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Review Of The Biological Effects Of Schiff Bases And Their Derivatives, Including Their Synthesis

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ABSTRACT:

Background : *Aldehyde and amine buildup can shape Schiff's base complex of metal. Amino and carbonyl mixtures address a sizable group of ligands used to make Schiff bases that can facilitate with metal particles by the nitrogen iota of an azomethine particle. There has been much interest in these ligands. The C=N connect, in which different azomethines have been researched and professed to overwhelm massive organic activity, like impacts against microorganisms, growths, and infections, as well as against jungle fever and disease, might be the reason for the significance of azomethine replacements. Schiff base metal complexes have recently proven valuable compounds in various fields, including industry and medicine. Schiff's bases are the ideal substance with unmatched organic and inorganic chemistry service. because of the extensive range of biological movements that Schiff base ligand display and their complexes collection, use in clinical applications is observed to have affected the chemistry of Schiff bases, their derivatives, synthesis methods, and the specific biological applications for these compounds, along with the ones for antibacterial, antifungal, anticancer, and antiviral objectives, are defined on this overview. The manufacture, characterization, and biological results of Schiff bases and their derivatives can be discussed in this assessment.*

Keywords: Biological Use, Antiviral, Antifungal, And Antibacterial Characteristics Of Schiff's Base.

Article Information

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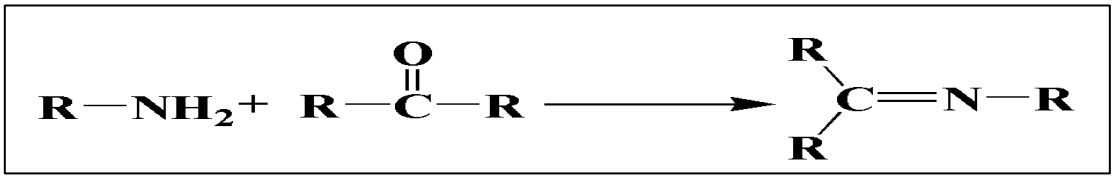
INTRODUCTION

Schiff bases' chemistry

According to Scheme 1. compounds of Schiff's base with a primary amine and a carbonyl molecule condense to form the chemical compound azomethine (-CH=N-).



Scheme 1: Condensation reaction resulting in a Schiff's base structure

Hugo Scientist made the preliminary discovery of Schiff base compounds in 1864. That attaches with the nitrogen atom to an alkyl organization (or aryl organization) in the carbon-nitrogen double

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bond makes up the Schiff base.$R1R_2C=NR_3$ is a standard chemical formula for Schiff's headquarters, where R3 denotes an alkyl or phenyl group [1-3].

Numerous molecules, including amino thiazoles, amino acids, triazole rings, thiosemicarbazides, and isatin compounds, have been exploited to create the Schiff bases[4]. Aliphatic aldehydes Compared to aromatic aldehydes, which are more stable and have a strong conjugation system existence, Schiff's bases can be eagerly polymerized and are generally unstable. When interacting with various transition metals on five- or six-membered chelate metals, Schiff bases, commonly di, tri, or tetradentate ligands, generate centered stable complexes.

The imine nitrogen of the azomethine group's low essential strength, monodentate Schiff bases cannot form stable complexes. Additionally, to interact with -OH/SH groups and azomethine, many metal ions can interact with dentate or tridentate Schiff base ligands[5], stabilizing them at various oxidation levels during chelation.

Since they may create carbon-nitrogen bonds, Schiff base reactions are crucial in synthesizing organic compounds. In many enzymatic processes where an enzyme interacts with an amino or carbon group in a substrate, Schiff bases can also be essential. In a process known as catalysis, an enzyme's initial amine commonly referred to as a base for Schiff [6–8]. In several procedures, including building molecular ferromagnets, catalysis, biological modeling, and complex cluster assembly, Schiff bases have been used. Schiff base metal complexes interest coordination chemists due to their simple synthesis, varied structural makeup, and wide range of uses. The uses of Schiff base metal complexes in organic chemistry are numerous. Potentiometric sensors use Schiff-based ligands as cation carriers because they provide targeted cations with good selectivity, sensitivity, and stability. Potentiometric sensors have used metal ions as cation carriers, such as Ag(I), Al(III), Co(II), Cu(II), Gd(III), Hg(II), and Ni(II)[10-12].

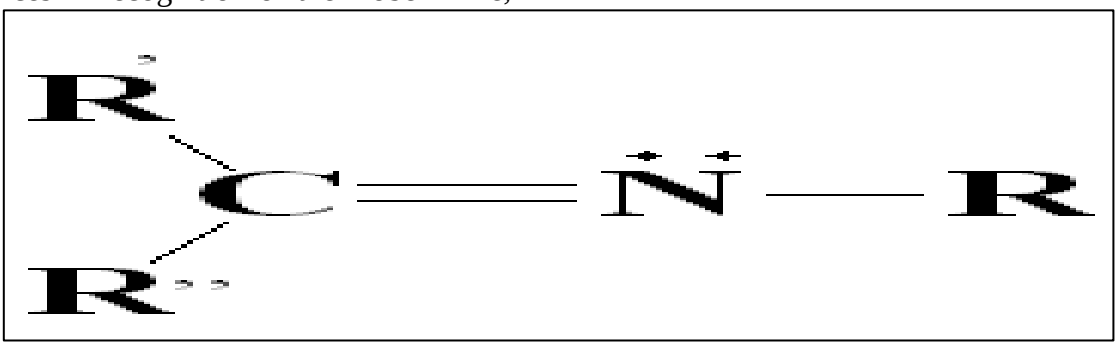
Additionally, olefin molecules can be hydrogenated with the aid of Schiff bases. Because a monolayer naturally forms on the surface to prevent corrosion, these materials can be employed in corrosion applications [10]. Inorganic, analytical, and biological chemistry are just a few fields where Schiff bases are helpful. Because of a wide range of bodily effects, including their anti-inflammatory qualities. There are several uses for Schiff bases in medicine and pharmaceuticals, including analgesic [8–12], antibacterial [16–17], anticonvulsant [18], antitubercular [19], anticancer [20, 21], antioxidant [22], and anthelmintic [23]. This nitrogen atom may be particularly relevant [24, 25]. Due to their wide range of therapeutic activity, thiosemicarbazone transition metal complexes have recently attracted attention. [26-29]This calls for several compounds with different functions. [30].

Recent developments in medicinal chemistry have focused on complexes of sulfur-containing ligands. According to research, isatin Schiff and Mannich bases have biological effects like antibacterial, antifungal, antiviral, anti-HIV, antiprotozoal, and antihelminthic activities [37–39]. Md developed several Schiff grounds and their metal complexes. Saddam Hossain and Md. Kudrat-E-Zahan [40–45]. It has been demonstrated that isatin and diethyldithiocarbamate Schiff base create a [46].

The creation of Schiff bases and their synthesis

Developed Schiff bases by condensing primary amines and carbonyl compounds [48]. A ketone (or aldehyde) that mimics Schiff base, commonly known as imine or azomethine, has the imine or azomethine group replaced for the carbonyl group (C=O) [49–52]. A molecule with an aryl or alkyl group (R) and a nitrogen atom connected, but not to hydrogen, is referred to as a Schiff base or a Schiff's base.

The same thing as an azomethine is a Schiff base. Hugo Schiff's name was given to these substances in recognition of the Nobel Prize, and they share the following characteristics in general, illustrated in Scheme **2.**



Schema 2: Schiff's overall organization

Generally speaking, Schiff bases may stabilize various metals with various oxidation states, improving their performance in several catalytic processes [54]. The oxygen atoms in NO or N_2O_2-donor groups are a typical component of Schiff bases; however, Sulfur, atoms of nitrogen or selenium, where R is an alkyl or aryl group, can alternatively be used to substitute the oxygen atoms. Compared to their alkyl equivalents, aryl Schiff bases are far more stable and less complicated to produce aldehydes aliphatic[58–60]. Compared to effectively conjugated aromatic, Schiff grounds are more brittle and highly polymerizable than aldehydes[56–57]. The first stage in producing a Schiff base is the synthesis of Schiff base ketones, as depicted in **Figure 1.** This reversible reaction frequently occurs during heating or when an acid or base is catalyzed.

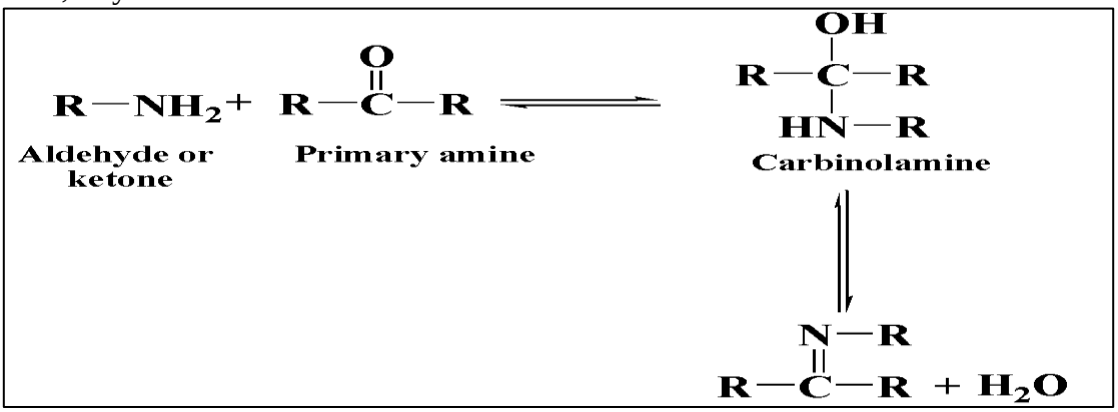


Figure 1 shows the reversible reaction of an aldehyde or ketone forming a Schiff base.

Removal of water, product separation, or a combination of the two processes produces this formation. Additionally, Numerous Schiff bases can hydrolyze back to their primary components (aldehydes, ketones, and amines) in an aqueous or basic. A different method of producing Schiff bases exists to address the issue of nucleophilic addition to the carbonyl group. The amine serves as the nucleophile in this instance. The amine combines with the aldehyde or ketone in the first step of the Schiff base production pathway to create the unstable addition chemical carbinolamine. We can use acid or base-catalyzed routes to extract water from carbinolamine. Carbinolamine undergoes acid-catalyzed dehydration since it is an alcohol. Usually, carbinolamine dehydration is viewed as the phase that determines how quickly Schiff bases develop, and then acids are used to catalyze the reaction. Due to the basicity of amines, the acid concentration is to be

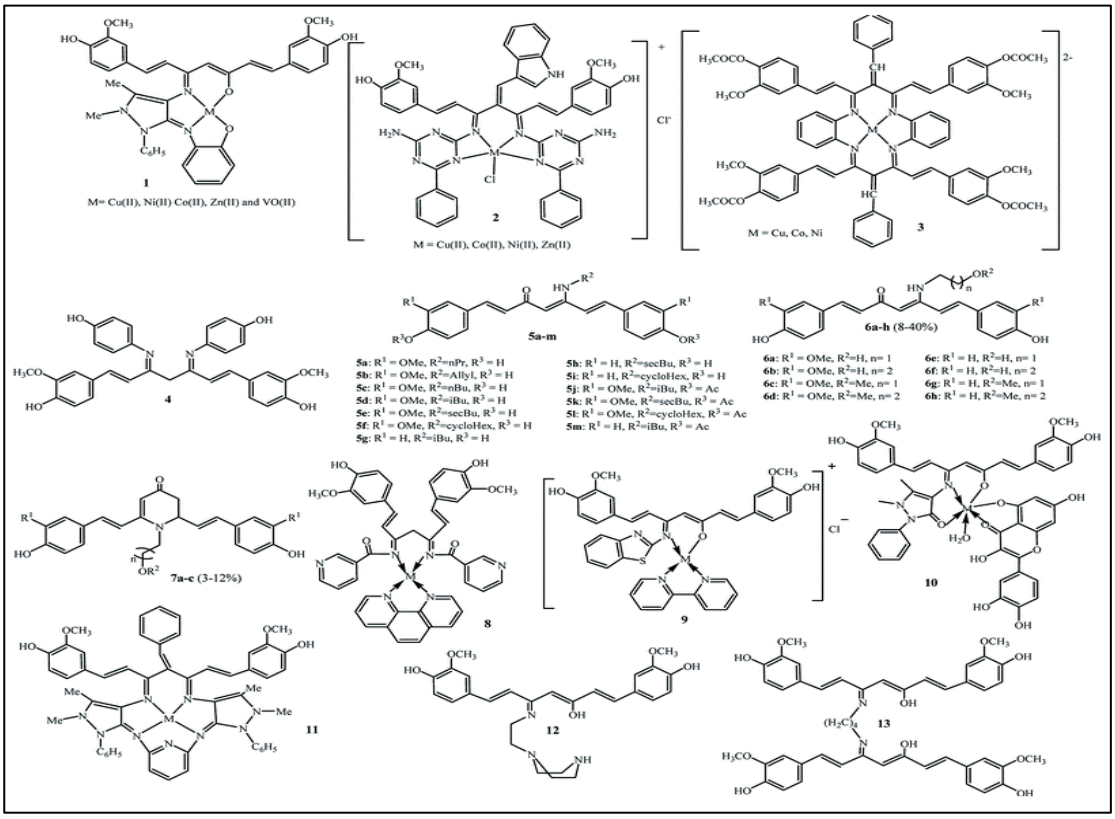
maintained. The amine no longer becomes nucleophilic if it is protonated, which causes equilibrium to be tugged to the left and prevents carbinolamine from forming. Therefore, it is desirable to synthesize a lot of Schiff bases in a somewhat acidic media. When exposed to bases, carbinolamines may lose moisture more quickly.

Except that it is not a coordinated reaction, this reaction is the same as removing E_2 alkyl halides. When an anionic intermediate is present, it passes through two processes: addition and subtraction [61].

Schiff base utilized in biology and its derivative is

Derivative of the curcumin Schiff base

The Schiff base method was used to assess the antibacterial and antifungal activity of particular ligands and their complexes against the microorganisms Candida albicans, Escherichia coli, Salmonella typhimurium, Staphylococcus aureus, Streptococci, and Pseudomonas aeruginosa. All investigated compounds demonstrated more significant biological potential than the unstudied ligand. On the other hand, the Zn(II) complex had solid antibacterial activity (Zone of Inhibition in mm: 9–14).



The structure of curcumin Schiff base derivatives is shown in Figure 2.

Curcumin can be transformed into the keto tautomer by the Knoevenagel condensation, which increases the likelihood that it will react with amines to form Schiff bases. Tharmaraj and colleagues employed this technique to convert indole-3-aldehyde into a di-ketone that curcumin cannot metabolize. The synthetic process was then used to grow the metal(II) complexes. They identified the compounds' nonlinear features, which are important in several photonic applications, and their pharmacological characteristics. In curcumin, Schiff base two, conjugated electron complexes can produce sizable nonlinear polarizabilities.

Additionally, the substances' effectiveness against fungi, including Aspergillus flavus and Penicillium digitatum, and bacteria like Streptococcus S. aureus with Streptococcus pyogenes. All metal(II) complexes had higher activity levels than compound 2's. Compared to amikacin, the copper complex showed stronger antibacterial activity Inhibitory zone against Staphylococcus aureus in mm: 23 [66,67]. The completed item and a green synthesis were then used to functionalize copper oxide nanoparticles [68]. Bio-functionalized copper oxide nanoparticles have demonstrated strong antibacterial action, especially against Aspergillus niger and Bacillus subtilis. The zone of inhibition is 19 mm. The spectroscopic methods in the UV-visible, emission, and circular dichroism ranges were used to examine the calf's thymus.

Porphyrins, tetra azo macrocycles occurring in nature, could be used as models for this structure [68], and showed greater interaction than the other chemicals. Figure 2 illustrates how Revathi improved curcumin using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay in the presence of methylene and keto groups. The generated 4-hydroxy benzaldehyde and N, N-dimethyl amino benzaldehyde were less energetic than curcumin (IC50 values about 50 M). By substituting at the keto site, compound 4's antioxidant activity was reduced, and even at 250 M, the compound's IC50 value was not reached [69]. Camp and D'hooghe assessed the labile-like structure in charge of curcumin's low bioavailability. As a result, they produced thirteen new -enaminone compounds using **Figure 2**, which illustrates microwave irradiation. DPPH was used to investigate the antioxidant activity, and ferric can reduce plasma (FRAP) testing accuracy.

In both experiments, the antioxidant activity of compounds 5a–f was exceptional and on par with that of curcumin. In the aromatic rings of substances, the -OCH3 group is in the same ortho position as the phenol group as it is on curcumin 5a through f. According to both investigations, the ortho methoxy-free molecules (5g-i) had very little antioxidant activity. No antioxidant action was detected in compounds 5j-m with phenolic groups retained after acetylation. different cell lines, including HT-29 and Caco-2, were tested against curcumin compounds in differentiated and undifferentiated conditions.

The results showed that differentiated Caco-2 cells were not cytotoxic to any derivatives. These cells resemble the enterocytes seen in the inner lining of the digestive tract[70]. The compounds and curcumin were both soluble in water. The solubility of the -enaminone molecule in water is improved by adding more polar amines, without affecting the biological activity of the resultant curcuminoids, according to studies by Camp and D'hooghe. Curcumin and hydroxyalkyl or methoxy alkyl amines were mixed, and polar hydroxyl and methoxy groups were to produce eight novel -enaminone analogs (6a-h) [71].

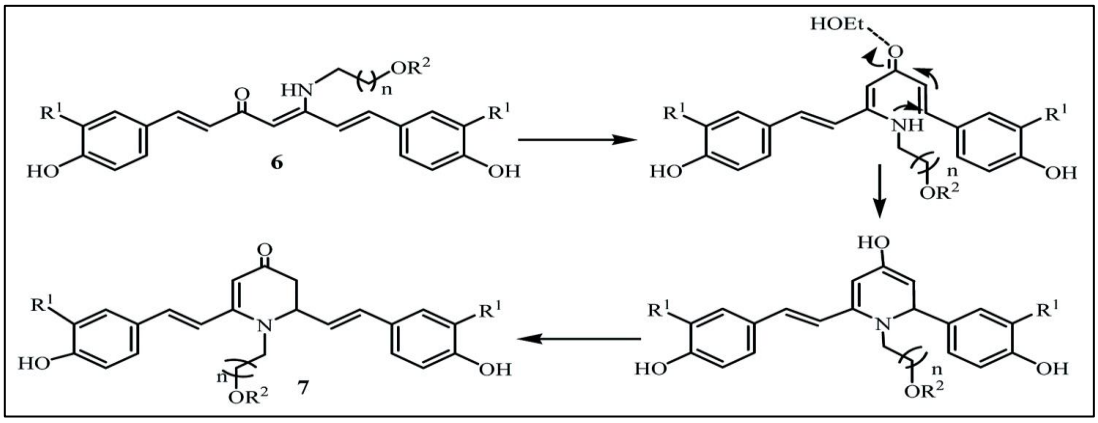


Figure 3 Depicts the proposed method for the manufacture of dihydropyridine-4-ones 7a-c.

A unique curcumin Schiff base 13, illustrated in Figure 2, has recently been discovered due to its high solubility in aqueous solutions and ability to operate during environmentally friendly manufacture. Compound 13 was more effective against E. coli and P. aeruginosa than curcumin but less effective against S. aureus and B. subtilis [72]. The experimental compounds (1–13) demonstrate a wide range of biological activity, synthesis methods, and yields.

Table 1 Lists the properties of compounds 1 through 13.

Compound	Condition of synthesis	Yield (%)	Activity	Outcome	Reference
1	6 h reflux of precursors in EtOH	80	Antibacterial	Zn(II) complex showed the highest activity but was not compared with curcumin	73
2	6 h stirrer of precursors in EtOH at room temperature and in presence of piperidine	72	Antibacterial and antifungal	Cu(II) complex showed the highest activities but was not compared with curcumin	74
3	24 h reflux of precursors in MeOH	No reported	DNA cleavage	Cu(II) complex showed the highest K_b	75
4	6 h stirrer of precursors in MeOH at room temperature and in presence of piperidine	56.9	Antioxidant	Lower antioxidant activity compared to curcumin	76
5a–i	Heating of precursors in 2-methyl-THF or $CHCl_3$ under microwave irradiation for 1–1.75 h at 80 °C in presence of MK10 clay and acetic acid	11–58	Anticancer and antioxidant	**5a–f** showed comparable antioxidant activity to curcumin, 5i was strongest anticancer agent	77
5j–m	Heating of **5d–g** and acetic anhydride in 2-methyl-THF in presence of pyridine	42–67	Anticancer and antioxidant	No antioxidant activity and low anticancer activity	78
6a–h	Heating of precursors in 2-methyl-THF or EtOH or DMF under microwave irradiation for 1–1.5 h at 70–100 °C in presence of MK10 clay and acetic acid	8–40	Anticancer and antioxidant	Enhanced water-solubility and anticancer activity and comparable antioxidant activity (**6a–d**) to curcumin	79
7a–c	Heating of precursors in EtOH under microwave irradiation for 1–1.5 h at 70–100 °C in presence of MK10 clay and acetic acid	3–12	Anticancer and antioxidant	Enhanced water-solubility compared to curcumin	80
8	12 h reflux of precursors in MeOH	74	Antibacterial and anthelmintic	Cu(II) complex showed the highest activities but was not compared with curcumin	81
9	4 h reflux of precursors in EtOH	66	Antibacterial/antifungal and DNA cleavage	Cu(II) complex showed the highest activities but was not compared with curcumin	82
10	3 h reflux of precursors in EtOH	75	Antibacterial/antifungal and DNA cleavage	Cu(II) complex showed the highest activities but was not compared with curcumin	83
11	24 h reflux of precursors in EtOH in presence of anhydrous K_2CO_3	No reported	Antibacterial/antifungal and anticancer	Cu(II) complex showed the highest activities but was not compared with curcumin	84
12	6 h reflux of precursors in MeOH	74	Anticancer and antioxidant	Cu(II) and Zn(II) complexes showed the highest activities but was not compared with curcumin	85
13	6 h reflux of precursors in EtOH in presence of acetic acid	85	Antibacterial	Higher activity against Gram-positive and lower activity against Gram-negative bacteria compared to curcumin	86

Sulfonamide Schiff bases

The pharmacological compounds used in the development of novel drugs **Figure 4**. The ability of A. niger, A. flavus, C. lunata, Trichoderma viride, S. aureus, Bacillus cereus, Salmonella typhi, Pseudomonas aeruginosa, and Salmonella typhi to suppress the growth of these substances was investigated. Several chemicals were tested for cytotoxicity in the cancer cell lines HeLa, Hep-G2, QG-56, and HCT-116. Paw edema caused by carrageenan was used to test the in vivo efficiency of an anti-inflammatory drug. The bioassay results revealed their activity increases when sulfonamides are coupled with curcumin. Compounds 14a-e with one sulfonamide molecule had higher antibacterial and antifungal activity than compounds 15a-e with two sulfonamide molecules connecting both carbonyls of curcumin. 14b-e and 14e (MIC 20 M against all bacteria) were the most efficacious compounds (MIC 20 M against all fungi except A. flavus). Among the 15a-e compounds, only 15e (IC50 values 25-50 M) surpassed curcumin in cytotoxicity. Furthermore, the anti-inflammatory effects of compounds 15e and 14e were the strongest, with percentage inhibitions of 40.3 and 38.7, respectively. This study's overall findings [87] show that the enolic group may be used for biological activities.

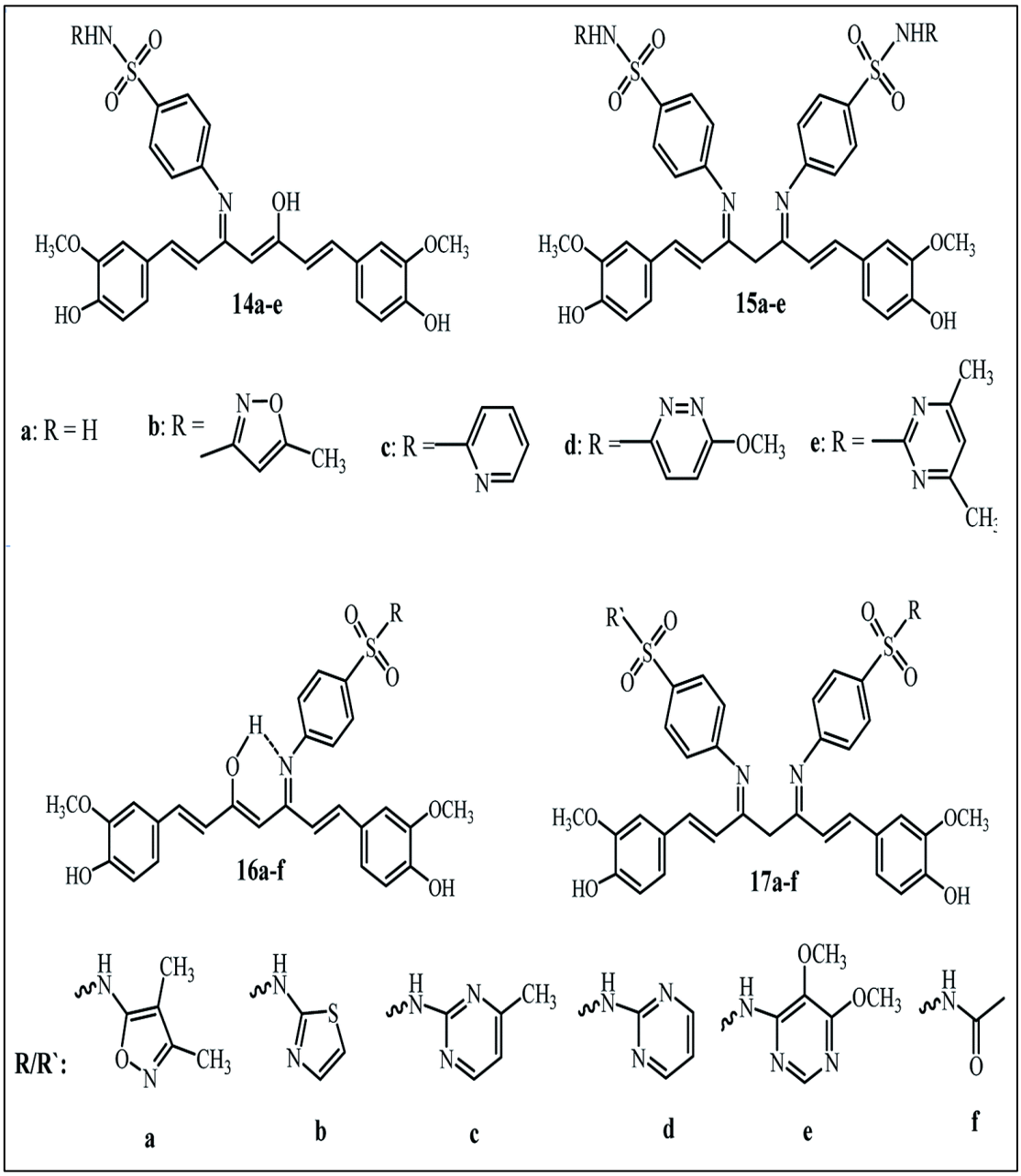


Figure. 4 depicts curcumin sulfonamide derivatives.

Ahmed et al. investigated the synthesis of various curcumin-Schiff bases, including one or two benzenesulfonamide moieties, as shown in Figure 4. (17a-f) and (16a-f). all demonstrated; also, it was revealed that 16a had powerful synergistic effects when combined with ciprofloxacin, a common antibacterial drug, or nystatin, a common antifungal drug. When combined, compound 16a (7.8 g mL1) with ciprofloxacin (0.12 g mL1) was eight times more efficient at preventing the growth of MRSA [88]. These substances are moderate to suitable inhibitors of the urease enzyme, according to in vitro experiments that this research team did on them [89]. 14-17 Materials **Table 2** details their synthesis, yields, and biological activity.

Table 2 summarizes the properties of compounds 14 through 17.

Compound	Condition of synthesis	Yield (%)	Activity	Outcome	Reference
14a–e	3–4 h reflux of precursors in EtOH	87–91	Antibacterial/antifungal and anti-inflammatory	**14b–e** showed higher activity compared to curcumin	**90**
15a–e	2–3 h heating of precursors in EtOH at 60 °C in presence of acetic acid	91–94	Antibacterial/antifungal and anti-inflammatory	Only **15e** showed higher activity compared to curcumin	**91**
16a–f and **17a–f**	Reflux of precursors in EtOH in presence of acetic acid	71.5–92.5	Antibacterial/antifungal and anti-inflammatory	**16a** was most potent compound	**92**

Schiff base metal compounds that are macrocyclic

Organic chemicals have piqued the interest of researchers in this sector more than inorganic and coordination compounds, which comprise most medications. Certain inorganic and coordinated compounds have shown favorable bioactive properties in recent decades [93-100]. The treatment for malignancies such as ovarian and testicular cancers [101–103]. Surprisingly, only two of the thousands of cisplatin analogs created and proven to be prospective anticancer medications operate (carboplatin and oxaliplatin). The others have remained dormant and have all been exhausted in the therapeutic management of neoplastic disorders [104–106]. Even though the equivalent frequently [107]. The capacity to explain elements of the reactivity of Schiff base coordination compounds that are usually impossible to investigate using less stable similar complexes of non-cyclic ligands has sparked interest in this class of substances. Several Schiff base macrocycles have been used for various purposes, including the modeling of cationic, anionic, and cationic-anionic metal-bio site neutral receptors [109].

The role of macrocyclic Schiff base-type ligands in metal ion complexes is gaining attention. The features and applications of naturally occurring biological macrocycles and their complexes have also been improved via synthetic macrocyclic chemistry [110]. Among all the macrocyclic Schiff base complexes, those produced by functionally substituted ligands with diverse donor groups are the most intriguing binuclear complexes that can be formed utilizing compartmental ligands [111].

Many medications based on this pharmacophore are already in use or are in advanced clinical studies. As antibacterial treatments, macrocyclic Schiff bases and their metal complexes hold immense biological promise. For instance, the acetylcholinesterase (AChE) inhibitor imperil has previously been used to treat Alzheimer's illness, even though dBET57 is an effective chimeras class medication that inhibits cancer proteolysis [112]; figure 5 shows how these intercalator's Pt (II) conjugates were created using direct Schiff base cyclo-condensation. This article describes a novel class of platinum-based antitumoral agents [113].

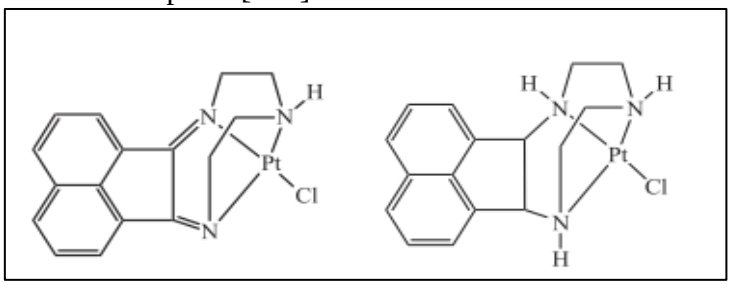


Figure 5: The structural features of platinum-based antitumoral

Figure 6. Show microbes, which included E. coli, S. aureus, S. epidermidis, B. subtilis, K. pneumonia, P. aeruginosa, and S. aureus bacteria strains [114].

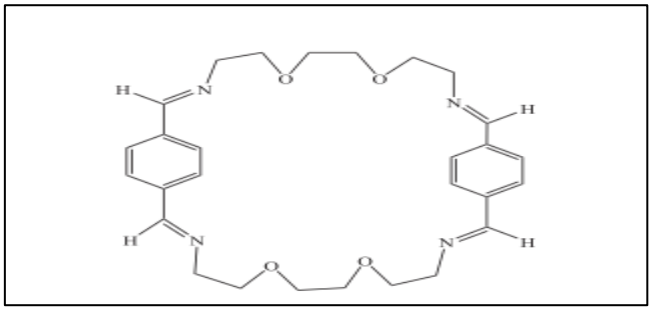
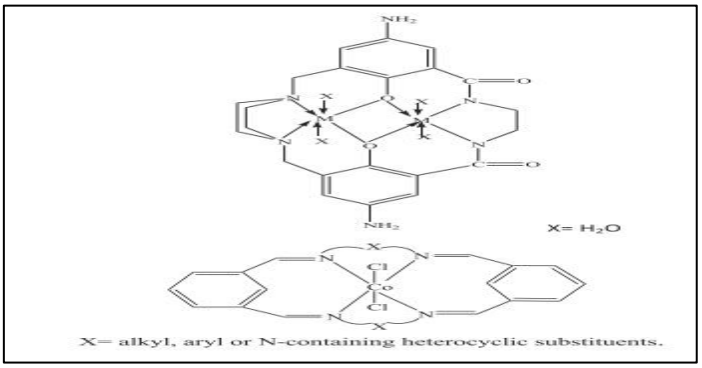


Figure 6. structures of macrocyclic

Figure 7 shows microbes and well-known antibacterial medications used to test each one's antibacterial potency. These compounds were all more efficient than streptomycin and ampicillin [115].



In Figure 7, the structures of ten compounds under investigation are displayed.

After non-template, o-phthalaldehyde is condensed with aromatic amino alcohols. P.M. Reddy and associates created a variety of novel macrocyclic compounds. Figure 8 demonstrates this approach. The substances' antimicrobial properties were discovered. The fungus A. flavus and Fusarium sp. also put the macro-cycles to the test in vitro [115].

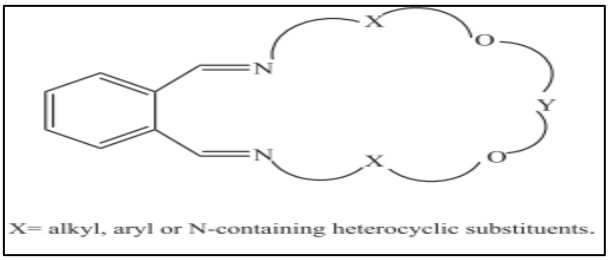
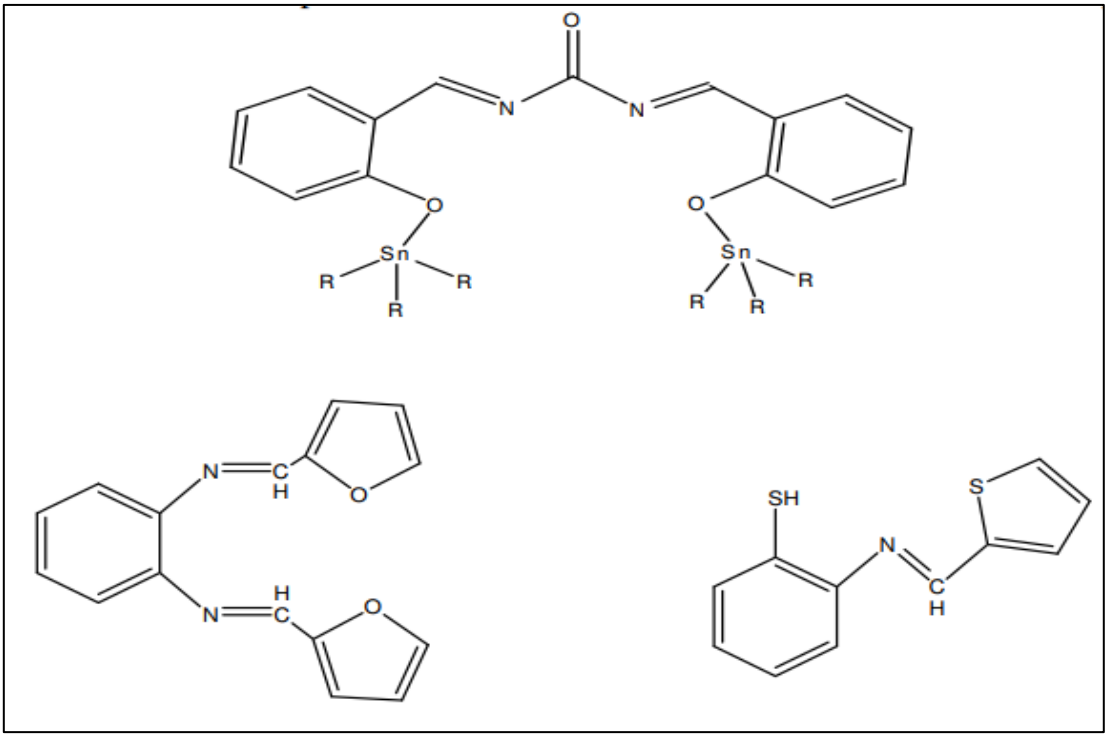


Figure 8 displays the structures of the compositions

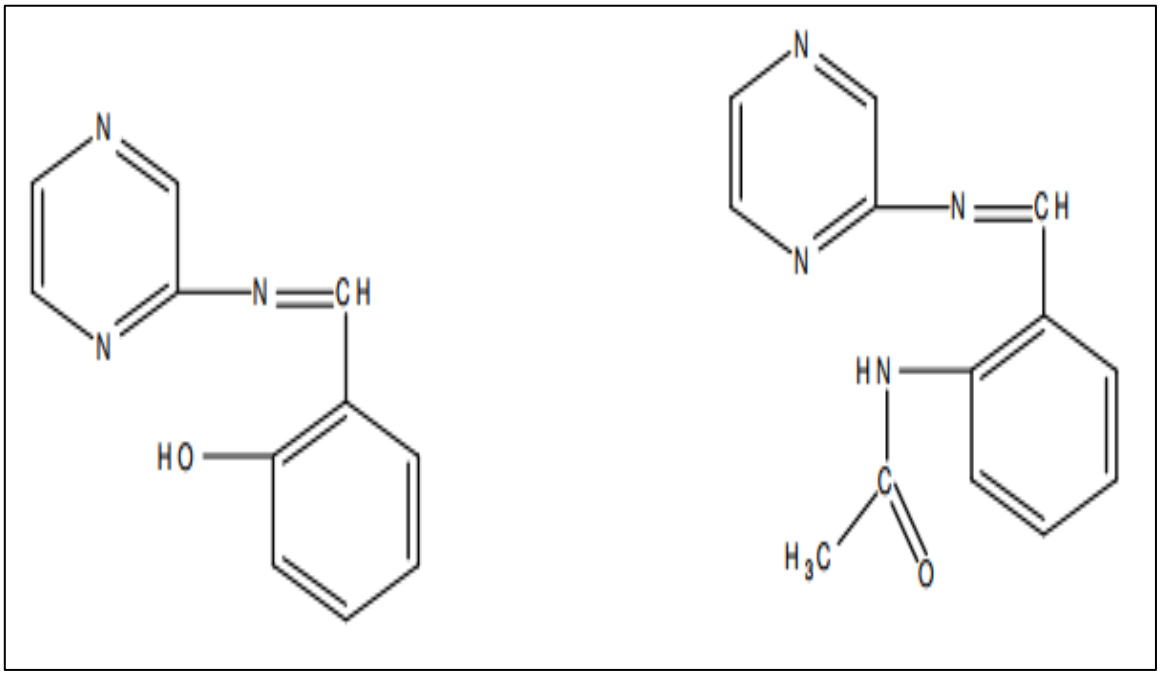
Several Schiff base metal complexes

Schiff's fundamental assumptions **Figure 9** depicts the results of Gehad and colleagues' investigations into metal complexes derived from 2-furan carboxaldehyde and o-phenylenediamine, 2-thiophene carboxaldehyde, and 2-amino thiophenol [116].



The compounds produced during the synthesis are depicted in Figure 9.

The condensation reaction of 2-aminopyrazine with salicylaldehyde and acetamido benzyl aldehyde produced some physiologically active pyrazine-derived Schiff base ligands, as shown in **Figure 10**



The compositions under research are shown in Figure 10

SARI et al. discovered several new amino acid Schiff bases. Discovered are shown in **Figure 11** in their synthesis and antibacterial activity [119]

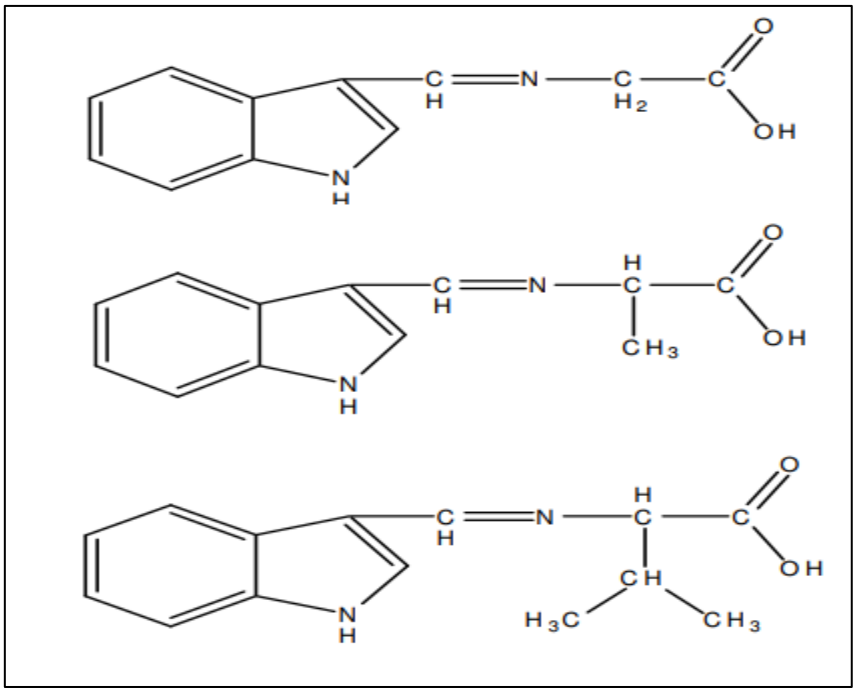


Figure 11 displays the structures of the artificial compounds

When O-hydroxybenzaldehyde condenses with amine, it produces transition metal complexes with Schiff base ligands Cu^{+2}, Ni^{+2}, and Co^{+2}, as shown in **Figure 12.** The ability of the compounds to battle bacteria and fungi was investigated and reported on [120]

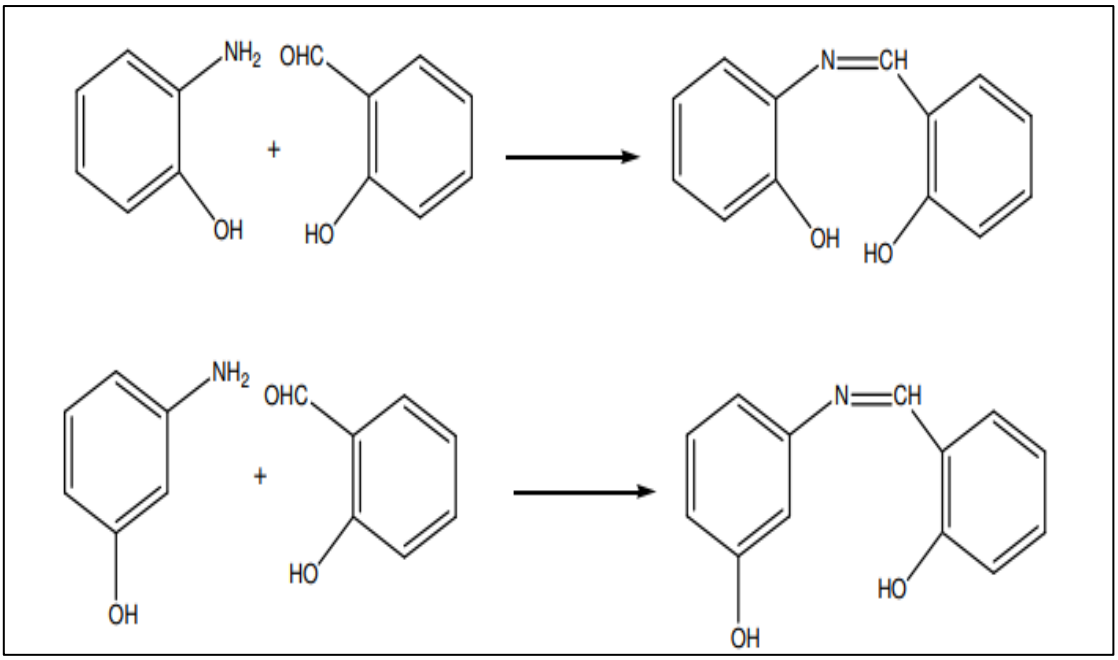


Figure 12: Compound structures from the synthesis

Figure 13 illustrates the research conducted by Daniel et al. on the chiral Schiff base Ruthenium (III) complex as well as diagnostic, catalytic, and antibacterial applications. For each of the novel compounds, these authors suggest an octahedral structure. These compounds also have proven catalytic and antibacterial properties [121].

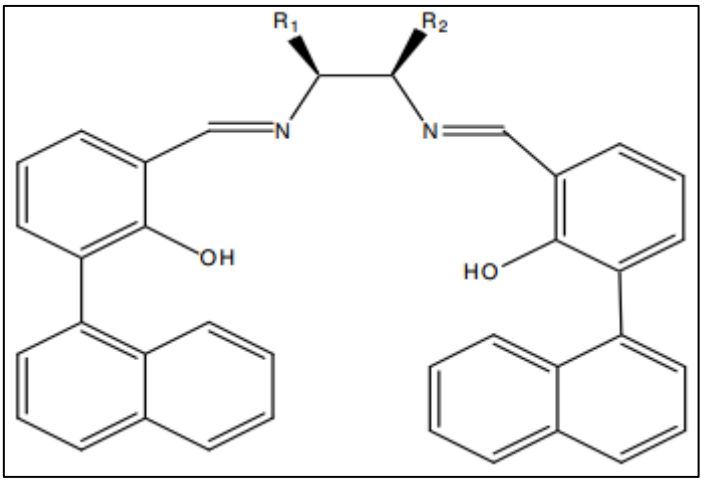


Figure 13 shows the compositions' structures.

Figure 14 depicts the findings of a study by Baluja et al. [122] on the biological activities of Schiff bases and their metal complexes.

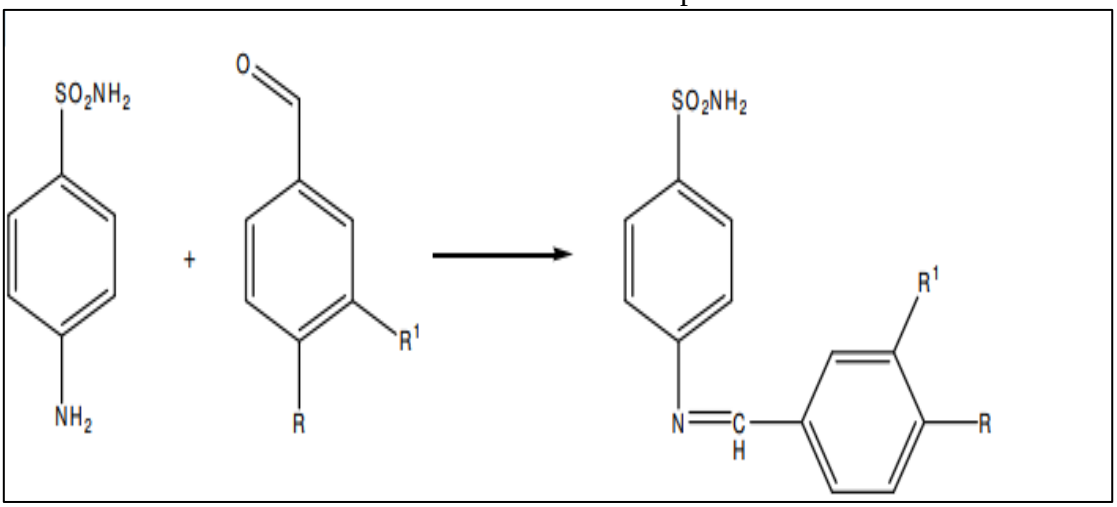


Figure .14 depicts the structures of the synthesized compounds.

Figure 15 shows how to produce three novel chitosan Schiff bases by combining chitosan with 2-chloroquinoline-3-carbaldehyde, quinazoline-6-carbaldehyde, and oxazole-4-carbaldehyde, in that order. Nuclear magnetic resonance (1H and 13C NMR) and FT-IR spectroscopy were used to verify the structural integrity of the newly generated derivatives. Gram-positive and Gram-negative bacteria, including E. coli, Klebsiella pneumoniae, Staphylococcus aureus, and Streptococcus mutants, were used to test the antibacterial activity of the produced compounds. Candida albicans with Aspergillus fumigatus, two different kinds of fungi, were also tested. An MTT screening test was used to gauge the novel chitosan Schiff bases' cytotoxicity. The results showed no cytotoxic action and a critical activity increase of the synthesized molecule compared to chitosan, typically examined by bacteria and fungus. According to our findings, these brand-new chitosan Schiff bases are fresh biomaterial contenders with improved antibacterial and nontoxic properties for biology and medicine use [123].

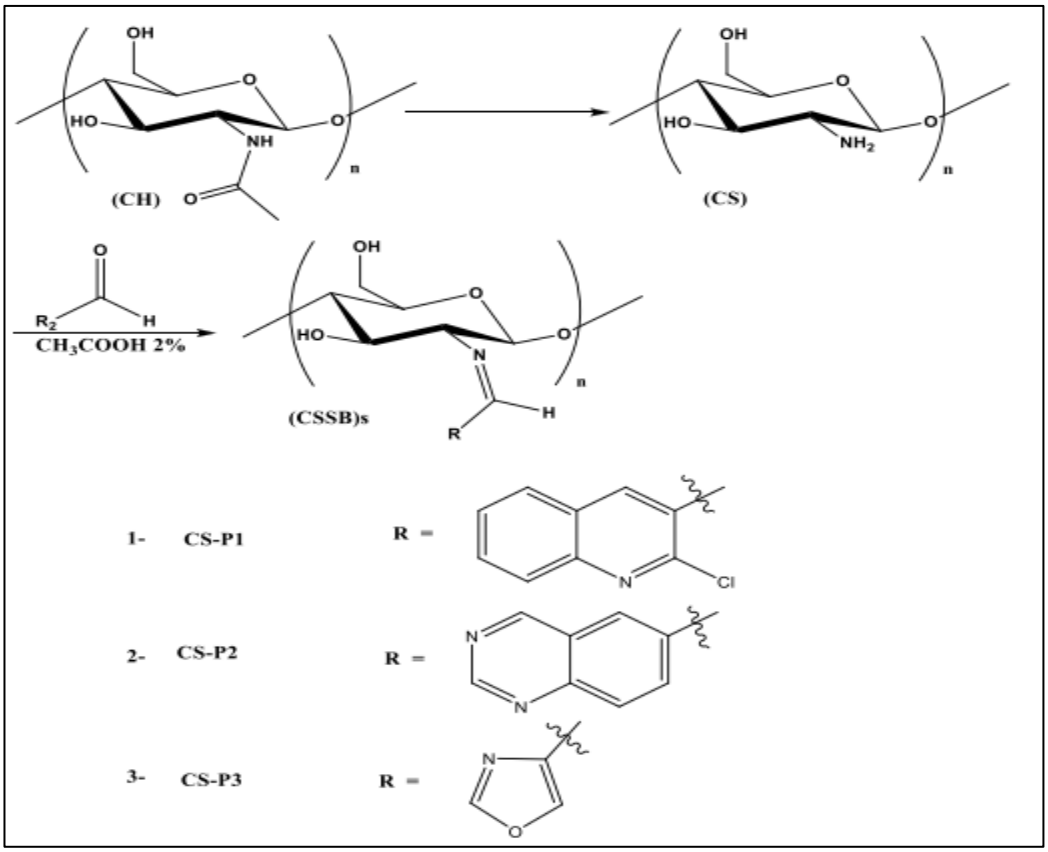


Figure 15: Creating new chitosan Schiff bases derivatives

CONCLUSION

This review paper may address the most recent advances in the research of Schiff bases and their derivatives, as well as their structure, characterization, and biological uses. These ligands and their metal complexes have found widespread application in industrial and medical settings. The Schiff bases are the primary investigators for industrial sector applications. As a result, further investigation into the biological effects of this class of Schiff base compounds is required. Despite the fact that Schiff bases and their derivatives have a growing body of research, more studies have recently focused on their potential as antibacterial and antiviral medicines.

REFERENCES

1. Q. Yao, Z. q. Ke, S. Guo, X. s. Yang, F. x. Zhang, X. f. Liu, X. Chen, H. g. Chen, H. Y. Ke and C. Liu, *J. Mol. Cell. Cardiol.*, 2018, 124, 26–34

2. D. Bagchi, S. Chaudhuri, S. Sardar, S. Choudhury, N. Polley, P. Lemmens and S. K. Pal, *RSC Adv.*, 2015, 5, 102516–102524

3. A. I. Joseph, R. L. Edwards, P. B. Luis, S. H. Presley, N. A. Porter, and C. Schneider, *Org. Biomol. Chem.*, 2018, 16, 3273–3281 X. X. Yang, C. M. Li, Y. F. Li, J. Wang and C. Z. Huang, *Nanoscale*, 2017, 9, 16086–16092.

4. S. Izui, S. Sekine, K. Maeda, M. Kuboniwa, A. Takada, A. Amano and

H. Nagata, *J. Periodontol.*, 2016, 87, 83–90

5. G. Djiokeng Paka, S. Doggui, A. Zaghmi, R. Safar, L. Dao, A. Reisch, A. Klymchenko, V. G. Roullin, O. Joubert and C. Ramassamy, *Mol. Pharm.*, 2016, 13, 391–403
6. J. Chen, Z. M. He, F. L. Wang, Z. S. Zhang, X. z. Liu, D. D. Zhai and W. D. Chen, *Eur. J. Pharmacol.*, 2016, 772, 33–42
7. H. Soleimani, A. Amini, S. Taheri, E. Sajadi, S. Shafikhani, L. A. Schuger, V. B. Reddy, S. K. Ghoreishi, R. Pouriran and S. Chien, *J. Photochem. Photobiol. B Biol.*, 2018, 181, 23–30
8. M. Qureshi, E. A. Al-Suhaimi, F. Wahid, O. Shehzad and A. Shehzad, *Neurol. Sci.*, 2018, 39, 207–214
9. F. N. Kaufmann, M. Gazal, C. R. Bastos, M. P. Kaster and G. Ghisleni, *Eur. J. Pharmacol.*, 2016, 784, 192–198
10. P. Kumaraswamy, S. Sethuraman and U. M. Krishnan, *J. Agric. Food Chem.*, 2013, 61, 3278–3285
11. R. K. Singh, D. Rai, D. Yadav, A. Bhargava, J. Balzarini and E. De Clercq, *Eur. J. Med. Chem.*, 2010, 45, 1078–1086
12. M. G. El-Gazzar, N. H. Zaher, E. M. El-Hossary and A. F. Ismail, *J. Photochem. Photobiol. B Biol.*, 2016, 162, 694–702
13. Y. P. Bharitkar, M. Das, N. Kumari, M. P. Kumari, A. Hazra, S. S. Bhayye, R. Natarajan, S. Shah, S. Chatterjee and N. B. Mondal, *Org. Lett.*, 2015, 17, 4440–4443
14. M. Singh, A. Hazra, Y. P. Bharitkar, R. Kalia, A. Sahoo, S. Saha, V. Ravichandran, S. Ghosh and N. B. Mondal, *RSC Adv.*, 2018, 8, 18938–18951
15. L. Rišiaňová, E. Fischer-Fodor, J. Valentová, C. Tatomir, N. C. Decea, P. Virag, I. Pechová, F. Devínsky and N. Miklášová, *Bioorg. Med. Chem. Lett.*, 2017, 27, 2345–2349
16. A. Arezki, G. G. Chabot, L. Quentin, D. Scherman, G. Jaouen and E. Brulé, *Med. Chem. Commun.*, 2011, 2, 190–195
17. F. C. Rodrigues, N. A. Kumar and G. Thakur, *Eur. J. Med. Chem.*, 2019, 177, 76–104
18. S. A. Noureddin, R. M. El-Shishtawy and K. O. Al-Footy, *Eur. J. Med. Chem.*, 2019, 182, 111631
19. S. Zhao, C. Pi, Y. Ye, L. Zhao and Y. Wei, *Eur. J. Med. Chem.*, 2019, 180, 524–535
20. P. Y. Khor, M. F. F. M. Aluwi, K. Rullah and K. W. Lam, *Eur. J. Med. Chem.*, 2019, 183, 111704
21. M. A. Tomeh, R. Hadianamrei and X. Zhao, *Int. J. Mol. Sci.*, 2019, 20, 1033
22. M. Thomas, A. Kulandaisamy and A. Manohar, *Int. J. Chem. Tech. Res.*, 2012, 4, 247–257.
23. S. Sumathi, P. Tharmaraj, C. Sheela and R. Ebenezer, *J. Coord. Chem.*, 2012, 65, 506–515
24. M. Jayandran, M. Haneefa and V. Balasubramanian, *Int. J. Chem. Nat. Sci.*, 2014, 2, 157–163
25. M. Jayandran, M. Haneefa and V. Balasubramanian, *Indian J Sci Technol*, 2016, 9, 1–9

26. J. Rajesh, A. Gubendran, G. Rajagopal and P. Athappan, *J. Mol. Struct.*, 2012, 1010, 169–178

27. M. H. Afsarian, M. Farjam, E. Zarenezhad, S. Behrouz and M. N. S. Rad, *Acta Chim. Slov.*, 2019, 66, 874–887

28. R. Revathi, D. A. Ananth, A. Rameshkumar and T. Sivasudha, *Asian J. Chem.*, 2015, 27, 1489–1494

29. R. De Vreese, C. Grootaert, S. D'hoore, A. Theppawong, S. Van Damme, M. Van Bogaert, J. Van Camp and M. D'hooghe, *Eur. J. Med. Chem.*, 2016, 123, 727–736

30. A. Theppawong, R. De Vreese, L. Vannecke, C. Grootaert, J. Van Camp and M. D'hooghe, *Bioorg. Med. Chem. Lett.*, 2016, 26, 5650–5656

31. A. Kareem, M. Arshad, S. A. Nami and N. Nishat, *J. Photochem. Photobiol. B Biol.*, 2016, 160, 163–171

32. N. Raman, T. Chandrasekar, G. Kumaravel and L. Mitu, *Appl. Organomet. Chem.*, 2018, 32, e3922

33. J. Porkodi and N. Raman, *Appl. Organomet. Chem.*, 2018, 32, e4030

34. A. Palanimurugan and A. Kulandaisamy, *Asian J. Chem.*, 2018, 30, 1262–1268

35. A. Kareem, M. S. Khan, S. A. Nami, S. A. Bhat, A. U. Mirza and N. Nishat, *J. Mol. Struct.*, 2018, 1167, 261–273

36. N. G. Gogoi and J. G. Handique, *J. Chem. Sci.*, 2019, 131, 74

37. J. Lal, S. K. Gupta, D. Thavaselvam and D. D. Agarwal, *Eur. J. Med. Chem.*, 2013, 64, 579–588

38. M. Ahmed, M. A. Qadir, M. I. Shafiq, M. Muddassar, Z. Q. Samra and A. Hameed, *Arab. J. Chem.*, 2019, 12, 41–53

39. M. Ahmed, M. A. Qadir, A. Hameed, M. N. Arshad, A. M. Asiri and M. Muddassar, *Biochem. Biophys. Res. Commun.*, 2017, 490, 434–440

40. T. Chandrasekar, N. Pravin and N. Raman, *Inorg. Chem. Commun.*, 2014, 43, 45–50

41. T. Chandrasekar, N. Pravin and N. Raman, *J. Mol. Struct.*, 2015, 1081, 477–485

42. T. Chandrasekar and N. Raman, *J. Mol. Struct.*, 2016, 1116, 146–154.

43. P. J. Dyson, G. Sava, *Dalton Trans.* 2006, 16, 1929.

44. S. Trzaska, *Chem. Eng. News.* 2005, 83, 25.

45. D. P. Carpenter, *Reputation and power: corporate image and pharmaceutical regulation at the FDA*, Princeton University Press, Princeton, NJ (USA) 2010.

46. 63 Approval Summary for cisplatin for Metastatic ovarian tumors. FDA Oncology Tools. Food and Drug Administration, Center for Drug Evaluation and Research 1978.

47. E. Wiltshaw, *Platinum Metals Rev.* 1979, 23, 90.

48. D. Lebwohl, R. Canetta, *Eur. J. Cancer* 1998, 34, 1522.

49. H. Brunner, P. Hankofer, U. Holzinger, B. Treittinger, H. Schönenberger, *Eur. J. Med. Chem.* 1990, 25, 35.

50. N. Farrell, Y. Qu, M. P. Hacker, *J. Med. Chem.* 1990, 33, 2179.

51. N. Farrell, Y. Qu, L. Feng, B. van Houten, *Biochemistry* 1990, 29, 9522.

52. J. D. Roberts, B. van Houten, Y. Qu, N. P. Farrell, *Nucleic Acids Res.* 1989, 17, 9719.

53. C. Navarro-Ranninger, F. Zamora, J. M. Perez, I. Lopez-Solera, S. Martinez-Carrera, J. R. Masaguer, C. Alonso, *J. Inorg. Biochem.* 1992, 46, 267.

54. P. A. Vigato, S. Tamburini, L. Bertolo, *Coord. Chem. Rev.* 2007, 251, 1311.

55. P. Guerriero, P. A. Vigato, D. E. Fenton, P. C. Hellier, *Acta Chem. Scand.* 1992, 46, 1025.

56. C. Schattschneider, S. D. Kettenmann, S. Hinojosa, J. Heinrich, N. Kulak, *Coord. Chem. Rev.* 2019, 385, 191.

57. J. Y. Jia, Q. H. Zhao, Y. Liu, Y. Z. Gui, G. Y. Liu, D. Y. Zhu, C. Yu, Z. Hong, *Acta Pharmacol. Sin.* 2013, 34, 976.

58. R. P. Nowak, S. L. De Angelo, D. Buckley, Z. He, K. A. Donovan, J. An, N. Safaee, M. P. Jedrychowski, C. M. Ponthier, M. Ishoey, T. Zhang, J. D. Mancias, N. S. Gray, J. E. Bradner, E. S. Fischer, *Nat. Chem. Biol.* 2018, 14, 706.

59. C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Delivery Rev.* 1997, 23, 3.

60. J. Gao, F. R. Woolley, R. A. Zingaro, *J. Med. Chem.* 2005, 48, 7192.

61. B. H. M. Mruthyunjayaswamy, Y. J. Omkar, B. Ijare, S. G. Patil, S. M. Kudari, *Transition Met. Chem.* 2005, 30, 234.

62. H. I. Ugras, I. Basaran, T. Kilic, U. Cakir, *J. Heterocyclic Chem.* 2006, 43, 1679.

63. N. Nishat, M. M. Haq, T. Ahamad, V. Kumar, *J. Coord. Chem.* 2007, 60, 85.

64. P. M. Reddy, A. V. S. S. Prasad, K. Shanker, V. Ravinder, *Spectrochim. Acta a* 2007, 68, 1000.

65. H. Khanmohammadi, R. Arabahmadi, M. H. Abnosi, H. R. Khavasi, *Polyhedron* 2007, 26, 4963.

66. S. Sreedaran, K. S. Bharathi, A. K. Rahiman, L. Jagadish, V. Kaviyarasan, V. Narayanan, *Polyhedron* 2008, 27, 2931.

67. D. P. Singh, R. Kumar, J. Singh, *Eur. J. Med. Chem.* 2009, 44, 1731.

68. P. M. Reddy, Y. P. Ho, K. Shanker, R. Rohini, V. Ravinder, *Eur. J. Med. Chem.* 2009, 44, 2621.

69. P. G. Avaji, C. H. V. Kumar, S. A. Patil, K. N. Shivananda, C. Nagaraju, *Eur. J. Med. Chem.* 2009, 44, 3552.

70. D. P. Singh, R. Kumar, J. Singh, *J. Enzyme Inhib. Med. Chem.* 2009, 24, 883.

71. H.I. Ugras, I. Basaran,T. Kilic and U. Cakir, J. Heterocyclic Chem., 43, 1679. (2006)

72. F.M. Morad, M.M.EL. Ajaily and S.B. Gweirif, Journal of Science and ItsApplications., 1, 72 (2007).

73. E.A. Elzahany, K.H. Hegab, S.K.H. Khalil and K.N.S. Youssef, Australian Journal of Basic and Applied Science., 2(2), 210(2008).

74. G.K. Rao, K.N. Venugopala and P.N. Sanjay pai, Journal of Pharmacology and Toxicology., 2(5), 481(2007)

75. S. Bairagi, A. Bhosale, and M.N. Deodhar, E-Journal of Chemistry., 6(3), 759(2009).

76. Yi. Y.I., X.Q. Wei, M.G. Xie, and Z.Y. L.U., Chinese Chemical Letters., 15, 525(2004)

77. M.V. Aanandhi, S. George and V. Vaidhyalingam, ARKIVOC., (xi), 187(2008)

78. G.K. Karaoglan, U.A. Aveiata and A. Gul, Indian Journal of Chemistry., 46A, 1273(2007)

79. P.A.M. Farias and M.B.R. Bastos, Int. J. Electrochem. Sci., 4, 458(2009).

80. R.A. Khalil, A.H. Jalil and A.Y.A. Alrazzak, Journal of the Iranian Chemical Society. 6, 345 (2009)

81. K. Jamil, M. Bakhtiar, A.R. Khan, F. Rubina, R. Rehana, R. Wajid, M. Qaisar, A.F. Khan, A.K. Khan, M. Danish, M. Awais, Z.A. Bhatti, M. Rizwan, A. Naveed, M. Hussani and A. Pervez,
Affrican Journal of Pure and Applied Chemistry., 3(4), 066(2009)

82. G.G. Mohamed, M.M. Omar and A.M. Hindy, Turk J Chem., 30, 361(2006)

83. Z.H. Chohan and S. Mushtaq, Pakistan Journal of Pharmaceutical Sciences. 13(1), 21(2000)

84. N.G.U. Sari, Journal of Science., 16(2), 283 (2003)

85. M.S. Islam, M.A Farooque, M.A.K. Bodruddoza, M.A. Mosaddik and M.S. Alam, Online Journal of Biological Sciences., 1(8), 711(2001)

86. T.D. Thangadurai and S.K. Ihm, J.Ind. Eng. Chem., 9, 563(2003).

87. S. Baluja, A. Solanki and N. Kachhadia, Journal of the Iranian Chemical Society., 3, 312 (2006).

88. J. Chen, Z. M. He, F. L. Wang, Z. S. Zhang, X. z. Liu, D. D. Zhai and W. D. Chen, Eur. J. Pharmacol., 2016, 772, 33–42.

89. H. Soleimani, A. Amini, S. Taheri, E. Sajadi, S. Shakhani, L. A. Schuger, V. B. Reddy, S. K. Ghoreishi, R. Pouriran and S. Chien, J. Photochem. Photobiol. B Biol., 2018, 181, 23–30.

90. M. Qureshi, E. A. Al-Suhaimi, F. Wahid, O. Shehzad and A. Shehzad, Neurol. Sci., 2018, 39, 207–214.

91. F. N. Kaufmann, M. Gazal, C. R. Bastos, M. P. Kaster and G. Ghisleni, Eur. J. Pharmacol., 2016, 784, 192–198.

92. P. Kumaraswamy, S. Sethuraman and U. M. Krishnan, J. Agric. Food Chem., 2013, 61, 3278–3285.

93. R. K. Singh, D. Rai, D. Yadav, A. Bhargava, J. Balzarini and E. De Clercq, Eur. J. Med. Chem., 2010, 45, 1078–1086.

94. M. G. El-Gazzar, N. H. Zaher, E. M. El-Hossary and A. F. Ismail, J. Photochem. Photobiol. B Biol., 2016, 162, 694–702.

95. Y. P. Bharitkar, M. Das, N. Kumari, M. P. Kumari, A. Hazra, S. S. Bhayye, R. Natarajan, S. Shah, S. Chatterjee and N. B. Mondal, Org. Lett., 2015, 17, 4440–4443.

96. M. Singh, A. Hazra, Y. P. Bharitkar, R. Kalia, A. Sahoo, S. Saha, V. Ravichandran, S. Ghosh and N. B. Mondal, RSC Adv., 2018, 8, 18938–18951.

97. L. Riˇsianov ˇ ´a, E. Fischer-Fodor, J. Valentov´a, C. Tatomir, N. C. Decea, P. Virag, I. Pechov´a, F. Dev´ınsky and N. Mikl´aˇsov´a, Bioorg. Med. Chem. Lett., 2017, 27, 2345–2349.

98. A. Arezki, G. G. Chabot, L. Quentin, D. Scherman, G. Jaouen and E. Brul´e, Med. Chem. Commun., 2011, 2, 190–195.

99. F. C. Rodrigues, N. A. Kumar and G. Thakur, Eur. J. Med. Chem., 2019, 177, 76–104.

100. A. Kareem, M. S. Khan, S. A. Nami, S. A. Bhat, A. U. Mirza and N. Nishat, J. Mol. Struct., 2018, 1167, 261–273.

101. N. G. Gogoi and J. G. Handique, J. Chem. Sci., 2019, 131, 74.

102. J. Lal, S. K. Gupta, D. Thavaselvam and D. D. Agarwal, Eur. J. Med. Chem., 2013, 64, 579–588.

103. M. Ahmed, M. A. Qadir, M. I. Sha□q, M. Muddassar, Z. Q. Samra and A. Hameed, Arab. J. Chem., 2019, 12, 41–53.

104. M. Ahmed, M. A. Qadir, A. Hameed, M. N. Arshad, A. M. Asiri and M. Muddassar, Biochem. Biophys. Res. Commun., 2017, 490, 434–440.

105. T. Chandrasekar, N. Pravin and N. Raman, Inorg. Chem. Commun., 2014, 43, 45–50.

106. T. Chandrasekar, N. Pravin and N. Raman, J. Mol. Struct., 2015, 1081, 477–485.

107. T. Chandrasekar and N. Raman, J. Mol. Struct., 2016, 1116, 146–154.

108. A. Theppawong, T. Van de Walle, C. Grootaert, M. Bultinck, T. Desmet, J. Van Camp and M. D'hooghe, ChemistryOpen, 2018, 7, 381–392.

109. A. Mahal, P. Wu, Z. H. Jiang and X. Wei, ChemistrySelect, 2019, 4, 366–369.

110. M. Massaro, R. Amorati, G. Cavallaro, S. Guernelli G. Lazzara, S. Milioto, R. Noto, P. Poma and S. Riela, Colloids Surf. B, 2016, 140, 505–513.

111. S. Pillarisetti, S. Maya, S. Sathianarayanan and R. Jayakumar, Colloids Surf. B, 2017, 159, 809–819.

112. T. Saranya, V. Rajan, R. Biswas, R. Jayakumar and S. Sathianarayanan, Int. J. Biol. Macromol., 2018, 110, 227–233.

113. N. Priyadharshini, I. S. Pillai, C. Joel, R. B. Bennie, S. Subramanian and P. Venkatesh, Indo Am. j. pharm. sci., 2015, 2, 1491–1505.

114. I. Ali, A. Haque, K. Saleem and M. F. Hsieh, Bioorg. Med. Chem., 2013, 21, 3808–3820.

115. I. Ali, K. Saleem, D. Wesselinova and A. Haque, Med. Chem. Res., 2013, 22, 1386–1398.

116. P. Jeyaraman, A. Alagarraj and R. Natarajan, J. Biomol. Struct. Dyn., 2020, 38, 488–499.

117. M. Cˇalinescu, M. Fiastru, D. Bala, C. Mihailciuc, T. Negreanu-Pˆırjol and B. Jurcˇa, J. Saudi Chem. Soc., 2019, 23, 817–827.

118. C. Canario, S. Silvestre, A. Falcao and G. Alves, Curr. Med. Chem., 2018, 25, 660–686.

119. D. S. Reddy, M. Kongot, S. P. Netalkar, M. M. Kurjogi, R. Kumar, F. Avecilla and A. Kumar, Eur. J. Med. Chem., 2018, 150, 864–875.

120. S. Dutta, A. Murugkar, N. Gandhi and S. Padhye, Metal-based drugs, 2001, 8, 183–188.

121. D. Simoni, M. Rizzi, R. Rondanin, R. Baruchello, P. Marchetti, F. P. Invidiata, M. Labbozzetta, P. Poma, V. Carina and M. Notarbartolo, Bioorg. Med. Chem. Lett., 2008, 18, 845–849.

122. H.-L. Qin, J. Leng, C.-P. Zhang, I. Jantan, M. W. Amjad, M. Sher, M. Naeem-ul-Hassan, M. A. Hussain and S. N. A. Bukhari, J. Med. Chem., 2016, 59, 3549–3561.

123. Haj, Nadia Q., Mohsin O. Mohammed, and Luqman E. Mohammood. "Synthesis and biological evaluation of three new chitosan Schiff base derivatives." *ACS omega* 5, no. 23 (2020): 13948-13954.

