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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Promising Schiff bases in antiviral drug design and discovery

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Abstract

Emerging and re-emerging illnesses will probably present a new hazard of infectious diseases and have fostered the urge to research new antiviral agents. Most of the antiviral agents are analogs of nucleosides and only a few are non-nucleoside antiviral agents. There is quite a less percentage of marketed/clinically approved non-nucleoside antiviral medications. Schiff bases are organic compounds that possess a well-demonstrated profile against cancer, viruses, fungus, and bacteria, as well as in the management of diabetes, chemotherapy-resistant cases, and malarial infections. Schiff bases resemble aldehydes or ketones with an imine/azomethine group instead of a carbonyl ring. Schiff bases have a broad application profile not only in therapeutics/medicine but also in industrial applications. Researchers have synthesized and screened various Schiff base analogs for their antiviral potential. Some of the important heterocyclic compounds like istatin, thiosemicarbazide, quinazoline, quinoyl acetohydrazide, etc. have been used to derive novel Schiff base analogs. Keeping in view the outbreak of viral pandemics and epidemics, this manuscript compiles a review of Schiff base analogs concerning their antiviral properties and structural-activity relationship analysis.

Keywords Schiff base · Antiviral agents · Istatin · Thiosemicarbazide · Quinazoline · COVID-19

Introduction

The worldwide emergence of viral pandemic and epidemic threats and the development of resistance to available therapeutics have turned into a severe menace. A sizable fraction of pandemics and/or epidemics that have dogged humanity throughout history are caused by infectious illnesses that are either from existing or newly emerging pathogenic viruses [1, 2]. At the end of 2019, atypical pneumonia caused by the novel coronavirus-2 or severe acute respiratory syndrome (SARS) within a population in Wuhan (China) was reported and is now known as COVID-19. The infection has been observed with a range of illnesses, from minor symptoms to life-threatening diseases, or it can be asymptomatic [3–5]. The pathogenic nature and mortality rate has warranted an urgent need to identify preventive and therapeutic interventions. In less than a year, the US Food and Drug Administration (USFDA) granted emergency use status to the vaccine developed by Pfizer/BioNTech based on a new platform consisting of mRNA encoding the virus spike protein, and therapeutics have now been approved for clinical use [6, 7].

Even though people are living longer and infectious outbreaks are curbed within a few years, the new hazards of infectious diseases will likely come from developing and resurfacing infections [8]. In the upcoming decades, the danger of disease outbreaks will grow due to climate change, increased urbanization, and shifting land use practices [9]. For instance, climate change may modify the range of global pathogens, allowing infections, especially vector-borne infections, to spread to new areas [10–12]. This has increased the desire to investigate novel antiviral medicines that target untapped pharmacological mechanisms with enhanced safety and limited toxicity [13–15]. Only a few non-nucleoside antiviral medicines are currently commercialized, and the majority of them are nucleoside analogs (example: Catherine, Fig. 1) [16].

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Zidovudine, a Human Immunodeficiency Virus (HIV) nucleoside reverse transcriptase inhibitor, received FDA approval in 1987, which sped up the efforts toward the development of nucleoside-based antiviral agents [17]. Several combination medicines are now being researched to stop the activity of the same or different viral macromolecules during various stages of their life cycle. They aim to obstruct the replication of the viral genome and thus control infection [18, 19]. Since the majority of antiviral medications only work against specific viral strains, it is crucial to continue looking for antiviral substances being active over a wide range of genotypes or subtypes of viruses [20, 21]. Efforts also aim to develop broad-spectrum antiviral agents for various genotypes or subtypes. As an illustration, many antiviral medications, such as Amprenavir, solely suppress HIV-1 and do not affect HIV-2 [22]. Numerous Hepatitis C Virus (HCV) inhibitors have been authorized exclusively for HCV genotype 1, and no other genotypes [23, 24]. However, several viral inhibitors (including Valacyclovir, PegIFN-2a, PegIFN-2b, Acyclovir, TDF, Foscarnet, Famciclovir, Lamivudine, and Ribavirin) have received approval to treat multiple viruses, which support the hypothesis that antiviral medications for a variety of infectious diseases may 1 day be developed [25]. In 1997, fixed-dose treatment combined with lamivudine/zidovudine was approved for use in HIV-infected patients [26, 27]. As a monotherapy against HCV, sofosbuvir was also authorized in 2013 [28, 29]. Imiquimod was authorized for the topical medication of solar keratoses, shallow basal cell carcinoma, and vaginal and perianal warts in 1997 [30–32]. In 2000, Docosanol was authorized for use as a supracutaneous cream to cure herpes labialis brought on by Herpes Simplex Virus (HSV) infections [33]. In 1998, it was thought that ribavirin worked through a variety of mechanisms, with modulation of the immune system and suppression of inosine-5'-monophosphate dehydrogenase (IMPDH) in humans [34, 35]. Topical sine catechins, an aqueous extract of leaves of green tea, were approved in 2006 for the cure of papilloma in genitalia brought on by HIV without having a known mechanism of action [36]. Polymerase inhibitors are known to be the most prevalent type of virus-targeting therapeutics and are classified as nucleoside and non-nucleoside analogs. Acyclovir, Zalcitabine, Didanosine, Lamivudine, Emtricitabine, Tenofovir, and Diisopropyl fumarate belong to the category of nucleoside analogs, whereas Nevirapine, Efavirenz, Rilpivirine hydrochloride, Delavirdine mesylate, and Etravirine are from the category of non-nucleoside analogs. For the treatment of HCV infection, only one non-nucleoside polymerase inhibitor is currently approved which is Dasabuvir [37, 38]. Saquinavir, a peptidomimetic-designed HIV-1 protease inhibitor, received approval in 1995 [39]. Raltegravir along with Elvitegravir was approved in 2007 and 2012, respectively as first-generation integrase inhibitors [40]. Second-generation integrase inhibitor Raltegravir has a greater genetic resistance barrier and maintains antiviral efficacy [41]. In 2014/2015, the FDA approved the first NS5A inhibitors, Ledipasvir, and Daclatasvir dihydrochloride followed by Ombitasvir, Velpatasvir, Pibrentasvir, and Elbasvir in 2016 and 2017 [42]. There are around 100 active medication candidates in research as of January 2018, with 29, 46, and 25 in Phase I, II, and III, respectively of clinical trials [43].

Imine or azomethine groups have been substituted for the group where a carbon atom is double bonded to an oxygen atom (C=O) to create the nitrogen cognate known as Schiff base (Fig. 2) [44, 45]. Frequently utilized carbon-based substances are Schiff bases. Their biological effects range from fungicidal to bactericidal, in treating malaria, suppressing cell growth, treating inflammation, treating viral diseases, and also in lowering the body temperature. They serve as catalysts, intermediates, pigments, and dyes in the production of chemicals [46–48]. Numerous naturally occurring, naturally produced, and artificially created substances contain imine or azomethine groups. For these molecules to have biological effects, an imine group must be present [49–51].

In the field of pharmaceutical sciences, Schiff base is used for a variety of purposes, including the following: as anticancer, antiviral, antifungal, and antibacterial chemicals; to treat HIV infections and diabetes; to combat cancer medication resistance; as antimalarial agents; and to immobilize enzymes [52–55].

In a study, a Schiff base ligand was produced by mixing the substances 5-nitropyridine-2-amine and 4-hydroxy-3-methoxy benzaldehyde in a 2:1 stoichiometric ratio (2HL:M). BHA was utilized as a positive control in the in vitro

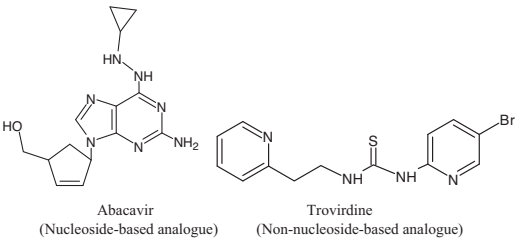
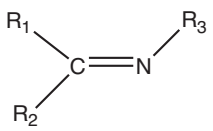


Fig. 1 Chemical structures of some antiviral agents



R_1, R_2 and/or R_3 = Alkyl or Aryl Substitution

Fig. 2 Basic structure of Schiff base

assay, which was carried out similarly to those for DPPH, ABTS, and superoxide. When compared to the ligand, it was discovered that the in vitro glucosidase inhibitory activities had a significant amount of inhibitory potential [56].

It is reported in a study that (*E*)-ethyl 2-(4-methoxybenzylidene) hydrazine carboxylate and 4-(nitro benzaldehyde) ethyl carbamate were synthesized and characterized as a new Schiff base ligand. Density functional theory and results from experiments limited to establishing the compound's structure have been found to have a positive association. The effectiveness of the Schiff base as a bioactive molecule has been demonstrated by molecular docking and antibacterial tests [57, 58].

A study discovered a connection between the zinc-Schiff base and the use of the peptide Novicidin that penetrates the membrane as a transporter for the delivery of zinc to cells of the prostate. It was discovered that the potency was toward PC3 tumor cells and the toxicity was normal in PNT1A cells. Additionally, both cell lines confirm zinc uptake. The combination has demonstrated a significant possibility for treating cancer, the activation of zinc stress (e.g., ZnT-1) and apoptosis was verified through a molecular analysis (e.g., CASP-1) [59, 60].

To create Schiff's bases, a series of (*S*)-flurbiprofen derivatives were synthesized using various aromatic or aliphatic aldehydes and ketones. Their structure was then validated using HR-ESI-MS, ^{1}H, and ^{13}C-NMR spectroscopy. It was shown that the newly synthesized compounds had considerable -gluta oxidase inhibiting actions. All of the active compounds' modes of binding were identified using the molecular docking method, and the compounds displayed potential anti-diabetic properties by obstructing high binding energies (between 7.51 and 3.36 kcal/mol) in the active site, which hinders the enzyme's capacity to operate [61]. (*E*)-2-((2-hydroxybenzylidene) amino)-4-methyl phenol (SL1) and (*E*)-2-((2-hydroxybenzylidene) amino) are two Schiff bases. The synthesis of -4-methyl phenol (SL2) and their solvent-free, non-toxic inclusion complexes with cyclodextrin (-CD) was carried out. Since these insertion complexes result in apoptosis, SL2—CD is more effective at combating cancer. For the first time, the bio-potency of CD was boosted by the addition of nanocrystalline Schiff bases [62–64].

The Schiff base has increased the curiosity of researchers immensely these days because of its versatile properties and applications in different areas. Some of the important applications of reported Schiff base derivatives are depicted in (Fig. 3).

Keeping in view the outbreak of COVID-19 and the requirement for potent antiviral drugs, the goal of the current manuscript is to give a thorough analysis of various significant chemical core's Schiff base analogs which have demonstrated antiviral properties in pre-clinical evaluation. It has focused on some important chemical cores, i.e., istatin, thiosemicarbazide, hydroxyguanidine tosylate, quinazoline, and quinolinyl to hydrazide been derivatized to prepare Schiff base analogs. It has also included details of some potential metal complexes with inhibition properties.

Antiviral Schiff bases

Isatin and its Schiff base derivatives

Isatin (1H-indole-2,3-dione) is a heterocyclic moiety having a well-demonstrated role in the control of numerous viral infections [65] Some of the well-reported antiviral agents with isatin nuclei are Sunitinib, Semaxanib, and Toceranib (Fig. 4).

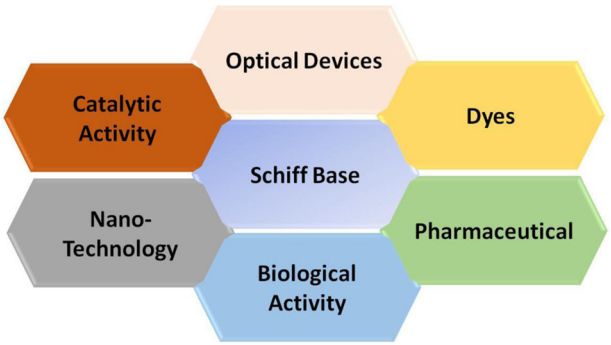


Fig. 3 Diverse applications of Schiff base analogs

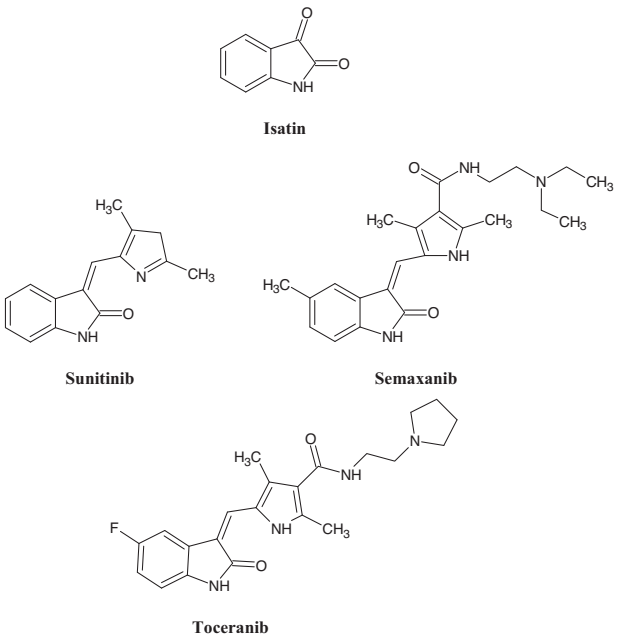


Fig. 4 Chemical structures of antiviral agents having isatin nuclei

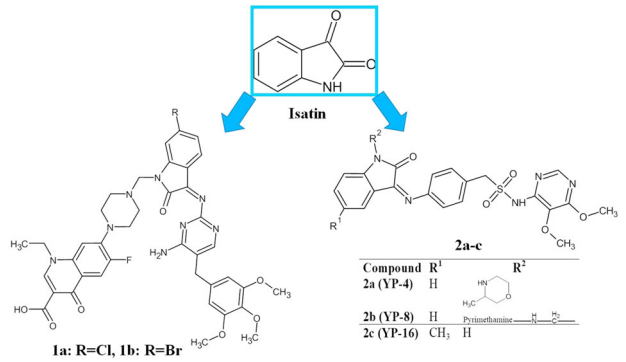


Fig. 5 Details of chemical structures of isatin and its Schiff base analogs

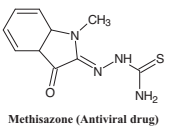


Fig. 6 Example of clinically approved antiviral drug with thiosemicarbazone nuclei

Pandeya et al. synthesized norfloxacin-isatin mannich base for checking anti-HIV activity [66]. Here two compounds **1a** and **1b** (Fig. 5) showed maximum potency with EC_{50} values of 11.3 and 13.9 µg/ml and protection in the range of 70–95%. Substitution of trimethoprim at the 3rd position and electron-withdrawing group at the 5th position showed maximum potency as compared to the other substituent.

In another series, 3(*N*)-sulphadoxine of Isatin derivatives (**2a–c**) were tested for their ability to inhibit HIV using the assay of MTT 3-(4,5-dimethyl thiazol-2-yl) (Fig. 5). It was found that a compound containing piperidinomethyl group (**2a**; YP-04) has shown activity up to 16% against HIV-2 (ROD) strain at an $EC_{50} > 2$ µg/ml and about 12% were effective against HIV-1 (IIIB) strain. In SAR, it was found that methyl-substituted isatin has shown less activity compared to the unsubstituted isatin derivatives, and 3-methyl morpholine substitution at position-1 of isatin showed better potency as compared to others. Two drug moieties of sulphadoxine and pyrimethamine (**2b**; YP-8) showed 13% protection against HIV-2 (ROD) at an EC_{50} of more than 2 µg/ml [67].

Isatinyl thiosemicarbazone Schiff base derivatives

The N-methyl-isatin ß-thiosemicarbazone i.e., Methisazone is an FDA-approved antiviral drug (Fig. 6) [68] Studies have demonstrated viral inhibitory properties of various thiosemicarbazone derivatives namely HSV-1, HSV-2, respiratory syncytial virus (RSV), dengue virus bovine viral diarrhea virus (BVDV), encephalitis virus, hepatitis C virus (HCV), and influenza virus [69–75]. Efforts have been

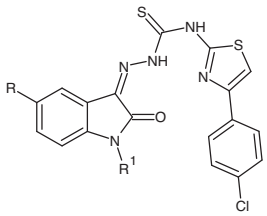


Fig. 7 Chemical structure of *N*-[4-(4'-Chlorophenyl) thiazol-2-yl] thiosemicarbazide (**3a–l**)

envisaged to investigate the viral inhibitory potential of its Schiff base analogs and these are reported here.

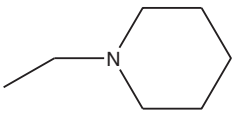
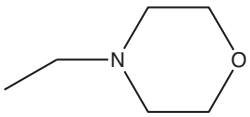
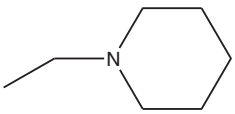
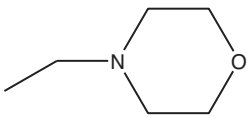
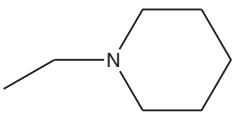
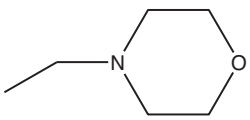
In an investigation conducted by Pandeya et al., 4-chloro acetophenone was used to manufacture *N*-[4-(4'-Chlorophenyl) thiazol-2-yl] thiosemicarbazides (**3a–l**; Fig. 7) [76]. In the human T cell line, the replication-inhibiting properties of HIV-1 were evaluated for the synthesized compounds. It was observed that none of them have substantial anti-HIV potential (Table 1). There was a belief that medications might not be able to stop HIV-1 reverse transcriptase (RT). It was assumed that a small hydrophobic molecule would be necessary for RT inhibitory activity, but the thiosemicarbazide end of these compounds has a large p-chlorophenyl thiazolyl group which may not favor the inhibition of HIV-1 reverse transcriptase.

Also, Banerjee et al. synthesized a series of isatinyl thiosemicarbazide analogs of 60 compounds and checked their anti-HIV and anti-tubercular activity. The EC_{50} values were found to be in the range of 1.69–129.96 µM. Out of these, hydroxy-substituted thiosemicarbazone compound **4b** showed EC_{50} 4.18 µM, and methoxy thiosemicarbazone analogs compound **4a** showed EC_{50} 1.69 µM (Fig. 8). So, methoxy thiosemicarbazones showed a better inhibitory profile and higher activity as compared to hydroxy thiosemicarbazones. On studying SAR, it was found that the chlorine present at the 4th position of phenyl piperazinyl methyl shows lipophilic interaction at the active site. The Methyl group at the 5th position of indolyl moiety shows interaction with the aromatic residue of the enzyme [77].

Quinoline and quinazoline Schiff base derivatives

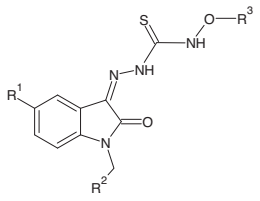
Quinoline and quinazoline are heterocyclic moieties with well-reported antiviral properties. During investigation of a potential drug to control the pandemic caused by SARS-CoV2, it has been found that RNA-dependent RNA polymerase (RdRp) has a pivotal viral life cycle and quinoline and quinazoline derivatives not only inhibit RNA virus-like HIV-1, Ebola virus, Influenza virus but also shows activity against DNA viruses such as HSV (Herpes simplex virus)

Table 1 Details of substitutions and anti-HIV activity for *N*-[4-(4'-chlorophenyl) thiazol-2-yl] thiosemicarbazide (**3a–l**, Fig. 7)

Compound No.	R	R^1	EC_{50} (μg)[a]
3a	H	H	>12
3b	Cl	H	>10
3c	Br	H	>10
3d	H	$-CH_2-N(CH_3)_2$	>54
3e	H		>57
3f	H		>19
3g	Cl	$-CH_2-N(CH_3)_2$	>10
3h	Cl		>12
3i	Cl		>12
3j	Br	$-CH_2-N(CH_3)_2$	>29
3k	Br		>21
3l	Br		>14

[a]MT-4 cells are 50% protected by an effective concentration of the chemical from HIV's cytotoxic effects

and Hepatitis B virus [78–82]. In continuation of exploring this moiety, Zhao et al. synthesized 101 quinoline and quinazoline derivatives and on screening using a cell-based assay, it was found that the inhibition activity shown by the compounds are **5e** = 95.03%, **5h** = 92.85%, and **5i** = 74.94%. On further study, it was found that these compounds **5e**, **5h**, and **5i** target the RNA replication which is driven by RdRp (Fig. 9). In respect of SAR, at the 2nd position of the quinoline ring, when the pyrrolidinyl group is replaced by another group like boc-piperazinyl (**5e**) and



4(a-b)

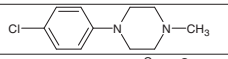
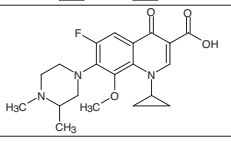
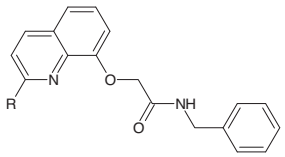
Compound No.	R^1	R^2	R^3
4a	CH_3		CH_3
4b	F		H

Fig. 8 Chemical structure of isatinyl thiosemicarbazide analogs



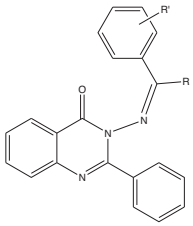
5(a-i)

Compound No.	R
5a	Diethylamino
5b	1-piperidyl
5c	N-morpholino
5d	4-eMthylpiperazin-1-yl
5e	4-Bocpiperazin-1-yl
5f	Dimethylamino
5g	Methylamino
5h	(*S*')-Boc-3-amino-pyrrolidinyl
5i	(*R*')-Boc-3-amino-pyrrolidinyl

Fig. 9 Chemical structure of quinoline and quinazoline derivatives

(s)-boc-3-amino-pyrrodinyl (**5h**) derivatives, a significant increase in activity was seen [83].

Through the development of 3-amino-2-phenyl quinazolines which is a Schiff base, a fresh sequence of 3-(benzylidene amino)-2-phenyl quinazolines (4(3H)-ones (**6a–l**; Fig. 10) was created [84]. Spectral analyses were used to interpret their chemical structures and viruses like HSV-1, Coxsackievirus, and coronavirus subtypes, etc. were tested for cytotoxicity and antiviral activity. Quinazoline derivatives were tested for the anti-influenza activity and cell-destroying capacity in the culture of the (MDCK) kidney cell line with the help of the MTS assay. It was found when compound **6a** was substituted with the hydroxyl group at R' position, the 50% cytotoxic concentration was found to be 2.6 μg/ml, and minimal cytotoxic concentration was found to be ≥0.8 μg/ml, while compounds **6b**, **6d**, **6e**, **6h**, and **6i** were found to have CC_{50}, >100.0 μg/ml when substituted with nitro, dimethyl amine, chlorine, and methyl group,



6(a-l)

Compd. No.	R	R'	Compd. No.	R	R'
6a	H	2-OH	**6g**	H	4-OH
6b	H	3-NO_2	**6h**	CH_3	H
6c	H	4-OCH_3	**6i**	CH_3	4-OH
6d	H	4-$N(CH_3)_2$	**6j**	H	4-Cl
6e	CH_3	4-Cl	**6k**	H	3-OH, 4-OCH_3
6f	H	H	**6l**	H	2-OCH_3

Fig. 10 Chemical structure and substitutions for compounds **6**(**a**–**l**)

respectively. Also, compounds **6c**, **6f**, **6g**, **6j**, and **6k** have shown activity against influenza virus with CC_{50} in the range of 8.0 to 50.0 µg/ml when substituted with methoxy, hydrogen, and a hydroxyl group at R' position. However, these compounds did not find to be active at a higher concentration for the anti-influenza activity of the H1N1 subtype, and H3N2 subtypes. When cytotoxicity and antiviral activity were calculated for the compounds **6a–l** in cell cultures of HEL, Compounds **6a** and **6c–6l** were found to have a minimum cytotoxic concentration ±100.0 µg/ml when substituted with hydroxy, methoxy, dimethyl amine, chlorine or H at R' while compound **6b** showed ≥20 µg/ml when substituted with the nitro group at R' position. While 50% effective concentration was calculated for compound **6a** substituted with R' = hydroxy group showing good activity with the quantity of 1.0 µg/ml against HSV-1 (KOS), HSV-1 TK-KOS ACVr, and HSV-2(G), 0.8 µg/ml for vaccinia virus and 15 µg/ml for vesicular stomatitis virus. Compound **6a** among all others demonstrated superior antiviral efficacy against all tested viruses. Compounds **6a–l** were also found to be effective at a culture of the Vero cell lineage extracted from the kidney's epithelial cells. It was found that the minimum cytotoxic concentration of compounds **6a**, **6c**, **6d**, **6e**, **6g**, **6h**, **6k**, and **6l** was found to be 100.0 µg/ml when substituted with hydroxy, methoxy, dimethylamine, chlorine, and H at R' position and H and methyl at R position. The 50% effective concentration to reduce virus-induced cytopathogenicity for compounds **6a**, **6c**, **6d**, **6e**, **6g**, **6h**, **6k**, and **6l** was found >20.0 µg/ml when substituted with hydroxy, methoxy, dimethylamine, chlorine, or H at R' position for Para influenza-3 virus, while it is >4.0 µg/ml for compounds **6b**, **6f**, and **6j**. For Reovirus-1, the EC_{50} was found to be 10.0 µg/ml in compound **6a**, >4.0 µg/ml in compounds **6b**, **6f**, **6j** and >20.0 µg/ml in compound **6c**, **6d**, **6e**, **6g**, **6h**, **6k** and **6l**. In case of Sindbis virus, the EC_{50} was shown to be 5 µg/ml by compound **6a**, >4 µg/ml for compound **6b**, **6f**, and **6j**, >20.0 µg/ml for **6c**, **6d**, **6e**, **6g**, **6h**, **6k** and **6l**, and >100.0 µg/ml for compound **6i**. So, it was seen that the substitution of the nitro or chloro group was found to be more effective as compared to the substitution of the hydroxy or methoxy group.

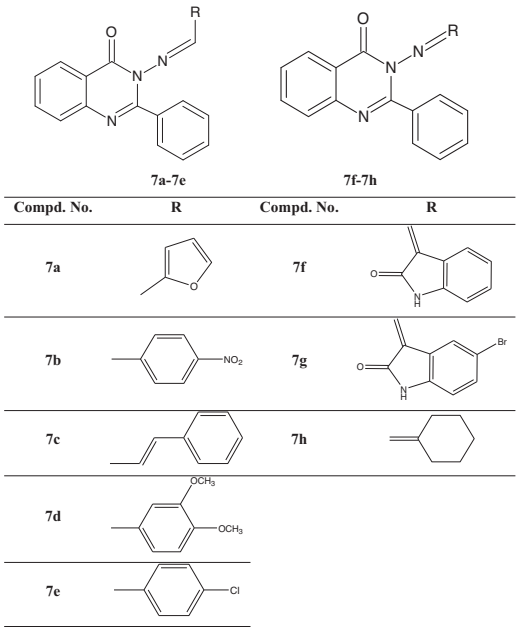


Fig. 11 Structural details of 3-(benzylidene amino)-2-phenyl. quinazoline-4(3H)-ones (**7a**–**h**) structure sizes proportion needs to be consistent

Compound **6a** was discovered to work well against viruses in culture developed from the Hela cell line at a minimum cytotoxic dosage of 4.0 g/ml, with an EC_{50} (g/ml) value of >0.8 for Vesicular stomatitis virus, >0.8 for Coxsackievirus B4, and >0.8 for the respiratory syncytial virus when substituted with a hydroxy group i.e., 2-OH at R' position.

In CRFK cell culture (FIPV), a minimum cytotoxic concentration of 11.2 µg/ml of compound **6a** was found to be effective against the virus with EC_{50} (µg/ml) value of >4.0 for Feline Coronavirus (FIPV) and >4.0 for Feline Herpes virus when substituted with a hydroxy group i.e., 2-OH at R' position.

In another study against viruses including feline herpes and feline coronavirus by synthetic 2-phenyl-3-substituted quinazoline-4(3H)-ones (**7a**–**h**, Fig. 11) by Krishnan et al. [85] structural characteristics were found to be correlated with the biological activity. It was observed that compound **7a** when substituted with 2-methyl furan ($CC_{50} = 14.1 \pm 2.3$ µg/ml, $EC_{50} = 4.0 \pm 0.5$ µg/ml) **7b**, when substituted with 1-methyl-4-nitrobenzene (CC_{50} 13.8 ± 1.8 µg/ml, $EC_{50} = 4.0 \pm 0.3$ µg/ml), **7d** when substituted with 1,2-dimethoxy-4-methylbenzene ($CC_{50} = 13.8 \pm 0.5$ µg/ml, $EC_{50} = 4.0 \pm 0.2$ µg/ml) and **7g** when substituted with 5-Bromo-3-methylidene-1,3-dihydro-2H-indol-2-one/5-bromoisatin ($CC_{50} = 16.2 \pm 0.8$ µg/ml, $EC_{50} > 4.0$ µg/ml) were close to each other while compound **7e** when substituted with 1-chloro-4-methylbenzene ($CC_{50} = 42.2 \pm 4.7$ µg/ml, $EC_{50} = 42.2 \pm 4.7$ µg/ml) which was higher as compared to **7a**, **7b** and **7d**. It was found that

the minimum cytotoxic concentration for compounds **7f** (substituted with 3-methylidene-1,3-dihydro-2*H*-indol-2-one)/ isatin and **7h** (methylidene cyclohexane) was equal to that of HHA (CC_{50} > 100.0 µg/ml, EC_{50} 2.6 ± 0.8 µg/ml), UDA (CC_{50} > 100 µg/ml, EC_{50} 117.6 ± 1.3 µg/ml) and Ganciclovir (CC_{50} > 100 µM, EC_{50} > 100.0 µg/ml). The selectivity index of the compounds **7c** and **7g** was found to be 4.0 which is much less as compared to the compounds HHA (SI 38), and UDA (SI 9).

On cultivated HeLa cells, the minimum concentration required to alter the morphology of the cells for compound **7a** was 100 ± 5.4 µg/ml, and **7g** was 100 ± 5.4 µg/ml when substituted with furan and indole derivatives at the **R** position. This concentration was reduced to $CC_{50} \geq 4.0$ µg/ml when substituted with elongated alkyl chain [(1*E*)-prop-1-en-1-yl] benzene in compound **7c**, the least cytotoxic concentration for the compounds **7d**, **7f**, and **7e** was near to 20.0 µg/ml when substituted with 1,2-dimethoxy-4-methylbenzene, 3-methylidene-1,3-dihydro-2*H*-indol-2-one, and 1-chloro-4-methylbenzene, respectively. Compound **7c** has shown the least value of less than 4.0 µg/ml for HeLa cells. The EC_{50} of the compounds for Vesicular stomatitis virus, Coxsackie virus, and RSV was found near 4 µg/ml for compounds **7a**, **7b**, **7c**, **7d**, **7e**, and **7f** when substituted with 2-methyl furan, 1-methyl-4-nitrobenzene, [(1*E*)-prop-1-en-1-yl]benzene, 1,2-dimethoxy-4-methylbenzene, 1-chloro-4-methylbenzene, and, 3-methylidene-1,3-dihydro-2*H*-indol-2-one, respectively, this value went to 20.0 µg/ml for compound **7g** when substituted with 5-bromo-3-methylidene-1,3-dihydro-2*H*-indol-2-one, the maximum value for EC_{50} was more than 100 µg/ml for the compound **7h** when substituted with methylidene cyclohexane. All the compounds from **7a**–**7h** were found to have a good response when compared with (*S*)-DHPA and Ribavirin with a minimum cytotoxic concentration above 250 µg/ml and EC_{50} in the range of 20 to 150 µg/ml for different viruses in Cultivated HeLa cells. Compound **7a** showed the highest selectivity index against 25 which is much higher as compared to reference compounds DS-5000, (*S*)-DHPA, and Ribavirin with selectivity index 0, 0, and 11, respectively.

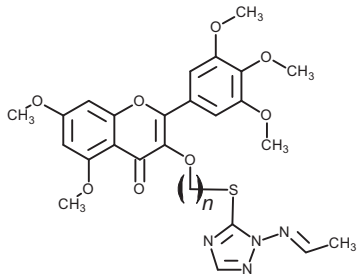
Compounds **7a**, **7d**, **7g**, and **7h** in the cultivated cell lineage of Vero were having the minimum concentration to alter the normal cell morphology by 50% around 100 g/ml when substituted with (2-methyl furan), (1,2-dimethoxy-4-methylbenzene), (5-bromo-3-methylidene-1,3-dihydro-2H-indol-2-one), and methylidene cyclohexane) respectively. The effective concentration of compounds **7b**, **7d**, **7e**, and **7f** to reduce the virus-induced pathogenicity in cells was found to be around 4 µg/ml when substituted with (1-methyl-4-nitrobenzene), (1,2-dimethoxy-4-methylbenzene), (1-chloro-4-methylbenzene) and, (3-methylidene-1,3-dihydro-2*H*-indol-2-one), respectively and above 20 µg/ml for the compounds **7a**, **7c**, **7g**, and **7h** when substituted with (2-methyl furan), ([(1*E*)-prop-1-en-1-yl]benzene), (5-bromo-3-methylidene-1,3-dihydro-2H-indol-2-one), and (methylidene cyclohexane) respectively in Para influenza-3, Reovirus-1, Sindbis, Punta Toro virus, and Coxsackie virus. The selectivity index value of compound **7d** was found to be 25 which is higher as compared to the reference.

Myricetin Schiff bases with triazole substitutions

A polyphenol flavonoid, called myricetin has a wide range of documented actions, including antiviral effects [86–92]. Similarly, heterocyclic compounds based on the derivatives of 1,2,4-triazole have high efficiency and a broad spectrum and are very popular. To test their potential for having antiviral effects against the tobacco mosaic virus (TMV), 1,2,4-Triazole Schiff base-based derivatives of myricetin were synthesized and evaluated [93]. Substitution at R with Phenyl; 3,4-dichloro phenyl; 3,4-dimethoxy phenyl; and 2-thiophene are some of the significant structural traits identified for effective therapeutic and protective effect. It was found when compounds **8a** and **8t** were substituted with a phenyl group, it showed curative percentage inhibition of around 52%, protection inhibition percentage of around 52% and 56%, respectively and inactivation inhibition percentage of around 67%, and 57% respectively, compound **8g** and **8w**, when substituted with 3,4-dimethoxy phenyl, showed curative percentage inhibition of around 53 for both, protection inhibition percent of around 55 and 58, respectively and inactivation inhibition percent of around 88 and 43 approximately. Compound **8j**, when substituted with 2-thiophene, showed a curative inhibition percentage of around 53%, a protection inhibition percentage of around 55, and an inactivation percentage inhibition of around 68. The antiviral activities of the synthesized compounds were compared against TMV (in vivo, 500 µg/ml). The above-mentioned results were compared with Ribavirin and Ningnanmycin and Myricetin. For Ribavirin and Ningnanmycin, curative percentage inhibition was found to be around 32% and 53, protection percentage inhibition, around 52 and 66, and inactivation percentage inhibition, around 74 and 92, respectively. For Myricetin, the curative percentage inhibition percentage was around 32, the protection inhibition percentage around 52, and the inactivation inhibition percentage around 52. Derivatives **8g** and **8j** were found to have a better therapeutic effect, **8p**, **8w**, and **8f** were having a good protective effect, and **8g** had a good passivation effect (Fig. 12) and have shown higher inhibitory percentage than that for Myricetin and Ribavirin while it is close to Ningnanmycin.

Copper complex [Cu(L)(phen)] with mixed ligands

According to a recent study, the primary protease (M^{pro}) of the COVID-19 virus is what causes the virus to become



8a-w (n = 3/4/5)

Compd No.	n	R	Compd No.	n	R	Compd No.	n	R	Compd No.	n	R
5a	3	Ph	**5g**	3	3,4 di-CH_3O-Ph	**5m**	4	3-CH_3-Ph	**5s**	4	4-*t*-Bu-Ph
5b	3	4-CH_3	**5h**	3	2,4-di-CH_3O-Ph	**5n**	4	4-CH_3O-Ph	**5t**	5	Ph
5c	3	CH_3-Ph	**5i**	3	4-*t*-Bu-Ph	**5o**	4	2-CH_3O-Ph	**5u**	5	4-CH_3-Ph
5d	3	4-CH_3O-Ph	**5j**	3	2-Thiophene	**5p**	4	3,4-di-CH_3-Ph	**5v**	5	4-CH_3O-Ph
5e	3	2-CH_3O-Ph	**5k**	4	Ph	**5q**	4	3,4-di-CH_3O-Ph	**5w**	5	3,4-di-CH_3O-Ph
5f	3	3,4-di-CH_3-Ph	**5l**	4	4-CH_3-Ph	**5r**	4	2,4-di-CH_3O-Ph			

Fig. 12 Structural details for Compounds **8a–w**

proteolytic and is crucial to the virus's life cycle [94–97]. Schiff bases have been discovered to be very significant in the medical and pharmaceutical industries, and the effectiveness of their complexes against COVID has been investigated. Computer modeling was done to determine the possibility against the virus by the compound [Cu(L)(phen)] of mixed ligands for copper (II) that was created by Bharti et al. (Fig. 13) shows the coordination of the Cu (II) ion with the Schiff base ligand (H2L) in the ONS-tridentate mode [98]. The complex formed with the copper having 8 molecules in one cell was having a square pyramidal shape when observed through X-ray crystallographic examination. Additionally, the functional characteristics of [Cu(L)(phen)] were investigated using quantum chemical calculations. The [Cu(L)(phen)] was practically created and developed in computer and assessed with the help of Swiss ADME, allowing for simple parameter analysis. The ligand and its copper complex underwent a molecular docking analysis, which reveals an attraction for the primary protease (M^{pro}) which is a spike protein for COVID-19. The results were quite positive when the binding affinity and inhibition constants were compared with current antiviral medications. According to the reports, the ligand's inhibition constant was 5.82 µM and the binding affinity was −7.14 kcal/mol for the H2L molecule (a Schiff base ligand) with Mpro, while the inhibition constant was 0.76 µM and the binding affinity was −6.18 kcal/mol for the complex [Cu(L)(phen)] with Mpro protein. The study is anticipated to provide scientific solutions and be found to be effective against COVID-19 viral suppression as a consequence of the recent issues it has posed throughout the world [99]. In comparison to previously developed antiviral medications, the binding affinity was fairly good. For instance, it was discovered that

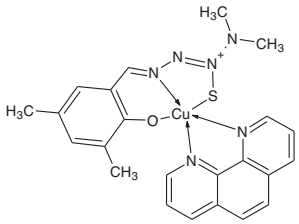


Fig. 13 Chemical structure of [Cu(L)(phen)]

the ligand and complex binding affinity was higher than the docking results of the drugs chloroquine, hydroxychloroquine, and remdesivir with the M^{pro} protein (−6.293 kcal/mol, −5.573 kcal/mol, and −6.352 kcal/mol, respectively).

Metallized Schiff base tridentate

A Schiff base ligand has a tendency to bind metal ions with a nitrogen atom of the azomethine group [100]. The main motive of this work was to create a Schiff base ligand. Using the crystal-structure inhibitor named UAW247, a molecular docking investigation looked at the produced compounds' affinity for the major SARS-CoV-2 protease (PDB-ID: 6XBH). The docking studies show the best conformation, free binding energy, and stability of the ligand along with other complexes and target proteins. The compounds in the formularies utilized to treat COVID-19 were predicted in silico to have antiviral activity [101–103]. Inhibitor UAW247 used molecular docking research to determine the ligand's and its metal complexes' mechanisms of attachment toward the complex's major protease. The binding models were found to have best confirmations with binding energies of 2.88, 3.38, 3.77, 2.86, 3.31, 3.08, 3.06, and 3.34 Å distances,

respectively. In 6XBH docking, many ligands were confirmed for binding like Fe (III), Nickel (III), Copper (II), Zinc (II), and Chromium (III). As per the interaction energies, it was found that Cr (III) complex was highly stable and has lesser binding energies. According to many studies, the ligand was successfully useful in combating coronavirus, and Chromium (III) complex was proven a strong antiviral because of its lower binding energy. This research opens a new door for the future development of coronavirus treatment [104].

Hydroxyguanidine tosylate Schiff base derivatives

1-Amino-3-hydroxyguanidine tosylate-salicylaldehyde Schiff bases are excellent starting points for the creation of novel antiviral medications [105]. When employed at levels as low as 3.2 µM, compound (**9a**) is one of the varieties of Schiff bases (**9a–l**, Fig. 14) synthesized from 1-amino-3-hydroxyguanidine tosylate, was found to be especially effective against mouse hepatitis virus, suppressing the half of the growth. Schiff bases (**9i–l**) obtained from abacavir were synthesized and tested for activity against the virus by Sriram et al. [106]. These substances belong to a brand-new class of abacavir prodrugs. Reverse transcriptase activity can be inhibited by the nucleoside analog abacavir. HIV-1 was strongly inhibited by compounds **9i–l**. These Schiff bases generated from Abacavir required a lower effective concentration of 6.0 µM to protect human leukemia cells from the cytotoxic effects of HIV half of its value. Molecule **9d** when substituted with H at R^1 and 4-CH_3C_6H at R^2 was discovered to be the most effective Schiff base, showing activity against CEM cells at levels greater than 100 µM and being effective at 50 nM, demonstrating its probability as a prime substance for the creation of new medications effective against HIV.

Quinolonylacetohydrazides

Quinolines/quinolones and their structural analogs have exhibited inhibitory properties against HIV, human cytomegalovirus (HCMV), SARS coronavirus, Zika virus, Chikungunya virus, hepatitis C virus (HCV), and Ebola virus [107–112]. The mechanism of action of antiviral quinolone remains unclear. Specific studies aimed at understanding the nature of drug's targets at the molecular level indicated that quinolones inhibit viral transcription [113]. Alshammari et al. created a novel of quinolonylacetohydrazides Schiff base derivatives (**10a–k**). Different spectroscopic techniques, such as NMR (^{1}H, ^{13}C, ^{15}N, ^{2}D), elemental analysis, and mass spectroscopy, were used to determine the chemical structures [114].

Using Autodock 4.2.6, calculations for docking were used to determine the attraction for binding of the synthesized molecules (**10a–k**; Fig. 15) with the Coronavirus-2 major protease (M^{pro}) and RNA polymerase (RdRp) with values between −7.0 and −9.7 kcal/mol, compounds (**10a–k**) have demonstrated strong binding tendencies for the M^{pro} of the Coronavirus-2. Compound (**10a–k**) had lower binding affinities for RdRP compared to M^{pro}, with docking values between −6 and −8 kcal/mol, whereas Remdesivir had affinities value of binding between −8.5 and −5.6 kcal/mol for M^{pro} and RdRp, respectively. Adenosine analog Remdesivir works well opposing various viruses that have RNA, including severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Coronavirus [115–117]. It is under clinical development for the treatment of the infection caused by the Ebola virus [118]. Studies reported compound (**10d**) had the highest ability to bind with M^{pro} of Coronavirus-2 causing SARS and could create four crucial hydrogen bonds with the amino acids LEU141, SER144, HIS163, and GLU166, with lengths of 2.02, 2.22, 1.83, and 2.07 Å, respectively. To determine, how alternative quinolone derivatives can be utilized as a cure for infection brought on by coronavirus, more research on these chemicals is necessary.

Toward termination and control of the epidemic, researchers from many medical specialties have worked together. Numerous research institutions and pharmaceutical businesses have recently presented 115 vaccine candidates and 249 potential therapies for COVID-19 disorders at various pre-clinical and clinical research stages. Around 330 clinical trials and 249 potential treatments for COVID-19 disorders were ongoing as of April 2020. This pandemic has posed a significant obstacle to the quick development of medications to combat this deadly illness [119]. This requirement has bent the interest of researchers toward metallodrugs, which could offer good opportunities to achieve the desired goals [120, 121]. Micronutrients like Zn, Se, and Vitamin D can intervene to stop the progression of COVID-19 [122, 123]. In addition to regulating the inflammatory response, zinc is known to control the effect of viruses, and bacteria. Along with all, the degree of COVID-19 severity can be altered, for which Schiff base shows itself to be a remarkably good candidate. Furthermore, co-ligands including NO, CO, and H_2S may strengthen the coronavirus impact against coronavirus. The interaction with spike protein and stopping RNA replication of coronavirus has a huge impact on the growth of anti-COVID agents [124]. Therefore, the use of Schiff base complexed metals in metallodrug-based design for the treatment of viral infection may be advantageous [125, 126].

Schiff bases are adaptable ligands that interact with several different metal ions. All transition metals, along with lanthanoids, are capable of forming complexes with Schiff bases. Because of their diverse biological characteristics, When Schiff bases made from sulfonamides

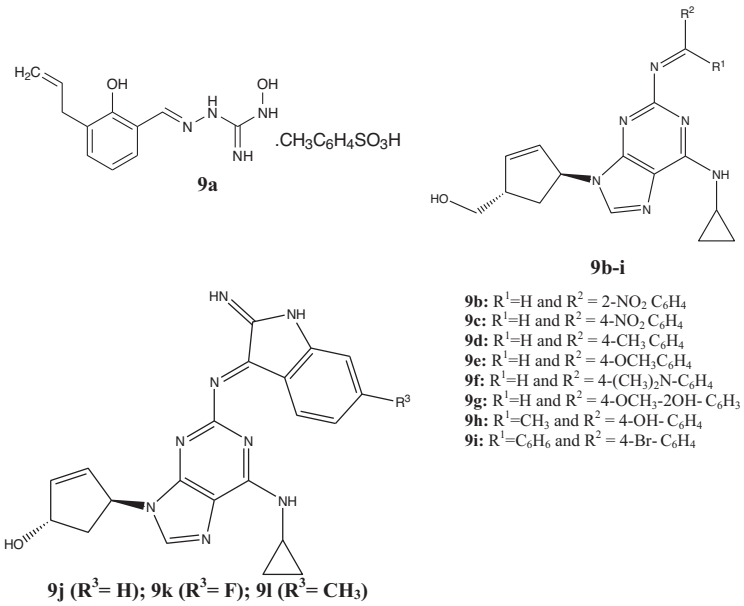
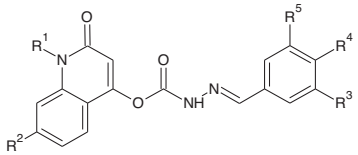


Fig. 14 Chemical structures of Compounds **9a–l**



10a: $R^1=R^3=R^4=R^5=H$, $R^2=Me$
10b: $R^1=R^3=R^5=H$, $R^2=Me$, $R^4=Br$
10c: $R^1=R^3=R^5=H$, $R^2=Me$, $R^4=NMe_2$
10d: $R^1=R^3=H$, $R^2=Me$, $R^5=OMe$
10e: $R^1=H$, $R^2=Me$, $R^3=R^4=R^5=OMe$
10f: $R^1=Me$, $R^2=R^3=R^4=R^5=H$
10g: $R^1=Me$, $R^2=R^3=R^5=H$, $R^4=Br$
10h: $R^1=Me$, $R^2=R^3=R^5=H$, $R^4=Cl$
10i: $R^1=Me$, $R^2=R^3=R^4=H$, $R^5=OMe$
10j: $R^1=Me$, $R^2=R^3=R^4=H$, $R^5=OMe$
10k: $R^1=Me$, $R^2=H$, $R^3=R^4=R^5=OMe$

Fig. 15 *N*-substituted-2-quinolonylacetohydrazides (**10a–k**)

form a metal complex it shows a specific role in pharmaceutical chemistry. For instance, different biological parameters were revealed by metal complexes of 5-chloro-2-hydroxybenzylidene aminobenzene sulfonamides [127], 4-(2-aminoethyl) benzenesulfonamide, 4-(2-aminomethyl) benzenesulfonamide, and sulfisoxazole [128]. In addition to this, the metal Schiff base complexes formed when various sulfonamides were combined with 5-chlorosalicyladehyde or indole-3-carboxaldehyde have demonstrated antibacterial and antifungal activities [129]. Additionally, carbonic anhydrase, an enzyme containing zinc, is significantly inhibited by Schiff bases [130–134]. There have been numerous Schiff base compounds so far. At the University of Manitoba, Malcolm Xing patented Schiff-base hydrogel as a potential wound treatment [135, 136]. Imine salts which are made from new pyrimidine have been patented to find against the pests that harm animals [137]. Consequently, it has been discovered that Schiff base has a variety of therapeutic properties; ranging from inhibitory action against bacteria, fungus, viruses, malaria, cancer, pests, inflammation, oxidation, and many enzymes [138–140].

Conclusion

Schiff bases have thus far been extensively investigated in numerous industrial and pharmacological applications. However, additional research is still needed to fully understand this compound class and its biological function. The formation of metal complexes by Schiff bases was found to be an important area for investigation in this review. Evaluation based on theoretical chemistry is preferred these days before attempting to synthesize a chemical that may ultimately produce useful outcomes. Although there are already analyzed molecules available, the biological properties of these Schiff base-metal complexes that have been made to be further investigated, and new complexes must be made with more features. Analysis of the links between the Schiff bases and the compounds mechanisms of action will be necessary for this field to advance. Additionally, molecular docking studies enable identifying potential binding mechanisms of highly effective drugs easier. The computation of potential receptor and ligand docking modes of novel/compounds is achievable with many molecular docking tools and molecular graphic programs. Pre-clinical and clinical reports are opening the doors of research for exploring the biological activity of Schiff base via several aspects.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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