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Synthetic Process and Recent applications of Schiffbases

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ABSTRACT
Schiff bases are aldehyde or ketone-like compounds with an imine or azomethine group in placeofthecarbonylgroup.They'recommonlyutilized inindustry,andtheyalsohaveawidespectrumof biological activity. There are a number of different reactions that can be utilized to synthesize the Schiff bases. The mostfrequentapproachistousemineralacidsascatalyst sinanacidcatalyzedcondensationreactionofprimary amine with an aldehyde or ketone under refluxing conditions. This brief study highlights the most promising antimalarial, antibacterial,antifungal,andantiviralSchiffbases.The numeroussynthesisprocessesandapplicationsofSchiffbasesand theirmetal complexes aresummarizedinthis article. Schiffbaseshavequiteachelatingconfigurationandare popularbecausetheyareeasytoproduceandaremodest electrondonorswithadjustableelectronicandstericeffects,makingthemflexible.Plant growth hormone, auxin, and cytokine all have outstanding growth regulator actions whenthiodiazole Schiff basesare used.Ithasbeenshownthatthe Schiff base complexesof 2-pyridinecarboxaldehyde and its derivatives have significant superoxide dismutase activity. Schiff bases can be further studied for other novel pharmacological activities by utilizing QSAR studies. Moreover, various derivatives could be synthesized with diverse therapeutic potential.

KEYWORDS: Schiff bases, Schiff base ligand, Auxiliary ligands, microwave irradiation, Schiff base derivatives

I. INTRODUCTION

Hugo Schiff was the namesake of the Schiff bases[1]. They're made when a primary aminecombineswithanaldehydeorketoneundercertainconditions.ASchiffbaseisstructurallyunique(alsoknownasimineorazomethine).isanitrogenanalogueofanaldehydeorketoneinwhichthecarbonyl group (CO) is substituted by an imine or azomethine group? Schiff bases are a class ofchemical molecules that are commonly employed. They're employed as pigments and dyes,catalysts, organic synthesis intermediates, and polymer stabilizers[2]. Schiff bases have also beenshowntoexhibitabroadrangeofbiologicalactivities,includingantifungal,antibacterial,antimalarial,antiproliferative,anti-inflammatory,antiviral,andantipyreticproperties[3]. Variousnatural,natural-derived,andnon-naturalsubstanceshaveimineorazomethinegroups.Thepresenceofaniminegroupinthesecompoundshasbeenproventobeimportantfortheirbiologicalactions[4-6].

II. CLASSIFICATION OF SCHIFFBASE

Schiff bases are categorized as bidentate (1), tridentate (2), tetradentate (3), or polydentate (4, 5)ligands that can form very stable complexes with transition metal ions in general. The resultantSchiff bases can act as mixed-donor ligands that can participate in bi-, tri-, tetra-, and highercoordination modes if they contain additional functional groups like –OH, –NH2, or –SH. As aresult,selectingtherightmetalsforapharmacologicallyactiveorganicscaffoldaltersitspharmacologicalactivity.Accordingtotheliterature,pharmacologicalactivityisdependentonthemetalion, chemical scaffold, and specificDNAbinding site[7].

Schiffbaseshavequiteachelatingconfigurationandare popularbecausetheyareeasytoproduceandaremodest electrondonorswithadjustableelectronicandstericeffects,makingthemflexible.Their derivatives are one of the few families of biologically active molecules that have beenextensivelyexploredinthesearchfornewpotentialagentsthatchemistscanemployforsynthesis [8]. These ligands have gotten a lot of attention because of their antimicrobial [9], anti-tuberculosis[10],anti-

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tumouractivity[11],anticonvulsant[12],anti-inflammatory[13],anti-HIV [14],anthelmintic[15],cardiovascular[16], andanti-carcinogenicproperties [17].

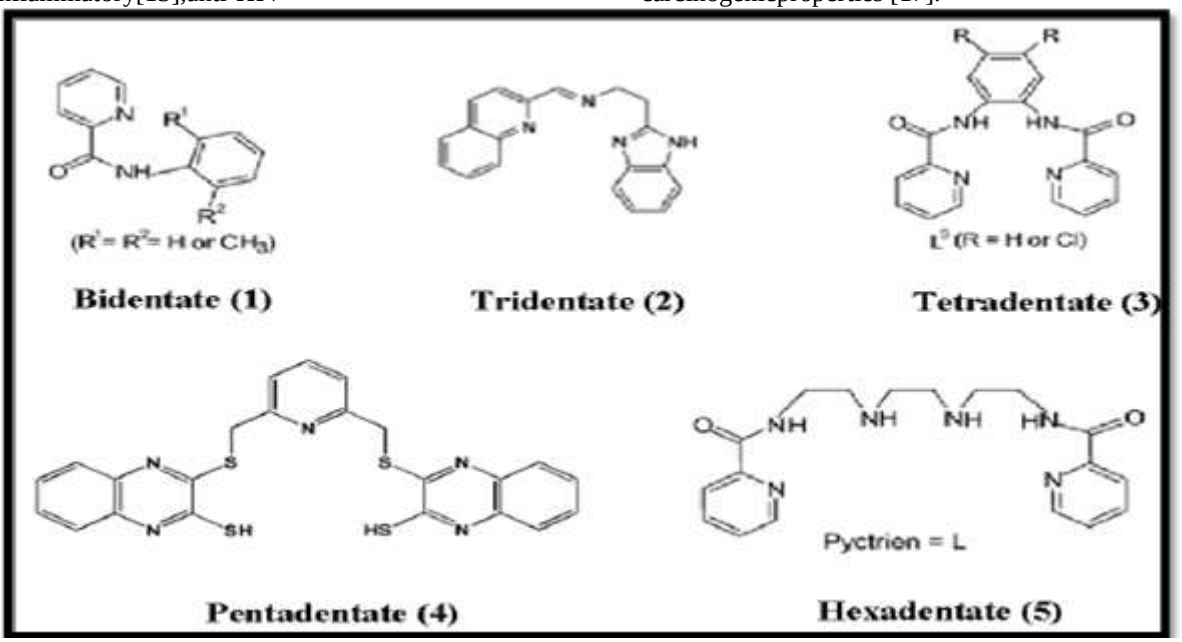

Figure1:Few classesofSchiffbasel

III. SYNTHESIS OF SCHIFFBASES

Schiff reported the first preparation of imines in the 19th century (1864). Since then, a variety ofimine production methods have been described[18]. Schiff describes a traditional synthesis thatinvolvesthecondensationofacarbonylmoleculew ith anamineusingazeotropicdistillation[19].The water that has developed in the system is subsequently entirely removed using molecularsieves[20].Inthe1990s,dehydratingsolutio nssuchastetramethylorthosilicateortrimethylorthofo rmate were used to develop an in-situ approach for water removal [21-22]. In 2004, Theefficacy of these approaches, according to Chakraborti et al., is contingent on the utilization ofhighly electrophilic carbonyl compounds and strongly nucleophilic amines. They recommendedusing compounds that serve as Bronsted-Lowry or Lewis acids to activate the carbonyl group ofaldehydes,catalysethenucleophilicattackbyamines ,anddehydratethesystem,leavingwaterout of the equation [23]. $ZnCl_2$, TiCl4, $MgSO_4$-PPTS, Ti $(OR)_4$, alumina, H_2SO_4, $NaHCO_3$, $MgSO_4$,Mg $(ClO_4)_2$, H_3CCOOH, Er $(OTf)_3$, P_2O_5/Al_2O_3, HCl are examples of Bronsted-Lowry or Lewisacidsemployed in thesynthesis of Schiffbases [24-27].

Auxiliaryligands,suchasSchiffbases,alterthestructur eandreactivityofthetransitionmetalioninthecomplex' scorewhileundergoingnoirreversibletransformations themselves,unlikereactiveligands.

IV. SOLVENT FREE SYNTHESIS BY MICRO WAVEIR RADIATION

The synthesis of Schiff bases with the use of microwaves is quick and easy, and it doesn't requirethe use of any solvent. Product yield and purification are also high. Some Schiff bases of 4-phenylthiosemicarbazidehavebeenmicrowavesynth esizedusingaromaticaldehydes(anisaldehyde,9-anthraldehyde,cinnamaldehyde,indole-3-carboxaldehyde,1-naphthaldehyde,andovanillin) [28].

Solventfreesynthesisby usingcatalyst

When the reaction mixture is pulverized in a mortar and pestle, the synthesis of Schiff basescanbedoneefficientlyatroom temperatureusing acatalystsuchasSnCl2andacetic acid.

Solventandcatalystfreesynthesis

Amortarandpestleareusedtogrindamixtureofamines andaldehydes/ketones.Thereactiontakesabout 2-3 minutes to complete.

Solventbasedsynthesis

When the mixture is refluxed in an acidic, basic, or neutral medium, a suitable solvent, suchasethanol

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ormethanol, is usually required [29].

V. TYPES OF SCHIFFBASE

The number of donor atoms in a ligand is used to classify them first. As a monodentate ligand,Schiff base 4-aminobenzenesulfonamide-1,3-benzodioxole-5-carbaldehyde can coordinate withtransitionmetals [30].SomebidentatearoylhydrazinebasedSchiffbases (ON)havebeencharacterizedasdioxo-uranium(VI)complexeswithacetone [31].Synthesizedandcharacterized5-(diethylamino) phenoland5-(diethylamino)-2-((2,6-diethylphenylimino) methyl) phenol.From3-aminopyridineand2,4-dihydroxyacetophenone, the tridentate Schiff base 1-pyridin-3-ylimino-ethyl benzene-1,3-diolwas produced and interacted with Ce(III), Pr(III), and Er(III) [32-33]. Condensation of 1,2-di-(4-fluoro-phenyl)ethylenediaminewithsalicylaldehydeyielded thetetradentate(ONNO)Schiffbaseligand [34]. A template technique based on condensation of an amine containing homopiperazineand 2,6-diacetylpyridine or 2,6-pyridine dicarboxaldehyde in a 1:1mol ratio in the presence ofmetalionswasusedtomakesymmetricalpentadentat emacrocyclicSchiffbases[35].Thereactionof 1-fluoro-2-nitrobenzene with homopiperazine yielded hexadentate macroacyclic Schiff baseligands (N_4O_2) of 2-hydroxybenzaldehyde (H2L1) or 2-hydroxy-3-methoxybenzaldehyde [36].From1,8-diamino-3,6-dioxaoctaneand3,5-dichlorosalicylaldehyde,theSchiffbaseligand(N_4O_2)(6,60-((1E,11E)-5,8-diazadodeca-1,11-diene-1,12-diyl)bis(2,4-dichlorophenol))[37].Condensationofpolyamine,2,20-(ethane-1,2-diylbis(piperazine-4,1-diyl))bis(ethan-1-amine)with 2-hydroxybenzaldehyde and 2-hydroxy-3-methoxybenzaldehyde yielded two macroacyclicoctadentate (N_6O_2) Schiffbaseligands [38].

VI. PREPARATION OF SCHIFFBASES

To make Schiff base, there are a number of different reactions that can be used. The mostfrequentapproachistousemineralacidsascatalyst sinanacidcatalyzedcondensationreactionofprimary amine with an aldehyde or ketone under refluxing conditions. The nucleophilic nitrogenatomoftheamineattacksthecarbonylcarboni nthisreaction,resultinginanunstableintermediate,car binolamine.AC14Nbondisproducedasaresultofthere movalofonemoleculeofwater,andtheproductisknow nasimine.Ingeneral,thereactivityofaldehydeinthepro ductionofSchiffbaseishigherthanthatofketonebecaus ethereactioncenterofaldehydeissterically lesshindere d than that of ketone. The pH of the solution, as well as the steric and electronic effects ofaminesandcarbonylcompounds,influencethecond ensationreaction.Acidscatalyzesuchreactionsbecaus ethedehydrationofthecarbinolamineistherate-determiningstepintheproductionofSchiffbases.It'sals oworthnotingthatalargeracidconcentrationwillproto natetheamine,limitingitsroleasanucleophileandredu cingcarbinolaminesynthesis.Asaresult,manySchiffb asesaresynthesizedatamildacidicpH.Similarly,thepr ocessisslowedatbasicconditionsdueto a lack of protons to catalyzethe removal ofthe carbinolamine hydroxylgroup [39].

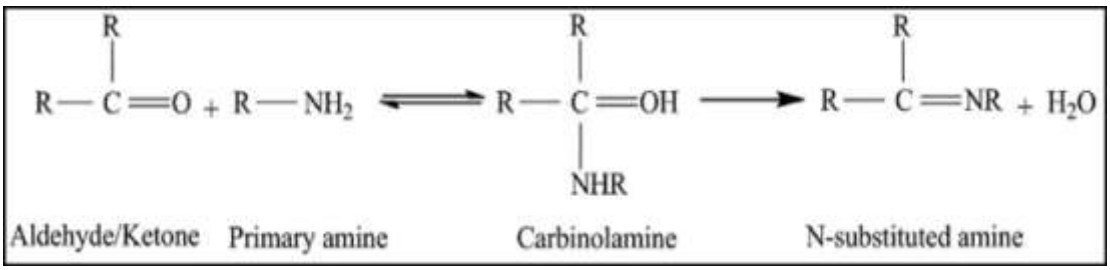

Figure2:Generalreaction forsynthesis ofSchiffbases

Auxiliaryligands,suchasSchiffbases,alterthestructur eandreactivityofthetransitionmetalioninthecomplex' scorewhileundergoingnoirreversibletransformations themselves,unlikereactiveligands.

VII. SCHIFF BASE DERIVATIVES WITH OTHER FUNCTIONAL GROUPS

Sulfonamides

Sulfonamidesarekeypharmacoresthatarefre quentlyusedinthedevelopmentofnovel drugs. Lal et

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al. synthesized two series of Schiff base-curcumins with sulfonamide moiety14a–eand15a–einthisregard.AntibacterialactivityagainstS.aureus, Bacilluscereus(B.cereus),Salmonella typhi, Pseudomonas aeruginosa, and E. coli, as well as antifungal activity against A.niger,A.avus,C.lunata,andTrichodermaviride(T.viride)weretestedforthesecompounds.Thecytotoxic activity of substances tested on cancer cell lines HeLa, Hep-G2, QG-56, and HCT-116.The carrageenan-induced paw oedema method was used to assess in vivo anti-inflammatoryefficacy. The bioassay results confirmed that when sulfonamides are combined with curcumin,theiractivity is enhanced [40].

Aminoacids

Aminoacidsincludebothamineandcarboxylicfunctionalgroupsandareessentialfor physiological activity. With compounds containing b-diketones, such as curcumin, the aminogroupcanperformtheSchiffbasereaction.In2013,Raman'steamproducedtheSchiffbaseligandby condensation of curcumin and cysteine a-amino acid in the search for specific anticancermedicines. The ligand's oxygen and nitrogen were coordinated to the metal ions Cu (II), Co (II),Ni(II),andZn(II).Theligand 18anditscomplexesaretested fortheirabilitytobindwithDNA.The electronic absorption spectra revealed that the complexes and DNA bases have a stronginteraction(Kb141.2–3.4104M1),whichcouldleadtoDNAcleavage.Gelelectrophoresistestswere conducted out in the presence of H2O2 as an oxidant using pBR322 circular plasmid DNA.Allof thecomplexes werediscoveredto be effectivecleavingagents [41].

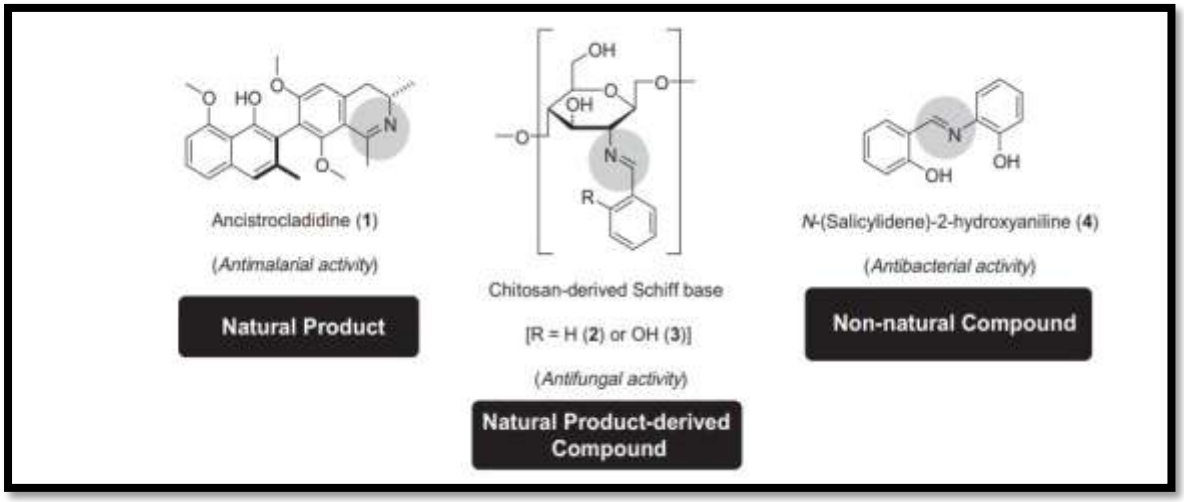

Figure3:BioactiveSchiffbases

VIII. BIOLOGICAL ACTIVITIES OF SCHIFF BASES

Antimalarialactivity

Schiff bases have been found to be useful components in the development of antimalarial drugs.Ancistrocladidineisasecondarymetabolitegeneratedbyplantsbelongingtothe Ancistrocladaceae and Dioncophyllaceae families, and it has an imine group in its molecularscaffold. The activity of Compound 1 against P. falciparum K1 and 3D7 has been demonstrated.Ancistrocladidine's minimal inhibitory concentrations (MIC values) were 0.3 and 1.9 lg/mL,respectively,tototallystopP.falciparumK1and 3D7development.Compound1was90-and10-foldmoreselectivetoP.falciparumK1and3D7thanratskeletalmyoblastL-6cells,respectively[42]. Rathelot et al. described the synthesis of Schiff base-functionalized 5-nitroisoquinolines, aswell as their in vitro efficacy against an ACC Niger chloroquine-resistant P. falciparum strain.Amongthe5-nitroisoquinolinederivativesproduced,Schiffbase5wasthemostpotentantimalarial drug. Compound 5 had to be at a concentration of 0.7 lg/mL to inhibit P. falciparumgrowth by 50% (IC50). Chloroquine's IC50 value was 0.1 lg/Ml under the identical experimentalcircumstances [43].

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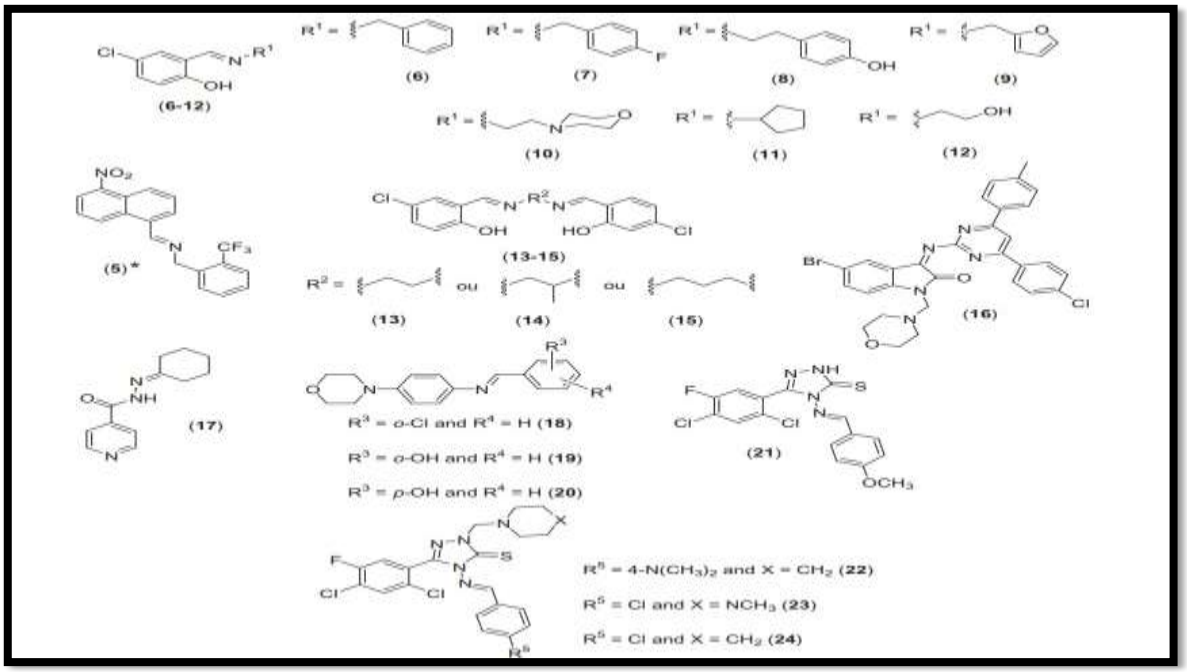

Figure4:ChemicalstructureofsomesyntheticantibacterialSchiffbases

Antibacterialactivity

Schiff bases have been suggested as potential antibacterial. N-(salicylidene)-2-hydroxyaniline,for example, has a MIC value of 8 lg/mL against Mycobacterium TB H37Rv [44]. Experimentsusing J774 macrophages were used to test chemical 4's selectivity. Compound 4 had no cytotoxiceffectonJ774macrophages,evenatconcentrationsashighas 1000lg/mL.Atthoseexperimentalconditions, more than 80% of macrophage cells were alive, demonstrating compound 4's greatselectivity. A series of Schiff bases produced from the condensation of 5-chloro-salicylaldehydeand primaryamineshaverecentlybeendescribedfortheirsynthesisandantibacterialactivity.Atleastoneofthetesteddbacterialspecieswasmoreactiveagainstthe5-chloro-salicylaldehyde-Shiffbasederivatives6–15.WithMICvaluesrangingfrom2.5to5.2lg/mL,Pseudomonasfluorescencewas the strain most sensitive to chemicals 6–11 and 13–15. The reference medication kanamycinhas a MIC of 3.9 lg/mL against the same bacterial strain. The MIC values for the Schiff bases 6,7, 9–11, 14, and 15 against Escherichia coli were 1.6–5.7 lg/mL, while the MIC value forkanamycin was 3.9 lg/mL. Only the Schiff base 14 was sensitive to Bacillus subtilis (MIC = 1.8lg/mL).Compounds6and7hadMICvaluesof3.1and1.6lg/mLagainstStaphylococcus aureus,respectively [45]. Aragon-Muriel et al.(2021)[46] investigated the antibacterial potential of fourbenzimidazole-basedSchiffbasesandtheirmetalcomplexesagainsttwoGram-positive(S.aureus25923, Listeria monocytogenes 19115) and two Gram-negative strains (S. aureus 25923, Listeriamonocytogenes 19115) and two Gram-negative strains (S. aureus 25923, Listeria monocytogenes1911 (E. coli 25922, P. aeruginosa 27583). The activity of the complexes was often higher thanthat of SBs alone. Furthermore, as is typically the case with biologically active substances,isomerismseems to play acritical rolein SBs [47].

Antifungalactivity

Fungal infections aren't always limited to the skin; in fact, there's been a rise in life-threateningsystemicfungalinfections.Atmicromolar quantities,piperonyl-derivedSchiffbaseswereeffectiveagainstfungus.Trichophytonrubrum(MIC=820–980lM)andEpidermophytonfloccosum (MIC = 200–930 lM) were both inhibited by these compounds [48]. Microsporumaudouinii (MIC values ranging from 2.4 to 9.7 lg/mL) and Microsporumgypseum (MIC valuesrangingfrom1.2to9.7lg/mL)werebothsignificantlyactiveagainsttheisatin-derivedSchiffbases16and41–51.Compounds16and41–51inhibitedCandidaalbicans,Aspergillusniger,Crypt

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ococcusneoformans,T.mentagrophytes,E.floccosum ,andHistoplasmacapsulatumgrowthwith MIC values greater than 10 lg/mL and less than 79 lg/mL [49]. Panneerselvam et al. foundthattreatmentwithcompound20at20lg/mLorco mpound52at30lg/mLinhibitedthedevelopmentof both C. albicans andA. niger inaseparateinvestigation [50].

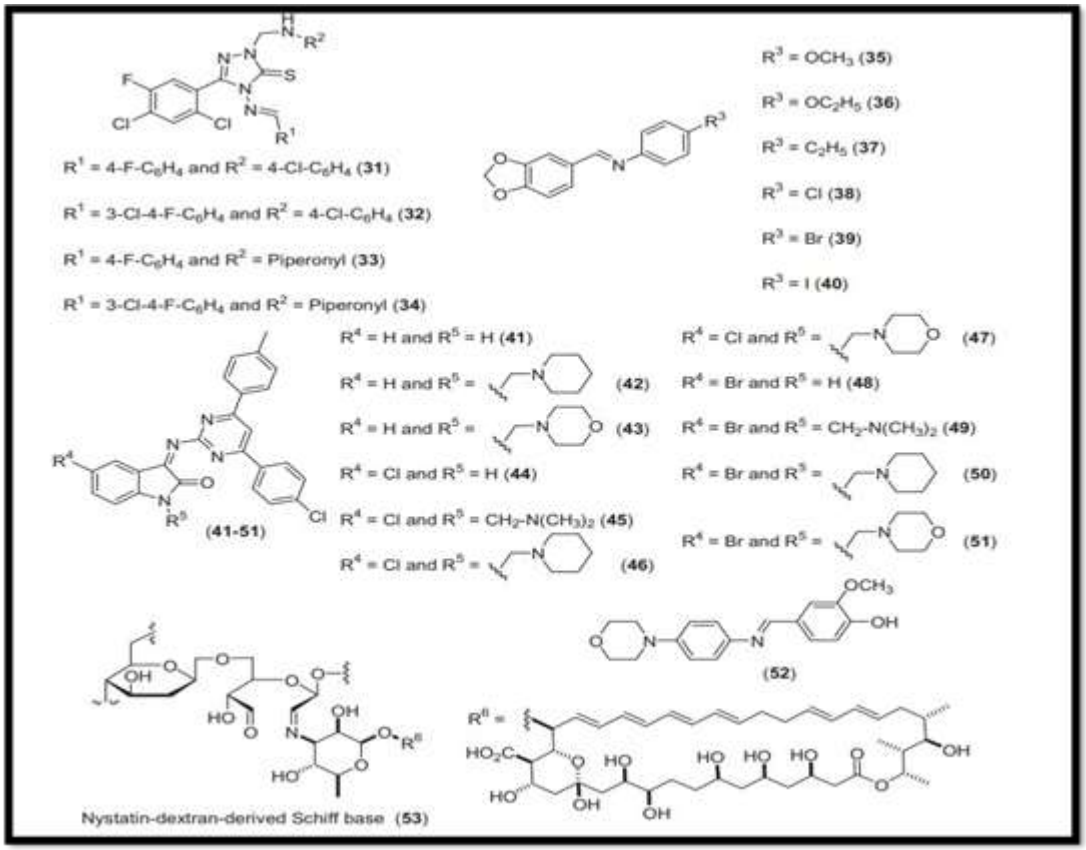

Figure 5: Chemical structure of some antifungal Schiff bases derived from natural or non-naturalcompounds

Antiviralactivity

1-amino-3-hydroxyguanidine tosylate salicylaldehyde Schiff bases are a good foundation fordesigning novel antiviral medicines [51]. Indeed, compound 54 was found to be particularlyefficient against mouse hepatitis virus (MHV) when used at concentrations as low as 3.2 lM, andwas produced from a collection of distinct 1-amino-3- hydroxyguanidinetosylate-derived Schiffbases.Abacavir is a nucleoside analogue that can stop reverse transcriptase fromworking.Itissoldunderthebrandname Ziagenand isusedtotreatthehumanimmunodeficiencyvirus(HIV)andAIDS(GlaxoSmithKline).Thecompounds55–65wasfoundtobehighlyefficientagainst human immunodeficiency virus type 1 (HIV-1) (HIV-1). The effective concentration(EC50) of these abacavir-derived Schiff bases required to protect human leukemic cells (CEM)50% against HIV-1's cytopathic effect was less than 6 lM. The most potent Schiff base wascompound 57, which was effective at 50 nM. Only at doses greater than 100 lM is this chemicalhazardous to CEM cells, indicating that it could be used as a lead compound in the developmentofnovel anti-HIV-1 drugs.

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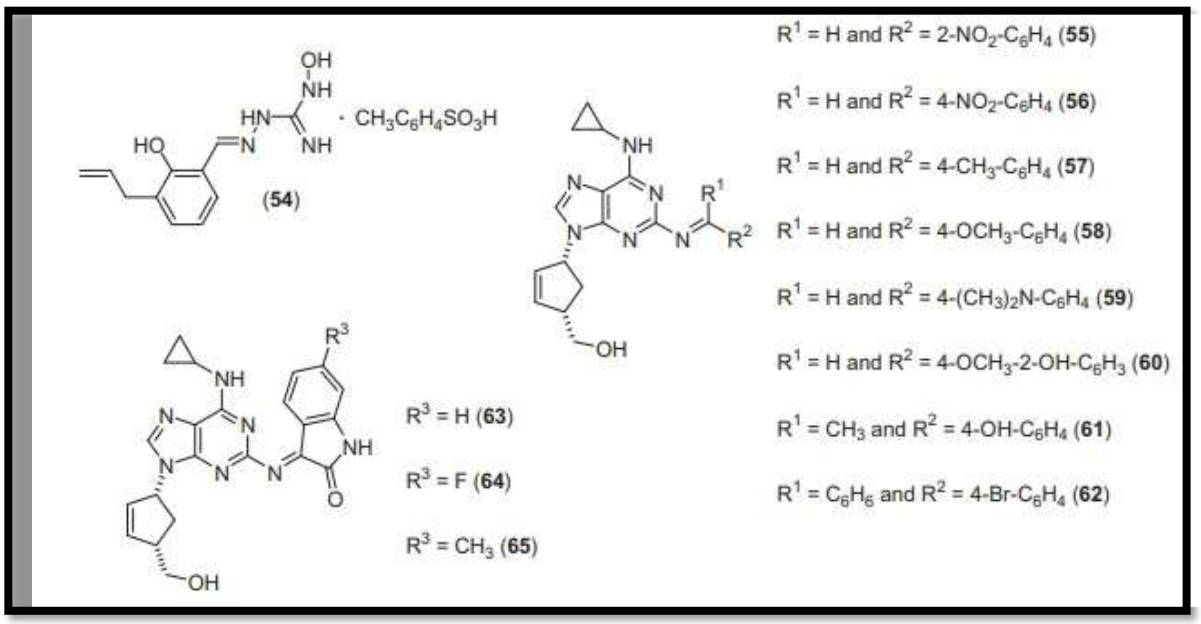

Figure6: ExamplesofantiviralsyntheticSchiffbases

Anticanceractivity

Cancerisanincurablediseasethatresultsindeath.Inthehumanbody,morethan200cancerformshave been identified. Cumarin and pyrazole aldehyde-derived Schiff bases were tested againstmalignant cell lines and shown to have moderate anti-cancer properties [52]. Furthermore, monoandbis-Schiffbaseswerefoundtobeeffectiveagainstfivecancercelllinesinanotherinvestigation [53]. Schiff bases can also form complexes with transition metals, and these metalcomplexes have been shown to have anticancer properties; Cu complexes with vaniline Schiffbases[54].Theanti-cancerpropertiesof-1,2-dihydro-pyrazol-3-oneSchiffbaseshavebeenreported.Becausethereisalargebodyofliteratureontheefficacyof Schiffbasesagainst cancer cell lines, more systematic and extensive study, both in vitro and in vivo, isrecommendedtoexpandtheirtherapeuticusagetoalleviatethe condition.

Actiononinsecticides

Whenthecellsurvivalrateofmungbeansproutswasincreased,Mo(II)complexesofSchiffbasesderivedfromthiadiazolederivativesandsalicylaldehydeoro-vanillinshowedinsecticidalactivityagainstbollworm [55].

Plantgrowthregulator/enzymaticactivity

Plant growth hormone, auxin, and cytokine all have outstanding growth regulator actions whenthiodiazole Schiff basesare used.Ithasbeenshownthatthe Schiff base complexesof 2-pyridinecarboxaldehyde and its derivatives have significant superoxide dismutase activity [56].Amylasetransportationacrossmembranewaspromotedby Mn(II)and Zn(II)complexescontainingtetradentateSchiffbaseligands,whereasitwashinderedby Ni(II)and Cu(II)complexes[57].AmidoSchiffbasechelatesofCu(II)andFe(II)serveasthrombininhibitors[58].

Applicationsof SchiffBases and Their Metal Complexes

Furtherresearchinthisareaisextremelydesirabledueto theversatilityofSchiffbaseligandsandthe biological, analytical, and commercial applications of their complexes. The Schiff bases,particularlythiosemicarbazones andtheir complexes,arebriefly discussedhere.

CatalyticApplications

ByattachingalternativesubstituentstotheligandinSchiffbasemetalcomplexes,theenvironmentat the coordination center can be changed, providing a useful range of steric and electricalpropertiesforfine-tuningstructureandreactivity.Thecatalyticactivityoftransitionmetalcomplexes, both simple and polymer

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anchored, were reviewed byGupta and Sutar. They haveemphasizedSchiffbasecomplex'spotentialasacatalystforoxidations,hydrogenations,polymerizations, different coupling processes, and ring closures [59]. Chemists have recentlybecomeinterestedinheterogeneousandhomogeneouscatalystsbecausetotheirimprovedselectivity andrecyclability.Thenumberofarticlesincatalysisbysupported Schiffbasecomplexeshasincreasedexponentiallyinrecentyears.Homogeneouscatalysis,ontheotherhand,ismoreimportantbecausethemechanismofthereactioncanbedetermined.Thestereoselective transformationsofBINAPligands(BINAPisanacronymfortheorganophosphoruschemical2,2'bis(diphenylphosphino)-1,1'-binaphthyl)arewellknown.Instereoselectiveorganictransformations, Cheand Huang examined the catalytic activity of chiral BINAP Schiff basecomplexes[60].

RibonucleotideReductase

Intheirneutralordeprotonatedform,thiosemicarbazonesactasN,N,S-thiodentateligands,formingchelateswithimportantmetalions.Theyinhibittumourcellproliferationinavarietyoftumourcelllines.TheenzymeRibonucleotideReductase(RR),whichisrequiredforDNAsynthesis, has been found to have a substantial correlation with tumour development rate [61].Brockmanetal.[62]publishedtheirfindingsin1956.In1965,Frenchetal.[63]proposedideasconcerningthemodeofactionofthe-(N)-heterocyclicthiosemicarbazones,claimingthattheactivemoleculessharedatridentatecharacter,allowingthemtobeeffectivechelators,andthatimprovingthearomaticsystemimprovedactivity.Theywereabletoanticipatetheactivityofpyrazinecarboxaldehydethiosemicarbazoneand1-formylisoquinolinethiosemicarbazoneusingthistechnique.Ribonucleotidereductaseisaniron-dependentenzymethatfacilitatesthereductionofribosetodeoxyriboseviaatyrosylradical-triggeredfreeradicalprocess.Whenthisenzymeisinhibited, the cell cycle's synthesis phase is halted, and the cell eventually dies through apoptosis.Theyalsoshowedthattheactivespecieswastheiron(II) complexof1-formylisoquinolinethiosemicarbazoneinanindirectway.Ironandcoppercomplexes,infact,wereeventuallyrevealed to be significantly moreactivethanthefreeligand [64].

IX. CONCLUSION

For industrial purposes, Schiff bases have been extensively researched. The biological activity ofthis class of chemicals, on the other hand, warrants additional exploration. When plant pathogensare taken into account, this becomes evident. Despite the fact that research on this topic is still initsearlystages,anumberofpapersrevealingtheeffectofSchiffbasesonpathogensoftherapeuticimportance have recently increased. Schiff base compounds have been identified as intriguingcandidates for the development of more effective antibacterial medicines. The structure–activityrelationshipsoftheSchiffbases,aswellasthemechanismofactionofthesecompounds,willbe studiedinordertoadvanceinthisfield.Thegoalofthisworkistogooverthechemistryof Schiffbasesandtheirmetalcomplexes,aswellastheircatalyticandRibonucleotideReductionactivities.

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