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Studies of Some Coordination Compounds with Schiff-Base Ligand Drived From Carbonyl and Amino "Hydroxamic" Acid

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Abstract – Schiff bases are versatile organic compounds typically used and synthesized by the condensation process of various aldehyde or ketone amino compounds such as imine. As they are easily synthesized by condensation, Schiff base ligands are classified as privileged ligands. They demonstrate a wide variety of uses and are often used as an O2 detector in medication, pharmacy, teamwork chemistry, biological processes, industries, product packets, dyes, and polymers. Semi carbazone is a derivative of imine derived from semi carbazide condensation and ideal for aldehyde and ketone. Excellent precursors for the production of metal or metal chalcogenide nanoparticles have been shown by imine ligands comprising transition metal complexes such as copper , zinc, and cadmium. In recent years , due to various pharmacological uses such as antiviral , antifungal, antimicrobial, antimalarial, antituberculosis, anticancer, anti-HIV, catalytic use in organic compound oxidation, and nanotechnology, researchers have drawn tremendous attention to Schiff bases, semi carbazones, thiosemicarbazones, and their metal complexes. The synthesis, structural, biochemical, and catalytic application of Schiff bases as well as their metal complexes are summarized in this study. Due to the capacity to chelate biologically essential metal ions to modulate different enzymes such as HDACs, urease, metallopeptidase, and carbonic anhydrase, substituted hydroxamic acid is one of the most widely researched pharmacophores. Syntheses and biological studies of various groups of hydroxamic acid derivatives have been published in multiple research articles in recent years, but this is the first study paper dedicated to their synthetic methods and their application for the synthesis of these specific molecules.

Keywords: Hydroxamic Acids, Hydroxylamine, Coupling Reactions, Catalytic Reaction, Mutagens, and Direct Synthesis.

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INTRODUCTION

Schiff 's base is identified by the name of Hugo Schiff, who first recorded the reversible acid-catalyzed condensation reaction of carbonyl compound primary amine. They are also classified as imines with a ReCH1⁄4NeR0 general form, where R and R0 are a linear or cyclic alkyl and/or aryl group that can be replaced differently . For coordination chemistry, Schiff bases are an essential class of ligands and coordinate with metal ions through azomethine nitrogen. In the area of coordination chemistry, Schiff base ligands have been extensively studied, primarily because of their simple synthesis, easy accessibility, and electronic properties. Schiff base coordination chemistry has gained a great deal of interest in recent times owing to In organic synthesis, analytical chemistry, metal mining, metallurgy, electroplating and photography, their importance is[5e7]. Schiff bases are commonly used in the pigment, catalysis, fungicidal and agrochemical industries . It is documented that some Schiff bases have remarkable antibacterial , antifungal, and anticancer activities. The C1⁄4N mould is essential for biological activity in such a class of compounds. By using a range of Schiff base ligands, Abdel-Rahman et al. have documented the number of transition metal complexes and researched their numerous biological activities such as antimicrobial , anticancer, antifungal, etc. For eg, using a variety of Schiff base ligands derived from 5-bromosalicylaldehyde (bs) and different a-amino acids such as Lalanine (ala), L-phenylalanine (phala), L-aspartic acid (aspa), Lhistidine (his), and L-arginine (arg), a number of Fe (II) complexes have been designed and synthesised. These complexes have been tested against Escherichia coli, Pseudomonas aeruginosa, and Bacillus cereus and various antifungal cultures such as Penicillium purpurogenium, Aspergillus flavus and Trichothecium rosium for their antibacterial and

antifungal function. Compared with the Schiff base ligands, Fe (II) complexes have demonstrated good antibacterial and antifungal action compared to the amino acids. These complexes were also tested using viscosity, UV-visible spectroscopy, and agarose gel electrophoresis measurements at pH 1/4 7.2 for their association with calf thymus (CT) DNA. The findings showed that different DNA binding constants based on the Schiff base ligands were seen by the studied complexes, and they bind strongly to CT DNA by intercalative mode[10b]. Several Schiff base ligand 2-[(2-Hydroxy-3-methoxy-benzylidene)-amino]pyridin-3-ol nanosized Fe(II), Cd(II) and Zn(II) complexes isolated from 2-amino-3-hydroxy-pyridine and 3-methoxysalicylaldehyde have been sonochemically prepared and both compounds have been tested for their antimicrobial action against such pathogens. The least antimicrobial behaviour towards fungi and bacteria was found to be demonstrated by the ligand, whereas all the complexes displayed more behaviour against the same fungi and bacteria. For colon carcinoma cells (HCT-116 cell line) and hepatic cell carcinoma cells (HepG-2), several complexes demonstrated great cytotoxic activity. Since the mid-19th century, metal Schiff base complexes have been recognised. Their usage as Schiff base ligands that are usually monodentate, bidentate, tridentate, tetradentate, etc. have been illustrated by a significant number of literature which rely on the existence of donor atoms.

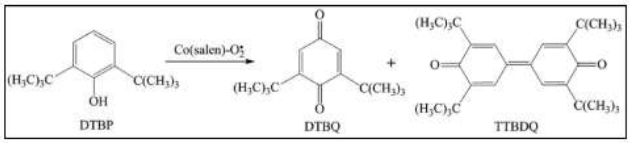
They are commonly applied to coordination chemistry since they are capable of creating stable transition metal complexes. Because of the stability of Schiff base metal complexes as well as biological activity, electrochemistry and possible applications in oxidation catalysis, researchers have based significant attention on the chemistry of Schiff base metal complexes containing nitrogen and other donor atoms owing to their comprehensive applications in dyes, polymers, enzyme preparation and catalyst applications. Because of their selectivity , sensitivity, and synthetic versatility to the central metal atom and the existence of the azomethine group, Schiff bases are widely studied, contributing to biological disclosure of the process of transformation reaction.

Via the use of Schiff base ligands derived from 2-amino-3-hydroxypyridine and 3-methoxysalicylaldehyde, several Cu(II), Co(II) and Ni(II) complexes have been identified and investigated for their in vitro antimicrobial activities against various bacteria and fungi. These complexes were also tested for DNA binding, and it was noticed that, by intercalative mode, these compounds could bind to DNA. However, the cytotoxicity of these Schiff metal base complexes on various cell lines, such as human colon carcinoma cells (HCT-116 cell line) and breast carcinoma cells (MCF-7 cell line), has demonstrated an important cytotoxicity activity against carcinoma cell growth relative to the vinblastine norm used clinically[16c]. Among the most common, metal coordination complexes based on salen / salophen have found immense applications in sensors, catalysis, biology, and material science. For a range of fascinating catalytic uses, several researchers have examined a significant number of Schiff base ligands as chelating compounds, such as metal chelates of copper , cobalt, etc. The N, N-bis(3,5-di-tert-butyl-salicylidene-1,2-cyclohexane deaminate) saline complex has been used as a catalyst for the oxidation of 2,6-di-tert-butylphenol (DTBP) and 3,5-di-tert-butylphenol (35-DTBP) into supercritical carbon dioxide (scCO2). The oxidation of DTBP, along with the side product of radical coupling, culminated in 2,6-di-tert-butyl-4,40-benzoquinone (DTBQ), i.e. 3,5,30-,50-tetra-tert-butyl-4,40-diphenoquinone (TTBDQ) (Scheme 1).

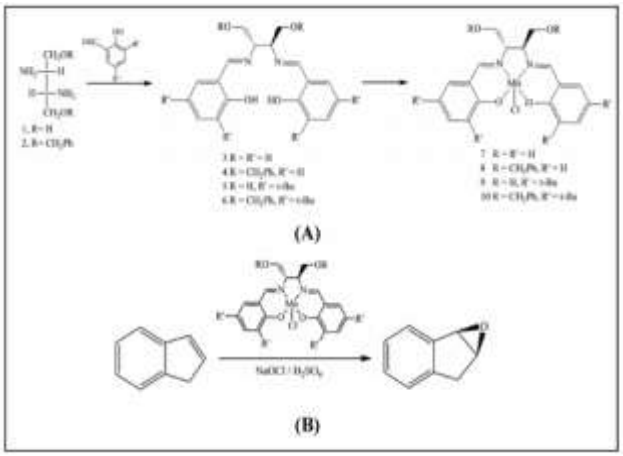
Catalyst conversion and selectivity have been studied as a feature of catalyst strain, temperature, and concentration. The transition and heavy metal ion complexes were synthesized utilising novel Schiff base ligands dependent on saline (3e6) obtained from the respective diamines (1 and 2) Chiral catalysts were the Mn (III) complexes (7e10) (Scheme 2A) of these Schiff base ligands and are stated to be useful for asymmetrical indene epoxidation (Scheme 2B). Some of the Mn(III) saline complexes is often used to catalyse the asymmetric epoxidation of conjugated olefins, e.g. the bis(2-pyridinaldehyde)-ethylenediamine, bis(2-pyridine-aldehyde)propylene diamine ligands of the Mn(II) bis(2-pyridinaldehyde)-ethylenediamine, bis(2-pyridine-aldehyde) complexes were used for olefin epoxidation, but reasonable epoxide selectivity was only possible in the presence of iodosobenzene (PhIO) as an oxidant[19]. Pt(II) complexes of Schiff base ligands N, N0-bis(salicylidene)-1,2-ethylene diamine (L1), N, N0-bis(salicylidene)-1,3-propane diamine (L2) and N, N0-bis(salicylidene)-1,1,2,2-tetramethylene diamine (L3) were recently reported by Che et al. and explained the use of vapour deposited Pt(II)-salen(11) triplet emitters as effective electro phosphorescent dyes in multilayer organic light e. They found that the efficiency of the OLEDs using the Schiff base dopant L3 was substantially greater than that of the Pt(II) emitters previously recorded. Many of the Schiff bases was synthesised with aromatic amines as well as aliphatic amines by salicylaldehyde condensation. Calvin and Baileshave recorded some imines with condensation reactions of salicylaldehyde and substituted anilines and other aromatic amines. Interesting electronic properties were discovered in the spectroscopic study of certain molecules containing nitrogen. It is stated that due to the presence of a loan pair of electrons in these substances, greater ligation of metal ions may be. A significant number of such azomethines with a range of transition metals and their complexes have been reported in the study papers in theLast years in the era. Tridentate Schiff base ligands 2-{(Z)-[(2-hydroxyphenyl)imino]methyl}phenol (12) and 2-{(Z)-[(2-hydroxyethyl)imino]methyl}phenol (13) containing ONO and 2-[(Z)-(pyridin-2-

ylimino)methyl]phenol (14) containing ONN or (2Z,4Z)-4-[(2-sulfanylphenyl)imino]pent-2-en-2-ol (15) containing donor atoms of NSO (Scheme 3) have been synthesised with binuclear complexes. These ligands are produced by condensing o-aminophenol's, o-amino thiophenols, amino alcohols, and aminothiols with salicylaldehyde or acetylacetone. The participation of imine nitrogen in coordination was indicated by IR spectroscopy.

Similarly, Gao and Zheun synthesised those Schiff base ligands 16, 17, and 18 by condensing 2-hydroxyacetophenone with various chiral diamines, such as 1,2-diamino-cyclohexane, 1,2-diphenylethylenediamine, and 2,20-diamino-1,10-binaphthalene, respectively (Scheme 4), to study the steric, electronic, and geometric effect of the methyl (-CH3) group on asymmetric azomethine carbon. Alkynyl functionalized salicylaldimine ligand 2-{(E)-[(4-trimethylsilylethynylphenyl)) has recently been identified by More et al..

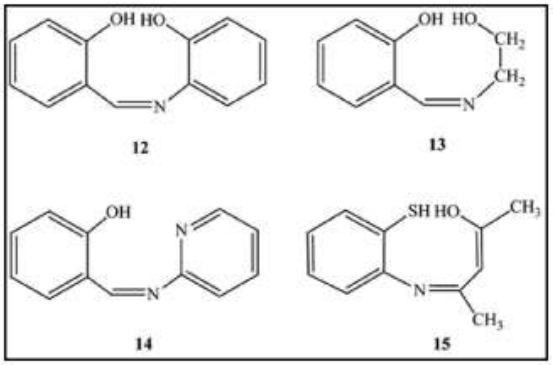


Scheme 1. Typical aerobic oxidation of DTBP by Co(salen). DTBP, 2,6-di-tert-butylphenol.



Scheme 2. (a) synthesis of derivatives of D-2,3-bis(arylidene amino)-1,4-butanediol (3e6) and their manganese complexes (7e10) and (b) indene epoxidation utilising the D-2,3-bis(di-t-butyl-salicylideneamino)-1,4-butanediol complexes of Mn(III).

imino]methyl}-4-(4-nitrophenylethynyl)phenol (19) and its Zn (II) and Ni (II) complexes. The emission properties of the complexes have been documented to be affected by p-conjugation, coligands (phen, bipy), and counter anion scale (ClO4, BF4, and PF6). More et al. have identified such luminescent complexes as promising non-linear optical material due to the impact of p-conjugation, Ni (II) and Zn (II) salophen complexes. (5th Scheme). As relatively effective models of biological compounds, a large number of Schiff base metal complexes are documented. They played a crucial role in the development of current coordination chemistry, as well as in the progress of inorganic biochemistry, catalysis and usable materials owing to their optical and magnetic properties[28e30]. For electronic devices such as solar cells and active components for image storage and data processing, technology focused on light emission or charge transport capability has been of special interest in recent years. They also play an significant role in the fields of stereochemistry, spectroscopy, and magnetic fields, because the Schiff base and its metal complexes have various functional groups. Similarly, semicarbazone is an imine derivative commonly derived from semicarbazide condensation with appropriate aldehyde or ketone. Semicarbazones can have a broad variety of biological uses, such as anti-cancer, antioxidants, and antifungals.



Scheme 3. Schiff base ligands containing ONO, ONN, and NSO donor atoms.

Hydroxamic acids are solid Fe(III) strongly chelated metal ion bidentate chelators; siderophores1,Zn(II); matrix metalloproteases (MMPs), carbonic anhydrase, and tumour necrosis factor-converting enzyme (TACE), Ni(II); urease, and Cu(II).2, 3. Under physiological conditions, hydroxamic acids, pKa values in the range of 9, are roughly 1% ionised and O-substitution improves the Coli methionine aminopeptidase,14 peptide deformylase,15 transforming enzyme tumour necrosis factor (TACE),16 matrix metalloproteinase enzyme MMP-13,17 tyrosinase,18 and aggrecanase.19 These unique molecules are also referred to as trypanocidal agents,20 stimulating effector of growth on queen bee larvae,21 up-regulating agents of high density lipoprotein (HDL) receptor CLA-1,22 in vitro antioxidant, antiradica,22 in vitro antioxidant

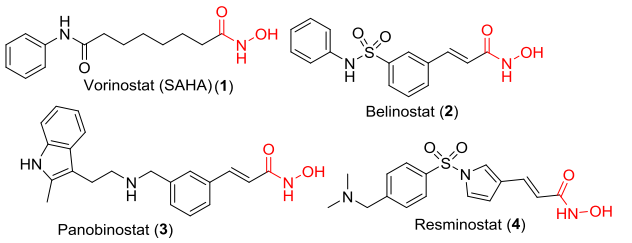


Figure 1: Approved hydroxamic acid based drugs

While a broad variety of biological behaviours are considered to exhibit hydroxamic acid derivatives, these compounds are best known for their anti-cancer properties. In order to treat various forms of cancers, four hydroxamic acid derivatives (Figure 1) have been licenced. On October 6, 2006, Suberoylanilide hydroxamic acid (SAHA) or Zolinza (US name) with antineoplastic activity was approved for the treatment of cutaneous T cell lymphoma (CTCL). SAHA (1) attaches to the HDAC catalytic domain, allowing the hydroxamic moiety to chelate the Zn(II) ion located at the active site of these enzymes, inhibiting deacetylation and inducing both hyperacetylated histones and transcription factors to accumulate. The upregulation of cyclin-dependent kinase (CDK) p21 accompanied by G1 arrest is induced by hyperacetylation of histone proteins. To achieve additional anti-proliferative results, SAHA is believed to influence hyperacetylation of non-histone proteins such as p53 (tumour suppressor), ⁇ -tubulin, and heat-shock protein 90 (HSP-90). Crossing the Blood Brain Boundary (BBB) is often accepted by SAHA. SAHA is in different stages of clinical trials to address a large range of cancers in conjunction with other antineoplastic drugs.39, 40Belinostat (BELEODAQTM, Continuum Pharmaceuticals, Inc.), a cinnamic hydroxamic acid extracted from sulfonamide (2), was given accelerated clearance by the Food and Drug Administration (FDA) on July 3, 2014 to treat patients with relapsed or refractory peripheral T-cell l By attacking HDAC enzymes, Belinostat (2) prevents tumour cell proliferation, triggering apoptosis, promoting cell differentiation, and inhibiting angiogenesis.41Panobinostat (3), another hydroxamic acid extracted from cinnamic acid, has been licenced for the treatment of multiple myeloma. Panobinostat (3) has been licenced for combined therapy with bortezomib and dexamethasone.42 Resminostat (4) is in clinical trials for the prevention of advanced hepatocellular carcinoma in patients with East Asian cancer (Figure 1).

The various phases in clinical research for the treatment of a wide variety of tumours contain a selection of hydroxamic acid compounds. Pracinostat (5) is a hydroxamic acid cinnamic acid analogue with potent HDAC inhibition action. This tiny molecule is in phase II and III clinical trials for the treatment of myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML).44 Givinostat (6), a variant of naphthalene-derived hydroxamic acid, is a powerful HDAC inhibitor that is an inclinical study for the treatment of different forms of cancers, including Hodgkin's lymphoma, chronic lymphocytic leukaemia (CLL) and multiple myeloma.45 Thi

Figure 2: Under clinical trials hydroxamic acid derivatives (5-9)[51] and a potent HDAC6 inhibitor (10)[50]

In order to combat a wide variety of cancers, a significant number of hydroxamic acid derivatives have been identified as active antineoplastic agents. Therefore, the synthesis of hydroxamic acid pharmacophore-bearing molecules is of considerable importance to both organic and medicinal chemists.

In contrast to the biological use of these compounds, synthetic approaches for hydroxamic acids are not so modern. Often synthetic chemists are satisfied with hydroxamic acid yields as poor as 10 percent from their precursors.52, 53 There is not a clear reagent or condition that can be used for a wide range of compounds, according to literature reports so far. However, various synthetic methods and reagents have been used to make a specific series of a few compounds.9 It will be helpful for synthetic and medicinal chemists to choose an appropriate or closely related reagent or method for a desired substrate to compile the following methods and reagents for the synthesis of hydroxamic acids.

Commercially available hydroxyl donating reagents

Free hydroxylamine (NH2OH) is brittle, explosive and mutagenic.54 It is often commercially available as hydrochloride salt in the form of salts (11) and in the form of a solution (12). In situ, free hydroxylamine is produced from hydrochloride salt by base treatment. Solutions of NH2OH are immediately used without pretreatment or drying in a reaction. Both N- and O-protected hydroxylamine are accessible from industrial outlets, although for hydroxamic acid synthesis, mainly O-protected hydroxylamine's (13–20) are used.

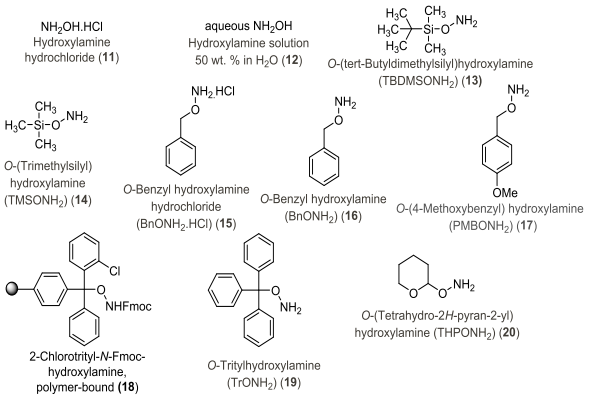


Figure3: Commonly available hydroxylamine donors

SYNTHESIS OF SUBSTITUTED HYDROXAMIC ACIDS

A. Direct reaction of hydroxylamine with ester derivatives:

Hydroxylamine's immediate response has also been used to synthesise hydroxamic acids from its ester precursors. Free hydroxylamine in a solution is slightly volatile, so to complete the reaction, a wide excess of the reagent is needed (~10 equivalent). Various polar solvents or solvent combinations are used for the direct reaction of esters with hydroxylamine produced in situ (Scheme 2). Solid bases (CH3ONa, NaOH or KOH) in methanol are used to produce free hydroxylamine in situ from hydroxylamine hydrochloride; i.e. tubastatin A(10), a highly selective HDAC6 inhibitor, has been synthesised at 31% yield by treating ester derivative37 with hydroxylamine hydrochloride and 25% sodium methoxide in methanol (Scheme 2).63, 64 The simplest reagent for hydroxylamine synthesis. A thio analogue (40) of trichostatin has been synthesised at moderate yield by using this reagent method. In this method, treatment of ester precursor (39) with 50 percent aqueous hydroxylamine (9 equivalent) accompanied by solution of potassium hydroxide in methanol produced trichostatin thio analogue 40 at 52 percent.65 In a significantly changed method, 50 percent aqueous NH2OH was used at room temperature in the presence of 1N NaOH in methanol. Through using this process, an 18F analogue of SAHA was synthesised from its ester precursor in modest yield (65 percent).66A series of effective and specific triazolylphenyl-based deacetylase inhibitors (e.g., 42) with action against pancreatic cancer cells and Plasmodium falciparum were synthesised from the ester precursors (e.g., by using hydroxylamine hydrochloride / KOH in MeOH) Low to moderate to large yields of compounds were obtained in this reagent method.68Chimaeric quinazoline dependent hydroxamic acids (e.g., 44) were synthesised in moderate to strong yields utilising this reagent method. This molecule (44) has shown in vitro inhibitory activity against HDAC, EGFR, and HER2 with IC50 values of 4.4, 2.4, and 15.7 nM , respectively (Scheme 2).

Scheme 2: Direct reaction of hydroxylamine with esters derivatives

OBJECTIVE

1. to research the synthesis, structural, biological and catalytic use, as well as their metal complexes, of Schiff bases.

2. Analysis of the synthesis and biological studies of multiple hydroxamic acid groups

CONCLUSION

For a long time, Schiff bases were documented and their uses were primarily restricted to chemistry of medicinal significance (biological significance) and catalysis. The spectrum of such compounds has grown in recent years, and their modern synthetic approach, focused on natural chemical reactions as well as solid state reactions, has advanced. Any papers on the usage of other forms of energy during their synthesis are also available. The current application that has spread to materials chemistry as well as nanotechnology is also illustrated in recent literature. In their coordination of the overwhelming majority of intermediate metals, Schiff bases and semicarbazones give a diversity and thus give considerable potential as precursors for next century nonmaterial of the respective metals or their compound semiconductors. Therefore, for catalytic, pharmacological, industrial, etc. uses, Imine ligands such as Schiff base, semi carbazones, and their derivatives have been extensively studied. Due to the ease of preparation with flexibility and variable dent city, Schiff base ligands are known as interesting ligands. Nowadays, the Schiff foundation and its metal complexes are a fascinating focus of study that constantly brings us fresh knowledge regarding freshly synthesised compounds. The biochemical, catalytic behaviour along with some miscellaneous applications of imine ligands and their metal complexes is described in this study, bringing the reach explicitly or indirectly into materials chemistry.

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