Metformin compounds: A review on the importance and the possible applications

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Abstract. Metformin is a particular compound able to coordinate metal ions and form complexes with Schiff bases that have unique properties and high stability, for a wide range of applications. This review describes and discusses organic and inorganic several reactions of synthesis of metformin complexes that coordinate some metal ions such as Ni, Co, Nd, Cr, Cu. These synthesis methods of metformin complexes are shown by the published results and characterization analyses. In medicine and pharmacy, these complexes are commonly applied and have shown a positive reaction in the fields. These complexes have been recommended to lower blood glucose levels and suggested as anti-cancer, anti-bacterial, and anti-leukemia compounds, and some have been used against leukemia. It has also been documented that the addition of specific ligands to metformin has also improved metformin's pharmacokinetic activity. Therefore, the preparation of many of the Schiff bases and complexes of metformin, such as [Nd (III) metformin Schiff Base, Co(TMP)(MET)(H₂O)Cl₂], [Ni(TMP)(MET)(H₂O)Cl₂, grapheneoxide-metformin-nickel, tetrachloro (metfor-min) platinum (IV) dimethyl, Cr(III)-2Mfn.HCl and others are described and discussed here. These complexes have the potential to be used for some biological activities, in addition to their potent as a catalyst of the carbon-carbon coupling reaction.

Keywords: metformin hydrochloride, metformin complex, metformin Schiff-bases
Graphical Abstract (GA)

GA Text: Metformin compound could coordinate metal ions such as Ni, Co, Nd, Cr, Cu and form complexes of Schiff bases with unique properties and high stability, which make them of high potential for a wide range of applications in medicine and pharmacy. The previously successfully synthesized complexes of metformin showed a positive response as anti-cancer, anti-bacterial, anti-leukemia. They also used to lower blood glucose levels and some were used as catalyst of the carbon-carbon coupling reaction.

1. Introduction
The history of metformin (Mtf) started in Europe where the plant “French lilac” or goat’s rue” was first used to extract metformin. This medicinal plant was used, among others, to treat the symptoms of diabetes mellitus (DM) in humans and to increase milk production in cattle (galactogenic properties)[1]. In the late 1940s, people focused on metformin after showing several reports about its ability to reduce blood sugar levels in human beings. In 1957, the French physician Jean Sterne published the first clinical trial of metformin as a treatment for diabetes [2]. Metformin hydrochloride (Mfn.HCl) structure is shown in Figure 1 [3].
Figure 1. Structure of metformin hydrochloride ligand, reused from [3].

Metformin hydrochloride (Met-HCL) is an anti-hyperglycemic agent [4]. It is known as 2-(N, N-dimethylcarbamimidoyl) guanidine (molecular formula C4, H11, N5, HCl). It consists of two imino and one amino group (primary, secondary, or tertiary) as donor centers. Met-HCL is a water soluble molecule and practically insoluble in acetone, ether and chloroform [5]. The pKa of metformin is 2.8 and 11.51 and the melting point is 222-226ºC[6,7]. Metformin has many great clinical applications. It can be used as a hypoglycemic substance after diagnosing a total pancreatectomy and absence of insulin[8]. It is well known to lowering the blood sugar level to the minimum physiological limit and destroys malarial parasites. It also uses as an antidiabetic, anti-malaria, analgesic, and as antimetabolites for microorganisms that inhibit folic acid metabolism [9]. Metformin coordinates with many elements of the transition series, especially copper (II), nickel (II), cobalt (II) and platinum (II) and produces highly colored chelate complexes[10,11]. This review aims to get insights into the most significant methods of preparing metformin and its complexes with the potential of its bio applications.

The aim: This review is to show the organic and inorganic materials used for preparing different metformin complexes with their possible applications.

The importance: This is a survey on the past and current methods used to prepare metformin complexes and their applications since 1963 until present. The process and the chemical properties have been discussed along with the importance of these complexes. The type of the ligand has a crucial effect on the propriety of the complex and ultimately on the field of application.

2. Synthesis of metformin complexes by organic reaction

2.1. Metal ions with Trimethoprim and metformin

Olawale Folorunso and his collaborators [12] coordinated a metal ion with trimethoprim and metformin [Co(TMP)(MET)(H$_2$O)Cl$_2$], [Ni(TMP)(MET)(H$_2$O)Cl$_2$], as shown in Scheme (1). This complex was characterized by Fourier transform infrared (FT-IR) and ultraviolet-visible (UV-VIS) spectroscopy. The geometry of the complex was octahedral coordination and its activity was tested against some bacteria. The results interestingly showed broad-spectrum antimicrobial activities against several selected bacterial isolates except B.subtilis, E.coli, and Pseudomonas aeruginosa. This confirmed that the coordinated metal ion complex was an active antibacterial agent more than the free ligands, or the control (streptomycin). Additionally, the investigation of antibacterial screening data revealed that most of the synthesized complexes possessed various antimicrobial
Scheme.1 Synthesis of the mixed ligand metal complex of trimethoprim and metformin, reused from [12].

2.2. Nd (III) Metformin Schiff-Base Complex
Recently, M. A. Mahmoud and his co-authors [17] prepared a complex of Nd(III)-metformin Schiff Base, Figure (2). This compound was diagnosed by IR, UV-Vis spectroscopy, GC-MS spectroscopy, X-Ray diffraction analysis (XRD), and thermal analysis. The geometry of the compound was octahedral. The Nd(III) complexes were previously tested for a wide range of biological applications, such as cellular recognition, immune response, and regulation of enzymatic activity by detecting saccharides in physiologically relevant conditions [13]. Such detection showed that any increase of the glucose concentration in phosphate buffer solution caused an increase in the viscosity of complexes; the Kb values indicated a good ability of the Nd$^{3+}$ complex to bind glucose in phosphate buffer [14,15]. Therefore, Nd-metformin complexes could certainly bind a glucose molecule and act as an indicator or rising glucose concentration.

Figure.2 Nd metformin Schiff-base of Nd (III) complex, reused from [15].

2.3. Schiff base of metformin
In 2020, Inas Al-Qadsy and Saeed et al [18] prepared two new Schiff bases of metformin hydrochloride, which were characterized by (FTIR), (UV-VIS), (NMR), (Mass spectroscopy) and
differential scanning calorimeter (DSC). The geometrical shape of the complex was octahedral and the resulting complexes were tested against different kinds of bacterial activity against, such as *S. aureus*, *K. pneumonia*, *E. coli*, and *E. faecalis*. The study confirmed a high activity of the ortho-metformin hydrochloride isomer compared with the para-isomer, but less than the positive control (streptomycin)[16], see Scheme 2.

**Graphene oxide-metformin-nickel catalyst**  
During 2020, the researcher Raoufi, Farveh and his collaborator [19] have prepared graphene oxide-metformin-nickel catalyst, see Scheme (3). This catalyst was diagnosed by (FT-IR), transmission electron microscopy (TEM), scanning electron microscopy (SEM), energy dispersive X-Ray analysis (EDX), (XRD), thermal gravimetric analysis (TGA), and coupled plasma/atomic emission spectroscopy (ICP). The geometry of the complex was octahedral. The study has also explored the potential of this complex to catalyze the carbon-carbon coupling reaction of a wide variety of aryl halides and phenyl boronic acids. The results indicated that the presented catalyst can reuse six runs without any noticeable decline in the coupling activity[17].

**Scheme 2.** Synthesis of metformin Schiff bases. Reused from [16].

**Scheme 3.** Synthesis of Ni coordinated to metformin –graphene oxide (GO-Mtf-Ni (0)). Reused from [17].

### 3. Synthesis of metformin complexes by inorganic reaction

#### 3.1. The tetrachloro (metformin) platinum (IV)

The complex tetrachloro (metformin) platinum (IV)dimethyl solvate was prepared by DisF. Bentefrit, et al in 1997 by solving [K2ptcl6] in hot water and then adding metformin hydrochloride (dissolved in water) and left for 36 days to form a yellow solid complex. The resulted complex was characterized by
FTIR, XRD and showed an octahedral coordination complex. This complex was tested against leukemia and the results indicated inhibition of the cell proliferation. Despite this bio effect, the metformin-platinum (IV) complex was less active than normal chemical therapy used to treat cancer tumors, although it’s polarity was higher [18].

3.2. The metformin of hydrochloride (Cr(III)-2Mfn.HCl)
In (2015), Samy M El-Megharbel prepared a complex of Cr (III)-2Mfn.HCl metformin hydrochloride and characterized by IR. The geometric shape of the complex was octahedral, as shown in Figure (3). The resulting complex has successfully decreased blood glucose parameters in diabetic rats. Therefore, the study proved that the pharmacological efficacy of the complex was toward antidiabetic application [3].

![Figure 3. The suggested chelating of [Cr(mfn.HCl)₂(Cl)₂] Cl. 6H₂O complex. Reused from [3].](image)

3.3. Mixed ligand complexes of Cu (II), Ni (II), and Co (II) with metformin (MTF) and cysteine residue
In 2015, Basim I. Al-Abdali et al prepared a complex of mixed ligands of Cu (II), Ni (II) and Co (II) with metformin (MTF) and the amino acid cysteine residue, Figure (4). The complex was analyzed by FTIR, UV-Vis, H nuclear magnetic resonance (H-NMR) and C-NMR spectral studies. The geometry of this complex indicated an octahedral coordination. The molar conductivity studies of the complexes demonstrated their non-electrolytic nature. The infrared and NMR spectral showed that the chelation behavior of the ligands towards selected transition metal ions was through two imino groups of metformin and the sulphur atom and the amino nitrogen of cysteine residue [19]. The other metformin complexes, ex Co(II)[11], Zn(II) [20] and Pt(II) [10] possessed antimicrobial activity and an interesting thermal behavior. Previous studies have shown that the amino acid cysteine residue may be biologically a relevant ligand that triggers the chelate rings consisting of different coordination active sites, such as N, S; O, S; or N, O[21],[22]. In a view of the biological and chemical properties, cysteine is a suitable ligand for synthesing complexes involve bioactive metals, for instance cobalt, nickel, and copper [23],[24]. Cysteine residue has been used as a co-ligand to form mixed ligand complexes of ranitidine, which is the most useful drug in the management of peptic and duodenal ulcers[25].
3.4. Copper and Nickel complexes of Metformin
During 2007, Nalamolu Koteswara Rao and co-authors prepared a complex of copper [II] metformin complex, [Cu (C₄H₁₀N₅)₂Cl₂] and nickel [II] metformin complex, [Ni (C₄H₁₀N₅)₂Cl₂]. These complexes were diagnosed by elemental analysis, IR and UV/VIS spectroscopy and thermal analysis [26] and showed planar coordination geometry. These metal complexes were evaluated for their hypoglycemic activity in alloxan-induced diabetic rabbits. These metal complexes showed a significant high hypoglycemic activity when compared to pure drugs. The study proved that the pharmacological efficiency of the metal complexes had a significant and sustained hypoglycemic effect for prolonged periods of time (10 h) [27].

3.5. A New Zinc-Mixed Ligand Complex
In 1995, Muruganantham Koothappan and his co-authors prepared a new zinc-mixed ligand complex (zinc-3-hydroxy flavone-metformin), which has been analyzed by (IR), (FTIR), (Mass spectroscopy) and (NMR) [28]. This complex was tested as a treatment for hyperglycemic patients. The study informed that the pharmacological efficiency of the complex possessed significant antidiabetic properties at less concentration than metformin-3-hydroxy flavone complex in ameliorating hyperglycemia [29], as shown in Table (1).

Table 1. Effect of zinc mixed ligand complex on oral glucose load test in experimental type 2 diabetic mellitus rats.

| Group                        | Fasting | 30 minutes | 60 minutes | 90 minutes | 120 minutes |
|------------------------------|---------|------------|------------|------------|-------------|
| Control                      | 88.15±8.18| 147.21±10.68| 179.82±14.57 | 130.59±12.38 | 102.16±10.12  |
| Diabetic                     | 263.55±18.26 | 300.93±21.64 | 393.18±20.51 | 351.17±22.85 | 316.83±20.36  |
| Diabetic+metformin-3-Hydroxyflavone | 155.41±10.77 | 184.27±18.28 | 245.91±20.64 | 199.17±21.91 | 139.81±13.99  |
| Diabetic+zinc-3-hydroxyflavone-metformin | 149.51±11.67 | 179.11±16.25 | 239.71±19.99 | 192.55±9.92  | 139.01±14.89  |
| Diabetic+metformine          | 136.34±10.19 | 171.66±15.84 | 227.85±20.98 | 175.84±19.69 | 128.97±12.81  |

Values are presented as mean ± standard error of the mean (n=6). One-way analysis of variance was done. There results were for diabetic rats compared to healthy rats (control) and values were statistically significant at p<0.05.

4. Conclusion
Although metformin is often used to treat diabetes type 2, metformin complexes is found their way to be very useful for treating many other diseases and disorders, such as cancer or bacterial infection, and some metformin complexes act against leukemia and other diseases. Furthermore, adding some
inorganic ligands such as Ni, Co, Cu, Nd, Pt to metformin enhanced the pharmacokinetic efficacy of metformin.

**Acknowledgement**
The authors would like to thank the head of the Department of Chemistry Sciences, Mustansiriyah University [https://uomustansiriyah.edu.iq/](https://uomustansiriyah.edu.iq/), and Alaa Abd AL-Karim in particular for kind help and support throughout writing this review.

**Availability of data and materials**
Authors are declared that all data generated or analyzed during this study are all available in this manuscript.

**Competing of interests**
The authors declare that they have no competing or conflict of interests.

**Funding**
This review received no fund from any government institution or private sector, however, it was formally registered in the scientific annual plan for PG in the Chemistry Department, Mustansiriyah University.

**Author’s contribution**
Authors have contributed equally.

**Consent for publication**
Not applicable.

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