IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2023 Vol.:28, Issue:4

Review on NSAID Metal Complexes: Synthesis, Characterization and Biological Activity

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 22 October 2023
Accepted: 27 October 2023
Published: 30 November 2023

HUMAN JOURNALS
ijppr.humanjournals.com

Keywords: NSAIDs, metal complexes, anticancer, antimicrobial, analgesic, anti-inflammatory

ABSTRACT

Metal complexes consist of a central metal atom or ion and surrounding molecules, which are called ligands. NSAIDs are a class of compounds with anti-inflammatory properties used to treat pain or fever. NSAIDs properties can be strongly improved when included in complexes using their compositional N and O donor atoms, which facilitate their coordination with metal ions. It is known that metal complexes, once bound to organic drugs, can enhance the drugs' biological activities, such as anticancer, antimicrobial, analgesic, and anti-inflammatory. The aim of the study is to achieve a metal-drug complex which can be less toxic and cause lower side effects with enhanced biological activity than the parent drug. From the systematic review study, it is observed that the most practised methods of characterization of metal complexes are: Elemental analyses, FTIR, UV–Visible spectroscopy, ^{1}H and ^{13}C NMR, X-ray diffraction, Melting point determination, Molar conductance and Mass spectroscopy. The widely reported biological activity of drug metal complexes includes Anti-inflammatory activity, Analgesic, Anti-microbial activity, Antioxidant activity and Anti-cancer activity. We can conclude that the complexation of NSAIDs with metal can have better biological activity when compared to the parent drug.

INTRODUCTION

Metal complexes consist of a central metal atom or ion which is called the coordination centre and a surrounding array of bound molecules, which are called ligands [1]. A ligand is an ion or molecule, which donates a pair of electrons to the central metal atom or ion to form a coordination centre. Ligands can be anions, cations, and neutral molecules [2].

The drug binds to the metal based on the coordination number, hence, the metal complexes can be classified into different types- (i) Binary complex: A binary complex is a noncovalent complex of two molecules that are bound together. E.g.: [Zn(*mef*)$_2$], [Zn(*dicl*)$_2$], [Cu (*Dopa*)$_2$] (ii) Ternary complex: A ternary complex is a protein complex containing three different molecules that are bound together. E.g.: [Mn(mef)$_2$(imi)$_2$(EtOH)$_2$], [Ni (metf)(en)$_2$] Cl_2 [3-4].

Complexes are widely used as therapeutic compounds to treat several human diseases such as carcinomas, lymphomas, infection control, diabetes, analgesic, anti-inflammatory and neurological disorders [5]. They are also used to improve the solubility of several pharmaceutical ingredients and subsequently the bioavailability of poorly water-soluble drugs [6]. Transition metal complexes are important in catalysis, material synthesis, photochemistry, and biological systems [7]. It is also a common strategy to improve the therapeutic potency and/or to reduce the toxicity of drug molecules [8].

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature. NSAIDs are useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, and migraines, and are used as opioid-sparing agents in certain acute trauma cases [9]. All drugs grouped in this class have analgesic, antipyretic and anti-inflammatory actions in different measures.

NSAIDs cause various adverse effects like gastrointestinal effects that include nausea, anorexia, gastric irritation, erosions, peptic ulceration, gastric bleeding/perforation, renal effects that include Na+ and water retention, chronic renal failure, nephropathy, CVS effects like rise in BP, risk of myocardial infarction (especially with COX-2 inhibitors), CNS effects like headache, mental confusion, vertigo, behavioural disturbances, seizure precipitation, Haematological effects like bleeding, thrombocytopenia, haemolytic anaemia, agranulocytosis which can possibly be reduced by complexation of these drugs with metal complexes [10].

Complexation shows significant effects that can limit the adverse effects of drugs. For example; the zinc–aceclofenac complex induced fewer ulcers in rat stomachs compared to the parent drug. This suggests that the complexation of NSAIDs with zinc may be an effective strategy for limiting the adverse gastrointestinal side effects of these agents [11]. Complexation also enhances the anti-inflammatory activity of drugs. E.g.: The anti-inflammatory properties of Ni (II), Zn (II) and Co (II) metal (diclofenac) complexes bearing Schiff base ligands derived from salicylaldehyde and glycine. Oral administration of the complexes reduced inflammatory oedema in rats challenged by carrageenan, with greater potency compared to the NSAID diclofenac [12].

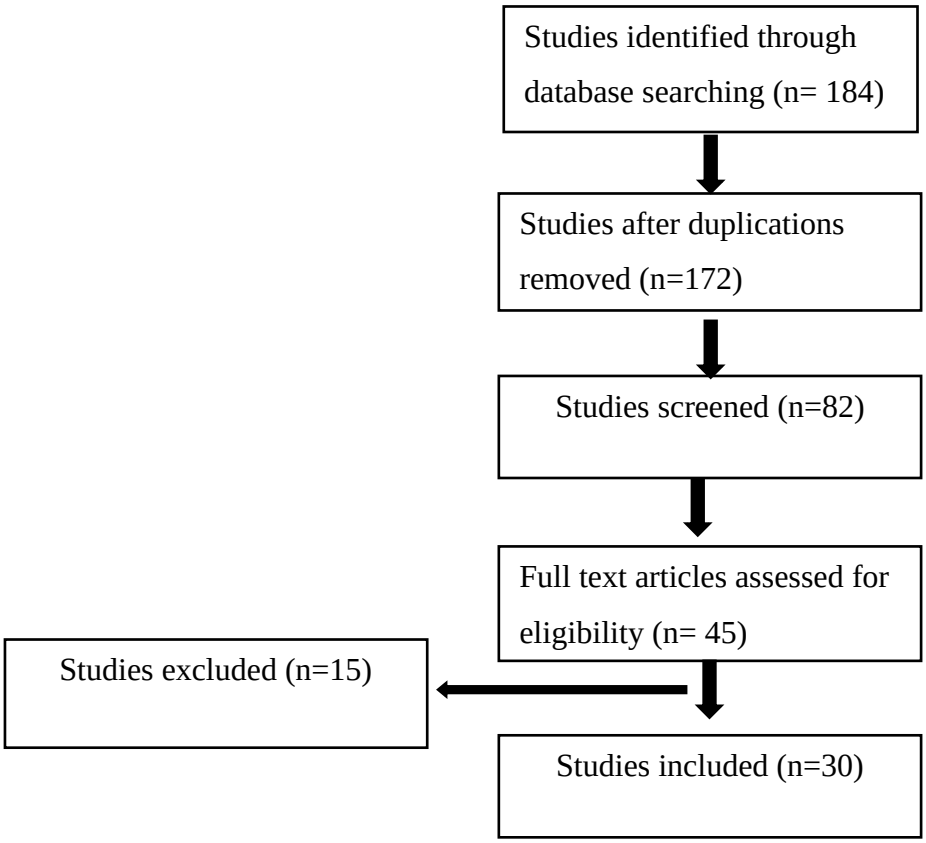
Many transition metal complexes act as extremely good anticancer agents and show their biological activity by stopping the replication of DNA, blocking the division of cancer cells and resulting in cell death [13]. The transition metal complexes frequently possess superior lipophilicity profiles compared to the free ligands, allowing them to more easily pass through cell membranes to exert their biological effects. For example, from antibiotic drug discovery, a Pt (II) tetracycline complex was six times more potent against *E. coli* compared to the free ligand [14].

Methodology:

Data sources and search strategy:

The search strategy refers to the methods employed to conduct methodologically sound research and might include information such as the data sources used and the specific terms applied to indistinct databases. The search locates articles relevant to answering the previously defined research question.

A comprehensive literature search was conducted from 2005 to 2023 using Google Scholar (https://scholor.google.co.uk/) Pub med (https://pubmed.ncbi.nlm.nih.gov), other databases and many journals for studies investigating the synthesis, characterization, and evaluation of NSAID metal complexes in pain and inflammation models. We first pooled results from different databases, and journals, performed the duplication removal step and then conducted title and abstract screening followed by full-text screening.



General Procedure for Synthesis of NSAID Metal Complexes: Equimolar metal salts dissolved in water were added to the ligands so that the ratio *n (metal): n (ligand)* of monovalent, divalent, and trivalent ions used was 1: 1, 1: 2 and 1: 3, respectively, in each case and immediate precipitation occurred. Then the solid complexes were isolated by filtration, washed until being free of chlorides with the corresponding solvent (methanol or water), and finally dried at room temperature [14].

General Methods Used for Characterization of NSAID Metal Complexes: Elemental analysis (C, H, N), FT-IR, ^{1}H NMR, ^{13}C NMR, DEPT-135 NMR Spectroscopy, Electronic spectra (SEM), Ultraviolet-Visible spectra, XRPD, Mass spectrum using LC-MS Spectrometer, Magnetic moments, Molar ratio measurements, and Molar conductance tests. The physicochemical and biological evaluation of drug-metal complexes is assayed in the below table.

Physicochemical and biological evaluation of drug-metal complexes:

S. No	Title	Primary ligand/ (NSAIDS) and Secondary ligand	Complexing agent	Type of Complex	Physicochemical Characterisation	Biological Activity	Conclusion	Ref
1	Synthesis, characterization, and antibacterial study of Co (II) and Cu (II) complexes of mixed ligands of piperaquine and diclofenac	Piperaquine and Diclofenac -	Cu (II) Co (II)	Binary complex	^{1}H NMR, ^{13}C NMR, DEPT-135 NMR Spectroscopy, Elemental Analyses, Ultraviolet-Visible spectra, FTIR, XRPD	Anti-inflammatory activity, Antioxidant Assay, Antibacterial activity	-The in vitro antioxidant and antibacterial assays portray the complexes with higher antioxidant and bactericidal efficacy than the parent ligands and some renowned standards	15
2	Zinc (II) complexes derived from ibuprofen Schiff base ligands: synthesis, characterization, and biological activity	Ibuprofen Schiff base	Zn (II)	Ternary complex	Elemental analyses (C, H, N), FT-IR, electronic spectra, magnetic moments, molar ratio measurements, and molar conductance tests	Antimicrobial activity-Antibacterial activity, Anti-fungal activity, and Anticancer activity	-Promising bioactivities against the tested pathogens. -Inhibited cell proliferation.	16
3	Synthesis, Characterization, In-Vitro Anti-Inflammatory, And Antimicrobial Screening of Metal (II) Mixed Diclofenac and Acetaminophen Complexes	Diclofenac and Acetaminophen -	Mn (II) Co (II) Ni (II) Cu (II) Zn (II)	Binary complex	Ultraviolet-visible spectra, FTIR, XRPD	In-vitro anti-inflammatory activity, antimicrobial screening	-Moderate anti-inflammatory activity compared to the diclofenac potassium salt (test standard. -Promising antidotes in metal chemotherapy.	17
4	Transition metal complexes of Naproxen: Synthesis, Characterization, Forced Degradation studies and Analytical method verification	Naproxen -	Co (II) Cu (II) Zn (II) Fe (III)	Binary complex	Elemental analyses, IR spectra, Thermal analysis, electronic photography (SEM), and Magnetic properties (NMR).	Anti-inflammatory activity	-The metal derivatives of Naproxen can be more potent anti-inflammatory agents with longer half-life and longer shelf life compared to Naproxen.	18

5	Synthesis and Characterization of Cu (II) Complexes of Salicylate Ligands	Acetylsalicylic acid -	Cu (II)	Binary complex	Elemental analyses, FTIR, electronic photography (SEM), and H-NMR.	-	The spectra of the ligands and the complexes formed proved that new products were formed and are stable.	19
6	Synthesis, Characterisation and Docking Studies of Metal (II) Complexes of Anti-inflammatory Drug Celecoxib	Celecoxib Schiff base	Cu (II) Co (II) Ni (II)	Ternary complex	Molar conductance test, FTIR, UV–visible spectrophotometer.	-	The nickel metal complex of Celecoxib is most active against the COX II enzyme.	20
7	Synthesis, characterization, docking and biological studies of M(II) (M= Mg, Ca, Sr) Piroxicam complexes	Piroxicam -	Mg (II) Ca (II) Sr (II)	Binary complex	UV Vis, IR, ^{1}H NMR, ^{13}C NMR, conductance, SEM-EDX, XRD and TGA.	Antioxidant, Anti-inflammatory, Analgesic, and Anxiolytic activity.	-Complexes possess higher biological potential with lower toxicity. -Ca (II) complex acts as a promising anti-inflammatory agent. -Sr (II) complex along with Ca (II) complex exhibited significant analgesic effects.	21
8	Synthesis, characterization, and biological activity of transition metals complexes with mefenamic acid (NSAIDs)	Mefenamic acid -	Co (II) Cu (II) Zn (II) Ni (II) Fe (III)	Binary complex	Elemental analysis, FTIR and UV-visible spectroscopy.	Antifungal, antibacterial, antitumor, antioxidant activity	-Nickle mefenamic acid complex exhibited pronounced activity against *F. solani*. -Antitumor activity of the products was higher than that of the free ligand.	22
9	Synthesis and characterization of silver(I) complexes with ligands having anti-inflammatory properties	Ibuprofen, Naproxen, Mefenamic acid, Aspirin, and salicylic acid. -	Ag (I)	Binary complex	Elemental analysis, FT-IR, ^{1}H and ^{13}C NMR, X-ray diffraction	Anti-inflammatory, Antimicrobial activity	Enhanced anti-inflammatory and antimicrobial properties.	23
10	Synthesis, characterization, the anti-inflammatory and analgesic activity of transition	3-[1-(2-hydroxyphenyl) ethylideamino]-2-phenyl-3,4-	Co (II) Cu (II) Zn (II) Ni (II)	Ternary complex	Elemental analysis, conductivity, magnetic moment measurements,	Anti-inflammatory and analgesic activity	-Anti-inflammatory activity was observed for Ni (II), Cu (II) and Zn (II) complexes. -The analgesic	24

	metal complexes of 3-[1-(2-hydroxyphenyl) ethylideamino]-2-phenyl-3,4-dihydroquinazolin-4(3H)-one	dihydroquinazolin-4(3H)-one Schiff base			IR, NMR, UV-vis and EPR spectroscopy.		activity of the complexes was greater than the standard.	
11	Quasi-Isostructural Co (II) and Ni (II) Complexes with Mefenamato Ligand: Synthesis, Characterization and Biological Activity	Mefenamic acid -	Co (II) Ni (II)	Binary complex	Elemental analysis (EA), flame atomic absorption spectrometry (FAAS), FTIR, and thermogravimetric analysis (TGA)	Antibacterial, Antioxidant and Antimicrobial Activities	All complexes showed an antioxidant activity higher than that of mefenamic acid.	25
12	Synthesis, characterization, antimicrobial and anti-inflammatory studies of some novel Schiff base metal complexes derived from the drug, diclofenac	Diclofenac Schiff Base	-	Ternary complex	Elemental analysis, Molar conductance, FTIR, Electronic spectra, 1H NMR spectrum, Mass spectrum using LC-MS Spectrometer.	Anti-inflammatory Antimicrobial activity	The ligand and metal complexes show better anti-microbial activities than the parent drug. The metal complexes possess satisfactory anti-inflammatory potential properties.	26
13	Synthesis, characterization, and anti-inflammatory effects of Cr (III), Mn (II), Fe (III) and Zn (II) complexes with diclofenac sodium	Diclofenac sodium -	Cr (III) Mn (II) Fe (III) Zn (II)	Binary complex	Elemental analysis, magnetic susceptibility, molar conductance, electronic and Infrared spectroscopy.	Anti-inflammatory Activity	Complexes may play a role in decreasing the synthesis of the proinflammatory PGE2 and concomitantly, increasing the synthesis of the anti-inflammatory PGF2a.	27
14	Copper (II) complexes of diclofenac: Spectroscopic studies and DNA strand breakage	Diclofenac sodium -	Cu (II)	Binary complex	Electronic and Infrared spectroscopy.	Anti-inflammatory Activity and DNA strand breakage (Anti-tumour)	Complexes possess promising anti-inflammatory properties. Binuclear copper (II) complexes, could have some relevance in the treatment of tumour cell lines	28
15	Diclofenac copper complexes with anti-inflammatory	Diclofenac sodium 1,3-propane	Cu (II)	Ternary complex	Elemental analysis, Molar conductance, FTIR,	Anti-inflammatory Activity	The complexes have better anti-inflammatory activity and lower	29

	activity, and preparation methods thereof	diamine			Electronic spectra, 1H NMR spectrum.		stomach side effects than ligands and can be used to prepare anti-inflammatory medicines.	
16	Transition metal complexes of diclofenac with potentially interesting anti-inflammatory activity.	Diclofenac sodium -	Cu (II)	Binary complex	Spectroscopic studies, X-ray crystallography and electrochemical studies	Anti-inflammatory Activity	Some of the complexes exhibit very promising anti-inflammatory activity and act as antioxidant compounds, a property that is absent from diclofenac.	30
17	Preparation, Diagnosis, Biological Activity, and Theoretical Studies of Some Mixed Drug Complexes	Mefenamic acid and metformin -	Cu (II) Co (II)	Binary complex	Magnetic susceptibility, molar conductance, TG analyses, FTIR and UV spectra	Analgesic, Antimicrobial activity	The Co (II) complexes have promising antibacterial properties. Cu (II) complexes showed significant analgesic property.	31
18	Synthesis, Characterization and Biological Activity of New Mefenamic Acid-- Oxoazetidine Derivatives	Mefenamic acid and Oxoazetidine Schiff's base	-	Ternary complex	Mp, TLC, UV, FT-IR, and elemental analysis	Analgesic, Antibacterial activity	Complexes were found to exhibit good antibacterial and analgesic activity	32
19	Comparative physicochemical, anti-inflammatory, and analgesic activity assay of synthesized chromium and nickel complexes of indomethacin	Indomethacin -	Cr (III) Ni (II)	Binary complex	FT-IR spectroscopy, UV–visible spectroscopy, atomic absorption spectroscopy, calorimetric DSC analysis, and melting point analysis.	Analgesic, Anti-inflammatory Activity	The Cr and Ni complex of indomethacin may show promising pharmacological effects which can be revealed by extensive analysis using PK-PD test model.	33
20	Synthesis and Characterization of New Ligands Attached to NSAIDs Moiety	Naproxen -	Zn (II)	Binary complex	Physical properties determination (melting points and Rf values), FTIR and 1H-NMR Spectroscopy.	Anti-inflammatory Activity	Acute anti-inflammatory activity indicated that nitro-containing analogue has a faster onset of action and significantly more effect than Naproxen.	34
21	Copper (II)	Benzimidaz	Cu (II)	Ternary	Elemental	Anti-	The synthesized	35

	complexes as potential anticancer and Nonsteroidal anti-inflammatory agents: *In vitro and in vivo studies*	ole-derived scaffolds Phenanthroline and 2,2′-bipyridyl		complex	analyses, FTIR and Mass Spectroscopy	inflammatory Activity, Anti-cancer activity	complexes are promising candidates to act as anticancer and COX 2 inhibitor (NSAID) agents	
22	Transition metal complexes with ibuprofen hydrazide: synthesis, characterization, and biological assays.	Ibuprofen hydrazide -	Pd (II) Pt (II)	Binary complex	Elemental analyses, FTIR, UV–Visible spectroscopy, 1H and 13C NMR, Electrospray ionization mass spectrometry (ESI-MS)	Anti-inflammatory Activity, Antimicrobial activity, Antiproliferative	Complexes show considerable anti-inflammatory and anti-microbial activity and higher antiproliferative activity	36
23	Antioxidant capacity and DNA-interaction studies of zinc complexes with a non-steroidal anti-inflammatory drug, mefenamic acid	Mefenamic acid 2,2’ Bipyridine	Zn (II)	Ternary complex	Elemental analyses, FTIR, UV-visible spectroscopy	Analgesic, Anti-inflammatory Activity, Antioxidant activity, DNA binding study.	Promising analgesic, anti-inflammatory Activity. The complexes can bind to DNA via intercalation as concluded by DNA solution viscosity measurements.	37
24	Synthesis and Characterization of Celecoxib Derivatives as Possible Anti-Inflammatory, Analgesic, Antioxidant, Anticancer and Anti-HCV Agents	Celecoxib N-substituted benzenesulfonamide	Cu (II)	Ternary complex	Elemental analyses, FTIR, UV-visible spectroscopy and molar conductance.	Anti-inflammatory, Analgesic, Antioxidant, Anticancer and Anti-HCV activity	The complex showed significant analgesic and promising anti-inflammatory activity with relatively reduced lipid peroxidation and did not cause tissue damage in the liver, or kidney.	38
25	Synthesis, characterization, anti-inflammatory and analgesic activity of transition metal complexes of Diclofenac sodium	Diclofenac sodium -	Zn (II) Fe (III)	Binary complex	Melting point determination, Elemental analyses, Molar conductance, FTIR, UV-Visible spectroscopy	Analgesic, Anti-inflammatory Activity, Antioxidant activity,	Acute anti-inflammatory activity and analgesic activity were reported. Significant antioxidant activity.	39
26	Synthesis, Characterization and Biological Activity of Ibuprofen hydrazide Cu (II)	Ibuprofen	Cu (II)	Binary complex	FT-IR spectroscopy, UV–Visible spectroscopy, AAS, TLC, MS	Anti-inflammatory Activity	Upon complexing Ibuprofen with Cu (II) we observed reduced GI adverse effects and toxicity.	40

	complex							
27	Synthesis and characterization of Mn (II) and Zn (II) complexes with Celecoxib	Celecoxib	Mn (II) Zn (II)	Binary complex	Elemental analyses, FTIR and Mass Spectroscopy	Analgesic, Anti-inflammatory Activity, Antioxidant activity,	Mn and Zn complex of Celecoxib may show promising pharmacological effects	41
28	Synthesis, Diagnosis, Biological Activity, and toxicity Studies of NSAID drug complexes	Naproxen -	Cu (II) Zn (II) Fe (III)	Binary complex	Elemental analyses, FTIR, UV- Visible spectroscopy, XRD, TGA	Analgesic, Anti-inflammatory Activity, Anti-microbial activity	The complexes have better anti-inflammatory activity and lower side effects than parent Celecoxib.	42
29	Synthesis, Characterization, and Biological Activity of Cu (II) Complexes of Aceclofenac	Aceclofenac -	Cu (II)	Binary complex	Elemental analyses, FTIR, UV–visible spectroscopy, NMR.	Analgesic, Anti-inflammatory Activity	Binuclear Cu (II) complexes with aceclofenac have promising anti-inflammatory activity.	43
30	Synthesis, Characterization and Anti-inflammatory assay of metal (II) complexes	Aspirin -	Cu (II) Zn (II)	Binary complex	Elemental analyses, FTIR, UV–Visible spectroscopy.	Anti-inflammatory Activity	Peak oedema develops within the first 3 to 4 hours, and is inhibited by oral doses of anti-inflammatory drug complexes synthesized.	44

From the above conducted systematic review study, it is observed that the most practised methods of characterization of metal complexes are: Elemental analyses, FTIR, UV–Visible spectroscopy, ^{1}H and ^{13}C NMR, X-ray diffraction, Melting point determination, Molar conductance and Mass spectroscopy.

The widely reported biological activity of drug metal complexes includes Anti-inflammatory activity, Analgesic, Anti-microbial activity, Antioxidant activity and Anti-cancer activity.

Metal complexes containing NSAIDs are a group of compounds that have attracted much interest among the scientific community. More specifically, d-block metals and their cations, namely, copper, cobalt, nickel, manganese, and zinc are by far the most exploited in NSAID-based metal complexes (metallodrugs).

Complexes were found to exhibit good antibacterial and antioxidant activity. Binuclear copper (II) complexes, could have some relevance in the treatment of tumour cell lines, thus indicating significant anticancer activity.

CONCLUSION

The complexation of NSAIDs with metal can have better biological activity when compared to the parent drug. It is also significant that after complexing, the drugs show promising anti-inflammatory and analgesic activities. The complexes also showed a faster onset of action and reduced GI adverse effects and toxicity, did not cause tissue damage in the liver, and kidney thereby reducing the side effects and enhancing the bioavailability.

In this review, the focus has been on the remarkable effects of these metallodrugs, including their wide range of biological activities. Since the pharmacologic effects of NSAIDs can be altered upon coordination to metal ions, it is possible to enhance the biological effects of the drugs and to decrease possible side effects, and eventually, it may allow the interaction with new biomolecular targets. This may be an advantageous path for the further optimization and consequent clinical development of metal−NSAID compounds.

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