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Metal Complexes and Their Role in Treatment of the Arthritis

Metal Kompleksleri ve Artrit Tedavisindeki Rolleri

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ABSTRACT

Worldwide, rheumatoid arthritis is a major cause of morbidity and mortality. In recent years, the domain of inorganic medicinal chemistry has shown more interest in metal-based drugs owing to their beneficial pharmacological activities. Since then, many useful anti-cancer metal-based drugs have been introduced. However, less attention has been paid to improving inflammatory drugs based on metal complexes. The objective of this review is to recapitulate previously published studies that concentrated on metal-based drugs used for the treatment of arthritis. It is anticipated that the current compilation of earlier studies will be helpful for the researcher to find the data and areas for future studies. The literature survey was done without any time limit using the help of various electronic databases, including ScienceDirect, SpringerLink, Web of Science, PubMed, and the Cochrane Library. Articles published in the English language are used for the current review. Only 20 studies were found to be pertinent to the present review. Metal complexes of non-steroidal anti-inflammatory drugs have been the subject of extensive research. To date, metal complexes of drugs such as aspirin, ibuprofen, anthranilic acid, methotrexate, indomethacin, and aceclofenac have been studied and evaluated for their possible antiarthritic activity. Gold metal complexes showed better efficacy and have been used in clinical practice as well. Due to their advantageous therapeutic properties, metals and their complexes are becoming more and more important today. To find new treatments for diseases, it is suggested that the mechanism of action and potential toxicity of metal complexes must be assessed.

Keywords: Rheumatoid arthritis, metal complexes, inflammation, NSAIDs, DMARs

ÖZ

Dünya çapında; romatoid artrit, morbidite ve mortalitenin önemli bir nedenidir. Son yıllarda, yararlı farmakolojik aktiviteleri nedeniyle inorganik tıbbi kimya alanında metal bazlı ilaçlara daha fazla ilgi gösterilmektedir. O zamandan beri, birçok yararlı kanser karşıtı metal bazlı ilaç piyasaya sürüldü. Ancak metal komplekslerine dayalı enflamatuvar ilaçların geliştirilmesine daha az ilgi gösterilmiştir. Bu derlemenin amacı, artrit tedavisinde kullanılan metal bazlı ilaçlara odaklanan daha önce yayınlanmış çalışmaları özetlemektir. Daha önce yapılmış çalışmaların mevcut derlemesinin, araştırmacılara gelecekteki çalışmalar için veri ve alan bulmada yardımcı olacağı öngörülmektedir. Literatür taraması ScienceDirect, SpringerLink, Web of Science, PubMed ve Cochrane Kütüphanesi gibi çeşitli elektronik veri tabanları kullanılarak herhangi bir zaman sınırlaması olmaksızın gerçekleştirildi. Mevcut inceleme için İngilizce dilinde yayınlanan makaleler kullanılmıştır. Mevcut incelemeyle ilgili olarak yalnızca 20 çalışma bulunmuştur. Non-steroidal anti-enflamatuvar ilaçların metal kompleksleri kapsamlı araştırmaların konusu olmuştur. Bugüne kadar aspirin, ibuprofen, antranilik asit, metotreksat, indometasin ve aseklofenak gibi ilaçların metal kompleksleri olası antiartritik aktiviteleri açısından incelenmiş ve değerlendirilmiştir. Altın metal kompleksleri daha iyi etkinlik göstermiş ve klinik uygulamada da kullanılmaya başlanmıştır. Metaller ve bunların kompleksleri, sağlığa yararlı özelliklerinden dolayı günümüzde giderek daha fazla önem kazanmaktadır. Hastalıklar için yeni tedaviler bulmak için, metal komplekslerinin etki mekanizmasının ve potansiyel toksisitesinin değerlendirilmesi önerilmektedir.

Anahtar Sözcükler: Romatoid artrit, metal kompleks, enflamasyon, NSAIDs, DMARs

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that usually affects the joints. It is caused by systemic autoimmunity, which destroys the joint lining and can have a negative impact on patient quality of life, such as undeviating disability, treatment financial burden, and premature death rates. According to estimation, 5 out of 1000 are victims of RA who might be presented with relentless joint damage and permanent disability (1-3). Flurbiprofen, ketoprofen, aceclofenac, diclofenac sodium, ibuprofen, diclofenac, sodium salicylate, magnesium salicylate, acetylsalicylic acid, indomethacin, phenylbutazone, salsalate, diflunisal, sulindac, nabumetone, tolmetin sodium salt dihydrate, piroxicam, naproxen, meloxicam, lornoxicam, chlorfenamic acid, etoricoxib, parecoxib, celecoxib, and ketorolac are the most frequently utilized non-steroidal anti-inflammatory drugs (NSAIDs). Dexamethasone, hydrocortisone, prednisolone, beclometasone dipropionate, betamethasone and methylprednisolone are the frequently used glucocorticoids. Disease-modifying antirheumatic drugs (DMARDs) prevent bone damage by diminishing synovial inflammation to control joint growth and increase rheumatoid factor and C-reactive protein. They have a healing impact on the joints, they are also linked to low white blood cell counts, rash, severe liver and kidney damage, and vomiting. DMARDs, including auranofin, azathioprine, cyclophosphamide, D-penicillamine, methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide, are usually used (4,5). New therapeutic modalities have dramatically changed how RA progresses. Although some patients do not respond well to treatment, many achieve remission if they are recognized early and receive adequate and consistent care. Early diagnosis, a treat-to-target strategy, and meticulous monitoring and management can increase the likelihood of remission in RA patients (6-8). Metals are frequently used in medicine and/or as diagnostic tools. Over the past 5,000 years, several human ailments have been treated using metals including iron, gold, and arsenic. There are now several medications with metals as ingredients. These materials contain a wide variety of metals, many of which are toxic to humans and can target DNA and/or proteins (9,10). Metal complexes have long been used in medicine to identify and treat various ailments. The discipline is undertaking a prototype modification; in the past, the major mechanism of action was examined after the discovery of a beneficial molecule; however, today, the mechanism of action is progressively employed to drive the innovation procedure. This method exploits the unique features of metal complexes, which can be modified to improve the metal compound's drug-like effects (11,12).

Recently, researchers have concentrated their attention on producing metal-based complexes to generate possible multi-targeted medicines due to the potential medical applications of metal complexes. This review's goal is to provide an overview of previously published research on arthritic treatments based on metal-based drugs. The literature was searched in the English language without any year limit using the help of various electronic databases, including ScienceDirect, SpringerLink, Web of Science, PubMed, and the Cochrane Library.

Metal Complexes of Drugs for the Treatment of Arthritis

Copper-Aspirin Metal Complex

NSAIDs are widely used to treat inflammatory disorders. Among NSAIDs class of the drugs, aspirin is commonly devoured to treat various inflammatory conditions, including arthritis. Aspirin causes a non-selective irremediable inhibition of the cyclooxygenase enzymes (COX-1 and COX-2) and, in return, blocks the synthesis of prostaglandin, which is essential to provoke an inflammatory response. COX-1 is found in many tissues, such as in the mucosa of the gastrointestinal tract, and it produces important prostaglandins. These prostaglandins exert cytoprotective effects by secreting mucus and protecting the stomach mucosa from the harmful effects of gastric hydrochloric acid. While COX-2 is turn out to be up-regulated in response to various inflammatory modulators that lead to the appearance of many symptoms of inflammatory disorders, such as RA and osteoarthritis. Hence, to treat inflammatory disorders it is recommended that COX-2-selective inhibitors should be used to avoid gastric ulceration and irritation (13,14). An attempt was made by researchers to bypass the harmful effects of aspirin by making its metal complex. This study proved that Cu-aspirin exhibited considerable inhibition of macrophages activated COX-2-mediated prostaglandin E_2 synthesis in contrast to aspirin. Further, the Cu-aspirin selectivity index was found to be 3.33 for COX-2 over COX-1 when compared to the selectivity index of aspirin which was 0.42. The outcome of the investigation demonstrated that the Cu-aspirin complex was seven times more selective for COX-2 than aspirin. The selective inhibition of the COX-2 by Cu-aspirin complex can be ascribed to the steric properties of the drug-metal complex and its interactions with inflammatory enzymes. Aspirin is a small molecule that can fit completely at cyclooxygenase enzymes (both COX-1 and COX-2) binding sites, which results in the non-selective inhibition of the enzyme. In contrast, selective COX-2 inhibitors like rofecoxib and celecoxib, have a bulky side chain of sulfanilamide in their structure, which prevents their interaction with the COX-1 enzyme. For the same reason, it is suggested that the Cu-aspirin complex is quite large compared with aspirin, which is why the drug-metal complex selectively inhibits COX-2. Further, aspirin, CuSO4, and the Cu-aspirin complex was tested in a control experiment. The results have shown that among all the tested chemicals, drug-metal complex exhibited an influential inhibition of COX-2 then CuSO4 and aspirin alone (15,16).

Metal Complexes of Anthranilic Acid

Iqbal et al. (17), reported that synthesis of transition metals Fe(II), Co(II), Mn(II), Ni(II), and Zn(II) with anthranilic acid and aldoses, whose description was done by different parameters. In an *in vivo* study, Mn(II) and Zn(II) complexes were administered in rats by oral route to assess the anti-inflammatory response in kaolin-induced paw edema. The COX-2/COX-1 selectivity index values were 0.34 to 0.52 and were similar to aspirin 7 values (0.41) (16,17).

Zinc-Aceclofenac Metal Complex

Kale et al. (18) conveyed that in 1992, the US FDA permitted aceclofenac, which was developed to overawe the un-wanted side effects associated with diclofenac. Gastric ulcer is still prevalent with aceclofenac, and to overcome this effect, zinc ions are most

best pronounced. The zinc ion has inherent antiarthritic activity, as well as a shield stomach. On this basis, an aceclofenac zinc complex was prepared. According to the findings of the *in vitro* hydrolysis investigation, the complex was more stable at acidic pH in the stomach than at alkaline pH in the intestine. The complex have anti-inflammatory effects as demonstrated by *in silico* analysis conducted using the Prediction of Activity Spectra of Substances software. This hypothesis was supported by an experiment on carrageenan-induced rat paw edema, the results of which included a decrease in the ulcer index and efficacy comparable to that of the parent medication. As a result, the aceclofenac-zinc complex and its derivatives can be used as anti-inflammatory agents as well as to treat ulcers (18).

Cobalt and Copper Metal Complexes of Mefenamic Acid

Cobalt (II) complexes with mefenamic acid have been created and studied, both with and without nitrogen donor heterocyclic ligands. Mefenamic acid appeared to function as a diprotonated monodentate ligand coupled to Co (II) ion, according to the experimental findings. CT-DNA can be bound by these metal complexes. When ethidium bromide and the complexes were evaluated in terms of how they bound to CT DNA, it became clear that the latter might outcompete the former by intercalating. These complexes can couple with human and bovine serum albumin, and complex 3 has the highest binding constant. Antioxidant activity is measured by their ability to repel reactive oxygen species (19). Cu-mefenamic acid complexes were also developed, characterized, and investigated. These complexes exhibited anti-inflammatory activity through interaction with CT-DNA. These complexes can effectively bind to albumin, and when reaching the target site, these complexes can easily dissociate (20).

Metal Complexes of Indomethacin

The inherent side effects of NSAIDs can be masked by the addition of beneficial effects by making a complex with the transition metals chromium and nickel. These complexes were screened for central, peripheral, and anti-inflammatory activity to identify potential pharmacological properties. 67.03% writhing inhibition and potent analgesic action was observed by nickel-indomethacin complex at a dose of 20 mg/kg. The anti-inflammatory profile of these compounds was conducted at 15 mg/kg dose, at 2 hr. inhibition of paw edema to 78.35% and 73.23%, respectively, which is comparable to the control indomethacin. Based upon the results, it can be expected that the chromium and nickel complexes of indomethacin have potential pharmacological effects that can be further verified by rigorous analysis (21,22).

Gold Metal Complexes

Various gold compounds of clinical importance, such as auranofin, solganal, and myochrysine, are being used in the treatment of arthritis. The indecisive picture about its innards procedure, it is assumed that its anti-inflammatory effects are due to certain reasons; gold(I), [Au(CN)2], or Au(III) are metabolites in the cell that can lead to the obsession of the selenium enzyme thioredoxin reductase. Auranofin is a new contender for the treatment of inflammation, cancer, and microbial infections because it inhibits inflammatory pathways and thiol redox enzymes (23).

Methotrexate Conjugated Gold Nanoparticles

Efficient drug delivery and therapeutic efficacy are the major interest of nanoparticles. The recent period is about nanoparticles, so methotrexate conjugated to gold nanoparticles (MTX-GNP), which have better antiarthritic potential than methotrexate alone in treating arthritis in experimental animal models. MTX-GNP was prepared by the adsorption method, and the particles formed were of 20-30 nm. The MTX-GNP was evaluated for its antiarthritic properties by studying urinary and serum parameters such as hydroxyproline, glucosamine, pyridoxine deoxypyridoxine, and serum cytokines. It has been revealed that MTX-GNP showed significant antiarthritic potential based on urinary and serum parameters than methotrexate alone. Therefore, it can be concluded that MTX-GNP has a better therapeutic advantage than MTX alone in the treatment of arthritis. A further detailed study is required on MTX-GNP (24).

Metal Complexes of Diclofenac

The most frequently prescribed therapeutic agents for RA are NSAIDs. Among the distinguished NSAIDs, diclofenac, a fenamic acid derivative, is generally administered due to its potency against pain and swelling in patients with RA. The synthesis of nociceptive prostaglandins in synovial tissue and blood and substance P, a pro-inflammatory neuropeptide, is inhibited by DCs, making it useful for the treatment of RA (25). Cobalt (II) diclofenac complexes were produced and categorized by chemical and spectroscopic analyses along with X-ray diffraction and thermal methods. The crystal structure was confirmed by spectroscopic and thermal data. The cobalt (II) coordination sphere has an octahedral structure with four waters and two diclofenac molecules. A polymeric chain extends down the crystal axis when an apical water molecule links two neighboring cobalt (II) ions. Compound 1 showed greater activity than diclofenac sodium, as revealed in the antioxidant activity experiments. The lower action of diclofenac sodium specifies that DPPH's lone pair of electrons most probably react with cobalt ions rather than sodium. The past investigations have shown comparable results (26). The interaction of [Cu(dicl)2(H_2O)2] (1), the copper(II) diclofenac complex, with the ligands N,N,N′,N′-tetramethylethylene-diamine (temed), propane-1,3-diamine (pn), ethylenediamine (en), unsymmetrical dimethylethylene-diamine (unsym-dmen), in methanol-water (4:1 v/v) produced the unique copper(II) complexes[Cu(temed)(dicl)2](2), [Cu(pn)2(H_2O)2](dicl)2·2H_2O(3), [Cu(en)2(H_2O)2](dicl)2·2H_2O(4) [Cu(unsym-dmen)2(H_2O)](dicl)2·H_2O_5), correspondingly. Spectroscopic (UV-vis, FT-IR) procedures were used to characterize each manufactured complex. The structures of complexes 2, 3, and 5 were explicitly discovered using single-crystal X-ray crystallography. The results exposed the ionic structures of complexes 4, 5 and the covalent structure of complex 2, and density functional theory calculations were used to improve the geometry of complex 3. The ability to bind to calf-thymus DNA of complexes 1-5 was observed through competitive studies with ethidium bromide and *in vitro* through cyclic voltammetry, viscosity measurements, and UV-vis spectroscopy. Fluorescence emission spectroscopy was utilized to find the interaction of complexes 1-5 with bovine serum albumin *in vitro* and the binding constants evaluated. The biological behaviors of complexes (1-5) was compared to those of previously described diclofenac complexes with Ni(II), Cu(II), and Mn(II). Complexes's (1-

5) current *in vitro* results with regard to their binding to CT-DNA and BSA might be encouraging for further biological study and their potential use as metallo-pharmaceutical compounds (27).

Ibuprofen and Naproxen Metal Complexes

Zinc can modify the body's natural defense mechanisms and is an effective antioxidant and anti-inflammatory agent. Zinc's role in accelerating wound healing, including ulcers, is widely accepted. The most extensively prescribed and utilized medicines are NSAIDs because of their several indications and widespread availability. Long-term and excessive use of NSAIDs can cause gastrointestinal impairment. As a result, in recent decades, increasing the curative indications of prevailing medicines has been top precedence. The metal complexes of NASAIDs have gotten a lot of attention in this area. The purpose of this research is to see how zinc complexation affects the naproxen and ibuprofen's ulcer-causing and anti-inflammatory effects in rats following intragastric injection. Anti-inflammatory activity was tested in male albino Wistar rats with inflammatory edema in the hindpaw initiated by carrageenan. In contrast to the control groups, both the complexes [zinc-naproxen and zinc-ibuprofen (20 mg/kg naproxen and ibuprofen)], as well as combinations with zinc hydroaspartate (in doses 14.37 and 16.05 mg/kg), and paternal drugs resulted in a substantial decrease in edema. After a single administration, there were insignificant statistical variations between the studied drugs. In contrast to control groups and parent NSAIDs, triple intragastric injection of the naproxen-ZHA and ibuprofen-ZHA mixture significantly improved anti-inflammatory action. Animals receiving ZHA and naproxen after 2 hours of carrageenan administration showed the most significant anti-inflammatory activity. Compared with the control group, these animals had 80.9 percent less edema. Ulcerations caused by parent NSAIDs were lessened by both mixtures of zinc hydroaspartate and zinc complexes combined with NSAIDs. However, following triple administration, the zinc hydroaspartate combinations of naproxen and ibuprofen were the minimum harmful. Based on these findings, by lowering the efficacious dosage of the paternal medicine while boosting its efficacy, zinc supplementation during NSAID treatment may assist to prevent and repair ulcers (28).

An innovative Zn (II)-naproxen combination [Zn(nap)2(dap)] has been synthesized. 1H NMR spectroscopy, elemental analysis, UV-Vis spectroscopy, and FT-IR were used to characterize the compound, which contained a 1,3-diamino propane ligand. X-ray crystallography was used to verify its single-crystal structure. *In vivo*, the Zn (II)-naproxen compound was tested for analgesic, ulcerogenic, and anti-inflammatory properties, as well as in vitro for antibacterial and antifungal properties. After 3 hours, the complex had a 57.8% edema inhibition rate, a 71 percent pain inhibition rate, and 8±1 as an ulcer index. The antioxidant and antibacterial actions of Zn(II)-Naproxen compound also examined and were found to be superior to naproxen (29).

Tenoxicam Metal Complexes

NSAIDs from the oxicam family, the most often used of which is tenoxicam, are one of the treatments for arthritis (30) and utilized to get rid of pain and swelling due to RA. TNX complexes of palladium(II), platinum(II), zinc(II), and copper(II) were produced in this study. They were characterized by analytical and instrumental procedures including differential thermal analysis, thermogravimetric analysis, UV-visible, inductively coupled plasma-optical emission spectrometry, and liquid chromatography-mass spectrometry. The complex FTIR spectra were calculated, and the results were reinforced by density functional theory calculations. [Pd(TNX)Cl2], [Pt(TNX)2], [Zn(TNX)2] and [Cu (TNX)2] are the proposed structures of these metal complexes. For the first time, the anti-inflammatory properties of the manufactured complexes were determined in comparison to the medication. The production of Tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine, was reduced more efficiently by metal complexes of the TNX as compared to tenoxicam alone. [Cu (TNX)2] exhibited the maximum anti-inflammatory activity. Molecular docking calculations showed the interactions amongst TNF-α and TNX complexes were of receptor-ligand type (31).

Folic Acid Conjugated Silver Nanoparticles

The origin of RA involves the invasion of inflammatory cells, particularly M1 macrophages that release a range of inflammatory cytokines. M1 macrophages should be removed/converted to the M2 phenotype (anti-inflammatory) to alleviate synovial inflammation. FA-AgNPs are folic-acid-based silver nanoparticles that can selectively transport into M1 macrophages. Effective RA treatment, they collaboratively decrease M1 macrophages and the polarization of M2 macrophages. The silver nanoparticles were simply made and then FA-modified to better comprehend M1 macrophage-focused transport through overexpressed folate receptors on their surface. FA-AgNPs melted after entering cells and freed Ag^{+} in reaction to intracellular glutathione, which is the main component for anti-inflammatory activities and hence helps in the management of RA. In high-biosafety mouse RA models, these nanoparticles may possibly gather into swollen joints, allowing for effective anti-inflammatory action and good healing. The body eventually rid itself of FA-AgNPs after treatment predominantly through feces, with no tissue accumulation and no long-term toxicity observed. This thesis is the first to apply bidirectional communication. The potential of folic acid-silver nanoparticles for RA treatment is highlighted in this study, which is the first study to use bioactive nanoparticles without the use of medicines (32).

CONCLUSION

Nowadays, the importance of metals and their complexes is increasing due to their beneficial therapeutic properties. However, little work has been reported previously on anti-arthritic metal complexes. It is suggested that the mechanism of action and possible toxicity of metal complexes must be evaluated to discover novel treatments against deadly ailments.

Ethics

Author Contributions

Concept: E.A., K.A., M.G.N., Ma.G., Mu.G., Design: E.A., K.A., M.G.N., Ma.G., Mu.G., Data Collection or Processing: E.A., K.A., M.G.N., Ma.G., Mu.G., Analysis or Interpretation: E.A., K.A., M.G.N., Ma.G., Mu.G., Literature Search: E.A., K.A., M.G.N., Ma.G., Mu.G., Writing: E.A., K.A., M.G.N., Ma.G., Mu.G.

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REFERENCES

1. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. JAMA. 2018; 320: 1360-72.
2. Ashiq K, Bajwa MA, Tanveer S, Qayyum M, Ashiq S, Khokhar R, et al. A comprehensive review on gout: The epidemiological trends, pathophysiology, clinical presentation, diagnosis and treatment. J Pak Med Assoc. 2021; 71: 1234-8.
3. Ashiq K, Ashiq S, Shehzadi N. Hyperuricemia and its association with hypertension: risk factors and management. Pak Heart J. 2022; 55: 200-1.
4. Zhou S, Zou H, Chen G, Huang G. Synthesis and Biological Activities of Chemical Drugs for the Treatment of Rheumatoid Arthritis. Top Curr Chem (Cham). 2019; 377: 28.
5. Ashiq K, Ashiq S, Shehzadi N, Hussain K, Khan MT. Prevalence and Control of the Hypertension in Patients Suffering from Rheumatoid Arthritis. Pak Heart [Internet]. 2024; 55: 421-2.
6. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Lancet. 2017; 389: 2338-48.
7. Ashiq K, Latif A, Ashiq S, Sundus A. A systematic review on the prevalence, pathophysiology, diagnosis, management and treatment of gout (2007-2018). GSC Biological and Pharmaceutical Sciences. 2018; 5: 50-5.
8. Cirri D, Fabbrini MG, Pratesi A, Ciofi L, Massai L, Marzo T, et al. The leading established metal-based drugs: a revisitation of their relevant physico-chemical data. Biometals. 2019; 32: 813-7.
9. Colotti G, Ilari A, Boffi A, Morea V. Metals and metal derivatives in medicine. Mini Rev Med Chem. 2013; 13: 211-21.
10. Barry NP, Sadler PJ. Challenges for metals in medicine: how nanotechnology may help to shape the future. ACS Nano. 2013; 7: 5654-9.
11. Boros E, Dyson PJ, Gasser G. Classification of Metal-based Drugs According to Their Mechanisms of Action. Chem. 2020; 6: 41-60.
12. Ashiq K, Naureen B, Ashiq S. Metal complexes and their potential therapeutic role against COVID-19: recent developments in drug designing. Sudan J Med Sci. 2021; 16: 540-5.
13. Jahnavi K, Reddy PP, Vasudha B, Narender B. Non-steroidal anti-inflammatory drugs: an overview. J Drug Deliv Ther. 2019; 9: 442-8.
14. Ngo SN, Addison CJ. Are COX-2 selective NSAIDs associated with less GI, renal, and cardiovascular side effects: evidence from animals treated with NSAIDs. Annual Res Rev Bio. 2018: 1-8.
15. Yun Y, Chen P, Zheng CL, Yang Y, Duan WG, Wang L, et al. Copper-aspirin complex inhibits cyclooxygenase-2 more selectively than aspirin. Yakugaku Zasshi. 2007; 127: 1869-75.
16. Leung CH, Lin S, Zhong HJ, Ma DL. Metal complexes as potential modulators of inflammatory and autoimmune responses. Chem Sci. 2015; 6: 871-84.
17. Iqbal MS, Khurshid SJ, Muhammad B. Anti-inflammatory and selective COX-2 inhibitory activities of metal complexes of Schiff bases derived from aldoses. Med Chem Res. 2013; 22: 861-8.
18. Kale MA, Shelke R, Nawale RB. Zinc-aceclofenac complex: synthesis, hydrolysis study and antiinflammatory studies. Antiinflamm Antiallergy Agents Med Chem. 2014; 13: 36-44.
19. Dimiza F, Papadopoulos AN, Tangoulis V, Psycharis V, Raptopoulou CP, Kessissoglou DP, et al. Biological evaluation of non-steroidal anti-inflammatory drugs-cobalt(II) complexes. Dalton Trans. 2010; 39: 4517-28.
20. Sharma RP, Kumar S, Venugopalan P, Ferretti V, Tarushi A, Psomas G, et al. New copper (II) complexes of the anti-inflammatory drug mefenamic acid: a concerted study including synthesis, physicochemical characterization and their biological evaluation. RSC Adv. 2016; 6: 88546-58.
21. Sukul A, Haque S, Poddar SK, Hossain MS, Niloy KK, Saha SK. Comparative physicochemical, anti-inflammatory, and analgesic activity assay of synthesized chromium and nickel complexes of indomethacin. Cogent Chem. 2017; 3: 1302312.
22. Lucas S. The pharmacology of indomethacin. J Headache Pain. 2016; 56: 436-46.
23. Madeira J, Gibson D, Kean W, Klegeris A. The biological activity of auranofin: implications for novel treatment of diseases. Inflammopharmacol. 2012; 20: 297-306.
24. Gomes A, Datta P, Sengupta J, Biswas A, Gomes A. Evaluation of anti-arthritic property of methotrexate conjugated gold nanoparticle on experimental animal models. J Nanopharm Drug Deliv. 2013; 1: 206-11.
25. Battu S, Yalavarthi PR, Gv SR, Radhakrishnan S, Thummaluru RMR, Konde A. Biopharmaceutical Process of Diclofenac Multi-particulate Systems for Chronotherapy of Rheumatoid Arthritis. Turkish J Pharm Sci. 2018; 15: 256.
26. Gacki M, Kafarska K, Wolf WM. A supramolecular polymeric chain in the cobalt (II) complex with diclofenac: Synthesis, crystal structure, spectroscopic, thermal and antioxidant activity. J Coord Chem. 2019; 72: 3481-94.
27. Kumar S, Sharma RP, Venugopalan P, Ferretti V, Perontsis S, Psomas G. Copper (II) diclofenac complexes: Synthesis, structural studies and interaction with albumins and calf-thymus DNA. J Inorganic Biochem. 2018; 187: 97-108.
28. Jarosz M, Szkaradek N, Marona H, Nowak G, Młyniec K, Librowski T. Evaluation of anti-inflammatory and ulcerogenic potential of zinc–ibuprofen and zinc–naproxen complexes in rats. Inflammopharmacol. 2017; 25: 653-63.
29. Chu YC, Wang TT, Wang LJ, Luo QY, Jia R, Hong TC, et al. Synthesis, characterization, and biological evaluation of a novel Zn (II)-Naproxen complex. Polyhedron. 2019; 163: 71-6.
30. Adam AMA. Ca (II), Sr (II) and Ba (II) ion interaction with the rheumatoid arthritis drug tenoxicam: Structural, thermal, and biological characterization. Applied Organometallic Chem. 2018; 32: e4055.
31. Muslu H, Kalaycıoğlu Z, Erdoğan T, Golcu A, Erim FB. Synthesis, characterization, anti-inflammatory evaluation, molecular docking and density functional theory studies of metal based drug candidate molecules of tenoxicam. Results Chem. 2021: 100111.
32. Yang Y, Guo L, Wang Z, Liu P, Liu X, Ding J, et al. Targeted silver nanoparticles for rheumatoid arthritis therapy via macrophage apoptosis and Re-polarization. Biomaterials. 2021; 264: 120390.