

Prodrug Approach: NSAID Conjugates of Platinum Compounds as Anti-Cancer Agents

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Abstract

Prodrug based synthetic approach is a very promising area of research to enhance the pharmacokinetic and pharmacodynamic properties of the drugs with a remarkable reduction of the side effects. Prodrugs can be used for drugs which are having poor solubility, poor transport properties and production of chronic side effects thus this approach provides a powerful tool for novel drug conjugates with improved therapeutic value. Platinum based anti-neoplastic agents are widely used in chemotherapeutic regimens but the side effects like hepatotoxicity, ototoxicity, cardiotoxicity, nausea and vomiting, diarrhea, mucositis, stomatitis, pain, alopecia, anorexia, cachexia, cytopenias and asthenia were reported. So, the development of prodrugs by using platinum compounds showed a better therapeutic value with the reduction of side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) are a broad class of drugs that showed Analgesic, Anti-inflammatory and Anti-pyretic activities based on the mechanism of cyclooxygenase (COX-1 and COX-2) enzyme inhibition and formation of prostaglandins. Also, Non-steroidal anti-inflammatory drugs (NSAIDs) have different targets to elicit various pharmacological actions and are beneficial for many other diseases. The different targets are nuclear factor kappa B (NF- κ B), Peroxisome proliferator-activated receptors (PPAR), Mammalian target of rapamycin (mTOR), Autophagy, Cytochrome C, NSAID activated gene (NAG-1), Angiogenesis, Resolvins, Protectins, Maresins. This review focused on the development of platinum prodrugs by conjugating with different NSAIDs and the therapeutic applications of the developed novel molecules including dual-action and triple-action prodrugs. This review discussed the different aspects of the prodrug-based approach, the detailed mechanism and other molecular targets of NSAIDs and the development of the platinum compounds –NSAID prodrugs.

Keywords: Anti-neoplastic agents, Anti-inflammatory agents, Non-steroidal anti-inflammatory drugs, Platinum compounds, Prodrugs.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a category of drugs that can be used widely for the treatment of various diseases characterized by inflammation. The use of anti-inflammatory drugs leads to gastric ulcers and gastro intestinal toxicity. A literature survey revealed that the applications of NSAIDs have analgesic, antipyretic and anti-inflammatory thus useful in various chronic diseases such as neurodegenerative disorders and different types of cancers⁽¹⁾. But the long-term use of NSAIDs may produce serious side effects in various physiological systems and the applications are limited due to the limitations in the transport properties across some of the physiological barriers. The disadvantages of NSAIDs can be overcome by the prodrug-based approach^(2,3).

A prodrug is an inactive form of the drug that can be converted into the pharmacologically active form of the drug at the site of action. Prodrug-based drug design is a valuable concept to overcome the barriers in the drug development

processes⁽⁴⁾. The prodrug approach can be used for drugs which are having poor solubility, poor transport properties and production of chronic side effects thus this approach provides a powerful tool for novel drug conjugate with improved therapeutic value. The prodrug approach leads to the discovery of different classes of drugs that is available on the market. Examples of prodrugs are Acyclovir, 5-Fluorouracil, Cyclophosphamide, Diethylstilbestrol diphosphate, L-Dopa, 6-Mercaptopurine, Mitomycin C, Zidovudine, Carbamazepine, Captopril, Carisoprodol, Sulindac, Loperamide, Oxyphenisatin, Sulfasalazine, Acetylsalicylate, Chloramphenicol succinate, Dipivefrin, Fosphenytoin etc^(4,5).

Ester, amide, phosphate prodrugs, etc. can be synthesized by using various conjugates⁽⁶⁾. The conjugates used for prodrug development are natural compounds, amino acids, carbohydrates etc. The conjugate possessed some ideal characteristics such as it must be non-toxic, easily eliminated from the body or some of the conjugates have beneficial effects on the organ systems. The selection of the

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conjugates is vital in the prodrug development process^(7,8). The NSAIDs elicit their therapeutic effects by inhibiting the cyclooxygenase enzyme and prostaglandin-mediated pathway⁽⁹⁾. Many research works were conducted in the area of NSAID prodrugs that is having different pharmacological activities and also mutual prodrugs reported synergistic pharmacological activities. The applications of the NSAIDs were extended to the different types of chronic diseases such as Alzheimer's disease, Parkinsonism diseases, different types of carcinomas, cardiovascular diseases and diabetes etc⁽¹⁰⁾.

Non-steroidal anti-inflammatory drugs

NSAIDs are well accepted for therapeutic activities such as Analgesic, Anti-inflammatory and Anti-pyretic activities based on the mechanism of cyclooxygenase (COX-1 and COX-2) isoenzyme inhibition and the formation of prostaglandins. The various pharmacological activities produced by the NSAIDs can be explained through different basic mechanisms such as the nitric oxide system and transcriptional factors that showed direct relationship with cytokine expression which is having a significant role in the anti-inflammatory process⁽¹¹⁾. The non-selective Food and drug administration (FDA) approved NSAIDs are diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, Ibuprofen, Indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin and COX-2 selective NSAIDs are celecoxib, rofecoxib and valdecoxib but the rofecoxib and valdecoxib were withdrawn. So the NSAIDs are utilized for the treatment of various diseases like headache, arthritis, gout, inflammatory arthropathies, dysmenorrhoea, sports injuries, migraine, post-operative pain, tissue injury, sciatica and rheumatism⁽¹²⁾.

The chemical structure of NSAIDs generally consists of an acidic group which is usually a carboxylic acid group, an enolic group, a hydroxamic acid group and a sulphonamide or tetrazole ring. The acidic group present in the structure is mainly responsible for receptor binding and lipophilic nature of NSAID is determined by the alkyl chain or the aromatic ring. The aromatic ring is substituted by halogens like chlorine, fluorine to get best activity. The general structural representation of NSAIDs was given in figure 1.

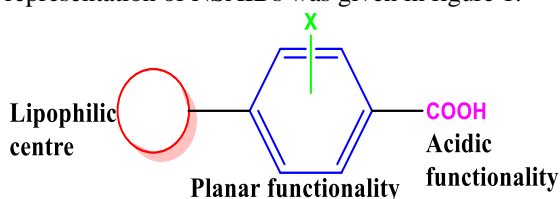


Figure 1. General structure of the NSAID

NSAIDs act on cyclooxygenase enzymes which is having the main function in the production

of prostaglandins. Prostaglandins are the biological mediators which showed an important function in the inflammatory process. The mechanism of action of NSAIDs is summarized in figure 2. The NSAIDs inhibit both the cyclooxygenase isoenzyme (COX-1 and COX-2) and that result in the reduction of inflammation. The biosynthesis of PG involves the release of arachidonic acid (AA) from damaged cell membranes by phospholipase enzymatic activity. AA is metabolized by cyclooxygenase (COX) into prostanoids and by lipoxygenase into leukotrienes respectively^(13, 14).

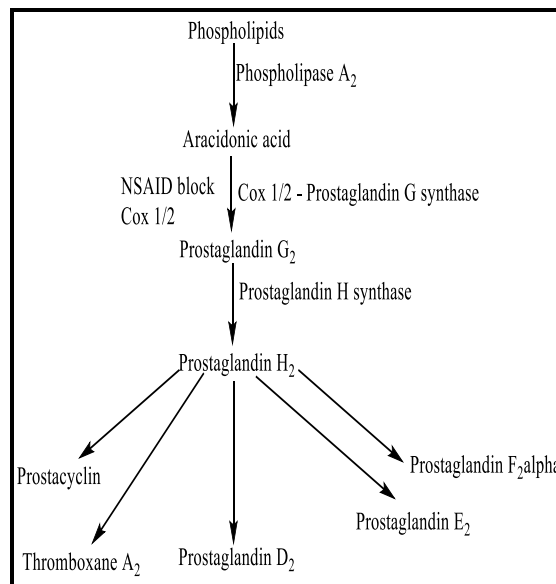


Figure 2. Mechanism of action of NSAIDs

The major side effects of NSAIDs are gastro-intestinal damage (nausea, vomiting, diarrhea, gastric ulceration and bleeding), cardiovascular side effects (congestive heart failure, increased arterial blood pressure, thrombotic events and palpitation), renal side effects (liver cirrhosis, congestive heart failure and chronic kidney diseases), hepatic side effects (acute liver damage and hepatic toxicity), CNS side effects (CNS side effects are very rare and it includes headache, mental confusion etc.), Hematological side effects (Platelet aggregation is inhibited by the use of NSAIDs thus prolongs the bleeding time), Other side effects (rashes, wheezing, throat swelling, asthma and exacerbation etc.)⁽¹⁵⁾. Since NSAIDs are associated with severe toxicities, newer approaches or alternative strategies were taken for "pharmacophore modification" to tame down the toxic side effects without compromising their beneficial health effects. In this regard, recently, prodrugs are gaining immense popularity.

Prodrugs

The term 'prodrug' or 'proagent' was introduced by Adrian Albert in 1958 who explained that this approach directly modifies the physical as well as chemical properties of drugs in a temporary

way that increases in the therapeutic effectiveness and decreases the toxicity ⁽¹⁶⁾. A prodrug should exert ideal properties like pharmacological inertness and rapid conversion into the pharmacologically active agent at the active site by different conversion methods and also the byproducts must be non-toxic. The objectives of prodrug-based concept include pharmaceutical objectives, Pharmacokinetic objectives and Pharmacodynamic objectives ⁽¹⁷⁾.

Functional groups susceptible to prodrug synthetic approach

The main factors affecting the development of prodrugs are the parent drug which is the compound that is used for the prodrug formation, promoiety and the synthesized novel prodrug should be evaluated by pharmacokinetic properties. The functional groups in the parent drug used for synthesizing prodrug are carboxylic acid, hydroxyl group, amino group, phosphate or phosphonate group and keto groups. The esters, carbonates, carbamates, amides, phosphates and oximes compounds were formed by the chemical modification of the drugs. The majority of the synthesized prodrugs are ester prodrugs and the active medicament is liberated by the enzymatic hydrolysis mainly by esterases. The prodrugs developed by the carbonates and carbamates linkage of carboxyl with hydroxyl or amine functionalities

are more than that of ester prodrugs and less than that of amide prodrugs. Carbonates are derived from the carboxyl group and alcohol functional groups, and the carbamates are acquired from the carboxyl group and amine functional groups. The use of amide prodrugs is limited due to their high *in vivo* stability and the amide linkage is hydrolyzed by the action of the amidase enzymes. Amide prodrugs are developed for increasing oral absorption. Oxime prodrugs were synthesized for enhancing the membrane permeability and rate of absorption of a parent drug. The drug is released by microsomal enzymes ⁽¹⁸⁾.

Other targets of NSAIDs and pharmacological effects

The studies proved that NSAIDs have different targets to elicit various pharmacological actions and are beneficial for many other diseases. The NSAIDs showed different actions in various targets such as nuclear factor kappa B (NF-Kb), Peroxisome proliferator-activated receptors (PPAR), Mammalian target of rapamycin (mTOR), Autophagy, Cytochrome c, NSAID activated gene (NAG-1), Angiogenesis, SPMs Lipoxins, Resolvins, Protectins, Maresins ⁽¹⁹⁾. From the literature, the table concluded the beneficial effects of NSAIDs on various targets that were given in Table 1.

Table 1. The different targets of NSAIDs

NSAID	Molecular target	References
Aspirin	NF-Kb,(PPAR), mTOR), Autophagy, Cytochrome c,NAG-1, Angiogenesis, SPMs Lipoxins, Resolvins, Protectins, Maresins	20, 21, 22, 23, 24, 25, 26,27,28
Diclofenac	NF-κB, Wnt/β-catenin, NAG-1	29,30,31
Sulindac	NF-κB, PPAR, MAPKs, Wnt/β-catenin, Cell kinetics, NAG-1, PDEs,	32, 33,34,35,36
Celecoxib	PDK-1/Akt, PPAR, MAPKs, mTOR, Autophagy, Cell kinetics, Cytochrome c, NAG-1, Ca ²⁺ mobilization, Carbonic Anhydrase	37, 38, 39,40, 41,42,43
Naproxen	PDK-1/Akt, Cell kinetics,	44,45
Ibuprofen	PPAR, NAG-1, Angiogenesis	46, 47,48
Indomethacin	PPAR, MAPKs, Wnt/β-catenin, Cytochrome c, NAG-1, Calcium mobilization, Carbonic Anhydrase	49,50,51, 52,53,54,55
Meloxicam	Autophagy, Carbonic Anhydrase	56,57
Flurbiprofen	NAG-1, β-secretase 1	58,59

Note: NF-Kb (Nuclear factor kappa B), PPAR (Peroxisome proliferator-activated receptors), mTOR (Mammalian target of rapamycin), NAG-1(NSAID-activated gene), SPMs Lipoxins (specialized pro-resolving lipid mediators), MAPKs (Mitogen-activated protein kinases), PDK-1/Akt (3-phosphoinositide-dependent kinase 1/ protein kinase B).

Platinum (II) based drug development

In the 1980s, Platinum-based drugs were developed and introduced in the medicinal field as an anticancer agent and the first developed effective platinum compound was Cisplatin. The white or yellowish-white colour Cisplatin or *cis*-diamminedichloroplatinum (II) is popular anti-

cancer drug and it is mainly used for the treatment of bladder, head and neck, lung, ovarian, and testicular cancers⁽⁶⁰⁾. Cisplatin is a coordination compound and exhibits planar geometry and it is slightly soluble in water and N, N -dimethyl formamide. The use of the platinum compound leads to many side effects because of that the less acceptability worldwide⁽⁶¹⁾.

Cisplatin was discovered by Barnett Rosenberg and it acted as an effective anti-cancer agent and it leads to the development of other platinum anticancer compounds⁽⁷³⁾. FDA-approved platinum drugs are cisplatin, carboplatin, oxaliplatin and another three compounds were approved nedaplatin, lobaplatin and heptaplatin⁽⁷⁴⁾. After the discovery of cisplatin, many platinum compounds were developed and came on clinical trials but only one platinum compound, carboplatin, showed a

remarkable advantageous effect over cisplatin. Carboplatin or *Cis* diammine (1, 1-cyclobutanecarboxylato) platinum (II), second-generation anti-cancer drug, is an anti-cancer drug used for tumor of ovaries, lungs, head and neck. Chemically carboplatin is a bidentate dicarboxylate and the structural properties. The detailed mechanism of carboplatin is not known but is expected to be acted by interacting with cellular targets such as DNA, tubulin and other proteins etc.⁽⁶²⁾.

Another platinum compound used for anti-neoplastic activity is oxaliplatin and the structural difference between oxaliplatin and cisplatin is the presence of diamino cyclohexane in the place of the amine functional group in cisplatin. The chemical name of oxaliplatin is oxalate (*trans*-1,1,2-diaminocyclohexane) platinum and the diaminocyclohexane is responsible for its identical properties. Oxaliplatin is a tetra-coordinated platinum complex that showed planar arrangement. Oxaliplatin is mainly used for the treatment of colorectal cancer and combining therapy with fluorouracil and folinic acid applied to advanced cancer treatments [Figure 3]^(63,64).

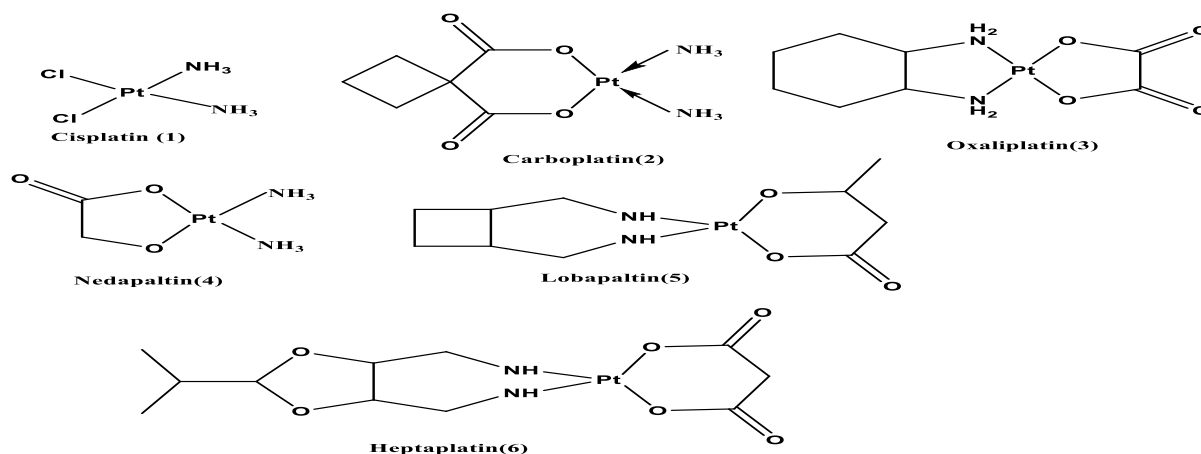


Figure 3. Platinum Compounds structure

Platinum (IV) complexes

The resistance developed by Cisplatin and related drugs leads to the development of platinum IV drugs that showed many advantages over platinum II drugs⁽⁶⁵⁾. Platinum IV drugs contain a ligand in the axial position that further allowed the modification. The high stability, oral bioavailability, fewer side effects and modification of the axial ligands resulted in the enhanced pharmacological and therapeutic properties⁽⁶⁶⁾. These complexes were categorized into three categories complex with bioactive axial ligand, complex without any bioactivatable axial ligand and photoactivatable which was given in the figures 4, 5 and 6. Tetraplatin, iproplatin and satraplatin are platinum (IV) complexes without bioactive axial ligand or targeting axial ligand. The studies reported the Pt

(IV) - estradiol conjugate, cisplatin-containing valproic acid and Pt (IV) complex with ethacrynic acid, which are examples of the complexes with bioactive axial ligands. Also, some photoactive platinum-complexes were reported by the researchers⁽⁶⁷⁾. The development of platinum (IV) complexes also opened a new scope in the design and development of the platinum-based anti-cancer therapy.

The polymer conjugates of platinum were also developed to improve the therapeutic index and the mainly used polymer is hydroxyl propyl methyl cellulose (HPMA). To enhance the properties and activity and also to reduce the toxicity of platinum compounds conjugated with another category of drugs or conjugates⁽⁶⁸⁾.

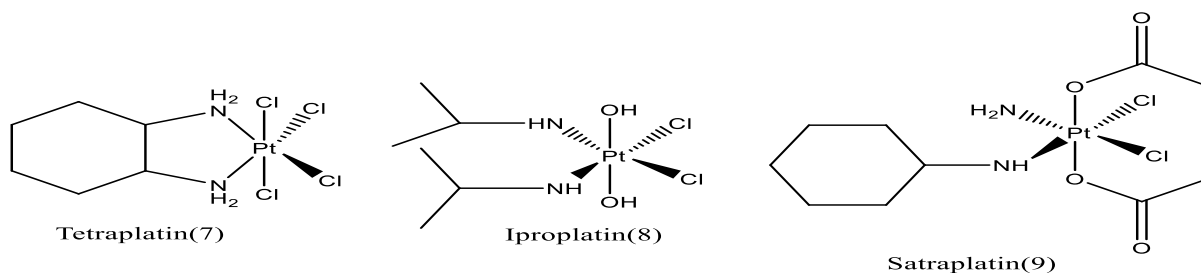


Figure 4. Chemical structure of the platinum (IV) complexes without any bioactivatable axial ligands

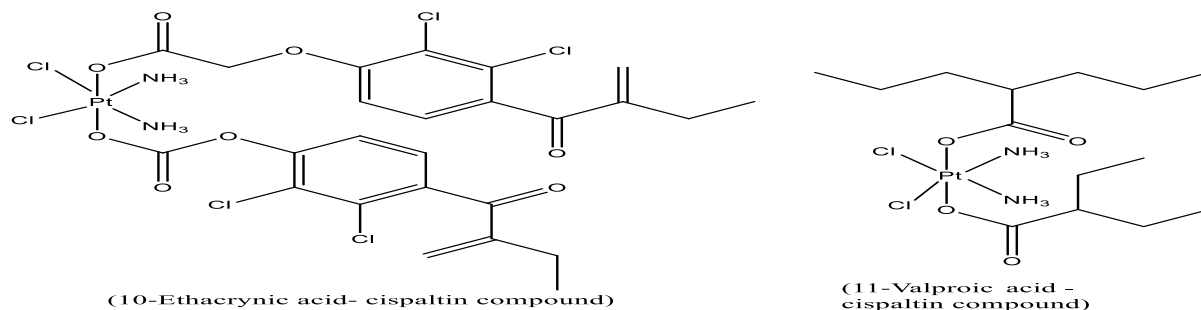


Figure 5. Chemical structures of Pt (IV) complex with bioactivatable ligands

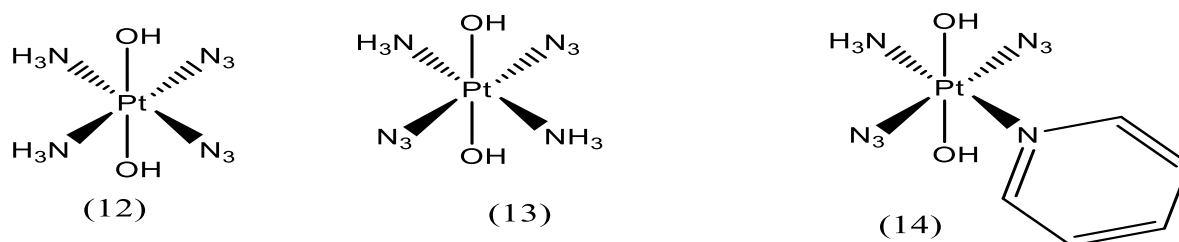


Figure 6. Photoactivatable Pt (IV) - diazido Complexes

Prodrugs of NSAIDs

The majority of the prodrugs of NSAIDs have been prepared by the derivatization of the carboxylic acid functional group present in the anti-inflammatory drugs. The conversion of the carboxylic acid functional group by using the different conjugates developed the carrier-linked and bioprecursor prodrugs. The prodrug-based approach successfully overcomes the disadvantages and the barriers to the effective application of the various drugs in the NSAIDs^(69,70).

NSAIDs – Metal complexes

The Metal-based complexes showed potential therapeutic activity but the number of compounds approved by FDA are very less, and the most notable compound is Cisplatin as anticancer agents. Metals have a beneficial role in the treatment of different diseases especially for cancer therapy. The widely used metal for the effective treatment of cancer is Platinum and other major metal utilized by

the medicinal field are ruthenium, cobalt, etc. A Literature survey suggested that metal prodrugs can effectively enhance the pharmacokinetic and pharmacodynamic properties^(71,72).

Platinum- NSAIDs prodrugs

The development of Pt (IV) prodrugs with NSAIDs as axial ligands can effectively produce enhancement in the activity by reducing the adverse effects produced by the platinum. Octahedral platinum is considered inert but the modification of the axial position can effectively be utilized for further design and development. Several studies were conducted by combining the platinum drugs with non-steroidal anti-inflammatory agents such as aspirin, ibuprofen, flurbiprofen, naproxen etc as axial ligands^(77,78). The General structures of the platinum-NSAID prodrugs were given in figure 7. The design and development of platinum prodrugs by conjugating with different categories of conjugates is a promising area of research in the treatment of various types of malignancy^(75,76).

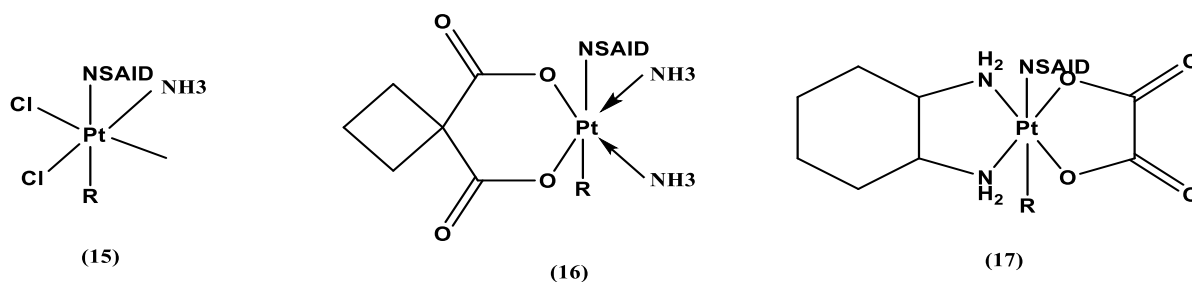


Figure 7. General structures of platinum compounds (cisplatin, oxaliplatin and carboplatin) -NSAID prodrugs

Development of Platinum-based prodrugs

In order to develop platinum prodrugs by using different conjugates researchers have adopted various schemes and the outline of the different schemes were given in the Figure 8. By using the various reagents, researchers can develop many types of prodrugs⁽⁷⁹⁾. Cisplatin produced a derivative in which hydroxyl group and -OR by reacting with hydrogen peroxide in the presence of alcohol (R-OH). Halogens can be added by the halogenation reaction and acetyl derivative can be obtained by the acetylation reaction.

The general structure of platinum compounds has different ligand types as shown in the figure. It contains leaving group ligand, non-leaving group ligand and axial ligand. The leaving ligands are usually N donors and they form a stable bond with platinum and any derivatization in this region retain in the final pharmacological action. Modification in the non-leaving group affects its lipophilicity, solubility, toxicity profile and reaction kinetics. The higher valent platinum complex

contains the axial ligands and this is the region of modification and different moieties can attach here thus altering its physical, chemical and pharmacological properties⁽⁸⁰⁾. Different schemes for synthesizing novel prodrugs were given in figure 9.

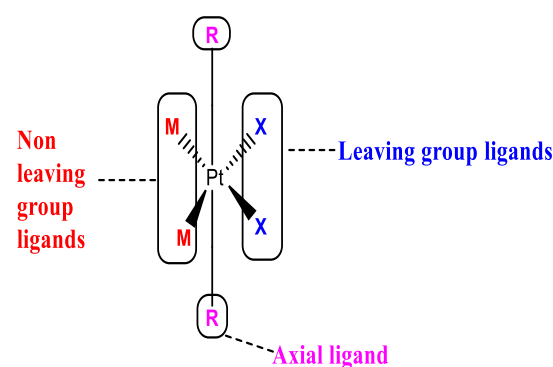


Figure 8. General structure of platinum based anticancer drugs

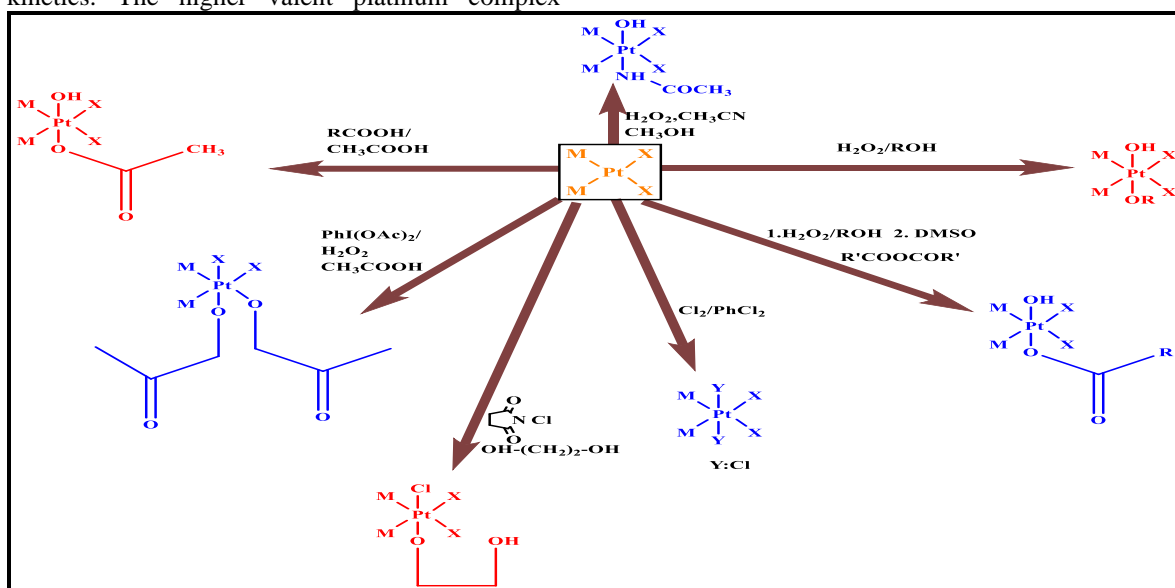


Figure 9. Different schemes for synthesizing new platinum compounds derivatives.

Mechanism of Platinum- NSAIDs prodrugs

The platinum complex with NSAIDs reported various advantages and the mechanism of action of the prodrugs because of the release of the active constituents intracellular and produced the toxic effect on the tumor cells. The Platinum-

NSAIDs prodrug approach enhances the lipophilic profile with a remarkable reduction in the toxic side-effects (81). The schematic representation of the mechanism of the Platinum- NSAIDs prodrugs was given in Figure 10.

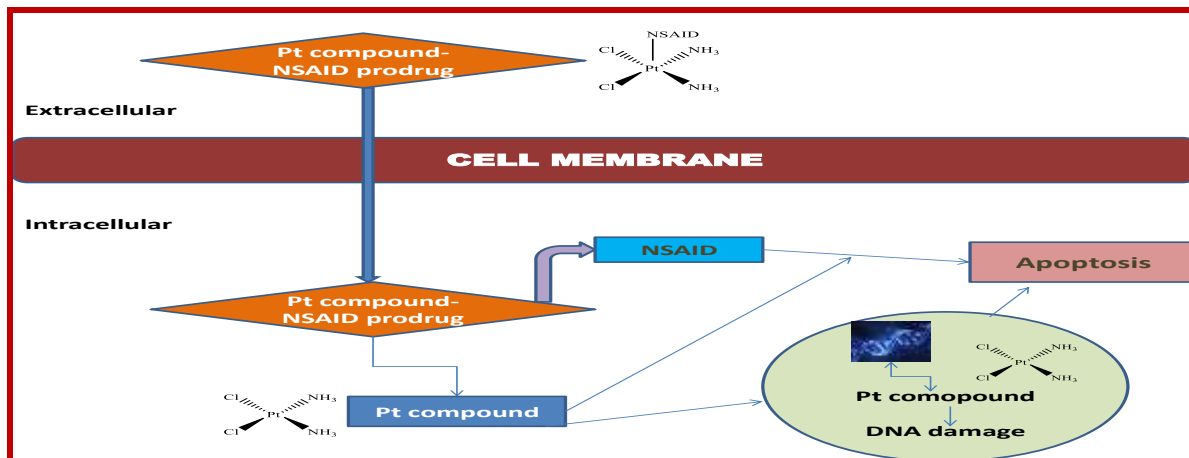


Figure 10. Schematic representation of the mechanism NSAID-Pt compound prodrugs

Chronic inflammation is one of the main indications of carcinoma by increasing the expressions of COX enzymes which is having an imperative role in prostaglandin synthesis. So current research focused on the combination of non-steroidal anti-inflammatory drugs with chemotherapeutic agents (82).

The interaction of NSAIDs with the platinum compounds such as cisplatin showed very beneficial pharmacological effects. The different classes of NSAIDs can be used for developing the various platinum compound conjugates. Many studies suggested the anti-cancer effects of the NSAIDs and this background is also contributing to

the development of effective prodrugs of platinum compounds as anti-cancer agents (83, 84).

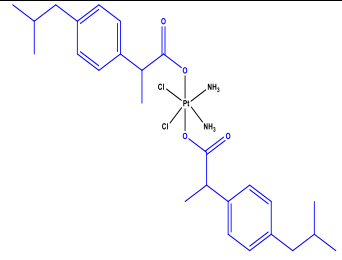
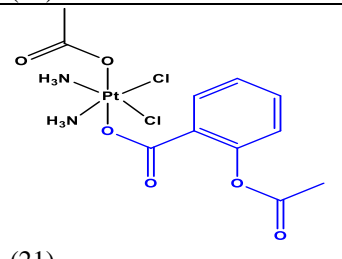
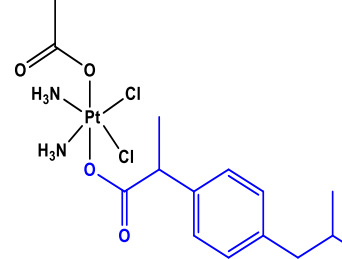
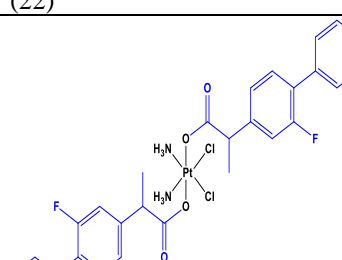
Dual-action platinum prodrugs with COX inhibitors

The dual-action platinum prodrugs were designed and developed by conjugating with cyclooxygenase inhibitors which were providing a promising area of oncology (table 1). The NSAIDs can be substituted in the axial position of Pt (IV) compounds and that can enhance the potency and reduce the side effects hence potent cytotoxic compounds were prepared.

Table 2. Chemical structures of the dual-action prodrugs

Compounds	Platinum containing drug	NSAID	Platinum-NSAID structure	Reference number
1	Cisplatin	aspirin	 (18)	(76)
2	Cisplatin	Indomethacin	 (19)	(45)

Continued table 2.

3	Cisplatin	Ibuprofen	 (20)	(46)
4	Cisplatin	Aspirin	 (21)	(85)
5	Cisplatin	Ibuprofen	 (22)	(86)
	Cisplatin	Flurbiprofen	 (23)	(87)

Triple action prodrugs of platinum-based drugs

Triple-action prodrugs were developed by conjugating with COX inhibitors and other bioactive ligands that resulted in the formation of highly active anti-cytotoxic agents. Maruyama *et al*⁽⁸⁸⁾, developed triple-action prodrugs of oxaliplatin by conjugating with COX inhibitors (COXi), histone deacetylase inhibitors (HDACi) and pyruvate dehydrogenase kinase inhibitors. The different

bioconjugated were substituted in the axial position producing very effective therapeutic agents. Platinum compound conjugated with the COX inhibitor and pyruvate dehydrogenase kinase inhibitor formed compounds 24 and 25 as shown in figure 11. The synthesis of platinum prodrugs with HDACi (histone deacetylase inhibitor) and one COXi (cyclooxygenase inhibitor) produced compounds 26, 27, 28 and 29. (Figure 11)

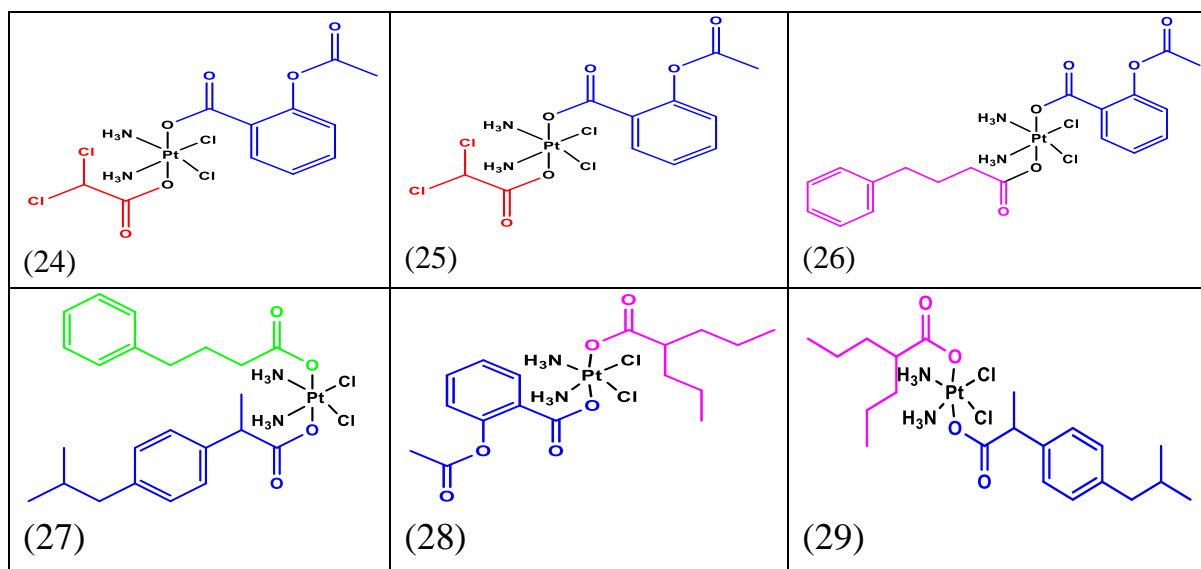


Figure 11. Triple-action prodrugs

In 2014, Pathak *et al* ⁽⁸⁹⁾, reported about the Aspirin and platinum compound that was the first reported platinum prodrug with NSAIDs. This study revealed that the aspirin-platinum complex has a similar therapeutic effect to cisplatin. Asplatin (aspirin and Cisplatin) caused the inflammatory response by suppressing the release of TNF-alpha and IL-4 factor and increasing the release of inflammatory mediators such as IL-10. Thus, the overall mechanisms of asplatin elicited dual action; anti-inflammatory and anti-cancer activity with a considerable reduction in the side effects such as ototoxicity.

Khoury *et al* ⁽⁹⁰⁾, developed a group of NSAID conjugated platinum (IV) compounds (with aspirin and indomethacin) and attempted to find out the effect of NSAIDs in the platinum-based

chemotherapeutics. The characterization was done by spectral methods and the cytotoxicity was determined by MTT assay. Further, they investigated COX-2 inhibition and cellular accumulation by using two different cell lines. The structure of the Pt (IV) prodrugs of aspirin and indomethacin were depicted in figure 12 and 13. The synthesis of the Platinum-indomethacin and aspirin prodrugs through the intermediate synthesis of the indomethacin N- hydroxy succinamide and aspirin anhydride. The study reported that the increase in the lipophilicity by RP-HPLC and also among the four synthesized compounds, the aspirin-conjugated platinum compounds have greater cytotoxicity and aspirin-conjugated prodrugs showed greater COX inhibition.

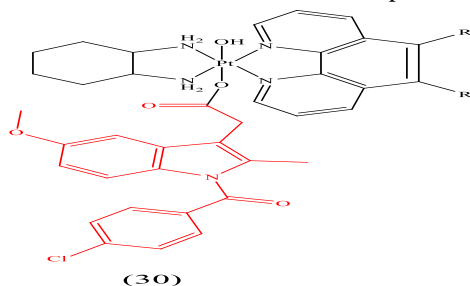


Figure 12. Structure of Indomethacin-platinum prodrugs

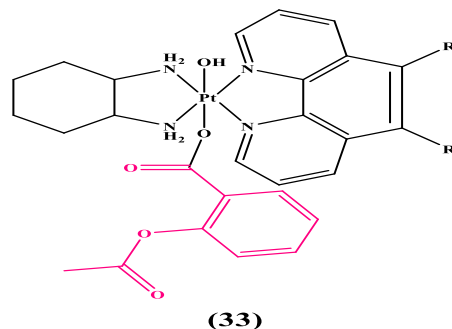
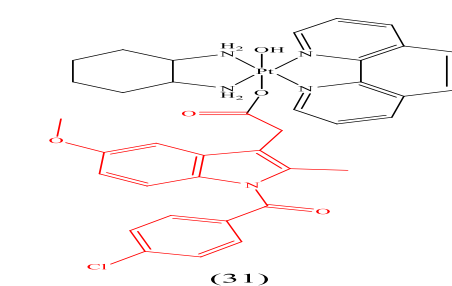
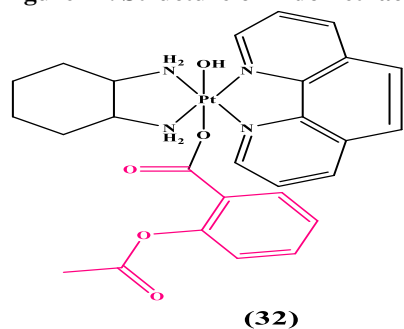


Figure 13. Structure of aspirin-platinum prodrugs

Several studies were conducted on cisplatin by conjugating with different NSAIDs such as aspirin, ibuprofen, naproxen and flurbiprofen. In 2019, Tolan *et al* ⁽⁹¹⁾, developed the prodrugs of naproxen with cisplatin, carboplatin and oxaliplatin. His study reported the novel platinum (IV) compounds – naproxen complexes, their characterization, cytotoxicity and anti-inflammatory activity. The cytotoxicity of the complexes was evaluated against breast tumors by MTT assay. The structure of the seven reported prodrugs was given

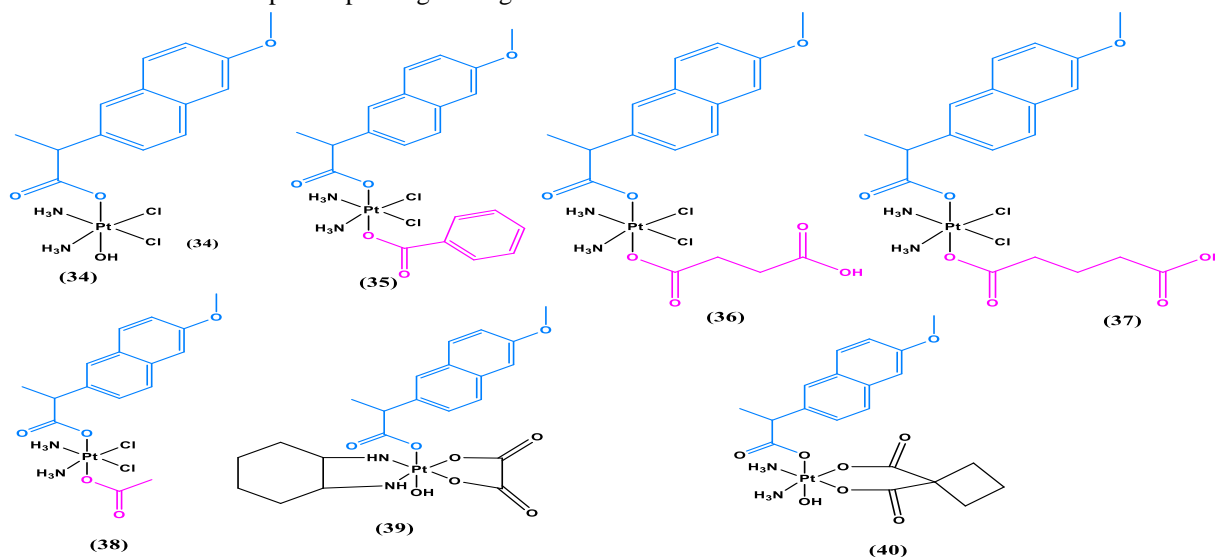


Figure 14. Chemical structures of the Naproxen-Platinum compounds prodrugs

Ravera *et al* ⁽⁹²⁾, reported that Cisplatin (Pt IV) conjugates of ketoprofen and naproxen provided synergistic anti-tumor activity and a study was conducted in various tumor cell lines. Ketoprofen and naproxen conjugates of Cisplatin resulted in dual action and effective anti-proliferative activity tested by using malignant pleural mesothelioma (MPM). This study revealed that the enhanced therapeutic activity due to the enhanced lipophilic profile thus enhanced cellular accumulation. The research work concluded that the NSAID as axial ligand enhances the lipophilic profile that leads to cellular accumulation through the NSAID activated gene-1 activation. Okamoto *et al* ⁽⁷⁸⁾, the use of diclofenac with cisplatin potentiates the anti-cancer action with the considerable reduction of the side effect ie nephrotoxicity. This study evaluated the effects of diclofenac or celecoxib on cisplatin induced nephrotoxicity and also its anti-cancer effects by using xenograft mouse models transplanted with A549/DDP cells. Li *et al* ⁽⁹³⁾, reported that the ketoprofen and loxoprofen complexes with platinum produced anti-proliferative and anti-metastatic actions. In this study, the prodrugs were investigating cyclooxygenase-2, matrix metalloproteinase-9, and programmed death-ligand-1 and reported that the compounds enhanced chronic DNA damage and

in the figure 14. This research work showed a favorable reduction pattern for complex 1 to the active Pt (II) drug with the release of the Anti-inflammatory drug naproxen. *In vitro* studies showed that the synthesized Pt (IV) complexes have thirteen-fold more cytotoxic than cisplatin by cell line studies. The Pt (IV) complexes showed Anti-inflammatory properties with remarkable NO inhibition, which indicated the reduced level of cancer associated with inflammation.

produced apoptosis of the tumor cells through mitochondrial apoptotic pathway Bcl-2-Bax-caspase-3. This approach produced a considerable immune response in tumor tissues. Many studies reported that triple-action cisplatin prodrugs are very interesting area of research and lead to the development of selective cytotoxic agents ⁽⁹⁴⁾. Hu *et al* ⁽⁹⁵⁾, developed oxaliplatin prodrugs of COX inhibitors carprofen, etodolac, ketoprofen and sulindac and reported the enhanced the platinum accumulation and cytotoxic activity.

The prodrug approach effectively synthesized the potent anti-tumor drugs with a remarkable reduction in toxicity. The NSAIDs used for the development of novel compounds were etodolac, carprofen and sulindac which lead to the synthesis of cisplatin-NSAID prodrugs. Cisplatin is a widely known anti-neoplastic agent but its application in the therapeutic field is limited due to poor solubility and toxicity. This research study revealed that NSAID conjugates have a beneficial role in the anti-tumour effect, among that etodolac prodrugs showed better pharmacological activity ⁽⁹⁶⁾.

Conclusion

This review concluded that the development of prodrugs of NSAIDs with platinum

compounds showed synergistic effects and a remarkable reduction of side effects produced by Platinum compounds. Studies reported the dual-action and triple-action prodrugs of platinum compounds with NSAIDs and other bio-conjugates. The development of platinum prodrugs by using the ligands in the axial position is a promising strategy to produce better pharmacological and therapeutic profile. Platinum compounds such as cisplatin and oxaliplatin are predominantly utilized for the synthesis of platinum prodrugs. The platinum compounds conjugated with different NSAIDs such as aspirin, naproxen, ibuprofen, flurbiprofen, diclofenac and different classes resulting in the formation of prodrugs that elicit dual action. Also, the triple action prodrugs of platinum compounds are the promising area of research and certain triple action prodrugs have reported. Development of very effective anti-neoplastic agents by using the prodrug-based approach with platinum compounds and NSAIDs is a promising area of investigation. Cisplatin and other platinum compounds conjugated with aspirin, ibuprofen, flurbiprofen, and naproxen resulting in better therapeutic activity.

Conflict of Interest

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