



Licofelone- Novel Analgesic and Anti-Inflammatory Agent for Osteoarthritis: An Overview

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ABSTRACT

Licofelone (2-[6-(4-chlorophenyl)-2, 2-dimethyl-7-phenyl-2, 3-dihydro-1H-pyrrolizin-5-yl] acetic acid) is the first member of a new class of analgesic and anti-inflammatory drugs acting by dual mechanism inhibiting both cyclooxygenase (COX) and 5-lipoxygenase (5-LOX). Inhibition of 5-LOX may reduce the gastrointestinal toxicity associated with other non steroidal anti-inflammatory drugs (NSAIDs), which only inhibit cyclooxygenase (COX). It has been evaluated for the treatment of osteoarthritis (OA), the most common form of arthritis. It has been found to be significantly effective in Phase III clinical trials conducted on patients of osteoarthritis. The present review describes the pharmacological and clinical developments of licofelone as a dual inhibitor for COX and 5-LOX.

Key words: Licofelone, analgesic, anti-inflammatory

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INTRODUCTION

Licofelone is developed by the German pharmaceutical company, Merckle GmbH, together with EuroAlliance partners Alfa Wassermann and Lacer, licofelone (ML3000). Licofelone is a dual COX/LOX inhibitor being considered as a treatment for osteoarthritis.^[1] Licofelone has both an analgesic and an anti-inflammatory action. Inhibition of 5-LOX may reduce the gastrointestinal toxicity associated with other non steroidal anti-inflammatory drugs (NSAIDs), which only inhibit COX. It has been tested in Phase III clinical trials.^[2]

The first generation of compounds showing the dual inhibition of LOX-5 and COX-2, such as Benoxaprofen,

are no longer in use due to their liver toxicity.^[3] A new generation of compounds has been developed that offers a more balanced inhibition of LOX-5 and COX-2 enzymes by acting as a substrate competitor. Licofelone is one of the most promising candidates for the treatment of osteoarthritis as an anti-inflammatory drug.^[4] Some other congener drugs in this category are Tepoxalin (ZubrinTM), Tebufelone, di-7-tert-butyl-2,3-dihydro-3, 3-dimethylbenzofuran (DHDMBF), Darbufelone, BF389, RJW63556, PGV20229, and C-1986. In humans, after oral administration of immediate release tablets, licofelone is rapidly absorbed from the gastrointestinal tract and maximum plasma concentrations are achieved approximately 2-3 h after administration. Systemic elimination follows bi-phasic characteristics with a rapid

initial decline of plasma concentration ($T_{1/2}(\alpha) = 1$ h) and a slow terminal elimination ($T_{1/2}(\beta) = 7-9$ h). In plasma, after single dosing, ML3000-1-O-acyl glucuronide (M1) and Hydroxy-ML3000 (M2) were detected as metabolites. Relative to the parent drug, the systemic exposure remained below 2%. After repeated administration, at steady-state, the exposure of M2 increased to approximately 20% relative to that of the parent drug and the rate of systemic elimination was below that of the parent drug (monophasic, $T_{1/2} = 10-12$ h). In contrast, M1 remained at the level of a trace metabolite. In that respect, the disposition of licofelone in humans is different from all standard animal species (mouse, rat, dog, monkey) in which systemic concentrations of M2 were negligible even upon chronic dosing. A further hydroxy metabolite of licofelone is M4. This compound

was initially identified in microsomal experiments but not in plasma samples from humans after single and repeated administration of therapeutic doses, i.e., 200 mg or 400 mg b.i.d. relevant concentrations were determined in plasma samples from subjects who were treated with increasing doses in order to determine the maximum tolerated dose. The chemical structures of licofelone and its metabolites are shown in Figure 1. The results from *in vitro* metabolism studies are presented, which demonstrate that in humans hydroxylation of the glucuronide M1 represents the pivotal step in the biosynthesis of M2. Although the cytochrome P-450 (CYP)-dependent hydroxylation of glucuronides has been described in literature,^{5,6} the formation of M2 represents 6 of 40 unique examples as the systemic exposure of humans to this major metabolite is based

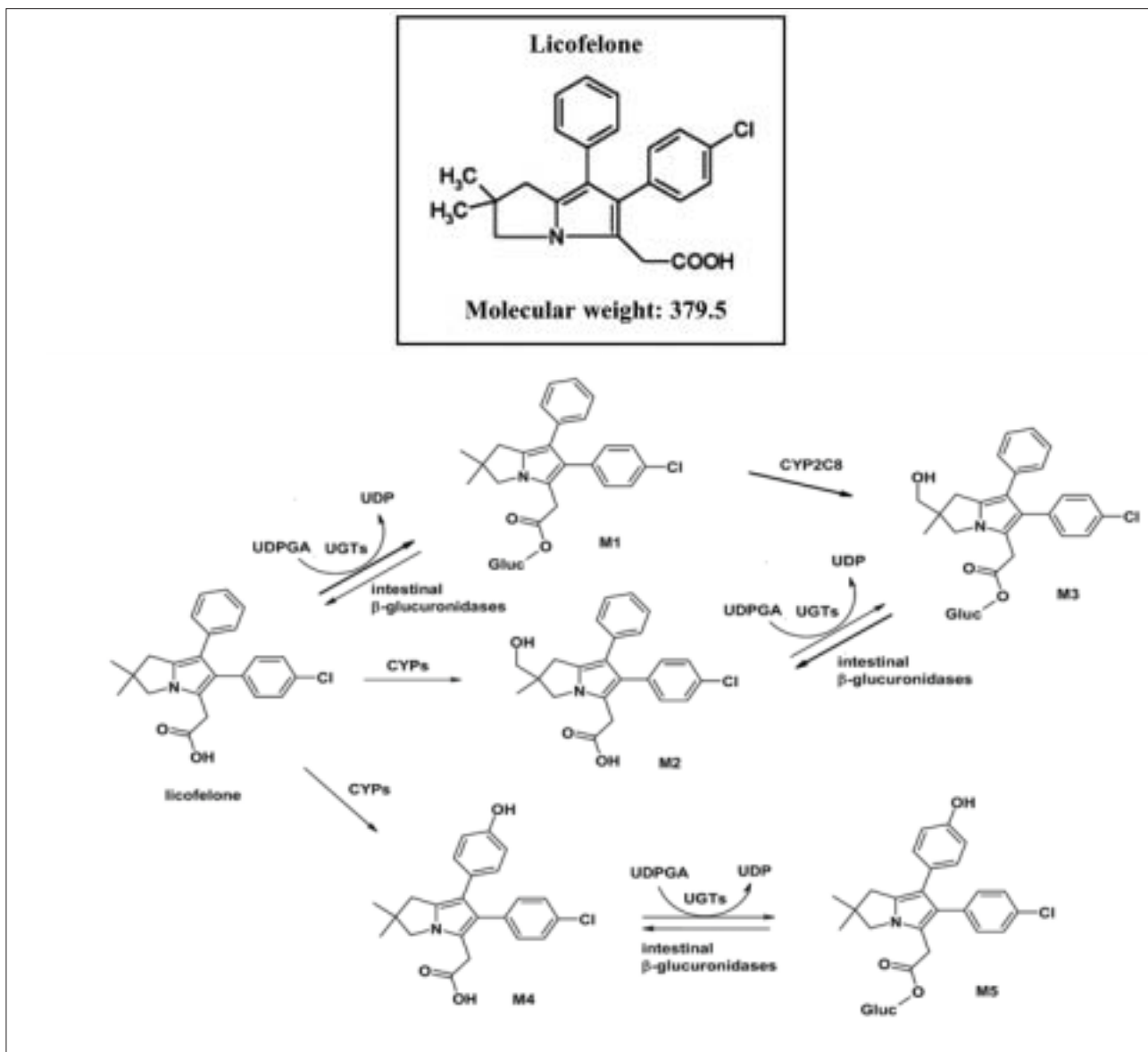


Figure 1: Chemical structure of licofelone and its proposed biotransformation pathway

on the glucuronidation of the parent drug followed by hydroxylation of the glucuronide.^[7]

Licofelone inhibits LOX-5, COX-1, and COX-2, decreases production of PGs and LTs,^[8,9] and presents lower GI toxicity compared with NSAIDs naproxen and rofecoxib.^[10-12] Interestingly, it has been reported recently that Licofelone inhibits LOX/COX pathways and induces apoptosis in HCA-7 colon cancer cells.^[13] Licofelone, designed to aim at a dual inhibition of the LOX and COX pathways, has proved to be effective in reducing growth in cancer cell lines. Interestingly, a recently published report that uses a mathematical model to study the interactions of the AA metabolic network, has revealed that a dual inhibitor against LOX/COX is more effective than a combination of single COX and LOX inhibitors.^[14,15]

Osteoarthritis (OA), a crippling disorder, is becoming an increasingly significant medical problem with the increase in the human lifespan. Presently, approximately 10% of the world's population is suffering from OA. OA is the leading cause of disability among the elderly population, yet the etiology, pathogenesis, and progression of this disease are still not fully understood.^[16,17] OA has a multifactorial origin and is slowly progressive. The disease process can be described as degradation and loss of articular cartilage accompanied by hypertrophic bone changes, with osteophyte formation and subchondral plate thickening. The process includes changes in articular cartilage and surrounding bone, an imbalance in the loss of cartilage (due to matrix degradation), and an attempt to repair this matrix.^[18,19] Specific interactions between the bone and cartilage in OA have not been clearly defined; however, mounting evidence indicates a direct role of the bone compartment in the initiation/progression of OA.^[20-22]

Arachidonic acid is released from membrane phospholipids following activation of phospholipase A₂. Several enzymatic complexes can further metabolize arachidonic acid into a number of prostanoids by specific syntheses in different cells,^[23] and osteoblasts mainly produce prostaglandin E₂ (PGE₂).^[24] The enzyme 5-lipoxygenase (5-LOX) catalyzes the formation of leukotrienes (LTs) from arachidonic acid. The first compound formed is LTA₄, which rapidly converts into LTB₄ or LTC₄. LTC₄ can be further catalyzed into LTD₄ and LTE₄.^[25,26]

Conventional NSAIDs inhibit cyclooxygenase 1 (COX-1) and/or COX-2, the key enzymes that metabolize arachidonic acid into prostaglandins and thromboxanes.^[27,28] Reduction of prostaglandins and thromboxane is probably the basis for the anti-inflammatory and analgesic activity

of NSAIDs, which are widely used for the treatment of OA. However, side effects have limited the utility of these drugs. The most common side effects are gastrointestinal and range from mild symptoms such as dyspepsia and abdominal discomfort to more serious events such as peptic ulcers and life-threatening gastric/duodenal bleeding and perforation.^[29] Long-term inhibition of COX could result in a shunt to the 5-LOX pathway leading to the formation of leukotrienes, which can induce gastric lesions and ulceration. Therefore, NSAIDs targeting both the COX and 5-LOX pathways may control the symptoms of OA without causing serious gastrointestinal side effects.^[30,31] Moreover, whether a shunt to the 5-LOX pathway and local production of leukotrienes in joint tissue are detrimental to tissue such as the subchondral bone compartment remains unknown.

Osteoblasts produce prostaglandins via both COX-1 and COX-2 activities.^[32,33] Prostaglandins stimulate bone resorption by increasing the number and activity of osteoclasts, and PGE₂ is the most potent agonist.^[34] The roles of a number of stimulators of formation of tartrate-resistant acid phosphatase-positive giant cells with osteoclast features are blocked by inhibiting endogenous prostaglandin synthesis.^[35-37] Prostaglandins also enhance bone formation by stimulating the replication and differentiation of osteoblasts along with an increase in the production of growth factors.^[38] In fully differentiated osteoblasts, a high concentration of prostaglandins can inhibit collagen synthesis.^[39] Prostaglandins may also mediate the response to mechanical forces in bone, because bone formation stimulated by impact loading can be blocked by NSAIDs.^[40]

Osteoblasts also synthesize leukotrienes *in vivo*, although their *in vitro* production has not been studied. Moreover, the exact levels of PGE₂ and leukotrienes observed *in vivo* in OA bone tissue are controversial^[41,42] and the levels of leukotrienes produced *in vitro* by OA osteoblasts have not been evaluated. Finally, whether leukotrienes may modulate the activity of OA osteoblasts and/or be involved in OA pathogenesis remains to be determined.

Licofelone distinctly differs from NSAIDs since it inhibits not only COX but also 5-LOX, which is associated with the production of pro-inflammatory and gastrototoxic leukotrienes. Inhibition of COX alone by NSAIDs is expected to shunt arachidonic acid metabolism to 5-LOX pathway leading to increased production of gastrototoxic leukotrienes.^[43] Thus, inhibition of 5-LOX in addition to COX is a new opening for having an agent possessing anti-inflammatory properties with reduced gastric toxicity. In

fact, 5-LOX now stands implicated in the deterioration of joints in OA. Inhibition of 5-LOX, therefore, can be said to protect cartilage and connective tissue from damage and also slow the progression of the disease.

Leucotriene-B₄ (LTB₄) protects the 5-LOX pathway. It has been shown to regulate the synthesis of interleukin-1 β (IL-1 β) by synovium. Excess production of LTB₄ leading to up regulation of IL-1 β synthesis in the synovium during osteoarthritis has been shown to be responsible for damage to the joints and progression of disease. NSAIDs by inhibiting only COX pathways are expected to make arachidonic acid more available for the formation of LTB₄ and thereby of IL-1 β . This also explains how some NSAIDs accelerate the progression of OA. A recent study has reported that reduction of structural changes by licofelone in OA is associated with the reduction of synthesis of LTB₄ and IL-1 β synthesis in the synovium.^[44] The occurrence of structural changes during the course of OA are related, besides the above factors, a number of complex pathways and mechanisms including the excessive production of proteolytic enzymes that can degrade the cartilage matrix and soft tissue around the joint. Among the proteolytic enzymes, the matrix metalloproteinase's (MMPs), especially MMP-13, Aggrecanase 1 & 2, and a cathepsin are the ones most likely to be involved in the degradation of cartilage. In a study focused on the effects of licofelone on the gene expression and protein synthesis of the major collagenolytic enzymes (MMP-13, aggrecanase & cathepsin K) in OA cartilage in an experimental model, licofelone has been found to markedly reduce the mRNA expression/synthesis of the above noted enzymes and prevent the death of chondrocytes indicative of a promising disease-modifying effect of licofelone in OA.^[45]

In summary, it is to be noted that licofelone, as a first member of a new class of COX and 5-LOX inhibitors, possesses analgesic and anti-inflammatory activities with a mechanism of action attributable to the inhibition of LTB₄, thereby IL-1 β arrests the production of proteolytic enzymes responsible for damaging the structural changes of joints. Thus, licofelone, by arresting the pathophysiology of OA, is going to be an ideal disease-modifying drug with better tolerability and acceptability.

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Licofelone- Novel Analgesic and Anti-Inflammatory Agent

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