CREATION OF ANTI-INFLAMMATORY PHARMACEUTICAL COMPOSITIONS (review)

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Abstract

The review article summarizes the data of literature and our own research on the creation of more effective and safe domestic combined drugs with a pronounced anti-inflammatory and analgesic effect. Untimely treatment of inflammatory processes often leads to long-term incapacity and even disability, so today there is an active search for new effective and safe domestic combination drugs with pronounced anti-inflammatory and analgesic effects. Due to the constant search for innovative drugs the treatment of a significant number of diseases and pathological conditions with existing drugs remains ineffective or causes addiction and a large number of side effects. As a result, inflammatory processes can be accompanied by severe pain, spasms, increased convulsive activity of the brain, other disorders, so non-narcotic analgesics and nonsteroidal anti-inflammatory drugs are combined with other agents that can cause complementary effects or potentiate each other's effects. Caffeine is a useful adjuvant of nonsteroidal anti-inflammatory drugs of various chemical structures in terms of anti-inflammatory and analgesic effects. The article presents a literature review of the current state of treatment of inflammation and pain, conducting research to expand the therapeutic capabilities of known pharmaceuticals, the creation of pharmaceutical compositions of nonsteroidal anti-inflammatory drugs with caffeine.

Keywords: *pain, inflammation, caffeine, non-narcotic analgesics, nonsteroidal anti-inflammatory drugs, pharmaceutical composition.*

The efficiency and continuous development of medical science involves the search for new drugs, as well as research to expand the therapeutic potential of known pharmaceuticals. An urgent problem at the present stage of development of medicine and pharmacy is the creation of new domestic combined drugs, the pharmacological effects of which are achieved through a rational combination of ingredients. The pharmaceutical composition of several components in one drug expands its pharmacological spectrum [1–4].

The combination of ingredients in multicomponent pharmaceutical compositions mutually enhances their pharmacological effects. Clinical studies have confirmed the advantages of combined drugs over single drugs for the pharmacotherapy of pain syndromes, inflammatory processes as they are more effective than each individual component [2]. Such pharmaceutical compositions make it possible to add to the composition of drugs active pharmaceutical ingredients in smaller doses, reducing toxicity and adverse side effects [3].

Recently, the world has seen an increase in the incidence of diseases accompanied by inflammatory processes, and their level continues to grow every year. Inflammation underlies most pathological processes and is the basis of more than 70% of known human diseases [1–4]. Inflammation as a typical pathological process developed in the process of evolution and occurs in response to any damage to body tissues. It is aimed at localization, destruction and removal from the body of pathogenic factors that cause inflammation, as well as to eliminate the consequences of their action. The cause of inflammation can be any factor or factor that can cause tissue damage (inflammatory agent or phlogogen (Greek *Phlogogen*, a substance, causing inflammation)) [5]. Classification of causes of inflammation depends on the nature and origin of phlogogenic factors [6].

Inflammatory processes can be accompanied by severe pain, spasms, increased convulsive

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activity of the brain, other disorders of the body, so non-narcotic analgesics (NNAs) and nonsteroidal anti-inflammatory drugs (NSAIDs) are combined with other drugs that can cause complementary effects or potentiate each other's effects.

Pharmacological regulation of pain is one of the most pressing problems of modern medicine [7]. Prevention and treatment of pain requires the use of drugs mainly from the group of analgesics. Pain is a clinical manifestation of inflammation and the main complaint of the patient with various inflammatory diseases.

In addition, long-term and combined use of non-narcotic analgesics and NSAIDs increases the incidence of complications of anti-inflammatory pharmacotherapy. Side effects of NSAIDs necessitate the search for safer anti-inflammatory drugs. Selective cyclooxogenase-2 (COX-2) inhibitors developed in recent years, which were supposed to solve the problem of NSAID side effects on the gastrointestinal tract, did not live up to the expectations of pharmacologists. Doses in which selectivity is maintained do not show sufficient clinical effect, and increasing the dose leads to loss of selectivity and gastrotoxicity.

Currently, there is an arsenal of modern NSAIDs, which are used to treat many diseases, ranging from fever to severe autoimmune processes [8]. But the current wide range of anti-inflammatory drugs does not solve the problem of successful treatment of inflammatory diseases and their recurrence, the frequency of which after discontinuation of drugs occurs in almost 100% of cases and whose use is complicated by many side effects [9].

Therefore, despite the saturation of the pharmaceutical market of Ukraine with NSAIDs, the search for new safe domestic drugs for the treatment of inflammatory processes that would be more effective and less toxic today remains relevant.

The group of traditional NSAIDs includes drugs that have different chemical structure and differ in the intensity of analgesic, antipyretic and anti-inflammatory effects and the frequency of side effects. General availability, fast and tangible analgesic effect, ease of use and the availability of a large number of dosage forms allows patients to use drugs without consulting a doctor, and this leads to their uncontrolled use [10]. Therefore, treatment with known non-narcotic analgesics or NSAIDs can worsen the quality of life of patients, and the lack of treatment of inflammatory processes, which is often accompanied by pain, leads to long-term disability and even disability [11].

NSAIDs are among the most commonly used symptomatic drugs. They are used to treat rheumatic diseases, deforming osteoarthritis, neuralgia and myalgia, osteochondrosis, cardiovascular disease, febrile conditions of infectious-inflammatory origin, headache and toothache and many other pathological conditions accompanied by inflammation and pain [12]. The dominant pharmacological effect of drugs in this group is anti-inflammatory action, which in its level is close to the action of anti-inflammatory drugs of steroidal structure (glucocorticoids and their synthetic analogues).

According to modern ideas, non-narcotic analgesics and NSAIDs have a complex mechanism of influence on various parts of the inflammatory response. The vast majority of non-narcotic analgesics and NSAIDs have been shown to indiscriminately inhibit the activity of COX-1 and COX-2 cyclooxygenase enzymes, which catalyze the production of prostaglandins from arachidonic acid and thus reduce inflammation and relieve pain. The therapeutic effect of NSAIDs is realized by inhibiting the activity of COX-2, and the main side effects occur due to inhibition of COX-1 [13, 14].

Simultaneously with the study of the clinical efficacy of the first NSAID salicylic acid, the first reports of its adverse effects on the gastrointestinal tract began to appear. Gastrointestinal complications are among the most common and dangerous side effects of NSAIDs [13]. The term "NSAID-gastropathy", introduced in 1986 by S.H. Roth, means erosive-ulcerative gastrointestinal lesions on the background of NSAIDs. NSAID gastropathies have some features: the appearance of ulcers on the background of NSAIDs, acute multiple erosions or ulcers, localization of ulcers in the antrum of the stomach, little or no asymptomatic course, frequent manifestations, disappearance after discontinuation of the drug. There are several factors that increase the risk of NSAID gastropathy: age (over 60 years), history of gastrointestinal pathology, high doses or concomitant use of multiple NSAIDs, concomitant use with glucocorticoids, long-term use of NSAIDs (over 3 months), therapy anticoagulants and/or antiplatelet agents [14–18]. NSAIDs are also characterized by a number of other side effects: sodium and water retention and, as a consequence, increased blood pressure; tendency to bleed; allergic reactions (bronchospasm, anaphylactic shock, Quincke's edema), etc. It is also known that renal dysfunction may be due to both the inhibitory effect of NSAIDs on the synthesis of vasodilators

prostaglandins and their nephrotoxic effect [16]. Liver damage from NSAIDs can be caused by both immune processes and their toxic effects. Almost all NSAIDs are able to change the dynamics of drugs of other pharmacological groups and are themselves under no less active influence from them. The use of NSAIDs should take into account the possibility of their interaction with other drugs, especially with indirect anticoagulants, antiplatelet agents (bleeding tendency), diuretics, antihypertensive drugs (reduced effectiveness of antihypertensive drugs) [17]. It is known that in patients with chronic heart failure NSAIDs may increase the incidence of decompensation due to reduced therapeutic effect of angiotensin-converting enzyme inhibitors and diuretics [18–20].

There is no doubt about the need for widespread use of NSAIDs, which is largely due to the rejuvenation of rheumatic diseases, increasing the number of patients with cardiovascular risks who take acetylsalicylic acid in low doses for a long time and others. In addition, these drugs are available, mostly available without a prescription. The clinical effect provides reliable compliance. The problem of eliminating the side effects of NSAIDs remains unresolved. In recent years, the mechanisms of gastroprotection and in particular the mechanisms of adaptation of the mucous membrane to the adverse effects of NSAIDs have been actively studied. Scientific research is aimed at studying the state of blood circulation, mechanisms of angiogenesis, balance of proliferation and apoptosis of gastric epitheliocytes, epidermal and transforming growth factors. However, despite the constant interest in studying the nature and characteristics of gastropathies, the problem of safe use of NSAIDs remains relevant, will require further research and new research, which will allow in the near future to create new effective and safe drugs that will improve patients' quality of life, safe even with long-term, if necessary, lifelong use. Modern ways to reduce the ulcerogenicity of NSAIDs (changes in tactics, combination with prostaglandins` analogues, H2-histamine blockers, proton pump inhibitors, drugs with antihypoxant and antioxidant activity) do not solve this problem. Therefore, the search for reliable and safe drugs remains an urgent problem.

Scientists have studied COX and found that this enzyme, which is detected in different tissues, usually shows a different spectrum of sensitivity, which allowed us to make assumptions about the existence of isoforms of the enzyme [21]. In the early 1990s a group of scientists led by J. Wayne found two isoforms of the enzyme COX in the body at the same time. The constructive isoform of COX-1 is responsible for the synthesis of prostaglandins, which are involved in the protection of the gastrointestinal mucosa, regulation of platelet function and renal blood flow, i.e., performs important physiological functions in the body [22]. The researchers also found COX-1 to be mostly in the cytoplasm or associated with the endoplasmic reticulum. Induced COX-2 is involved in the synthesis of prostaglandins in inflammation [23–30].

Depending on the nature of COX blockade, NSAIDs are divided into selective and non-selective COX inhibitors. Classification of NSAIDs depending on their ability in therapeutic doses to selectively block the activity of COX-1, COX-2 and COX-3 [30] is presented in *Table 1*.

Table 1. Classification by the mechanism of inhibition of COX activity [30].

Group of drugs	Drugs
Selective COX-1	Low doses of acetylsalicylic acid
Non-selective COX-1 and COX 2 inhibitors	Diclofenac, ketorolac, ibuprofen, naproxen, ketoprofen, indomethacin, etodolac, aspirin, paracetamol, metamizole, piroxicam and most other modern NSAIDs
Selective COX-2 inhibitors	Lornoxicam, meloxicam, nabumetone and nimesulide
Highly selective COX-2 inhibitors	Parecoxib, rofecoxib, celecoxib, etoricoxib
COX-3 inhibitors	Paracetamol

Traditional NSAIDs include non-selective COX-1 and COX-2 inhibitors. Selective COX-2 inhibitors have less effect on COX-1. Highly selective COX-2 inhibitors (coxibs) have virtually no effect on COX-1. Modern views on the mechanism of action of paracetamol are based on the fact that it is not a typical NSAID due to the fact that it blocks COX-3, which is synthesized in the CNS [31–37]. In addition to affecting prostaglandins synthesis, NSAIDs affect various links in the pathogenetic chain of inflammation – inhibit lipid peroxidation, stabilize lysosomal membranes, etc. [38].

Literature sources analysis showed that combined anti-inflammatory and analgesic drugs often include 1,3,7-trimethylxanthine – caffeine, $C_8H_{10}N_4O_2$ (*Fig. 1*) [39–40].

Caffeine is an alkaloid of the purine series, colorless or white bitter crystals. The structural struc-

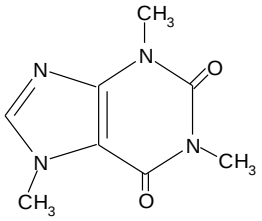

Fig. 1. Caffeine (1,3,7-trimethylxanthine).

ture is a heterocyclic alkaloid of the purine series. It was first extracted from coffee extract in 1821. It is known to be a psychostimulant, found in coffee, tea, energy and many beverages. Caffeine is found in plants such as coffee, tea, cocoa and others [41–52].

According to the literature, caffeine is known to have a positive effect on the bioavailability of NSAIDs and non-narcotic analgesics. As a result, the anti-inflammatory and analgesic effects of these drugs increase [41, 42]. Enhancement of the analgesic effect of non-narcotic analgesics is associated with caffeine induction of central cholinergic analgesia [43, 45], structural similarity of adenosine and caffeine molecules, which contributes to the neurochemical mechanism of action of the latter in the form of blocking P1 "purine" brain receptors [47].

At the Department of Medical and Bioorganic Chemistry of KhNMU the created pharmaceutical compositions of NSAIDs of different chemical structure (analben (potassium salt of 2,4-dichlorobenzoic acid), acetic acid derivative – diclofenac-sodium (2-[(2,6-Dichlorophenyl)amino]benzeneacetic acid sodium salt), a derivative of propionic acid – ibuprofen (((±)-2(4-isobutylphenyl)-propionic acid), a derivative of amino-phenol – paracetamol (N-(4-hydroxyphenyl)acetamide), oxycams – NSAIDs are derivatives of pyridin-2-ylamide 3-carboxylic acid: meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) and piroxicam (4-hydroxy-2-methyl-N-2-pyridinyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide), a secondary analgesic – carbamazepine (5H-dibenz-[b, f]-azepine-5-carboxamide)) and others with caffeine were studied. Our long-term research has shown that caffeine enhances the pharmacological effects of NSAIDs of different chemical structure and analgesics [41–52], so we believe that caffeine is a suitable adjuvant of NSAIDs of different chemical structure in terms of anti-inflammatory and analgesic effects [41–52]. Due to the fact that pharmaceutical compositions with coxibs are not available on the pharmaceutical market, we decided to create such pharmaceutical compositions and investigate the above types of biological activity.

The main advantage of coxib drugs compared to other NSAIDs is their much smaller negative impact on the gastrointestinal tract. The objects of our research in the framework of the departmental initiative research work "Chemical-pharmaceutical substantiation of biologically active compounds, conjugates and drug compositions with anti-inflammatory and analgesic activities", we chose celecoxib and rofecoxib [19, 22]. These drugs belong to the group of highly selective inhibitors of COX-2 and their pharmacological action is to inhibit the biosynthesis of prostaglandins – mediators of pain and inflammation [19]. Since COX-2 is the main trigger of inflammation and neoangiogenesis, these signs accompany a wide range of pathological conditions and diseases [22]. Therefore, the therapeutic properties of celecoxib, which is very widely used, in particular, have been studied in all areas of medical practice [18]. Celecoxib has shown a high therapeutic effect in the treatment of acute pathologies of the musculoskeletal system, surgery, post-traumatic stress disorder [18, 19]. This drug is used in rheumatology [22] and even as an urgent analgesic. Positive results have been obtained in the treatment of celecoxib even schizophrenia [53]. Due to the antitumor effect the drug is used in oncology. Celecoxib is one of the few NSAIDs that can be taken for a long time [53–72] because it is well tolerated and virtually free from the risk of complications from both the gastrointestinal tract and the cardiovascular system [22].

The chemical structure of coxibs is based on the structure of benzenesulfonic acid. Celecoxib is 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (*Fig. 2*):

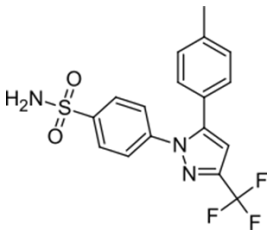

Fig. 2. Celecoxib (4-(5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide), $C_{17}H_{14}F_3N_3O_2S$.

Rofecoxib [[4-[4-(Methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone]) is an NSAID, a synthetic drug of the coxib group. In its structure it contains a side sulfone chain (*Fig. 3*):

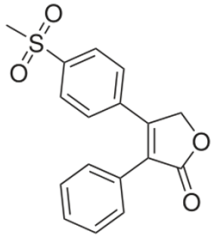

Fig. 3. Rofecoxib ([4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone]), $C_{17}H_{14}O_4S$.

Rofecoxib is also widely used in clinical practice in Ukraine [58]. The mechanism of its pharmacological action is identical to highly selective NSAIDs [22]. The drug is highly effective as an analgesic and antipyretic in the treatment of rheumatic conditions, dysmenorrhea [58] and migraine [59]. In the treatment of musculoskeletal disorders, it shows not only anti-inflammatory and analgesic, but also chondroprotective properties [59–61]. Oncologists note the positive effect of rofecoxib on the course of familial pollinosis, colon cancer in combination therapy of these diseases. Rofecoxib has a positive effect on the course of neurodegenerative processes [61]. There are no combined drugs based on celecoxib and rofecoxib in the arsenal of pharmaceuticals, so we have created such pharmaceutical compositions and are conducting research on them.

Studies of domestic and foreign scientists in recent years indicate the prospects for the search for biologically active molecules among the derivatives of 1,2,4-triazole [62–72]. It should be noted that drugs derived from 1,2,4-triazole are among the 200 drugs with the highest sales (alprozalam, trazodone, fluconazole).

The viability of this heterocyclic system is due to many factors: high reactivity, low toxicity, availability of reagents for synthesis, solubility in most solvents and, especially, a wide range of biological activity. Amino derivatives of 1,2,4-triazole and 1,2,4-triazole-3-thione provide great opportunities for the search for biologically active compounds [62–72].

Compounds of this class have proven to be low-toxic and highly effective substances [62–72]. Relying on data on the high pharmacological activity of various 4-R-3-thio-1,2,4-triazoles and their derivatives with analgesic, antibacterial, antiviral, antifungal, anti-inflammatory, antitumor, anticonvulsant, antituberculous effects, which is covered in the works of O. I. Panasenko, E. Knysha, J. B. Polya, A. Kumar, etc., and taking into account the insufficient amount of data on the pharmacological properties of 3,4,5-trisubstituted 1,2,4-triazole, we considered it appropriate to obtain substances with improved pharmacological activity and increased safety, which would be the basis for the creation of original drugs. Thus, the heterocyclic system of 1,2,4-triazole is a promising fragment for the synthesis of new biologically active substances with different types of pharmacological action, in particular with anti-inflammatory and analgesic effects [62–72].

The study in the framework of PhD dissertation of the senior lecturer of the Department of Medical and Bioorganic Chemistry of KhNMU N. M. Chalenko involved an assessment of literature sources on the synthetic and biological potential of 4-amino-3-thio-5-R-4H-1,2,4-triazoles and selection of the basic structures that are the most promising for modification and production of new biologically active substances, determination of the optimal directions of structural modification and elaboration of new derivatives on the grounds of basic structures, for which virtual screening was performed and compounds with the highest predicted anti-inflammatory activity were selected for synthetic studies, a synthesis of starting compounds 4-amino-3-thio-5-R-4H-1,2,4-triazoles, proposal of optimal conditions for their alkylation with chloroacetic anilides to obtain a number of 4-amino-(1H-pyrrol-1-yl)-5-R-4H-1,2,4-triazol-3-ylthio-acetanilide, a modification of the amino group in the synthesized substances; modeling of structures and purposeful synthesis of new surfactants based on 4-amino-3-thio-5-R-4H-1,2,4-triazoles along with a study of their reactivity, physicochemical, anti-inflammatory and analgesic properties with a search of structures with the most promising compounds of anti-inflammatory and analgesic action [62, 63].

According to the results of pharmacological screening, 15 "hit compounds" with anti-inflammatory activity from the group of 4-amino-(1H-pyrrol-1-yl)-5-R-4H-1,2,4-triazol-3-ylthio-acetanilide, for which the laws of connection "chemical structure-antiexudative and analgesic activity" in a number of synthesized derivatives were established.

Based on SAR-analysis, recommendations for the rational design of NSAIDs in the group of 4-amino-(1H-pyrrol-1-yl)-5-R-4H-1,2,4-triazole-3-ylthio-acetanilides [62, 63]. According to the results of pharmacological screening of analgesic and antiexudative activities [64], 3 new "leader compounds" were selected for further experimental studies (*Fig. 4–6*):

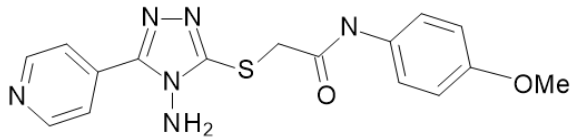

Fig. 4. N-(4-methoxyphenyl) -2- [4-amino-5-(pyridin-4-yl) -4H-1,2,4-triazol-3-ylthio] acetamide (Compound 1).

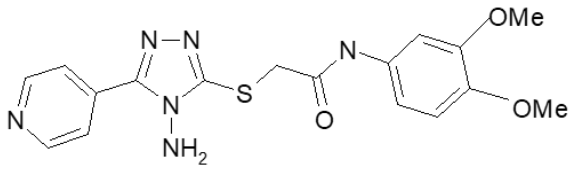

Fig. 5. N-(3,4-dimethoxyphenyl) -2- [4-amino-5-(pyridin-4-yl) -4H-1,2,4-triazol-3-ylthio] acetamide (Compound 2).

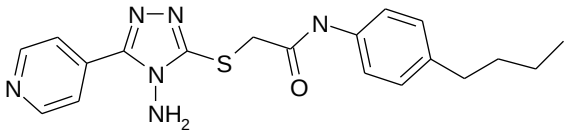

Fig. 6. N-(4-butylphenyl)-2- [4-amino-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-ylthio] acetamide (Compound 3).

Based on these 3 new "leader compounds", we have also created pharmaceutical compositions with caffeine adjuvant. We see the prospect of increasing efficiency, reducing toxicity and side effects in the development of pharmaceutical compositions based on coxibs (rofecoxib and celeco¬xib) and caffeine and derivatives of 4-amino-(1H-pyrrol-1-yl)-5-R-4H-1, 2,4-triazole-3-ylthio-acetanilides and caffeine, which is what the staff of the Department of Medical and Bioorganic Chemistry [62–63].

Thus, the review of literature sources, including our own experimental studies, indicate the prospects for the development of two-component pharmaceutical compositions based on NSAIDs of different chemical structure and derivatives of 4-amino-5-(pyridin-4-yl)-1,2,4-triazole(4H)-3-yl-thioacetanilides. As an adjuvant, it is advisable to choose 1,3,7-trimethylxanthine (caffeine). This is the basis for the creation of new domestic two-component pharmaceutical compositions with anti- inflammatory and analgesic effects.

DECLARATIONS:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

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Data Transparency

The data can be requested from the authors.

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