

Uracil as the basis for medication creation

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ABSTRACT

The article under review is dedicated to the main biochemical and pharmacological properties of uracil. The pharmacodynamics of its derivative methyluracil in different medications is highlighted. It also focuses on the antineoplastic activity mechanisms of fluorouracil and its derivatives containing fluorine. Furthermore, the cardiotropic, antihypoxic and antiviral properties of the uracil-based compounds are described.

KEYWORDS: uracil, methyluracil, fluorouracil, anti-inflammatory, antineoplastic, cardiotropic, antiviral action, new uracil-based compounds.

INTRODUCTION

Uracil is a pyrimidine nitrogenous base [2,4-dioxypyrimidine], which is the essential part of the ribonucleic acid nucleotide. It possesses amphoteric properties, and is subject to tautomerism; that is, it exists in tautomeric forms - lactims or lactams. At pH 7-9, the lactam form of uracil predominates. It was first identified in the nucleic acid-splitting products of yeast in 1902 [1].

The method of uracil formation remained unknown for a long time, although it was established that some forms of *Neurospora* are able to synthesize uracil from oxaloacetic acid. Moreover, these organisms turned out to be capable of producing uracil from orotic acid (vitamin B₉) which belongs to carboxyuracil according to its composition

(orotic acid is present in the blood colostrum). A study on *Lactobasillus fulguricus* indicated that orotic acid was the source of uracil; this was proved by adding uracil to the growth medium labeled with the radioactive carbon in orotic acid position 2. Further studies conducted proved that orotic acid is used for uracil synthesis not only by bacteria but by animals as well [2].

Also, some minor pyrimidine bases such as dihydrouracil, pseudouracil, methyluracil, carboxyuracil, and thiouracil, which account for 10% of all the tRNA nucleotides, have been identified; they are of great physiological importance since they are the ones that protect the RNA molecule from the effect of hydrolytic enzymes.

1. Specific regenerative features of uracil-based compounds

Among the minor nitrogen bases methyluracil is used in medical practice. Methyluracil improves tissue metabolism, regeneration, possesses anabolic/anti-catabolic effects and activates leucopoiesis. In case of local (topical) administration, this drug possesses photoprotective effect; it increases tissues granulation and epithelization. The anabolic effect of methyluracil is associated with the increase in hypophyseal prolactin production [3]. It has been established that methyluracil normalizes nucleic metabolism, accelerates cell regeneration (recovery) and inhibits the proteolytic enzyme activity as it possesses anti-inflammatory effect.

Organs traumatized by wounds and burns are characterized by the violation of tissue respiration, and accumulation of active forms of oxygen and

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acyl hydroperoxide. The very antioxidant-specific features of 4-methyluracil determine its regeneration properties. The decrease in the levels of free radical oxidation products is observed not only in the wounded tissues, but in the blood serum as well, which proves the wound-healing and antioxidant properties of 4-methyluracil [4]. In patients with chronic neurodermatitis 4-methyluracil increased the number of T-lymphocytes and their functional activity, reducing itching, redness, infiltration, and lichenification [5]. The ability to stimulate erythropoiesis and specifically Willebrand factor is the typical characteristic feature of the drug [6].

Methyluracil 10% ointment, a domestic drug that has anti-inflammatory and immunostimulatory effect, improves trophic tissues, and stimulates regeneration [7]. It has been established that it promotes thermal burn healing in rats and lowers the content of cytokines IL-1 β and IL-8 to normal level on day 14 and tumor necrosis factor alpha on day 21 [8]. In the case of local ultra-violet irradiation of guinea pig skin in the background of proliferative hyperplastic and degenerative process development, the application of methyluracil 10% ointment as a curative and preventive treatment reduced the erythema duration, the intensity of hyperplastic and degenerative changes in the epidermis, and the inflammatory and proliferative changes in the dermis within the post-operative period [9]. Methyluracil ointment administration during the post-operative period led to the decrease in nitric oxide metabolites, the rate of which was provoked by the irradiation [10]. In the case of the non-specific vulvovaginitis treatment, methyluracil ointment with myramistin is recommended as methyluracil also stimulates the metabolic processes, while myramistin is an antiseptic with antifungal and antimicrobial effects [11].

Also, the low-toxic water-soluble methyluracil-6 and its derivative compounds in complexes with succinic and fumaric acids have been synthesized; their anti-hypoxic action has been defined [12]. The obtained oxymethyluracil has antioxidant and immunomodulatory effects, and shows reparative activity [13].

New uracil-based compounds, such as 5-hydroxy-6-Methyluracilum, 6 aminouracil, 5-hydroxy-6-methyl-1 (thietanil 3) uracil, suppressed the

generation of active oxygen forms in modeled systems, including blood cells, which indicates free radical oxidation inhibition. Also, the stimulating effect of the drugs 6 methyluracil, 5-bromo-6- methyluracil, 6-methyl-5-piperidino-methyl-1-(3-thietanil) uracil, and NN1- β (6-methyl-1 (thietanil- 3) uracil-5-methyl) piperazine on oxygen-dependent mechanism of phagocytosis has been established [14].

2. Application in gastroenterology

Methyluracil tends to raise phytocytosis and antibody production, thereby increasing the resistance of tissues to pathological effects and improving the hepatocyte function. The drug is successfully used in the treatment of digestive system disorders such as esophagitis in the background of chronic gastritis, duodenitis, peptic ulcers, stomach and duodenum erosion. An experiment showed the ability of methyluracil to stimulate regenerative processes in the pancreas, and to inhibit the activity of lipid peroxidation, trypsin, and lipase acute pancreatitis. In patients with chronic enteritis, methyluracil, that has anti-inflammatory effects, improved postoperative period dynamics by means of reducing complications, stimulating hematopoiesis, and general and local regenerative processes [15]. When cytostatic therapy is administered, the functional failure of the digestive tube, that is, the changes in the connective tissues in the wall of rat small intestine, in terms of quantity and location, is a frequent complication. Methyluracil acts as a modifier of toxicity, by inducing morphometric changes in the wall of the rat small intestine, restoring the proportion of connective tissue [16]. In the case of carrageenan edema in rats, methyluracil at a dose of 5 mg favors the preservation of superoxide dismutase activity in blood, gastric mucosa, and liver, due to a decrease in the nitric oxide metabolism and blockade of free radical oxidation of lipids [17].

3. Application perspectives of uracil-based compounds

3.1. In the case of systemic and metabolic disorders

Methyluracil has been studied as an anabolic immunomodulatory and as an antiphlogistic in

experimental diabetes in rats. Such a study showed that in case of inflammation methyluracil increased the insulin level in the background of alloxan diabetes and decreased the rats' blood glucose, thus showing antiexudative action [3]. The administration of methyluracil as part of a complex therapy in a group of people showed some positive results in the treatment of diabetes mellitus. This is confirmed by the decrease in the lactate level and pyruvate to lactate ratio, and by the tendency towards a decrease in glycaemia levels and positive changes in glucose metabolism in them [18].

Uracil-based compounds are still a subject of intense interest. Thus, the N-substituted 6-methyl-1 (tiethanyl 3) uracil-based compounds, which are the intermediate products of organic synthesis as well as biologically active substances, were synthesized [19]. Among these uracil-based compounds 6-methyl-5-morpholinomethyl-1 (thietanyl-3) uracil reduces emotional anxiety, increases the reserve capacity of phagocytes, and exhibits antioxidant activity [14].

3.2. As a neuromuscular blocking agent

6-methyluracil tetraalkylammonium-based compounds have shown the fundamental potential for developing anticholinesterase drugs with selective effects on locomotor muscles with lasting relaxant effect up to 5 days. The intensity and duration of the muscle relaxant effect of bis- ω -ammonioalkyluracil bromide was found to be much higher in experiments on animals. The increase in the efficiency and action of tetraalkylammonium compounds as cholinesterase inhibitors was attributed to the location of the uracil fragment in the structure in the tetraalkylammonium pharmacophore [20].

Because of the fact that the 'peripheral anionic site', consisting of aromatic rings of amino acids, is located in the anticholinesterase active center, it is believed that there could be places inside the 'peripheral anionic site' which form the point of interaction for uracil-containing ligands. It is the uracil fragment which favours the increase in selectivity and formation of non-covalent bonds with residues of aromatic amino acids [21]. Biochemical studies have demonstrated that some methylphosphoric acid-based compounds containing

6 methyluracil remnants in thioester radicals are potent cholinesterase inhibitors.

3.3. As a prospective cardioprotective agent

Several papers are dedicated to the research of the cardiotropic properties of uracil-based compounds. Thus, the rubomycium-induced cardiac decompensation served the basis for demonstrating the cardioprotective effect of carbicil (crown ether derivative of uracil). Carbicil substantially corrected peroxide homeostasis in the myocardium and liver of rats misbalanced in terms of heart failure. Carbicil also restores the activity of glutathione reductase and glutathione peroxidase in myocardium and liver of rats in the case of experimental cardiac decompensation, reduces the severity of disorders of energy metabolism, increases the intracellular concentration of nucleotides DPN (Nicotinamide adenine dinucleotide) and NADP (Nicotinamide adenine dinucleotide phosphate) and increases ATP, creatine and glycogen [22, 23].

The membrane-active properties of carbicil have also been investigated; its ability to interact with the phospholipid bilayers of the cell membranes has been revealed [24]. A derivative of uracil, 1,3-bis (2-hydroxyethyl)-uracil, which possesses an inotropic activity, has also been developed. Pharmacological studies have been conducted on the papillary muscles of rat heart. It has been established that a significant increase in the inotropic activity of 1,3-bis (2-hydroxyethyl)-uracil as well as of strophanthine is observed at the concentration $1 * 10^{-7} \mu$ (31%). The maximum increase in the force of contraction is observed at the concentration $1 * 10^{-4} \mu$ and equals 41% [25].

3.4. Mechanism of action and prospective antitumor specific features

The first uracil antimetabolite, fluorouracil, was created in 1962. It possesses cytostatic activity, violates the synthesis of nucleic acids and is a phase-specific agent that mostly affects the 5th phase of the cell cycle. The cytostatic action of fluorouracil occurs due to its transformation into an active thymidylate synthetase enzyme inhibitor [26]. Fluorouracil is transformed into 5-fluoro-2'-deoxyuridine monophosphate and 5-fluorouracil triphosphate. 5-fluoro-2'-monophosphate and deoxyuracil and folate cofactor N5-10 methylhidrat form a complex that inhibits the thymidylate synthetase

and violates the thymidylate formation - thymidine triphosphate precursor which is necessary for the DNA synthesis. During the RNA synthesis, the transcriptional enzymes can wrongly incorporate the 5-fluorine uridine triphosphate instead of uridine triphosphate that interferes with RNA synthesis and protein synthesis. There is also a drug named tegafur which is hydrolyzed in the body.

The mechanism of fluorouracil action is still under study. The active drug metabolites inhibit thymidylate synthetase that inhibits DNA formation and/or are incorporated into the RNA structure, which leads to the inhibition of protein synthesis. It has also been shown that fluorouracil decreases the thymidine phosphorylase activity due to inhibition of the expression of the enzyme that enhances apoptosis in cancer cells [27]. Fluorouracil is widely used in oncology as one of the integrated colorectal cancer treatment methods [28]. Fluorouracil modifies conformal chronomodulated radiation therapy used in the treatment of head and neck, lowering radiation reactions and pain [29]. Administration of phtorafurum as a radiomodulator during combined radiotherapy for locally advanced uterine cancer increases the rate and extent of tumor regression [30]. Tegafur is less toxic compared to fluorouracil. Caletcetam is the new fluorouracil modification, which is administered orally and not intravenously (IV). Caletcetam is converted to 5-fluorouracil under the influence of thymidine phosphorylase. Sequential enzymatic biotransformation of caletcetam to 5-fluorouracil promotes higher drug concentration in tumor tissues than in surrounding tissues. A drug called UFT containing uracil and tegafur in the ratio 1:4 has been developed. It prevented the disintegration of 5-fluorouracil by competing for dihydropyridine dehydrogenase. A prolonged-release drug of 5-fluorouracil has also been developed which has shown efficacy in ovarian cancer in experiments where it was combined with the systemic administration of a drug with local effects [31]. The tegafur-uracil plus intravenous cisplatin therapy is a safe and effective treatment for patients with docetaxel-refractory prostate cancer, although large-scale, multicenter, prospective studies are needed to validate this finding [32].

Fluorouracil is a toxic agent. The correlation between toxicity and pharmacokinetic parameters has been established [33]. Fluorouracil toxicity appears in the form of reversible encephalopathy with a pre-stroke condition that requires medical intervention. [34]. Asiatic acid, a triterpene compound, is recommended for the treatment of cognitive deficits caused by fluorouracil [35].

Newly designed methods of synthesis of bis-uracil-based compounds with the pharmacological group = C = SBrCl have been developed. The high antitumor activity of the synthesized heterocyclic bis-based compounds allows considering these compounds as potential anticancer medicinal products and opens new perspectives in oncopharmacology. It has been established that some of the synthesized compounds that are closely similar to 5-fluorouracil in terms of the chemical structure have a low-toxicity with LD₅₀ values ranging from 485 mg/kg to 120 mg/kg. The similarity of the chemical structure of the synthesized compounds with that of the antitumor drug 5-fluorouracil allows considering them as potential anticancer medicinal products taking the toxicity values into account [36].

The interest of scientists in finding new pyrimidine antimetabolites as a means of treatment for tumor diseases has not decreased. Taking into consideration the fact that tumors absorb uracil molecules better than normal cells, it seems to be appropriate to develop fluorouracil-based compounds which can serve as a substrate and/or enzyme inhibitors and are absorbed by the tumor tissue [37].

Phosphorylated uracil was developed on the basis of fluorouracil. It possesses anti-proliferative activity against experimental tissues cells, which often causes an increase in the apoptotic index in tumor tissues and enhances blood circulation disorders. It also possesses the ability to influence the formation of new blood vessels in tumors by inhibiting the synthesis of vascular wall components [38].

The number of studies aimed at the synthesis and activity of new 5- or 6-substituted uracil-based compounds is increasing. The modification of 5 (6)-substituted uracil molecules by introducing halogens (fluoride pharmacophore) leads to an increase in their solubility towards lipids and

makes medicines more effective due to their ease of transport in the body [39]. Thus, in the experiment involving human brain tumors, the expressed antitumor effect of the bis-derivative 6-methyluracil was established [40].

The synthetic mono- and bis 5-methyluracil-based compounds, the molecules of which have one or two heterocycles tied by the fluoroethane residue molecules, belong to the class of low-toxic compounds and are less toxic than the 5-fluorouracil drug (1.3-1.5 times). Bis-derived 5 methyluracil has a curative effect against heterotransplanted human glioma, which is 1.2 times higher than the accepted activity criterion in the treatment of glioblastomas using fluorouracil (25%) [34].

The new substituted uracil-1'(N)-acetic acid esters of camptothecins (CPTs) have been evaluated for their *in vitro* antitumor activity against tumor cell lines A549, Bel7402, BGC-823, HCT-8 and A2780. *In vitro* results showed that most of the derivatives exhibited comparable or superior cytotoxicity compared to CPT and topotecan (TPT). Prospective compounds were selected for evaluation of *in vivo* antitumor activity against H22, BGC-823 and Bel-7402 in mice. These findings indicate that 20(S)-O-fluorouracil-1'(N)-acetic acid ester derivative of CPTs could be developed as an antitumor drug candidate for clinical trials [41].

3.5. As antivirals and antibacterials

Antiviral and anti-tumour are the two most widely reported activities of uracil analogues; however they also possess herbicidal, insecticidal and bactericidal activities. Their antiviral potential is based on the inhibition of key steps in viral replication pathway resulting in potent activities against HIV, hepatitis B and C, the herpes viruses etc. [42]. The synthesis of a new series of 1,3-disubstituted uracil-based compounds as a potential broad-spectrum inhibitors of viral reproduction has been performed [43].

DNA templates containing 5-hydroxymethyluracil or 5-hydroxymethylcytosine were used in an *in vitro* transcription assay with RNA polymerase from *Escherichia coli*. A strong enhancement of transcription was observed in the DNA containing the Pveg promoter whereas a decrease was observed in the DNA containing the rrnB P1

promoter, suggesting that they may act as epigenetic marks [44].

The development of antiviral drugs based on uracil for HIV treatment is very important. It has been established that 5-arylamino-uracil-based compounds that have previously proven themselves as agents capable of inhibiting the growth of *mycobacterium tuberculosis* at a concentration of 5-10 mg/kg are also uncompetitive non-nucleoside inhibitors of non-toxic HIV-1 reverse transcriptase *in vitro* (on cells MT -4) and *ex vivo* (human tonsil tissue) [45]. The synthesis of (1-[ω - (phenoxy) alkane or alkyl and alkenyl]uracil derivative has been carried out in order to find new HIV-1 non-nucleoside inhibitors by condensing equimolar amounts of 2,4-bis (trimethylsilylox) pyrimidine and 1-halo- ω (phenoxy) alkane or alkene. Their anti-HIV-1 activity in the cell culture, as well as against the HIV-1 reverse transcriptase has been studied [46]. Furthermore, 1-[3- (phenoxy) benzyl]-5-(phenylamino) uracil was obtained by means of condensation of 2,4-bis (trimethylsilylox) -5- (phenylamino) pyrimidine obtained by assimilation of the corresponding 5- (phenylamino) uracil and 3- (phenoxy) bromomethyl benzene in a dichloroethane 1,2- solution while boiling, which in later experiments showed itself to be a potential inhibitor of virus C hepatitis reproduction [47].

A series of 1,6-bis[(benzyloxy)methyl]uracil derivatives with the combined structural features of both diphenyl ether and pyridone types of non-nucleoside reverse transcriptase inhibitors have been synthesized. Target compounds were found to inhibit HIV-1 reverse transcriptase at micro- and submicromolar levels of concentrations and exhibited anti-HIV-1 activity in MT-4 cell culture, demonstrating resistance profile similar to first generation NNRTIs. The synthesized compounds also showed profound activity against influenza virus (H1N1) in MDCK cell culture without detectable cytotoxicity [48].

A library of mono- and bis-uracil isatin conjugates have been synthesized and subjected for the assessment of their *in vitro* activity against the protozoal pathogen *Trichomonas vaginalis*. The structure activity studies (SAR) revealed that the bis-uracil isatin-based conjugates were more effective than their corresponding mono conjugates in inhibiting the growth of *T. vaginalis* at a

concentration of approximately 10 μM with no visual effect on mammalian cells at the same concentration [49].

4. Dosage forms and specific physical and chemical features of uracil-based compounds

Nowadays methyluracil is produced in the form of pills, pure ointments (consisting of methyluracilum) or in the form combined with sulfadimidine, trimecaine, laevomecolum. It is also the component of betamycin (along with tetracaine hydrochloride) and aerosol (with sea buckthorn oil and sodium etazol).

The pharmacokinetic characteristics of methyluracil during its release from the gel and ointment are different. Kinetic processes of the methyluracil released from the dosage form are compared to the creams and ointment. At first, the release from the dosage form decreases, but then it increases; the rate of release process decreases with the increase in the half-life period. It is estimated that the ointment has a longer effect on the wound's surface than the gel (ointment>cream) [50].

It has been shown that the uracil-based compounds (6 methyluracil, 5-hydroxy-6-methyluracilum) form rather stable complexes (1:1 proportion) with the polyfunctional acids (citrus pectin, citrus pectin fraction oxidized and 5-aminosalicylic acid). It has also been established that the complex combination of 6 methyluracil, a citrus pectin oxygenized fraction, 5-hydroxy-6-methyluracilum and aminosalicylic acid is characterized by low toxicity and increased anti-flammable effect [51].

A polyurethane implantation material immobilized with methyluracil was recently designed. The C=O and NH groups of methyluracil influence the redistribution of bound and free polyurethane groups, leading to the formation of hydrogen bonds between polyurethane and methyluracil. The release of 75.5% methyluracil immobilized on a polymer was prolonged for 84 days. At the same time, over 50% of methyluracil are released till the 14th day of the study which may promote the increase in the effectiveness of the regenerative processes at the implantation area. Model surgery on animals has established that the composite material combined with methyluracil is biocompatible and bioactive. Implant samples

made of polymers with prolonged release of methyluracil promoted the reduction of the effects of alteration and exudation in the area of the implant placement, the activation of regeneration processes and the formation of ripe and thin connective tissue cells around the implant at the early stages of the experiment [28].

CONCLUSION

The significance of finding new uracil-based compounds is emphasized by the wide range of their pharmacological activity and their influence on various aspects of metabolism.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest with respect to this article.

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