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Synthesis and Biological Activity of Monastroll

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ABSTRACT

Dihydropyrimidine-5-carboxylates are known to possess anti-hypertensive, anti-viral, anti-tumor, anti-staphylococcal, anti-cancer, etc. biological activity. The structure of dihydropyrimidines is of interest for studying the reactivity of a molecule and preparing new derivatives. In the specialized literature, a large number of different derivatives of dihydropyrimidine-5-carboxylates are described, however, most of them are obtained from the condensations of 1,3-dicarbonyl bonds with various aldehydes, urea or thiourea, catalyzed by different catalysts through different schemes of synthesis, which damages the finite yield.

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Introduction

The reaction products are easily accessible in large quantities and are used in the pharmaceutical industry as active substances or as precursors in their synthesis. Due to the importance of dihydropyrimidines, several new methodologies have recently been developed for the synthesis of monastrol and its derivatives. Chemical transformation of dihydropyrimidines by introducing specific pharmacophore groups into their structure is considered one of the promising methods for obtaining new classes of compounds with various biological properties. Attention is drawn to the presence of nucleophilic centers that allow a variety of mono- and dialkylations, as well as very promising cyclization reactions based on them. Some of them, depending on the substituted groups, possess the corresponding anti-hypertensive, anti-viral, anti-rumoral, anti-staphylococcal, anti-cancer biological activity. This reaction has been known for more than a century, but it is ambiguous. The literature describes the mechanisms of this reaction, which proceeds in more than five directions, with the formation of various intermediate products. The synthesis is catalyzed by inorganic acids or under microwave or infrared radiation. The synthesis is catalyzed by inorganic acids or under microwave or infrared radiation. The most useful and elegant methodology currently used to synthesize dihydropyrimidines is the Biginelli reaction. The Biginelli reaction is a multicomponent chemical reaction that gives 3,4-dihydropyrimidin-2(1H)-one(thione). The hydrogen atoms of the CH_3 group in position 6 of the 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate molecule have sufficient mobility for condensation reactions.

In recent years, efforts have been aimed at developing green solvents, called «eutectic solvents», derived from renewable and biodegradable components. They play an important role in human activities, and their use in research drugs has stimulated the development of a wide spectrum of synthetic methods for their preparation, preparative accessibility and chemical transformations, such as modulators of calcium channel antagonists, adrenergic receptors, antibacterial agents of the α1 receptor series, mitotic inhibitors, kinesin (family of motor proteins of eukaryotic cells, these are tubulin-dependent ATPases), anticancer, antihypertensive activity, antiviral agents and others, which makes further searches among them very promising [1].

In the synthesis of dihydropyrimidines, the target is the selection of reagents and the testing of various catalysts and conditions, especially in the development of strategies that enable the approach of environmentally friendly catalytic conditions for further use in the work. Eutectic alloys, natural polysaccharides can serve as an environmentally friendly and financially attractive alternative to toxic and expensive catalysts. During experiments, catalysis and its role, their environmental characteristics, environmental pollution, waste and costs, as well as the application of these concepts to the synthesis of the biologically important structure of the bioactive derivative of 3,4-dihydropyrimidine-2(1H)-thione, known as its common name - Monastrol.

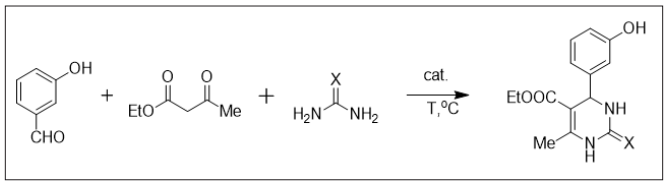

Figure 1: Biginelli reaction: monoreactive three-component synthesis of monastrol based on acetoacetic ester, thiourea or urea and 3-hydroxybenzaldehyde with the formation of monastrol and oxymonastrol (ethyl 6-methyl-4-(3-hydroxyphenyl)-2-(thi) oxo-1,2,3,4-tetrahydropyrimidine-5 carboxy)

Monastrol synthesized in the one-step, multicomponent Biginelli reaction in the presence of various bioavailable and biodegradable catalysts is of interest in its cell permeability as a molecular

inhibitor small protein belonging to the Kinesin-5 protein family, protein for the bipolar motor. These mitotic blocking agents may be useful in the treatment of cancer. Monastrol and related compounds that bind proteins other than tubulin may have less toxicity and fewer side effects than currently used tubulin-binding agents. The above properties are typical for racemic monastrol [1].

The target of monastrol synthesis is reagent selection. To increase the yield, selectivity, reduced reaction time and minimization of excess reagent, formation of side products, high temperatures, pollution, waste and costs in the synthesis of Biginelli catalysis have emerged unequaled especially in the development of strategies that allow to address the ecological catalytic conditions for further use of the works. Monastrol syntheses were performed with various catalysts and in various ratios, the results of which are presented in the corresponding reports [2]. The accessibility, the high efficiency, the mild reaction conditions, the ease of separation of the catalyst after the completion of the synthesis, the more directed progress of the reaction allow us to conclude in their favor. Therefore, the improvement of the asymmetric synthesis of S-monastrol (enantiomer with higher biological activity) represents a current topic. In the search for low molecular weight compounds that could interfere with mitosis, monastrol, a compound that blocks the motor activity of specific kinesins whose functions are restricted to the mitotic spindle, was proposed. Together with the role played by microtubules in disease pathogenesis, these cytoskeletal elements may be targets for new drugs. These mitotic blocking agents may be useful in the treatment of cancer, namely, it is currently proven, breast cancer. Monastrol and related compounds that bind proteins other than tubulin may have less toxicity and fewer side effects than currently used tubulin-binding substances. Monastrol has been shown to inhibit kinesin-5, a motor protein important for spindle bipolarity. A high molecular weight, cell-permeable, potent inhibitor of mitosis that does not interact with tubulin. It arrests cells in mitosis and specifically inhibits the mobility of mitotic kinesin Eg5, the motor protein required for the formation and maintenance of the mitotic spindle. Among the dihydropyrimidines, monastrol ranks prominently. Of considerable interest is cell permeability as a small molecule inhibitor of the spindle protein kinesin-5, as a motor protein for spindle bipolarity.

Monastrol, as an antiprotozoal drug, is used to treat and prevent infections caused by protozoan parasites belonging to the genus Leishmania, affects the activity of urease, etc. Monastrol and its analogues oxymonastrol differ from each other by replacing the sulfur atom present in monastrol with an oxygen atom in oxymonastrol. Oxymonastrol induced DNA damage, reduced cell proliferation, and increased the mRNA level of a member of the Kinesin subfamily of the cytochrome P-450 family. However, oxymonastrol was cytotoxic only at the highest concentrations used, without compromising cell proliferation and viability. Moreover, no genotoxic damage or changes in mRNA level were detected. Monastrol has greater antiproliferative activity compared to oxymonastrol, and this effect is probably associated with DNA damage caused by monastrol and its possible bioactivation, demonstrated by increased mRNA expression. In addition, these effects are apparently associated with the presence of a sulfur atom in its structure [3].

The general and specific objectives of the given theme are: the development of methods for the synthesis of substituted dihydropyrimidine-5-carboxylates and their use for obtaining biologically active polyfunctional organic compounds. The synthesis of substituted dihydropyrimidine-5-carboxylates consists in the variation of the substituents in the initial aldehyde, urea, thiourea, aceto-acetic acid ethers. Substituted dihydropyrimidine-5-carboxylates can be converted to the desired product by reaction with a suitable nucleophile. Obtaining "eutectic solvents" based on native components (tartaric acid, choline chloride, dihydroabietic acid, urea, pectin, etc.) and researching the catalytic properties of "eutectic solvents" in order to obtain substituted dihydropyrimidine-5-carboxylates. Obtaining and researching the catalytic properties of materials made using 3D printing technology based on local minerals (from the region of Naslavcea village, etc.) and insoluble polymers.

Relevance and Purpose

In the synthesis of monastrol, the objective is to select reagents and test various biodegradable and bioavailable catalysts to achieve maximum product yield. Eutectic alloys can serve as straight environmentally friendly alternative from a financial point of view and the toxicity of catalysts in the synthesis of monostrol.

Materials

To confirm the structure of the synthesized compounds, analyzes were performed using the following tools:

- IR-spectrum recorded in the database by Perkin Elmer. Spectrum 100FT-IR with a range of 3600-650 cm^{-1}.
- NMR spectra were recorded in DMSO-d6 with 1% TMS on a Bruker-Avance III spectrometer (400.13 and 100.61 MHz).

Commercially available reagents, biodegradable catalysts, with permitted toxicity, were used as initial compounds. Solvents were used after prior distillation.

The Results

During the experiments, catalysis and its role, the importance of multicomponent reactions and their ecological, biodegradable and bioavailable characteristics, as well as the application of these concepts to the synthesis of the important biological structure of monastrol (1,2,3,4-tetrahydro-4-(3 -hydroxyphenyl)-6 methyl-2-thioxo-5-pyrimidinecarboxylic). To increase yield, selectivity, reduce reaction time, and minimize excess reactants, side products, high temperatures, pollution, waste, and costs in Biginelli synthesis, catalysis has emerged unparalleled, especially in the development of strategies, which favors the achievement of eco-friendly catalytic conditions for its continued use in the chemical field. The syntheses of monastrol were carried out with different catalysts and in various ratios.

Conclusion

Syntheses of monastrol were carried out with the participation of different catalysts and in different ratios. The availability of eutectic solvents, waste and by-products from the food industry as catalysts in the Biginelli reaction, high efficiency, mild reaction conditions, ease of separation of the catalyst after finishing the synthesis, more targeted reaction, allows to we conclude in favor of eutectic or green solvents, and secondary products of the food industry, which allows us to bear minimal losses in the food industry. The linear nature of the dependences of the course of reactions on the corresponding catalysts was presented as the result of the conducted research.

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