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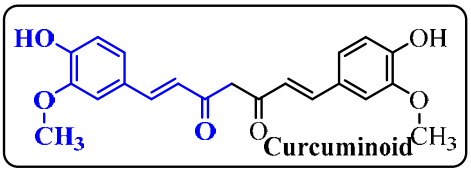
3,5-BIS(ARYLIDENE)PIPERIDIN-4-ONES AS SYNTHETIC CURCUMIN ANALOGUES

Abstract. The synthesis of divinyl ketones based on various cyclic ketones, in particular piperid-4-ones, with aromatic aldehydes is considered. The dependence of pharmacological activity on the nature of substituents in the aromatic ring and at nitrogen of the piperidine cycle is shown. The perspectivity of searching for anticancer drugs in a family of substituted 3,5-bis(arylidene)piperidin-4-ones has been established.

Keywords: divinyl ketones, piperidine, aldol-crotonic condensation, synthesis, pharmacological activity.

Nitrogen-containing heterocycles play an important role in the activities of vital organisms. Many of most highly effective drugs relate to compounds of this family. There is a highly interest of α,β-unsaturated ketones due to their availability, reactivity and practical application in various fields [1]. Hydrogenated divinyl ketones possess a wide range of biological activities (antitumoral, antimicrobial, antifungal and etc.) and can be potentially used for creation of pharmacological preparations. It should be noted that α,β-unsaturated ketones show the similar structure as natural curcumin [2], which is the main active ingredient in turmeric roots, also known for its biological activity such as antioxidant, antidiabetic, anti-inflammatory and и anti-cancer drugs.

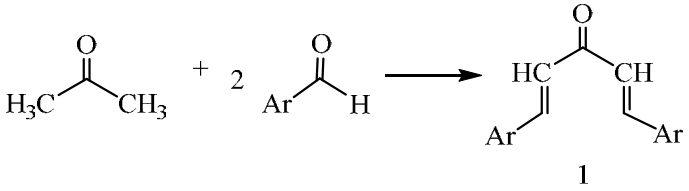


This Research relates to the analysis of literature based on synthesis of aromatic divinyl ketones with piperidine fragment and pharmacological activities of diarylidene ketones and their derivatives.

A lot of publications are dedicated to the elaboration of synthesis methods of divinyl ketones in order towards more complex and high functional systems. Some ways such as aldol-crotonic condensation, acylation of olefins with carboxylic acid anhydrides and acid halides (Friedel-Crafts reaction), also methods based on vinylacetylene carbinols developed by I.N. Nazarov and others have become traditional. The large group of α,α'-conjucated dienones is make up the condensation products of acetone or other ketones with aromatic aldehydes, usually represents symmetrical dienones with same or mixed aryl radicals.

The most common way of dienone's synthesis is aldol-crotonic condensation of ketones with aldehydes that proceeds under alkaline or acidic conditions which are created by different agents. In case of condensation between acetone and

2 moles of aromatic aldehyde symmetrical dienone - diarylidene acetone are formed (1) [3]:



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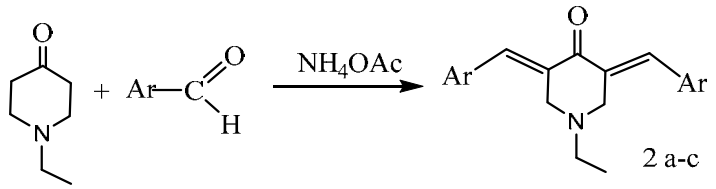
A detailed analysis of this reaction's mechanism describes in Becker's monograph [4].

Reactions of aldol-crotonic condensation between cyclic ketones and aromatic aldehydes under alkaline conditions had known for a long time.

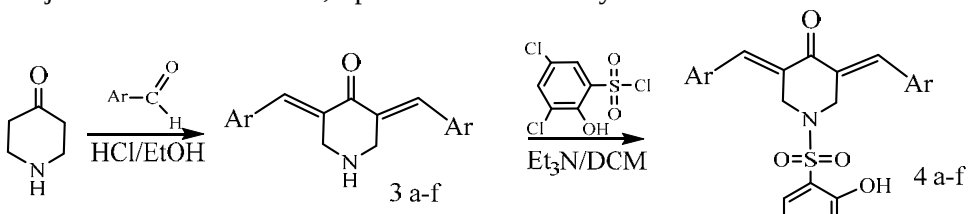
Attempt of increasing the number of 3,5-dialkyl substituted piperidones by using cyclic ketones as carboxylic component of Mannich reaction was made by Vatsadze S.Z. and co-authors. As it turned out, interaction between cyclohexanone, different aromatic aldehydes and ammonium acetate leads to formation of bicyclic compounds. But, for example in case of 1-ethylpiperidine-4 the final product was divinyl ketone 2a–c [5]:



2 a-c

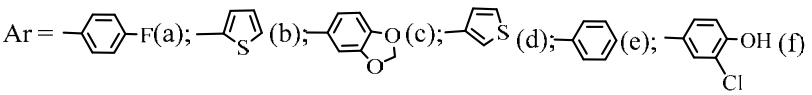
Ar = Ph (a); *p*-$CH_3OC_6H_4$ (b); *p*-$(CH_3)_2NC_6H_4$ (c)

Synthesis, based on norpiperidone-4 and aromatic aldehydes made by Kulathooran Singaram and co-authors [6], are the great examples of obtaining of conjucated dienones with 1,4-pentadiene-3-one's system:



3 a-f

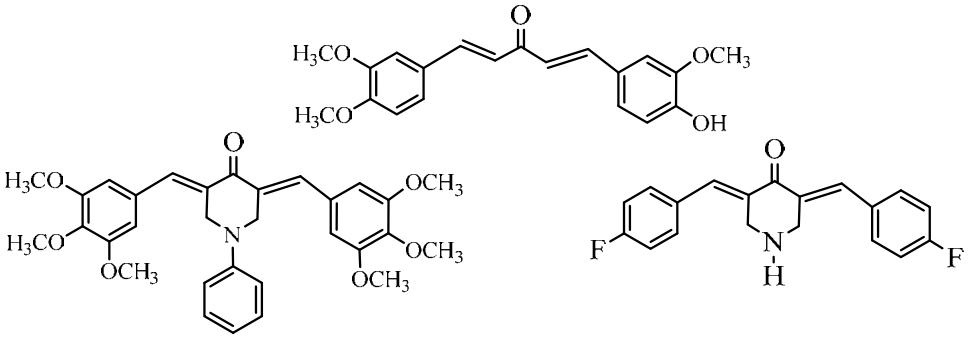
4 a-f



Three types of heteroaromatic analogues (twenty seven compounds) with monoketones as linkers were synthesized. After that, the antibacterial activity of synthesized compounds was studied against six strain of bacteria. Among them, 3,5-dibenzylidene-1-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]piperidine-4-one

(4e) possess the best antifungal activity against *Aspergillus niger* and *A. fumigatus*. The chemical structures of the synthesized compounds were defined by various spectroscopy techniques [6].

Twenty one novel NH- и N-methyl-3,5-bis-(arylidenyl)-4-piperidone's analogues of curcumin were synthesized by Mattew Gregory and co-authors [7]. Twelve of them were tested for the cytotoxicity against *B16 cells* (*mouse melanoma*) and *L1210* (*mouse lymphoma*). Compounds have a significant activity against *B16* cells. It has been shown that the main role at cytotoxicity plays the position of hydroxyl group. Amino containing analogues are usually less active than their halogen and oxygen containing analogues, therefore N-substitution in the 4-piperidinone fragment increases the cytotoxicity of the compounds [7]:

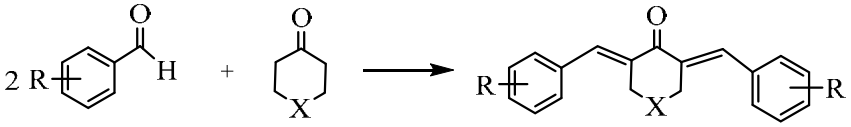


Condensation of cyclic ketone with aromatic aldehydes in the presence of ammonium acetate under ethanol media made by Natesan Sundaramurthy Karthikeyan and co-authors affords the corresponding 5-aryl-7,8,13,14-tetrahydrodibenzo[a,i]phenanthridine with excellent yield. This mild and effective procedure also can be used in synthesis of 2,4-diaryl-6,7-belizo-3-azabicyclo[3.3.1]nonan-9-one and α,α'-bis-(benzylidene substituted)cycloalkanes [8].

Indian scientists has investigated the structure of the synthesized three dibenzylidene-4-piperidone derivatives. In the *para*-fluorine-substituted dibenzylidene compound, fluorine participates in the C-H ... F interaction, resulting in a one-dimensional packing fragment. In addition, fluorine has a significant ability to form exclusive intermolecular interactions, as well as compete with oxygen as an acceptor [9].

It is known that curcumin (diferuloylmethane) and its synthetic derivatives has antioxidant [10], anti-inflammatory [11], antiviral [12], antibacterial [13] effects, and thus has potential application for the treatment of various malignant tumors, diabetes, allergies, arthritis and other chronic diseases [14-17]. Various search groups has been carried out chemical modifications of curcumin's analogues, with the aim of exploring new derivatives with increased systemic bioavailability and improved pharmacological activity [18, 19]. 3,5-bis(benzylidene)-4-piperidone exhibit cytotoxic activity, especially on leukocyte cell and colon cancer [20].

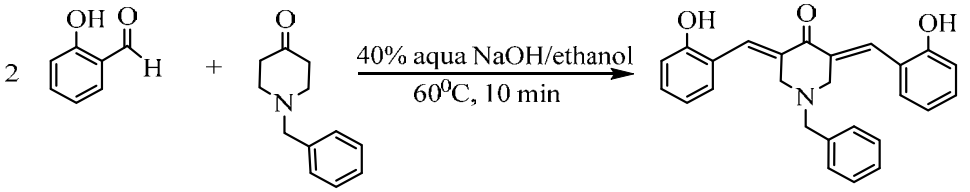
A number of novel curcumin's analogues was synthesized and screened for anti-cancer and antiangiogenic at Emory University and at the National Cancer Insitute (NCI). The majority of the analogs demonstrated a moderate degree of anti-cancer activity. Compounds (X=CH_2, O или NCH_3; R=*o*-OH) showed a high level of cytotoxicity in the NCI *in vitro* anti-cancer cell line screen. In addition, this compounds inhibit the growth of tumor cells growth with higher efficiency than the commonly used chemotherapeutic drug, cisplatin. [21].



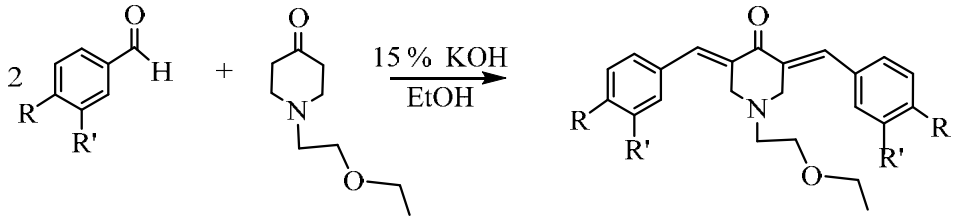
X= CH_2; O; NCH_3; NH·HOAc

R= *o*-OH; *o*-F

With the purpose of exploring of novel curcumin's derivatives, Yum Eryanti and his team synthesized 3,4-bis(2-hydroxybenzilydene)-4-piperidone [21, 22] by the reaction of condensation between 2-hydroxybenzaldehyde and N-benzyl-4-piperidone in precence of 10% NaOH under microwave radiation:



The simplicity of the synthesis and the availability of the reagents are the most important criteria of the searching novel potential biologically active compounds. We [23-25] have synthesized α,β-unsaturated piperidine-4-ones under the conditions of Klassen-Schmidt reaction by condensation of 1-(2-ethoxyethyl)piperidone-4 with benzoic, anisic and veratric aldehydes. The reaction is carried out in ethanol in the presence of an alkaline agent:



R, R = H or OCH_3

According to various examples of 3,5-bis(arylidene)-4-oxopiperidines which are exhibit biological activity, they can be attributed to synthetic cucumin's analogues. Thus, using the example of various 3,5-bis-(arylidene)-4-oxopiperi-

dines, having biological activity, it has been shown that ones can be attributed to synthetic analogues of curcumin. The most promising in this family of chemical compounds is the search for anticancer drugs.

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Резюме

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КУРКУМИННЫҢ СИНТЕТИКАЛЫҚ АНАЛОГТАРЫ РЕТІНДЕГІ 3,5-БИС(АРИЛИДЕН)ПИПЕРИД-4-ОНДАРЫ

Әртүрлі циклдік кетондарға негізделген дивинил кетондардың синтезі, атап айтқанда, ароматты альдегидтермен пиперид-4-ондардың синтезі қарастырылған, фармакологиялық белсенділіктің ароматты сақинадағы және пиперидин цикліндегі азот атомындағы орынбасарлардың табиғатына тәуелділігі көрсетілген. 3,5-бис (арилиден) орыналмасқан пиперидин-4-ондардың арасында ісікке қарсы препараттарды іздеу перспективасы белгіленді.

Түйін сөздер: дивинилкетон, пиперидон, альдол-кротонды конденсация, синтез, фармакологиялық белсенділік.

Резюме

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3,5-БИС(АРИЛИДЕН)ПИПЕРИДИН-4-ОНЫ
КАК СИНТЕТИЧЕСКИЕ АНАЛОГИ КУРКУМИНА

Рассматривается синтез дивинилкетонов на основе различных циклических кетонов, в частности пиперид-4-онов, с ароматическими альдегидами. Показана зависимость фармакологической активности от природы заместителей в ароматическом кольце и у атома азота пиперидинового цикла. Установлена перспективность поиска противоопухолевых препаратов в ряду замещенных 3,5-бис(арилиден)пиперидин-4-онов.

Ключевые слова: дивинил кетоны, пиперидин, альдольно-кротоновая конденсация, синтез, фармакологическая активность.