CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

ISSN 2686-7575 (Online)

https://doi.org/10.32362/2410-6593-2022-17-3-210-230

UDC 547.78:54.057

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RESEARCH ARTICLE

Obtaining substituted phenol derivatives with potential antimicrobial activity

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Abstract

Objectives. *With the growing resistance of pathogenic microorganisms to antibiotics, the development of new antimicrobial drugs offering specific mechanisms of action becomes an urgent task. Only few antimicrobials offer a broad spectrum of activity against gram-positive and gram-negative bacteria, molds, and yeasts. In this regard, the purpose of the work was to develop methods for synthesizing biologically active derivatives of alkyl-substituted phenols (reactions at the hydroxy group) to study their biological effect.*

Methods. *The synthesis of imidazole acetates of substituted phenols was carried out in two stages. At the first stage, the chloroacetyl derivative of the selected compounds was obtained, to which imidazole was then added. O-acylation reactions at the first stage of the synthesis were carried out under varying conditions. The first version of the synthesis was carried out using chloroacetyl chloride as an acylating agent together with a high-boiling solvent. In the second variant, chloroacetic anhydride was used, along with an attempt to replace the solvent with a low-boiling one. A thymol methoxy derivative was additionally synthesized by a known method using methyl iodide and varying the reaction parameters.*

Results. *The parameters of chloroacetylation and methoxylation of aromatic alcohols were optimized with rational selection of solvents and the ratio of reagents in the reactions. Synthesized thymol (2-isopropyl-5-methylphenol) and propofol (2,6-isopropylphenol) derivatives contained imidazole as an additional pharmacophore with affinity for microorganism cell membrane proteins. A thymol methoxy derivative comprising an aromatic ether exhibiting increased hydrophobicity was also obtained. The synthesized compounds were characterized by NMR spectroscopy.*

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Conclusions. *Chloroacetyl derivatives of aromatic alcohols can be effectively synthesized by cooling the reaction mixture using an excess quantity of an acylating agent and increasing the reaction time (compared to literature data). The yield of thymol chloroacetate was 75%, while that of propofol chloroacetate was 30%. This can be explained by the sterically hindered reaction of the propofol alcohol group, which has isopropyl substituents at the second and sixth positions of the benzene ring.*

Keywords: *alkyl-substituted phenols, imidazole, thymol, propofol, chloroacetate*

For citation: Sokhraneva V.A., Yusupova D.A., Boriskin V.S., Groza N.V. Obtaining substituted phenol derivatives with potential antimicrobial activity. *Tonk. Khim. Tekhnol. = Fine Chem. Technol.* 2022;17(3):210–230 (Russ., Eng.). https://doi.org/10.32362/2410-6593-2022-17-3-210-230

НАУЧНАЯ СТАТЬЯ

Получение производных замещенных фенолов с потенциальной антимикробной активностью

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Аннотация

Цели. *В связи с растущей резистентностью патогенных микроорганизмов к антибиотикам актуальной задачей является разработка новых противомикробных препаратов с уникальным механизмом действия. Немногие антимикробные препараты обладают широким спектром действия на грамположительные и грамотрицательные бактерии, плесени и дрожжи. В связи с этим, цель нашей работы – разработать способы синтеза биологически активных производных алкил-замещенных фенолов (реакций по гидроксигруппе) для исследования их биологического действия.*

Методы. *Синтез имидазолацетатов замещенных фенолов проводился в две стадии. На первой стадии было получено хлорацетильное производное выбранных соединений, к которому далее присоединялся имидазол. Реакции О-ацилирования на первой стадии синтеза проводились в различных условиях. Первый вариант синтеза проводили с использованием хлорацетилхлорида в качестве ацилирующего агента и высококипящего растворителя. Во втором варианте использовали хлоруксусный ангидрид, и была предпринята попытка заменить растворитель на низкокипящий. Также было синтезировано метоксипроизводное тимола по известной методике, с применением метилйодида и варьирования параметров реакции.*

Результаты. *Проведена оптимизация параметров хлорацетилирования и метоксилирования ароматических спиртов. Осуществлен подбор растворителей и соотношения реагентов в реакциях. Были синтезированы производные тимола (2-изопропил-5-метилфенола) и пропофола (2,6-изопропилфенола), содержащие имидазол в*

качестве дополнительного фармакофора, имеющего сродство к белкам клеточных мембран микроорганизмов. Также было получено метоксипроизводное тимола – ароматический простой эфир с повышенной гидрофобностью. Синтезированные соединения были охарактеризованы методом ЯМР-спектроскопии.

Выводы. *Синтез хлорацетильных производных ароматических спиртов при охлаждении реакционной массы с использованием избытка ацилирующего агента и увеличением времени реакции (по сравнению с литературными данными) является более предпочтительным. Выход хлорацетета тимола составил 75%, хлорацетата пропофола – 30%, что можно объяснить стерически затрудненным реагированием спиртовой группы пропофола, имеющего изопропильные заместители по 2 и 6 положениям бензольного кольца.*

Ключевые слова: *алкил-замещенные фенолы, имидазол, тимол, пропофол, хлорацетат*

Для цитирования: Сохранева В.А., Юсупова Д.А., Борискин В.С., Гроза Н.В. Получение производных замещенных фенолов с потенциальной антимикробной активностью. *Тонкие химические технологии*. 2022;17(3):210–230. https://doi.org/10.32362/2410-6593-2022-17-3-210-230

INTRODUCTION

Infectious diseases remain highly prevalent, posing a continuing serious threat to human health. This risk is also associated with the growing resistance of pathogenic microorganisms to antibiotics. Despite significant advances in the understanding of antimicrobials, their use in the treatment of infections is impeded due to their high toxicity. It is also worth noting that few antimicrobials offer a wide spectrum of action on gram-positive and gram-negative bacteria, as well as fungi. Therefore, the development of new antimicrobial drugs that offer a unique mechanism of action is a relevant research direction [1].

Currently, there is increasing data indicating the positive effect on the human body of various diets rich in plant products. Products containing phenolic and polyphenolic compounds are considered to be one of the most valuable components of nutrition [2, 3]. Studies show that the consumption of natural substituted phenols can reduce the risk of developing many diseases, including cardiovascular and neurodegenerative pathologies, as well as some forms of cancer. Phenols have also been found to affect lipid metabolism [4]. In addition, it is known that natural phenols can suppress the negative effects of bacterial, viral and fungal infections, as well as interact with a wide number of proteins, such as enzymes, tissue proteins and membrane receptors, to modulate their activity [5].

Due to their antibacterial, antiviral, anti-inflammatory, antioxidant, and antitumor properties, phenolic compounds are among the most attractive potential antimicrobial agents [6].

On the other hand, imidazole compounds have been of interest to researchers for more than a century. As well as occupying a unique position in the chemistry of heterocycles, imidazole derivatives have recently been used more widely in chemistry and pharmacology. Imidazole is a nitrogen-containing five-membered heterocyclic ring of biological and pharmaceutical significance. The imidazole ring is part of several important natural molecules, including purine, histamine, histidine, and nucleic acid. Being a polar and ionizable aromatic compound, imidazole is used to optimize the parameters of solubility and bioavailability of poorly soluble drugs by improving the pharmacokinetic characteristics of synthesized complex molecules [7]. Moreover, the availability of several viable methods for synthesizing imidazole-containing compounds opens up wide opportunities in the field of medical chemistry. Imidazole derivatives, as well as substituted phenols, have a wide range of biological activity: antibacterial, anticancer, anti-tuberculosis, and antifungal.

In this regard, the aim of the present work was to develop methods for the synthesis of imidazole-containing derivatives of alkyl-substituted phenols in order to study their possible antimicrobial activity. In addition, there are suggestions that two types of bioactivity may occur during the hydrolysis of such conjugates. In this work, the initial phenolic compounds from which imidazolacetates were synthesized were thymol (2-isopropyl-5-methylphenol) and propofol (2,6-isopropylphenol).

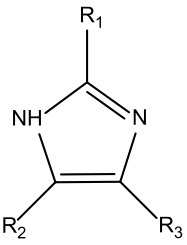

Fig. 1. General structure of imidazoles.

Examples of conjugation of phenols and polyphenols with imidazole and their biological activity

Imidazoles are well-known and widespread heterocyclic compounds (Fig. 1). As is known from many literary sources, imidazole derivatives exhibit various biological activities, including antitumor, antifungal [8] and antibacterial [9] ones.

Imidazole and nafimidone derivatives were obtained according to the schemes shown in Figs. 2 and 3 according to the methodology described in [10].

The compounds were evaluated *in vitro* in comparison with three *Candida* fungi, which are frequent pathogens of nosocomial infections and pathogenic to people with weakened immune systems: *Candida albicans* (ATCC 90028), *C. krusei* (ATCC 6258), and C. parapsilosis (ATCC 22019) [11], as well as against four conditionally pathogenic bacteria pathogens of nosocomial infections: *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853) [12] (Table 1).

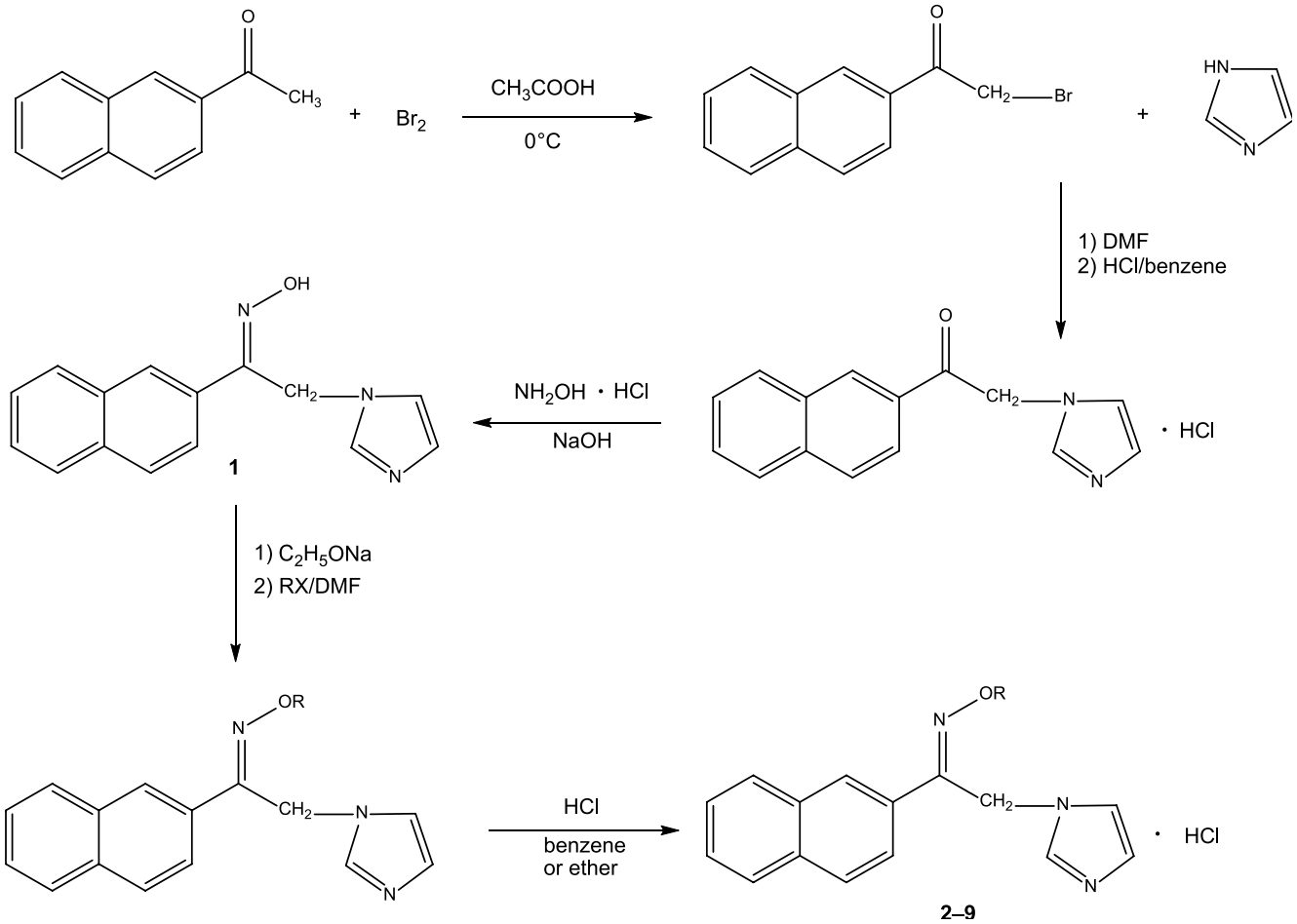

Fig. 2. Synthesis of nafimidone oxime and oxime ethers by *O*-alkylation of the oxime with an alkyl halide.

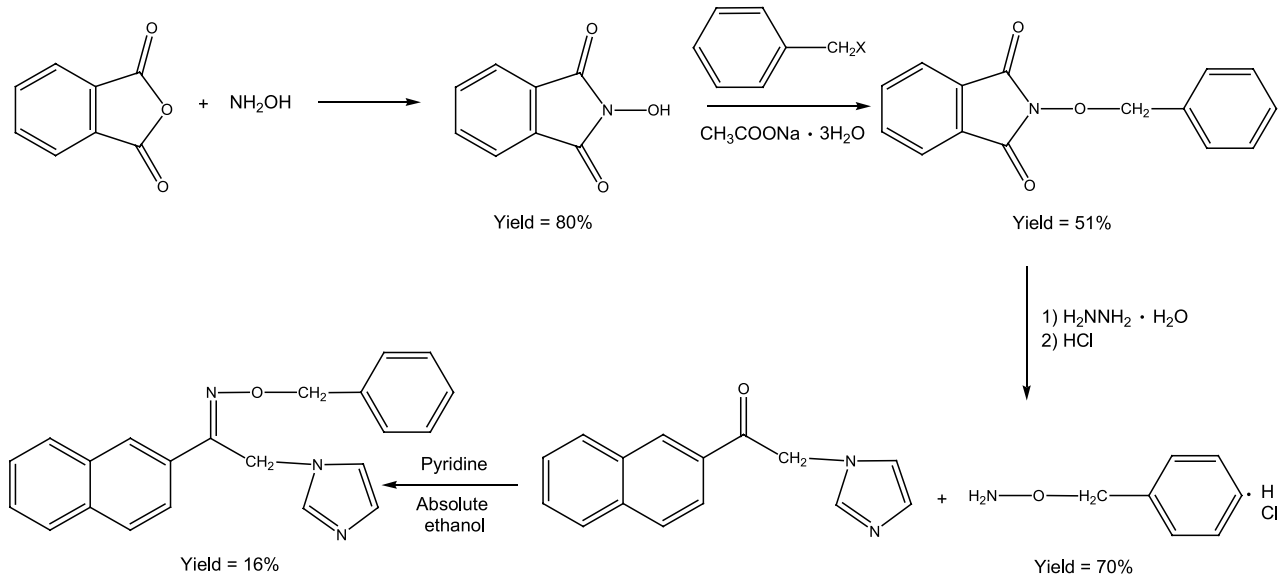

Fig. 3. Synthesis of nafimidone *O*-benzyloxime (**7**) by condensation of a ketone with an *O*-substituted hydroxylamine.

The results of the studies showed that only compound **1** was inactive against both bacteria and fungi. Most compounds (**2**, **3a**, **3b**, **4**, **6**, **7**, **8**, and **9**) were active against gram-positive bacteria, especially *S. aureus*, at low values of the minimum inhibitory concentration (MIC, Eng. minimum inhibitory concentration, MIC). Compounds **2**, **3a**, **3b**, **4**, and **9** demonstrated effective activity against *E. faecalis* at concentrations of 4–16 μg/mL, while the reference substance, amikacin, was active at a concentration

Table 1. Antibacterial and antifungal activity of compounds (MIC in μg/mL)

Compound	Bacteria (MIC μg/mL)				Fungi (MIC μg/mL)		
	S. aureus ATCC25923	*E. faecalis* ATCC 29212	*E. coli* ATCC 25922	*P. auruginosa* ATCC 27853	*C. albicans* ATCC 90028	*C. krusei* ATCC 6258	*C. parapsilosis* ATCC 22019
1	>64	>64	>64	>64	>64	>64	>64
2	32	16	>64	>64	64	32	64
3a	0.5	16	>64	>64	1	1	2
3b	8	16	>64	>64	2	4	4
4	8	4	>64	>64	16	32	32
5	>64	>64	>64	>64	8	16	8
6	1	>64	>64	>64	>64	>64	>64
7	0.5	>64	>64	>64	>64	>64	>64
8	0.5	>64	>64	>64	>64	>64	>64
9	2	4	32	>64	>64	>64	>64
Fluconazole	–	–	–	–	0.25	16	1
Amikacin	4	64	1	2	–	–	–

of 64 μg/mL. All derivatives (except compound **9** against *E. coli*) were inactive against gram-negative bacteria. Only five compounds (**2**, **3a**, **3b**, **4**, and **5**) demonstrated activity against fungi. In relation to *C. krusei* compounds, **3a** and **3b** showed even better activity than fluconazole. Compound **3a** showed the best activity against both bacteria and fungi [13].

The general structure of nafimidone oxime and oxime esters is shown in Fig. 4.

In order to study the effect of stilbenes conjugated with 2-aminoimidazole on biofilms *P. Aeruginosa* resistant to many known antibiotics, compounds **10**, **11**, and **13a-b** were synthesized (Fig. 5). Biofilms were grown in a modified M9 medium in 96-well microtiter plates. As a result, it was found that compounds **10** and **11** are able to inhibit the growth of *P. aeruginosa* film up to 24 h by 56% and 48%, respectively. Compounds **13a-b** did not demonstrate any antibacterial activity [14].

A series of new imidazole derivatives **17a-m** (Fig. 6) was synthesized to evaluate their antifungal activity *in vitro*. Five species of conditionally pathogenic *Candida* were selected for the tests, including *Candida glabrata* 80, *Candida glabrata* 67, *Candida albicans* 135, *Candida parapsilosis* 208, and *Candida pseudotropicalis* 801 [14].

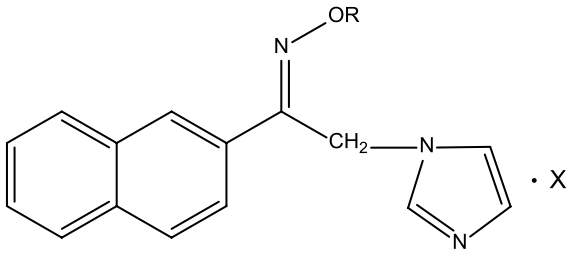

Fig. 4. General structure of nafimidone oxime and oxime ethers.

The synthesis was carried out in accordance with the scheme in Fig. 6. The synthesis of intermediates of (±)-2-bromo-1-(5-aryl-3-pyridine-2-yl-4,5-dihydro-pyrazole-1-yl)-ethanones (**16a-m**) was carried out by reacting bromoacetyl chloride with (±)-5-aryl-3-(pyridine-2-yl)-4,5-dihydro-1*H*-pyrazoles (**15a-m**), which were obtained from the corresponding 3-aryl-1-(pyridine-2-yl)-propenones (**14a-m**) treated with hydrazine hydrate. Further, the corresponding 4,5-dihydro-1*H*-pyrazoles (**15a-m**) were isolated, from which compounds **16a-m** were obtained. After that, treatment of compounds **16a-m**

Table 2. Structures, solvents used for recrystallization, yields (%) and melting points ($T_{m.p.}$) of compounds

Compound	R	X	Solvent used for recrystallisation	Yield, %	$T_{m.p.}$, °C
1	–H	HCl	Methanol	82	193–196
2	$–CH_3$	HCl	Methanol/Ethyl acetate	47	167–168
3a (E)	$–C_2H_5$	HCl	(1) Methanol/water, (2) Methanol/ Ethyl acetate	46	92–94
3b (Z)	$–C_2H_5$	HCl	Methanol/Ethyl acetate	33	82–84
4	$–C_3H_7$	HCl	(1) Methanol/water, (2) Methanol/Ethyl acetate	84	170–172
5	$–CH_2–CH=CH_2$	HCl	Methanol/Ethyl acetate	58	164–166
6	$–C_6H_{11}$ (cyclo)	HCl	(1) Ethyl acetate, (2) Benzene	34	179–181
7	$–CH_2C_6H_5$	HCl	(1) Methanol/water, (2) Benzene	97	158–160
8	$4–CH_2C_6H_4Cl$	HCl	(1) Methanol/water, (2) Dioxane	87	188–190
9	$2,4–CH_2C_6H_3Cl_2$	HCl	Dioxane/ether	56	186–187

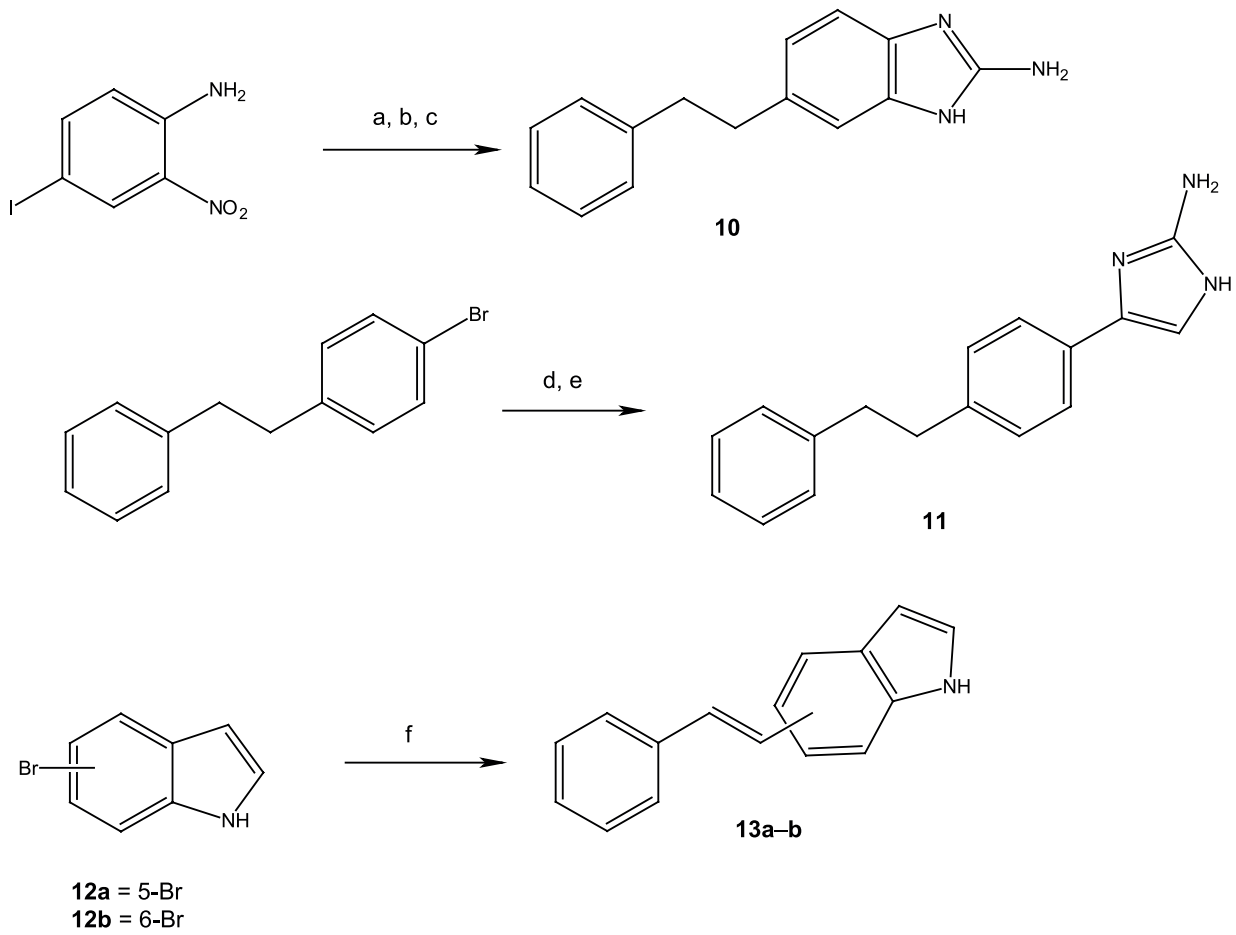

Fig. 5. Scheme for the synthesis of stilbene derivatives.
(a) Styrene, $Pd(OAc)_2$, CH_3CN, DIPEA, 80°C, 76%; (b) $SnCl_2 \cdot 2H_2O$, EtOAc, 80°C; (c) CNBr, MeOH/H_2O (1:1), 50°C, 91%; (d) imidazo [1,2-a]pyrimidine hydrobromide, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, 1,4-dioxane, 100°C, 82%; (e) 20% N_2H_4/EtOH, 105°C, 84%; (f) styrene, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, NEt_3, 100°C, 73–76%. DIPEA = *N*,*N*-diisopropylethylamine.

with imidazole in the presence of acetonitrile led to (±)-1-(5-aryl-3-pyridine-2-yl-4,5-dihydro-pyrazole-1-yl)-2-imidazole-1-yl-ethanones (**17a-m**) being obtained.

The synthesized compounds showed different antifungal activity *in vitro* against the tested *Candida* strains (Table 3). The following substances were used as reference substances: miconazole (Mic), 5-fluorouracil (5FC), and amphotericin B (AMB). Compounds **17a**, **17b**, **17e**, **17f**, and **17j** were equally active against *C. pseudotropicalis* 801 (CPs 801) and *C. glabrata* 80 (CG 80), MIC values were 62.5 μg/mL after 24 and 48 h. At the same time, with respect to the *C. glabrata* 67, MIC values from 62.5 μg/mL were increased to 125 μg/mL and 500 μg/mL after 24 and 48 h, respectively. With respect to *C. parapsilosis* 208 (CP 208), MIC values of 62.5 μg/mL showed only compounds **17h**, **17i**, and **17k**. None of the tested compounds demonstrated activity against *C. albicans* 135 [13].

Hydroxylated derivatives of thymol (**20a-e**) were synthesized to evaluate the inhibitory effect on fungal tyrosinase (Fig. 7). The intermediate chloroacetyl product **18** was obtained by esterification of the hydroxyl group of thymol with chloroacetyl chloride in the presence of triethylamine and methylene chloride as a solvent. The target synthesis product **20a-e** was obtained by nucleophilic substitution in the intermediate compound **18** with hydroxysubstituted benzoic acids **19a-e**.

The synthesis of mono- and dihydroxylated thymol derivatives with different positions of the hydroxyl group in the phenyl ring was carried out to study the role of multiple hydroxyl groups in tyrosinase inhibition. As a result, it was found out that the determining factor of inhibitory ability is not the number of hydroxyl groups, but their position [15]. Thus, the compound **20d** containing the 3,4-dihydroxy-substituted part of benzoic acid showed higher activity (IC_{50} = 45.0 μM) than **20c** and

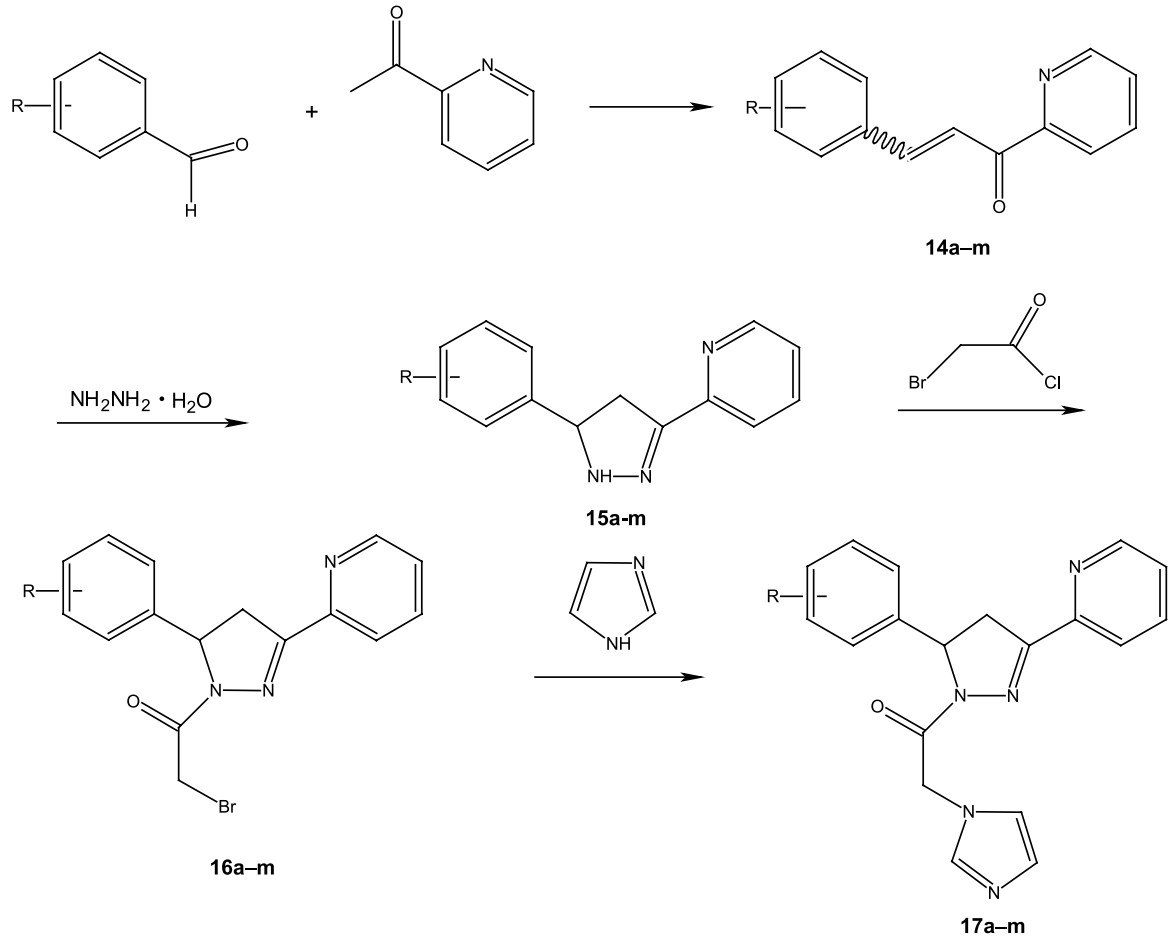

Fig. 6. Scheme for synthesis of (±)-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanones (**17a-m**).

Table 3. Activity of derivatives of (±)-1-(5-aryl-3-pyridine-2-yl-4,5-dihydro-pyrazole-1-yl)-2-imidazole-1-yl-ethanones (**17**) against three strains of *Candida*

Compound	R	Yield, %	Range, μg/mL	CP 208		CPs 801		CG 80	
				24 h	48 h	24 h	48 h	24 h	48 h
AMB	–	–	0.5–8	1	2	2	<0.5	2	2
Mic	–	–	5–80	<5	<5	<5	<5	<5	<5
5FC	–	–	2–32	<2	4	<2	8	<2	<2
17a	H	53	1000–16	–	–	62.5	62.5	62.5	62.5
17b	2–Cl	45	1000–16	–	–	62.5	62.5	62.5	62.5
17e	2–Br	55	1000–16	–	–	62.5	62.5	62.5	62.5
17f	3–Br	56	1000–16	–	–	62.5	62.5	62.5	62.5
17h	2–F	48	1000–62.5	62.5	62.5	–	–	–	–
17i	3–F	46	1000–16	62.5	62.5	–	–	–	–
17j	4–F	49	1000–16	–	–	62.5	62.5	62.5	62.5
17k	2–CH_3	55	1000–16	62.5	62.5	–	–	–	–

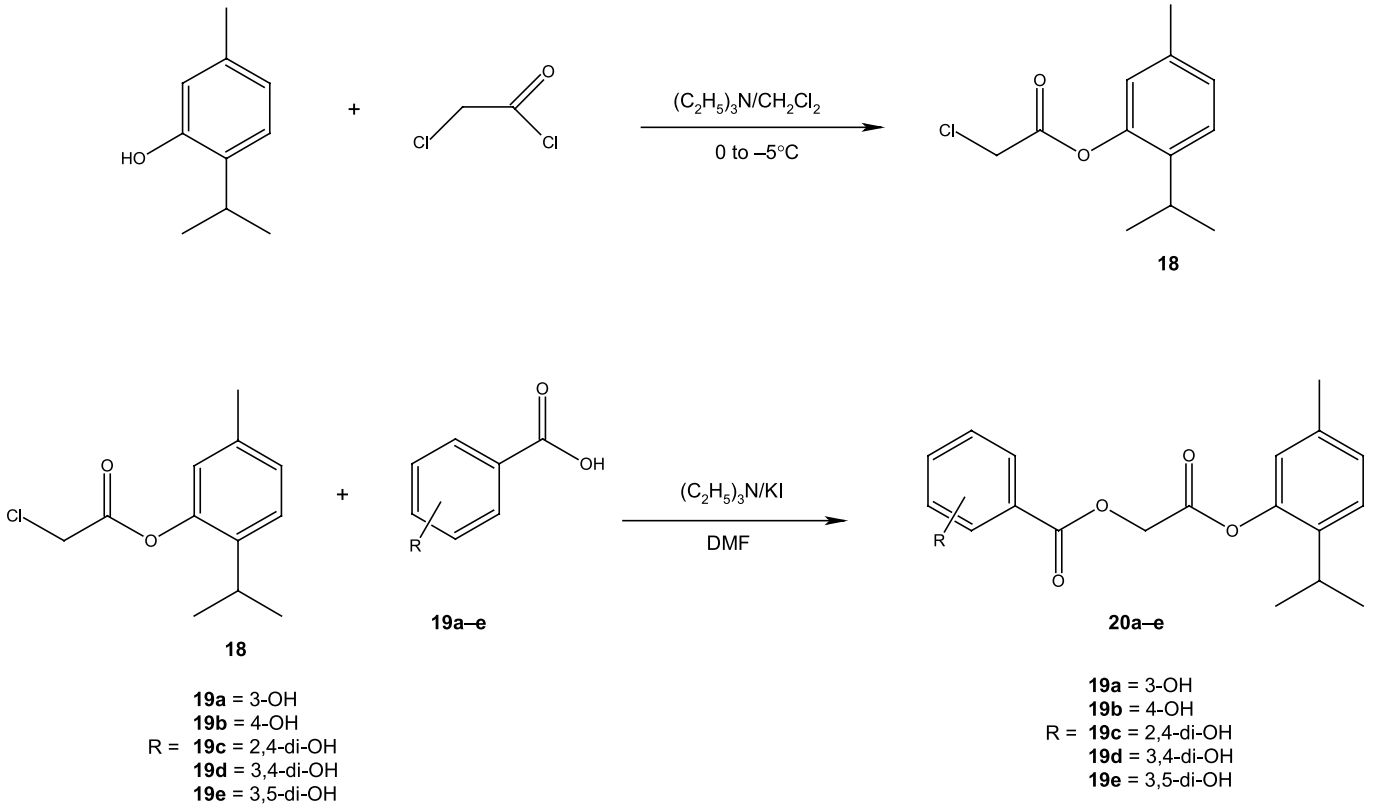

Fig. 7. Scheme for the synthesis of thymol derivatives (**20a-e**).

20e, for which the IC_{50} value was 56.1 and 220.9 μM, respectively. Derivatives **20c** and **20e** contain 2.4- and 3.5-dihydroxy-substituted benzoic acid residues, respectively. In the case of compound **20d**, two hydroxy groups are present in adjacent positions of the phenyl ring. This prevents the molecule from interacting well with the enzyme. This structural feature correlates well with L-3,4-dihydroxyphenylalanine (L-DOPA), which is used as a substrate for the enzyme tyrosinase during bioanalysis. Thus, the compound **20d** is the most active among the dihydroxylated thymol derivatives due to its close structural similarity to L-DOPA. Table 4 shows the IC_{50} values of synthesized thymol analogues. It can be seen that kojic acid exhibits better activity than all synthesized thymol derivatives [15].

In order to determine the optimal conditions for carrying out the acylation reaction of phenolic compounds, Uzbek scientists carried out syntheses under various conditions described in [16] (Fig. 8, Table 5). The chloroacetylation reaction of 4-hydroxyacetanilide was carried out in the presence of various catalysts and solvents. As a result of chloroacetylation of 4-hydroxyacetanilide in the presence of Lewis acids as a catalyst, two products are formed: 4-*N*-acetaminophenyl chloride and 5-*N*-acetamino-2-hydroxyphenacyl chloride. When the reaction is carried out in the absence of a catalyst, the *O*-acylation reaction predominates, resulting in a high observed yield of 4-*N*-acetaminophenyl chloroacetate. Table 5 shows that the best yield is observed when using chloroform as a solvent [16].

In this experimental work, we synthesized derivatives of thymol (2-isopropyl-5-methylphenol) and propofol (2,6-isopropylphenol) with imidazole via *O*-chloroacetates. A methoxy derivative of thymol was also obtained.[1]

EXPERIMENTAL

Devices and materials

^1H and ^{13}C NMR spectra was recorded on a pulsed Fourier spectrometer MSL-300 (*Bruker*, Germany) in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard. Chemical shifts are given in ppm; spin-spin interaction constants are in hertz. Column chromatography was performed using silica gel Kieselgel 60 (*Merck*,

[1] The numbering of connections in this and the following sections is autonomous.

Table 4. Activity of thymol derivatives **20a-e** against fungal tyrosinase

Compound	Tyrosinase inhibition activity	
	% Inhibition, 25 μg/mL	IC_{50} ± SEM μM
20a	48 ± 1	79.3 ± 5.3
20b	33 ± 2	91.5 ± 9.4
20c	68 ± 2	56.1 ± 5.9
20d	55 ± 3	45.0 ± 1.5
20e	5 ± 2	220.9 ± 11.6
Kojic acid	100	16.69 ± 2.8

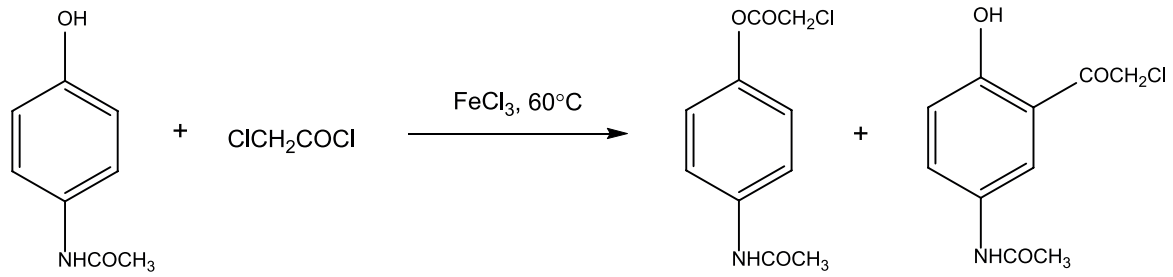

Fig. 8. Scheme for the synthesis of 4-*N*-acetaminophenylchloroacetate and 5-*N*-acetamino-2-hydroxyphenacyl chloride.

Table 5. Chloroacetylation of 4-hydroxyacetanilide in the presence of various solvents [16]

Reagents	Reagent ratio	Temperature, °C	Solvent	Yield, %
4-Hydroxyacetanilinide / chloroacetyl chloride	1:1	60–61	Chloroform	86
4-Hydroxyacetanilide / chloroacetyl chloride	1:1	98–100	Heptane	75
4-Hydroxyacetanilide / chloroacetyl chloride	1:1	83–84	Dichloroethane	79

Germany, particle size 40–63 μm). Silica Gel 60 F254 plates (*Merck*) were used for thin-layer chromatography (TLC) of the obtained compounds. The solvents were additionally dried or high purity reagents from *Merck* (Germany) and *Sigma-Aldrich* (USA) were used. The glassware was dried at 140°C before use.

Preparation of solvents for use in synthesis

The following solvents were used in the synthesis: methylene chloride (CH_2Cl_2), petroleum ether 40/70 (PE), ethyl acetate (EA), acetone, *N*,*N*-dimethylformamide (DMFA), tetrahydrofuran (THF),

and isopropyl alcohol (IPA). Drying and distillation of solvents was carried out according to standard methods.

Synthesis techniques of chloroacetyl derivatives of substituted phenols and polyphenols

The synthesis of 2-isopropyl-5-methylphenyl-2-chloroacetate (1) by heating is shown in Fig. 9.

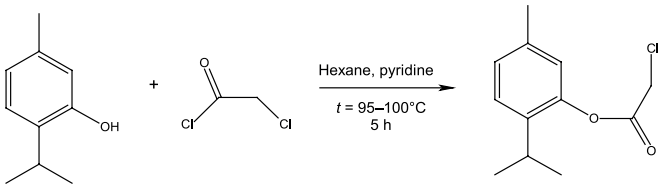

Fig. 9. Scheme for the synthesis of 2-isopropyl-5-methylphenyl-2-chloroacetate (**1**) by heating (method **I**).

Thymol (2.33 mmol, 350 mg) was dissolved in 15 mL of hexane and transferred to a flask fitted with a magnetic stirrer. After adding chloroacetyl chloride (3.26 mmol, 0.26 mL) dissolved in 5 mL of hexane to the thymol solution, the mixture was stirred and heated using a sand bath to a temperature of 95–100°C for 3 h. Then pyridine (0.36 mmol, 0.2 mL) was added to the reaction mass, which was continuously stirred for another 2 h under heating. The course of the reaction was controlled using TLC in a PE/EA solvent system in a ratio of 4:1. The reaction mass was washed from pyridine, dried over anhydrous sodium sulfate Na_2SO_4, and purified by column chromatography (PE/EA, 20:1→5:1). The yield was 254 mg (48%), R_f = 0.77 (PE/EA, 4:1).

^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ=1.22–1.24(Ar–CH–$(CH_3)_2$, 6H), 2.35 (Ar–CH_3, 3H), 3.01 (Ar–CH, 1H), 4.34(–CH_2–Cl, 2H), 6.88(Ar–H4, 1H), 7.10 (Ar–H1, 1H), 7.23 (Ar–H2, 1H).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 20.92 (C6), 23.14 (C7, C9), 27.19 (C8), 40.90 (C12), 122.36 (C4), 126.77 (C1), 127.81 (C2), 136.95 (C3, C5), 147.62 (C10), 166.27 (C14).

The synthesis of 2-isopropyl-5-methylphenyl-2-chloroacetate (2) by heating is shown in Fig. 10.

Thymol (0.67 mmol, 100 mg) was dissolved in 10 mL of methylene chloride and transferred to a flask with a magnetic stirrer. Chloroacetic anhydride (1.27 mmol, 216 mg) dissolved in 5 mL of pyridine was added to the thymol solution, and the mixture was stirred and heated using a sand bath to a temperature of 50–60°C for 5 h. The course of the reaction was controlled using TLC in a

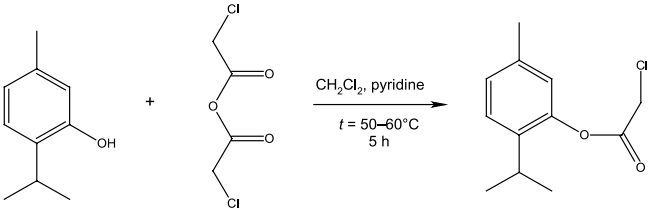

Fig. 10. Scheme for the synthesis of 2-isopropyl-5-methylphenyl-2-chloroacetate (**2**) by heating (method **II**).

PE/EA solvent system in a 10:1 ratio. The reaction mass was washed from pyridine, dried over Na_2SO_4 and purified by column chromatography (PE/EA, 25:1→10:1). The yield was 29 mg (19%), R_f = 0.67 (PE/EA, 10:1).

^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ = 1.11–1.13 (Ar–CH–$(CH_3)_2$, 6H), 2.27 (Ar–CH_3, 3H), 2.96 (Ar–CH, 1H), 4.72 (–CH_2–Cl, 2H), 6.90 (Ar–H4, 1H), 7.09 (Ar–H1, 1H), 7.25 (Ar–H2, 1H).

The synthesis of 2-isopropyl-5-methylphenyl-2-chloroacetate (3) during cooling is shown in Fig. 11.

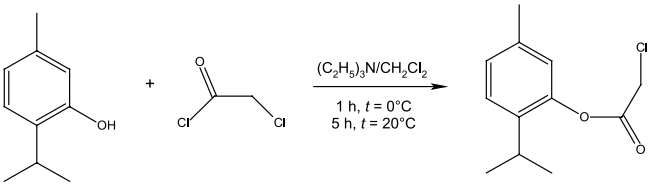

Fig. 11. Scheme for the synthesis of 2-isopropyl-5-methylphenyl-2-chloroacetate (**3**) during cooling (method **III**).

Thymol (1.26 mmol, 189 mg) and triethylamine (1.26 mmol, 0.18 mL) were dissolved in 20 mL of methylene chloride and transferred to a flask with a magnetic stirrer. The mixture was cooled in an ice bath to 0°C. Then chloroacetyl chloride (1.26 mmol, 0.1 mL) dissolved in 5 mL of methylene chloride was added to the reaction mixture drop by drop and cooled for 1 h. After that, the reaction continued at 20°C for another 5 h. The course of the reaction was controlled using TLC in a PE/EA solvent system in a 5:1 ratio. The reaction mass was extracted with 1% hydrochloric acid solution, 5% alkali solution, and with saturated salt solution and dried over Na_2SO_4. Further, the reaction mixture was purified by column chromatography (PE/EA, 30:1→10:1). The yield was 113 mg (40%), R_f = 0.63 (PE/EA, 5:1).

^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ = 1.11–1.13 (Ar–CH–$(CH_3)_2$, 6H), 2.27 (Ar–CH_3, 3H),

2.96 (Ar–CH, 1H), 3.36 (Ar–OH, 4H), 4.72 (–CH_2–Cl, 2H), 6.90 (Ar–H4, 1H), 7.09 (Ar–H1, 1H), 7.25 (Ar–H2, 1H).

The synthesis of 2-isopropyl-5-methylphenyl-2-chloroacetate (4) during cooling is shown in Fig. 12.

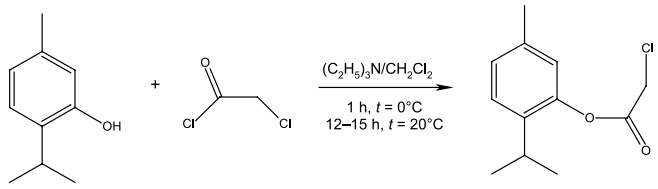

Fig. 12. Scheme for the synthesis of 2-isopropyl-5-methylphenyl-2-chloroacetate (**4**) during cooling (method **IV**).

Thymol (2.66 mmol, 400 mg) and triethylamine (5.32 mmol, 0.74 mL) were dissolved in 10 mL of methylene chloride and transferred to a flask with a magnetic stirrer. The mixture was cooled in an ice bath to 0°C. Then chloroacetyl chloride (13.32 mmol, 1.06 mL) dissolved in 7 mL of methylene chloride was added to the reaction mixture drop by drop and cooled for 1 h. After that, the reaction continued at 20°C for another 12–15 h. The course of the reaction was controlled using TLC in a PE/EA solvent system in a 10:1 ratio. The reaction mass was extracted with 1% hydrochloric acid solution, 5% alkali solution, and with saturated salt solution and dried over Na_2SO_4. Further, the reaction mixture was purified by column chromatography (PE/EA, 30:1→10:1). The yield was 450 mg (75%), R_f = 0.57 (PE/EA, 10:1).

^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ = 1.22–1.24 (Ar–CH–$(CH_3)_2$, 6H), 2.35 (Ar–CH_3, 3H), 3.01 (Ar–CH, 1H), 4.34 (–CH_2–Cl, 2H), 6.88 (Ar–H4, 1H), 7.10 (Ar–H1, 1H), 7.23 (Ar–H2, 1H).

The synthesis of 2,6-diisopropylphenylchloroacetate (5) during cooling is shown in Fig. 13.

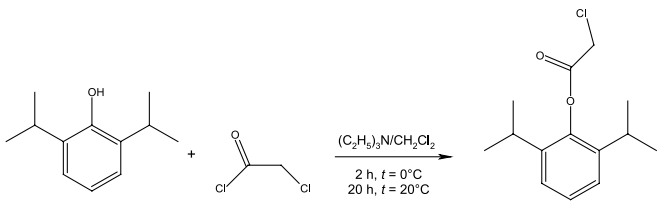

Fig. 13. Scheme for the synthesis of 2,6-diisopropylphenylchloroacetate (**5**) during cooling (method **IV**).

A mixture of propofol (1) (0.799 mmol), triethylamine (0.799 mmol) in anhydrous dichloromethane (25 mL) was cooled in a mixture of ice salt to 0–5°C. Chloroacetyl chloride (2) (0.799 mmol) was added to this reaction mixture in dry dichloromethane drop by drop with constant stirring for 2 h, maintaining a constant temperature. Then the reaction mixture was stirred at 20°C and left overnight, after that washed with 1% HCl and 5% sodium hydroxide solution. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous sodium sulfate, and filtered and the solvent was removed at reduced pressure. The course of the reaction was controlled using TLC in a PE/EA solvent system in a 10:1 ratio. The mixture was purified by column chromatography (PE, PE/EA ratio was 15:1, 12:1, 10:1, 8:1, 6:1). The yield was 43 mg (30.3%). R_f = 0.72 (PE/EA, 10:1).

^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ = 1.64–1.69 (Ar–CH–$(CH_3)_2$, 6H), 3.42–3.44 (Ar–CH, 1H), 5.33 (–CH_2–Cl), 7.73 (Ar–H3, 1H), 7.74 (Ar–H5, 1H), 7.76 (Ar–H4, 1H).

Methods of synthesis of imidazole derivatives of substituted phenols and polyphenols

The synthesis of 2-isopropyl-5-methylphenyl-2-(1*H*-imidazole-1-yl)acetate (6) at 20°C is shown in Fig. 14.

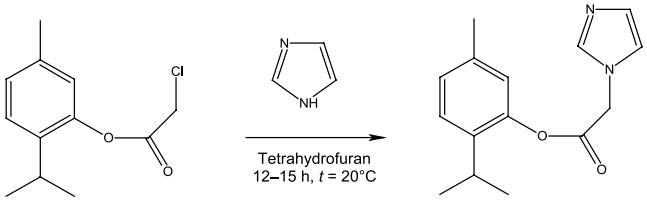

Fig. 14. Scheme for the synthesis of 2-isopropyl-5-methylphenyl-2-(1*H*-imidazol-1-yl) acetate (**6**) at 20°**C** (method **V**).

Imidazole (21.83 mmol, 1486 mg) and 2-isopropyl-5-methylphenyl 2-chloroacetate (1.98 mmol, 450 mg) were dissolved in 7 mL of THF and transferred to a flask with a magnetic stirrer. The mixture was continuously stirred at 20°C for 12–15 h. The course of the reaction was controlled using TLC in the IPS/CH_2Cl_2 solvent system in a 3:2 ratio. The reaction mass was washed with water and dried over Na_2SO_4. Further, the reaction mixture was purified by column chromatography (IPS/CH_2Cl_2, 2:3→3:1). The yield was 20 mg (4%), R_f = 0.85 (IPS/CH_2Cl_2, 3:2).

^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ = 0.85–0.89 (Ar–CH–$(CH_3)_2$, 6H), 2.27 (Ar–CH_3, 3H),

2.91 (Ar–CH, 1H), 4.57–4.71 (–CH_2–N, 2H), 6.55 (Ar–H4, 1H), 6.70 (–N–CH=CH=, 1H), 6.72 (=CH–N–, 1H), 6.80 (Ar–H1, 1H), 6.95 (–N=CH–N–, 1H), 7.02 (Ar–H2, 1H).

The synthesis of 2-isopropyl-5-methylphenyl-2-(1*H*-imidazole-1-yl)acetate (7) at low temperature is shown in Fig. 15.

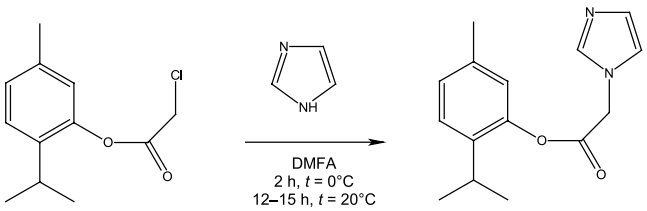

Fig. 15. Scheme for the synthesis of 2-isopropyl-5-methylphenyl-2-(1*H*-imidazol-1-yl) acetate (**7**) during cooling (method **VI**).

Imidazole (4.4 mmol, 300 mg) and 2-isopropyl-5-methylphenyl 2-chloroacetate (0.44 mmol, 100 mg) were dissolved in 3 mL of DMFA and transferred to a flask with a magnetic stirrer and cooled in an ice bath to 0°C for 2 h. After that, the reaction continued at a temperature of 20°C for 12–15 h. The course of the reaction was controlled using TLC in the IPS/CH_2Cl_2 solvent system in a 3:2 ratio. The reaction mass was diluted with water and extracted with CH_2Cl_2, then dried over Na_2SO_4 and evaporated using a rotary evaporator. After removing the solvent, the substance crystallized. The yield was 64 mg (57%), R_f = 0.85 (IPS/CH_2Cl_2, 3:2).

^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ = 0.85–0.89 (Ar–CH–$(CH_3)_2$, 6H), 2.27 (Ar–CH_3, 3H), 2.91 (Ar–CH, 1H), 4.57–4.71 (–CH_2–N, 2H), 6.55 (Ar–H4, 1H), 6.70 (–N–CH=CH=, 1H), 6.72 (=CH–N–, 1H), 6.80 (Ar–H1, 1H), 6.95 (–N=CH–N–, 1H), 7.02 (Ar–H2, 1H).

The synthesis of 2,6-diisopropylphenylimidazol-acetate (8) at 20°C is shown in Fig. 16.

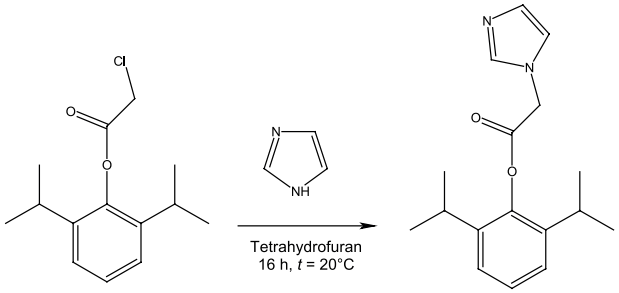

Fig. 16. Scheme for the synthesis of 2,6-diisopropyl-phenylimidazole acetate (**8**) at 20°C.

The ester of propofol and chloroacetyl chloride (130 mg, 0.51 mmol) and imidazole (521 mg, 7.65 mmol) were dissolved in 10 mL of THF and transferred to a round-bottomed flask with a magnetic stirrer. The reaction was placed in the shade because of the fact that under the influence of light, THF can form peroxides. The reaction was left overnight. Then the THF was evaporated on a rotary evaporator and the substance was re-dissolved into CH_2Cl_2. After that, the reaction mixture was washed twice with water and dried over Na_2SO_4. The course of the reaction was controlled using TLC in an isopropanol/CH_2Cl_2 solvent system in a 4:1 ratio. The mixture was purified by column chromatography (CH_2Cl_2, isopropanol/CH_2Cl_2 ratio was 2:3, 1:1, 3:2, 2:1, 3:1). The yield was 32 mg (23.3%). R_f = 0.80 (Isopropanol/CH_2Cl_2, 4:1).

^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ = 1.31–1.35 (Ar–CH–$CH_3)_2$, 6H), 3.09–3.11 (Ar–CH, 1H), 5.62 (–CH_2–Im), 7.40 (Ar–H3, 1H), 7.41 (Ar–H5, 1H), 7.42 (Ar–H4, 1H), 7.15 (Im–H5, 1H), 7.17 (Im–H4, 1H), 7.45 (Im–2H, 1H).

Method of synthesis of methoxy derivatives of substituted phenols

The synthesis of methoxythymol (1-isopropyl-2-methoxy-4-methylbenzene) (9) is shown in Fig. 17.

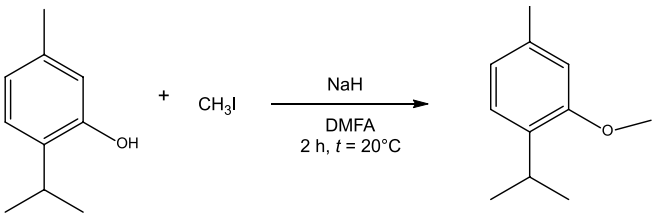

Fig. 17. Scheme for the synthesis of methoxythymol (1-isopropyl-2-methoxy-4-methylbenzene) (**9**).

A suspension of NaH (1.58 mmol, 38 mg) in DMFA was added to thymol (0.8 mmol, 120 mg) dissolved in 1 mL of DMFA and placed in a flask with a magnetic stirrer. The mixture was stirred for 45 min at 20°C. Then CH_3I (2.4 mmol, 0.15 mL) was added to the reaction mixture drop by drop and kept for 1 h at 20°C. The course of the reaction was controlled using TLC in a PE/EA solvent system in a 3:1 ratio. The reaction mass was decomposed with water, acidified with 1% hydrochloric acid solution to pH 4.0, extracted with methylene chloride, and dried over Na_2SO_4. Further, the reaction mixture was purified by column chromatography (PE/EA, 15:1→4:1). The yield was 60 mg (46%), R_f = 0.69 (PE/EA, 3:1).

^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ = 1.11–1.13 (Ar–CH–$(CH_3)_2$, 6H), 2.26 (Ar–CH_3, 3H), 3.15–3.18 (Ar–CH–, 1H), 3.76 (–O–CH_3), 6.74 (Ar–H6, 1H), 6.77 (Ar–H4, 1H), 7.03 (Ar–H3, 1H).

RESULTS AND DISCUSSION

Preparation of chloroacetyl derivatives of substituted phenols and polyphenols

The synthesis of imidazole derivatives of alkyl-substituted phenols was carried out in two stages (Fig. 18). At the first stage of synthesis, *O*-chloroacetyl derivatives of selected alcohols, thymol, and propofol were obtained, to which imidazole was then added.

Chloroacetyl derivatives of aromatic alcohols were obtained using several techniques described in the literature. In particular, syntheses carried out during heating [16] and cooling [15] of the reaction mass were used.

In order to obtain a chloroacetyl derivative of thymol using heating, two syntheses were carried out under different conditions (Figs. 9 and 10). The first synthesis (method **I**) was carried out using chloroacetyl chloride as an acylating agent and *n*-hexane as a high-boiling solvent. In the second case (method **II**) involving the use of chloroacetic anhydride, an attempt was made to replace the solvent with low-boiling methylene chloride. As a result, the following product yields were obtained: for compound **1** (method **I**), the yield was 48%, whereas for compound **2** (method **II**), the yield was 19%, from which it follows that the change in the conditions of the synthesis did not lead to a better result.

We also investigated the possibilities of improving synthesis methods using reduced (0°C) and room temperature (20°C) using the example of two methods with chloroacetyl chloride as an *O*-acylating reagent, which differed in reaction time and reagent ratios (Figs. 11 and 12). Chloroacetyl derivatives of thymol were obtained with yields of 40% (method **III**) and 75% (method **IV**) for compounds **3** and **4**, respectively. Therefore, the synthesis by cooling the reaction mass using an excess of an acylating agent and increasing the reaction time is more preferable when obtaining chloroacetyl derivatives of aromatic alcohols. The results are presented in Table 6.

The *O*-acylation reaction of propofol proceeded similarly to the reaction with thymol, but the reaction time increased due to steric difficulties in attaching the chloroacetate fragment to propofol (Fig. 13). The product yield was 30%.

Preparation of imidazole chloroacetyl derivatives of alkyl-substituted phenols

We conducted a synthetic study to obtain imidazole derivatives of 2-isopropyl-5-methylphenyl--2-chloroacetate. In the course of the study, two syntheses were carried out according to the methods described in [15, 16], in which different temperatures and solvents were used (Figs. 14 and 15), and we also increased the reaction time in comparison with the literature sources used. When synthesizing at 20°C and using THF as a reaction medium (method **V**), the yield of product **6** was 4%, which is not a satisfactory result. In order to increase the yield of the product, synthesis was carried out using DMFA as a solvent, as well as at lower and room temperatures (method **VI**) the yield of product 7 was 57%.

The reaction of 2,6-isopropylphenylchloro-acetate with imidazole was carried out according to method **V**, similarly to the reaction with a thymol derivative, the yield was 23%. The results are presented in Table 7.

Preparation of methoxy derivatives of substituted phenols

The methoxy derivatives of thymol were synthesized according to the method [17]. Due to steric difficulties in attaching the methyl residue, the reaction time was increased (Fig. 17). In this case, methoxythymol (1-isopropyl-2-methoxy-4-methyl-benzene) (9) was obtained with a yield of 46%.

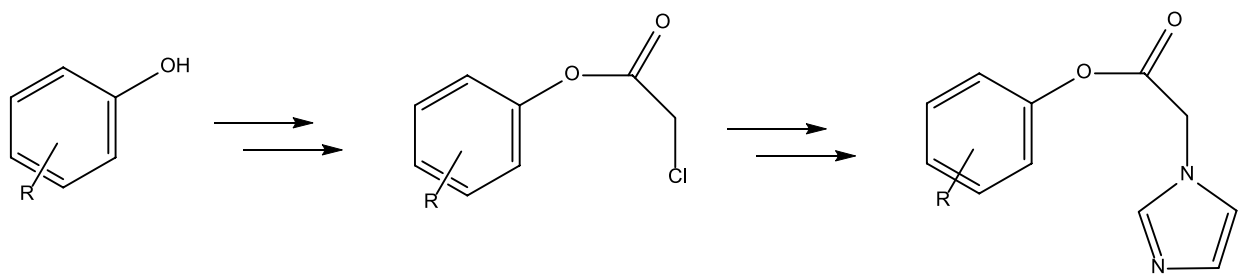

Fig. 18. General scheme for the synthesis of imidazole derivatives of substituted phenols and polyphenols.

Table 6. Chloroacetylation of thymol in the presence of various solvents

Reagents	Reagent ratio	Temperature, °C	Solvent	Yield, %
Thymol/Chloroacetyl chloride	1:1	95–100	Hexane	48
Thymol/Chloroacetic anhydride	1:1.9	50–60	Methylene chloride	19
Thymol/Chloroacetyl chloride	1:2	0–5	Methylene chloride	40
Thymol/Chloroacetyl chloride	1:4	0–5	Methylene chloride	75

Table 7. Preparation of imidazole chloroacetyl derivatives of alkyl-substituted phenols in the presence of various solvents

Reagents	Reagent ratio	Temperature, °C	Solvent	Yield, %
Thymol chloroacetyl chloride / imidazole	1:3	20	THF	4
Thymol chloroacetyl chloride / imidazole	1:10	0–5	DMFA	57
Propofol chloroacetyl chloride / imidazole	1:10	0–5	DMFA	23

Note: THF is tetrahydrofuran; DMFA is *N*,*N*-dimethylformamide.

Confirmation of the structure of the obtained compounds

The structures of the obtained compounds were confirmed by methods ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR spectrum of 2-isopropyl-5-methylphenyl-2-chloroacetate (Fig. 19). Methyl protons of the isopropyl chain of the ring were observed at δ = 1.22–1.24 ppm. The signal belonging to Ar–CH_3 was recorded at δ = 2.35 ppm. The proton Ar–CH– gives a multiplet at 3.01 ppm. The spectrum also showed a signal at δ = 4.34 ppm, which indicates the presence of –CH_2–Cl. Aromatic protons appeared in the characteristic range from 6.88 to 7.23 ppm.

^{13}C NMR spectrum of 2-isopropyl-5-methylphenyl-2-chloroacetate (Fig. 20). The methyl carbon of the ring (Ar–CH_3) gave a signal at 20.92 ppm. The methyl carbons of the isopropyl chains of the ring were present at δ = 23.14 ppm. The carbon corresponding to Ar–CH resonated at δ = 27.19 ppm. The signal at δ = 40.90 ppm confirms the presence of chloroacetate (–CH_2–Cl). Signals in the range from 122.36 to 136.95 ppm confirm the presence of the aromatic ring. The signal at δ = 147.62 ppm corresponds to carbon, through which a complex ester bond is formed by oxygen. The spectrum also showed a signal at δ = 166.27 ppm, characteristic of the carboxyl group atom (C=O).

^{1}H NMR spectrum of 2,6-diisopropylphenyl-chloroacetate (Fig. 21). A multiplet corresponding to the methyl protons of the isopropyl chains of the ring was observed at δ = 1.64–1.69 ppm. The proton Ar–CH– gives a multiplet at δ = 3.42–3.44. The signal at δ = 5.33 ppm corresponded to protons –CH_2–Cl. The protons of the aromatic ring appeared in the range of 7.73–7.76 ppm.

^{1}H NMR spectrum of 2-isopropyl-5-methylphenyl-2-(1*H*-imidazole-1-yl)acetate (Fig. 22). Methyl protons of the isopropyl chain of the ring were observed at δ = 0.85–0.89 ppm. The signal belonging to Ar–CH_3 was recorded at δ = 2.27 ppm. The proton Ar–CH– gives a multiplet at 2.91 ppm. The spectrum

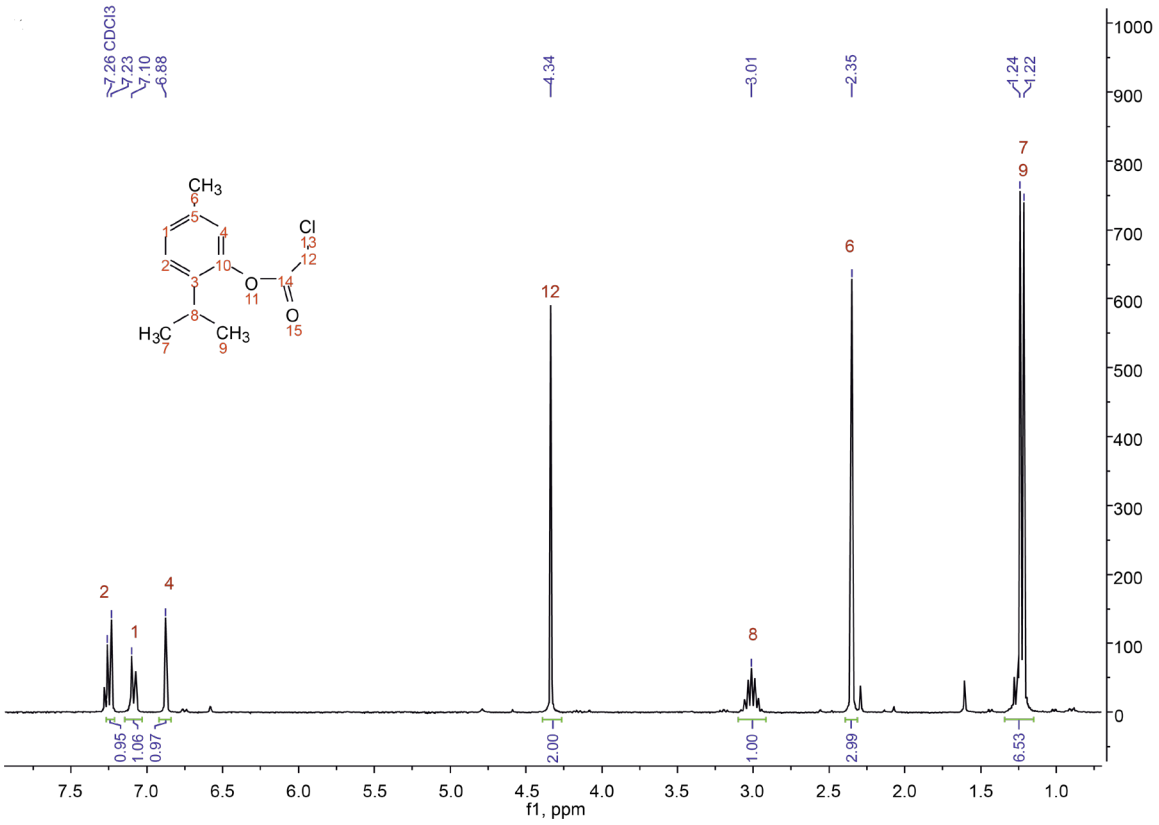

Fig. 19. [1]H NMR spectrum of 2-isopropyl-5-methylphenyl-2-chloroacetate.

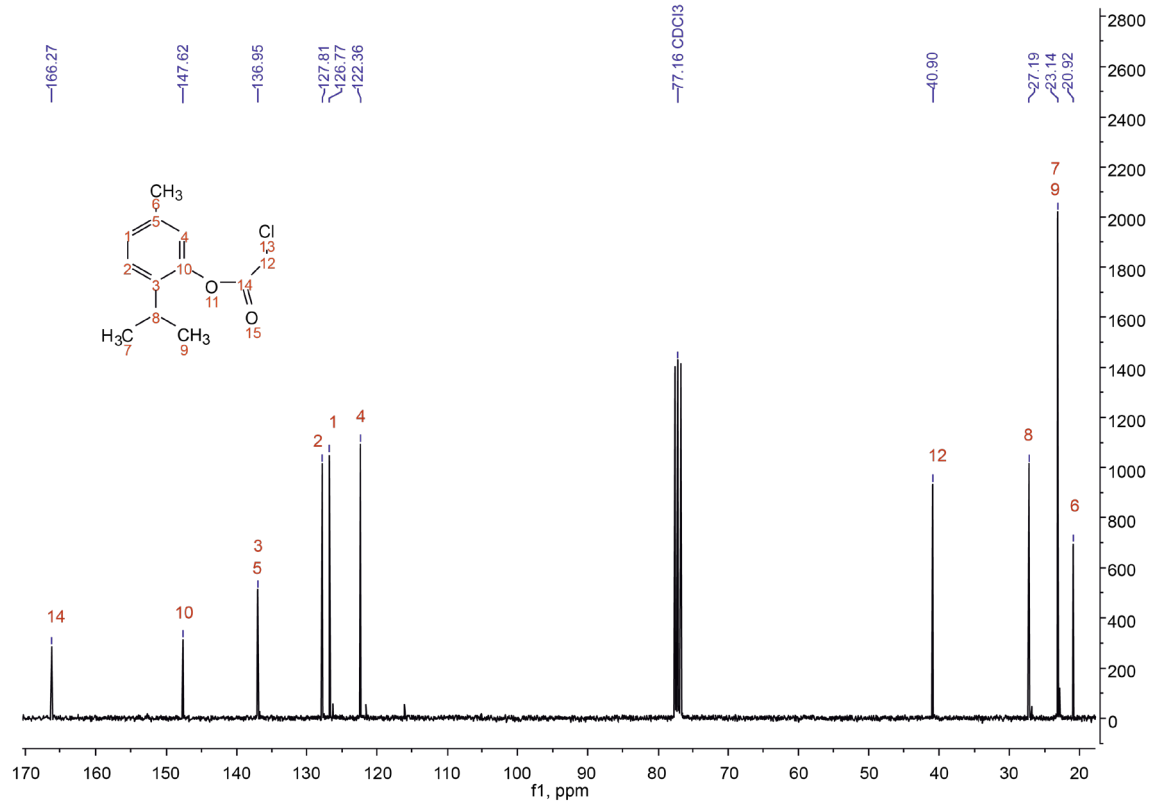

Fig. 20. [13]C NMR spectrum of 2-isopropyl-5-methylphenyl-2-chloroacetate.

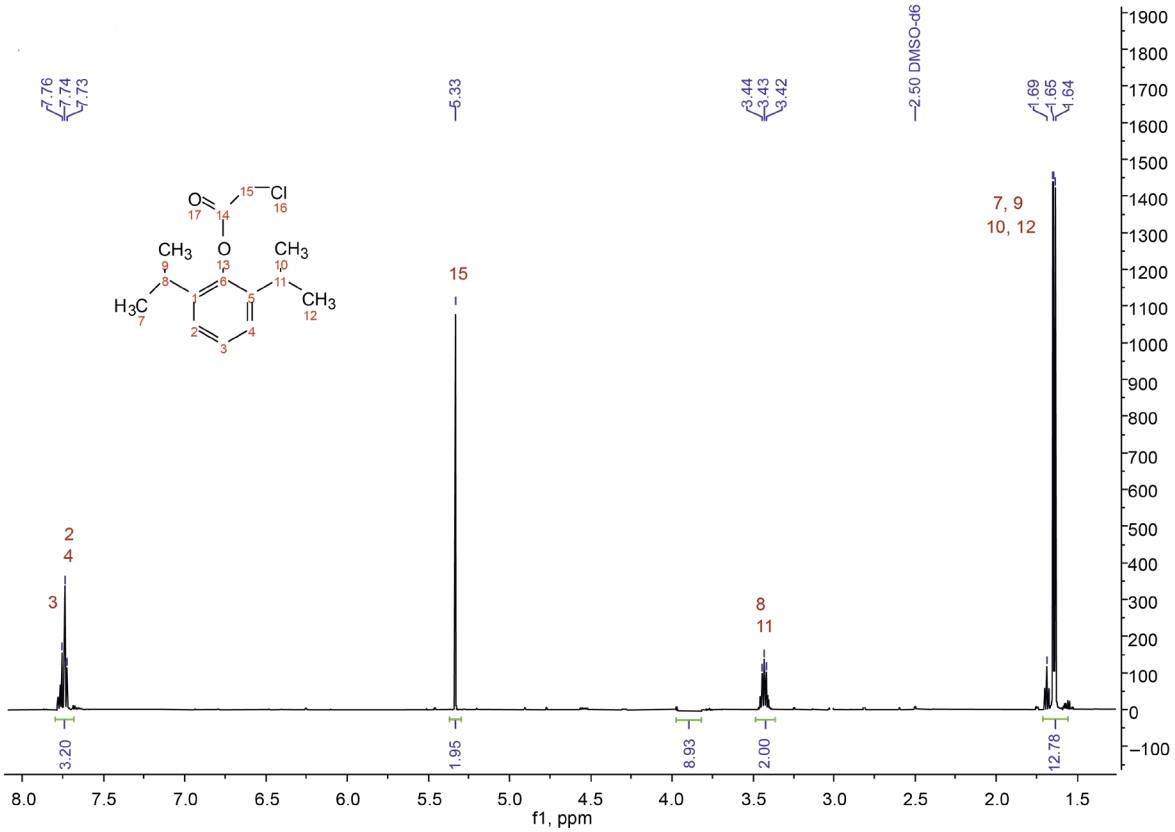

Fig. 21. [1]H NMR spectrum of 2,6-diisopropylphenylchloroacetate.

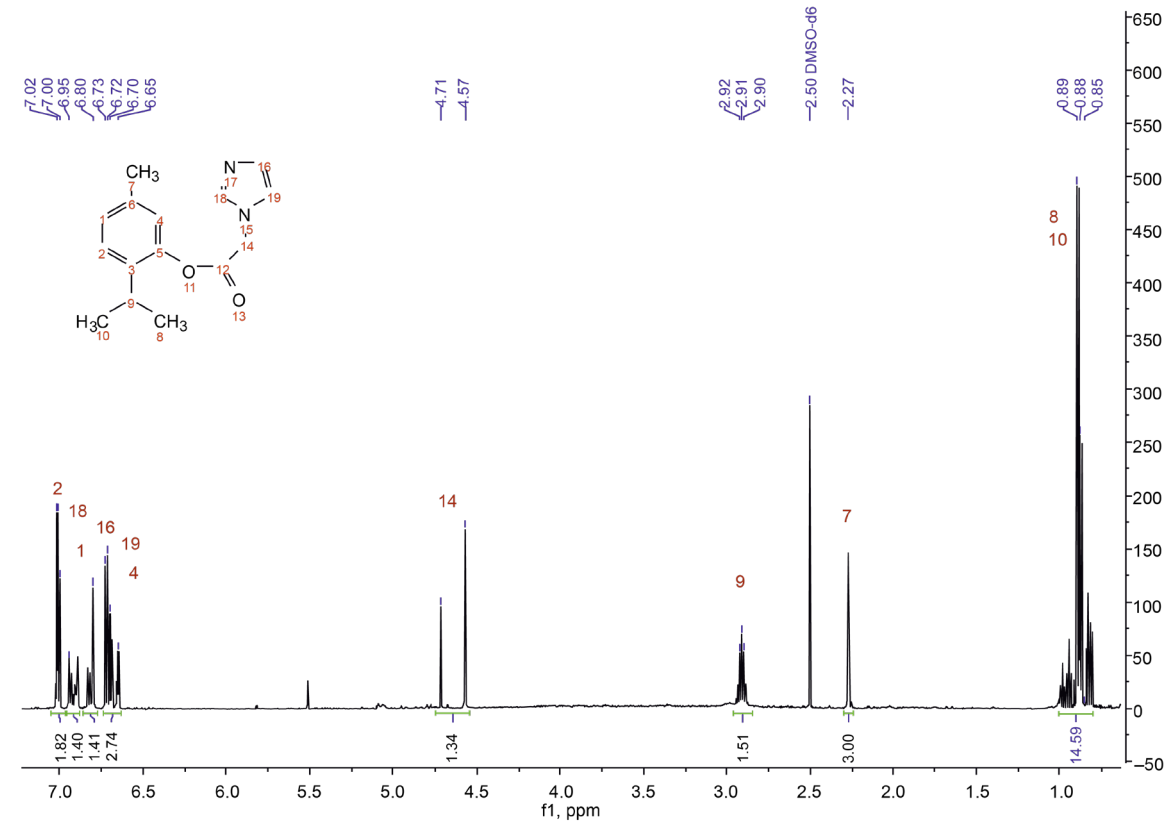

Fig. 22. [1]H NMR spectrum of 2-isopropyl-5-methylphenyl-2-(1*H*-imidazol-1-yl) acetate.

also showed signals at δ = 4.57–4.71 ppm, which indicates the splitting of protons –CH_2– groups located between –N– and –C=O groups.

It can be explained by the fleximeric structure of this molecule, which is confirmed by 3D modeling data (Fig. 23). Aromatic protons appeared in the characteristic range from 6.65 to 7.02 ppm. The protons of the imidazole fragment were observed in the range from 6.70 to 7.00 ppm. The split signal of the proton –CH– between two nitrogen atoms (δ = 7.00 ppm) also testifies in favor of the formation of a fleximer analog.

^{1}H NMR spectrum of 2,6-diisopropylphenyl-imidazolacetate (Fig. 24). A multiplet corresponding to the methyl protons of the isopropyl chains of the ring was observed at δ = 1.31–1.35 ppm. The proton Ar–CH– gives a multiplet at δ = 3.09–3.11. The signal at δ = 5.62 ppm corresponded to the protons –CH_2–Im. The protons of the aromatic ring appeared in the range of 7.40–7.42 ppm, and the protons of the imidazole ring in the range of 7.15–7.45 ppm.

^{1}H NMR spectrum of methoxythymol (Fig. 25). A doublet corresponding to the methyl protons of the isopropyl chain of the ring was observed at δ = 1.11–1.13 ppm. At δ = 2.26 ppm, a signal corresponding to Ar–CH_3 was recorded. The proton Ar–CH– gives a multiplet at δ = 3.15–3.18 ppm. The signal at δ = 3.76 ppm corresponded to the protons –O–CH_3. The protons of the aromatic ring appeared in the range of 6.74–7.03 ppm.

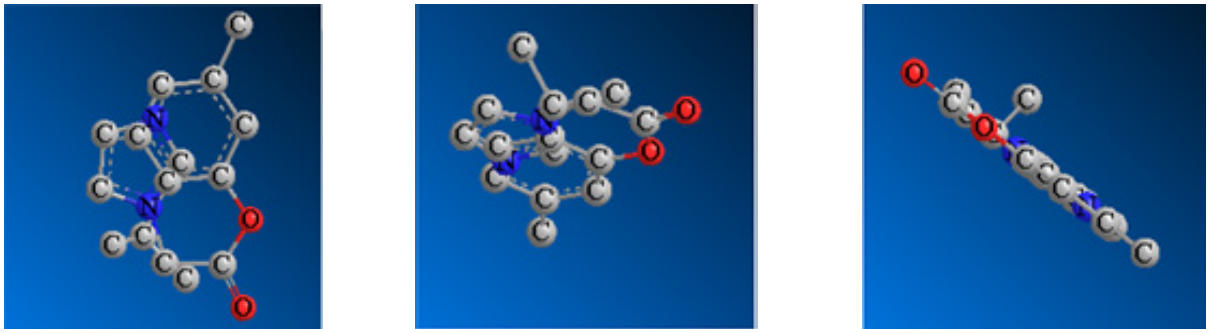

Fig. 23. 3D model of 2-isopropyl-5-methylphenyl-2-(1*H*-imidazol-1-yl) acetate.

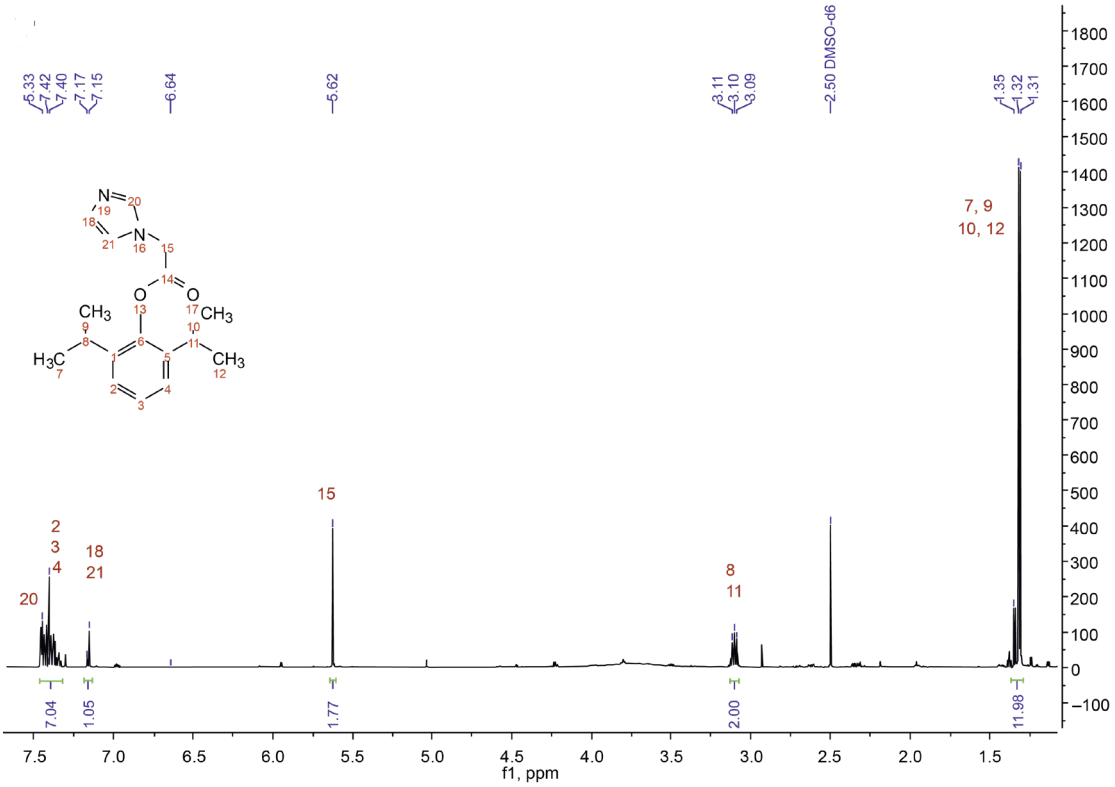

Fig. 24. ^{1}H NMR spectrum of 2,6-diisopropylphenylimidazole acetate.

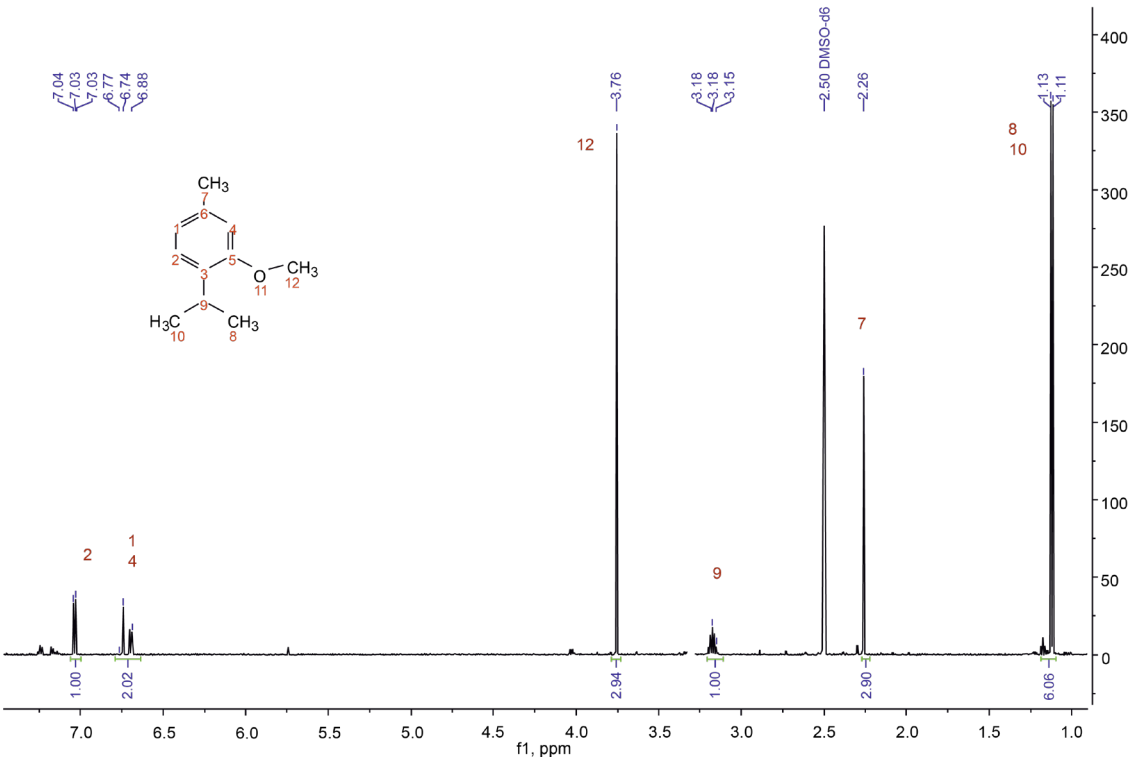

Fig. 25. ^{1}H NMR spectrum of methoxythymol.

CONCLUSIONS

When studying various approaches for the *O*-acylation of thymol and propofol, it was found that synthesis carried out during cooling of the reaction mass using an excess of chloroacetyl chloride in dichloromethane in the presence of triethylamine gives the highest yield, as well as allowing the conversion of the initial reagent to be controlled. For the stage of pharmacophore (heterocycle) administration, a reaction with imidazole in tetrahydrofuran at room temperature was worked out. The structure of the compounds was confirmed by NMR spectroscopy. Samples of the obtained compounds were transferred for biological studies on model yeast strains. Such methods are likely to be useful for obtaining a number of hydrophobic derivatives of aromatic alcohols.

Acknowledgments

The work was supported by a grant from the Ministry of Science and Higher Education of the Russian Federation (project No. 0706-2020-0019) using the equipment of the RTU MIREA Center for Collective Use.

Authors' contributions

V.A. Sokhraneva – conducting experiments on the synthesis of thymol–imidazole conjugates, processing the material, and writing the text of the article;

D.A. Yusupova – conducting experiments on the synthesis of thymol–imidazole conjugates, synthesis of thymol methoxy derivative;

V.S. Boriskin – conducting experiments on the synthesis of conjugates of propofol with imidazole;

N.V. Groza – development of the research concept, scientific guidance at all stages of the study.

The authors declare no conflicts of interest.

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The article was submitted: December 21, 2021; approved after reviewing: March 10, 2022; accepted for publication: June 17, 2022.

Translated from Russian into English by N. Isaeva
Edited for English language and spelling by Thomas Beavitt