Original research article

SYNTHESIS OF NEW 3,4-DIHYDROPYRIMIDIN-2(1H)-ONES: OPTIMISATION OF SYNTHESIS CONDITIONS AND ANALYSIS OF ANTIFUNGAL ACTIVITY OF THE OBTAINED COMPOUNDS

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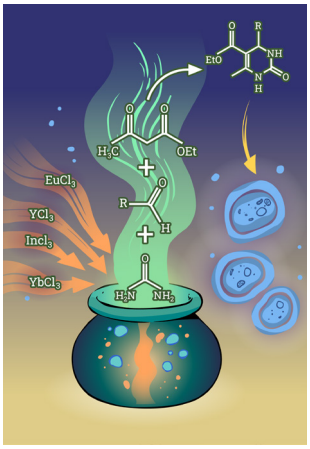

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Abstract: This paper for the first time presents an efficient method for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (3,4-DHPMs) bearing aliphatic and cyclopropane-containing aldehyde residues, using europium(III) chloride hexahydrate as a catalyst in the Biginelli multicomponent reaction (MCR). A high permeability through the phospholipid bilayer and the potential for passive diffusion facilitating participation in intracellular interactions were determined. A preliminary evaluation of the antifungal properties of the obtained compounds against a range of fungal species was carried out using *in silico* methods. Experiments on the effect of 3,4-dihydropyrimidinones on the growth of *Yarrowia lipolytica* yeast showed no acute toxicity of the tested compounds within the micromolar concentration range.

Keywords: 3,4-dihydropyrimidin-2(*1H*)-ones, Biginelli multicomponent reaction, aliphatic and cyclopropane-containing aldehydes, europium (III) chloride, indium (III) chloride, yttrium (III) chloride, ytterbium (III) chloride, PerMM service, Pass Online service, *in silico* analysis, *Yarrowia lipolytica*

Оригинальная исследовательская статья

СИНТЕЗ НОВЫХ 3,4-ДИГИДРОПИРИМИДИН-2(1Н)-ОНОВ: ОПТИМИЗАЦИЯ УСЛОВИЙ СИНТЕЗА И АНАЛИЗ БИОАКТИВНОСТИ ПОЛУЧЕННЫХ СОЕДИНЕНИЙ

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Резюме: Впервые разработан эффективный метод получения 3,4-дигидропиримидин-2(1Н)-онов (3,4-ДГП), содержащих остаток алифатических и циклопропан содержащих альдегидов с применением гексагидрата хлорид европия(III) как катализатора для мультикомпонентной реакции (МКР) Биджинелли. Проведена комплексная оценка возможных биологических свойств полученных соединений методами *in silico*. Расчитана высокая проницаемость через фосфолипидные бислой и возможность пассивной диффузии для участия во внутриклеточных взаимодействиях. Опыты по влиянию 3,4-дигидропиримидинонов на рост дрожжей *Yarrowia lipolytica* показали отсутствие острой токсичности у протестированных соединений в микромолярном диапазоне концентраций. Расчеты показывают, что 3,4-ДГП-ы могут обладать цитотоксическими свойствами относительно многих линий раковых клеток, что перспективно для биомедицинских исследований.

Ключевые слова: 3,4-дигидропиримидин-2(1Н)-оны, мультикомпонентная реакция Биджинелли, алифатические и циклопропансодержащие альдегиды, хлорид европия (III), хлорид индия (III), хлорид иттрия (III), хлорид иттербия (III), сервис PerMM, сервис Pass Online; анализ *in silico*, *Yarrowia lipolytica*

Introduction

Pyrimidine (1,3-diazine) derivatives have various therapeutic applications in medicinal chemistry [1]. One of the proposed reasons for the compounds' activity is the presence of a pyrimidine base in cytosine, thymine and uracil, which are essential building blocks of nucleic acids, including DNA and RNA [1].

A number of chemical compounds containing the common 3,4-dihydropyrimidin-2(1H)-one fragment **1—3** (Fig. 1) as a core have garnered significant interest from researchers due to a wide range of therapeutic and pharmacological properties [2—4], including antitumour [5; 6] and antitubercular activity [7—9].

3,4-DHPMs can be synthesised via the Biginelli MCR, a powerful tool with a focus on generating diverse structural fragments [3; 4; 10; 11].

The use of multicomponent reactions provides a viable synthetic approach, offering several advantages: selectivity, efficient substrate utilisation, environmental friendliness, cost-effectiveness and experimental simplicity [3; 4; 10; 11]. The Biginelli reaction is unique and promising in that it provides compounds with a distinct set of cycles and functional groups [3; 4; 10; 11].

Aliphatic aldehydes typically give very low yields in the Biginelli reaction [12]. Despite the limited availability of 3,4-DHPMs bearing aliphatic aldehyde residues, considerable data exist on these compounds and their biological activities (Fig. 1) [13—16].

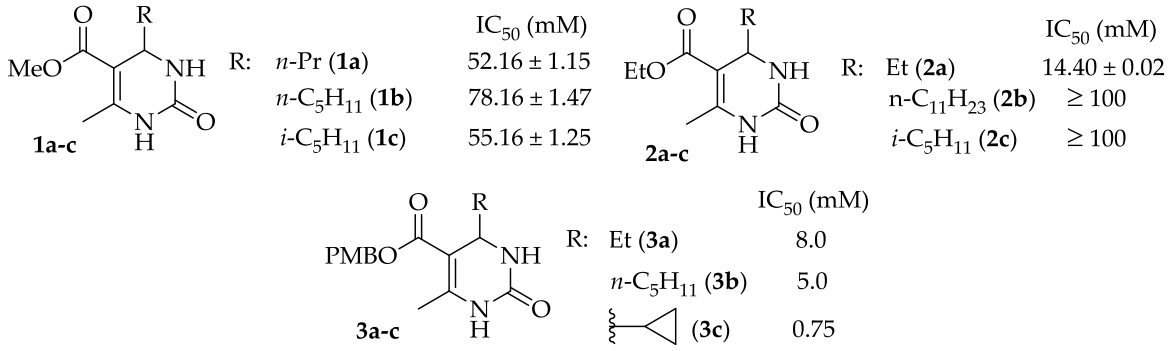

Fig. 1. Bioactive 3,4-DHPs 1-4 with an aliphatic aldehyde fragment in the side chain

Indeed, compounds **1a-c** are effective inhibitors of the enzyme β-glucuronidase, useful in combating a variety of pathological conditions [13]. Compound **2a** exhibits inhibitory activity against xanthine oxidase, an enzyme that is an important pharmacological target for the treatment of hyperuricemia in gout and arthritis [14], whereas compounds **2b**,**c** (Fig. 1) are potent and selective inhibitors of Punta Toro virus, *Bunyaviridae* group and *Phlebovirus* genus, and Rift Valley fever virus, comparable to ribavirin [15]. Compounds **3a-c** (Fig. 1) are sodium iodide symporter (NIS) inhibitors and radioprotective molecules capable of blocking the uptake of radioactive iodine [16].

Cyclopropane derivatives are bioactive compounds found in animals, plants and microorganisms; generated during both primary and secondary metabolism, they display diverse biological properties [17—20].

Hybrid and multifunctional drugs attract considerable attention because they combine two pharmacophore moieties within a single molecule, prompting a continual search for new 3,4-DHPMs capable of modulating known processes or revealing novel bioactivities — a practice now well established in organic synthesis [21].

To implement this idea, potential modifications of the standard Biginelli reaction product **5** (Fig. 2) were planned, taking into account the substitution of aldehyde **6** with an aliphatic aldehyde residue 7, including those containing a cyclopropane fragment **8—11**.

Thus, compounds prepared via the Biginelli reaction using aliphatic aldehydes **7—11** [22] may exhibit distinct biological properties, as they incorporate two pharmacophore groups: the 3,4-dihydropyrimidin-2(1H)-one ring and a cyclopropane moiety (Fig. 2).

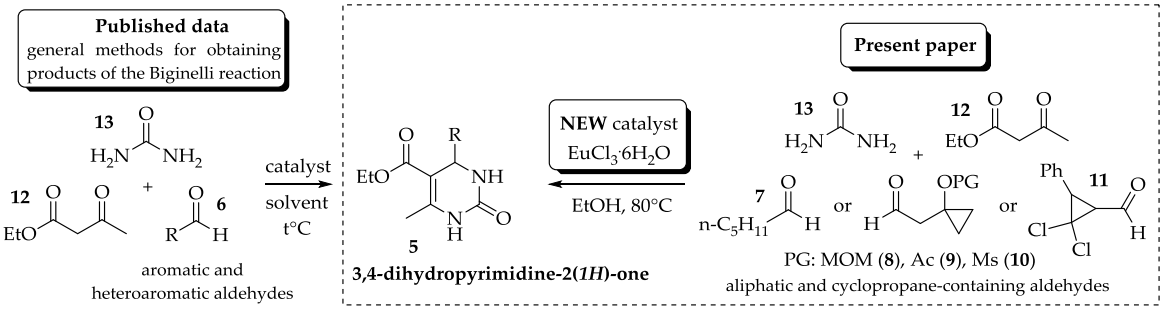

Fig. 2. Strategy for the synthesis of 3,4-DHPMs using Biginelli MCRs

Aldehydes **8—11** are labile compounds because they contain a cyclopropane ring, which can be easily opened in strongly acidic media or in the presence of strong Lewis acids; they also undergo elimination reactions in basic media. The *gem*-dihalogenecyclopropane moieties are labile under the action of basic reagents and many nucleophiles. These factors significantly limit the choice of catalysts and solvents for Biginelli MCRs involving aliphatic aldehydes **8—11**.

This study aims to identify new mild and selective catalysts and conditions for the Biginelli reaction, enabling the efficient use of aliphatic aldehydes **7—11** of various structures to achieve high yields, as well as to evaluate the antifungal properties of the resulting compounds against ascomycetous yeast of the *Yarrowia lipolytica species*, including through *in silico* approaches. Such studies have not been conducted previously, as evidenced by the lack of relevant information in the literature. To accomplish this, a series of experiments was conducted to identify catalysts — rare-earth metal chlorides — that possess sufficient Lewis acidity to accelerate the reaction without disrupting the small cyclic fragment. The central idea is that these compounds should readily undergo cyclopropane ring opening under the action of various enzymatic systems, thereby laying groundwork for bioconjugation by activating them without chemical intervention in the biosphere. For example, in an organism, compound 16 is likely to undergo transfer of the acyl moiety under the influence of an acetyl-CoA molecule, potentially leading to the formation of an open-chain cyclopropanol moiety, which is known to be highly reactive toward numerous nucleophiles, electrophiles and radicals present in the system.

Materials and methods

The reagents and solvents used in this study were of 'pure' and 'pure for analysis' grade. Solvents were purified and dried according to established literature methods. The identity of the synthesised compounds was confirmed and reaction progress was monitored by thin-layer chromatography (TLC) on Sorbfil plates. Solvent mixtures of petroleum ether and ethyl acetate in various ratios were used as eluents. Individual compounds were isolated by column chromatography on silica gel (70—230 mesh, Merck) using the same solvent mixtures as eluents.

^{1}H and ^{13}C NMR spectra of 5 % solutions of the studied compounds in $CDCl_3$ or $(CD_3)_2SO$ were obtained on a Bruker Avanse-500 spectrometer (operating frequencies 500 and 125 MHz). Chemical shifts were recorded on the δ scale, using the residual proton signals of $CDCl_3$ (δ = 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C) and $(CD_3)_2SO$

(δ = 2.50 ppm for ^{1}H and 39.4 ppm for ^{13}C) as references. IR spectra of the investigated substances were recorded in film on a Vertex 70, Bruker FT-IR Alpha spectrophotometer. Mass spectra were recorded on an Agilent 8860 GS system mass spectrometer using 70 eV electron impact ionisation, an Agilent 1990 1s-433e column and an HP-5 MS column over a temperature range of – 60 to 350 °C. The melting point was determined on a Stuart SMP 50 Cole-Parmer instrument. The masses of the substances were measured using Radwag AS 220/C/2/N analytical balance with an accuracy of 0.1 mg.

The yeast strain *Yarrowia lipolytica* DE5.54-1 from the collection of the A. N. Bach Institute of Biochemistry of the Russian Academy of Sciences was used in the study, with its subsequent cultivation at the Laboratory of Pharmaceutical Biochemistry at the Research Institute for Physical Chemical Problems of Belarusian State University. *Yarrowia lipolytica* expresses CYP11A1 and CYP17A1 genes from bovine adrenal glands using isocitrate lyase as a promoter. Yeast cultures were grown in standard YPD nutrient medium (1 % yeast autolysate, 2 % peptone, 2 % glucose; Difco, USA) at 30 °C with mechanical agitation at 200 rpm for 24 h. After 24 h, the culture was transferred to a fresh portion of nutrient medium [23].

Microbiological experiments to evaluate the effect of the compounds on yeast growth were conducted at 30 °C and 200 rpm × min^{-1} in a UHTM shaker-incubator (Elion, Russia) using YPD 0.4 nutrient medium (1 % yeast extract, 2 % peptone, 0.4 % glucose). The number of cells was estimated by absorbance at 600 nm (A_{600}, A_{600} = 1 correlated with 24 × 10^{6} cells [24]. The tested compounds were added as ethanol solution to a concentration of 100 μM and 1 % ethanol. 1 % ethanol was added to the control sample. The initial number of cells corresponded to an optical density of A_{600} = 0.5. The cultures were incubated for 24 h. For A_{600} growth control, aliquots of 100 μl were determined by mixing 100 μl with 900 μl of growth medium at 0, 3, 6, 18 and 24 h.

The general procedure for the synthesis of Biginelli products **14—18** was as follows: in a solution of 0.100 g (1.0 mmol) hexanal **7**, or 0.144 g (1. 0 mmol) aldehyde **8**, or 0.142 g (1.0 mmol) aldehyde **9**, or 0.178 g (1.0 mmol) aldehyde **10,** or 0.215 g (1.0 mmol) aldehyde **11**, 0.130 g (1.0 mmol) acetoacetic ester **12**, 0.072 g (1. 2 mmol) urea **13** with a selected catalyst in EtOH (3 mL) [15.2 mg (0.05 mmol), or 30.4 mg (0.15 mmol) $YCl_3 \cdot 6H_2O$, 11.0 mg (0.05 mmol), or 33.1 mg (0.15 mmol) $InCl_3 \cdot 6H_2O$, 18. 3 mg (0.05 mmol), or 55.0 mg (0.15 mmol) $EuCl_3 \cdot 6H_2O$, 19.4 mg (0.05 mmol), or 58.1 mg (0.15 mmol) $YbCl_3 \cdot 6H_2O$] was boiled for 4—12 h until the reaction was complete (controlled by TLC). The mixture was cooled, the precipitate was separated and recrystallised from EtO H. If no crystals formed, the solvent was removed under reduced pressure, and the product was separated by column chromatography using a petroleum ether/ethyl acetate mixture in varying proportions as the eluent.

Results

1. Selection of optimal conditions

Initially, experiments were carried out to select optimal conditions for the Biginelli reaction using hexanal **7**, acetoacetic ester **12** and urea **13** (Fig. 3).

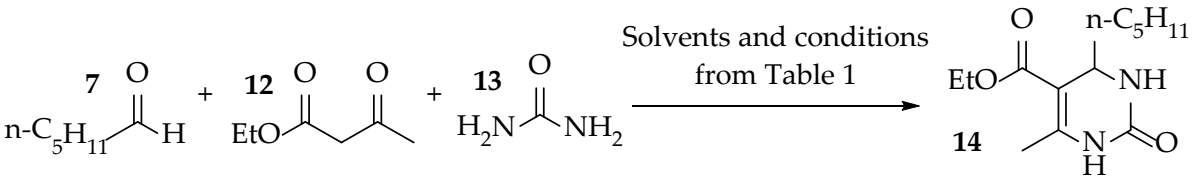

Fig. 3. Model Biginelli MCR involving hexanal **7**, acetoacetic ester **12** and urea **13**

Hexanal was chosen because 3,4-DHPMs containing pentyl fragments (**1b**, **1c**, **2c** and **3b**) are known to exhibit promising biological properties for biomedical research (see Fig. 1).

The experiments explored both established systems for aliphatic aldehydes employing a wide range of soft catalysts [12, 25—45] and newly developed systems based on rare-earth metal salts and ionic liquids (Table 1). The results of the experiments are summarised in Table 1.

Table 1

Results of Biginelli MCR experiments involving hexanal 7, acetoacetic ester 12 and urea 13 under the action of different catalysts[1]

№	Catalyst (mmol)	Ratio of reagents 7/12/13	Solvent	t, °C	τ, h[2]	Yield 14, %[3]
1	2	3	4	5	6	7
1	TsOH (0.15) [25]	1/1.2/1.5	EtOH	80	2.5	—
2	I_2 (0.50) [26]	1/1/1.5	PhMe	105	5	10
3	I_2 (0.40) [27]	1/1/1.25	MeCN	82	9	—
4	TEBA (0.10) [28]	1/1/1.5	—	100	3	31
5	NH_4Cl (0.40) [29]	1/1/1.5	—	100	3	8
6	$NaIO_4$ (0.20) [30]	1/1/2	—	20	6	14
7	$NaIO_4$ (0.20) [30]	1/1/2	EtOH	80	7	6
8	$LiClO_4$ (0.20) [31]	1/1/2	MeCN	82	7	72
9	LiBr (2.00) [32]	1/1/1	THF	80	7	—
10	LiBr (0.10) [33]	1/1.2/1.2	MeCN	82	7	16
11	CuI (0.15) [34]	1/1/1.5	MeCN	90	3	22
12	CuI (0.15)	1/1/1.5	EtOH	80	8	12
13	$Sc(OTf)_3$ (0.10) [35]	1/1/1.2	EtOH	80	16	29
14	$Sc(OTf)_3$ (0.10) [36]	1/1/1.5	MeCN	82	16	33
15	$Cu(OTf)_2$ (0.01) [37]	1/1/1	MeCN	82	14	16
16	$Cu(OTf)_2$ (0.20) [38]	1/1/1.5	EtOH	80[5)]	12	65
17	$Zn(OTf)_2$ (0.20) [39]	1/1.5/1.5	—	100	0.3	67
18	$Zn(OTf)_2$ (0.20) [12]	1/1.2/1.5	EtOH	80	7	76
19	$Zn(OTf)_2$ (0.15)	1/1.1/1.2	EtOH	80	8	74
20	$In(OTf)_3$ (0.10) [40]	1/1.1/1.3	MeCN	90	5	11
21	$In(OTf)_3$ (0.15)	1/1.1/1.2	EtOH	80	8	19
22	$Yb(OTf)_3$ (0.05) [41]	1/1/1.5	—	100	1.5	62
23	$Yb(OTf)_3$ (0.15)	1/1.1/1.2	EtOH	80	8	79
24	$InCl_3 \cdot 3H_2O$ (0.05) [42]	1/1/1.2	EtOH	80	11.5	39
25	$InCl_3 \cdot 3H_2O$ (0.15)	1/1/1.2	EtOH	80	16	76
26	$LaCl_3 \cdot 6H_2O$ (0.05) [43]	1/1/1.2	EtOH	80	7	53
27	$LaCl_3 \cdot 6H_2O$ (0.15)	1/1/1.2	EtOH	80	7	60
28	$CoCl_2 \cdot 6H_2O$ (0.05)	1/1/1.2	EtOH	80	10	5
29	$CoCl_2 \cdot 6H_2O$ (0.15)	1/1/1.2	EtOH	80	10	12
30	$YbCl_3 \cdot 6H_2O$ (0.05) [44]	1/1/1.2	EtOH	80	7	75
31	$YbCl_3 \cdot 6H_2O$ (0.15)	1/1/1.2	EtOH	80	6	89
32	$YCl_3 \cdot 6H_2O$ (0.05)	1/1/1.2	EtOH	80	6	86
33	$YCl_3 \cdot 6H_2O$ (0.15)	1/1/1.2	EtOH	80	10	90
34	$CeCl_3 \cdot 7H_2O$ (0.25) [45]	1/1/3	EtOH	80	5	16
35	$CeCl_3 \cdot 7H_2O$ (1.00)	1/1/3	EtOH	80	2.5	81
36	$EuCl_3 \cdot 6H_2O$ (0.05)	1/1/1.2	EtOH	80	10	50
37	$EuCl_3 \cdot 6H_2O$ (0.10)	1/1/1.2	EtOH	80	9	77

The end of Table 1

№	Catalyst (mmol)	Ratio of reagents 7/12/13	Solvent	t, °C	τ, h[2]	Yield 14, %[3]
1	2	3	4	5	6	7
38	$EuCl_3 \cdot 6H_2O$ (0.15)	1/1/1.2	EtOH	80	5.5	92
39	$EuCl_3 \cdot 6H_2O$ (0.15)	1/1/1.2	MeCN	82	15	18
40	$Eu(OTf)_3$ (0.15)	1/1/1.2	EtOH	80	8	74
41	$Eu(NO_3)_3$ (0.15)	1/1/1.2	EtOH	80	8	77
42	$Eu_2(CO_3)_3$ (0.15)	1/1/1.2	EtOH	80	8	19
43	$Eu(OAc)_3$ (0.15)	1/1/1.2	EtOH	80	8	10
44	$Eu_2(SO_4)_3$ (0.15)	1/1/1.2	EtOH	80	8	0
45	—	1/1/1.2	IL[4]	100	1.5	74
46	$EuCl_3 \cdot 6H_2O$ (0.05)	1/1/1.2	IL	100	1.5	84
47	$EuCl_3 \cdot 6H_2O$ (0.15)	1/1/1.2	IL	100	1.5	90

Notes:

[1] The reactions were carried out for 1 mmol of starting aldehyde **7**; 3 ml of solvent was used; the ratio of reagents and the amount of catalyst are given in Table 1.

[2] Time required for complete conversion of the aldehyde in the reaction.

[3] Yield of the reaction product after isolation from the reaction mixture.

[4] 1 ml of Ost(imid)BF_4 ionic liquid (IL) was applied, and the product was precipitated in water.

The involvement of aliphatic aldehydes in these transformations was significant (experiments 1—44, Table 1), as was the assessment of the effects of catalyst and ionic liquid additions, which had not been previously investigated (experiments 45—47, Table 1).

2. Synthesis of cyclopropane-containing 3,4-dihydropyrimidin-2(1H)-ones

The obtained optimal reaction conditions were transferred to aldehydes **8—11** containing the cyclopropanol moiety (Fig. 4) and new 3,4-DHPMs **15—18** were thus obtained in moderate yields (Table 2).

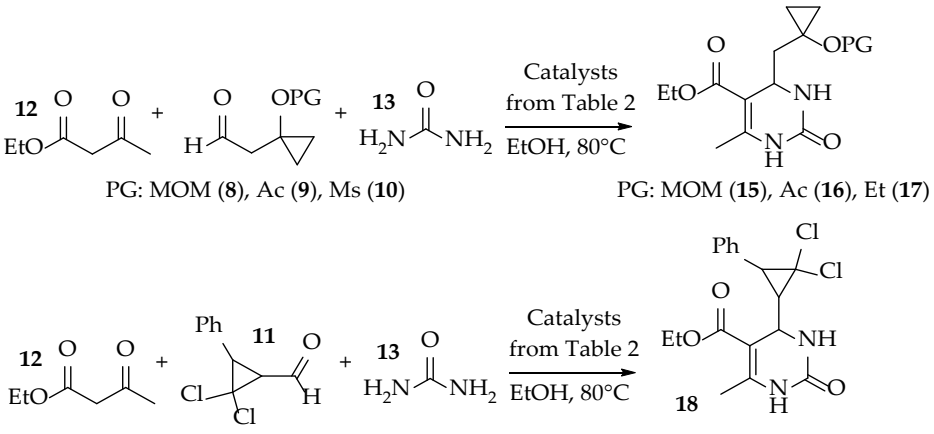

Fig. 4. Biginelli reaction involving cyclopropane-containing aldehydes **8—11**, acetoacetic ester **12** and urea **13**

Table 2

Biginelli reaction involving aldehydes 8—11, acetoacetic ester 12 and urea 13[1, 2]

Catalyst	Yield of target products depending on the amount of catalyst, %[3]					
	0.05 mmol		0.15 mmol			
	15	16	15	16	17	18
$YCl_3 \cdot 6H_2O$	53	23	62	—	—	45
$InCl_3 \cdot 6H_2O$	15	27	—[4]	—	—	—
$EuCl_3 \cdot 6H_2O$	5	30	10	43	51	55
$YbCl_3 \cdot 6H_2O$	24	19	—	—	—	47

Notes:

[1] Reaction completion time: 4—8 hours (monitored by TLC).

[2] The reactions were carried out using 1 mmol of starting aldehyde 8—11, 1 mmol of acetoacetic ester **12**, 1.2 mmol of urea **13** in 3 mL of ethanol at 80 °C and a selected amount of catalyst.

[3] The yield of the reaction product after chromatographic separation.

[4] The experiment was not conducted.

3. Physicochemical characteristics of the obtained compounds

Ethyl-6-methyl-2-oxo-4-pentyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (14). M. p. = 148—150 °C. IR, ν/cm^{-1}: 3303, 3247, 1648, 1593, 1224, 1084. ^{1}H NMR ($CDCl_3$), δ/ppm: 8.20 (s, 1H, NHC=); 5.92 (s, 1H, CHNH); 4.34 (d. t, 1H, CH_2CHNH, J_1 = 7.7, J_2 = 3.7 Hz); 4.22 (m, 2H, CH_3CH_2O); 2.32 (s, 3H, CH_3C=); 1.67—1.51 (m, 2H, $CHCH_2$); 1.48—1.29 (m, 9H, $CH_2(CH_2)_3CH_3$, CH_3CH_2O); 0.92 (t, 3H, $CH_3(CH_2)_4$, J = 6.7 Hz). ^{13}C NMR ($CDCl_3$), δ/ppm: 166.0 (OCC=), 154.6 (NCO), 146.7 (CH_3C=), 101.7 (OCC=), 60.0 (CH_3CH_2O), 51.6 (CHN), 36.9 ($CHCH_2$), 31.5 ($C_2H_5CH_2$), 24.1 ($C_3H_7CH_2$), 22.6 ($CH_3CH_2CH_2$), 18.6 (CH_3C=), 14.4 (CH_3CH_2O), 14.1 ($CH_3(CH_2)_4$). MS, m/z ($I_{rel.}$, %): 209 (4.2), 184 (10.1), 183 (100.0), 155 (39.6), 137 (35.4), 110 (4.2), 96 (4.2).

Ethyl-4-((1-(methoxymethoxy)cyclopropyl)methyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (15). M. p. = 170—172 °C. IR, ν/cm^{-1}: 3236, 3110, 1697, 1648, 1225, 1085, 1037. ^{1}H NMR ($CDCl_3$), δ/ppm: 8.68 (s, 1H, NHC=); 5.93 (br. s, 1H, CHNH); 4.80—4.72 (m, 2H, CH_3OCH_2); 4.68 (d. t, 1H, CH_3CHNH, J_1 = 10.4, J_2 = 3.0 Hz); 4.20 (d. q, 2H, CH_3CH_2O, J_1 = 7.1 Hz, J_2 = 2.8 Hz); 3.40 (s, 3H, CH_3OCH_2); 2.30 (s, 3H, CH_3C=); 1.95 (m, 1H, $CHCH_2$); 1.67 (m, 1H, $CHCH_2$); 1.31 (t, 3H, CH_3CH_2O, J = 7.1 Hz); 1.03 (d. t, 1H, $C(CH_2)_2$, J_1 = 11.6, J_2 = 6.0 Hz); 0.91 (d. t, 1H, $C(CH_2)_2$, J_1 = 11.3, J_2 = 5.9 Hz); 0.60 (d. t, 1H, $C(CH_2)_2$, J_1 = 10.1, J_2 = 5.9 Hz); 0.52—0.38 (m, 1H, $C(CH_2)_2$). ^{13}C NMR ($CDCl_3$), δ/ppm: 165.9 (OCC=), 154.6 (NCO), 147.6 (CH_3C=), 101.2 (OCC=), 95.3 (CH_3OCH_2), 60.1 (CH_3CH_2O), 58.9 (CH_3OCH_2), 56.3 ($C(CH_2)_2$), 50.3 ($CHCH_2$), 41.6 ($CHCH_2$), 18.7 (CH_3C=), 14.5 (CH_3CH_2O), 13.3 ($C(CH_2)_2$), 10.2 ($C(CH_2)_2$).

Ethyl-4-((1-acetoxycyclopropyl)methyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16). M. p. = 175—177 °C. IR, ν/cm^{-1}: 3232, 3107, 1745, 1698, 1651, 1481, 1465, 1228. 1211, 1090, 1029. ^{1}H NMR, δ/ppm: 8.41 (s, 1H, NHC=); 6.14—5.99 (m, 1H, CHNH); 4.50 (d. t, 1H, CH_2CHNH, J_1 = 10.6, J_2 = 3.0 Hz); 4.20 (d. q, 2H, CH_3CH_2O, J_1 = 7.1, J_2 = 5.0 Hz); 2.31 (s, 3H, CH_3C=); 2.28—2.19 (m, 1H, $CHCH_2$); 2.07 (s, 3H, CH_3CO); 1.73—1.58 (m, 1H, $CHCH_2$); 1.32 (t, 3H, CH_3CH_2O, J = 7.1 Hz); 1.07 (d. t, 1H, $C(CH_2)_2$, J_1 = 10.8, J_2 = 6.9 Hz); 0.97 (d. t, 1H, $C(CH_2)_2$, J_1 = 10.2, J_2 = 6.8 Hz); 0.87 (d. t, 1H, $C(CH_2)_2$, J_1 = 11.2, J_2 = 6.6 Hz); 0.68—0.55 (m, $C(CH_2)_2$, 1H). ^{13}C NMR, δ/ppm: 171.5 (CH_3CO), 165.6 (OCC=), 154.3 (NCO), 147.8 (CH_3C=), 100.9 (OCC=),

60.0 ($CH_3\underline{C}H_2O$), 56.9 ($\underline{C}(CH_2)_2$), 49.8 (CHN), 41.3 ($CH\underline{C}H_2$), 21.3 ($\underline{C}H_3CO$), 18.5 ($\underline{C}H_3C=$), 14.3 ($\underline{C}H_3CH_2$), 13.3 ($C(\underline{C}H_2)_2$), 10.4 ($C(\underline{C}H_2)_2$). MS, m/z ($I_{rel.}$, %): 278 $[M\text{-}H_2O]^+$ (3.2), 253 (15.4), 252 (100.0), 224 (30.7), 196 (33.5), 179 (4.9), 178 (6.2), 150 (8.2), 106 (5.1).

Ethyl-4-((1-ethoxycyclopropyl)methyl)-6-methyl-2-oxo-1,2,3,4-tetra-hydropyrimidine-5-carboxylate (17). M. p. = 165—167 °C. IR, ν/cm^{-1}: 3254, 3109, 1699, 1647, 1229, 1087. ^{1}H NMR, δ/ppm: 8.45 (s, 1H, NHC=); 5.80 (s, 1H, CHN$\underline{H}$); 4.65 (d. t, 1H, $CH_2C\underline{H}NH$, J_1 = 7.7, J_2 = 3.6 Hz); 4.21 (m, 2H, $CH_3C\underline{H}_2OCO$); 3.64—3.45 (m, 2H, $CH_3C\underline{H}_2OC(CH_2)_2$); 2.32 (s, 3H, CH_3C=); 1.84—1.74 (m, 2H, $CHC\underline{H}_2$); 1.32 (t, 3H, $C\underline{H}_3CH_2OC(CH_2)_2$, J = 7.1 Hz); 1.22 (t, 3H, $C\underline{H}_3CH_2OCO$, J = 7.0 Hz); 0.90 (d. t, 1H, $C(C\underline{H}_2)_2$, J_1 = 11.2, J_2 = 5.8 Hz); 0.80 (d. t, 1H, $C(C\underline{H}_2)_2$, J_1 = 11.0, J_2 = 5.6 Hz); 0.56 (d. d.d, 1H, $C(C\underline{H}_2)_2$, J_1 = 9.9, J_2 = 6.3, J_3 = 5.1 Hz); 0.42 (d. d. d, 1H, $C(C\underline{H}_2)_2$, J_1 = 10.0, J_2 = 6.5, J_3 = 5.0 Hz). ^{13}C NMR, δ/ppm: 165.8 (O$\underline{C}$C=), 154.3 (NCO), 147.6 ($CH_3\underline{C}$=), 100.9 (OC$\underline{C}$=), 61.9 ($CH_3\underline{C}H_2OCO$), 59.9 ($CH_3\underline{C}H_2OC(CH_2)_2$), 59.3 ($\underline{C}(CH_2)_2$), 50.6 ($\underline{C}HCH_2$), 39.2 ($CH\underline{C}H_2$), 18.6 ($\underline{C}H_3C$=), 15.5 ($\underline{C}H_3CH_2OC(CH_2)_2$), 14.4 ($\underline{C}H_3CH_2OCO$), 13.8 ($C(\underline{C}H_2)_2$), 10.5 ($C(\underline{C}H_2)_2$). MS, m/z ($I_{rel.}$, %): 184 (10.3), 183 (100.0) $[M - C_2H_5O]$+, 155 (40.3), 137 (36.4), 110 (4.3), 96 (4.5), 71 (5.3).

Ethyl-4-(2,2-dichloro-3-phenylcyclopropyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (18). M. p. = 172—174 °C. IR, ν/cm^{-1}: 3223, 3099, 1693, 1642, 1220, 1086. ^{1}H NMR, δ/ppm: 9.37 (s, 1H, NHC=); 9.31 (s, 1H, NHC=); 7.79 (br. s, 1H, CHN$\underline{H}$), 7.58 (br. s, 1H, CHN$\underline{H}$); 7.41—7.08 (m, 10H, C_6H_5); 4.21 (d. d, 1H, C$\underline{H}$NH, J_1 = 8.9, J_2 = 4.2 Hz); 4.16 (d.d, 1H, C$\underline{H}$NH, J_1 = 6.8, J_2 = 3.4 Hz); 4.14—4.05 (m, 2H, $CH_3C\underline{H}_2O$); 4.05—3.88 (m, 2H, $CH_3C\underline{H}_2O$); 3.02 (d, 1H, $C_6H_5C\underline{H}$, J = 9.0 Hz); 2.90 (d, 1H, $C_6H_5C\underline{H}$, J = 8.5 Hz); 2.29 (t, 1H, $C\underline{H}CHNH$, J = 8.7 Hz); 2.23 (s, 3H, CH_3C=); 2.21 (s, 3H, CH_3C=); 1.22 (t, 3H, $C\underline{H}_3CH_2O$, J = 7.1 Hz); 1.07 (t, 3H, $C\underline{H}_3CH_2O$, J = 7.1 Hz). ^{13}C NMR, δ/ppm: 165.5 (O$\underline{C}$C=), 165.3 (O$\underline{C}$C=), 155.3 (NCO), 154.8 (NCO), 148.6 ($CH_3\underline{C}$=), 147.7 ($CH_3\underline{C}$=), 134.2 ($C(1)_{Ph}$), 133.8 ($C(1)_{Ph}$), 128.8 ($C(2)_{Ph}$), 128.7 ($C(6)_{Ph}$), 128.4 ($C(3)_{Ph}$, $C(5)_{Ph}$), 127.8 ($C(4)_{Ph}$), 101.2 (OC$\underline{C}$=), 99.4 (OC$\underline{C}$=), 64.4 ($CH_3\underline{C}H_2O$), 63.4 ($CH_3\underline{C}H_2O$), 60.5 (CCl_2), 60.4 (CCl_2), 53.1 (CHNH), 49.8 (CHNH), 41.8 ($\underline{C}HCHNH$), 40.9 ($\underline{C}HCHNH$), 40.0 ($C_6H_5\underline{C}H$), 37.6 ($C_6H_5\underline{C}H$), 18.7 ($\underline{C}H_3C$=), 18.3 ($\underline{C}H_3C$=), 14.5 ($\underline{C}H_3CH_2O$), 14.3 ($\underline{C}H_3CH_2O$). MS, m/z ($I_{rel.}$, %): 323 (1.8), 259 (1.8), 183 (100), 155 (28.4), 155 (40.3), 149 (8.3), 137 (20.1), 127 (1.2), 115 (9.4), 96 (2.5), 89 (1.9), 77 (1.2).

4. In silico *prediction of permeability through cell membranes*

In further studies, the permeability of all newly synthesised products via passive diffusion through the phospholipid bilayer was theoretically evaluated through *in silico* 3D structure simulations using the PerMM service (Table 3) [46].

PerMM calculates the membrane binding energies (ΔG_{bind}) and the transfer energy profiles ($\Delta G_{transf}(z)$) of permeants in membranes and obtains their optimal spatial positions and conformations during rotational and translational motion along the membrane normal *z* [46]. The membrane-bound state of a permeant is defined as its conformation and the spatial position in the membrane with the lowest transfer energy from water [46]. Integrating the free energy profile along the permeation pathway allows the evaluation of permeability coefficients (P) of molecules through artificial and natural membranes [46].

3D coordinates for molecules were generated using molecular Chem3D modeling software (PerkinElmer Informatics, Inc.) with subsequent local energy minimisation. To calculate the lowest transfer energy pathway of a molecule along the membrane normal, the drag method was employed, in which energy transfer is locally minimised with respect to the rotational variables of the molecule at each $z + \Delta z$ point along the transmembrane pathway, starting from the optimal rotational orientation

determined at the preceding point *z*. The modelling conditions were as follows: pH = 7.35, T = 37 °C; cholesterol and glucose were chosen as reference standards for comparison.

Table 3

Values of logP and free energy of binding by the Biginelli MCR product for different types of membranes

Number of compound	Free energy of binding, kcal/mol	Logarithm of the permeability coefficient (logP)			
		BLM[1]	BBB[2]	Caco-2[3]	PAMPA DS[4]
14	– 3.70	– 1.30	– 3.35	– 3.81	– 2.43
15	– 2.88	– 2.70	– 3.85	– 4.17	– 3.72
16	– 3.85	– 1.32	– 3.36	– 3.82	– 2.45
17	– 4.39	– 0.23	– 2.98	– 3.54	– 1.44
18	– 4.69	– 1.22	– 3.32	– 3.79	– 2.35
Glucose	– 1.82	– 9.08	– 6.10	– 5.80	– 9.60
Cholesterol	– 10.25	6.08	– 0.75	– 1.92	4.39

Notes:

[1] Black lipid membrane (artificial).

[2] Blood-brain barrier (natural).

[3] The cell membrane of human colorectal adenocarcinoma of the colon used as a model of the intestinal epithelial barrier (natural).

[4] Double-Sink Parallel Artificial Membrane Permeability Assay: the lipid solution consists of 20 % dodecane solution and a mixture of phospholipids; the acceptor solution contains a mixture of surfactants (an in vitro model of passive transcellular permeability over a large pH range).

5. In silico *prediction of antifungal activity against a variety of fungi*

A powerful set of methods for the computer prediction of the biological activity of chemical compounds is based on Bayesian probability. The PASS software package is capable of predicting the biological activity spectra of currently known chemical compounds [47]. The approach employed in PASS to predict the biological activity of a chemical compound rests on the assumption that Activity = Structure. The structure of a compound is, in turn, characterised by its individual functional elements (descriptors), such as radicals and functional groups of atoms [47].

Using the AntiFun Pred platform, potential cytotoxicity calculations were performed for a wide range of fungi with the obtained compounds. The results are presented in Table 4.

Table 4

Results of *in silico* prediction of antifungal activity for compounds 14—18

Number of compound	Confidence	Binomial name
14	0.2661	*Rhizopus oryzae*
	0.1552	*Mucor hiemalis*
	0.1429	*Saccharomyces cerevisiae*
	0.0278	*Yarrowia lipolytica*

The end of Table 4

Number of compound	Confidence	Binomial name
15	0.0513	*Cryptococcus bacillisporus*
	0.0482	*Pichia guilliermondii*
	0.0268	*Yarrowia lipolytica*
	0.0132	*Galactomyces geotrichum*
16	0.1981	*Clavispora lusitaniae*
	0.0950	*Galactomyces geotrichum*
	0.0730	*Pichia guilliermondii*
	0.0704	*Cryptococcus bacillisporus*
17	0.1303	*Pichia guilliermondii*
	0.1179	*Galactomyces geotrichum*
	0.1143	*Candida dubliniensis*
	0.1096	*Cryptococcus bacillisporus*
18	0.1446	*Rhizopus oryzae*
	0.1186	*Absidia corymbifera*
	0.1051	*Cryptococcus bacillisporus*
	0.0173	*Yarrowia lipolytica*

6. Experiments on yeast fungi of the Yarrowia lipolytica *species*

The obtained compounds, **14—18**, were tested for activity against *Yarrowia lipolytica* yeast, which provides a convenient model for glycolysis, apoptosis and gene expression in tumours [48—50]. The experiment demonstrated no significant suppression of culture growth at 6, 18 and 24 h of incubation (Table 5).

Table 5

Number of *Yarrowia lipolytica* yeast cells (millions, rounded to whole numbers) incubated with 100 μM of the tested compounds

Compound number	Sampling time				
	0 h	3 h	6 h	18 h	24 h
1	2	3	4	5	6
14	12	28	58	458	814
15	12	27	59	450	816
16	12	22	55	408	818
17	12	24	57	418	836
18	12	23	60	420	804
Control	12	17	41	384	792

Discussion

In the MCR model with hexanal, europium (III) chloride proved to be the most efficient catalyst, consistently forming a well-shaped dense precipitate upon cooling, with the possibility of reusing catalyst-containing solution. High to moderate yields were obtained with ytterbium (III), yttrium (III) and indium (III) chloride hexahydrates.

As for the cyclopropane-containing aldehydes, the best results for compound **9** were also obtained using europium (III) chloride as catalyst, whereas in the case of aldehyde **8**, yttrium(III) chloride performed best, which is likely due to the partial removal of the methoxymethyl protection by europium (III) salt acting as a Lewis acid (Fig. 4, Table 2).

The involvement of aldehyde **10** in the Biginelli reaction, catalysed by europium (III) chloride and yttrium (III) chloride, resulted in the formation of an unexpected product **17**. This product arose from the elimination of methanesulfonate and the Michael addition of ethanol to the intermediate aldehyde **19**, with aldehyde **20** directly participating in the MCR (Fig. 5).

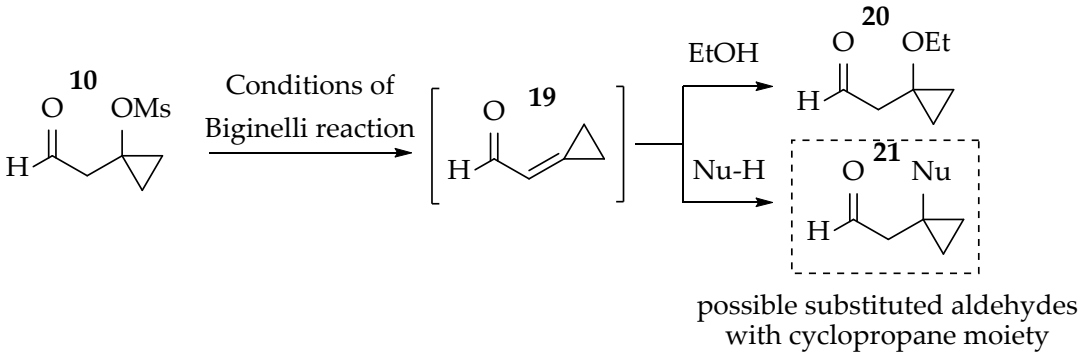

Fig. 5. Suggested scheme for the formation of aldehyde 20

It can be assumed that, with appropriate optimisation of conditions, a similar transformation with other nucleophiles (Nu—H) will yield aldehydes of species 21, capable of mild and selective Michael addition, thereby expanding the range of synthesised 3,4-DHPM structural species in this transformation (Fig. 5).

It can be assumed that, with an appropriate selection of optimal conditions, a similar transformation with other nucleophiles (Nu—H) will yield aldehydes of species **21**, capable of mild and selective Michael addition, thereby expanding the range of synthesised 3,4-DHPM compounds in this transformation (Fig. 5).

Data obtained from the PerMM server indicate that all studied compounds can passively penetrate model cell membranes and participate in intracellular regulatory processes, as a logarithm of the permeability coefficient (logP) greater than −4.35 suggests a compound's potential for passive transport across the cell membrane [46]. Compounds **17** and **18** exhibit the highest binding energy.

Notably, this calculation is essential, as further increases or decreases in antifungal activity can be explained by Overtone's concept of cell permeability, which suggests that the lipid membrane surrounding the cell favours the passage of only lipid-soluble materials [51]. Therefore, liposolubility is an important factor controlling antifungal activity.

Comprehensive in silico prediction of antifungal properties (Table 4) indicated that the studied compounds may have potential for the treatment of zygomycosis, caused primarily by micromycetes of the genus *Rhizopus* (mainly *Rhizopus oryzae*) and, less frequently, by those of the genus *Mucor* [52]. This is indicated by the high probability of activity against these fungal species for compounds **14** and **18**. At the same time, compound **16** is predicted with high confidence to possess antifungal activity against *Clavispora lusitaniae* yeast, which may have potential applications in the treatment of disseminated candidiasis, including septicaemia and pyelonephritis [53].

The in vitro experiment on *Yarrowia lipolytica* yeast showed that the compounds exhibited no antifungal activity against these microorganisms and no toxicity through mechanisms common to eukaryotes [54]. These findings are consistent with the earlier computational analysis, as the predicted reliability of detecting cytotoxic properties against this yeast species was extremely low.**Funding:** This research was funded by SRP, state registration number 20240340.

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