



Single-stage synthesis of heterocyclic alkaloid-like compounds from (+)-camphoric acid and their antiviral activity

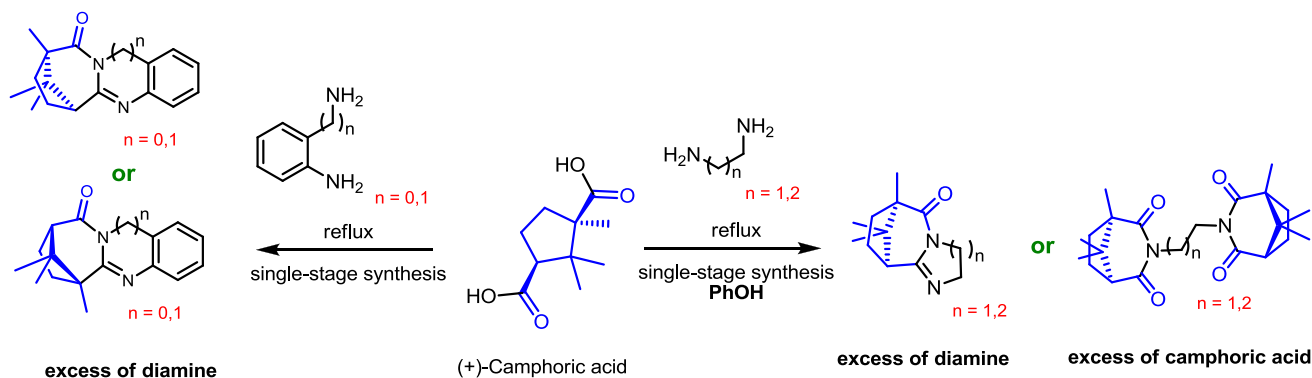
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Abstract

An effective technique for one-stage synthesis of new polycyclic nitrogen-containing compounds has been developed. The procedure involves refluxing mixtures of camphoric acid with aliphatic or aromatic diamine without catalysts. In cases where the starting amine has a low boiling point (less than 200 °C), phenol is used as a solvent, as it is the most optimal one for obtaining products with good yields. It has been shown that the use of Lewis acids as catalysts reduces the yield of the reaction products. A set of compounds have been synthesized, which can be attributed to synthetic analogues of alkaloids. In vitro screening for activity influenza virus A was carried out for the obtained compounds. The synthesized quinazoline-like agent **14** has inhibitory activity against different strains of influenza viruses.

Graphical abstract



Keywords (+)-Camphoric acid · Single-stage synthesis · Alkaloid analogues · Influenza virus · Antiviral activity · Antivirals

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Introduction

Influenza represents one of the most serious challenges to medical science and health care all over the world. It causes annual epidemics and from time to time pandemics, both resulting in significant increase in morbidity and mortality [1]. Due to fast replicative cycle, ability to reassort the fragments of segmented genome and lack of correcting activity of viral polymerase influenza virus can quickly select mutants that do not match the virus-inhibiting antibodies and can therefore escape from the immune response [2]. Several

classes of chemically distinct compounds are currently used for treatment of influenza: amantadine and rimantadine (two blockers of M2 proton channel) [3, 4], four neuraminidase inhibitors (oseltamivir, zanamivir, peramivir and laninamivir) prevent budding of viral progeny [5], umifenovir (Arbidol) is used against influenza in Russia and China [6, 7], pyrazinecarboxamide derivative favipiravir (T-705) was approved for stockpiling for potential treatment of pandemic influenza [8, 9], and baloxavir marboxil (Xofluza[®]) that has been recently approved by FDA interferes with endonuclease activity of viral PA subunit of polymerase complex [10].

The same features of influenza virus that cause the emergence of antibody-escape mutants lead also to the selection of drug resistance to direct-acting antivirals. Indeed, all current isolates of influenza virus are resistant to adamantane derivatives so that WHO does not recommend their use for treatment of influenza anymore [10–12]. In 2007–2009 almost total resistance of seasonal influenza A(H1N1) viruses to oseltamivir was achieved. These strains were further replaced with oseltamivir-susceptible pandemic influenza viruses A(H1N1)pdm09 [13, 14]. Taken together, these facts suggest that novel anti-influenza drugs of alternative mechanism(s) of activity and viral target(s) are therefore of high priority for medicinal science and health care.

The abundance, crystallinity and variety of transformations of (+)-camphor were interesting throughout the history of organic chemistry. Our work is devoted to the investigation of chemical properties of (+)-camphoric acid (product of oxidation of (+)-camphor). Camphoric acid is a cyclopentane derivative containing two carboxylic acid functional groups on the first and third carbon atoms. The C-1 atom has an additional methyl group, thereby converting camphoric acid into an enantiomeric ditopic organic linker with different coordination regimes. Moreover, the coordination chemistry of camphoric acid specifically gives rise to many interesting chiral features applicable to both materials and life sciences, such as asymmetrical synthesis or crystallization, homochiral structural design, chiral induction, absolute helical control and ligand handedness [15]. There are examples of the use of camphoric acid derivatives as ligands [16–18].

The condensation of carboxylic acids with amines and anilines is known to be a classical way of preparing amides. This interaction is shown for a wide spectrum of various substrates [19]. The methods for preparing 2-substituted benzimidazoles based on direct cyclocondensations of carboxylic acids with benzene-1,2-diamine are also well known, but almost all of them involve rigid conditions, high temperatures or acidic conditions [20–22]. For example, many carboxylic acids are condensed with benzene-1,2-diamine at temperatures of about 200° [23–25].

Thus, we consider it relevant to study the interaction of camphoric acid with various aliphatic and aromatic diamines. This study is important, because all

nitrogen-containing heterocyclic compounds play a great role in medicinal and organic chemistry in whole.

Results and discussion

Chemistry

The present work is devoted to the synthesis of new polycyclic nitrogen-containing compounds from (+)-camphoric acid and aliphatic or aromatic diamines. The first investigated reaction was interaction between ethylenediamine **2** and (+)-camphoric acid **1**. As a result of refluxing 1 eq. camphoric acid with 2 eq. ethylenediamine in phenol, product **3** was obtained (Scheme 1). This technique led to an almost quantitative conversion to **3** after 2 h with 80% yield. Product **3** was not observed, if refluxing the starting reagents was carried out without a solvent, apparently due to the low boiling point of the starting amine **2**. Also we used toluene, DMSO and *o*-xylene as a solvent for this interaction. It should be noted that using toluene or xylene significantly increased the conversion time to 24 h. The use of DMSO as a solvent resulted in a double decrease in the desired product. Thus, using phenol as a solvent proved to be the most optimal for the production of the tricyclic product **3**.

Refluxing a tenfold excess of camphoric acid with diamine **2** in *i*-PrOH gives us a mixture of cyclic amide of symmetrical structure **4** and product **3** (1:1). Product **4** was purified by column chromatography and isolated with 9% yield.

Further, the interaction of 1,3-diaminopropane **5** with camphoric acid was investigated. Refluxing **5** with **1** in phenol for 3 h led to compound **6** with 90% yield (Scheme 1). Unfortunately, we were unable to isolate the cyclic amide of a symmetric structure based on 1,3-diaminopropane.

Product **8** was obtained by refluxing **1** with **7** in an *i*-PrOH with 25% yield. This interaction allows us to obtain compound **8** and presumably mixture of polycyclic compounds with a similar structure to the compound **6**, which, unfortunately, are not received in a pure form. For compounds **3**, **8** and perchlorate of the compound **6** (**6**·HClO₄) X-ray crystallographic analysis was carried out (Fig. 1).

Then, we decided to investigate the possibility of obtaining compounds of a similar structure from aromatic amines. Thus, *o*-phenylenediamine **9** was chosen as the next object of our research.

We show that refluxing of mixture of **9** with **1** without a solvent for 3 h leads to the formation of a mixture of two benzimidazole derivatives **10a** and **10b** with a total yield of 70% (Scheme 2). In this case, we carried out a study of the conversion rate and the ratio of the final products, by replacing camphoric acid **1** with its anhydride, and also by adding 5 mol% of Lewis acid to the reaction mixture,

Scheme 1 Interaction of camphoric acid with aliphatic diamines

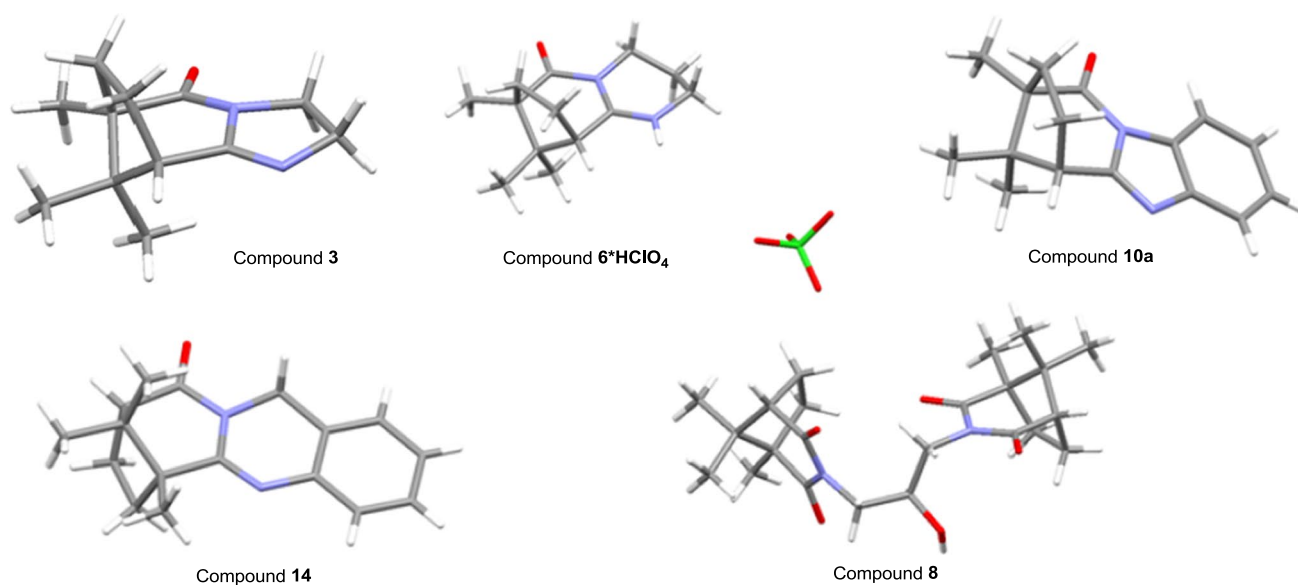
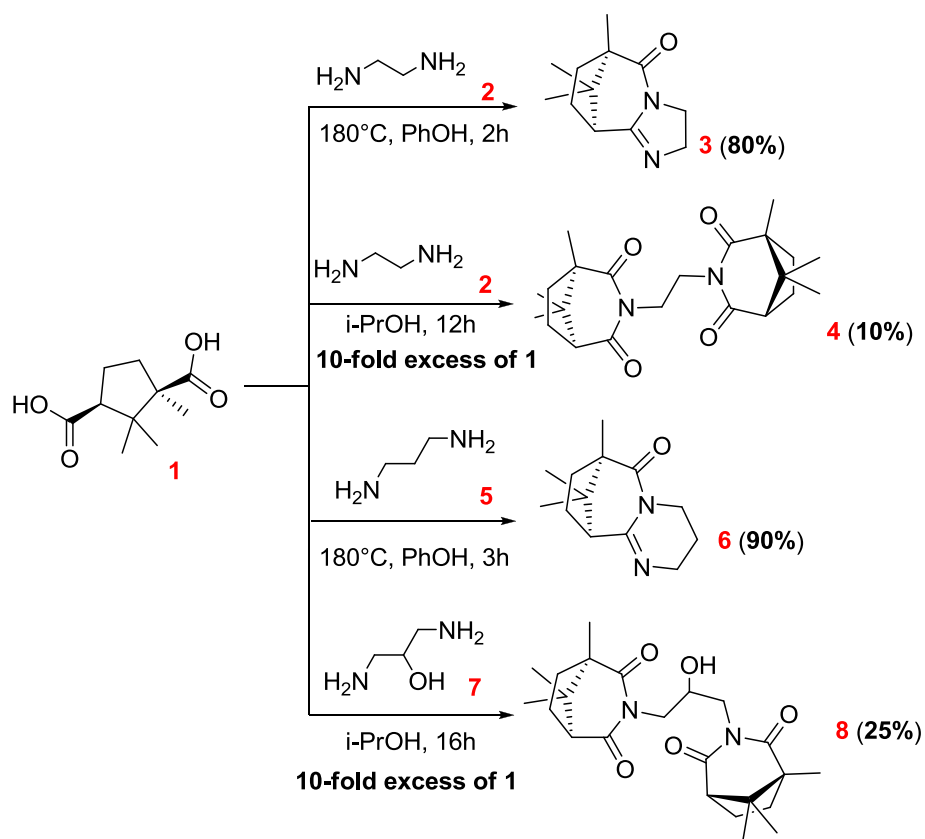
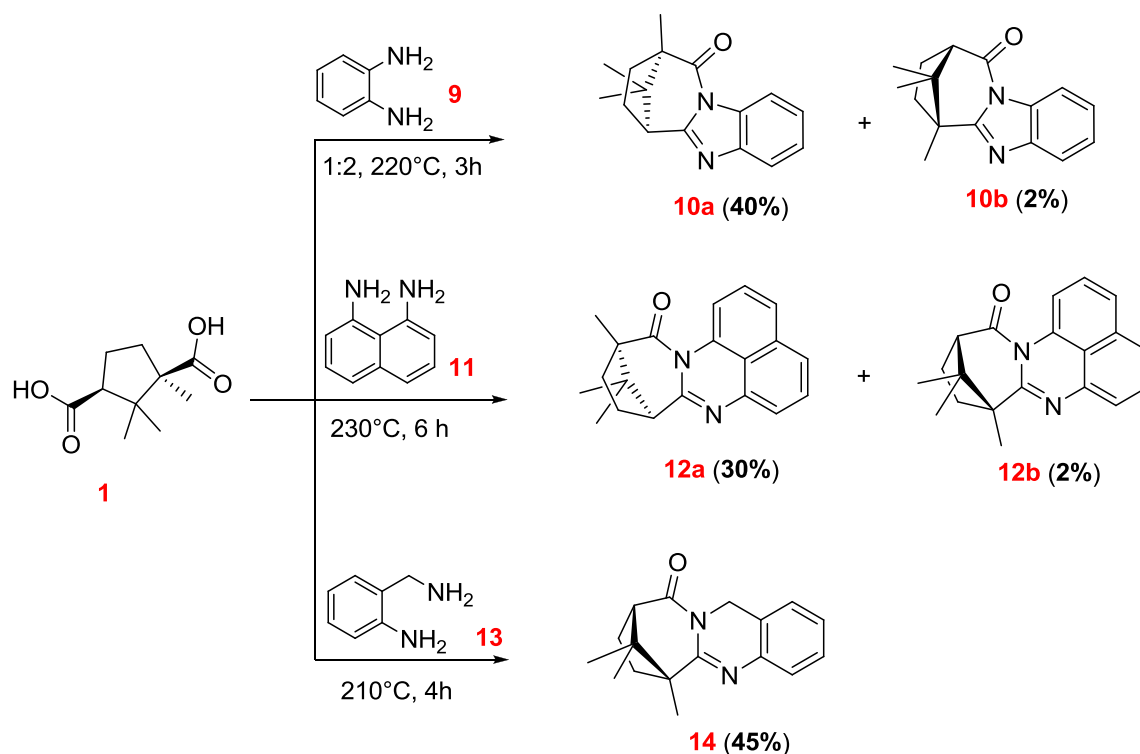


Fig. 1 Crystallographic data (excluding structure factors) for the structures **3**, **6**· HClO_4 , **10a**, **14**, **8** in this paper have been deposited with the Cambridge Crystallographic Data Centre (Deposition Nos. CCDC 1838812–1838815 and 1874453) as supplementary publication

for example, anhydrous zinc chloride. It is shown that the use of the Lewis acid increases the conversion time from 3 to 5 h and decreases the total yield of the reaction products to 55% and the quantity of the major isomer **10a** in the

final mixture. Using camphoric acid anhydride as a starting reagent slightly reduces the overall yield of the reaction products. Compounds **10a** and **10b** have been isolated after the column chromatography with a yield of 40% and 2%,



Scheme 2 Interaction of camphoric acid with aromatic diamines

respectively. The structure of compound **10a** has been confirmed by X-ray crystallographic analysis (Fig. 1).

The benzimidazole derivative **10a** was previously described [19]. The procedure involved refluxing the mixture of reagents with 10 mol% of boric acid in toluene for 48 h, and a Dean–Stark trap was used for the azeotropic removal of H₂O. We have also shown the possibility of synthesizing compound **10a** by single-stage synthesis without solvent and catalysts, which significantly reduced the reaction time.

Then, we chose naphthalene-1,8-diamine **11** as parent aromatic diamine. Refluxing double excess of **11** with **1** without a solvent for 6 h led to the mixture of compounds **12a** and **12b** with a total yield of 50% (Scheme 2). Compounds **12a** and **12b** have been isolated by column chromatography with a yield of 30% and 2%, respectively. We consider that the *minor* product in all the transformations above is obtained by the primary nucleophilic attack to a more sterically hindered carboxylic group. This assumption is confirmed by ¹H, ¹³C and 2D NMR spectra (see Supporting Information).

Also, the interaction of *o*-aminobenzylamine **13** with **1** was studied. Refluxing the mixture of **1** and excess of **13** without a solvent for 4 h resulted in compound **14** with 45% yield (Scheme 2). X-ray crystallographic analysis shows that, in this case, the *main* product is the compound formed as a result of the primary nucleophilic attack to a more sterically hindered carboxyl group (Fig. 1).

Biological part

Synthesized polycyclic nitrogen-containing compounds **3**, **6**, **10a**, **10b**, **12a**, **12b**, **14** can be referred to as synthetic analogues of natural quinazoline alkaloids. Nowadays, natural and synthetic quinazolines attract considerable attention due to their diverse and sometimes very high biological activity [26]. For example, the most common active metabolites of plants of the genus *Peganum* are quinazoline alkaloids (such as vasicine **15a**, desoxyvasicine **15b**, vasicinone **16a**, deoxyvasicinone **16b** [27]). These natural compounds have a broad spectrum of native biological activity, in particular: anti-AD for **15a–b** [28], anti-parasitic for **16a–b** [29], insecticidal for **15a** [30]. At the same time, synthetic derivative of quinazoline diproqualone **17** was previously used as an analgesic for osteoarthritis and rheumatoid arthritis [31] (Fig. 2).

Along with the pronounced biological activity, the compounds of the quinazoline series can be successfully used as chiral catalysts [32, 33]. Thus, the use of vasicine **15a** as an organic catalyst for direct C–H arylation of unactivated arenes with aryl iodides/bromides without assistance of any transition metal catalyst has been described [34]. Vasicine **15a**, a quinazoline alkaloid, from the leaves of *Adhatoda vasica*, has been utilized as an efficient catalyst for metal- and base-free Henry reaction of various aldehydes with nitro alkanes [35]. The quinazoline structure possibly imparts rigidity to the ligand and hence consistently high

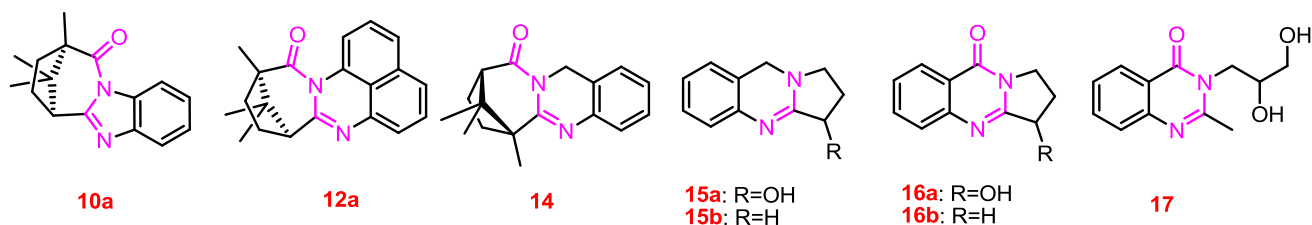


Fig. 2 Similarity of the structure of quinazoline alkaloids and synthesized compounds

Table 1 Antiviral activity of compounds **3**, **4**, **6**, **10a**, **12a–b**, **14** against influenza virus A/Puerto Rico/8/34 (H1N1)

Entry	Compound	CC ₅₀ ^a (μM)	IC ₅₀ ^b (μM)	SI ^c
1	3	> 1456.3	51.5 ± 6.0	28
2	4	> 772.2	> 772.2	1
3	6	> 1361.7	36.8 ± 4.1	37
4	10a	264.2 ± 2.2	43.3 ± 3.2	6
5	10b	1179.6 ± 91.2	55.1 ± 6.1	21
6	12a	136.7 ± 10.8	18.7 ± 1.9	7
7	12b	> 985.6	> 985.6	1
8	14	> 1117.9	17.9 ± 2.0	62
9	Rimantadine	374 ± 26	61 ± 5	6
10	Amantadine	329 ± 21	60 ± 7	5
11	Deitiforin	956 ± 68	142 ± 11	7

^aCC₅₀—cytotoxic concentration; the concentration resulting in 50% death of cells

^bIC₅₀—effective concentration; the concentration resulting in 50% inhibition of virus replication

^cSI—selectivity index, ratio CC₅₀/IC₅₀

enantioselectivity [36]. At present time, attention of numerous groups is being paid to the synthesis of analogues of natural alkaloids.

Antiviral activity

Synthetic and natural quinazoline alkaloids can exhibit pronounced antiviral properties [37, 38]. The compounds synthesized in this work contain both the monoterpene fragment and the N-heterocycle. We have previously shown that

various derivatives of monoterpene, in particular compounds including a 1,7,7-trimethylbicyclo[2.2.1]heptane scaffold and N-heterocyclic fragment, exhibit antiviral properties against the influenza virus [39, 40]. In this regard, the obtained derivatives were screened for their inhibitory activity against influenza virus A H1N1. For each compound, the values of 50% cytotoxic dose (CC₅₀), 50% virus-inhibiting dose (IC₅₀) and selectivity index (SI) were calculated. The results are shown in Table 1. Adamantane- and norbornane-based derivatives were used as reference compounds due to their close similarity to the compounds under investigation in having rigid cage fragments in their structures. It is worth noting that compounds **3**, **6**, **10b**, **12b**, **14** are less cytotoxic than reference compounds. Compounds **3**, **6**, **10b**, **14** are most effective in inhibiting the influenza virus A (H1N1) and can be used for further studies this type of activity. We believe that aliphatic polycyclic compounds (with a similar structure to compounds **3**, **6**) or compounds containing an additional aromatic cycle may exhibit potentially high antiviral activity, but in this case, we are particularly interested in the isomers with the hem-dimethyl bridge directed upwards.

For compound **14**, which showed the highest activity, we studied the antiviral activity against different strains of influenza virus (Table 2). It has been shown that compound **14** has inhibitory activity against different strains of influenza virus A. The compound synthesized has inhibitory activity against strain H5N2 (comparable to reference compounds) and strain H1N1 (exceeding that of reference compounds). Unfortunately, the inhibitory activity of compound **14** against strain H3N2 is lower than that of the reference compounds.

Table 2 Antiviral activity of compound **14** and reference standards

Compound	CC50 (μM)	Antiviral activity					
		A/PR/8/34 (H1N1)		A/Aichi/2/68 (H3N2)		A/mallard/Pennsylvania (H5N2)	
		IC ₅₀ (μM)	SI	IC ₅₀ (μM)	SI	IC ₅₀ (μM)	SI
14	> 1118	18 ± 2	62	27 ± 4	41	21 ± 3	53
Rimantadine	374 ± 26	61 ± 5	6	5 ± 1	75	7 ± 2	53
Amantadine	329 ± 21	60 ± 7	5	4 ± 0	82	6 ± 1	55
Deitiforin	956 ± 68	142 ± 11	7	17 ± 2	56	19	50

Conclusion

In conclusion, a simple and effective method of single-stage synthesis of polycyclic nitrogen-containing heterocyclic compounds, synthetic analogues of natural alkaloids, is suggested for the first time. It was shown that the optimal technique of synthesis is refluxing mixtures of parent compounds in phenol or without solvent and catalysts. Using this method, we synthesized a number of polycyclic amides containing in their structure both a heterocyclic fragment and a bicyclic fragment (**3**, **6**, **10a**, **10b**, **12a**, **12b**, **14**) and two cyclic symmetrical amides (**4**, **8**). The structures of all synthesized compounds were confirmed by a complete set of spectral data, including X-ray crystallographic analyses of crystalline products **3**, **6**, **8**, **10a** and **14**. In vitro screening for inhibitory activity against influenza virus was carried out for the obtained compounds and compound **14**, was shown, exhibits inhibitory activity against different strains of influenza virus A (H1N1, H3N2, H5N2). Compounds **3**, **6**, **10b** and their derivatives, in turn, can be used in the further study of this type of activity.

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Compliance with ethical standards

Conflict of interest The authors confirm that this article content has no conflict of interest.

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