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Synthesis of esters and amides of 2-aryl-1-hydroxy-4-methyl-1H-imidazole-5-carboxylic acids and study of their antiviral activity against orthopoxviruses

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Abstract
Smallpox was eradicated 40 years ago but it is not a reason to forget forever about orthopoxviruses pathogenic to humans. Though in 1980 the decision of WHO to cease vaccination against smallpox had seemed logical, it led to the decrease of cross immunity against other infections caused by orthopoxviruses. As a result, in 2022 the multi-country monkeypox outbreak becomes a topic of great concern. In spite of existing FDA-approved drugs for the treatment of such diseases, the search for new small-molecule orthopoxvirus inhibitors continues. In the course of this search a series of novel 2-aryl-1-hydroxyimidazole derivatives containing ester or carboxamide moieties in position 5 of heterocycle has been synthesized and tested for activity against Vaccinia virus in Vero cell culture. Some of the compounds under consideration revealed a selectivity index higher than that of the reference drug Cidofovir. The highest selectivity index SI = 919 was exhibited by ethyl 1-hydroxy-4-methyl-2-[4-(trifluoromethyl)phenyl]-1H-imidazole-5-carboxylate 1f. The most active compound also demonstrated inhibitory activity against the cowpox virus (SI = 20) and the ectromelia virus (SI = 46).

Introduction
In the second half of the XX century smallpox became a first disease totally eradicated by means of vaccination. The Smallpox Eradication Program was carried out in 1966–1980 and after its termination the global immunization of population that provided cross immunity against orthopoxviruses was also ceased. Consequently, now, 40 years later, most of the people do not have any immunity against orthopoxviruses. Such is indeed one of the reasons of the multi-country monkeypox outbreak of 2022 that affected >100 countries. It should be mentioned that there is not only a hazard that zoonotic infections caused by other already known representatives of orthopoxvirus family can transfer to a human, but also new pathogenic strains of orthopoxviruses may evolve in the course of mutations. Unfortunately, the possibility of the return of our “old friend” smallpox must not be ruled out because it may be regarded as a potential bioterrorism agent that may either be contained somewhere in illegal repositories or be artificially obtained on the basis of primary DNA structure data. The virus may also “peacefully” persist in the remains buried in permafrost.

It should be noted that there are only three drugs approved for the treatment of the diseases caused by orthopoxviruses: they are Cidofovir, Brincidofovir and Tecovirimat (ST-246) (Figure 1). Following the successful preclinical trials, clinical trials of the fourth effective and bioavailable anti-smallpox compound NIOCH-14 are currently being carried out in Russia.

Due to the likeliness of the structures of the most effective antivirals against orthopoxviruses (Tecovirimat and NIOCH-14) and to the fact that in mammal organism NIOCH-14 transforms into ST-246, it may be supposed that they obtain a similar mechanism of action that may cause problems with resistance. So, the search for new structures possessing antiviral activity against orthopoxviruses continues. As one of the reasons of this search is the possibility of the development of resistance against existing drugs, it is not surprising that the researchers consider different classes of organic compounds. Promising results were demonstrated by the derivatives of adamantane, 1,2,4-triazine, 1,2,4-triazine, 1,2,4-triazine, 1,2,4-triazine.
terpenoids.\textsuperscript{23–29} We propose the search for such structures in the series of small molecules containing imidazole moiety. This structurally simple aromatic heterocycle plays an important role in medicinal chemistry. Imidazole-containing molecules demonstrate a wide variety of antiviral activities. Only recently papers on antiviral activity of imidazole derivatives against Hepatitis C virus,\textsuperscript{30–37} Hepatitis B virus,\textsuperscript{38} influenza A virus,\textsuperscript{39–40} dengue virus,\textsuperscript{41,42} Chikungunya virus,\textsuperscript{43} rhabdoviridae,\textsuperscript{44–48} herpesviridae,\textsuperscript{49} Human Cytomegalovirus,\textsuperscript{50} HIV-1\textsuperscript{51} and coronaviruses\textsuperscript{52} have been published.

Previously a perspective of 1-hydroxyimidazole derivatives as potential anti-viral compounds against the Vaccinia virus (VACV) was revealed.\textsuperscript{53} The present work is a continuation of our search for structures possessing inhibitory activity against orthopoxviruses in the series of 1-hydroxyimidazoles. For further modifications one of the most promising structures was chosen, i.e. ethyl 1-hydroxy-2-(2-hydroxyphenyl)-4-methyl-1\textsubscript{H}-imidazole-5-carboxylate 1\textsubscript{a} (Fig. 2). In the present work we aim to reveal the influence of the substituents in phenyl moiety in the position 2 of imidazole on cytotoxicity and virus-inhibiting activity against orthopoxviruses in the series of ethyl 2-aryl-1-hydroxy-1\textsubscript{H}-imidazole-5-carboxylates. We also aim to evaluate the changes in biological activity that accompany the substitution of an ester moiety in position 5 of 1-hydroxyimidazole by a carboxamide one.

One of the most convenient and wide-spread methods to synthesize 1-hydroxyimidazole derivatives is the cyclization of aldehydes with corresponding oximes and ammonium acetate.\textsuperscript{54} 1-Hydroxyimidazoles 1\textsubscript{b–f} were obtained in glacial acetic acid at room temperature (Scheme 1).

Starting oxime was obtained by the nitrosation of ethyl acetoacetate by known technique.\textsuperscript{55} Commercially available benzaldehyde, its mono- and 4-(trifluoromethyl)benzaldehyde were used as starting aldehydes for the evaluation of the effect of functional groups in 2-aryl substituent. This choice of substituents was determined by the fact that in the course of the development of Tecovirimat or NIOCH-14 that also contain aryl moieties the best results were demonstrated by the structures with electron-withdrawing groups.\textsuperscript{15,18}

As usual, esters of carboxylic acids, including heterocyclic compounds, react with amines to form amides at room temperature,\textsuperscript{56} upon heating,\textsuperscript{57} or in the presence of metal salts.\textsuperscript{58} In our case, 2-aryl-1-hydroxy-4-methyl-1\textsubscript{H}-imidazole-5-carboxamides 2\textsubscript{a–l} were obtained by refluxing esters 1\textsubscript{a–f} in butylamine (6–10 h) or cyclopropylamine (36–54 h) (Scheme 2).

All the novel 1-hydroxyimidazole derivatives 1\textsubscript{b–f}, 2\textsubscript{a–l} were tested for activity against VACV in Vero cell culture. The results are given in Table 1.

Ethyl 2-aryl-1-hydroxy-1\textsubscript{H}-imidazole-5-carboxylates containing either non-substituted phenyl moiety (1\textsubscript{b}) or 2- or 3-nitrophenyl...
Table 1

Cytotoxicity and antiviral activity of 1-hydroxyimidazoles 1a–f, 2a–l against Vaccinia virus (Copenhagen strain) in Vero cell culture.

| N° | M.C. | R² | R³ | CC50 (M ≤ SD, n = 3) μM | IC50 (M ≤ SD, n = 3) μM | SI (CC50/IC50) |
|----|------|----|----|----------------|----------------|--------------|
| 1a  | 262 | 2- | – | 1825.57 ± 15.53 | 117 | – |
| 1b  | 246 | H | – | 171.54 ± 55.26 | N/A | – |
| 1c  | 291 | 2- | NO2 | 343.30 ± 33.68 | N/A | – |
| 1d  | 291 | 3- | NO2 | 374.91 ± 38.14 | N/A | – |
| 1e  | 291 | 4- | NO2 | 45.70 ± 8.93 | 0.45 ± 0.03 | 102 |
| 1f  | 314 | 4- | CF3 | >321.97 | – | 919 |
| 2a  | 289 | 2- | CF3 | 196.89 ± 15.02 | 13 | – |
| 2b  | 273 | 2- | cycle | 298.90 ± 2.70 | N/A | – |
| 2c  | 273 | H | cycle | 436.26 ± 15.42 | 6 | – |
| 2d  | 275 | H | cycle | >389.11 | N/A | – |
| 2e  | 318 | 2- | NO2 | >314.47 | N/A | – |
| 2f  | 302 | 2- | cycle | >331.13 | N/A | – |
| 2g  | 318 | 2- | NO2 | 164.47 ± 17.64 | 9 | – |
| 2h  | 302 | 3- | NO2 | 30.19 ± 5.91 | – | – |
| 2i  | 328 | 4- | NO2 | 260.93 ± 63.91 | N/A | – |
| 2j  | 318 | 4- | NO2 | 200.63 ± 3.02 | 66 | – |
| 2k  | 302 | 4- | cycle | 356.95 ± 10.73 | 33 | – |
| 2l  | 314 | 4- | CF3 | 33.44 ± 2.02 | – | – |
| 2m  | 325 | 4- | CF3 | 26.10 ± 4.40 | 5.34 ± 2.55 | 8 |
| 2n  | 325 | 4- | cycle | 201.85 ± 20.58 | 10 | – |
| 2o  | 279 | H | cycle | 989.25 ± 32.47 | 30 | – |
| 2p  | 394 | H | cycle | 1193.40 ± 0.0076 | 156,733 | – |
| 2q  | 228 | H | cycle | 228.68 | 0.0025 | – |

Notes: M.W. – molecular weight; CC50 = 50 % cytotoxicity concentration, at which 50 % of cells in uninfected monolayers are destroyed; IC50 = 50 % virus inhibitory concentration, at which 50 % of cells in infected monolayers are preserved; SI – selectivity index, ratio CC50/IC50; M = mean value; SD = standard deviation; n = 3 – the number of repeats of measurement of CC50 and IC50; N/A = not active.

Table 2

Antiviral activity of 1-hydroxyimidazoles 1a,e,f and 2i,j against cowpox virus (Grishak strain) and ectromelia virus (strain K-1) in Vero cell culture.

| N° | M.C. | R² | R³ | Activity against cowpox virus (IC50/IC50/IC50) | Activity against ectromelia virus (IC50/IC50/IC50) |
|----|------|----|----|---------------------------------------------|---------------------------------------------|
| 1a  | 262 | 2- | – | 1825.6 ± 103.4 | 1.07 ± 0.38 | 43 |
| 1e  | 291 | 2- | NO2 | 45.70 ± 8.93 | 0.38 ± 0.03 | 14 |
| 1f  | 314 | 2- | NO2 | 321.97 ± 29.62 | 1.88 ± 0.88 | 46 |
| 2i  | 318 | 2- | NO2 | 200.63 ± 12.30 | 6.75 ± 0.67 | 23 |
| 2j  | 302 | 356.95 ± 33.44 | 41.4 ± 14.70 | 24 |
| Cidofovir | 279 | 989.25 ± 46.38 | 33.98 ± 23 | 29 |
| NIOCH-14 | 394 | 1193.40 ± 0.0076 | 9.25 ± 9.25 | 33 |

Notes: M.W. – molecular weight; CC50 = 50 % cytotoxicity concentration, at which 50 % of cells in uninfected monolayers are destroyed; IC50 = 50 % virus inhibitory concentration, at which 50 % of cells in infected monolayers are preserved; SI – selectivity index, ratio CC50/IC50; M = mean value; SD = standard deviation; n = 3 – the number of repeats of measurement of CC50 and IC50; N/A = not active.

Antiviral activity as well. Compound 2a exhibited activity comparable by values with the one of 1a, but its increased cytotoxicity resulted in the decrease of selectivity index value by an order of magnitude (SI = 13 for 2a and SI = 117 for 1a). Presence of the butylamine moiety in the structure of a molecule led to a display of some virus-inhibitory activity by 1-hydroxy-2-phenylimidazole 2b and 1-hydroxy-2-(4-nitrophenyl)imidazole 2g, but in both cases their selectivity indices were not high (less than 10), so these derivatives could not be considered as perspective virus-inhibiting compounds.

For the most promising structures 1e,f the substitution of ester moiety by a carboxamide one (2i–l) led to a decrease of antiviral activity. Interestingly, in the case of a more cytotoxic starting 2-(4-nitrophenyl)imidazole 1e transfer to carboxamides 2i,j resulted in the decrease of cytotoxicity, while for the non-cytotoxic 2-[4-(trifluoro- methyl)phenyl]imidazole 1f such a change in the structure led to an acute increase in cytotoxicity and, as a result, to low values of selectivity indices for 2k,l. Thus, in the series of carboxamides the most promising results were exhibited by 2-(4-nitrophenyl)derivatives 2i,j (SI = 66 and 33, respectively).

Compounds with the highest selectivity indices were also tested for antiviral activity against other orthopoxviruses, i.e., the cowpox virus (CPXV) and the mouselop or ectromelia virus (ECTV). The results are given in Table 2.

Activities exhibited by compounds 1a,e,f and 2i,j against ECTV and CPXV were lower than the ones against VACV. At that, esters 1a,e,f demonstrated more promising antiviral activity against ECTV (SI_{ECTV} = 77 for 1a, 43 for 1e and 46 for 1f) than the one of amides 2i,j (SI_{ECTV} = 29 for 2i and 24 for 2j). If we take into consideration only the values of virus-inhibiting concentrations of the derivatives 1a,e,f and 2i,j, then the most perspective antiviral activity against these orthopoxviruses was displayed by 1-hydroxyimidazole 1e (SI_{ECTV} = 1.07 μM, IC_{50/IC_{50}} = 3.23 μM) containing 4-nitrophenyl moiety in position 2, and ethoxycarbonyl group in position 4 of imidazole. But as the same compound 1e was the most cytotoxic in the series (CC_{50} = 45.7 μM), its cytotoxicity adversely affected the demonstrated selectivity indices (SI_{ECTV} = 43; SI_{CPXV} = 14). At the same time, due to its low cytotoxicity (CC_{50} = 1825.5 μM) 1-hydroxyimidazole 1a showing not quite perspective virus inhibiting concentrations (CC_{50/IC_{50}} = 23.63 μM; IC_{50/CPXV} = 31.37 μM) had the highest selectivity indices (SI_{ECTV} = 77; SI_{CPXV} = 58). By the order of values selectivity indices of compounds 1a,e,f and 2i,j.
were comparable with the ones of Cidofovir but were significantly lower than the ones of NIOCH-14.

Cytotoxicity and antiviral activity of 1-hydroxyimidazoles $1a-f$, $2a-l$ against influenza A/H1N1pdm09 virus (strain A/California/07/2009 (H1N1)v strain) in MDCK cell culture had revealed the lack of activity (Table 3). Therefore, the compounds under consideration may be regarded as specific inhibitors of orthopoxviruses.

Interestingly, the transfer from Vero cell culture to MDCK cell culture resulted in the alteration of cytotoxicity of 1-hydroxyimidazoles $1a-f$, $2a-l$. All the ethyl esters $1a-f$ were not cytotoxic while in the series of amides containing n-butyl moiety rather toxic compounds may be found, i.e. $2a$ (CC$_{50}$ = 42.9 $\mu$M); $2l$ (CC$_{50}$ = 27.2 $\mu$M); $2k$ (CC$_{50}$ = 12.9 $\mu$M).

We have screened a series of newly synthesized ethyl esters and carboxamides of 2-aryl-1-hydroxy-4-methyl-1H-imidazole-5-carboxylic acids against the Vaccinia virus. It was revealed that the compounds exhibited the most promising activity possessed electron-withdrawing groups (NO$_2$, CF$_3$) in 2-phenyl substituent in para-position. The most active substances $1a$, $f$ and $2l$, $j$ also demonstrated inhibitory activity against other orthopoxviruses, namely, the cowpox virus and the mousepox virus (ectromelia).

It was also revealed that the compounds under consideration had been devoid of activity against the influenza A/H1N1 virus.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Data availability

Data will be made available on request.

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### Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2022.129080. These data include MOL files and InChIKeys of the most important compounds described in this article.

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