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A. V. Fedyk, B. A. Chalyk
Institute of Organic Chemistry of the National Academy of Sciences of Ukraine,
5 Academician Kukhar str., Kyiv 02660, Ukraine

The synthesis of functionalized 4,5-dihydroisoxazoles decorated with the dimethylphosphinoyl group

Abstract

Aim. To synthesize a hybrid molecular platform incorporating dimethylphosphinoyl and 4,5-dihydroisoxazole moieties suitable for the creation of focused combinatorial libraries of compounds.

Results and discussion. The base-promoted interaction of halogenoxides with dimethyl(vinyl)phosphine oxide under mild conditions allowed us to obtain 11 isoxazoline–dimethylphosphine oxide hybrids in moderate yields. The reaction was found to be regio- though non-stereoselective. Furoxans were identified as possible side products of the reaction.

Experimental part. The one-pot interaction with dimethyl(vinyl)phosphine oxide was used for the synthesis of the target compounds. Nitrile oxides were obtained *in situ* from the corresponding halogenoximes by base-promoted generation. The ADME parameters for a synthesized 5-P(O)Me_2-isoxazoline compared to its isosters with the same core structure were predicted using a SwissADME Web Tool. The compounds obtained were characterized by ^{1}H, ^{13}C, ^{19}F, ^{31}P NMR spectroscopy and HPLC-MS spectrometry methods, as well as the elemental analysis.

Conclusions. A practical approach to the isoxazoline platform decorated with a 5-P(O)Me_2 "magic" group and containing 3-substituent with an easy-to-modify functionality has been developed. On example of the piperidine derivative, the effect of the dimethylphosphinoyl group on physicochemical properties and ADME parameters compared to its isosters has been determined.

Keywords: dimethylphosphine oxide; isoxazoline; dipolar cycloaddition; nitrile oxide; halogenoximes; selectivity; ADME profile

А. В. Федик, Б. А. Чалик
Інститут органічної хімії Національної академії наук України,
вул. Академіка Кухаря, 5, м. Київ, 02660, Україна

Синтез функціоналізованих 4,5-дигідроізоксазолів, які містять диметилфосфіноїльну групу

Анотація

Мета. Синтезувати гібридну молекулярну платформу, яка містить диметилфосфіноїльну групу та фрагмент 4,5-дигідроізоксазолу і в подальшому може бути використана для створення фокусованих комбінаторних бібліотек сполук.

Результати та їх обговорення. Взаємодія галогеноксимів із диметил(вініл)фосфіноксидом у присутності основи у м'яких умовах дозволила одержати із помірними виходами 11 гібридних сполук, які містять фрагменти ізоксазоліну та диметилфосфіноксиду. Виявлено, що реакція є регіо-, хоча й нестереоселективною. Фуроксани було ідентифіковано як можливі побічні продукти реакції.

Експериментальна частина. Для синтезу цільових сполук було використано взаємодію нітрилоксидів з диметил(вініл)фосфіноксидом. Нітрилоксиди було одержано *in situ* з відповідних галогеноксимів дією основи. Для одного з представників цільових 5-P(O)Me_2-ізоксазолінів було спрогнозовано ADME-профіль та порівняно одержані значення з аналогічними характеристиками для його ізостерів з базовою структурою ізоксазоліну. Розрахунки було здійснено за допомогою вебресурсу SwissADME. Одержані сполуки схарактеризовано методами ^{1}H, ^{13}C, ^{19}F, ^{31}P ЯМР-спектроскопії та ВЕРХ-мас-спектрометрії, а також елементного аналізу.

Висновки. Розроблено практичний підхід до одержання ізоксазолінової платформи, що містить «магічну» 5-P(O)Me_2 групу та функціоналізований замісник у положенні 3. На прикладі похідної піперидину окреслено вплив диметилфосфіноїльної групи на фізико-хімічні властивості та ADME-параметри порівняно з її ізостерами.

Ключові слова: диметилфосфін оксид; ізоксазолін; диполярне циклоприєднання; нітрилоксид; галогеноксими; селективність; ADME-профіль

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Supporting information: Copies of ^{1}H, ^{13}C, ^{19}F, ^{31}P NMR spectra of the synthesized compounds.
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■ Introduction

Phosphorus along with carbon, oxygen, and nitrogen is an essential element undoubtedly required for the growth and development of all known forms of life. Either in the form of inorganic phosphates or being incorporated in the biomolecules (nucleotides, DNA, RNA, phospholipids, phosphorylated proteins, etc.) phosphorus is involved in multiple vital biochemical processes, like storing and transferring genetic information, transporting cellular energy, functioning the cell membrane, including several transport mechanisms and protection of the interior of all cells. Hence, no wonder that this element gained much attention from agriculture [1], biochemistry [2], and medicinal chemistry [3] researchers. Thus, organophosphates make up much part of insecticides and have been investigated for application in the veterinary field [4, 5]. The medical application of phosphorus-containing organic substances started with the release of menadiol sodium diphosphate by Roche in 1941 [6]. Further research has led to expansion of the nomenclature of "P"-containing functional groups embedded in drug molecules, and now it is possible to find pharmaceutical agents belonging to phosphoric amides [7], phosphonates [8], phosphinates [9], bisphosphonates [10], phosphoric anhydrides [11], etc., which have achieved commercial success [12]. Recently, excellent reviews highlighting and summarizing the phosphorus-containing drugs currently available at the market, their structural features, biological mechanism, as well as historical aspects of their development, have been published [13, 14].

Broadly, a phosphorus-containing functionality is added to the molecule to create selectivity- and bioavailability-enhanced pro-drugs and does not constitute a pharmacophoric part of the molecule [15]. This strategy is also frequently used to improve the aqueous solubility of sparingly soluble molecules and achieve a suitable pharmacokinetics profile by introducing a charged phosphate and related units [16]. A major obstacle associated with the latter approach is a low cell permeability and poor oral bioavailability of the charged molecules [17]. In view of this, it is surprising that their uncharged counterparts, namely phosphine oxides, have been largely neglected in drug discovery. It is quite strange as the phosphine oxide residue is usually easily formed and becomes (bio)chemically inert after its incorporation into the molecular structure. It also does not display much redox properties compared to carbonyl and alcohol functional groups. Furthermore, its capacity to act as an H-bond acceptor makes the phosphine oxide group an excellent alternative to existing common H-bond acceptors like carbonyls and sulfones [18].

A real breakthrough in understanding that a phosphine oxide fragment can be a game changer in creating innovative drugs have come with the accelerated FDA granted approval of brigatinib (Alunbrig®) for the treatment of metastatic non-small cell lung cancer [19]. A unique structural feature of brigatinib is the presence of the dimethyl phosphine oxide (DMPO) moiety, which solely causes the selectivity profile of brigatinib over anaplastic lymphoma kinase. It is amazing that such a simple group within a long thread-like brigatinib structure 70 times increases its potency compared to unsubstituted counterparts. Moreover, DMPO provides brigatinib with remarkable water solubility and reduced lipophilicity [20].

Later, after the release of brigatinib, a magnificent work by *Finkbeiner et al.* comprehensively showed that phosphine oxides (including DMPO) were outstanding polar structural elements deserving to become a routine part of medicinal chemistry toolkit [21]. In particular, the authors thoroughly investigated *in vitro* properties of a series of phosphorus(V)-containing compounds and came to conclusion that phosphine oxides gave high solubility and metabolic stability to organic substrates, but occasionally due to the worsened cell membrane permeability. All of the above has led to a revision of the generally accepted paradigm of medical chemistry, according to which phosphine oxides are considered an undesirable group. This change of views has

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given rise to several clinical candidates containing the trialkylphosphine oxide group (Figure 1, **A**) and, in particular, the DMPO moiety (Figure 1, **B**) [13, 21]. Among them, Fosazepam deserves attention; it is a water-soluble analog of Diazepam and indicates the magic effect of the DMPO fragment on the physicochemical properties of organic molecules.

Turning to the synthetic side of the issue it should emphasized that the ability to readily incorporate new functional groups into molecular frameworks is what determines how well these groups are adopted by medicinal chemistry. Taking into account the importance of the last statement, as well as the lack of methods suitable for introducing the DMPO fragment into low molecular-weight saturated heterocyclic amines, we have lately disclosed several scalable synthetic approaches to DMPO-containing azetidine, pyrrolidine, piperidine, and morpholine derivatives [22]. This work significantly contributed to medicinal chemistry and provided valuable sp^3-enriched building blocks for the use in early drug discovery. Proceeding with the creation of MedChem relevant DMPO containing functionalized "bricks" with a high potential to generate lead-like compounds, in this report we describe an efficient strategy towards a hybrid molecular platform incorporating the $Me_2P(O)$ and 4,5-dihydroisoxazole moiety along with a ready-to-modify functionality.

Interestingly, although the isoxazole ring is among the top heterocycles used in medicinal chemistry [23], its 4,5-dihydro analog is overlooked by major pharmaceutical players. The search over different databases returned no marketed drugs approved for the use in human medicine, and only 3 examples undergoing experimental clinical trials with 2 of them approved for veterinary use (Figure 2, **A**) [24–26]. On the other hand, naturally occurring 4,5-dihydroisoxazoles are a well-known class of heterocyclic compounds often with outstanding pharmacological properties (Figure 2, **B**) [27–29].

One should note that our research group has a profound experience in construction of polysubstituted isoxazoles and 4,5-dihydro analogs [30, 31]. We have devised new and optimized known methods towards the heterocyclic platforms, which rely on 1,3-dipolar addition of *in situ* generated nitrile oxides from halogenoximes to diverse unsaturated partners. It has been proven that the use of a component containing an alkene fragment is a simple and effective way to obtain isoxazolines [32]. It is worth mentioning that we have successfully exploited this way to reach diethyl phosphonates (Scheme 1, **A**) [33]. In this way, it becomes obvious that the target for working derivatives can be achieved by replacing diethyl

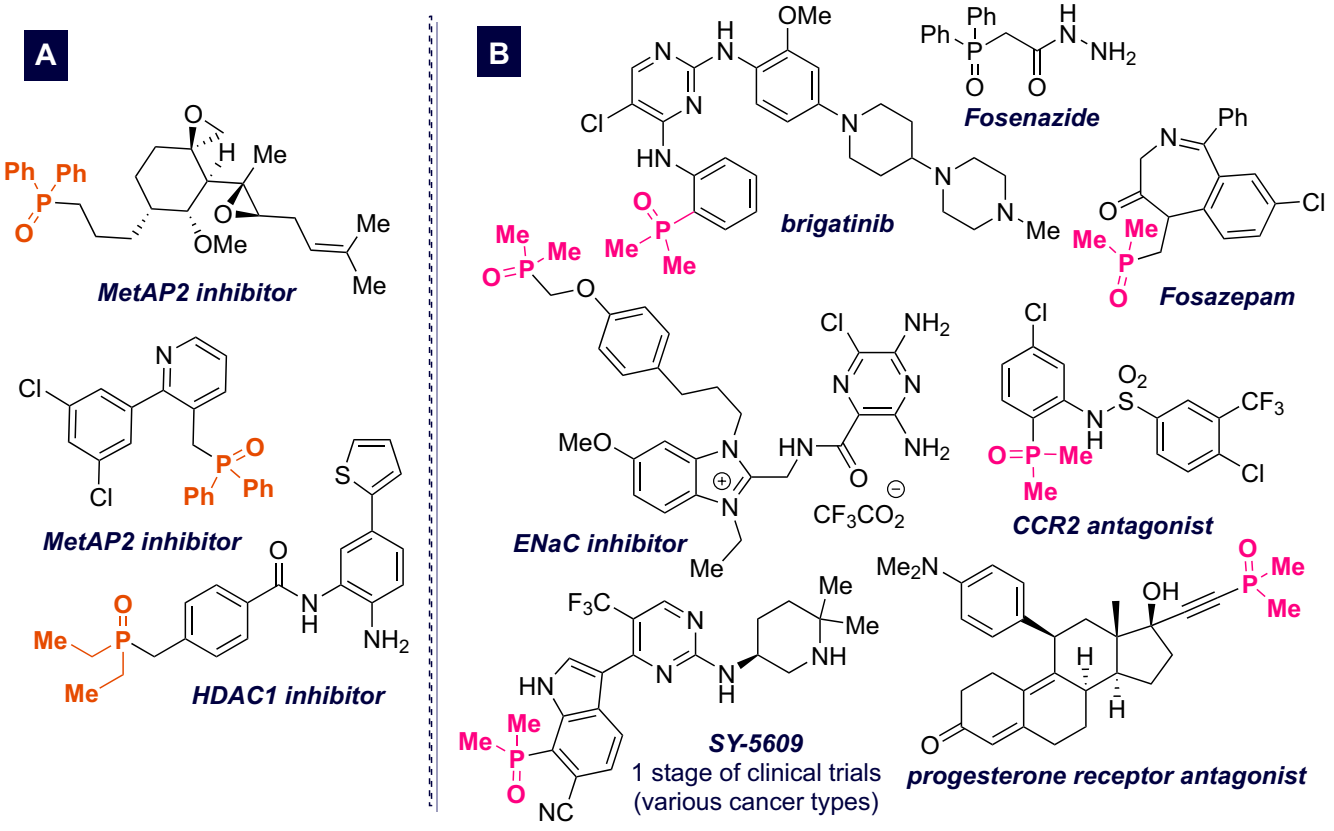


Figure 1. Recent examples (or investigational and approved drugs) of the use of phosphine oxides in medicine

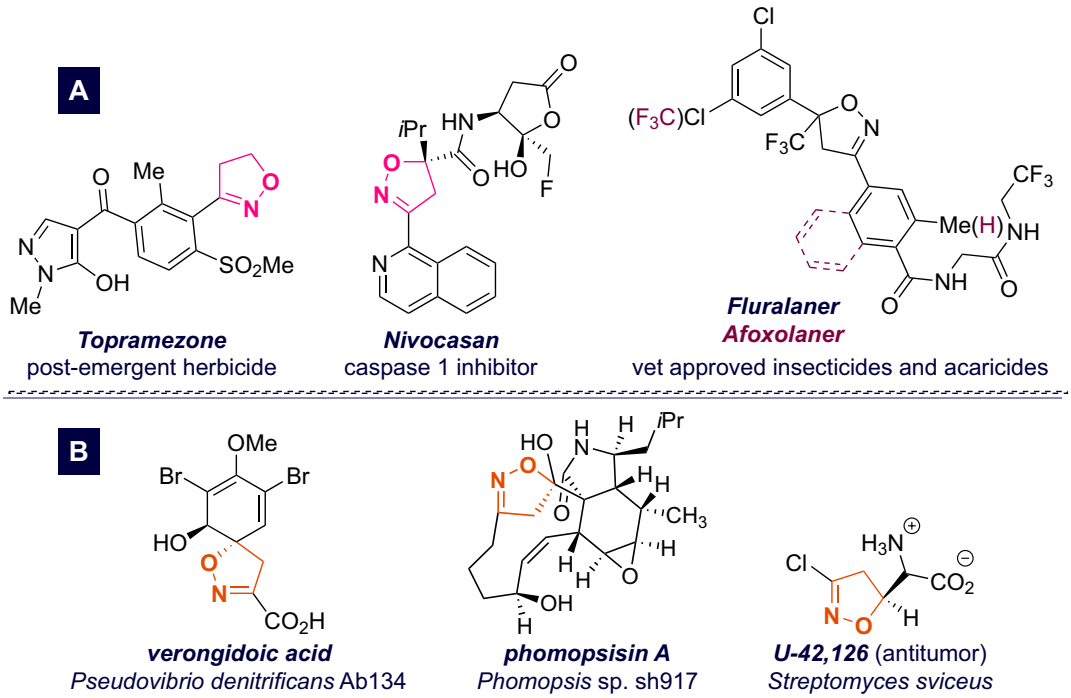
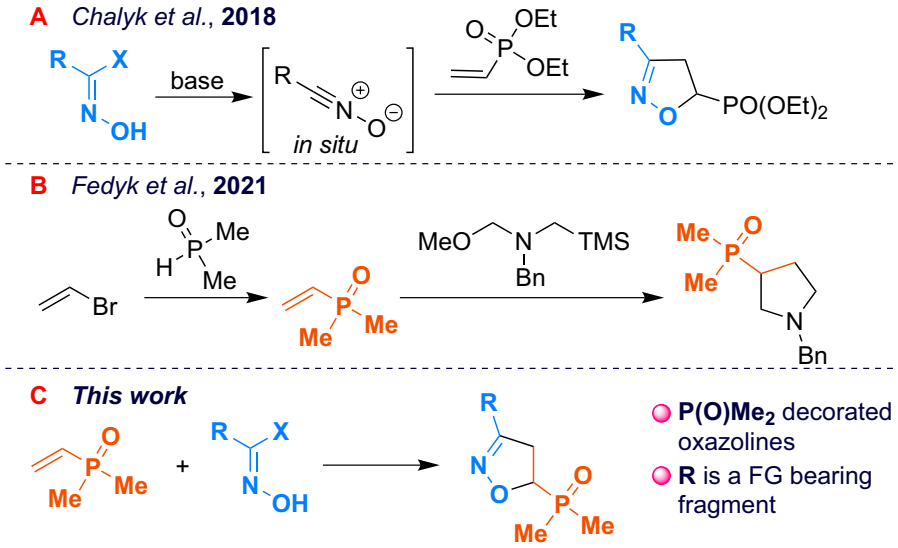


Figure 2. Experimental (**A**) and natural (**B**) 4,5-dihydroisoxazoles



Scheme 1. Aim and background of this work

vinylphosphonate with dimethyl(vinyl)phosphine oxide in the last reaction. In turn, recently in our work, the procedure for preparing the latter on a scale of more than 100 g was disclosed [22]. Notably, the phosphine oxide was fruitfully examined in 1,3-dipolar addition with N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine giving the corresponding pyrrolidine in a high yield (Scheme 1, **B**).

Thus, herein we discuss the interaction of dimethyl(vinyl)phosphine oxide with halogenoximes with an intention to assemble $P(O)Me_2$ decorated isoxazolines having an easy-to-modify randomization point (Scheme 1, **C**).

■ Results and discussion

According to the planned research strategy, we relied on the method for the synthesis of 3,5-disubstituted isoxazolines based on [3+2]-cycloaddition of nitrile oxides and dimethyl(vinyl) phosphine oxide (Scheme 2) [34]. The corresponding nitrile oxides **12a–k** could be produced *in situ* from halogenoximes **4a–h**, **6i**, **8j** and **11k**, which, in turn, were obtained from the corresponding N-Boc-protected amino acids **1a–h** (through their sequential reduction to alcohols **2** and generation of aldehydes **3**) (Scheme 2, **A**), glyoxalic acid (**5i**) (Scheme 2, **B**) [35], hemiacetal **7j**

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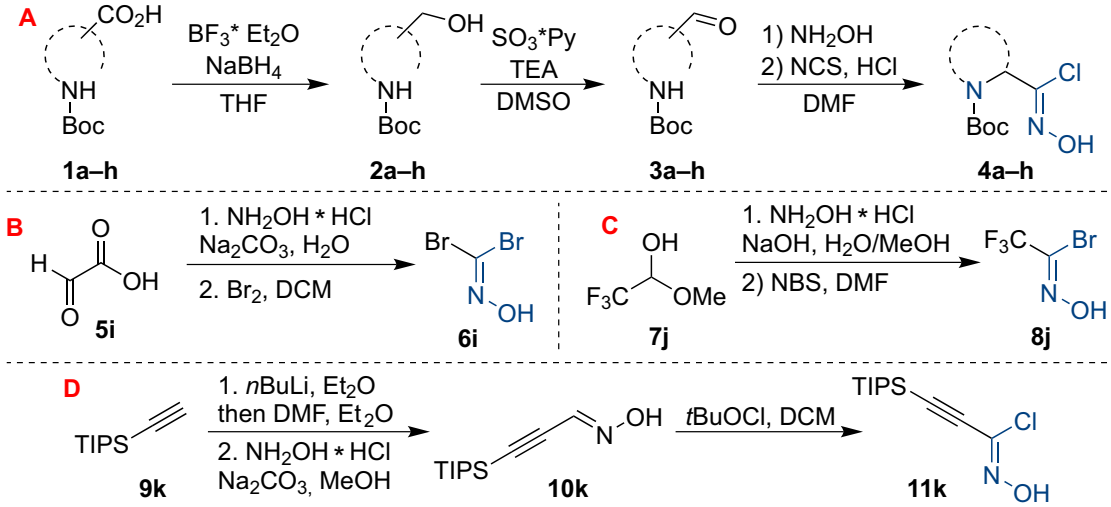


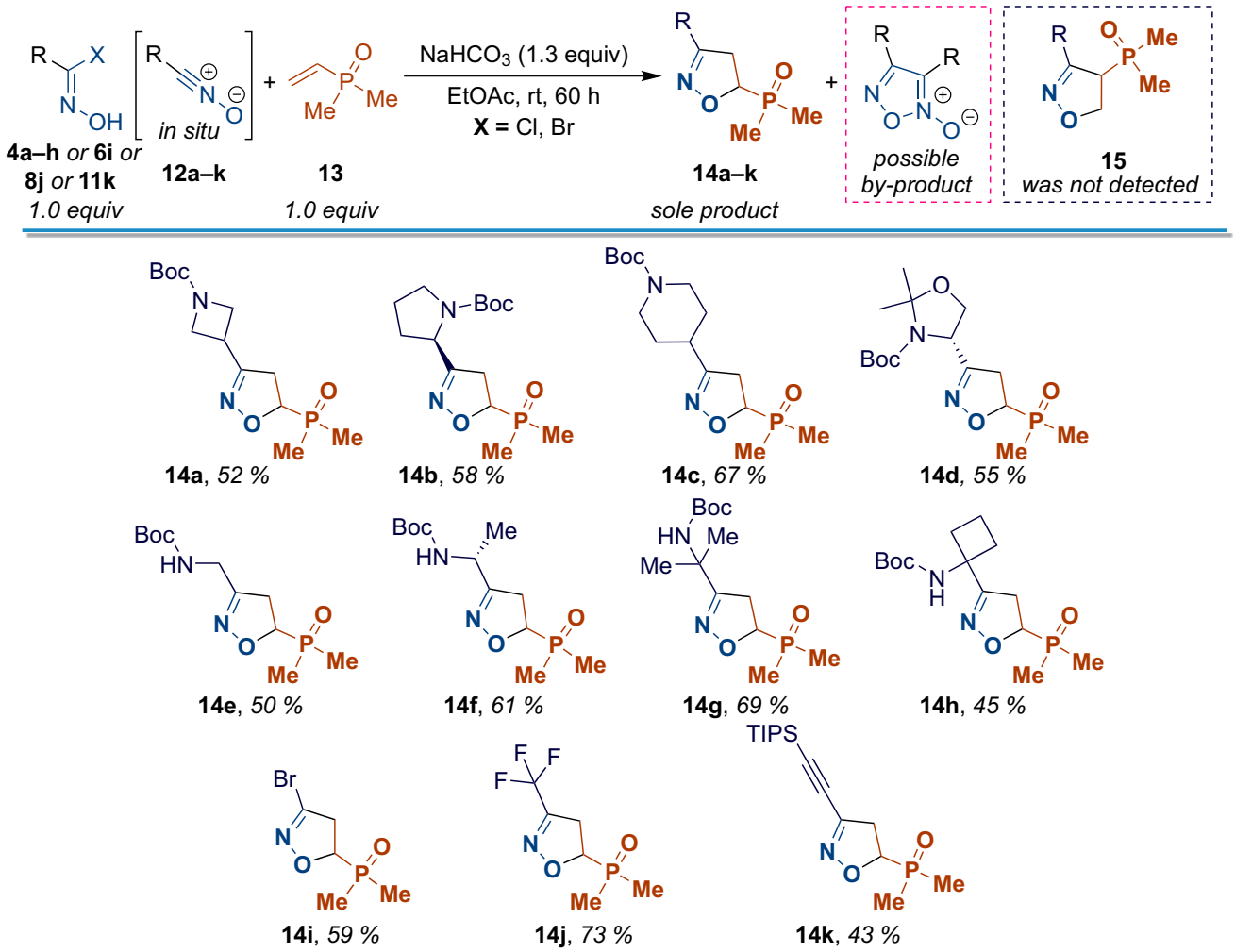
Scheme 2. Synthesis of the starting halogen oximes

(Scheme 2, **C**) [36], or TIPS-protected acetylene **9k** (Scheme 1, **D**) [37, 38] according to the procedures previously published. The choice of R-substituents in halogenoximes was justified by the utility of the [3+2]-adducts derived from them for subsequent synthetic transformations (e.g., the presence of protected NH_2 and alkyne groups or bromine atom) and their attractiveness for medicinal chemistry in the case of the CF_3-substituent.

Having intermediate halogenoximes, we started studying their interaction with dimethyl(vinyl)phosphine oxide (**13**). For the reaction, we chose conditions that previously proved themselves as efficient and reliable ones for a wide range of substrates [30]. Precisely, the reactions were carried out using a 1-to-1 ratio of the starting materials in the presence of a 1.3-fold excess of a weakly basic sodium bicarbonate in the ethyl acetate medium at room temperature. Such gentle conditions allowed keeping intact all functional groups besides the reaction centers. The progress of the reaction was monitored by HPLC indicating that the reaction usually completed within 60 h. One should point out that application of insoluble base in this setup made it possible gradual generation of nitrile oxides, thus mostly avoiding dimerization of the latter with the formation of the corresponding furoxans (Scheme 3). However, during the HPLC-monitoring, we sometimes noticed the formation of this by-product although there were no obvious reasons for this fact. In this case, an additional portion of nitrile oxide should be added to the reaction mixture in order to use up the remaining dipolarophile. As the result, the target isoxazolines **14a–k** were obtained in moderate yields though all entries needed additional chromatography purification step to isolate the substance with 95%+ purity. Importantly, all the products were stable enough to store them at ambient conditions and did not show any noticeable sign of decomposition within 2 years after preparation.

Another issue to be addressed is the regioselectivity of the reaction. 1,3-Dipolar cycloaddition is known to give several regioisomers when non-symmetrical dipolarophiles are used [39]. Previously, we observed a lack of regioselectivity in the case of utilization of diethyl ethynylphosphonate as the reaction partner with the formation of a mixture of 4- and 5-isomers in different ratios [33]. However, the switch to diethyl vinylphosphonate restored the selectivity providing 5-phosphonate solely. According to all spectral data recorded, only one isomer was formed in the cycloaddition. Assignment of its structure to 5-dimethylphosphinoyl **14** was made based on ^{13}C NMR spectral data (Figure 3, **A**). Thus, C-5 atom of the isoxazoline core was seen as a doublet with the *ipso*-coupling constant of ~81 Hz; C-4, in turn, was found as a doublet though with much lower J ~ 6 Hz. We did not detect any traces of another feasible isomer **15** neither in NMR nor in HPLC spectra of the crude products.

The regioselectivity of the process might be governed by steric and/or electronic factors (Figure 3, **B**). In particular, the transition state **TS1** leading to the formation of 3,4-disubstituted isoxazolines **15** is unfavorable compared to **TS1** (giving 3,5-disubstituted isomer) due to the steric repulsion between the R-group and the dimethylphosphinoyl fragment. In addition, information complying with the above-stated one can be derived from the analysis of the atomic charges over alkene carbons in compound **13**. The values



Scheme 3. Synthetic approach to dimethyl phosphine oxide – isoxazoline hybrids

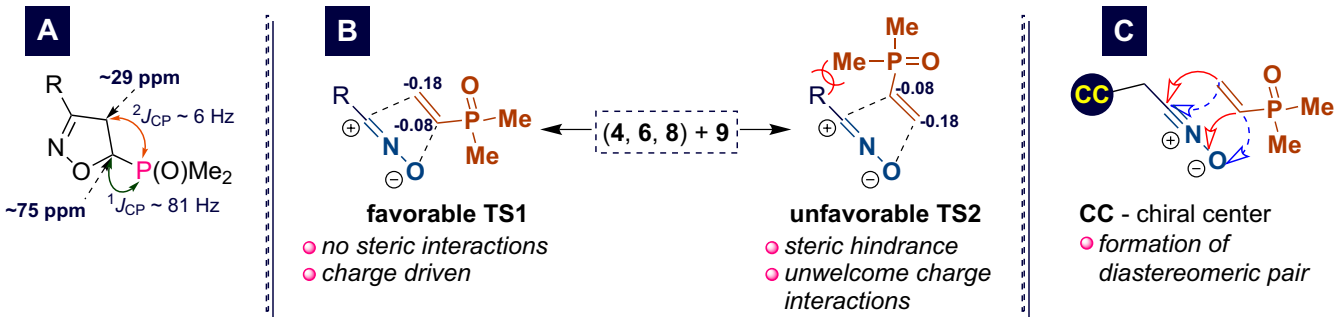


Figure 3. Regio- and stereoselective aspects of the reaction studied

retrieved from the Hückel molecular orbital theory calculations (ChemBio3D Ultra, *ver. 14.0*, https://www.cambridgesoft.com/Ensemble_for_Chemistry/details/Default.aspx?fid=13&pid=668) demonstrate a favored C···C interaction (attraction of positive and negative charges) and less pronounced C···O repulsion than in **TS1** compared to **TS2**. Thus, the charge distribution also favors the product structures identical to those found experimentally.

Unlike the regioselectivity, the reaction was not stereoselective with reference to C-5 atom of isoxazolidine. This was judged from the formation of a diastereomeric pair in the cases of chiral oximes **4b,d,f** shown by NMR and HPLC data (Figure 3, **C**).

Further, we studied suitable ways to remove protecting Boc- (on the example of compound **14h**) and TIPS-groups. Previously, the Boc-protection was washed out from similar isoxazoles with HCl dissolved in MeOH [34]. Surprisingly, our attempt to apply this method to **14h** failed, and we obtained inseparable mixture of products. Changing the reaction setup to TFA/DCM enabled the

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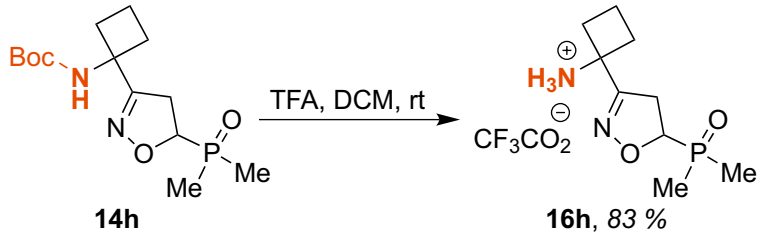

Scheme 4. Boc-deprotection of compound **14h**

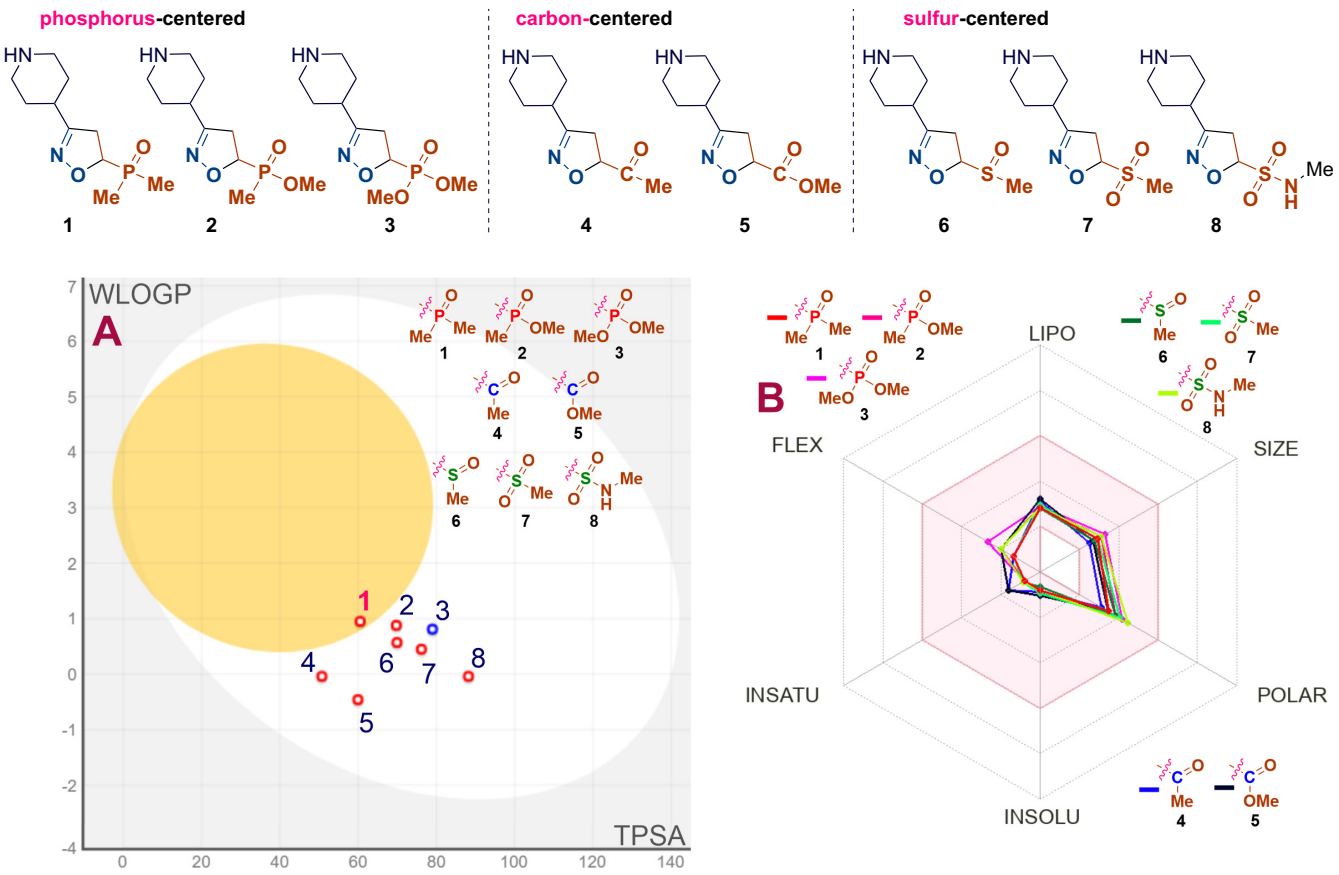

Figure 4. (**A**) The BOILED-Egg model; WLOGP – lipophilicity; TPSA – the Topological Polar Surface Area; blue dots for P-gp substrates, red dots for P-gp non-substrate. (**B**) The bioavailability radar: LIPO – lipophilicity from −0.7 to +5.0; SIZE – the molecular weight from 150 to 500 g mol^{-1}; POLAR – the topological polar surface area from 20 to 130 Å^2; INSOLU – the decimal logarithm of water solubility less than 6; INSATU – the fraction of sp^3 hybridized carbons not less than 0.25; FLEX – rotatable bonds not more than 9

isolation of the desired amine in the form of a trifluoroacetate salt (Scheme 4). Unfortunately, all our attempts to deprotect alkyne **14k** under standard conditions (TBAF, THF; HF, MeCN; Et_3N*3HF) did not result in a satisfactory result.

Currently, the above-mentioned unique properties of P(O)Me_2 the substituent are widely used by MedChem researchers, e.g. to dramatically increase solubility and decrease lipophilicity of organic compounds. For instance, this tactic was used to improve the solubility of the antihypertensive drug prazosin without affecting its biological profile [40]. Broadly, available chemical space of small molecular "bricks", as well as powerful operational instruments allow altering the ADME properties of potential drug candidates to achieve necessary characteristics. This becomes possible with a right choice of pieces within complex thread-like molecules. Therefore, we decided to trace how some properties of the target compounds **14** changed with the replacement of the DMPO group with its isosters. The analysis was performed on the example of piperidine derivative **14c**. As isosteric substituents, P-, C- and S-centered functionalities were selected (Figure 4). The calculation was carried out with the aid of a SwissADME web tool [41, 42] and concerned two issues:

- prediction of the passive gastrointestinal absorption (HIA) and penetration of the blood-brain barrier (BBB) (BOILED-Egg method, Figure 4, **A**);

• retrieval of the Bioavailability radar that provides predicted information about 6 important physicochemical characteristics – lipophilicity, size, polarity, solubility, flexibility and saturation of molecules. An optimal range for each value is represented as a red area.

One can see that the DMPO derivative (1) falls into the "yolk" area meaning its highly probable BBB permeation; it is not also a subject to active efflux by means of P-glycoprotein (a red dot). The presence of other functional groups decreases likelihood of this process, and the isosters are predicted as well-absorbed in the gastrointestinal tract, but not accessing the brain (a white region). As for the Bioavailability radar, for all isosters examined the plots perfectly fit the red region leaving a wide gap to alter the characteristics of molecules. All derivatives feature close calculated characteristics with none of them falling out significantly.

■ Conclusions

A practical approach to the isoxazoline platform decorated with a 5-P(O)Me_2 substituent and based on 1,3-dipolar addition between *in situ* generated nitrile oxides and dimethyl(vinyl)phosphine oxide has been developed. The base-promoted interaction of halogenoxides with dimethyl(vinyl)-phosphine oxide under mild conditions has allowed us to obtain 11 isoxazoline–dimethylphosphine oxide hybrids in moderate yields. The reaction has been found to be regio- though non-stereoselective. The approach to the Boc-deprotection has been also described. On the example of the piperidine derivative, the effect of the dimethylphosphinoyl group on physicochemical properties and ADME parameters compared to its isosters has been determined.

■ Experimental part

All starting compounds and solvents were obtained from commercial sources and used without further purification. Melting points were measured in open capillary tubes and given uncorrected. NMR experiments were performed on a Bruker 170 Avance 500 (at 500 MHz for ^{1}H NMR, 470 MHz for ^{19}F NMR, 202 MHz for ^{31}P NMR, and 126 MHz for ^{13}C NMR) or a Varian Unity Plus 400 (at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR) spectrometers in the DMSO-d_6 or $CDCl_3$ solution. NMR chemical shifts were reported in ppm units using the δ scale and referenced using the solvent peaks at 7.26 and 77.1 ppm ($CDCl_3$) for ^{1}H and ^{13}C nuclei, respectively, and 2.48 and 39.5 ppm (DMSO-d_6) for ^{1}H and ^{13}C nuclei, respectively. For ^{19}F NMR experiments hexafluorobenzene was used as an internal standard. The chemical shifts in ^{31}P NMR studies were referenced to external 85% H_3PO_4. HPLC experiments were carried out on an Agilent LC/MSD SL 1100 instrument (atmospheric pressure electrospray ionization (ES-API)), GCMS spectra were taken on an Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). According to chromatographic studies, all compounds had purity of more than 95%. Elemental analyses were performed in the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.

The general procedure for the synthesis of 3-(5-dimethylphosphoryl)-4,5-dihydroisoxazoles 14

To the solution of the corresponding halogenoxime **4** *or* **6** *or* **8** *or* **11** (5 mmol, 1.0 equiv) and dimethyl(vinyl)phosphine oxide (**13**, 0.52 g, 5 mmol, 1.0 equiv) in EtOAc (10 mL), $NaHCO_3$ (0.57 g, 6.5 mmol, 1.3 equiv) was added. The mixture was vigorously stirred at room temperature for 60 h. Then the inorganic precipitate was filtered off, the filtrate was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by the preparative high-performance liquid chromatography or flash column chromatography (details are given for each compound below) resulting in the target 4,5-dihydroisoxazoles **14**.

***tert*-Butyl 3-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)azetidine-1-carboxylate (14a)**

A colorless oil, solidified upon standing. HPLC purification: 9% water-acetonitrile 0.5–6.5 min; flow 30 mL min^{-1} (loading pump 4 mL min^{-1} acetonitrile); column SunFireC18 100×19 mm 5um (R). Yield – 0.78 g (52%). Anal. Calcd for $C_{13}H_{23}N_2O_4P$, %: C 51.65; H 7.67; N 9.27. Found, %: C 51.82; H 7.74; N 9.11. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.42 (9H, s, 3×CH_3); 1.46 (3H, d, $^2J_{HP}$ = 12.7 Hz, CH_3P); 1.61 (3H, d, $^2J_{HP}$ = 12.8 Hz, CH_3P); 3.31–3.45 (2H, m); 3.53 (1H, dq, J = 8.8, 4.4 Hz); 3.99 (2H, dd, J = 9.2, 4.9 Hz); 4.17 (2H, t, J = 8.7 Hz); 4.70–4.81 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 11.40 (d, $^1J_{CP}$ = 68 Hz, $\underline{C}H_3P$); 14.79 (d, $^1J_{CP}$ = 68 Hz, $\underline{C}H_3P$); 26.53; 28.24; 35.93; 52.09; 77.66; 79.95 ($\underline{C}(CH_3)_3$); 155.91 (C=O); 158.30 (d, $^3J_{CP}$ = 3.7 Hz, C-3 isoxazoline). ^{31}P NMR (202 MHz, $CDCl_3$), δ, ppm: 43.38. LC-MS (ES-API), m/z: 325.2 $[M+Na]^+$.

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***tert*-Butyl (2R)-2-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)pyrrolidine-1-carboxylate (14b)**

A colorless oil. HPLC purification: 20–45% water-acetonitrile 2–7 min; flow 30 mL min^{-1} (loading pump 4 mL min^{-1} acetonitrile); column SunFireC18 100×19 mm 5um (R). Yield – 0.91 g (58%). Anal. Calcd for $C_{14}H_{25}N_2O_4P$, %: C 53.16; H 7.97; N 8.86. Found, %: C 53.04; H 7.92; N 9.03. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.37–1.48 (12H, m, 3×CH_3 + CH_3P); 1.58 (3H, d, $^2J_{HP}$ = 12.9 Hz, CH_3P); 1.82–2.29 (4H, m); 3.19–3.58 (4H, m); 4.55–4.80 (2H, m). ^{13}C and ^{31}P NMR spectra are not informative due to hindered rotation (see *Supporting information file*). LC-MS (ES-API), *m/z*: 317.0 $[M+H]^+$.

***tert*-Butyl 4-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)piperidine-1-carboxylate (14c)**

A yellow oil. Flash column chromatography (FCC) purification: $CHCl_3$:MeOH (10:1), R_f = 0.27. Yield – 1.1 g (67%). Anal. Calcd for $C_{15}H_{27}N_2O_4P$, %: C 54.54; H 8.24; N 8.48. Found, %: C 54.73; H 8.11; N 8.54. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.38 – 1.47 (12H, m); 1.49–1.65 (5H, m); 1.83 (2H, d, *J* = 13.0 Hz); 2.56 (1H, tt, *J* = 11.1, 3.2 Hz); 2.79 (2H, t, *J* = 12.3 Hz); 3.24–3.37 (2H, m); 4.11 (2H, d, *J* = 13.5 Hz); 4.63–4.73 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 10.60 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 13.24 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 27.90; 28.75 (d, $^2J_{CP}$ = 6.3 Hz, C-4 isoxazoline); 34.88; 35.87; 42.80; 75.91 (d, $^1J_{CP}$ = 81 Hz, C-5 isoxazoline); 79.25 (C(CH_3)$_3$); 154.09 (C=O); 160.77 (d, $^3J_{CP}$ = 3.8 Hz, C-3 isoxazoline). ^{31}P NMR (202 MHz, $CDCl_3$), δ, ppm: 44.13. LC-MS (ES-API), *m/z*: 331.1 $[M+H]^+$.

***tert*-Butyl (4S)-4-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)-2,2-dimethyloxazolidine-3-carboxylate (14d)**

A white amorphous solid. HPLC purification: 20–45% water-acetonitrile 2–7 min; flow 30 mL min^{-1} (loading pump 4 mL min^{-1} acetonitrile); SunFireC18 100×19 mm 5um (R). Yield – 0.95 g (55%). Anal. Calcd for $C_{15}H_{27}N_2O_5P$, %: C 52.02; H 7.86; N 8.09. Found, %: C 52.10; H 7.97; N 8.01. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.40 – 1.73 (21H, m); 3.31–3.53 (2H, m); 3.93–4.11 (1H, m); 4.13–4.30 (1H, m); 4.67–4.99 (2H, m). ^{13}C and ^{31}P NMR spectra are not informative due to hindered rotation and diastereomeric (see *Supporting information file*). LC-MS (ES-API), *m/z*: 347.2 $[M+H]^+$.

***tert*-Butyl ((5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)methyl)carbamate (14e)**

A colorless oil. HPLC purification: 0–15% water-acetonitrile 0.5–6.5 min; flow 30 mL min^{-1} (loading pump 4 mL min^{-1} acetonitrile); column SunFireC18 100×19 mm 5um (R). Yield – 0.69 g (50%). Anal. Calcd for $C_{11}H_{21}N_2O_4P$, %: C 47.82; H 7.66; N 10.14. Found, %: C 47.98; H 7.57; N 10.04. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.31–1.47 (16H, m); 3.09–3.33 (2H, m); 3.78–3.93 (2H, m); 4.70 (1H, ddd, *J* = 12.0, 9.5, 6.5 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 11.62 (d, $^1J_{CP}$ = 68 Hz); 13.76 (d, $^1J_{CP}$ = 68 Hz); 28.09; 36.22; 36.63; 76.83 (d, $^1J_{CP}$ = 81 Hz, C-5 isoxazoline); 78.24 (C(CH_3)$_3$); 155.58 (C=O); 157.55 (d, $^3J_{CP}$ = 3.8 Hz, C-3 isoxazoline). ^{31}P NMR (162 MHz, DMSO-d_6), δ, ppm: 41.17. LC-MS (ES-API), *m/z*: 355.2 $[M+DMSO+H]^+$.

***tert*-Butyl ((1R)-1-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)ethyl)carbamate (14f)**

A white amorphous solid. HPLC purification: 9% water-acetonitrile 0.5–6.5 min; flow 30 mL min^{-1} (loading pump 4 mL min^{-1} acetonitrile); column SunFireC18 100×19 mm 5um (R). Yield – 0.88 g (61%). Anal. Calcd for $C_{12}H_{23}N_2O_4P$, %: C 49.65; H 7.99; N 9.65. Found, %: C 49.58; H 7.95; N 9.78. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.41–1.54 (15H, m); 1.60–1.69 (3H, m, CH_3P); 3.41 (2H, dd, *J* = 20.2, 11.7 Hz); 4.58 (1H, s); 4.71–4.91 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 10.41 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 10.70 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 13.98 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 14.05 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 18.09; 18.21; 27.78; 35.19; 35.80; 43.78; 43.98; 76.35 (d, $^1J_{CP}$ = 81 Hz, C-5 isoxazoline); 76.48 (d, $^1J_{CP}$ = 81 Hz, C-5 isoxazoline); 79.18 (C(CH_3)$_3$); 154.50; 154.63; 160.26; 160.57. ^{31}P NMR (202 MHz, $CDCl_3$), δ, ppm: 43.71, 44.19. LC-MS (ES-API), *m/z*: 291.4 $[M+H]^+$.

***tert*-Butyl (2-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)propan-2-yl)carbamate (14g)**

A white amorphous solid. HPLC purification: 10–35% water-acetonitrile 2–7 min; flow 30 mL min^{-1} (loading pump 4 mL min^{-1} acetonitrile); column sunfire SunFireC18 100×19 mm 5um (R). Yield – 1.05 g (69%). Anal. Calcd for $C_{13}H_{25}N_2O_4P$, %: C 51.31; H 8.28; N 9.21. Found, %: C 51.25; H 8.34; N 9.29. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.40 (9H, s, 3×CH_3); 1.44–1.51 (6H, m, CH_3P + CH_3CNH); 1.53 (3H, s, CH_3CNH); 1.60 (3H, d, $^2J_{HP}$ = 12.8 Hz, CH_3P); 3.37 (2H, dd, *J* = 20.5, 10.7 Hz, CH_2CH oxazoline); 4.74 (1H, t, *J* = 10.2 Hz, CH oxazoline); 4.85 (1H, s, NH). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 10.67 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 14.67 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 26.11; 26.79; 28.26; 35.80; 51.79; 76.98 (d, $^1J_{CP}$ = 82 Hz, C-5 isoxazoline); 79.71 (C(CH_3)$_3$); 154.38 (C=O); 164.18 (d, $^3J_{CP}$ = 4 Hz,

C-3 isoxazoline). ^{31}P NMR (202 MHz, $CDCl_3$), δ, ppm: 44.93. LC-MS (ES-API), m/z: 327.2 $[M+Na]^+$.

***tert*-Butyl (1-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)cyclobutyl)carbamate (14h)**

A white amorphous solid. HPLC purification: 12% water-acetonitrile 0.5–6.5 min; flow 30 mL min^{-1} (loading pump 4 mL min^{-1} acetonitrile); column SunFireC18 100×19 mm 5um (R). Yield – 0.71 g (45%). Anal. Calcd for $C_{14}H_{25}N_2O_4P$, %: C 53.16; H 7.97; N 8.86. Found, %: C 53.25; H 7.93; N 8.92. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.45 (9H, s, 3×CH_3); 1.54 (3H, d, $^2J_{HP}$ = 12.6 Hz, CH_3P); 1.68 (3H, d, $^2J_{HP}$ = 12.9 Hz, CH_3P); 1.96–2.12 (2H, m); 2.21–2.34 (2H, m); 2.50 (1H, s); 2.69 (1H, s); 3.33–3.54 (2H, m); 4.86 (1H, t, J = 8.6 Hz, CH oxazoline); 5.05 (1H, s, NH). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 14.74; 28.30; 28.38; 32.71; 32.97; 35.51; 54.39; 80.16; 154.38; 162.10. ^{31}P NMR (202 MHz, $CDCl_3$), δ, ppm: 45.55. LC-MS (ES-API), m/z: 317.2 $[M+H]^+$.

(3-Bromo-4,5-dihydroisoxazol-5-yl)dimethylphosphine oxide (14i)

A white amorphous solid. HPLC purification: 0–20% water-acetonitrile 0.5–6.5 min; flow 30 mL min^{-1} (loading pump 4 mL min^{-1} acetonitrile); column SunFireC18 100×19 mm 5um (R). Yield – 0.66 g (59%). Anal. Calcd for $C_5H_9BrNO_2P$, %: C 26.57; H 4.01; N 6.20. Found, %: C 26.43; H 4.04; N 6.25. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.40 (3H, d, $^2J_{HP}$ = 12.8 Hz, CH_3P); 1.51 (3H, d, $^2J_{HP}$ = 13.1 Hz, CH_3P); 3.48 (2H, dd, J = 19.4, 11.0 Hz, C$\underline{H_2}$CH oxazoline); 4.73 (1H, td, J = 11.0, 4.4 Hz, CH oxazoline). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 11.30 (d, $^1J_{CP}$ = 69 Hz, CH_3P); 14.65 (d, $^1J_{CP}$ = 68 Hz, CH_3P); 42.27 (C-4 isoxazoline); 78.07 (d, $^1J_{CP}$ = 79 Hz, C-5 isoxazoline); 137.59 (d, $^3J_{CP}$ = 5 Hz, C-3 isoxazoline); 137.61. ^{31}P NMR (202 MHz, $CDCl_3$), δ, ppm: 42.66. LC-MS (ES-API), m/z: 226.0 $[M+H]^+$.

Dimethyl(3-(trifluoromethyl)-4,5-dihydroisoxazol-5-yl)phosphine oxide (14j)

A white amorphous solid. FCC purification: $CHCl_3$:MeOH (10:1), R_f = 0.35. Yield – 0.78 g (73%). Anal. Calcd for $C_6H_9F_3NO_2P$, %: C 33.50; H 4.22; N 6.51. Found, %: C 33.55; H 4.32; N 6.43. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.49 (3H, d, $^2J_{HP}$ = 12.6 Hz, CH_3P); 1.65 (3H, d, $^2J_{HP}$ = 12.9 Hz, CH_3P); 3.48–3.64 (2H, m, C$\underline{H_2}$CH oxazoline); 4.98 (1H, ddt, J = 11.6, 9.5, 2.8 Hz, CH oxazoline). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 11.53 (d, $^1J_{CP}$ = 69 Hz, CH_3P); 14.58 (d, $^1J_{CP}$ = 69 Hz, CH_3P); 33.27; 79.99 (d, $^1J_{CP}$ = 78 Hz, C-5 isoxazoline); 119.30 (q, $^1J_{CF}$ = 272 Hz, CF_3); 149.45 (qd, $^2J_{CF}$ = 38 Hz, $^3J_{CP}$ = 5 Hz, C-3 isoxazoline). ^{19}F NMR (470 MHz, $CDCl_3$), δ, ppm: -66.15. ^{31}P NMR (202 MHz, $CDCl_3$), δ, ppm: 41.84. GC-MS (EI), m/z: 215.0 $[M]^{\bullet+}$; 78.0 $[HP(O)Me_2]^{\bullet+}$ (100%).

Dimethyl(3-((triisopropylsilyl)ethynyl)-4,5-dihydroisoxazol-5-yl)phosphine oxide (14k)

A white amorphous solid. FCC purification: $CHCl_3$:MeOH (10:1), R_f = 0.32. Yield – 0.70 g (43%). Anal. Calcd for $C_{16}H_{30}NO_2PSi$, %: C 58.68; H 9.23; N 4.28. Found, %: C 58.77; H 9.27; N 4.11. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.03–1.19 (21H, m, 3×*i*Pr); 1.49 (3H, d, $^2J_{HP}$ = 12.6 Hz, CH_3P); 1.64 (3H, d, $^2J_{HP}$ = 12.8 Hz, CH_3P); 3.46 (2H, dd, J = 19.9, 11.0 Hz, C$\underline{H_2}$CH oxazoline); 4.83 (1H, td, J = 11.2, 3.9 Hz, CH oxazoline). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 10.51; 10.77 (d, $^1J_{CP}$ = 69 Hz, CH_3P); 14.34 (d, $^1J_{CP}$ = 69 Hz, CH_3P); 17.97; 38.67; 77.76 (d, $^1J_{CP}$ = 81 Hz, C-5 isoxazoline); 92.76; 103.29; 142.70 (d, $^3J_{CP}$ = 3.8 Hz, C-3 isoxazoline). ^{31}P NMR (202 MHz, $CDCl_3$), δ, ppm: 43.34. LC-MS (ES-API), m/z: 328.0 $[M+H]^+$.

The synthesis of 1-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)cyclobutan-1-aminium 2,2,2-trifluoroacetate (16h)

tert-Butyl (1-(5-(dimethylphosphoryl)-4,5-dihydroisoxazol-3-yl)cyclobutyl)carbamate (**14h**) (0.316 g, 1.0 mmol) was dissolved in DCM (20 mL), the solution was cooled to 0 °C. Then 10 equiv of TFA was added dropwise to the solution, and the mixture was allowed to stir overnight at room temperature. All volatile components were evaporated under reduced pressure resulting in the title compound.

A white amorphous solid. Yield – 0.27 g (83%). Anal. Calcd for $C_{11}H_{18}F_3N_2O_4P$, %: C 40.01; H 5.49; N 8.48. Found, %: C 40.32; H 5.69; N 8.21. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.40–1.70 (6H, m), 1.83–2.14 (3H, m), 2.32–2.47 (3H, m), 3.37–3.73 (2H, m), 4.85–4.98 (1H, m), 8.72 (3H, s). ^{19}F NMR (470 MHz, $CDCl_3$), δ, ppm: -75.21. ^{31}P NMR (202 MHz, DMSO-d_6), δ, ppm: 40.63. LC-MS (ES-API), m/z: 217.1 $[M-C_2F_3O_2]^+$.

References

1. Bhattu, M.; Verma, M.; Kathuria, D., Recent advancements in the detection of organophosphate pesticides: a review. *Analytical Methods* **2021,** *13* (38), 4390–4428. https://doi.org/10.1039/D1AY01186C.
2. Thakur, M.; Medintz, I. L.; Walper, S. A., Enzymatic Bioremediation of Organophosphate Compounds — Progress and Remaining Challenges. *Frontiers in Bioengineering and Biotechnology* **2019,** *7*. https://doi.org/10.3389/fbioe.2019.00289.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

3. Iaroshenko, V. Phosphorus in Chemical Biology and Medicinal Chemistry. In *Organophosphorus Chemistry*, V. Iaroshenko (Ed.). 2019; pp 499–544. https://doi.org/10.1002/9783527672240.ch10.
4. Denoix, J. M.; Thibaud, D.; Riccio, B., Tiludronate as a new therapeutic agent in the treatment of navicular disease: a double-blind placebo-controlled clinical trial. *Equine Veterinary Journal* **2003,** *35* (4), 407–413. https://doi.org/10.2746/042516403776014226.
5. Akre, C. The Use of Pyrethroids, Carbamates, Organophosphates, and Other Pesticides in Veterinary Medicine. In *Chemical Analysis of Non-antimicrobial Veterinary Drug Residues in Food*, 2016; pp 383–426. https://doi.org/10.1002/9781118696781.ch7.
6. Pharmaceutical Manufacturing Encyclopedia. 3rd Ed. William Andrew Publishing, Norwish NY: Elsevier; 2007; pp. 56m–57m. https://doi.org/10.1016/B978-0-8155-1526-5.50017-9.
7. Garnock-Jones, K. P., Fosaprepitant Dimeglumine: A Review in the Prevention of Nausea and Vomiting Associated with Chemotherapy. *Drugs* **2016,** *76* (14), 1365–1372. https://doi.org/10.1007/s40265-016-0627-7.
8. Nordgren, I.; Bengtsson, E.; Holmstedt, B.; Pettersson, B.-M., Levels of Metrifonate and Dichlorvos in Plasma and Erythrocytes during Treatment of Schistosomiasis with Bilarcil®. *Acta Pharmacologica et Toxicologica* **1981,** *49* (s5), 79–86. https://doi.org/10.1111/j.1600-0773.1981.tb03256.x.
9. Duchin, K. L.; Waclawski, A. P.; Tu, J. I.; Manning, J.; Frantz, M.; Willard, D. A., Pharmacokinetics, Safety, and Pharmacologic Effects of Fosinopril Sodium, an Angiotensin-Converting Enzyme Inhibitor in Healthy Subjects. *The Journal of Clinical Pharmacology* **1991,** *31* (1), 58–64. https://doi.org/10.1002/j.1552-4604.1991.tb01887.x.
10. Ala-Houhala, I.; Saha, H.; Liukko-Sipi, S.; Ylitalo, P.; Pasternack, A., Pharmacokinetics of clodronate in haemodialysis patients. *Nephrology Dialysis Transplantation* **1999,** *14* (3), 699–705. https://doi.org/10.1093/ndt/14.3.699.
11. Roberti, G.; Tanga, L.; Michelessi, M.; Quaranta, L.; Parisi, V.; Manni, G.; Oddone, F. Cytidine 5'-Diphosphocholine (Citicoline) in Glaucoma: Rationale of Its Use, Current Evidence and Future Perspectives. *Int. J. Mol. Sci.* **2015**, *16*, 28401–28417. https://doi.org/10.3390/ijms161226099.
12. Smith, B. R.; Eastman, C. M.; Njardarson, J. T., Beyond C, H, O, and N! Analysis of the Elemental Composition of U.S. FDA Approved Drug Architectures. *J. Med. Chem.* **2014,** *57* (23), 9764–9773. https://doi.org/10.1021/jm501105n.
13. Yu, H.; Yang, H.; Shi, E.; Tang, W. Development and Clinical Application of Phosphorus-Containing Drugs. *Medicine in Drug Discovery* **2020,** *8*, 100063. https://doi.org/10.1016/j.medidd.2020.100063.
14. Rodriguez, J. B.; Gallo-Rodriguez, C. The Role of the Phosphorus Atom in Drug Design. *ChemMedChem* **2019,** *14* (2), 190–216. https://doi.org/10.1002/cmdc.201800693.
15. Buckner, F. S.; Urbina, J. A. Recent developments in sterol 14-demethylase inhibitors for Chagas disease. *International Journal for Parasitology: Drugs and Drug Resistance* **2012,** *2*, 236–242. https://doi.org/10.1016/j.ijpddr.2011.12.002.
16. Rodriguez, J. B.; Falcone, B. N.; Szajnman, S. H. Detection and treatment of Trypanosoma cruzi: a patent review (2011-2015). *Expert Opinion on Therapeutic Patents* **2016,** *26* (9), 993–1015. https://doi.org/10.1080/13543776.2016.1209487.
17. Wiemer, A. J.; Wiemer, D. F. Prodrugs of Phosphonates and Phosphates: Crossing the Membrane Barrier. In *Phosphorus Chemistry I: Asymmetric Synthesis and Bioactive Compounds*, Montchamp, J.-L., Ed. Springer International Publishing: Cham, 2015; pp 115–160. https://doi.org/10.1007/128_2014_561.
18. Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. The pKBHX Database: Toward a Better Understanding of Hydrogen-Bond Basicity for Medicinal Chemists. *J. Med. Chem.* **2009,** *52* (14), 4073–4086. https://doi.org/10.1021/jm801331y.
19. National Cancer Institute. FDA Grants Brigatinib Accelerated Approval for Metastatic Non-Small Cell Lung Cancer. https://www.cancer.gov/news-events/cancer-currents-blog/2017/brigatinib-fda-lung-cancer (accessed Apr 15, 2023).
20. Bedi, S.; Khan, S. A.; AbuKhader, M. M.; Alam, P.; Siddiqui, N. A.; Husain, A. A comprehensive review on Brigatinib – A wonder drug for targeted cancer therapy in non-small cell lung cancer. *Saudi Pharmaceutical Journal* **2018,** *26* (6), 755–763. https://doi.org/10.1016/j.jsps.2018.04.010.
21. Finkbeiner, P.; Hehn, J. P.; Gnamm, C. Phosphine Oxides from a Medicinal Chemist's Perspective: Physicochemical and in Vitro Parameters Relevant for Drug Discovery. *J. Med. Chem.* **2020,** *63* (13), 7081–7107. https://doi.org/10.1021/acs.jmedchem.0c00407.
22. Fedyk, A.; Slobodyanyuk, E. Y.; Stotska, O.; Vashchenko, B. V.; Volochnyuk, D. M.; Sibgatulin, D. A.; Tolmachev, A. A.; Grygorenko, O. O. Heteroaliphatic Dimethylphosphine Oxide Building Blocks: Synthesis and Physico-chemical Properties. *Eur. J. Org. Chem.* **2021,** *2021* (47), 6591–6603. https://doi.org/10.1002/ejoc.202100581.
23. Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014,** *57* (24), 10257–10274. https://doi.org/10.1021/jm501100b.
24. Nath, C. P.; Kumar, N.; Hazra, K. K.; Praharaj, C. S.; Singh, S. S.; Dubey, R. P.; Sharma, A. R. Topramezone: A selective post-emergence herbicide in chickpea for higher weed control efficiency and crop productivity. *Crop Protection* **2021,** *150*, 105814. https://doi.org/10.1016/j.cropro.2021.105814.
25. Arends, J. E.; Hoepelman, A. I. M.; Nanlohy, N. M.; Höppener, F. J. P.; Hirsch, K. R.; Park, J. G.; van Baarle, D. Low doses of the novel caspase-inhibitor GS-9450 leads to lower caspase-3 and -8 expression on peripheral CD4+ and CD8+ T-cells. *Apoptosis* **2011,** *16* (9), 959–966. https://doi.org/10.1007/s10495-011-0620-2.
26. Walther, F. M.; Allan, M. J.; Roepke, R. K. A.; Nuernberger, M. C. The effect of food on the pharmacokinetics of oral fluralaner in dogs. *Parasites & Vectors* **2014,** *7* (1), 84. https://doi.org/10.1186/1756-3305-7-84.
27. Martin, D. G.; Chidester, C. G.; Mizsak, S. A.; Duchamp, D. J.; Baczysnkyj, L. The isolation, structure, and absolute configuration of U-43,795, a new antitumor agent. *J. Antibiot. (Tokyo)* **1975,** *28* (1), 91–93. https://doi.org/10.7164/antibiotics.28.91.
28. Nicacio, K. J.; Ióca, L. P.; Fróes, A. M.; Leomil, L.; Appolinario, L. R.; Thompson, C. C.; Thompson, F. L.; Ferreira, A. G.; Williams, D. E.; Andersen, R. J.; Eustaquio, A. S.; Berlinck, R. G. S. Cultures of the Marine Bacterium Pseudovibrio denitrificans Ab134 Produce Bromotyrosine-Derived Alkaloids Previously Only Isolated from Marine Sponges. *J. Nat. Prod.* **2017,** *80* (2), 235–240. https://doi.org/10.1021/acs.jnatprod.6b00838.
29. Tang, J.-w.; Hu, K.; Su, X.-z.; Li, X.-n.; Yan, B.-c.; Sun, H.-d.; Puno, P.-t. Phomopsisins A–C: Three new cytochalasans from the plant endophytic fungus Phomopsis sp. sh917. *Tetrahedron* **2020,** *76* (39), 131475. https://doi.org/10.1016/j.tet.2020.131475.
30. Chalyk, B. A.; Hrebeniuk, K. V.; Gavrilenko, K. S.; Shablykin, O. V.; Yanshyna, O. O.; Bash, D.; Mykhailiuk, P. K.; Liashuk, O. S.; Grygorenko, O. O. Synthesis of Bi- and Polyfunctional Isoxazoles from Amino Acid Derived Halogenoximes and Active Methylene Nitriles. *Eur. J. Org. Chem.* **2018,** *2018* (22), 2753–2761. https://doi.org/10.1002/ejoc.201800311.
31. Chalyk, B. A.; Hrebeniuk, K. V.; Gavrilenko, K. S.; Kulik, I. B.; Rozhenko, A. B.; Volochnyuk, D. M.; Liashuk, O. S.; Grygorenko, O. O. Synthesis of 4-Hetarylisoxazoles from Amino Acid-Derived Halogenoximes and Push-Pull Enamines. *Eur. J. Org. Chem.* **2018,** *2018* (40), 5585–5595. https://doi.org/10.1002/ejoc.201800753.

32. Chalyk, B. A.; Khutorianskyi, A. V.; Vashchenko, B. V.; Danyleiko, K.; Grynyova, A.; Osipova, A. O.; Kozytskiy, A.; Syniuchenko, D.; Tsymbaliuk, A.; Gavrilenko, K. S.; Biitseva, A. V.; Volochnyuk, D. M.; Komarov, I. V.; Grygorenko, O. O. Reductive Recyclization of sp3-Enriched Functionalized Isoxazolines into α-Hydroxy Lactams. *J. Org. Chem.* **2022,** *87* (2), 1001–1018. https://doi.org/10.1021/acs.joc.1c02301.
33. Chalyk, B. A.; Sosedko, A. S.; Volochnyuk, D. M.; Tolmachev, A. A.; Gavrilenko, K. S.; Liashuk, O. S.; Grygorenko, O. O. Regioselective synthesis of isoxazole and 1,2,4-oxadiazole-derived phosphonates via [3 + 2] cycloaddition. *Org. Biomol. Chem.* **2018,** *16* (47), 9152–9164. https://doi.org/10.1039/C8OB02257G.
34. Chalyk, B. A.; Kandaurova, I. Y.; Hrebeniuk, K. V.; Manoilenko, O. V.; Kulik, I. B.; Iminov, R. T.; Kubyshkin, V.; Tverdokhlebov, A. V.; Ablialimov, O. K.; Mykhailiuk, P. K. A base promoted multigram synthesis of aminoisoxazoles: valuable building blocks for drug discovery and peptidomimetics. *RSC Adv.* **2016,** *6* (31), 25713–25723. https://doi.org/10.1039/C6RA02365G.
35. Leng, L.; Zhou, X.; Liao, Q.; Wang, F.; Song, H.; Zhang, D.; Liu, X.-Y.; Qin, Y. Asymmetric Total Syntheses of Kopsia Indole Alkaloids. *Angew. Chem. Int. Ed.* **2017,** *56* (13), 3703–3707. https://doi.org/10.1002/anie.201700831.
36. Poh, J.-S.; García-Ruiz, C.; Zúñiga, A.; Meroni, F.; Blakemore, D. C.; Browne, D. L.; Ley, S. V., Synthesis of trifluoromethylated isoxazoles and their elaboration through inter- and intra-molecular C–H arylation. *Org. Biomol. Chem.* **2016,** *14* (25), 5983–5991. https://doi.org/10.1039/C6OB00970K.
37. Kusakabe, K.-I.; Yoshida, S.; Nakahara, K.; Hasegawa, T.; Tadano, G.; Fuchino, K. Dihydrooxazine or oxazepine derivatives having bace1 inhibitory activity. WO2014065434A1, May 5, 2014.
38. Minter, A. R.; Fuller, A. A.; Mapp, A. K. A Concise Approach to Structurally Diverse β-Amino Acids. *J. Am. Chem. Soc.* **2003,** *125* (23), 6846–6847. https://doi.org/10.1021/ja0298747.
39. Breugst, M.; Reissig, H.-U., The Huisgen Reaction: Milestones of the 1,3-Dipolar Cycloaddition. *Angew. Chem. Int. Ed.* **2020,** *59* (30), 12293–12307. https://doi.org/10.1002/anie.202003115.
40. Stambirskyi, M. V.; Kostiuk, T.; Sirobaba, S. I.; Rudnichenko, A.; Titikaiev, D. L.; Dmytriv, Y. V.; Kuznietsova, H.; Pishel, I.; Borysko, P.; Mykhailiuk, P. K. Phosphine Oxides (−$POMe_2$) for Medicinal Chemistry: Synthesis, Properties, and Applications. *J. Org. Chem.* **2021,** *86* (18), 12783–12801. https://doi.org/10.1021/acs.joc.1c01413.
41. Daina, A.; Michielin, O.; Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports* **2017,** *7* (1), 42717. https://doi.org/10.1038/srep42717.
42. SwissADME. http://www.swissadme.ch/index.php (accessed Mar 13, 2023).

Information about the authors:
Andrii V. Fedyk (*corresponding author*), Ph.D. Student of the Biologically Active Compounds Department, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; e-mail for correspondence: andrefedyk@ukr.net.
Bohdan A. Chalyk, Ph.D. Student of the Biologically Active Compounds Department, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.

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