



Scientific article

UDC 547.793, 547.313

DOI: 10.52957/2782-1900-2026-7-3-123-133

SYNTHESIS, ANTIOXIDANT ACTIVITY, AND SPECTRAL CHARACTERIZATION OF (E)-3-ARYL-5-(ARYLETHENYL) - 1,2,4-OXADIAZOLES

A.V. Migalkina¹, I.K. Proskurina¹, E.A. Vasilyeva^{1,2}, A.A. Shetnev^{1,3},
M.V. Tarasenko^{1,3}, L.A. Komshina¹, Zh.V. Chirkova⁴

Anastasia Vladimirovna Migalkina, Student; Irina Konstantinovna Proskurina, Candidate of Biological Sciences, Associate Professor; Elena Andreevna Vasilyeva, Post-graduate Student, Senior Lecturer; Anton Andreevich Shetnev, Candidate of Chemical Sciences, Associate Professor; Marina Vladimirovna Tarasenko, Candidate of Chemical Sciences, Senior Researcher; Lyudmila Aleksandrovna Komshina, Candidate of Chemical Sciences, Associate Professor; Zhanna Vyacheslavovna Chirkova, Doctor of Chemical Sciences, Professor

¹ Yaroslavl State Pedagogical University named after K.D. Ushinsky, 150000, Russia, Yaroslavl, Respublikanskaya Street, 108/1; a.shetnev@list.ru

² Russian State University named after A.N. Kosygin (Technology. Design. Art), Russia, 119071, Moscow, Malaya Kaluzhskaya St., 1

³ Yaroslavl State Medical University of the Ministry of Health of Russia, 150000, Yaroslavl, Russia. Yaroslavl, Revolutsionnaya str., 5

⁴ Yaroslavl State Technical University, 150023, Russia, Yaroslavl, 88 Moskovsky pr.; chirkovazhv@ystu.ru

Keywords:
oxadiazole, olefin,
Wittig reaction,
antioxidant activity

Abstract. The article discusses the synthesis and characterization of 5-(alkenyl)-3-aryl-1,2,4-oxadiazoles. The synthesis scheme includes two steps: preparation of the triphenylphosphonium chloride and its subsequent condensation with aldehydes. The synthesis conditions for the target products were improved by replacing the base. It increases their yields and allows previously synthetically inaccessible compounds obtaining. The ¹H NMR spectra of the products contain doublets characteristic of double-bond protons with a coupling constant J = 16.1–16.4 Hz, indicating the E-configuration of the obtained compounds. Fluorescent and antioxidant properties were found for compounds containing electron-donating substituents.

For citation:

Migalkina A.V., Proskurina I.K., Vasilyeva E.A., Shetnev A.A., Tarasenko M.V., Chirkova Zh.V. Synthesis, antioxidant activity, and spectral characterization of (E)-3-aryl-5-(arylethenyl) - 1,2,4-oxadiazoles // From Chemistry towards Technology Step-by-Step. 2026. Vol. 7, Iss. 3. P. 123-133. URL: <https://chemintech.ru/en/nauka/issue/7500/view>

Introduction

The Wittig reaction is a method for the synthesis of alkenes consisting in the interaction of aldehydes or ketones with phosphorus ylides. The advantages of this transformation include regioselectivity, relatively mild reaction conditions, and the availability of the starting reagents [1]. Of great interest for medicinal chemistry is the synthesis of heterocyclic systems containing an

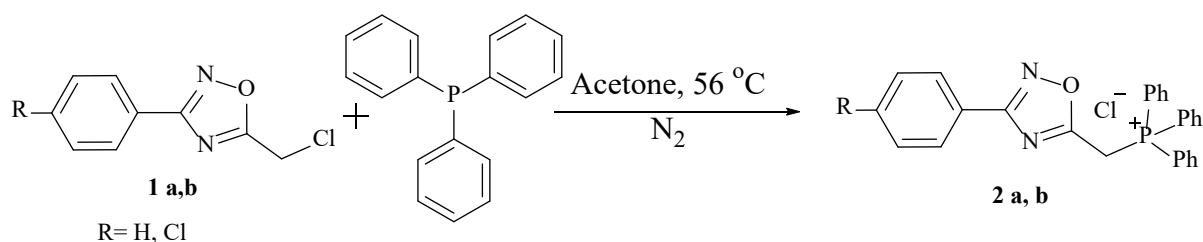


alkenyl fragment. These compounds exhibit antitumor, antiviral, and antiparasitic biological activity [2–4]. In addition, the alkenyl fragment is a convenient substance for further chemical modifications – addition and cyclization reactions. It provides the construction of new carbo- and heterocyclic systems [5, 6].

Nitrogen-containing heterocyclic compounds play a particularly important role in medicinal chemistry. According to statistical data for 2013–2023, 82% of 321 FDA-approved drugs were synthesized on the basis of heterocycles containing a nitrogen atom [7]. 1,2,4-Oxadiazoles are the structures widely used in drug design due to their diverse biological activity [8–13]. In this regard, the synthesis of olefins containing a 1,2,4-oxadiazole fragment is an urgent task of organic synthesis.

Results and discussions

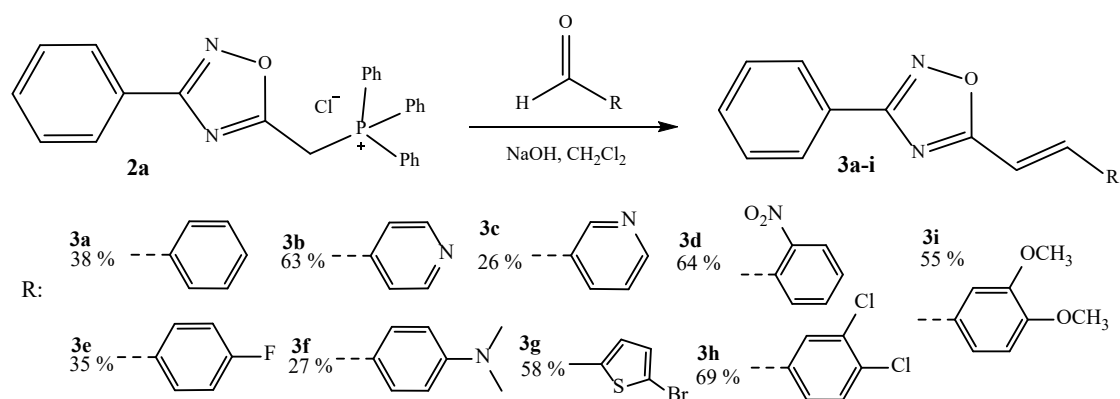
Olefins containing a 1,2,4-oxadiazole fragment were obtained according to a two-step scheme. The first step is the synthesis of ((3-aryl-1,2,4-oxadiazol-5-yl)methyl)triphenylphosphonium chloride **2** (Scheme 1).



Scheme 1

The first step was conducted according to the procedure described in [14], by reacting 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole with triphenylphosphine under an inert atmosphere for 12 h at the boiling point of acetone. The reaction progress was monitored by TLC (eluent – toluene : acetone : petroleum ether = 3 : 5 : 5). The precipitate of the corresponding phosphonium salt was filtered off and washed with acetone.

Initially, for the synthesis of 5-alkenyl-3-aryl-1,2,4-oxadiazoles **3**, a protocol for the Wittig reaction under phase-transfer conditions, used for the preparation of *trans*-stilbene [14, 15], was selected (Scheme 2).



Scheme 2



Reaction conditions: triphenylphosphonium salt-to-aldehyde-to-NaOH ratio of 1 : 1 : 12, solvent – methylene chloride, stirring at room temperature for 24 h. Under these conditions, 9 target products were obtained; the yields of some of them are low (27–38%). For this reason, optimization of the conditions was conducted using the synthesis of compounds **3e** and **3f** as examples (Table 1).

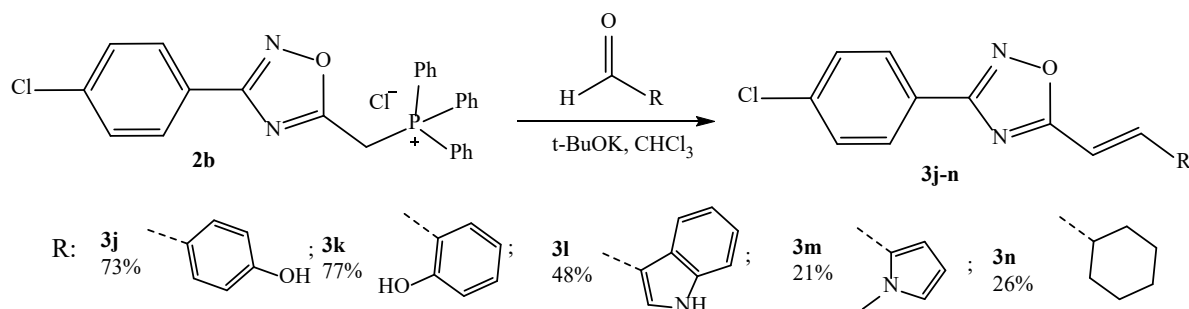
Table 1. Optimization of the synthesis conditions for 5-alkenyl-1,2,4-oxadiazoles **3e** and **3f**

Product	Ylide-to-aldehyde ratio	Base, equiv.	Solvent	T, °C	$\Delta\tau$, h	Yield, %
3e	1:1	NaOH, 12	CH ₂ Cl ₂	20	24	36
3e	1:1	NaOH, 12	CH ₂ Cl ₂	40	24	39
3e	1:1.2	NaOH, 12	CH ₂ Cl ₂	20	24	40
3e	1:1	<i>t</i> BuOK, 1	CHCl ₃	20	24	54
3e	1:1.5	<i>t</i> BuOK, 1	CHCl ₃	20	24	58
3e	1:1.5	<i>t</i> BuOK, 1	CHCl ₃	50	4	76
3f	1:1	NaOH, 12	CH ₂ Cl ₂	20	24	27
3f	1:1	<i>t</i> BuOK, 1	CHCl ₃	20	24	38
3f	1:1.5	<i>t</i> BuOK, 1	CHCl ₃	20	24	40
3f	1:1.5	<i>t</i> BuOK, 1	CHCl ₃	50	3	51

Indeed, increasing of the temperature of the reaction mixture in the CH₂Cl₂/H₂O system promoted higher yield of reaction product **3e**. Therefore, it was decided to replace the solvent with the higher-boiling chloroform. Furthermore, to ensure high conversion of the starting triphenylphosphonium salts **2** (**a**, **b**), the use of a large excess of aldehyde is required.

The data in Table 1 allow us to conclude that the conditions close to optimal for the synthesis of 5-alkenyl-1,2,4-oxadiazoles **3e**, **3f** are as follows: triphenylphosphonium salt 2-to-aldehyde-to-*t*-BuOK ratio of 1 : 1.5 : 1; solvent is chloroform; temperature is about 50–70 °C. Under these conditions, the yield of the target products increased twofold.

The use of potassium *tert*-butoxide as the base made it possible to obtain a series of target products **3** (**j**–**k**) in good and moderate yields. It is impossible when using the procedure involving sodium hydroxide (Scheme 3).



Scheme 3

At the same time, we did not observe the formation of products of dichlorocarbene insertion at the double bond of compounds **3**, which could theoretically be formed as a result of the interaction of potassium *tert*-butoxide with chloroform in the reaction mixture [16, 17]. In the ¹H NMR spectra of the substances, doublets corresponding to the double bond are observed, with spin-spin coupling constants $J = 16.1\text{--}16.4$ Hz, characteristic of *trans*-isomeric alkenes.



Furthermore, the observed regioselective formation of *trans*-olefination products is apparently related to the structure of the triphenylphosphonium ylides **2(a, b)** stabilized by the electron-withdrawing 1,2,4-oxadiazole ring. It is in good agreement with known literature data [1].

Due to the presence of chromophoric fragments in the structure of the obtained compounds, some photophysical and antioxidant properties (AOA) of 3-aryl-5-alkenyloxadiazoles **3(a-n)** were studied (Table 2).

Table 2. Photophysical and antioxidant properties of compounds **3(a-n)**

Product	Compound formula	Antioxidant activity (AOA), $\mu\text{g/mL}$	Fluorescence color at λ_{max} 365 nm	UV spectrum λ_{max} , nm
3a		-	green	Peaks at 300, 323, 373 nm
3b		-	intense green	Peak at 299 nm, trough at 360 nm
3c		-	yellow-green	Peak at 300 nm, trough at 351 nm
3d		-	orange-yellow	Peak at 299, 346 nm, trough at 344 nm
3i		-	weak yellow-green	Peak at 299 nm, trough at 356 nm
3e		128	green	Peak at 325, 395, 404 nm, trough at 360 nm
3f		-	weak yellow-green	Peak at 298, 378 nm, trough at 349 nm
3g		-	not observed	Peak at 300 nm, trough at 358 nm
3h		256	blue-green	Peak at 300, 390 nm, trough at 206, 254, 278, 348 nm



Conclusion of Table 2

Product	Compound formula	Antioxidant activity (AOA), $\mu\text{g/mL}$	Fluorescence color at λ_{max} 365 nm	UV spectrum λ_{max} , nm
3j		256	green	Peak at 299, 378 nm, trough at 344 nm
3k		256	green	Peak at 300 nm, trough at 358 nm
3l		256	blue-violet	Peak at 299, 394 nm, trough at 348 nm
3m		256	orange-green	Peak at 299, 407 nm, trough at 350 nm
3n		-	not observed	Peak at 287 nm, trough at 339 nm

In the series of synthesized (*E*)-5-(*R*-styryl)-3-phenyl-1,2,4-oxadiazoles, antioxidant activity was evaluated *in vitro*. Antioxidant activity was determined spectrophotometrically by the ability of the compounds to reduce the 2,2-diphenyl-1-picrylhydrazyl radical in an *in vitro* model according to the procedure described in [18].

According to Table 2, not containing strong electron-donating groups compounds do not exhibit AOA in the test used. In contrast, for compounds with 4- $\text{N}(\text{CH}_3)_2$ substituent (**3e**) at a concentration of 128 $\mu\text{g/mL}$, as well as for 3,4-(OCH_3)₂ (**3h**), 4-OH (**3j**), 2-OH (**3k**), 3-indolyl (**3l**), and *N*-methylpyrrolyl (**3m**), the AOA value was 256 $\mu\text{g/mL}$.

Thus, antioxidant activity in the studied series correlates with the donor ability of the substituent *R*. The absence of activity in compounds with acceptor groups (2- NO_2 , 4-F, 3,4-dichlorophenyl) confirms the ability of the substituent to stabilize radical intermediates through resonance and/or inductive effects as a key factor.

In addition, the UV absorption spectra and fluorescent properties of the obtained products were studied. Upon irradiation at a wavelength of 365 nm, all compounds possessing AOA (**3e**, **3h–3m**) have intense fluorescence in the visible region (green, blue-green, orange-green, blue-violet). However, the presence of fluorescence alone is not a sufficient condition for the manifestation of AOA: compounds **3 (a–d)** (substituents Ph, 4-Py, 3-Py, 2- NO_2 -phenyl) also fluoresce but are inactive. The manifestation of antioxidant activity requires a combination of two factors: the ability to fluoresce (indicating the presence of an efficient π -conjugated system) and the presence of a donor substituent that provides intramolecular charge transfer. In the UV spectra of all compounds, a characteristic peak is observed in the region of 298–300 nm, corresponding to the $\pi \rightarrow \pi^*$ transition in the styryl fragment.



Compound **3n** (R = cyclohexyl) has no conjugation between the substituent and the styryl system. It does not fluoresce, does not exhibit AOA, and its absorption spectrum is represented by a single peak at 287 nm without long-wavelength transitions. Therefore, in this case we use as a negative control. It confirms the necessity of an extended π -system for the manifestation of both antioxidant activity and fluorescence.

Conclusion

The paper presents a preparative method for the synthesis of (*E*)-5-(*R*-styryl)-3-phenyl-1,2,4-oxadiazoles via the Wittig reaction, using previously undescribed stabilized 1,2,4-oxadiazole-containing triphenylphosphine ylides as reagents in the potassium *tert*-butoxide–chloroform system, providing yields of *trans*-olefins up to 73%. For compounds with electron-donating substituents providing intramolecular charge transfer, antioxidant activity was found at concentrations of 128–256 $\mu\text{g/mL}$. It correlates with the appearance of an additional long-wavelength absorption band (>370 nm) in the UV spectra and intense fluorescence in the visible region.

Experimental part

Organic and inorganic reagents and solvents were obtained from commercial sources (Aldrich, Vekton, Ecos) and used without additional purification. We monitored the reaction progress by thin layer chromatography (TLC) on silica gel on Silufol UV aluminium plates using the following eluent - toluene : acetone : petroleum ether in the volume ratio of 3:5:5. We performed elemental analysis on a PerkinElmer 2400 unit. Melting points were measured using a Reach Devices RD-MP melting point apparatus (China). UV spectra were recorded on an Ecos PE-5400 UV spectrophotometer (Russia). NMR spectra were recorded on a Varian 400 Unity Plus instrument (400 MHz for ^1H and 100 MHz for ^{13}C , respectively) for solutions in $\text{DMSO}-d_6$. The signals of residual solvent protons were used as a reference for chemical shifts in ^1H NMR (δ 2.50 ppm) or ^{13}C NMR (δ 39.5 ppm); tetramethylsilane was used as a marker.

General procedure for the synthesis of 1,2,4-oxadiazole-containing triphenylphosphonium ylides

Triphenylphosphine (10 mmol) was added to a solution of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazole (10 mmol) in acetone under a nitrogen atmosphere. The reaction mixture was stirred for 18 h at 56 °C. The reaction progress was monitored by TLC (eluent: toluene : acetone : petroleum ether in a ratio of 3:5:5 (v/v)). The reaction mixture was then cooled, and the resulting precipitate was filtered off and washed with acetone. The products required no additional purification.

((3-Phenyl-1,2,4-oxadiazol-5-yl)methyl)triphenylphosphonium chloride (2a). Yield is 9 g (64%), white crystalline substance. T melt. 240–242°C. NMR spectrum ^1H (400 MHz, $\text{DMSO}-d_6$), δ , ppm: 6.31 (d, 2H, CH_2P J 16.0), 7.63 – 7.48 (m, 3H, C_6H_5), 7.84 – 7.76 (m, 8H, C_6H_5 , Ph-P), 7.97 – 7.88 (m, 9H, Ph-P). NMR spectrum ^{13}C (101 MHz, $\text{DMSO}-d_6$), δC , ppm: 22.63 (d, CH_2P , J 54.3), 118.10 (d, 3C, C-P, J 88.4), 125.90 (C-Het), 127.59 (2C, C_6H_4), 130.07 (2C, C_6H_4), 130.89 (d, 6C, Ph, J 13.0), 132.69 (C_6H_4) 134.69 (d, 6C, Ph, J 10.7), 136.12 (3C, Ph),



168.52 (N-C=N_{oxadiazole}), 171.85 (N=CO_{oxadiazole}). Found, %: C 71.02; H 4.84; N 6.17. C₂₇H₂₂ClN₂OP. Calculated, %: C 70.98; H 4.85; N 6.13.

((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)triphenylphosphonium chloride (2b) Yield is 3.43 g (70%), white powder, T melt. 256-258 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 6.31 (d, 2H, CH₂P, *J* 16.0), 7.62 (d, 2H, C₆H₄, *J* 8.3), 7.80 (td, 8H, C₆H₄, Ph-P, *J* 7.1, 5.7, 2.6), 7.93 (dd, 9H, Ph-P, *J* 13.6, 7.8). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 22.54 (d, CH₂P, *J* 54.4), 117.99 (d, 3C, C-P, *J* 88.3), 124.77 (C-Het), 129.40 (2C, C₆H₄), 130.28 (2C, C₆H₄), 130.91 (d, 6C, C Ph, *J* 13.1), 134.67 (d, 6C, C Ph, *J* 11.0), 136.17 (3C, Ph), 137.44 (C-Cl), 167.78 (N-C=N_{oxadiazole}), 171.97 (N=CO_{oxadiazole}). Found, %: C 66.14; H 4.34; N 5.73. C₂₇H₂₁Cl₂N₂OP. Calculated, %: C 66.00; H 4.31; N 5.70.

General procedure for the synthesis of 5-alkenyl-3-aryl-1,2,4-oxadiazoles (3a-n)

Method A (compounds 3a-3i): To 1 mmol of the oxadiazole triphenylphosphonium salt in methylene chloride, NaOH (12 mmol) in 0.5 mL of water was added dropwise, and the aldehyde (1 mmol) was added. The mixture was stirred at room temperature for 24 h. Then the reaction mixture was washed with water and dried over Na₂SO₄. The solvent was evaporated under vacuum. The residue was dissolved in hot ethyl alcohol and then cooled with ice. The precipitated products were filtered off and purified by recrystallization from ethyl alcohol.

Method B (compounds 3j-3n): To 1 mmol of the oxadiazole triphenylphosphonium salt in chloroform, the corresponding aldehyde (1.5 mmol) and potassium *tert*-butoxide (1 mmol) were added. The reaction mixture was stirred at 50-70 °C for 2-4 h. The reaction was stopped when the starting materials were consumed (TLC monitoring). The reaction mass was then washed with water, dried over Na₂SO₄, and the solvent was removed under vacuum. The obtained substance was purified by recrystallization from ethanol.

3-Phenyl-5-[(1E)-2-phenylethenyl]-1,2,4-oxadiazole (3a) [19]. Yield is 94 mg (38%), white crystalline substance, T melt. 90-92 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 7.53 – 7.41 (m, 4H, C₆H₄ and Het-CH=), 7.64 – 7.54 (m, 3H, C₆H₄), 7.85 (dd, 2H, C₆H₄, *J* 6.5, 2.9), 7.95 (d, 1H, Ar-CH, *J* 16.4), 8.06 (dt, 2H, C₆H₄, *J* 7.6, 1.6). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 110.92 (Het-CH=), 126.98 (C_{Ar}), 127.71 (2C_{Ar}), 129.09 (2C_{Ar}), 129.69 (2C_{Ar}), 129.94 (2C_{Ar}), 131.35 (C_{Ar}), 132.25 (C_{Ar}), 134.92 (C_{Ar}), 143.56 (Ph-CH=), 168.70 (N-C=N_{oxadiazole}), 176.11 (N=CO_{oxadiazole}). Found, %: C 77.45; H 4.89; N 11.31. C₁₆H₁₂N₂O. Calculated, %: C 77.40; H 4.87; N 11.28.

(E)-3-Phenyl-5-(2-(pyridin-4-yl)ethenyl)-1,2,4-oxadiazole (3b) Yield is 313 mg (63%), yellow crystalline substance, T melt. 103-105 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 7.54 (d, 3H, CH_{Ar}, *J* 7.2), 7.63 (d, 1H, Het-CH=, *J* 16.4), 7.73 (d, 2H, C₅H₄N pyridin, *J* 5.1), 7.83 (d, 1H, Ar-CH=, *J* 16.4), 8.01 (d, 2H, CH_{Ar}, *J* 6.9), 8.64 (d, 2H, C₅H₄N pyridin, *J* 5.1). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm.: 115.45 (Het-CH=), 122.56 (2C_{pyridin}), 127.06 (C_{Ar}), 127.78 (2C_{Ar}), 129.77 (2C_{Ar}), 132.11 (C_{Ar}), 140.84 (Ph-CH=), 142.04 (C_{pyridin}), 151.08 (2C_{pyridin}), 169.07 (N-C=N_{oxadiazole}), 175.37 (N=CO_{oxadiazole}). Found, %: C 72.30; H 4.48; N 16.90. C₁₅H₁₁N₃O. Calculated, %: C 72.28; H 4.45; N 16.86.

(E)-3-Phenyl-5-(2-(pyridin-3-yl)vinyl)-1,2,4-oxadiazole (3c) Yield is 132 mg (26%), yellow crystalline substance, T melt. 105-107 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 7.49 (s, 1H, C₅H₄N_{pyridin}), 7.59 (t, 4H, CH_{Ar}, Het-CH=, *J* 7.8), 7.97 (d, 1H, Ar-CH=, *J* 16.3), 8.05 (d, 2H, CH_{Ar}, *J* 6.8), 8.30 (d, 1H, C₅H₄N_{pyridin}, *J* 7.9), 8.62 (s, 1H, C₅H₄N_{pyridin}),



8.99 (s, 1H, C₅H₄N_{pyridin}). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm.: 112.85 (Het-CH=), 124.66 (C_{pyridin}), 126.88 (C_{Ar}), 127.71 (2C_{Ar}), 129.95 (2C_{Ar}), 130.81 (C_{Ar}), 132.29 (C_{pyridin}), 135.29 (C_{pyridin}), 140.27(Ph-CH=), 150.66 (C_{pyridin}), 151.76 (C_{pyridin}), 168.76 (N-C=N_{oxadiazole}), 175.73 (N=CO_{oxadiazole}). Found, %: C 72.31; H 4.47; N 16.89. C₁₅H₁₁N₃O. Calculated, %: C 72.28; H 4.45; N 16.86.

5-[(1E)-2-(4-Nitrophenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (3d). Yield is 187 mg (64%), white crystalline substance, T melt. 142-144 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 7.49 (d, 1H, Het-CH=, *J* 16.2), 7.67 – 7.54 (m, 3H, C₆H₅), 7.77 – 7.68 (m, 1H, C₆H₅), 7.85 (t, 1H, C₆H₄NO₂ *J* 7.3), 8.09 – 8.02 (m, 2H, C₆H₅), 8.13 (t, 2H, C₆H₄NO₂ *J* 8.0), 8.23 (d, 1H, Ar-CH=, *J* 16.3). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 115.24 (Het-CH=), 125.58 (C_{Ar}-Het), 126.76 (C₆H₄NO₂), 127.77 (2C_{Ar}), 129.97 (2C_{Ar}), 130.75 (C₆H₄NO₂), 131.87 (C₆H₄NO₂), 132.37 (C₆H₄NO₂), 134.69 (C₆H₄NO₂), 138.53(C₆H₄NO₂), 141.65 (C_{Ar}), 148.95 (Ph-CH=), 168.86 (N-C=N_{oxadiazole}), 175.40 (N=CO_{oxadiazole}). Found, %: C 65.57; H 3.80; N 14.35. C₁₆H₁₁N₃O₃. Calculated, %: C 65.53; H 3.78; N 14.33.

5-[(1E)-2-(4-Fluorophenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (3e) [20]. Yield is 95 mg (35%), white crystalline substance, T melt. 130-132 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 7.29 (t, 2H, CH_{Ar}, *J* 8.7), 7.38 (d, 1H, Het-CH=, *J* 16.4), 7.57 (d, 3H, CH_{Ar}, *J* 6.9), 7.96 – 7.87 (m, 3H, CH_{Ar}, Ar-CH=), 8.07 – 8.00 (m, 2H, CH_{Ar}). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 110.73 (Het-CH=), 116.69 (d, 2C, Ph-F, *J* 21.7), 126.97 (C_{Ar}), 127.68 (2C_{Ar}), 129.88 (2C_{Ar}), 131.42 (d, 2C, Ph-F, *J* 8.5), 131.89 (d, C, Ph-F, *J* 59.6), 142.25 (Ph-CH=), 164.06 (d, C, Ph-F, *J* 249.2), 168.66 (N-C=N_{oxadiazole}), 176.01 (N=CO_{oxadiazole}). Found, %: C 72.19; H 4.86; N 10.54. C₁₆H₁₁FN₂O. Calculated, %: C 72.17; H 4.84; N 10.52.

(E)-4-(2-(3-Phenyl-1,2,4-oxadiazol-5-yl)ethenyl)-N,N-dimethylaniline (3f). Yield is 79 mg (27%), yellow crystalline substance, T melt. 139-141 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 2.98 (s, 6H, 2CH₃), 6.73 (d, 2H, C₆H₄N, *J* 8.4), 7.05 (d, 1H, Het-CH=, *J* 16.1), 7.57 (d, 3H, CH_{Ar}, *J* 6.4), 7.64 (d, 2H, C₆H₄N, *J* 8.4), 7.79 (d, 1H, Ar-CH=, *J* 16.2), 8.04 (dd, 2H, CH_{Ar}, *J* 7.3, 2.8). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 104.44 (Het-CH=), 111.82 (NCH₃), 112.45 (2C C₆H₄N), 122.25 (C₆H₄N), 127.34 (C_{Ar}), 127.65(2C_{Ar}), 129.84 (2C_{Ar}), 130.75 (2C C₆H₄N), 132.01(C_{Ar}), 133.41 (NCH₃), 144.11 (Ph-CH=), 152.54 (C₆H₄N), 168.45 (N-C=N_{oxadiazole}), 176.95 (N=CO_{oxadiazole}). Found, %: C 74.50; H 5.90; N 14.47. C₁₈H₁₇N₃O. Calculated, %: C 74.20; H 5.88; N 14.42.

(E)-5-(2-(5-Bromothiophen-2-yl)ethenyl)-3-phenyl-1,2,4-oxadiazole (3g). Yield is 193 mg (58%), beige crystalline substance, T melt. 108-110 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 7.08 (d, 1H, Het-CH=, *J* 16.1), 7.34 (d, 1H, CH_{thienyl}, *J* 3.8), 7.51 (d, 1H, CH_{thienyl}, *J* 3.9), 7.65 – 7.57 (m, 3H, CH_{Ar}), 8.08 – 8.00 (m, 3H, CH_{Ar}, Ar-CH=). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 109.71 (Het-CH=), 116.81 (C_{thienyl}), 126.92 (C_{thienyl}), 127.68 (2C_{Ar}), 129.93 (2C_{Ar}), 132.26 (C_{Ar}), 132.71 (C_{thienyl}), 133.61 (C_{thienyl}), 135.29 (C_{Ar}), 141.58 (Het-CH=), 168.69 (N-C=N_{oxadiazole}), 175.66 (N=CO_{oxadiazole}). Found, %: C 50.49; H 2.75; N 8.45. C₁₄H₉BrN₂OS. Calculated, %: C 50.47; H 2.72; N 8.41.

5-[(1E)-2-(3,4-Dichlorophenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (3h). Yield is 218 mg (69%), white crystalline substance, T melt. 164-166 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 7.59 (k, 4H, C₆H₅, Het-CH=, *J* 9.3, 7.8), 7.72 (d, 1H, C₆H₅, *J* 8.4), 7.85 (dd,



1H, C₆H₃, *J* 8.3, 2.1), 7.91 (d, 1H, Ar-CH=, *J* 16.4), 8.04 (dd, 2H, C₆H₅, *J* 7.5, 2.1), 8.19 (s, 1H, C₆H₃). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 113.12 (Het-CH=), 126.85 (C_{Ar}), 127.70 (2C_{Ar}), 129.06 (C₆H₃), 129.95 (2C_{Ar}), 130.71 (C₆H₃), 131.75 (C_{Ar}), 132.30 (C₆H₃), 132.57 (C₆H₃), 133.51 (C₆H₃), 135.77 (C₆H₃), 140.83 (Ph-CH=), 168.77 (N-C=N_{oxadiazole}), 175.70 (N=CO_{oxadiazole}). Found, %: C 60.62; H 3.21; N 8.85. C₁₆H₁₀Cl₂N₂O. Calculated, %: C 60.59; H 3.18; N 8.83.

5-[(1E)-2-(3,4-Dimethoxyphenyl)ethenyl]-3-phenyl-1,2,4-oxadiazole (3i). Yield is 170 mg (55%), white crystalline substance, T melt. 110-113 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 3.81 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 7.02 (d, 1H, C₆H₃, *J* 8.3), 7.39 – 7.30 (m, 2H, C₆H₃, Het-CH=), 7.50 (d, 1H, C₆H₃, *J* 2.0), 7.64 – 7.53 (m, 3H, CH_{Ar}), 7.85 (d, 1H, Ar-CH=, *J* 16.3), 8.05 (dd, 2H, CH_{Ar}, *J* 7.3, 2.3). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 56.25 (OCH₃), 56.34 (OCH₃), 108.35 (Het-CH=), 110.90 (C₆H₃), 112.19 (C₆H₃), 123.95 (C₆H₃), 127.13 (C_{Ar}), 127.66 (2C_{Ar}), 127.79 (C₆H₃), 129.89 (2C_{Ar}), 132.14 (C_{Ar}), 143.70 (Ph-CH=), 149.75 (C₆H₃), 151.89 (C₆H₃), 168.58 (N-C=N_{oxadiazole}), 176.49 (N=CO_{oxadiazole}). Found, %: C 70.14; H 5.25; N 9.13. C₁₈H₁₆N₂O₃. Calculated, %: C 70.12; H 5.23; N 9.09.

(E)-4-(2-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)ethenyl)phenol (3j). Yield is 263 mg (73%), yellow crystalline substance, T melt. 198-200 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 6.85 (d, 2H, C₆H₄OH, *J* 8.1), 7.18 (d, 1H, Het-CH=, *J* 16.1), 7.65 (d, 2H, C₆H₄Cl, *J* 7.9), 7.69 (d, 2H, C₆H₄OH, *J* 8.1), 7.85 (d, 1H, Ar-CH=, *J* 16.3), 8.05 (d, 2H, C₆H₄Cl, *J* 7.9), 10.13 (s, 1H, OH). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 106.90 (Het-CH=), 116.54 (2C_{Ar}), 126.01 (C_{Ar}), 128.12 (C_{Ar}), 129.47 (2C_{Ar}), 130.09 (2C_{Ar}), 131.20 (2C_{Ar}), 136.86 (2C_{Ar}), 144.01 (Ph-CH=), 160.81 (C_{Ar}), 167.76 (N-C=N_{oxadiazole}), 176.82 (N=CO_{oxadiazole}). Found, %: C 64.35; H 3.74; N 9.41. C₁₆H₁₁ClN₂O₂. Calculated, %: C 64.33; H 3.71; N 9.38.

(E)-2-(2-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)ethenyl)phenol (3k). Yield is 277 mg (77%), white crystalline substance, T melt. 193-195 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 6.88 (t, 1H, C₆H₄OH, *J* 7.5), 6.96 (d, 1H, C₆H₄OH, *J* 8.3), 7.28 (t, 1H, C₆H₄OH, *J* 8.4), 7.38 (d, 1H, Het-CH=, *J* 16.5), 7.63 (d, 2H, C₆H₄Cl, *J* 8.5), 7.73 (d, 1H, C₆H₄OH, *J* 7.8), 8.05 (d, 2H, C₆H₄Cl, *J* 8.5), 8.10 (d, 1H, Ar-CH=, *J* 16.4), 10.47 (s, 1H, OH). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 105.83 (Het-CH=), 115.00 (C_{Ar}), 119.68 (C_{Ar}), 121.82 (C_{Ar}), 126.30 (C_{Ar}), 129.48 (2C_{Ar}), 130.01 (2C_{Ar}), 130.85 (C_{Ar}), 132.59 (C_{Ar}), 136.65 (C_{Ar}), 142.76 (Ph-CH=), 161.73 (C_{Ar}), 167.60 (N-C=N_{oxadiazole}), 178.07 (N=CO_{oxadiazole}). Found, %: C 64.36; H 3.73; N 9.42. C₁₆H₁₁ClN₂O₂. Calculated, %: C 64.33; H 3.71; N 9.38.

(E)-5-(2-(1H-Indol-3-yl)ethenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (3l). Yield is 184 mg (48%), beige crystalline substance, T melt. 185-187 °C. NMR spectrum ¹H (400 MHz, DMSO-*d*₆), δ, ppm: 7.07 (d, 1H, Het-CH=, *J* 16.4), 7.29 – 7.17 (m, 2H, Ind), 7.54 – 7.47 (m, 1H, Ind), 7.69 – 7.62 (m, 2H, C₆H₄), 8.11 – 8.01 (m, 4H, C₆H₄, Ind), 8.15 (d, 1H, Ar-CH=, *J* 16.3), 11.91 (s, 1H, NH). NMR spectrum ¹³C (101 MHz, DMSO-*d*₆), δC, ppm: 108.53 (Het-CH=), 118.04 (d, *J* 26.7, C_{Ind}), 124.17 (C_{Ind}), 125.79 (C_{Ind}), 126.90 (C_{Ar}), 128.47 (C_{Ind}), 130.49 (C_{Ind}), 131.28 (C_{Ind}), 134.46 (2C_{Ar}), 135.07 (2C_{Ar}), 138.19 (C_{Ar}), 141.74 (C_{Ind}), 143.09 (C_{Ind}), 143.42 (Ph-CH=), 164.14 (N-C=N_{oxadiazole}), 172.61 (N=CO_{oxadiazole}). Found, %: C 67.21; H 3.79; N 13.10. C₁₈H₁₂ClN₃O. Calculated, %: C 67.19; H 3.76; N 13.06.



(E)-5-(2-(1-Methyl-1H-pyrrol-2-yl)ethenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (3m). Yield is 74 mg (21%), beige crystalline substance, T melt. 105-107 °C. NMR spectrum ^1H (400 MHz, DMSO- d_6), δ , ppm: 3.78 (s, 3H, CH_3), 6.21 – 6.15 (m, 1H, Pyr), 7.00 – 6.90 (m, 2H, Het-CH=, Pyr), 7.07 (t, 1H, Pyr, J 2.1), 7.68 – 7.60 (m, 2H, C_6H_4), 7.78 (d, 1H, Ar-CH=, J 16.0), 8.07 – 8.01 (m, 2H, C_6H_4). NMR spectrum ^{13}C (101 MHz, DMSO- d_6), δC , ppm: 34.66 (N-CH_3), 109.65 (C_{Pyr}), 110.14 (C_{Pyr}), 113.72 (C_{Pyr}), 117.91 (Het-CH=), 126.10 (C_{Ar}), 129.46 (2C_{Ar}), 129.70 (C_{Pyr}), 130.05 (2C_{Ar}), 131.78 (Ph-CH=), 136.79 (C_{Ar}), 167.68 ($\text{N-C=N}_{\text{oxadiazole}}$), 177.08 ($\text{N=CO}_{\text{oxadiazole}}$). Found, %: C 63.08; H 4.25; N 14.74. $\text{C}_{15}\text{H}_{12}\text{ClN}_3\text{O}$. Calculated, %: C 63.05; H 4.23; N 14.71.

(E)-5-(2-Cyclohexylethenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (3n). Yield is 92 mg (26%), white crystalline substance, T melt. 68-70 °C. NMR spectrum ^1H (400 MHz, DMSO- d_6), δ , ppm: 1.40 – 1.02 (m, 5H, C_6H_{11}), 1.65 (d, 1H, C_6H_{11} J 11.7), 1.84 – 1.68 (m, 4H, C_6H_{11}), 2.35 – 2.26 (m, 1H, C_6H_{11}), 6.55 (dd, 1H, CH=, J 16.3, 1.5), 7.11 (dd, 1H, Ar-CH=, J 16.2, 6.8), 7.63 (d, 2H, C_6H_4 , J 8.2), 8.01 (d, 2H, C_6H_4 , J 8.2). NMR spectrum ^{13}C (101 MHz, DMSO- d_6), δC , ppm: 25.84 ($2\text{C}_{\text{cyclohexane}}$), 26.08 ($\text{C}_{\text{cyclohexane}}$), 31.67 ($2\text{C}_{\text{cyclohexane}}$), 41.05 ($\text{C}_{\text{cyclohexane}}$), 111.57 (Het-CH=), 125.81 (C_{Ar}), 129.45 (2C_{Ar}), 130.05 (2C_{Ar}), 136.91 (C_{Ar}), 154.00 (Ph-CH=), 167.68 ($\text{N-C=N}_{\text{oxadiazole}}$), 175.96 ($\text{N=CO}_{\text{oxadiazole}}$). Found, %: C 66.58; H 5.97; N 9.73. $\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{O}$. Calculated, %: C 66.55; H 5.93; N 9.70.

Funding

This research was financially supported by the Russian Science Foundation (Project No. 25-23-20245).

Conflict of interest

The authors declare no conflict of interest in financial or any other sphere.

References:

1. Byrne P.A., Gilheany D.G. The modern interpretation of the Wittig reaction mechanism. *Chem. Soc. Rev.*, 2013, 42(16), 6670-6696. DOI: 10.1039/c3cs60105f
2. Ryu H., Seo S., Cho S.-H., Kim H.S., Jung A., Kang D.W., Son K., Cui M., Hong S.-h., Sharma P.K., Choi S., Blumberg P.M., Frank-Foltyn R., Bahrenberg G., Stockhausen H., Schiene K., Christoph T., Frommann S., Lee J. 2-Alkyl/alkenyl substituted pyridine C-region analogues of 2-(3-fluoro-4-methylsulfonylaminophenyl)propanamides as highly potent TRPV1 antagonists. *Bioorg. Med. Chem. Lett.*, 2014, 24(16), 4039-4043. DOI: 10.1016/j.bmcl.2014.05.074
3. Girgis A.S., Panda S.S., Srouf A.M., Abdelnaser A., Nasr S., Moatasim Y., Kutkat O., El Taweel A., Kandeil A., Mostafa A., Ali M.A., Fawzy N.G., Bekheit M.S., Shalaby E.M., Gigli L., Fayad W., Soliman A.A.F. 3-Alkenyl-2-oxindoles: Synthesis, antiproliferative and antiviral properties against SARS-CoV-2. *Bioorg. Chem.*, 2021, 114, 105131. DOI: 10.1016/j.bioorg.2021.105131
4. Varela M.T., Lima M.L., Galuppo M.K., Tempone A.G., de Oliveira A., Lago J.H.G., Fernandes J.P.S. New alkenyl derivative from Piper malacophyllum and analogues: Antiparasitic activity against Trypanosoma cruzi and Leishmania infantum. *Chem. Biol. Drug Des.*, 2017, 90(5), 1007-1011. DOI: 10.1111/cbdd.12986
5. Wang J., Wu Y., Wang P. Modular and diverse synthesis of oxaheterocycles via Pd-catalyzed migratory 1,n-cycloannulation of alkenes. *Chem. Sci.*, 2025, 16, 20292-20299. DOI: 10.1039/d5sc06539a
6. Zhang Z., Li B., Liu Y., Li Y., Xiao Y., Wu H., Zhang Y. Synergistic In/amine-catalyzed cascade Michael-Aldol reactions of alkenyl pyridines with diverse 1,4-dipoles. *J. Org. Chem.*, 2025, 90(38), 13573-13588. DOI: 10.1021/acs.joc.5c01612



7. **Marshall C.M., Federice J.G., Bell C.N., Cox P.B., Njardarson J.T.** An update on the nitrogen heterocycle compositions and properties of U.S. FDA-approved pharmaceuticals (2013–2023). *J. Med. Chem.*, 2024, 67(14), 11622–11655. DOI: 10.1021/acs.jmedchem.4c00841
8. **Cherkasova A., Astolfi R., Nawrozki M., Gladkikh B., Proia E., Giuliani L., Rotili D., Ragno R., Ivanov R.** 1,2,4-Oxadiazoles in medicinal chemistry: trends of the last years. *Eur. J. Med. Chem.*, 2025, 297, 117935. DOI: 10.1016/j.ejmech.2025.117935
9. **Avanzo R. E., Padrón J. M., D'Accorso N. B., Fascio M. L.** Synthesis and in vitro antiproliferative activities of (5-aryl-1,2,4-oxadiazole-3-yl) methyl d-ribofuranosides. *Bioorg. Med. Chem. Lett.*, 2017, 27, 3674–3677. DOI: 10.1016/j.bmcl.2017.07.015
10. **Kulkarni R., Manjunatha K., Joy M. N. et al.** Exploration of NMI-MsCl mediated amide bond formation for the synthesis of novel 3,5-substituted-1,2,4-oxadiazole derivatives: synthesis, evaluation of anti-inflammatory activity and molecular docking studies. *Mol. Div.*, 2023, 27, 1867–1878. DOI: 10.1007/s11030-022-10536-z
11. **Rangaswamy S., Sreenivasulu R., Babu V. R. et al.** Design, synthesis, anticancer evaluation, and molecular docking studies of oxazole-incorporated naphthyridine derivatives. *Chem. Biodivers.*, 2023, 20, e202300466. DOI: 10.1002/cbdv.202300466
12. **Stebletsova I. A., Larin A. A., Fershtat L. L.** Recent advances in the synthesis of pharmacologically active 1,2,3-, 1,2,4-, and 1,2,5-oxadiazole-based lead compounds. *Russ. Chem. Rev.*, 2025, 94(10), RCR5185. DOI: 10.59761/RCR5185
13. **Varaprasadu B. D., Haridasym S. B., Koppula S. K.** Synthesis of novel pyrido[3,4-d] pyrimidine-thiazolidione-1,2,4-oxadiazoles as potent EGFR targeting anticancer agents. *J. Heterocycl. Chem.*, 2024, 61(5), 789–798. DOI: 10.1002/jhet.4859
14. **Vasil'eva E.A., Alexeev M.A., Tarasenko M.V., Ivanovskiy S.A., Blumina M. V., Shetnev A.A.** Wittig Olefination with Novel 1,2,4-Oxadiazole-Substituted Triphenylphosphonium Ylides. *Russ J. Gen. Chem.*, 2026, 96, 162. DOI: 10.1134/S1070363225608075
15. **Yanovskaya L.A., Yufit S.S.** Organicheskiy sintez v dvukhfaznykh sistemakh. M.: Khimiya, 1982, 184 s. (in Russian).
16. **Mohamadi F., Still W. C.** Dichlorocarbene cyclopropanation of allylic alcohols. *Tetrahedron Lett.*, 1986, 27(8), 893–896. DOI: 10.1016/s0040-4039(00)84130-1
17. **Fedorynski M., Ziolkowska W., Jonczyk A.** Tetramethylammonium salts: highly selective catalysts for the preparation of gem-dichlorocyclopropanes from electrophilic alkenes and chloroform under phase-transfer catalysis conditions. *J. Org. Chem.*, 1993, 58(22), 6120–6121. DOI: 10.1021/jo00074a047
18. **Blois, M.** Antioxidant Determinations by the Use of a Stable Free Radical. *Nature*, 1958, (181), 1199–1200. DOI: 10.1038/1811199a0
19. **Yu L., Yang K., Yao L., Wang N., Kang H., Yao G., Li X., Qin B.** Synthesis and Antifungal Activity of 1,2,4-Oxadiazole Derivatives. *Molecules*, 2025, 30(8), 1851. DOI: 10.3390/molecules30081851
20. **Kumar S., Wadhwa P.** Synthesis, molecular docking and biological evaluation of 1,2,4-oxadiazole based novel non-steroidal derivatives against prostate cancer. *Bioorg. Chem.*, 2024, 143, 107029. DOI: 10.1016/j.bioorg.2023.107029

Received 28.06.2026

Approved after reviewing 22.07.2026

Accepted 20.08.2026