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REGIOSELECTIVITY OF THE S_EAR REACTION OF 8-CHLORO-3,4-DIHYDRO-1*H*-[1,4]OXAZINO[4,3-*A*]BENZIMIDAZOLE

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Abstract. *The article investigates the impact of process temperature and electrophilic agent addition time on the regioselectivity of the S_EAr reaction. The purpose is an efficient functionalisation of the bifarmacophore molecule 8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole in electrophilic nitration and halogenation reactions. Two isomeric 7- and 9-substituted products were formed during these reactions. A larger amount of 7-R-8-chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole was formed. Reducing the reaction temperature and the concentration of the electrophilic agent in the reaction mixture increased the selectivity of the process for forming the isomer.*

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Introduction

Inclusion of several pharmacophore fragments into the molecular structure is one of the promising directions in the design of substances with high biological activity [1-7]. As a result, the synergistic action of the pharmacophore groups is observed. It leads to the enhancement of the therapeutic effect of the drug under development.

For example, this approach is used to synthesise dual-action antibiotics [1]. These drugs are essential for overcoming the issue associated with the development of antibiotic resistance in microorganisms. The two pharmacophores of such a drug can be connected via a spacer directly or with a slight overlap. It is suggested that covalent bonding, unlike non-covalent bonding, makes the pharmacokinetic characteristics of the resulting molecule more predictable.

The most common pharmacophores in medicinal substances are benzimidazole [8-10] and morpholine [11-16] cycles. There are a lot of benzimidazole derivatives. For example, omeprazole is used as an antiulcer agent; candesartan, telmisartan, and azilsartan medoxomil are used as antihypertensive drugs; dibazol shows the antispasmodic properties effect, etc. (Fig. 1). Moreover, the most of these compounds contain substituents in the 1st and 2nd positions of the heterocycle.

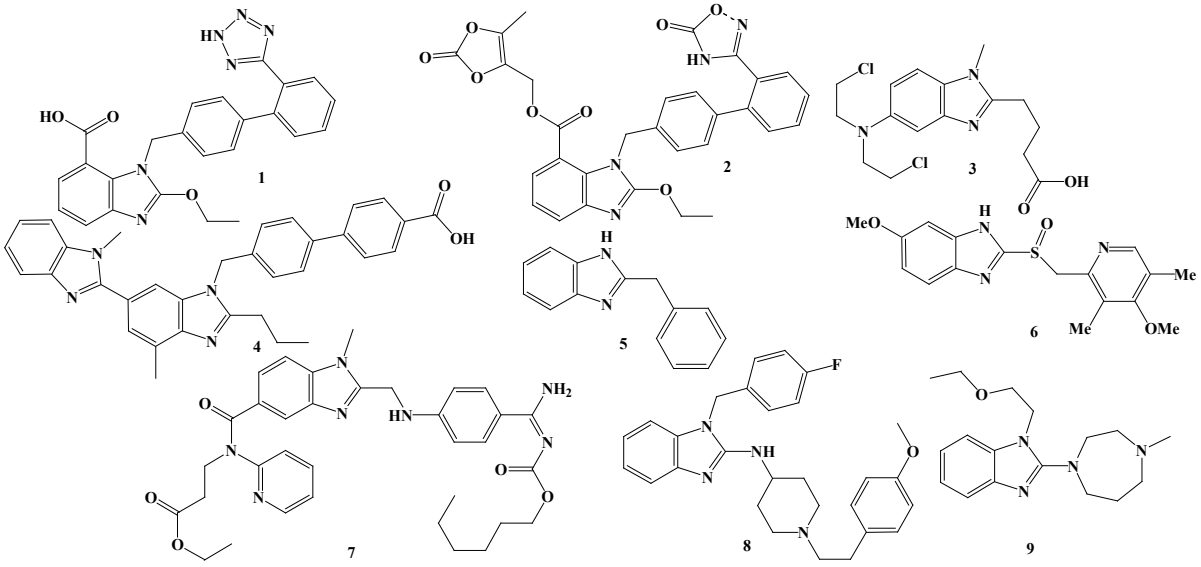


Fig. 1. Medicinal products containing a benzimidazole ring: 1 – candesartan, 2 – azilsartan medoxomil, 3 – bendamustine, 4 – telmisartan, 5 – dibazol, 6 – omeprazole, 7 – dabigatran etexilate mesylate, 8 – astemizole, 9 – emedastine

The morpholine cycle includes the following drugs: new-generation antibiotic linezolid, the antidepressant moclobemide, the antiemetic aprepitant, and the antiarrhythmic agent etmozin (Fig. 2). The drug gefitinib is used to treat cancer.

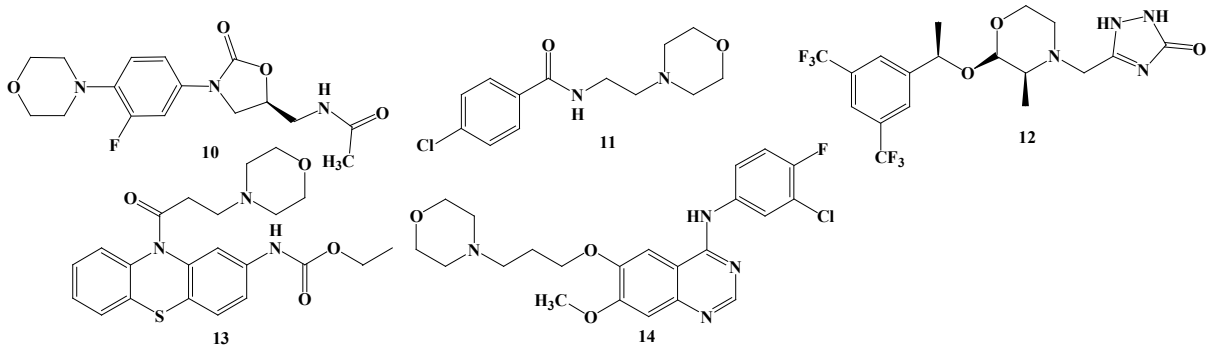


Fig. 2. Structural formulas of morpholine-containing drugs: 10 – linezolid, 11 – aprepitant, 12 – moclobemide, 13 – etmozin, 14 – getifib

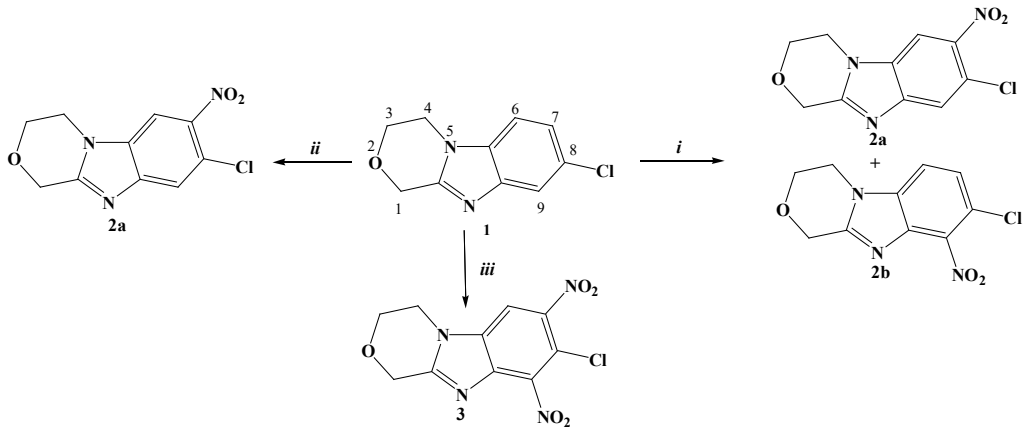
We have previously developed an effective method for synthesising a new benzimidazole derivative. It contains a morpholine ring annulated at positions 1 and 2 - 8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**1**) [17].

Compounds containing this condensed heterocycle are utilized in the development of potent pharmaceutical substances [18, 19], such as antiviral [20] and antitumor [21] agents.

Continuing the work on the synthesis of new bipharcophore molecules, this study investigated one of the ways of functionalising condensed benzimidazole **1** during aromatic electrophilic substitution reactions: nitration and halogenation. They allow new highly reactive centres to be formed in the molecule.

Main body

A nitrating mixture of potassium nitrate and sulphuric acid was used to introduce the nitro group. It was quickly added to the solution of heterocycle **1** in sulphuric acid. We conducted the reaction at 30 °C for 1 hour. We have used these conditions previously for the nitration of pyrid[1,2-a]benzimidazoles [22]. A mixture of two isomeric nitro compounds **2a** and **2b** in a ratio of 1 : 0.33 was isolated from the reaction mass (Scheme 1, ***i***). The total yield of isomers **2a** and **2b** was 97%.



Scheme 1. Reagents and conditions: ***i*** KNO_3, H_2SO_4, 30 °C, rapid addition of nitrating agent, reaction time is 1 hour; ***ii*** KNO_3, H_2SO_4, 20 °C, gradual addition of nitrating agent is made during 2 hours; ***iii*** KNO_3, H_2SO_4, 90 °C, rapid addition of nitrating agent, reaction time is 4 hours.

Patent [18] reports the formation of two isomers upon nitration of condensed benzimidazole **1**. However, the isomer ratio was not specified in the patent, and their separation and identification were not performed. Only high-resolution mass spectrometry data (MS m/z (ESI): 254.2 [M^{+1}]) for the mixture of substances was provided.

These compounds **2a** and **2b** were isolated individually during the research. Their structure was proved by ^{1}H, ^{13}C NMR spectroscopy and high-resolution mass spectrometry. Proton signals were assigned based on ^{1}H-^{1}H NOESY spectroscopy data.

Fig. 3 shows the 2D NMR spectrum of one of the nitration reaction products, which was formed in larger quantities. Two proton signals in the form of singlets were present in the ^{1}H NMR spectrum (horizontal part of the spectrum) in the weak field region of 7.9-8.5 ppm. A cross peak of interaction between protons $H^{4,4}$ of the morpholino cycle and aromatic proton H^{6} was recorded in the 2D NMR spectrum. This type of proton signal and the absence of a substituent in the 6th position indicated the introduction of a nitro group in the 7th position of the heterocycle. Thus, the substance obtained was identified as 7-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**2a**). Data from ^{13}C NMR spectroscopy and mass spectrometry confirmed the structure of nitro compound **2a**.

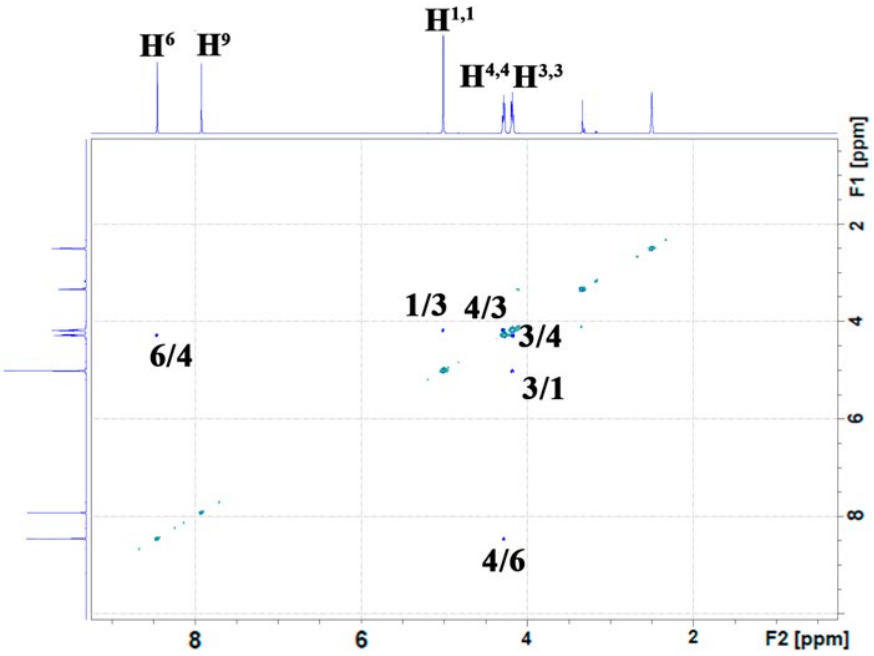


Fig. 3. ^{1}H-^{1}H NOESY NMR spectrum of 7-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**2a**) (DMSO-d_6)

The formation of the 9-substituted product, 9-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**2b**), was evidenced by the presence in the ^{1}H NMR spectrum (Fig. 4, horizontal part of the spectrum) of two signals of aromatic protons H^{6} and H^{7}, which had the form of a doublet with J = 8.6 - 8.7 Hz. The signal H^{6} appeared in a weaker field. It had a cross-peak with methylene protons H^{4,4}. Compared to compound **2a**, the proton signals of isomer **2b** were shifted to the more strongly polar region of the NMR spectrum at 7.5–7.9 m.d.

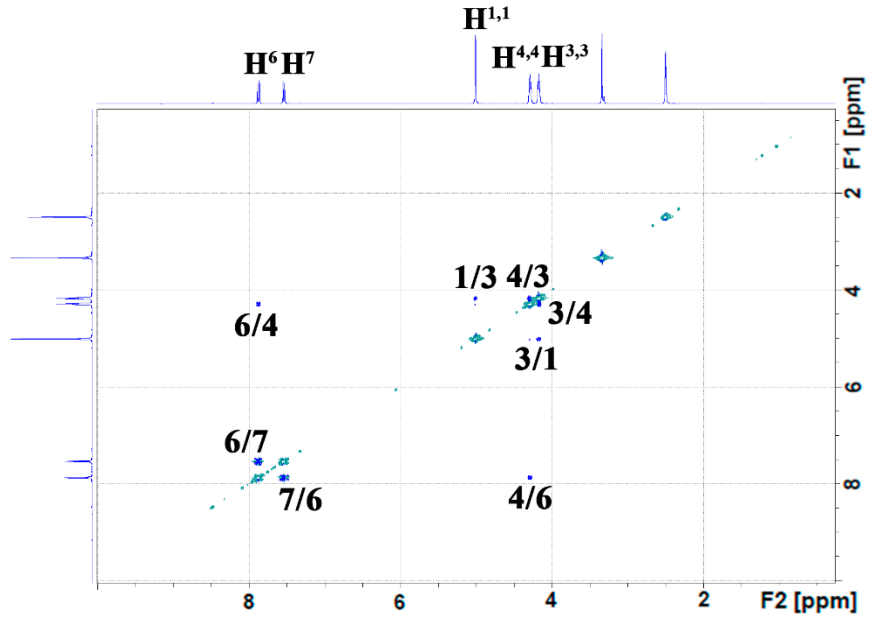


Fig. 4. ^{1}H-^{1}H NOESY NMR spectrum of 9-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**2b**) (DMSO-d_6)

We studied the effect of temperature and timing of nitrating agent addition on the regioselectivity of aromatic electrophilic substitution reactions (Table 1).

Table 1. The impact of temperature and timing of nitrating agent addition on the ratio of nitroisomers **2a** and **2b** formed

№	T, °C	Time of reagent addition	Reaction time, h	Σ yield (%) **2a** and **2b**	Ratio **2a** and **2b***
1	10	≈ 5 sec	3	89	1 : 0.19
2	20	≈ 5 sec	1.5	91	1 : 0.22
3	30	≈ 5 sec	1	94	1 : 0.33
4	40	≈ 5 sec	0.75	96	1 : 0.35
5	50	≈ 5 sec	0.75	93	1 : 0.39
6	30	2 h	2**	97	1 : 0.05
7	20	2 h	2**	96	1 : 0.03

* according to ^{1}H NMR spectroscopy

** S_EAr reaction proceeded during the gradual introduction of the nitrating mixture over a period of 2 hours.

As can be seen from the data in the table, the amount of 9-nitro-substituted product **2b** in the reaction mass increased with rising reaction temperature (experiments 1-5). The highest selectivity of the reaction at substrate **1** position 7 was observed at temperatures of 10 and 20 °C (experiments 1 and 2). At the same time, the reaction time of S_EAr increased, and isomer **2b** was always present in the reaction mass.

Subsequently, in order to increase the selectivity of the nitration process, the reaction was conducted with a shortage of nitrating agent (experiments 6 and 7). A stepwise addition of the nitrating mixture over 2 hours led to the formation of mainly nitrocompound **2a**. Another isomer, **2b**, was present in trace amounts in the reaction mixture. After recrystallisation in methanol, benzimidazole **2a** was isolated with a yield of 89%. Thus, the conditions for the synthesis of 7-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**2a**) (Scheme 1, ***ii***) via an individual nitration reaction were optimized.

The use of an excess of the nitrating agent afforded 7,9-dinitro-8-chloro-3,4-dihydro-1***H***-[1,4]oxazino[4,3-*a*]benzimidazole (*3*) (Scheme 1, **iii**) in 89% yield. The introduction of two nitro groups into substrate **1** proceeded only at temperatures above 80 °C. The reaction was conducted for 4 hours.

According to 2D NMR spectroscopy data (Fig. 5), the nitro groups were introduced in accordance with the directing effect of the substituent, specifically at the 7- and 9-positions of the condensed benzimidazole **1**.

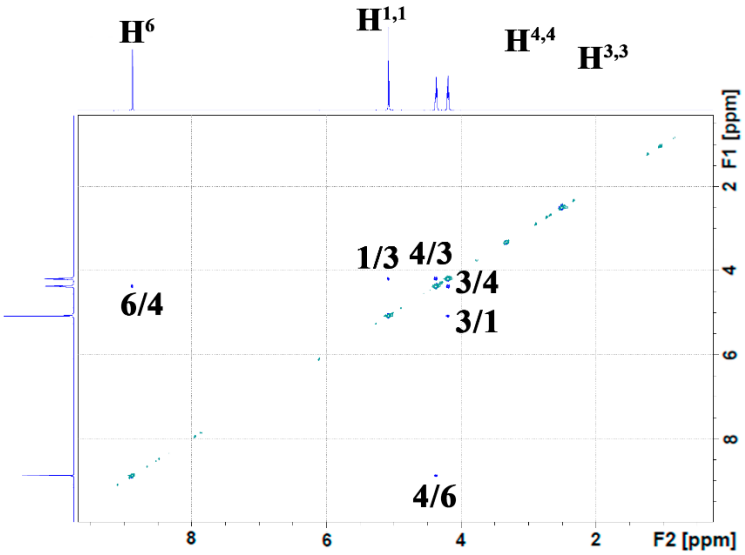
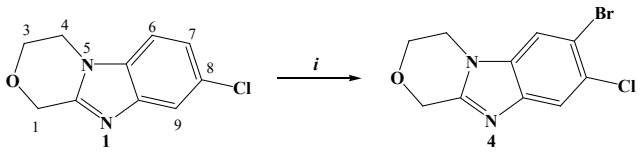


Fig. 5. ^{1}H-^{1}H NOESY NMR spectrum of 9-dinitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**3**)

Halogenation of condensed benzimidazole **1** with N-bromosuccinimide in concentrated sulfuric acid followed patterns analogous to the mononitration reaction (Scheme 1, ***i***). It should be noted that this reaction proceeded much more slowly than the nitration process. Therefore, bromination was performed at 40 °C for 9 hours. Complete consumption of substrate **1** in the reaction was observed when using 1.4 equivalents of NBS.

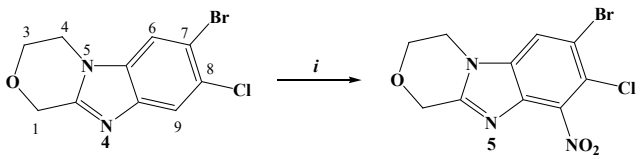
When the brominating agent was added rapidly, two isomers were formed. Two proton signals were present in the ^{1}H NMR spectrum of the mixture obtained, in the form of a singlet of the 7,8-dihalogen-substituted isomer, and two signals in the form of a doublet with a *J*-coupling of 8.6 Hz, of another isomer, which was formed in smaller quantities. As the reaction temperature increased, the amount of this compound in the reaction mass also increased.

Stepwise addition of N-bromosuccinimide solution over 9 hours at 40 °C to the reaction mixture yielded 7-bromo-8 -chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (4) after recrystallisation in isopropanol with a yield of 91% (Scheme 2).



Scheme 2. Reagents and conditions ***i*** NBS, H_2SO_4, 40 °C, stepwise addition of halogenating agent over 9 hours.

It was of interest to determine the regioselectivity of the S_EAr reaction during the nitration of dihalogenated derivative **4**. In this case, the halogen atoms direct the introduction of the nitro group to different positions in the molecule. Rapid addition of the nitrating agent at 40 °C yielded two nitration products at the 9- and 6-positions in a ratio of 1:0.21, respectively. The proportion of the 9-substituted product in the reaction mixture could be increased by the slow, dropwise addition of the nitrating mixture over a period of 3 hours. After recrystallization from isopropanol, the yield of 7-bromo-8-chloro-9-nitro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**5**) was 91%.



Scheme 3. Reagents and conditions: ***i*** KNO_3, H_2SO_4, 40 °C, stepwise addition of halogenating agent over 3 hours.

In 2D NMR spectrum (Fig. 6) of compound **5**, a cross-peak corresponding to the interaction between the $H^{4,4}$ protons of the morpholine ring and the aromatic proton H^6 was observed, confirming the introduction of the nitro group at the 9-position.

Thus, the formation of two isomers occurred during the nitration and halogenation of 8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**1**): 7,8- and 8,9-disubstituted products. The selectivity of aromatic electrophilic substitution was affected by the reaction temperature and, in particular, by the concentration of the electrophilic agent in the reaction mixture.

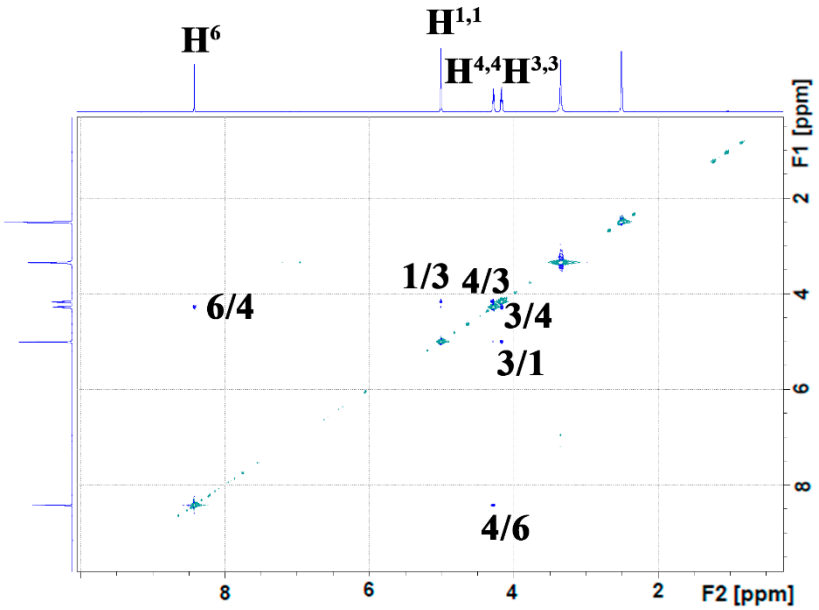


Fig. 6. ^{1}H-^{1}H NOESY NMR spectrum of 7-brom-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**5**) (DMSO-d_7)

When the process temperature and reagent concentration were reduced, the electrophilic particle was introduced predominantly into position 7 of the condensed heterocycle. Electrophilic attack predominantly occurred at the 9-position in 7-bromo-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (**4**), where the substituents exhibit mismatched directing effects. As a result, the conditions for the functionalisation of the bipharcophore molecule 8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole in the S_EAr reaction were developed. The resulting halonitro derivatives can be used for further functionalisation in aromatic nucleophilic substitution and reduction reactions. It will significantly expand the range of known 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole derivatives.

Experimental part

We determined the melting points on a PolyTherm A device at a heating rate of 3 °C/min and did not adjust. We recorded NMR spectra on a Bruker DRX-400 for DMSO-d_6 solutions. We used the signals of residual solvent protons in ^{1}H NMR (δ 2.5 ppm) or in ^{13}C NMR (δ = 39.5 ppm) as a reference for counting chemical shifts.

High-resolution mass spectra for substances **3** and **5** were recorded on a Bruker micrOTOF (time-of-flight mass analyser) (Germany) equipped with an electrospray ionisation (ESI) source. The scanning range was *m/z* 50-2000. External calibration of the mass scale was performed using a low-concentration calibration solution 'Tuning mix' (Agilent Technologies). Samples were injected using a Hamilton RN 1750 syringe (Switzerland) with a capacity of 500 µl. Measurements were performed in positive ion (+) mode (grounded spray needle, high-voltage capillary 4500 V; potential difference with spray shield –500 V). The flow rate during injection was controlled by a syringe pump (3 µl/min). Nitrogen was used as the nebuliser gas (1.0 bar) and desiccant gas (4.0 l/min, 200 °C). The data were processed using the BrukerData Analysis 4.0 software package.

High-resolution mass spectra (HRMS) for compounds **2a**, **2b**, and **4** were recorded on an Agilent 6546 time-of-flight (TOF) mass spectrometer (Agilent Technologies) equipped with an electrospray ionization (ESI) source in positive ion mode. Sample injection volume was 10 μL. Source parameters: sheath gas temperature is 350 °C; sheath gas flow is 11 psi (0.758 bar); drying gas temperature is 320 °C; drying gas flow rate is 3 L/min; nebulizer gas is 35 psi (2.413 bar); capillary voltage is 3500 V. The calibration solution contained two internal reference masses (purine, $C_5H_4N_4$, *m/z* 121.050873; and HP-921 [hexakis(1H,1H,3H-tetrafluoropropoxy)phosphazene], $C_{18}H_{18}O_6N_3P_3F_{24}$, *m/z* 922.009798). Data acquisition and processing were performed using MassHunter Workstation 10.0 software (Agilent Technologies). All masses were obtained with an error of less than 5 ppm.

General method for the synthesis of 7-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (2a) and 9-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (2b)

We added a solution of 0.51 g (0.005 mol) of KNO3 in 20 ml of H2SO4 to a solution of 1 g (0.0048 mol) of benzimidazole $_1$ in 20 ml of H2SO4 at 30 °C. The reaction mixture was then stirred for 1 h. Then we poured the reaction mixture into ice and treated it with NH_4OH to pH 8. We filtered out the precipitate, dried it, and recrystallised in methanol. Upon cooling, isomer **2a** precipitated. We evaporated the filtrate and recrystallised the dry residue obtained in isopropanol. Upon cooling, isomer 2b precipitated from the isopropanol.

7-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (2a) Yield is 64%. T melt. 212-215 °C. Spectrum ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H, H^6), 7.92 (s, 1H, H^9), 5.01 (s, 2H, $H^{1,1}$), 4.29-4.25 (m, 2H, $H^{4,4}$), 4.19-4.16 (m, 2H, $H^{3,3}$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ 155.02, 145.63, 142.70, 132.84, 121.16, 119.33, 109.60, 64.93, 63.68, 43.17. ESI-HRMS: *m/z* calculated $C_{10}H_9ClN_3O_3$: 254.0327 $[M+H]^+$, found 254.0331; Δ = 1.60 ppm.

9-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (2b). Yield is 17%. T melt. 156-160 °C. Spectrum ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 8.7 Hz, 1H, H^6), 7.54 (d, J = 8.6 Hz, 1H, H^7), 5.01 (s, 2H, $H^{1,1}$), 4.31-4.27 (m, 2H, $H^{4,4}$), 4.19-4.15 (m, 2H, $H^{3,3}$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6) δ 153.35, 138.99, 135.97, 135.70, 123.30, 117.61, 114.96, 64.80, 63.63, 43.16. ESI-HRMS: *m/z* calculated $C_{10}H_9ClN_3O_3$: 254.0327 $[M+H]^+$, found 254.0333; Δ = 1.78 ppm.

Synthesis methodology of 7-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (2a).

We added a solution of 0.51 g (0.005 mol) of KNO3 in 20 ml of H2SO4 to a solution of 1 g (0.0048 mol) of benzimidazole $_1$ in 20 ml of H_2SO_4 at 20 °C for 2 hours. Then we poured the reaction mixture into ice and treated it with NH_4OH to pH 8. We filtered out the precipitate, dried it, and recrystallised in methanol. Yield is 1,08 g (89%).

Synthesis methodology of 7,9-dinitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (3).

We added a solution of 1.02 g (0.010 mol) of KNO3 in 20 ml of H2SO4 to a solution of 1 g (0.0048 mol) of benzimidazole **1** in 20 ml of H_2SO_4 at 60 °C. The reaction mixture was then stirred at 90 °C for 4 hours. Then we poured the reaction mixture into ice and treated it with

NH_4OH to pH 8. We filtered out the precipitate, dried it, and recrystallised in isopropanol and DMF.

Yield is 1.28 g (89 %). T melt. 244-247 °C. Spectrum ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H, H^6), 5.08 (s, 2H, $H^{1,1}$), 4.38-4.36 (m, 2H, $H^{4,4}$), 4.21-4.18 (m, 2H, $H^{3,3}$). Spectrum ^{13}C NMR (101 MHz, DMSO-d_6) δ 217.93, 157.59, 142.05, 139.31, 137.70, 134.69, 112.44, 111.71, 64.81, 63.43, 43.80. ESI-HRMS: *m/z* calculated $C_{10}H_8ClN_4O_5$: 299.0178 $[M+H]^+$, found 299.0190; Δ = 4.01 ppm.

Synthesis methodology of 7-nitro-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (4).

We added a solution of 1.2 g (0.0067 mol) of NBS in 30 ml of H**2**SO_4 to a solution of 1.0 g (0.0048 mol) of benzimidazole **1** in 20 ml of H_2SO_4 at 40 °C for 9 hours. Then we poured the reaction mixture into ice and treated it with NH_4OH to pH 8. We filtered out the precipitate, dried it, and recrystallised in isopropanol.

Yield 1.26 g (91 %). T melt. 192-199 °C. ^{1}H NMR (400 MHz, ДМСО-d_6) δ 8.02 (s, 1H, H^6), 7.84 (s, 1H, H^9), 4.94 (s, 2H, $H^{1,1}$), 4.09-4.23 (m, 4H, $H^{3,3,4,4}$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.43, 143.09, 134.71, 126.78, 120.64, 115.57, 114.42, 65.01, 63.91, 43.12. ESI-HRMS: *m/z* calculated $C_{10}H_9BrClN_2O$: 288.9559$[M+H]^+$, found 288.9562; Δ = 1.12 ppm.

Synthesis methodology of 7-brom-8-chloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazole (5).

We gradually added a solution of 0.37 g (0.0036 mol) of KNO_3 in 20 ml of H_2SO_4 to a solution of 1 g (0.0035 mol) of benzimidazole **4** in 20 ml of H_2SO_4 at 40 °C for 3 hours. Then we poured the reaction mixture into ice and treated it with NH_4OH to pH 8. We filtered out the precipitate, dried it, and recrystallised in isopropanol.

Yield is 1.06 g (91 %). Tmelt. 237-240 °C. Spectrum ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 5.01 (s, 2H, $H^{1,1}$), 4.30-4.26 (m, 2H, $H^{4,4}$), 4.18-4.14 (m, 2H, $H^{3,3}$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.25, 139.60, 136.28, 135.13, 118.47, 117.85, 114.86, 64.77, 63.55, 43.45. ESI-HRMS: calculated $C_{10}H_7BrClN_3O_3$: 333.9411$[M+H]^+$, found 333.9418; Δ = 2.10 ppm.

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Conflict of interest

The authors declare that there are no conflicts of interest to report in this paper.

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2025. The topic of the research is: 'Development of new drugs for targeted chemotherapy of oncological diseases based on condensed benzimidazole derivatives with a nodal nitrogen atom.'

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