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Synthesis and anti-inflammatory activity of S-oxides of pyridinyloxy substituted imidazo[2,1-*b*][1,3]thiazines

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A B S T R A C T

Here derivatives of imidazo[2,1-*b*][1,3]thiazines are attractive objects for organic and medicinal chemists. In the present work chemoselective conditions for oxidation of the sulfur atom in the 6-(2-pyridinyloxy)substituted (benzo)imidazo[2,1-*b*][1,3]thiazines to the corresponding sulfoxides were proposed and their synthesis was performed. Synthesized sulfoxides exist in the diastereomeric mixture and individual diastereomers **2a-e** and **3a-e** were obtained using a chromatographic technique. The structure of compounds **2a-e** and **3a-e** were characterized using ^{1}H, ^{13}C NMR, LC-MS spectra, and X-ray analysis for derivative **2b**. The anti-inflammatory activity screening *in vivo* was performed using the carrageenan model of inflammatory paw edema in white rats for all the diastereomeric mixtures and individual diastereomers. Diastereomer **2c** possessed an anti-inflammatory effect with an inflammation inhibition index of 46.1% which was equal to the activity of the reference drug diclofenac sodium.

1. Introduction

The oxidation reaction of sulfur atoms in organic molecules is a powerful tool for their modification for the purpose of design of new derivatives important for both synthetic transformations and structural and biomedical researches.[1,2] In particular, a number of effective approaches have been developed for the selective oxidation of sulfides to sulfoxides and sulfones, among which a special role is assigned to chemo- and biocatalytic methods.[3,4] Acyclic and (hetero)cyclic compounds, which contain a pharmacologically attractive sulfoxide function, in a significant number of cases tend to enhance the biological effect and reduce toxicity or are important intermediate products and building blocks for the design of several bioactive compounds.[5] Conformationally stable chiral sulfoxides are key structural fragments of many natural products and some important pharmaceutical agents. There are among these molecules deserving to the attention drug for the treatment of gastric ulcer esomeprazole,[6] cardiotonic drug sulmazole,[7] non-steroidal anti-inflammatory drug sulindac,[8] drug for the treatment of nervous system disorders modafinil,[9] anti-HIV-CCR5 antagonist[10] and the natural antibacterial component of garlic garlicnin B-2[11] (**Fig. 1**).

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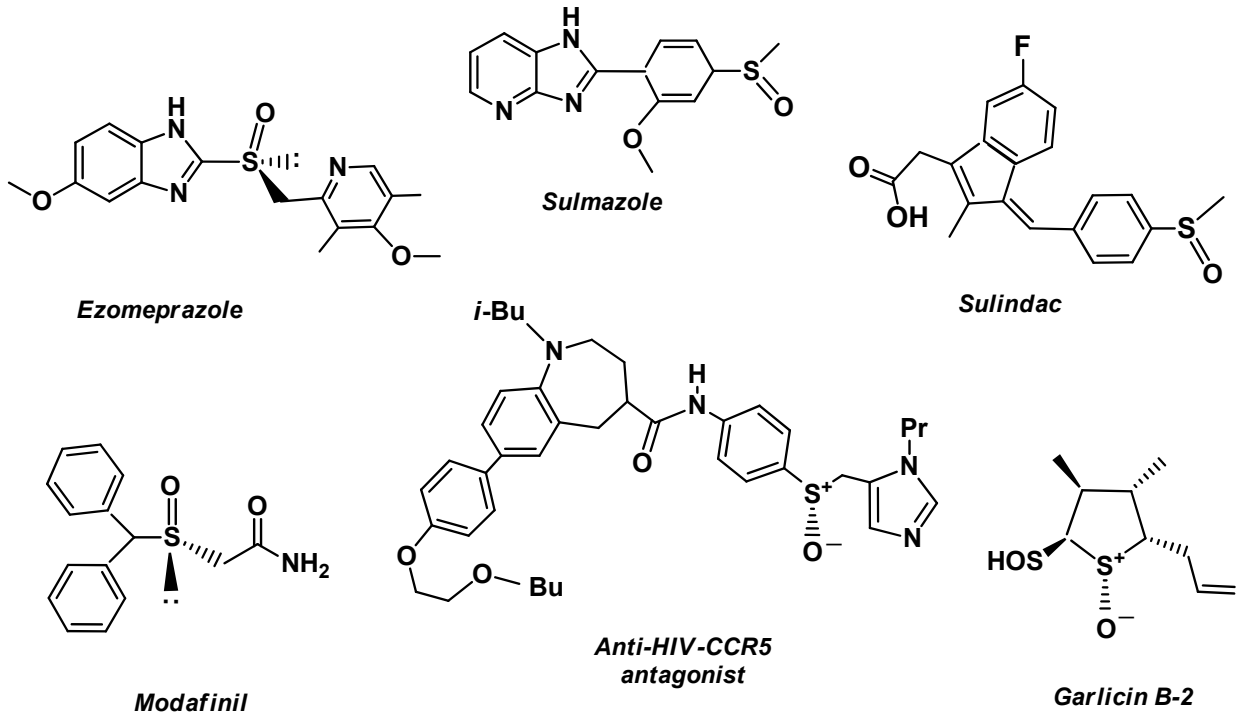


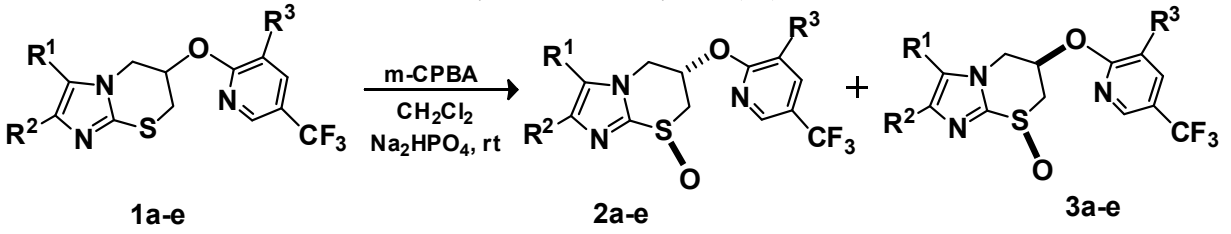
Fig. 1. Approved drugs and biologically active molecules containing sulfoxide group.

A detailed review of the literature allows us to conclude that the main efforts of researchers were focused at the study of structures in which the sulfoxide group is connected to alkyl, aryl, or heteroaryl substituents. Among them, substances with vasodilator,[12] antitumor[13] and antiallergic[14] effects were identified and reported. At the same time, compounds in which the S=O function is an endocyclic element of the heterocycle have been studied to a much lesser extent and mainly concern S-oxides of thiophene,[15] its saturated[16,17] and benzoannelated[18,19] derivatives. In recent years, several publications reported on S-oxides of cepham-type β-lactams with pronounced antibacterial activity[20] and imidazo[2,1-b][1,3]thiazine derivatives[21-25] with antituberculosis[21,22] and antitrypanosomal action[25]. Recently we reported on the efficient synthetic approaches to the series of new pyridinyloxy-substituted imidazo[2,1-*b*][1,3]thiazines, which are characterized by satisfactory drug-like parameters and anti-inflammatory activity *in vivo*.[26-28] In the present work, we describe the application of developed conditions for selective oxidation of the sulfur atom in the molecules of pyridinyloxy-substituted imidazo[2,1-*b*][1,3]thiazines to the corresponding sulfoxides and their anti-inflammatory activity screening results.

2. Results and Discussion

2.1 Chemistry

Oxidants such as oxone,[24] diacetoiodobenzene,[23] Davis reagent,[21] and *meta*-chloroperbenzoic acid (*m*-CPBA)[22, 25] are widely used in the modern preparative organic chemistry for the selective oxidation of the sulfur atom to the corresponding S-oxide function in the imidazothiazine core. Considering the high efficiency of *m*-CPBA for the conversion of 6-oxysubstituted 2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazines[25] into the corresponding S=O derivatives, this reagent was selected and used for the oxidation of 6-(2-pyridinyloxy)substituted (benzo)imidazo[2,1-*b*][1,3]thiazines **1a-e**. It was established that interaction of **1a-e** with *m*-CPBA in a ratio of 1:1 in a solution of dichloromethane in the presence of sodium hydrogen phosphate at room temperature for 24 h is characterized by high chemoselectivity and leads to the formation of a mixture of diastereomeric sulfoxides **2a-e** and **3a-e**, the content of which in the reaction medium according to LC-MS was 94-99 %, and which after the simple preparative procedures was isolated with yields of 74-87 %. The stereochemical result of the reaction is clearly confirmed by ^{1}H NMR spectra, in which a doubling of all signals was observed. Comparison of the integral intensities of doubled multiplets of H-6 protons (at 6.41-6.65 ppm and at 5.80-6.15 ppm) made it possible to determine the ratio of the formed diastereomers: **2a**:**3a** = 1.2:1; **2b**:**3b** = 1.3:1; **2c**:**3c** = 1.9:1; **2d**:**3d** = 1:3.2; **2e**:**3e** = 1.4:1, which were separated by column chromatography using the eluent MeOH-$CHCl_3$ (1:50) (**Scheme 1, Table 1**).



Scheme 1. Synthesis of the 5-(trifluoromethyl)pyridine-2-yl-oxy-substituted (benzo)imidazo[2,1-b][1,3]thiazine oxides **2a-e** and **3a-e**.

Table 1. Structure characterization and yields of compounds **2a-e** and **3a-e**.

Compounds	R^1	R^2	R^3	Yields, %
2a	H	H	Cl	34
2b	Ph	Ph	H	26
2c	Ph	Ph	Cl	28
2d	(-CH=CH-)$_2$		H	25
2e	(-CH=CH-)$_2$		Cl	35
3a	H	H	Cl	21
3b	Ph	Ph	H	34
3c	Ph	Ph	Cl	23
3d	(-CH=CH-)$_2$		H	29
3e	(-CH=CH-)$_2$		Cl	19

The data of ^{1}H, ^{13}C NMR and LC-MS spectra (see the experimental part) confirm the structure of the synthesized compounds, however, do not provide clear insights regarding the stereochemistry of the appropriate diastereomers. The stereostructure of type **2** isomers was reliably confirmed in the example of compound **2b** by X-ray analysis (**Fig. 2**). This diastereomer (chemical shift of the H6 atom in the range 6.41-6.48 ppm) is a racemic mixture of molecules with a relative configuration of asymmetric centres (*6R*,*8S*).

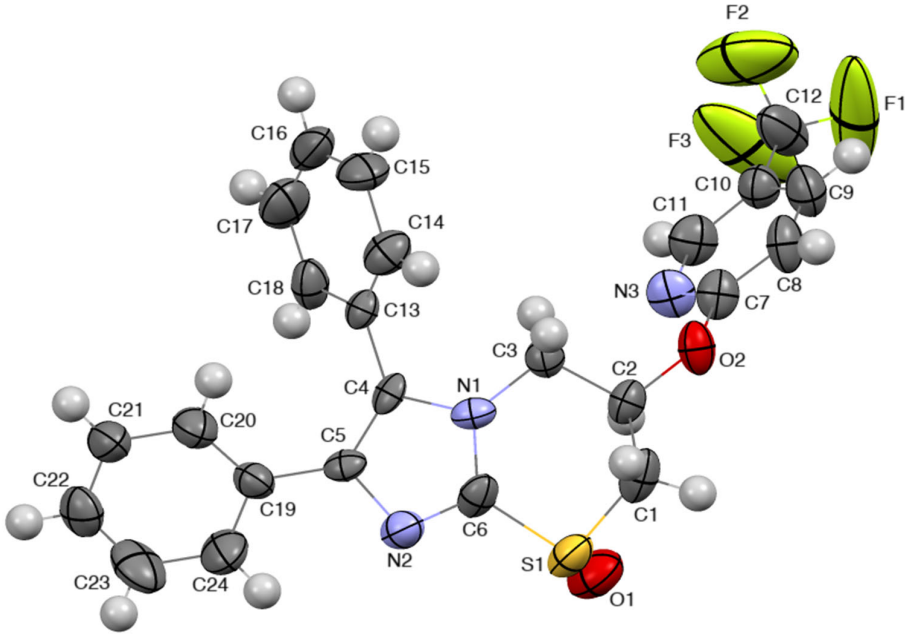


Fig. 2. Molecular structure of compound **2b** according to X-ray diffraction data. Thermal ellipsoids are shown at the 50% probability level.

The partially saturated six-membered heterocycle of compound **2b** adopts a half-chair conformation, where the S1, C6, N1, and C3 atoms lie in a plane with an accuracy of 0.001 Å, and the C1 and C2 atoms deviate from this plane by 0.49 Å and -0.38 Å, respectively. The substituent at the C2 atom is located in an equatorial position (the N1–C3–C2–O2 torsion angle is -172.2(7)º), and the para-trifluoropyridine fragment is almost orthogonal to the C2–C3 endocyclic bond and turned coplanar to the C2–O2 exocyclic bond (the C3–C2–O2–C7 and C2–O2–C7–N3 torsion angles are -84(1)º and 3(1)º,

respectively). This position of the substituent is due to the steric repulsion between the partially saturated heterocycle and the pyridine ring, as evidenced by the shortened C3...N3 intramolecular contact of 3.14 Å (the van der Waals radii sum[29] is 3.21 Å). The presence of two phenyl substituents in the vicinal position leads to disruption of conjugation between their aromatic systems and the π-system of the imidazole ring (the C5–C4–C13–C18 and C4–C5–C19–C20 torsional angles are -52(2)º and -25(2)º, respectively) due to significant steric repulsion (the shortened intramolecular contacts C20...C13 3.33 Å, C14…C3 3.15 Å (the van der Waals radii sum is 3.42 Å) and H20...C13 2.77 Å (2.87 Å)).

Taking into account the molecular structure of diastereomer **2b** as well as data of paper[30], according to which S=O group in six-membered cycles has axial position, (*6S,8S*) configuration can be assigned to diastereomer **3b.** Similar relative configurations of the stereogenic centres of the **2a, c-e** and **3a, c-e** diastereomers are given in the experimental part.

2.2 Anti-inflammatory activity

Synthesized diastereomeric mixtures and individual diastereomers were studied for their anti-inflammatory activity in the carrageenin model of inflammatory paw edema in white rats (diclofenac sodium was used as a reference drug).[31] The screening results (Table 2) showed that all tested diastereomeric mixtures demonstrate anti-inflammatory activity with the index of inhibition of the inflammatory process at 20-35%. Whereas the same indicator for the individual diastereomers was characterized by values of 30-45%. At the same time, the value of inflammation inhibition index for diclofenac sodium in the experiment condition was 52.5 %. Obtained data suggest that peculiarities of the stereoconfiguration of the derivatives of **2a-e** and **3a-e** do not significantly impact on their anti-inflammatory effect. Although, worth noting, that anti-inflammatory activity of diastereomeric mixtures **2a-2e**/**3a-3e** was lower compared to the activity of the corresponding individual diastereomers. In general, the highest level of activity was observed for diastereomer **2c**, which contains a chlorine atom in the pyridine core and two phenyl substituents in the imidazole ring in the molecule (see **Table 2**).

Comparing the results of the anti-inflammatory activity of the synthesized diastereomers **2a-e**/**3a-e** with similar non-oxidized imidazo[2,1-*b*][1,3]thiazines,[26] for which the index of inhibition of the inflammatory process was 13.9-26.4%, suggests that the presence of a sulfoxide group leads to an increase in anti-exudative activity.

Table 2. *In vivo* anti-inflammatory activity of compounds **2a-e, 3a-e** and their mixtures on carrageenin-induced paw edema in white rats (intraperitoneally use; doses: carrageenin 1%, 0.1 mL; diclofenac sodium – 8 mg/kg, tested compounds – 50 mg/kg; M±m; n=6 in each group)

Compounds/ Reference drug	Rat hind limb volume increase, 4 h, %	Inflammation inhibition index, %
Carrageenin	124.9±9.3	-
Diclofenac sodium	59.3±6.4	52.5
2a/3a	98.5±9.3	17.6
2b/3b	83.4±8.4	35.1
2c/3c	82.6±6.5	35.5
2d/3d	93.6±8.6	24.5
2e/3e	84.2±7.9	34.9
2a	86.2±7.9	31.0
2b	78.2±6.3	37.4
2c	67.3±5.4	46.1
2d	75.7±4.9	39.4
2e	72.8±6.1	41.7
3a	82.8±9.1	33.7
3b	83.4±7.0	33.2
3c	74.4±6.2	40.4
3d	80.4±7.2	35.6
3e	69.6±5.3	44.3

3. Conclusions

In the present paper, the chemoselective approach to the synthesis of [(pyridin-2-yl)oxy]benzo[4,5]imidazo[2,1-*b*][1,3]thiazines sulfoxides is proposed. The method is based on the application of m-chlorobenzoic acid and leads to the obtaining of the diastereomeric mixtures of the appropriate sulfoxides. The synthesized diastereomeric mixtures were divided chromatographically and the structures of the individual diastereomers were characterized by spectral and X-ray analysis. The synthesized derivatives were screened for their anti-inflammatory activity *in vivo* (carrageenin test) and hit-compound was identified as the most potent with a value of inflammation inhibition index of 46.1%. Obtained data contribute to the organic and medicinal chemistry of this type of heterocycles. Thus, this work confirms that heterocycle chemistry is one of the most developing branches of science due to its various applications as reported before[34-45].

4. Experimental

4.1 Chemistry

All the reagents and solvents used in the present work were of the purity grade „chemically pure“. No additional purification of the reactants was applied before the syntheses. All the solvents were cleaned by standard methods before use. Melting points were measured on a Kofler melting point device and are uncorrected. ^{1}H NMR spectra were acquired in pulsed Fourier transform mode on a Varian VXR-400 spectrometer (400 MHz), while ^{13}C NMR spectra were acquired on a Bruker Avance DRX-500 spectrometer (126 MHz), using DMSO-d_6 as a solvent, reference: δ (TMS) = 0 ppm. Mass spectra were recorded on an Agilent LC/MSD SL chromatograph equipped with Zorbax SB-C_{18} column (4.6x15mm), particle size 1.8 μm (PN 82(c)75-932), solvent DMSO, electrospray ionization at atmospheric pressure. Elemental analysis was performed on a PerkinElmer 2400 CHN Analyzer. The individuality of the obtained compounds was monitored by TLC on Silutol UV-254 plates (eluent MeOH-$CHCI_3$, 1:50).

4.1.1 General procedure for the synthesis of sulfoxides pyridinyloxy substituted (benzo)imidazo[2,1-b][1,3]thiazines **2a-e, 3a-e**. *m*-Chloroperbenzoic acid (8.3 mmol of 60% purity) was added to the mixture of appropriate [(pyridine-2-yl)oxy](benzo)imidazo[2,1-b][1,3]thiazine 1a-e (5 mmol) and Na_2HPO_4 (8.3 mmol) in CH_2Cl_2 (25 mL) and stirred at room temperature for 24 h. The organic layer was washed twice with an aqueous solution of Na_2SO_3 and dried with Na_2SO_4. Solvent was evaporated in vacuum, diastereomers were separated by column chromatography (eluent MeOH-$CHCI_3$, 1:50).

4.1.2 (6R, 8S*)-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-6,7-dihydro-5H-imidazo[2,1-b] [1,3]thiazine 8-oxide* (**2a**). White solid, mp 170-171°C (chloroform); yield 34%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.41-3.47 (m, 1H), 3.86-3.90 (m, 1H), 4.26-4.32 (m, 1H), 4.92 (dd, ^{2}J = 12.0, ^{3}J = 8.0 Hz, 1H), 6.48-6.54 (m, 1H), 7.13 (s, 1H), 7.37 (s, 1H), 7.95 (s, 1H), 8.39 (s, 1H). ^{13}C, NMR (125 MHz, $CDCl_3$): δ = 48.8, 50.2, 65.0, 119.6, 122.1, 122.9 (q, $^2J_{C,F}$ = 33.75 Hz), 123.0 (q, $^1J_{C,F}$ = 270.75 Hz), 130.8, 136.7 (q, $^4J_{C,F}$ = 3.0 Hz), 142.1, 142.5 (q, $^3J_{C,F}$ = 4.25 Hz), 159.0. MS: m/z 352 (M + H). Anal. Calcd. for $C_{12}H_9ClF_3N_3O_2S$ (%): C, 40.98; H, 2.58; N, 11.95. Found: C, 41.15; H, 2.56; N, 12.08.

4.1.3 (6R,8S*)- 2,3-Diphenyl-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-6,7-dihydro-5H-imidazo[2,1-b] [1,3]thiazine 8-oxide* (**2b**). White solid, mp 192-193°C (chloroform); yield 26%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.49-3.55 (m, 1H), 3.80-3.84 (m, 1H), 4.06 (dd, ^{2}J = 16.0, ^{3}J = 8.0 Hz, 1H), 4.50 (dd, ^{2}J = 12.0, ^{3}J = 4.0 Hz, 1H), 6.41-6.48 (m, 1H), 6.83 (d, ^{3}J = 8.0 Hz, 1H), 7.24-7.25 (m, 3H), 7.34-7.36 (m, 2H), 7.48-7.54 (m, 5H), 7.84 (d, ^{3}J = 8.0 Hz, 1H), 8.41 (s, 1H). ^{13}C, NMR (125 MHz, $CDCl_3$): δ = 46.7, 49.6, 63.6, 110.9, 120.9 (q, $^2J_{C,F}$ = 33.75 Hz), 123.1 (q, $^1J_{C,F}$ = 270.0 Hz), 126.5, 126.8, 127.8, 128.1, 128.9, 129.1, 129.9, 131.0, 132.5, 136.0 (d, $^4J_{C,F}$ = 2.5 Hz), 140.2, 141.4, 144.4 (q, $^3J_{C,F}$ = 5.0 Hz), 163.9. MS: m/z 470 (M + H). Anal. Calcd. for $C_{24}H_{18}F_3N_3O_2S$ (%): C, 61.40; H, 3.86; N, 8.95. Found: C, 61.59; H, 3.88; N, 8.87.

4.1.4(6R,8S*)-[(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)oxy]-2,3-diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine 8-oxide* (**2c**). White solid, mp 228-229°C (chloroform); yield 28%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.41 (dd, ^{2}J = 14.0, ^{3}J = 10.0, Hz, 1H), 3.93 (dd, ^{2}J = 12.0, ^{3}J = 4.0, Hz, 1H), 4.09 (dd, ^{2}J = 12.0, ^{3}J = 8.0, Hz, 1H), 4.56 (dd, ^{2}J = 14.0, ^{3}J = 6.0 Hz, 1H), 6.46-6.52 (m, 1H), 7.21-7.25 (m, 3H), 7.37-7.39 (m, 2H), 7.49-7.52 (m, 5H), 7.91 (m, 1H), 8.32 (s, 1H). ^{13}C, NMR (125 MHz, DMSO-d_6): δ = 47.1, 48.8, 65.9, 118.6, 121.2 (q, $^2J_{C,F}$ = 33.75 Hz), 123.5 (q, $^1J_{C,F}$ = 271.25 Hz), 126.8, 127.6, 128.8, 128.9, 129.8, 130.0, 130.9, 131.4, 133.7, 137.8 (d, $^4J_{C,F}$ = 2.5 Hz), 139.4, 142.9, 143.3 (q, $^3J_{C,F}$ = 5.0 Hz), 159.7. MS: m/z 504 (M + H). Anal. Calcd. for $C_{24}H_{17}ClF_3N_3O_2S$ (%): C, 57.20; H, 3.40; N, 8.34. Found: C, 57.02; H, 3.43; N, 8.41.

4.1.5 (1S,3R*)-{[5-(Trifluoromethyl)pyridin-2-yl]oxy}-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine 1-oxide* (**2d**). White solid, mp 222-223°C (chloroform); yield 25%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.66 (dd, ^{2}J = 12.0, ^{3}J = 8.0 Hz, 1H), 3.93-3.97 (m, 1H), 4.42 (dd, ^{2}J = 12.0, ^{3}J = 8.0 Hz, 1H), 5.00 (dd, ^{2}J = 12.0, ^{3}J = 4.0 Hz, 1H), 6.59-6.65 (m, 1H), 7.28 (s, 1H), 7.42-7.50 (m, 3H), 7.93-7.96 (m, 2H), 8.41 (s, 1H). ^{13}C, NMR (150 MHz, DMSO-d_6): δ = 46.1, 48.7, 65.6, 111.6, 118.2, 120.3, 120.9 (q, $^2J_{C,F}$ = 33.15 Hz), 123.1 (q, ^{1}J = 270.6 Hz), 123.7, 124.8, 134.5, 136.7 (d, $^4J_{C,F}$ = 3.6 Hz), 142.2, 143.0 (q, $^3J_{C,F}$ = 4.2 Hz), 148.9, 159.2. MS: m/z 368 (M + H). Anal. Calcd. for $C_{16}H_{12}F_3N_3O_2S$ (%): C, 52.31; H, 3.29; N, 11.44. Found: C, 52.50; H, 3.25; N, 11.56.

4.1.6 (1S,3R*)-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-3,4-dihydro-2H-benzo[4,5]-imidazo[2,1-b][1,3]thiazine 1-oxide* (**2e**). White solid, mp 217-219°C (chloroform); yield 35%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.67 (dd, ^{2}J = 14.0, ^{3}J = 10.0 Hz, 1H), 3.90-3.93 (m, 1H), 4.41 (dd, ^{2}J = 12.0, ^{3}J = 8.0 Hz, 1H), 4.97 (dd, ^{2}J = 12.0, ^{3}J = 4.0 Hz, 1H), 6.56-6.61 (m, 1H), 7.39-7.47 (m, 3H), 7.91-7.95 (m, 2H), 8.41 (s, 1H). ^{13}C, NMR (125 MHz, DMSO-d_6): δ = 46.1, 48.7, 65.6, 111.6, 118.2, 120.4, 120.9 (q, $^2J_{C,F}$ = 32.5 Hz), 123.1 (q, $^1J_{C,F}$ = 271.25 Hz), 123.7, 124.9, 134.5, 136.8 (d, $^4J_{C,F}$ = 2.5 Hz), 142.2, 143.0 (d, $^3J_{C,F}$ = 5.0 Hz), 148.9, 159.6. MS: m/z 402 (M + H). Anal. Calcd. for $C_{16}H_{11}ClF_3N_3O_2S$ (%): C, 47.83; H, 2.76; N, 10.46. Found: C, 47.65; H, 2.72; N, 10.57.

4.1.7 (6S, 8S*)-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-6,7-dihydro-5H-imidazo[2,1-b][1,3] thiazine 8-oxide* (**3a**). White solid, mp 152-153°C (chloroform); yield 21%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.96-4.06 (m, 2H), 4.49-4.54 (m, 1H), 4.72-4.77 (m, 1H), 6.10-6.15 (m, 1H), 7.09 (s, 1H), 7.25 (s, 1H), 7.93 (s, 1H), 8.37 (s, 1H). ^{13}C, NMR (125 MHz,

$CDCl_3$): δ = 48.6, 54.3, 67.5, 118.8, 121.4, 122.2 (q, $^2J_{C,F}$ = 33.75 Hz), 122.3 (q, $^1J_{C,F}$ = 271.25 Hz), 130.1, 136.0 (d, $^3J_{C,F}$ = 6.25 Hz), 141.4, 141.8 (q, $^4J_{C,F}$ = 3.75 Hz), 158.3. MS: m/z 352 (M + H). Anal. Calcd. for $C_{12}H_9ClF_3N_3O_2S$ (%): C, 40.98; H, 2.58; N, 11.95. Found: C, 41.20; H, 2.60; N, 11.85.

4.1.8 (6S, 8S*)-2,3-Diphenyl-6-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-6,7-dihydro-5H-imidazo[2,1-b] [1,3]thiazine 8-oxide* (**3b**). White solid, mp 129-130°C (chloroform); yield 34%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.98-4.06 (m, 2H), 4.21 (dd, ^2J = 14.0, ^3J = 6.0, Hz, 1H), 4.34 (dd, ^2J = 12.0, ^3J = 4.0 Hz, 1H), 6.07-6.12 (m, 1H), 6.89 (d, ^3J = 8.0 Hz, 1H), 7.22-7.23 (m, 3H), 7.33 (d, ^3J = 8.0 Hz, 2H), 7.46-7.54 (m, 5H), 7.84-7.87 (m, 1H), 8.40 (s, 1H). ^{13}C, NMR (125 MHz, $CDCl_3$): δ = 47.0, 54.5, 66.3, 111.4, 121.4 (q, $^2J_{C,F}$ = 32.5 Hz), 123.9 (q, $^1J_{C,F}$ = 270.0 Hz), 126.7, 127.1, 127.8, 128.0, 129.0, 129.4, 130.0, 130.1, 132.1, 136.3 (d, $^4J_{C,F}$ = 3.75 Hz), 139.3, 140.8, 144.2 (q, $^3J_{C,F}$ = 3.75 Hz), 162.5. MS: m/z 470 (M + H). Anal. Calcd. for $C_{24}H_{18}F_3N_3O_2S$ (%):C, 61.40; H, 3.86; N, 8.95. Found: C, 61.63; H, 3.83; N, 8.88.

4.1.9 (6S, 8S*)-[(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)oxy]-2,3-diphenyl-6,7-dihydro-5H-imidazo [2,1-b] [1,3]thiazine 8-oxide* (**3c**). White solid, mp 235-236°C (chloroform); yield 23%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.80-3.85 (m, 2H), 4.25 (dd, ^2J = 12.0, ^3J = 4.0 Hz, 1H), 4.49 (dd, ^2J = 12.0, ^3J = 8.0 Hz, 1H), 5.80-5.86 (m, 1H), 7.21-7.26 (m, 3H), 7.39-7.41 (m, 2H), 7.52-7.55 (m, 5H), 7.90 (m, 1H), 8.30 (s, 1H). ^{13}C, NMR (150 MHz, DMSO-d_6): δ = 46.8, 48.4, 66.9, 118.8, 120.7 (q, $^2J_{C,F}$ = 33.0 Hz), 123.6 (q, $^1J_{C,F}$ = 271.5 Hz), 126.7, 127.5, 128.8, 129.3, 130.0, 130.1, 130.9, 131.0, 133.9, 136.7 (d, $^4J_{C,F}$ = 3.0 Hz), 138.8, 142.9, 143.1 (q, $^3J_{C,F}$ = 6.0 Hz), 160.2. MS: m/z 504 (M + H). Anal. Calcd. for $C_{24}H_{17}ClF_3N_3O_2S$ (%): C, 57.20; H, 3.40; N, 8.34. Found: C, 57.39; H, 3.45; N, 8.27.

4.1.10 (1S,3S*)-{[5-(Trifluoromethyl)pyridin-2-yl]oxy}-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine 1-oxide* (**3d**). White solid, mp 231-232°C (chloroform); yield 29%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.83-3.87 (m, 1H), 3.96 (dd, ^2J = 13.6, ^3J = 7.6 Hz, 1H), 4.66-4.71 (m, 1H), 4.76 (dd, ^2J = 12.6, ^3J = 6.6 Hz, 1H), 5.99-6.05 (m, 1H), 7.39-7.47 (m, 4H), 7.92-7.96 (m, 2H), 8.36 (s, 1H). ^{13}C, NMR (400 MHz, $CDCl_3$): δ = 46.4, 48.9, 65.9, 111.8, 118.4, 120.6, 121.1 (q, $^2J_{C,F}$ = 33.15 Hz), 123.3 (q, $^1J_{C,F}$ = 270.6 Hz), 123.9, 125.1, 134.7, 137.0 (d, $^4J_{C,F}$ = 3.6 Hz), 142.5, 143.3 (q, $^3J_{C,F}$ = 4.2 Hz), 149.1, 159.5. MS: m/z 368 (M + H). Anal. Calcd. for $C_{16}H_{12}F_3N_3O_2S$ (%): C, 52.31; H, 3.29; N, 11.44. Found: C, 52.48; H, 3.31; N, 11.36.

4.1.11 (1S,3S*)-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine 1-oxide* (**3e**). White solid, mp 234-235°C (chloroform); yield 19%. ^{1}H, NMR (400 MHz, $CDCl_3$): δ 3.85-3.90 (m, 1H), 3.98 (dd, ^2J = 12.0, ^3J = 8.0 Hz, 1H), 4.70 (dd, ^2J = 12.0, ^3J = 4.0 Hz, 1H), 4.78 (dd, ^2J = 14.0, ^3J = 6.0 Hz, 1H), 6.01-6.07 (m, 1H), 7.42-7.48 (m, 3H), 7.94-7.97 (m, 2H), 8.38 (s, 1H). ^{13}C, NMR (150 MHz, DMSO-d_6): δ = 46.8, 47.5, 66.6, 111.9, 118.9, 120.7, 120.8 (q, $^2J_{C,F}$ = 33.0 Hz), 123.6 (q, ^1J = 270.0 Hz), 123.9, 125.0, 134.8, 136.8 (d, $^4J_{C,F}$ = 3.0 Hz), 142.4, 143.2 (d, $^3J_{C,F}$ = 4.5 Hz), 149.2, 160.2. MS: m/z 402 (M + H). Anal. Calcd. for $C_{16}H_{11}ClF_3N_3O_2S$ (%): C, 47.83; H, 2.76; N, 10.46. Found: C, 48.01; H, 2.71; N, 10.35.

4.2. X-Ray crystal structure determination

The colorless crystals of **2b** ($C_{24}H_{18}F_3N_3O_2S$) are orthorhombic. At 293 K **a** = 21.4821(18), **b** = 19.7731(14), c = 5.0929(4) Å, V = 2163.3(3) Å^3, M_r = 469.47, Z = 4, space group $Pna2_1$, d_{calc}= 1.441 g/cm^3, μ(MoK$_\alpha$) = 0.203 mm^{-1}, F(000) =968. Intensities of 18341 reflections (3807 independent, R_{int}=0.109) were measured on the « Bruker APEX-II CCD» diffractometer (graphite monochromated MoK$_\alpha$ radiation, CCD detector, phi- and ω-scaning, $2\Theta_{max}$ = 50°).

The structure was solved by the direct method using SHELXTL package.[32, 33] Positions of the hydrogen atoms were located from electron density difference maps and refined by the "riding" model with U_{iso} = 1.2U_{eq} of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 3807 reflections was converged to wR_2 = 0.165 (R_1 = 0.091 for 2058 reflections with F>4σ(F), S = 1.110).
The final atomic coordinates and crystallographic data for molecule 2b have been deposited to with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 2214033).

4.3 In vivo anti-inflammatory screening

The male albino rats weighing 180-220 g were used for the anti-exudative activity study. The animals were treated humanely throughout the study period adhering to the guideline for the use and care of animals in the declaration of Helsinki (National Research Council, 2011). The experiment design and study protocol were approved by the Animal Ethics Committee of the Danylo Halytsky Lviv National Medical University, protocol No.10, March 17, 2021. The carrageenin-induced hind paw edema was produced by the method of Winter et al.[31] The compounds synthesized were intraperitoneally injected in a dose of 50 mg/kg (in saline solution with one drop of Tween-80™). Diclofenac (tablets "Diclofenac sodium", "Zdorovja narodu", Ukraine) in dose 8 mg/kg was used as a reference drug. The antiexudative activity (inflammation inhibition) was expressed as a decrease in rats paw edema, was calculated using the equation, and was given in percentage:

$$Inhibition\ index,\% = (\Delta Vcontrol - \Delta Vexperiment)/\Delta Vcontrol * 100\%$$

where, ΔVcontrol and ΔVexperiment – the mean values of the volume difference for control and experimental animals hinds respectively.

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