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Graphical Abstracts

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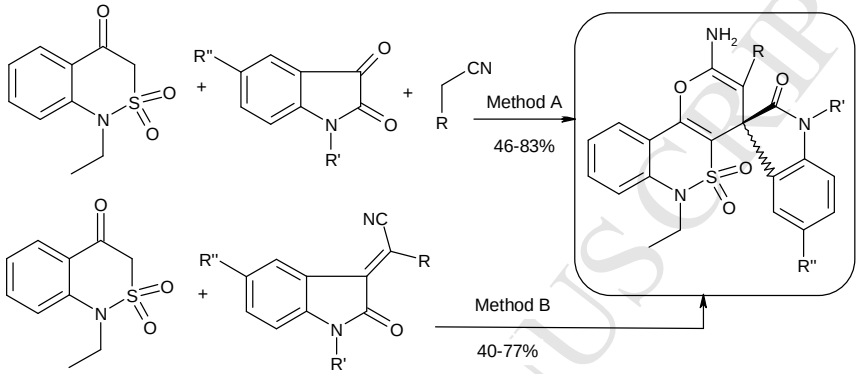

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AN EFFICIENT, THREE-COMPONENT SYNTHESIS AND MOLECULAR STRUCTURE OF DERIVATIVES OF 2-AMINO-3-R-6-ETHYL-4,6-DIHYDROPYRANO[3,2-C][2,1]BENZOTHIAZINE-5,5-DIOXIDE SPIROCOMBINED WITH A 2-OXINDOLE NUCLEUS

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Abstract — Spiro[(2-amino-3-R-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-5,5-dioxide)-4,3'-(1'-R'-5'-R"-indolin-2'-one)] compounds were synthesized based on the three-component interaction of benzo[c][2,1]thiazin-4-on 2,2-dioxide with corresponding isatins and appropriate methylene active nitriles in the presence of a base as a catalyst. The molecular structures of the target compounds were proved uniquely by the X-ray diffraction analysis method.

Keywords: benzo[c][2,1]thiazine, 2-oxindoles, methylene active nitriles, spirocyclic compounds, 4,6-dihydropyrano[3,2-c][2,1]benzothiazine-5,5-dioxide, X-ray diffraction analysis.

1. Introduction

Currently, synthetic organic chemistry provides medicine with new and effective heterocyclic compounds for treating a variety of diseases. In this regard, derivatives of benzothiazinone S,S-dioxide occupy a special place, since they are very perspective compounds to create new drugs. This is associated with their fairly wide range of biological activities. Sedative, anticonvulsant, hypnotic, hypoglycemic, muscle relaxant, anti-arrhythmic hypotensive and other activities are the most typical for them.[1,2]

Among ten possible structural isomers of benzothiazinone S,S-dioxide,[3,4] benzo[c][2,1]thiazin-4-on 2,2-dioxide attracted our attention, due to insufficient studies of the biological activity spectra for different derivatives of this benzothiazinone and insufficient studies of its chemical properties.

Derivatives of 3,4-dihydro-2,1-benzothiazine-2,2-dioxide are characterized by such biological activities as IL-8 receptor antagonism,[5] selective inhibition of focal adhesion kinase,[6] antiviral (reverse transcriptase inhibitory activities),[7] anticancer[8] and antibacterial activities.[9]

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Also, they demonstrate potent biological activities such as lipoxygenase inhibition and are applied as agents for heart diseases.[10] On the other hand, being structural isomers, the benzo[c][2,1]thiazine-4(3*H*)-on 2,2-dioxide core is bioisosteric to the benzo[e][1,2]thiazine one. It serves as a base for such drugs as piroxicam®, droxicam® and meloxicam® (Fig. 1), which one to efficient analgesic and anti-inflammatory agents.[11] Some of these compounds showed anti-bacterial activity.[12]

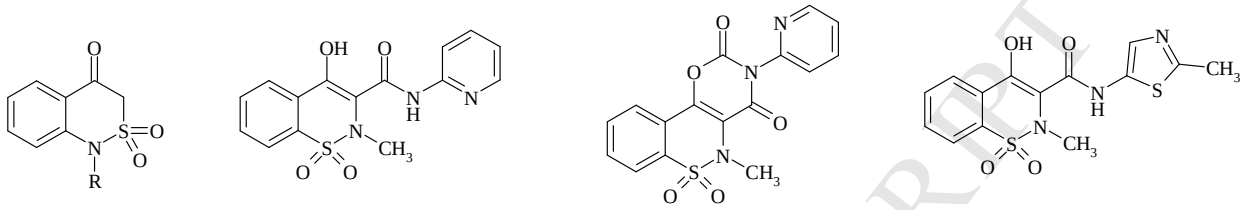


Figure 1. Initial benzo[c][2,1]thiazin-4-on 2,2-dioxide and bioisosteric biologically active benzothiazine derivatives

Benzo[c][2,1]thiazine-4(3*H*)-on 2,2-dioxide represents the methylene active CH-acid. Its structure is an analogue of a cyclic methyleneactive 1,3-dicarbonyl compound, which makes it a very convenient and promising intermediate for building new heterocyclic systems based on it. Although this compound, unlike its carbonyl analogue, exists entirely in the 4-oxo form,[13,14] it exhibits a number of specific properties that are not characteristic for carbonyl compounds. In particular, it is not reduced in 4-hydroxy derivatives by the direct route and does not form enamines with secondary amines. The carbonyl group of the given heterocycle is distinguished by a high propensity for enolization in when of introducing alkyl or acyl groups into position 3.[15,16] This property opens up great opportunities for the synthesis of condensed heterocyclic systems using CH_2CO-group in this compound in particular using multi-component reactions.

Multicomponent reactions of enol-nucloephilic compounds, carbonyl compounds and the appropriate active nitriles have recently attracted the interest of the synthetic community, because the formation of diverse condensation products can be expected depending on the specific conditions and structure of the building blocks. This interaction is the direct route for construction of the 2-amino-4*H*-pyrane core.[17] The mechanism of this coupling is based on a domino Knoevenagel/Michael cyclization sequence between carbonyl compounds, appropriate nitriles and carbonyl CH-acids.[18] There are no data about these interactions for benzo[c][2,1]thiazine-4(3H)-on 2,2-dioxide. No information is available about the synthesis of the condensed heterocyclic systems including benzo[c][2,1]thiazine-4(3*H*)-on 2,2-dioxide and the 4*H*-pyranic ring as well.

Using isatins in this reaction as the carbonyl component allows construction of the spiro[4*H*-pyran-oxindole] core[19] in a one-pot synthesis. For example, a three-component reaction

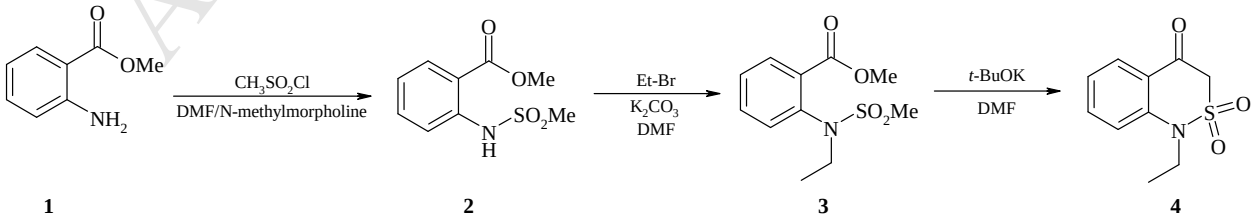
of isatins, ethylcyanoacetate or malononitrile, and 3-methylpyrazol-5-one in the presence of base catalysts[20] or under ultrasound irradiation,[21] or in the presence of $NaHCO_3$ under grinding,[22] leads to the spiro[pyrano[2,3-*c*]pyrazolo-2-oxindoles] with good yields. The same principle was used by us in the preparation and study of the previously reported 4-hydroxy-2-quinolones annelated by a spiro[indole-3,4'-pyran] ring.[23]

In this aspect, N-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-on-2,2-dioxide is new synthon for the one-step three-component synthesis of condensed system of 2-amino-6-ethyl-3-R-4-R'-4-R"-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide.

This article is devoted to a new spirocyclic system of spiro[(2-amino-3-R-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-5,5-dioxide)-4,3'-(2'-oxindole)]. Experiments carried out by us have shown that exchange of the 4-hydroxycoumarin or 4-hydroxy-2-oxo-1,2-dihydroquinoline for heteroanalog, in particular, N-ethyl-1*H*-2,1-benzothiazin-4(3H)-on-2,2-dioxide **4**, does not have any kind of effect on the course of the reaction and thus, it gives spiro[(2-amino-3-R-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-5,5-dioxide)-4,3'-(2'-oxindole)] **10-11**.

2. Results and discussion

The synthesis of the initial N-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-on-2,2-dioxide **4** was described in the literature,[24] and included esters of anthranilic acids **1** as initial compounds (Scheme 1). Different authors used different conditions for the synthesis of compound **2**, such as THF(dioxane)-triethylamine, methylenechloride/pyridine, pyridine, etc. We found that using the DMF/N-methylmorpholine system in this reaction allows pure compound **2** to be obtained with excellent yields in a short time. Moreover, all authors[21,24] used only NaH in DMF for heterocyclization of alkylated compound **3**. We also found that replacement of NaH with *t*BuOK increases the yield of compound **4**, obtaining it in analytically pure form, which did not need further purification.



1 **2** **3** **4**

Scheme 1. Synthesis of N-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-on-2,2-dioxide **4**

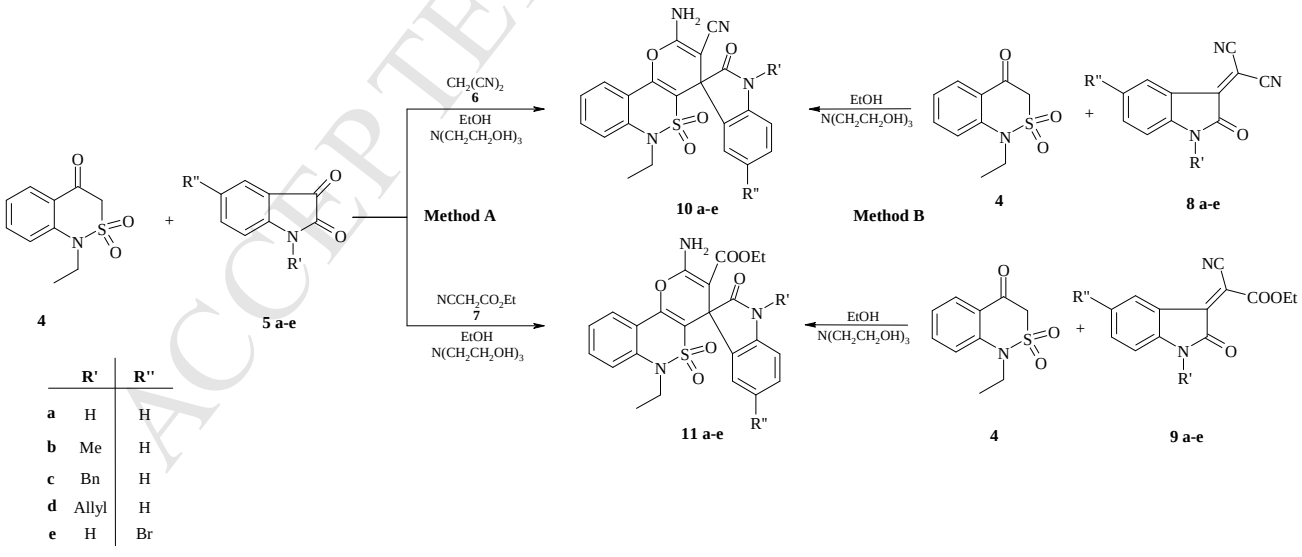
The synthesis of target compounds **10a-e** and **11a-e** was carried out according to transformations presented on Scheme 2.

A three-component one-pot reaction of equimolar quantities of benzothiazinone **4**, malonodinitrile and the appropriate isatins **5a-e** in the presence of triethanolamine under reflux for 30 min in ethanol, gave to derivatives of 2-amino-3-R-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-5,5-dioxide **10a-e** spiricombined with a 2-oxindole core with the yields of 64-83% (Scheme 2, Table 1).

Using ethylcyanoacetate in the three-component condensation as the methyleneactive nitrile increases the time of interaction to about 2 h. The yields of target compounds **11a-e** were 46-63% (Scheme 2, Table 1).

It was possible to carry out a two-step synthesis of target compounds **10a-e** and **11a-e** using the corresponding Knoevenagel condensation products, namely 2-oxoindolinilidenes **8a-e** and **9a-e**, in accordance with the mechanism of the reaction. Synthesis of compounds **8a-e** and **9a-e** was carried out pursuant to a procedure presented in our previous work.[20] Interaction of benzothiazinone **4** with 3-cyanomethylidene-2-oxindoles **8a-e** and **9a-e** proceeded by reflux in ethanol in the presence of a base. In the case of compounds **8a-e**, heating continued for 1 h; as a result, compounds **10a-e** were formed with the yields of 53-77%. For 2-oxoindolinilidenes **9a-e**, the duration of heating was 3-4 h, and the yields of target compounds were 40-52% (Scheme 2, Table 1).

Compounds **10 a-e** and **11 a-e** were obtained in the form of stable, refractory, fine colourless powders, which, if necessary, were recrystallized from a ethanol/DMF mixture (1:1).



Scheme 2.

Table 1. Yields for the compounds **10a-e** and **11a-e** synthesized by two methods

Compound	R'	R''	Yield, %

			Method A	Method B
10a	H	H	83	77
10b	Me	H	70	61
10c	Bn	H	65	53
10d	Allyl	H	81	73
10e	H	Br	64	56
11a	H	H	63	52
11b	Me	H	55	49
11c	Bn	H	58	41
11d	Allyl	H	57	52
11e	H	Br	46	40

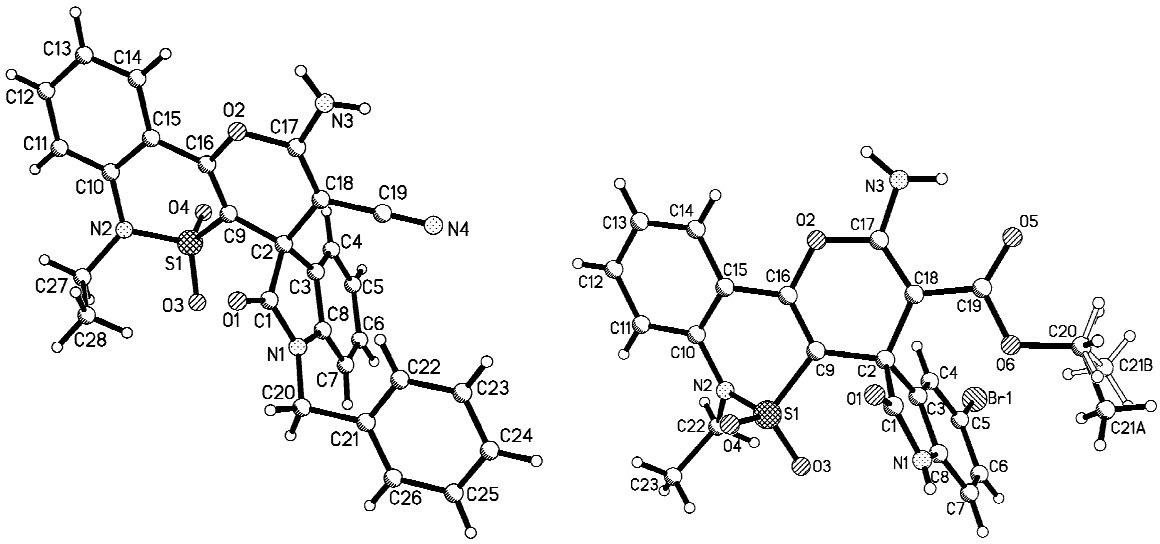
Using cyanoacetamide **8** as methyleneactive nitrile in the three-component reaction, we did not obtain the expected 3-carbamide derivatives. In the case of N-methylisatin **5b**, 3-ethoxycarbonyl derivative **11b** was a product of the reaction, which can be explained by alcoholysis of the amide group.

The infrared spectrum of the compounds features absorption bands of valence and deformation oscillations of amino, cyano groups for **10a-e** or amino, carbethoxy groups for **11a-e**.

The ^{1}H NMR spectra of **10a-e** and **11a-e** compounds feature a characteristic set of signals: an extended high-intensity singlet of the α-amino group of the pyran ring at 7.6-7.7 ppm for 3-cyano derivatives **10a-e** and at 7.8-8.1 ppm for 3-ethoxycarbonyl derivatives **11a-e**. The corresponding non-alkylated compounds **10-11a,e,** (R' = H) also feature a proton singlet from the NH group of the 2-oxindole ring in a higher field at 10.45-10.85 ppm. A triplet can be observed in all of the compounds at 0.9-1.1 ppm and at 0.6-0.7 ppm for **11c** corresponding to the methyl group of the N-ethyl function. Protons from the NH group of the 2-oxindole rings as well as of the α-amino group of the pyran ring can be easily exchanged in the presence of D_2O in DMSO-D_6 solution.

The ^{13}C NMR spectra also confirmed the structures of the synthesized compounds. Furthermore, full assignment of the ^{13}C NMR data confirmed structures **10,11a-e**, where the key signals at δ175─178 ppm was assigned to the 2-oxindolic carbonyl group; at δ57 ppm for **10a-e** and at δ59 ppm for **11a-e** was assigned to the quaternary sp^3 carbon.[20,25] The signal at δ118 ppm was assigned to the nitrile carbon in the pyran ring for compounds **10a-e** and the signal at δ167 ppm was assigned to the carbonyl carbon of the ester group for compounds **11a-e**. Full spectral data for all new compounds are presented in Section 4.

The structures of the compounds **10c** and **11e** have been confirmed by X-ray diffraction study (Fig. 2)



10d **11f**

Figure 2. Molecular structure of the compounds **10c** and **11e** according to the X-ray diffraction study.

The molecules **10c** and **11e** differ from each other by substituents at the C18, C5 and N1 atoms and details of molecular and crystal structures as consequence. The benzothiazine ring adopts a twist-boat conformation in both molecules (the puckering parameters[26] are S = 0.64, Θ = 51.8°, Ψ = 27.2° for **10c** and S = 0.66, Θ = 50.9°, Ψ = 21.3° for **11e**). However, the S1 and C9 atoms deviate from the mean plane of the remaining atoms of the ring in opposite directions with respect to the indolone fragment. In the case of molecule **10c** both atoms are shifted toward the benzene ring of indolone (deviations are -0.89 Å and -0.30 Å for the S1 and C9 atoms, respectively) while both atoms in molecule **11e** deviate in the opposite direction by 0.90 Å and 0.26 Å, respectively. Such a difference in conformation of the benzothiazine ring results in appearance of steric repulsion between atoms of the sulfonyl group and bicyclic fragment in the molecule **10c** in contrast to the molecule **11e** (the shortened intramolecular contacts O3…C3 2.96 and S1…C4 3.44 Å as compared with van der Waals radii sum[27] 3.00 Å and 3.55 Å, respectively). This leads to slightly non-planar conformation of the five-membered heterocycle of bicyclic fragment in **10c** (deviation of the C1 atom from the mean plane of the remaining atoms of the ring is 0.11 Å), some bending of the bicyclic fragment (the angle between the -N-C(=O)-C- planar fragment and aromatic ring is 11.6°) and deviation from the orthogonal orientation of the spiro-joined fragments to each other (the angle between mean planes of the dihydroindolone fragment and pyran ring is 84.1°). In contrast to **10c**, the bicyclic fragment in **11e** is planar within 0.03 Å, and the angle between the bicyclic fragment and planar within 0.01

Å pyran ring is 92.0°. It can be noted that the pyran ring in **10c** is slightly non-planar and adopts a flattened boat conformation (the puckering parameters are S = 0.25, Θ = 69.6°, Ψ = 0.0°) with the deviations of the O2 and C2 atoms by 0.10 Å and 0.22 Å, respectively.

3. Conclusion

In conclusion, we have demonstrated that the original spiro-joined heterocyclic system containing the spiro[(4,6-dihydropyrano[3,2-c][2,1]benzothiazine-5,5-dioxide)-4,3'-(indolin-2'-one)] core **10-11** was synthesized based on the domino Knoevenagel/Michael cyclization sequence between benzo[c][2,1]thiazin-4-on-2,2-dioxide with corresponding isatins and appropriate methylene active nitriles in the presence of an organic base as a catalyst. Experiments carried out by us have shown that N-ethyl-1*H*-2,1-benzothiazin-4(3H)-on-2,2-dioxide **4** is a proper analogue of cyclic methyleneactive 1,3-dicarbonyl compounds in this reaction. The isolated yields in this one-pot protocol were moderate to high (46–83%) and provided the desired target compounds with a high purity after a simple filtration or recrystallization from an ethanol/DMF mixture (1:1).

4. Experimental section

4.1. General

Starting isatins and methylenactive nitriles were obtained from commercial sources and used without further purification. Dry solvents were prepared in accordance with standard methods. Melting points were obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. ^{1}H NMR spectra were recorded on a Varian WXR-400 (200 MHz) spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts in parts per million). ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz, the references at the signal of the solvent 39.5 ppm for DMSO-d_6. IR spectra were taken on a Perkin–Elmer 298 spectrophotometer in KBr pellets. Elemental analyses were carried out using Carlo Erba CHNS-O EA 1108 analyzer. Mass spectra were taken on a Varian 1200L DIP (EI, 70 eV).

4.2. X-ray diffraction study

The crystals of **10c** ($C_{28}H_{22}N_4O_4S$) are monoclinic. At 100 K a = 13.9801(5), b = 18.7160(7), c = 9.4293(3) Å, β = 99.037(4)°, V = 2436.6(2) Å^3, Mr = 510.56, Z = 4, space group $P2_1/c$, d_{calc}= 1.392 g/cm^3, μ(MoKα) = 0.177 mm^{-1}, F(000) = 1,064. Intensities of 24,624 reflections (7,111 independent, R_{int} = 0.052) were measured on the Xcalibur-3 diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 60°).

The crystals of **11e** ($C_{23}H_{20}N_3O_6BrS$) are triclinic. At 293 K a = 9.7567(5), b = 11.2376(5), c = 12.0580(6) Å, α = 99.984(4)°, β = 94.389(4)°, γ = 112.110(4)°, V = 1191.6(1) Å^3, Mr =

546.39, Z = 2, space group P1, d_{calc}= 1.523 g/cm^3, μ(MoKα) = 1.857 mm^{-1}, F(000) = 556. Intensities of 11080 reflections (6931 independent, R_{int} = 0.022) were measured on the«Xcalibur-3» diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 60°).

The structures were solved by the direct method using the SHELXTL package.[28] The restrictions on the bond lengths in the disordered fragments for the **11e** were applied (Csp^3-Csp^3 1.54 Å). The absorption correction was performed using the multi-scan method (T_{min} = 0.708, T_{max} = 0.913). Position of the hydrogen atoms were located from electron density difference maps and refined by "riding" model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl and hydroxyl groups and for water molecule and n = 1.2 for other hydrogen atoms) in the case of the structure **11e**. The hydrogen atoms of the molecule **10c** and the hydrogen atoms of **11e** taking part in the formation of the hydrogen bonds are refined in isotropic approximation. Full-matrix least-squares refinement of the structures against F^2 in anisotropic approximation for non-hydrogen atoms using 7090 (**10c**), 6877 (**11e**) reflections was converged to: wR_2 = 0.111 (R_1 = 0.049 for 5188 reflections with F>4σ(F), S = 1.038) for structure **10c** and wR_2 = 0.197 (R_1 = 0.070 for 4381 reflections with F>4σ(F), S = 1.051) for structure **11e**. The final atomic coordinates, and crystallographic data for molecules **10c** and **11e** 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 (1002460 for **10c** and CCDC 1002461 for **11e**).

4.3. Procedure for the synthesis of N-ethyl-benzo[c][2,1]thiazin-4-on 2,2-dioxide. Starting methylanthranilate (13 mL, 0.1 mol) was added to a mixture of DMF (25 mL) and N-methylmorpholine (0.1 mol, 11 mL). After that methansulphonylchloride (0.1 mol, 7.7 mL) was added to the solution dropwise, while cooling the reaction mixture with ice. The resulting suspension was mixed using a magnetical stirrer for 10 min at room temperature, then the temperature was gradually increased to 50-60°C and the suspension was mixed for 1.5 h. Next, was added water (100 mL) to the resulting suspension. The resulting precipitate was filtered off, washed with water and dried in air, giving pure product **2** (m.p. 80-83°C) in a yield of 80-85%. Product **2** (0.1 mol, 22.9 g) was dissolved in DMF (80 mL) and potassium carbonate (0.205 mol, 29 g) was added to this solution. The resulting suspension was stirred for 30 min and ethylbromide (0.128 mol, 9.6 mL) was added dropwise. This mixture was stirred at 80°C for 8-10 h, cooled down and poured on to water. The obtained precipitate was filtered off and dried in air. Recrystallisation from *i*-PrOH gave pure product **3** (m.p. 58-60°C) in a yield of 77-80%. To a magnetically stirred suspension of potassium *tert*-butoxide (90 mmol) in dry DMF (15 mL), a

solution of methyl 2-ethylmethylsulfonylamidobenzoate **3** (60 mmol) in dry DMF (25 mL) was added at room temperature, and then the suspension was stirred for 4 hours at 70°C. When mixing was completed, diluted hydrochloric acid was added to the resulting suspension. The precipitate was filtered off, washed with water and dried. As a result, analytically pure product **4** was obtained (m.p. 84-86°C) in a yield of 85-90%.

4.4. General procedure for the synthesis of spiro[(2-amino-3-R-6-ethyl-4,6-dihydropyrano[3,2-c][2,1]benzothiazine-5,5-dioxide)-4,3'-(1'-R'-5'-R''-indolin-2'-one)] (10a-e, 11a-e).

Method A. Three-component one-pot procedure. To a solution of the respective isatins **5a–e** (0.001 mol) in ethanol (5.0 mL), triethanolamine (0.13 mL, 0.001 mol) and malonodinitrile **6** (0.066 g, 0.001 mol) or cyanoacetic acid ethyl ester **7** (0.11 mL, 0.001 mol) were added. After that the N-ethyl-1*H*-2,1-benzothiazin-4(*3H*)-one-2,2-dioxide **4** (0,23 g, 0.001 mol) was added to the resulting solution. When compound **6** was used, the reaction mixture was heated until the precipitate of compounds **10a–e** was observed (usually about 30 min). When compound **7** was used, the resulting reaction mixture was refluxed for 2 h and cooled down to room temperature. After cooling, the mixture was allowed to form the precipitate of **11a–e**. The resulting precipitates of compounds **10a–e** and **11a-e** were filtered, washed with ethanol and then dried. When necessary, the precipitates were recrystallized from an ethanol and DMF mixture.

Method B. Synthesis using 3-cyanomethyliden-2-oxindoles. A solution of 3-cyanomethyliden-2-oxindoles **8a–e** or **9a–e** (0.001 mol), compound **4** (0.225 g, 0.001 mol), and triethanolamine (0.13 mL, 0.001 mol) was refluxed in ethanol (10.0 mL). When **8a–e** was used, the reaction mixture was refluxed for 1 h and in the case of synthesis with **9a–e** nitriles – for 3-4 h. The resulting precipitates of **10a–e** and **11a-e** were treated as mentioned in *method A.*

The yields for the synthesized compounds **10a–e** and **11a-e** are presented in Table 1.

4.4.1. Spiro[(2-amino-3-cyano-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(indolin-2'-one)] (10a).

Beige powder; mp 232–234°C (decomp.); ν_{max} (KBr) 3583, 3411, 3371, 3324, 3212, 2198, 1721, 1670, 1598, 1469, 1384, 1320 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 10.69 (s, 1H), 7.98 (d, J=7.6 Hz, 1H), 7.79 - 7.56 (m, 4H), 7.47 (t, J=7.3 Hz 1H), 7.35-7.20 (m, 2H), 7.01 (t, J=7.3, 1H), 6.87 (d, J=7.6, 1H), 3.86 (br. q, J=7.2 Hz, 2H), 1.06 (t, J=7.0, 3H);δ ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 176.49, 159.34, 148.00, 142.12, 137.86, 132.75, 131.22, 129.63, 124.57, 124.38, 122.21, 120.57, 117.86, 116.79, 112.02, 109.87, 57.26, 56.06, 48.64, 43.96, 18.58, 13.19; EI-MS (m/z) = 420 ($[M]^+$). Anal. Calcd for $C_{21}H_{16}N_4O_4S$: C, 59.99; H, 3.84; N, 13.33; S, 7.63. Found: C, 60.19; H, 3.79; N, 13.26; S, 7.65.

4.4.2. Spiro[(2-amino-3-cyano-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(1'-methyl-indolin-2'-one)] (10b).

Light gray crystalline powder; mp 224-225^{o}C (decomp.); ν_{max} (KBr) 3397, 3318, 3210, 3129, 2204, 1706, 1673, 1609, 1490, 1470, 1417, 1325, 1169 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.96 (d, J=7.63 Hz, 1H), 7.78-7.54 (m, 4H), 7.53-7.31 (m, 3H), 7.19-7.01 (m, 2H), 3.82 (q, J=7.12 Hz, 2H), 3.20 (s, 3H), 0.99 (t, J=7.02 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 175.39, 159.85, 148.46, 143.95, 138.30, 133.26, 130.89, 130.27, 125.78, 124.86, 123.39, 121.03, 118.25, 117.11, 112.33, 109.30, 57.23, 44.40, 27.19, 13.65; EI-MS (m/z) = 434 ([M]$^{+}$). Anal. Calcd for $C_{22}H_{18}N_4O_4S$: C, 60.82; H, 4.18; N, 12.90; S, 7.38. Found: C, 61.01; H, 4.25; N, 12.81; S, 7.33.

4.4.3. Spiro[(2-amino-3-cyano-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(1'-benzyl-indolin-2'-one)] (10c).

Light brown crystalline powder; mp 230-232^{o}C (decomp.); ν_{max} (KBr) 3595, 3392, 3308, 3197, 2202, 1707, 1667, 1591, 1488, 1466, 1410, 1326 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.99 (d, J=7.63 Hz, 1H), 7.78-7.56 (m, 4H), 7.53-7.18 (m, 8H), 7.06 (t, J=7.5 Hz, 1H), 6.87 (d, J=7.63 Hz, 1H), 4.94 (dd, J=34, 16 Hz, 2H), 3.84 (q, J=7.83 Hz, 2H), 1.00 (t, J=6.87 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 175.76, 160.02, 148.72, 143.16, 138.34, 136.19, 133.33, 130.87, 130.17, 128.86, 127.65, 125.96, 125.11, 123.49, 121.08, 118.28, 117.29, 112.16, 109.94, 57.03, 44.49, 44.07, 13.68; EI-MS (m/z) = 510 ([M]$^{+}$). Anal. Calcd for $C_{28}H_{22}N_4O_4S$: C, 65.87; H, 4.34; N, 10.97; S, 6.28. Found: C, 65.93; H, 4.37; N, 11.01; S, 6.23.

4.4.4. Spiro[(2-amino-3-cyano-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(1'-allyl-indolin-2'-one)] (10d).

Beige crystalline powder; mp>250^{o}C; ν_{max} (KBr) 3534, 3457, 3296, 3131, 2203, 1649, 1610, 1487, 1320, 1175, 1148, 1108 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.97 (d, J=6.71 Hz, 1H), 7.77-7.54 (m, 4H), 7.54-7.27 (m, 3H), 7.07 (t, J=7.50 Hz, 1H), 6.98 (d, J=7.63 Hz, 1H), 5.93-5.75 (m, 1H), 5.34 (d, J=17.09 Hz, 1H), 5.16 (d, J=10.68 Hz, 1H), 4.34 (q, J=14.5, 2H), 3.82 (q, J=7.3 Hz, 2H), 0.99 (t, J=6.87 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 175.23, 159.90, 148.63, 143.06, 138.32, 133.31, 131.86, 130.85, 130.14, 125.87, 124.85, 123.38, 120.99, 118.21, 117.22, 112.17, 109.95, 57.37, 48.70, 44.41, 42.68, 13.67; EI-MS (m/z) = 460 ([M]$^{+}$). Anal. Calcd for $C_{24}H_{20}N_4O_4S$: C, 62.60; H, 4.38; N, 12.17; S, 6.96. Found: C, 62.56; H, 4.42; N, 12.23; S, 6.91.

4.4.5. Spiro[(2-amino-3-cyano-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(5'-bromo-indolin-2'-one)] (10e).

Light gray crystalline powder; mp>250^{o}C; ν_{max} (KBr) 3421, 3285, 3194, 2204, 1740, 1710, 1667, 1591, 1471, 1411, 1328, 1206, 1178 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 10.85

(s, 1H), 7.94 (d, J=7.63 Hz, 1H), 7.79-7.34 (m, 7H), 6.83 (d, J=8.55 Hz, 1H), 3.85 (q, J=7.02 Hz, 2H), 1.00 (t, J=6.80, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 176.61, 159.84, 148.70, 141.91, 138.24, 133.99, 133.28, 128.95, 124.86, 121.03, 118.29, 117.22, 114.22, 112.29, 111.62, 56.97, 44.42, 13.62; EI-MS (m/z) = 499 ($[M]^+$). Anal. Calcd for $C_{21}H_{15}BrN_4O_4S$: C, 50.51; H, 3.03; N, 11.22; S, 6.42. Found: C, 50.47; H, 3.08; N, 11.25; S, 6.46.

4.4.6. Spiro[(2-amino-3-ethoxycarbonyl-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(indolin-2'-one)] (11a).

Green-gray crystalline powder; mp>250^{o}C; ν_{max} (KBr) 3349, 3249, 2987, 1716, 1687, 1646, 1533, 1325, 1278, 1175, 1150, 1104 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 10.45 (br. s., 1H), 8.13-7.93 (m, 3H), 7.67-7.35 (m, 3H), 7.22-7.03 (m, 2H), 6.86 (d, J=7.32, 1H), 6.74 (d, J=7.63 Hz, 1H), 3.89-3.59 (m, 4H), 0.95 (t, J=6.87, 3H), 0.74 (t, J=7.17 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 178.17, 167.38, 159.66, 147.09, 144.10, 138.46, 134.31, 132.81, 128.85, 125.11, 124.68, 121.63, 120.94, 118.66, 115,59, 109.33, 76.22, 59.46, 49.16, 44.59, 13.56; EI-MS (m/z) = 467 ($[M]^+$). Anal. Calcd for $C_{23}H_{21}N_3O_6S$: C, 59.09; H, 4.53; N, 8.99; S, 6.86. Found: C, 59.03; H, 4.48; N, 9.06; S, 6.93.

4.4.7. Spiro[(2-amino-3-ethoxycarbonyl-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(1'-methyl-indolin-2'-one)] (11b).

Light green crystalline powder; mp 230-232^{o}C (decomp.); ν_{max} (KBr) 3325, 2933, 1689, 1608, 1528, 1468, 1322, 1279, 1176, 1102 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.20-7.98 (m, 3H), 7.71-7.49 (m, 2H), 7.43 (t, J=7.50, 1H), 7.26 (t, J=7.70 Hz, 1H), 7.15 (d, J=7.50 Hz, 1H), 7.04-6.87 (m, 2H), 3.90-3.59 (m, 4H), 3.14 (s, 3H), 0.95 (t, J=6.87 Hz, 3H), 0.68 (t, J=7.17 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 176.53, 167.23, 159.75, 147.13, 145.18, 138.43, 133.44, 132.93, 129.13, 125.13, 124.87, 122.44, 120.95, 118.57, 115.40, 108.17, 75.78, 59.39, 44.58, 26.92, 13.60; EI-MS (m/z) = 481 ($[M]^+$). Anal. Calcd for $C_{24}H_{23}N_3O_6S$: C, 59.87; H, 4.81; N, 8.73; S, 6.65. Found: C, 59.82; H, 4.86; N, 8.77; S, 6.53.

4.4.8. Spiro[(2-amino-3-ethoxycarbonyl-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(1'-benzyl-indolin-2'-one)] (11c).

Yellow-green crystalline powder; mp 226-228^{o}C (decomp.); ν_{max} (KBr) 3366, 3258, 1688, 1608, 1529, 1487, 1328, 1283, 1171, 1106 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 7.96-7.67 (m, 3H), 7.40-6.79 (m, 10H), 6.68-6.49 (m, 2H), 4.53 (s, 2H), 3.61-3.30 (m, 4H), 0.65 (t, J=7.02 Hz, 3H), 0.04 (t, J=7.02 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 176.95, 167.18, 159.86, 147.34, 144.84, 138.47, 137.03, 133.66, 132.96, 128.89, 128.70, 127.79, 125.21, 124.77, 124.56, 122.52, 121.02, 118.61, 115.10, 108.83, 75.94, 59.09, 44.69, 13.78, 13.59; EI-MS (m/z) = 557 ($[M]^+$). Anal. Calcd for $C_{30}H_{27}N_3O_6S$: C, 64.62; H, 4.88; N, 7.54; S, 5.75. Found: C, 64.48; H, 4.97; N, 7.42; S, 5.86.

4.4.9. Spiro[(2-amino-3-ethoxycarbonyl-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(1'-allyl-indolin-2'-one)] (11d).

Gray powder; mp 225-226^{o}C (decomp.); ν_{max} (KBr) 3354, 3197, 2976, 1693, 1644, 1613, 1532, 1341, 1282, 1171, 1103 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 8.11 (s, 2H), 8.04 (d, J=7.90, 1H), 7.73-7.50 (m, 2H), 7.43 (t, J=7.30 Hz, 1H), 7.31-7.10 (m, 2H), 7.01-6.82 (m, 2H), 5.99-5.73 (m, 1H), 5.51 (d, J=17.50 Hz, 1H), 5.23 (d, J=10.07 Hz, 1H), 4.52-4.08 (m, 2H), 3.87 - 3.53 (m, 4H), 0.94 (t, J=7.00 Hz, 3H), 0.64 (t, J=7.02 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 176.31, 167.17, 159.79, 147.29, 144.58, 138.45, 133.54, 132.85, 128.93, 125.18, 124.60, 122.41, 120.93, 118.40, 115.20, 108.80, 75.98, 59.24, 48.62, 44.59, 43.33, 14.05, 13.59; EI-MS (m/z) = 507 ([M]$^{+}$). Anal. Calcd for $C_{26}H_{25}N_3O_6S$: C, 61.53; H, 4.96; N, 8.28; S, 6.32. Found: C, 61.65; H, 5.07; N, 8.36; S, 6.15.

4.4.10. Spiro[(2-amino-3-ethoxycarbonyl-6-ethyl-4,6-dihydropyrano[3,2-c][2,1] benzothiazine-5,5-dioxide)-4,3'-(5'-bromo-indolin-2'-one)] (11e).

Light broun crystalline powder; mp>250^{o}C; ν_{max} (KBr) 3322, 2981, 1715, 1698, 1645, 1531, 1473, 1326, 1281, 1171, 1103 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ (ppm) 10.61 (s, 1H), 8.11 (s, 2H), 8.02 (d, J=7.63 Hz, 1H), 7.73-7.51 (m, 2H), 7.43 (t, J=7.20, 1H), 7.37-7.26 (m, 2H), 6.71 (d, J=7.94 Hz, 1H), 3.94-3.65 (m, 4H), 0.96 (t, J=7.02 Hz, 3H), 0.78 (t, J=7.32 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 177.86, 167.18, 159.78, 147.40, 143.50, 138.40, 136.70, 132.94, 131.63, 127.66. 124.91, 124.71, 120.94, 118.61, 114.79, 113.15, 111.27, 75.60, 59.61, 49.28, 44.61, 13.53; EI-MS (m/z) = 546 ([M]$^{+}$). Anal. Calcd for $C_{23}H_{20}BrN_3O_6S$: C, 50.56; H, 3.69; N, 7.69; S, 5.87; Found: C, 50.70; H, 3.54; N, 7.81; S, 5.75.

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References and notes

[1] Franzén, R. G. *J. Comb. Chem.* **2000,** 2**,** 195.

[2] Grover, S.; Alderwick, L. J.; Mishra, A. K.; Krumbach, K.; Marienhagen, J; Eggeling, L; Bhatt, A.; Besra, G. S. *J. Biol Chem.* **2014**, 28, 289(9), 6177.

[3] Garigipati, R. S.; Weinreb, S. M. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; *Pergamon: Oxford*, **1996**; Vol. 6, pp 349–382.

[4] Catsoulacos, P.; Camoutsis, Ch. *J. Heterocyclic Chem.* **1979**, 16, 1503.

[5] Nie, H.; Widdowson, K.L. WO 9834929, 1998; Chem. Abstr. **1998**, 129, 1756451.

[6] Iwatani, M.; Iwata, H.; Okabe, A.; Skene, R. J., Tomita, N., Hayashi, Y., Aramaki, Y.; David J. Hosfield Akira Hori, A.; Baba, A.; Miki, H. *Eur. J. Med. Chem.*. **2013**, *61*, 49-60.

[7] Yoakim, C.; O'Meara, J.; Simoneau, B.; Ogilie, W. W.; Deziel, R. WO 2004026875, 2004; *Chem. Abstr*. **2004**, 140, 303707.

[8] Fairhurst, J.; Gallagher, P. WO 2001087881, 2001; *Chem. Abstr*. **2001**, 136, 6015

[9] Pieroni, M.; Sabatini, S.; Massari S.; Kaatz, G. W.; Cecchetti, V., Tabarrini, O. *Med.Chem.Commun.*, **2012**, 3, 1092.

[10] Misu Y.; Togo H. *Org. Biomol. Chem.* **2003**, 1**,** 1342-1346.

[11] Lazer, E. S.; Miao, C. K.; Cywin, C. L.; Sorcek, R.; Wong, H.-C.; Meng, Z.; Potocki, I.; Hoermann, M. A.; Snow, R. J.; Tschantz, M. A.; Kelly, T. A.; McNeil, D. W.; Coutts, S. J.; Churchill, L.; Graham, A. G.; David, E.; Grob, P. M.; Engel,W.; Meier, H.; Trummlitz, G. *J. Med. Chem.* **1997**, 40, 980.

[12] Shafiq, M.; Zia-Ur-Rehman, M.; Khan, I.U.; Arshad, M.N.; Khan, S.A. *J. Chil. Chem. Soc*. **2011**, 56, 1, 527.

[13] Jeon, M.-K.; Kim, M. S; Kwon, J. J.; Gong, Y. D.; Lee, D. H. *Tetrahedron***. 2008**, 64, 9060.

[14] Shafiq, M.; Khan, I.U.; Tahir, M.N.; Siddiqui, W.A..*Acta Crystallogr Sect E Struct Rep* Online. **2008**, 64, o558.

[15] Lombardino, J. G.;Treadway, N. W., *Jr. Org. Prep. Proced. Int.* **1971**, 3, 33–36.

[16] Coppo, F.T.; Fawzi, M. M.; *J. Heterocyclic Chem.* **1998,** 35, 983.

[17] Pore, M. D.; Hegade, G.; Gaikwad, P. S.; Patil, D. B.; P., & D Patil, J. *Letters in Organic Chemistry*. **2014**, 11, 131.

[18] Shaterian, H. R.; Arman, M.; Rigi, F. *J. Mol. Liquids.* **2011**, 158, 145.

[19] Singh G.S.; Desta, Z.Y. *Chem. Rev.* **2012**, 112, 6104.

[20] Redkin, R.G.; Shemchuk, L. A.; Chernykh, V. P.; Shishkin, O. V.; Shishkin, S. V. *Tetrahedron*. **2007**. 63, 11444.

[21] Zou, Y.; Hu, Y.; Liu, H.; Shi, D. *ACS Comb. Sci.* **2012**, 14, 38.

[22] Liu, Y.; Ren, Z.; Cao, W.; Chen, J.; Deng H.; Shao, M. *Synth. Commun.* **2011,** 41, 3620.

[23] Ukrainets, I.V.; Redkin, R.G.; Sidorenko L.V.; Turov A.V. *Chem. Heterocycl. Compd. (Engl.Transl.); Khim. Geterotsikl. Soedin.; RU.*2009, **12**, 1834.

[24] Volovenko, Yu.; Volovenko, T.; Popov, K. *J. Heterocycl. Chem.* **2007**, 44, 1413.

[25] Kapiller-Dezsőfi, R.; Volk, B. *New J . Chem.* **2004** , 28 , 1214.

[26] Zefirov, N. S.; Palyulin, V. A.; Dashevskaya, E. E. *J. Phys. Org. Chem.*, **1990**, *3*, 147.

[27] Zefirov, Yu. V. *Kristallographiya* (Russian), **1997**, 42, 936.

[28] Sheldrick, G.M. *Acta Crystallogr., Sect. A.* **2008**, A64, 112.