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Synthesis of novel spiro-condensed 2-amino-4*H*-pyrans based on 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide

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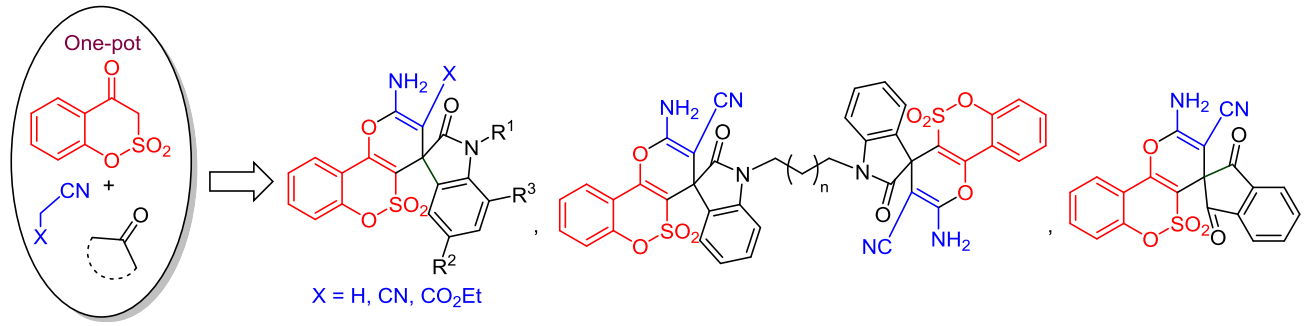


A series of new spiro-condensed 2-amino-4*H*-pyrans were synthesized by three-component interaction of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide, malononitrile, and cyclic carbonyls in moderate to high yields. This is one of the first examples of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide application in multicomponent transformations.

Keywords: active methylene nitrile, 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide, isatin, ninhydrin, spiro compounds, multicomponent reactions.

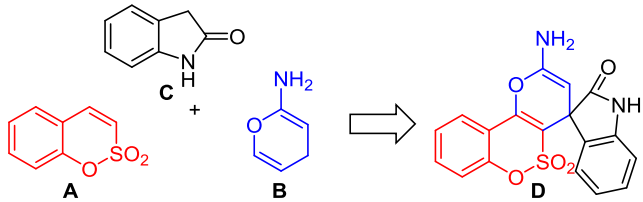
New drug development is one of the challenging tasks for modern science. Current innovations in this area led to impressive changes in the ability to improve the quality of life and treatment of diseases.

Creation of novel medicines can proceed through different pathways, but the general model of such development was designed at the end of the last century.[1] This process is not only a long-termed and sophisticated, it is also expensive enough.[2,3] Therefore, the first step toward new drug creation – synthesis of novel molecules – is so valuable and important, since their targeted construction can significantly decrease the time and costs required for new medicine development. That is why pharmacophore approach became one of the major tools in drug discovery after the past century's development.[4] The concept of pharmacophore was first introduced in 1909 by Ehrlich,[5] who defined the pharmacophore as a molecular framework that carries the essential features responsible for a drug's biological activity. Application of such frameworks and their combinations in medicinal chemistry is nowadays widely used in virtual screening, *de novo* and multitarget drug design.[6,7]

In the present study, we turned our attention to three pharmacophores at once – 1,2-benzoxathiine 2,2-dioxide, 2-amino-4*H*-pyran, and indolin-2-one, aiming to unite them into one molecular framework (Scheme 1).

As for 1,2-benzoxathiine 2,2-dioxide **A**, its chemical and biological properties are relatively little studied. However, one can consider its structure as an isostere for two groups of heterocycles that are responsible for wide range of

Scheme 1. Combination of three starting pharmacophores into the target molecule **D**

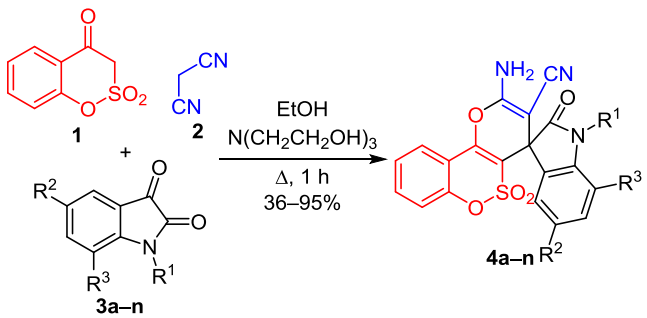


biological activities. The first group contains 2*H*-chromen-2-one core, derivatives of which are well-known anticoagulants. The second one comprises 1*H*-2,1-benzothiazine 2,2-dioxide frame which has shown high prospects for creating new effective NSAIDs based on it.[8,9] 2-Amino-4*H*-pyrans **B** constitute another well-known group in medicinal chemistry, whose representatives possess antimicrobial[10] and anticancer[11] properties. Finally, antiviral and tuberculostatic effects, as well as anxiogenic, sedative, anticonvulsant, anticancer, fibrinolytic, muscle relaxant, antiallergic, immunosuppressant, and antithrombotic activities have been found for the derivatives of indolin-2-one **C**.[12]

Being united into molecular system **D**, these pharmacophores produce spiro frame that also displays pronounced antimicrobial, analgesic, anti-inflammatory, antibacterial, antifungal, antitumor, and antiviral activities.[13]

Previously we described targeted synthesis of compounds similar to structure **D** as domino Knoevenagel/Michael/hetero-Thorpe–Ziegler cyclization reaction sequence[14] of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with active methylene nitriles and isatins.[15] Application of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide instead of the benzothiazine may result in target system **D**. For this purpose, a wide range of substituted isatins were applied in the reaction. Starting isatins **3a**–**n** were synthesized following known synthetic approaches.[16] The three-component interaction of equimolar amounts of starting compounds was carried out in the presence of triethanolamine as a catalyst under reflux for 1 h in EtOH (Scheme 2). The target compounds **4a**–**n** were isolated in 36–95% yields as crystalline precipitates that can be recrystallized from EtOH–DMF, 1:1 mixture. Utilization of other catalysts with more pronounced basic properties (such as Et_3N or DBU) as well as the prolongation of the reaction time did not lead to the increase in yields of compounds **4a**–**n**.

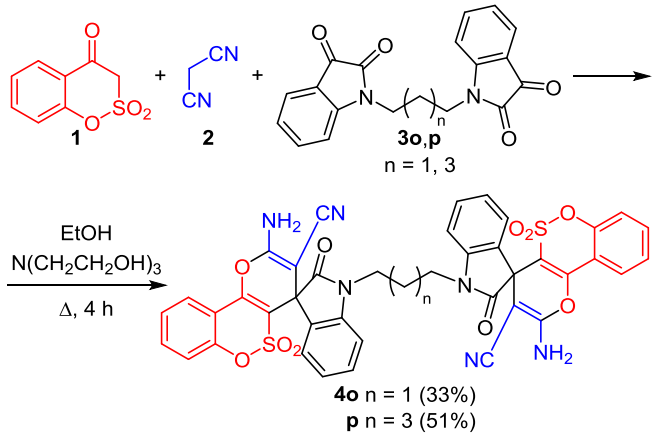
Scheme 2. Three-component synthesis of the target compounds **4a**–**n**



a $R^1 = R^2 = R^3 = H$; **b** $R^1 = CH_2CO_2Et$, $R^2 = R^3 = H$; **c** R^1 = Allyl, $R^2 = R^3 = H$; **d** $R^1 = Et$, $R^2 = R^3 = H$; **e** R^1 = Bn, $R^2 = R^3 = H$; **f** $R^1 = Me$, $R^2 = R^3 = H$; **g** $R^1 = H$, $R^2 = Me$, $R^3 = H$; **h** $R^1 = H$, $R^2 = NO_2$, $R^3 = H$; **i** $R^1 = H$, $R^2 = Br$, $R^3 = H$; **j** R^1 = Allyl, $R^2 = Br$, $R^3 = H$; **k** R^1 = Bn, $R^2 = Br$, $R^3 = H$; **l** $R^1 = Me$, $R^2 = Br$, $R^3 = H$; **m** $R^1 = R^2 = Me$, $R^3 = H$; **n** $R^1 = H$, $R^2 = R^3 = Br$

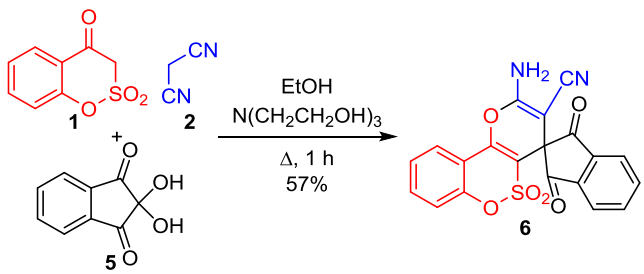
Bis-isatins **3o**,**p** were also examined as a carbonyl component in the above-mentioned interaction. Applying 0.5 equiv of compounds **3o**,**p** and prolongation of the reaction time up to 4 h led to the symmetrical bis-products **4o**,**p** (Scheme 3). Aiming to obtain nonsymmetrical 2-amino-4*H*-pyran-3-carbonitriles, equimolar quantities of starting compounds were also used under the same reaction conditions. Nevertheless, only mixtures of starting isatins and products of their condensation with malononitrile were isolated in both cases.

Scheme 3. Synthesis of bis-spiro compounds **4o**,**p**



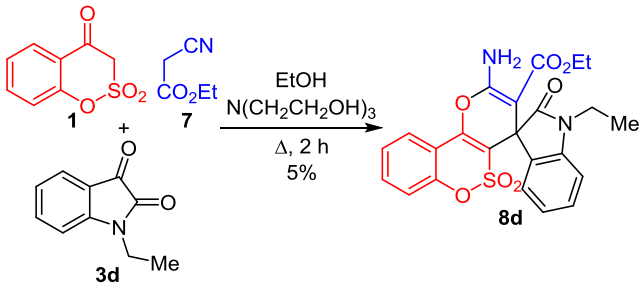
Literature data provide, in most cases, information about application of isatins for the construction of spiro-built 2-amino-4*H*-pyrans, whereas other possible carbonyls for such purpose are overlooked.[17] In this regard ninhydrin (**5**) was additionally applied in the three-component interaction as a compound containing endocyclic hidden carbonyl group (Scheme 4). This allowed us to obtain spiro-2-amino-4*H*-pyran **6** in 57% yield.

Scheme 4. Utilization of ninhydrin (**5**) in the three-component interaction



We also made an attempt to vary the nitrile component, namely, to utilize ethyl cyanoacetate (**7**) instead of malononitrile[18] under the same reaction conditions. However, no consistent results were obtained in most cases for such interaction, and complex mixtures of the starting compounds, the Knoevenagel condensation intermediates, and the target products – ethyl 2-amino-2'-oxospiro[4*H*-pyrano[3,2-*c*]-[1,2]benzoxathiine-4,3'-indoline]-3-carboxylate 5,5-dioxides were isolated. In this regard, *N*-ethylisatin appeared to be the only example for which target ethyl 2-amino-4*H*-pyran-3-carboxylate **8d** was obtained, but in extremely low yield of 5% (Scheme 5). Our efforts to achieve higher yields by variation of catalysts (Et_3N, DBU, AcONa), solvents, and heating modes (either room temperature or reflux up to 10 h) did not significantly affect the reaction efficiency.

Scheme 5. Utilization of ethyl cyanoacetate in the three-component interaction



Thus, the three-component reactions involving ethyl cyanoacetate revealed unusual reactivity of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide compared to 1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (as its N-containing analog). As it has been shown before,[15] the latter easily gives corresponding ethyl 2-amino-4*H*-pyran-3-carboxylates, whereas 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide is rather inert in these reactions.

The structures of the obtained compounds were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry as well as elemental analysis.

Structural features of 2-amino-4*H*-pyrans containing *N*-substituted (compound **4b**) and 5-substituted (compound **4h**) indoline fragment have been additionally confirmed by single crystal X-ray diffraction study (Fig. 1). Non-hydrogen atoms are drawn as 30% probability displacement ellipsoids and H atoms are drawn as spheres of an arbitrary size. Detailed information about molecular and crystal structures of compounds **4b**,**h** see in the Supplementary information file.

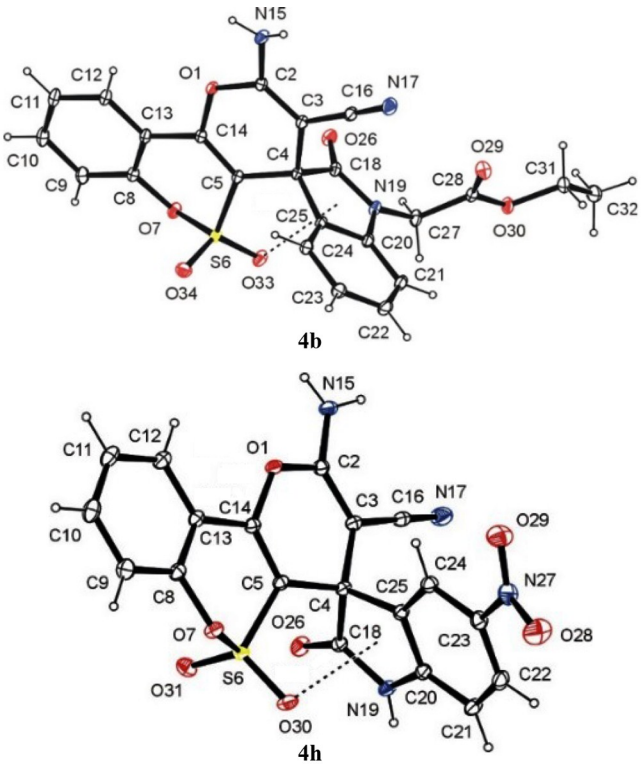


Figure 1. Molecular structures of compounds **4b**,**h** with atoms represented by thermal vibration ellipsoids of 30% probability.

In conclusion, we succeeded in construction of two novel spiroheterocyclic systems comprising three pharmacophore units based on one-pot three-component interaction of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide with malononitrile and wide range of isatins or ninhydrin. The benzoxathiinone is a new enol nucleophile for such reactions. Moreover, this paper allowed us to disclose some aspects of its reactivity in multicomponent reactions, since it was not used in this type of interactions before.

Experimental

IR spectra were recorded on a PerkinElmer 298 spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Varian MR-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, using TMS as internal standard. Mass spectra were recorded on a Bruker 320-MS apparatus by the electron ionization (EI) technique, operating at 70 eV. LCMS were recorded with an Agilent 1100 Series high-performance liquid chromatograph equipped with an Agilent 1100 Series diode array detector and with an Agilent LC/MSD SL mass selective detector (atmospheric pressure electrospray ionization – ES-API). Elemental analyses were carried out using a Carlo Erba CHNS-O EA 1108 analyzer. Melting points were determined on a Gallenkamp MFB-595 melting point apparatus in open capillary tubes.

Starting active methylene nitriles, catalysts, and solvents were obtained from commercial sources and used without further purification. 1,2-Benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) was synthesized according to previously described procedure.[19] Starting isatins **3a**–**n** were synthesized according to known synthetic methods.[16]

Synthesis of 2-amino-2'-oxospiro[4*H*-pyrano[3,2-*c*]-[1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxides 4a–n (General method). Triethanolamine (20 mol %) was added to a solution of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) (0.198 g, 0.001 mol), malononitrile (**2**) (0.066 g, 0.001 mol), and appropriate isatin **3a**–**n** (0.001 mol) in EtOH (5–10 ml). The mixture was refluxed for 1 h. The obtained precipitates of compounds **4a**–**n** were filtered off, washed with EtOH, dried in air, and recrystallized from EtOH–DMF, 1:1.

2-Amino-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4a). Yield 0.28 g (71%), light-yellow crystalline powder, mp 299–301°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3317 (NH_2, st asym), 3186 (NH_2, st sym), 2207 (C≡N, st), 1673 (C=O, st), 1378 (SO_2, st asym), 1186 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.87 (1H, d, *J* = 7.6, H Ar); 7.01 (1H, t, *J* = 7.6, H Ar); 7.27 (1H, t, *J* = 7.6, H Ar); 7.35 (1H, d, *J* = 7.3, H Ar); 7.51 (1H, d, *J* = 8.2, H Ar); 7.55–7.62 (1H, m, H Ar); 7.66 (2H, br. s, NH_2); 7.70–7.77 (1H, m, H Ar); 7.94 (1H, d, *J* = 7.6, H Ar); 10.75 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 48.0; 56.9; 110.1; 110.3; 114.9; 116.5; 119.0; 122.5; 125.1; 126.0; 126.8; 129.8; 130.2; 134.5; 142.1; 148.6; 148.8; 159.1; 176.1. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 393 [M]$^+$

(30), 329 [M^+–SO_2] (100). Found, %: C 57.92; H 2.64; N 10.55; S 8.02. $C_{19}H_{11}N_3O_5S$. Calculated, %: C 58.01; H 2.82; N 10.68; S 8.15.

Ethyl 2-(2-amino-3-cyano-5,5-dioxido-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-4,3'-indoline]-1'-yl)acetate (4b). Yield 0.22 g (45%), light-violet crystalline powder, mp 291–293°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3309 (NH_2, st asym), 3181 (NH_2, st sym), 2208 (C≡N, st), 1755 (C=O, st), 1669 (C=O, st), 1375 (SO_2, st asym), 1190 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.0, CH_3); 4.11 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.47–4.60 (2H, m, NCH_2); 7.04–7.15 (2H, m, H Ar); 7.36 (1H, t, *J* = 7.7, H Ar); 7.44 (1H, d, *J* = 7.3, H Ar); 7.52 (1H, d, *J* = 8.2, H Ar); 7.56–7.62 (1H, m, H Ar); 7.68–7.77 (3H, m, NH_2, H Ar); 7.95 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 13.9; 41.8; 47.4; 56.5; 61.0; 109.5; 110.1; 114.8; 115.8; 118.9; 123.3; 125.1; 125.8; 126.8; 128.5; 130.2; 134.52; 142.6; 148.6; 149.0; 159.4; 167.0; 174.7. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 479 $[M]^+$ (100), 415 [M^+–SO_2] (73). Found, %: C 57.53; H 3.49; N 8.69; S 6.51. $C_{23}H_{17}N_3O_7S$. Calculated, %: C 57.62; H 3.57; N 8.76; S 6.69.

1'-Allyl-2-amino-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]-benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4c). Yield 0.25 g (58%), light-brown crystalline powder, mp 290–292°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3308 (NH_2, st asym), 3202 (NH_2, st sym), 2202 (C≡N, st), 1673 (C=O, st), 1366 (SO_2, st asym), 1193 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.23–4.44 (2H, m, CH_2–CH=C$\underline{H}_2$); 5.12–5.36 (2H, m, $C\underline{H}_2$–CH=CH_2); 5.74–5.86 (1H, m, CH_2–C$\underline{H}$=CH_2); 6.99 (1H, d, *J* = 7.9, H Ar); 7.10 (1H, t, *J* = 7.5, H Ar); 7.35 (1H, t, *J* = 7.6, H Ar); 7.45 (1H, d, *J* = 7.6, H Ar); 7.52 (1H, d, *J* = 8.2, H Ar); 7.55–7.62 (1H, m, H Ar); 7.65–7.79 (3H, m, NH_2, H Ar); 7.95 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 42.2; 47.6; 56.6; 109.7; 110.0; 114.8; 116.3; 116.8; 118.9; 123.1; 125.1; 125.7; 126.8; 129.0; 130.2; 131.2; 134.5; 142.6; 148.6; 149.0; 159.1; 174.4. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 433 $[M]^+$ (75), 392 [M^+–C_3H_5] (100), 369 [M^+–SO_2] (36). Found, %: C 60.78; H 3.39; N 9.58; S 7.25. $C_{22}H_{15}N_3O_5S$. Calculated, %: C 60.96; H 3.49; N 9.69; S 7.40.

2-Amino-1'-ethyl-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]-benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4d). Yield 0.27 g (65%), light-brown crystalline powder, mp >300°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3308 (NH_2, st asym), 3175 (NH_2, st sym), 2194 (C≡N, st), 1671 (C=O, st), 1375 (SO_2, st asym), 1184 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.0, CH_3); 3.74 (2H, q, *J* = 6.8, CH_2); 7.05–7.15 (2H, m, H Ar); 7.37 (1H, t, *J* = 7.6, H Ar); 7.43 (1H, d, *J* = 7.3, H Ar); 7.51 (1H, d, *J* = 8.2, H Ar); 7.55–7.62 (1H, m, H Ar); 7.66–7.77 (3H, m, NH_2, H Ar); 7.95 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 12.0; 34.8; 47.5; 56.6; 109.2; 110.1; 114.9; 116.2; 119.0; 123.0; 125.1; 125.9; 126.8; 129.3; 130.3; 134.5; 142.4; 148.6; 148.9; 159.0; 174.1. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 421 $[M]^+$ (100), 392 [M^+–C_2H_5] (22), 357 [M^+–SO_2] (46). Found, %: C 59.76; H 3.45; N 9.91; S 7.44. $C_{21}H_{15}N_3O_5S$. Calculated, %: C 59.85; H 3.59; N 9.97; S 7.61.

2-Amino-1'-benzyl-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]-benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4e). Yield 0.41 g (85%), light-brown crystalline powder, mp 295–298°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3468 (NH_2, st asym), 3259 (NH_2, st sym), 2209 (C≡N, st), 1672 (C=O, st), 1372 (SO_2, st asym), 1189 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.84–5.04 (2H, m, CH_2); 6.87 (1H, d, *J* = 7.9, H Ar); 7.08 (1H, t, *J* = 7.5, H Ar); 7.20–7.32 (4H, m, H Ar); 7.36–7.42 (2H, m, H Ar); 7.46 (1H, d, *J* = 7.3, H Ar); 7.53 (1H, d, *J* = 8.2, H Ar); 7.57–7.64 (1H, m, H Ar); 7.70–7.81 (3H, m, NH_2, H Ar); 7.97 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 43.6; 47.7; 56.7; 109.7; 109.9; 114.8; 116.4; 118.9; 123.2; 125.1; 125.8; 126.8; 127.1; 127.4; 128.4; 129.0; 130.2; 134.5; 135.5; 142.6; 148.6; 149.0; 159.2; 174.9. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 483 $[M]^+$ (26), 419 [M^+–SO_2] (20), 392 [M^+–C_7H_7] (100). Found, %: C 64.48; H 3.45; N 8.57; S 6.49. $C_{26}H_{17}N_3O_5S$. Calculated, %: C 64.59; H 3.54; N 8.69; S 6.63.

2-Amino-1'-methyl-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]-benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4f). Yield 0.37 g (91%), light-pink crystalline powder, mp 293–295°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3338 (NH_2, st asym), 3177 (NH_2, st sym), 2208 (C≡N, st), 1668 (C=O, st), 1372 (SO_2, st asym), 1189 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.17 (3H, s, CH_3); 7.07–7.14 (2H, m, H Ar); 7.39 (1H, t, *J* = 7.8, H Ar); 7.44 (1H, d, *J* = 7.3, H Ar); 7.53 (1H, d, *J* = 7.9, H Ar); 7.59 (1H, t, *J* = 7.6, H Ar); 7.70–7.76 (1H, m, H Ar); 7.79 (2H, s, NH_2); 7.93 (1H, d, *J* = 7.9, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.8; 47.6; 56.4; 109.2; 110.2; 114.9; 116.4; 119.0; 123.2; 125.1; 125.7; 126.8; 129.1; 130.4; 134.5; 143.5; 148.6; 148.9; 159.2; 174.7. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 407 $[M^+]$ (100), 343 [M^+–SO_2] (70). Found, %: C 58.89; H 3.15; N 10.25; S 7.70. $C_{20}H_{13}N_3O_5S$. Calculated, %: C 58.96; H 3.22; N 10.31; S 7.87.

2-Amino-5'-methyl-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]-benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4g). Yield 0.39 g (95%), white needles, mp 241–243°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3315 (NH_2, st asym), 3186 (NH_2, st sym), 2207 (C≡N, st), 1670 (C=O, st), 1378 (SO_2, st asym), 1187 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 (3H, s, CH_3); 6.75 (1H, d, *J* = 7.7, H Ar); 7.07 (1H, d, *J* = 8.0, H Ar); 7.19 (1H, s, H-5'); 7.53 (1H, d, *J* = 8.0, H Ar); 7.59 (1H, t, *J* = 7.6, H Ar); 7.68–7.77 (3H, m, NH_2, H Ar); 7.92 (1H, d, *J* = 7.7, H Ar); 10.71 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 21.1; 48.6; 57.6; 110.3; 110.9; 115.4; 116.9; 119.4; 125.5; 126.8; 127.2; 130.5; 131.0; 131.8; 134.9; 140.1; 149.1; 149.2; 159.4; 176.5. Mass spectrum (ES-API), *m*/*z*: 408 $[M+H]^+$. Found, %: C 58.88; H 3.16; N 10.24; S 7.68. $C_{20}H_{13}N_3O_5S$. Calculated, %: C 58.96; H 3.22; N 10.31; S 7.87.

2-Amino-5'-nitro-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]-benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4h). Yield 0.37 g (84%), colorless crystalline powder, mp >300°C (DMF). IR spectrum, ν, cm^{-1}: 3320 (NH_2, st asym), 3207 (NH_2, st sym), 2207 (C≡N, st), 1667 (C=O, st), 1524 (NO_2, st asym), 1359 (NO_2, st sym), 1327 (SO_2, st asym), 1185 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm

(*J*, Hz): 7.11 (1H, d, *J* = 8.6, H Ar); 7.54 (1H, d, *J* = 8.2, H Ar); 7.58–7.64 (1H, m, H Ar); 7.73 (1H, d, *J* = 7.6, H Ar); 7.86–7.97 (3H, m, NH_2, H Ar); 8.26 (1H, d, *J* = 8.9, H Ar); 8.52 (1H, s, H-5′); 11.58 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 48.1; 55.6; 108.6; 110.6; 115.0; 116.4; 119.0; 122.3; 125.3; 126.9; 127.4; 131.1; 134.6; 142.9; 148.4; 148.6; 149.6; 159.3; 176.9. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 438 [M^+] (6), 374 [M^+–SO_2] (12), 210 (100). Found, %: C 51.98; H 2.22; N 12.69; S 7.16. $C_{19}H_{10}N_4O_7S$. Calculated, %: C 52.06; H 2.30; N 12.78; S 7.31.

2-Amino-5'-bromo-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]-benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4i). Yield 0.41 g (88%), light-blue crystalline powder, mp >300°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3333 (NH_2, st asym), 3207 (NH_2, st sym), 2206 (C≡N, st), 1668 (C=O, st), 1369 (SO_2, st asym), 1184 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.84 (1H, d, *J* = 8.2, H Ar); 7.42–7.48 (1H, m, H Ar); 7.52 (1H, d, *J* = 8.2, H Ar); 7.59 (1H, t, *J* = 7.6, H Ar); 7.64–7.77 (4H, m, NH_2, H Ar); 7.92 (1H, d, *J* = 7.6, H Ar); 10.90 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 48.1; 56.3; 109.4; 112.0; 113.9; 114.9; 116.3; 118.9; 125.1; 126.7; 128.8; 132.2; 132.9; 134.4; 141.3; 148.6; 149.0; 159.0; 175.7. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 471 $[M]^+$ (15), 407 [M^+–SO_2] (28), 273 [M^+–$C_8H_6O_4S$] (100). Found, %: C 48.49; H 2.20; N 8.75; S 6.63. $C_{19}H_{10}BrN_3O_5S$. Calculated, %: C 48.32; H 2.13; N 8.90; S 6.79.

1'-Allyl-2-amino-5'-bromo-2'-oxospiro[4*H*-pyrano[3,2-*c*]-[1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4j). Yield 0.47 g (92%), light-brown crystalline powder, mp >300°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3306 (NH_2, st asym), 3175 (NH_2, st sym), 2211 (C≡N, st), 1672 (C=O, st), 1378 (SO_2, st asym), 1192 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.24–4.44 (2H, m, CH_2=CH–C<u>H</u>$_2$); 5.12–5.33 (2H, m, C<u>H</u>$_2$=CH–CH_2); 5.71–5.84 (1H, m, CH_2=C<u>H</u>–CH_2); 6.94–7.00 (1H, m, H Ar); 7.51–7.64 (3H, m, H Ar); 7.71–7.78 (1H, m, H Ar); 7.81 (1H, d, *J* = 1.8, H-4'); 7.87 (2H, s, NH_2); 7.90–7.95 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 42.3; 47.7; 56.0; 109.1; 111.7; 114.9 (2C); 116.4; 117.0; 118.9; 125.2; 126.8; 128.8; 130.9; 131.5; 133.0; 134.5; 141.8; 148.6; 149.3; 159.2; 174.1. Mass spectrum (ES-API), *m*/*z*: 512 $[M(^{79}Br)+H]^+$, 514 $[M(^{81}Br)+H]^+$. Found, %: C 51.67; H 2.83; N 8.07; S 6.05. $C_{22}H_{14}BrN_3O_5S$. Calculated, %: C 51.58; H 2.75; N 8.20; S 6.26.

2-Amino-1'-benzyl-5'-bromo-2'-oxospiro[4*H*-pyrano-[3,2-*c*][1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4k). Yield 0.29 g (51%), light-brown crystalline powder, mp >300°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3304 (NH_2, st asym), 3172 (NH_2, st sym), 2213 (C≡N, st), 1674 (C=O, st), 1378 (SO_2, st asym), 1191 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.85–5.03 (2H, m, CH_2); 6.84 (1H, d, *J* = 8.2, H Ar); 7.21–7.32 (3H, m, H Ar); 7.34–7.39 (2H, m, H Ar); 7.48 (1H, d, *J* = 7.6, H Ar); 7.55 (1H, d, *J* = 8.2, H Ar); 7.59–7.64 (1H, m, H Ar); 7.73–7.78 (1H, m, H Ar); 7.82 (1H, s, H-4'); 7.88 (2H, s, NH_2); 7.94 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 43.6; 47.8; 56.1; 109.0; 111.7; 114.9; 115.1; 116.5; 119.0; 125.3; 126.8; 127.1; 127.5; 128.5; 129.0; 131.5; 133.1; 134.6; 135.2; 141.9; 148.6; 149.4; 159.2; 174.6. Mass spectrum (ES-API), *m*/*z*: 562 $[M(^{79}Br)+H]^+$, 564 $[M(^{81}Br)+H]^+$. Found, %: C 55.70; H 2.95; N 7.33; S 5.58. $C_{26}H_{16}BrN_3O_5S$. Calculated, %: C 55.53; H 2.87; N 7.47; S 5.70.

2-Amino-5'-bromo-1'-methyl-2'-oxospiro[4*H*-pyrano-[3,2-*c*][1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4l). Yield 0.44 g (91%), light-gray crystalline powder, mp >300°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3275 (NH_2, st asym), 3169 (NH_2, st sym), 2202 (C≡N, st), 1667 (C=O, st), 1376 (SO_2, st asym), 1189 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.16 (3H, s, CH_3); 7.09 (1H, d, *J* = 8.2, H Ar); 7.52–7.63 (3H, m, H Ar); 7.71–7.77 (1H, m, H Ar); 7.79 (1H, d, *J* = 2.1, H-4'); 7.84 (2H, s, NH_2); 7.92 (1H, dd, *J* = 7.8, *J* = 1.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 26.9; 47.7; 55.8; 109.2; 111.2; 114.9; 115.0; 116.4; 119.0; 125.2; 126.8; 128.8; 131.5; 133.1; 134.5; 142.7; 148.6; 149.2; 159.2; 174.3. Mass spectrum (ES-API), *m*/*z*: 486 $[M(^{79}Br)+H]^+$, 488 $[M(^{81}Br)+H]^+$. Found, %: C 49.61; H 2.58; N 8.52; S 6.42. $C_{20}H_{12}BrN_3O_5S$. Calculated, %: C 49.40; H 2.49; N 8.64; S 6.59.

2-Amino-1',5'-dimethyl-2'-oxospiro[4*H*-pyrano[3,2-*c*]-[1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4m). Yield 0.39 g (93%), light-gray crystalline powder, mp >300°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3300 (NH_2, st asym), 3171 (NH_2, st sym), 2201 (C≡N, st), 1668 (C=O, st), 1373 (SO_2, st asym), 1185 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24 (3H, s, 5'-CH_3); 3.14 (3H, s, N–CH_3); 6.98 (1H, d, *J* = 7.9, H Ar); 7.18 (1H, d, *J* = 7.6, H Ar); 7.27 (1H, s, H-4'); 7.53 (1H, d, *J* = 8.2, H Ar); 7.56–7.62 (1H, m, H Ar); 7.72 (1H, d, *J* = 7.9, H Ar); 7.77 (2H, s, NH_2); 7.93 (1H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 20.6; 26.8; 47.7; 56.6; 108.9; 110.3; 114.9; 116.4; 119.0; 125.1; 126.1; 126.8; 129.2; 130.6; 132.2; 134.5; 141.1; 148.6; 148.8; 159.1; 174.5. Mass spectrum (ES-API), *m*/*z*: 422 $[M+H]^+$. Found, %: C 59.71; H 3.65; N 10.12; S 7.49. $C_{21}H_{15}N_3O_5S$. Calculated, %: C 59.85; H 3.59; N 9.97; S 7.61.

2-Amino-5',7'-dibromo-2'-oxospiro[4*H*-pyrano[3,2-*c*]-[1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4n). Yield 0.20 g (36%), light-brown powder, mp >300°C (EtOH–DMF, 1:1). IR spectrum, ν, cm^{-1}: 3346 (NH_2, st asym), 3197 (NH_2, st sym), 2207 (C≡N, st), 1672 (C=O, st), 1376 (SO_2, st asym), 1179 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm: 7.54–7.64 (2H, m, H Ar); 7.72–7.79 (2H, m, H Ar); 7.79–7.83 (1H, m, H Ar); 7.85–7.94 (3H, m, NH_2, H Ar); 11.34 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 49.3; 56.0; 103.2; 108.9; 114.6; 114.9; 116.4; 119.0; 125.3; 126.9; 128.4; 133.4; 134.6; 135.0; 141.1; 148.6; 149.3; 159.1; 175.9. Mass spectrum (ES-API), *m*/*z*: 550 $[M(^{79}Br^{79}Br)+H]^+$, 552 $[M(^{79}Br^{81}Br)+H]^+$, 554 $[M(^{81}Br^{81}Br)+H]^+$. Found, %: C 41.17; H 1.73; N 7.49; S 5.70. $C_{19}H_9Br_2N_3O_5S$. Calculated, %: C 41.40; H 1.65; N 7.62; S 5.82.

Synthesis of bis-spiro derivatives 4o,p (General method). Triethanolamine (20 mol %) was added to a solution of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) (0.198 g, 0.001 mol), malononitrile (**2**) (0.066 g, 0.001 mol), and appropriate isatin **3o**,**p** (0.0005 mol) in EtOH (5–10 ml). The mixture was refluxed for 4 h. The obtained precipitates were filtered off, washed with EtOH, dried in air, and recrystallized from DMF.

2-Amino-1'-[3-(2-amino-3-cyano-5,5-dioxido-2'-oxospiro-[4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-4,3'-indolin]-1'-yl)-propyl]-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4o). Yield 0.14 g (33%), gray powder, mp >300°C (DMF). IR spectrum, ν, cm^{-1}: 3415, 2199 (C≡N, st), 1708 (C=O, st), 1372 (SO_2, st asym), 1176 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.89–1.99 (2H, m, $NCH_2C\underline{H_2}CH_2N$); 3.84 (4H, t, *J* = 7.3, $NC\underline{H_2}CH_2C\underline{H_2}N$); 7.10 (2H, t, *J* = 7.5, H Ar); 7.16 (2H, d, *J* = 7.6, H Ar); 7.32–7.39 (2H, m, H Ar); 7.47 (2H, d, *J* = 7.3, H Ar); 7.54 (2H, d, *J* = 7.9, H Ar); 7.60 (2H, t, *J* = 7.6, H Ar); 7.71–7.78 (2H, m, H Ar); 7.83 (4H, br. s, NH_2); 7.94 (2H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum, δ, ppm: 38.8; 48.1; 57.1; 109.6; 110.5; 115.3; 116.8 (2C); 119.5; 123.7; 125.7; 126.5; 127.4; 129.7; 130.9; 135.1; 143.1; 149.1; 149.5; 159.6; 175.2. Mass spectrum (ES-API), *m*/*z*: 827 $[M+H]^+$. Found, %: C 59.40; H 3.25; N 10.33; S 7.57. $C_{41}H_{26}N_6O_{10}S_2$. Calculated, %: C 59.56; H 3.17; N 10.16; S 7.76.

2-Amino-1'-[5-(2-amino-3-cyano-5,5-dioxido-2'-oxospiro-[4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-4,3'-indolin]-1'-yl)-pentyl]-2'-oxospiro[4*H*-pyrano[3,2-*c*][1,2]benzoxathiine-4,3'-indoline]-3-carbonitrile 5,5-dioxide (4p). Yield 0.22 g (51%), light-gray crystalline powder, mp 298–300°C (DMF). IR spectrum, ν, cm^{-1}: 3311 (NH_2, st asym), 3184 (NH_2, st sym), 2198 (C≡N, st), 1670 (C=O, st), 1380 (SO_2, st asym), 1186 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37–1.49 (2H, m, $NCH_2CH_2C\underline{H_2}$); 1.55–1.67 (4H, m, $2NCH_2C\underline{H_2}CH_2$); 3.58–3.75 (4H, m, $2NC\underline{H_2}CH_2CH_2$); 7.05–7.13 (4H, m, H Ar); 7.31–7.38 (2H, m, H Ar); 7.44 (2H, d, *J* = 7.3, H Ar); 7.53 (2H, d, *J* = 8.2, H Ar); 7.60 (2H, t, *J* = 7.8, H Ar); 7.74 (2H, t, *J* = 7.8, H Ar); 7.80 (4H, s, NH_2); 7.93 (2H, d, *J* = 7.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 23.2; 26.3; 47.6; 56.8; 109.2; 110.1; 114.8; 116.3; 118.9; 122.9; 125.1; 125.8; 126.8; 129.2; 130.3; 134.4; 142.8; 148.6; 148.9; 159.1; 174.4. Mass spectrum (ES-API), *m*/*z*: 855 $[M+H]^+$. Found, %: C 60.58; H 3.65; N 9.70; S 7.33. $C_{43}H_{30}N_6O_{10}S_2$. Calculated, %: C 60.42; H 3.54; N 9.83; S 7.50.

2-Amino-1',3'-dioxo-1',3'-dihydrospiro[4*H*-pyrano[3,2-*c*]-[1,2]benzoxathiine-4,2'-indene]-3-carbonitrile 5,5-dioxide (6). Triethanolamine (20 mol %) was added to a solution of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) (0.198 g, 0.001 mol), malononitrile (**2**) (0.066 g, 0.001 mol), and ninhydrin (**5**) (0.178 g, 0.001 mol) in EtOH (10 ml). The mixture was allowed to reflux, and 10 min after starting of heating, precipitate of compound **6** started to form. The mixture was continued to reflux for 1 h and cooled to room temperature. The obtained precipitate of compound **6** was filtered off, washed with EtOH, dried in air, and recrystallized from DMF. Yield 0.23 g (57%), yellow powder, mp >300°C (DMF). IR spectrum, ν, cm^{-1}: 3356 (NH_2, st asym), 3195 (NH_2, st sym), 2204 (C≡N, st), 1710 (C=O, st), 1667 (C=O, st), 1381 (SO_2, st asym), 1177 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.56–7.67 (2H, m, H Ar); 7.79 (1H, t, *J* = 7.7, H Ar); 7.95 (1H, d, *J* = 7.7, H Ar); 8.11–8.23 (6H, m, NH_2, H Ar). ^{13}C NMR spectrum, δ, ppm: 53.4; 53.7; 108.0; 114.8; 116.4; 119.6; 124.8; 125.7; 127.6; 135.6; 138.6; 140.5; 149.3; 151.4; 160.4; 196.9. Mass spectrum (ES-API), *m*/*z*: 407 $[M+H]^+$. Found, %: C 59.31; H 2.55; N 6.73; S 7.71. $C_{20}H_{10}N_2O_6S$. Calculated, %: C 59.11; H 2.48; N 6.89; S 7.89.

Ethyl 2-amino-1'-ethyl-2'-oxospiro[4*H*-pyrano[3,2-*c*]-[1,2]benzoxathiine-4,3'-indoline]-3-carboxylate 5,5-dioxide (8d). Triethanolamine (20 mol %) was added to a solution of 1,2-benzoxathiin-4(3*H*)-one 2,2-dioxide (**1**) (0.198 g, 0.001 mol), ethyl cyanoacetate (**7**) (0.113 g, 0.001 mol), and *N*-ethylisatin (**3d**) (0.175 g, 0.001 mol) in EtOH (10 ml). The mixture was refluxed for 2 h. The solvent was removed under reduced pressure, and MeOH was added to the residue. The mixture was allowed to reflux for 1 min, cooled to room temperature, precipitate of compound **8d** was filtered off, washed with cold MeOH, and dried in air. Yield 0.03 g (5%), colorless prisms, mp 255–258°C. IR spectrum, ν, cm^{-1}: 3346 (NH_2, st asym), 3195 (NH_2, st sym), 1693 (C=O, st), 1653 (C=O, st), 1374 (SO_2, st asym), 1172 (SO_2, st sym). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.63 (3H, t, *J* = 7.0, CH_3); 1.18 (3H, t, *J* = 7.2, CH_3); 3.57–3.67 (2H, m, CH_2); 3.69–3.81 (2H, m, CH_2); 6.91–7.02 (2H, m, H Ar); 7.20–7.30 (2H, m, H Ar); 7.45–7.50 (1H, m, H Ar); 7.54–7.60 (1H, m, H Ar); 7.67–7.74 (1H, m, H Ar); 7.98–8.04 (1H, m, H Ar); 8.13 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 12.4; 13.9; 35.2; 48.0; 59.4; 75.5; 108.6; 113.6; 115.6; 119.2; 122.6; 125.1; 125.7; 127.1; 129.6; 132.6; 134.6; 144.2; 147.9; 149.1; 159.4; 167.0; 175.8. Mass spectrum (ES-API), *m*/*z*: 469 $[M+H]^+$. Found, %: C 59.11; H 4.22; N 5.83; S 6.98. $C_{23}H_{20}N_2O_7S$. Calculated, %: C 58.97; H 4.30; N 5.98; S 6.84.

X-ray diffraction study of compounds 4b,h. Crystals of compound **4b** ($C_{23}H_{17}N_3O_7S$, M_r 479.45) were triclinic, space group $P\bar{1}$, at 130.0(1) K: *a* 8.3540(2), *b* 8.7015(3), *c* 14.6369(4) Å; α 91.732(2), β 93.570(2), γ 98.462(3)°; *V* 1049.53(5) $Å^3$; *Z* 2. A violet pillar (EtOH) crystal of 0.28 × 0.25 × 0.23 mm was used to record 30131 (Mo*K*α radiation, θ_{max} 31.82°) intensities on a Rigaku SuperNova Dual Atlas diffractometer with CrysAlis PRO software[20] using mirror monochromatized Mo*K*α radiation from a high-flux microfocus source. Accurate unit cell parameters were determined by least-squares techniques from the θ values of 14124 reflections, θ range 2.51–31.76°. The data were corrected for Lorentz polarization and for absorption effects. The 1460 total unique reflections (R_{int} 0.031) were used for structure determination. The structure was solved by direct methods (SHELXT),[21] and refined against F^2 for all data (SHELXL-97).[22] The positions of the H atoms bonded to N atom were obtained from the difference Fourier maps and were refined freely. The remaining H atoms were placed geometrically in calculated positions and were refined with a riding model, with C–H 0.98 Å (CH_3), 0.99 Å (CH_2), 0.95 Å ($C(sp^2)$–H) and $U_{iso}(H) = 1.2U_{eq}(C)$ or $1.5U_{eq}(C)$. The methyl group was refined as a rigid group, which was allowed to rotate. Final refinement converged with *R* 0.036 (for 5941 data with $F^2 > 4\sigma(F^2)$), *wR* 0.099 (on F^2 for all data), and *S* 1.042 (on F^2 for all data). The largest difference peak and hole was 0.464 and –0.465 $eÅ^3$. The molecular illustrations were drawn using ORTEP-3 for Windows.[23] The complete crystallographic data was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1865664).

Crystals of compounds **4h** ($C_{19}H_{10}N_4O_7S$, M_r 438.37) were monoclinic, at 130.0(1) K: space group *C*2/*c*, *a* 24.6902(6), *b* 12.4406(2), *c* 13.6861(4) Å; β 120.088(3)°; *V* 3637.39(18) Å^3; *Z* 8. A colorless block (EtOH) crystal of 0.25 × 0.12 × 0.10 mm was used to record 18942 (Cu*K*α radiation, θ_{max} 76.74°) intensities on a Rigaku SuperNova Dual Atlas diffractometer[20] using mirror monochromatized Cu*K*α radiation from a high-flux microfocus source. Accurate unit cell parameters were determined by least-squares techniques from the θ values of 11269 reflections, θ range 3.69–76.52°. The data were corrected for Lorentz polarization and for absorption effects. The 3811 unique reflections (R_{int} 0.021) were used for structure determination. The structure was solved by dual-space algorithm (SHELXT),[21] and refined against F^2 for all data (SHELXL-97).[22] The positions of the H atoms bonded to N atoms were obtained from the difference Fourier maps and were refined freely. The remaining H atoms were placed geometrically in calculated positions and were refined with a riding model, with C–H 0.95 Å (C(sp^2)–H) and U_{iso}(H) =1.2U_{eq}(C). Final refinement converged with *R* 0.033 (for 3696 data with $F^2 > 4\sigma(F^2)$), *wR* 0.094 (on F^2 for all data), and *S* 1.075 (on F^2 for all data). The largest difference peak and hole was 0.346 and –0.507 eÅ^3. The molecular illustrations were drawn using ORTEP-3 for Windows.[23] The complete crystallographic data was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1865665).

Supplementary information file containing full spectroscopic data (^{1}H and ^{13}C NMR, IR, MS) for compounds **4a**–**p**, **6**, and **8d** as well as X-ray crystallographic data for compounds **4b**,**h** is available from the journal website at http://hgs.osi.lv.

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