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2,1-BENZOTHIAZINE 2,2-DIOXIDES. 3*. 4-HYDROXY-1-METHYL-2,2-DIOXO-*N*-(1,3-THIAZOL-2-YL)-1*H*-2λ^6,1-BENZOTHIAZINE-3-CARBOXAMIDES – A NEW GROUP OF POTENTIAL ANALGETICS

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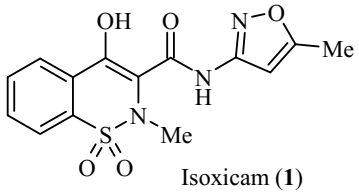
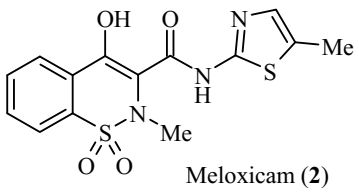
We have developed an effective synthetic method and prepared several 4-hydroxy-1-methyl-2,2-dioxo-N-(1,3-thiazol-2-yl)-1H-2λ^6,1-benzothiazine-3-carboxamides and a few structurally related heterocyclic arylamides. The structural features of one of the substituted thiazolyl-2-amides obtained have been investigated. Compounds with a high analgesic activity have been identified within this group by pharmacological screening.

Keywords: amides, 2-aminothiazoles, 2,1-benzothiazines, esters, analgesic activity.

N-Hetaryl-4-hydroxy-2-methyl-1,1-dioxo-2*H*-1λ^6,2-benzothiazine-3-carboxamides, such as isoxicam (**1**) and the widely used meloxicam (**2**) have been drugs of high importance for the suppression of pain and pain syndromes of various etiology [2-6]. However, despite their value, these drugs (similarly to other analgetics from different pharmacological groups) are not completely free of various drawbacks, which are the reason for many contraindications and limitations to their use [7]. Therefore, the search for novel, highly active and, most importantly, safe pain medications has never lost its importance.



Isoxicam (**1**)



Meloxicam (**2**)

*For Communction 2, see [1].

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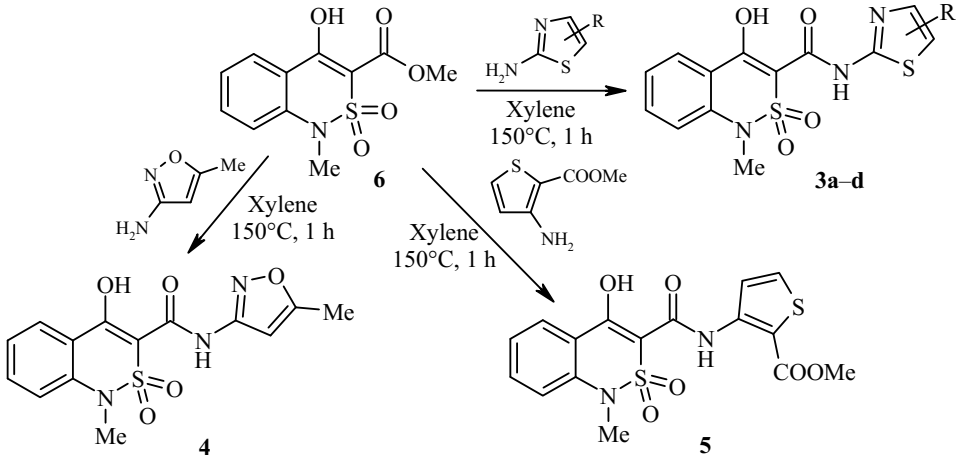
From this perspective, *N*-hetaryl-substituted 4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides are of great interest. On the one hand, these compounds are 2-sulfo analogs of strong analgesic agents – *N*-R-amides of 4-hydroxy-1,2-dihydroquinoline-3-carboxylic acids [8-10], while on the other hand, they represent isomers of the aforementioned drugs isoxicam (**1**) and meloxicam (**2**). It should be noted that the seemingly trivial modifications of isoxicam (changing 2-C=O group to SO_2 group) or meloxicam (switching places the nitrogen and sulfur atoms in the thiazine ring) with the purpose of obtaining new target molecules proved to be difficult synthetic challenges. *N*-hetaryl-4-hydroxy-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides therefore remain hitherto unexplored both from the chemical and pharmacological aspects despite the obvious value of such investigations.

As we have repeatedly demonstrated before, the reactions of lower alkyl esters of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids with primary and even secondary alkyl-, aryl-, and hetarylamines at elevated temperature easily and rapidly produced the corresponding amides. It should be especially emphasized that such syntheses often gave the best results in high-boiling inert solvents. The solvent volume, however, must not be excessively high: the optimal amount was 0.5-2 ml per 0.01 mol of the starting ester, otherwise the reaction rate dropped significantly, and the reaction completion required several hours instead of 3-5 minutes [11, 12].

According to our experiments, this scheme was also suitable for obtaining *N*-hetaryl-4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides **3**-**5**. For example, the methyl ester of 4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylic acid (**6**) reacted with equimolar amounts of thiazolyl-2-amines or structurally related compounds in a dry xylene at 150°C, giving good yields of the respective target hetarylamides **3**-**5**. It should be noted, however, that the reactivity of their 2-sulfo analog **6** was considerably lower than that of 4-hydroxyquinolin-2-one esters. The apparent reason was the strong effect of the sulfo group, which increased the acidity of the 4-OH group of ester **6** to such an extent that the desired course of the reaction was impeded by salt formation. Nevertheless, the amide formation still occurred, even though it required much longer time (approximately 1 h according to the reaction monitoring by ^{1}H NMR spectroscopy).

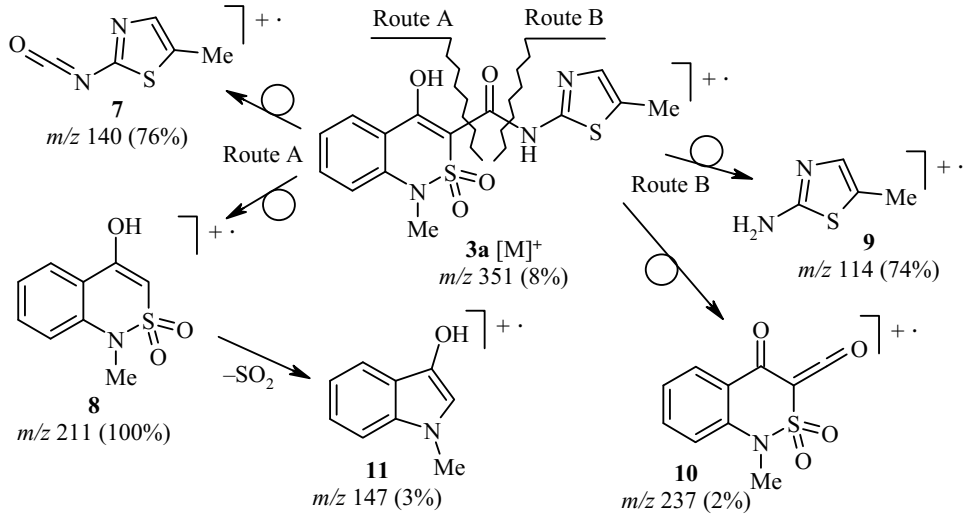


3 a R = 5-Me, **b** R = 4-CH_2COOEt, **c** R = 4-Ph, **d** R = 4-(adamant-1-yl)

All *N*-hetaryl-4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides **3**-**5** obtained were white crystals with a yellowish tinge, with narrow melting ranges (in some cases with decomposition), very well soluble at elevated temperatures in DMF, DMSO, and dioxane, sparingly soluble in alcohols, and practically insoluble in water. The structures of these compounds were confirmed with elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, as well as mass spectra.

Interestingly, aryl- and hetarylamides of 4-hydroxy-2-oxo-1,2-dihydroquinolin-3-carboxylic acids formed molecular ions under the conditions of electron impact ionization that were prone to primary fragmentation mainly by the cleavage of the acyclic amide bond, while their probability of fragmentation at the

C(3)–CONHHet(Ar) bond was much lower, or even absent [13-15]. The situation was the opposite with 2-sulfo analogs **3-5**, the molecular ions of which fragmented mainly at the bond between the heterocycle and the carbamide fragment (route A). This is shown in the scheme below, which uses the example of 5-methyl-thiazolyl-2-amide **3a** to explain the appearance of high intensity peaks with *m/z* 140 (76) and 211 (100), which is typical in the mass spectra of the *N*-hetaryl-4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides **3-5**, and indicating a fragmentation that formed the isocyanate **7** and benzothiazine **8** ions, respectively. It is important to note here that the molecular ion fragmentation according to the route A consists not of one, but rather of two different processes, which represent rearrangements with hydrogen atom migration. The charge during these rearrangements may be localized on either one of the fragments, but with different probabilities. In other words, the fragmentation of the molecular radical cation **3a** may produce either isocyanate radical cation **7** with *m/z* 140 and simultaneously a neutral fragment with the mass of 211 au, or benzothiazine radical cation **8** with *m/z* 211 by elimination of a neutral fragment with the mass of 140 au. The neutral fragments are not detected in mass spectra and have been omitted from the scheme for clarity.



The primary fragmentation of the molecular radical cation similarly occurred at the carbamide bond (route B). This direction was less characteristic for most of heterocyclic arylamides **3-5** despite the fairly high intensity of the peaks due to the corresponding hetarylamines. For instance, amide **3a** gave a mass spectrum with 74% intensity of the characteristic peak (*m/z* 114) due to the liberation of 2-amino-5-methylthiazole (**9**). At the same time, the associated peak of the bicyclic ketene **10**, which was common to all the compounds studied, had the intensity of only 2%. The ketene route of molecular ion fragmentation became more pronounced only in the case of 5-methyl-1,2-oxazol-3-ylamide **4** when ketene **10** peak intensity was 69%. However, the strongest peak in the mass spectrum was still that of benzothiazine **8** with *m/z* 211, thus the initial fragmentation in this case also occurred at the benzothiazine–carbamide bond.

Remarkably, *N*-hetaryl-4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides **3-5** under the conditions of mass spectrometry did not eliminate SO_2. This typical high-temperature reaction of many heterocycles containing a sulfo group [16-18] was quite insignificant in this case, and did not occur with the molecular ion, but rather only during the fragmentation of the benzothiazine fragment ion **8**. This was evidenced by the very low intensity of the peaks produced by such fragmentation of hydroxyindole **11**, which in none of the examined cases reached even 10%.

According to our X-ray structural analysis data, the dihydrothiazine ring in the molecule of ethyl ({[(4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazin-3-yl)carbonyl]amino}-1,3-thiazol-4-yl)acetate (**3b**) was in an intermediate conformation between a "twist-boat" and a "sofa" (the folding parameters [19]: S 0.64, Θ 48.9°, Ψ 17.3°). The S(1) and C(8) atoms deviated from the least-squares plane of the remaining ring atoms by -0.85 and -0.21 Å, respectively (Fig. 1).

The repulsion of the 1-*N*-methyl substituent and the aromatic ring (shortened intramolecular contact H(2)···C(17) 2.71 Å at the sum of the van der Waals radii equal to 2.87 Å [20]) resulted in the lengthening of the C(1)–N(1) bond to 1.408(3) Å, compared to its average length of 1.375 Å [21]. The carbamide group of the substituent at the C(8) atom was practically coplanar with the endocyclic C(7)–C(8) double bond (the dihedral angle C(7)–C(8)–C(9)–O(2) was 8.5(3)°), which was facilitated by the formation of intramolecular hydrogen bonds O(1)–H···O(2) (H···O 1.79 Å, O–H···O 157°) and N(2)–H···O(4) (H···O 1.99 Å, N–H···O 143°). This conformation involved a redistribution of electron density as indicated by the lengthening of the C(9)–O(2) and C(7)–C(8) bonds to 1.236(3) and 1.374(3) Å, respectively (with the average values 1.210 and 1.326 Å) and shortening of the C(7)–O(1) bond to 1.315(3) Å (the average value 1.362 Å).

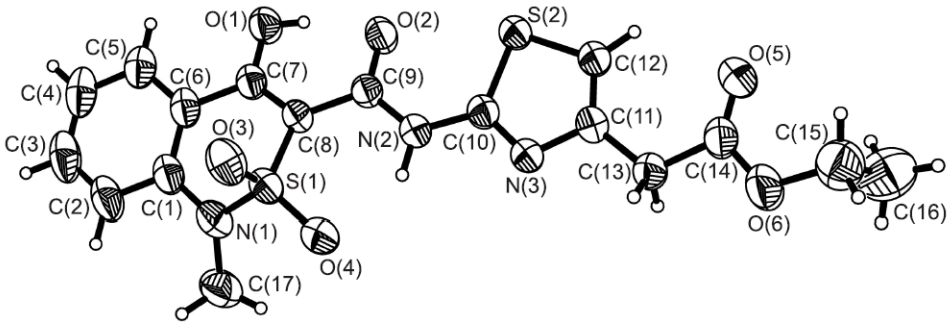


Fig.1. The molecular structure of amide **3b** with atoms represented by thermal vibration ellipsoids of 50% probability.

The thiazole ring was in an antiperiplanar position relative to the C(8)–C(9) bond and was coplanar with the carbamide fragment (the torsion angles C(10)–N(2)–C(9)–C(8) -175.5(2)°, C(9)–N(2)–C(10)–S(2) 1.6(3)°). The spatial relationship between the C(9)=O(2) bond and the thiazole ring in combination with the distance between the sulfur and oxygen atoms (2.76 Å, sum of van der Waals radii 3.13 Å) indicated σ-hole interaction between them. The ester group of the substituent in the thiazole ring was in *sp* conformation relative to the C(12)–C(11) bond and was practically coplanar to the C(11)–C(13) bond, with the torsion angles C(12)–C(11)–C(13)–C(14) 13.5(4)°, C(11)–C(13)–C(14)–O(5) -6.6(4)°. The ethyl group was in *ap* conformation relative to the C(13)–C(14) bond, while the C(15)–C(16) bond was practically orthogonal to the COO fragment plane, with the torsion angles C(15)–O(6)–C(14)–C(13) -172.0(3)°, C(14)–O(6)–C(15)–C(16) -91.2(4)°. Weak intramolecular hydrogen bonds C(12)–H···O(5) (H···O 2.40 Å, C–H···O 116°), C(17)–H(17a)···O(4) (H···O 2.30 Å, C–H···O 114°) were also identified in this molecule, and there was a shortened intramolecular contact H(5)···O(1) 2.41 Å (sum of van der Waals radii 2.46 Å).

The analgesic properties of hetarylamides **3-5** were studied with the standard thermal tail-flick test in white rats, the procedure of which we have previously described in detail [22]. Each of the compounds studied was tested in 7 animals. The experimental results obtained (Table 1) clearly demonstrated that the screening oral dose of 20 mg/kg of the compounds studied and the reference drugs noticeably decreased the sensitivity of the animals to pain. This was evidenced by the appropriate lengthening of the latent period of tail flick, as compared to the control group of animals received only solvents.

Statistically significant analgesic activity (assuming the level of statistical significance at $p \leq 0.05$) was demonstrated for all *N*-hetaryl-4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides **3-5** described in this work. However, the magnitude of this analgesic effect varied quite widely and depended on the structure of the amide fragment. First of all we should note that (5-methylthiazol-2-yl)amide **3a** is an actual isomer of meloxicam (**2**), and its higher activity confirms our approach in searching novel analgesic compounds. Unfortunately, we were not able to directly compare two other isomers, isoxicam (the manufacture of which has

Table 1. The Analgesic Activity of Hetarylamides **3-5** and Reference Drugs

Compound	The latent period after 1 h from administering of the compounds, s	Change of the latent period, compared to control, %
3a	6.29±0.20	+61.5
3b	7.27±0.22	+86.4
3c	4.26±0.14	+9.4
3d	5.03±0.19	+28.9
4	4.79±0.16	+22.9
5	4.32±0.12	+10.8
Meloxicam	5.78±0.15	+48.2
Piroxicam	4.87±0.17	+24.9
Control	3.90±0.18	—

been discontinued) and 5-methylisoxazol-3-ylamide **4**. However, taking into account the very similar analgesic properties of isoxicam and piroxicam [23], we may assume that the reversed positions of sulfur and nitrogen in the benzothiazine ring had practically no effect on the activity in this case. Of particular interest among all the compounds studied was ethyl ({[(4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazin-3-yl)carbonyl]amino}-1,3-thiazol-4-yl)acetate (**3b**), which was much more effective than piroxicam and meloxicam in suppressing the pain reaction caused by heat, and thus should be studied as a potential lead compound for further pharmacological development of analgesic agents.

We conclude that the method proposed for the synthesis of *N*-hetaryl-substituted 4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamides has provided good yields and purity of the target compounds, and thus can be recommended for a larger scale preparation of these compounds. The biological testing has indicated that changing the molecular structure from 1,2-benzothiazines to the isomeric 2,1-analogs is a promising approach that can successfully improve the analgesic properties of drug candidates.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra of the compounds synthesized were acquired on a Varian Mercury 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6, with TMS as internal standard. Mass spectra were recorded of a Varian 1200L instrument in full scan mode in the range of 35-700 *m*/*z*, with EI ionization (70 eV) and direct sample introduction. Elemental analysis was performed on a EuroVector EA-3000 elemental analyzer. Melting points were determined in a capillary by using an SMP10 Stuart digital melting point apparatus. The starting methyl 4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxylate (**6**) was synthesized according to a literature procedure [22].

4-Hydroxy-1-methyl-*N*-(5-methyl-1,3-thiazol-2-yl)-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamide (3a). A mixture of ester **6** (2.69 g, 0.01 mol), 2-amino-5-methylthiazole (1.14 g, 0.01 mol), and absolute xylene (2 ml) was kept for 1 h at 150°C on a liquid metal bath using a suitable air-cooled distilling column that allowed to distill off the methanol formed without removing the xylene solvent. The reaction mixture was cooled, EtOH (5 ml) was added, and the mixture was left for several hours at room temperature. The crystalline amide **3a** precipitated was filtered off, washed with cold EtOH, and dried. Yield 3.12 g (89%), yellowish crystals; mp 277-279°C (decomp., DMF–EtOH, 1:5). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.09 (1H, s, OH); 8.82 (1H, s, NH); 8.00 (1H, d, *J* = 7.7, H-5); 7.50 (1H, t, *J* = 7.6, H-7); 7.18-7.11 (2H, m, H-6,8); 6.93 (1H, s, H-4 thiazole); 3.27 (3H, s, NCH_3); 2.37 (3H, s, 5'-CH_3). ^{13}C NMR spectrum, δ, ppm: 169.9 (C-4); 162.3 (C=O); 159.9 (C-2 thiazole); 141.1 (C-8a); 133.1 (C-5); 128.9 (C-4 thiazole); 127.7 (C-5 thiazole); 125.5 (C-7); 123.5 (C-6); 122.8 (C-8); 117.2 (C-4a); 104.4 (C-3); 30.5 (NCH_3); 12.1 (5'-CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 351 $[M]^+$ (8), 237

(2), 211 (100), 147 (3), 140 (76), 114 (74), 105 (35), 91 (53), 72 (50). Found, %: C 47.76; H 3.65; N 12.03; S 18.11. $C_{14}H_{13}N_3O_4S_2$. Calculated, %: C 47.85; H 3.73; N 11.96; S 18.25.

Hetarylamides **3b-d**, **4**, and **5** were obtained similarly as white crystals with a yellowish tinge.

Ethyl ({[(4-Hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazin-3-yl)carbonyl]amino}-1,3-thiazol-4-yl)acetate (3b). Yield 83%; mp 144-146°C (DMF–EtOH, 1:8). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.08 (1H, s, OH); 9.67 (1H, s, NH); 8.01 (1H, d, *J* = 7.8, H-5); 7.58 (1H, t, *J* = 7.8, H-7); 7.25-7.18 (2H, m, H-6,8); 7.04 (1H, s, H-5 thiazole); 4.17 (2H, q, *J* = 7.2, OC<u>H</u>$_2$CH$_3$); 3.79 (2H, s, C<u>H</u>$_2$COOEt); 3.32 (3H, s, NCH$_3$); 1.29 (3H, t, *J* = 7.2, OCH$_2$C<u>H</u>$_3$). ^{13}C NMR spectrum, δ, ppm: 172.6 (<u>C</u>OOEt); 169.6 (C-4); 162.8 (C=O); 162.6 (C-2 thiazole); 141.2 (C-8a); 135.0 (C-4 thiazole); 133.7 (C-5); 127.6 (C-7); 123.3 (C-6); 123.1 (C-8); 117.5 (C-4a); 111.5 (C-5 thiazole); 105.0 (C-3); 61.6 (O<u>C</u>H$_2$CH$_3$); 34.3 (<u>C</u>H$_2$COOEt); 30.7 (NCH$_3$); 14.7 (OCH$_2$<u>C</u>H$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 423 [M]$^+$ (14), 237 (2), 212 (47), 211 (89), 186 (58), 147 (5), 139 (100), 118 (21), 105 (35), 91 (54), 71 (31). Found, %: C 48.15; H 3.96; N 9.98; S 15.02. $C_{17}H_{17}N_3O_6S_2$. Calculated, %: C 48.22; H 4.05; N 9.92; S 15.14.

4-Hydroxy-1-methyl-2,2-dioxo-*N*-(4-phenyl-1,3-thiazol-2-yl)-1*H*-2λ6,1-benzothiazine-3-carboxamide (3c). Yield 90%; mp 256-258°C (DMF–EtOH, 1:5). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.12 (1H, s, OH); 9.97 (1H, s, NH); 8.05 (1H, d, *J* = 7.8, H-5); 7.84 (2H, d, *J* = 7.5, H-2,6 Ph); 7.60 (1H, t, *J* = 7.5, H-4 Ph); 7.51 (1H, s, H-5 thiazole); 7.46 (2H, t, *J* = 7.5, H-3,5 Ph); 7.39 (1H, t, *J* = 7.7, H-7); 7.27-7.21 (2H, m, H-6,8); 3.35 (3H, s, NCH$_3$). ^{13}C NMR spectrum, δ, ppm: 169.7 (C-4); 162.5 (C=O); 161.8 (C-2 thiazole); 143.7 (C-4 thiazole); 141.2 (C-8a); 133.4 (C-5); 132.2 (C-*i* Ph); 129.6 (C-3,5 Ph); 129.3 (C-4 Ph); 127.7 (C-7); 126.5 (C-2,6 Ph); 123.9 (C-6); 123.0 (C-8); 117.5 (C-4a); 108.5 (C-5 thiazole); 105.1 (C-3); 30.7 (NCH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 413 [M]$^+$ (25), 237 (8), 211 (55), 202 (100), 176 (74), 147 (4), 134 (51), 118 (12), 105 (21), 91 (29), 77 (25). Found, %: C 55.28; H 3.75; N 10.23; S 15.42. $C_{19}H_{15}N_3O_4S_2$. Calculated, %: C 55.19; H 3.66; N 10.16; S 15.51.

***N*-[4-(Adamant-1-yl)-1,3-thiazol-2-yl]-4-hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamide (3d)**. Yield 96%; mp 251-253°C (DMF–EtOH, 1:5). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.04 (1H, s, OH); 9.54 (1H, s, NH); 8.02 (1H, d, *J* = 7.5, H-5); 7.55 (1H, t, *J* = 7.3, H-7); 7.24-7.17 (2H, m, H-6,8); 6.68 (1H, s, H-5 thiazole); 3.31 (3H, s, NCH$_3$); 2.11 (3H, s, 3,5,7-CH adamantane); 1.94 (6H, s, 2,8,9-CH$_2$ adamantane); 1.78 (6H, s, 4,6,10-CH$_2$ adamantane). ^{13}C NMR spectrum, δ, ppm: 173.1 (C-4); 162.4 (C=O); 152.4 (C-2 thiazole); 141.3 (C-8a); 137.3 (C-4 thiazole); 133.5 (C-5); 127.6 (C-7); 124.2 (C-6); 123.0 (C-8); 117.5 (C-4a); 105.7 (C-5 thiazole); 105.0 (C-3); 43.2 (2,8,9-CH$_2$ adamantane); 36.6 (4,6,10-CH$_2$ adamantane); 35.4 (C-1 adamantane); 30.7 (NCH$_3$); 28.6 (3,5,7-CH adamantane). Mass spectrum, *m*/*z* (I_{rel}, %): 471 [M]$^+$ (12), 260 (59), 237 (4), 234 (100), 211 (30), 203 (18), 177 (13), 147 (4), 105 (12), 91 (25), 77 (20). Found, %: C 58.69; H 5.45; N 9.03; S 13.53. $C_{23}H_{25}N_3O_4S_2$. Calculated, %: C 58.58; H 5.34; N 8.91; S 13.60.

4-Hydroxy-1-methyl-*N*-(5-methyl-1,2-oxazol-3-yl)-2,2-dioxo-1*H*-2λ^6,1-benzothiazine-3-carboxamide (4). Yield 84%; mp 178-180°C (DMF–EtOH, 1:5). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.43 (1H, s, OH); 10.06 (1H, s, NH); 8.08 (1H, d, *J* = 7.6, H-5); 7.77 (1H, t, *J* = 7.7, H-7); 7.48 (1H, d, *J* = 8.3, H-8); 7.37 (1H, t, *J* = 7.4, H-6); 6.68 (1H, s, H-4 oxazole); 3.49 (3H, s, NCH$_3$); 2.45 (3H, s, 5'-CH$_3$). ^{13}C NMR spectrum, δ, ppm: 170.3 (C-4); 162.3 (C=O); 158.4 (C-3 oxazole); 137.3 (C-8a); 133.9 (C-5); 128.8 (C-5 oxazole); 124.2 (C-7); 123.7 (C-6); 122.6 (C-8); 119.4 (C-4 oxazole); 118.2 (C-4a); 106.2 (C-3); 31.5 (NCH$_3$); 12.9 (5'-CH$_3$). Mass spectrum, *m*/*z* (I_{rel}, %): 335 [M]$^+$ (23), 237 (69), 211 (100), 146 (28), 133 (25), 124 (53), 105 (63), 98 (64), 91 (79), 77 (62). Found, %: C 50.03; H 3.99; N 12.44; S 9.47. $C_{14}H_{13}N_3O_5S$. Calculated, %: C 50.14; H 3.91; N 12.53; S 9.56.

Methyl 3-{[(4-Hydroxy-1-methyl-2,2-dioxo-1*H*-2λ^6,1-benzothiazin-3-yl)carbonyl]amino}thiophene-2-carboxylate (5). Yield 80%; mp 222-224°C (DMF–EtOH, 1:8). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.57 (1H, s, OH); 11.40 (1H, s, NH); 8.10 (1H, d, *J* = 7.8, H-5); 8.06 (1H, d, *J* = 5.5, H-5 thiophene); 7.82 (1H, d, *J* = 5.5, H-4 thiophene); 7.77 (1H, t, *J* = 7.5, H-7); 7.48 (1H, d, *J* = 8.3, H-8); 7.39 (1H, t, *J* = 7.5, H-6); 3.93 (3H, s, OCH$_3$); 3.51 (3H, s, NCH$_3$). ^{13}C NMR spectrum, δ, ppm: 170.6 (<u>C</u>OOMe); 164.7 (C-4); 163.3 (C=O); 155.9 (C-3 thiophene); 137.3 (C-8a); 133.6 (C-5); 133.0 (C-2 thiophene); 128.8 (C-5 thiophene); 124.4 (C-7);

123.9 (C-6); 121.0 (C-8); 119.3 (C-4 thiophene); 118.9 (C-4a); 104.8 (C-3); 52.9 (OCH_3); 32.3 (NCH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 394 $[M]^+$ (32), 237 (3), 211 (3), 157 (100), 125 (30), 105 (5), 91 (6), 77 (11). Found, %: C 48.64; H 3.67; N 7.18; S 16.16. $C_{16}H_{14}N_2O_6S_2$. Calculated, %: C 48.72; H 3.58; N 7.10; S 16.26.

X-ray Structural Study of Compound 3b. Compound **3b** ($C_{17}H_{17}N_3O_6S_2$, *M* 423.47) formed monoclinic crystals (DMF), at 20°C: *a* 10.7511(7), *b* 7.2105(5), *c* 23.998(1) Å; β 97.665(5)°; *V* 1843.7(2) $Å^3$; *Z* 4; space group $P2_1/c$; d_{calc} 1.526 g/cm^3; μ(MoKα) 0.331 mm^{-1}; *F*(000) 880. Unit cell parameters and intensities of 18008 reflections (5367 independent, R_{int} 0.034) were measured on an Xcalibur-3 diffractometer (MoKα-radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ 60°).

The structure was solved directly with the SHELXTL software package [24]. The structure was refined with the constrained bond length in the ethyl group (1.54 Å). The hydrogen atom positions were identified by differential synthesis of electron density and refined with the "rider" model with $U_{iso} = nU_{eq}$ for each non-hydrogen atom linked to the corresponding hydrogen atom (n = 1.5 for methyl groups and n = 1.2 for the rest of the hydrogen atoms). The hydrogen atoms involved in hydrogen bonding were refined in isotropic approximation. The structure was solved by F^2 full-matrix method of least squares in anisotropic approximation for the non-hydrogen atoms to wR_2 0.172 using 5257 reflections (R_1 0.056 using 3391 reflections with $F > 4\sigma(F)$, S 1.017). The complete crystallographic data set was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 969536).

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