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# Studies on Reactions of 3-Benzoyl-4-hydroxypyrido[3,2-*e*]-1,2-thiazines with Primary Amines and N-Methylhydrazine

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Reaction of the appropriate 3-benzoyl-4-hydroxypyrido[3,2-*e*]-1,2-thiazine-1,1-dioxides **2** bearing a methyl or a 3-(4-arylpiperazin-1-yl)propyl group at the nitrogen atom of the thiazine ring with primary amines resulted in enamines of type (E)-**3**. The related products **8** were obtained by alkylation of 3-phenylpyrazolo[4,3-*c*]pyrido[3,2-*e*]-1,2-thiazine-5,5-dioxide **7** with the corresponding 1-aryl-4-(3-chloropropyl)piperazines **9**. The structures of the new heterocycles **3** and **8**, synthesized for pharmaceutical purposes, and of the model compounds **4**–**6**, prepared for comparison of spectral properties, were proven through elemental, IR, $^1$H NMR and, in some cases (**3d, 8a**), X-ray data.

**Key words**: pyrido-1,2-thiazines, pyrazolopyrido-1,2-thiazines, syntheses, X-ray study

Oxicams (Fig. 1) represent a newer chemical category of the enolic acids, used in the treatment of chronic rheumatic diseases [1]. In previous communications we reported the synthesis and antiinflammatory evaluation of their pyridine-analogues of general structure **I** (Fig. 1) [2] and the related 2-substituted-3-acyl-4-hydroxypyrido[3,2-*e*]-1,2-thiazines **II** (Fig. 1). Some of the heterocycles **II**, obtained in connection with various projects, exhibited, depending on the substituents R and R′, antimycobacterial **IIa** [3], psychopharmacological **IIb** [4], or analgesic **IIc** [5] activity under preliminary pharmacological screening.

The pronounced biological action of the pyridothiazines **IIa–c** stimulated us to continue our search and prepare their analogues, modified at the $\beta$-dicarbonyl grouping, partially incorporated in the 1,2-thiazine ring, in order to evaluate the influence of this structural change on biological activity. Based on our preliminary results [3–5], the 2-substituted-3-benzoylpyridothiazines **II** (R = $C_6H_5$, R′ ≠ H ) were chosen for further development. In this study, we report the conversion of some compounds **II** into enamines (E)-**3** (Scheme 1) and an investigation on determination of their

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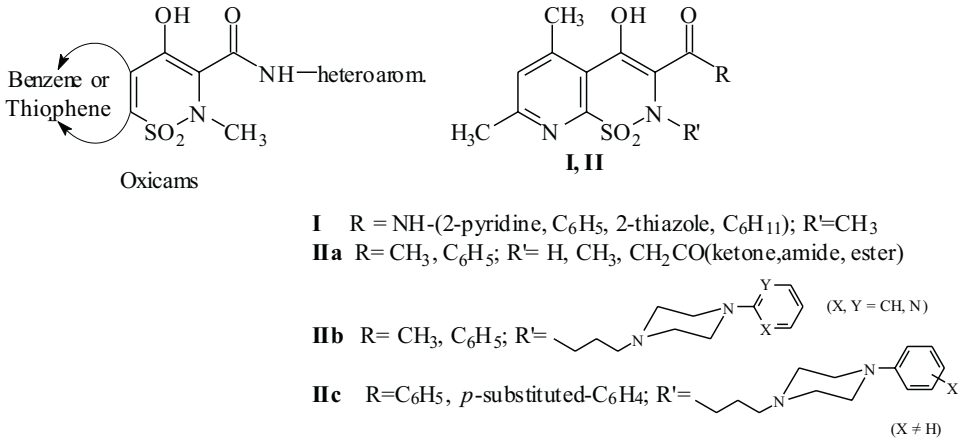



**Figure 1.**

structure. Additionally, model compounds **4–6** (Scheme 2) were synthesized for comparison of spectral data and derivatives of the triheterocyclic system of pyrazolo-pyridothiazine **8** (Scheme 3), which can be considered as partially rigid analogues of enamines **3**, were prepared for a comparison of biological effects.

## RESULTS AND DISCUSSION

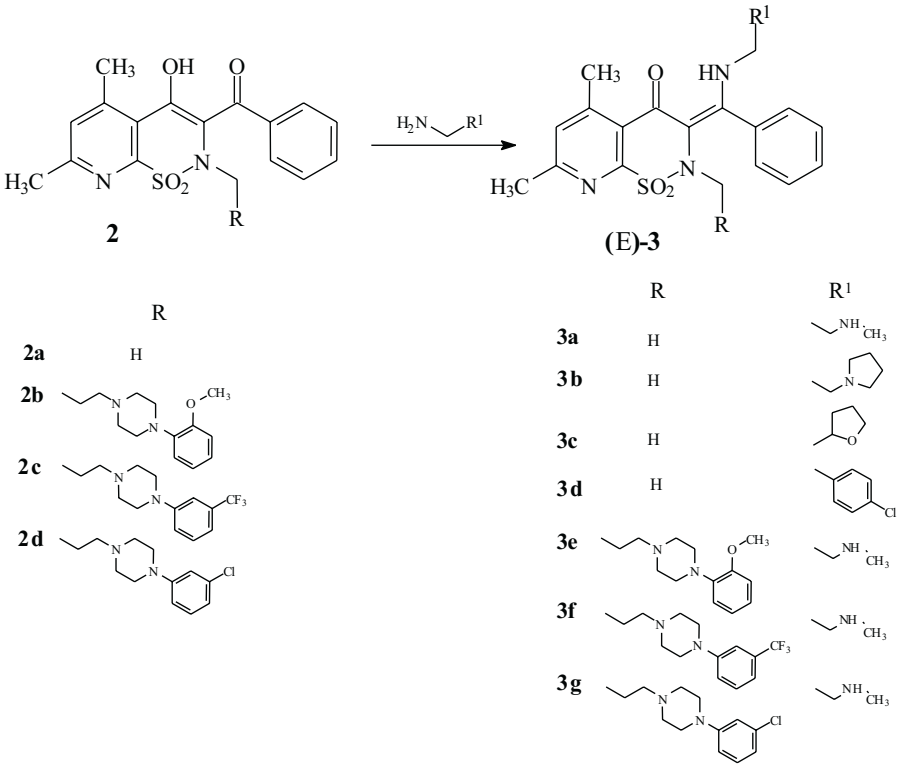
In the present work we found that 2-substituted-3-benzoyl-4-hydroxypyridothiazines **2** (Scheme 1) show a high reactivity toward some primary amines [N-methylethylenediamine, 1-(2-aminoethyl)pyrrolidine, tetrahydrofurfurylamine, *p*-chlorobenzylamine], resulting in the corresponding enamine derivatives of type (E)-**3**.

The synthesis of compounds **3** was carried out by heating equimolar amounts of pyridothiazines **2a–d** [5,6] and the corresponding amines in ethanol solution. The reactions yields were moderate to high (30–72%). The model compounds **4–6** (Scheme 2) were also prepared for comparison of spectral data.

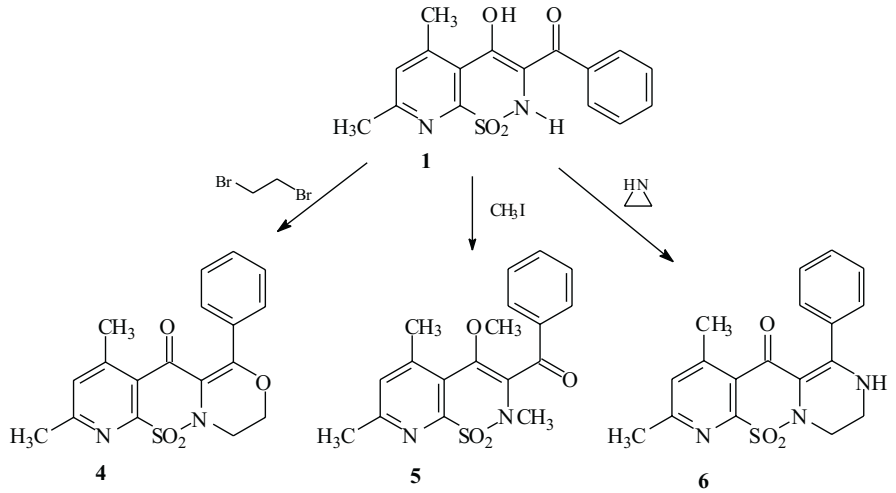
Compound **4** was formed by heating 3-benzoyl-4-hydroxypyrido-1,2-thiazine **1** [6] in DMF, containing an excess of dibromoethane/NaOEt, **5** by methylation of the substrate **1** with $CH_3I/K_2CO_3$ in acetonitrile, whereas **6** by reaction of **1** and ethylenediamine in DMF. It should be noted, that compounds **4** and **6** belong to the previously unreported new heterocyclic ring systems – pyrido[3′,2′:5,6]-1,2-thiazino[3,2-*c*]-1,4-oxazine and pyrido[3,2-*e*]pyrazino[3,4-*b*]-1,2-thiazine, respectively.

The experiments with the preparation of the model compounds **4–6** demonstrated, that starting 3-benzoyl-4-hydroxypyrido-1,2-thiazine **1** possesses the capability

Scheme 1




Scheme 2



of reacting in two tautomeric forms – 4-hydroxy (Scheme 2) and 4-oxo (tautomer is not shown). Therefore, the enol-imine (A, B) and oxo-enamine (C, D) structures, shown in Fig. 2, were possible for the products **3** obtained. Additionally, in the case of the isomer B and C, which possesses an exocyclic C=C double bond, two geometric forms E and Z or an E/Z-mixture of them may by present (Fig. 2).

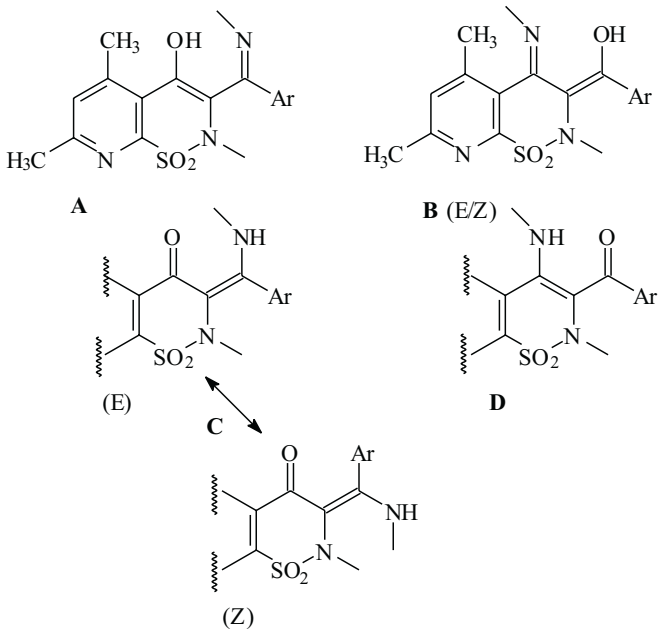



**Figure 2.**

Structures of enamines **3** and the model compounds **4–6** were fully characterized by elemental analysis, IR and $^1$H NMR spectra and, in some cases (**3d, 8a**), also with the X-ray method.

The IR spectra of **4–6** (Scheme 2) showed absorption at 1625–1655 cm$^{-1}$ of medium intensity, confirming the presence of the C=O bound. In the $^1$H NMR of compound **5**, similar to the recently described substrates **2** [5,6] (Scheme 1), the aromatic region of the 3-benzoyl group was split into two signal groups, centered at ~8.2 (2H) and ~7.6 (3H) ppm. In contrast, the aromatic protons of the benzylidene grouping of **4** and **6** appeared as a sharp multiplet (br s) at ~7.4 ppm. In addition, the structure of compound **4**, which gave crystals suitable for X-ray measurement, was confirmed by X-ray determination [7].

The (E)-C (Fig. 2) type structure of the enamines **3** was established on the base of elemental and spectroscopic (IR, $^1$H NMR) data, by comparison of their spectral data with those of the model compounds **4–6** and by X-ray analyses of **3d**. The structures of (E)-**3** were supported by the following proofs:

a) All the products **3** showed only one set of signals in the $^1$H NMR spectra. This proves the existence of one predominant form with no indication of a tautomerization.

b) The $^1$H-NMR ($CDCl_3$) spectrum of the *p*-chlorobenzyl derivative **3d** (as an example), revealed a doublet of -$CH_2$- benzyl protons, centered at 4.27 ppm ($J$ = 6.3 Hz) and a broad exchangeable 1H (NH) signal at 12.0 ppm. Addition of $D_2O$ results in an exchange of the 12.0 ppm signal and the 4.27 ppm doublet collapsed into a singlet (4.27 ppm, 2H), indicating the coupling between NH-$CH_2$-Ar. This excludes the enol-imine A and B forms (Fig. 2), where the $CH_2$-benzyl protons would appear as a singlet.

c) The enamines **3a–g** (Scheme 1), in contrast to the substrates **2a–d**, did not produce an intense coloration with iron(III) chloride, indicating the lack of an enolic hydroxy group. This also excludes the enol-imine forms A and B.

d) The aromatic protons of the 3-substituent of **3a–d**, similar to the model compounds **4** and **6** with a benzylidene substructure, always appeared as a sharp multiplet (br s) at ~7.48 ppm. These data suggest, that the oxo-enamine form D (Fig. 2) can be ruled out, because in the case of this isomer, as for the 3-benzoyl derivative **5** and substrates **2** described recently [5,6], the aromatic region of the 3-substituent should be split into two signal groups, centered at ~8.2 (2H) and ~7.6 (3H) ppm. Hence, the data presented above for compounds **3a–d** are compatible with the isomer C.

The aromatic region of the enamines **3e–g**, possessing the 4-arylpiperazine moiety, exhibited lines at ~6.7–7.9 (m, 10H, 9ArH + $H_\beta$-pyridine). Because these compounds were obtained under conditions identical to those of **3a–d**, we hope that the preferential formation of the required analogues of type **3**-C (Fig. 2) also occurs in this case.

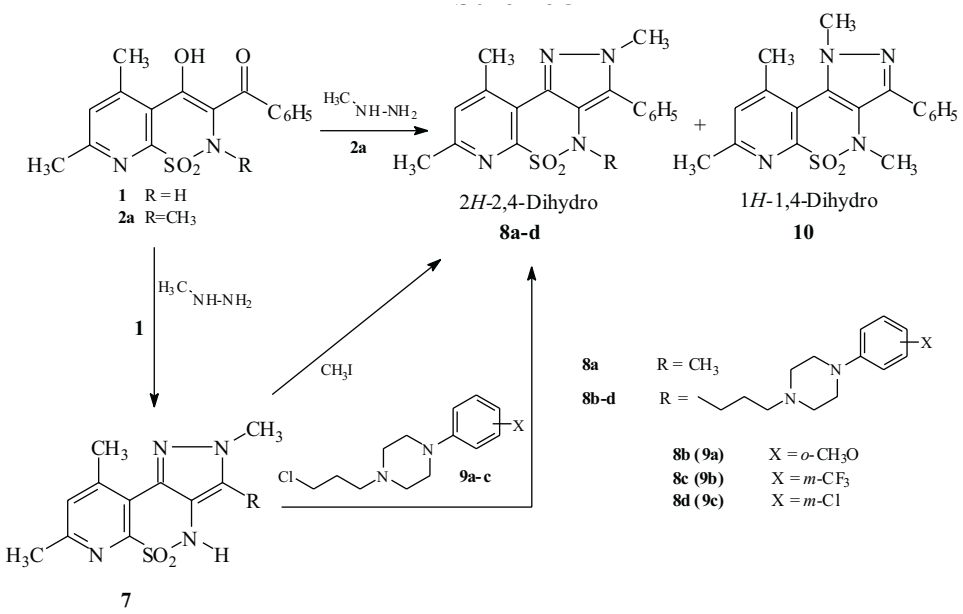
e) Enamines **3**-C (Fig. 2) may be present at their geometric form (Z) or (E). The ~20–25 $cm^{-1}$ bathochromic shift of the 4-oxo bound, observed in the IR spectra of **3a–g** with respect to that of **6**, suggests the existence of an intramolecular hydrogen bonding with the NH enamine proton and (E)-configuration around the exocyclic C=C bond. The (E)-configuration of enamines **3** is clearly evident from crystallographic data of **3d** (the solid state conformation is depicted in Fig. 3). Consequently, it is reasonable to propose the (E)-configuration for all the all remaining enamines **3**, as shown in Scheme 1.

The 2-methyl enamines (E)-**3a–c** (Scheme 1) were evaluated for their ability to produce an antimycobacterial effect. In this context, it should be noted that the model compound **6** (Scheme 2) can be partially considered as a (Z)-analogue of the enamines (E)-**3**, and this derivative was also included in the antimycobacterial investigation. The results of the primary screening indicated, that enamines **3a–c** did not show appreciable activity at the assayed concentration of 6.25 $\mu$g/ml against *Mycobacterium tuberculosis* H37Rv (10–15% inhibition) [8]. Their **IIa** precursors exhibited activity in the range 10–40%, however, this activity refers to a concentration of 12.5 $\mu$g/ml [3]. For compound **6** we have not got biological data yet. Enamines (E)-**3e–g** are currently under investigation as potential analgesic agents, because the pyrido-

thiazines **2b–d** (Scheme 1) with a 3-(4-arylpiperazinyl)propyl side chain, starting their synthesis, were promising analgesic candidates for chemical development [5]. For the comparison of the biological effects of enamines (E)-**3e–g**, pyrazolopyrido-1,2-thiazines **8b–d** (Scheme 3), which can be considered as their partially rigid analogues, were prepared.

It has been reported, that hydrazines show excellent reactivity towards the $\beta$-dicarbonyl grouping of different compounds, giving the respective pyrazole derivatives [9]. In the course of a recent investigation [10], we observed that the $\beta$-dicarbonyl grouping of 3-benzoyl-4-hydroxy-2-methylpyrido[3,2-*e*]-1,2-thiazine **2a** in the presence of an excess of N-methylhydrazine undergoes cyclization to the isomeric derivatives 2*H*-2,4-dihydro-**8a** and 1*H*-1,4-dihydro-**10** (Scheme 3) of the new system pyrazolo[4,3-*c*]pyrido[3,2-*e*]-1,2-thiazine with preferred formation of **8a**.

Scheme 3




As we previously reported [10], the IR and $^1$H NMR spectra of **8a** and **10** were quite similar and these isomeric heterocycles were differentiated on the basis of UV spectra only. Since these compounds exhibited biological (antimycobacterial) activity [11], we were encouraged to reconfirm their structures with X-ray method, the more so that crystallographic data of the pyrazolo[4,3-*c*]pyrido[3,2-*e*]-1,2-thiazine ring system has not yet been measured. Therefore, in this study X-ray investigations were undertaken using **8a** as a model compound, which gives suitable crystals for crystallogaphic measurement. The X-ray data confirmed, that the recent UV characteri-

zation of **8a** was in accordance with the proposed structure (the single-crystal X-ray structure of **8a** is shown in Fig. 3).

As we recently reported [10], compound **8a** was also formed in a methylation reaction of the substrate **7** with $CH_3I$ in an ethanol/NaOEt solution (Scheme 3). Employing these conditions, the target analogues **8b–e** of the enamines (E)-**3e–g** were prepared by alkylation of the pyrazolopyridothiazine **7** [10] with the corresponding 1-aryl-4-(3-chloropropyl)piperazines **9a–c** (Scheme 3), with yields of ~30–50%. Intermediates **9** were obtained from commercially available 1-arylpiperazines and 1-bromo-3-chloropropane [5,12]. The elemental analysis and $^1$H NMR spectral data confirmed the proposed structures of the heterocycles **8b–d**. It is noteworthy that, as in the case of the (E)-enamines **3a–d**, the aromatic protons of the 3-substituent appeared at ~7.55 ppm, as a singlet.

The biological activity (analgesic action) of the heterocycles **8b–d** is currently under investigation.

*Crystal and molecular structure of **3d** and **8a***. Selected geometrical parameters (bond distances, angles) for X-ray investigated crystal structures of (E)-**3d** and **8a** [10] are given in Table 1. A view of the molecules with numbering of the atoms are shown in Fig. 3.

The pyrido[3,2-*e*]-1,2-thiazine rings system is common for both analyzed structures and the geometry (bond lengths, angles and planarity) of this molecular fragment in (E)-**3d** and **8a** is very similar. The pyridine rings are planar to within 0.007(4) and 0.008(2) Å for **8a** and (E)-**3d**, respectively. The methyl substituents in the pyridine ring are displaced from the best pyridine plane by 0.003(6) Å for C71, –0.028(6) Å for C91 in **8a** and –0.076(3) Å for C15 and –0.055(3) Å for C16 in (E)-**3d**. The analysis of the torsion angles and calculated asymmetry parameters [13] indicates that the six-numbered partially saturated thiazine rings adopt diplanar conformation with two torsion angle close to 0° (S1–C11–C13–C6 = –3.3(5)°, N2–C12–C6–C13 = –0.1(6)° in **8a** and S1–C9–C10–C4 = 1.8(2)° and N2–C3–C4–C10 = 1.7(3)° in [(E)-**3d**] and domination of 2-fold symmetry axis bisecting S1–N2 bond; adequate asymmetry parameters $\Delta C_2^{S1,N2}$, are 3.5° for **8a** and 5.3° for (E)-**3d**. To minimize the steric effect of the adjacent $SO_2$ and N-$CH_3$ groups, O11 atom and the lone pair on N2 atom occupy equatorial positions, while the second O12 atom and $CH_3$ methyl group occupy axial positions in opposite side of S1–N2 bond for both thiazine rings. The geometry at the S atoms exhibit distorted tetrahedral configuration with the largest deviations in the O–S–O and N–S–C angles [O12–S1–O11 = 119.65(19)°, N2–S1–C11 = 103.26(17)° in **8a** and O12–S1–O11 = 119.74(9)° and N2–S1–C9 = 100.61(9)° for (E)-**3d**]. These angles and S–C, two S–O and S–N bond lengths do not differ significantly from mean values of those observed in similar substructures [14]. The N2 atoms have flattened pyramidal configuration; the sums of the bonds angles around these atoms are 342.0(3)° for **8a** and 345.4(1)° for (E)-**3d**, intermediate values between expected $sp^3$ and $sp^2$ hybridization.

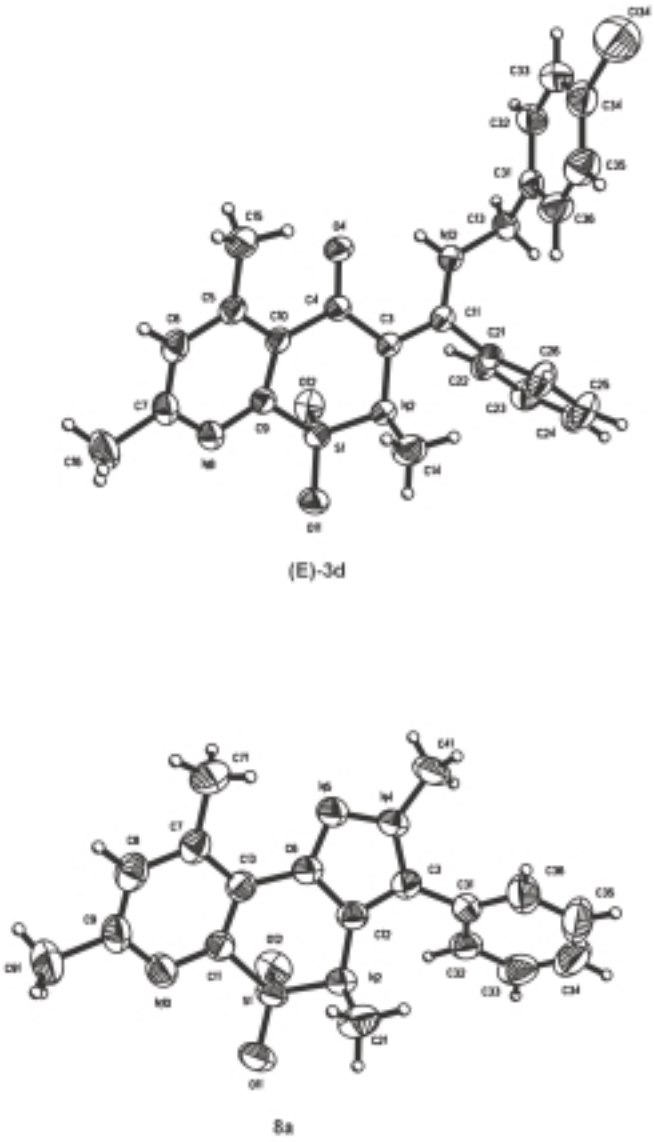



**Figure 3.** A view of the molecules **3d** and **8a** with the atomic labelling. Non-H atoms are represented by displacement ellipsoids of 50% probality.

The bond lengths in the pyrazole ring of **8a** are typical for the delocalized $\pi$-electrons system. This ring is planar to within 0.006(4) Å and inclined at an angle of 20.1(1)° to pyridine ring. The methyl substituent is displaced from the best plane of the pyrazine ring by –0.149(6) Å.

**Table 1.** Selected bond distances (Å) and angles (°) for **3d** and **8a**.

| | Compound **3d** | | Compound **8a** |
|---|---|---|---|
| Bond distances | | | |
| S(1)–O(11) | 1.422(3) | S(1)–O(11) | 1.4231(14) |
| S(1)–O(12) | 1.426(3) | S(1)–O(12) | 1.4229(14) |
| S(1)–N(2) | 1.649(3) | S(1)–N(2) | 1.6311(16) |
| S(1)–C(11) | 1.789(4) | S(1)–C(9) | 1.7792(19) |
| N(2)–C(12) | 1.431(4) | N(2)–C(3) | 1.448(2) |
| N(2)–C(21) | 1.474(6) | N(2)–C(14) | 1.477(3) |
| N(4)–C(3) | 1.351(4) | N(12)–C(11) | 1.325(2) |
| N(4)–N(5) | 1.363(4) | | |
| N(4)–C(41) | 1.453(5) | N(12)–C(13) | 1.461(2) |
| N(5)–C(6) | 1.343(5) | O(4)–C(4) | 1.249(2) |
| C(3)–C(12) | 1.368(5) | C(3)–C(11) | 1.394(2) |
| C(3)–C(31) | 1.481(5) | C(11)–C(21) | 1.492(2) |
| C(6)–C(12) | 1.396(5) | C(3)–C(4) | 1.426(2) |
| C(6)–C(13) | 1.463(5) | C(4)–C(10) | 1.499(2) |
| C(11)–C(13) | 1.402(5) | C(9)–C(10) | 1.392(3) |
| | | C(13)–C(31) | 1.504(3) |
| Bond angles | | | |
| O(11)–S(1)–O(12) | 119.65(19) | O(11)–S(1)–O(120) | 119.74(9) |
| O(11)–S(1)–N(2) | 107.47(18) | O(11)–S(1)–N(2) | 108.57(8) |
| O(12)–S(1)–N(2) | 107.64(17) | O(12)–S(1)–N(2) | 108.40(9) |
| O(11)–S(1)–C(11) | 110.16(18) | O(11)–S(1)–C(9) | 109.68(9) |
| O(12)–S(1)–C(11) | 107.43(17) | O(12)–S(1)–C(9) | 108.14(8) |
| N(2)–S(1)–C(11) | 103.26(17) | N(2)–S(1)–C(9) | 100.61(9) |
| C(12)–N(2)–C(21) | 115.7(3) | C(3)–N(2)–C(14) | 116.84(16) |
| C(12)–N(2)–S(1) | 110.0(2) | C(3)–N(2)–S(1) | 113.12(11) |
| C(21)–N(2)–S(1) | 116.3(3) | C(14)–N(2)–S(1) | 115.48(14) |
| C(3)–N(4)–N(5) | 113.1(3) | | |
| C(3)–N(4)–C(41) | 127.5(4) | C(11)–N(12)–C(13) | 127.31(17) |
| N(5)–N(4)–C(41) | 118.9(3) | | |
| C(6)–N(5)–N(4) | 104.0(3) | | |
| N(4)–C(3)–C(12) | 105.6(3) | N(12)–C(11)–C(3) | 121.18(17) |
| N(4)–C(3)–C(31) | 124.6(3) | N(12)–C(11)–C(21) | 117.23(16) |
| C(12)–C(3)–C(31) | 129.8(3) | C(3)–C(11)–C(21) | 121.56(17) |
| N(5)–C(6)–C(12) | 110.7(3) | O(4)–C(4)–C(3) | 122.03(17) |

Table 1 (continuation)

| | | | |
|---|---|---|---|
| N(5)–C(6)–C(13) | 126.5(3) | O(4)–C(4)–C(10) | 118.56(16) |
| C(12)–C(6)–C(13) | 122.8(3) | C(3)–C(4)–C(10) | 119.37(16) |
| C(13)–C(11)–S(1) | 119.1(3) | C(10)–C(9)–S(1) | 117.26(14) |
| C(3)–C(12)–C(6) | 106.7(3) | C(11)–C(3)–C(4) | 122.44(17) |
| C(3)–C(12)–N(2) | 128.5(3) | C(11)–C(3)–N(2) | 117.78(15) |
| C(6)–C(12)–N(2) | 124.8(3) | C(4)–C(3)–N(2) | 119.76(15) |
| C(11)–C(13)–C(6) | 117.3(3) | C(9)–C(10)–C(4) | 120.77(16) |
| | | N(12)–C(13)–C(31) | 110.68(17) |

The rings of phenyl substituents C31–C36 in **8a** and C21–C26 in (E)-**3d** are planar; their least-squares planes are inclined by 40.32(15)° and 78.72(7)° with respect to the pyridine planes for **8a** and (E)-**3d**, respectively. The influence of the steric hindrance of the large *p*-chlorobenzyl substituent on mutual orientation of phenyl and pyridothiazine parts in (E)-**3d** is observed.

In compound (E)-**3d**, the enamine H on N12 is involved in an intramolecular hydrogen bond to O4 of the carbonyl group [N12–H12 = 0.86(2), N12…O4 = 2.601(2), H12…O4 = 1.90(2) Å and N12–H12…O4 = 137(2)°] is observed. The planarity of the atomic group C10, O4, C4, C3, C11, N12 to within 0.034(2) Å and the bond lengths C4–O4 [1.249(2) Å], C3–C4 [1.426(2) Å], C3–C11 [1.394(2) Å] and C11–N12 [1.325(2) Å] point at delocalization of the $\pi$ electrons in the oxo-enamine substructure.

The molecular packing in the crystals of both investigated compounds is influenced by the presence of the weak C–H…X intermolecular hydrogen bonds. In the crystal structure of **8a**, the molecules are joined in molecular chains parallel to Y crystallographic axis by C33–H331…O11 (–x, ½ + y, ½ – z) hydrogen bonds: C33–H331 = 1.01(6), C33…O11 = 3.214(6), H331…O11 = 2.35(6) Å and C33–H331…O3 = 144(5)°. Inversion-related molecules in the crystal of (E)-**3d** form dimers by the pair of C22–H221…O4 (–x + 1, –y, –z) hydrogen bonds: C22–H221 = 0.97(3), C22…O4 = 3.503(3), H221…O4 = 2.56(2) Å and C22–H221…O3 = 165(2)°. Neighbouring chains in **8a** and dimers in (E)-**3d** are held together by van der Waals forces only.

A search of the Cambridge Structural Data base (CSD, version November 2002) [15,16] revealed only two structures of the compounds containing pyrido[4,3-*c*]-1,2-thiazine moiety [17] and 34 organic structures with benzo[3,2-*e*]-1,2-thiazine part; *e.g.* the non-steroidal anti-inflammatory and analgesic agents as PIROXICAM in neutral [18] and zwitterions [19] forms, MELOXICAM in neutral enol, anion, cation and zwitterions forms [20], and DROXICAM [21] and also one tricyclic condensed pyrazolobenzothiazine derivative [22]. The bond lengths, angles and conformation of pyridothiazine part in both investigated compounds (E)-**3d** and **8a** do not differ significantly from those reported for searched benzothiazine derivatives. Differences are observed in the geometry and conformation of the side chains, caused by several possibilities of intramolecular hydrogen bonds formation.

## CONCLUSIONS

a) In order to evaluate the significance of modification of the $\beta$-dicarbonyl grouping in some 2-substituted-3-benzoyl-4-hydroxypyrido[3,2-*e*]-1,2-thiazines of type **II** (Fig. 1) on biological activity, we prepared seven enamines (E)-**3** (Scheme 1) and three related pyrazolopyridothiazines **8** (Scheme 3). Additionally, the model compounds **4–6** (Scheme 2) were obtained for comparative spectral data. b) Reaction between 2-substitued-3-benzoyl-4-hydroxypyrido[3,2-*e*]-1,2-thiazines (**1** or **2**) and primary amines or N-methylhydrazine in ethanol solution shifts the tautomeric equilibrium of the $\beta$-dicarbonyl grouping in substrates **1** and **2** from 4-hydroxy to 4-oxo tautomers. This was necessary for the predominant formation of the corresponding enamines (E)-**3** and pyrazolopyridothiazines **8**. c) The structure of the new compounds **3–6** and **8** was evident from elemental, spectral (IR, $^1$H NMR) and X-ray (**3d**, **4** and **8a**) data. d) A search of the Cambridge Structural Data base revealed, that compounds containing the title pyrido[3,2-*e*]-1,2-thiazine ring system has not yet been measured with X-ray method. e) The biological data currently available on the enamines (E)-**3a–c** seems to indicate, that structural modification of the $\beta$-dicarbonyl grouping of pyridothiazines **IIa** (Fig. 1) to improve their antimycobacterial potency, rather does not lead to advantageous results. Biological evaluations of the enamines (E)-**3e–g**, substituted with 4-arylpiperazinylpropyl moiety and their triheterocylic analogues **8b–d**, are in progress and their results will be the subject of a separate paper.

## EXPERIMENTAL

Melting points are uncorrected. $^1$H NMR spectra in $CDCl_3$ were recorded on a Tesla (80 MHz) or a Brucker (200 MHz) spectrometer, the chemical shifts are reported in $\delta$ (ppm). IR (KBr) spectra were recorded on Specord-75 IR spectrometer. Elemental C, H, N analyses were run on a Carlo Erba NA-1500 analyzer, the results were within 0.4% of the values calculated for the corresponding formulas. Chromatographic separations were performed on a silica gel [Kieselgel 60 (70–230 mesh), Merck] column (CC).

**General procedure for preparation of pyrido-1,2-thiazine-1,1-dioxides of enamine type (E)-3**. A solution of 1.5 mmol of 2-substituted-3-benzoyl-4-hydroxypyrido-1,2-thiazine-1,1-dioxide **2** [5,6] and 2 mmol of corresponding amine in ethanol (20 ml) was refluxed (5–15 hrs). After cooling the product precipitated [(E)-**3a–d**) was filtered off and purified by crystallization. In the case of enamines (E)-**3e–g** ethanol was distilled off and the residue was treated with water. Then, the solid formed was filtered off and purified by crystallization [(E)-**3f**, **g**] or with CC [(E)-**3e**] to give pure enamines.

(E)-**3a:** Yield 0.24 g (40%) from 3-benzoyl-4-hydroxy-2-methylpyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide (**2a**) [6] and N-methylethylenediamine (5 hrs), m.p. 209–211°C (ethanol). Anal. Calcd. for $C_{20}H_{24}N_4O_3S$ (400.49): C, 60.0; H, 6.0; N, 14.0. Found: C, 60.2; H, 5.8; N, 14.4. $^1$H NMR (80 MHz): 1.35 s (1H, NH, $D_2O$ exchangeable), 2.4 s (3H, $NCH_3$), 2.51 s (3H, $CH_3$), 2.61 s (3H, $CH_3$), 2.78 m (5H, 2-$NCH_3$ + $NCH_2$), 3.11–3.32 m (2H, $CH_2$N-enamine), 7.28 s (1H, $H_\beta$-pyridine), 7.48 br s (5H, ArH), 11.8 br (1H, HN-enamine, $D_2O$ exchangeable). IR: 1600 (C=O), 1570–1540 (C=C).

(E)-**3b:** Yield 0.3 g (46%) from 3-benzoyl-4-hydroxy-2-methylpyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide (**2a**) [6] and 1-(2-aminoethyl)pyrrolidine (10 hrs), m.p. 172–174°C (ethanol). Anal. Calcd. for $C_{23}H_{28}N_4O_3S$ (440.56): C, 62.7; H, 6.4; N, 12.7. Found: C, 62.6; H, 6.1; N, 12.4. $^1$H NMR (80 MHz): 1.7–1.9 m (4H, CH), 2.4–2.7 m [12H, 2x$CH_3$ + N($CH_2$)$_3$], 2.78 s (3H, 2-$NCH_3$), 3.04–3.3 m (2H, $CH_2$N-enamine), 7.25 s (1H, $H_\beta$-pyridine), 7.47 br s (5H, ArH), 11.8 br (1H, HN, $D_2O$ exchangeable). IR: 1600 (C=O), 1540–1570 (C=C).

(E)-**3c:** Yield 0.19 g (30%) from 3-benzoyl-4-hydroxy-2-methylpyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide (**2a**) [6] and tetrahydrofurfurylamine (5 hrs), m.p. 250–252°C (ethanol). Anal. Calcd. for $C_{22}H_{25}N_3O_4S$ (427.51): C, 61.8; H, 5.9; N, 9.8. Found: C, 62.1; H, 6.1; N, 9.5. $^1$H NMR (80 MHz): 1.3–1.9 m (4H, CH), 2.51 s (3H, $CH_3$), 2.64 s (3H, $CH_3$), 2.78 s (3H, 2-$NCH_3$), 3.0–3.3 m (2H, $CH_2$N-enamine), 3.7–4.05 m (3H, CH-O-$CH_2$), 7.29 s (1H, H$_\beta$-pyridine), 7.49 br s (5H, ArH), 11.9 br (1H, HN, $D_2O$ exchangeable): IR: 1600 (C=O), 1570–1540 (C=C).

(E)-**3d:** Yield 0.51 g (72%) from 3-benzoyl-4-hydroxy-2-methylpyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide (**2a**) [6] and *p*-chlorobenzylamine (15 hrs), m.p. 218–220°C (ethanol). Anal. Calcd. for $C_{24}H_{22}ClN_3O_3S$ (467.96): C, 61.6; H, 4.7; N, 9.0. Found: C, 61.7; H, 4.5; N, 8.7. $^1$H NMR (80 MHz): 2.53 s (3H, $CH_3$), 2.64 s (3H, $CH_3$), 2.76 s (3H, 2-$NCH_3$), 4.27 d (2H, NH-$CH_2$, $J$ = 6.3 Hz), 7.0–7.4 m (5H, 4ArH + H$_\beta$-pyridine), 7.48 br s (5H, ArH), 12.0 br (1H, HN, $D_2O$ exchangeable). IR: 1600 (C=O), 1570–1540 (C=C).

(E)-**3e:** Yield 0.43 g (46%) from 3-benzoyl-4-hydroxy-2-{3-[4-(*o*-methoxyphenyl)piperazin-1-yl]propyl}pyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide **2b** [5] and N-methylethylenediamine (15 hrs), CC [ethyl acetate-methanol (1:2), $R_f$ = 0.36], m.p. 105–107°C (cyclohexane). Anal. Calcd. for $C_{33}H_{42}N_6O_4S$ (618.79): C, 64.1; H, 6.8; N, 13.6. Found: C, 63.7; H, 6.5; N, 13.7. $^1$H NMR (80 MHz): 1.0–1.25 m (2H, $CH_2$**$CH_2$**$CH_2$), 1.85–2.15 m [3H, $CH_2$N-piperazine + NH ($D_2O$ exchangeable)], 2.35–2.45 m [7H, $NCH_3$ + $CH_2N$(**$CH_2$**)$_2$], 2.63 s (3H, $CH_3$), 2.77 m (5H, $CH_3$ + $NCH_2$), 2.87–3.4 m [8H, 2-$NCH_2$ + ArN($CH_2$)$_2$ + $CH_2$N-enamine], 3.85 s (3H, OCH3), 6.9–7.9 m (10H, 9ArH + H$_\beta$-pyridine), 11.9 br (1H, HN-enamine, $D_2O$ exchangeable). IR: 1605 (C=O), 1540–1570 (C=C).

(E)-**3f:** Yield 0.64 g (65%) from 3-benzoyl-4-hydroxy-2-{3-[4-(*m*-trifluoromethylphenyl)piperazin-1-yl]propyl}pyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide **2c** [5] and N-methylethylenediamine (15 hrs), m.p. 173–175°C (cyclohexane/toluene 1.25:1). Anal. Calcd. for $C_{33}H_{39}F_3N_6O_3S$ (656.76): C, 60.1; H, 5.8; N, 13.1. Found: C, 60.4; H, 5.5; N, 13.5. $^1$H NMR (200 MHz): 0.9–1.45 m [3H, $CH_2$**$CH_2$**$CH_2$ + NH ($D_2O$ exchangeable)], 1.91 t [2H, $CH_2$N-piperazine, $J$ = 7.0 Hz], 2.29 t [4H, $CH_2N$(**$CH_2$**)$_2$, $J$ = 5.0 Hz], 2.37 s (3H, $NCH_3$), 2.63 s (3H, $CH_3$), 2.70–2.77 m (5H, $CH_3$ + $NCH_2$), 2.91 t (2H, $CH_2$N-enamine, $J$ = 7.8 Hz), 3.08–3.36 m [6H, ArN($CH_2$)$_2$ + 2-$NCH_2$), 6.98–7.18 m (3H, ArH), 7.23 s (1H, H$_\beta$-pyridine), 7.27–7.36 m (2H, ArH), 7.44–7.59 m (3H, ArH), 7.78–7.86 m (1H, ArH), 11.9 br (1H, HN-enamine, $D_2O$ exchangeable). IR: 1605 (C=O), 1540–1570 (C=C).

(E)-**3g:** Yield 0.41 g (44%) from 3-benzoyl-4-hydroxy-2-{3-[4-(*m*-chlorophenyl)piperazin-1-yl]propyl}pyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide **2d** [5] and N-methylethylenediamine (15 hrs), m.p. 170–172°C (cyclohexane). Anal. Calcd. for $C_{32}H_{39}ClN_6O_3S$ (623.21): C, 62.4; H, 6.4; N, 13.3. Found: C, 62.7; H, 6.1; N, 13.7. $^1$H NMR (200 MHz): 0.84–1.42 m (2H, $CH_2$**$CH_2$**$CH_2$), 1.65 br (1H, NH, $D_2O$ exchangeable), 1.91 t [2H, $CH_2$N-piperazine, $J$ = 7.1 Hz], 2.27 t [4H, $CH_2N$(**$CH_2$**)$_2$, $J$ = 5.0 Hz], 2.40 s (3H, $NCH_3$), 2.63 s (3H, $CH_3$), 2.71–2.77 m (5H, $NCH_2$ + $CH_3$), 2.90 t (2H, $CH_2$N-enamine, $J$ = 7.9 Hz), 3.07 t [4H, ArN($CH_2$)$_2$, $J$ = 5.0 Hz], 3.15–3.37 m (2H, 2-$NCH_2$], 6.70–7.83 m (3H, ArH), 7.10–7.31 m (3H, 2ArH + H$_\beta$-pyridine), 7.41–7.58 m (3H, ArH), 7.78–7.82 m (1H, ArH), 11.9 br (1H, NH-enamine, $D_2O$ exchangeable). IR: 1605 (C=O).

**11*H*-8,10-Dimethyl-1-phenyl-3,4-dihydro-pyrido[3′,2′:5,6]-1,2-thiazino[3,2-*c*]-1,4-oxazin-11-one-6,6-dioxide (4)**. The solution of sodium ethoxide prepared from 0.23 g of Na and 50 ml of anhydrous ethanol was evaporated and to the residue were added 10 ml of anhydrous DMF, 1.65g (5 mmol) of 3-benzoyl-4-hydroxypyridothiazine **1** [6] and 1.7 ml of 1,2-dibromoethane. The reaction mixture was heated with stirring at 100°C for 2 hrs. After cooling the mixture was diluted with an excess of water. The precipitate separated was filtered off and purified by crystallization to give **4**.

1.1 g (62% yield), m.p. 202–204°C (toluene). Anal. Calcd. for $C_{18}H_{16}N_2O_4S$ (356.39): C, 60.7; H, 4.5; N, 7.9. Found: C, 60.9; H, 4.7; N, 7.7. $^1$H NMR (200 MHz): 2.55 s (3H, $CH_3$), 2.65 s (3H, $CH_3$), 4.06 t (2H, $NCH_2$, J = 4.8 Hz), 4.58 t (2H, $OCH_2$, $J$ = 4.8 Hz), 7.26 s (1H, H$_\beta$-pyridine, 7.45 br s (5H, ArH). IR: 1650 (C=O), 1550 (C=C).

**2*H*-3-Benzoyl-4-methoxy-2,5,7-trimethylpyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide (5)**. A solution of 1.65 g (5 mmol) of 3-benzoyl-4-hydroxypyrido-1,2-thiazine **1** [6], 7.0 g of anhydrous $K_2CO_3$ and 3 ml of methyl iodide in 50 ml of acetonitrile was refluxed with stirring for 12 hrs. After filtration, the solvent was distilled off, the residue was dissolved at $CHCl_3$, filtered with charcoal and after evaporation chromatographed (CC) eluting with ethyl acetate/chloroform (1:15). The fractions containing the product of $R_f$ = 0.71 were combined and evaporated to provide **5** (an analytical sample was obtained after crystallization).

0.45 g (25% yield), m.p. 159–161°C (cyclohexane). Anal. Calcd. for $C_{18}H_{18}N_2O_4S$ (358.41): C, 60.3; H, 5.1; N, 7.8. Found: C, 60.6; H, 4.9; N, 7.6. $^1$H NMR (80 MHz): 2.64 s (3H, $CH_3$), 2.67 s (3H, $CH_3$), 3.0 s (3H, 2-$NCH_3$), 3.49 s (3H, $OCH_3$), 7.31 s (1H, H$_\beta$-pyridine), 7.6–7.8 m (3H, ArH), 8.25–8.35 m (2H, ArH). IR: 1655 (C=O), 1570 (C=C).

**2*H*-8,10-Dimethyl-1-phenyl-3,4-dihydropyrido[3,2-*e*]pyrazino[3,4-*b*]-1,2-thiazin-11-one-6,6-dioxide (6)**. A solution of 0.8 g (2.4 mmol) of 3-benzoyl-4-hydroxyprido-1,2-thiazine **1** [6] and 0.1 ml (2.4 mmol) of ethylenimine in 10 ml of DMF was stirred at 50°C for 12 hrs. After evaporation the residue was chromatographed (CC) eluting with ethyl acetate/chloroform (1:1). The fractions containing the product of $R_f = 0.66$ were combined and evaporated to provide 6 (an analytical sample was obtained after crystallization).

0.15 g (18% yield), m.p. 243–245°C (ethanol). Anal. Calcd. for $C_{18}H_{17}N_3O_3S$ (355.41): C, 60.8; H, 4.8; N, 11.8. Found: C, 61.0; H, 4.9; N, 12.2. $^1$H NMR (200 MHz): 2.46 s (3H, $CH_3$), 2.53 s (3H, $CH_3$), 3.54–3.61 m (2H, $CH_2$), 3.80–3.85 m (2H, $CH_2$), 7.11 s (1H, H$_\beta$-pyridine), 7.36 br s (5H, ArH). The position of NH proton signal was not established. IR: 3295 (NH), 1625 (C=O), 1500 (C=C).

**2*H*-2,7,9-Trimethyl-3-phenyl-4-{3-[4-(substituted-phenyl)piperazin-1-yl]propyl}-2,4-dihydropyrazolo[4,3-*c*]pyrido[3,2-*e*]-1,2-thiazine-5,5-dioxides (8b–d)**. To a solution of sodium ethoxide (40 ml), prepared from 0.23 g of Na and 100 ml of anhydrous ethanol, 1.36 g (4 mmol) of pyrazolo[4,3-*c*]pyrido[3,2-*e*]-1,2-thiazine-5,5-dioxide **7** [10] and 4 mmol of corresponding 1-(substituted-phenyl)-4-(3-chloropropyl)piperazine **9** were added. The reaction mixture was refluxed for 10 hrs and evaporated. The residue was dissolved in chloroform, filtered and the solvent was removed. The crude product obtained was purified by crystallization (**8b, c**) or with CC (**8d**).

**8b**: Yield 0.94 g (41%) from pyrazolopyrido-1,2-thiazine **7** [10] and 1-(*o*-methoxyphenyl)-4-(3-chloropropyl)piperazine (**9a**) [5], m.p. 218–220°C (ethanol). Anal. Calcd. for $C_{31}H_{36}N_6O_3S$ (572.72): C, 65.0; H, 6.3; N, 14.7. Found: C, 64.7; H, 6.1; N, 14.8. $^1$H NMR (80 MHz): 1.25–1.55 m (2H, $CH_2\mathbf{CH_2}CH_2$), 1.9–2.1 m [2H, $CH_2$N-piperazine], 2.2–2.35 m [4H, $CH_2N(\mathbf{CH_2})_2$], 2.64 s (3H, $CH_3$), 2.8–3.0 m [7H, $CH_3$ + $(CH_2)_2$NAr], 3.36 t [2H, 4-$NCH_2$), $J$ = 7.6 Hz], 3.83 s (3H, $OCH_3$), 3.92 s (2H, 2-$NCH_3$), 6.8–7.05 m (4H, ArH), 7.28 s (1H, H$_\beta$-pyridine), 7.55 br s (5H, ArH).

**8c:** Yield 1.27 g (52%) from pyrazolopyrido-1,2-thiazine **7** [10] and 1-(*m*-trifluoromethylphenyl)-4-(3-chloropropyl)piperazine (**9b**) [12], m.p. 139–141°C (ethanol). Anal. Calcd. for $C_{31}H_{33}F_3N_6O_2S$ (610.69): C, 61.0; H, 5.4; N, 13.8. Found: C, 60.8; H, 5.2; N, 14.2. $^1$H NMR (80 MHz): 1.25–1.6 m (2H, $CH_2\mathbf{CH_2}CH_2$), 1.85–2.05 m (2H, $CH_2$N-piperazine), 2.1–2.3 m [4H, $CH_2N(\mathbf{CH_2})_2$], 2.65 s (3H, $CH_3$), 2.82 s (3H, $CH_3$), 2.95–3.15 m [4H, $(CH_2)_2$NAr], 3.37 t [2H, 4-$NCH_2$), $J$ = 7.4 Hz], 3.92 s (2H, 2-$NCH_3$), 6.95–7.35 m (5H, 4ArH + H$_\beta$-pyridine), 7.56 br s (5H, ArH).

**8d:** Yield 0.72 g (31%) from pyrazolopyrido-1,2-thiazine **7** [10] and 1-(*m*-chlorophenyl)-4-(3-chloropropyl)piperazine (**9c**) [12], CC [ethyl acetate/chloroform (1:2), $R_f = 0.55$], m.p. 172–174°C (ethanol). Anal. Calcd. for $C_{30}H_{33}ClN_6O_2S$ (577.14): C, 62.4; H, 5.8; N, 14.6. Found: C, 62.7; H, 5.9; N, 14.3. $^1$H NMR (80 MHz): 1.2–1.55 m (2H, $CH_2\mathbf{CH_2}CH_2$), 1.9–2.3 m [6H, $N(CH_2)_3$], 2.66 s (3H, $CH_3$), 2.83 s (3H, $CH_3$), 2.9–3.2 m [4H, $(CH_2)_2$NAr], 3.36 t [2H, 4-$NCH_2$), $J$ = 7.4 Hz], 3.93 s (2H, 2-$NCH_3$), 6.7–7.15 m (4H, ArH), 7.3 s (1H, H$_\beta$-pyridine), 7.57 br s (5H, ArH).

X-ray structure analysis of 2*H*-3-[$\alpha$-(4-chlorobenzylamino)benzylidene]-2,5,7-trimethyl-4-oxo-3,4-dihydropyrido[3,2-*e*]-1,2-thiazine-1,1-dioxide [(E)-**3d**] and 2*H*-2,4,7,9-tetramethyl-3-phenyl-2,4-dihydropyrazolo[4,3-*c*]pyrido[3,2-*e*]-1,2-thiazine-5,5-dioxide (**8a**). Colourless prismatic crystals, suitable for X-ray diffraction analysis, were grown by slow evaporation of an ethanol solution in the case of both investigated compounds. X-ray data were collected on the Nonius MACH3 four-circle diffractometer for **1** and Kuma KM-4 CCD area-detector diffractometer for (E)-**3d** at room temperature; crystal sizes: 0.35×0.20×0.10 mm and $\omega$-2$\theta$ scans of **8a** and 0.28×0.12× 0.07 mm and $\omega$ scan of (E)-**3d**. The structures were solved by direct methods using SHELXS86 [23] for **8a** and SHELXS97 [24] for (E)-**3d** and refined by full-matrix least-squares with SHELXL97 [24]. All hydrogen atoms were located from $\Delta\rho$ map and their coordinates were refined with isotropic displacement parameters, taken as 1.5 times those of the respective parent atoms. All crystal and experimental data are listed in Table 2. Molecular graphics were prepared using ORTEP3 [25]. PARST [26] was used for geometrical calculations and PLATON/PLUTON [27] were used for analyse of the hydrogen bonds. All calculations were performed using WINGX ver. 1.64.05 package [28].

**Table 2.** Crystal data and structure refinement.

| | Compound **3d** | Compound **8a** |
|---|---|---|
| Empirical formula | $C_{18}H_{18}N_4O_2S$ | $C_{24}H_{22}N_3O_3SCl$ |
| Formula weight | 354.42 | 467.96 |
| Crystal system | orthorhombic | triclinic |
| Space group | Pbca | P-1 |
| Unit cell parameters | $a$ = 13.9948(11) | $a$ = 8.9327(9) Å |
| | $b$ = 14.0474(5) | $b$ = 9.8674(11) Å |
| | $c$ = 17.8879(7) | $c$ = 13.1444(14) Å |
| | | $\alpha$ = 73.537(9)° |
| | | $\beta$ = 88.049(8)° |
| | | $\gamma$ = 89.527(8)° |
| Volume, $V$ | 3516.6(3) | 1110.4(2) Å$^3$ |
| Molecular multiplicity, $Z$ | 8 | 2 |
| Density (calculated) | 1.339 | 1.400 g/cm$^3$ |
| Radiation | CuK$\alpha$ | MoK$\alpha$ |
| Wavelength | $\lambda$ = 1.54178 Å | $\lambda$ = 0.71073 Å |
| Cell parameters from | 25 | 2612 reflections |
| $\theta$ range for lattice parameters | 20.80–46.11° | 1.60–21.30° |
| Absorption coefficient, $\mu$ | 1.797 | 0.298 mm$^{-1}$ |
| Absorption correction | $\psi$ – scan [29] | numerical [30] |
| $T_{max}/T_{min}$ | 0.747/0.997 | 0.828/0.986 |
| $\theta$ range for data collection | 4.94–74.04 | 3.04–28.70° |
| Index ranges h, k, l | 0/17, 0/17, –21/21 | –11/10, –13/13, –17/17 |
| Intensity decay | 0.0 | 0.0% |
| No. of measured reflections | 2264 | 14149 |
| No. of independent reflections | 2184 ($R_{int}$ = 0.00) | 5322 ($R_{int}$ = 0.0436) |
| No. of observed reflections | 2059 with $I > 2\sigma(I)$ | 3089 with $I > 2\sigma(I)$ |
| *Refinement* | | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Final $R$ indices: $R$, $wR(F^2)$ | 0.0513, 0.1202 | 0.0432, 0.0971 |
| Goodness-of-fit on $F^2$, $S$ | 1.170 | 0.884 |
| Data/parameters | 2184/281 | 5322/356 |
| Extinction coefficient | 0.0024(3) | 0.0043(14) |
| Largest diff. peak and hole | +0.236 and –0.254 | +0.244 and –0.376 eÅ$^{-3}$ |
| $(\Delta/\sigma)_{max}$ | 0.002 | 0.000 |

**Supplementary materials**: Crystallographic data for structures reported in this paper have been deposited at Cambridge Crystallographic Data Centre; Numbers CCDC-236974 [(E)-**3d**], 236973 (**8a**). These data can be obtained free of charge *via* deposit@ccdc.cam.ac.uk.

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