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Expeditious one-pot synthesis of highly substituted thiazolo[3,2-*a*]pyridines involving chromones

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ABSTRACT

The 1,4-zwitterion derived from 4,5-dimethylthiazole and acetylenedicarboxylates has been shown to react at low temperature readily with 3-formylchromones (chromone-3-carboxaldehydes) resulting, after an unusual rearrangement, in the facile synthesis of thiazolo[3,2-*a*]pyridine derivatives; in the case of electron-donating substituents in the chromone ring tetracyclic chromenothiazolopyridines are isolated as the main reaction products. However, at higher temperature after an unexpected 1,2-aroyl migration 8-formyl-5*H*-[1,3]thiazolo[3,2-*a*]pyridines are formed as a mixture of two rotamers. Structural assignments of the new compounds as well as complete assignment of ^{1}H and ^{13}C NMR signals were based on the analysis of their ^{1}H and ^{13}C NMR (1D and 2D), IR, MS and elemental analysis data. Plausible mechanisms are proposed.

1. Introduction

The thiazolopyridine ring system is found in a broad range of biologically active compounds.[1] Specifically, thiazolo[3,2-*a*]pyridine derivatives are found to exhibit a broad spectrum of potent anticancer activity and are useful for chemotherapy of various cancers, such as leukemia, lung cancer, and melanoma.[2] Due to their biological importance, thiazolo[3,2-*a*]pyridine derivatives have become synthetic targets for many organic and medicinal chemists.[3,4] On the other hand, the rich and fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest.[5] *N*-Heterocycles are known to form zwitterions with activated acetylenic compounds, which can be trapped by a variety of electrophiles and proton donors leading thus to the facile synthesis of heterocyclic compounds.[6] In the light of our interest on the development of new routes toward heterocyclic systems,[7] we have exploited the reactivity profile of a thiazole-dimethyl acetylenedicarboxylate (DMAD) zwitterion in bringing about three-component reactions with 3-formylchromones speculating formation of either thiazolopyridines or chromenylthiazolooxazines. The use of 3-formylchromones and thiazole would give to the reaction a new perspective, since 3-formylchromones represent a very reactive system owing to the presence of an unsaturated keto function, a conjugated second carbonyl group at C-3 and, above all, a very reactive electrophilic center at C-2 and the thiazole ring is liable to molecular rearrangement.[8]

2. Results and discussion

Our studies were initiated by the reaction of DMAD with 3-formylchromone **1a** and 4,5-dimethylthiazole at −10 °C to rt to afford the thiazolo[3,2-*a*]pyridinedicarboxylate **5a** in 45% yield,[9] instead of the expected chromenylthiazolooxazine **7a** or thiazolopyridine **8a** (and/or **9a**) (Scheme 1). A minor product, identified as chromenothiazolopyridinedicarboxylate **6a** (~4% yield), was also detected. The reaction appears to be general with a number of substituted 3-formylchromones affording thiazolo[3,2-*a*]pyridinedicarboxylates **5** in moderate yield. However, in the case of 3-formylchromones **1b** and **1c** with electron-donating substituents in 6-position, the tetracyclic derivatives **6** were the main reaction products, whereas **5** were formed as minor products in ~5% yield (Table 1).

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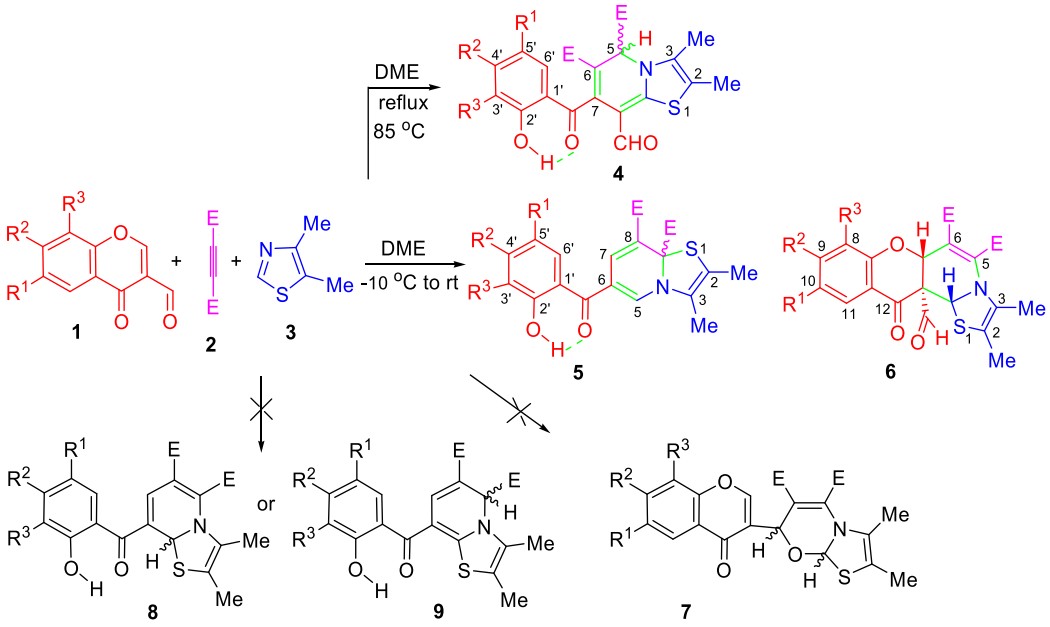


Scheme 1. Reaction of 3-formylchromones **1** with acetylenedicarboxylates **2** and thiazole **3** to afford compounds **4**, **5**, and **6**.

Table 1
Synthesis of thiazolopydines **4**, **5**, and benzopyranothiazolopydines **6**

Chromone				Ester	Products			
	R^1	R^2	R^3	E	**4**[a] (%)	Rotameric ratio A:B	**5**[b] (%)	**6**[b] (%)
1a	H	H	H	COOMe	**4a** (45)	1.4:1.0	**5a** (45)	**6a** (4)[c]
1b	Me	H	H	COOMe	**4b** (50)	1.9:1.0	**5b** (5)[d]	**6b** (38)
1c	*i*-Pr	H	H	COOMe	**4c** (45)	2.5:1.0	**5c** (10)[d]	**6c** (32)
1d	Cl	H	H	COOMe	**4d** (41)	2.2:1.0	**5d** (41)	
1e	Cl	Me	H	COOMe	**4e** (37)	2.4:1.0	**5e** (37)	**6e** (5)[c]
1f	NO_2	H	H	COOMe	**4f** (23)	2.6:1.0	**5f** (23)	—
1g	Br	H	Br	COOMe	**4g** (38)	2.5:1.0	**5g** (38)	—
1a	H	H	H	COOEt	**4h** (45)	1.6:1.0	—	—
1d	Cl	H	H	COOEt	**4i** (41)	2.3:1.0	—	—

[a] Reaction conditions: 85 °C in DME (reflux).
[b] Reaction conditions: −10 °C to rt in DME.
[c] As an inseparable mixture with **5**.
[d] As an inseparable mixture with **6**.

Unexpectedly, when the reaction was repeated in boiling dimethoxyethane (DME), 8-formyl-5*H*-thiazolo[3,2-*a*]pyridines **4** were isolated, as the only reaction products, as a mixture of two rotamers in moderate yields (23–50%). The rotameric ratio, as expected, was greatly dependent on the size of the R^1 chromone substituents varying from 1.4:1 in the unsubstituted derivative **4a** to 2.6:1 in the nitro-substituted **4f** (Table 1 and Fig. 2). The same products **4** were also isolated, when the reaction was carried out with diethyl acetylenedicarboxylate. A MO reaction path calculation for the estimation of the rotational energy barrier of the benzoyl group, with the assumption that the hydrogen bond of the salicylate moiety is preserved, gave comparable results by both AM1 and PM3 methods.[10] In Figure 1 the calculated sinusoid-like curve (PM3) for compound **4b** for the variation of relative energy of formation ($\Delta\Delta H_f$) versus the dihedral angle between the atoms in group C14-C8-C7-C6 (Fig. 4) showing two energy barriers of 26.8 and 31.4 kcal (PM3) for a full rotation, is depicted. The minima of energy at 90° and 270° correspond to the major and minor rotamers, respectively. Moreover, as already mentioned, the rotameric ratio greatly depends on the size of the chromone 5′-substituents. This ratio remains unchanged even by refluxing in DME for 4 h, because the rotational restriction energy is relatively high, as was also confirmed by computation. Concerning the initial formation of the non interconvertible rotamers, most probably, during the [1,3]*H* shift (**17**–**4**, Scheme 2) *syn* hydride migration leading to the major rotamer appears to be more favorable compared to the *anti* leading to the minor rotamer, on account of

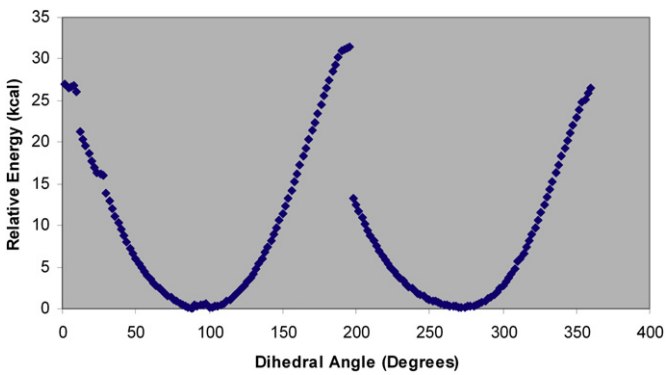


Figure 1. Variation of relative energy of formation ($\Delta\Delta H_f$) versus the dihedral angle between C14-C8-C7-C6 atoms (Fig. 4) as the salicylate group is rotating in compound **4b** (PM3).

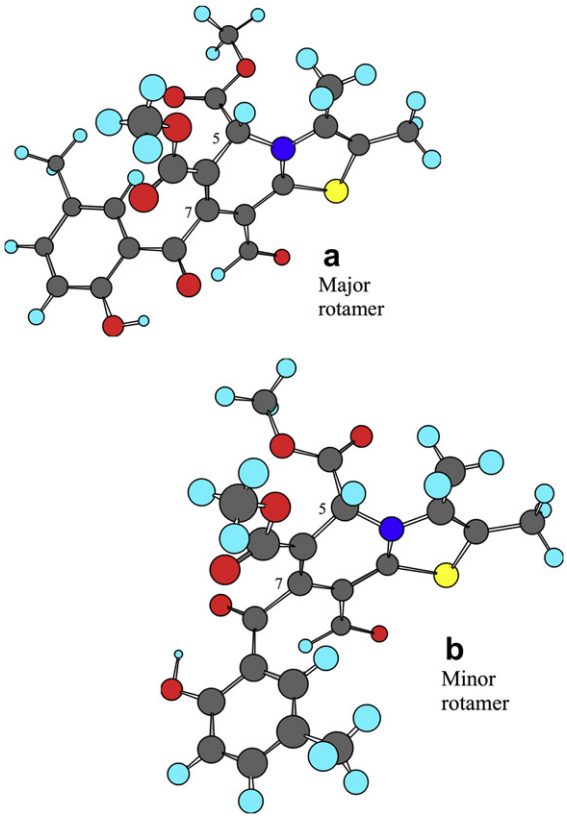


Figure 2. Global lower energy conformations of **4b** major (a) and minor (b) rotamers calculated by DFT (B3LYP/6-31G(d)).

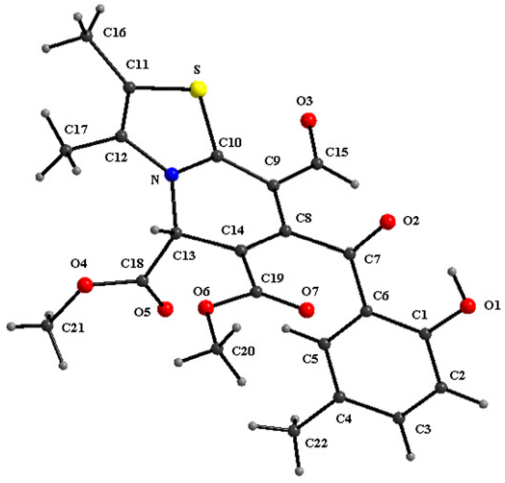


Figure 3. Crystal structure of compound **4b** (major component).

stereochemical interactions, irrespective of the initial configuration of salicyloyl moiety. In Figure 2 the global lower energy conformations of **4b** rotamers calculated by DFT (B3LYP/6-31G(d))[11,12] are depicted. The two rotamers could also be regarded as diastereomers, since there is a chiral center at C5 and the inability of free rotation of salicyloyl moiety at C7 can be considered to create a second chiral center. However, for the sake of clarity, the isomers will be referred to as rotamers throughout this work.

The following mechanistic postulate (Scheme 2) may be invoked to rationalize the reaction. The Huisgen zwitterion **10** formed from thiazole and DMAD attacks initially the C-2 chromone carbon

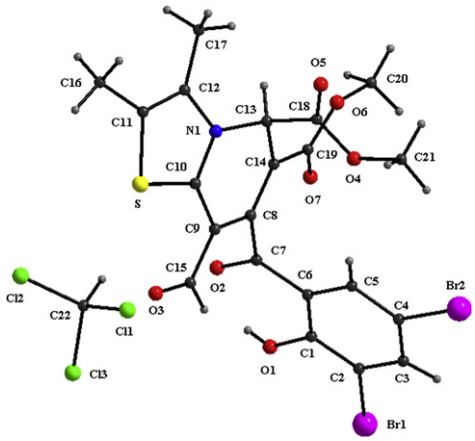


Figure 4. Crystal structure of compound **4g** cocrystallized with $CHCl_3$ (major component).

(instead of the expected aldehyde carbon)[6,13] giving intermediate **11**, which, by chromone ring opening (path a) leads initially to **12** and then by ring closure and formation of a new six-member ring to **13**. Deformylation of **13** followed by 1,5-sigmatropic shift results in **5** through the intermediacy of the vinyl sulfide zwitterion **15** bearing an aromatic pyridine ring. However, when R^1 is an electron-donating substituent, the ether bond of the chromone moiety in intermediate **11** is stabilized resulting, before deformylation, in the formation of the cyclohexene ring, through path b, leading thus stereoselectively to compound **6**. Nevertheless, **6c** was completely transformed to **5c** during column purification. Finally, when the reaction is carried out at higher temperature 1,2-aroyl migration in intermediate **13** seems to be more favorable to deformylation leading through **16** to the isolated products **4**.

2.1. Structure assignments of the new compounds

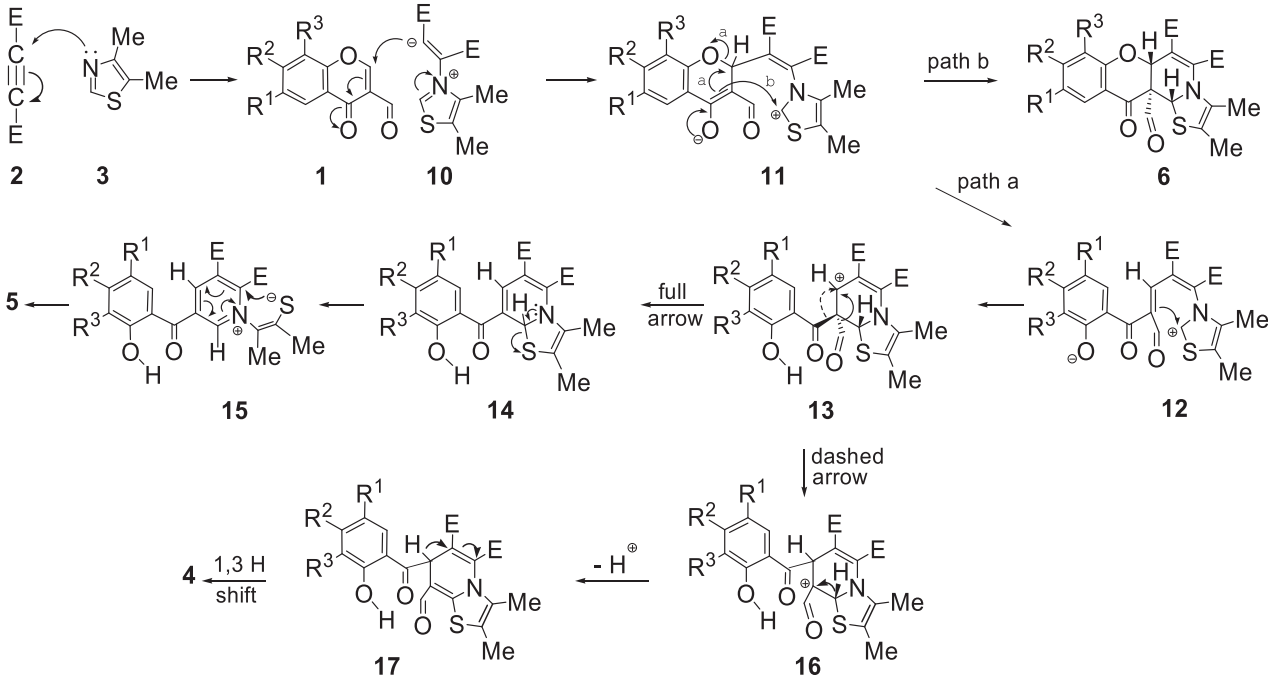
The assigned molecular structures of the new compounds **4**, **5**, and **6** were based on rigorous spectroscopic analysis including IR, NMR (^{1}H, ^{13}C, COSY, NOESY, HETCOR, and COLOC), MS and elemental analysis data.

Concerning the structural assignment of the major and minor rotamers of compounds **4** a substantial difference was observed in the ^{1}H NMR chemical shift of the C-6′ proton, being always shifted downfield, approximately 0.5 ppm, in the major rotamer. This difference can be attributed to the influence of the 5-ester moiety being in close proximity compared to the minor rotamer, as is depicted in Figure 2.

However, in order to eliminate any ambiguity about the structure of compounds **4**, the structures of the major rotamers of **4b** and **4g** were independently confirmed by crystal structure analysis[14] (Fig. 3 and Fig. 4). In both structures the salicylate carbonyl is in *anti* configuration with the 5-carboxymethylo group. The thiazolo ring is planar and the dihydropyridine ring has the boat conformation. The dihedral angle between oxadiazole plane and C9-C8-C14-C13 is about 30° and the salicylate moiety is almost perpendicular to the plane of atoms C9-C8-C14 (Fig. 3).

Concerning the structure of **6b** COLOC correlations in conjunction with the NOESY correlations (Fig. 5) confirmed the structure and the *syn*-approximation of protons 6a-H and 12b-H. In Figure 5 the COLOC correlations of protons with carbons via ^2J and ^3J coupling for compounds **4c**, **5a**, and **6b** are depicted.

The global lower energy conformation of **6b**, in accordance with COLOC and NOESY data, calculated by DFT (B3LYP/6-31G(d)) is depicted in Figure 6.



Scheme 2. Proposed plausible mechanism for the formation of compounds **4**, **5**, and **6**.

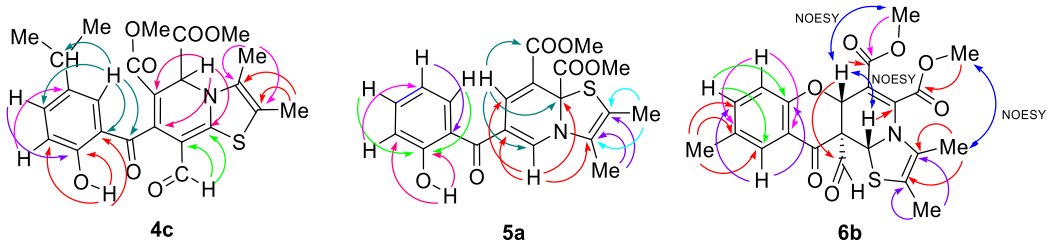


Figure 5. Diagnostic COLOC correlations between protons and carbons (via $^{2}J_{C\text{-}H}$ and $^{3}J_{C\text{-}H}$) in compounds **4c**, **5a**, and **6b**. In **6b** some important diagnostic NOESY correlations (in blue color) are also included.

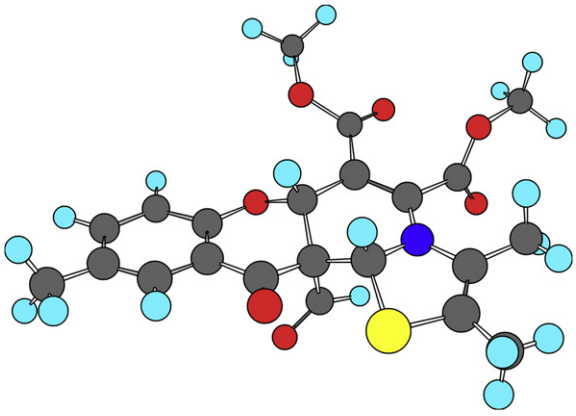


Figure 6. Global lower energy conformation of **6b** calculated by DFT (B3LYP/6-31G(d)).

3. Conclusions

In conclusion, we have devised the first three-component reaction involving a thiazole-DMAD zwitterion for the synthesis of novel thiazolo- and chromenothiazolopyridines. The outcome of the reaction was found to be temperature depended. So, at −10 °C to rt, through an unusual rearrangement of the thiazole ring, salicylate derivatives of [1,3]thiazolo[3,2-*a*]pyridines (**5**) were mainly obtained along with promising new tetracyclic chromenothiazolopyridines (**6**), since they combine two biologically active ring systems 1,4-chromenone with [1,3]thiazolo[3,2-*a*]pyridine,[2] whereas at higher temperature through an unexpected 1,2-aroyl migration 8-formyl-5*H*-[1,3]thiazolo[3,2-*a*]pyridines (**4**) were isolated as a mixture of two non interconvertible rotamers. Moreover, the present work demonstrates the versatility of chromones in bringing about one-pot synthetic procedures.

4. Experimental

4.1. General

Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel. TLC was performed using precoated silica gel glass plates 0.25 mm containing fluorescent indicator UV_{254} purchased from Macherey–Nagel using a 3:1 mixture of petroleum ether/ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80 °C. NMR spectra were recorded at room temperature (rt) on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. Chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Coupling constants ^{n}J are reported in Hertz. Second order ^{1}H spectra in the aromatic region, where it was possible, were

analyzed by simulation.[15] IR spectra were recorded on a Perkin–Elmer 297 spectrometer or on a Perkin–Elmer 1600 series FTIR spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution electron impact mass spectra were recorded on a 6890 N GC/MS system (Agilent Technology) and elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer.

4.2. General procedure for the reaction of 3-formylchromones (1a–1g) with acetylenedicarboxylates and 4,5-dimethylthiazole at 85 °C

To a stirred solution of 3-formylchromone **1** (1.0 mmol) and 4,5-dimethylthiazole (1 mmol) in DME (20 mL) kept at −10 °C under argon, methyl (or ethyl) acetylene (1.2 mmol) was added. The system was then allowed to attain room temperature and was refluxed for 12 h. The solvent was distilled off and the resulting residue was subjected to column chromatography on silica gel using petroleum ether/AcOEt (7:1) as eluent, slowly increasing the polarity up to 3:1 to give.

*4.2.1. 5,6-Dimethoxycarbonyl-2,3-dimethyl-8-formyl-7-(2′-hydroxybenzoyl)-5H-[1,3]thiazolo[3,2-a]pyridine (**4a**).* Yellow crystals as 1.4:1 inseparable mixture of rotamers (0.193 g, 45%), mp 227–230 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3444 (br), 1736, 1695, 1632 cm^{-1}. MS (LCMS) *m*/*z* (%) 452 (100, $M^{+\bullet}$+Na). Anal. Calcd for $C_{21}H_{19}NO_7S$ (429.44): C, 58.73; H, 4.46; N, 3.26. Found: C, 58.56; H, 4.50; N, 3.33.

Major rotamer: ^{1}H NMR: 2.34 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 3.61 (s, 3H, 5-OCH_3), 3.82 (s, 3H, 6-OCH_3), 6.19 (s, 1H, 5-H), 6.87 (ddd, *J*=8.2, 7.5, 1.1 Hz, 1H, 5′-H), 7.05 (dd, *J*=8.0, 1.1 Hz, 1H, 3′-H), 7.50 (ddd, *J*=8.0, 7.5, 1.5 Hz, 1H, 4′-H), 7.67 (dd, *J*=8.3, 1.5 Hz, 1H, 6′-H), 9.00 (s, 1H, CHO), 11.61 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 51.8 (5-OCH_3), 53.5 (6-OCH_3), 57.2 (C-5), 98.4 (C-7), 104.4 (C-8), 118.3 (C-3′), 119.7 (C-5′), 120.6 (C-2), 120.8 (C-1′), 131.7 (C-6′), 132.1 (C-3), 136.9 (C-4′), 146.1 (C-6), 157.8 (C-8a), 161.8 (C-2′), 164.4 (5-C=O), 168.9 (6-C=O), 180.1 (8-C=O) 200.7 (7-C=O).

Minor rotamer: ^{1}H NMR: 2.34 (s, 3H, 2-CH_3), 2.35 (s, 3H, 3-CH_3), 3.57 (s, 3H, 5-OCH_3), 3.77 (s, 3H, 6-OCH_3), 6.27 (s, 1H, 5-H), 6.73 (ddd, *J*=8.3, 7.5, 1.1 Hz, 1H, 5′-H), 7.02 (dd, *J*=8.0, 1.1 Hz, 1H, 3′-H), 7.20 (dd, *J*=8.3, 1.5 Hz, 1H, 6′-H), 7.43 (ddd, *J*=8.0, 7.5, 1.5 Hz, 1H, 4′-H), 9.05 (s, 1H, CHO), 11.61 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 52.0 (5-OCH_3), 53.7 (6-OCH_3), 57.4 (C-5), 98.6 (C-7), 103.1 (C-8), 118.4 (C-3′), 119.4 (C-5′), 119.7 (C-1′), 120.5 (C-2), 131.3 (C-6′), 132.3 (C-3), 136.7 (C-4′), 145.1 (C-6), 157.6 (C-8a), 162.0 (C-2′), 164.4 (5-C=O), 168.6 (6-C=O), 180.1 (8-C=O) 199.8 (7-C=O).

*4.2.2. 5,6-Dimethoxycarbonyl-2,3-dimethyl-8-formyl-7-(2′-hydroxy-5′-methyl-benzoyl)-5H-[1,3]thiazolo[3,2-a]pyridine (**4b**).* Yellow crystals as an inseparable mixture of rotamers in a 1.9:1 ratio (0.222 g, 50%), mp 238–240 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3447 (br), 1736, 1699, 1637 cm^{-1}. MS (LCMS) *m*/*z* (%) 466 (100, $M^{+\bullet}$+Na), 444 (25, $M^{+\bullet}$+1). Anal. Calcd for $C_{22}H_{21}NO_7S$ (443.47): C, 59.58; H, 4.77; N, 3.16. Found: C, 59.46; H, 4.68; N, 3.23.

Major rotamer: ^{1}H NMR: 2.24 (s, 3H, 5′-CH_3), 2.34 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 3.63 (s, 3H, 5-OCH_3), 3.83 (s, 3H, 6-OCH_3), 6.20 (s, 1H, 5-H), 6.96 (d, *J*=8.5 Hz, 1H, 3′-H), 7.32 (dd, *J*=8.5, 2.2 Hz, 1H, 4′-H), 7.41 (d, *J*=2.2 Hz, 1H, 6′-H), 9.00 (s, 1H, CHO), 11.45 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 52.0 (5-OCH_3), 53.5 (6-OCH_3), 57.2 (C-5), 98.2 (C-7), 104.5 (C-8), 118.1 (C-3′), 120.4 (C-2), 120.5 (C-1′), 128.4 (C-5′), 131.4 (C-6′), 132.1 (C-3), 138.0 (C-4′), 146.2 (C-6), 157.9 (C-8a), 159.8 (C-2′), 164.4 (5-C=O), 168.9 (6-C=O), 180.3 (8-C=O) 200.5 (7-C=O).

Minor rotamer: ^{1}H NMR: 2.15 (s, 3H, 5-CH_3), 2.35 (s, 3H, 2-CH_3), 2.35 (s, 3H, 3-CH_3), 3.58 (s, 3H, 5-OCH_3), 3.77 (s, 3H, 6-OCH_3), 6.28 (s, 1H, 5-H), 6.92 (d, *J*=8.5 Hz, 1H, 3′-H), 6.93 (d, 2.2 Hz, 1H, 6′-H), 7.25 (dd, *J*=8.5, 2.2 Hz, 1H, 4′-H), 9.03 (s, 1H, CHO), 11.51 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 20.4 (5-CH_3), 52.0 (5-OCH_3), 53.5(6-OCH_3), 57.5 (C-5), 98.1 (C-7), 103.2 (C-8), 118.2 (C-5′), 119.3 (C-1′), 120.5 (C-2), 128.4 (C-3′), 132.1 (C-3), 131.4 (C-6′), 138.1 (C-4′), 145.2 (C-6), 157.7 (C-8a), 160.0 (C-2′), 164.6 (5-C=O), 168.6 (6-C=O), 180.1 (8-C=O), 199.7 (7-C=O).

*4.2.3. 5,6-Dimethoxycarbonyl-2,3-dimethyl-8-formyl-7-(2′-hydroxy-5′-isopropylbenzoyl)-5H-[1,3]thiazolo[3,2-a]pyridine (**4c**).* Yellow crystals, as a 2.5:1 inseparable mixture of rotamers (0.212 g, 45%), mp 212–214 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3448 (br), 1734, 1696 cm^{-1}. MS (LCMS) *m*/*z* (%) 472 (100, $M^{+\bullet}$+1). Anal. Calcd for $C_{24}H_{25}NO_7S$ (471.52): C, 61.13; H, 5.34; N, 2.97. Found: C, 61.01; H, 5.48; N, 3.13.

Major rotamer: ^{1}H NMR: 1.178 (d, *J*=6.9 Hz, 3H, 5′-CH(CH_3)$_2$), 1.183 (d, *J*=6.9 Hz, 3H, 5′-CH(CH_3)$_2$), 2.35 (s, 6H, 2-CH_3, 3-CH_3), 2.78 (sept, *J*=6.9 Hz, 1H, 5′-CH), 3.61 (s, 3H, 5-OCH_3), 3.79 (s, 3H, 6-OCH_3), 6.21 (s, 1H, 5-H), 6.98 (d, *J*=8.6 Hz, 1H, 3′-H), 7.39 (dd, *J*=8.6, 2.3 Hz, 1H, 4′-H), 7.49 (d, *J*=2.3 Hz, 1H, 6′-H), 8.99 (s, 1H, CHO), 11.46 (s, 1H, OH). ^{13}C NMR: 10.9 (3-CH_3), 11.8 (2-CH_3), 23.7, and 24.05 (CHMe_2), 33.2 (CHMe$_2$), 51.9 (5-OCH_3), 53.5 (6-OCH_3), 57.2 (C-5), 98.4 (C-7), 104.5 (C-8), 118.0 (C-3′), 120.4 (C-2), 120.5 (C-1′), 129.0 (C-6′), 132.0 (C-3), 135.4 (C-4′), 139.7 (C-5′), 146.3 (C-6), 157.9 (C-8a), 159.9 (C-2′), 164.4 (5-C=O), 168.9 (6-C=O), 180.2 (8-C=O), 200.6 (7-C=O).

Minor rotamer: ^{1}H NMR: 1.08 (d, *J*=6.9 Hz, 3H, 5′-CH_3), 1.09 (d, *J*=6.9 Hz, 3H, 5′-CH_3), 2.33 (s, 3H, 2-CH_3, 3-CH_3), 2.69 (sept, *J*=6.9 Hz, 1H, 5′-CH), 3.55 (s, 3H, 5-OCH_3), 3.76 (s, 3H, 6-OCH_3), 6.29 (s, 1H, 5-H), 6.96 (d, *J*=8.6 Hz, 1H, 3′-H), 6.97 (d, *J*=2.3 Hz, 1H, 6′-H), 7.34 (dd, *J*=8.6, 2.3 Hz, 1H, 4′-H), 9.04 (s, 1H, CHO), 11.50 (s, 1H, OH). ^{13}C NMR: 10.9 (3-CH_3), 11.8 (2-CH_3), 23.83, and 24.05 (CHMe_2), 33.0 (CHMe$_2$), 51.8 (5-OCH_3), 53.6 (6-OCH_3), 57.4 (C-5), 98.2 (C-7), 103.1 (C-8), 118.3 (C-3′), 120.5 (C-2), 120.5 (C-1′), 128.5 (C-6′), 132.3 (C-3), 134.8 (C-4′), 139.6 (C-5′), 145.1 (C-6), 157.7 (C-8a), 160.3 (C-2′), 164.6 (5-C=O), 168.6 (6-C=O), 180.1 (8-C=O), 199.7 (7-C=O).

*4.2.4. 7-(5′-Chloro-2′-hydroxybenzoyl)-5,6-dimethoxycarbonyl-2,3-dimethyl-8-formyl-5H-[1,3]thiazolo[3,2-a]pyridine (**4d**).* Yellow crystals, as a 2.2:1 inseparable mixture of rotamers (0.190 g, 41%), mp 273–276 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3448 (br), 1736, 1693, 1640 cm^{-1}. MS (LCMS) *m*/*z* (%) 462/464 (100, $M^{+\bullet}$−1). Anal. Calcd for $C_{21}H_{18}ClNO_7S$ (463.89): C, 54.37; H, 3.91; N, 3.02. Found: C, 54.46; H, 3.84; N, 3.09.

Major rotamer: ^{1}H NMR: 2.35 (s, 3H, 2-CH_3), 2.38 (s, 3H, 3-CH_3), 3.65 (s, 3H, 5-OCH_3), 3.89 (s, 3H, 6-OCH_3), 6.18 (s, 1H, 5-H), 7.02 (d, *J*=8.5 Hz, 1H, 3′-H), 7.44 (dd, *J*=8.5, 2.5 Hz, 1H, 4′-H), 7.62 (d, *J*=2.5 Hz, 1H, 6′-H), 8.98 (s, 1H, CHO), 11.52 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 52.1 (5-OCH_3), 53.8 (6-OCH_3), 57.2 (C-5), 98.2 (C-7), 104.5 (C-8), 120.1 (C-3′), 120.9 (C-2), 121.4 (C-1′), 124.0 (C-5′), 130.7 (C-6′), 132.4 (C-3), 136.7 (C-4′), 145.4 (C-6), 157.8 (C-8a), 160.3 (C-2′), 164.2 (5-C=O), 168.7 (6-C=O), 179.8 (8-C=O), 200.0 (7-C=O).

Minor rotamer: ^{1}H NMR: 2.34 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 3.62 (s, 3H, 5-OCH_3), 3.77 (s, 3H, 6-OCH_3), 6.24 (s, 1H, 5-H), 7.00 (d, *J*=8.5 Hz, 1H, 3′-H), 7.15 (d, *J*=2.5 Hz, 1H, 6′-H), 7.38 (dd, *J*=8.5, 2.5 Hz, 1H, 4′-H), 9.02 (s, 1H, CHO), 11.57 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 52.1 (5-OCH_3), 53.7 (6-OCH_3), 57.4 (C-5), 98.2 (C-7), 103.0 (C-8), 120.2 (C-3′), 120.4 (C-1′), 120.9 (C-2), 124.0 (C-5′), 129.9 (C-6′), 132.4 (C-3), 136.7 (C-4′), 144.7 (C-6), 157.8 (C-8a), 160.5 (C-2′), 164.2 (5-C=O), 168.4 (6-C=O), 179.6 (8-C=O), 199.1 (7-C=O).

*4.2.5. 7-(5′-Chloro-2′-hydroxy-4′-methylbenzoyl)-5,6-dimethoxycarbonyl-2,3-dimethyl-8-formyl-5H-[1,3]thiazolo[3,2-a]pyridine (**4e**).* Yellow crystals as a 2.4:1 inseparable mixture of rotamers (0.177 g, 37%), mp 262–266 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3448 (br), 1739, 1695, 1638 cm^{-1}. MS (LCMS) *m*/*z* (%) 500/502 (100, $M^{+\bullet}$+Na). Anal. Calcd for $C_{22}H_{20}ClNO_7S$ (477.91): C, 55.29; H, 4.22; N, 2.93. Found: C, 55.40; H, 4.14; N, 3.01.

Major rotamer: ^{1}H NMR: 2.34 (s, 3H, 4′-CH_3), 2.36 (s, 3H, 2-CH_3), 2.39 (s, 3H, 3-CH_3), 3.64 (s, 3H, 5-OCH_3), 3.89 (s, 3H, 6-OCH_3), 6.18

(s, 1H, 5-H), 6.95 (s, 1H, 3′-H), 7.59 (s, 1H, 6′-H), 8.98 (s, 1H, CHO), 11.47 (s, 1H, OH). ^{13}C NMR: 10.9 (3-CH_3), 11.9 (2-CH_3), 20.9 (4′-CH_3), 52.1 (5-OCH_3), 53.8 (6-OCH_3), 57.2 (C-5), 98.1 (C-7), 104.4 (C-8), 119.8 (C-1′), 120.4 (C-3′), 120.5 (C-2), 124.6 (C-5′), 131.0 (C-6′), 132.3 (C-3), 145.5 (C-4′), 146.2 (C-6), 157.8 (C-8a), 160.1 (C-2′), 164.2 (5-C=O), 168.8 (6-C=O), 179.9 (8-C=O), 199.3 (7-C=O).

Minor rotamer: ^{1}H NMR: 2.36 (s, 3H, 2-CH_3), 2.37 (s, 3H, 4′-CH_3), 2.39 (s, 3H, 3-CH_3), 3.62 (s, 3H, 5-OCH_3), 3.76 (s, 3H, 6-OCH_3), 6.25 (s, 1H, 5-H), 6.92 (s, 1H, 3′-H), 7.13 (s, 1H, 6′-H), 9.02 (s, 1H, CHO), 11.52 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.8 (2-CH_3), 20.9 (4′-CH_3), 52.0 (5-OCH_3), 53.7 (6-OCH_3), 57.4 (C-5), 98.2 (C-7), 103.0 (C-8), 118.8 (C-1′), 120.5 (C-3′), 120.7 (C-2), 124.6 (C-5′), 130.3 (C-6′), 132.4 (C-3), 144.8 (C-4′), 146.1 (C-6), 157.7 (C-8a), 160.4 (C-2′), 164.3 (5-C=O), 168.5 (6-C=O), 179.7 (8-C=O), 198.5 (7-C=O).

*4.2.6. 5,6-Dimethoxycarbonyl-2,3-dimethyl-8-formyl-7-(2′-hydroxy-5′-nitrobenzoyl)-5H-[1,3]thiazolo[3,2-a]pyridine (**4f**).* Orange crystals as an inseparable mixture of rotamers 2.6:1 (0.109 g, 23%), mp 273–276 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3448 (br), 1736, 1694, 1692 cm^{-1}. MS (LCMS) *m*/*z* (%) 475 (100, $M^{+\bullet}$+1). Anal. Calcd for $C_{21}H_{18}N_2O_9S$ (474.44): C, 53.16; H, 3.82; N, 5.90. Found: C, 53.32; H, 3.84; N, 6.03.

Major rotamer: ^{1}H NMR: 2.36 (s, 3H, 2-CH_3), 2.38 (s, 3H, 3-CH_3), 3.67 (s, 3H, 5-OCH_3), 3.93 (s, 3H, 6-OCH_3), 6.19 (s, 1H, 5-H), 7.18 (d, *J*=9.3 Hz, 1H, 3′-H), 8.38 (dd, *J*=9.3, 2.7 Hz, 1H, 4′-H), 8.60 (d, *J*=2.7 Hz, 1H, 6′-H), 8.97 (s, 1H, CHO), 12.25 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 52.3 (5-OCH_3), 54.4 (6-OCH_3), 57.3 (C-5), 98.4 (C-7), 104.6 (C-8), 119.6 (C-3′), 119.9 (C-2), 121.2 (C-1′), 127.8 (C-6′), 131.3 (C-4′), 132.5 (C-3), 140.2 (C-5′), 144.9 (C-6), 158.1 (C-8a), 164.2 (C-2′), 166.3 (5-C=O), 168.6 (6-C=O), 179.3 (8-C=O), 200.6 (7-C=O).

Minor rotamer: ^{1}H NMR: 2.37 (s, 3H, 2-CH_3), 2.38 (s, 3H, 3-CH_3), 3.65 (s, 3H, 5-OCH_3), 3.78 (s, 3H, 6-OCH_3), 6.23 (s, 1H, 5-H), 7.15 (d, *J*=9.3 Hz, 3′-H), 8.13 (d, *J*=2.7 Hz, 1H, 6′-H), 8.32 (dd, *J*=9.3, 2.7 Hz, 1H, 4′-H), 9.01 (s, 1H, CHO), 12.30 (s, 1H, OH). ^{13}C NMR: 11.1 (3-CH_3), 11.9 (2-CH_3), 52.3 (5-OCH_3), 53.8 (6-OCH_3), 57.5 (C-5), 98.5 (C-7), 104.5 (C-8), 119.7 (C-3′), 119.9 (C-2), 121.4 (C-1′), 127.4 (C-6′), 131.2 (C-4′), 132.5 (C-3), 140.2 (C-5′), 144.9 (C-6), 158.2 (C-8a), 164.1 (C-2′), 166.6 (5-C=O), 168.3 (6-C=O), 179.1 (8-C=O), 200.7 (7-C=O).

*4.2.7. 7-(3′,5′-Dibromo-2′-hydroxybenzoyl)-5,6-dimethoxycarbonyl-2,3-dimethyl-8-formyl-5H-[1,3]thiazolo[3,2-a]pyridine (**4g**).* Yellow crystals, as an inseparable mixture of rotamers 2.5:1 (0.223 g, 38%), mp 236–237 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3445 (br), 1740, 1690, 1636 cm^{-1}. MS (LCMS) *m*/*z* (%) 586/588/590 (100, $M^{+\bullet}$+1). Anal. Calcd for $C_{21}H_{17}Br_2NO_7S$ (587.24): C, 42.95; H, 2.92; N, 2.39. Found: C, 42.81; H, 2.84; N, 2.31.

Major rotamer: ^{1}H NMR: 2.35 (s, 3H, 2-CH_3), 2.38 (s, 3H, 3-CH_3), 3.66 (s, 3H, 5-OCH_3), 3.89 (s, 3H, 6-OCH_3), 6.17 (s, 1H, 5-H), 7.76 (d, *J*=3.0 Hz, 6′-H), 7.87 (d, *J*=3.0 Hz, 4′-H), 8.94 (s, 1H, CHO), 12.20 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 52.1 (5-OCH_3), 53.8 (6-OCH_3), 57.2 (C-5), 98.3 (C-7), 104.5 (C-8), 111.0 (C-3′), 113.1 (C-5′), 121.1 (C-2), 122.3 (C-1′), 132.4 (C-3), 132.9 (C-6′), 141.8 (C-4′), 145.0 (C-6), 157.4 (C-2′), 157.6 (C-8a), 164.1 (5-C=O), 168.6 (6-C=O), 179.5 (8-C=O), 199.8 (7-C=O).

Minor rotamer: ^{1}H NMR: 2.36 (s, 3H, 2-CH_3), 2.37 (s, 3H, 3-CH_3), 3.64 (s, 3H, 5-OCH_3), 3.77 (s, 3H, 6-OCH_3), 6.22 (s, 1H, 5-H), 7.28 (d, *J*=3.0 Hz, 1H, 6′-H), 7.82 (d, *J*=3.0 Hz, 1H, 4′-H), 8.98 (s, 1H, CHO), 12.27 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.9 (2-CH_3), 52.1 (5-OCH_3), 53.8 (6-OCH_3), 57.2 (C-5), 98.4 (C-7), 103.0 (C-8), 111.0 (C-3′), 113.3 (C-5′), 121.3 (C-2), 121.3 (C-1′), 132.5 (C-3), 132.1 (C-6′), 141.8 (C-4′), 144.4 (C-6), 157.6 (C-8a), 157.8 (C-2′), 164.1 (5-C=O), 168.3 (6-C=O), 179.3 (8-C=O), 198.9 (7-C=O).

*4.2.8. 5,6-Diethoxycarbonyl-2,3-dimethyl-8-formyl-7-(2′-hydroxybenzoyl)-5H-[1,3]thiazolo[3,2-a]pyridine (**4h**).* Yellow crystals as an inseparable mixture of rotamers 1.6:1 (0.206 g, 45%), mp 186–189 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3447 (br), 1749, 1730. 1696 cm^{-1}. MS (LCMS) *m*/*z* (%) 480 (100, $M^{+\bullet}$+Na). Anal. Calcd for $C_{23}H_{23}NO_7S$ (457.50): C, 60.38; H, 5.07; N, 3.06. Found: C, 60.15; H, 4.92; N, 3.15.

Major rotamer: ^{1}H NMR: 0.99 (t, *J*=7.1 Hz, 3H, 5-CH_2CH_3), 1.29 (t, *J*=7.1 Hz, 3H, 6-CH_2CH_3), 2.33 (s, 3H, 2-CH_3), 2.35 (s, 3H, 3-CH_3), 4.06 (q, *J*=7.0 Hz, 2H, 5-OCH_2CH_3), 4.21 (q, *J*=7.1 Hz, 1H, 6-OCH_2CH_3), 4.30 (q, *J*=7.1 Hz, 1H, 6-OCH_2CH_3), 6.19 (s, 1H, 5-H), 6.85 (ddd, *J*=8.3, 7.0, 1.2 Hz, 1H, 5′-H), 7.04 (dd, *J*=8.1, 1.2 Hz, 1H, 3′-H), 7.50 (ddd, *J*=8.1, 7.0, 1.5 Hz, 1H, 4′-H), 7.71 (dd, *J*=8.3, 1.5 Hz, 1H, 6′-H), 8.99 (s, 1H, CHO), 11.66 (s, 1H, OH). ^{13}C NMR: 10.9 (3-CH_3), 11.8 (2-CH_3), 13.5 (5-OCH_2CH_3), 14.1 (6-OCH_2CH_3), 57.4 (C-5), 61.1 (5-OCH_2), 62.8 (6-OCH_2), 99.1 (C-7), 104.3 (C-8), 118.2 (C-3′), 119.3 (C-5′), 120.3 (C-2), 121.0 (C-1′), 131.9 (C-6′), 132.2 (C-3), 136.9 (C-4′), 145.2 (C-6), 157.8 (C-8a), 161.8 (C-2′), 164.1 (5-C=O), 168.4 (6-C=O), 180.0 (8-C=O) 200.8 (7-C=O).

Minor rotamer: ^{1}H NMR: 0.94 (t, *J*=7.4 Hz, 3H, 5-CH_2CH_3), 1.25 (t, *J*=7.1 Hz, 3H, 6-CH_2CH_3), 2.33 (s, 3H, 2-CH_3), 2.34 (s, 3H, 3-CH_3), 4.02 (q, *J*=7.0 Hz, 2H, 5-OCH_2CH_3), 4.20 (q, *J*=7.1 Hz, 1H, 6-OCH_2CH_3), 4.33 (q, *J*=7.1 Hz, 1H, 6-OCH_2CH_3), 6.26 (s, 1H, 5-H), 6.74 (ddd, *J*=8.3, 7.0, 1.2 Hz, 1H, 5′-H), 7.00 (dd, *J*=8.1, 1.2 Hz, 1H, 3′-H), 7.24 (dd, *J*=8.3, 1.5 Hz, 1H, 6′-H), 7.43 (ddd, *J*=8.1, 7.0, 1.5 Hz, 1H, 4′-H), 9.05 (s, 1H, CHO), 11.67 (s, 1H, OH). ^{13}C NMR: 10.9 (3-CH_3), 11.8 (2-CH_3), 13.4 (5-OCH_2CH_3), 14.0 (6-OCH_2CH_3), 57.4 (C-5), 61.1 (5-OCH_2), 62.8 (6-OCH_2), 98.9 (C-7), 103.0 (C-8), 118.3 (C-3′), 119.3 (C-5′), 119.9 (C-1′), 120.3 (C-2), 131.5 (C-6′), 132.2 (C-3), 136.7 (C-4′), 144.3 (C-6), 157.6 (C-8a), 162.1 (C-2′), 164.2 (5-C=O), 168.0 (6-C=O), 180.0 (8-C=O) 199.8 (7-C=O).

*4.2.9. 7-(5′-Chloro-2′-hydroxybenzoyl)-5,6-diethoxycarbonyl-2,3-dimethyl-8-formyl-5H-[1,3]thiazolo[3,2-a]pyridine (**4i**).* Yellow crystals as an inseparable mixture of rotamers 2.3:1 (0.202 g, 41%), mp 175–178 °C (CH_2Cl_2/pet. ether); IR (KBr) ν_{max}: 3448 (br), 1732, 1690, 1637 cm^{-1}. MS (LCMS) *m*/*z* (%) 514 (100, $M^{+\bullet}$+Na). Anal. Calcd for $C_{23}H_{22}ClNO_7S$ (491.94): C, 56.15; H, 4.51; N, 2.85. Found: C, 56.26; H, 4.54; N, 3.01.

Major rotamer: ^{1}H NMR: 1.06 (t, *J*=7.1 Hz, 3H, 5-OCH_2CH_3), 1.31 (t, *J*=7.1 Hz, 3H, 6-OCH_2CH_3), 2.34 (s, 3H, 2-CH_3), 2.36 (s, 3H, 3-CH_3), 4.10 (q, *J*=7.1 Hz, 2H, 5-OCH_2), 4.32 (q, *J*=7.1 Hz, 2H, 6-OCH_2), 6.19 (s, 1H, 5-H), 7.02 (d, *J*=9.0 Hz, 1H, 3′-H), 7.45 (dd, *J*=9.0, 2.7 Hz, 1H, 4′-H), 7.63 (d, *J*=2.7 Hz, 1H, 6′-H), 8.96 (s, 1H, CHO), 11.60 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.8 (2-CH_3), 13.7 (5-OCH_2CH_3), 14.2 (6-OCH_2CH_3), 57.4 (C-5), 61.2 (5-OCH_2), 63.1 (6-OCH_2), 99.1 (C-7), 104.2 (C-8), 120.0 (C-3′), 120.6 (C-2), 121.6 (C-1′), 124.0 (C-5′), 130.6 (C-6′), 132.4 (C-3), 136.7 (C-4′), 144.5 (C-6), 157.8 (C-8a), 160.3 (C-2′), 163.9 (5-C=O), 168.2 (6-C=O), 179.6 (8-C=O), 200.1 (7-C=O).

Minor rotamer: ^{1}H NMR: 1.01 (t, *J*=7.1 Hz, 3H, 5-OCH_2CH_3), 1.25 (t, *J*=7.3 Hz, 3H, 6-OCH_2CH_3), 2.36 (s, 6H, 2-CH_3, 3-CH_3), 4.09 (q, *J*=7.1 Hz, 2H, 5-OCH_2), 4.20 (q, *J*=7.3 Hz, 2H, 6-OCH_2), 6.24 (s, 1H, 5-H), 6.98 (d, *J*=9.0 Hz, 3′-H), 7.19 (d, *J*=2.7 Hz, 1H, 6′-H), 7.39 (dd, *J*=9.0, 2.7 Hz, 1H, 4′-H), 9.01 (s, 1H, CHO), 11.63 (s, 1H, OH). ^{13}C NMR: 11.0 (3-CH_3), 11.8 (2-CH_3), 13.6 (5-OCH_2CH_3), 14.0 (6-OCH_2CH_3), 57.4 (C-5), 61.2 (5-OCH_2), 62.8 (6-OCH_2), 98.9 (C-7), 102.8 (C-8), 120.1 (C-3′), 120.7 (C-2), 121.6 (C-1′), 123.95 (C-5′), 130.0 (C-6′), 132.5 (C-3), 136.6 (C-4′), 143.9 (C-6), 157.6 (C-8a), 160.6 (C-2′), 163.9 (5-C=O), 167.9 (6-C=O), 179.5 (8-C=O), 199.1 (7-C=O).

4.3. General procedure for the reaction of 3-formylchromones (1a–1g) with DMAD and 4,5-dimethylthiazole at −10 °C

DMAD (1.2 mmol) was added to a stirred solution of 3-formylchromone **1** (1.0 mmol) and 4,5-dimethylthiazole (1 mmol) in DME (20 mL) kept at −10 °C under argon. The system was then allowed to attain room temperature and was stirred for 12 h. The solvent was distilled off and the resulting residue was subjected to

column chromatography on silica gel using petroleum ether/AcOEt (7:1) as eluent, slowly increasing the polarity up to 3:1 to give in elution order.

4.3.1. From compound ***1a****. 4.3.1.1. 8,8a-Dimethoxycarbonyl-2,3-dimethyl-6-(2′-hydroxybenzoyl)-8aH-[1,3]thiazolo[3,2-a]pyridine (****5a****).* Orange crystals, (0.180 g, 45%), mp 208–209 °C (CH_2Cl_2/Et_2O); IR (Nujol) ν_{max}: 3458, 1738, 1698 cm^{-1}. ^1H NMR δ: 2.02 (s, 3H, 2-CH_3), 2.03 (s, 3H, 3-CH_3), 3.75 (s, 3H, 8a-OCH_3), 3.84 (s, 3H, 8-OCH_3), 6.91 (ddd, *J*=7.6, 7.4, 1.1 Hz, 1H, 5′-H), 7.03 (dd, *J*=8.3, 1.1 Hz, 1H, 3′-H), 7.45 (ddd, *J*=8.3, 7.4, 1.75 Hz, 1H, 4′-H), 7.50 (dd, *J*=7.6, 1.75 Hz, 1H, 6′-H), 7.90 (d, *J*=1.0 Hz, 1H, 5-H), 7.98 (d, *J*=1.0 Hz, 1H, 7-H), 11.63 (s, 1H, OH). ^{13}C NMR δ: 11.2 (3-CH_3), 12.7 (2-CH_3), 52.1 (8-OCH_3), 53.7 (8a-OCH_3), 72.8 (C-8a), 109.5 (C-6), 118.3 (C-3′), 118.6 (C-5′), 119.1 (C-2), 120.1 (C-1′), 125.5 (C-3), 130.9 (C-6′), 132.1 (C-7), 134.9 (C-4′), 141.6 (C-5), 161.9 (C-2′), 165.2 (8-C=O), 169.3 (8a-C=O), 192.8 (6-C=O). MS (LCMS) *m*/*z* (%) 402 (100, $M^{+\bullet}$+1). Anal. Calcd for $C_{20}H_{19}NO_6S$ (401.43): C, 59.84; H, 4.77, N, 3.49. Found: C, 59.93; H, 4.83; N, 3.40.

*4.3.1.2. 12a,12b-Dihydro-5,6-dimethoxycarbonyl-2,3-dimethyl-12a-formyl-12-oxo-6aH,12H-chromeno[3,2-c][1,3]thiazolo[3,2-a]pyridine (****6a****).* From a 5:1 mixture of **5a**:**6a** some ^1H NMR data were deduced. ^1H NMR δ: 1.83 (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 3.75 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 5-OCH_3), 5.61 (s, 1H, 6a-H), 5.68 (s, 1H, 12b-H), 7.02 (dd, *J*=8.4, 1.0 Hz, 1H, 8-H), 7.08 (ddd, *J*=8.0, 7.2, 1.0 Hz, 1H, 10-H), 7.55 (ddd, *J*=8.4, 7.2, 1.75 Hz, 1H, 9-H), 7.89 (dd, *J*=8.0, 1.75 Hz, 1H, 11-H), 10.16 (s, 1H, CHO).

4.3.2. From compound ***1b****. 4.3.2.1. 8,8a-Dimethoxycarbonyl-2,3-dimethyl-6-(2′-hydroxy-5′-methylbenzoyl)-8aH-[1,3]thiazolo[3,2-a]pyridine (****5b****).* From a 1:2 mixture of 5b:6b some ^1H NMR data were deduced. ^1H NMR δ: 2.02 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.32 (s, 3H, 5′-CH_3), 3.76 (s, 3H, 8a-OCH_3), 3.84 (s, 3H, 8-OCH_3), 6.93 (d, *J*=8.0 Hz, 1H, 3′-H), 7.26 (dd, *J*=8.0, 2.0 Hz, 1H, 4′-H), 7.89 (d, *J*=1.0 Hz, 1H, 5-H), 7.98 (d, *J*=1.0 Hz, 1H, 7-H), 11.36 (s, 1H, OH).

*4.3.2.2. 12a,12b-Dihydro-5,6-dimethoxycarbonyl-12a-formyl-12-oxo-2,3,10-trimethyl-6aH,12H-chromeno[3,2-c][1,3]thiazolo[3,2-a]pyridine (****6b****).* Orange crystals, (0.169 g, 38%), mp 189–192 °C (CH_2Cl_2/Et_2O); IR (Nujol) ν_{max}: 1735, 1708, 1662 cm^{-1}. ^1H NMR δ: 1.83 (q, *J*=1.0 Hz, 3H, 3-CH_3), 1.93 (q, *J*=1.0 Hz, 3H, 2-CH_3), 2.32 (s, 3H, 10-CH_3), 3.78 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 5-OCH_3), 5.60 (s, 1H, 6a-H), 5.64 (s, 1H, 12b-H), 6.92 (d, *J*=8.5 Hz, 1H, 8-H), 7.36 (dd, *J*=8.5, 2.2 Hz, 1H, 9-H), 7.67 (d, *J*=2.2 Hz, 1H, 11-H), 10.16 (s, 1H, 12a-CHO). ^{13}C NMR δ: 11.9 (3-CH_3), 13.6 (2-CH_3), 20.5 (10-CH_3), 52.0 (6-OCH_3), 53.2 (5-OCH_3), 58.7 (C-12a), 63.0 (C-6a), 71.1 (C-12b), 114.2 (C-2), 117.6 (C-6), 118.3 (C-8), 119.8 (C-11a), 126.8 (C-11), 127.4 (C-3), 132.1 (C-10), 138.5 (C-9), 144.1 (C-5), 159.1 (C-7a), 164.2 (5-C=O), 165.7 (6-C=O), 187.4 (C-12), 196.8 (12a-C=O). MS (LCMS) *m*/*z* (%) 444 (100, $M^{+\bullet}$+1), 416 (91). Anal. Calcd for $C_{22}H_{21}NO_7S$ (443.47): C, 59.58; H, 4.77, N, 3.16. Found: C, 59.43; H, 4.68; N, 3.22.

4.3.3. From compound ***1c****. 4.3.3.1. 8,8a-Dimethoxycarbonyl-2,3-dimethyl-6-(2′-hydroxy-5′-isopropylbenzoyl)-8aH-[1,3]thiazolo[3,2-a]pyridine (****5c****).* Yellow crystals (0.044 g, 10%), mp 178–180 °C (CH_2Cl_2/Et_2O); IR (KBr) ν_{max}: 3448, 1735, 1701 cm^{-1}. ^1H NMR δ: 1.23 (d, *J*=6.9 Hz, 3H, 5′-CHCH_3), 1.26 (d, *J*=6.9 Hz, 3H, 5′-CHCH_3), 2.02 (s, 6H, 2-CH_3, 3-CH_3), 2.88 (sept, *J*=6.9 Hz, 1H, 5′-CH), 3.75 (s, 3H, 8a-OCH_3), 3.84 (s, 3H, 8-OCH_3), 6.96 (d, *J*=8.0 Hz, 1H, 3′-H), 7.32 (dd, *J*=8.0, 2.0 Hz, 1H, 4′-H), 7.36 (d, *J*=2.0 Hz, 1H, 6′-H), 7.86 (d, *J*=1.0 Hz, 1H, 5-H), 8.00 (d, *J*=1.0 Hz, 1H, 7-H), 11.36 (s, 1H, OH). ^{13}C NMR δ: 11.2 (3-CH_3), 12.7 (2-CH_3), 24.0, and 24.2 (5′-CH(*C*H_3)$_2$), 33.2 (5′-CH), 52.0 (8-OCH_3), 53.7 (8a-OCH_3), 72.7 (C-8a), 107.5 (C-8), 109.5 (C-6), 117.8 (C-3′), 119.0 (C-2), 119.8 (C-1′), 125.4 (C-3), 128.3 (C-6′), 132.2 (C-7), 133.6 (C-4′), 138.8 (C-5′), 141.7 (C-5), 159.7 (C-2′), 165.2 (8-C=O), 169.3 (8a-C=O), 192.9 (6-C=O). MS (LCMS) *m*/*z* (%) 466 (100, $M^{+\bullet}$+Na), 444 (70, M^++1). Anal. Calcd for $C_{23}H_{25}NO_6S$ (443.51): C, 62.29; H, 5.68, N, 3.16. Found: C, 62.53; H, 5.52; N, 3.21.

*4.3.3.2. 12a,12b-Dihydro-5,6-dimethoxycarbonyl-12a-formyl-10-isopropyl-12-oxo-2,3-dimethyl-6aH,12H-chromeno[3,2-c][1,3]thiazolo[3,2-a]pyridine (****6c****).* Oil, 32% yield, estimated from the ^1H NMR of the mixture with **5c**. From a 1:3 mixture of **5c**:**6c** the NMR data were deduced. ^1H NMR δ: 1.23 (d, *J*=6.9 Hz, 6H, 5′-CH(CH_3)$_2$), 1.84 (q, *J*=1.0 Hz, 3H, 3-CH_3), 1.93 (q, *J*=1.0 Hz, 3H, 2-CH_3), 2.90 (sept, 1H, 5′-CH), 3.78 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 5-OCH_3), 5.61 (s, 1H, 6a-H), 5.65 (s, 1H, 12b-H), 6.95 (d, *J*=8.5 Hz, 1H, 8-H), 7.43 (dd, *J*=8.5, 2.2 Hz, 1H, 9-H), 7.72 (d, *J*=2.2 Hz, 1H, 11-H), 10.17 (s, 1H, 12a-CHO). ^{13}C NMR δ: 11.6 (3-CH_3), 13.6 (2-CH_3), 23.8 (10-CH(CH_3)$_2$), 33.4 (10-CH), 52.3 (6-OCH_3), 53.2 (5-OCH_3), 58.6 (C-12a), 63.0 (C-6a), 71.1 (C-12b), 114.2 (C-2), 118.3 (C-6), 118.4 (C-8), 119.8 (C-11a), 126.2 (C-11), 127.4 (C-3), 138.5 (C-9), 144.1 (C-5), 147.8 (C-10), 159.3 (C-7a), 164.2 (5-C=O), 165.7 (6-C=O), 187.4 (C-12), 196.8 (12a-C=O).

4.3.4. From compound ***1d****. 4.3.4.1. 6-(5′-Chloro-2′-hydroxybenzoyl)-8,8a-dimethoxycarbonyl-2,3-dimethyl-8aH-[1,3]thiazolo[3,2-a]pyridine (****5d****).* Orange crystals (0.178 g, 41%), mp 182–183 °C (CH_2Cl_2/Et_2O); IR (Nujol) ν_{max}: 3448, 1736, 1695 cm^{-1}. ^1H NMR δ: 2.03 (s, 3H, 3-CH_3), 2.06 (s, 3H, 2-CH_3), 3.76 (s, 3H, 8a-OCH_3), 3.85 (s, 3H, 8-OCH_3), 6.99 (d, *J*=8.8 Hz, 1H, 3′-H), 7.39 (dd, *J*=8.8, 2.5 Hz, 1H, 4′-H), 7.45 (d, *J*=2.5 Hz, 1H, 6′-H), 7.91 (d, *J*=1.1 Hz, 1H, 5-H), 7.94 (d, *J*=1.1 Hz, 1H, 7-H), 11.48 (s, 1H, OH). ^{13}C NMR δ: 11.2 (3-CH_3), 12.8 (2-CH_3), 52.2 (8-OCH_3), 53.9 (8a-OCH_3), 72.8 (C-8a), 107.9 (C-8), 109.0 (C-6), 119.1 (C-2), 119.8 (C-3′), 120.9 (C-1′), 123.3 (C-5′), 125.5 (C-3), 129.9 (C-6′), 131.7 (C-7), 134.5 (C-4′), 141.8 (C-5), 160.2 (C-2′), 165.0 (8-C=O), 169.0 (8a-C=O), 191.3 (6-C=O). MS (LCMS) *m*/*z* (%) 436/438 (100, $M^{+\bullet}$+1). Anal. Calcd for $C_{20}H_{18}ClNO_6S$ (435.88): C, 55.11; H, 4.16, N, 3.21. Found: C, 54.98; H, 4.13; N, 3.30.

4.3.5. From compound ***1e****. 4.3.5.1. 6-(5′-Chloro-2′-hydroxy-4′-methylbenzoyl)-8,8a-dimethoxycarbonyl-2,3-dimethyl-8aH-[1,3]thiazolo[3,2-a]pyridine (****5e****).* Yellow crystals (0.167 g, 37%), mp 215–217 °C (CH_2Cl_2/Et_2O); IR (Nujol) ν_{max}: 3437, 1734, 1693 cm^{-1}. ^1H NMR δ: 2.03 (s, 3H, 3-CH_3), 2.05 (s, 3H, 2-CH_3), 2.39 (s, 3H, 4′-CH_3), 3.77 (s, 3H, 8a-OCH_3), 3.85 (s, 3H, 8-OCH_3), 6.92 (d, *J*=0.6 Hz, 1H, 3′-H), 7.45 (d, *J*=0.6 Hz, 1H, 6′-H), 7.89 (d, *J*=1.0 Hz, 1H, 5-H), 7.94 (d, *J*=1.0 Hz, 1H, 7-H), 11.56 (s, 1H, OH). ^{13}C NMR δ: 11.3 (3-CH_3), 12.8 (2-CH_3), 20.7 (4′-CH_3), 52.2 (8-OCH_3), 53.8 (8a-OCH_3), 72.8 (C-8a), 107.7 (C-8), 109.1 (C-6), 118.9 (C-2), 119.5 (C-1′), 120.4 (C-3′), 123.8 (C-5′), 125.5 (C-3), 130.4 (C-6′), 131.8 (C-7), 141.6 (C-5), 143.7 (C-4′), 160.3 (C-2′), 165.1 (8-C=O), 169.1 (8a-C=O), 191.2 (6-C=O). MS (LCMS) *m*/*z* (%) 450/452 (100, $M^{+\bullet}$+1). Anal. Calcd for $C_{21}H_{20}ClNO_6S$ (449.90): C, 56.06; H, 4.48, N, 3.11. Found: C, 56.13; H, 4.53; N, 3.24.

*4.3.5.2. 10-Chloro-12a,12b-dihydro-5,6-dimethoxycarbonyl-12a-formyl-12-oxo-2,3,9-trimethyl-6aH,12H-chromeno[3,2-c][1,3]thiazolo[3,2-a]pyridine (****6e****).* From a 2:1 mixture of **5e**:**6e** some ^1H NMR data were deduced. ^1H NMR δ: 1.83 (s, 3H, 3-CH_3), 1.93 (s, 3H, 2-CH_3), 2.39 (s, 3H, 9-CH_3), 3.79 (s, 3H, 6-OCH_3), 3.89 (s, 3H, 5-OCH_3), 5.56 (s, 1H, 6a-H), 5.64 (s, 1H, 12b-H), 6.91 (s, 1H, 8-H), 7.82 (s, 1H, 11-H), 10.13 (s, 1H, 12a-CHO).

4.3.6. From compound ***1f****. 4.3.6.1. 8,8a-Dimethoxycarbonyl-2,3-dimethyl-6-(2′-hydroxy-5′-nitrobenzoyl)-8aH-[1,3]thiazolo[3,2-a]pyridine (****5f****).* Yellow crystals (0.103 g, 23%), mp 187–189 °C (CH_2Cl_2/Et_2O); IR (Nujol) ν_{max}: 3449, 1740, 1698 cm^{-1}. ^1H NMR δ: 2.05 (s, 3H, 3-CH_3), 2.07 (s, 3H, 2-CH_3), 3.79 (s, 3H, 8a-OCH_3), 3.86 (s, 3H, 8-OCH_3), 7.13 (d, *J*=9.2 Hz, 1H, 3′-H), 7.94 (d, *J*=1.0 Hz, 1H, 5-H), 7.99 (d, *J*=1.0 Hz, 1H, 7-H), 8.33 (dd, *J*=9.2, 2.7 Hz, 1H, 4′-H), 8.51 (d, *J*=2.7 Hz, 1H, 6′-H), 12.62 (br s, 1H, OH). ^{13}C NMR δ: 11.3 (3-CH_3), 12.9 (2-CH_3), 52.3 (8-OCH_3), 54.0 (8a-OCH_3), 65.9 (C-8a), 108.47 (C-

8), 108.54 (C-6), 118.9 (C-2), 119.2 (C-3′), 121.0 (C-1′), 125.4 (C-3), 126.9 (C-6′), 129.6 (C-4′), 131.3 (C-7), 139.3 (C-5′), 142.0 (C-5), 164.9 (8-C=O), 167.2 (8a-C=O), 167.9 (C-2′), 190.7 (6-C=O). MS (LCMS) *m/z* (%) 446 (30, $M^{+\bullet}$), 374 (100). Anal. Calcd for $C_{20}H_{18}N_2O_8S$ (446.43): C, 53.81; H, 4.06, N, 6.27. Found: C, 53.73; H, 4.00; N, 6.40.

4.3.7. From compound ***1g****. 4.3.7.1. 6-(3′,5′-Dibromo-2′-hydroxybenzoyl)-8,8a-dimethoxycarbonyl-2,3-dimethyl-8aH-[1,3]thiazolo[3,2-a]pyridine (****5g****).* Yellow crystals (0.212 g, 38%), mp 233–235 °C (CH_2Cl_2/Et_2O); IR (Nujol) ν_{max}: 3450, 1735, 1680 cm^{-1}. ^1H NMR δ: 2.03 (s, 3H, 3-CH_3), 2.05 (s, 3H, 2-CH_3), 3.77 (s, 3H, 8a-OCH_3), 3.85 (s, 3H, 8-OCH_3), 7.56 (d, *J*=2.3 Hz, 1H, 6′-H), 7.83 (d, *J*=2.3 Hz, 1H, 4′-H), 7.90 (d, *J*=1.0 Hz, 1H, 5-H), 7.92 (d, *J*=1.0 Hz, 1H, 7-H), 11.56 (s, 1H, OH). ^{13}C NMR δ: 11.2 (3-CH_3), 12.8 (2-CH_3), 52.2 (8-OCH_3), 53.9 (8a-OCH_3), 73.0 (C-8a), 108.3 (C-8), 108.7 (C-6), 110.1 (C-5′), 113.1 (C-3′), 120.6 (C-2), 122.0 (C-1′), 125.4 (C-3), 131.5 (C-6′), 132.2 (C-7), 139.7 (C-5), 142.1 (C-4′), 157.4 (C-2′), 164.9 (8-C=O), 168.9 (8a-C=O), 190.5 (6-C=O). Anal. Calcd for $C_{20}H_{17}Br_2NO_6S$ (559.23): C, 42.95; H, 3.06, N, 2.50. Found: C, 43.11; H, 3.09; N, 2.41.

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14. Complete crystallographic data for compounds **4b** and **4g** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 694985 and CCDC 694986. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax (int. code): +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk).
15. Simulated with SpinWorks simulation program, version 2.5, available from http://davinci.chem.umanitoba.ca/pub/marat/SpinWorks/.