Synthesis and Characterization of New Trifluoromethyl Substituted 3-Ethoxycarbonyl- and 3-Pyrimidin-2-yl)-(1,2,3)-Oxathiazinane-S-Oxides

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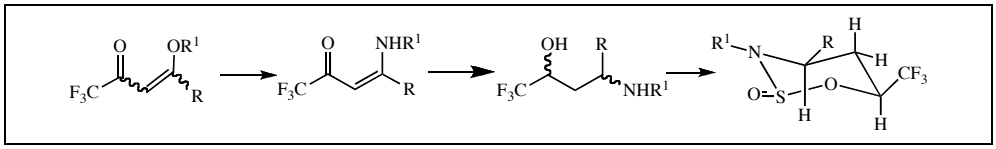

This paper describes the synthesis and characterization of a new series of 4-substituted-3-ethoxycarbonyl-6-trifluoromethyl-(1,2,3)-oxathiazinane-S-oxides and 3-(4,6-diphenyl-pyrimidin-2-yl)-6-trifluoromethyl-(1,2,3)oxathiazinane-S-oxides from the cyclization reaction of 4,4,4-trifluoro-3-hydroxybutylcarbamates and 4-(4,6-diphenyl-pyrimidin-2-ylamino)-1,1,1-trifluoro-butan-2-ols with thionyl chloride. The analysis of the NMR data allowed us to define important features of the molecular structure. Significant chemical and structural differences were observed between the trifluoromethylated oxathiazinanes obtained in this work from other analogue compounds reported in the literature.

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INTRODUCTION

A wide variety of chemically and biologically important molecules has been prepared from 2-oxo-[1,2,3]-oxathiazinanes and 2,2-dioxo-[1,2,3]oxathia-zinanes, also known as cyclic sulfamidites and sulfamidates, respectively [1]. For example, cyclic sulfamidate has been used as a chiral educt for the synthesis of enantiopure γ-substituted α-amino acids [2], for the enantioselective synthesis of the bromopyrrole alkaloid manzacidin A and C [3], for the generation of a variety of unnatural α,α-dissubstituted amino acid derivatives [4] and optical active hydroxy amino acids [5], and for the synthesis of a variety of aliphatic compounds through the opening of the cyclic sulfamidates with azides, cyanide, amines, phenol, thiophenol, thioisocyanides, and potassium acetate [6]. In addition, cyclic sulfamidites have been used as starting material for the preparation of enantiomerically enriched sulfinamides and sulfoximides [7,8].

Only a single method has been reported to synthesize six-membered sulfamidites, which is through the reaction of a γ-amino alcohols with thionyl chloride [9]. Curiously, most six-membered sulfamidites bear bulky substituents at the nitrogen as well as at the α-endocyclic nitrogen position. In addition, it has been shown that carbamoyl-ation of the NH improves the electrophilic reactivity of these compounds [10]. However, it is relatively rare to find such compounds bearing substituents at the α-oxygen position and, to our knowledge, oxathiazinanes containing a trifluoromethyl group at the α-oxygen position have not yet been reported.

Due to its modest steric requirements, high lipophilicity and electron-withdrawing effect and difficult metabolization, fluorine compounds have been extensively utilized in medicinal chemistry [12]. In this context, trifluoromethyl substituted heterocycles have been receiving special attention due to their broad scope of biological activity [13]. However, to the best of our knowledge, no example of oxathiazinanes bearing a trifluoromethyl group has been submitted to biological evaluation prior to our study.

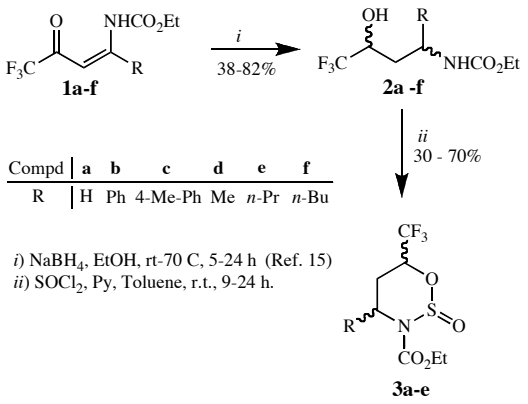
In this context, we were primarily interested in the synthesis of (1,2,3)-oxathiazinane-S-oxides containing a trifluoromethyl group at the α-position of the endocyclic oxygen atom. The trifluoromethyl group has a strong electron-withdrawing effect and we were interested to know how this group could affect the reactivity and the structure of the title compounds. As an extension of our study we are proposing the synthesis of *N*-substituted 6-trifluoromethyl-(1,2,3)-oxathiazinane-S-oxides with groups such as ethyl ester and pyrimidines. The influence of an α-substituent at the endocyclic nitrogen atom on the reactivity of the cyclization reaction and configuration of the oxathiazinane ring system is also the subject of this study. The (1,2,3)-oxathiazinane-S-oxides obtained in this study could be used as the starting material to synthesize acyclic compounds functionalized at the $-CF_3$ α-position, which are difficult to achieve by other methods.

RESULTS AND DISCUSSION

The strategy utilized to synthesize the 1,2,3-oxathiazinanes **3a-e** is shown in Scheme 1. In this

Scheme, the synthesis starts with the reaction of the readily available 4-alkoxy-1,1,1-trifluoro-alk-3-en-2-ones [14], with ethyl carbamate in dichloromethane or chloroform in the presence of a catalytic amount of *p*-toluene sulfonic acid, to give (4,4,4-trifluoro-3-oxo-but-1-enyl)-carbamic acid ethyl esters **1a-f** [15]. Compounds **1a-f** were reduced with sodium borohydrade in ethanol to give the ethyl 4,4,4-trifluoro-3-hydroxybutylcarbamates **2a-f** [15].

Scheme 1

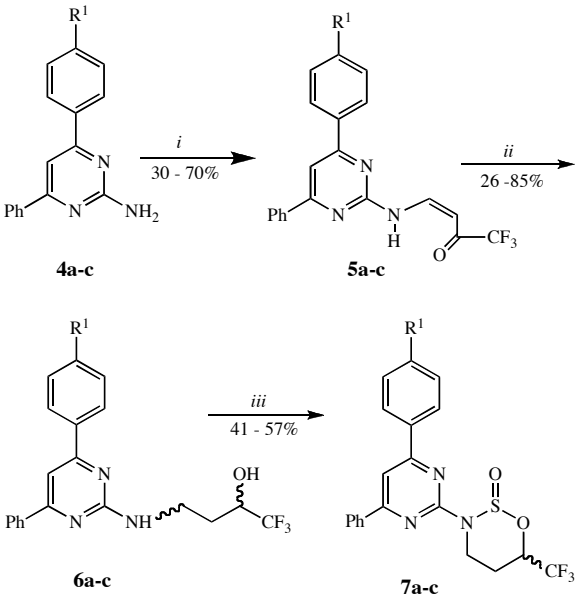


Compd	a	b	c	d	e	f
R	H	Ph	4-Me-Ph	Me	*n*-Pr	*n*-Bu

i) $NaBH_4$, EtOH, rt-70 C, 5-24 h (Ref. 15)
ii) $SOCl_2$, Py, Toluene, r.t., 9-24 h.

Although, the synthesis of **1a-d** and **2a-d** has been recently reported [15], in this paper we are extending these reactions to include two new substituents to obtain **1e-f** and **2e-f**. The 4-substituted-3-ethoxycarbonyl-6-trifluoromethyl-(1,2,3)-oxathiazinane-S-oxides **3a-e** were obtained through the cyclization reaction of the ethyl 4,4,4-trifluoro-3-hydroxybutylcarbamates **2a-e** with thionyl chloride, in toluene, and in the presence of pyridine. It was necessary to use an excess of the thionyl chloride to improve yields. When an equivalent of thionyl chloride was used, unreacted starting material 2 (Scheme 1) and 6 (Scheme 2) was obtained, especially with compounds with bulky groups at the 4-position. The best reaction condition was achieved when a 1.5 equivalent of thionyl chloride was used. The cyclic products 3 (Scheme 1) or 7 (Scheme 2) were not obtained when the reactions were carried out under reflux, using triethylamine instead of pyridine, or other solvents such as $CHCl_3$ or CH_2Cl_2. When the reaction was carried in THF for 24 h, the products were obtained but some starting material remained unreacted. Longer reaction times as well as larger amounts of thionyl chloride did not improve the yields of the cyclization products. It has been reported that the cyclization of homoserine by using a similar protocol required the addition of a large excess of imidazole to obtain the corresponding 1,2,3-oxathiazinane-S-oxides, and when the imidazole was omitted from the reaction mixture, the major isolated product was a symmetrical sulfite [2a]. For the reaction of the amino alcohols **2a-e** (Scheme 1) and **6a-c** (Scheme 2) with thionyl chloride in toluene and in the presence of pyridine, the use of imidazole was not required to obtain the 1,2,3-oxathiazinane-S-oxides **3a-e** and **7a-c**.

Scheme 2



Compd	a	b	c
R^1	H	Cl	OMe

i) 4-Ethoxy-1,1,1-trifluoro-but-3-en-2-one, EtOH, reflux, 18 h
ii) $NaBH_4$, EtOH, rt-70 ºC, 5-24 h (Ref. 15).
iii) $SOCl_2$, py, toluene, r.t., 24 h.

The strategy used for the synthesis of compounds **7a-c** is shown in Scheme 2. This strategy starts with the reaction of pyrimidin-2-amines **4a-c**, which synthesis has been reported elsewhere [16]. The reactions of the pyrimidin-2-amines **4a-c** with 4-ethoxy-1,1,1-trifluoro-but-3-en-2-one were carried out in ethanol under reflux for 18 hours to obtain the desired 1,1,1-trifluoro-4-(pyrimidin-2-ylamino)but-3-en-2-ones **5a-c**. Although the Michael addition reaction of amines to 4-alkoxy-1,1,1-trihalo-alk-3-en-2-ones (enones), followed by the elimination of the 4-alkoxy group, leading to the corresponding enamino ketones has been widely reported [17], the reaction of weak nitrogen nucleophiles such as pyrimidin-2-amines with these enones was not yet reported. It was observed that the substitution on the β-carbon of the enones makes the attack of the pyrimidin-2-amines to this carbon more difficult. For the reaction of the 4-substituted enones with pyrimidin-2-amines **4**, other reaction conditions such as changing solvents and the use of acid catalysis was tested, but no positive result for these reactions was found.

The reduction of compounds **5a-c**, using the same procedure described above for compounds **1a-f**, furnished the corresponding 4-(pyrimidin-2-ylamino)-1,1,1-trifluoro-butan-2-ol **6a-c** (Scheme 2), in moderate to good yields. The cyclization of compounds **6a-c** with thionyl chloride to give a series of 3-(4,6-diphenyl-pyrimidin-2-yl)-6-trifluoromethyl-(1,2,3)oxathiazinane-S-oxides **7a-c** was carried out using the same procedure as described for the synthesis of compounds **3a-e**.

The structure of the enamino ketones **1** and **5**, amino alcohols **2** and **6** and oxathiazinanes **3** and **7** were analyzed by GC-MS, elemental analysis, ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, and 2-D NMR COSY to confirm the hydrogen assignments. These data are reported in the experimental part. The atom numbering used for the NMR assignment of compounds **1**, **3**, **5**, and **7** is presented in Figure 1. Compounds **2** and **6** follow the same numbering of the compounds **1** and **5**, respectively.

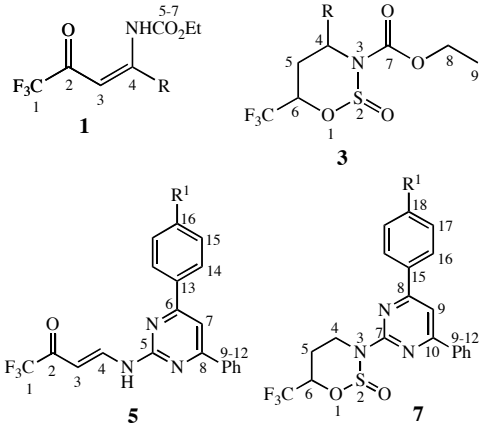
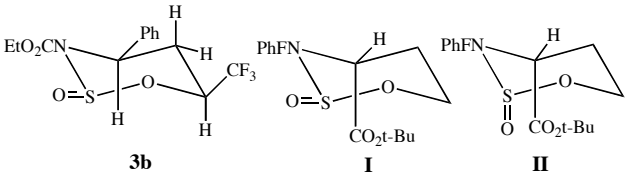


Figure 1. atom numbering for the NMR assignment of compounds **1**, **3**, **5**, and **7**.

Structural Considerations. For the reduced compounds **2b-c** that presented more than one stereogenic center, as well as for 1,2,3-oxathiazinanes **3b-c**, only a single set of signals was observed in both ^{1}H and ^{13}C-NMR spectra. In addition, a single peak was observed in the total ion chromatogram registered on a GC-MS equipped with a non-chiral capillary column. For compound **3c**, a gas-chromatogram registered on a chiral column showed two peaks of about the same intensity for the oxathiazinanes containing two asymmetric carbons and a sulfoxide group. This indicates that only a pair of enantiomers was formed and that the reduction and cyclization reactions were stereoselective. However, for compounds **3d-e**, two peaks were observed in the total ion chromatogram and for compound **3d**, a gas-chromatogram registered using a chiral column showed four peaks, which is an indication that a pair of diastereoisomers and two pairs of enantiomers were formed. The reaction, however, was stereoselective because the minor diastereoisomer was formed at 10% of the major isomer. This result confirms the data observed on the NMR spectroscopy and GC-MS.

The 1,2,3-oxathiazinane-S-oxides **3** and **7** show both ^{1}H- and ^{13}C-NMR spectra similar to the corresponding amino alcohol precursors. The formation of compounds **3** and **7** was evidenced by the multiplicity of H-4 of the cyclic products, showing a signal with well defined coupling constants, as well as by the molecular ion on the mass spectra, which showed that the 1,2,3-oxathiazinane-S-oxides had 46 mass units more than the corresponding amino alcohols **2**.

The interpretation of the coupling constants of H-4 and H-5 furnished important information about the spatial position of the substituents attached to the oxathiazinane six-membered ring. It was observed that the H-4 of compound **3b** shows a coupling constant with one of the H-5 with 13.0 Hz and with the other with 6.0 Hz. These coupling constants are consistent with the position of the phenyl group in a *pseudo*-equatorial position. The coupling constant of one of the H-5 (axial) shows a geminal coupling constant with the other H-5 (equatorial) and vicinal coupling constants with H-4 and with H-6 with about 13.0 Hz for all of these nuclei (Figure 2). This indicates that the CF_3 group is in equatorial position and confirms the *pseudo*-equatorial position of the 4-phenyl group. The same analysis done for the other sulfamidites **3** and **7** shows the same trend as presented for **3b**. It is interesting to note that in a recent study with analogues of 1,2,3-oxathiazinane-S-oxides derived from homoserine [2a], the 4-*t*-butyl carboxyl group was reported in axial position. Figure 2 shows the structure of the oxathiazinane **3b** drawn according to the interpretation of the ^{1}H NMR coupling constants and the structure of analogue oxathiazinanes reported in the literature [2a].



$J_{H4\text{-}H5ax}$ = 13.2 Hz
$J_{H4\text{-}H5eq}$ = 6.0 Hz
$J_{H5eq\text{-}H5ax}$ = 14.0 Hz
$J_{H5eq\text{-}H6}$ = 3.0 Hz
$J_{5ax\text{-}H6}$ = 13.2 Hz

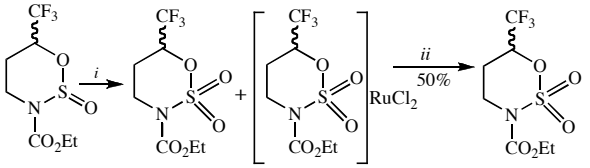
I = (2*S*)-3-(4-Fluoro-phenyl)-2-oxo-[1,2,3]oxathiazinane-4-carboxylic acid *tert*-butyl ester
II = (2*R*)-3-(4-Fluoro-phenyl)-2-oxo-[1,2,3]oxathiazinane-4-carboxylic acid *tert*-butyl ester

Figure 2. Structure and ^{1}H NMR coupling constants of compound **3b** and structure of oxathiazinanes from Reference 2a.

Oxidation of ethyl 2-oxo-6-trifluoromethyl-(1,2,3)-oxathiazinane-3-carbamate (**3a**) to ethyl 2-dioxo-6-trifluoromethyl-(1,2,3)-oxathiazinane-3-carbamate (**8a**) was performed using two methods: *m*-chloroperbenzoic

acid and potassium periodate catalized by ruthenium trichloride. The reaction with the first oxidant was not effective and the starting compound **3a** was recovered. The oxidation carried out with potassium periodate catalyzed by ruthenium trichloride [2a] (Scheme 3) furnished the desired product **8a** (in a small amount) and a ruthenium dichloride-sulfamidate complex **9a** (as the major product) that was analyzed by GC-MS. For **9a**, a typical molecular ion of m/z 447 with several characteristic peaks due to natural isotopes of ruthenium was observed [18]. We were not able to completely hydrolyze the ruthenium-sulfamidate complex **9a** following procedures from the literature [2a]. Compound **8a** was isolated, as a pure compound, only after column chromatography in silica gel in a 50% yield. In addition, it has been reported that the reaction of γ-amino alcohols derived from homoserine with thionyl chloride furnished a mixture of 2*R* and 2*S* sulfamidites and that only the 2*R* (equatorial oxygen) could be oxidized to the correspondent sulfamidate [2a]. For the oxathiazinane **3a** obtained in this work, it seems that only the equatorial oxygen-sulfoxide was obtained and this conclusion rises from the following evidences: (*i*) Only one set of signals in both ^{1}H and ^{13}C NMR was observed, (*ii*) a single peak was observed in the total ion chromatogram registered on a GC-MS equipped with a non chiral capillary column, and (*iii*) oxathiazinane **3a** was completely oxidized to 2-dioxo-(1,2,3)oxathiazinane **8a** (Scheme 3).

Scheme 3



i) $RuCl_3.2H_2O$, KIO_4, CH_3CN, 0 °C, 15 min.
ii) Column chromatography 60A (230-400 mesh)

In conclusion, this paper showed the synthesis and characterization of a new series of 4-substituted-3-ethoxycarbonyl-6-trifluoromethyl-(1,2,3)-oxathiazinane-S-oxides and 3-(4,6-diphenyl-pyrimidin-2-yl)-6-trifluoromethyl-(1,2,3)oxathiazinane-S-oxides. The structure of the oxathiazinanes was studied by GC-MS, GC-chiral chromatography, and ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy as well as 2-D NMR experiments. The interpretation of the ^{1}H NMR coupling constants showed conclusive information about the spatial positions of the substituents bonded to the oxathiazinane ring. GC-chiral chromatography showed the nature of the enantiomeric/diastereomeric composition of the obtained products. Significant chemical and structural differences were observed between the trifluoromethylated oxathiazinanes obtained in this work and other analogue compounds reported in the literature, as discussed in the text. The oxathiazinanes were assessed against a panel of microorganisms including yeast like fungi, bacteria and algae, but no activity was observed.

EXPERIMENTAL

The solvents were purified and dried before use and the 4-alkoxy-1,1,1-trifluoro-alk-3-en-2-ones were prepared according to procedures from the literature [14]. Column chromatography was carried out in silica gel Aldrich 60A (230-400 mesh), using mixtures of adequate solvents as eluants. Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) or on a Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) in $CDCl_3$ or DMSO-d_6 and using TMS as internal reference. ^{19}F NMR spectra were registered on a Bruker DPX 400 at 376.6 MHz in $CDCl_3$ or DMSO-d_6 and using fluorobenzene as the external reference. Mass spectra were registered on a HP 5973 MSD connected to a HP 6890 GC and interfaced by a pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP 5MS capillary column (30 m of length, 0.32 mm of internal diameter, and 0.25 μm of film thickness), and helium was used as the carrier gas. The chiral cromatography was registered on a Varian 3800 GC equipped with a split-splitless injector, FID detector, and a home made capillary column of 2,3-di-O-pentyl-6-O-*iso*-butyril (25 m of length, 0.25 mm of internal diameter, and 0.25 μm of film thickness) and/or lipodex E (25 m of length, 0.25 mm of internal diameter, and 0.25 μm of film thickness). The following conditions were used: initial temperature 40 °C, final temperature 180 °C, rate of heat of 3 °C/min, pressure of the hydrogen carrier gas 7 Psi, temperature of the injector 220 °C, and temperature of the detector 280 °C. Compounds **1a-d** and **2a-d** were prepared according to reference [15] and compounds **1e-f**, **2e-f** and **6a-c** are new and were synthesized using the same methods [15]. Compounds **1e-f** and **2e-f** were purified by silica gel column chromatography Aldrich 60A (230-400 Mesh) using hexane/dichloromethane 2:1 as the eluant. Compounds **6a-c** were purified by recrystallization from ethanol.

General procedure for the preparation of 1,1,1-trifluoro-4-(4,6-diphenyl-pyrimidin-2-ylamino)-but-3-en-2-one (5a-c). To a solution of pyrimidin-2-amine 4 (5.0 mmol) in ethyl alcohol (15.0 mL) the 4-ethoxy-1,1,1-trifluoro-alk-3-en-2-one (0.84 g, 5.0 mmol) was added at room temperature. The mixture was stirred under reflux for 18 h. The solid obtained was filtered and compounds 5a-c were purified by recrystallization from ethanol.

4-(4,6-Diphenyl-pyrimidin-2-ylamino)-1,1,1-trifluoro-but-3-en-2-one (5a). This compound was obtained as a colorless solid, yield 30 %; mp. 154 °C (ethanol); MS, EI (70ev): *m/z* (%) decomposed in the GC-column. ^{1}H NMR (200.13 MHz, DMSO-d_6) δ: 6.24 (d, $J_{H3\text{-}H4}$=12.1 Hz, 1H, H-3), 7.60 (m, 7H, H-7, H-11, H-12), 8.31 (m, 4H, H-10), 9.03 (t, 1H, $J_{H4\text{-}H3\text{-}NH}$=12.1 Hz, 1H, H-4), 11.79 (d, 1H, $J_{NH\text{-}H4}$=12.1 Hz, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 95.4 (C-3), 108.0 (C-7), 117.0 (q, $^{1}J_{C\text{-}F}$=289.9 Hz, CF_3), 127.4 (C-10, C-14), 129.0 (C-12, C-16), 131.5 (C-11, C-

15), 135.9 (C-9, C-13), 148.0 (C-5), 157.5 (C-4), 165.8 (C-6, C-8), 178.0 (q, $^2J_{C\text{-}F}$ = 33.1 Hz, C-2). Anal. Calcd. for $C_{20}H_{14}F_3N_3O$. Found: C, 65.04; H, 3.82; N, 11.38.

4-[4-(4-Chloro-phenyl)-6-phenyl-pyrimidin-2-ylamino]-1,1,1-trifluoro-but-3-en-2-one (5b). This compound was obtained as an orange solid, yield 60 %; mp. 117°C (ethanol); MS, EI (70ev): *m/z* (%) decomposed in the GC-column; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 5.79 (d, $J_{H3\text{-}H4}$=8.2 Hz, 1H, H-3), 7.40–7.55 (m, 5H, H-11, H-12, H-15), 7.77 (s, 1H, H-7), 8.05–8.14 (m, 4H, H-10, H-14), 8.51 (dd, $J_{H4\text{-}NH}$=12.4 Hz, $J_{H4\text{-}H3}$=8.2 Hz, 1H, H-4) 11.50 (d, $J_{H4\text{-}NH}$=12.4 Hz, 1H, H-3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 92.2 (C-3), 107.9 (C-7), 116.5 (q, $^1J_{C\text{-}F}$=286.9 Hz, CF_3), 127.2 (C-10), 128.4 (C-14), 129.0 (C-11), 129.2 (C-15), 131.5 (C-12), 134.6 (C-16), 136.0 (C-13), 137.7 (C-9), 147.5 (C-4), 157.2 (C-8), 165.0 (C-6), 166.5 (C-5), 180.8 (q, $^2J_{C\text{-}F}$=34.4 Hz, C-2). *Anal.* Calcd. for $C_{20}H_{13}ClF_3N_3O$: C, 59.49; H, 3.25; N, 10.41. Found: C, 59.72; H, 3.29; N, 10.26.

4-[4-(4-Methoxy-phenyl)-6-phenyl-pyrimidin-2-ylamino]-1,1,1-trifluoro-but-3-en-2-one (5c). This compound was obtained as an orange solid, yield 70 %; mp. 111 °C (ethanol); MS, EI (70ev): *m/z* (%) decomposed in the GC-column; ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 5.77 (d, $J_{H3\text{-}H4}$=8.0 Hz, 1H, H-3), 7.00–7.04 (m, 2H, H-15), 7.47–7.54 (m, 3H, H-11, H-12), 7.74 (s, 1H, H-7), 8.00–8.13 (m, 4H, H-10, H-14), 8.53 (dd, $J_{H4\text{-}NH}$=12.6 Hz, $J_{H4\text{-}H3}$=8.0 Hz, 1H, H-4) 11.50 (d, $J_{H4\text{-}NH}$=12.6 Hz, 1H, N-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 55.2 (OCH_3), 101.0 (C-3), 107.0 (C-7), 114.1 (C-15), 116.8 (q, $^1J_{C\text{-}F}$=290.0 Hz, CF_3), 127.1 (C-10), 128.0 (C-13), 128.7 (C-14), 128.9 (C-12), 131.1 (C-11), 135.9 (C-9), 148.2 (C-4), 161.9 (C-16, C-8), 165.0 (C-5, C-6), 178.0 (q, $^2J_{C\text{-}F}$=33.1 Hz, C-2). *Anal.* Calcd. for $C_{21}H_{16}F_3N_3O_2$: C, 63.16; H, 4.04; N, 10.52. Found: C, 63.54; H, 4.12; N, 10.59.

General procedure for the preparation of 3- and 4-substituted 6-trifluoromethyl-(1,2,3)-oxathiazinane-S-oxides (3a-e, 7a-c). The γ-amino alcohols **2** and **6** (1.0 mmol) in toluene (8.0 mL) were stirred at 110 °C in Dean-Stark under argon for 1 h. The reaction was allowed to cool to room temperature, then pyridine (0.16 mL, 2.0 mmol) was added and after five minutes the mixture was cooled at 0°C. Thionyl chloride (0.1 mL, 1.5 mmol) was added, the ice bath was removed, and the stirring was continued for 9 to 24 h at room temperature. A solid (pyridine hydrochloride) was observed at the end of the reaction and was filtered off. The solvent was removed by rotatory evaporator, CH_2Cl_2 (15.0 mL) was added and the solution was washed with water (3 × 10.0 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10.0 mL). The organic layers were combined, dried ($MgSO_4$), and the solvent was removed by rotatory evaporator. Compounds **3a-e** were purified by silica gel column chromatography, Aldrich 60A (230-400 Mesh) using hexane/methyl chloride 1:1 as the eluant. The compounds **7a-c** were purified by recrystallization from ethanol.

6-trifluoromethyl-2λ^4-[1,2,3]oxathiazinane-3-carboxylic acid ethyl ester (3a). This compound was obtained as a yellow oil, yield 70%; MS, EI (70ev): *m/z* (%) 261 (M^+, 6), 233 (20), 217 (12), 189 (10), 172 (36), 152 (14), 109 (32), 56 (100); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.33 (t, $J_{H9\text{-}H8}$=7.0 Hz, 3H, H-9), 1.93–2.03 (dddd, $J_{H5eq\text{-}H5ax}$=13.8 Hz, $J_{H5eq\text{-}H4eq}$=3.8 Hz, $J_{H5eq\text{-}H4ax}$=3.2 Hz, $J_{H5eq\text{-}H6}$=3.0 Hz, 1H, H-5), 2.07–2.29 (dtd, $J_{H5ax\text{-}H5eq}$=13.8 Hz, $J_{H5ax\text{-}H6}$=12.0 Hz, $J_{H5ax\text{-}H4ax}$=12.0 Hz, $J_{H5ax\text{-}H4eq}$=4.4 Hz, 1H, H-5), 3.82–3.96 (ddd, $J_{H4ax\text{-}H4eq}$=13.4 Hz, $J_{H4ax\text{-}H5ax}$=12.0 Hz, $J_{H4ax\text{-}H5eq}$=3.2 Hz, 1H, H-4), 4.02–4.13 (ddd, $J_{H4eq\text{-}H4ax}$=13.4 Hz, $J_{H4eq\text{-}H5ax}$=4.4 Hz, $J_{H4eq\text{-}H5eq}$=3.8 Hz, 1H, H-4), 4.30 (q, $J_{H8\text{-}H9}$=7.0 Hz, 3H, H-8), 5.05–5.20 (m, 1H, H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.4 (C-9), 30.3 (C-5), 36.5 (C-4), 61.4 (C-8), 67.8 (q, $^2J_{C\text{-}F}$=31.0 Hz, C-6), 125.1 (q, $^1J_{C\text{-}F}$=279.5 Hz, CF_3), 157.9 (C-7); ^{19}F NMR (376.5 MHz, $CDCl_3$, fluorobenzene) δ: -79.42. *Anal.* Calcd. for $C_7H_{10}F_3NO_4S$: C, 32.19; H, 3.86; N, 5.36. Found: C, 32.29; H, 3.86; N, 5.30.

2-Oxo-4-phenyl-6-trifluoromethyl-2λ^4-[1,2,3]oxathiazinane-3-carboxylic acid ethyl ester (3b). This compound was obtained as a colorless oil, yield 42 %; MS, EI (70ev): *m/z* (%) 337 (M^+, 2), 272 (14), 244 (25), 200 (49), 185 (12), 104 (100), 77 (38); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 1.15 (t, $J_{H9\text{-}H8}$=7.0 Hz, 3H, H-9), 2.36–2.42 (ddd, $J_{H5eq\text{-}H5ax}$=14.0 Hz, $J_{H5eq\text{-}H4ax}$=6.0 Hz, $J_{H5eq\text{-}H6}$=3.0 Hz, 1H, H-5), 3.20–3.30 (dt, $J_{H5ax\text{-}H5eq}$=14.0 Hz, $J_{H5ax\text{-}H6}$=13.2 Hz, $J_{H5ax\text{-}H4ax}$=13.2 Hz, 1H, H-5), 4.14 (q, $J_{H8\text{-}H9}$=7.0 Hz, 2H, H-8), 4.64–4.70 (m, 1H, H-6), 5.06–5.11 (dd, $J_{H4ax\text{-}H5ax}$=13.2 Hz, $J_{H4ax\text{-}H5eq}$=6.0 Hz, 1H, H-4), 7.25–7.43 (m, 5H, Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0 (C-9), 27.0 (C-5), 57.1 (C-4), 63.3 (C-8), 73.8 (q, $^2J_{C\text{-}F}$=35.3 Hz, C-6), 122.4 (q, $^1J_{C\text{-}F}$=278.7 Hz, CF_3), 126.7, 128.1, 128.9, 140.0 (Ph), 152.3 (C-7). *Anal.* Calcd. for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 46.37; H, 4.26; N, 4.09.

4-(4-Methyl-phenyl)-2-oxo-6-trifluoromethyl-2λ^4-[1,2,3]-oxathiazinane-3-carboxylic acid ethyl ester (3c). This compound was obtained as a colorless oil, yield 30 %; MS, EI (70ev): *m/z* (%) 351 (M^+, 3), 258 (12), 214 (15), 200 (41), 118 (100), 91 (33), 65 (12); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.18 (t, $J_{H9\text{-}H8}$=7.2 Hz, 3H, H-9), 2.33 (s, 3H, H-14), 2.39–2.43 (ddd, $J_{H5eq\text{-}H5ax}$=15.0 Hz, $J_{H5eq\text{-}H4ax}$=5.8 Hz, $J_{H5eq\text{-}H6}$=3.2 Hz, 1H, H-5), 3.14–3.34 (ddd, $J_{H5ax\text{-}H5eq}$=15.0 Hz, $J_{H5ax\text{-}H6}$=13.0 Hz, $J_{H5ax\text{-}H4ax}$=13.2 Hz, 1H, H-5), 4.14 (q, $J_{H8\text{-}H9}$=7.2 Hz, 2H, H-8), 4.61–4.72 (m, 1H, H-6), 5.01–5.10 (dd, $J_{H4ax\text{-}H5ax}$=13.2 Hz, $J_{H4ax\text{-}H5eq}$=5.8 Hz, 1H, H-4), 7.17 (d, *J*=8.0 Hz, 2H, Ph), 7.32 (d, *J*=8.0 Hz, 2H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0 (C-9), 21.0 (CH_3), 27.1 (C-5), 56.8 (C-4), 63.3 (C-8), 73.8 (q, $^2J_{C\text{-}F}$ = 34.6 Hz, C-6), 122.4 (q, $^1J_{C\text{-}F}$=278.7 Hz, CF_3), 126.7, 129.5, 137.0, 137.9 (Ph), 152.3 (C-7); ^{19}F NMR (376.6 MHz, $CDCl_3$, fluorobenzene) δ: -78.70. *Anal.* Calcd. for $C_{14}H_{16}F_3NO_4S$: C, 47.86; H, 4.59; N, 3.99. Found: C, 48.47; H, 4.88; N, 3.64.

4-Methyl-2-oxo-6-trifluoromethyl-2λ^4-[1,2,3]oxathiazinane -3-carboxylic acid ethyl ester (3d). This compound was obtained as an orange oil, yield 64 %. Data for the major isomer: MS, EI (70ev): *m/z* (%) 260 (M^+-15, 53), 230 (5), 188 (89), 56 (100); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.33 (t, $J_{H9\text{-}H8}$=7.0 Hz, 3H, H-9), 1.50 (d, $J_{H10\text{-}H4}$ = 6.2 Hz, 3H, CH_3), 2.26–2.38 (ddd, $J_{H5eq\text{-}H5ax}$=14.6 Hz, $J_{H5eq\text{-}H4ax}$=6.9 Hz, $J_{H5eq\text{-}H6}$=2.8 Hz, 1H, H-5), 2.92–3.12 (ddd, $J_{H5ax\text{-}H5eq}$=14.6 Hz, $J_{H5ax\text{-}H6}$=12.6 Hz, $J_{H5ax\text{-}H4ax}$=12.4 Hz, 1H, H-5), 4.24–4.37 (m, 1H, H-4), 4.29 (q, $J_{H8\text{-}H9}$=7.0 Hz, 2H, H-8), 4.42–4.58 (m, 1H, H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.2 (C-9), 22.6 (CH_3), 26.0 (C-5), 48.4 (C-4), 63.3 (C-7), 73.7 (q, $^2J_{C\text{-}F}$=34.4 Hz, C-6), 122.5 (q, $^1J_{C\text{-}F}$=278.6 Hz, CF_3), 152.27 (C-7); ^{19}F NMR (376.5 MHz, $CDCl_3$, fluorobenzene) δ: -79.00. *Anal.* Calcd. for $C_8H_{12}F_3NO_4S$: C, 34.91; H, 4.39; N, 5.09. Found: C, 35.26; H, 4.77; N, 5.18.

2-Oxo-4-propyl-6-trifluoromethyl-2λ^4-[1,2,3]oxathiazinane-3-carboxylic acid ethyl ester (3e). This compound was obtained as a yellow oil, yield 30 %; MS, EI (70ev): *m/z* (%) 260 (M^+-43, 80), 188 (100), 124 (44); ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 0.94 (t, *J*=7.2 Hz, 3H, CH_3), 1.32 (t, $J_{H8\text{-}H9}$=7.2 Hz, 3H, H-9), 1.25–1.35 (m, 2H, CH_2), 1.72–2.04 (m, 2H, CH_2), 2.28–2.40 (ddd, $J_{H5eq\text{-}H5ax}$=14.4 Hz, $J_{H5eq\text{-}H4ax}$=7.4 Hz, $J_{H5eq\text{-}H6}$=2.8 Hz, 1H, H-5), 2.81–3.00 (ddd, $J_{H5ax\text{-}H5eq}$=14.4 Hz, $J_{H5ax\text{-}H6}$=12.5 Hz, $J_{H5ax\text{-}H4ax}$=11.8 Hz, 1H, H-5), 4.23–4.34 (m, 1H, H-4), 4.29 (q, $J_{H8\text{-}H9}$=7.2 Hz, 2H, H-8), 4.42–4.52 (m, 2H, H-6); ^{13}C NMR

(100.6 MHz, $CDCl_3$): δ 13.7 (C-12), 13.9 (C-9), 14.4 (C-11), 18.8 (C-10), 37.3 (C-5), 48.7 (C-4), 61.1 (C-8), 69.0 (q, $^2J_{C\text{-}F}$=31.6 Hz, C-6), 125.0 (q, $^1J_{C\text{-}F}$=280.2 Hz, CF_3), 157.0 (C-7). *Anal.* Calcd. for $C_{10}H_{16}F_3NO_4S$: C, 39.60; H, 5.32; N, 4.62. Found: C, 39.86; H, 5.46; N, 4.32.

2-(2-Oxo-6-trifluoromethyl-2λ⁴-[1,2]oxathian-3-yl)-4,6-diphenyl-pyrimidine (7a). This compound was obtained as a colorless solid, yield 42 %; mp. 130–135 °C (ethanol); MS, EI (70ev): *m/z* (%) 419 (M^+, 22), 328 (79), 273 (43), 232 (8), 129 (50), 77 (53); ^{1}H NMR (200.13 MHz, DMSO-d_6) δ: 1.78–2.07 (m, 1H, H-5), 2.07–2.12 (m, 1H, H-5), 3.97–4.20 (m, 1H, H-4), 4.71–4.80 (ddd, $J_{H4eq\text{-}H4ax}$=13.8 Hz, $J_{H4eq\text{-}H5ax}$=3.4 Hz, $J_{H4eq\text{-}H5eq}$=3.8 Hz, 1H, H-4), 5.44–5.58 (m, 1H, H-6), 7.53–7.62 (m, 6H, H-13, H-14, H-17, H-18), 7.76 (s, 1H, H-9), 8.29–8.38 (m, 4H, H-12, H-16); ^{13}C NMR (50.6 MHz, DMSO-d_6): δ 29.4 (C-5), 37.1 (C-4), 66.7 (q, $^2J_{C\text{-}F}$=29.5 Hz, C-6), 101.7 (C-9), 127.0 (C-12, C-16), 128.6 (C-13, C-17), 130.7 (C-14, C-18), 137.0 (C-11, C-15), 162.2 (C-7), 164.5 (C-8, C-10). *Anal.* Calcd. for $C_{20}H_{16}F_3N_3O_2S$: C, 57.27; H, 3.85; N, 10.02. Found: C, 57.38; H, 4.21; N, 9.63.

4-(4-Chloro-phenyl)-2-(2-oxo-6-trifluoromethyl-2λ⁴-[1,2]-oxathian-3-yl)-6-phenyl-pyrimidine (7b). This compound was obtained as a yellow solid, yield 57 %; mp. 151 °C (ethanol); MS, EI (70ev): *m/z* (%) 453 (M^+, 9), 362 (47), 307 (38), 293 (100), 266 (64), 231 (53), 189 (10), 163 (27), 77 (76); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 2.09–2.18 (dddd, $J_{H5eq\text{-}H5ax}$=14.0 Hz, $J_{H5eq\text{-}H4eq}$=3.4 Hz, $J_{H5eq\text{-}H4ax}$=3.1 Hz, $J_{H5eq\text{-}H6}$=3.2 Hz, 1H, H-5), 2.32–2.39 (dtd, $J_{H5ax\text{-}H5eq}$=14.0 Hz, $J_{H5ax\text{-}H6}$=12.0 Hz, $J_{H5ax\text{-}H4ax}$=12.0 Hz, $J_{H5ax\text{-}H4eq}$=4.1 Hz, 1H, H-5), 4.07–4.22 (ddd, $J_{H4ax\text{-}H4eq}$=14.0 Hz, $J_{H4ax\text{-}H5ax}$=12.0 Hz, $J_{H4ax\text{-}H5eq}$=3.1 Hz, 1H, H-4), 4.73–4.80 (ddd, $J_{H4eq\text{-}H4ax}$=14.0 Hz, $J_{H4eq\text{-}H5ax}$=4.1 Hz, $J_{H4eq\text{-}H5eq}$=3.4 Hz, 1H, H-4), 5.18–5.27 (m, 1H, H-6), 7.46–7.54 (m, 5H, H-13, H-17, H-18); 7.70 (s, 1H, H-9); 8.04–8.12 (m, 4H, H-12, H-16); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.0 (C-5), 34.5 (C-4), 64.6 (q, $^2J_{C\text{-}F}$=34.3 Hz, C-6), 106.2 (C-9), 123.3 (q, $^1J_{C\text{-}F}$=277.2 Hz, CF_3), 127.2 (C-16), 128.5 (C-12), 128.9 (C-18), 129.1 (C-17), 131.3 (C-13), 134.9 (C-14), 136.3 (C-11), 137.5 (C-15), 159.8 (C-8), 164.5 (C-10), 166.1 (C-7); ^{19}F NMR (376.5 MHz, $CDCl_3$, fluorobenzene) δ: -78.11. *Anal.* Calcd. for $C_{20}H_{15}ClF_3N_3O_2S$: C, 52.93; H, 3.33; N, 9.26. Found: C, 53.16; H, 3.30; N, 9.16.

4-(4-Methoxy-phenyl)-2-(2-oxo-6-trifluoromethyl-2λ⁴-[1,2]-oxathian-3-yl)-6-phenyl-pyrimidine (7c). This compound was obtained as a colorless solid, yield 41 %; mp. 137–140 °C (ethanol); MS, EI (70ev): *m/z* (%) 449 (M^+, 22), 358 (46), 303 (32), 289 (100), 262 (53), 159 (22), 77 (61); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 2.09–2.15 (dddd, $J_{H5eq\text{-}H5ax}$=14.0 Hz, $J_{H5eq\text{-}H4eq}$=3.4 Hz, $J_{H5eq\text{-}H4ax}$=3.1 Hz, $J_{H5eq\text{-}H6}$=3.2 Hz, 1H, H-5), 2.30–2.41 (dtd, $J_{H5ax\text{-}H5eq}$=14.0 Hz, $J_{H5ax\text{-}H6}$=12.0 Hz, $J_{H5ax\text{-}H4ax}$=12.0 Hz, $J_{H5ax\text{-}H4eq}$=4.1 Hz, 1H, H-5), 4.10–4.18 (ddd, $J_{H4ax\text{-}H4eq}$=14.0 Hz, $J_{H4ax\text{-}H5ax}$=12.0 Hz, $J_{H4ax\text{-}H5eq}$=3.1 Hz, 1H, H-4), 4.74–4.79 (ddd, $J_{H4eq\text{-}H4ax}$=14.0 Hz, $J_{H4eq\text{-}H5ax}$=4.1 Hz, $J_{H4eq\text{-}H5eq}$=3.4 Hz, 1H, H-4), 5.18–5.26 (m, 1H, H-6), 7.01 (d, $J_{H17\text{-}H16}$=8.8 Hz, 2H, H-17), 7.50–7.52 (m, 3H, Ph), 7.67 (s, 1H, H-9), 8.08–8.11 (m, 4H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 23.1 (C-5), 34.6 (C-4), 55.4 (OCH_3), 64.7 (q, $^2J_{C\text{-}F}$=34.30 Hz, C-6), 105.7 (C-9), 114.3 (C-17), 123.4 (q, $^1J_{C\text{-}F}$=277.2 Hz, CF_3), 127.2 (C-16), 128.8 (C-12), 128.9 (C-13), 129.1 (C-14), 131.0 (C-15), 136.8 (C-11), 159.9 (C-7), 162.4 (C-18), 165.4 (C-8), 165.6 (C-10); ^{19}F NMR (376.5 MHz, $CDCl_3$, fluorobenzene) δ: -78.11. *Anal.* Calcd. for $C_{21}H_{18}F_3N_3O_3S$: C, 56.12; H, 4.04; N, 9.35. Found: C, 56.02; H, 4.04; N, 9.25.

Procedure for the preparation of 2-Dioxo-6-trifluoromethyl-2λ⁴-[1,2,3]oxathiazinane-3-carboxylic acid ethyl ester (8a). To a solution of **3a** (0.26 g, 1.0 mmol) in CH_3CN (12.0 mL) stirred in an ice bath and under argon atmosphere, ruthenium chloride ($RuCl_3.2H_2O$) in catalytic amount (5.0 mg) and KIO_4 (0.23 g, 2.0 mmol) was added. After 15 min water (10.0 mL) was added and stirring was continued for 6 h at 0 °C. The reaction mixture was extracted with ethyl ether (3 × 10.0 mL) and the organic layer were combined and washed with saturated sodium bicarbonate solution (10.0 mL) and with 50% sodium chloride solution. The organic phase was dried ($MgSO_4$) and the solvent was removed by rotatory evaporator. Compound **8a** was purified by silica gel column chromatography, Aldrich 60A (230-400 Mesh) using hexane/methyl chloride 2:1 as the eluant. Yield 50 %; oil; MS EI (70ev): *m/z* (%) 277 (M, 1), 232 (14), 205 (42), 109 (100), 56 (26). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.0 Hz, 3H, CH_3), 2.16–2.27 (m, 2H, H-5), 3.83–3.97 (m, 1H, H-4), 4.35 (q, *J* = 7.0 Hz, 2H, CH_2), 4.43–4.50 (m, 1H, H-4), 5.00–5.16 (m, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.7 (C-5), 44.7 (C-4), 64.9 (C-8), 79.0 (q, $^2J_{C\text{-}F}$ = 35.5 Hz, C-6), 121.5 (q, $^1J_{C\text{-}F}$ = 277.2 Hz, CF_3), 151.1 (C=O).

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