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AN EFFICIENT SYNTHESIS OF 2,4'-BI-1,3-OXA(THIA)ZOLES AS SCAFFOLDS FOR BIOACTIVE PRODUCTS

S. Peña[1], L. Scarone[1], E. Manta[1], and G. Serra[1]*

A rapid and efficient methodology to prepare 2,4'-bi-1,3-azoles as scaffolds for biologically active marine natural products is described. Hantzsch reaction and oxidative cyclodehydration of β-hydroxy amides or thioamides were used to construct the azole rings. The obtained biheterocycles displayed no cytotoxicity on HCT-15 cell line.

Keywords: bi-1,3-azoles, α-halo ketone, β-hydroxy amides, Hantzsch reaction, oxidative cyclodehydration.

It is well known that natural products play an important role in drug development, particularly that of anticancer, antibiotic, and antiparasitic drugs [1]. The structural diversity of natural products has served as an inspiration source for research of pharmacologically active molecules.

Bioxazoles, bithiazoles, and oxazole-thiazole scaffolds are present in numerous structurally novel and biologically active marine products [2–4]. Representative examples include hennoxazoles, with a 2,4'-bioxazole system, isolated from the sponge *Polifibrospongia* as potent anti-herpes virus agents [5], bengazoles, containing an uncommon 2,5'-bioxazole, isolated from the sponge *Jaspis* sp. as anthelmintic, antifungal, and antitumor agents [6–8], leucamide A, a cyclic heptapeptide with an oxazole-thiazole system, isolated from the sponge *Leucetta microraphis*, as moderately cytotoxic towards several tumor cell lines [9], and largazole, a depsipeptide containing a thiazoline-thiazole system, isolated from the cyanobacterium *Symploca* sp., a potent histone deacetylase (HDAC) inhibitor [10].

The 2,4'-biazole fragment is a more common moiety in marine natural products than 2,5'-biazole system. This is consistent with the biogenesis of those heterocycles that are derived from serine, threonine, or cysteine residues in peptides by a cyclodehydration and oxidation process [3].

The interest in synthesis of these biheterocycles has stimulated the development of different methodologies. To construct the 2,4'-bioxazole moiety of (+)-hennoxazole A, Wipf and co-workers employed the cyclodehydrating Burgess reagent and cupric bromide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and hexamethylenetetramine (HMTA) to prepare one of the oxazole rings, and Dess-Martin oxidation and 1,2-dibromotetrachloroethane to prepare the other ring [11]. Later, Williams' group synthetized (–)-hennoxazole A using diethylaminosulfur trifluoride (DAST) to prepare oxazoline rings from the appropriate β-hydroxy amides and bromotrichloromethane in the presence of DBU to obtain the corresponding oxazoles [12].

*To whom correspondence should be addressed, e-mail: gserra@fq.edu.uy.

[1]Quimica Farmaceutica Facultad de Quimica, 2124 Montevideo, Uruguay.

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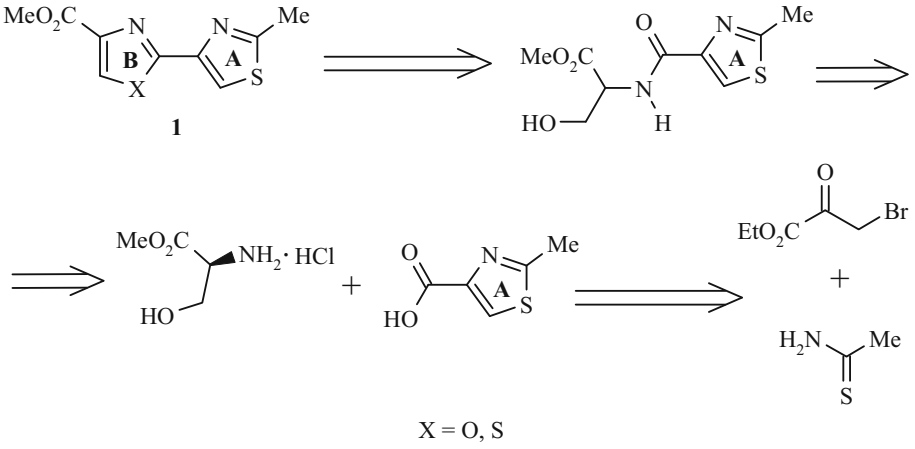
In 2003, Nan and co-workers reported the synthesis of 2,4'-biheterocycles as intermediates toward the total synthesis of leucamide A [13, 14]. The methodology used involves Holzapfel's modified Hantzsch procedure to obtain the thiazole component, followed by a coupling reaction, DAST-mediated cyclization, and treatment with bromotrichloromethane with DBU to obtain the oxazole component [15]. A few years later, in 2009, Nan's group reported the synthesis of C(7)-demethyl largazole analogs containing 2,4'-bithiazole using two consecutive Hantzsch reactions [16].

As a part of our search for anticancer or antiparasitic drugs candidates employing molecular simplification [17–22], we focused on the synthesis of 2,4'-biheterocycles as scaffolds of bioactive products using Hantzsch and cyclodehydration-oxidation reactions. In the present work, we report the synthesis of biheterocycles of type **1** (Scheme 1) using commercially available starting materials: L-serine methyl ester hydrochloride, ethyl bromopyruvate, and thioacetamide.

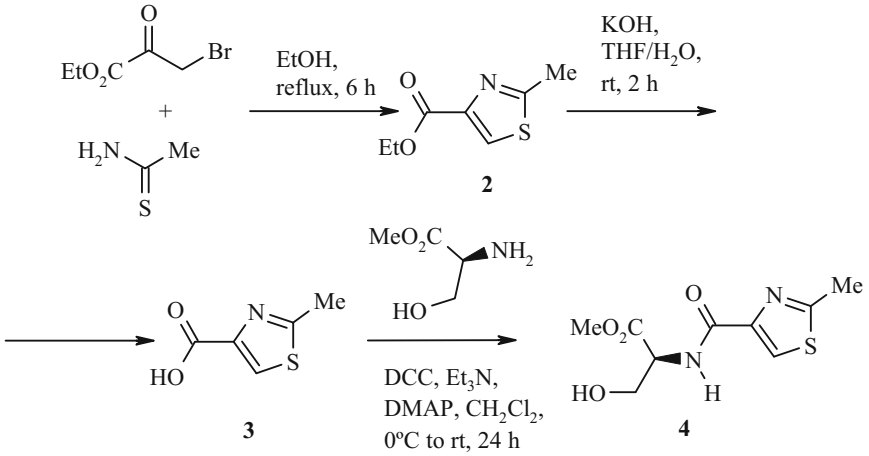
Scheme 1



In order to prepare the thiazole ring **A**, ethyl bromopyruvate and thioacetamide were refluxed in ethanol. Thiazole **2** was obtained in 81% yield (Scheme 2). Conventional hydrolysis using lithium hydroxide in tetrahydrofuran–water gave carboxylic acid **3** in low yield (44%). In contrast, hydrolysis using 10% aqueous potassium hydroxide produced the acid **3** in very good yield (86%).

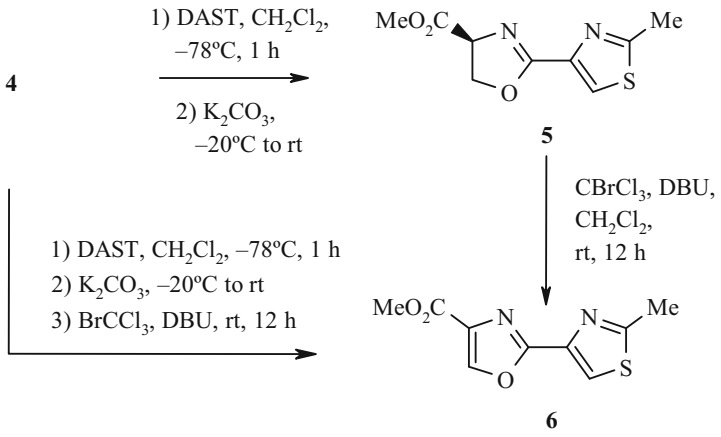
The next step to prepare the β-hydroxy amide **4** involved amide bond formation to obtain the precursor of ring **B** (Scheme 1). The use of N,N'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as coupling agent allowed us to obtain amide **4** in 83% yield.

Scheme 2



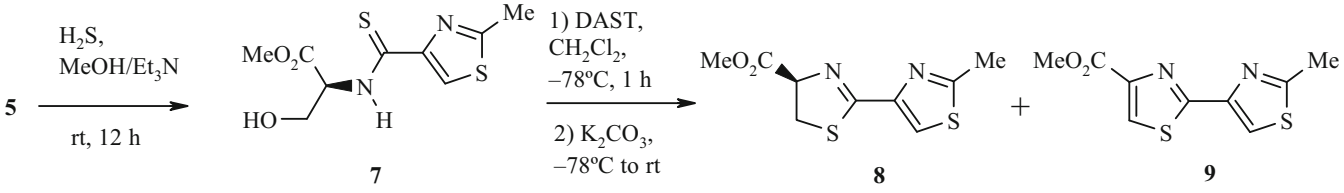
Cyclodehydration reaction of β-hydroxy amide **4** to obtain the corresponding oxazoline **5** was performed using DAST (Scheme 3). Subsequent oxidation employing bromotrichloromethane and DBU resulted in the formation of 2-(thiazol-4-yl)oxazole **6** in 78% yield. Consequently, compound **6** was obtained from **4** in 67% overall yield. The one-pot procedure gave oxazole **6** from β-hydroxy amide **4** in 53% yield. The isolation of oxazoline **5** not only allows to improve the yield of oxazole **6**, but also to use it as a precursor in the synthesis of thiazolinylthiazole **8** (Scheme 4).

Scheme 3



Thiolysis of oxazoline **5** employing Wipf's methodology [23], followed by cyclodehydration, permitted the transformation of β-hydroxy thioamide **7** into 4-(thiazolin-2-yl)thiazole **8**, as well as the unexpected 2,4'-bithiazole **9**. Air oxidation of thiazolines to thiazoles during the purification of tantazole A has been observed previously by Carmelli [24]. Recently, Yao reported the oxidation of thiazoline-4-carboxylates to thiazole-4-carboxylates by molecular oxygen [25]. Consequently, the formation of bithiazole **9** could be explained by air oxidation of thiazolinylthiazole **8**.

Scheme 4

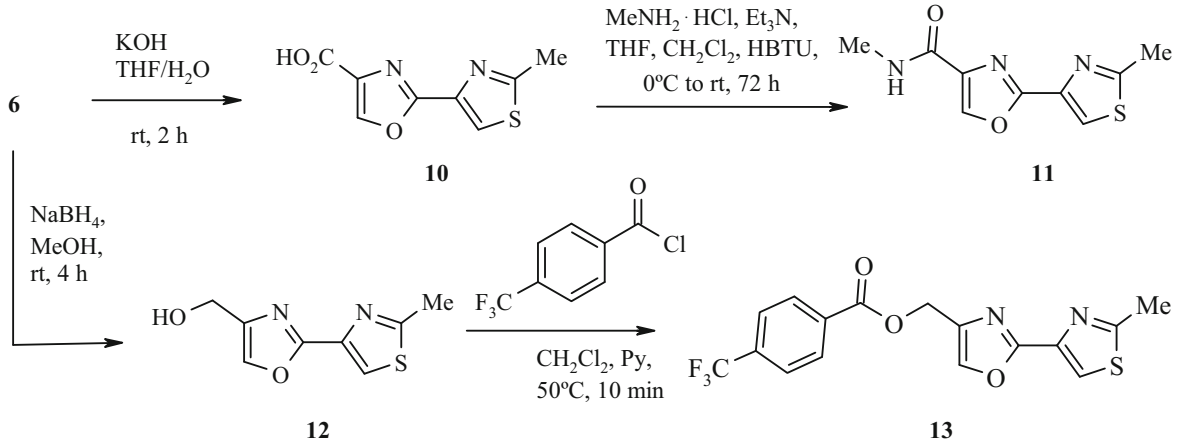


In order to introduce some structural modifications for biological evaluation, the ester group of compound **6** was first hydrolyzed to acid **10**, and N-methylamide **11** was obtained using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) as the coupling agent (Scheme 5).

Alcohol **12** was obtained from ester **6** in very good yield employing an excess of $NaBH_4$ in methanol. Then a bulky and electron-withdrawing group was introduced by esterification of compound **12** to obtain the protected alcohol **13.**

We have obtained 2,4'-biheterocycles from readily available precursors using a rapid and efficient synthetic pathway. These compounds were modified to prepare new derivatives. Our preliminary evaluation of the biological activities demonstrated no cytotoxicity on HCT-15 cell line [26]. All of the obtained biheterocycles exhibited an activity about 1000 times lower than that of Mytomicin C (GI 50 (Mytomicin C) = 2.5 μM). Insights gained from these studies will serve for further preparations of new potential and selective antiparasitic compounds. Our process could be used for construction of natural products and their analogs containing 2,4'-biazoles.

Scheme 5



EXPERIMENTAL

Optical rotation was measured using a Kruss Optronic GmbH P8000 polarimeter with a 0.5 ml cell. IR spectra were recorded on a Shimadzu FTIR 8101A spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 instrument (400 and 100 MHz, respectively) in $CDCl_3$ (all compounds) or MeOD (compound **10**) using TMS as internal standard. High-resolution mass spectra (ESI) were obtained on a Bruker Daltonics MicrOTOF-Q instrument. Flash column chromatography was carried out on Silica gel 60 (J.T. Baker, 40 μm average particle diameter). All reactions and chromatographic separations were monitored by TLC (Macherey/Nagel, Polygram SIL G/UV 254). TLC plates were analyzed under 254 nm UV light, by iodine vapor, *p*-hydroxybenzaldehyde spray, or ninhydrine spray.

Ethyl 2-Methyl-1,3-thiazole-4-carboxylate (2). A solution of ethyl bromopyruvate (3.9 g, 20 mmol) and thioacetamide (1.5 g, 20 mmol) in dry EtOH (14.0 ml) was refluxed under N_2 for 6 h. Then, the reaction mixture was concentrated under reduced pressure and $NaHCO_3$ (sat. sol.) was added until pH 8. The aqueous layer was extracted with Et_2O (4×20 ml), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (eluent *n*-hexane–AcOEt, 2:1) to give 2.78 g (81%) of thiazole **2** as an orange oil. R_f = 0.65 (*n*-hexane–AcOEt, 2:1). ^{1}H NMR spectrum δ, ppm (*J*, Hz): 1.41 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 2.77 (3H, s, 2-CH$_3$); 4.43 (2H, q, *J* = 7.1, CH$_3$C<u>H</u>$_2$); 8.04 (1H, s, H-5). ^{13}C NMR spectrum δ, ppm: 14.4; 19.4; 61.4; 127.3; 146.9; 161.4; 166.8.

2-Methyl-1,3-thiazole-4-carboxylic Acid (3). To a stirred solution of thiazole **2** (0.54 g, 3.15 mmol) in THF (3.0 ml), 10% KOH solution (3.0 ml) was added at room temperature. Stirring was continued for 2 h. HCl (5 M) was added until pH 3. The aqueous phase was extracted with ethyl acetate (4×15 ml). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Thiazole **3** (0.39 g, 86%) was obtained and used without further purification; R_f 0.37 ($CHCl_3$–AcOEt, 3:1). ^{1}H NMR spectrum δ, ppm: 2.82 (3H, s, CH_3); 8.19 (1H, s, H-5); 10.51 (1H, s, COOH). ^{13}C NMR spectrum δ, ppm: 19.2; 128.9; 145.9; 164.8; 167.5.

Methyl (*S*)-3-Hydroxy-2-{[(2-methyl-1,3-thiazol-4-yl)carbonyl]amino}propanoate (4). To a stirred solution of acid **3** (0.2 g, 1.4 mmol) in dry CH_2Cl_2 (10 ml) cooled at 0ºC under N_2, Et_3N (0.2 ml, 1.4 mmol), L-serine methyl ester hydrochloride (0.22 g, 1.4 mmol), and DMAP (0.017 g, 0.14 mmol) were added. The reaction mixture was stirred for 30 min. Then DCC (0.32 g, 1.54 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. The precipitated dicyclohexylurea was filtered off, water (10 ml) was added and the mixture was extracted with AcOEt (4×15 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt) to obtain β-hydroxy amide **4** (0.28 g, 83%) as a white solid; R_f 0.44 (AcOEt). IR spectrum, ν, cm^{-1}:

3399, 2956, 1746, 1653, 1545, 1215, 1181, 756. ^{1}H NMR spectrum, δ, ppm: 2.73 (3H, s, CH_3); 3.09–3.06 (1H, m, OH); 3.83 (3H, s, OCH_3); 4.14–4.03 (2H, m, CH_2OH); 4.86 (1H, m, NCH); 7.98 (1H, s, H thiazole); 8.14 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 19.1; 52.9; 54.8; 63.5; 123.9; 148.8; 161.3; 166.4; 170.7. Found: *m/z* 245.0592 $[M+H]^+$. $C_9H_{13}N_2O_4S$. Calculated: 245.0596.

Methyl (*S*)-2-(2-Methyl-1,3-thiazol-4-yl)-4,5-dihydro-1,3-oxazole-4-carboxylate (5). To a solution of β-hydroxy amide **4** (0.2 g, 0.82 mmol) in dry CH_2Cl_2 (8 ml) at –78°C under N_2, DAST (0.13 ml, 0.92 mmol) was added dropwise. After stirring for 1 h, the reaction mixture was quenched with K_2CO_3 solution (0.17 g, 1.23 mmol) at –20°C. After warming to room temperature, the mixture was further diluted with a saturated aqueous solution of Na_2CO_3 and then extracted with CH_2Cl_2 (4×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (AcOEt) to obtain oxazoline **5** (0.16 g, 86%) as a white solid; mp 123–124°C; $[\alpha]^{20}_D$ +127° (*c* 0.5, MeOH); R_f 0.44 (AcOEt). IR spectrum, ν, cm^{-1}: 3407, 2956, 1740, 1651, 1210, 1179. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.77 (3H, s, CH_3); 3.82 (3H, s, OCH_3); 4.63 (1H, dd, J_1 = 8.7, J_2 = 10.5, CH_2); 4.74 (1H, dd, J_1 = 8.7, J_3 = 8.0, CH_2); 4.98 (1H, dd, J_2 = 10.5, J_3 = 8.0, CH); 7.91 (1H, s, H thiazole). ^{13}C NMR spectrum, δ, ppm: 19.3; 52.1; 68.6; 69.9; 124.1; 142.9; 161.5; 167.2; 171.4. Found: *m/z* 227.0484 $[M+H]^+$. $C_9H_{11}N_2O_3S$. Calculated: 227.0490.

Methyl 2-(2-Methyl-1,3-thiazol-4-yl)-1,3-oxazole-4-carboxylate (6). Oxazoline **5** (0.159 g, 0.709 mmol) was dissolved in dry CH_2Cl_2 (14 ml). The reaction mixture was cooled to –20ºC, and $CBrCl_3$ (0.25 ml, 2.54 mmol) was slowly added. Then it was allowed to reach 0ºC and DBU (0.38 ml, 2.54 mmol) was added dropwise. The reaction mixture was quenched with a saturated solution of $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (AcOEt) to obtain oxazole **6** (0.12 g, 78%) as a white-yellow solid; R_f 0.44 (AcOEt). IR spectrum, ν, cm^{-1}: 3129, 2953, 1717, 1566, 1323, 1294. ^{1}H NMR spectrum, δ, ppm: 2.82 (3H, s, CH_3); 3.96 (3H, s, OCH_3); 8.06 (1H, s, H thiazole); 8.31 (1H, s, H oxazole). ^{13}C NMR spectrum, δ, ppm: 19.3; 52.3; 121.3; 134.3; 142.1; 143.6; 157.8; 161.6; 167.7. Found: *m/z* 225.0334 $[M+H]^+$. $C_9H_9N_2O_3S$. Calculated: 225.0328.

Methyl (*S*)-3-Hydroxy-2-{[(2-methyl-1,3-thiazol-4-yl)carbonothioyl]amino}propanoate (7). A solution of oxazoline **5** (0.2 g, 0.88 mmol) in MeOH–Et_3N (8 ml, 2:1) was saturated with H_2S, prepared from Na_2S and H_2SO_4, under continuous stirring at room temperature. The production of H_2S was maintained for 10 min; the reaction mixture was left at room temperature, while progress of the reaction was controlled by TLC. Excess H_2S, MeOH, and Et_3N were removed by evaporation *in vacuo* through a solution of bleach. The residue was purified by flash chromatography (*n*-hexane–AcOEt, 1:3) to obtain β-hydroxy thioamide **7** (0.18 g, 77%) as a yellow oil; R_f 0.56 (AcOEt–*n*-hexane, 3:1). IR spectrum, ν, cm^{-1}: 3129, 1717, 1566, 1323, 1294. ^{1}H NMR spectrum δ, ppm: 2.77 (3H, s, CH_3); 3.99 (3H, s, OCH_3); 4.25–4.21 (2H, m, CH_2); 5.52–5.48 (1H, m, CH); 8.25 (1H, s, H thiazole); 9.92 (1H, s, NH). ^{13}C NMR spectrum δ, ppm: 19.3; 52.9; 59.2; 62.5; 126.0; 153.3; 165.9; 170.1; 187.4. Found: *m/z* 283.0182 $[M+Na]^+$. $C_9H_{12}N_2NaO_3S_2$. Calculated: 283.0187.

Methyl (*R*)-2'-Methyl-4,5-dihydro-2,4'-bi-1,3-thiazole-4-carboxylate (8) and **Methyl 2'-Methyl-2,4'-bi-1,3-thiazole-4-carboxylate (9).** To a solution of β-hydroxy thioamide **7** (0.15 g, 0.58 mmol) in dry CH_2Cl_2 (6 ml) at –78°C under N_2, DAST (0.09 ml, 0.65 mmol) was added dropwise. After stirring for 1 h, the reaction mixture was quenched with K_2CO_3 solution (0.12 g, 0.27 mmol) at –20ºC. After warming to room temperature, the mixture was further diluted with a saturated aqueous solution of Na_2CO_3 and then extracted with CH_2Cl_2 (4×20 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (*n*-hexane–AcOEt, 1:4) to obtain thiazoline **8** (0.060 g, 43%) as a yellow oil that subsequently solidified and thiazole **9** (0.020 g, 14%) as a yellow solid. Compound **8**: mp 59–60°C; $[\alpha]^{20}_D$ +18° (*c* 2.2, CH_2Cl_2); R_f 0.44 (*n*-hexane–AcOEt, 1:4). IR spectrum, ν, cm^{-1}: 3114, 29525, 1742, 1605, 1435, 1202, 1161. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73 (3H, s, CH_3); 3.70–3.58 (2H, m, CH_2); 3.81 (3H, s, OCH_3); 5.27 (1H, t, *J* = 9.3, CH); 7.86 (1H, s, H thiazole). ^{13}C NMR spectrum, δ, ppm: 19.2; 35.1; 52.8; 78.3; 121.1; 148.2; 165.5; 166.4; 171.2. Found: *m/z* 243.0250 $[M+H]^+$. $C_9H_{11}N_2O_2S_2$. Calculated: 243.0262.

Compound **9**: mp 157–158°C; R_f 0.60 (*n*-hexane–AcOEt, 1:4). IR spectrum, ν, cm^{-1}: 3129, 2994, 1713, 1495, 1238, 1165. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.78 (3H, s, CH_3); 3.99 (3H, s, OCH_3); 8.01 (1H, s, H thiazole); 8.25 (1H, s, H thiazole). ^{13}C NMR spectrum, δ, ppm: 19.2; 52.6; 117.1; 127.9; 147.5; 147.9; 161.9; 166.9; 163.5. Found: *m/z* 241.0097 $[M+H]^+$. $C_9H_9N_2O_2S_2$. Calculated: 241.0105.

2-(2-Methyl-1,3-thiazol-4-yl)-1,3-oxazole-4-carboxylic Acid (10). Following the procedure for the conversion of ester **2** into acid **3**, ester **6** (0.042 g, 0.19 mmol) was transformed into acid **10**. The crude product was purified by flash chromatography (AcOEt–MeOH, 1:1) to obtain acid **10** (0.036 g, 91%) as a colorless solid; R_f 0.47 (AcOEt–MeOH, 1:1). ^1H NMR spectrum, δ, ppm: 2.79 (3H, s, CH_3); 8.18 (1H, s, H thiazole); 8.23 (1H, s, H oxazole).

N-Methyl-2-(2-methyl-1,3-thiazol-4-yl)-1,3-oxazole-4-carboxamide (11). A stirred solution of acid **10** (0.027 g, 0.13 mmol) in DMF (2 ml) and CH_2Cl_2 (5 ml) was cooled to 0ºC; then $MeNH_2 \cdot HCl$ (0.060 g, 0.89 mmol) and Et_3N (0.61 mmol) were added. After 15 min, the reaction mixture was left to reach room temperature, and HBTU (0.088 g, 0.23 mmol) was added. It was stirred during three days at room temperature. A 5% HCl solution was added until pH 5. The aqueous layer was extracted with Et_2O (4×10 ml), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (AcOEt) to obtain the desired amide **11** (0.012 g, 40%) as a colorless solid; R_f 0.44 (AcOEt). ^1H NMR, spectrum, ppm (*J*, Hz): 2.84 (3H, s, CH_3); 3.00 (3H, d, J = 4.9, NCH_3); 7.87 (1H, s, H thiazole); 8.25 (1H, s, H oxazole). ^{13}C NMR spectrum, δ, ppm: 19.4; 25.1; 120.7; 137.5; 140.6; 142.2; 156.8; 160.8; 168.2. Found: *m/z* 224.0488 $[M+H]^+$. $C_9H_{10}N_3O_2S$. Calculated: 224.0494.

[2-(2-Methyl-1,3-thiazol-4-yl)-1,3-oxazol-4-yl]methanol (12). To a solution of ester **6** (0.050 g, 0.22 mmol) in MeOH (6 ml), $NaBH_4$ (0.37 g, 9.74 mmol) was slowly added at room temperature with continuous stirring. After no more starting material was observed by TLC, MeOH was distilled under reduced pressure, and 20 ml of H_2O was added. The aqueous layer was extracted with AcOEt (5×25 ml), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography with MeOH–AcOEt (1:5) to obtain alcohol **12** (0.039 g, 86%) as a white solid; R_f = 0.64 (MeOH–AcOEt, 1:5). ^1H NMR spectrum, δ, ppm: 2.83 (3H, s, CH_3); 4.70 (2H, s, CH_2); 7.66 (1H, s, H thiazole); 7.84 (1H, s, H oxazole). Found: *m/z* 197.0381 $[M+H]^+$. $C_8H_9N_2O_2S$. Calculated: 197.0385.

[2-(2-Methyl-1,3-thiazol-4-yl)-1,3-oxazol-4-yl]methyl 4-Trifluoromethylbenzoate (13). 4-Trifluoromethylbenzoyl chloride (0.03 ml, 0.19 mmol) was added to a stirred solution of alcohol **12** (0.03 g, 0.15 mmol) and pyridine (0.01 ml, 0.15 mmol) in CH_2Cl_2 (6 ml), and then the mixture was heated at 50ºC. After 90 min, the reaction was quenched with ice water. A solution of HCl 5% was added until pH 2. The aqueous layer was extracted with AcOEt (3×15 ml) and washed with a 5% solution of $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane–AcOEt, 2:1) to obtain the desired ester **13** (0.047 g, 84%) as a white solid; mp 145–146°C; R_f 0.76 (AcOEt–*n*-hexane, 3:1). IR spectrum, ν, cm^{-1}: 3137, 3092, 2923, 1719, 1595, 1325, 1287. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.82 (3H, s, CH_3); 5.40 (2H, s, CH_2); 7.72 (2H, d, J = 8.3, H Ar); 7.83 (1H, s, H oxazole); 7.87 (1H, s, H thiazole); 8.20 (2H, d, J = 8.3, H Ar). ^{13}C NMR spectrum, δ, ppm: 19.3; 58.9; 119.8; 119.9; 125.4; 130.1; 130.3; 133.0; 136.7; 137.5; 137.6; 142.8; 157.8; 165.2; 167.7. Found: *m/z* 391.0331 $[M+Na]^+$. $C_{16}H_{11}F_3N_2NaO_3S$. Calculated: 391.0340.

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REFERENCES

1. D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, **70**, 461 (2007).
2. Z. Jin, *Nat. Prod. Rep.*, **23**, 464, (2006).
3. E. Riego, D. Hernández, F. Albericio, and M. Álvarez, *Synthesis*, 1907 (2005).

4. V. S. C. Yeh, *Tetrahedron*, **60**, 11995 (2004).
5. T. Ichiba, W. Y. Yoshida, P. J. Scheuer, T. Higa, and D. G. Gravalos, *J. Am. Chem. Soc.*, **113**, 3173 (1991).
6. M. Adamczeski, E. Quiñoa, and P. Crews, *J. Am. Chem. Soc.,* **110**, 1598 (1988).
7. J. Rodríguez, R. M. Nieto, and P. Crews, *J. Nat. Prod.*, **56**, 2034 (1993).
8. A. Rudi, Y. Kashman, Y. Benayahu, and M. Schleyer, *J. Nat. Prod.*, **57**, 829 (1994).
9. S. Kehraus, G. M. Konig, A. D. Wright, and G. Woerheide, *J. Org. Chem*., **67**, 4989 (2002).
10. K. Taori, V. J. Paul, and H. Luesch, *J. Am. Chem. Soc.*, **130**, 1806 (2008).
11. P. Wipf and S. Lim, *J. Am. Chem. Soc.*, **117**, 558 (1995).
12. D. R. Williams, D. A. Brooks, and M. A. Berliner, *J. Am. Chem. Soc.*, **121**, 4924 (1999).
13. W.-L. Wang and F.-J. Nan, *J. Org. Chem.*, **68**, 1636 (2003).
14. H.-J. Chen, W.-L. Wang, G.-F. Wang, L.-P. Shi, M. Gu, Y.-D. Ren, L.-F. Hou, P.-L. He, F.-H. Zhu, X.-G. Zhong, W. Tang, J.-P. Zuo, and F.-J. Nan, *Chem. Med. Chem.*, **3**, 1316 (2008).
15. M. W. Brendenkamp and C. W. Holzapfel, *Synth. Commun.*, **20**, 2235 (1990).
16. F. Chen, A.-H. Gao, J. Li, and F.-J. Nan, *Chem. Med. Chem.*, **4**, 1269 (2009).
17. L. Scarone, D. Sellanes, E. Manta, P. Wipf, and G. Serra, *Heterocycles*, **63**, 773 (2004).
18. D. Sellanes, L. Scarone, G. Mahler, E. Manta, A. Baz, S. Dematteis, J. Saldaña, L. Dominguez, P. Wipf, and G. Serra, *Lett. Drug Des. Discovery*, **3**, 35 (2006).
19. G. Mahler, G. Serra, S. Dematteis, J. Saldaña, L. Domínguez, and E. Manta, *Bioorg. Med. Chem. Lett.*, **16**, 1309 (2006).
20. D. Sellanes, E. Manta, and G. Serra, *Tetrahedron Lett*., **48**, 1827 (2007).
21. M. Incerti, C. Fontana, L. Scarone, G. Moyna, and E. Manta, *Heterocycles*, **75**, 1385 (2008).
22. L. Scarone, J. Fajardo, J. Saldaña, L. Domínguez, P. Espósito, S. Dematteis, P. Wipf, E. Manta, and G. Serra, *Lett. Drug Des. Discovery*, **6**, 413 (2009).
23. P. Wipf, C. P. Miller, S. Venkataraman, and P. C. Fritch, *Tetrahedron Lett.*, **36**, 6395 (1995).
24. S. Carmeli, R. E. Moore, G. M. L. Patterson, T. H. Corbett, and F. J. Valeriote, *J. Am. Chem. Soc.*, **112**, 8195 (1990).
25. Y. Huang, H. Gan, S. Li, J. Xu, X. Wu, and H. Yao, *Tetrahedron Lett.*, **51**, 1751 (2010).
26. P. V. Skehan, in: *Cell Biology. A Laboratory Handbook*, 2nd Ed., 1998, Vol. 1, p. 313.