

Accepted Manuscript

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PII: S0040-4020(13)01474-9

DOI: [10.1016/j.tet.2013.09.052](https://doi.org/10.1016/j.tet.2013.09.052)

Reference: TET 24827

To appear in: *Tetrahedron*

Received Date: 22 July 2013

Revised Date: 10 September 2013

Accepted Date: 17 September 2013

Please cite this article as: Ribeiro Laia FM, Gomes CSB, Pinho e Melo TMVD, Reactivity of Sarcosine and 1,3-Thiazolidine-4-carboxylic Acid Towards Salicylaldehyde-derived Alkynes and Allenes, *Tetrahedron* (2013), doi: 10.1016/j.tet.2013.09.052.

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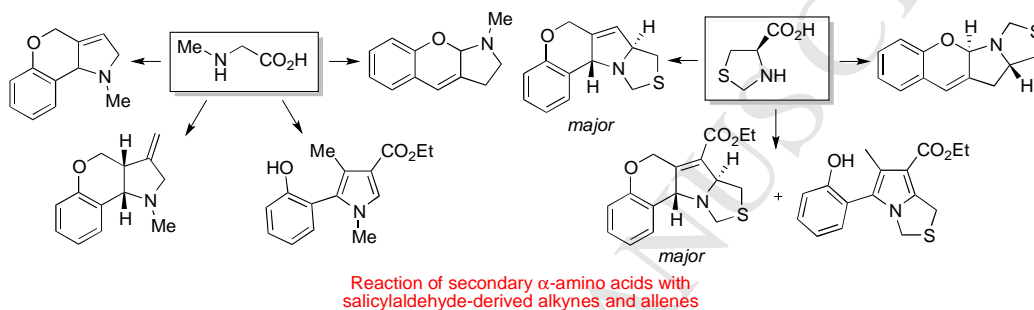
Reactivity of Sarcosine and 1,3-Thiazolidine-4-carboxylic Acid Towards Salicylaldehyde-derived Alkynes and Allenes

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Abstract – The reaction of sarcosine and 1,3-thiazolidine-4-carboxylic acid with salicylaldehyde-derived alkynes and allenes opened the way to new chromeno[4,3-*b*]pyrrole and chromeno[2,3-*b*]pyrrole derivatives. Tetrahydro-chromeno[4,3-*b*]pyrroles were obtained from the reaction of these secondary amino acids with *O*-propargylsalicylaldehyde. Interestingly, sarcosine reacted with ethyl 4-(2-formylphenoxy)but-2-ynoate to give a monocyclic pyrrole resulting from rearrangement of the initially formed 1,3-dipolar cycloadduct. Decarboxylative condensation of ethyl 4-(2-formylphenoxy)but-2-ynoate with 1,3-thiazolidine-4-carboxylic acid afforded in a stereoselective fashion the expected chromeno-pyrrolo[1,2-*c*]thiazole, which structure was unambiguously established by X-ray crystallography. However, the 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole resulting from the opening of the pyran ring was also isolated. The reaction with *O*-buta-2,3-dienyl salicylaldehyde afforded 3-methylene-hexahydrochromeno[4,3-*b*]pyrrole. *O*-Allenyl salicylaldehyde reacted with sarcosine and 1,3-thiazolidine-4-carboxylic acid to give new type of chromeno-pyrroles. A mechanism proposal for the synthesis of these chromeno[2,3-*b*]pyrroles has been presented.

Keywords: Cycloaddition / Azomethine ylides / Chromeno[4,3-*b*]pyrroles / Chromeno-pyrrolo[1,2-*c*]thiazoles / Chromeno[2,3-*b*]pyrrole / Pyrroles / Allenes / Sarcosine / Thiazolidine

1. Introduction

Chromene and chromane substructures are frequently found in naturally occurring compounds, many of which exhibit useful biological activity.¹ This led to the search for new compounds inspired on these structural motifs in order to obtain molecules with relevance in medicinal chemistry. In this context, hetero-annulated chromene

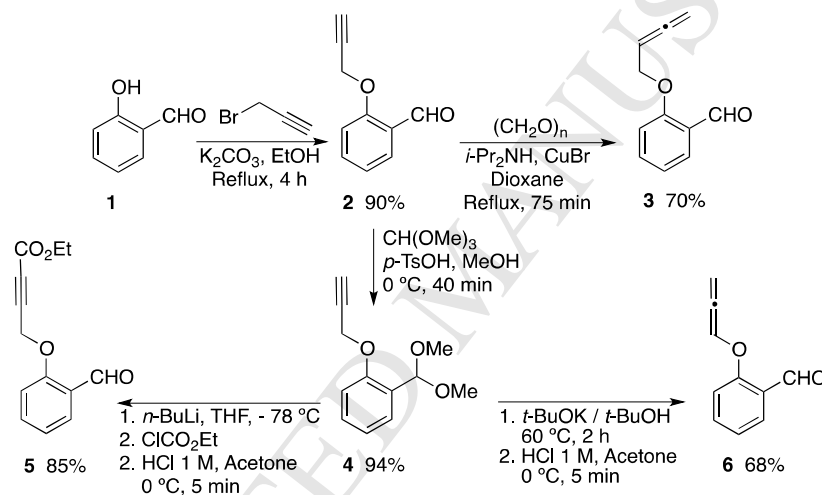
and chromane derivatives, namely chromeno[4,3-*b*]pyrrole derivatives, are important target molecules. Reports on the construction of the chromeno[4,3-*b*]pyrrole ring system include the condensation of alkenyl and alkynyl ethers of salicylaldehydes with either α -amino acid esters or secondary amino acids followed by intramolecular 1,3-dipolar cycloaddition of the *in situ* generated azomethine ylides.² Intramolecular cycloaddition of mesoionic 2-[2-(prop-2-ynoxy)phenyl]oxazolium-5-olates prepared from the corresponding *N*-acylamino acids is an alternative approach to chromeno[4,3-*b*]pyrroles.³ 2-Fluorochromeno[4,3-*b*]pyrroles have also been prepared by intramolecular cycloaddition of azomethine ylides generated from the reaction of difluorocarbenes with imines derived from alkenyl and alkynyl ethers of salicylaldehydes.⁴ A similar approach involving the generation of azomethine ylides from ethoxycarbonylcarbenoids and Schiff bases of *O*-alkynyl salicylaldehydes is known.⁵ On the other hand, it has been demonstrated that the reaction of imines derived from *O*-alkenyl salicylaldehydes and acid chlorides mediated by PhP(2-catechyl) leads to chromeno[4,3-*b*]pyrrole derivatives via intramolecular cycloaddition of phosphorus-containing 1,3-dipoles.⁶

Despite the existing methods for the synthesis of chromeno[4,3-*b*]pyrrole derivatives, there still is demand for strategies to achieve wider structural diversity. Our approach was to study the reactivity of sarcosine and 1,3-thiazolidine-4-carboxylic acid with a variety of salicylaldehydes bearing internal dipolarophiles, including derivatives with an allenic moiety which could give access to new types of tetrahydrochromeno-pyrrole derivatives.

2. Results and Discussion

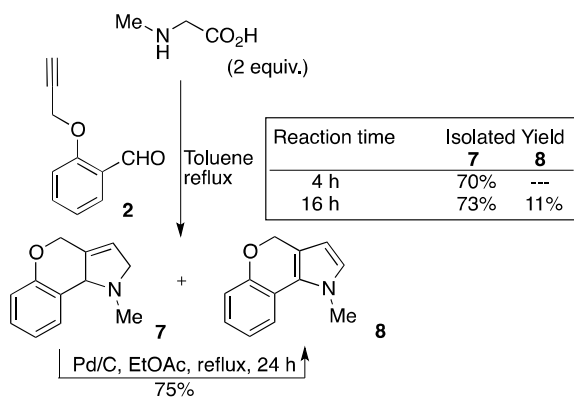
O-Propargylsalicylaldehyde (**2**) was efficiently obtained from the reaction of salicylaldehyde with propargyl bromine in refluxing ethanol in the presence of potassium carbonate. The Crabbé homologation of terminal alkynes was applied to the synthesis of *O*-buta-2,3-dienyl salicylaldehyde (**3**).⁷ Thus, the copper(I) bromide mediated reaction of salicylaldehyde **2** with formaldehyde and *N,N'*-diisopropylamine in refluxing dioxane afforded the corresponding allenic derivative **3** in 70% yield. The protection of the aldehyde functionality of compound **2** was achieved by treatment with a 5:1 methanol-trimethyl orthoformate solution in the presence of *p*-

toluenesulfonic acid following previously reported general procedures.⁸ The acetal protected salicylaldehyde **4** reacted with potassium *t*-butoxide in *t*-butanol at 60 °C to give the aryloxyallene derivative after 1.5 h, as described for other aryl propargyl ethers.⁹ The acetal group was smoothly hydrolysed with 1 M HCl to afford *O*-allenyl salicylaldehyde (**6**) in good yield.^{8a} Attempts to prepare aldehyde **6** from *O*-propargylsalicylaldehyde (**2**) without resorting to aldehyde protection, following a reported methodology,¹⁰ were not successful. The functionalization of terminal alkyne **2** with a carboxylate group was carried out by reacting it with butyllithium followed by the reaction with ethyl chloroformate.¹¹ Deprotection^{8a} of the acetal group gave the target *O*-propargylsalicylaldehyde **5** in 85% overall yield (Scheme 1).



Scheme 1. Synthesis of *O*-propargylic, *O*-allenyl and *O*-buta-2,3-dienyl salicylaldehyde derivatives.

Initially, we looked again into the reaction of *O*-propargylsalicylaldehyde (**2**) with sarcosine (Scheme 2). Under the reported reaction conditions,²ⁱ condensation of aldehyde **2** with sarcosine (2 equiv.) in toluene at reflux for 4 h, the expected tetrahydro-chromeno[4,3-*b*]pyrroles **7** was obtained in 70% yield. Increasing the reaction time to 16 h gave 1,2,4,9b-tetrahydrochromeno[4,3-*b*]pyrrole **7** in 73% yield together with the formation of the corresponding aromatized derivative **8** obtained in low yield (11%). Oxidation of compound **7**, using Pd/C in refluxing ethyl acetate for 24 h, afforded 1,4-dihydrochromeno[4,3-*b*]pyrrole **8** in 75% yield.



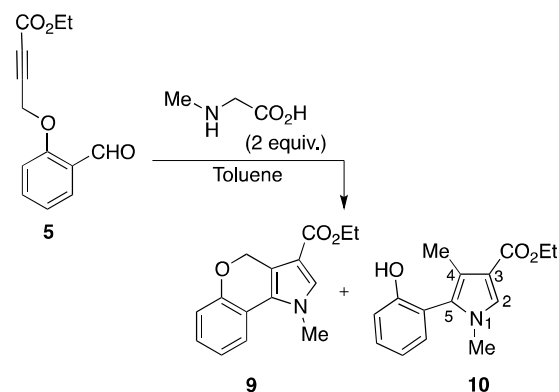
Scheme 2. Synthesis of tetrahydrochromeno[4,3-*b*]pyrrole **7** and dihydrochromeno[4,3-*b*]pyrrole **8** from *O*-propargylsalicylaldehyde (**2**) and sarcosine.

We extended the study to the reactivity of sarcosine towards salicylaldehyde **5**, bearing an activated alkyne (Table 1). Carrying out the reaction in refluxing toluene for 1 h, the corresponding 1,2,4,9b-tetrahydrochromeno[4,3-*b*]pyrrole was not formed and instead pyrrole **10** was isolated in 16% yield (Entry 1). The structural assignment of this compound was based on one-dimensional ^1H and ^{13}C NMR spectra and confirmed by two-dimensional HMQC spectrum. The ^1H NMR spectrum showed a signal with a chemical shift of 2.14 ppm corresponding to methyl protons. In the HMQC spectrum, a proton having a chemical shift of 7.40 ppm showed connectivity with the carbon with the chemical shift 128.9 ppm, which was assigned to carbon C-2. On the other hand, no connectivity was observed for a proton with the chemical shift of 5.32 ppm confirming that it belongs to the hydroxyl group.

The conventional thermolysis of aldehyde **5** in toluene in the presence of sarcosine was performed using different reaction times (Table 1). Refluxing for 2 h gave pyrrole **10** in 75% yield, together with the formation of 1,4-dihydrochromeno[4,3-*b*]pyrrole **9** in low yield (Entry 2). Increasing the reaction time to 4 h afforded pyrrole **10** in 81% yield (Entry 3). The formation of compound **9** in very low yield was again observed. However, a longer reaction time did not lead to improvements (Entry 4). On the other hand, the use of milder reaction conditions did not favour the formation of chromeno[4,3-*b*]pyrrole **9** (Entry 5).

The synthesis of pyrrole **10** was also achieved under microwave induced reaction conditions (Table 1). Irradiation at 120 °C for 5 min did not lead to any products (Entry 6) but setting the temperature to 150 °C for 15 min allowed the isolation of pyrrole **10** in 52% yield (Entry 7).

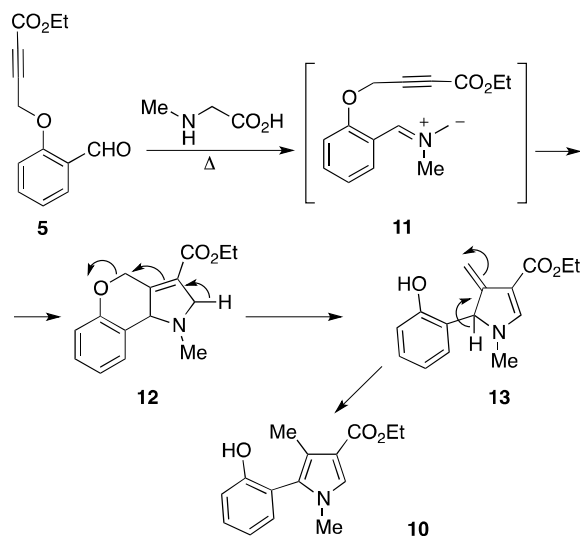
Table 1. Synthesis of chromeno[4,3-*b*]pyrrole **9** and pyrrole **10** from salicylaldehyde **5** and sarcosine.



Entry	Reaction conditions	Isolated Yield	
		9	10
1	Reflux, 1 h ^a	---	16%
2	Reflux, 2 h ^a	< 5% ^b	75%
3	Reflux, 4 h ^a	< 1% ^b	81%
4	Reflux, 15.5 h ^a	< 3% ^b	81%
5	95 °C, 4 h ^c	< 3% ^b	15%
6	MW, 120 °C, 5 min	---	---
7	MW, 150 °C, 15 min	< 3% ^b	52%

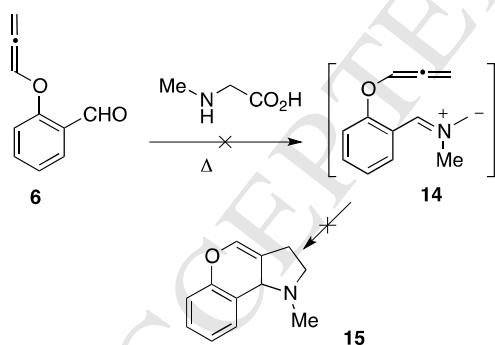
^aDean-Stark apparatus was used; ^bcompound **9** could not be isolated in pure form; ^cmolecular sieves (4Å).

The synthesis of the monocyclic pyrrole **10** can be rationalized as outlined in Scheme 3. The initially formed 1,3-dipolar cycloadduct **12** undergoes opening of the pyran ring to give intermediate **13**, which is converted into the final product by prototropy.



Scheme 3. Mechanism proposal for the synthesis of pyrrole **10**.

The reactivity of sarcosine towards the salicylaldehyde-derived allene derivative **6** was also studied. It was expected that the decarboxylative condensation of salicylaldehyde-derived allene derivative **6** with sarcosine would lead to tetrahydrochromeno[4,3-*b*]pyrrole **15** in a process where the β,γ -carbon-carbon double bond of the allene would act as dipolarophile on reacting with the *in situ* generated azomethine ylide **14** (Scheme 4).

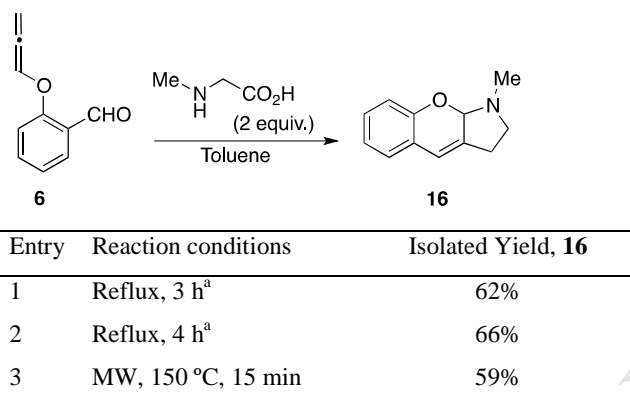


Scheme 4. The expected outcome of the reaction of *O*-allenyl salicylaldehyde (**6**) with sarcosine.

However, an unexpected result was obtained. In fact, the reaction of *O*-allenyl salicylaldehyde (**6**) with sarcosine afforded chromeno[2,3-*b*]pyrrole **16** instead of the chromeno[4,3-*b*]pyrrole **15** (Table 2). Carrying out the reaction in refluxing toluene for 3 h chromeno[2,3-*b*]pyrrole **16** was obtained in 62% yield (Table 2, Entry 1). A slight improvement of the yield was achieved when the reaction time was increased to

4 h (Entry 2). Compound **16** was also obtained in good yield under microwave induced reaction conditions (Entry 3).

Table 2. Synthesis of 1-methyl-1,2,3,9a-tetrahydrochromeno[2,3-*b*]pyrrole (**16**) from *O*-allenyl salicylaldehyde (**6**) and sarcosine.



^aDean-Stark apparatus was used.

The assignment of the structure of compound **16** was supported by two-dimensional HMQC and HMBC spectra (400 MHz). From HMQC spectrum, it was established that the carbon with the chemical shift 117.2 ppm corresponds to C-4 since it shows connectivity with the vinylic proton having a chemical shift of 6.24 ppm. The carbon with the chemical shift 93.8 ppm was assigned to C-9a since it shows connectivity with the proton chemical shift 4.92 ppm. On the other hand, protons of the two methylene groups, observed in the ¹H NMR spectrum at 2.66 ppm and 2.97 ppm, show connectivity with carbons with chemical shift 25.6 ppm (C-3) and 51.3 ppm (C-2), respectively. In the HMBC spectrum, methyl protons correlate with carbon C-2 (51.3 ppm) and carbon C-9a (93.8). On the other hand, proton H-4 correlates with carbons C-3 (25.6 ppm) and C-9a (93.8 ppm), C-8a (151.6 ppm) and with the aromatic carbon observed at 125.2 ppm (Figure 1). From the HMBC spectrum, it was also established that the quaternary carbons with the chemical shift 123.3 ppm and 135.5 ppm correspond to C-4a and C-3a, respectively, since connectivity was observed between carbon C-4a and the protons H-6 and H-5 but no correlation was observed between these protons and carbon C-3a. In addition, the values of the chemical shift observed for C-4 (117.2 ppm) and C-3a (135.5 ppm) confirmed the structural assignment and ruled out the alternative isomeric structure **15**.

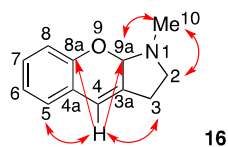
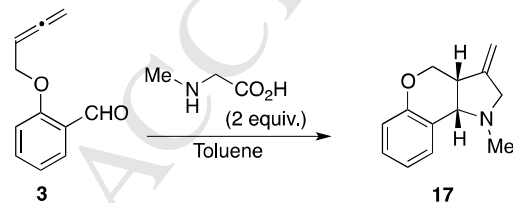


Figure 1. Main connectivities found in the HMBC spectrum of 1-methyl-1,2,3,9a-tetrahydrochromeno[2,3-*b*]pyrrole **16**.

The reaction of sarcosine with *O*-buta-2,3-dienyl salicylaldehyde (**3**) was also explored under conventional thermolysis and under microwave irradiation (Table 3). The best result was achieved carrying out the reaction in refluxing toluene for 27 h giving 3-methylene-hexahydrochromeno[4,3-*b*]pyrrole **17** in 58% yield. The synthesis of this compound can be explained considering the generation of the expected azomethine ylide which participates in intramolecular 1,3-dipolar cycloaddition with the α,β -carbon-carbon double bond of the allenic moiety. The stereochemistry of the ring fusion was assigned considering that the benzylic methine proton was observed as a doublet with a coupling constant of 5.2 Hz, which is the value expected for a *cis* relationship. On the other hand, in the NOESY spectrum cross-peaks were observed between protons H-9b and H-3a.

The structure of this chromeno[4,3-*b*]pyrrole derivative is of particular interest since the presence of the methylene group allows further elaboration.

Table 3. Synthesis of 1-methyl-3-methylene-1,2,3,3a,4,9b-hexahydrochromeno[4,3-*b*]pyrrole (**17**) from *O*-buta-2,3-dienyl salicylaldehyde (**3**) and sarcosine.



Entry	Reaction conditions	Isolated Yield, 17
1	Reflux, 4 h ^a	28%
2	Reflux, 6 h ^a	31%
3	Reflux, 19.5 h ^a	56%
4	Reflux, 27 h ^a	58%

5 MW, 150 °C, 15 min

6%

^aDean-Stark apparatus was used.

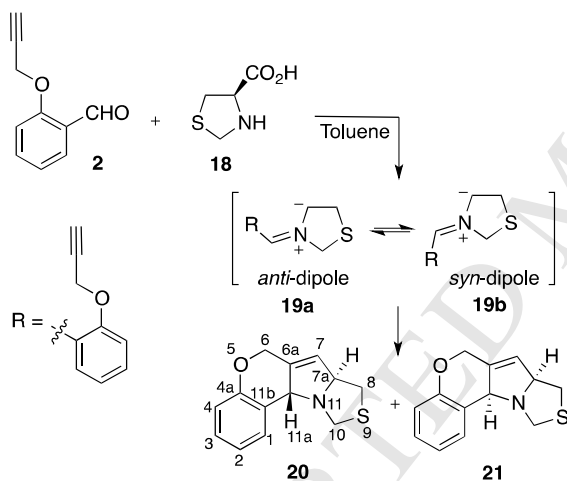
In recent past, we have been interested in exploring the intermolecular cycloaddition of nonstabilized ylides generated via the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acids with aldehydes.¹² On the other hand, the reaction of *O*-propargylsalicylaldehyde (**2**) with 1,3-thiazolidine-4-carboxylic acid (**18**) has been reported.^{2d} The authors reported that carrying out the reaction in toluene at 100 °C for 17 h, chromeno-pyrrolo[1,2-*c*]thiazole **20** was obtained in 37% yield via the *anti*-dipole but no product resulting from the cycloaddition of the *syn*-dipole was detected. In this context, we decided to look into this reaction and to extend the study to the reaction of 1,3-thiazolidine-4-carboxylic acid with other salicylaldehyde-derived alkynes and allenes.

Carrying out the reaction of *O*-propargylsalicylaldehyde (**2**) with 1,3-thiazolidine-4-carboxylic acid using conditions similar to those previously described^{2b} did not lead to the same outcome (Table 4, Entry 1). In fact, chromeno-pyrrolo[1,2-*c*]thiazole **20** was isolated in 36% yield as previously reported, but the chromeno-pyrrolo[1,2-*c*]thiazole **21**, derived from the cycloaddition of the *syn*-dipole, was also obtained in 16% yield. Performing the reaction with a shorter reaction time (7 h or 4 h) also afforded compound **20** (37-40%) as the major product together with the formation of the stereoisomer **21** (16-18%) (Entries 2 and 3). The microwave-induced condensation of *O*-propargylsalicylaldehyde (**2**) with 1,3-thiazolidine-4-carboxylic acid led to the chromeno-pyrrolo[1,2-*c*]thiazoles **20** and **21** in lower yields and the aromatized derivative **22** was also isolated (Entry 4).

The assignment of the structure of compounds **20** and **21** was supported by two-dimensional NOESY, HMQC and HMBC spectra (400 MHz). From the HMQC spectrum of compound **20**, it was established that the carbon with 67.3 ppm chemical shift corresponds to C-11a since it shows connectivity with the proton having a chemical shift of 4.69 ppm. On the other hand, the carbon with 76.3 ppm chemical shift corresponds to C-7a since it shows connectivity with the proton observed as a multiplet at 4.60-4.61 ppm. The carbon at 123.7 ppm corresponds to C-7 since it shows connectivity with the vinylic proton (5.65 ppm). In the HMBC spectrum, H-7

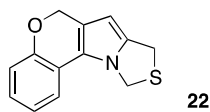
correlates with carbons C-7a (76.3 ppm), C-6a (136.4 ppm) and C-11a (67.3 ppm) and protons H-6 correlate with carbons C-7 (123.7 ppm), C-6a (136.4 ppm), C-4a (153.2 ppm) and C-11a (67.3 ppm). From the HMBC spectrum, it was also established that the quaternary carbons with the chemical shift 127.3 ppm and 136.4 ppm correspond to C-11b and C-6a, respectively, since connectivity was observed between carbon C-11b and two aromatic protons but no correlation was observed between these protons and carbon C-6a. In the NOESY spectrum of compound **20**, no connectivity was observed between H-7a and H-11a. The same spectroscopy analysis was carried out for derivative **21**. In this case, connectivity between H-7a and H-11a was observed in the NOESY spectrum.

Table 4. Synthesis of chromeno-pyrrolo[1,2-*c*]thiazoles from *O*-propargylsalicylaldehyde (**2**) and 1,3-thiazolidine-4-carboxylic acid (**18**).



Entry	Reaction conditions	Isolated Yield	
		20	21
1	Reflux, 17 h ^a	36%	16%
2	Reflux, 7 h ^a	37%	18%
3	Reflux, 4 h ^a	40%	16%
4	MW, 150 °C, 15 min	19% ^b	6% ^b

^aDean-Stark apparatus was used; ^bcompound **22** was also isolated in < 10%.



We have previously described quantum-chemistry calculations, which were carried

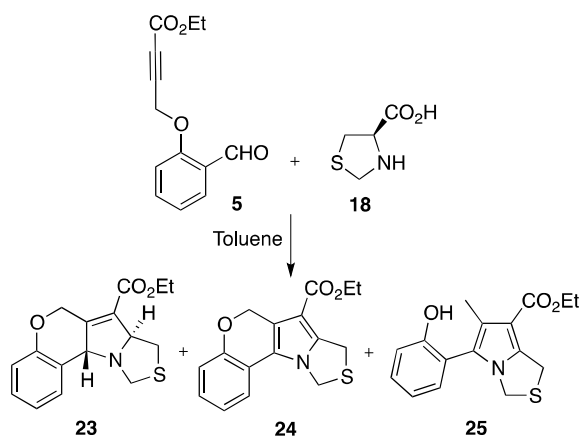
out in order to explain the *anti/syn* selectivity of the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acid with aldehydes. Based on the gas-phase calculations the *anti* 1,3-dipole was expected to be more stable than the *syn* form by ca. 17 kJ mol⁻¹ for R = Ph. Moreover, according to the calculations, the barrier height for *syn-anti* interconversion is low. This suggests that, once produced, the *syn* and *anti* dipoles exist in equilibrium. The theoretical calculations predicted that the produced amount of *syn* 1,3-dipole should be significantly higher (ca. 92%) than that of the *anti* 1,3-dipole (ca. 8%). However, after being formed in a comparatively larger amount, the *syn* 1,3-dipole is expected to partially convert to the *anti* form.¹² These observations are also in agreement with selective formation of chromeno-pyrrolo[1,2-*c*]thiazole **20** resulting from the cycloaddition of the *anti* 1,3-dipole **19a** generated from *O*-propargylsalicylaldehyde (**2**) and 1,3-thiazolidine-4-carboxylic acid (**18**).

The work was then extended to the study of the reactivity of 1,3-thiazolidine-4-carboxylic acid (**18**) towards salicylaldehyde **5** (Table 5). Carrying out the reaction in refluxing toluene a mixture of chromeno-pyrrolo[1,2-*c*]thiazoles **23** and **24** and pyrrolo[1,2-*c*]thiazole **25** were isolated (Entries 1-3). The best result was achieved when the thiazolidine and salicylaldehyde **5** were left to react for 7 h giving a 94:6 mixture of compounds **23** and **24** in 73% yield and pyrrolo[1,2-*c*]thiazole **25** in 12% yield (Entry 2). Interestingly, selective crystallization of the mixture of **23** and **24** with ethyl acetate/hexane afforded **23** as a white crystalline solid whereas compound **24** was obtained as a yellow solid by crystallization with ethyl acetate/petroleum ether. The synthesis of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **25** can be explained considering a similar pathway to the one leading to pyrrole **10** (see Scheme 3) although in this case the process is less favoured which is an indication of the higher stability of the initially formed cycloadduct. The reaction was also carried out at 95 °C for 30 h with the aim of favouring the formation of chromeno-pyrrolo[1,2-*c*]thiazoles **23** (Entry 4). However, under these reaction conditions a 80:20 mixture of compounds **23** and **24** was obtained in only 62% yield and 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **25** in 4%. The microwave-induced reaction was less efficient (Entry 5).

The structure of chromeno-pyrrolo[1,2-*c*]thiazole **23** was unambiguously established by X-ray crystallography (Figure 2). Two molecules of opposite chirality were present in the crystal structure. There are two chirogenic centres, C-11a and C-7a, in

each molecule. The hydrogen atoms bonded to these carbons are placed on opposite faces of the 3-pyrroline ring. The results described above show that selective formation of the product resulting from the cycloaddition of the *anti*-dipole was again observed.

Table 5. Decarboxylative condensation of salicylaldehyde **5** with 1,3-thiazolidine-4-carboxylic acid (**18**).



Entry	Reaction conditions	Isolated Yield	
		(23:24) ^c	25
1	Reflux, 16 h ^a	58% (96:4)	10%
2	Reflux, 7 h ^a	73% (94:6)	12%
3	Reflux, 5 h ^a	51% (96:4)	7%
4	95 °C, 30 h ^b	62% (80:20)	4%
5	MW, 150 °C, 15 min	42% (86:14)	15%

^aDean-Stark apparatus was used; ^bMolecular sieves were used; ^cratio of isomers determined by ¹H NMR.

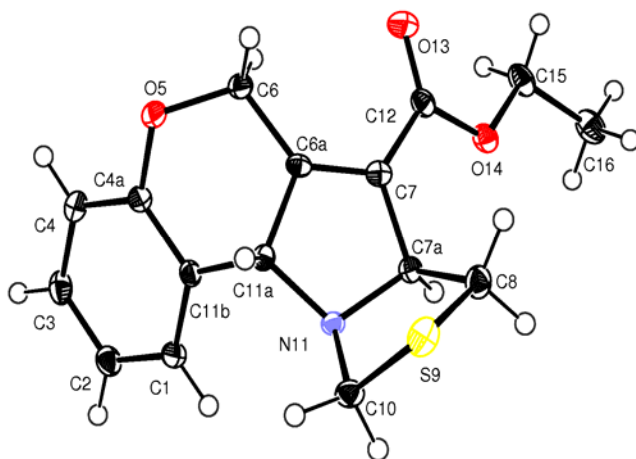
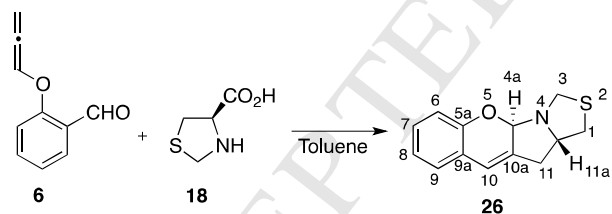


Figure 2. ORTEP-3 diagram of compound **23**, using 50% probability level ellipsoids. For clarity reasons, only one of the molecules present in the asymmetric unit is shown.

The reactivity of 1,3-thiazolidine-4-carboxylic acid (**18**) towards salicylaldehyde-derived allene **6** was also explored (Table 6). We were pleased to find that this reaction leads to tetrahydro-1*H*-chromeno[3',2':4,5]pyrrolo[1,2-*c*]thiazole **26** instead of the expected 7*a*,8,10,11*a*-tetrahydro-7*H*-chromeno[3',4':4,5]pyrrolo[1,2-*c*]thiazole, which would be formed via the generation of the corresponding azomethine ylide followed by the addition to the β,γ -carbon-carbon double bond of the allene. Thus, the chemical behaviour of salicylaldehyde **6** towards sarcosine was also observed in the reaction of this compound with 1,3-thiazolidine **18**.

The reaction carried out in refluxing toluene for 17 h resulted in the chromeno-pyrrolo[1,2-*c*]thiazole **26** on 42% yield isolated as single stereoisomer (Table 6, Entry 1). The same yield was obtained heating the reaction mixture for a shorter period (Table 6, Entry 2). Under microwave irradiation compound **26** was isolated in very low yield (Table 6, Entry 3).

Table 6. Synthesis of chromeno-pyrrolo[1,2-*c*]thiazole **26** from salicylaldehyde **6** and 1,3-thiazolidine-4-carboxylic acid (**18**).



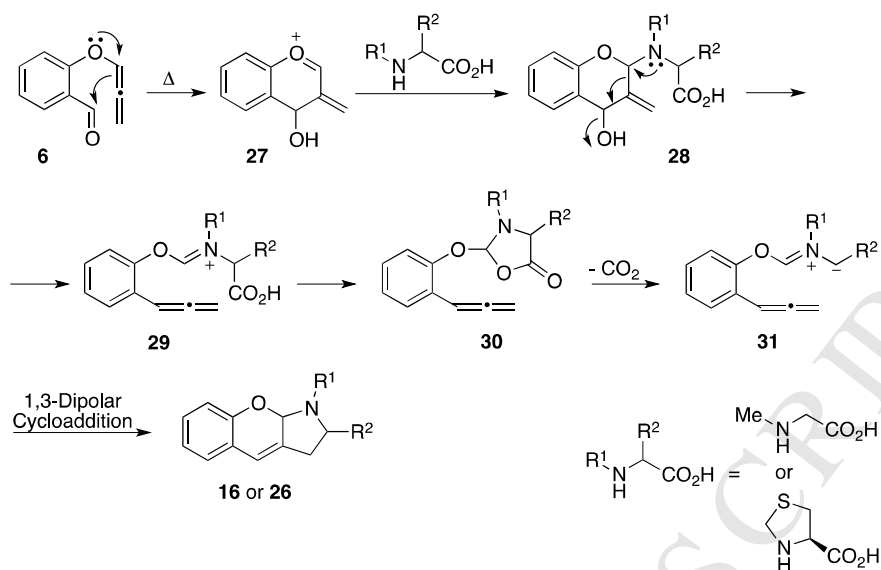
Entry	Reaction conditions	Isolated Yield, 26
1	Reflux, 17 h ^a	42%
2	Reflux, 7 h ^a	42%
3	MW, 150 °C, 15 min	9%

^aDean-Stark apparatus was used.

The assignment of the structure of chromeno-pyrrolo[1,2-*c*]thiazole **26** was supported by two-dimensional NOESY, HMQC and HMBC spectra (400 MHz). From the HMQC spectrum, it was established that the carbon with 119.5 ppm chemical shift was assigned to C-10 since it shows connectivity with the vinylic proton observed at 6.30 ppm. The carbon with chemical shift 33.3 ppm corresponds to methylene group

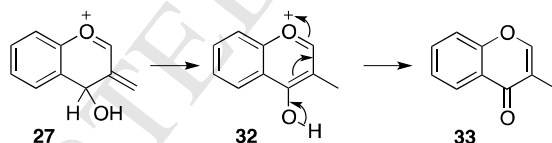
of pyrrolidine ring (C-11) since it shows connectivity with two protons with different chemical shifts, 2.50-2.55 ppm and 3.03-3.09 ppm. In the HMBC spectrum, proton H-10 correlates with carbons C-11 (33.3 ppm) and C-4a (93.5 ppm), C-5a (152.4 ppm) and with the aromatic carbon observed at 126.4 ppm. The protons H-1 correlate with carbons C-11 (33.3 ppm), C-11a (66.8 ppm) and C-3 (58.1 ppm). On the other hand, protons H-11 correlate with carbons C-1 (38.7 ppm), C-11a (66.8 ppm), C-10 (119.5 ppm) and C-10a (134.6 ppm). From the HMBC spectrum, it was also established that the quaternary carbons with the chemical shift 123.5 ppm and 134.6 ppm correspond to C-9a and C-10a, respectively, since connectivity was observed between carbon C-9a and two aromatic protons but no correlation was observed between these protons and carbon C-10a. Thus, similar spectroscopic features were observed between chromeno[2,3-*b*]pyrrole **16** and chromeno-pyrrolo[1,2-*c*]thiazole **26**. In the NOESY spectrum no connectivity was observed between H-11a and H-4a, which is in agreement with the stereochemistry assignment.

A mechanism proposal for the synthesis of chromeno[2,3-*b*]pyrrole **16** and chromeno-pyrrolo[1,2-*c*]thiazole **26** is outlined in Scheme 5. The initial cyclization of *O*-allenyl salicylaldehyde (**6**) affords intermediate **27**, which undergoes nucleophilic addition on reacting with the secondary amino acid to give **28**. Opening of the dihydro-pyran ring, followed by the elimination of carbon dioxide gives azomethine ylide **31** bearing an allene moiety. The subsequent 1,3-dipolar cycloaddition, with the internal addition to the allene β,γ -carbon-carbon, leads to the final product.



Scheme 5. Mechanism proposal for the synthesis of chromeno[2,3-*b*]pyrrole **16** and chromeno-pyrrolo[1,2-*c*]thiazole **26**.

Interestingly, 3-methyl-4*H*-chromen-4-one (**33**)¹³ was formed in low yield (4-9%) as byproduct from the reaction of the salicylaldehyde **6** with 1,3-thiazolidine-4-carboxylic acid (**18**). This observation reinforces the mechanism proposal for the synthesis of chromeno-pyrrolo[1,2-*c*]thiazole **26** since 4*H*-chromen-4-one **33** derives from the postulated intermediate **27** (Scheme 6).



Scheme 6. 3-Methyl-4*H*-chromen-4-one (**33**) formed as byproduct of the synthesis of chromeno-pyrrolo[1,2-*c*]thiazole **26**.

Attempts to carry out the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acid with *O*-buta-2,3-dienyl salicylaldehyde (**3**) led to complex mixtures.

3. Conclusions

The reactivity of sarcosine and 1,3-thiazolidine-4-carboxylic acid towards salicylaldehyde-derived alkynes and allenes was explored as a strategy to obtain new chromeno[4,3-*b*]pyrrole derivatives.

The decarboxylative condensation of sarcosine and 1,3-thiazolidine-4-carboxylic acid with *O*-propargylsalicylaldehyde led to the synthesis of the corresponding tetrahydrochromeno[4,3-*b*]pyrroles. Stereoselectivity was observed in the reaction with the 1,3-thiazolidine with the formation of the cycloadduct resulting from the *anti*-dipole as the major product.

A different outcome was observed from the reaction of sarcosine with ethyl 4-(2-formylphenoxy)but-2-ynoate. In this case, the initially formed 1,3-dipolar cycloadduct undergoes opening of the pyran ring followed by prototropy to give a monocyclic pyrrole. Decarboxylative condensation of ethyl 4-(2-formylphenoxy)but-2-ynoate with 1,3-thiazolidine-4-carboxylic acid afforded the expected chromeno-pyrrolo[1,2-*c*]thiazole with the selective formation of the product derived from the *anti*-dipole which structure was unambiguously established by X-ray crystallography. However, the 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole resulting from the opening of the pyran ring was also isolated.

A 3-methylene-hexahydrochromeno[4,3-*b*]pyrrole derivative was obtained from the reaction of *O*-buta-2,3-dienyl salicylaldehyde and sarcosine via intramolecular 1,3-dipolar cycloaddition of the expected dipole with the α,β -carbon-carbon double bond of the allenic moiety.

The synthesis of a new type of chromeno-pyrrole derivatives was also achieved from the reaction of *O*-allenyl salicylaldehyde with secondary amino acids. *O*-Allenyl salicylaldehyde reacted with sarcosine and 1,3-thiazolidine-4-carboxylic acid to afford 1-methyl-1,2,3,9a-tetrahydrochromeno[2,3-*b*]pyrrole and 3,4a,11,11a-tetrahydro-1*H*-chromeno[3',2':4,5]pyrrolo[1,2-*c*]thiazole, respectively.

4. Experimental Section

4.1. General

Microwave reactions were carried out in a microwave reactor CEM Focused Synthesis System Discover S-Class. Flash column chromatography was performed

with silica gel 60 as the stationary phase. ^1H NMR spectra were recorded on an instrument operating at 400 MHz and ^{13}C NMR at 100 MHz. Chemical shifts are expressed in ppm relatively to internal tetramethylsilane (TMS), and coupling constants (J) are in hertz. IR spectra were recorded on a Fourier Transform spectrometer. HRMS spectra were obtained on an electron impact (EI) or electrospray (ESI) TOF mass spectrometer. Melting points were determined in open glass capillaries and are uncorrected. Sarcosine was purchased from Aldrich. 1,3-Thiazolidine-4-carboxylic acid was prepared by a literature procedure.¹⁴

4.2. Procedures for the synthesis of salicylaldehyde derivatives

4.2.1. 2-(Prop-2-ynoxy)benzaldehyde (**2**)

Benzaldehyde **2** was prepared by modifying a literature procedure.¹¹ To a solution of salicylaldehyde (11.13 mL, 100 mmol) in ethanol (60 mL) anhydrous K_2CO_3 (15.20 g, 110 mmol) was added and the resulting mixture was stirred for 5 min at room temperature. After the formation of a yellow solid, propargyl bromide (80% in toluene, 11.85 mL, 110 mmol) was added and the reaction mixture was heated at reflux for 4 hours under N_2 atmosphere. After cooling to room temperature, water was added, the aqueous layer was extracted with diethyl ether, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Recrystallization from diethyl ether afforded **2** (14.36 g, 90%) as a white solid. Mp 71-73 °C (lit.¹¹ 64-66 °C) (from diethyl ether). ^1H NMR (CDCl_3) 10.49 (1H, s, CHO), 7.86 (1H, dd, $J = 7.6, 1.2$ Hz, Ar-H), 7.55-7.59 (1H, m, Ar-H), 7.07-7.13 (2H, m, Ar-H), 4.83 (2H, d, $J = 2.0$ Hz, $\text{OCH}_2\text{C}\equiv\text{CH}$), 2.58 (1H, t, $J = 2.0$ Hz, $\text{OCH}_2\text{C}\equiv\text{CH}$).

4.2.2. 2-(Buta-2,3-dienyloxy)benzaldehyde (**3**)

Benzaldehyde **3** was prepared according to a literature procedure.⁷ A mixture of salicylaldehyde derivative **2** (2.50 g, 15.62 mmol), paraformaldehyde (1.17 g, 39.05 mmol), N,N' -di-isopropylamine (4.38 mL, 31.24 mmol) and anhydrous cuprous bromide (1.12 g, 7.81 mmol) in dioxane (25 mL) was heated at reflux for 75 min. After cooling to room temperature, saturated aqueous NaCl solution was added to the reaction mixture, the aqueous layer was extracted with diethyl ether, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography [ethyl acetate/hexane (1:6)] to give

allene **3** (1.90 g, 70%) as a yellow liquid. IR (film, cm^{-1}): 1957, 1689, 1238; ^1H NMR (CDCl_3) 10.51 (1H, s, CHO), 7.82-7.85 (1H, m, Ar-H), 7.51-7.55 (1H, m, Ar-H), 6.98-7.05 (2H, m, Ar-H), 5.38-5.45 (1H, m, $\text{OCH}_2\text{CH}=\text{C}=\text{CH}_2$), 4.88-4.91 (2H, m, $\text{OCH}_2\text{CH}=\text{C}=\text{CH}_2$), 4.68-4.69 (2H, m, $\text{OCH}_2\text{CH}=\text{C}=\text{CH}_2$); ^{13}C NMR (CDCl_3) 209.5, 189.8, 160.8, 135.7, 128.4, 125.3, 120.9, 113.1, 86.6, 77.1, 66.2; HRMS (ESI): calculated $\text{C}_{11}\text{H}_{11}\text{O}_2$ [$\text{M}+\text{H}^+$] 175.07536. Found: 175.07484.

4.2.3. 1-(Dimethoxymethyl)-2-(prop-2-ynoxy)benzene (**4**)

Acetal **4** was prepared according to a literature procedure.⁸ A mixture of salicylaldehyde derivative **2** (5.00 g, 31.24 mmol) and trimethyl orthoformate (20.50 mL, 187 mmol) in 100 mL of dry methanol was cooled to 0 °C under nitrogen atmosphere. *p*-Toluenesulfonic acid (0.30 g, 1.56 mmol) was added and the resulting mixture was stirred at 0 °C for 40 min. The reaction mixture was treated with saturated aqueous K_2CO_3 solution, the aqueous layer was extracted with ethyl acetate, washed with water and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure to give the pure product. Compound **4** (5.96 g, 94%) was obtained as a low melting solid. IR (film, cm^{-1}): 2120, 1222; ^1H NMR (CDCl_3) 7.54-7.57 (1H, m, Ar-H); 7.28-7.32 (1H, m, Ar-H), 7.00-7.04 (2H, m, Ar-H), 5.68 (1H, s, $\text{CH}(\text{OMe})_2$), 4.73 (2H, d, $J = 2.4$ Hz, $\text{OCH}_2\text{C}\equiv\text{CH}$), 3.37 (6H, s, OMe), 2.51 (1H, t, $J = 2.4$ Hz, $\text{OCH}_2\text{C}\equiv\text{CH}$); ^{13}C NMR (CDCl_3) 149.8, 124.2, 122.2, 121.8, 116.0, 107.3, 93.7, 73.4, 70.4, 51.0, 48.3; HRMS (ESI): calculated $\text{C}_{12}\text{H}_{14}\text{NaO}_3$ [M^+Na]: 229.0835. Found: 229.0832.

4.2.4. Ethyl 4-(2-formylphenoxy)but-2-ynoate (**5**)^{8a,11}

A solution of acetal **4** (1.63 g, 7.90 mmol) in dry THF (42 mL) was stirred at -78 °C for 10 min under nitrogen atmosphere. Butyllithium (2.5M in hexane) (4.74 mL, 11.85 mmol) was slowly added to the reaction mixture over 40 min and the resulting solution was stirred for 30 min at the same temperature. Ethyl chloroformate (1.28 mL, 13.43 mmol) was slowly added to the reaction mixture and stirred another 40 min at -78 °C. After warming to room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (80 mL) and diluted with ethyl acetate (200 mL). The organic layer was washed with water (3×200 mL), brine (2×40 mL), dried over Na_2SO_4 and the solvent was removed in vacuum. The crude product was dissolved in acetone (25 mL), the solution cooled to 0 °C, followed by the dropwise

addition of a HCl aqueous solution (1 M, 56.40 mL) and the resulting solution was stirred at 0 °C for 5 min. The reaction mixture was treated with saturated aqueous NaHCO₃ solution, extracted with dichloromethane and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [ethyl acetate/hexane (1:5)] to give compound **5** (1.55 g, 85%) as pale white solid. Mp 49-51 °C (lit.¹¹ 50-52 °C) (from ethyl acetate/hexane); ¹H NMR (CDCl₃) 10.47 (1H, s, CHO), 7.86-7.88 (1H, m, Ar-H), 7.57-7.60 (1H, m, Ar-H), 7.06-7.14 (2H, m, Ar-H), 4.96 (2H, s, OCH₂C≡C), 4.25 (2H, q, *J* = 6.8 Hz, CO₂CH₂CH₃), 1.31 (3H, t, *J* = 6.8 Hz, CO₂CH₂CH₃).

4.2.5 2-(Propa-1,2-dienyloxy)benzaldehyde (**6**)

Allene **6** was prepared by modifying a literature procedure.^{8a,9} A solution of acetal **4** (2.50 g, 12.10 mmol) in *tert*-butyl alcohol (7.0 mL) was added dropwise to a solution of potassium *tert*-butoxide (0.54 g, 4.80 mmol) in *tert*-butyl alcohol (2.5 mL). The resulting mixture was heated at 60 °C for 1.5 hours. After cooling to room temperature, water was added to the reaction mixture and the aqueous layer was extracted with diethyl ether, dried over Na₂SO₄ and the solvent removed in vacuum. The crude product was dissolved in acetone (30 mL), the solution cooled to 0 °C, followed by the dropwise addition of a HCl aqueous solution (1M, 116.0 mL) and the resulting mixture was stirred at 0 °C for 5 min. The reaction mixture was treated with saturated aqueous NaHCO₃ solution, extracted with dichloromethane and dried over Na₂SO₄. The solvent was removed under reduce pressure and the crude product was purified by flash chromatography [ethyl acetate/hexane (1:5)] to give compound **6** (1.32 g, 68%) as pale yellow liquid. IR (film, cm⁻¹): 1964, 1691, 1230; ¹H NMR (CDCl₃) 10.47 (1H, s, CHO), 7.87 (1H, dd, *J* = 7.6, 1.2 Hz, Ar-H), 7.54-7.59 (1H, m, Ar-H), 7.13-7.21(2H, m, Ar-H), 6.91 (1H, t, *J* = 6.0 Hz, OCH=C=CH₂), 5.49 (2H, d, *J* = 6.0 Hz, OCH=C=CH₂); ¹³C NMR (CDCl₃) 202.6, 189.2, 159.4, 135.6, 128.4, 126.2, 123.1, 118.0, 116.7, 90.6; HRMS (ESI): calculated C₁₀H₈NaO₂ [M⁺+Na]: 183.04165. Found: 183.04100.

4.3. General procedures for the synthesis of chromeno-pyrroles and pyrrole derivatives **10** and **25**

Method A: A solution of the appropriated aldehyde and sarcosine or 1,3-thiazolidine-4-carboxylic acid in toluene (10 mL) was heated at reflux, using a Dean-Stark

apparatus, except where indicated otherwise, for the time indicated in each case. The reaction was monitored by TLC. After the reaction was complete, the solvent was removed under reduced pressure and the crude product was dissolved in dichloromethane. The organic layer was washed several times with water and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography.

Method B: A solution of the appropriate aldehyde and sarcosine or 1,3-thiazolidine-4-carboxylic acid in toluene (1-1.5 mL) was irradiated in the microwave reactor for 15 min with the temperature set to 150 °C. The solvent was removed under reduced pressure and the crude product was dissolved in dichloromethane. The organic layer was washed several times with water and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography.

4.3.1. *1-Methyl-1,2,4,9b-tetrahydrochromeno[4,3-b]pyrrole (7) and 1-Methyl-1,4-dihydrochromeno[4,3-b]pyrrole (8)*

Prepared by *method A* from aldehyde **2** (160 mg, 1.00 mmol) and sarcosine (178 mg, 2.00 mmol) using 4Å molecular sieves instead of the Dean-Stark apparatus. The reaction mixture was stirred for 16 hours and solvent was removed under reduced pressure. Purification by flash chromatography [ethyl acetate/hexane (1:2) to ethyl acetate/hexane (2:1), then ethyl acetate] afforded, in order of elution, compound **8** (21 mg, 11%) and compound **7** (137 mg, 73%) as white solids.

1-Methyl-1,4-dihydrochromeno[4,3-b]pyrrole (8). Mp 62-64 °C (from ethyl acetate/hexane); IR (KBr, cm⁻¹): 1224, 1185; ¹H NMR (CDCl₃) 7.43 (1H, d, *J* = 7.6 Hz, Ar-H), 7.05-7.09 (1H, m, Ar-H), 6.93-6.97 (2H, m, Ar-H), 6.60 (1H, d, *J* = 2.0 Hz, H-2), 5.95 (1H, d, *J* = 2.0 Hz, H-3), 5.21 (2H, s, H-4), 3.89 (3H, s, N-Me); ¹³C NMR (CDCl₃) 153.1, 126.6, 125.0, 123.9, 121.5, 120.2, 119.9, 117.3, 116.6, 103.1, 66.2, 36.7; HRMS (ESI): calculated C₁₂H₁₂NO [M⁺+H]: 186.09134. Found: 186.09178

1-Methyl-1,2,4,9b-tetrahydrochromeno[4,3-b]pyrrole (7). Mp 63-65 °C (from ethyl acetate/hexane); IR (KBr, cm⁻¹): 1235, 1222; ¹H NMR (CDCl₃) 7.37 (1H, d, *J* = 7.6 Hz, Ar-H), 7.12-7.15 (1H, m, Ar-H), 6.93-6.96 (1H, m, Ar-H), 6.83 (1H, d, *J* = 8.4 Hz, Ar-H), 5.71 (1H, br s, H-3), 4.74 (1H, d, *J* = 12.8 Hz, H-4), 4.64-4.68 (1H, m, H-4), 4.43 (1H, br s, H-9b), 4.04-4.07 (1H, m, H-2), 3.48-3.51 (1H, m, H-2), 2.81 (3H, s,

N-Me); ^{13}C NMR (CDCl_3) 153.8, 135.7, 128.3, 127.5, 126.2, 121.6, 121.4, 117.3, 67.1, 65.0, 64.3, 44.0; HRMS (ESI): calculated $\text{C}_{12}\text{H}_{14}\text{NO}$ [M^+H]: 188.10699. Found: 188.10642.

4.3.2. *Ethyl 1-methyl-1,4-dihydrochromeno[4,3-b]pyrrole-3-carboxylate (9) and Ethyl 5-(2-hydroxyphenyl)-1,4-dimethyl-1H-pyrrole-3-carboxylate (10)*

Prepared by *method A* from aldehyde **5** (232 mg, 1.00 mmol) and sarcosine (178 mg, 2.00 mmol) in toluene (10 mL) was heated at reflux, using a Dean-Stark apparatus, for 4 hours. Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:4)] afforded, in order of elution, compound **9** (<1%) as a yellow oil and compound **10** (211 mg, 81%) as a white solid.

Prepared by *method B* from aldehyde **5** (116 mg, 0.50 mmol) and sarcosine (89 mg, 1.00 mmol) in toluene (1 mL). Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:4)] afforded in order of elution, compound **9** (<3%) and compound **10** (68 mg, 52%).

Ethyl 1-methyl-1,4-dihydrochromeno[4,3-b]pyrrole-3-carboxylate (9). ^1H NMR (CDCl_3) 7.40-7.42 (1H, m, Ar-H), 7.23 (1H, s, H-2), 7.08-7.12 (1H, m, Ar-H), 6.92-6.97 (2H, m, Ar-H), 5.45 (2H, s, H-4), 4.26 (2H, q, $J = 7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.90 (1H, s, N-Me), 1.34 (3H, t, $J = 7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); HRMS (EI): calculated $\text{C}_{15}\text{H}_{15}\text{NO}_3$ [M^+] 257.1052. Found: 257.1063.

Ethyl 5-(2-hydroxyphenyl)-1,4-dimethyl-1H-pyrrole-3-carboxylate (10). Mp 130-132 °C (from ethyl acetate/hexane); IR (KBr, cm^{-1}): 3342, 1691, 1252, 1233; ^1H NMR (CDCl_3) 7.40 (1H, s, H-2), 7.33 (1H, t, $J = 8.0, 7.6$ Hz, Ar-H), 7.12 (1H, d, $J = 7.2$ Hz, Ar-H), 7.02 (1H, d, $J = 8.0$ Hz, Ar-H), 6.98 (1H, t, $J = 7.6, 7.2$ Hz, Ar-H) 5.32 (1H, s, OH), 4.28 (2H, q, $J = 7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.41 (3H, s, N-Me), 2.14 (3H, s, C-Me), 1.35 (3H, t, $J = 7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) 165.2, 154.6, 132.0, 130.6, 128.9, 126.1, 121.1, 120.4, 117.3, 115.6, 114.2, 59.4, 34.8, 14.5, 11.1; HRMS (EI): calculated $\text{C}_{15}\text{H}_{17}\text{NO}_3$ [M^+] 259.1208. Found: 259.1206.

4.3.3. *1-Methyl-1,2,3,9a-tetrahydrochromeno[2,3-b]pyrrole (16)*

Prepared by *method A* from aldehyde **6** (237 mg, 1.48 mmol) and sarcosine (264 mg, 2.96 mmol). The reaction mixture was stirred for 4 hours and evaporation of the solvent under reduced pressure afforded **16** (184 mg, 66%) as a red oil. Compound **16** was also prepared by *method B* in 59% yield (165 mg) from aldehyde **6** (237 mg, 1.48

mmol) and sarcosine (264 mg, 2.96 mmol). Compound **16**: IR (film, cm^{-1}): 1229, 1207; ^1H NMR (CDCl_3) 7.08 (1H, t, $J=8.0$, 7.2 Hz, Ar-H), 7.01 (1H, d, $J=7.2$ Hz, Ar-H), 6.91 (1H, d, $J=7.6$ Hz, Ar-H), 6.88 (1H, t, $J=8.0$, 7.6 Hz, Ar-H), 6.24 (1H, br s, H-4), 4.92 (1H, br s, H-9a), 2.97 (2H, m, H-2), 2.66-2.67 (2H, m, H-3), 2.64 (3H, s, N-Me); ^{13}C NMR (CDCl_3) 151.6, 135.5, 127.1, 125.2, 123.3, 120.6, 117.2, 115.3, 93.8, 51.3, 37.9, 25.6; HRMS (ESI): calculated $\text{C}_{12}\text{H}_{14}\text{NO}$ [$\text{M}^+\text{+H}$]: 188.10699. Found: 188.10694.

4.3.4. 1-Methyl-3-methylene-1,2,3,3a,4,9b-hexahydrochromeno[4,3-b]pyrrole (**17**)

Prepared by *method A* from aldehyde **3** (270 mg, 1.56 mmol) and sarcosine (278 mg, 3.12 mmol). The reaction mixture was stirred for 27 hours and purification by flash chromatography [ethyl acetate/hexane (1:6)] afforded **17** (181 mg, 58%) as an orange oil. IR (film, cm^{-1}): 1261, 1231; ^1H NMR (CDCl_3) 7.18-7.25 (2H, m, Ar-H), 6.88-6.91 (2H, m, Ar-H), 5.06 (1H, br s, $\text{C}=\text{CH}_2$), 5.03 (1H, br s, $\text{C}=\text{CH}_2$) 3.94-4.05 (2H, m, H-4), 3.66 (1H, d, $J=14.0$ Hz, H-2), 3.13 (1H, d, $J=5.2$ Hz, H-9b), 3.02 (1H, br d, $J=14.0$ Hz, H-2), 2.84-2.90 (1H, m, H-3a), 2.47 (3H, s, N-Me); ^{13}C NMR (CDCl_3) 154.9, 146.5, 131.5, 129.0, 120.4, 119.9, 117.1, 107.1, 66.3, 62.6, 60.3, 41.2, 39.9; HRMS (ESI): calculated $\text{C}_{13}\text{H}_{16}\text{NO}$ [$\text{M}^+\text{+H}$]: 202.12264. Found: 202.12247.

4.3.5. 7a,8,10,11a-Tetrahydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole (**20**), 7a,8,10,11a-Tetrahydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole (**21**) and 8,10-Dihydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole (**22**)

Prepared by *method A* from aldehyde **2** (120 mg, 0.75 mmol) and 1,3-thiazolidine-4-carboxylic acid (200 mg, 1.5 mmol) in toluene (10 mL) was heated at reflux for 7 hours, using a Dean-Stark apparatus. Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:4), then ethyl acetate/hexane (1:2) to ethyl acetate/hexane (2:1), then ethyl acetate] afforded, in order of elution, compound **20** (65 mg, 37%) as pale yellow solid and compound **21** (30 mg, 18%) as orange oil.

Prepared by *method B* from aldehyde **2** (120 mg, 0.75 mmol) and 1,3-thiazolidine-4-carboxylic acid (200 mg, 1.5 mmol) in toluene (1 mL). Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:4), then ethyl acetate/hexane (1:2) to ethyl acetate/hexane (2:1), then ethyl acetate] afforded in order of elution, compound **22** (<10%) as orange oil, compound **20** (32.5 mg, 19%) and compound **21** (10 mg, 6%).

7a,8,10,11a-Tetrahydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole (20). Mp 87-89 °C (from diethyl ether/petroleum ether); IR (film, cm⁻¹): 1223, 1109, 754; ¹H NMR (CDCl₃) 7.37 (1H, d, *J* = 7.6 Hz, Ar-H), 7.14 (1H, pseudo-t, *J* = 7.6 Hz, Ar-H), 6.97 (1H, pseudo-t, *J* = 7.2 Hz, Ar-H), 6.82 (1H, d, *J* = 8.4 Hz, Ar-H), 5.65 (1H, br s, H-7), 4.79 (1H, d, *J* = 13.2 Hz, H-6), 4.74 (1H, d, *J* = 13.2 Hz, H-6), 4.69 (1H, br s, H-11a), 4.60-4.61 (1H, m, H-7a), 4.42 (1H, d, *J* = 10.8 Hz, H-10), 4.33 (1H, d, *J* = 10.8 Hz, H-10), 3.08 (1H, dd, *J* = 11.2, 8.0 Hz, H-8), 2.85 (1H, dd, *J* = 11.2, 2.4 Hz, H-8); ¹³C NMR (CDCl₃) 153.2, 136.4, 128.3, 127.3, 126.0, 123.7, 121.3, 117.0, 76.3, 67.3, 64.5, 62.9, 39.1; HRMS (EI): calculated C₁₃H₁₃NOS [M⁺] 231.0718. Found: 231.0717.

7a,8,10,11a-Tetrahydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole (21). IR (film, cm⁻¹): 1224, 1112, 759; ¹H NMR (CDCl₃) 7.40 (1H, d, *J* = 7.6 Hz, Ar-H), 7.18 (1H, pseudo-t, *J* = 7.6 Hz, Ar-H), 6.98 (1H, pseudo-t, *J* = 7.2 Hz, Ar-H), 6.87 (1H, d, *J* = 8.4 Hz, Ar-H), 5.69 (1H, br s, H-7), 5.15 (1H, br s, H-11a), 4.83 (1H, d, *J* = 12.4 Hz, H-6), 4.75-4.78 (1H, m, H-7a), 4.55-4.59 (1H, m, H-6), 3.65 (1H, d, *J* = 8.6 Hz, H-10), 3.58 (1H, d, *J* = 8.6 Hz, H-10), 3.32 (1H, dd, *J* = 11.2, 7.6 Hz, H-8), 3.08 (1H, dd, *J* = 11.2, 2.8 Hz, H-8); ¹³C NMR (CDCl₃) 154.6, 136.1, 128.6, 127.8, 125.6, 120.5, 120.2, 116.7, 72.8, 63.5, 63.3, 52.2, 33.8; HRMS (EI): calculated C₁₃H₁₃NOS [M⁺] 231.0718. Found: 231.0720.

8,10-Dihydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole (22). ¹H NMR (CDCl₃) 7.21-7.23 (1H, m, Ar-H), 7.02-7.05 (1H, m, Ar-H), 6.89-6.92 (2H, m, Ar-H), 5.73 (1H, s), 5.23 (2H, s), 5.22 (2H, s), 4.07 (2H, s); HRMS (EI): calculated C₁₃H₁₁NOS [M⁺] 229.0561. Found: 229.0561.

4.3.6. *Ethyl 7a,8,10,11a-tetrahydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole-7-carboxylate (23)*, *Ethyl 8,10-dihydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole-7-carboxylate (24)* and *Ethyl 5-(2-hydroxyphenyl)-6-methyl-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxylate (25)*

Prepared by *method A* from aldehyde **5** (174 mg, 0.75 mmol) and 1,3-thiazolidine-4-carboxylic acid (200 mg, 1.5 mmol) in toluene (10 mL) was heated at reflux for 7 hours, using a Dean-Stark apparatus. Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:4)] afforded, in order of elution, a 94:6 mixture of the compounds **23** and **24** (166 mg, 73%) and 1*H,3H*-pyrrolo[1,2-*c*]thiazole **25** (27 mg, 12%) as a white solid. Selective crystallization of the mixture of

23 and **24** with ethyl acetate/hexane afforded **23** as a white crystalline solid whereas compound **24** was obtained as a yellow solid by crystallization with ethyl acetate/petroleum ether.

Prepared by *method B* from aldehyde **5** (174 mg, 0.75 mmol) and 1,3-thiazolidine-4-carboxylic acid (200 mg, 1.5 mmol) in toluene (1 mL). Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:4)] afforded in order of elution, a 86:14 mixture of the compound **23** and the corresponding aromatized derivative **24** (96.5 mg, 42%) and *1H,3H*-pyrrolo[1,2-*c*]thiazole **25** (35 mg, 15%).

Ethyl 7a,8,10,11a-tetrahydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole-7-carboxylate (23). Mp 84-86 °C (from ethyl acetate/hexane); IR (KBr, cm^{-1}): 1707, 1216, 1125, 771; ^1H NMR (CDCl_3) 7.43 (1H, d, $J = 7.2$ Hz, Ar-H), 7.21 (1H, pseudo-t, $J = 7.6$ Hz, Ar-H), 7.07 (1H, pseudo-t, $J = 7.4$ Hz, Ar-H), 6.95 (1H, d, $J = 8.0$ Hz, Ar-H), 5.11 (2H, s, H-6), 4.86 (1H, br s, H-11a), 4.76 (1H, m, H-7a), 4.32 (1H, d, $J = 10.8$ Hz, H-10), 4.28 (1H, d, $J = 10.8$ Hz, H-10), 4.18-4.26 (2H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.24 (1H, dd, $J = 11.6, 8.0$ Hz, H-8), 3.08 (1H, dd, $J = 11.6, 2.4$ Hz, H-8), 1.30 (3H, t, $J = 7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C NMR (CDCl_3) 163.1, 153.5, 152.4, 128.4, 128.3, 124.6, 122.7, 117.4, 75.5, 69.1, 66.6, 61.9, 60.8, 39.3, 14.3; HRMS (EI): calculated $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{S} [\text{M}^+]$ 303.0929. Found: 303.0915.

Ethyl 8,10-dihydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole-7-carboxylate (24). Mp 143-145 °C (from ethyl acetate/petroleum ether); IR (KBr, cm^{-1}): 1690, 1227, 1139, 767; ^1H NMR (CDCl_3) 7.19 (1H, d, $J = 7.6$ Hz, Ar-H), 7.08 (1H, pseudo-t, $J = 7.4$ Hz, Ar-H), 6.87-6.91 (2H, m, Ar-H), 5.46 (2H, s), 5.26 (2H, s), 4.31 (2H, s), 4.26 (2H, q, $J = 7.2$ Hz), 1.34 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3) 164.1, 152.7, 142.8, 127.7, 121.4, 121.0, 120.1, 119.2, 117.6, 117.1, 104.7, 65.5, 59.9, 49.1, 29.4, 14.5; HRMS (EI): calculated $\text{C}_{16}\text{H}_{15}\text{NO}_3\text{S} [\text{M}^+]$ 301.0773. Found: 301.0775.

Ethyl 5-(2-hydroxyphenyl)-6-methyl-1H,3H-pyrrolo[1,2-c]thiazole-7-carboxylate (25). Mp 175-177 °C (from ethyl acetate/hexane); IR (film, cm^{-1}): 3390, 1682, 1108, 757; ^1H NMR (CDCl_3) 7.30 (1H, pseudo-t, $J = 7.2$, Ar-H), 7.15 (1H, d, $J = 6.8$ Hz, Ar-H), 6.95-7.01 (2H, m, Ar-H), 5.62 (1H, br s), 4.88 (1H, d, $J = 8.4$ Hz), 4.78 (1H, d, $J = 8.4$ Hz), 4.35-4.40 (2H, m), 4.28 (2H, q, $J = 7.2$ Hz), 2.17 (3H, s), 1.34 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (CDCl_3) 165.0, 154.2, 141.8, 131.4, 130.5, 124.8, 121.5, 120.6, 117.2, 115.9, 107.5, 59.6, 48.5, 31.2, 14.6, 11.8; HRMS (EI): calculated $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{S} [\text{M}^+]$ 303.0929. Found: 303.0931.

4.3.7. 3,4a,11,11a-Tetrahydro-1H-chromeno[3',2':4,5]pyrrolo[1,2-c]thiazole (**26**)

Prepared by *method A* from aldehyde **6** (120 mg, 0.75 mmol) and 1,3-thiazolidine-4-carboxylic acid (200 mg, 1.5 mmol) in toluene (10 mL) was heated at reflux for 7 hours, using a Dean-Stark apparatus. Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:4)] afforded compound **26** (73 mg, 42%) as a yellow oil.

Prepared by *method B* from aldehyde **6** (120 mg, 0.75 mmol) and 1,3-thiazolidine-4-carboxylic acid (200 mg, 1.5 mmol) in toluene (1 mL). Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:4)] afforded compound **26** (17 mg, 9%).

3,4a,11,11a-Tetrahydro-1H-chromeno[3',2':4,5]pyrrolo[1,2-c]thiazole (26). IR (film, cm^{-1}): 1230, 1204, 755; ^1H NMR (CDCl_3) 7.10 (1H, pseudo-t, $J = 7.6$ Hz, Ar-H), 7.01 (1H, d, $J = 7.2$ Hz, Ar-H), 6.88-6.92 (2H, m, Ar-H), 6.30 (1H, br s, H-10), 5.34 (1H, br s, H-4a), 4.42 (1H, d, $J = 10.4$ Hz, H-3), 4.31 (1H, d, $J = 10.4$ Hz, H-3), 3.96-4.02 (1H, m, H-11a), 3.14 (1H, dd, $J = 11.2, 7.0$ Hz, H-1), 3.03-3.09 (1H, m, H-11), 2.62 (1H, dd, $J = 11.2, 6.0$ Hz, H-1), 2.50-2.55 (1H, m, H-11); ^{13}C NMR (CDCl_3) 152.4, 134.6, 128.6, 126.4, 123.5, 121.8, 119.5, 116.4, 93.5, 66.8, 58.1, 38.7, 33.3; HRMS (EI): calculated $\text{C}_{13}\text{H}_{13}\text{NOS} [\text{M}^+]$ 231.0718. Found: 231.0719.

4.4. 1-Methyl-1,4-dihydrochromeno[4,3-b]pyrrole (**8**)

To a solution of compound **7** (135 mg, 0.72 mmol) in ethyl acetate (10 mL) Pd/C 10% (14 mg, 10 w%) was added. The resulting solution was heated at reflux for 24 hours. After cooling to room temperature, the reaction mixture was filtered on celite to remove the oxidant and the solvent was concentrated under reduced pressure. Purification of the crude product by flash chromatography [ethyl acetate/hexane (1:2)] afforded **8** (100 mg, 75%) as a white solid. Compound **8** was identified by comparison with the specimen previous prepared (see above).

4.5. X-ray Diffraction. A crystal of compound **23** was selected, covered with polyfluoroether oil, and mounted on a nylon loop. Crystallographic data for this compound was collected at the IST using graphite monochromated Mo-K α radiation ($\lambda=0.71073\text{\AA}$) on a Bruker AXS-KAPPA APEX II diffractometer equipped with an Oxford Cryosystem open-flow nitrogen cryostat, at 150 K. Cell parameters were retrieved using Bruker SMART software and refined using Bruker SAINT on all

observed reflections. Absorption corrections were applied using SADABS.¹⁴ Structure solution and refinement were performed using direct methods with the program SIR2004¹⁵ included in the package of programs WINGX-Version 1.80.05¹⁶ and SHELXL.¹⁷ All hydrogen atoms were inserted in idealised positions and allowed to refine riding on the parent carbon atom, with C–H distances of 0.95 Å, 0.98 Å, 0.99 Å and 1.0 Å for aromatic, methyl, methylene and methine H atoms, respectively, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$. The figure of the molecular structure was generated using ORTEP-III.¹⁸

4.5.1. Crystallographic data for 3,4a,11,11a-Tetrahydro-1H-chromeno[3',2':4,5]pyrrolo[1,2-c]thiazole 23. $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{S}$, $M = 303.38$, orthorhombic, $Pca2_1$ with unit cell, $a = 23.4004(6)$ Å, $b = 6.9636(2)$ Å, $c = 17.3619(4)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $V = 2829.14(13)$ Å³. $\rho_{\text{calcd}} = 1.424$ Mg/m³, $Z = 8$, $\mu = 0.239$ mm⁻¹. $R [I > 2\sigma(I)] = 0.0366$ and $R_w = 0.0860$ for 8484 independent reflections.

Supplementary data. ¹H NMR, ¹³C NMR, HMQC, HMBC and NOESY spectra for selected compounds. Crystallographic data of compound **23**.

Acknowledgments

Thanks are due to *Fundação para a Ciência e a Tecnologia* (SFRH/BD/69941/2010, SFRH/BPD/64623/2009, PEst-C/QUI/UI0313/2011 and PEst-OE/QUI/UI0100/2013) for financial support. We acknowledge the Nuclear Magnetic Resonance Laboratory of the Coimbra Chemistry Center (www.nmrccc.uc.pt), University of Coimbra for obtaining the NMR spectroscopic data. C.S.B.G. thanks Prof. M. Teresa Duarte for valuable discussions on X-ray crystallography.

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Reactivity of Sarcosine and 1,3-Thiazolidine-4-carboxylic Acid Towards Salicylaldehyde-derived Alkynes and Allenes

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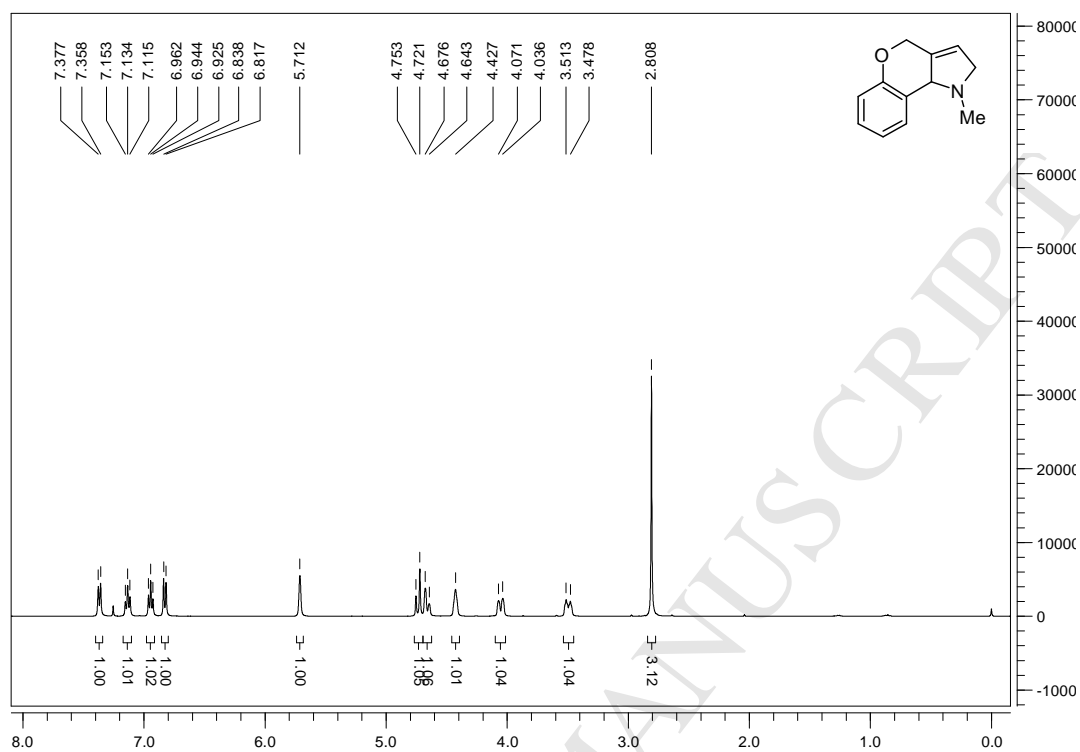
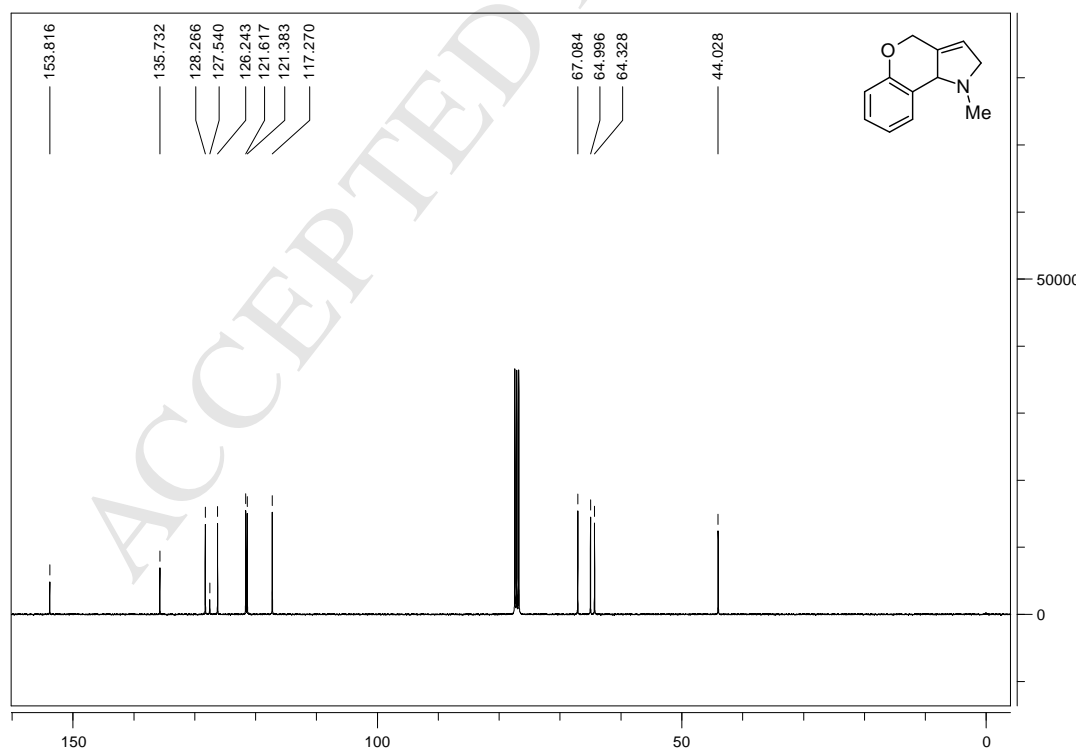
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Supplementary data

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1. ^1H and ^{13}C NMR, HMQC, HMBC and NOESY spectra of selected compoundsFigure S1. ^1H NMR spectrum of compound 7.Figure S2. ^{13}C NMR spectrum of compound 7.

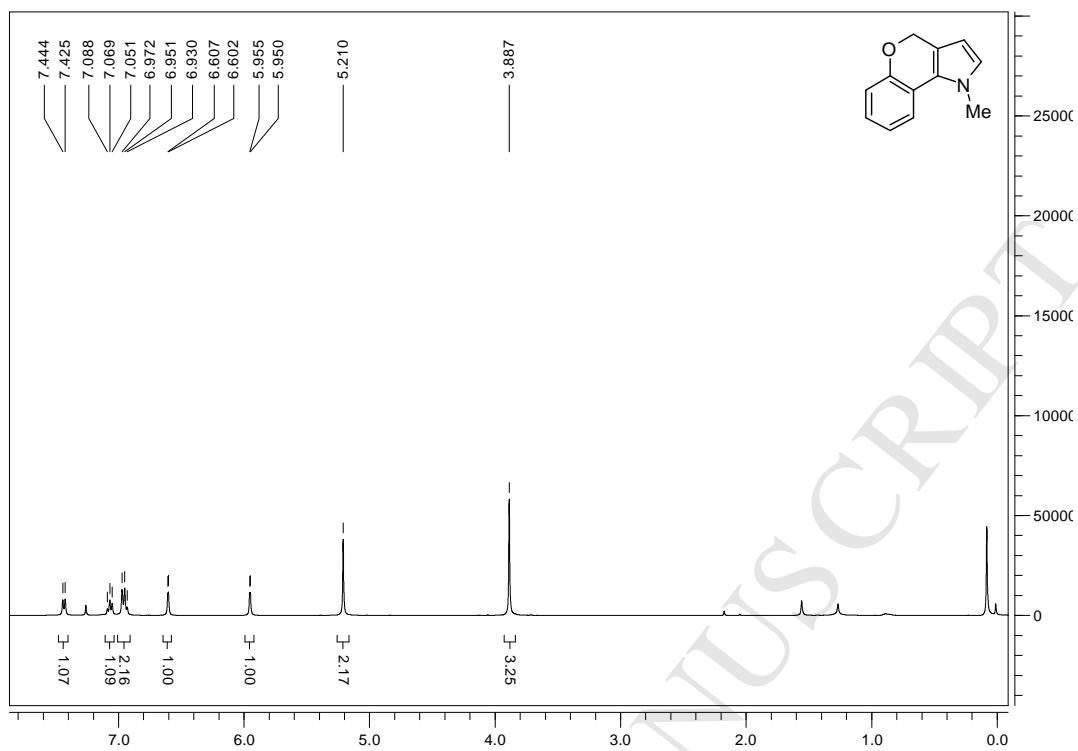


Figure S3. ¹H NMR spectrum of compound 8.

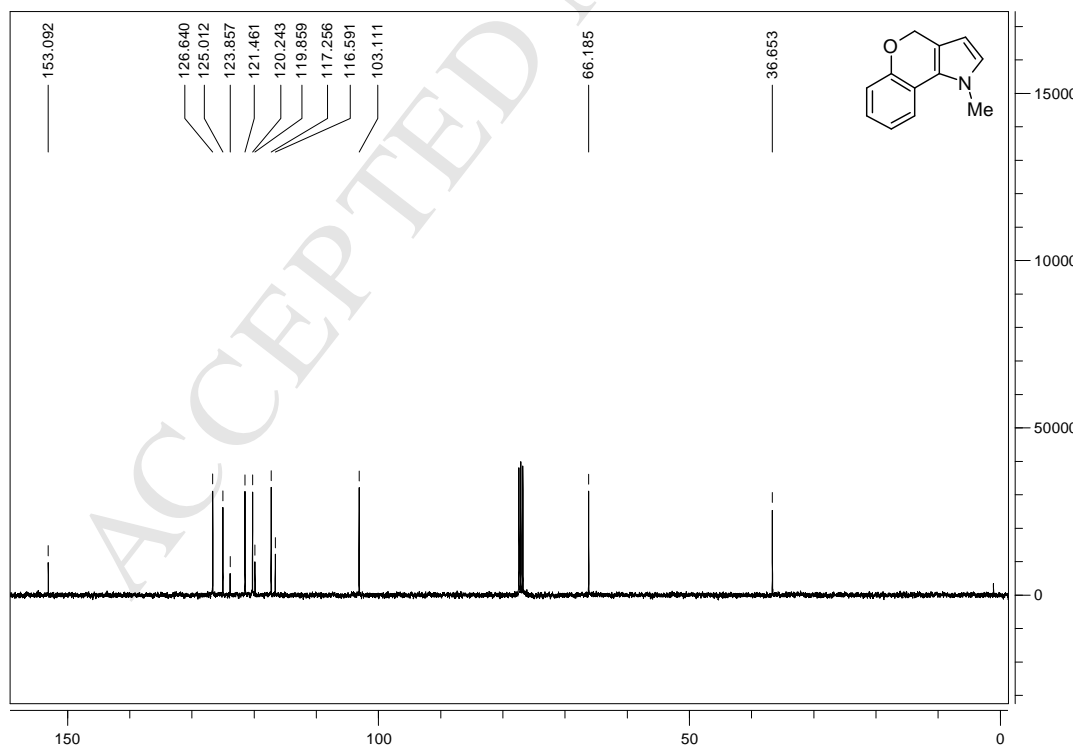


Figure S4. ¹³C NMR spectrum of compound 8.

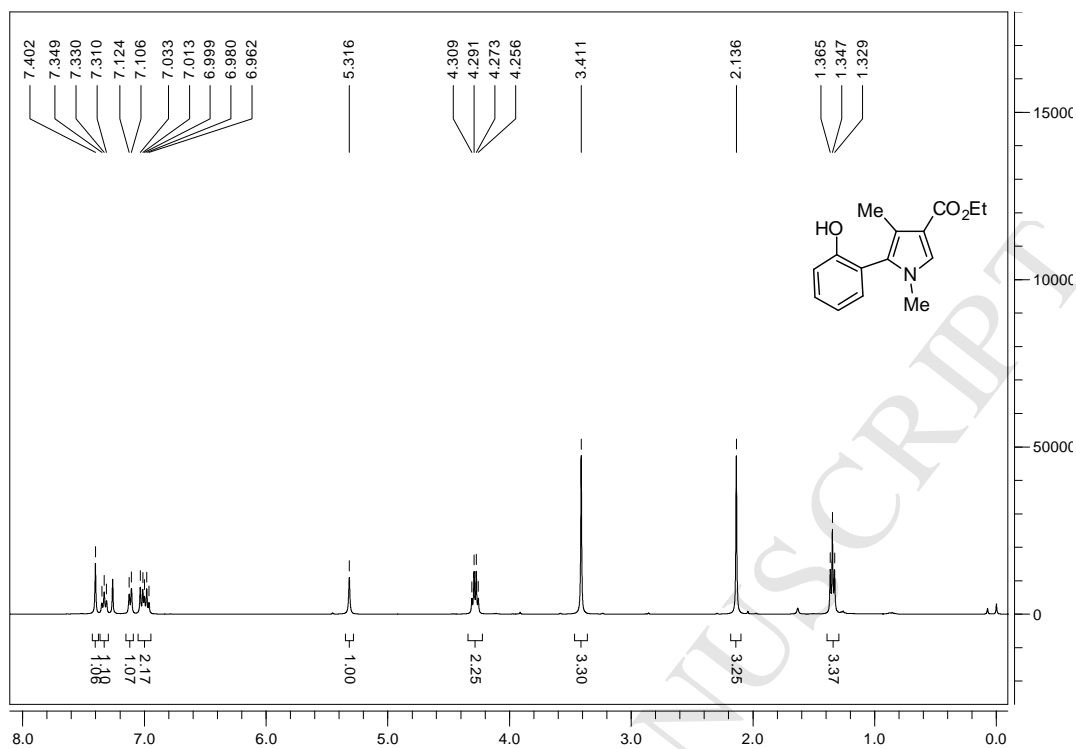


Figure S5. ¹H NMR spectrum of compound **10**.

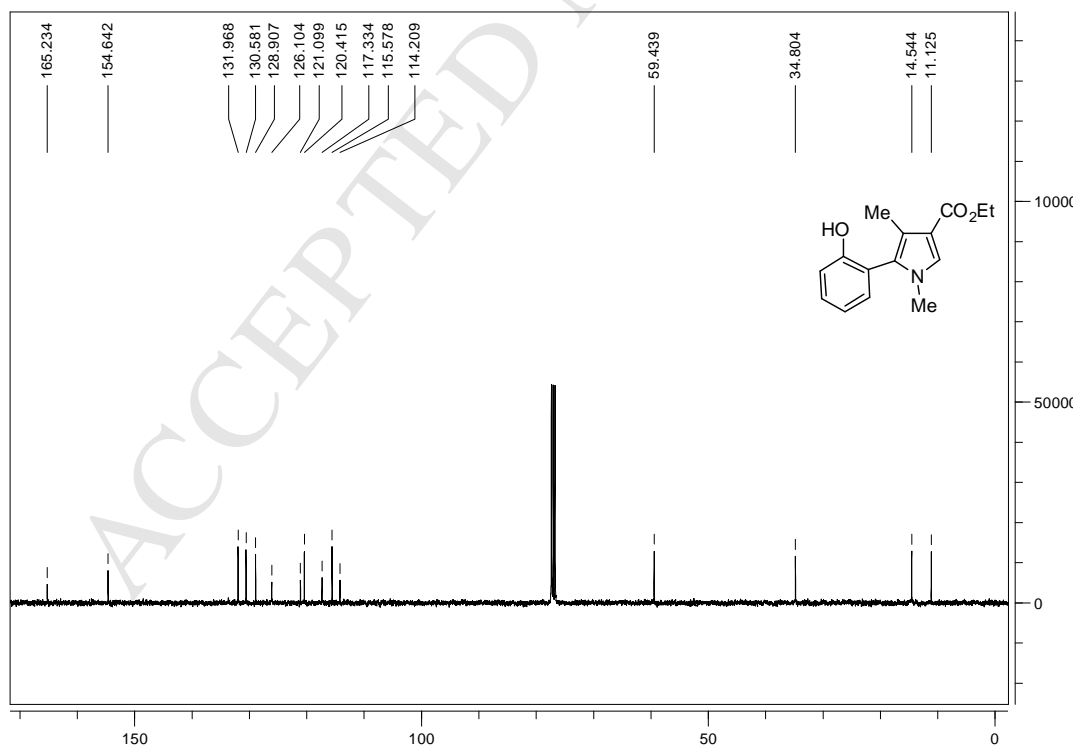


Figure S6. ¹³C NMR spectrum of compound **10**.

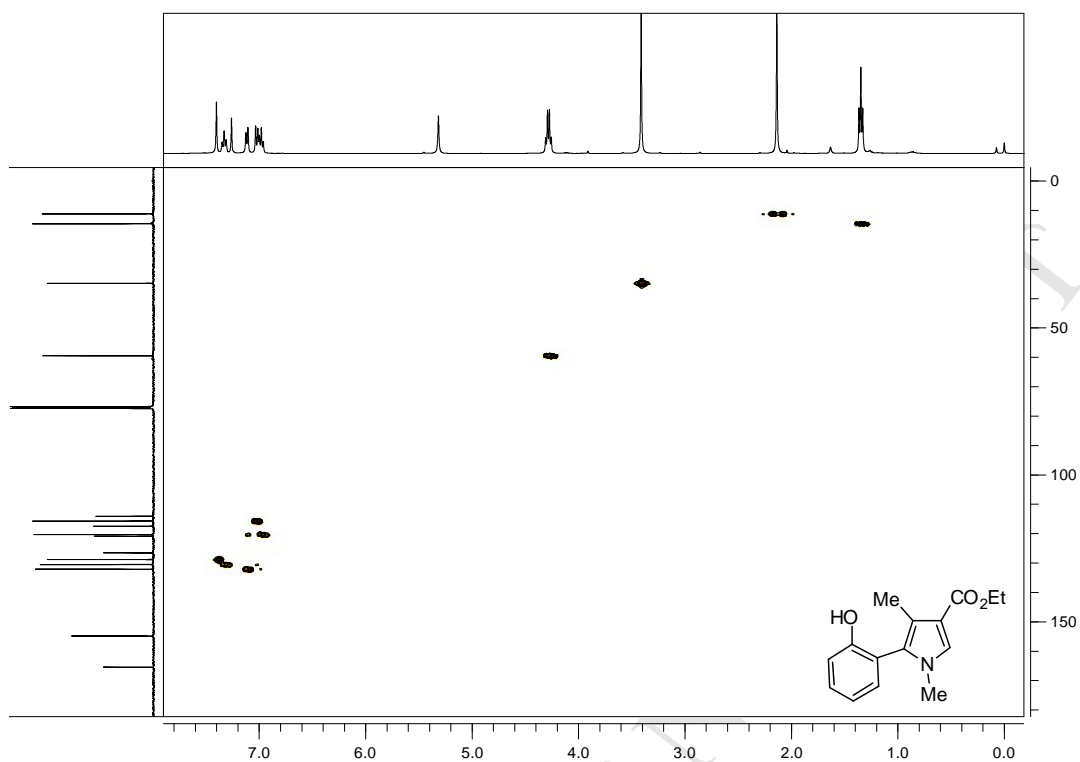


Figure S7. HMQC spectrum of compound 10.

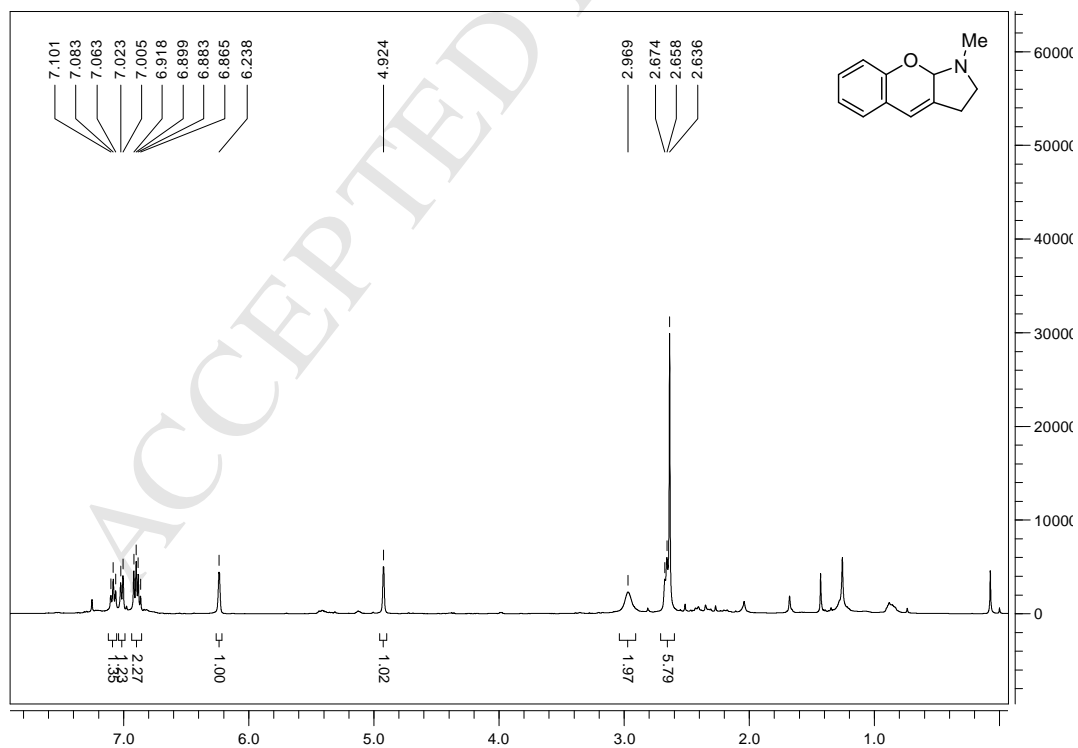


Figure S8. ^1H NMR spectrum of compound 16.

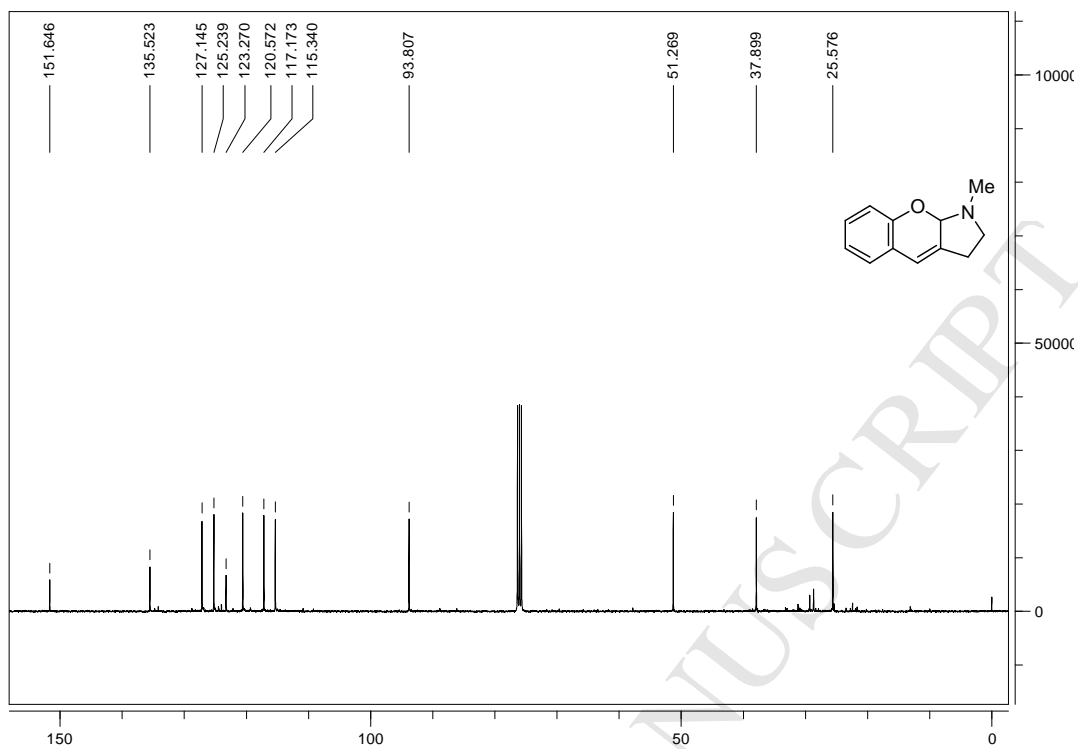


Figure S9. ^{13}C NMR spectrum of compound 16.

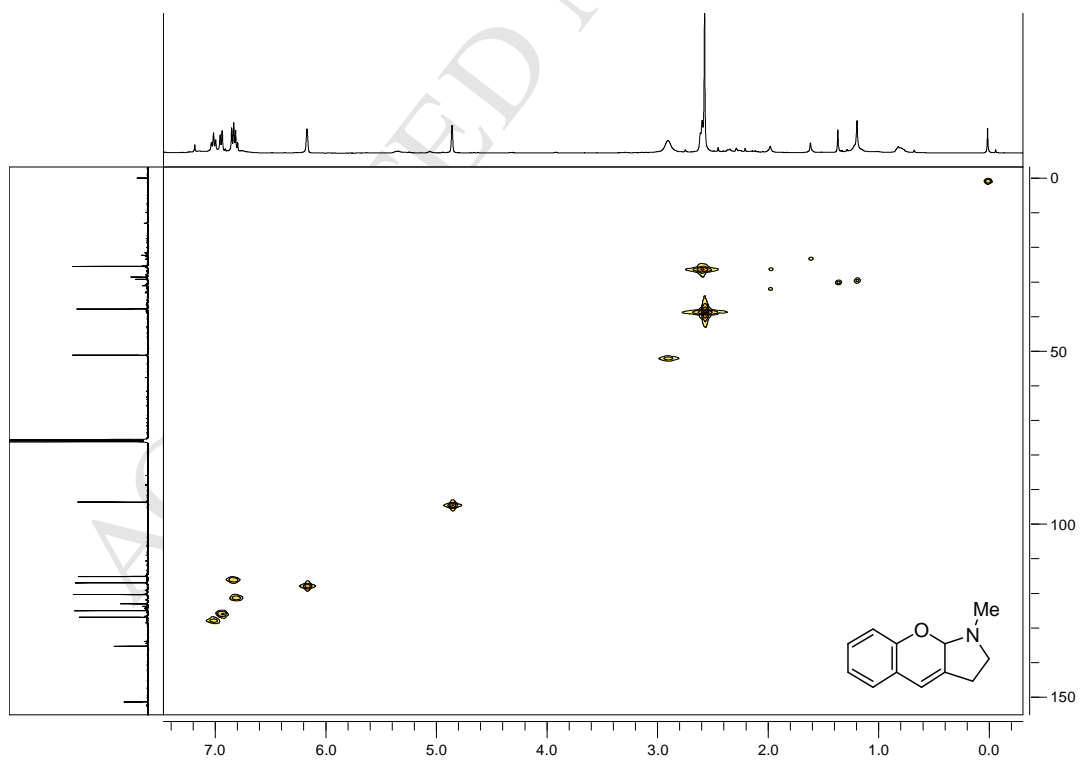


Figure S10. HMQC spectrum of compound 16.

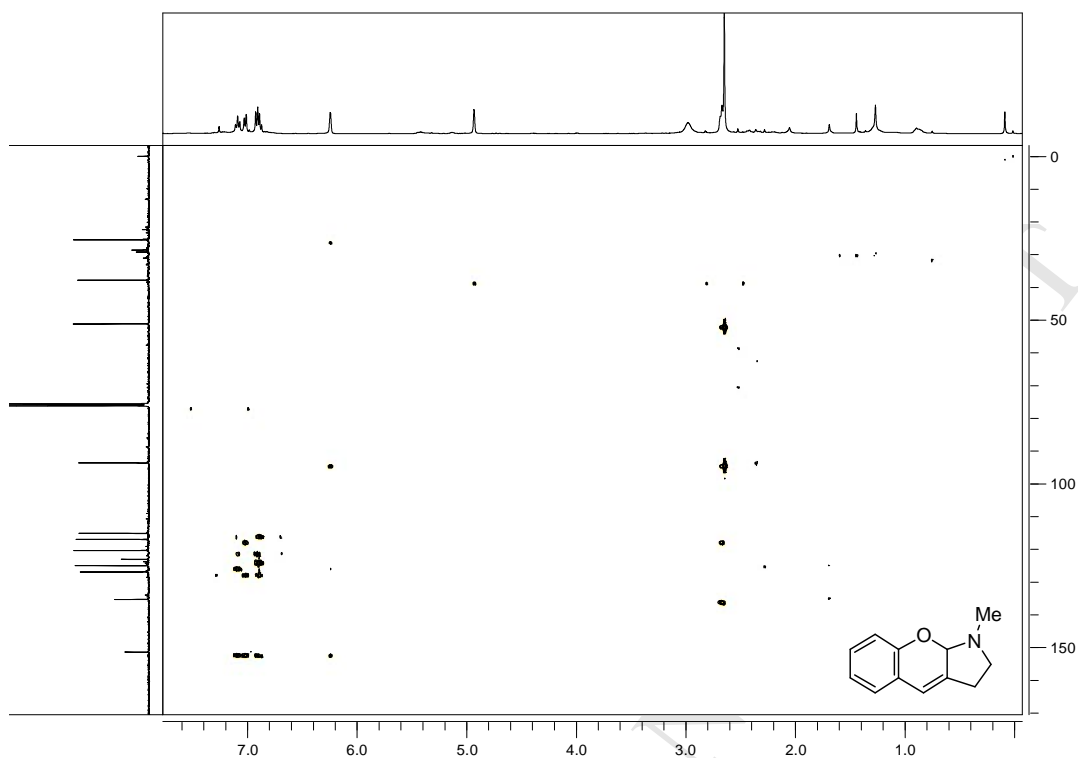


Figure S11. HMBC spectrum of compound 16.

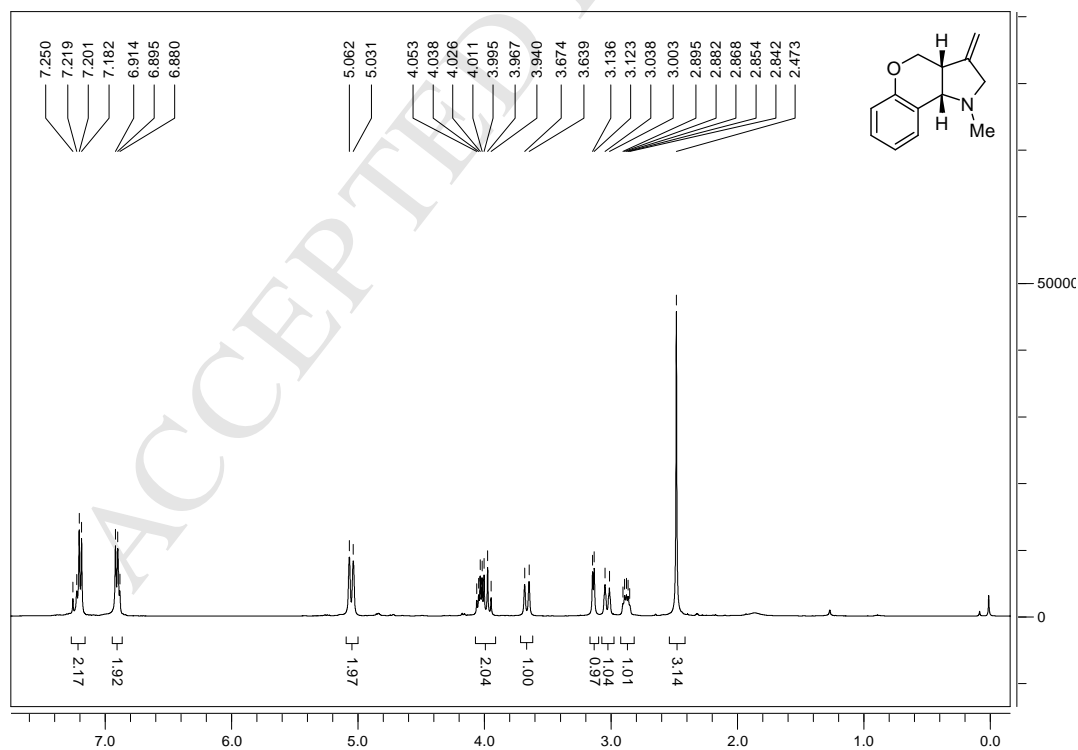


Figure S12. ^1H NMR spectrum of compound 17.

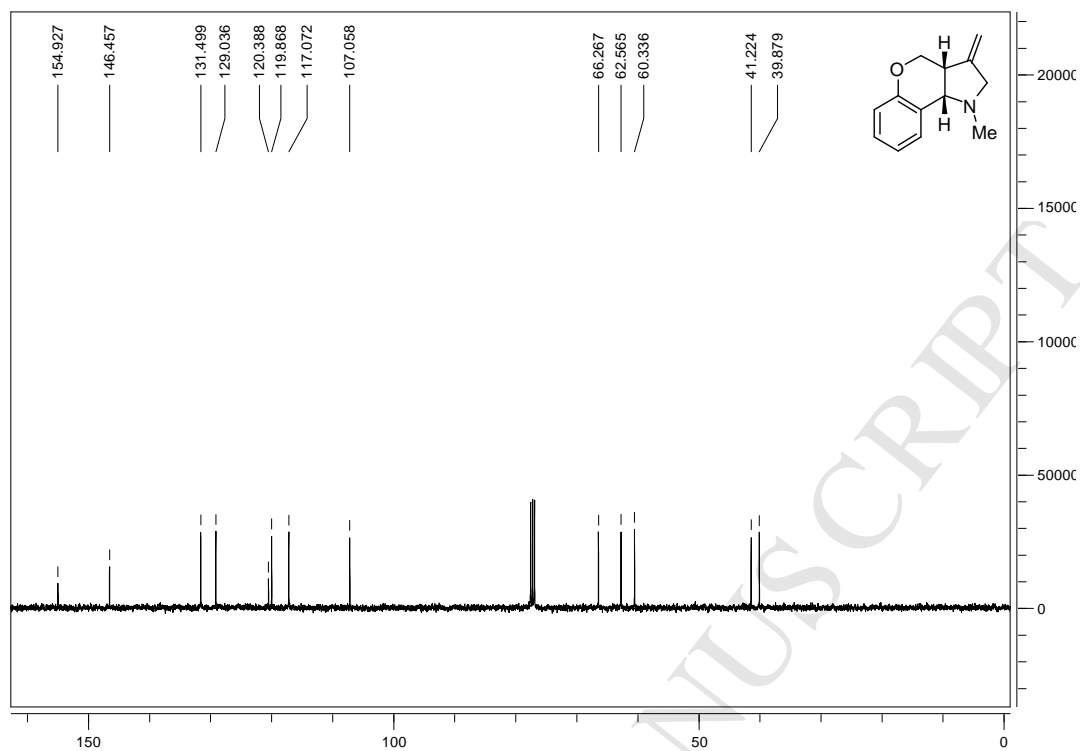


Figure S13. ¹³C NMR spectrum of compound 17.

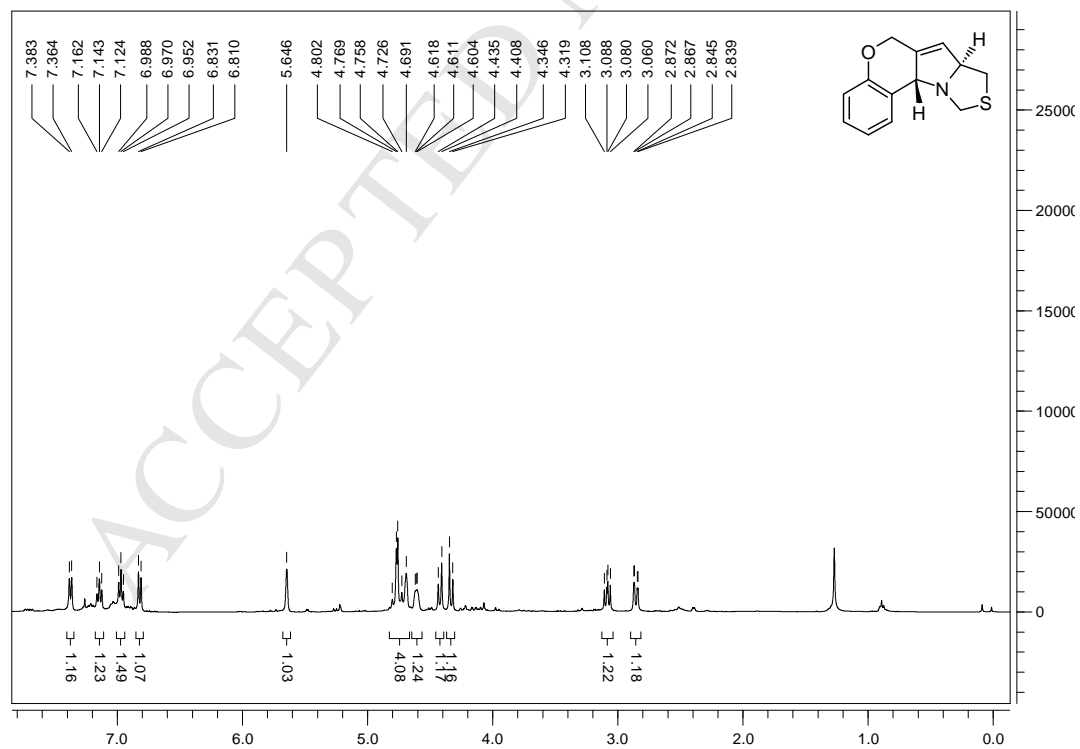


Figure S14. ¹H NMR spectrum of compound 20.

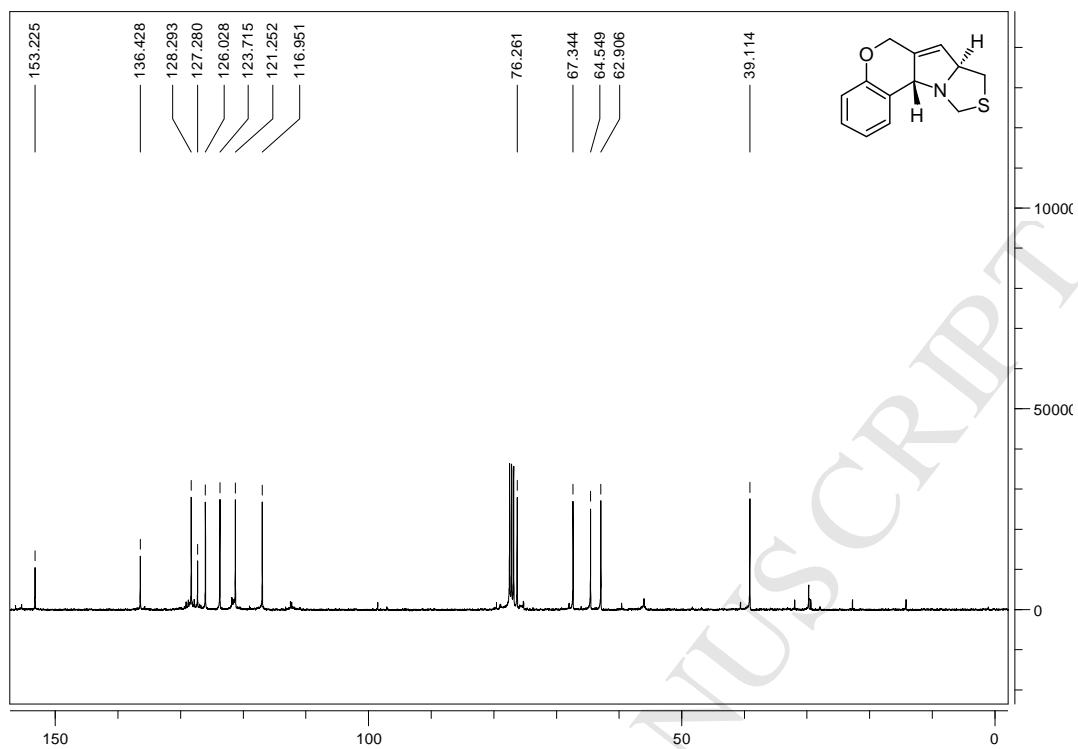


Figure S15. ^{13}C NMR spectrum of compound 20.

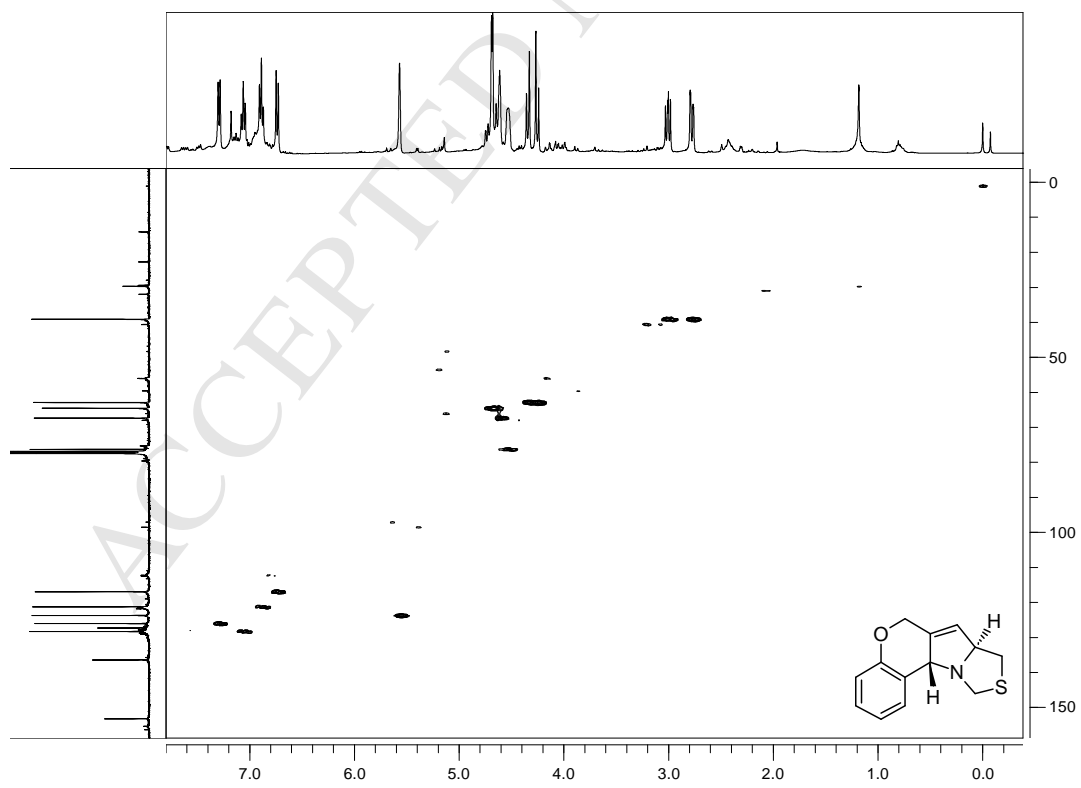


Figure S16. HMBC spectrum of compound 20.

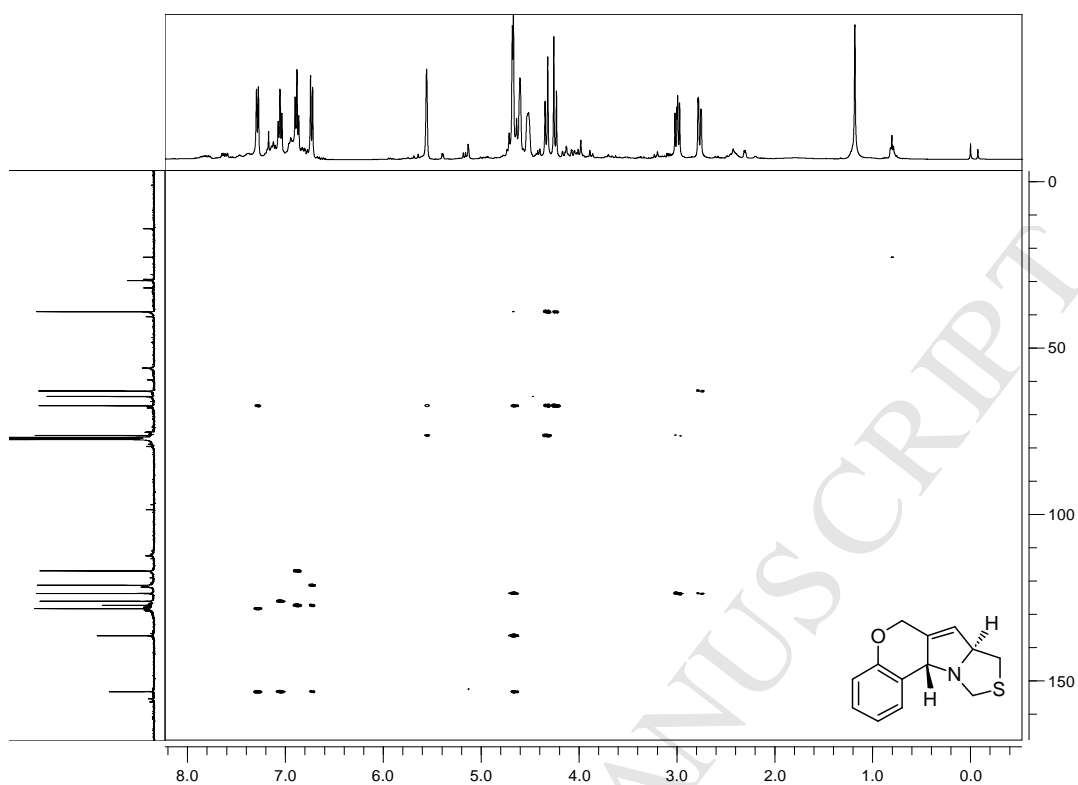


Figure S17. HMBC spectrum of compound 20.

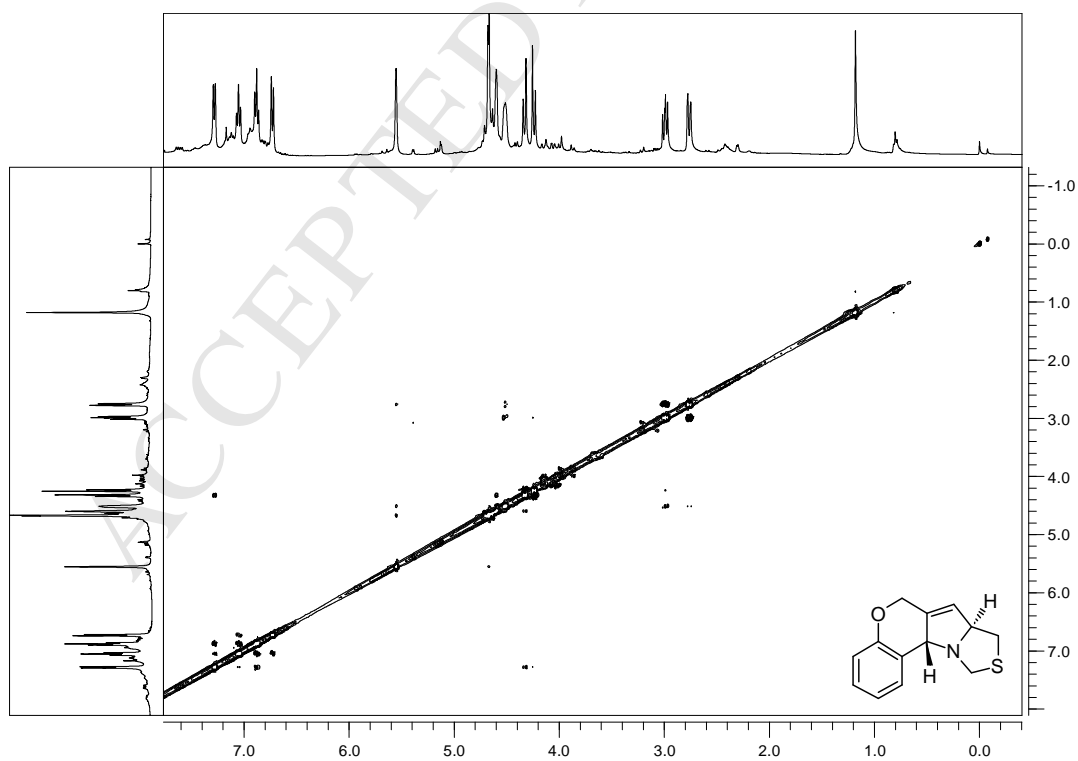


Figure S18. NOESY spectrum of compound 20.

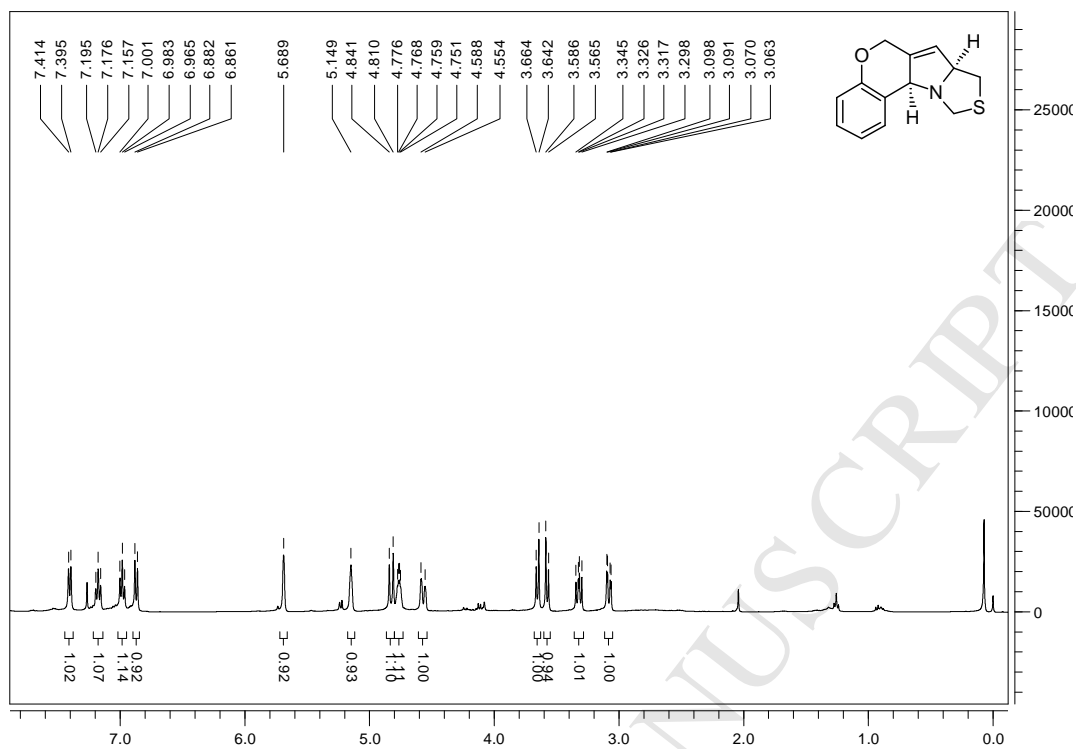


Figure S19. ^1H NMR spectrum of compound **21**.

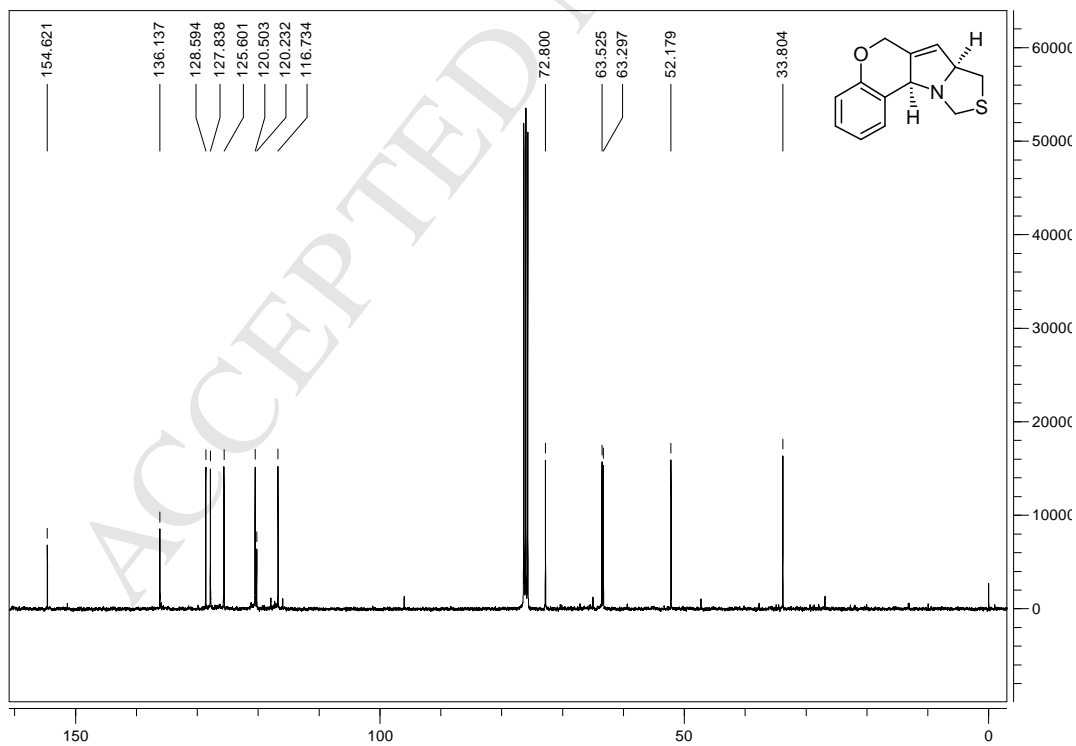


Figure S20. ^{13}C NMR spectrum of compound **21**.

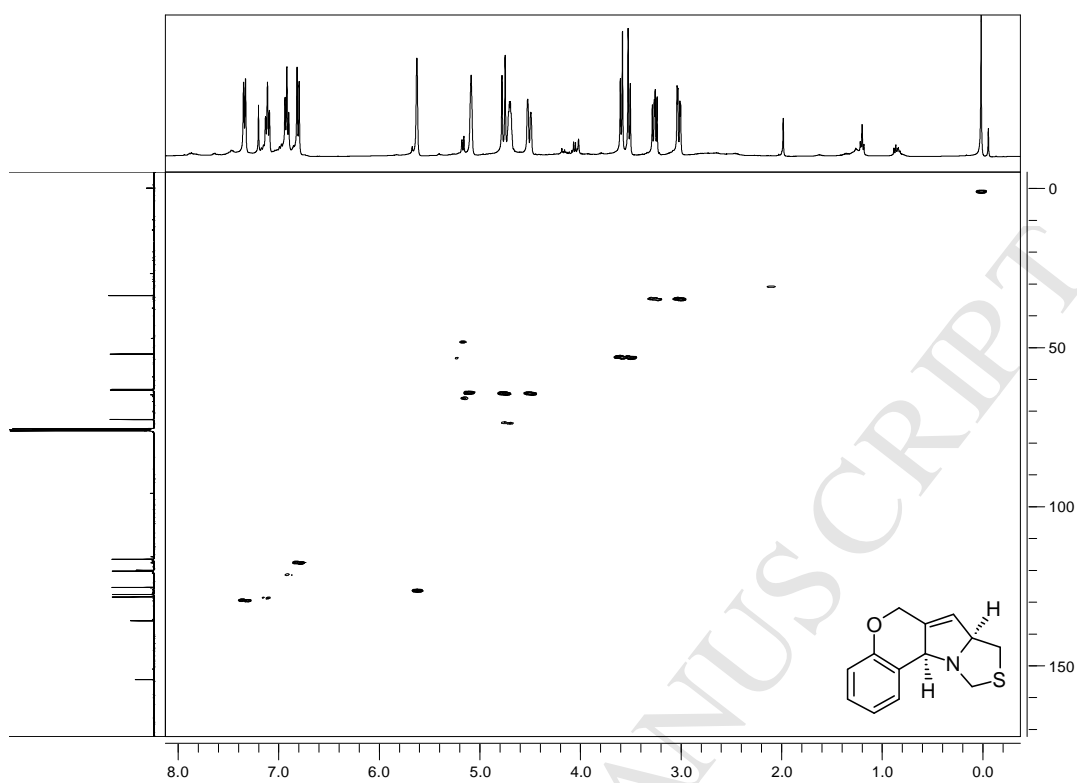


Figure S21. HMBC spectrum of compound **21**.

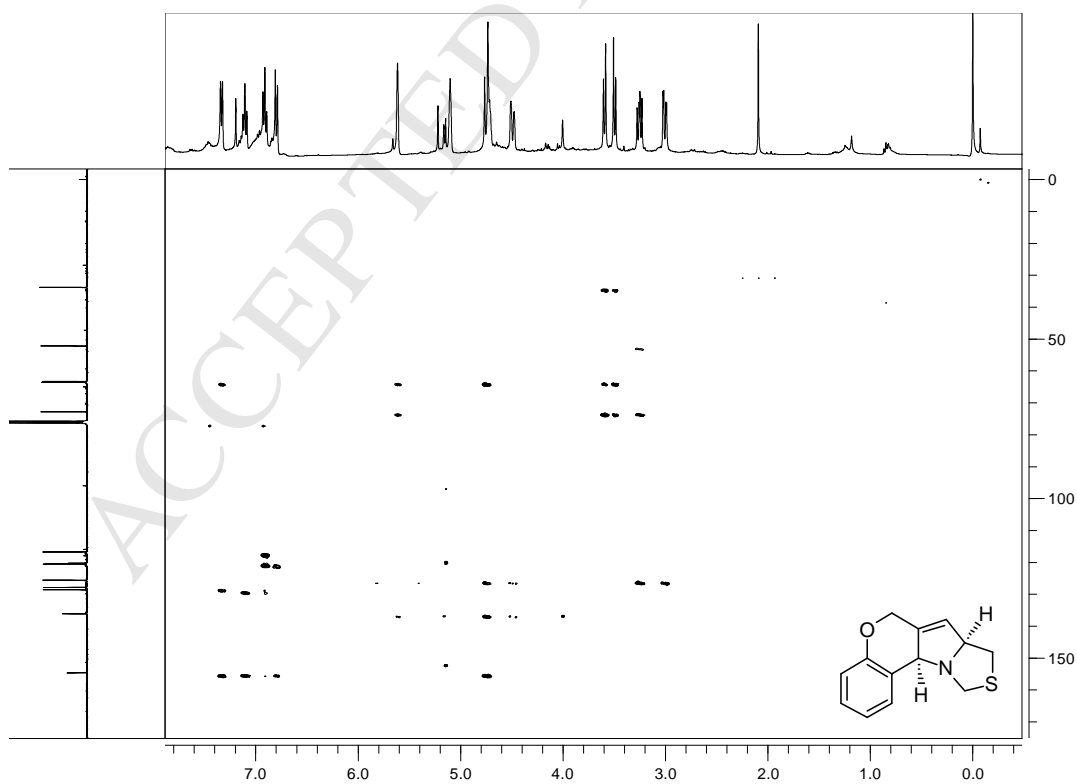


Figure S22. HMBC spectrum of compound **21**.

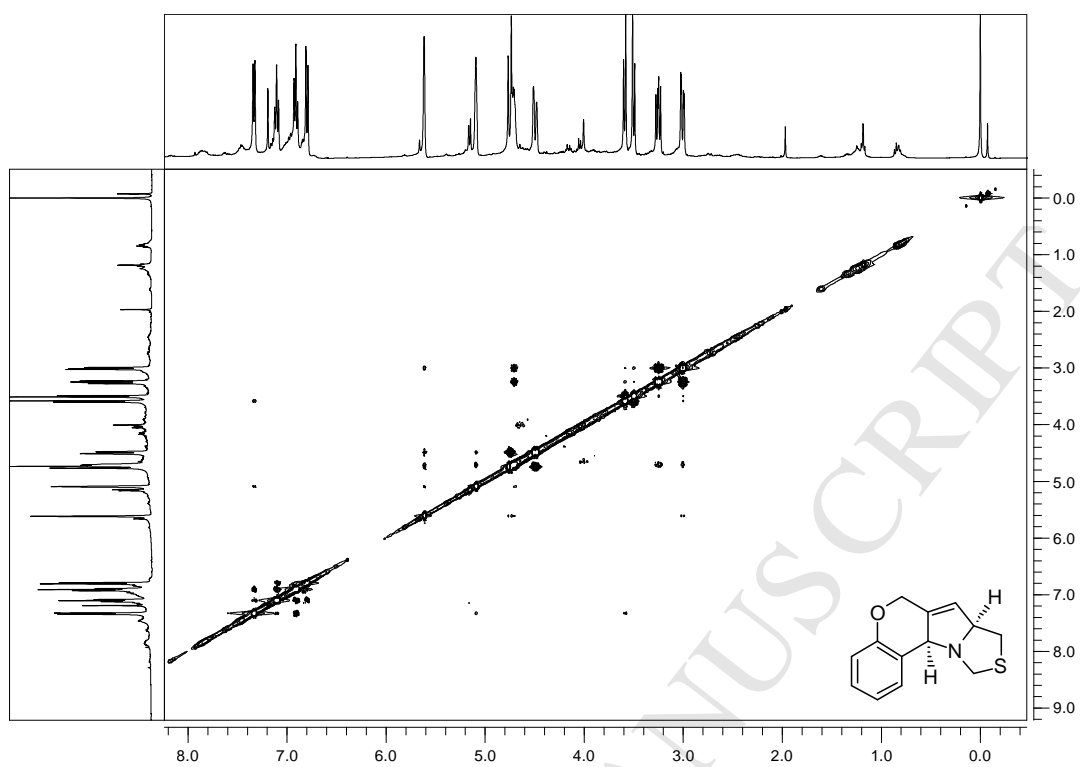


Figure S23. NOESY spectrum of compound 21.

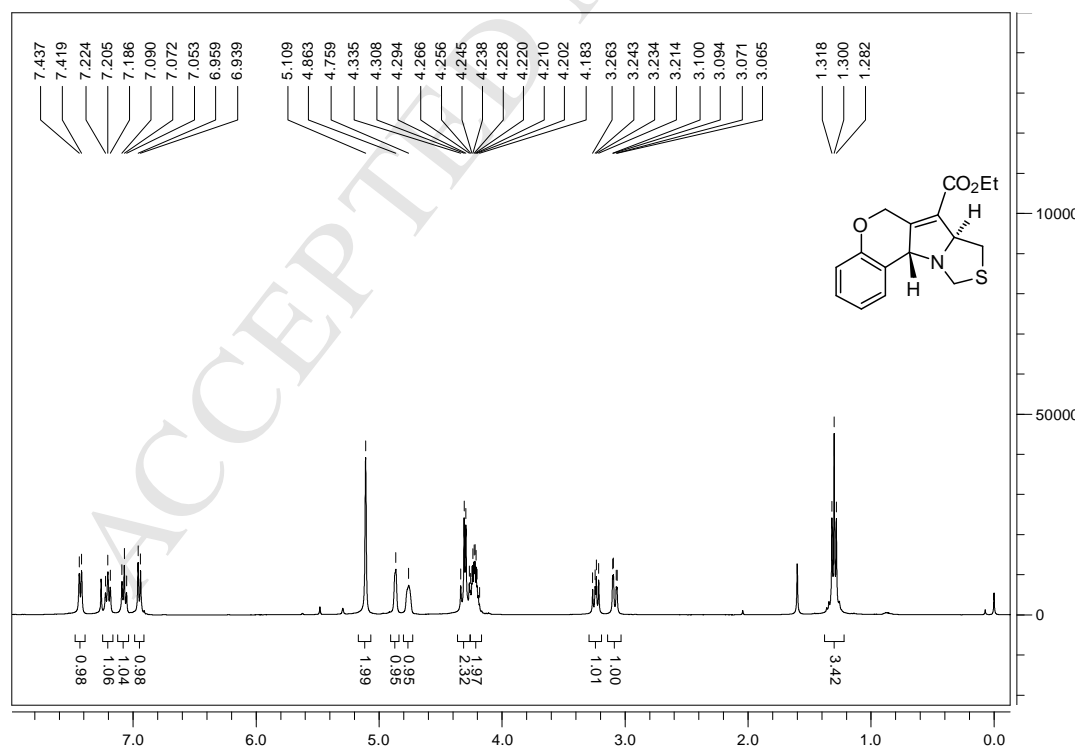


Figure S24. ¹H NMR spectrum of compound 23.

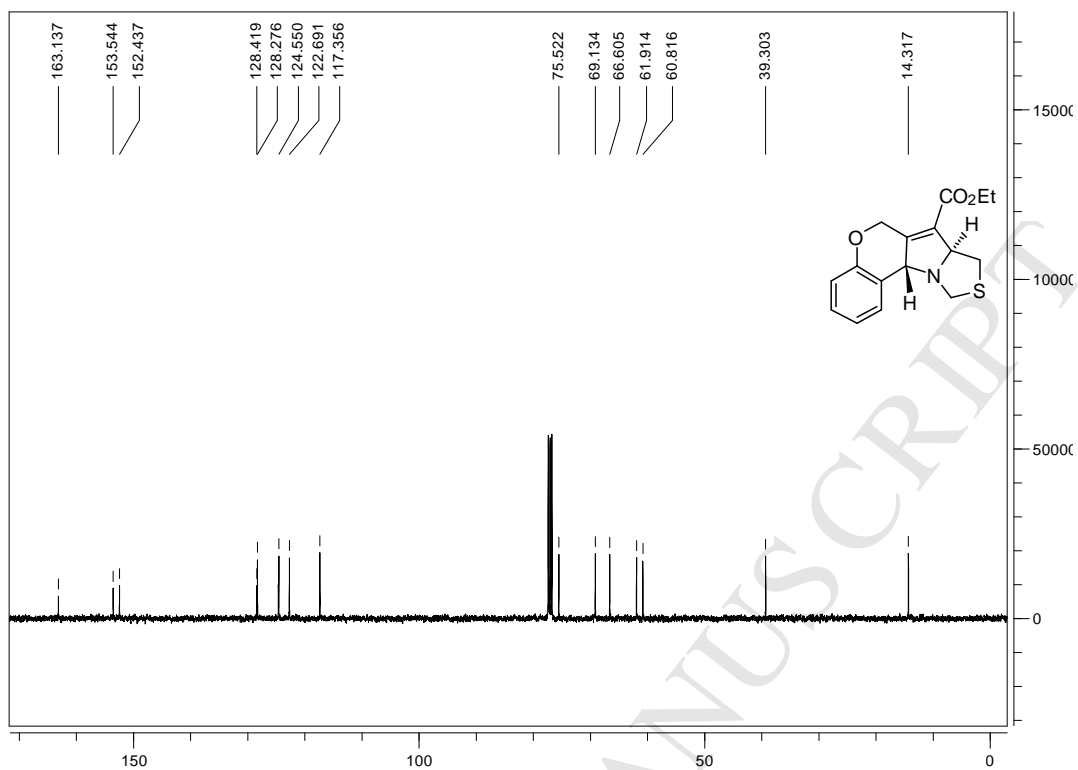


Figure S25. ^{13}C NMR spectrum of compound 23.

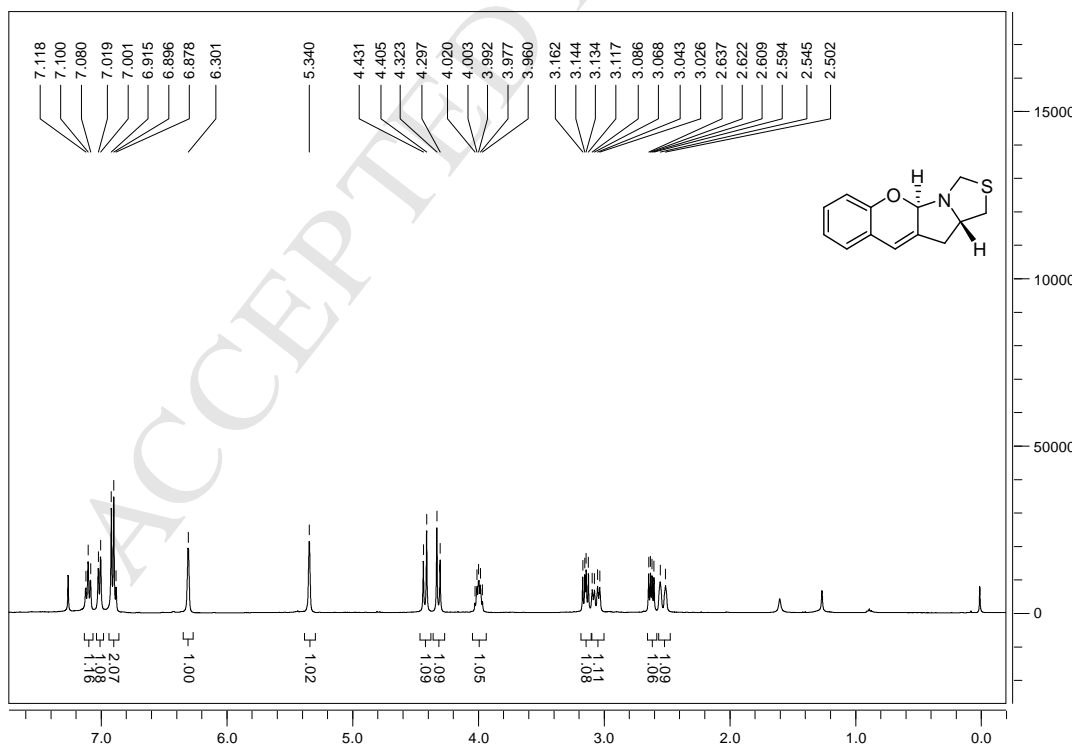


Figure S26. ^1H NMR spectrum of compound 26.

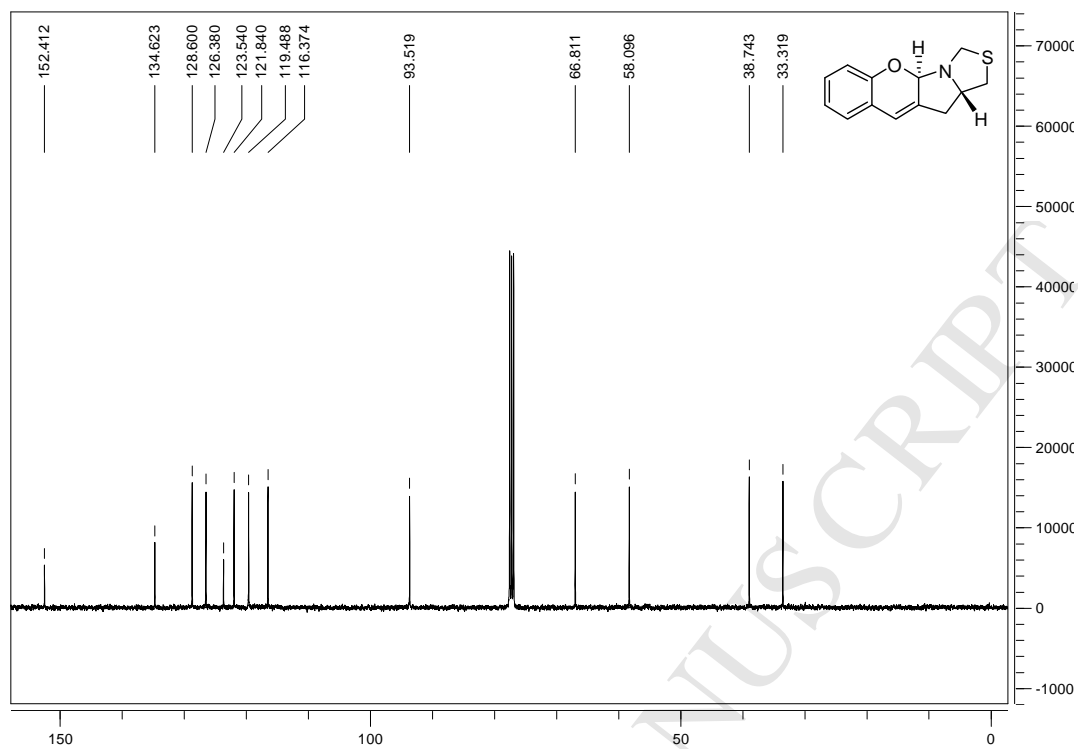


Figure S27. ^{13}C NMR spectrum of compound 26.

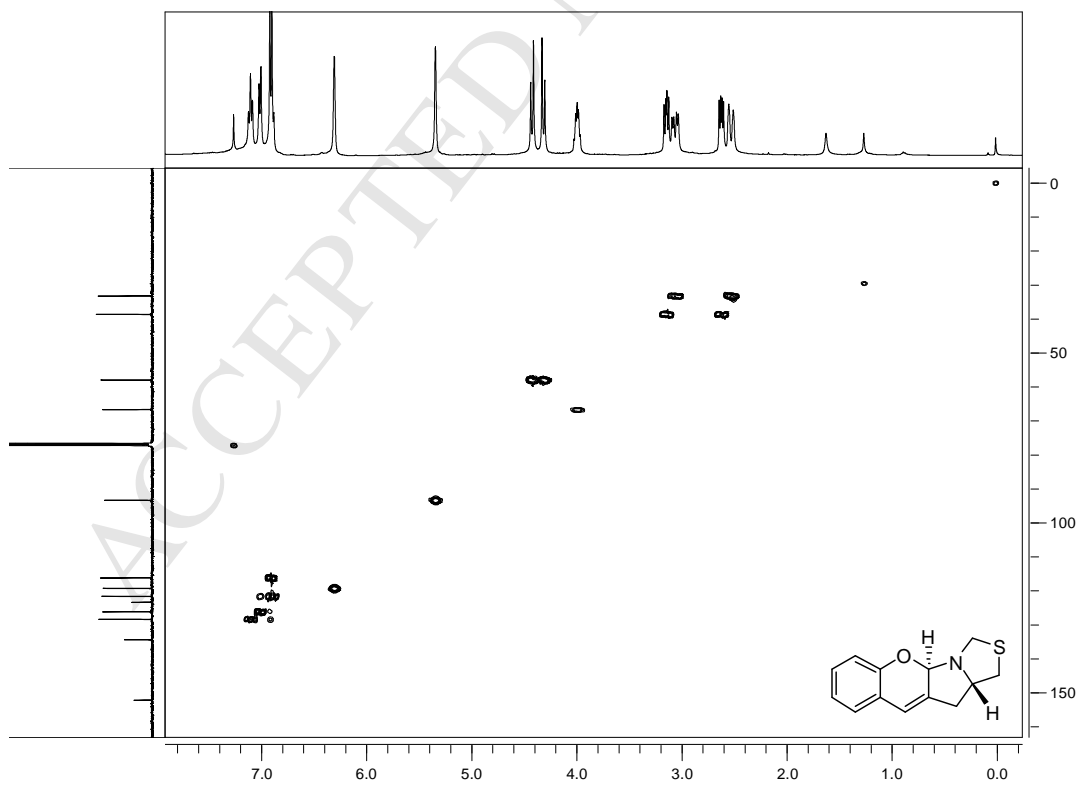


Figure S28. HMQC spectrum of compound 26.

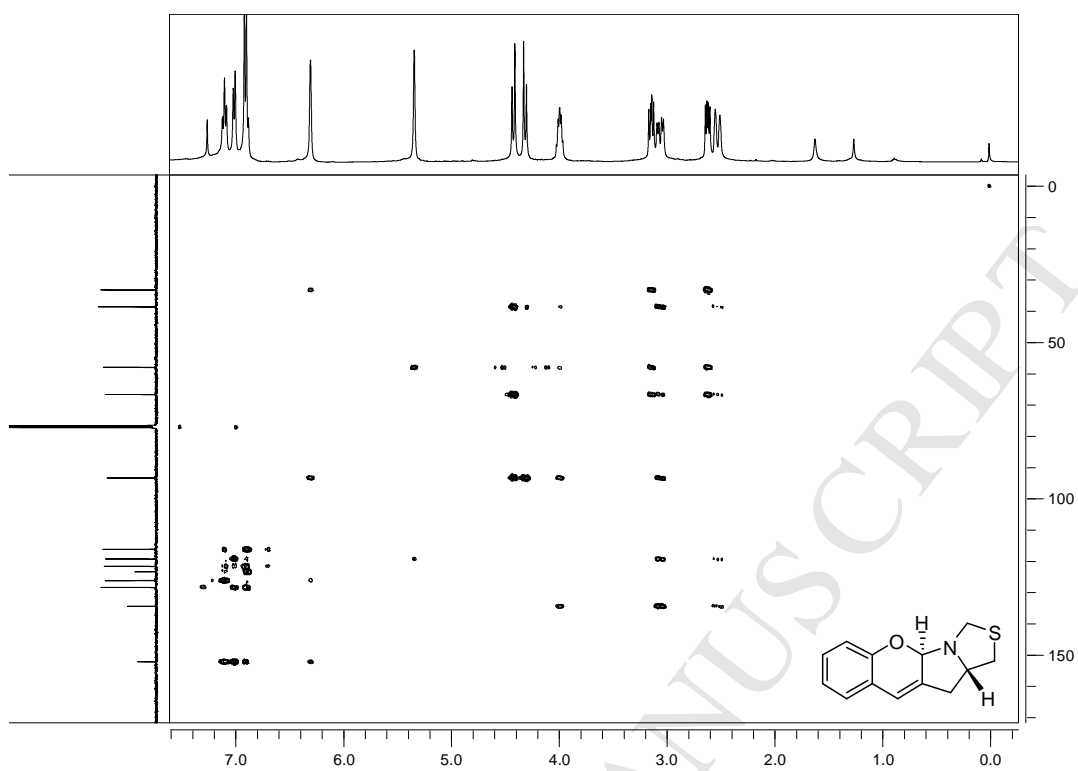


Figure S29. HMBC spectrum of compound 26.

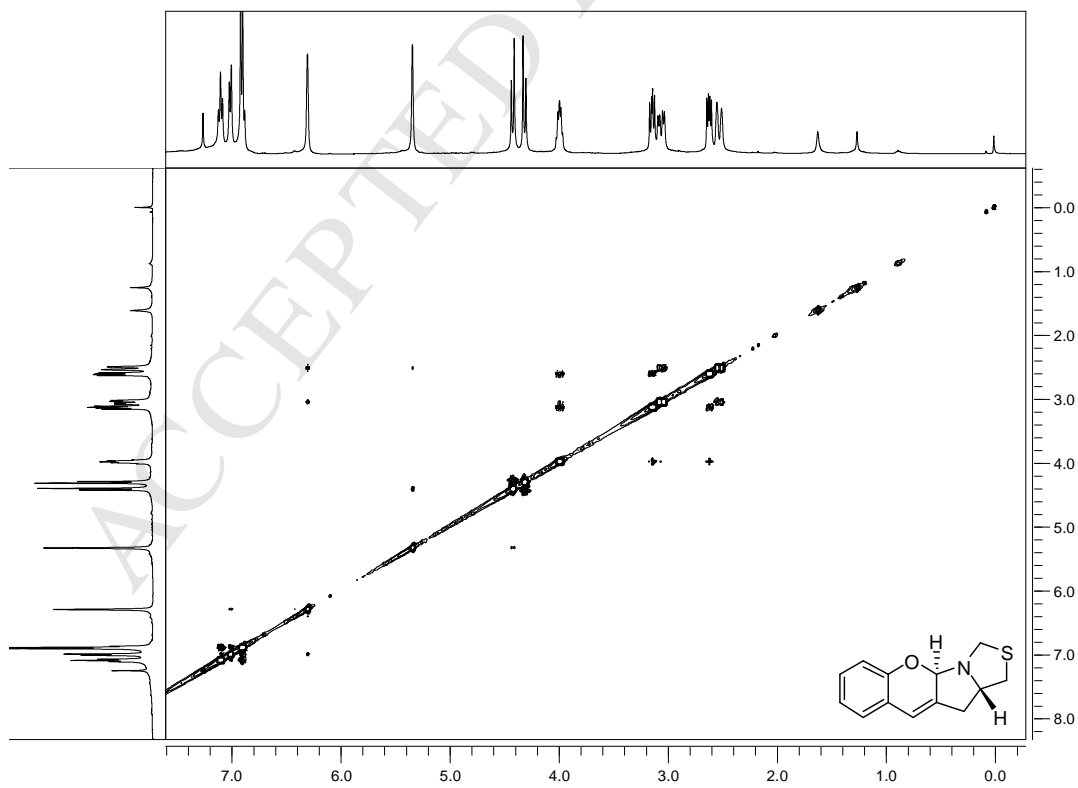


Figure S30. NOESY spectrum of compound 26.

2. Crystallographic data for ethyl 7a,8,10,11a-tetrahydro-6H-chromeno[3',4':4,5]pyrrolo[1,2-c]thiazole-7-carboxylate (**23**)

A crystal of compound **23** was selected, covered with polyfluoroether oil, and mounted on a nylon loop. Crystallographic data for this compound was collected at the IST using graphite monochromated Mo-K α radiation ($\lambda=0.71073\text{\AA}$) on a Bruker AXS-KAPPA APEX II diffractometer equipped with an Oxford Cryosystem open-flow nitrogen cryostat, at 150 K. Cell parameters were retrieved using Bruker SMART software and refined using Bruker SAINT on all observed reflections. Absorption corrections were applied using SADABS.¹ Structure solution and refinement were performed using direct methods with the program SIR2004² included in the package of programs WINGX-Version 1.80.05³ and SHELXL.⁴ All hydrogen atoms were inserted in idealised positions and allowed to refine riding on the parent carbon atom, with C-H distances of 0.95 \AA , 0.98 \AA , 0.99 \AA and 1.0 \AA for aromatic, methyl, methylene and methine H atoms, respectively, and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$. The figure of the molecular structure was generated using ORTEP-III.⁵

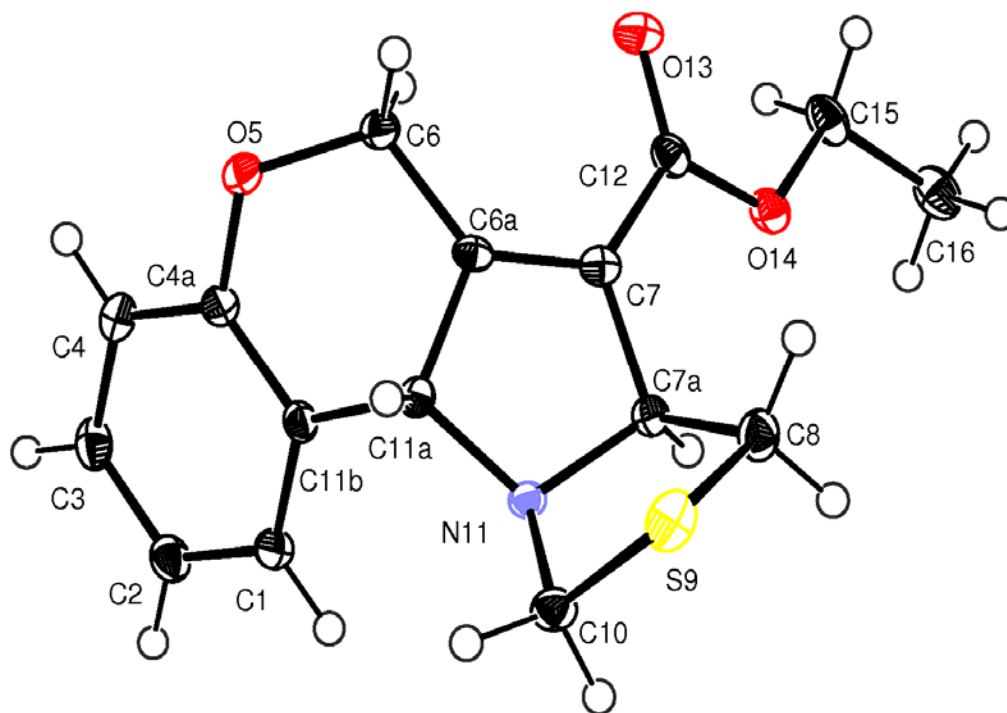


Figure S31. ORTEP-3 diagram of compound **23**, using 50% probability level ellipsoids. For clarity reasons, only one of the molecules present in the asymmetric unit is shown.

Table S1. Crystal data and structure refinement for compound **23**.

Empirical formula	C ₁₆ H ₁₇ N O ₃ S
Formula weight	303.37
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	<i>P c a 2</i> ₁
Unit cell dimensions	a = 23.4004(6) Å α = 90°. b = 6.9636(2) Å β = 90°. c = 17.3619(4) Å γ = 90°.
Volume	2829.14(13) Å ³
Z	8
Density (calculated)	1.424 Mg/m ³
Absorption coefficient	0.239 mm ⁻¹
F(000)	1280
Crystal size	0.50 x 0.40 x 0.20 mm ³
Theta range for data collection	2.10 to 30.34°.
Index ranges	-32 ≤ h ≤ 33, -9 ≤ k ≤ 9, -24 ≤ l ≤ 24
Reflections collected	32535
Independent reflections	8484 [R(int) = 0.0472]
Completeness to theta = 30.34°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9538 and 0.8900
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	8484 / 1 / 381
Goodness-of-fit on F ²	1.043
Final R indices [I > 2σ(I)]	R1 = 0.0366, wR2 = 0.0860
R indices (all data)	R1 = 0.0444, wR2 = 0.0892
Absolute structure parameter	0.04(4)
Largest diff. peak and hole	0.315 and -0.235 e.Å ⁻³

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **23**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S(9)	848(1)	-6856(1)	5178(1)	22(1)
S(25)	1746(1)	2249(1)	3036(1)	23(1)
O(5)	-462(1)	-17(2)	5961(1)	20(1)
O(13)	1297(1)	145(2)	6784(1)	26(1)
O(14)	1944(1)	-668(2)	5875(1)	18(1)
O(21)	3010(1)	-4624(2)	2232(1)	21(1)
O(29)	1262(1)	-4486(2)	1398(1)	23(1)
O(30)	608(1)	-3566(2)	2277(1)	18(1)
N(11)	643(1)	-3378(2)	4640(1)	14(1)
N(27)	1939(1)	-1225(2)	3588(1)	14(1)
C(10)	588(1)	-5340(2)	4388(1)	18(1)
C(8)	1419(1)	-5150(2)	5328(1)	20(1)
C(7A)	1186(1)	-3139(2)	5078(1)	14(1)
C(7)	1019(1)	-1846(2)	5735(1)	14(1)
C(6A)	452(1)	-1637(2)	5772(1)	13(1)
C(6)	100(1)	-358(2)	6277(1)	15(1)
C(4A)	-481(1)	178(2)	5164(1)	17(1)
C(4)	-814(1)	1618(3)	4851(1)	21(1)
C(3)	-856(1)	1759(3)	4051(1)	21(1)
C(2)	-559(1)	486(3)	3580(1)	21(1)
C(1)	-219(1)	-932(2)	3904(1)	17(1)
C(11B)	-183(1)	-1112(2)	4698(1)	14(1)
C(11A)	168(1)	-2632(2)	5110(1)	13(1)
C(12)	1421(1)	-719(2)	6202(1)	17(1)
C(15)	2350(1)	668(3)	6219(1)	22(1)
C(16)	2917(1)	371(3)	5829(1)	26(1)
C(26)	2014(1)	746(2)	3826(1)	19(1)
C(24)	1159(1)	588(2)	2938(1)	21(1)
C(23A)	1391(1)	-1424(2)	3157(1)	14(1)
C(23)	1552(1)	-2659(2)	2482(1)	13(1)
C(22A)	2113(1)	-2940(2)	2441(1)	14(1)
C(22)	2452(1)	-4211(2)	1924(1)	16(1)

C(20A)	3029(1)	-4896(2)	3024(1)	17(1)
C(20)	3352(1)	-6389(3)	3312(1)	20(1)
C(19)	3398(1)	-6598(2)	4108(1)	22(1)
C(18)	3113(1)	-5343(3)	4599(1)	21(1)
C(17)	2781(1)	-3867(2)	4299(1)	17(1)
C(27B)	2742(1)	-3611(2)	3506(1)	14(1)
C(27A)	2408(1)	-2025(2)	3119(1)	14(1)
C(28)	1140(1)	-3644(2)	1985(1)	16(1)
C(31)	183(1)	-4648(3)	1853(1)	22(1)
C(32)	-360(1)	-4640(3)	2312(1)	29(1)

Table S3. Bond lengths [Å] and angles [°] for **23**.

S(9)-C(8)	1.8057(17)
S(9)-C(10)	1.8355(17)
S(25)-C(24)	1.8037(17)
S(25)-C(26)	1.8359(18)
O(5)-C(4A)	1.392(2)
O(5)-C(6)	1.4443(19)
O(13)-C(12)	1.210(2)
O(14)-C(12)	1.3493(19)
O(14)-C(15)	1.4576(19)
O(21)-C(20A)	1.389(2)
O(21)-C(22)	1.4398(19)
O(29)-C(28)	1.2098(19)
O(30)-C(28)	1.3454(19)
O(30)-C(31)	1.4481(19)
N(11)-C(10)	1.441(2)
N(11)-C(11A)	1.4728(19)
N(11)-C(7A)	1.4889(19)
N(27)-C(26)	1.444(2)
N(27)-C(27A)	1.4740(19)
N(27)-C(23A)	1.4904(19)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(8)-C(7A)	1.564(2)

C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(7A)-C(7)	1.504(2)
C(7A)-H(7A)	1.0000
C(7)-C(6A)	1.337(2)
C(7)-C(12)	1.469(2)
C(6A)-C(6)	1.497(2)
C(6A)-C(11A)	1.497(2)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(4A)-C(4)	1.381(2)
C(4A)-C(11B)	1.394(2)
C(4)-C(3)	1.395(2)
C(4)-H(4)	0.9500
C(3)-C(2)	1.392(2)
C(3)-H(3)	0.9500
C(2)-C(1)	1.388(2)
C(2)-H(2)	0.9500
C(1)-C(11B)	1.386(2)
C(1)-H(1)	0.9500
C(11B)-C(11A)	1.520(2)
C(11A)-H(11A)	1.0000
C(15)-C(16)	1.504(3)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(26)-H(26A)	0.9900
C(26)-H(26B)	0.9900
C(24)-C(23A)	1.550(2)
C(24)-H(24A)	0.9900
C(24)-H(24B)	0.9900
C(23A)-C(23)	1.502(2)
C(23A)-H(23A)	1.0000
C(23)-C(22A)	1.329(2)
C(23)-C(28)	1.465(2)
C(22A)-C(22)	1.489(2)

C(22A)-C(27A)	1.507(2)
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(20A)-C(20)	1.380(2)
C(20A)-C(27B)	1.398(2)
C(20)-C(19)	1.395(2)
C(20)-H(20)	0.9500
C(19)-C(18)	1.391(3)
C(19)-H(19)	0.9500
C(18)-C(17)	1.389(2)
C(18)-H(18)	0.9500
C(17)-C(27B)	1.391(2)
C(17)-H(17)	0.9500
C(27B)-C(27A)	1.511(2)
C(27A)-H(27A)	1.0000
C(31)-C(32)	1.501(2)
C(31)-H(31A)	0.9900
C(31)-H(31B)	0.9900
C(32)-H(32A)	0.9800
C(32)-H(32B)	0.9800
C(32)-H(32C)	0.9800
C(8)-S(9)-C(10)	88.57(8)
C(24)-S(25)-C(26)	87.99(8)
C(4A)-O(5)-C(6)	114.98(11)
C(12)-O(14)-C(15)	115.81(13)
C(20A)-O(21)-C(22)	115.02(11)
C(28)-O(30)-C(31)	114.92(12)
C(10)-N(11)-C(11A)	115.77(12)
C(10)-N(11)-C(7A)	109.79(12)
C(11A)-N(11)-C(7A)	108.75(11)
C(26)-N(27)-C(27A)	115.29(12)
C(26)-N(27)-C(23A)	109.63(12)
C(27A)-N(27)-C(23A)	109.15(11)
N(11)-C(10)-S(9)	106.70(11)
N(11)-C(10)-H(10A)	110.4
S(9)-C(10)-H(10A)	110.4
N(11)-C(10)-H(10B)	110.4

S(9)-C(10)-H(10B)	110.4
H(10A)-C(10)-H(10B)	108.6
C(7A)-C(8)-S(9)	106.94(11)
C(7A)-C(8)-H(8A)	110.3
S(9)-C(8)-H(8A)	110.3
C(7A)-C(8)-H(8B)	110.3
S(9)-C(8)-H(8B)	110.3
H(8A)-C(8)-H(8B)	108.6
N(11)-C(7A)-C(7)	103.46(12)
N(11)-C(7A)-C(8)	109.80(12)
C(7)-C(7A)-C(8)	114.63(13)
N(11)-C(7A)-H(7A)	109.6
C(7)-C(7A)-H(7A)	109.6
C(8)-C(7A)-H(7A)	109.6
C(6A)-C(7)-C(12)	123.37(14)
C(6A)-C(7)-C(7A)	111.05(13)
C(12)-C(7)-C(7A)	124.96(14)
C(7)-C(6A)-C(6)	129.75(14)
C(7)-C(6A)-C(11A)	110.65(13)
C(6)-C(6A)-C(11A)	118.76(13)
O(5)-C(6)-C(6A)	112.14(12)
O(5)-C(6)-H(6A)	109.2
C(6A)-C(6)-H(6A)	109.2
O(5)-C(6)-H(6B)	109.2
C(6A)-C(6)-H(6B)	109.2
H(6A)-C(6)-H(6B)	107.9
C(4)-C(4A)-O(5)	118.69(14)
C(4)-C(4A)-C(11B)	121.41(16)
O(5)-C(4A)-C(11B)	119.86(14)
C(4A)-C(4)-C(3)	118.83(16)
C(4A)-C(4)-H(4)	120.6
C(3)-C(4)-H(4)	120.6
C(2)-C(3)-C(4)	120.34(15)
C(2)-C(3)-H(3)	119.8
C(4)-C(3)-H(3)	119.8
C(1)-C(2)-C(3)	120.04(15)
C(1)-C(2)-H(2)	120.0
C(3)-C(2)-H(2)	120.0

C(11B)-C(1)-C(2)	120.11(15)
C(11B)-C(1)-H(1)	119.9
C(2)-C(1)-H(1)	119.9
C(1)-C(11B)-C(4A)	119.24(14)
C(1)-C(11B)-C(11A)	124.23(14)
C(4A)-C(11B)-C(11A)	116.53(13)
N(11)-C(11A)-C(6A)	104.69(11)
N(11)-C(11A)-C(11B)	113.23(12)
C(6A)-C(11A)-C(11B)	106.19(12)
N(11)-C(11A)-H(11A)	110.8
C(6A)-C(11A)-H(11A)	110.8
C(11B)-C(11A)-H(11A)	110.8
O(13)-C(12)-O(14)	123.76(15)
O(13)-C(12)-C(7)	124.94(15)
O(14)-C(12)-C(7)	111.19(13)
O(14)-C(15)-C(16)	107.63(14)
O(14)-C(15)-H(15A)	110.2
C(16)-C(15)-H(15A)	110.2
O(14)-C(15)-H(15B)	110.2
C(16)-C(15)-H(15B)	110.2
H(15A)-C(15)-H(15B)	108.5
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
N(27)-C(26)-S(25)	106.65(11)
N(27)-C(26)-H(26A)	110.4
S(25)-C(26)-H(26A)	110.4
N(27)-C(26)-H(26B)	110.4
S(25)-C(26)-H(26B)	110.4
H(26A)-C(26)-H(26B)	108.6
C(23A)-C(24)-S(25)	106.80(11)
C(23A)-C(24)-H(24A)	110.4
S(25)-C(24)-H(24A)	110.4
C(23A)-C(24)-H(24B)	110.4
S(25)-C(24)-H(24B)	110.4

H(24A)-C(24)-H(24B)	108.6
N(27)-C(23A)-C(23)	103.27(11)
N(27)-C(23A)-C(24)	109.94(12)
C(23)-C(23A)-C(24)	114.44(13)
N(27)-C(23A)-H(23A)	109.7
C(23)-C(23A)-H(23A)	109.7
C(24)-C(23A)-H(23A)	109.7
C(22A)-C(23)-C(28)	123.33(14)
C(22A)-C(23)-C(23A)	111.93(13)
C(28)-C(23)-C(23A)	124.29(13)
C(23)-C(22A)-C(22)	130.29(14)
C(23)-C(22A)-C(27A)	110.34(13)
C(22)-C(22A)-C(27A)	118.57(13)
O(21)-C(22)-C(22A)	112.27(13)
O(21)-C(22)-H(22A)	109.2
C(22A)-C(22)-H(22A)	109.2
O(21)-C(22)-H(22B)	109.2
C(22A)-C(22)-H(22B)	109.2
H(22A)-C(22)-H(22B)	107.9
C(20)-C(20A)-O(21)	118.61(14)
C(20)-C(20A)-C(27B)	121.90(16)
O(21)-C(20A)-C(27B)	119.43(14)
C(20A)-C(20)-C(19)	118.69(16)
C(20A)-C(20)-H(20)	120.7
C(19)-C(20)-H(20)	120.7
C(18)-C(19)-C(20)	120.32(16)
C(18)-C(19)-H(19)	119.8
C(20)-C(19)-H(19)	119.8
C(17)-C(18)-C(19)	120.27(16)
C(17)-C(18)-H(18)	119.9
C(19)-C(18)-H(18)	119.9
C(18)-C(17)-C(27B)	120.12(15)
C(18)-C(17)-H(17)	119.9
C(27B)-C(17)-H(17)	119.9
C(17)-C(27B)-C(20A)	118.67(14)
C(17)-C(27B)-C(27A)	124.60(14)
C(20A)-C(27B)-C(27A)	116.73(14)
N(27)-C(27A)-C(22A)	104.52(12)

N(27)-C(27A)-C(27B)	114.56(13)
C(22A)-C(27A)-C(27B)	105.98(12)
N(27)-C(27A)-H(27A)	110.5
C(22A)-C(27A)-H(27A)	110.5
C(27B)-C(27A)-H(27A)	110.5
O(29)-C(28)-O(30)	123.88(14)
O(29)-C(28)-C(23)	124.52(14)
O(30)-C(28)-C(23)	111.56(13)
O(30)-C(31)-C(32)	108.03(14)
O(30)-C(31)-H(31A)	110.1
C(32)-C(31)-H(31A)	110.1
O(30)-C(31)-H(31B)	110.1
C(32)-C(31)-H(31B)	110.1
H(31A)-C(31)-H(31B)	108.4
C(31)-C(32)-H(32A)	109.5
C(31)-C(32)-H(32B)	109.5
H(32A)-C(32)-H(32B)	109.5
C(31)-C(32)-H(32C)	109.5
H(32A)-C(32)-H(32C)	109.5
H(32B)-C(32)-H(32C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **23**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(9)	24(1)	13(1)	29(1)	5(1)	5(1)	1(1)
S(25)	26(1)	14(1)	29(1)	4(1)	4(1)	-1(1)
O(5)	17(1)	30(1)	14(1)	0(1)	2(1)	6(1)
O(13)	26(1)	32(1)	20(1)	-9(1)	-2(1)	0(1)
O(14)	16(1)	17(1)	20(1)	-2(1)	-3(1)	-4(1)
O(21)	16(1)	30(1)	16(1)	0(1)	3(1)	5(1)
O(29)	23(1)	28(1)	16(1)	-7(1)	-1(1)	2(1)
O(30)	16(1)	20(1)	17(1)	-5(1)	-2(1)	-4(1)
N(11)	16(1)	12(1)	12(1)	-1(1)	0(1)	1(1)

N(27)	13(1)	15(1)	14(1)	-2(1)	2(1)	-2(1)
C(10)	20(1)	15(1)	19(1)	-3(1)	-1(1)	-1(1)
C(8)	19(1)	16(1)	24(1)	0(1)	-2(1)	3(1)
C(7A)	14(1)	14(1)	15(1)	0(1)	0(1)	-1(1)
C(7)	18(1)	11(1)	13(1)	3(1)	1(1)	-1(1)
C(6A)	18(1)	11(1)	9(1)	2(1)	-1(1)	-1(1)
C(6)	16(1)	16(1)	14(1)	0(1)	0(1)	1(1)
C(4A)	14(1)	21(1)	14(1)	-1(1)	0(1)	0(1)
C(4)	15(1)	23(1)	23(1)	-1(1)	2(1)	4(1)
C(3)	16(1)	25(1)	23(1)	6(1)	-1(1)	3(1)
C(2)	18(1)	28(1)	16(1)	4(1)	-1(1)	0(1)
C(1)	16(1)	21(1)	16(1)	-2(1)	0(1)	-1(1)
C(11B)	11(1)	17(1)	15(1)	1(1)	-1(1)	-1(1)
C(11A)	12(1)	13(1)	14(1)	1(1)	2(1)	-1(1)
C(12)	18(1)	16(1)	16(1)	3(1)	-3(1)	1(1)
C(15)	21(1)	19(1)	27(1)	-1(1)	-10(1)	-4(1)
C(16)	22(1)	31(1)	24(1)	5(1)	-3(1)	-7(1)
C(26)	21(1)	18(1)	18(1)	-5(1)	0(1)	-1(1)
C(24)	19(1)	18(1)	25(1)	-2(1)	0(1)	3(1)
C(23A)	13(1)	16(1)	13(1)	0(1)	2(1)	-3(1)
C(23)	16(1)	13(1)	11(1)	2(1)	1(1)	-2(1)
C(22A)	19(1)	12(1)	11(1)	2(1)	1(1)	-2(1)
C(22)	18(1)	16(1)	14(1)	0(1)	1(1)	3(1)
C(20A)	13(1)	21(1)	17(1)	1(1)	2(1)	-1(1)
C(20)	14(1)	20(1)	26(1)	0(1)	1(1)	1(1)
C(19)	15(1)	20(1)	30(1)	6(1)	-4(1)	-1(1)
C(18)	18(1)	25(1)	19(1)	4(1)	-4(1)	-5(1)
C(17)	15(1)	20(1)	18(1)	-1(1)	0(1)	-3(1)
C(27B)	11(1)	16(1)	17(1)	2(1)	-2(1)	-3(1)
C(27A)	14(1)	14(1)	13(1)	0(1)	1(1)	-1(1)
C(28)	17(1)	15(1)	14(1)	2(1)	-1(1)	0(1)
C(31)	19(1)	23(1)	23(1)	-8(1)	-5(1)	-3(1)
C(32)	22(1)	37(1)	28(1)	-7(1)	-2(1)	-12(1)

Table S5. Torsion angles [°] for **23**.

C(11A)-N(11)-C(10)-S(9)	-84.35(13)
C(7A)-N(11)-C(10)-S(9)	39.23(14)
C(8)-S(9)-C(10)-N(11)	-40.58(11)
C(10)-S(9)-C(8)-C(7A)	29.73(11)
C(10)-N(11)-C(7A)-C(7)	-139.55(13)
C(11A)-N(11)-C(7A)-C(7)	-11.96(15)
C(10)-N(11)-C(7A)-C(8)	-16.75(17)
C(11A)-N(11)-C(7A)-C(8)	110.84(14)
S(9)-C(8)-C(7A)-N(11)	-13.32(15)
S(9)-C(8)-C(7A)-C(7)	102.62(13)
N(11)-C(7A)-C(7)-C(6A)	10.20(16)
C(8)-C(7A)-C(7)-C(6A)	-109.33(15)
N(11)-C(7A)-C(7)-C(12)	-161.00(14)
C(8)-C(7A)-C(7)-C(12)	79.47(18)
C(12)-C(7)-C(6A)-C(6)	-2.3(2)
C(7A)-C(7)-C(6A)-C(6)	-173.66(14)
C(12)-C(7)-C(6A)-C(11A)	166.87(13)
C(7A)-C(7)-C(6A)-C(11A)	-4.50(17)
C(4A)-O(5)-C(6)-C(6A)	-37.50(18)
C(7)-C(6A)-C(6)-O(5)	158.53(15)
C(11A)-C(6A)-C(6)-O(5)	-9.89(19)
C(6)-O(5)-C(4A)-C(4)	-136.76(15)
C(6)-O(5)-C(4A)-C(11B)	45.50(19)
O(5)-C(4A)-C(4)-C(3)	-176.92(15)
C(11B)-C(4A)-C(4)-C(3)	0.8(2)
C(4A)-C(4)-C(3)-C(2)	-1.0(3)
C(4)-C(3)-C(2)-C(1)	-0.1(3)
C(3)-C(2)-C(1)-C(11B)	1.4(2)
C(2)-C(1)-C(11B)-C(4A)	-1.7(2)
C(2)-C(1)-C(11B)-C(11A)	178.98(14)
C(4)-C(4A)-C(11B)-C(1)	0.6(2)
O(5)-C(4A)-C(11B)-C(1)	178.26(14)
C(4)-C(4A)-C(11B)-C(11A)	179.96(14)
O(5)-C(4A)-C(11B)-C(11A)	-2.4(2)
C(10)-N(11)-C(11A)-C(6A)	133.77(13)
C(7A)-N(11)-C(11A)-C(6A)	9.65(15)

C(10)-N(11)-C(11A)-C(11B)	-111.01(15)
C(7A)-N(11)-C(11A)-C(11B)	124.87(13)
C(7)-C(6A)-C(11A)-N(11)	-3.22(16)
C(6)-C(6A)-C(11A)-N(11)	167.29(12)
C(7)-C(6A)-C(11A)-C(11B)	-123.26(13)
C(6)-C(6A)-C(11A)-C(11B)	47.25(17)
C(1)-C(11B)-C(11A)-N(11)	23.8(2)
C(4A)-C(11B)-C(11A)-N(11)	-155.56(13)
C(1)-C(11B)-C(11A)-C(6A)	138.11(15)
C(4A)-C(11B)-C(11A)-C(6A)	-41.23(17)
C(15)-O(14)-C(12)-O(13)	-6.2(2)
C(15)-O(14)-C(12)-C(7)	170.13(13)
C(6A)-C(7)-C(12)-O(13)	18.9(2)
C(7A)-C(7)-C(12)-O(13)	-170.98(16)
C(6A)-C(7)-C(12)-O(14)	-157.42(14)
C(7A)-C(7)-C(12)-O(14)	12.7(2)
C(12)-O(14)-C(15)-C(16)	174.49(14)
C(27A)-N(27)-C(26)-S(25)	85.71(13)
C(23A)-N(27)-C(26)-S(25)	-37.91(14)
C(24)-S(25)-C(26)-N(27)	41.37(11)
C(26)-S(25)-C(24)-C(23A)	-32.34(11)
C(26)-N(27)-C(23A)-C(23)	136.09(13)
C(27A)-N(27)-C(23A)-C(23)	8.93(15)
C(26)-N(27)-C(23A)-C(24)	13.56(16)
C(27A)-N(27)-C(23A)-C(24)	-113.59(14)
S(25)-C(24)-C(23A)-N(27)	17.04(15)
S(25)-C(24)-C(23A)-C(23)	-98.61(13)
N(27)-C(23A)-C(23)-C(22A)	-7.76(16)
C(24)-C(23A)-C(23)-C(22A)	111.72(15)
N(27)-C(23A)-C(23)-C(28)	164.80(13)
C(24)-C(23A)-C(23)-C(28)	-75.72(18)
C(28)-C(23)-C(22A)-C(22)	0.3(2)
C(23A)-C(23)-C(22A)-C(22)	172.96(15)
C(28)-C(23)-C(22A)-C(27A)	-169.09(13)
C(23A)-C(23)-C(22A)-C(27A)	3.56(17)
C(20A)-O(21)-C(22)-C(22A)	38.21(18)
C(23)-C(22A)-C(22)-O(21)	-159.27(15)
C(27A)-C(22A)-C(22)-O(21)	9.40(19)

C(22)-O(21)-C(20A)-C(20)	136.77(15)
C(22)-O(21)-C(20A)-C(27B)	-45.92(19)
O(21)-C(20A)-C(20)-C(19)	176.38(14)
C(27B)-C(20A)-C(20)-C(19)	-0.9(2)
C(20A)-C(20)-C(19)-C(18)	1.3(2)
C(20)-C(19)-C(18)-C(17)	-0.2(2)
C(19)-C(18)-C(17)-C(27B)	-1.4(2)
C(18)-C(17)-C(27B)-C(20A)	1.8(2)
C(18)-C(17)-C(27B)-C(27A)	-178.24(14)
C(20)-C(20A)-C(27B)-C(17)	-0.6(2)
O(21)-C(20A)-C(27B)-C(17)	-177.86(14)
C(20)-C(20A)-C(27B)-C(27A)	179.36(14)
O(21)-C(20A)-C(27B)-C(27A)	2.1(2)
C(26)-N(27)-C(27A)-C(22A)	-131.01(13)
C(23A)-N(27)-C(27A)-C(22A)	-7.13(15)
C(26)-N(27)-C(27A)-C(27B)	113.45(15)
C(23A)-N(27)-C(27A)-C(27B)	-122.67(13)
C(23)-C(22A)-C(27A)-N(27)	2.25(16)
C(22)-C(22A)-C(27A)-N(27)	-168.56(13)
C(23)-C(22A)-C(27A)-C(27B)	123.64(13)
C(22)-C(22A)-C(27A)-C(27B)	-47.17(17)
C(17)-C(27B)-C(27A)-N(27)	-23.9(2)
C(20A)-C(27B)-C(27A)-N(27)	156.13(13)
C(17)-C(27B)-C(27A)-C(22A)	-138.56(15)
C(20A)-C(27B)-C(27A)-C(22A)	41.45(17)
C(31)-O(30)-C(28)-O(29)	2.6(2)
C(31)-O(30)-C(28)-C(23)	-174.94(13)
C(22A)-C(23)-C(28)-O(29)	-15.8(2)
C(23A)-C(23)-C(28)-O(29)	172.48(15)
C(22A)-C(23)-C(28)-O(30)	161.74(14)
C(23A)-C(23)-C(28)-O(30)	-10.0(2)
C(28)-O(30)-C(31)-C(32)	172.11(15)

Symmetry transformations used to generate equivalent atoms:

3. References

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