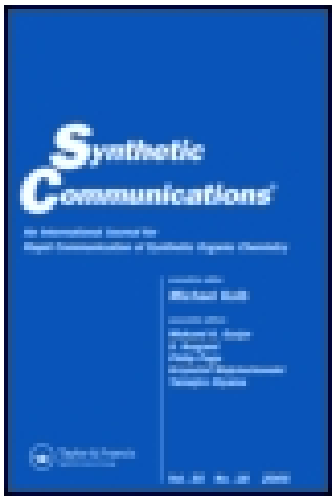

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Synthesis of Novel Dispiro 1,4-Benzothiazine Hybrid Heterocycles Through 1,3-Dipolar Cycloaddition

Malathi Karuppiah[a], Jeyachandran Veerappan[a], Kalaiselvan Karumpan[a] & Raju Ranjith Kumar[a]

[a] Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai, Tamil Nadu, India

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SYNTHESIS OF NOVEL DISPIRO 1,4-BENZOTHIAZINE HYBRID HETEROCYCLES THROUGH 1,3-DIPOLAR CYCLOADDITION

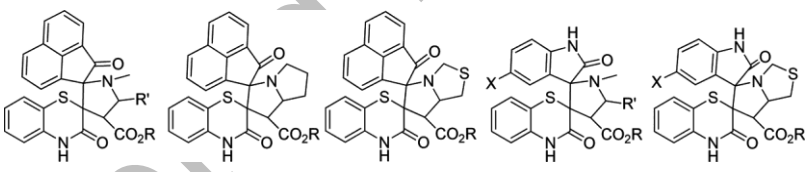
Malathi Karuppiah[1], Jeyachandran Veerappan[1], Kalaiselvan Karumpan[1], Raju Ranjith Kumar[1]

[1]Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University Madurai, Tamil Nadu, India

Address correspondence to Raju Ranjith Kumar, Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625021, Tamil Nadu, India. E-mail: raju.ranjithkumar@gmail.com

Abstract

The 1,3-dipolar cycloaddition of azomethine ylides generated in situ from the reaction of acenaphthylene-1,2-dione or isatins and α-amino acids to (E)-methyl/ethyl 2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]thiazin-2-ylidene)acetate led to the stereoselective formation of novel dispiro 1,4-benzothiazine hybrid heterocycles in good yields.



KEYWORDS: 1,3-Dipolar cycloaddition, Azomethine ylide, Dispiro oxindole, Pyrrolidine, Pyrrolizine

INTRODUCTION

1,3-Dipolar cycloadditions form a subject of intensive research in organic synthesis in view of their enormous synthetic applications.[1] In particular, the cycloaddition of non-stabilized azomethine ylides generated *in situ* from the decarboxylative condensation of

α-amino acids and non-enolizable 1,2-diketones to exocyclic olefins represent one of the most convergent approaches for the construction of novel dispiro oxindole or acenaphthene–pyrrolidine, pyrrolizine, pyrrolothiazole or octahydroindolizine hybrid heterocycles.[2] Spiro oxindoles are present in many natural products such as coerulescine, horsfiline and elacomine, which are endowed with wide range of biological activities.[3] Furthermore, compounds constituting spiro pyrrolidine motif exhibit significant biological activities such as anticonvulsant,[4] potential antileukaemic,[5] local anaesthetic[6] and antiviral.[7]

On the other hand, 1,4-benzothiazines[8] are significant class of heterocycles possessing wide spectrum of biological activities such as analgesic,[9] anticancer,[10] antifungal,[11] antibacterial,[12] antitubercular,[13] antithyroid[14] and calcium antagonist.[15] These heterocycles form the core of antibiotic and cholesterol lowering drugs.[16] In addition, 1,4-benzothiazines are also known for their applications as dyes, photographic developers and UV absorbers.[17]

The importance of spiro compounds and 1,4-benzothiazines, prompted us to envisage the construct novel hybrids comprising the above motifs. In this context, the present work discloses the outcome of 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the decarboxylative condensation of various α-amino acids with acenaphthenequinone or isatins to 1,4-benzothiazine dipolarophiles comprising an excocyclic alkene. Acenaphthenequinone, though less explored in terms of biological activity, is a versatile precursor for azomethine ylide cycloaddition as it reacts with α-

amino acids generating reactive 1,3-dipoles. The present work also pertains to our continuous effort in the synthesis of novel dispiro hybrid heterocycles employing 1,3-dipolar cycloaddition reactions.[18]

RESULTS AND DISCUSSION

Initially, the dipolarophiles *viz*. (*E*)-methyl or ethyl 2-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazin-2-ylidene)acetate **3** were synthesized from the reaction of 2-aminothiophenol **1** with DMAD **2a** or DEAD **2b** respectively (**Scheme 1**) following a literature procedure.[19] The structure of the exocyclic dipolarophiles **3a** and **3b** was elucidated with the help of NMR spectroscopy. The melting point and the NMR data of these synthesized exocyclic dipolarophiles **3a** and **3b** agree well with those reported in the literature.

Subsequently, the 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the reaction of sarcosine **5**, phenylglycine **6**, proline **7** or 1,3-thiazolane-4-carboxylic acid **8** with acenaphthenequinone **4** to the above dipolarophiles **3a** and **3b** afforded novel dispiro 1,4-benzothiazine hybrid heterocycles **9–12** (**Scheme 2**). The cycloadditions were effected by heating an equimolar mixture of the reactants to reflux in ethanol on a water bath. After the reaction was complete as evident from TLC the reaction mixture was poured into ice water and the resultant solid was subjected to column chromatography to obtain pure product.

The reaction proceeds *via* the generation of azomethine ylide **A** *in situ* from the

decarboxylative condensation of acenaphthenequinone **4** and α-amino acids, which then reacts with the exocyclic dipolarophiles **3** to afford the dispiro hybrid heterocycles **9–12** (**Scheme 3**). It is well known that the azomethine ylide exists in resonance forms **A** and **B**, either of which can react with the dipolarophile **3** to afford the respective isomers (**Scheme 3**). However, the above cycloaddition occurs selectively involving the dipolarophile **A** leading to the formation of **9**. The other isomer **9′** arising from the cycloadditon of dipole **B** is not obtained in the course of the reaction, which may presumably be attributed to the steric factors. This selectivity is also apparent form the ^{1}H NMR spectrum of the product **9**, wherein three triplets due to H-4′ and H-5′ are observed in the range 3–4 ppm. If the other isomer **9′** was formed, a singlet would have been expected due to H-3′ instead of a triplet. In addition, the above cycloaddition reaction occur stereoselectively resulting in the exclusive formation of one diastereomer in all the cases **9–12**, although up to four new contiguous stereo centers are generated during the course of the cycloaddition in a single step.

The structure of all the dispiro 1,4-benzothiazine hybrid heterocycles **9–12** was elucidated with the help of one- and two- dimensional NMR spectroscopy. As a representative case the ^{1}H and ^{13}C chemical shift assignment of **12b** are discussed. In the ^{1}H NMR spectrum of **12b**, a triplet and a quartet at 1.28 and 4.23 ppm (J = 7.2 Hz) can be readily assigned to the protons of the -OEt group. The C,H-COSY correlation of these protons assigns the carbon signals at 13.3 and 60.5 ppm to -CH_3 and -CH_2 carbons respectively. Further, the HMBC correlation of the above –CH_2 protons assigns the signal at 167.8 ppm to the carboxylate carbon. A doublet at 4.59 ppm with J value 10.2 Hz can

be assigned to H-7′ on the basis of its multiplicity. This proton shows C,H-COSY correlation with a carbon signal at 51.6 ppm assigning it to 7′-C. From the HMBC correlation of H-7′ the 3-C amide carbonyl carbon appears at 161.7 ppm. Further, H-7′ has a H,H-COSY correlation with a multiplet at 4.84–4.87 ppm, which can be assigned to H-7a′. The C,H-COSY correlation of H-7a′ assigns the carbon signal at 66.9 ppm to 7a′-C. It is evident from the H,H-COSY correlation of H-7a′ that the doublets of doublets at 3.11 and 3.33 ppm (J = 11.1, 6.3 Hz) are due to 1′-CH_2 and from the C,H-COSY spectrum it is clear that 1′-CH_2 carbon appears at 35.0 ppm. The two doublets at 3.42 and 3.78 ppm with J = 8.7 Hz which can be assigned to 3′-CH_2 protons show (i) C,H-COSY correlation with a carbon signal at 50.5 ppm due to 3′-C and (ii) HMBC correlation with one of the spiro carbons 5′-C at 79.6 ppm thereby assigning the carbon signal at 63.0 to the other spiro carbon 6′-C. The NH of the 1,4-benzothiazine ring appears as singlet at 9.74 ppm and shows HMBC correlation with the 2-C spiro carbon at 63.0 ppm. The doublet at 5.89 ppm (J = 7.8 Hz) and the triplet at 6.70 ppm (J = 7.8 Hz) can be assigned to H-5 and H-7 respectively on the basis of the shielding effect of NH through resonance. The H,H-COSY correlations of the above protons assigns the triplet and doublet at 6.79 and 7.08 ppm (J = 7.5 Hz) to 6-C and 8-C respectively whereas the C,H-COSY correlations assigns the carbon signals at 115.2, 122.3, 126.9 and 127.6 ppm to 5-C to 8-C respectively. The two doublets observed at 7.26 ppm (J = 6.9 Hz) and 7.91 ppm (J = 7.2 Hz) can be assigned to 8″- and 3″-CH protons respectively from the fact that the former shows HMBC correlation with the C-1″ carbonyl carbon at 200.1 ppm and the latter shows with the spiro carbon 5′-C at 79.6 ppm. Further, from the H,H-COSY correlation the triplets at 7.61 ppm (J = 8.1 Hz) and 7.46 ppm (J = 7.5 Hz) are due to 4″-

and 7″-CH protons and the doublets at 7.83 ppm (J = 8.4 Hz) and 7.98 ppm (J = 6.9 Hz) are due to 5″- and 6″-CH protons respectively. The C,H-COSY correlations of these protons assigns the carbon signals at 126.4, 125.0, 130.5, 126.8 and 119.4 ppm to 3″-C to 8″-C carbons respectively. The ^{1}H and ^{13}C chemical shifts of **12b** are shown in **Figure 1**. The structure of **12b** elucidated from NMR spectroscopy was further confirmed from single crystal X-ray studies. The ORTEP diagram shoen in **Figure 2**[20] reveal that the 7′-H and 8′-H are *trans* and the two carbonyls attached to C-5′ and C-2 are also *trans*. Similarly, by straightforward considerations the ^{1}H and ^{13}C chemical shift assignments for all the other dispiro 1,4-benzothiazine hybrid heterocycles **9–12** were done and the data are given in the experimental section.

Then the cycloaddition of azomethine ylides generated *in situ* from the reaction of α-amino acids and isatins **13** to these dipolarophiles **3** was investigated with a view to synthesize novel dispiro oxindole–1,4-benzothiazine hybrid heterocycles **14–16** (**Scheme 4**). The reaction under similar conditions afforded excellent yields of the products. However, the reaction failed to occur in the case of proline. The structure of these compounds was elucidated with one- and two-dimensional NMR spectroscopy as done for the above cases. As a representative example, the ^{1}H and ^{13}C NMR chemical shifts of **14b** are shown in **Figure 3**.

EXPERIMENTAL

General Procedure For The Synthesis Of Dispiro 1,4-Benzothiazine Hybrid Heterocycles

A mixture of (**3**, 1 mmol), acenaphthylene-1,2-dione or isatins (**4** or **13**, 1.2 mmol) and the respective α-amino acid (**5–8**, 1.5 mmol) in ethanol (10 mL) was heated to reflux on a water bath for 3 h. After completion of the reaction as evident from TLC, the mixture was poured into crushed ice and the resulting solid was filtered off and purified by column chromatography on silica gel employing ethyl acetate/petroleum ether (10:90 v/v) as eluent to obtain pure products **9–12** and **14–16**.

Compound 12b

Obtained as pale white solid; Yield 71%; m.p. 222–224°C; Anal. Calcd. for $C_{27}H_{22}N_2O_4S_2$: C, 64.52; H, 4.41; N, 5.57; S, 12.76. Found: C, 64,59; H, 4.34; N, 5.63; S, 12.68. ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 1.28 (t, *J*=7.2Hz, 3H), 3.30-3.36 (m, 1H), 3.42 (d, *J*=8.7Hz, 1H), 3.77 (d, *J*=8.7Hz, 1H), 4.23 (dd, *J*=14.1, 7.2Hz, 2H), 4.59 (d, *J*=10.2Hz, 1H), 4.83–4.9 (m, 1H), 5.84 (d, *J*=7.8Hz, 1H),6.68 (t, *J*=7.8Hz, 1H), 6.79 (t, *J*=7.5Hz, 1H), 7.08 (d, *J*=7.5Hz, 1H), 7.26 (d, *J*=6.9Hz 1H), 7.46 (t, *J*=7.5Hz, 1H), 7.59–7.64 (m, 1H), 7.83 (d, J=8.4Hz, 1H), 7.91 (d, *J*=7.2Hz, 1H), 7.98 (d, *J*=8.1Hz, 1H), 9.74 (s, 1H). ^{13}C NMR (75 MHz, CDCl3) δ_C: 13.3, 35.0, 38.1, 50.5, 51.6, 60.5, 63.0, 66.9, 79.6, 115.2, 116.5, 119.4, 122.3, 123.5, 125.0, 126.4, 126.8, 126.9, 127.6, 128.8, 130.0, 130.4, 132.4, 135.6, 139.6, 161.7, 167.8, 200.1.

Compound 14b

Obtained as pale white solid; Yield 70%; m.p. 279–281°C; Anal. Calcd. for $C_{22}H_{21}N_3O_4S$: C, 62.40; H, 5.00; N, 9.92, S, 7.57. Found: C, 62.32; H, 4.93; N, 9.98; S, 7.49. ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 1.29 (t, *J*=7.2Hz, 3H), 2.05 (s, 3H),

3.32 (t, *J*=8.7Hz, 1H), 4.06 (t, *J*=9.0Hz, 1H), 4.21 (dd, *J*=14.4, 7.2Hz, 2H), 4.81 (t, *J*=8.7Hz, 1H), 6.22 (d, *J*=7.5Hz, 1H), 6.28 (d, *J*=7.8Hz, 1H), 6.75 (t, *J*=6.3Hz, 2H), 6.79–6.88 (m, 2H), 7.06 (d, *J*=7.2Hz, 1H), 7.14 (d, *J*=6.9Hz, 1H), 9.52 (s, 1H), 10.26 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 12.8, 33.7, 44.6, 52.0, 55.2, 59.2, 76.6, 107.2, 113.9, 115.2, 119.6, 121.1, 123.2, 124.3, 125.6, 128.0, 135.0, 141.7, 164.4, 168.3, 173.3.

CONCLUSIONS

The 1,3-dipolar cycloaddition of unstabilized azomethine ylides generated *in situ* from the decarboxylative condensation of acenaphthylene-1,2-dione/ isatins and α-amino acids to (*E*)-ethyl/methyl 2-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]-thiazin-2-ylidene)acetate resulted in the formation of novel dispiro 1,4-benzothiazine hybrid heterocycles. These cycloadditions proceeded stereo-selectively affording a single isomer of the product in excellent yields. The structure of all the dispiro heterocycles was elucidated with the help of one and two dimensional NMR spectroscopy. The prominent advantages of this reaction comprise a facile one-pot three-component protocol, formation of two C–C and one C–N bonds in a single step in addition to the generation of four new contiguous stereo centers.

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University Grants Commission, New Delhi for funds under UGC-BSR meritorious fellowship.

SUPPLEMENTARY INFORMATION

Full experimental detail, characterization data for all compounds, and copies of ^{1}H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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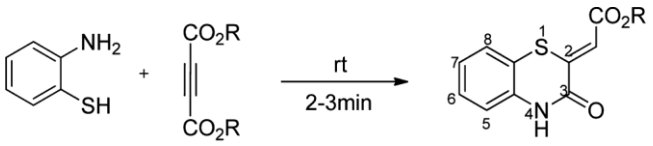
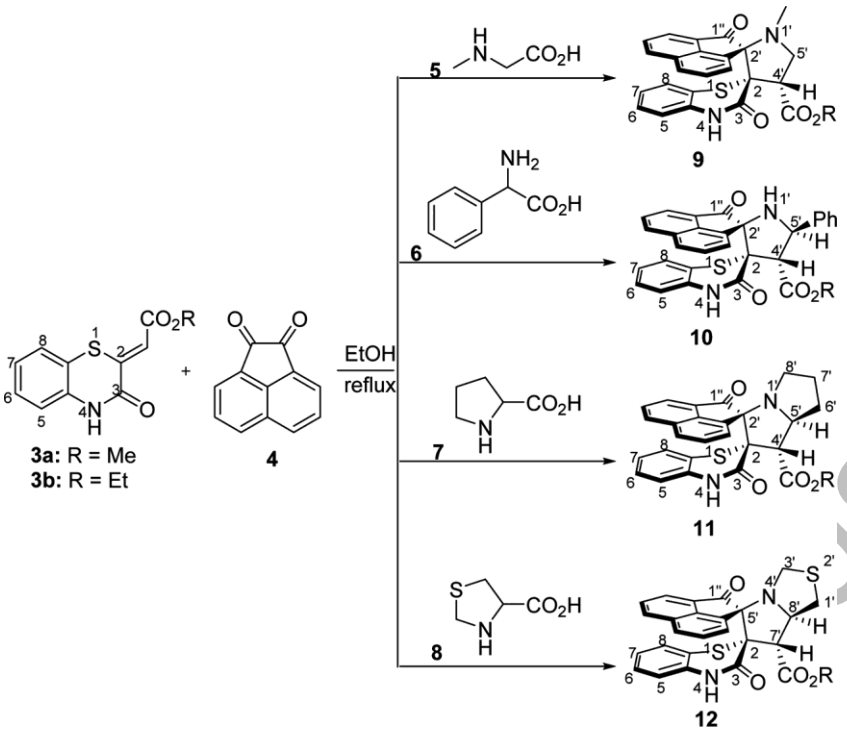
20. Crystallographic data (excluding structure factors) for compound **12b** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 1021459. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 762911 or e-mail: deposit@ccdc.cam.ac.uk].

Scheme 1. Synthesis of dipolarophiles **3**



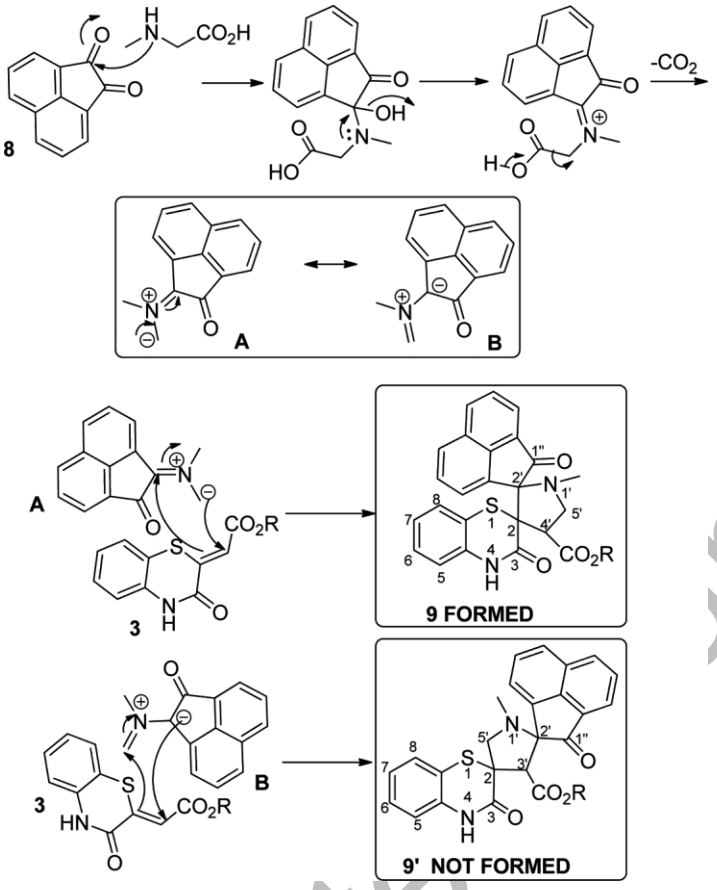
1 **2a:** R = Me **2b:** R = Et **3a:** R = Me, 90 % **3b:** R = Et, 82 %

Scheme 2. Synthesis of dispiro acenaphthene1,4-benzothiazine hybrid heterocycles **9–12**

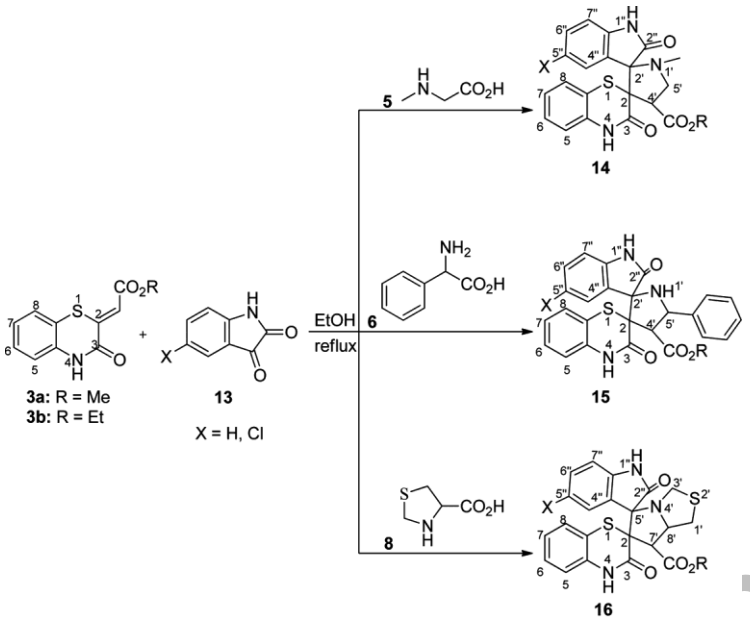


Entry	Compound	R	Yield (%)
1	**9a**	Me	75
2	**9b**	Et	72
3	**10a**	Me	75
4	**10b**	Et	84
5	**11a**	Me	68
6	**11b**	Et	86
7	**12a**	Me	74
8	**12b**	Et	71

Scheme 3. Formation of azomethine ylides *via* decarboxylative route and the cycloaddition



Scheme 4. Synthesis of dispiro oxindole 1,4-benzothiazine hybrid heterocycles **14–16**



Entry	Compound	R	X	Yield (%)
1	**14a**	Me	H	71
2	**14b**	Et	H	70
3	**14c**	Me	Cl	81
4	**14d**	Et	Cl	82
5	**15a**	Me	H	99
6	**15b**	Et	H	73
7	**15c**	Me	Cl	99
8	**15d**	Et	Cl	98
9	**16a**	Me	H	73
10	**16b**	Et	H	88
11	**16c**	Me	Cl	76
12	**16d**	Et	Cl	94

Figure 1. ^{1}H and ^{13}C NMR chemical shifts of **12b**

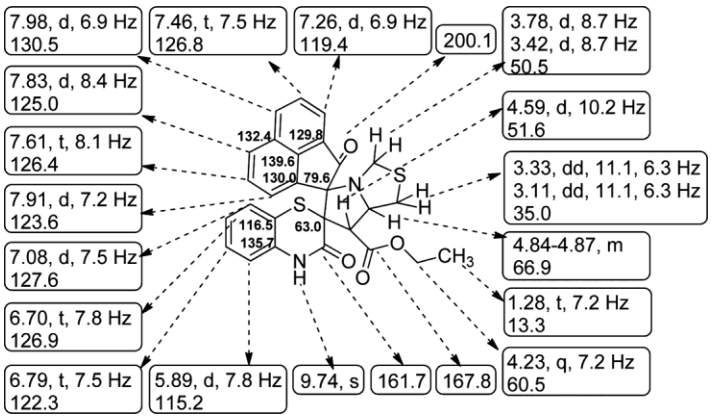


Figure 2. ORTEP diagram of **12b**

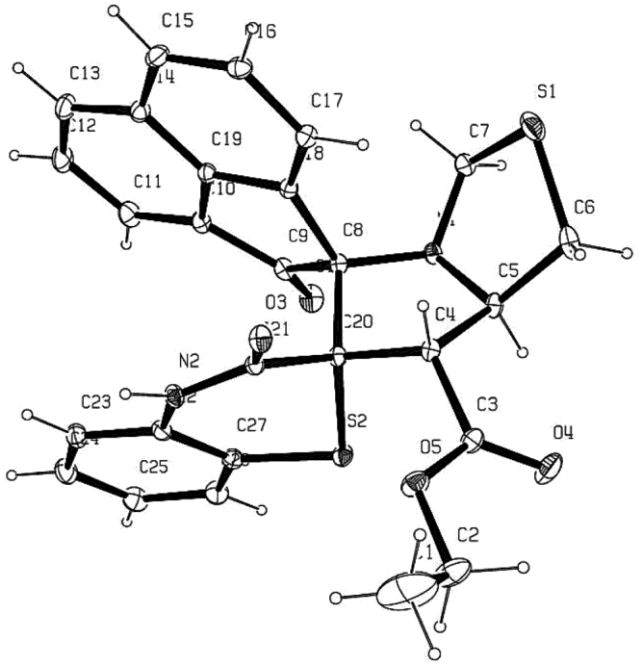


Figure 3. ^{1}H and ^{13}C NMR chemical shifts of **14b**