Electrocyclization and Unexpected Reactions of Non-Stabilised α,β:γ,δ-Unsaturated Azomethine Ylides. Experimental and Theoretical Study.

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Synthesis Paper

Electrocyclization and Unexpected Reactions of Non-Stabilised α,β:γ,δ-Unsaturated Azomethine Ylides. Experimental and Theoretical Study.

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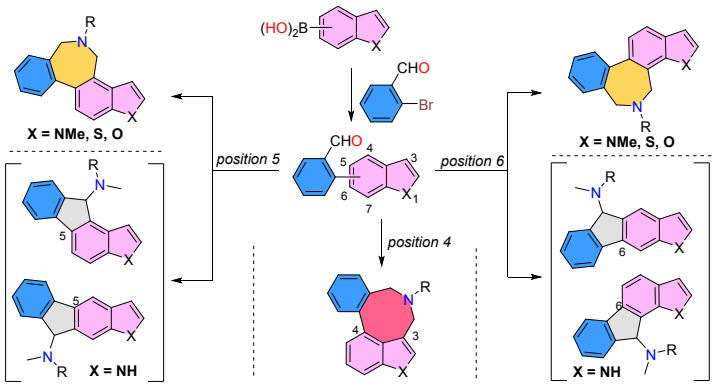
This paper is dedicated to professor Ferenc Fülöp.



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Abstract Versatile, two-step synthesis of dihydro-dibenzo[c,e]azepine, carbazole derivatives and other alkaloid type drug-like scaffolds, by in situ generated azomethine ylide induced intramolecular electrocyclization reaction from commercially available materials are presented. The reaction mechanisms of transition-metal- free carbon–carbon bond formation and the role of the kinetic control, resulting in the good regioselectivity, were confirmed by theoretical calculations.

Key words alkaloid, azomethine ylide, dihydro-5H-dibenzo[c,e]azepine, electrocyclization, NICS

The rigid key-lock hypothesis has been outdated in the course of the modern pharmaceutical research and is looking for looser and more flexible drug candidates. The rigid and constrained conformations of 4, 5 and 6 membered unsaturated rings (containing a heteroatom) limits their effectivity for larger and more dynamic binging packets on the protein side. In most of the cases, these binding pockets were not “designed” for drug-like cyclic organic molecules, of that require adoptancy to bind. On the other hand, the larger ring motifs (ring size larger than 10) have already exhibit too many flexible bonds and provides a too large available conformational space for a precise binding. The 7 and 8 membered unsaturated rings, like azepanes and azocanes, however, comply with these criteria, because they have limited number of rotatable bonds, but furnish the required flexibility. Heterocycles containing azepine ring anellated to indoles can be found in many important alkaloid families presented a few example in Figure 1A, while their synthetic variants are of uttermost importance to the pharmaceutical industry due to their diverse biological activities and larger freedom to operate.[1]

In spite of the pharmacological needs, the available synthetic methods are still not routine. The 1,3-dipolar cycloaddition of azomethine ylides is a versatile and efficient tool for the construction of five-membered nitrogen heterocycles.[2] When the azomethine ylide is conjugated with double bonds, other pericyclic pathways become available, including 1,5- or 1,7-electrocyclizations, with the latter 8 π-electron process having only recently emerged as a potentially useful method for the formation of seven-membered heterocycles.[3]

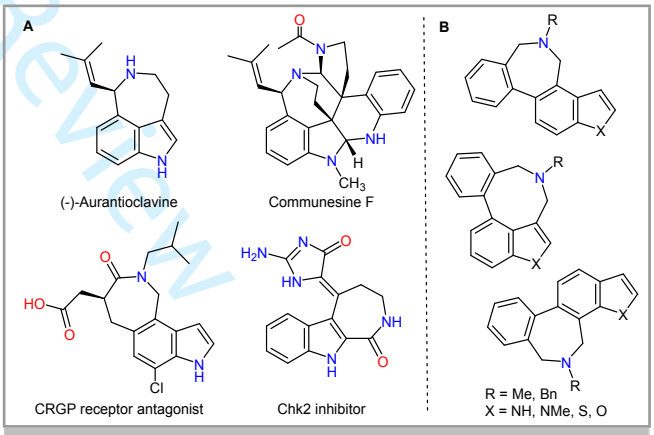
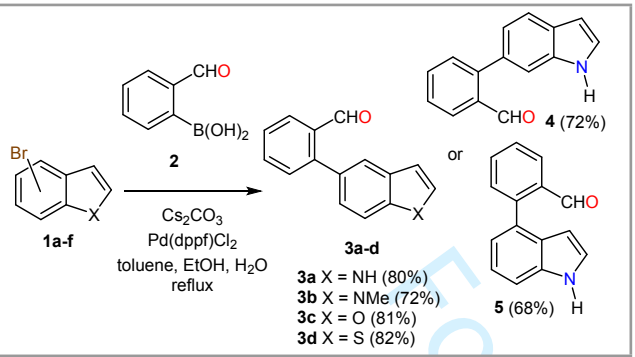


Figure 1 (A) Representative bioactive natural alkaloids and drug candidate molecules with a indolo-azepine scaffold. (B) Main types of scaffolds prepared in this project.

As a continuation of these studies, our aim was to show the generality of these methods as useful tools for the annelation of benzazepine ring to different heterocyclic derivatives in a single step (Figure 1B). Earlier we have already shown that this allows for a not only elegant but also efficient way of synthesizing isoquinoline,[4] β-carboline[5] and some indole[6] fused azepine ring systems. In this paper, we describe the synthesis of some hitherto unknown heterocycles using the 1,7-electrocyclisation of conjugated azomethine ylides on indole (Ind), benzofuran (Bff) and benzothiophene (Bth) along with the observations of alternative reaction pathways which also resulted in the formation of new heterocyclic scaffolds.

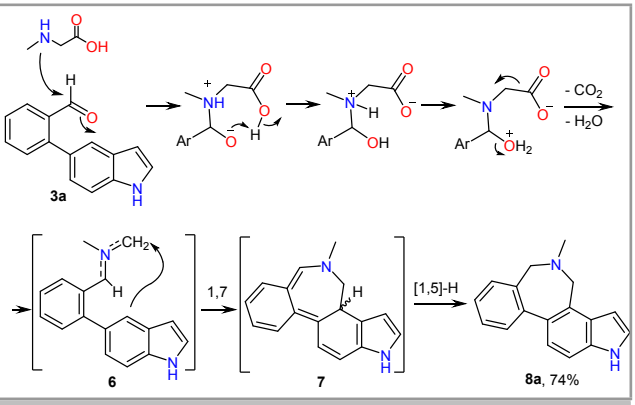
Herein we report new, two-step reactions to indole fused *N*-heterocycles from bromo indoles, along with the results of quantum chemical calculations, for the confirmation of the proposed reaction mechanism.

The starting materials **3-5** were prepared from the commercially available bromoindoles, 5-bromobenzofuran and 5-bromobenzothiophene derivatives (**1a-f**) using 2-formyl phenyboronic acid (**2**) via Suzuki coupling (Scheme 1).



Scheme 1 Synthesis of indolylbenzaldehydes and their analogues by Suzuki coupling reactions.

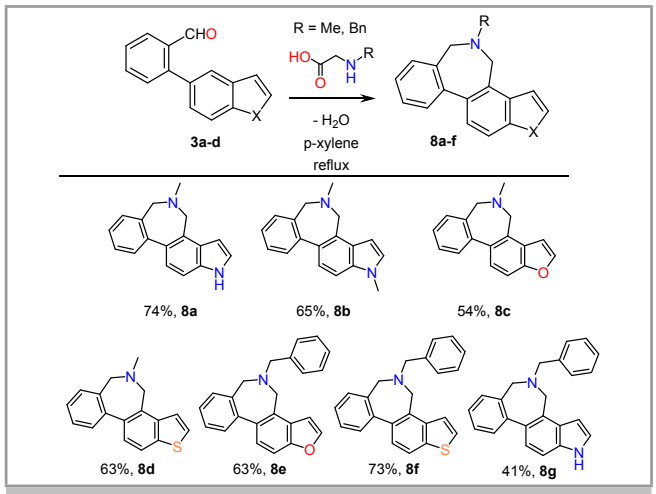
Our initial study applied the generation of non-stabilised azomethine ylide **6** by the decarboxylation method, involving the condensation step of the corresponding aldehyde with amino acid. In the first experiment, a mixture of sarcosine and **3a** benzaldehyde was heated under reflux in *p*-xylene (the water formed was removed by a *Dean-Stark* trap) for three hours. (Scheme 2).[7]



Scheme 2 Plausible mechanism of the formation of 1,4,5,6-tetrahydrobenzo[5,6]azepino[3,4-e]indole (**8a**) from **3a** and sarcosine.

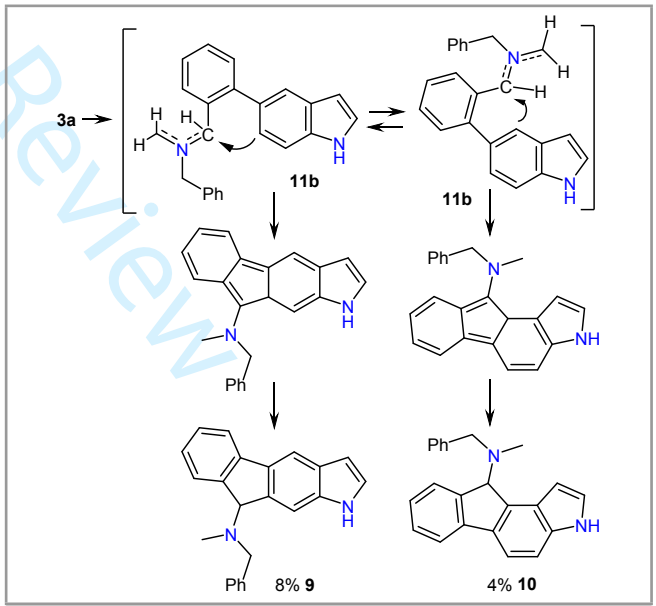
Under these conditions the formed α,β:γ,δ –conjugated azomethine ylide~~s~~ **6** reacted in a 1,7-electrocyclisation followed by a 1,5-sigmatropic hydrogen shift giving rise to the formation of the expected benzazepine derivative **8a** which was obtained after column chromatography in good yield (74%, Scheme 2).

Similar reactions were carried out using **3b-d** aldehydes in the same conditions. In addition, N-benzylglycine as a reactant was also used. ~~The formation of t~~The desired benzazepine derivatives **8a-g** ~~which~~ were obtained after chromatography in good yields (Scheme 3).



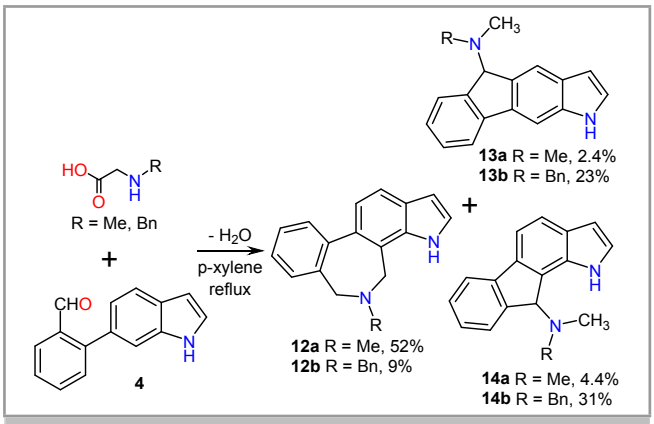
Scheme 3 Synthesis of azepines **8a-f** via a 1,7-electrocyclisation of α,β:γ,δ –conjugated azomethine ylides.

However, when **3a** and *N*-benzyl glycine were reacted under the same conditions three products were formed (**8g**, **9**, **10**) and isolated. The expected azepine derivative **8g** were prepared as the major product in 41% yield, together with two regioisomeric by-products **9** and **10** indeno[1,2-*f*]indoles[8] in 8% and 4% isolated yields after preparative HPLC purification, respectively (Scheme 4). Reactions of **3a** with secondary amino acids, such as proline, pipecolinic acid and 1,3-thiazolidine-4-carboxylic acid, gave a complex mixture of unidentified products.



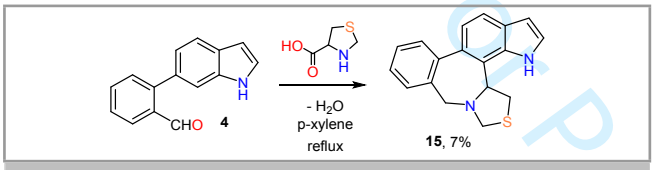
Scheme 4. Proposed mechanism of the formation of 1,9-dihydroindeno[1,2-f]indole coproducts (**9** and **10**) from in situ generated azomethine ylide **11b**.

A very similar reactivity pattern was observed with the regioisomeric 2-(1*H*-indol-5-yl)benzaldehyde **4**. The reaction with sarcosine provided the expected product **12a** in moderate yield and some interesting by-products **13a** and **14a** in traces. However, interestingly in the presence of *N*-benzyl glycine, the **13b** and **14b** indeno[1,2-*f*]indoles became the main products (23% and 31%, respectively), while the expected benzazepine derivative **12b** was only the minor component (9%, Scheme 5).



Scheme 5 The reaction of 2-(1H-indol-5-yl)benzaldehyde with sarcosine, N-benzyl-glycine or 1,3-thiazolidine-4-carboxylic acid.

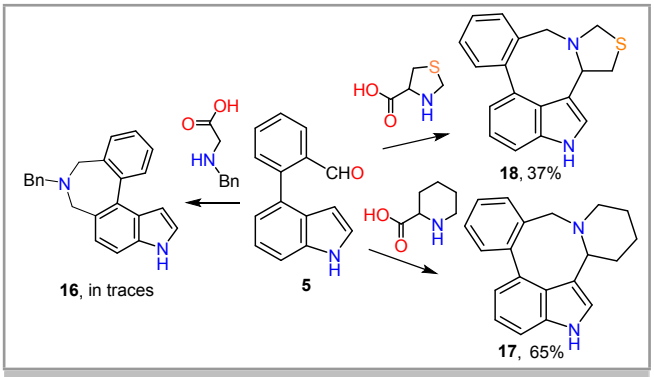
The reaction with the cyclic 1,3-thiazolidine-4-carboxylic acid again gave the benzazepine type product **15,** albeit in poor isolated yield (7%, Scheme 6).



Scheme 6 The reaction of 2-(1H-indol-5-yl)benzaldehyde with 1,3-thiazolidine-4-carboxylic acid.

Most surprisingly, the 2-(1H-indol-4-yl)benzaldehyde **5** showed totally different behavior in the reactions with the above-applied amino acids, under the same conditions. *N*-benzyl-glycine provided only a complex mixture of products, which contained only traces of the expected product **16** (proved by HPLC-HRMS MW(M+H) = 325.1686 Da, but not isolated) from 1,7-electrocyclisation process, while with the secondary amino acids regioselective formations of **17** and **18** were observed in good to moderate yields (65% and 37%), which are hitherto unknown heterocycles containing a very unusual eight-membered central core with four fused rings (Scheme 7).

Before attempting to propose any plausible explanation for the differences observed in the reactivity of aldehydes **3-5**, we aimed at proving whether or not the formation of the supposed azomethine intermediate can take place under the reaction conditions used. For this, we repeated the reactions with sarcosine in the presence of a dipolarophile trapping agent, *N*-phenyl-maleimide, while keeping the reaction conditions unchanged.

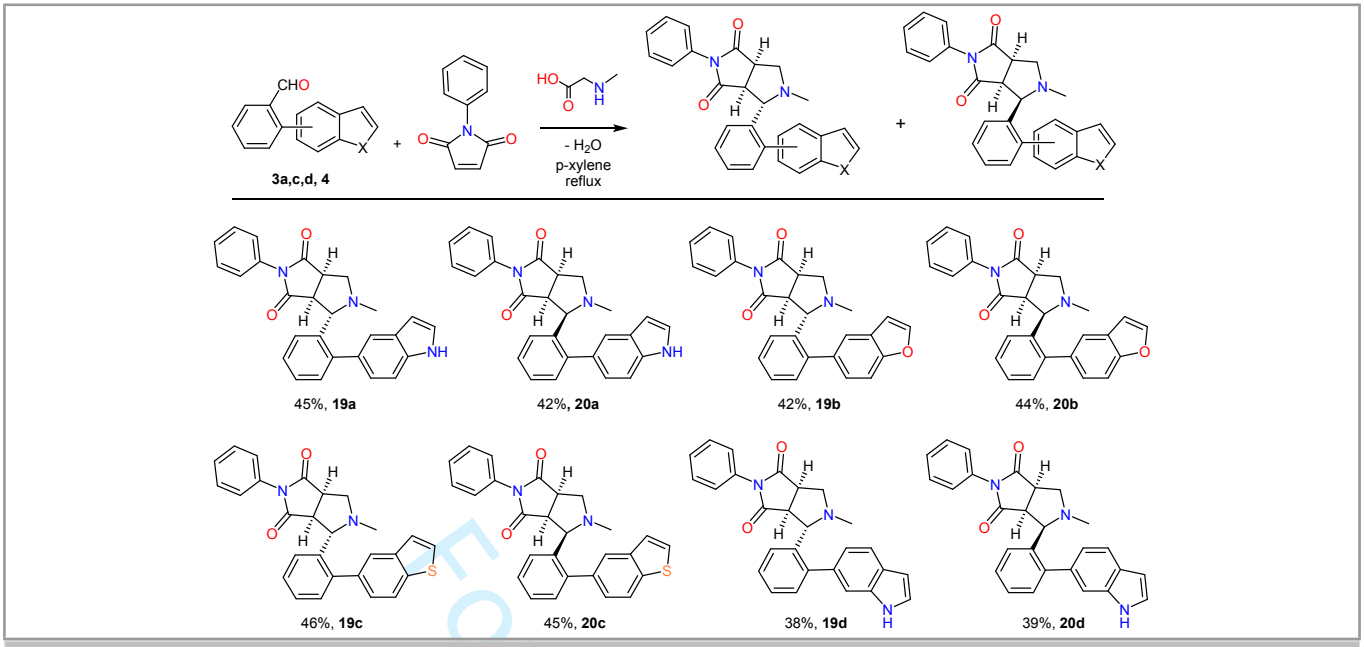


Scheme 7 Ring closing reaction of azomethin ylide formed in situ from 2-(1H-indol-4-yl)benzaldehyde (**5**) and amino acids.

In all cases, various diastereomeric mixtures of the expected *endo*- and *exo*-cycloadducts (**19** and **20**) were formed in good yields except for one: the 2-(1*H*-Indol-4-yl)benzaldehyde (**5**) gave again a complex mixture of products in contrast to the other four analogues (Scheme 8).

Based on these observations, we can suggest that the formation of **8a-g, 12a-b** goes evidently through a conjugated azomethine ylide intermediate stabilized by a 1,7-electrocyclisation pathway (as described in Scheme 2), which proceeds in all cases in a regioselective manner. The concurrent occurrence of the 1,5-electrocyclisation in such reactions is known, but not in this manner, with the exclusion of two atoms of the azomethine ylide. The pair of products (**9**, **10** and **13**, **14**) most probably arise from a non-regioselective 1,5-electrocyclisation process (Scheme 8).

In the reactions of 2-(1*H*-indol-4-yl)benzaldehyde (**5**) with amino acids even involvement of the azomethine ylide intermediate cannot be justified, most probably due to the steric proximity of the indol-3 position during the condensation reaction of the aldehyde function a cationic intermediate was trapped, resulting in the formation of the unexpected eight-membered ring.



Scheme 8 The reaction of N-phenylmaleimide and the corresponding ylides formed in situ from sarcosine and 2-arylbenzaldehydes.

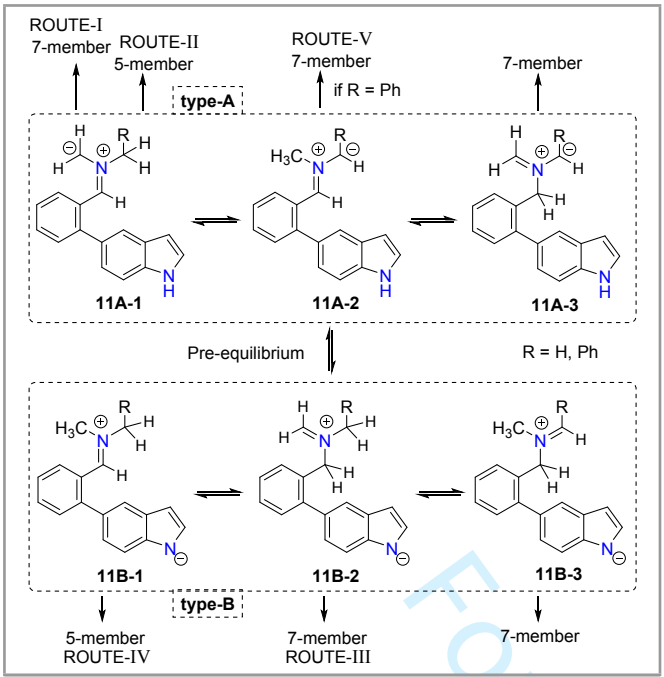
Theoretical study

~~All the structures were optimized by G16[9] at M06-2X /6-31++G(d,p) level of theory[10] with IEF-PCM implicit solvent method (ε = 12.2)[11].~~

In order to explain the surprising formation of ~~some selected unexpected~~the 5- and 8-membered cyclic products ~~(~~, such as **9**, **10** and **~~18~~17**~~)~~, the reaction mechanisms ~~of the transformations of~~from the azomethine ylide ~~intermediates~~ **11b** (R = Ph, Scheme 4) and **11a** (R = H) to all the theoretically possible products were ~~discovered~~ scouted systematically ~~by theoretical methods~~. Such an extensive and comprehensive theoretical study has not been published in the literature yet, comparing the alternate and competing routes. The formations of **9**, **10** and **17** avoid the general [1,7] pericyclic mechanism. All the structures were optimized by G16[9] at M06-2X /6-31++G(d,p) level of theory[10] with IEF-PCM implicit solvent method (ε = 12.2)[11]. Although, the rate determining step of the overall process is the formation of the azomethine ylide ~~(the elimination of the CO_2), which demands the elevated reaction temperature~~, this part of the mechanism was skipped from this study, since it is already discussed widely ~~and published~~ in the literature[12].

The product distribution of the process~~, however,~~ is determined by the enthalp~~h~~y difference between the transition states (TSs) of the various ring closure steps~~, starting form the conjugated azomethine ylides~~ from **11a**, **11b**. These species take part in a complex equilibria, as illustrated in Scheme 9. ~~In this scheme, s~~Structures ~~in~~ type-A (**11Aa**; **11Ab**) represent the ~~usual structural variations~~typical forms of azomethine ylides (**11A-1**, **2**, **3**). However, an alternate protonation equilibrium ~~were~~ should be also considered, where the proton of the ~~NH of~~ indole NH ~~protonates~~ migrates to one of the side-chain carbon atoms at azomethin ylide, resulting **11Ba** and **11Bb** as zwitterionic structures (Type-B, **11B-1**, **2**, **3**). Noteworthy, that ~~in the case of~~for R = H (**11a**), the most stable form is **11Ba-1**, in contrast to the expected form (**11Aa-1** ≡ **11Aa-2**), which is only the second lowest with a significant enthalpy difference (see Table 1). The situation is changed for the ~~benzyl derivative~~R = Bn (**11b**), where the two most stable forms are the expected to be **11Ab-2** and the zwitterionic form **11Bb-1** is less stable from the aspect of enthalpy values. ~~The~~ All the possible 7- and 5-membered products can be derived from the different forms of **11a** and **11b** *via* the corresponding ring closure steps through ROUTEs I–IV, represented by the arrows in Sh~~c~~cheme 11 and 12. Each of these routes involve the ring closure towards both the position 4 and 6 of the indole ring.

~~In the case of the reaction with sarcosine, the ROUTE-I represents the generally accepted mechanism of the [1,7] pericyclic ring closure reaction, *via* low enthalpy transition states (TS) to position 4 and 6. Subsequently, the forming intermediates **22A1** and **22A2** take place in [1,5] sigmatrope hydride shifts, resulting the products (**8a**, **23a**). The activation enthalpy of the ROUTE-I-4 is more preferred by ca. 25 kJ mol^{-1}, allowing the formation of the isomer **8a**. Noteworthy, that the theoretically possible ROUTE-III provides somewhat higher but even low enthalpy transitions, which cannot be ignored beside ROUTE-I.~~



Scheme 9 The complex preequilibrium of the azomethine ylide intermediates of **11Aa/11Ab** and **11Ba/11Bb** formed from **3a** respectively. The thermodynamic data are given in Table 1.

Table 1. The ΔH and ΔG (kJ mol^{-1}) values of the preequilibrium comp-uted for **11Aa/11Ab** and **11Ba/11Bb**. The energy values were calculated at M06-2X /6-31++G(d,p)//PCM(THF)) level of theory level of theory.

		11A		11B	
		ΔH	ΔG	ΔH	ΔG
a; R = H	1	17.3	18.3[a]	**0.0**	**0.0**
	2	17.3	18.3[a]	26.3	29.7
	3	49.2	45.1	18.1	21.6
b; R = Ph	1	33.1	22.6	17.1	8.2
	2	**0.0**	**0.0**	29.5	30.8
	3	33.4	22.1	34.9	34.8

Reaction with sarcosine (ROUTE-I in Scheme 10 and Table 2) represents the generally accepted mechanism of the [1,7] pericyclic ring closure reaction, *via* low enthalpy transition states (TS) to position 4 and 6. The calculated Nucleus Independent Chemical Shift (NICS)[13] values are also confirming the aromatic character of the TSs. Subsequently, intermediates **22A1** and **22A2** take place in a [1,5] sigmatrope hydride shifts, resulting the expected products (**8a, 23a**). From regioselectivity aspect, the activation enthalpy of the ROUTE-I-4 is more preferred by ca. 25 kJ mol^{-1}, allowing the selective formation of the isomer **8a** against **23a**, in agreement with the experiments. This regioselectivity can be explained by the more preserved aromaticity of the indole ring in the **TS-A1a** compared to **TS-A2a**. Noteworthy, that the analogues zwitterionic [1,7] pericyclic ring closure, ROUTE-III provides somewhat higher, but even low enthalpy transitions to the same products, which may be considered as an alternative of ROUTE-I. Comparing the standard formation of the pericyclic product **8a** with the formation of the 5-member isomers (**24a** and **25a**), via ROUTE-II, all ROUTE-II and ROUTE-IV exhibit significantly higher enthalpies of activations (TSB), due to the non-aromatic character (see nearly zero NICS values). However, the zwitterionic ROUTE-IV exhibits lower TS values, but these are higher than ROUTE-I and III. for the related TSs, excluding their probability This is in agreement with in the mechanism and confirming again the experimental findings about the practically exclusive formation of **8a**.

In the case of the reaction with benzyl glycine (R = Ph), the ROUTE-I also represents the normal [1,7] ring closure mechanism, which results analogue aromatic TS structures and related enthalpies, preferring the formation of product **8g** against the regioisomers **23b, 9** and **10**. The regioselectivity of the azepine formation (**8g** orvs **23b**) also depends on the transition statestwo TSs, preferring **8g**. TThe he calculated enthalpies of the non-aromatic TSs via ROUTE-II from the zwitterionic **11B-1**, belong to the formationtoward of the two 5-member products via ROUTE-II are quite high, as expected. However, here ROUTE-IV, which leadsleading also to the 5-member products (**9**, **10**) from the zwitterionic intermediate **11B-1**, already provides equally low enthalpies of activation and these values to really compete with ROUTE-I. and III. This result confirms the parallel formation of **8g, 9** and **10**. The regioselectivity of the azepine formation (**8** or **23**) also depends on the transition states. In the case of Route I-4 with much lower activation energy (ΔG =+46.5 kJ/mol), the indole ring remains more aromatic than in Route I-6 (ΔG =+71.5 kJ/mol), which explain the corresponding TSs (Scheme 10, Table 2).

ConsideringComparing the TSs of ROUTE-I and IIIV, they undoubtedly finely explain the experimentally observed product distribution. The somewhat higher activation enthalpies of TSs in ROUTE-III IV already represents somewhat higher activation enthalpies, but they could be consideredrepresent the minor products. Theoretically, the ring closure reaction at the benzylic C atom via ROUTE-V in Scheme 11 and Table 2 is also possibility, however, they showed somewhat higher activation enthalpies, then ROUTE-I and ROUTE-IV. According to the activation enthalpiesy, the related products (**26, 27**) can may form as a small amount side-products, which were not identified experimentally form the complex reaction mixtures.

One of the most reliable confirmations of the pericyclic reaction is the probe of the aromatic character, which can be easily measured by the method of Nucleus Independent Chemical Shift (NICS)[13]. It places a probe atom (ghost atom) into the center of the ring of the TS structure and its calculated chemical shift (in ppm) indicates the existence of the aromatic ring current (it is - 9.4 ppm for benzene at the given level of theory). Due to the fact, that in this case the rings in TSs is are not planar, rather a cylinder shaped, so not one, but 11 probe atoms were placed on the axes of the cylinder, passing through the plane. The given NICS values represents the maximal value among them. For [1,7] pericyclic processes (ROUTE I and V), the NICS valueas are lower than -10 ppm, referring to their pure aromatic character, as expected. In contrast to that, tThe moderate low values between 0 and –4 ppm, calculated for 5-member ring formation in TSs (ROUTE II, ROUTE IV) prove the absence of the aromatic or pericyclic character. Here,, the ring closure is rather a classical electrophilic attact of the carbocation. Not suprisinglyInterestingly, ROUTE III also belongs to the previous category. In summary, the pericyclic ring closure compete with the classic electrophilic ring closure.

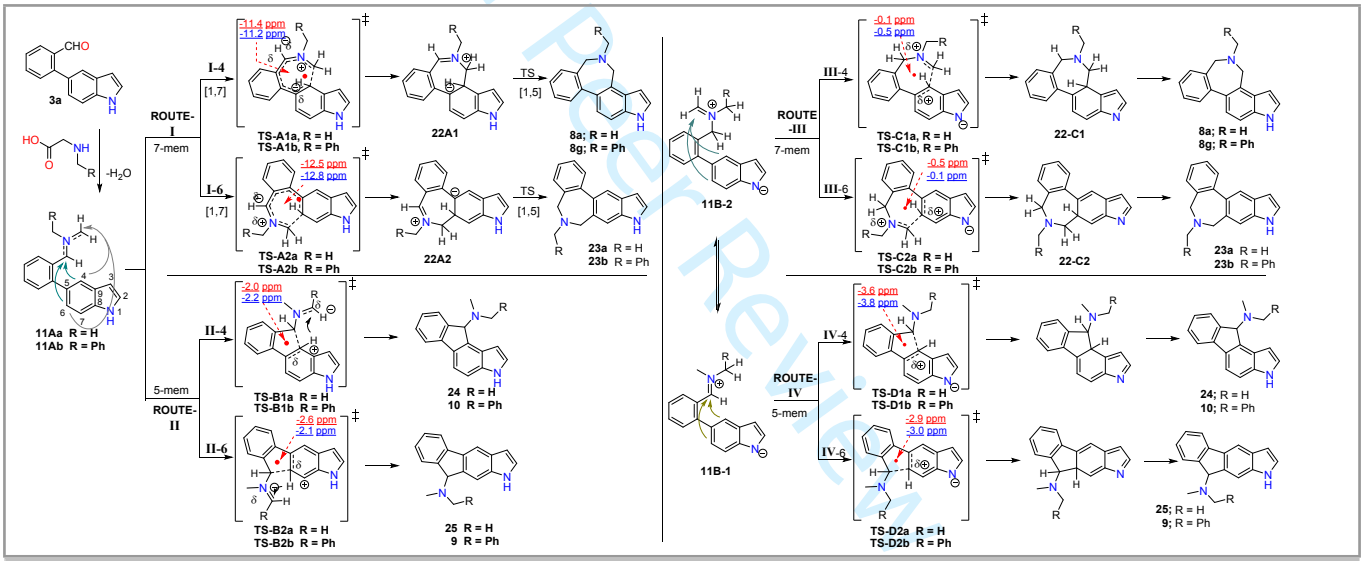
In order to exclude the deprotonation of the indole NH and prove the hypothesis about the competing ROUTEs, the N-Me indole derivative (**3b**) was also studied experimentally. The The experimentally registeredobserved exclusive formation of **8b** from the N-Me indole derivative (**3b**) undoubtedly confirm that the absence of the zwitterionicour hypothesis about the unusual zwitterionic-type ring closure mechanism (ROUTE-IV) excludes the formation of 5-member products for benzyl-glycine derivative. Due to the N-Me substitution of **8b**, there is no option for the indole

deprotonation, so the azomethine ylide remain the dominant intermediate, leading to ~~exclusively to~~ the expected 7-member product **8b** via ROUTE-I.

For the sake of simplicity, only the ring closure reaction of compound **5** with pipecolinic acid ~~was studied~~is discussed ~~by theoretical tools in a more straightforward manner~~ (Scheme 12 and Table 3~~3~~), ~~.~~ ~~The~~ the reaction with other amino acids, such as L-thiaproline~~,~~ ~~results~~ leads to analogues conclusions. In this case, t~~T~~he ~~preliminary~~ forming azomethine ylide~~s~~ also takes part in an equilibrium, as showed earlier. The expected 7-member product (**29**) can be derived from the usual intermediate via [1,7] pericyclic ring closure reaction (ROUTE-VI-5), however, the calculated activation enthalpy was higher (+50 kJ mol^{-1}), in contrast with the previous isomers. It can be explained ~~with~~ by the ~~higher enthalpy TS and intermediate, which are less stable, compared to their isomers (Table 3)~~lower aromatic character of the indole in the intermediate state. Interestingly ~~enough~~, that the direct formation of the 8-membered product (**17**) via ROUTE-VI-3 can not be ~~expected~~explain, due to the formation of a ~~dead end~~ strange~~d~~ multicycle intermediate, which leads to a dead end. The alternate route, ~~which leads to~~providing the 8-member product (ROUTE-VII-3), starts from ~~a~~ the stable zwitterionic intermediate **28B** and goes through a very low activation barrier (15.3 kJ mol^{-1}, Table 3), which undoubtedly explain the exclusive formation of the product **17**., against **29**.

The calculated NICS values for the four ~~route~~ROUTE-VI and VII also explain the aromatic character.~~,~~ Obviously, ROUTE-VI-5 ~~is~~ is firmly ~~obvious~~aromatic, but noteworthy, that ROUTE-VI-3 also exhibit high NICS value for at the center of the ring in TSs, in spite of the fact that it does not belong strictly to the classical pericyclic reaction. It seems to be rather a ~~a double~~consecutive [3+2]-[3+2] cycloaddition.

In conclusion, a versatile and selective synthetic procedure were ~~developded~~developed to provide novel molecular scaffolds by [1,7] ring closure for flexible protein biding sites as medchem target. Unexpected and, formally [1,5] ring closure products were observed in selected cases, which compete with the usual [1,7] pericyclic route. In order to understand the switching between the two reaction mechanisms ~~of~~to the 7 and 5 ring-closure reaction of aryl indoles, theoretical methods were used, proving explanations to the outcaome of the synthetic work.

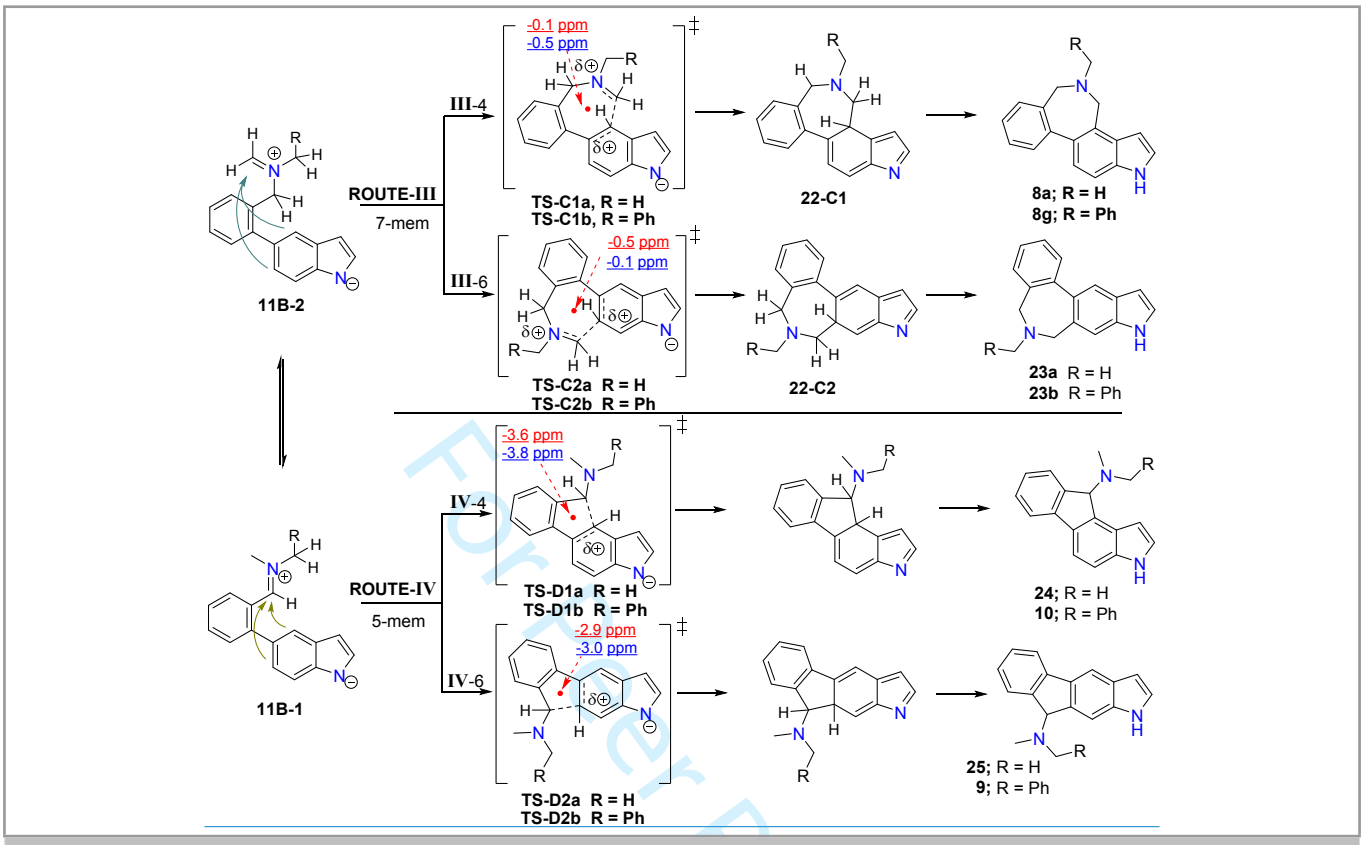


Scheme 10 Detailed reaction mechanism of the transformation of **11Ba** *via* ROUTE I ~~and II-IV~~ to synthetically isolated (**8a**, **8g**, **9** and **10**) and hypothetical products (**23a**, **23b**, **24** and **25**) in the presence of sarcosine or N-benzyl glycine. For computed values see Table 2. The energy values were calculated at M06-2X /6-31++G(d,p)//PCM(THF)) level of theory level of theory.

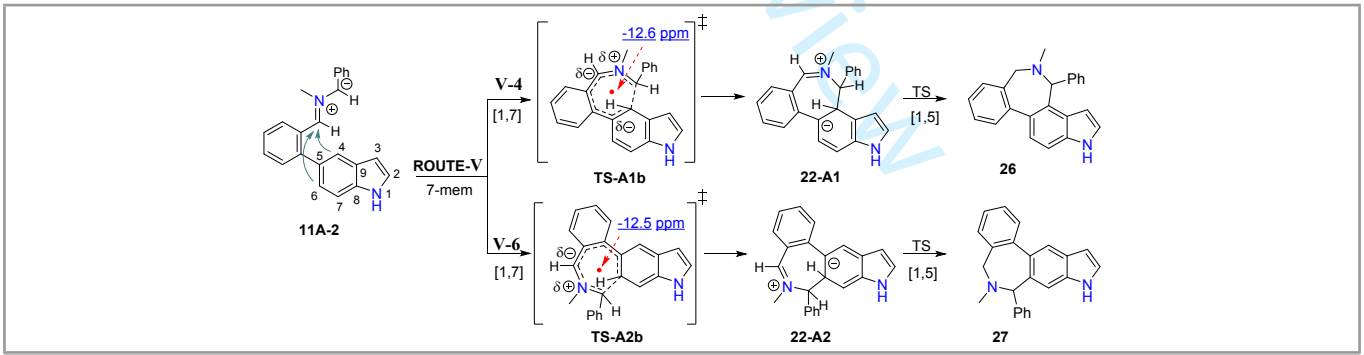
Table 2. The computed themodynamic ΔH, ΔG (kJ mol^{-1}) and ΔS (J mol^{-1} K^{-1}) values of transition states (TS), intermediates (INT) and product states for ROUTE-I–V.

		ROUTE	TS			INT			Product		
			ΔH	ΔG	ΔS	ΔH	ΔG	ΔS	ΔH	ΔG	ΔS
a; R = H	7-memb	I-4	39.3	46.5	-24.1	-10.4	-5.2	-17.2	-171.6	-162.1	-31.9
		I-6	64.6	71.5	-23.2	40.9	44.0	-23.2	-172.0	-162.6	-31.7
		II-4	131.9	139.4	-25.2	–	–	–	-170.7	-165.7	-16.5
		II-6	133.2	142.8	-24.1	–	–	–	-167.1	-161.1	-20.0
	5-memb	III-4	69.4	76.0	-22.3	-10.0	-2.7	-24.3	-171.6	-162.1	-31.9
		III-6	71.1	77.7	-22.0	-14.9	-7.7	-24.3	-172.0	-162.6	-31.7
		IV-4	+46.3	+50.7		-13.7			-170.7	-165.7	-16.5
		IV-6	+49.8	+54.2		-22.3	-18.4	-13.3	-167.1	-161.1	-20.0
b; R = Ph	7-memb	I-4	43.9	49.3	-17.9	-8.7	-5.2	-11.5	-132.1	-125.5	-22.2
		I-6	69.5	72.7	-10.7	45.9	46.1	-0.9	-153.6	-147.6	-20.1
		II-4	119.5	125.3	-19.6	–	–	–	-161.0	-163.6	8.7
		II-6	131.1	137.2	-20.5	–	–	–	-162.2	-156.2	-20.0
	5-mem	III-4	84.8	84.0	2.6	-3.7	-3.7	0.2	-132.1	-125.5	-22.2
		III-6	86.8	85.7	3.5	-5.4	-5.6	0.4	-153.6	-147.6	-20.1
		IV-4	49.6	47.2	8.2	-2.6	-5.4	9.6	-161.0	-163.6	8.7

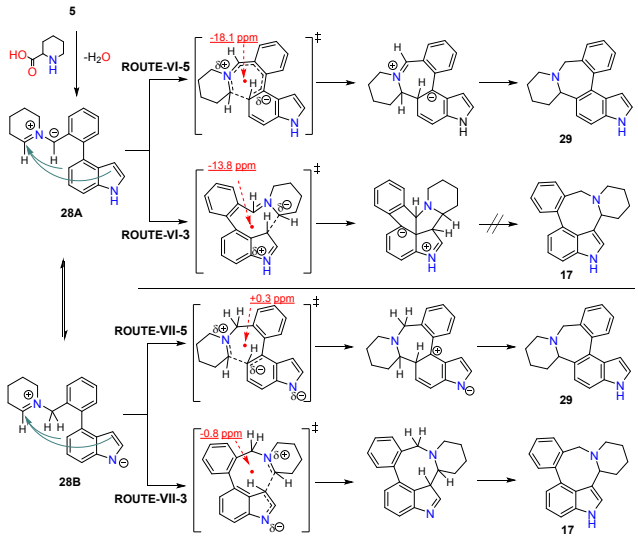
IV-6	42.2	35.3	23.2	-12.5	-17.9	18.0	-162.2	-156.2	-20.0
7-m V-4	41.7	44.8	-10.4	15.2	16.5	-4.2	-158.9	-153.3	-18.8
V-6	72.1	74.6	-8.4	71.4	69.0	7.8	-162.1	-157.2	-16.6



Scheme 11. Detailed reaction mechanism of the transformation of **11** *via* ROUTE III and IV to synthetically isolated (**8a, 8g, 9** and **10**) and hypothetical products (**23a, 23b, 24** and **25**) in the presence of sarcosine or N-benzyl glycine. For computed values see **Table 2**. The energy values were calculated at M06-2X /6-31++G(d,p) //PCM(THF)) level of theory level of theory.



Scheme 12 11 Detailed reaction mechanism of the transformation of **11** *via* ROUTE V to hypothetical products (**26, 27**) in the presence of *N*-benzyl glycine. For computed values see **Table 2**. The energy values were calculated at M06-2X /6-31++G(d,p)//PCM(THF)) level of theory level of theory.



Scheme 13 12 Detailed reaction mechanism of the transformation of **5** *via* ROUTE VI and VII to synthetically isolated (**17**) and hypothetical product (**29**) in the presence pipecolic acid. For computed values see **Table 3**. The energy values were calculated at M06-2X /6-31++G(d,p) level of theory.

Table 3. The computed themodynamic ΔH, ΔG (kJ mol^{-1}) and ΔS (J mol^{-1} K^{-1}) values of transition states (TS), intermediates (INT) and product states for ROUTE-VI and VII. The energy values were calculated at M06-2X /6-31++G(d,p//PCM(THF)) level of theory.

ROUTE	Start			TS			INT			Product		
	ΔH	ΔG	ΔS	ΔH	ΔG	ΔS	ΔH	ΔG	ΔS	ΔH	ΔG	ΔS
VI-5	47.0	41.8	17.3	**88.6**	**94.4**	-19.3	**47.0**	**41.8**	17.4	**-91.4**	**-85.2**	-20.6
VI-3				**271.7**	**278.3**	-22.2	**240.4**	**243.2**	-9.3	**-54.7**	**-49.5**	-17.6
VII-5	0.0	0.0	0.0	**89.7**	**96.3**	-21.9	**68.0**	**74.3**	-20.9	**-91.4**	**-85.2**	-20.6
VII-3				**15.3**	**17.7**	-8.1	–	–	–	**-54.7**	**-49.5**	-17.6

~~In conclusion, a versatile and selective synthetic procedure were developdedto provide novel molecular scaffolds by [1,7] ring closure for flexible protein biding sites as medchem target. Unexpected and, formaly [1,5] ring closure products were observed in selected cases, which compete with the usual [1,7] pericyclic route. In order to understand the switching between the two reaction mechanism of the ring-closure reaction of aryl indoles, theoretical methods were used, proving the outcame of the synthetic work.~~

The experimental section has no title; please leave this line here.

IR spectra were recorded with a Bruker Tensor 27 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-*d6* using TMS as an internal reference with a Bruker Avance III. spectrometer operating at 600 MHz and 125 MHz respectively (1H-, DEPTQ-, HSQC-, HMBC-, NOE-NMR). High-resolution MS spectra were measured by Agilent 6230 TOF LC/MS spectrometer. Elemental analysis was performed on FlashEA 1112 Elemanalyzer.

Synthesis of the hetaryl-benzaldehydes (3a-d, 4 and **5) – General procedure:** The mixture of 15 mmol of the corresponding bromoarene (**1a-1f**,), 3.44 g (22.95 mmol) of (2-formylphenyl)boronic acid (**2**), 0.34 g (0.46 mmol) of 1,1'-bis(diphenilphosphino)-ferrocene-palladium(II)-chloride and 15.3 ml (30.6 mmol) of a 2 M aqueous solution of Cs_2CO_3, 78 ml of toluene and 24 ml of ethanol was refluxed for 1.5 h. After cooling, the reaction mixture was filtered through a pad of Celite and concentrated. The residue was taken up in 150 ml of dichloromethane and washed with water and brine, dried, and concentrated. The crude product was purified by column chromatography on silica gel with ethyl acetate – heptane eluent.

2-(1*H*-Indol-5-yl)benzaldehyde (3a): 2.72 g (80%) pale brown solid;

IR: 3257, 1650 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d$_6$): 11.31 (bs, 1H, -NH), 9.90 (s,1H, HC=O), 7.89 (dd, *J* = 7.5 and 1.5 Hz, 1H, H-6), 7.73 (td, *J* = 7.5 Hz and 1.5 Hz, 1H, H-5), 7.60-7.50 (m, 4H, H-3, H-4, Ind-4 and 7), 7.45 (t, J = 2.8 Hz, 1H, Ind-2), 7.15 (dd, *J* = 8.3 and 1.7 Hz, 1H, Ind-6), 6.52 (m, 1H, Ind-3).

^{13}C NMR (125 MHz, DMSO-d$_6$): 192.8 (CH), 147.4 (q), 136.1 (q), 134.1 CH), 133.8 (q), 131.7 CH), 128.4 (q), 128.2 (q), 127.5 (CH), 127.4 (CH), 127.1 (CH), 123.8 (CH), 122.3 (CH), 111.9 (CH), 102.0 (CH).

HRMS [M+H]+$_{found}$ = 222.0905, $C_{15}H_{11}NO$ required 222.0918.

2-(1-Methylindol-5-yl)benzaldehyde (3b): 2.61 g (72%) pale brown solid;

IR: 1648 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d$_6$): 9.88 (s,1H, HC=O), 7.90 (dd, *J* = 7.5 and 1.5 Hz, 1H, H-6), 7.73 (td, *J* = 7.5 Hz and 1.5 Hz, 1H, H-5), 7.60-7.55 (m, 3H, Ind-2, 4 and 7), 7.54 (t, J = 7.5 Hz, 1H, H-4), 7.43 (d, J 7.5 Hz, 1H, H-3), 7.22 (dd, *J* = 8.2 and 1.5 Hz, 1H, Ind-6), 6.54 (m, 1H, Ind-3), 3.85 (s, 3H, *N*Me).

^{13}C NMR (125 MHz, DMSO-d$_6$): 192.7 (CH), 147.2 (q), 136.5 (q), 134.1 (CH), 134.0 (q), 133.8 (CH), 1129.25 (q), 129.2 (q), 128.55 (CH), 128.5 (CH), 127.5 (CH), 123.8 (CH), 122.6 (CH), 110.3 (CH), 101.2 (CH), 33.1 (CH_3).

HRMS [M+H]+$_{found}$ = 236.1070, $C_{16}H_{13}NO$ required 236.1070.

2-(1-Benzofuran-5-yl)-benzaldehyde (3c): 2.70 g, (81%); pale yellow oil;

IR: 1683 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d$_6$): δ 9.89 (s, 1H, HC=O), 8.10 (d, 1H, *J* = 2.2 Hz, Bf-2), 7.93 (d, 1H, *J* = 7.8 Hz, H-6), 7.76 (m, 1H, H-5), 7.75-7.72 (m, 2H, Bf-4 and 6), 7.61-7.56 (m, 2H, H-3, Bf-5), 7.38 (dd, J = 8.5 and 1.8 Hz, 1H, H-4), 7.04 (dd, J = 2.2 Hz and 0.9 Hz, 1H, Bf-3).

^{13}C NMR (125 MHz, DMSO-d$_6$): 192.4 (CH), 154.5 (q), 147.6 (CH), 145.9 (q), 134.3 (CH), 133.9 (q), 132.7 (q), 131.8 (CH), 128.2 (CH), 128.0 (q), 127.8 (CH), 127.0 (CH), 123.3 (CH), 111.7 (CH), 107.4 (CH).

HRMS [M+H]+$_{found}$ = 223.0749, $C_{15}H_{11}O_2$ required 223.0759.

2-(1-Benzothiophen-5-yl)-benzaldehyde (3d): 2.93 g, (82%); pale yellow solid;

IR: 1682 cm^{-1};

^1H NMR (500 MHz, DMSO-d_6): δ 9.91 (s, 1H, HC=O), 8.14 (d, *J* = 8.2 Hz, 1H,H-6), 7.96-7.93 (m, 2H, H-5 and Bt-2), 7.87 (d, *J* = 5.4 Hz, 1H, Bt-5), 7.78 (t, *J* = 8.2 Hz, 1H, H-4), 7.63-7.58 (m, 2H, Bt-3 and 4), 7.54 (d, J = 5.4 Hz, 1H, Bt-6), 7.46 (dd, *J* = 8.2 and 1.7 Hz, 1H, H-3).

^{13}C NMR (125 MHz, DMSO-d_6): 192.4 (CH), 145.7 (q), 140.1 (q), 139.4 (q), 134.4 (CH), 134.0 (q), 133.8 (q), 131.7 (CH), 129.2 (CH), 128.4 (CH), 127.9 (CH), 126.7 (CH), 125.5 (CH), 124.6 (CH), 123.1 (CH).

HRMS $[M+H]^+_{found}$ = 239.0521, $C_{15}H_{11}OS$ required 239.0530.

2-(1H-Indol-6-yl)benzaldehyde (4): 2.45 g (72%); pale brown solid;

IR: 3260, 1678 cm^{-1};

^1H NMR (500 MHz, DMSO-d_6): δ 11.28 (br s, 1H, NH,), 9.91 (s, 1H, HC=O), 7.90 (m, 1H), 7.74 (m, 1H), 7.67 (d, *J* = 8,0 Hz, 1H), 7.59 (d, *J* = 7.6 Hz1H), 7.54 (t, *J* = 7.6 Hz, 1H,), 7.46 (dd, J = 3.2 Hz and 2.5 Hz, 1H), 7.42 (m, 1H), 7.06 (dd, *J* = 8.0 and 1.6 Hz, 1H), 6.52 (m, 1H).

^{13}C NMR (125 MHz, DMSO-d_6): 192.8 (CH), 147.1 (q), 136.3 (q), 134.2 (CH), 133.9 (q), 131.6 (CH), 130.4 (CH), 127.9 (q), 127.7 (q), 127.5 (CH), 127.2 (CH), 121.9 (CH), 120.5 (CH), 113.6 (CH), 101.5 (CH).

HRMS $[M+H]^+_{found}$ = 222.0907, $C_{15}H_{12}NO$ required 222.0918.

2-(1*H*-Indol-4-yl)benzaldehyde (5): 2.31 g (68%); brown solid;

IR: 3339, 1681 cm^{-1};

^1H NMR (500 MHz, DMSO-d_6): δ 11.40 (1H, bs, -NH), 9.71 (1H, bs, HC=O), 7.95 (d, J = 7 7.5 Hz, 1H, H-6), 7.78 (t, J = 7.5 Hz, 1H, H-5), 7.62-7.57 (2H, m, H-3 and 4), 7.52 (1H, d, *J* = 8.1 Hz, Ind-7), 7.42 (1H, t, *J* = 2.8 Hz, Ind-2), 7.23 (1H, dd, *J* = 8.1 and 7.2 Hz, Ind-6), 6.98 (1H, dd, 7.2 and 1.8 Hz, Ind-5), 6.13 (s, 1H, Ind-3).

^{13}C NMR (125 MHz, DMSO-d_6): δ 192.3 (CH), 145.2 (q), 136.2 (q), 134.5 (CH), 133.9 (q), 131.5 (CH), 129.3 (q), 128.2 (CH), 128.2 (q), 127.2 (CH), 127.0 (CH), 121.6 (CH), 121.6 (CH), 112.2 (CH), 100.2 (CH).

HRMS $[M+H]^+_{found}$ = 222.0912, $C_{15}H_{12}NO$ required 222.0918.

Reactions the aldehydes (3a-d, 4, 5) with amino acids – General procedure

The mixture of 1 mmol of the corresponding aldehyde and 3 mmol of sarcosine, *N*-benzyl-glycine, pipecolinic acid or 1,3-thiazolidine-4-carboxylic acid in 30 ml of *p*-xylene was refluxed for two hours. After cooling, the reaction mixture was filtered through a pad of Celite and concentrated. The crude product was purified by column chromatography on silica gel with methanol - dichloromethane eluent.

9-Methyl-1,4,5,6-tetrahydro-indolo[4,5-*d*][2]benzazepine (8a): 183 mg (74%);

IR: 1439 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ 11.28 (br s, 1H, NH), 7.52 (dd, *J* = 7.8 and 1.1 Hz, 1H, H-4), 7.47 (dd, *J* = 7.8 and 0.8 Hz, 1H, H-5), 7.49 (dd, J = 7.5 and 1.3 Hz, 1H, H-2), 7.41 (t, *J* = 2.7 Hz, 1H, H-12), 7.40 (d, *J* = 7.6 Hz, 1H, H-7), 7.33 (td, *J* = 7.3 and 1.3 Hz, 1H, H-6), 7.27 (d, *J* = 8.3 Hz, 1H, H-3), 6.67 (m, 1H, H-11), 3.62 (s, 2H, H_2-10), 3.25 (s, 2H, H_2-8), 2.40 (s, 3H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ 142.5 (q), 136.0 (q), 134.6 (q), 131.2 (q), 130.2 (CH), 129.0 (q), 128.6 (CH), 128.2 (CH), 127.0 (CH), 126.6 (CH), 125.2 (q), 121.6 (CH), 111.6 (CH), 100.3 (CH), 57.7 (CH_2), 53.0 (CH_2), 43.7 (CH_3).

HRMS $[M+H]^+_{found}$ = 249.1381, $C_{17}H_{17}N_2$ required 249.1391.

1,9-Dimethyl-1,4,5,6-tetrahydro-indolo[4,5-*d*][2]benzazepine (8b):

IR: 1682 cm^{-1};

^1H NMR (500 MHz, DMSO-d_6): 7.53 (d, J = 7.5 Hz, 1H, H-4), 7.52 (d, J = 7 8.5 Hz, 1H, H-2), 7.46 (t, J = 7.5 Hz, 1H, H-5), 7.40 (m, 2H, H.7 and H-12), 7.34 (t, J = 7.5 Hz, 1H, H.6), 7.33 (d, J = 8.5 Hz, 1H, H-3), 6.66 (d, J = 3Hz, 1H, H-11), 3.84 (s, 3H, *N1*-Me), 3.59 (s, 2H, CH_2-10), 3.24 (s, 2H, CH_2-8), 2.40 (s, 3H, *N9*-Me).

^{13}C NMR (125 MHz, DMSO-d_6): 142.4 (q), 136.5 (q), 135.0 (q), 131.4 (q), 130.9 (CH), 130.1 (CH), 129.2 (q), 128.5 (CH), 128.2 (CH), 127.1 (CH), 125.8 (q), 121.7 (CH), 109.8 (CH), 99.5 (CH), 57.8 (CH_2), 43.8 (CH_3), 52.9 (CH_2), 33.1 (CH_3).

HRMS $[M+H]^+_{found}$ = 263,1551, $C_{18}H_{18}N_2$ required 263,1550.

9-Methyl-1,4,5,6-tetrahydro-benzfurano[4,5-d][2]benzazepine (8c): 135 mg (54%); yellow solid;

IR: 2785 cm^{-1};

^1H NMR (500 MHz, DMSO-d_6): 8.07 (d, J = 2.2 Hz, 1H, H-12), 7.68 (d, J = 8.5 Hz, 1H, H-2), 7.54 (d, J = 7.6 Hz, 1H, H-4), 7.48 (t, J = 8.5 Hz, 1H, H-3), 7.47 (t, J = 7.6 Hz, 1H, H-5), 7.42 (d, J = 7.6 Hz, 1H, H-7), 7.38 (d, J = 7.6 Hz, 1H, H-6), 7.24 (d, J = 2.2 Hz, 1H, H-11), 3.56 (br s, 2H, CH_2-10), 3.24 (br s, 2H, CH_2-8), 2.38 (s, 3H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): 154.2 (q, C-1a), 147.2 (CH, C-12), 141.2 (q, C-3b), 135.5 (q, C-3a), 135.1 (q, C-7a), 130.2 (CH, C-7), 128.6 (CH, C-5), 128.5 (q, C-10b), 128.3 (CH, C-4), 127.8 (CH, C-6), 127.3 (q, C-10a), 124.6 (CH, C-3), 111.2 (CH, C-2), 106.1 (CH, C-11), 57.5 (CH_2, C-8), 53.0 (CH_2, C-10), 43.6 (CH_3).

HRMS $[M+H]^+_{found}$ = 250.1226, $C_{17}H_{16}NO$ required 250.1231.

9-Methyl-1,4,5,6-tetrahydro-benzthiophen[4,5-d][2]benzazepine (8d): 167 mg (63%), pale yellow solid;

IR: 2784 cm^{-1};

^1H NMR (500 MHz, DMSO-d_6): 8.06 (d, J = 8.3 Hz, 1H, H-2), 7.85 (d, J = 5.5 Hz, 1H, H-12), 7.78 (dd, J = 5.5 Hz and 0.7 Hz, 1H, H-11), 7.57 (d, J = 7.7 Hz, 1H, H-4), 7.53 (d, J = 8.3 Hz, 1H, H-3), 7.49 (td, J = 7.7 Hz and 1.8 Hz, 1H, H-5), 7.44 (dd, J = 7.7 Hz and 1.5 Hz, 1H, H-7), 7.40 (td, J = 7.7 Hz and 1.5 Hz, 1H, H-6), 3.67 (br s, 2H, CH_2-10), 3.22 (br s, 2H, CH_2-8), 2.38 (3H, s, -CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): 141.2 (q, C-3b), 140.2 (q, C-10b), 139.2 (q, C-1b), 136.9 (q, C-3a), 135.5 (q, C-7a), 130.1 (CH, C-7), 129.2 (q, C-10a), 128.6 (2 x CH, C-6 and C-12), 128.4 (CH, C-4), 128.0 (CH, C-6), 124.6 (CH, C-3), 123.1 (CH, C-11), 122.5 (CH, C-2), 57.6 (CH_2, C-8), 53.1 (CH_2, C-10), 43.7 (CH_3).

HRMS $[M+H]^+_{found}$ = 266.1001, $C_{17}H_{16}NS$ required 266.1003.

9-Benzyl-1,4,5,6-tetrahydro-benzfurano[4,5-d][2]benzazepine (8e): 205 mg (63%); pale yellow solid;

IR: 1452 cm^{-1};

^1H NMR (500 MHz, DMSO-d_6): 8.08 (d, J = 2.2 Hz, 1H, H-12), 7.69 (d, J = 8.5 Hz, 1H, H-12), 7.55 (d, J = 7.6 Hz, 1H, H-4), 7.49 (d, J = 8.5 Hz, 1H, H-3), 7.48 (td, J = 7.5 Hz and 1.5 Hz, 1H, H-5), 7.43 (d, J = 7.0 Hz, Bn-2 and 6), 7.39 (t, J = 7.0 Hz, 2H, Bn-3 and 5), 7.39 (td, J = 7.5 Hz and 1.5 Hz, 1H, H-6), 7.35 (1H, dd, J J = 7.5 Hz and 1.5 Hz, 1H, H-7), 7.30 (t, J = 7.0, 1H, Bn-4), 7.01 (dd, J = 2.2 Hz and 0.9 Hz, 1H, H-11), 3.71 (s, 2H, $BnCH_2$), 3.60 (br s, 2H, CH_2-10), 3.22 (br s, 2H, CH_2-8).

^{13}C NMR (125 MHz, DMSO-d_6): 154.2 (q, C-1a), 147.3 (CH, C-12), 141.3 (q, C-3b), 139.6 (q, Bn-1'C), 135.6 (q, C-3a), 135.3 (q, C-7a), 130.1 (CH, C-7), 129.1 (2 x CH, Bn-2' and 6'C), 128.9 (2 x CH, Bn-3' and 5'C), 128.6 (CH, C-5), 128.3 (CH, C-4), 128.2 (CH, C-11a), 127.9 (CH, C-6), 127.7 (q, C-10a), 127.5 (CH, Bn-4'C), 124.6 (CH, C-3), 111.2 (CH, C-2), 105.8 (CH, C-11), 59.9 (CH_2, Bn), 55.4 (CH_2, C-8), 51.5 (CH_2, C-10).

HRMS $[M+H]^+_{found}$ = 326.1526, $C_{23}H_{20}NO$ required 326.1544.

9-Benzyl-1,4,5,6-tetrahydro-benzthiophen[4,5-d][2]benzazepine (8f): 249 mg (73%); pale yellow solid;

IR: 1451 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): 8.10 (d, J = 8.3 Hz, 1H, H-2), 7.86 (d, J = 5.5 Hz, 1H, H-12), 7.59 (d, J = 7.6 Hz, 1H, H-4), 7.55 (d, J = 8.3 Hz, 1H, H-3), 7.53 (d, J = 5.5 Hz, 1H, H-11), 7.50 (td, J = 7.6 Hz and 1.4 Hz, 1H, H-5), 7.44 (d, J = 7.2 Hz, 2H, Bn-2 and 6), 7.41 (td, J = 7.6 Hz and 1.4 Hz, 1H, H-6), 7.39 (t, J = 7.2 Hz, 2H, Bn-3 and 5), 7.37 (dd, J = 7.6 Hz and 1.4 Hz, 1H, H-7), 7.30 (t, J = 7.2 Hz, 1H, Bn-4), 3.73 (s, 2H, Bn-CH_2), 3.71 (br s, 2H, CH_2-10), 3.24 (br s, 2H, CH_2-8).

^{13}C NMR (125 MHz, DMSO-d_6): δ 141.3 (q, C-3b), 140.0 (q, C-10b), 139.6 (q, Bn-1'C), 139.2 (q, C-1a), 137.1 (q, C-3a), 135.3 (q, C-7a), 130.1 (CH, C-7), 129.5 (q, C-10a), 129.0 (2 x CH, Bn-2' and 6'C), 128.9 (2 x CH, Bn-3' and 5'C), 128.8 (CH, C-12), 128.6 (CH, C-5), 128.3 (CH, C-4), 128.1 (CH, C-6), 127.5 (CH, Bn-4'C), 124.6 (CH, C-3), 122.6 (CH, C-2), 122.6 (CH, C-11), 59.9 (CH_2, Bn), 55.4 (CH_2, C-8), 51.8 (CH_2, C-10).

HRMS [M+H]+$_{found}$ = 342.1301, $C_{23}H_{20}NS$ required 342.1316.

9-Benzyl-1,4,5,6-tetrahydro-indolo[4,5-*d*][2]benzazepine (8g):

IR: 2925, 1441 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): 11.25 (br s, 1H, NH), 7.51 (d, J = 7.5 Hz, 1H, H-4), 7.47 (d, J = 8.5 Hz, 1H, H-2), 7.45 (t, J = 7.5 Hz, 1H, H-5), 7.44 (d, J = 7.8 Hz, 2H, Bn-2 and 6), 7.41 (m, 1H, H-12), 7.39 7.44 (t, J = 7.8 Hz, 2H, Bn-3 and 5), 7.35 (d, J = 7.5 Hz, 1H, H-7), 7.34 (d, J = 7.5 Hz, 1H, H-6), 7.30 (t, J = 7.8 Hz, 1H, Bn-4), 7.27 (d, J = 8.5 Hz, 1H, H-3), 6.43 (m, 1H, H-11), 3.71 (s, 2H, BnCH_2), 3.58 (s, 2H, CH_2-10), 3.24 (s, 2H, CH_2-8).

^{13}C NMR (125 MHz, DMSO-d_6): 142.7 (q, C-3b), 140.0 (q, Bn-1'C), 136.0 (q, C-1a), 135.4 (q, C-7a), 131.3 (q, C-3a), 130.0 (CH, C-7), 129.0 (2xCH, Bn-2' and 6'C), 128.8 (2xCH, Bn-3' and 5'C), 128.8 (q, C-10b), 128.3 (CH, C-5), 128.1 (CH, C-4), 127.4 (CH, Bn-4'C), 127.0 (CH, C-6), 126.5 (CH, C-12), 126.1 (q, C-10a), 121.5 (CH, C-3), 111.4 (CH, C-2), 100.0 (CH, C-11), 60.1 (Bn-CH_2), 56.1 (CH_2-8), 51.3 (CH_2-10).

HRMS [M+H]+$_{found}$ = 325.1626, $C_{23}H_{20}N_2$ required 325.1624.

***N*-Benzyl-*N*-methyl-1,9-dihydroindeno[1,2-f]indole-9-amine (9):** 26 mg (8%); pale yellow solid;

IR: 2922, 1602 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): 11.13 (br s, 1H, -NH), 7.94 (s, 1H, H-4), 7.79 (d, J = 7.5 Hz, 1H, H-5), 7.69 (s, 1H, H-10), 7.67 (d, J = 7.5 Hz, 1H, H-8), 7.42 (d, J = 7.5 Hz, 2H, Bn-2 and 6), 7.36 (m, 1H, H-2), 7.35 (t, J = 7.5 Hz, H-6), 7.33 (t, J = 7.5 Hz, 2H, Bn-3 and 5), 7.23 and 7.21 (2 x t, J = 7.5 Hz, 2H, H-7 and Bn-4), 6.76 (1H, s, H-3), 5.03 (1H, s, H-9), 3.81 (d, J = 13 Hz, 1H, Bn-CH_2), 3.67 (d, J = 13 Hz, 1H, Bn-CH_2), 2.06 (3H, s, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): 144.3 (q, C-9a), 142.3 (q, C-4b), 140.4 (q, Bn-1'C), 138.4 (q, C-9a), 136.6 (q, C-10a), 133.0 (q, C-4a), 128.7 (4 x CH, Bn-2',3',5'and 6'C), 128.5 (CH, C-6), 128.4 (q, C-3a), 127.3 (CH, Bn-4'C), 126.3 (CH, C-7), 126.2 (CH, C-2), 126.0 (CH, C-8), 119.5 (CH, C-5), 111.4 (CH, C-4), 109.2 (CH, C-10), 102.0 (CH, C-3), 68.6 (CH, C-9), 57.9 (Bn-CH_2), 38.0 (*N*CH_3).

HRMS [M+H]+$_{found}$ = 325.1684, $C_{23}H_{21}N_2$ required 325.1704.

***N*-Benzyl-*N*-methyl-1,4-dihydro-indeno[1,2-*e*]indole-4-amine (10):** 13 mg (4%); pale yellow solid;

IR: 3378, 1434 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): 11.25 (br s, 1H, -NH), 7.74 (d, J = 7.0 Hz, 1H, H-8), 7.72 (d, J = 7.0 Hz, 1H, H-5), 7.55 (d, *J* = 8.3 Hz, 1H, H-9), 7.45-7.40 (m, 4H, H-2, H-10, Bn-2 and 6), 7.37-7.30 (m, 3H, H-7, Bn-3 and 5), 7.23 (t, J = 7.6 Hz, Bn-4), 7.21 (t, 1H, J = 7.0, 1H, H-6), 6.76 (m, 1H, H-3), 5.16 (s, 1H, H-4), 3.81 (d, *J* = 13.4 Hz, 1H, BnCH_2), 3.67 (d, J = 13.4 Hz, 1H, BnCH_2), 2.06 (s, 3H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): 143.5 (q, C-4a), 143.2 (q, C-8a), 140.5 (q, Bn-4'C), 137.1 (q, C-10a), 136.3 (q, C-3b), 131.8 (q, C-8b), 128.9 (2 x CH, Bn-2' and 6'C), 128.7 (2 x CH, Bn-3' and 5'C), 128.3 (CH, C-7), 127.3 (CH, Bn-4'C), 126.6 (CH, C-2), 126.2 (CH, C-5), 125.6 (q, C-4b), 125.4 (CH, C-6), 119.3 (CH, C-8), 113.7 (CH, C-9), 112.1 (CH, C-10), 101.1 (CH, C-3), 69.5 (CH, C-4), 58.6 (CH_2), 37.8 (CH_3).

HRMS [M+H]+$_{found}$ = 325.1699, $C_{23}H_{21}N_2$ required 325.1704.

11-Methyl-1,10,11,12-tetrahydro-indolo[5,6-*d*][2]benzazepine (12a): 129 mg (52%); pale yellow solid;

IR: v: 3161, 1512 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): 11.33 (s, 1H, NH), 7.59 (d, J = 8.0 Hz, 1H, H-4), 7.51 (dd, J =7.5 and 1.0 Hz, 1H, H-6), 7.44 (td, J =7.5 and 1.0 Hz, 1H, H-7), 7.41 (d, J = 3.0 Hz, 1H, H-2), 7.38 (dd, J =7.5 and 1.0 Hz, 1H, H-4), 7.33 (td, J =7.5 and 1.0 Hz, 1H, H-5), 7.17 (d, J = 8.0 Hz, 1H, H-5), 6.50 (dd, J = 3.0 and 1.5 Hz, 1H, H-3), 3.59 (s, 2H, CH_2-12), 3.22 (s, 2H, CH_2-10), 2.37 (s, 3H, *N*CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): 142.3 (q, C-5b), 136.4 (q, C-12b), 133.8 (q, C-5a), 135.4 (q, C-9a), 130.0 (CH, C-4), 128.3 (CH, C-6), 128.2 (CH, C-7), 128.0 (q, C-3a), 127.1 (CH, C-8), 126.6 (CH, C-2), 119.7 (CH, C-7), 119.6 (CH, C-5), 102.0 (CH, C-3), 58.1 4 (CH_2, C-10), 51.1 4 (CH_2, C-8), 44.0 (NCH_3).

[M+H]+$_{found}$ = 249,1383, $C_{17}H_{17}N_2$ required 249.1391.

11-Benzyl-1,10,11,12-tetrahydro-indolo[5,6-*d*][2]benzazepine (12b): 29 mg (9%); pale yellow solid;

IR: 1452 cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6): 11.34 (br s, 1H, NH), 7.62 (d, J = 8.4 Hz, 1H, H-4), 7.53 (d, J = 7.2 Hz, 1H, H-6), 7.44-7.36 (m, 4H, H-2, H-7, Bn-3 and 5), 7.36-7.29 (m, 4H, H-8, Bn-3, 4 and 5), 7.22 (d, J = 7.2 Hz, 1H, H-9), 7.18 (d, J = 8.4 Hz, 1H, H-5), 6.54 (br s, 1H, H-3), 3.81 (s, 2H, CH_2-12), 3.76 (s, 2H, CH_2-Bn), 3.13 (s, 2H, CH_2-10).

^{13}C NMR (125 MHz, DMSO-d_6): 142.5 (q, C-5b), 139.7 (q, Bn-1'C), 135.9 (q, C-12b), 134.9 (q, C-9a), 133.7 (q, C-5a), 130.0 (CH, C-9), 129.2 (2 x CH, Bn-2' and 6'C), 128.8 (2 x CH, Bn-3' and 5'C), 128.3 (CH, C-7), 128.2 (CH, C-6), 128.2 (q, C-3a), 127.7 (CH, Bn-4'C), 127.1 (CH, C-8), 126.6 (CH, C-2), 119.9 (CH, C-4), 119.6 (CH, C-5), 118.5 (q, C-12a), 102.1 (CH, C-3), 60.3 (Bn-CH_2), 54.5 (CH_2-10), 51.2 (CH_2-12).

HRMS [M+H]+$_{found}$ = 325.1703, $C_{23}H_{21}N_2$ required 325.1704.

***N,N*-Dimethyl-1,5-dihydro-indeno[1,2-*f*]indole-5-amine (13a):** 6 mg (2.4 %); pale yellow solid;

IR: v: 3160, 1511 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): 11.15 (br s, 1H, NH), 7.80 (d, *J* = 8.5 Hz, 1H, H-9), 7.74 (s, 1H, H-10), 7.71 (s, 1H, H-4), 7.54 (d, *J* = 8.5 Hz, 1H, H-6), 7.34 (m, 2H, H-2 and H-8), 7.22 (d, *J* = 8.5 Hz, 1H, H-7), 6.44 (m, 1H, H-3), 4.88 (s, 1H, H-5), 2.22 (s, 6H, Me);

^{13}C NMR (125 MHz, DMSO-d_6): 144.6 (q, C-5a), 142.0 (q, C-9a), 136.6 (q, C-10a), 135.4 (q, C-4a), 135.1 (q, C-9b), 128.4 (CH, C-8), 128.3 (q, C-3a), 126.5 (CH, C-7), 126.3 (CH, C-2),126.1 (CH, C-6), 119.7 (CH, C-9), 117.6 (CH, C-4), 102.9 (CH, C-10), 102.0 (CH, C-3), 69.3 (CH, C-5), 41.2 (2 x CH_3);

HRMS [M+H]+$_{found}$ = 248.1315, $C_{17}H_{16}N_2$ required 248.1313.

***N*-Benzyl-*N*-methyl-1,5-dihydro-indeno[1,2-*f*]indole-5-amine (13b):** 75 mg (23%); pale yellow solid;

IR v: 3405, 1447 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.16 (brs,1H, NH), 7.84 (s, 1H, H-4), 7.82 (d, J = 7.5 Hz, 1H, H-9), 7.78 (s, 1H, H-10), 7.67 (d, J = 7.5 Hz, 1H, H-6), 7.43 (d, J = 7.8 Hz, 2H, Bn-2' and 6'H), 7.38 (t, J = 7.5 Hz, 1H, H-8), 7.36 (br s, 1H, H-2), 7.33 (t, J = 7.8 Hz, 2H, Bn-3' and 5'H),7.27 (t, J = 7.5 Hz, 1H, H-7), 7.23 (t, J = 7.8 Hz, 1H, Bn-4'H), 6.49 (br s, 1H, H-3), 5.00 (s, 1H, H-5), 3.68 (d, J = 12.5 Hz, 1H, NCH_2), 3.63 (d, J = 12.5 Hz, 1H, NCH_2), 2.10 (s, 3H, NMe);

^{13}C NMR (125 MHz, DMSO-d_6): δ 144.9 (q, C-5a), 142.1 (q, C-9a), 140.4 (q, Bn-1'C), 136.7 (q, C-10a), 135.7 (q, C-9b), 135.1 (q, C-4a), 128.8 (2xCH, Bn-2' and 6'C), 128.6 (2xCH, Bn-3' and 5'C), 128.4 (CH, C-8), 127.2 (CH, Bn-4'C), 126.6 (CH, C-7), 126.4 (CH, C-2), 126.0 (CH, C-6), 119.7 (CH, C-9), 117.4 (CH, C-4), 103.0 (CH, C-10), 102.0 (CH, C-3), 68.4 (CH, C-5), 58.0 (CH_2), 37.9 CH_3).

HRMS [M+H]+$_{found}$ = 325.1700, $C_{23}H_{21}N_2$ required 325.1704.

***N,N*-Dimethyl-1,10-dihydro-indeno[1,2-*g*]indole-10-amine (14a):**

11 mg (4.4 %); colorless oil;

IR: 1451 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): 10.78 (br s, 1H, NH), 7.75 (d, *J* = 7.5 Hz, 1H, H-6), 7.63 (d, *J* = 7.5 Hz, 1H, H-9), 7.56 (d, *J* = 8.5 Hz, 1H, H-4), 7.45 (d, *J* = 8.5 Hz, 1H, H-5), 7.34 (t, *J* = 7.5 Hz, 1H, H-7), 7.31 (t, *J* =3.0 Hz, 1H, H-2), 7.19 (t, *J* = 7.5 Hz, 1H, H-8), 6.49 (dd, *J* =3.0 and 1.5 Hz, 1H, H-3), 5.11 (s, 1H, H-10), 2.26 (s, 6H, NMe_2).

^{13}C NMR (125 MHz, DMSO-d_6): 143.4 (q, C-5b), 142.7 (C-9a), 134.0 (q, C-5a), 133.1 (q, C-10b), 128.9 (q, C-3a), 128.4 (CH, C-7), 127.7 (q, C-10a), 126.5 (CH, C-2), 126.4 (CH, C-9), 125.6 (CH, C-8), 120.8 (CH, C-4), 119.7 (CH, C-6), 111.9 (CH, C-5), 102.3 (CH, C-3), 69.3 (CH, C-10), 41.4 (2 x CH_3).

HRMS [M+H]+$_{found}$ = 248.1310, $C_{17}H_{16}N_2$ required 248.1313.

***N*-Benzyl-*N*-methyl-1,10-dihydro-indeno[1,2-*g*]indole-10-amine (14b):** 100 mg (31%); white solid;

IR: 2918, 1450 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): δ 10.83 (br s, 1H, NH), 7.78 (d, J = 7.4 Hz, 1H, H-6), 7.73 (d, J = 7.4 Hz, 1H, H-9), 7.60 (d, J = 8.1 Hz, 1H, H-4), 7.49 (d, J = 8.1 Hz, 1H, H-5), 7.42 (brs, 1H, H-2), 7.40-7.31 (m, 5H, H-7 and Bn-H), 7.24 (t, J = 7.4 Hz, 1H, H-8), 7.18 (t, J = 7.5 Hz, Bn-4'H), 6.54 (brs, 1H, H-3), 5.29 (s, 1H, H-10), 3.57 (1H, d, J = 13,3 Hz, $BnCH_2$), 3.47 (1H, d, J = 13,3 Hz, $BnCH_2$), 2.22 (s, 3H, CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 143.3 (q, C-9a), 143.0 (q, C-5b), 140.1 (q, Bn-1'C), 134.4 (q, C-5a), 133.2 (q, C-10b), 129.1 (2 xCH, Bn-2' and 6'C), 128.9 (q, C-3a), 128.5 (2 xCH, Bn-3' and 5'C), 128.4 (CH, C-7), 127.4 (q, C-10a), 127.2 (CH, Bn-4'C), 126.7 (CH, C-2), 126.4 (CH, C-9), 125.8 (CH, C-8), 120.9 (CH, C-4), 119.8 CH, C-6), 111.9 (CH, C-5), 102.4 (CH, C-3), 69.1 (CH, C-10), 57.5 (CH_2), 38.7 (CH_3).

HRMS [M+H]+$_{found}$ = 325.1705, $C_{23}H_{21}N_2$ required 325.1704.

1,9,10,12,12a,13-Hexahydro-indolo[6,7-*d*]thiazolo[3,4-*b*][2]benzazepine (15): 20 mg (7%); yellow solid;

IR: 2924, 1436 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.32 (brs, 1H, NH), 7.64 (d, J = 8.1 Hz, 1H, H-4), 7.46 (d, J = 8.2 Hz, 1H, H-6), 7.42 (t, J = 2.8 Hz, 1H, H-2), 7.41-7.38 (m, 2H, H-7 and H-9), 7.23 (t, J = 8.2 Hz, 1H, H-8), 7.19 (d, J = 8.1 Hz, 1H, H-5), 6.53 (1H, t, J = 2.8 Hz, H-3), 4.88 (dd, J = 9.5 Hz and 8.1 Hz, 1H, H-13a), 4.68 (d, J = 9,8 Hz1H,H-12), 4.47 (d, J = 9,8 Hz1H,H-12), 3.80 (d, J = 14.4 Hz, 1H, H-10), 3.71 (d, J = 14.4 Hz, 1H, H-10), 2.66 (1H, dd, J = 9.5 Hz and 8.0 Hz, H-13), 2.03 (1H, dd, J = 9.5 Hz and 8.0 Hz, H-13);

^{13}C NMR (125 MHz, DMSO-d_6): δ 141.3 (q, C-5b), 137.7 (q, C-9a), 135.9 (q, C-14c), 132.4 (q, C-6b), 130.1 (CH, C-9), 128.6 (CH, C-7), 128.2 (q, C-3a), 127.1 (CH, C-8), 127.8 (CH, C-6), 126.7 (CH, C-2), 121.5 (CH, C-5), 120.5 (CH, C-4), 120.0 (q, C-14b), 102.3 (CH, C-3), 64.8 (CH, C-14a), 62.4 (CH_2, C-12), 57.0 (CH_2, C-10), 37.5 (CH_2, C-13).

HRMS [M+H]+$_{found}$ = 293.1099, $C_{18}H_{17}N_2S$ required 293.1112.

2,3,4,5,5a,15-Hexahydro-1H-pyrido[1,2-b]indolo[2,3,4-k,l][2]benzazocine (17): 187 mg (65%); brown-red solid;

IR: 2934, 1447 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.11 (brs, 1H, NH), 7.53 (d, J = 7.7 Hz, 1H, H-11), 7.42 (t, J = 7.7 Hz, 1H, H-12), 7.35 (m, 2H, H-8 and H-13), 7.25 (m, 1H, H-6 and H-14), 7.15 (t, J = 7.6 Hz, 1H, H-9), 6.87 (d, J = 7.6 Hz, 1H, H-10), 4.29 (1H, d, J = 13.6 Hz, H-15), 3.43 (1H, d, J = 13.6 Hz, H-15), 3.12 (brs, 1H, H-5a), 2.89 (br s, 1H,H-2), 1.93 (m, 1H, H-5), 1.80 -(m, 1H, H-5), 1.75 (m, 1H, H-4), 1.63 (m, 1H, H-3), 1.54 (m, 1H, H-3),1.10 (m, 1H, H-4);

^{13}C NMR (125 MHz, DMSO-d_6): δ 142.2 (q, C-910b), 136.3 (q, C-67a), 132.4 (q, C-910a), 131.8 (CH, C-134), 131.4 (q, C-134a), 129.7 (CH, C-101) 128.6 (CH, C-112), 128.0 (q, C-4b7b1), 126.8 (CH, C-123), 123.7 (CH, C-65), 122.1 (CH, C-89), 121.6 (CH, C-910), 116.8 (q, C-45b), 111.3 (CH, C-78), 56.9 (CH_2, C-145), 534.1 (CH, C-15a), 53.1 (CH_2, C-21), 30.9 (CH_2, C-45), 26.4 (CH_2, C-23), 24.9 (CH_2, C-34).

HRMS [M+H]+$_{found}$ = 289.1703, $C_{20}H_{21}N_2$ required 289.1704.

2,3,4,5,5a,15-Hexahydro-1H-thiazolo[3,4-b]indolo[2,3,4-k,l][2]benzazocine (18): 108 mg (37%); brown solid;

IR: v: 1411 cm^{-1};

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.23 (br s, 1H, NH), 7.52 (dd, J = 7.5 and 1.4 Hz, 1H, H-11), 7.45 (td, J = 7.5 and 1.4 Hz, 1H, H-10), 7.41 (d, J = 3.4 Hz, 1H, H-2),7.39 (d, J = 7.5 Hz, 1H, H-14), 7.38 (td, J = 7.5 and 1.4 Hz, 1H, H-9), 7.33 (dd, J = 7.5 and 1.4 Hz, 1H, H-8), 7.19 (t, J = 7.5 Hz, 1H, H-13), 6.92 (dm, J = 7.3 Hz, 1H, H-12), 3.99 (t, J = 5.8 Hz, 1H, H-2*b*), 3.81 (d, J = 6.3 Hz, 1H, H-5), 3.78 (2, 2H, 7-CH_2), 3.52 (d, J = 6.3 Hz, 1H, H-5), 3.25 (dd, J = 9.8 Hz and 5.7 Hz, 1H, H-3), 3.02 (dd, J = 9.8 Hz and 5.7 Hz, 1H, H-3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 141.9 (q, C-11a), 136.6 (q, C-14a), 133.2 (q, C-7a), 132.5 (q, C-11b), 131.8 (CH, C-8), 130.2 (CH, C-11), 129.0 (CH, C-10), 127.6 (CH, C-9), 127.4 (q, C-14b), 123.8 CH, C-2), 122.4 (CH, C-13), 121.5 (CH, C-12), 111.5 (CH, C-14), 110.5 (q, C-2a), 57.1 (CH, C-2b), 32.7 (CH_2, C-3), 52.9 (CH_2, C-5), 52.5 (CH_2, C-7).

HRMS [M+H]+$_{found}$ = 293.1103, $C_{18}H_{17}N_2S$ required 293.1112.

Synthesis of 1,3-dipolar cycloadducts. General procedure:

The mixture of the corresponding aldehyde (**3a,c,d, 4,** 0.5 mmol), 136 mg (1.5 mmol) of sarcosine and 89 mg (0.5 mmol) of *N*-phenyl-maleimide in dry toluene (5 ml) was refluxed for 1 h. After cooling, the reaction mixture was filtered through a pad of Celite and concentrated. The crude product was purified by column chromatography on silica gel with ethyl acetate – heptane eluent.

4-[2-(1H-Indole-5-yl)-phenyl]-5-methyl-2-phenyl-octahydro-pyrrolo[3,4-c]pyrrol-1,3-dione (19a): 95 mg (45 %), white powder;

IR: v: 1708, 1382 cm^{-1};

^{1}H NMR (500 Hz, DMSO,-d_6): δ 11.18 (s, 1H, NH), 7.59 (d, J = 7.6 Hz, 1H, Ph-6'H), 7.47-7.37 (m, 7H, Ind-2', 4' and 7'H, *N*Ph-3',4' and 5'H, Ph-5'H), 7.35 (t, *J* = 7.7 Hz, 1H, Ph-4'H), 7.23 (d, *J* = 7.7 Hz, 1H, Ph-3'H), 7.03 (brd, *J* = 7.0 Hz, 2H, NPh-2' and 6'H), 6.97 (d, *J* = 8.4 Hz, 1H, Ind-6'H), 6.41 (brs, 1H, Ind-3'H), 3.73 (m, 1H, H-6a), 3.66 (d, *J* = 7.8 Hz, 1H, H-4), 3.52 (dd, J = 8.6 Hz and 7.8 Hz, 1H, H-3a), 3.45 (t, J = 9.5 Hz, 1H, H-6), 2.27 (dd, *J* = 9.5 Hz and 7.3 Hz, 1H, H-6), 1.84 (s, 3H, *N*CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 177.6 (q, C-1), 176.1 (q, C-3), 145.1 (q, Ph-2'C), 137.2 (q, Ph-1'C), 135.3 (q, Ind-7'C), 132.5 (q, *N*Ph-1'C), 131.6 (q, Ind-5'C), 130.7 (CH, Ph-3'C), 129.3 (2xCH, *N*Ph-3' and 5'C), 128.8 (CH, *N*Ph-4'C), 128.1 (CH, Ph-6'C), 127.9 (CH, Ph-5'C), 127.8 (q, Ind-3a'C), 127.5 (CH, Ph-4'C), 127.3 (2xCH, *N*Ph-2' and 6'C), 126.4 (CH, Ind-2'C), 123.6 (CH, Ind-6'C), 121.5 (CH, Ind-4'C), 111.2 (CH, Ind-7'C), 101.6 (CH, Ind-3'C), 67.8 (CH, C-4), 57.1 (CH_2, C-6), 54.7 (CH, C-3*a*), 44.5 (CH, C-6*a*), 38.8 (CH_3).

HRMS [M+H]+$_{found}$ = 422.1847, $C_{27}H_{24}N_3O_2$ required 422.1868.

4-[2-(1H-Indole-5-yl)-phenyl]-5-methyl-2-phenyl-octahydro-pyrrolo[3,4-c]pyrrol-1,3-dione (20a): 89 mg (42 %), white powder;

IR v: 1704, 1383 cm^{-1};

^1H NMR (500 MHz, DMSO,-d_6): δ 11.21 (s, 1H, NH), 7.53 (brs, 1H, Ind-4'H), 7.48 (t, *J* = 7.5 Hz, 2H, *N*Ph-3' and 5'H), 7.46 (d, J = 7.4 Hz, Ind-7'H), 7.42-7.38 (m, 3H, *N*Ph-4'H, Ph-6'H and Ind-2'H), 7.33 (t, *J* = 7.5 Hz, 1H, Ph-5'H), 7.26 (t, *J* = 7.5 Hz, 1H, Ph-4'H), 7.20-7.16 (m, 3H, Ph-3'H, *N*Ph-2' and 6'H), 7.11 (brd, *J* = 7.4 Hz, 1H, Ind-6'H), 6.46 (br s, 1H, Ind-3'H), 3.42 (d, *J* = 9.2 Hz, 1H, H-4), 3.40 (m, 1H, H-6), 3.38 (m, 1H, H-6a), 3.28 (dd, *J* = 9.2 and 8.3 Hz, 1H, H-3a), 2.37 (dd, *J* = 9.4 6.6 Hz, 1H, H-6), 2.00 (s, 3H,*N*CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 179.0 (q, C-1), 175.7 (q, C-3), 144.5 (q, Ph-2'C), 135.9 (q, Ph-2'C), 135.6 (q, Ind-7a'C), 133.0 (q, NPh-1'C), 132.1 (q, Ind-5'C), 130.5 (CH, Ph-3'C), 129.4 (2xCH, *N*Ph-3' and 5'C), 128.7 (CH, NPh-4'C), 127.9 (q, Ind-3a'C), 127.3 (CH, Ph-5'C), 127.2 (3xCH, Ph-4'C, *N*Ph-2' and 6'C), 127.0 (CH, Ph-6'C), 126.5 (CH, Ind-2'C), 122.5 (CH, Ind-6'C), 120.3 (CH, Ind-4'C), 111.4 (CH, Ind-4'C), 101.7 (CH, Ind-3'C), 69.8 (CH, C-4), 57.6 (CH_2, C-6), 51.1 (CH, C-3*a*), 45.3 (CH, C-6*a*), 39.9 (CH_3).

HRMS $[M+H]^+_{found}$ = 422.1857, required $C_{27}H_{24}N_3O_2$ 422.1868.

4-(2-Benzofuran-5-yl-phenyl)-5-methyl-2-phenyl-octahydro-pyrrolo[3,4-c]pyrrole-1,3-dione (19b): 88 mg (42 %), white powder;

IR v: 1709, 1176 cm^{-1};

^1H NMR (500 Hz, DMSO,-d_6): δ 8.07 (d, *J* = 2.2 Hz, 1H, Bf-2'H), 7.62 (d, *J* = 8,3 Hz, 2H, Bf-7 and Ph-6'H), 7.51 (d, *J* = 1.5 Hz, 1H, Bf-4'H), 7.49 (t, *J* = 8.0 Hz, 1H, Ph-5'H), 7.47-7.39 (m, 3H, *N*Ph-3', 4' and 5'H), 7.38 (t, *J* = 8.0 Hz, 1H, Ph-4'H), 7.24 (1H, d, *J* = 8.0 Hz, Ph-4'H), 7.19 (d, *J* = 8.5 Hz, 1H, Bf-6'H), 7.03 (br m, 2H, *N*Ph-2' and 6'H), 6.95 (d, *J* = 2.1 Hz, 1H, Bf-3'H), 3.72 (m, 1H, H-6*a*), 3.55 (d, *J* = 7.8 Hz, 1H, H-4), 3.51 (dd, *J* = 7.8 and 8.4 Hz, 1H, H-4*a*), 3.46 (t, *J* = 9.4 Hz, 1H, H-6), 2.31 (dd, *J* = 9.4 Hz and 7.6 Hz, 1H, H-6), 1.87 (s, 3H, *N*CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 177.4 (q, C-1), 176.2 (q, C-3), 153.9 (q, Bf-7*a*'C), 147.2 (CH, Bf-2'C), 143.7 (q, Ph-2'C), 137.5 (q, Ph-1'C), 135.7 (q, Bf-5'C), 132.9 (q, *N*Ph-1'C), 130.5 (CH, Ph-3'C), 129.4 (2xCH, *N*Ph-3' and 5'C), 128.8 (CH, *N*Ph-4'C), 128.5 (CH, Ph-5'C), 128.3 (CH, Ph-6'C), 127.7 (CH, Ph-4'C), 127.3 (2xCH, *N*Ph-2' and 6'C), 126.7 (CH, Bf-6'C), 122.8 (CH, Bf-4'C), 111.0 (CH, Bf-7'C), 107.3 (CH, Bf-3'C), 67.8 (CH, C-4), 57.1 (CH_2, C-6), 54.9 (CH, C-3*a*), 44.5 (CH, C-6*a*), 38.8 (CH_3).

HRMS $[M+H]^+_{found}$ = 423.1678, $C_{27}H_{23}N_2O_3$ required 423.1708.

4-(2-Benzofuran-5-yl-phenyl)-5-methyl-2-phenyl-octahydro-pyrrolo[3,4-*c]*pyrrole-1,3-dione (20b): 92 mg (44 %), white powder;

IR v: 1709, 1180 cm^{-1};

^1H NMR (500 MHz, DMSO,-d_6): δ 8.07 (d, *J* = 2.2 Hz, 1H, Bf-2'H), 7.69 (d, *J* = 8.4 Hz, 1H, Bf-7'H), 7.66 (d, *J* = 1.5 Hz, 1H, Bf-4'H), 7.48 (t, *J* = 7.0 Hz, 2H, *N*Ph-3' and 5'H), 7.46 (d, *J* = 7.5 Hz, 1H, Ph-6'H), 7.40 (t, *J* = 7.0 Hz, 1H, *N*Ph-4'H), 7.37 (t, *J* = 7.5 Hz, 1H, Ph-5'H), 7.33 (dd, *J* = 8.4 Hz and 1.2 Hz, 1H, Bf-6'H), 7.29 (t, *J* = 7.5 Hz, 1H, Ph-4'H), 7.20 (d, *J* = 7.5 Hz, 1H, Ph-3'H), 7.16 (d, *J* = 7.0 Hz, 2H, *N*Ph-2' and 6'H), 7.02 (dd, *J* = 2.2 and 0.9 Hz, 1H, Bf-3'H), 3.40 (m, 1H, H-6), 3.39 (m, 1H, H-6*a*), 3.37 (d, *J* = 9.0 Hz, 1H, H-4), 3.24 (dd, *J* = 9.0 and 8.2 Hz, 1H, H-3*a*), 2.41 (dd, *J* = 9.5 and 6.5 Hz, 1H, H-6*a*), 2.03 (s, 3H, *N*CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 178.9 (q, C-1), 175.6 (q, C-3), 154.1 (q, Bf-7*a*'C), 147.2 (CH, Bf-2'C), 143.1 (q, Ph-2'C), 136.2 (q, Bf-5'C), 135.9 (q, Ph-1'C), 132.9 (q, *N*Ph-1'C), 130.3 (CH, Ph-3'C), 129.4 (2xCH, NPh-3' and 5'H), 128.7 (CH, Ph-4'C), 127.9 (CH, Ph-5'C), 127.6 (q, Bf-3*a*'C), 127.4 (CH, Ph-4'C), 127.2 (2xCH, NPh-2' and 6'H), 127.0 (CH, Ph-6'C), 125.7 (CH, Bf-6'C), 121.6 (CH, Bf-4'C), 111.3 (CH, Bf-7'C), 107.4 (CH, Bf-3'C), 69.6 (CH, C-4), 57.5 (CH_2, C-4), 50.9 (CH, C-3*a*), 45.3 (CH, C-6*a*), 39.9 (CH_3).

HRMS $[M+H]^+_{found}$ = 423.1697, $C_{27}H_{23}N_2O_3$ required 423.1708.

4-(2-Benzo[b]thiophen-5-yl-phenyl)-5-methyl-2-phenyl-octahydro-pyrrolo[3,4-c]pyrrole-1,3-dione (19c): 100 mg (46 %), white powder;

IR, v: 1711, 1380 cm^{-1};

^1H NMR (500 MHz, DMSO,-d_6): δ 8.04 (d, *J* = 8.3 Hz, 1H, Bt-7'H), 7.84 (d, *J* = 5.4 Hz, 1H, Bt-2'H), 7.76 (d, *J* = 1.3 Hz, 1H, Bt-4'H), 7.64 (d, *J* = 7.9 Hz, 1H, Ph-6'H), 7.51 (t, *J* = 7.9 Hz, 1H, Ph-5'H), 7.44-7.37 (m, 5H, *N*Ph-3',4' and5'H, Ph-4'H and Bt-3'H), 7.27 (dm, *J* = 8.0 Hz, 2H, Ph-3'H and Bt-6'H), 6.97 (br m, 2H, *N*Ph-2' and 6'H), 3.72 (m, 1H, H-6*a*), 3.59 (d, *J* = 7.7 Hz, 1H, H-4), 3.51 (dd, *J* = 9.0 and 7.7 Hz, 1H, H-3*a*), 3.46 (t, *J* = 9.5 Hz, 1H, H-6), 2.34 (dd, *J* = 9.5 and 7.6 Hz, 1H, H-6), 1.90 (s, 3H, *N*CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 177.4 (q, C-1), 176.2 (q, C-3), 143.5 (q, Ph-2'C), 139.7 (q, Bt-3*a*'H), 138.4 (q, Bt-7*a*'H), 137.5 (q, Ph-1'C), 137.1 (q, Bt-5'H), 132.5 (q, *N*Ph-1'C), 130.4 (CH, Ph-3'H), 129.3 (2xCH, *N*Ph-3' and 5'C), 128.8 (CH, *N*Ph-4'C), 128.7 (CH, Bt-2'C), 128.6 (CH, Ph-5'C), 128.3 (CH, Ph-6'C), 127.8 (CH, Ph-4'C), 127.3 (2xCH, *N*Ph-2' and 6'C), 126.7 (CH, Bt-6'C), 125.1 (CH, Bt-4'C), 124.5 (CH, Bt-3'C), 122.5 (CH, Bt-7'C), 67.8 (CH, C-4), 57.0 (CH_2, C-6), 54.9 (CH, C-3*a*), 44.5 (CH, C-6*a*), 38.8 (CH_3).

HRMS $[M+H]^+_{found}$ = 439.1468, $C_{27}H_{23}N_2O_2S$ required 439.1480.

4-(2-Benzo[b]thiophen-5-yl-phenyl)-5-methyl-2-phenyl-octahydro-pyrrolo[3,4-c]pyrrole-1,3-dione (20c): 95 mg (45 %), white powder;

IR, v: 1708, 1500 cm^{-1};

^1H NMR (500 MHz, DMSO,-d_6): δ 8.10 (d, *J* = 8.2 Hz, 1H, Bt-7'H), 7.89 (br s, 1H, Bt-4'H), 7.85 (d, *J* = 5.4 Hz, 1H, Bt-2'H), 7.52 (d, *J* = 5.4 Hz, 1H, Bt-3'H), 7.48 (t, *J* = 7.5 Hz, 2H, *N*Ph-3' and 5'H), 7.47 (d, *J* =7.4 Hz, 1H, Ph-6'H), 7.40 (m, 3H, *N*Ph-4'H, Ph-5'H, Bt-6'H), 7.31 47 (t, *J* =7.4 Hz, 1H, Ph-4'H), 7.22 47 (d, *J* =7.4 Hz, 1H, Ph-3'H), 7.17 (d, *J* = 7.5 Hz, 2H, *N*Ph-2' and 6'H), 3.40 (m, 3H, H-4, H-6, H-6*a*), 3.28 (dd, *J* = 9.2 and 8.3 Hz, 1H, H-3*a*), 2.42 (dd, 1H, *J* = 9.2 and 6.9 Hz, H-6), 2.03 (s, 3H, *N*CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 178.9 (q, C-1), 175.6 (q, C-3), 142.9 (q, Ph-2'C), 139.9 (q, Bt-3*a*'C), 138.6 (q, Bt-7*a*'C), 137.6 (q, Bt-5'C), 135.8 (q, Ph-1'C), 132.9 (q, *N*Ph-1'C), 130.3 (CH, Ph-3'C), 129.4 (2xCH, *N*Ph-3' and 5'C), 128.8 (CH, Bt-2'C), 128.7 (CH, *N*Ph-4'C), 128.0 (CH, Ph-5'C), 127.4 (CH, Ph-4'C), 127.2 (2xCH, *N*Ph-2' and 6'C), 127.1 (CH, Ph-6'C), 126.7 (CH, Bt-6'C), 124.7 (CH, Bt-3'C), 123.9 (CH, Bt-4'C), 122.8 (CH, Bt-7'C), 69.6 (CH, C-4), 57.5 (CH_2, C-6), 51.0 (CH, C-3*a*), 45.3 (CH, C-6*a*), 39.9 (CH_3).

HRMS $[M+H]^+_{found}$ = 439.1471, $C_{27}H_{23}N_2O_2S$ required 439.1480.

4-[2-(1H-Indole-6-yl)-phenyl]-5-methyl-2-phenyl-octahydro-pyrrolo[3,4-c]pyrrol-1,3-dione (19d): 78 mg (38 %), white powder;

IR, v: 1706 cm^{-1};

^1H NMR (500 MHz, DMSO,-d_6): δ 11.20 (s, 1H, NH), 7.60 (d, *J* = 7.5 Hz, 1H, Ph-6'H), 7.53 (d, *J* = 7.9 Hz, 1H, Ind-4'H), 7.46 (t, *J* = 7.5 Hz, 1H, Ph-5'H), 7.38 (m, 4H, Ind-2'H, *N*Ph-3',4' and 5'H), 7.36 (t, *J* = 7.6 Hz, 1H, Ph-4'H), 7.27 (s, 1H, Ind-7'H), 7.24 (d, *J* = 7.6 Hz, 1H, Ind-6'H), 6.93 (br s, 2H, *N*Ph-2' and 6'H), 6.88 (d, *J* = 7.9 Hz, 1H, Ind-5'H), 6.47 (s, 1H, Ind-3'H), 3.72 (m, 1H, H-6*a*), 3.67 (d, *J* = 7.6 Hz, 1H, H-2), 3.47 (d, *J* = 7.6 Hz, 1H, H-3*a*), 3.46 (t, *J* = 9.1 Hz, 1H, H-6), 2.31 (dd, *J* = 9.1 and 7.2 Hz, 1H, H-6), 1.92 (s, 3H, *N*CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 177.5 (q, C-1), 176.0 (q, C-3), 144.9 (q, Ph-2'C), 137.3 , 136.1, 133.7, 132.5, 130.6, 129.3, 128.7, 128.0, 128.0, 127.6, 127.3, 127.0, 126.3, 121.6, 119.6, 113.1, 101.4, 67.8, 57.0, 54.8, 44.5, 38.9.

HRMS $[M+H]^+_{found}$ = 422.1846, $C_{27}H_{24}N_3O_2$ required 422.1868.

4-[2-(1H-Indole-6-yl)-phenyl]-5-methyl-2-phenyl-octahydro-pyrrolo[3,4-c]pyrrol-1,3-dione (20d): 82 mg (39 %), white powder;

IR, v: 1703, 1383 cm^{-1};

^1H NMR (500 MHz, DMSO,-d_6): δ 11.17 (1H, s, -NH), 7.60 (1H, d, J = 8.1 Hz), 7.49 (2H, m), 7.45-7.38 (4H, m), 7.34 (1H, m), 7.28 (1H, m), 7.20 (1H, dm, J = 9.0 Hz), 7.18 (2H, m), 7.02 (1H, brd, J = 8.1 Hz), 6.48 (1H, brt), 3.45 (1H, d, J = 9.2 Hz, -CH-), 3.40 (1H, m, -CH_2-), 3.40 (1H, m, -CH-), 3.29 (1H, dd, J = 9.2 Hz and 8,1 Hz, -CH-), 2.39 (1H, dd, J = 9.4 Hz and 6.6 Hz, -CH_2-), 2.01 (3H, s, -CH_3);

^{13}C NMR (125 MHz, DMSO-d_6): δ 179.0 (q), 175.6 (q), 144.3 (q), 136.1 (q), 135.8 (q), 134.3 (q), 132.9 (q), 130.3 (CH), 129.4 (2 x CH), 128.7(CH), 127.4 (2

x CH), 127.2 (2 x CH), 127.2 (q), 127.1 (CH), 126.3 (CH), 120.6 (CH), 120.0 (CH), 111.9 (CH), 101.5 (CH), 69.7 (CH), 57.6 (CH_2), 51.0 (CH), 45.3 (CH), 39.9 (CH_3).

HRMS $[M+H]+_{found}$ = 422.1842, $C_{27}H_{24}N_3O_2$ required 422.1868.

Computational method: All computations were carried out with the Gaussian16 program package (G16)[9], using convergence criteria of 3.0×10^{-4}, 4.5×10^{-4}, 1.2×10^{-3} and 1.8×10^{-3}, for the gradients of the root mean square (RMS) force, maximum force, RMS displacement, and maximum displacement vectors, were used, respectively. Computation was carried out at at M06-2X/6-31++G(d,p) level of theory[10], using integral equation formalism-polarisable continuum model (IEFPCM) method with the parameters of THF.[14] The method and basis sets were chosen for their reliability shown in earlier studies.[15] The vibrational frequencies were computed at the same levels of theory, as used for geometry optimisation, in order to properly confirm that all structures reside at minima on their potential energy hypersurfaces (PESs). Thermodynamic functions, such as energy (*U*), enthalpy (*H*), Gibbs free energy (*G*), and entropy (*S*) were computed for 298.15 K, using the quantum chemical, rather than the conventional thermodynamic reference state.

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Supporting Information

There is **Supporting Information** to be published.

Primary Data

There is no **Primary Data** to be associated with this manuscript.

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SUPPORTING INFORMATION

for

Electrocyclization and Unexpected Reactions of Non-Stabilised α,β:γ,δ-Unsaturated Azomethine Ylides. Experimental and Theoretical Study.

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SUPPORTING INFORMATION

^{1}H-NMR and ^{13}C-APT Spectra of Synthesized Compounds

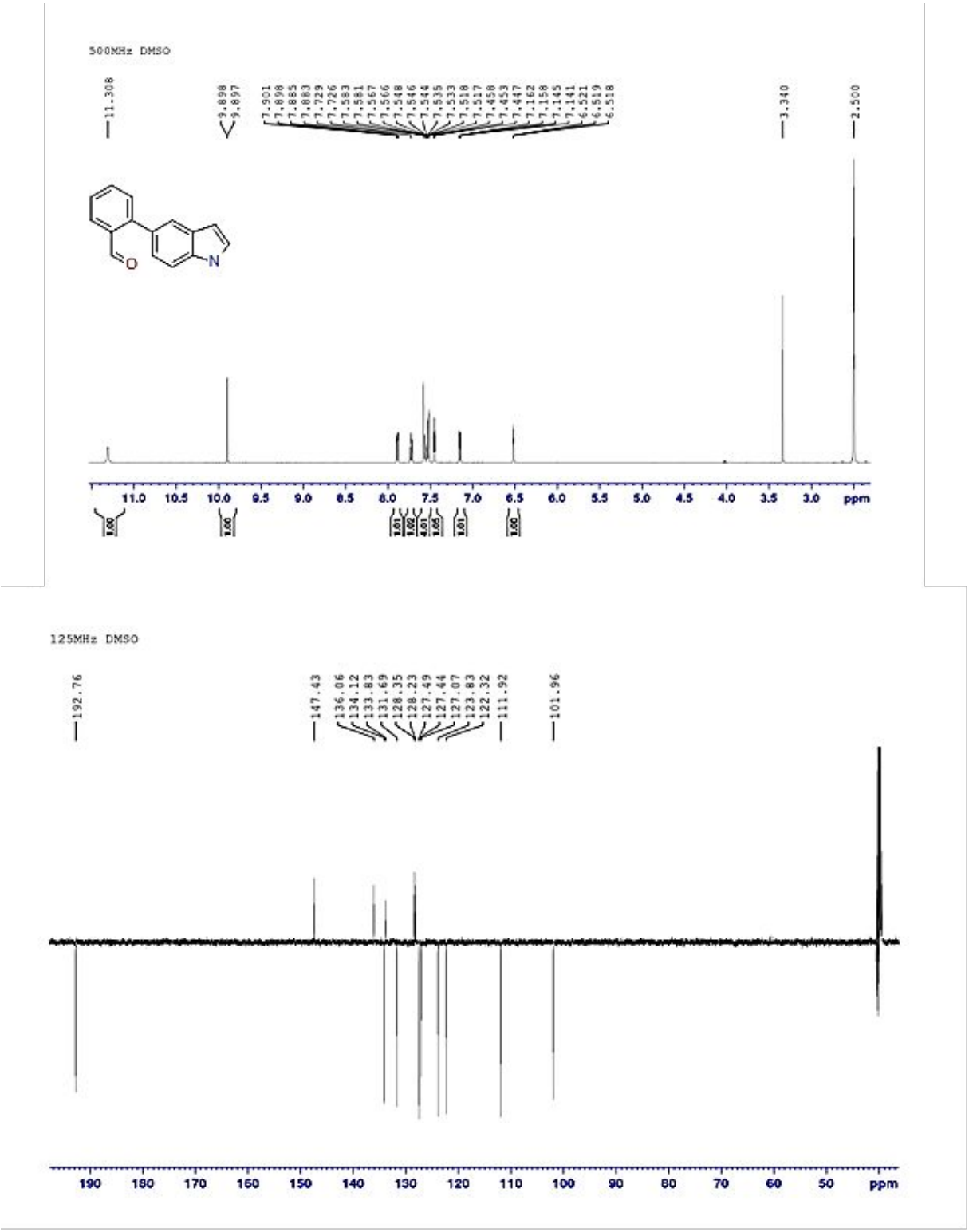
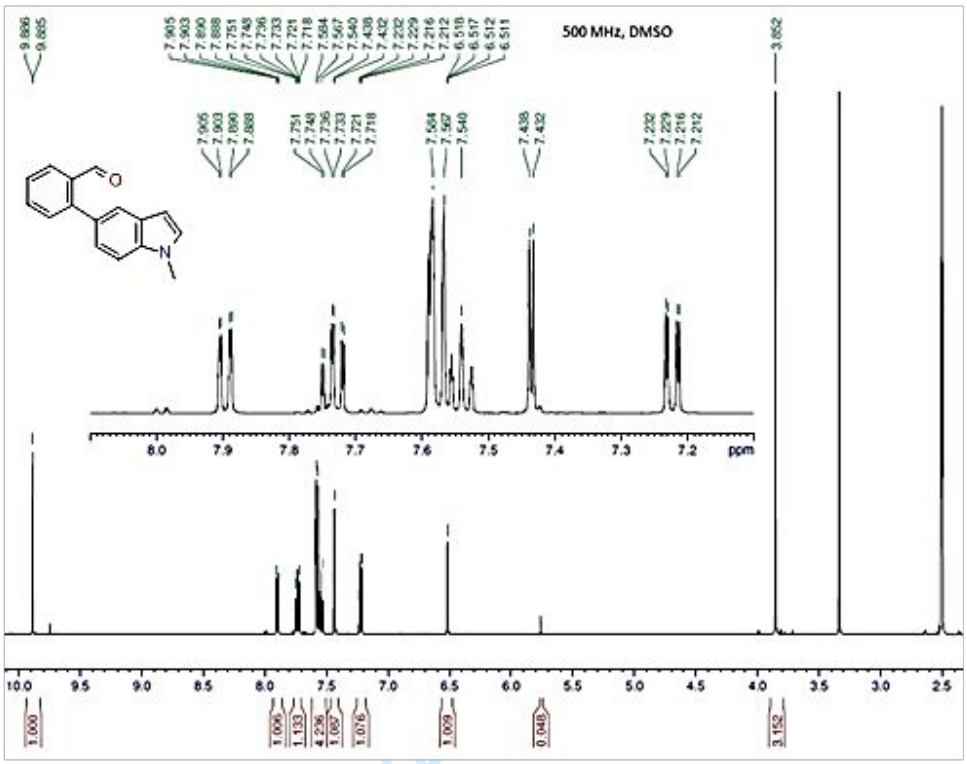


Figure S1. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **3a** in DMSO-d_6

SUPPORTING INFORMATION



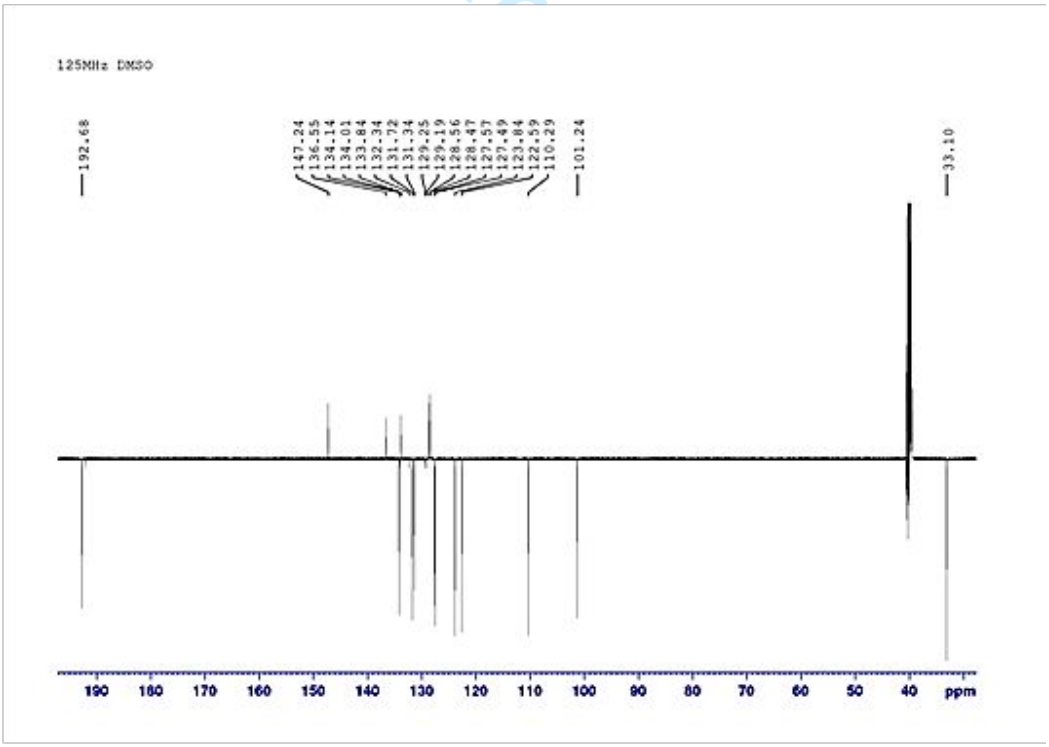


Figure S2. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **3b** in DMSO-d_6

SUPPORTING INFORMATION

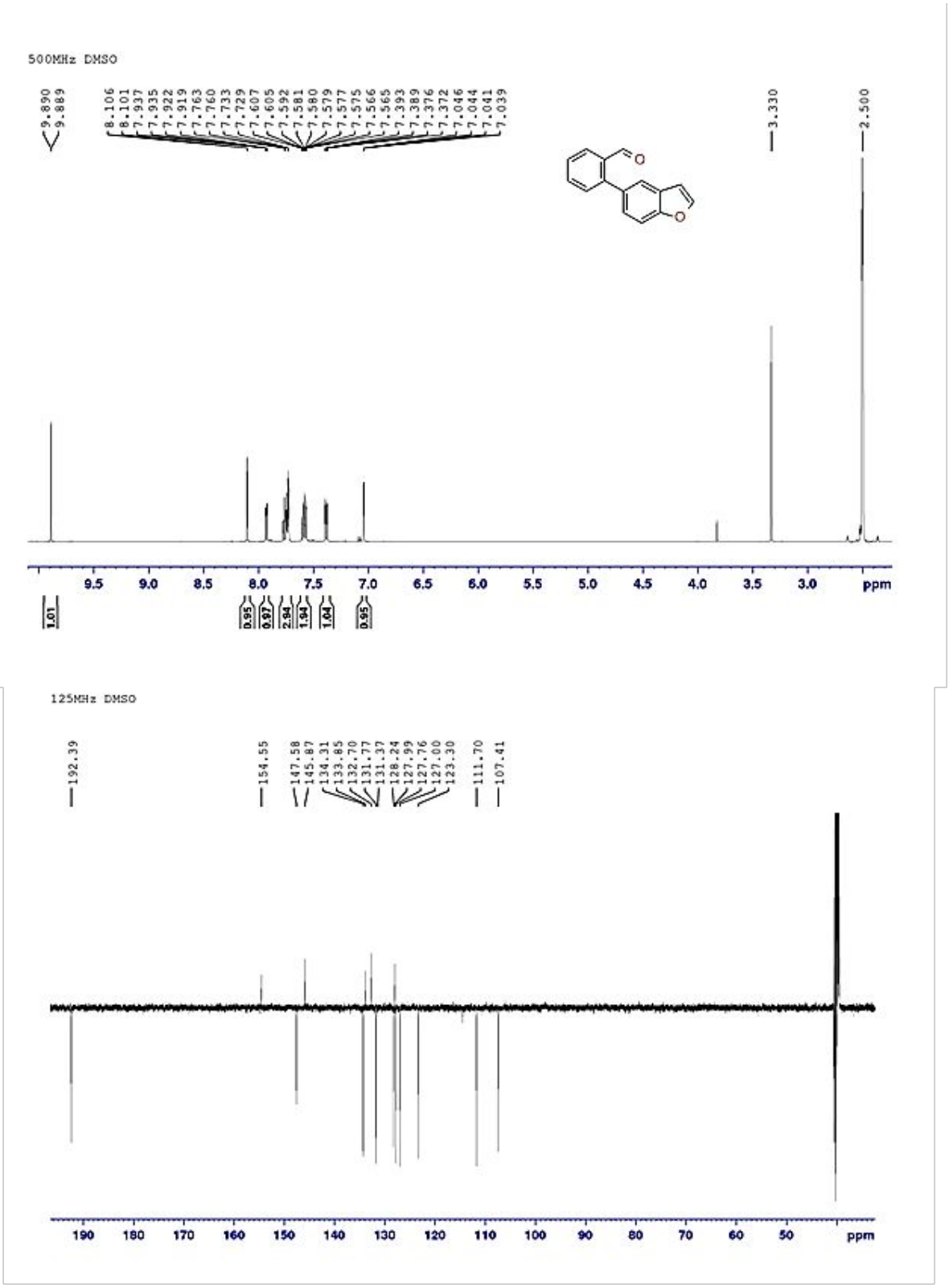


Figure S3. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **3c** in DMSO-d_6

SUPPORTING INFORMATION

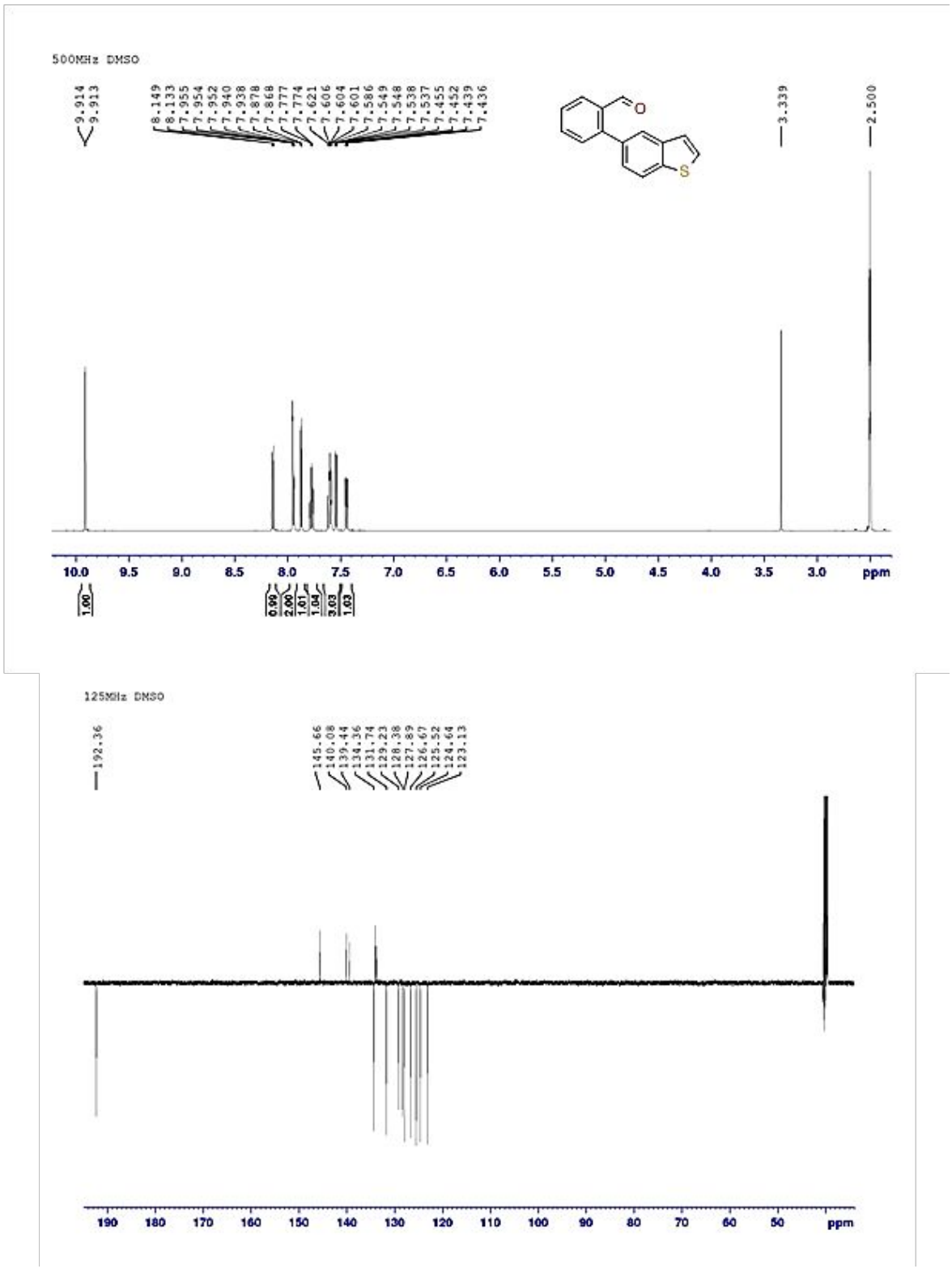
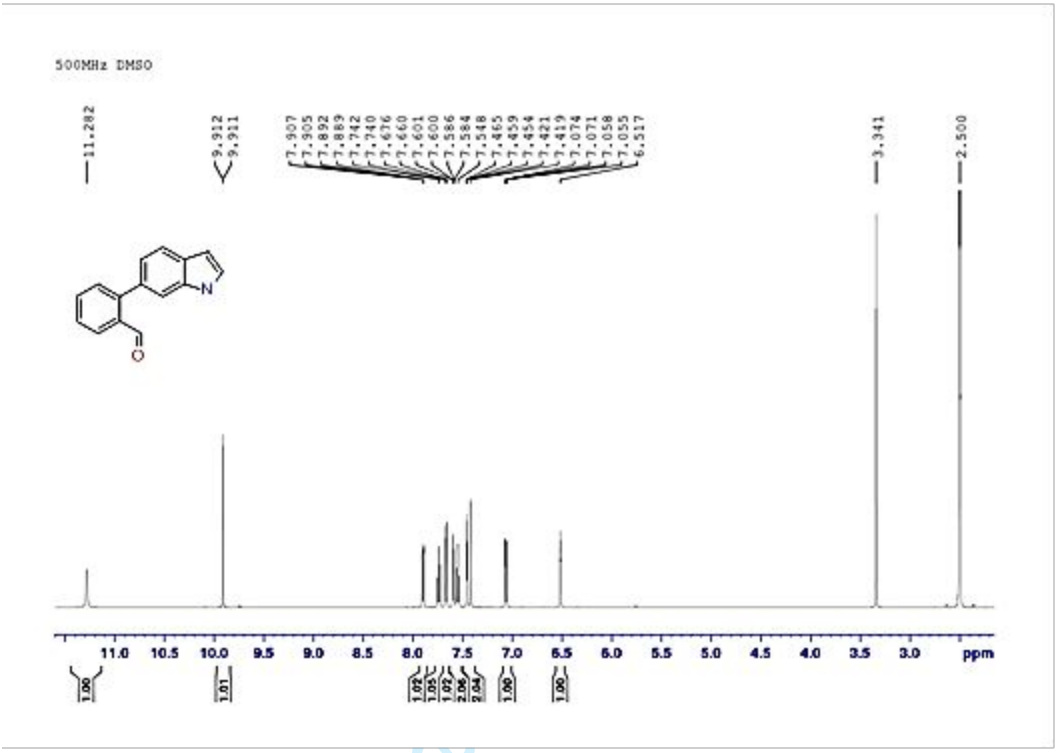


Figure S4. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **3d** in DMSO-d_6

SUPPORTING INFORMATION



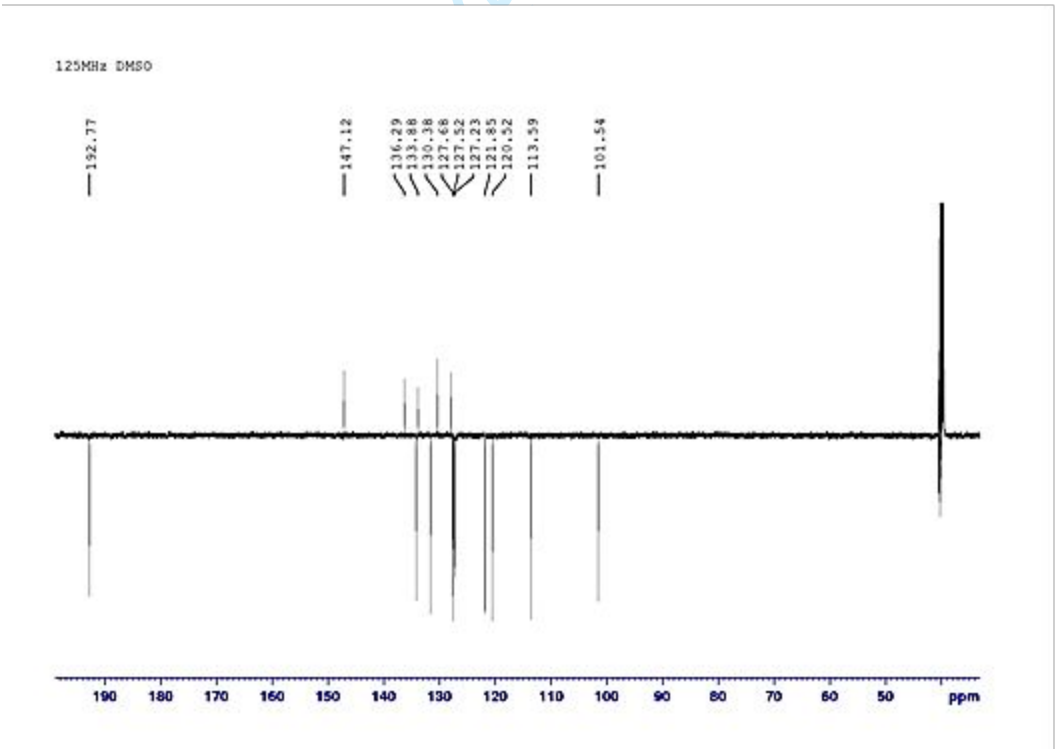
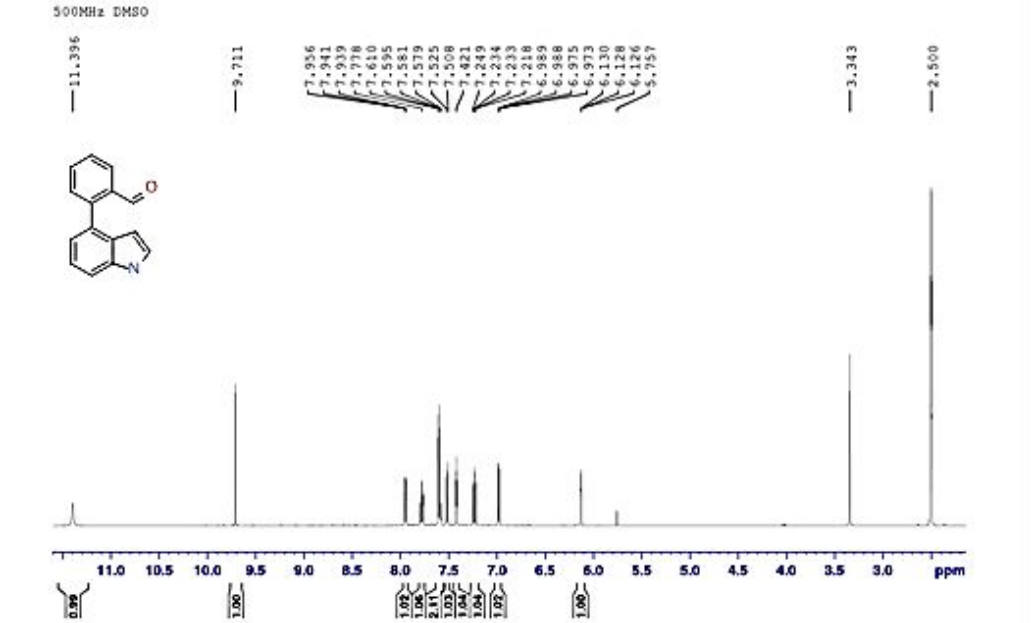


Figure S5. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **4** in DMSO-d_6

SUPPORTING INFORMATION



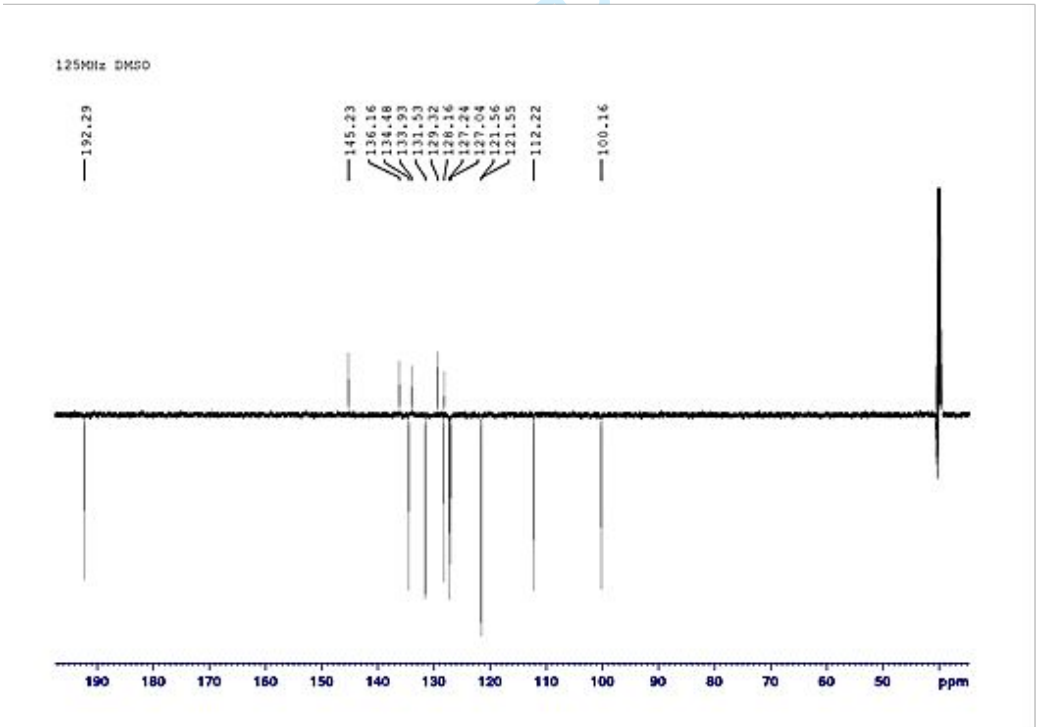
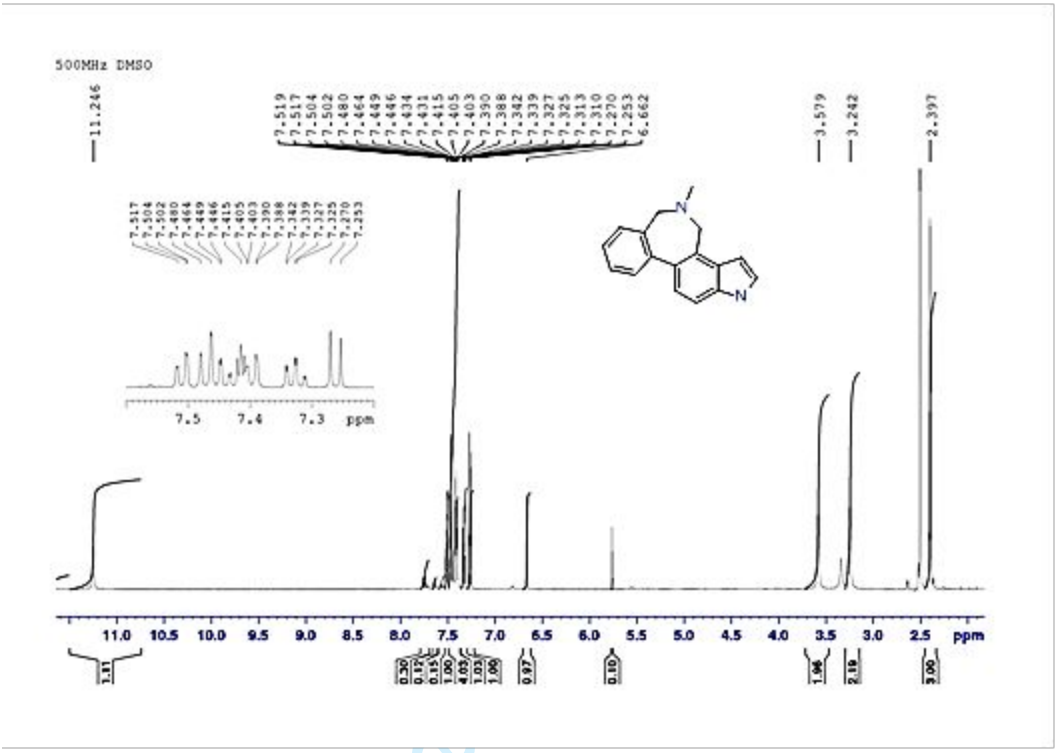


Figure S6. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **5** in DMSO-d_6

SUPPORTING INFORMATION



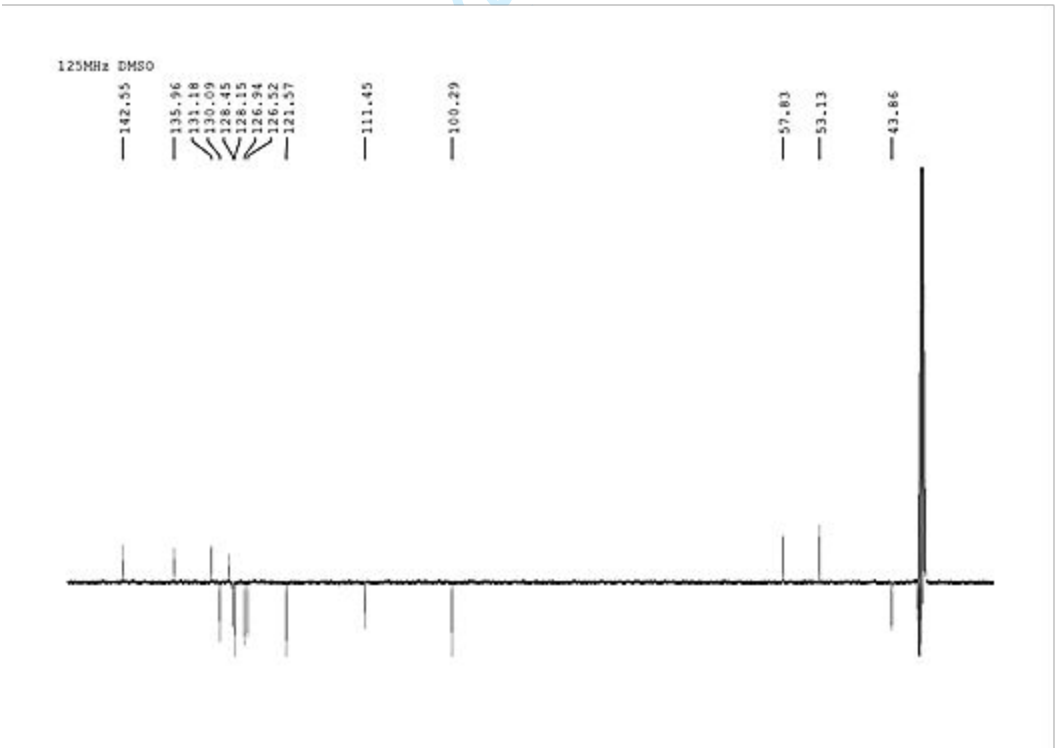
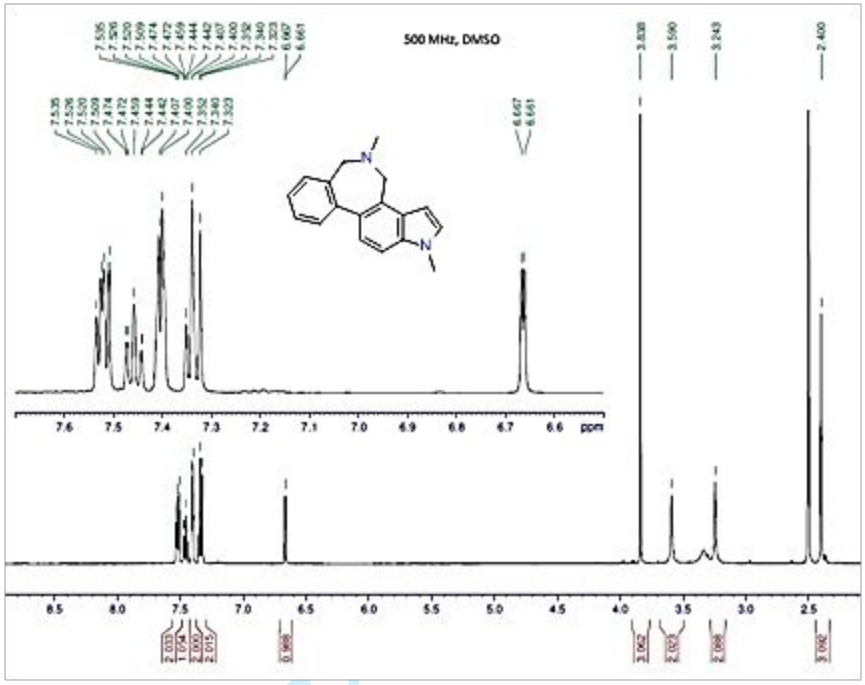


Figure S7. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **8a** in DMSO-d_6

SUPPORTING INFORMATION



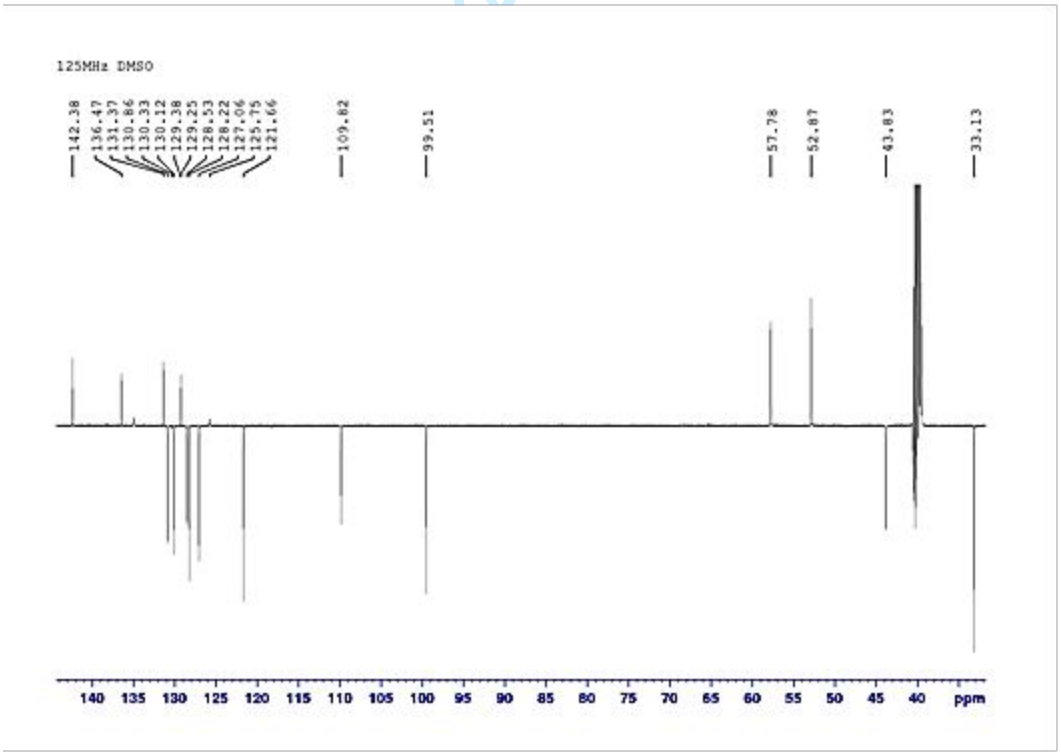


Figure S8. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **8b** in DMSO-d_6

SUPPORTING INFORMATION

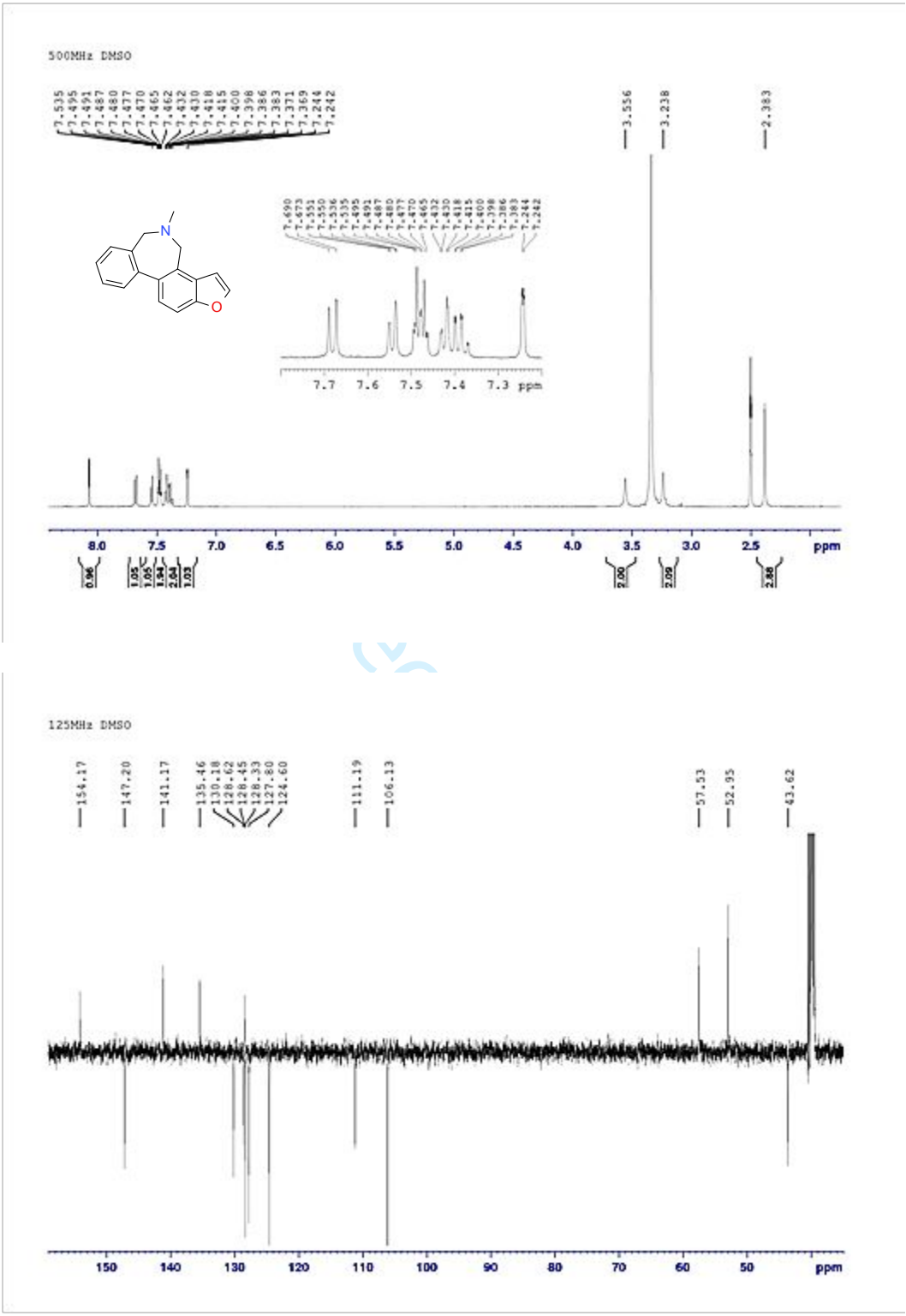
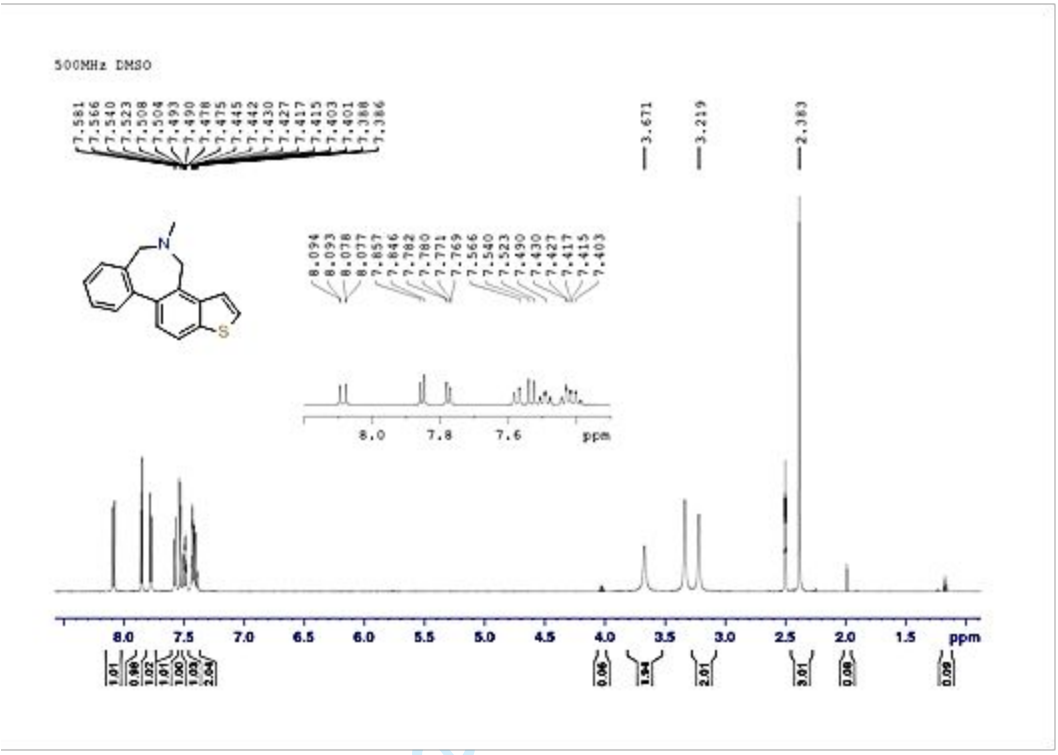


Figure S9. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **8c** in DMSO-d_6

SUPPORTING INFORMATION



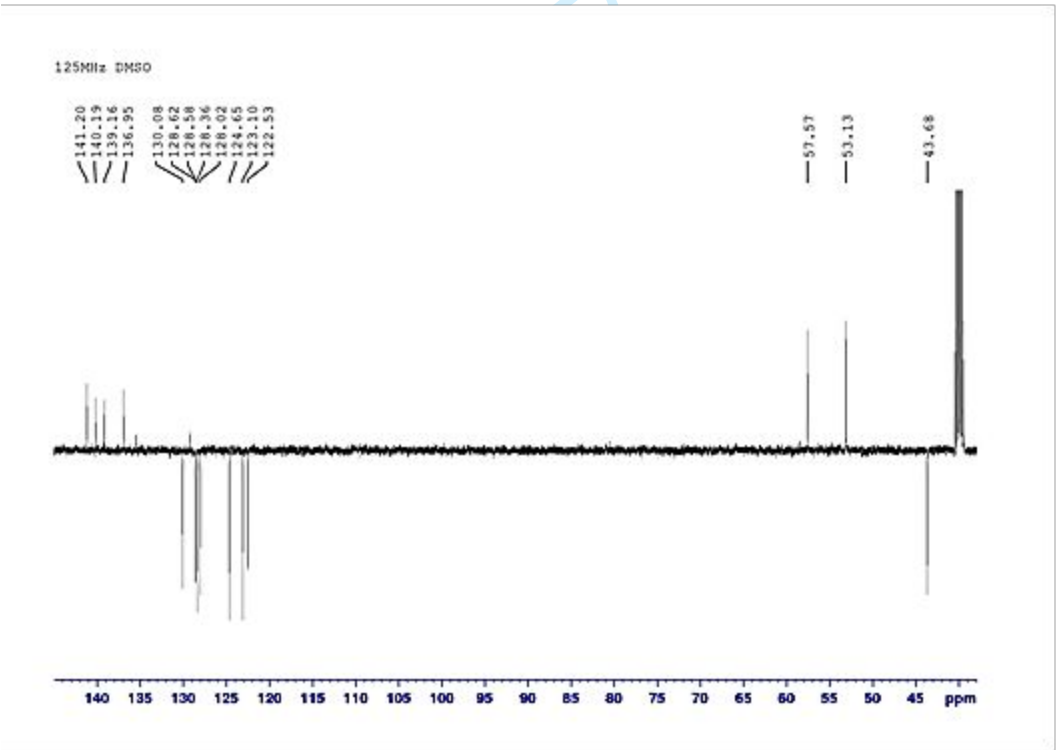
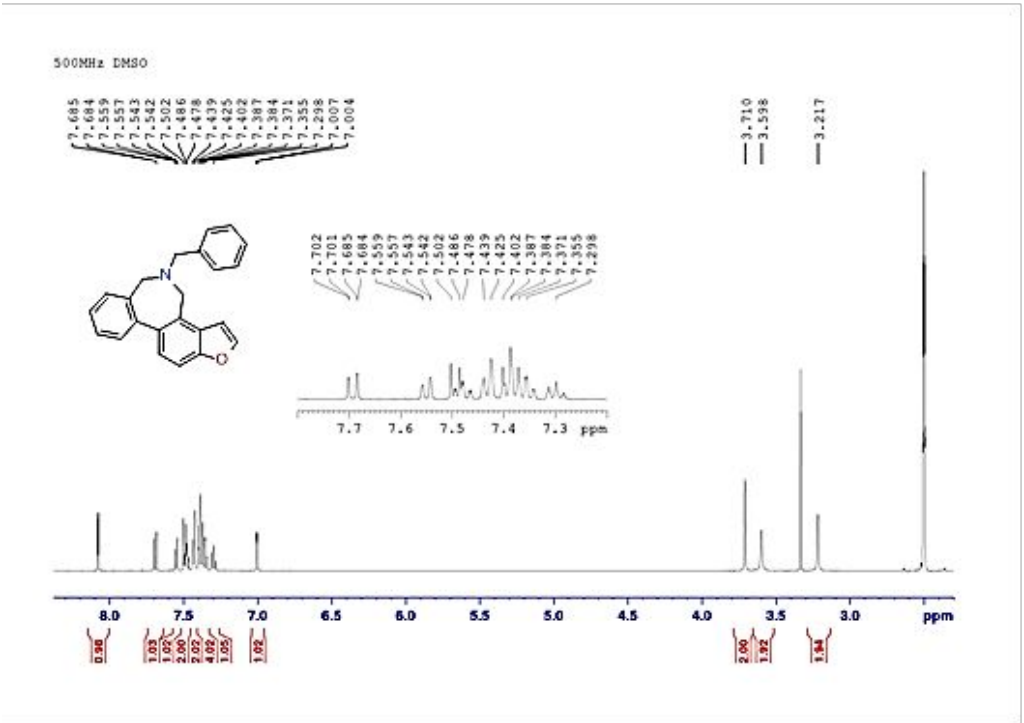


Figure S10. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **8d** in DMSO-d_6

SUPPORTING INFORMATION



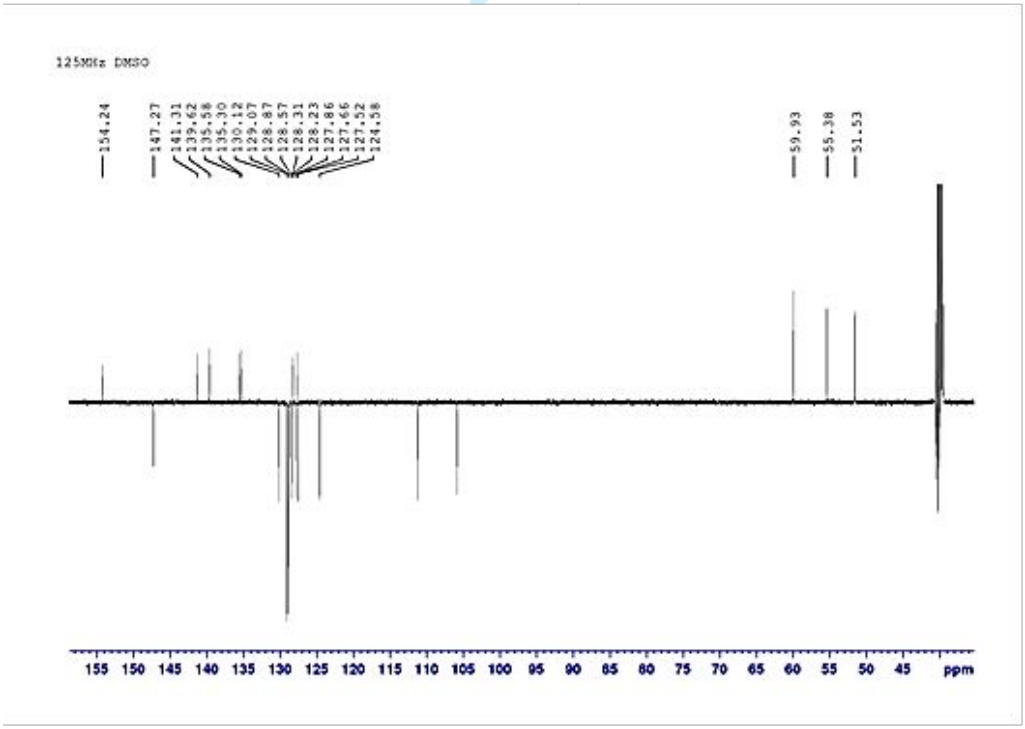
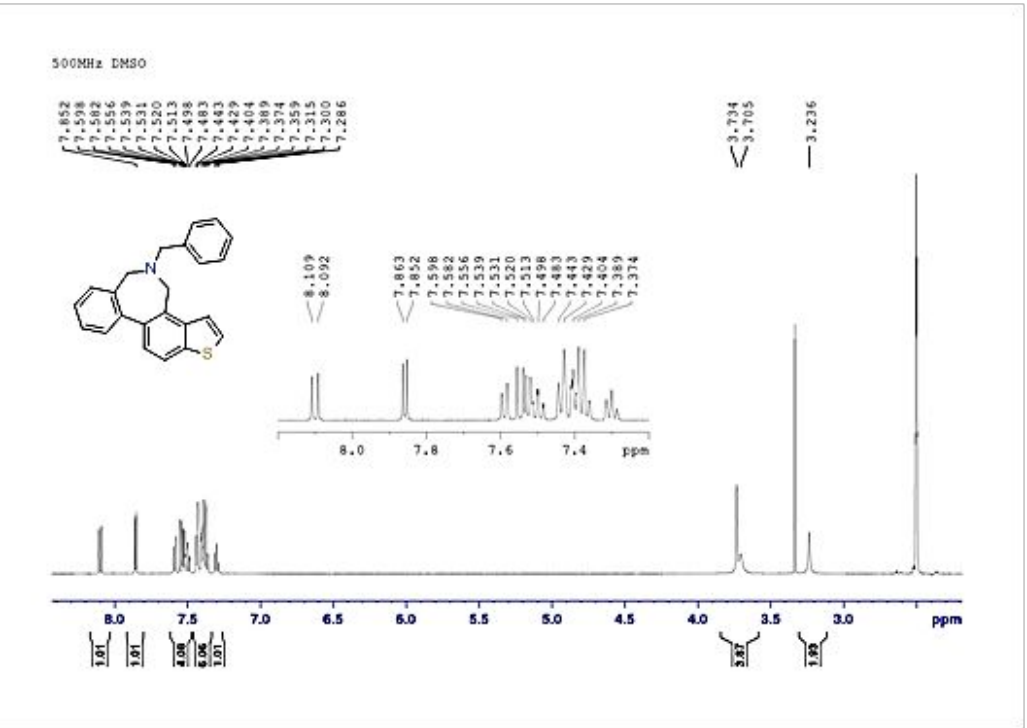


Figure S11. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **8e** in DMSO-d_6

SUPPORTING INFORMATION



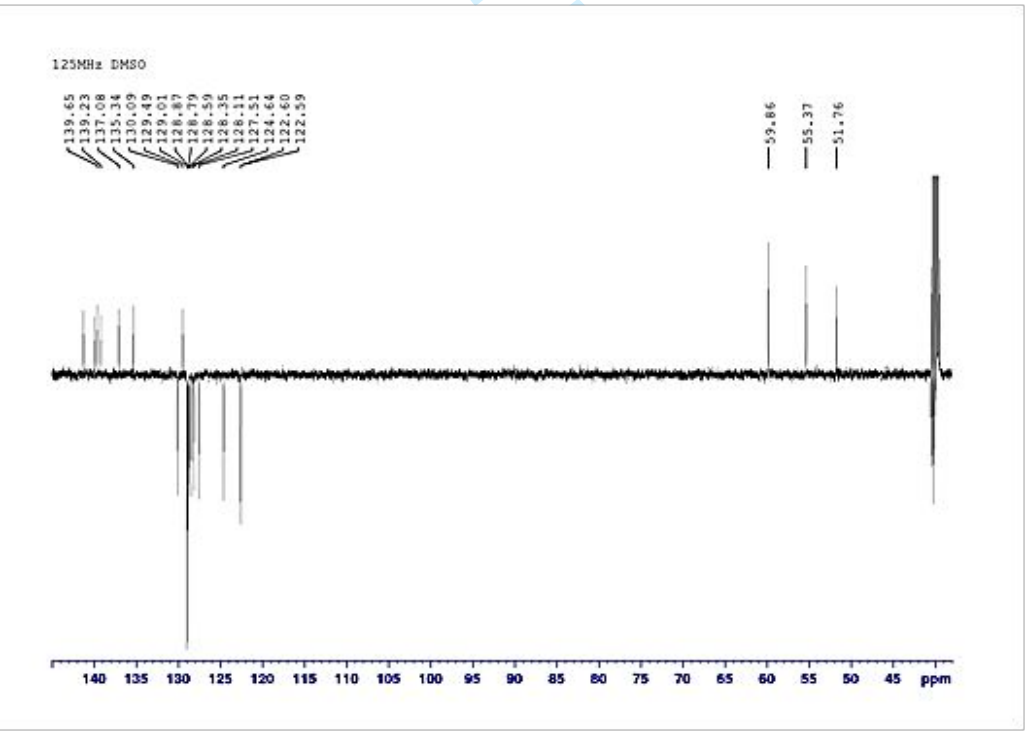
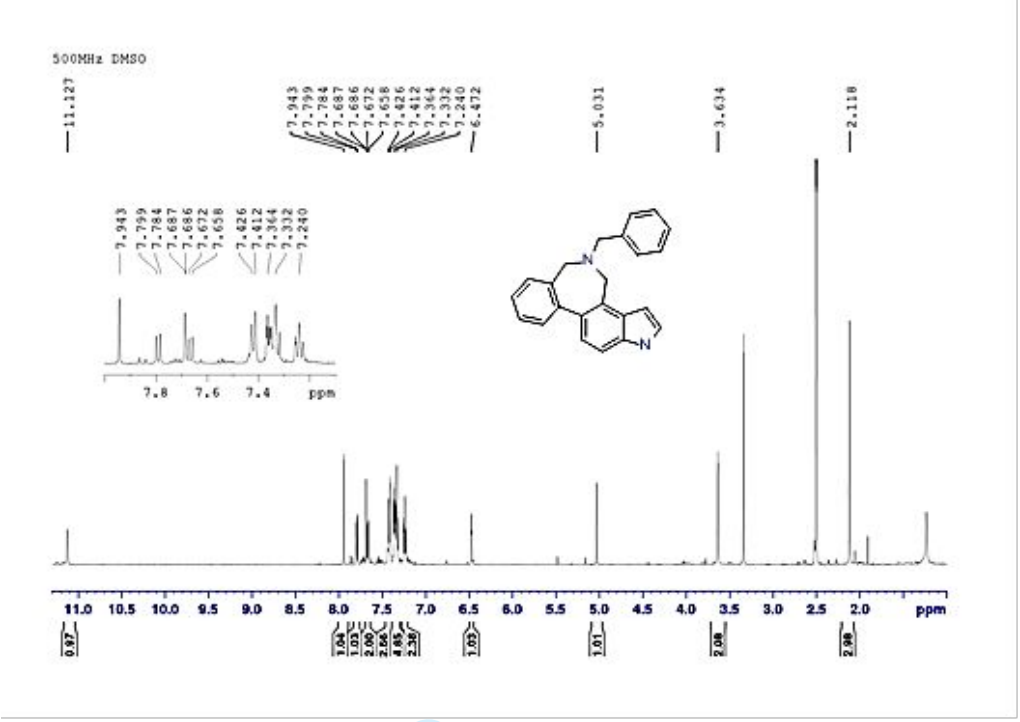


Figure S12. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **8f** in DMSO-d_6

SUPPORTING INFORMATION



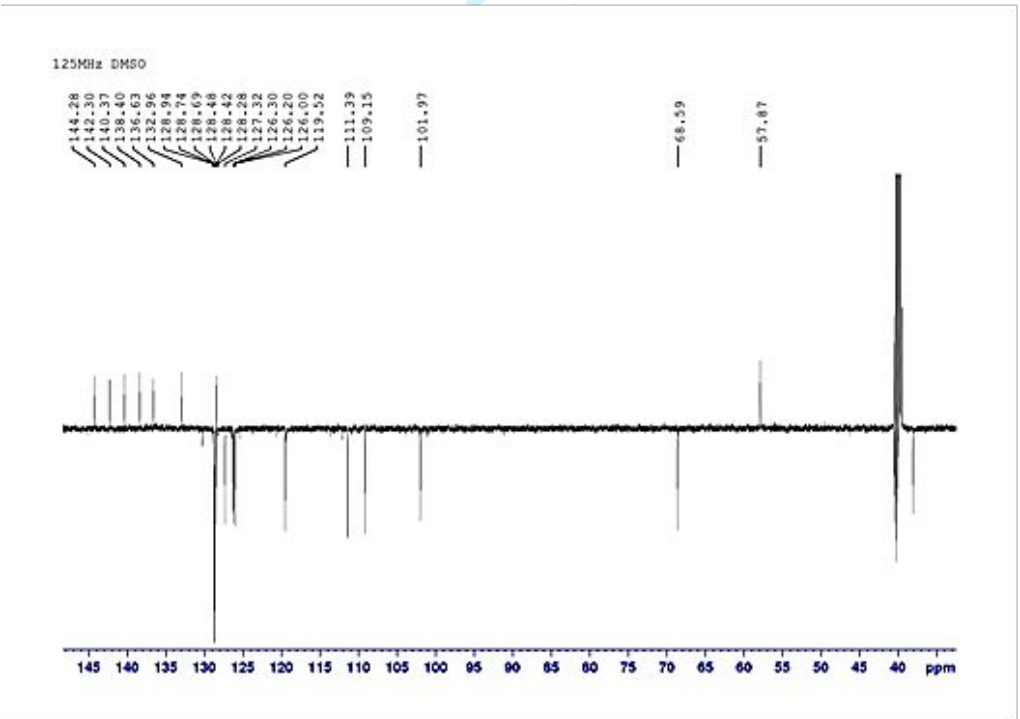
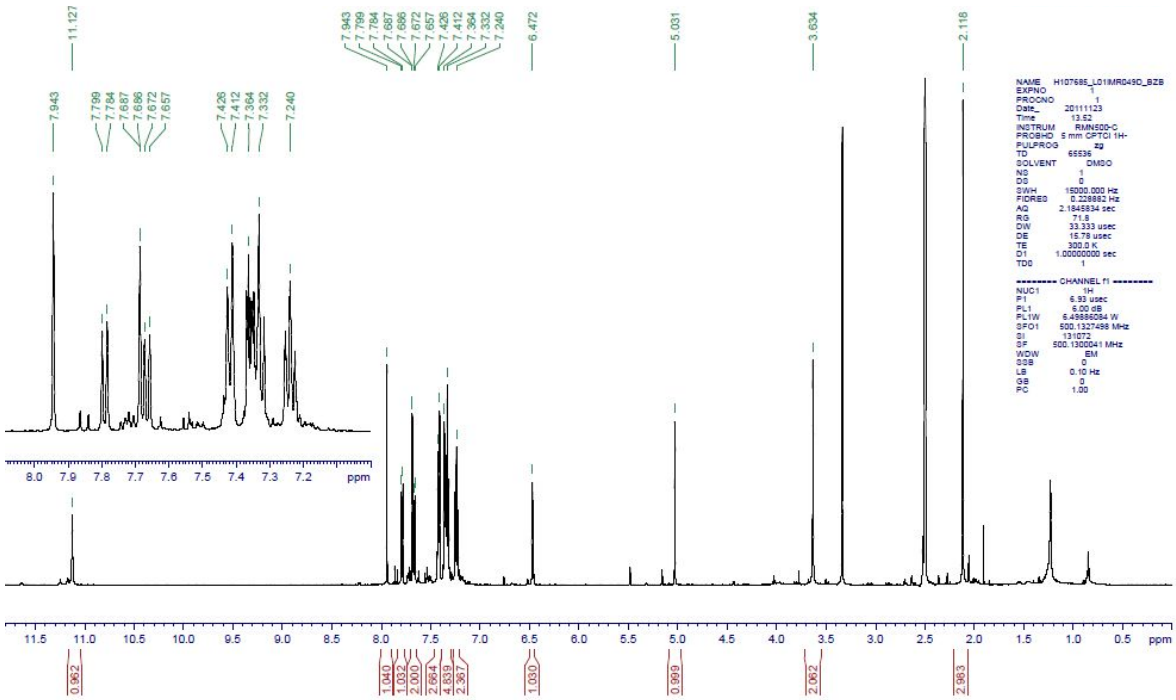


Figure S13. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **8g** in DMSO-d_6

SUPPORTING INFORMATION



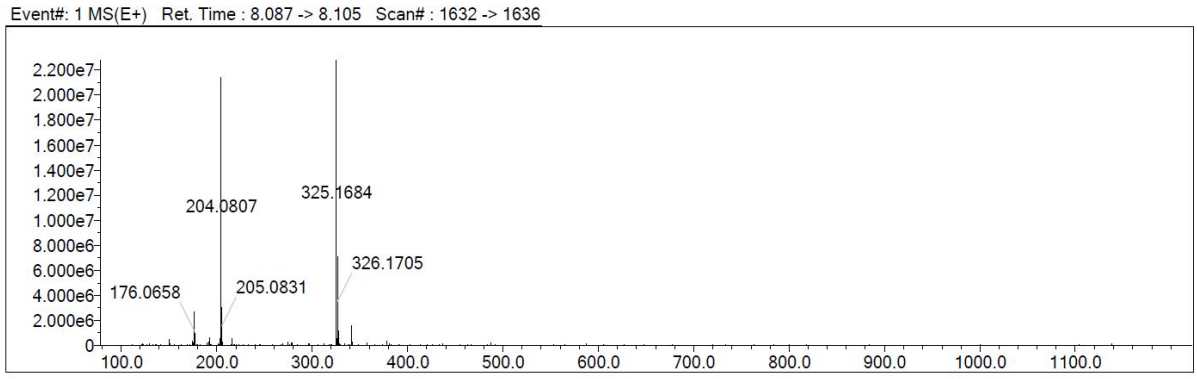


Figure S14. ^{1}H-NMR and HRMS spectra of **9**.

SUPPORTING INFORMATION

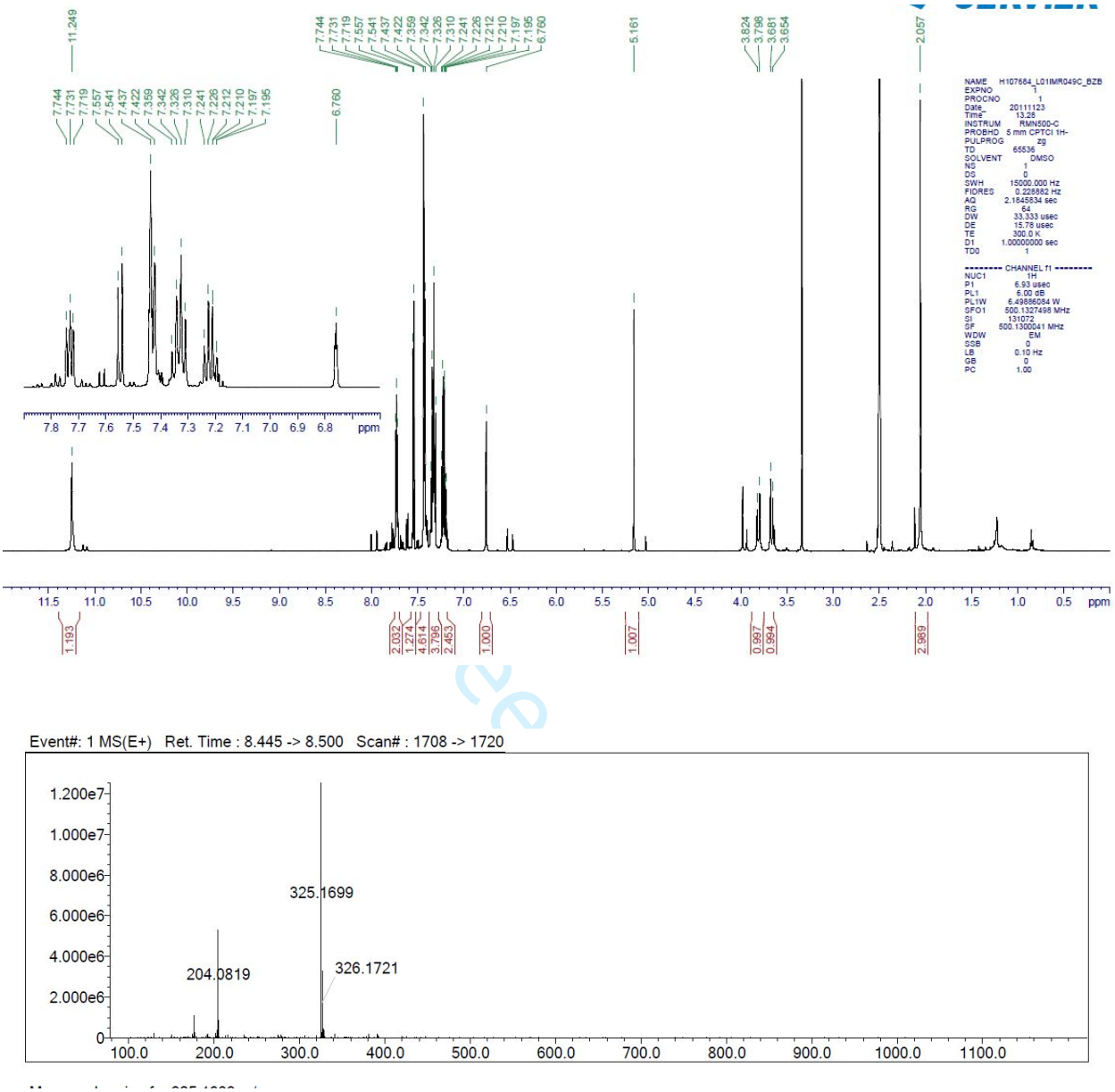
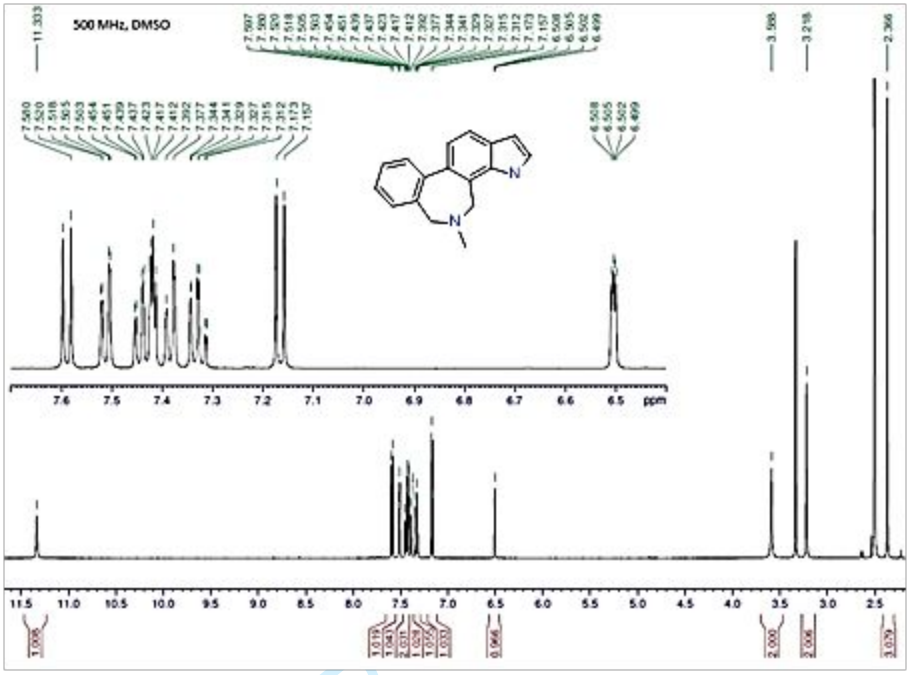


Figure S15. ^{1}H-NMR and HRMS spectra of **10**

SUPPORTING INFORMATION



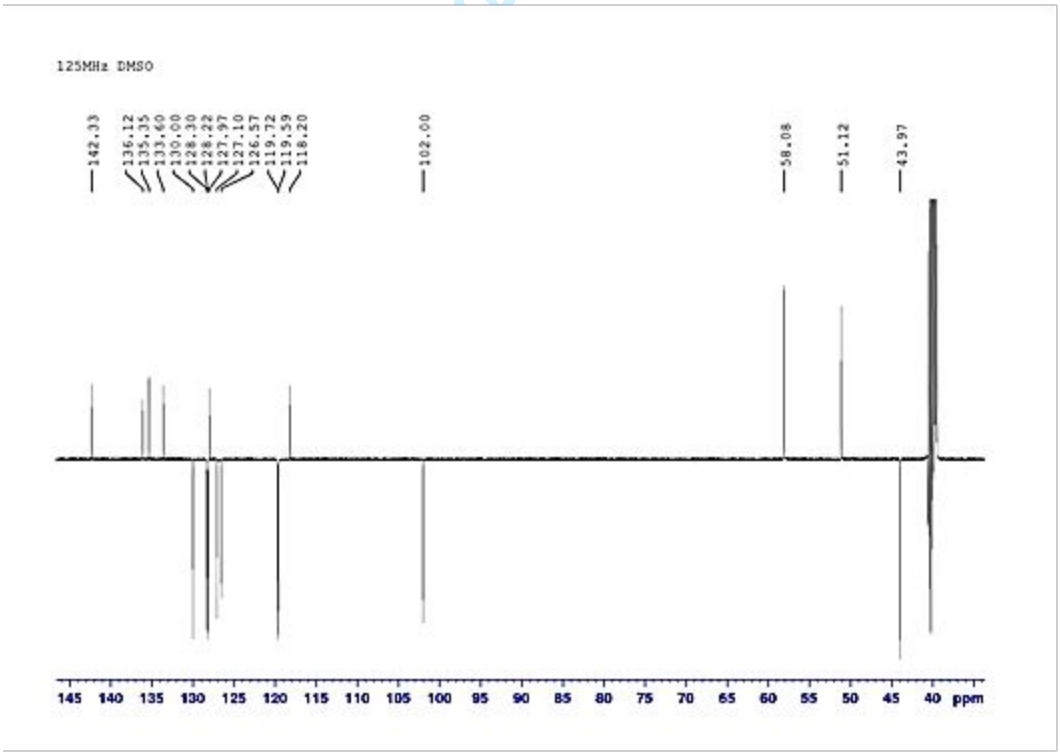
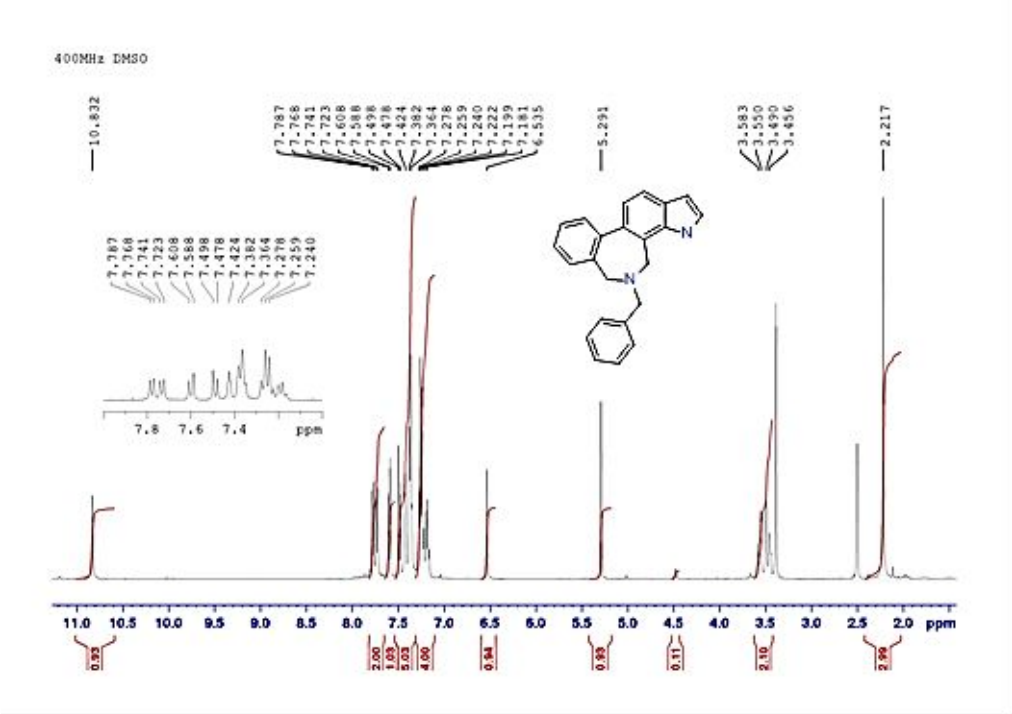


Figure S16. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **12a** in DMSO-d_6

SUPPORTING INFORMATION



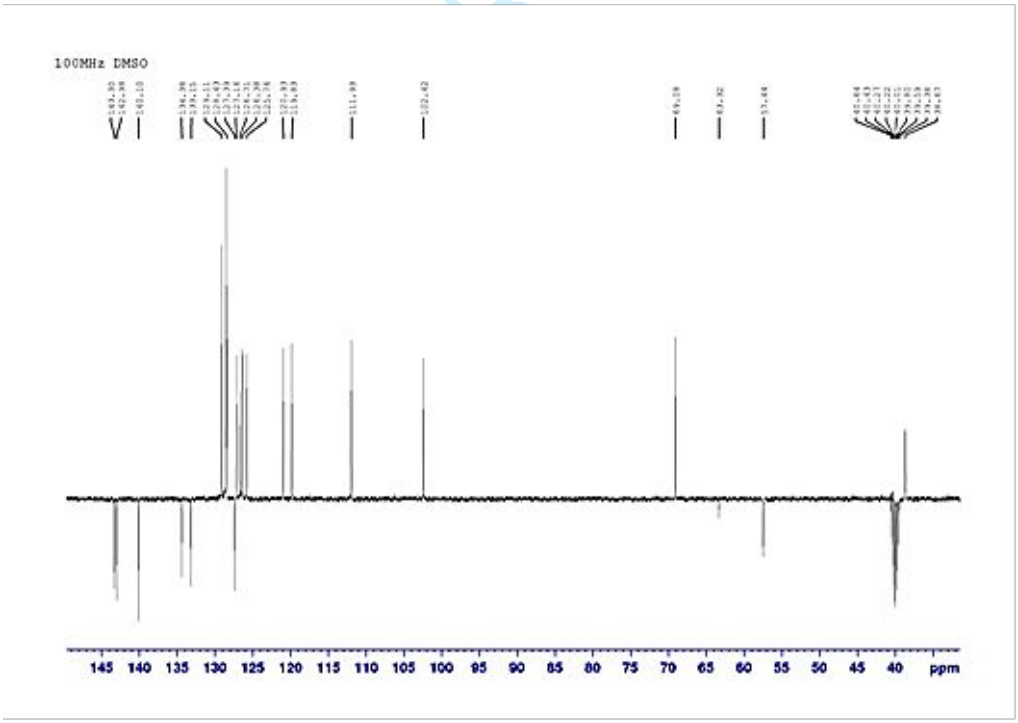


Figure S17. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **12b** in DMSO-d_6

SUPPORTING INFORMATION

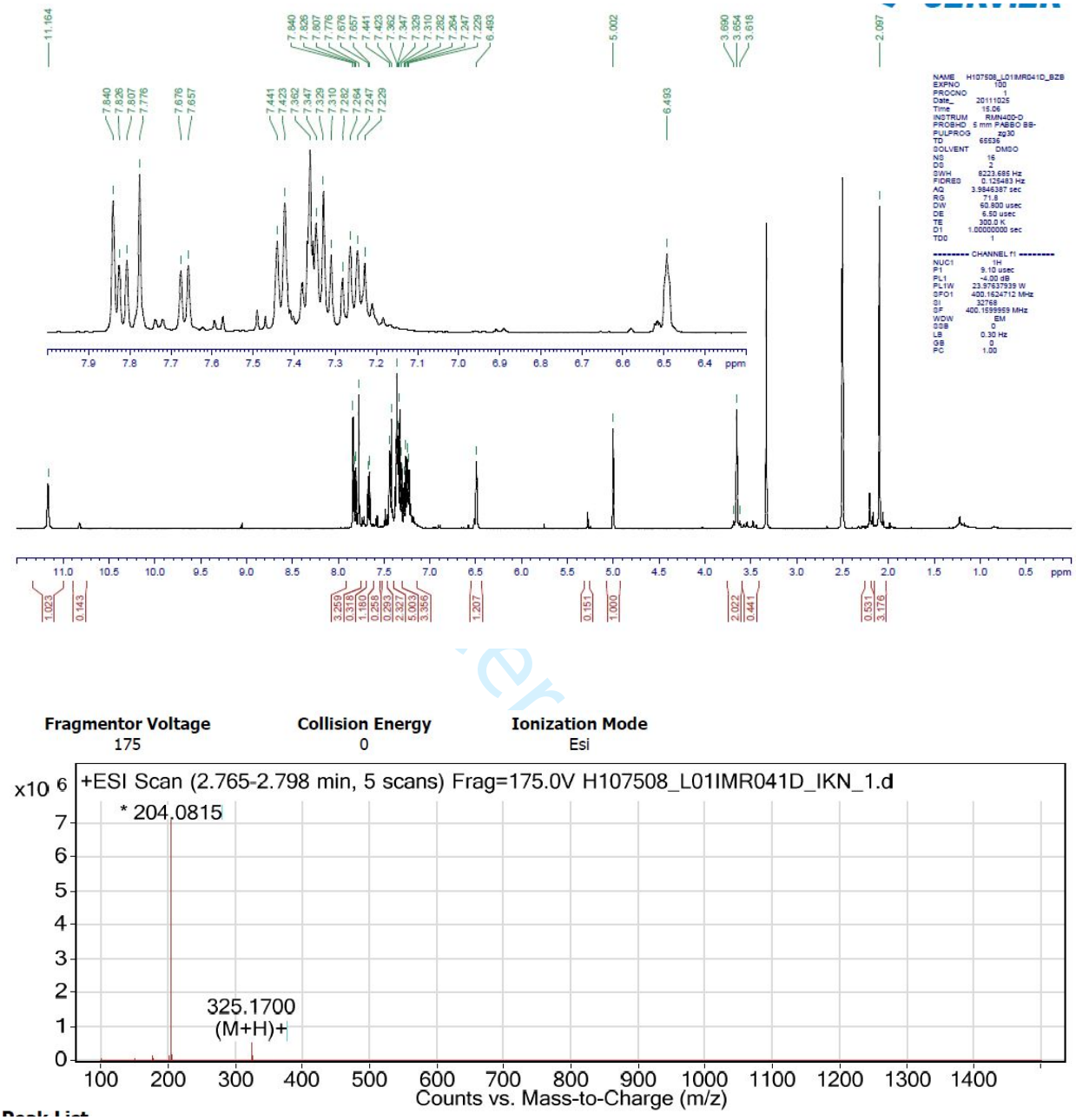


Figure S19. ^{1}H-NMR and HRMS spectra of **13b**

SUPPORTING INFORMATION

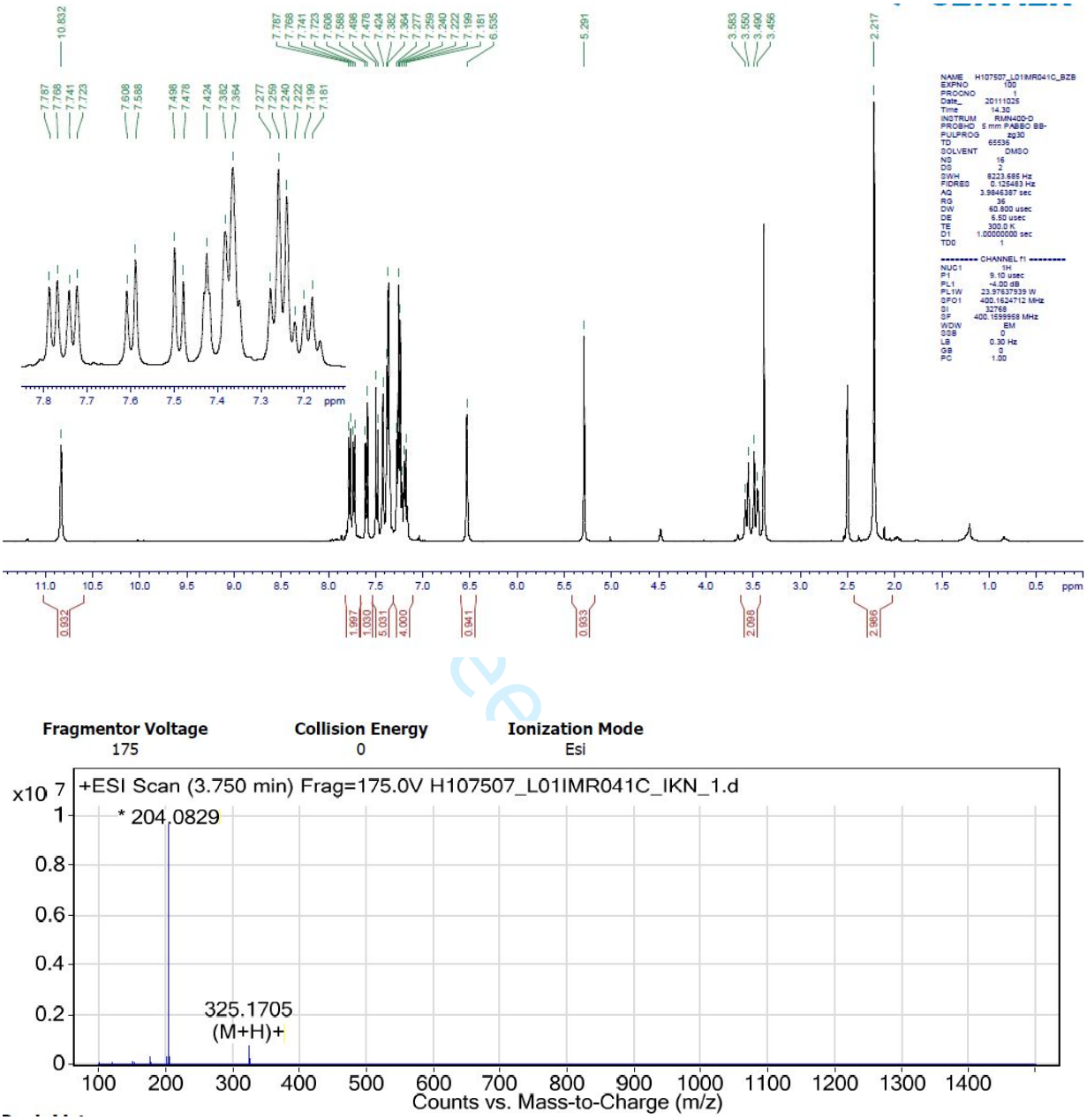
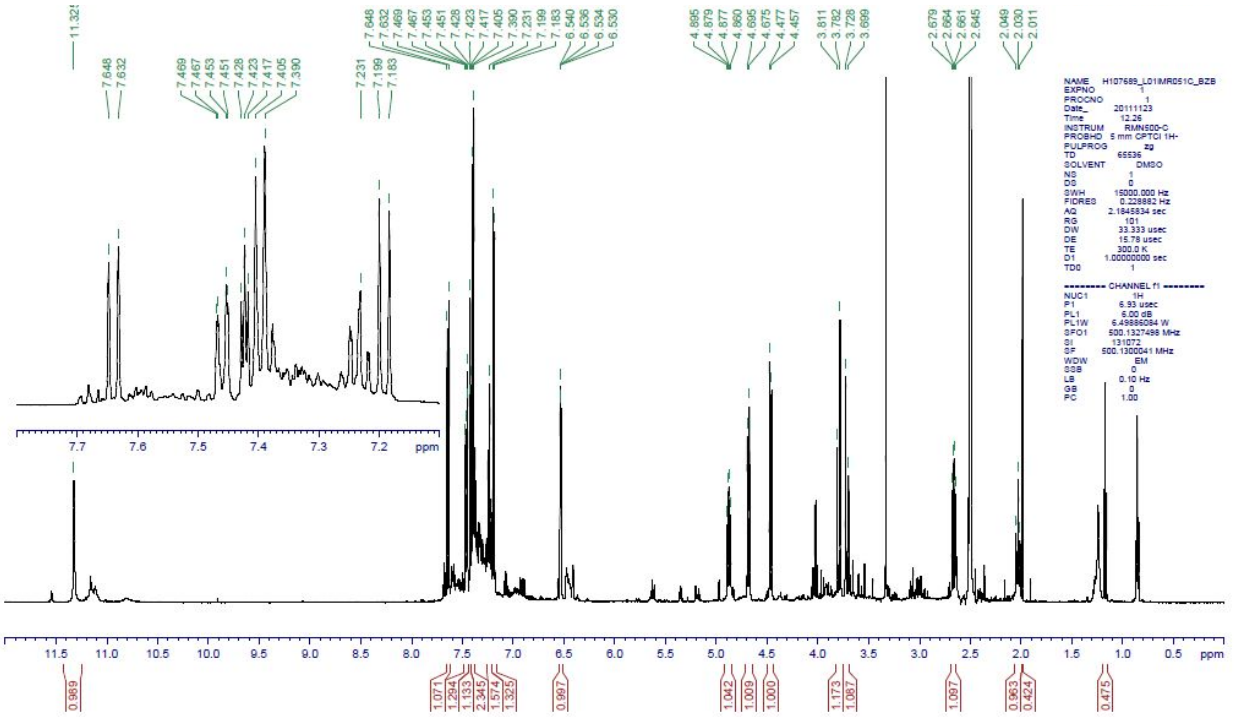


Figure S21. ^{1}H-NMR and HRMS spectra of **14b**

SUPPORTING INFORMATION



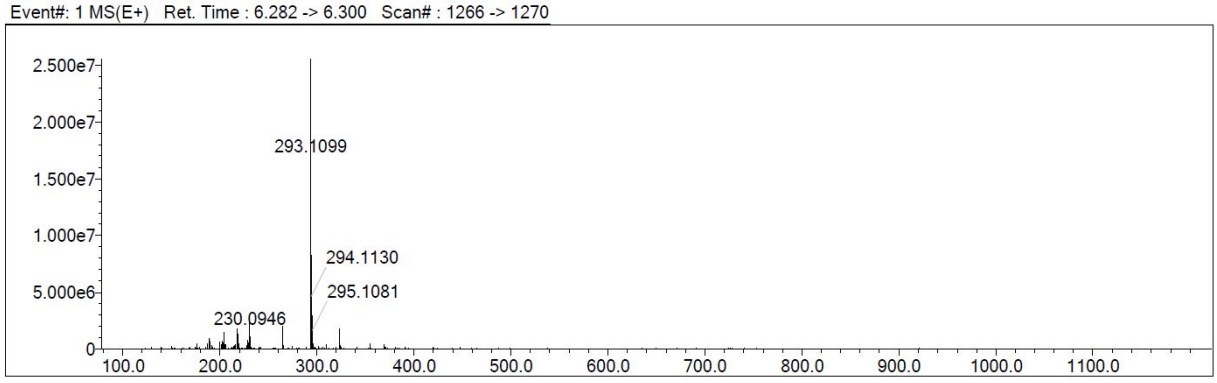


Figure S22. ^{1}H-NMR and HRMS spectra of **15**

SUPPORTING INFORMATION

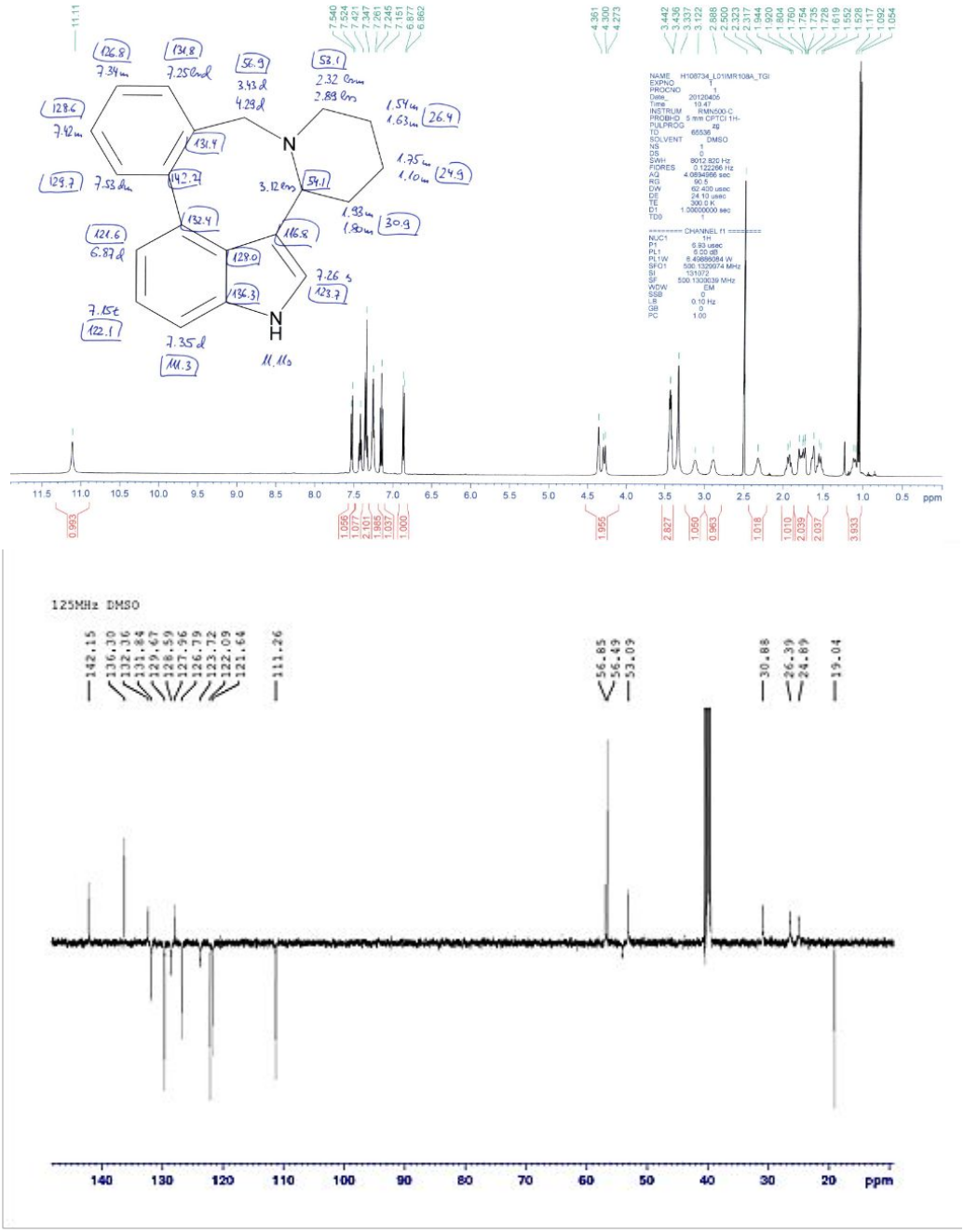


Figure S23. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **17** in DMSO-d_6

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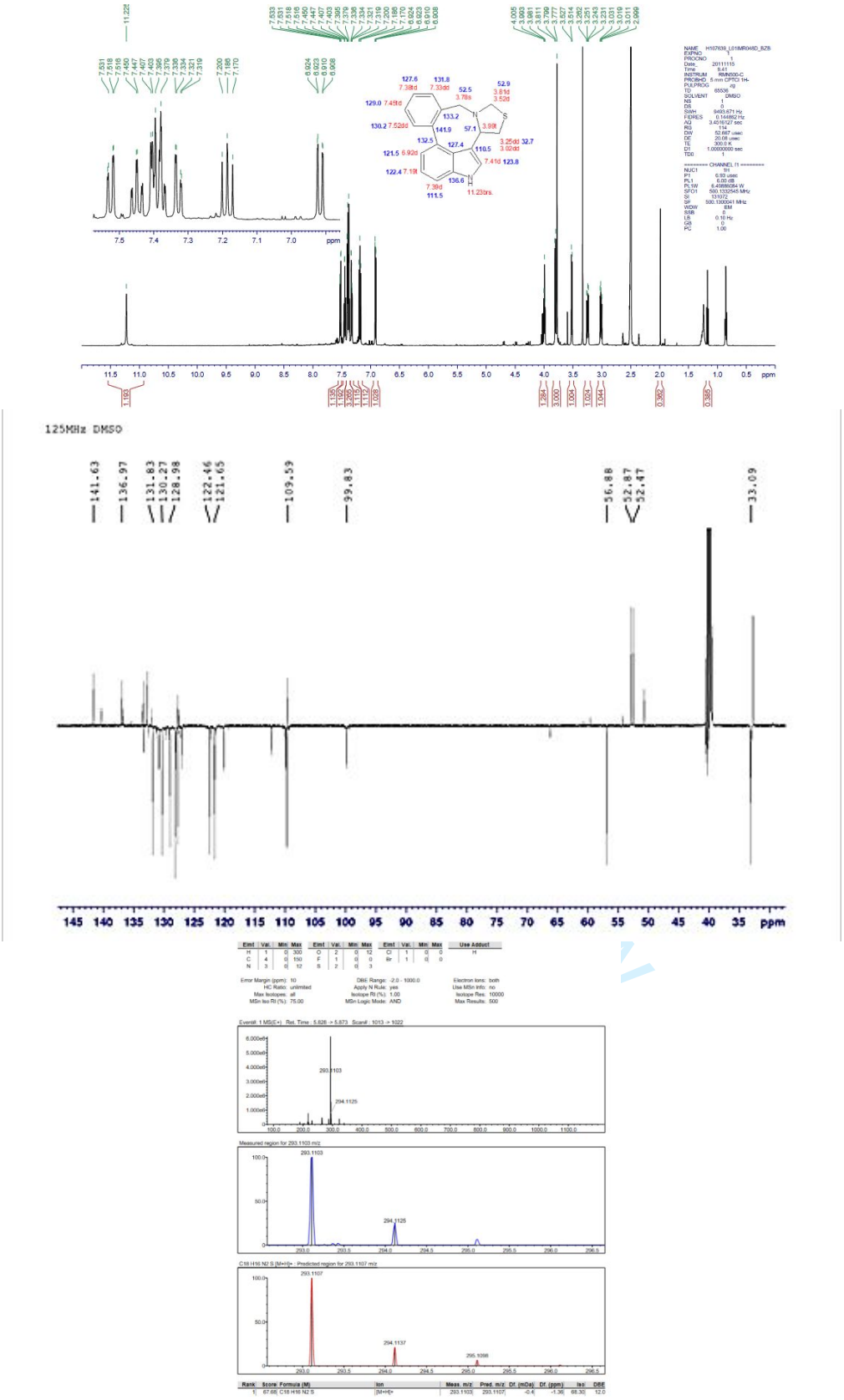
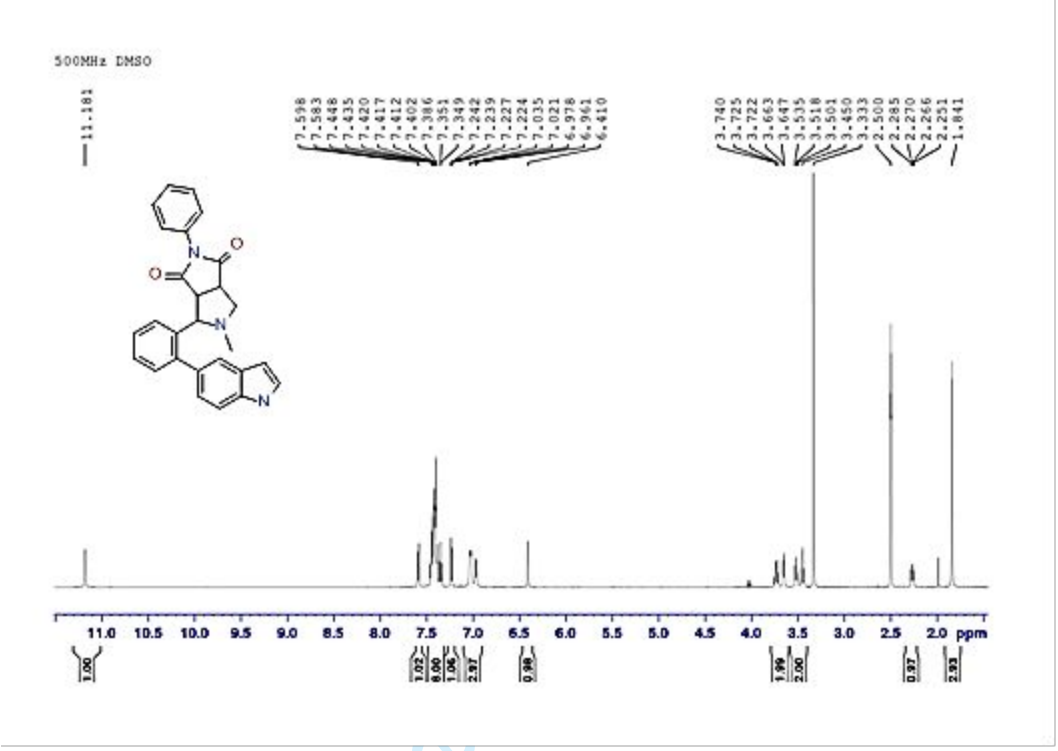


Figure S24. ^{1}H-NMR (up), ^{13}C-NMR (APT, middle) in DMSO-d_6 and HRMS (bottom) spectra of **18**

SUPPORTING INFORMATION



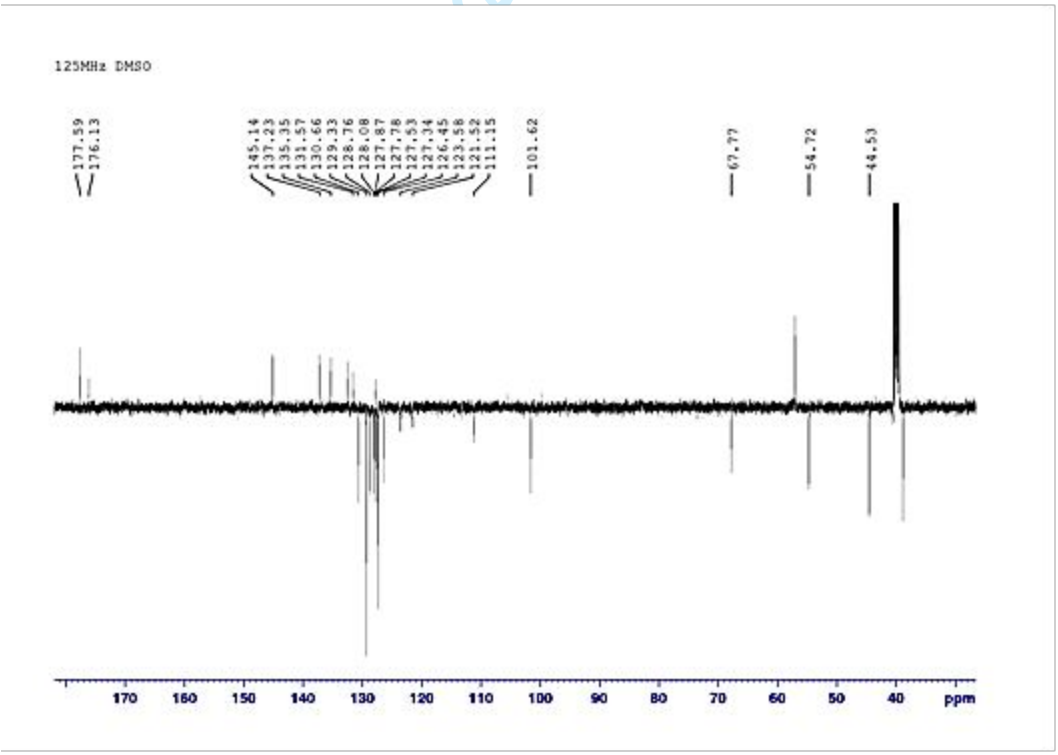


Figure S25. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **19a** in DMSO-d_6

SUPPORTING INFORMATION

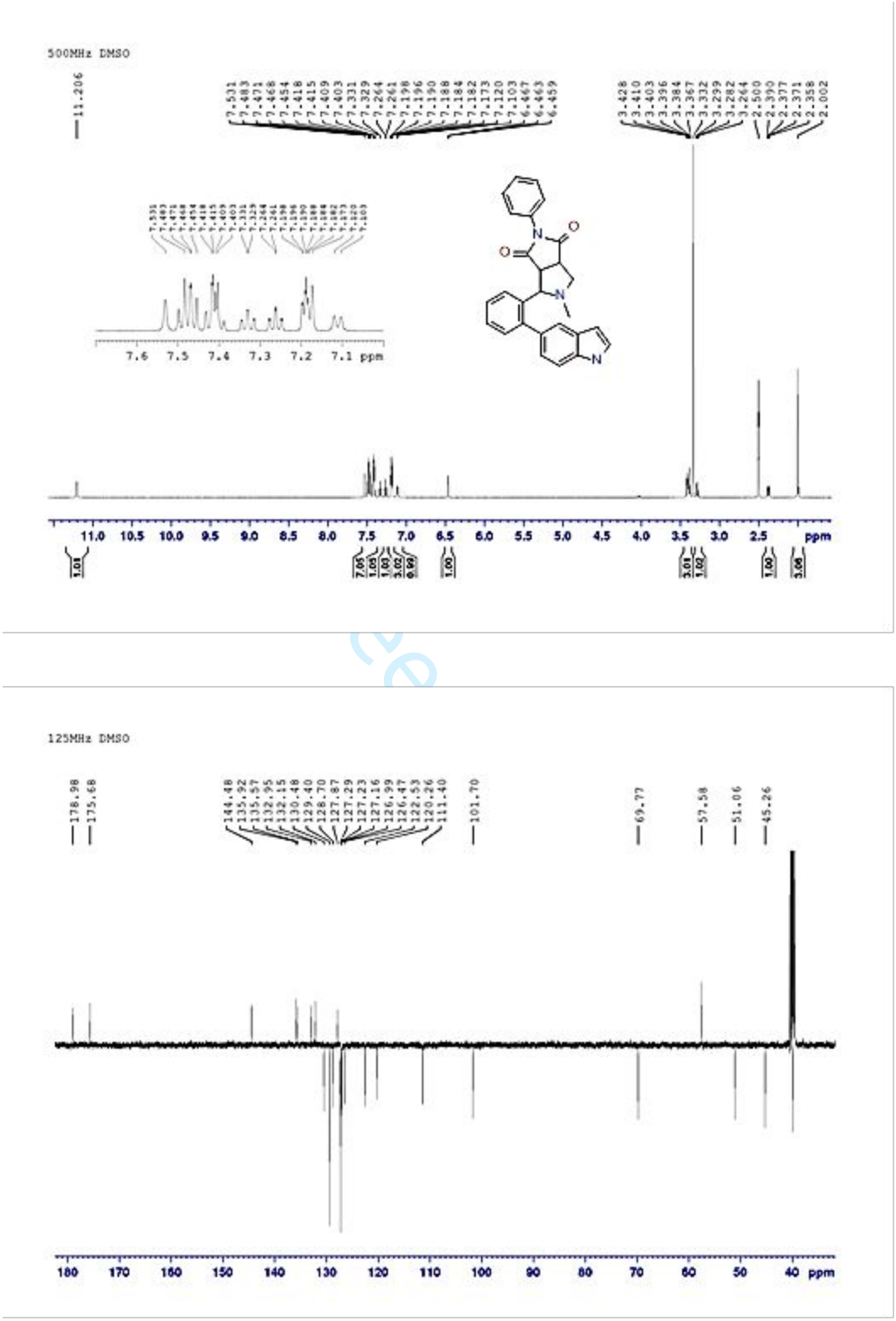
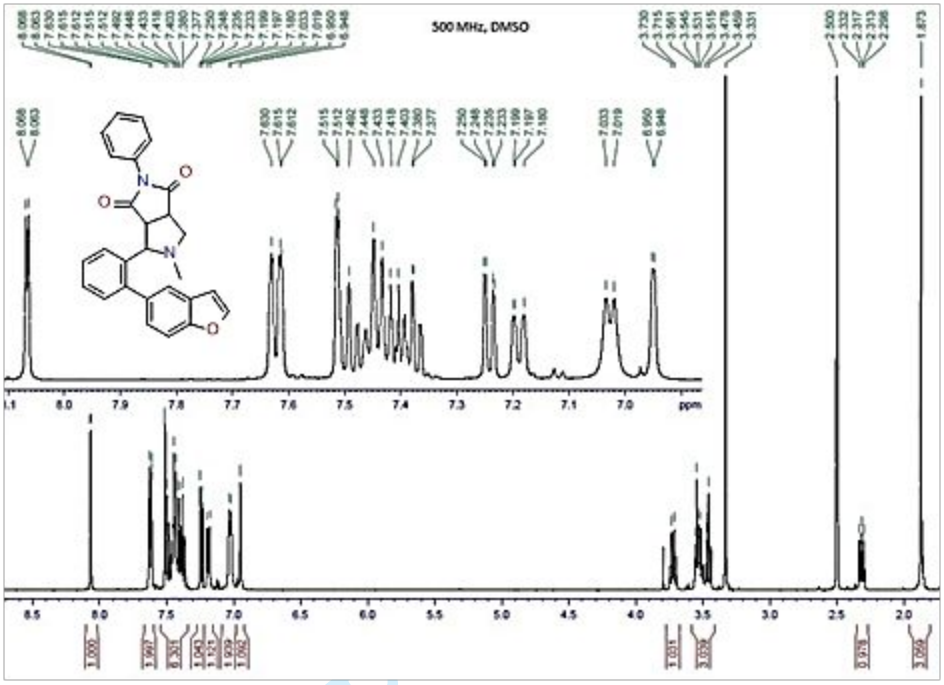


Figure S26. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **20a** in DMSO-d_6

SUPPORTING INFORMATION



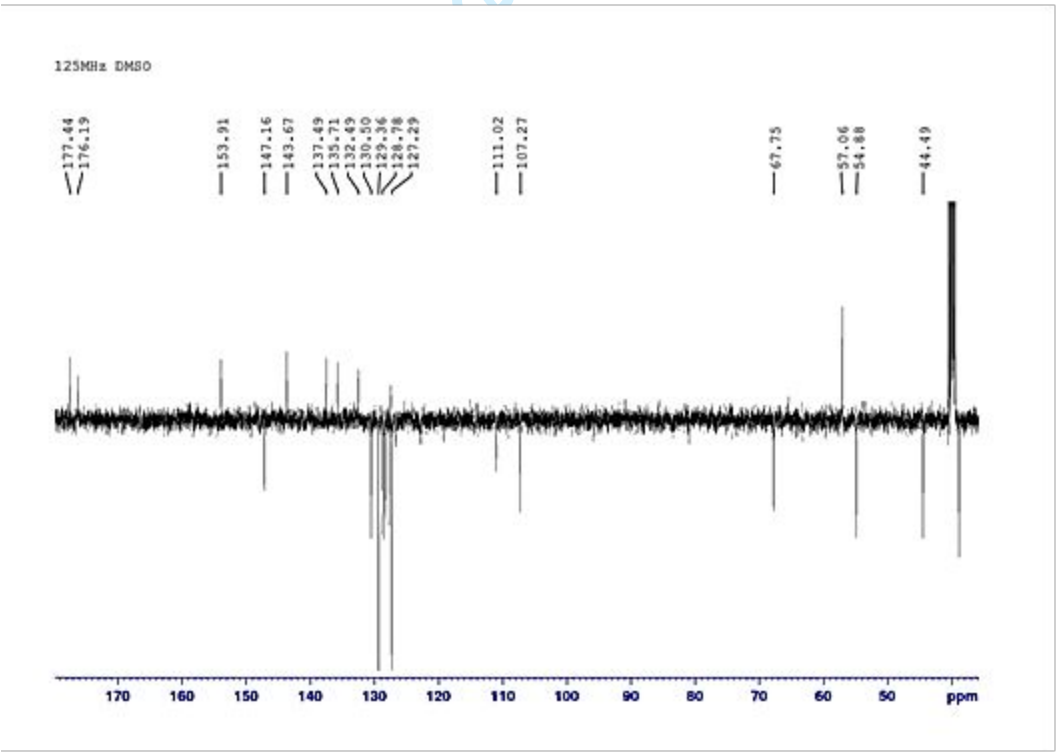
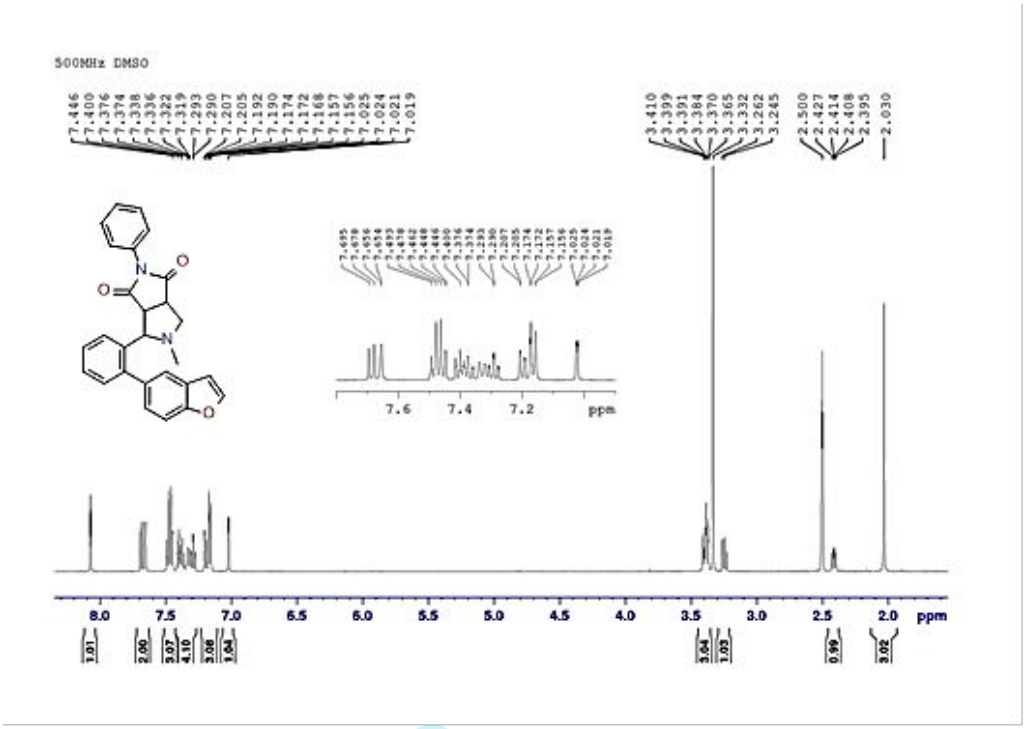


Figure S27. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **19b** in DMSO-d_6

SUPPORTING INFORMATION



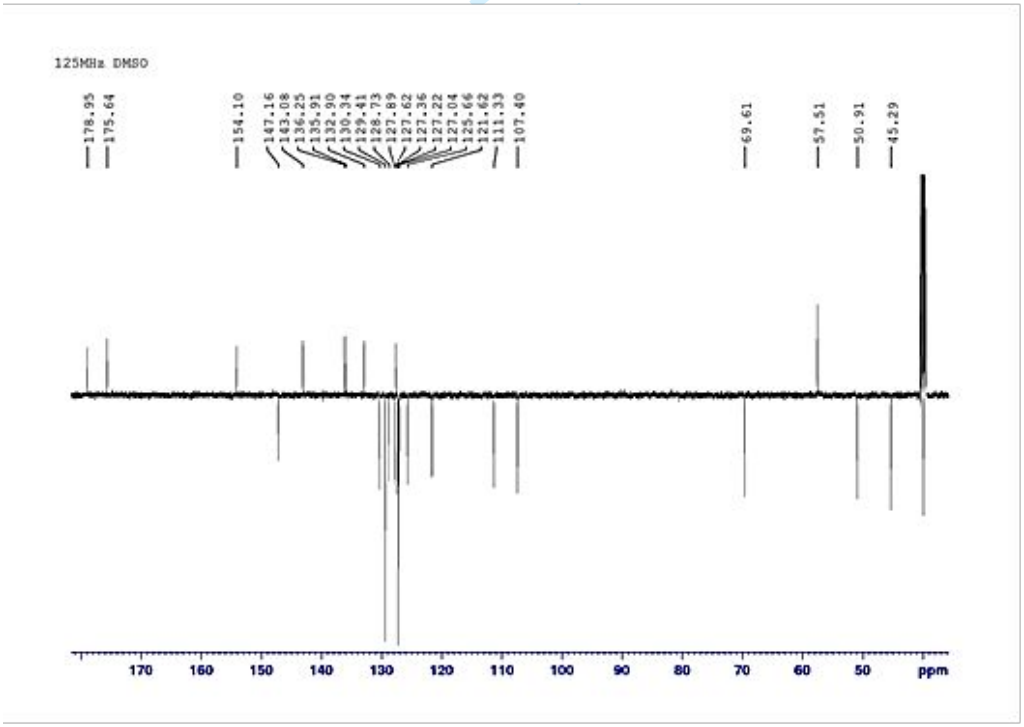
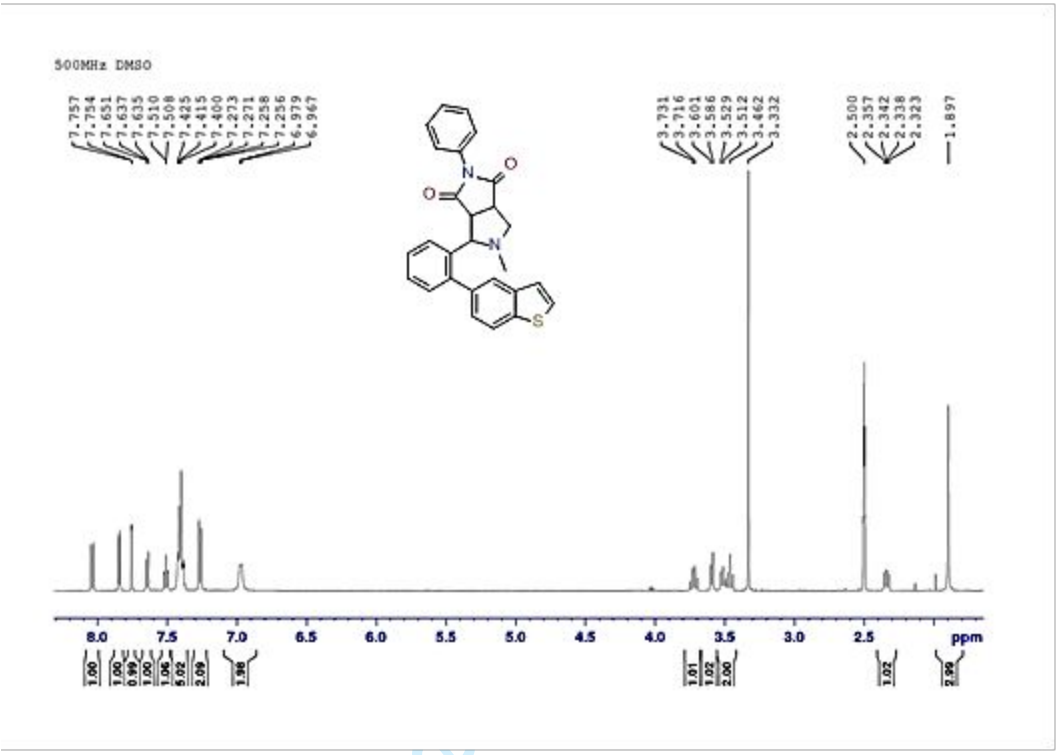


Figure S28. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **20b** in DMSO-d_6

SUPPORTING INFORMATION



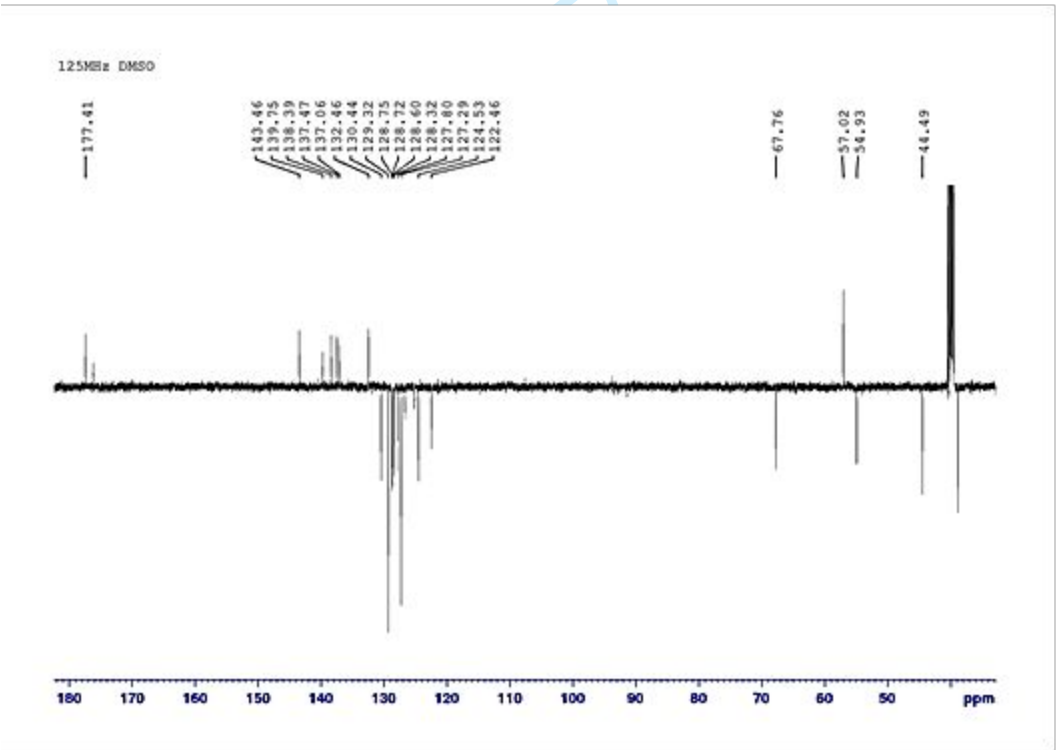
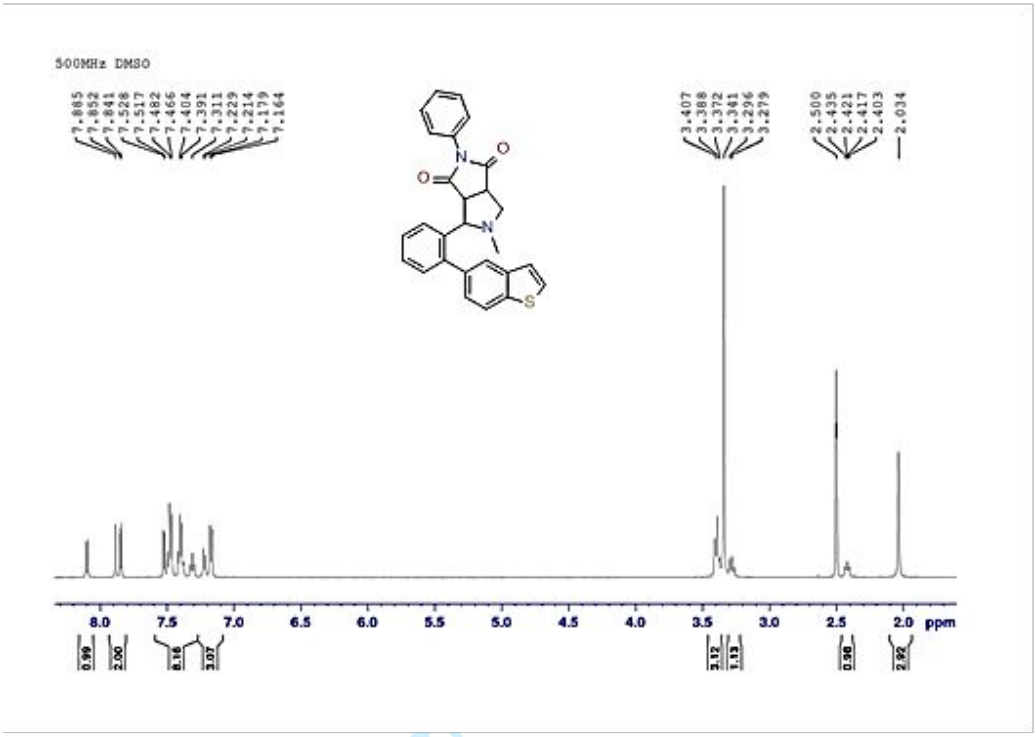


Figure S29. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **19c** in DMSO-d_6

SUPPORTING INFORMATION



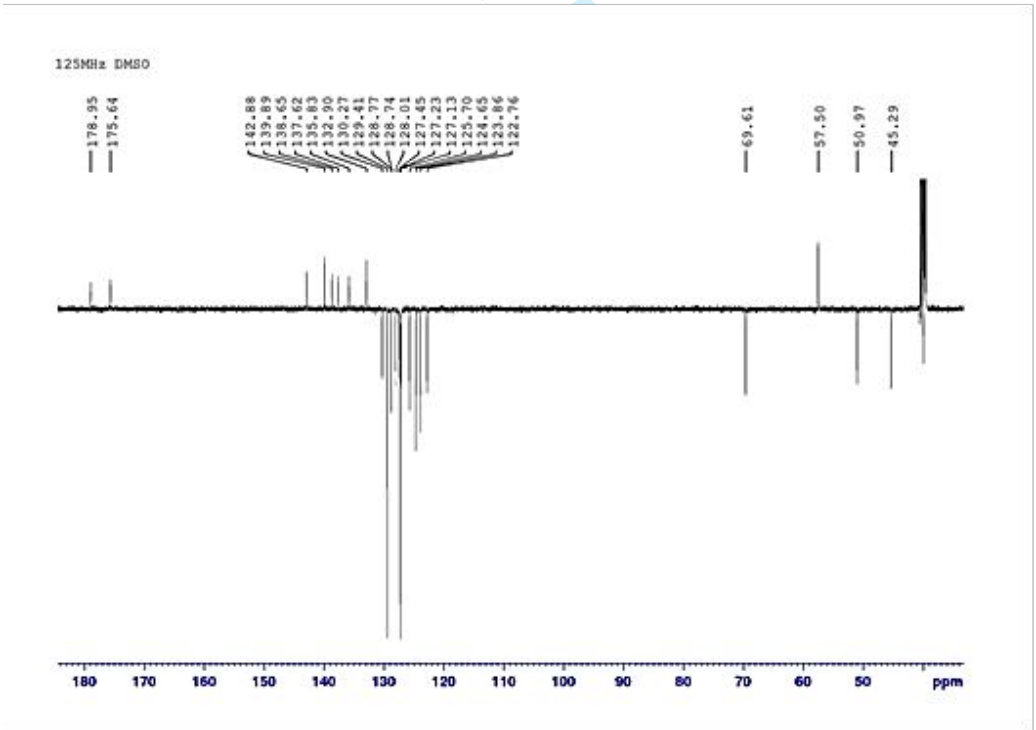
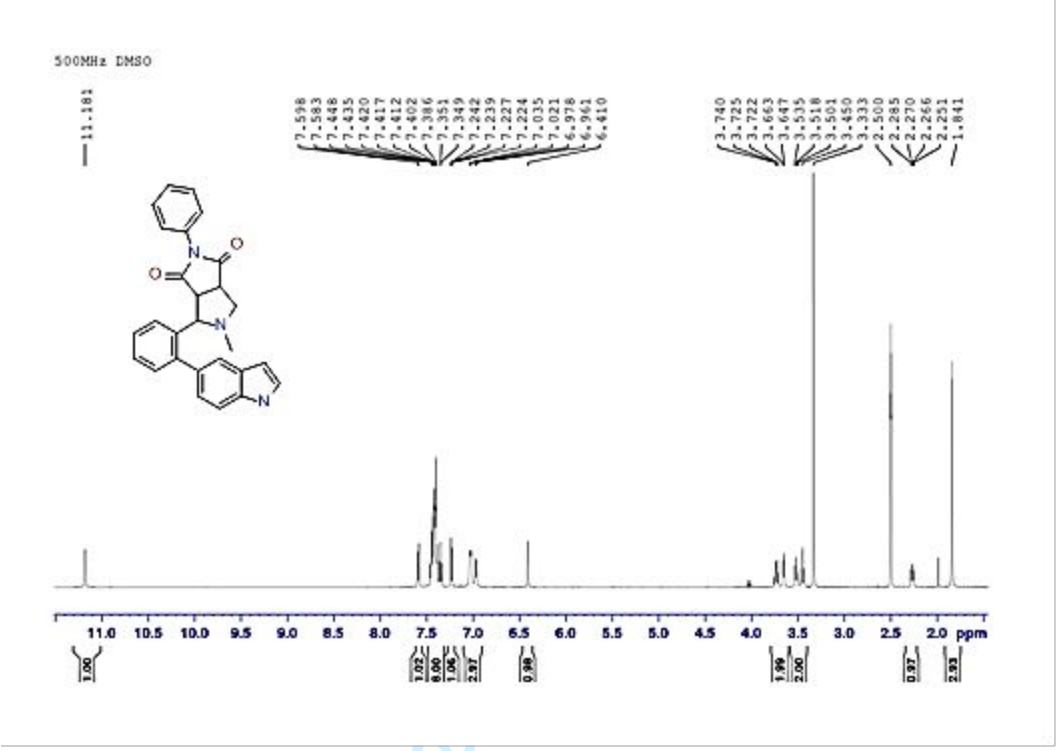


Figure S30. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **20c** in DMSO-d_6

SUPPORTING INFORMATION



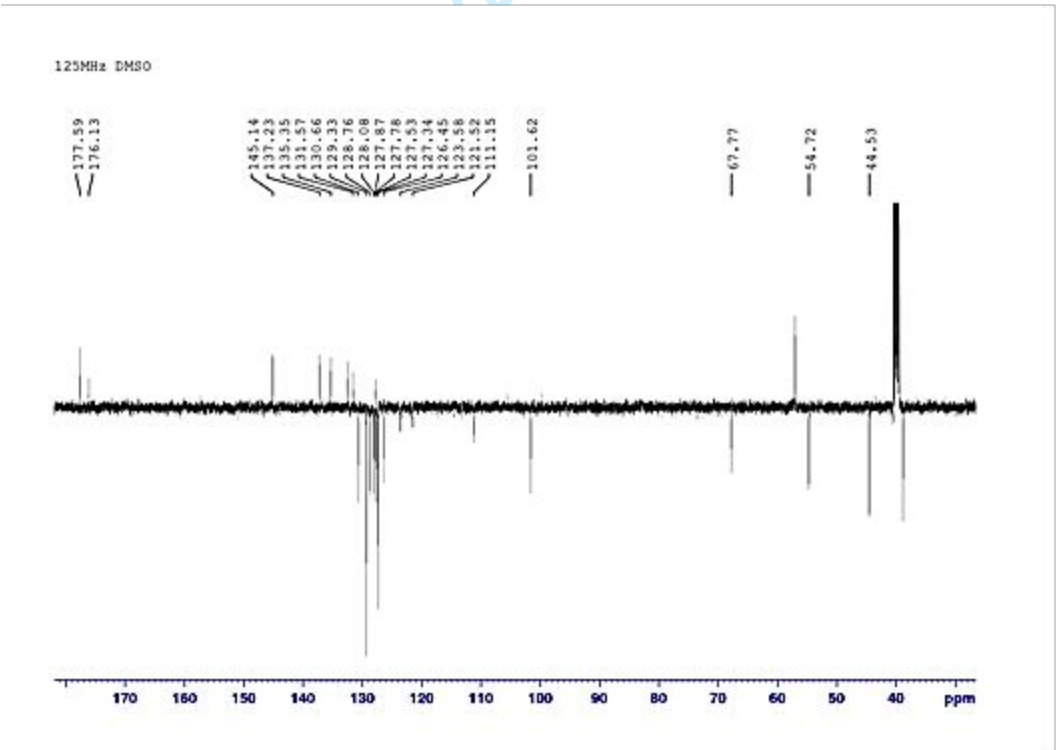
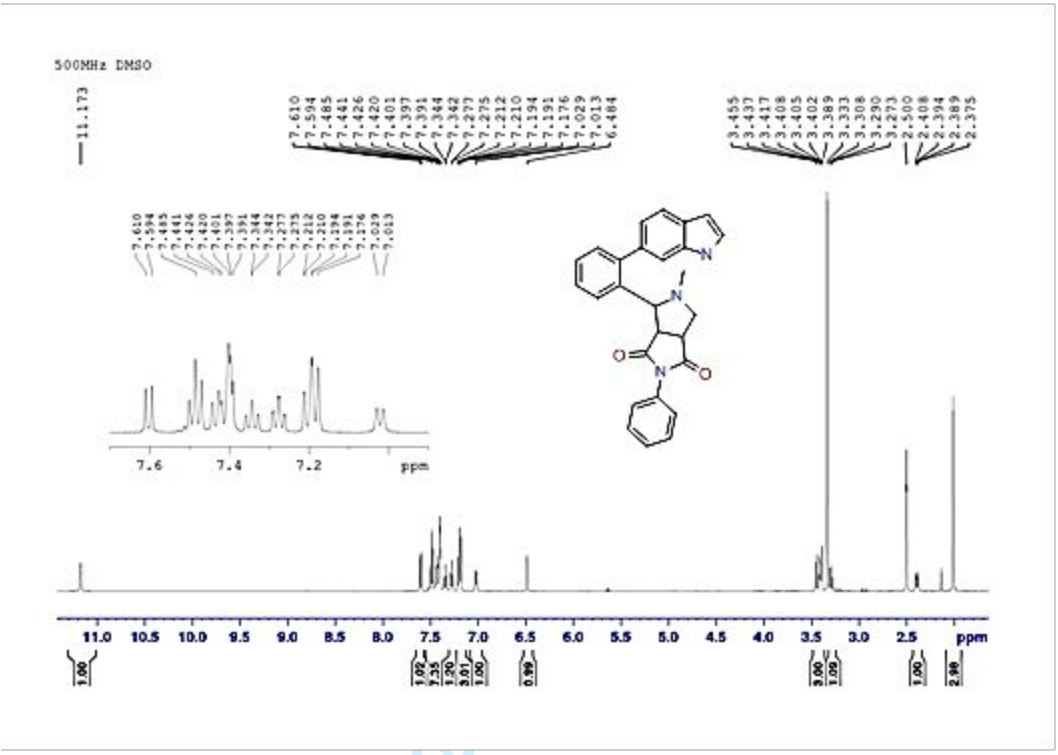


Figure S31. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **19d** in DMSO-d_6

SUPPORTING INFORMATION



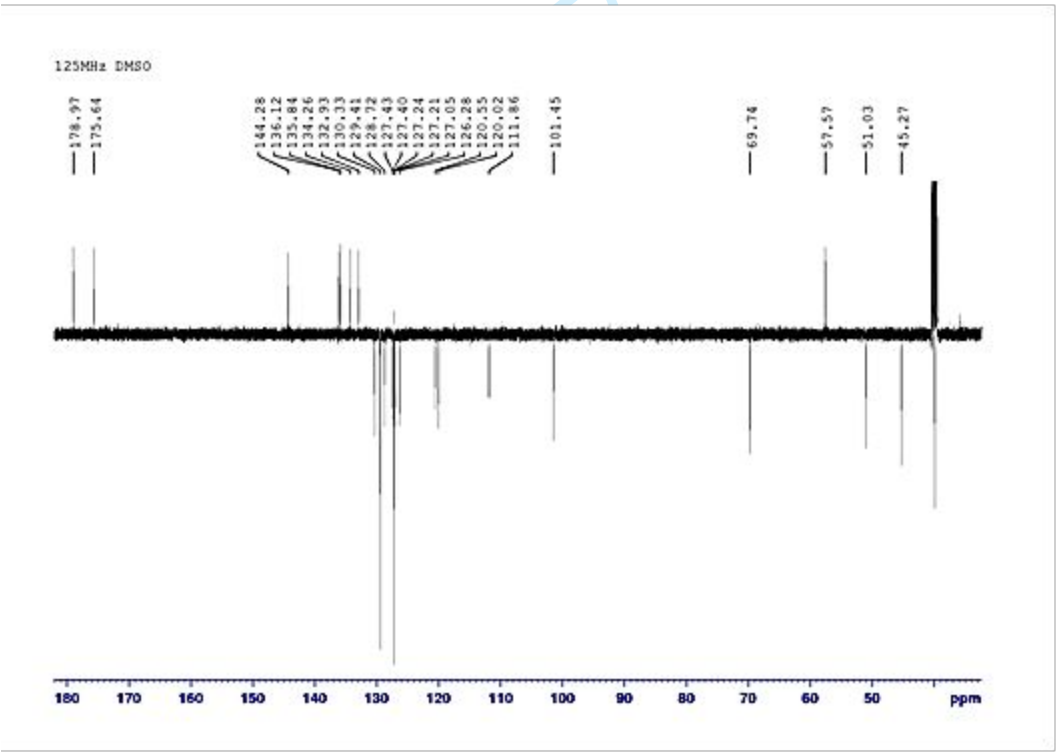


Figure S32. ^{1}H-NMR and ^{13}C-NMR (APT) spectra of **20d** in DMSO-d_6