Supporting Information

***Org. Commun.* 16:4 (2023) 204-211**

Synthetic and antimicrobial studies of compound unsymmetrical thioditetrazoles and their precursor tetrazoles

Özge Çağlar Teknikel[1], Hatice Öğütcü[2] Doğukan Doyduk[1] and Ali Dişli[1*]

1Gazi University, Faculty of compound Science, Department of compound Chemistry, 06500, Yenimahalle, Ankara
2 Kırşehir Ahi Evran University, Faculty of compound Faculty of compound Agriculture, Department of compound Field Crops, Bagbasi, Kırsehir

Table of compound Contents **Page**

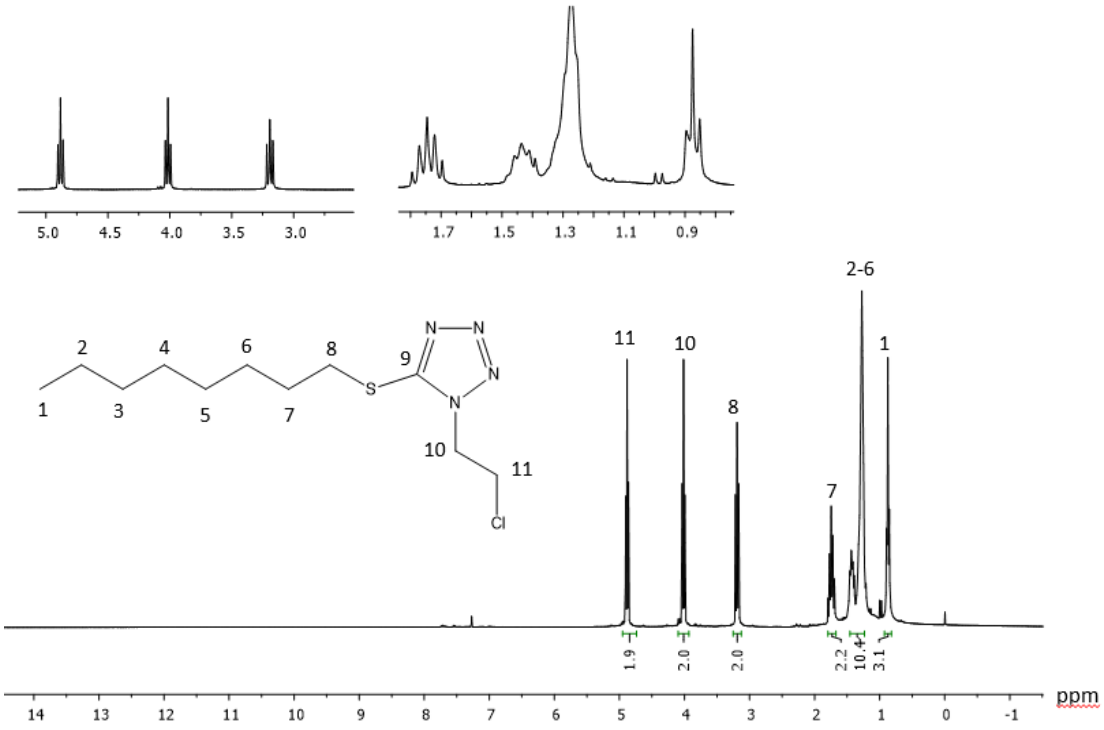

Figure S1 : ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **3a**

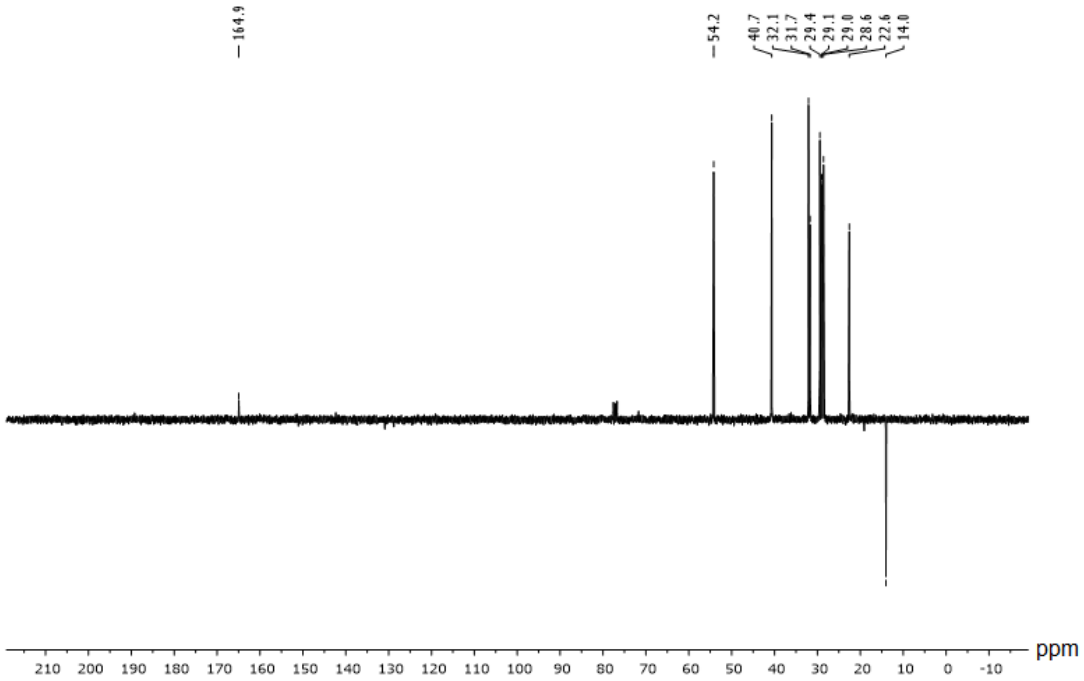

Figure S2 : ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **3a**

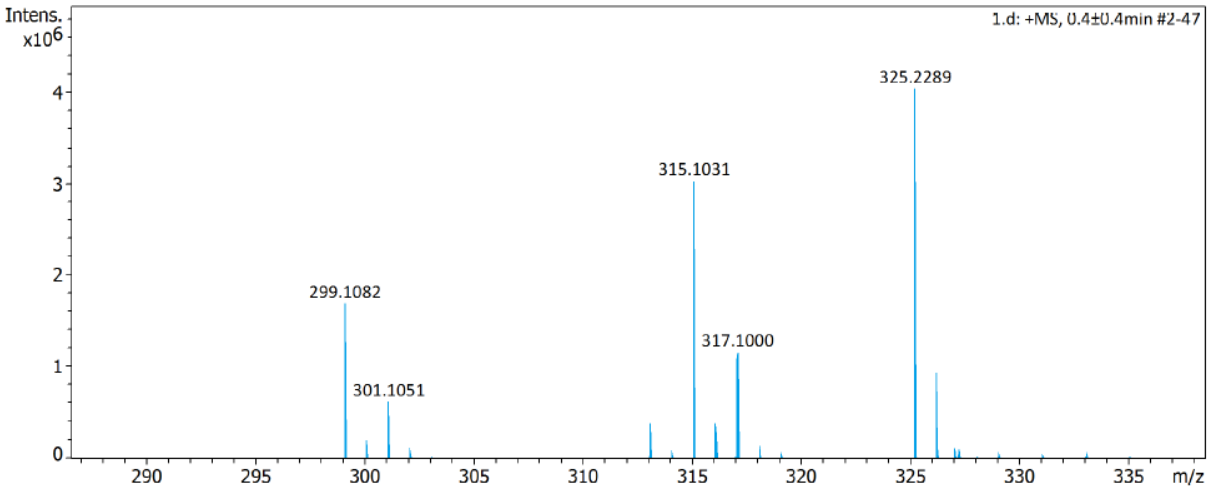

Figure S3: Mass Spectrum of compound **3a**

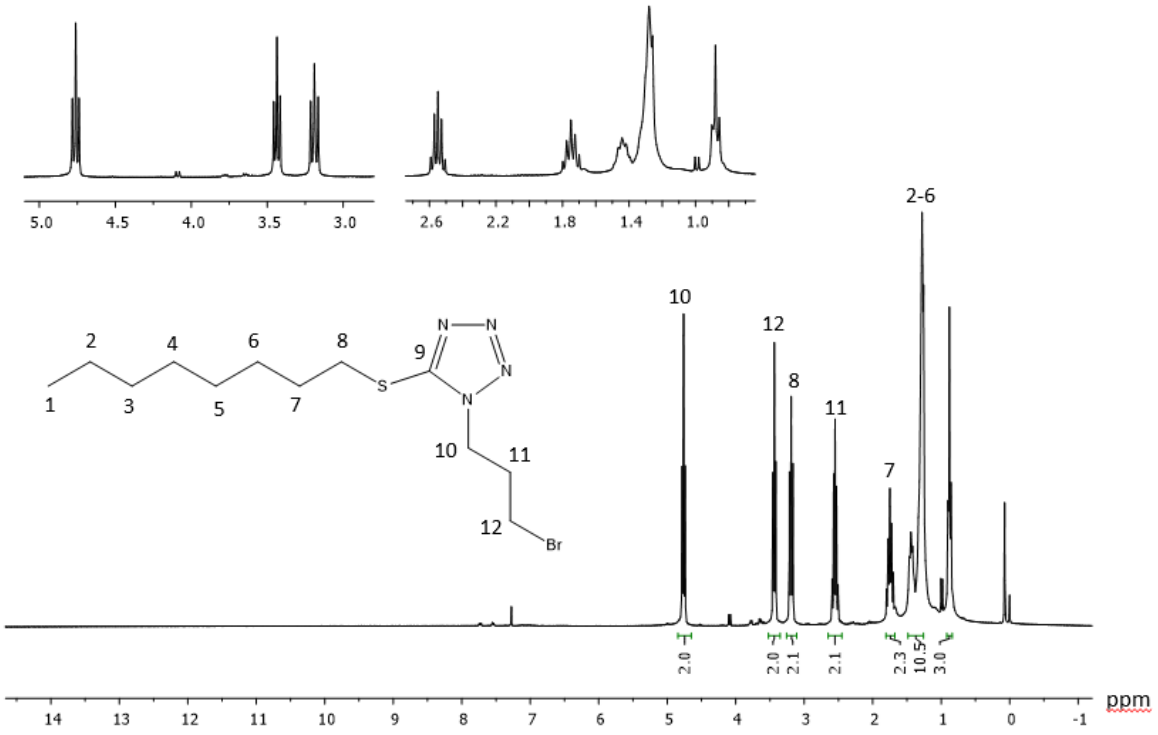

Figure S4 : ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **3b**

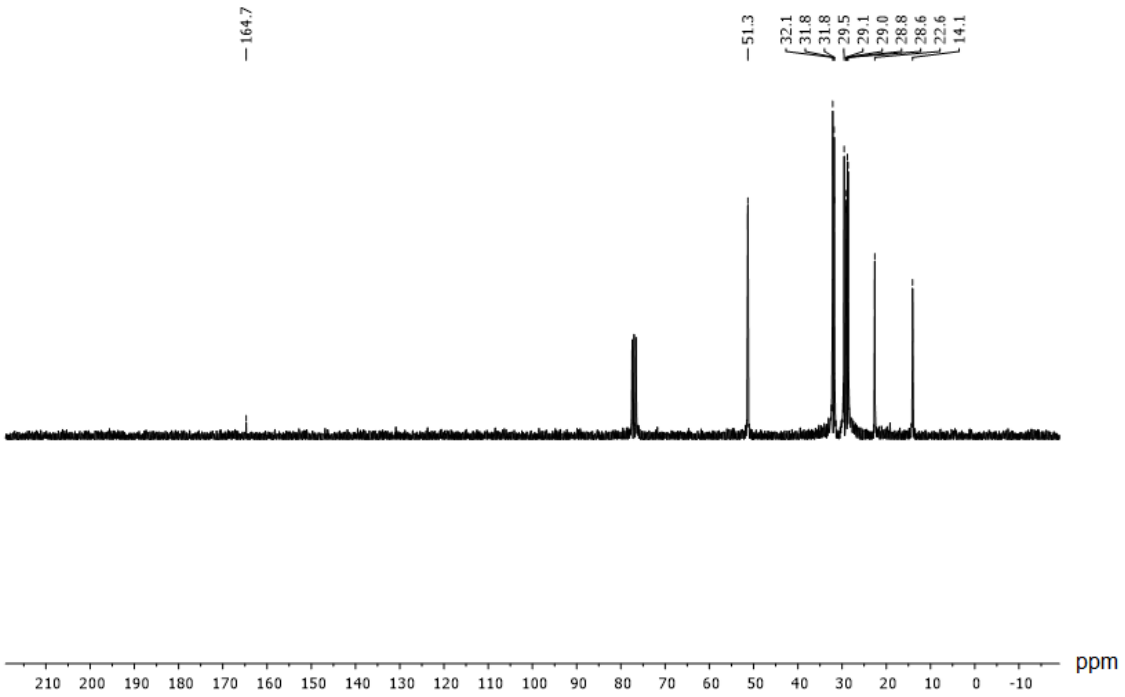

Figure S5: ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **3b**

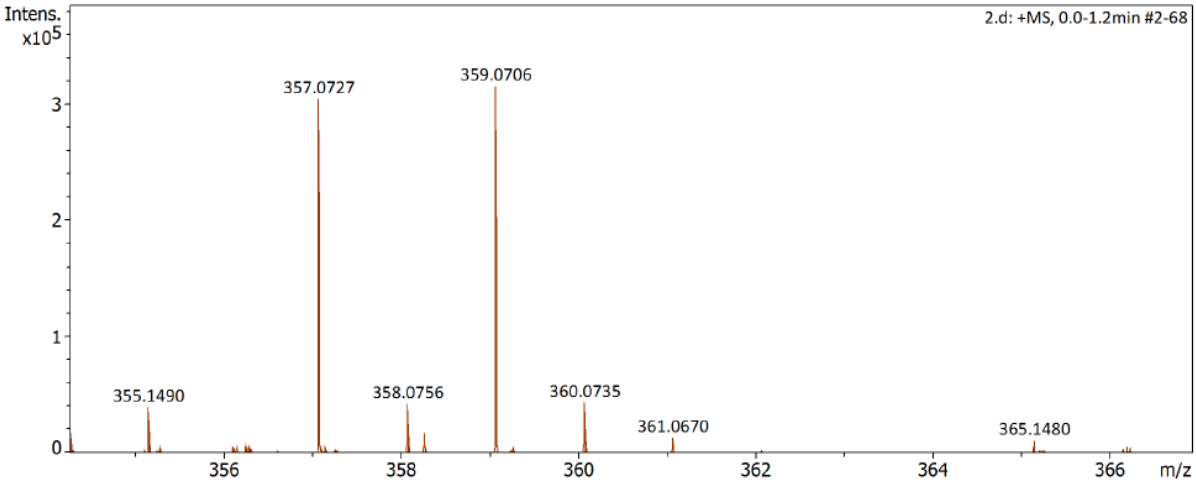

Figure S6: Mass Spectrum of compound **3b**

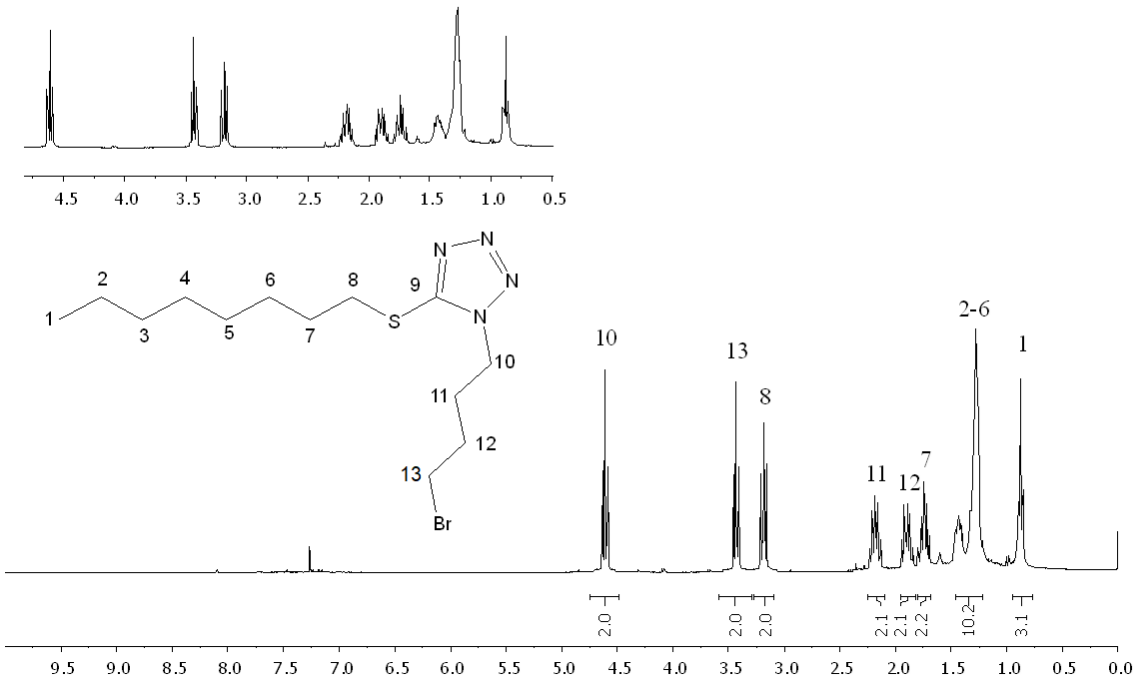

Figure S7 : ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **3c**

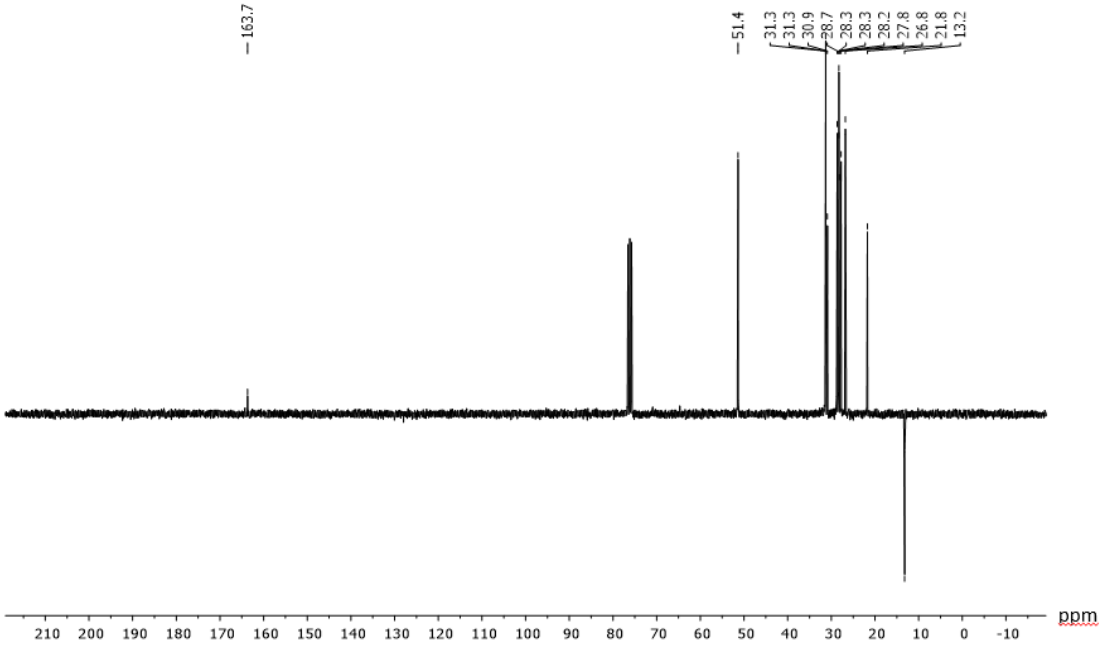

Figure S8 : ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **3c**

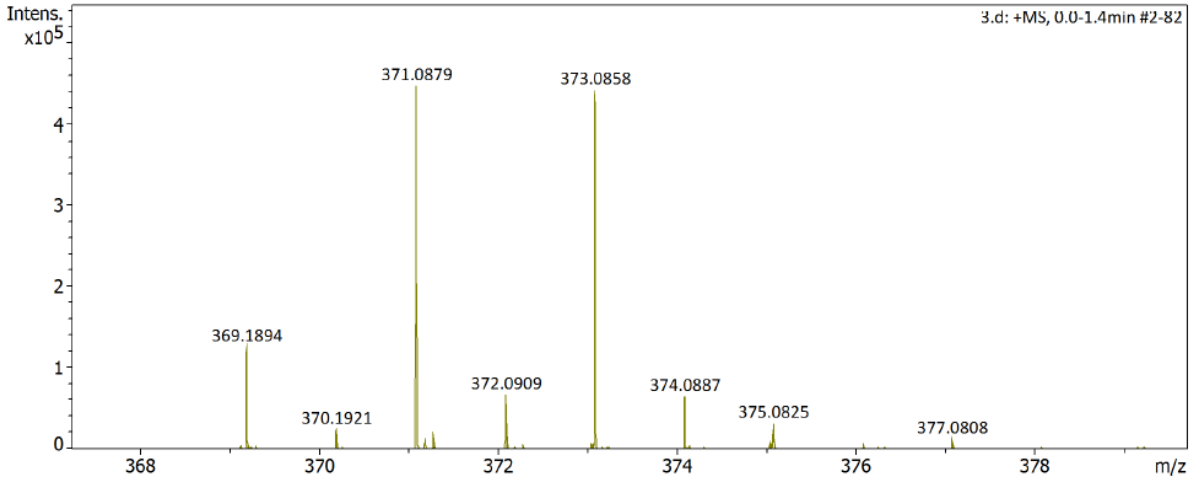

Figure S9 : Mass Spectrum of compound **3c**

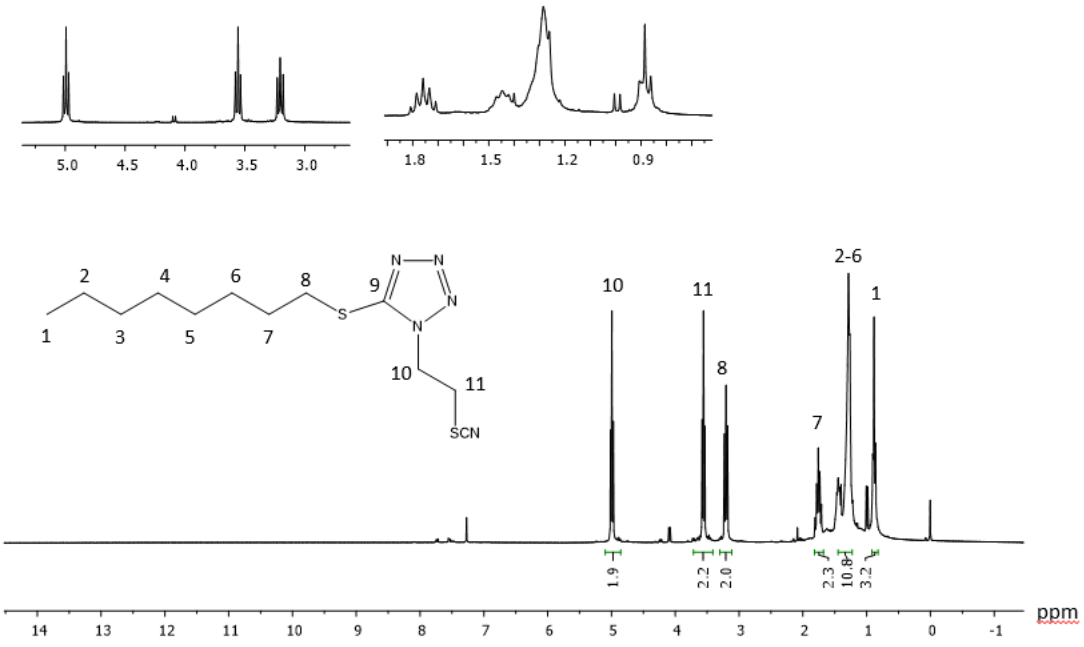

Figure S10 : ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **4a**

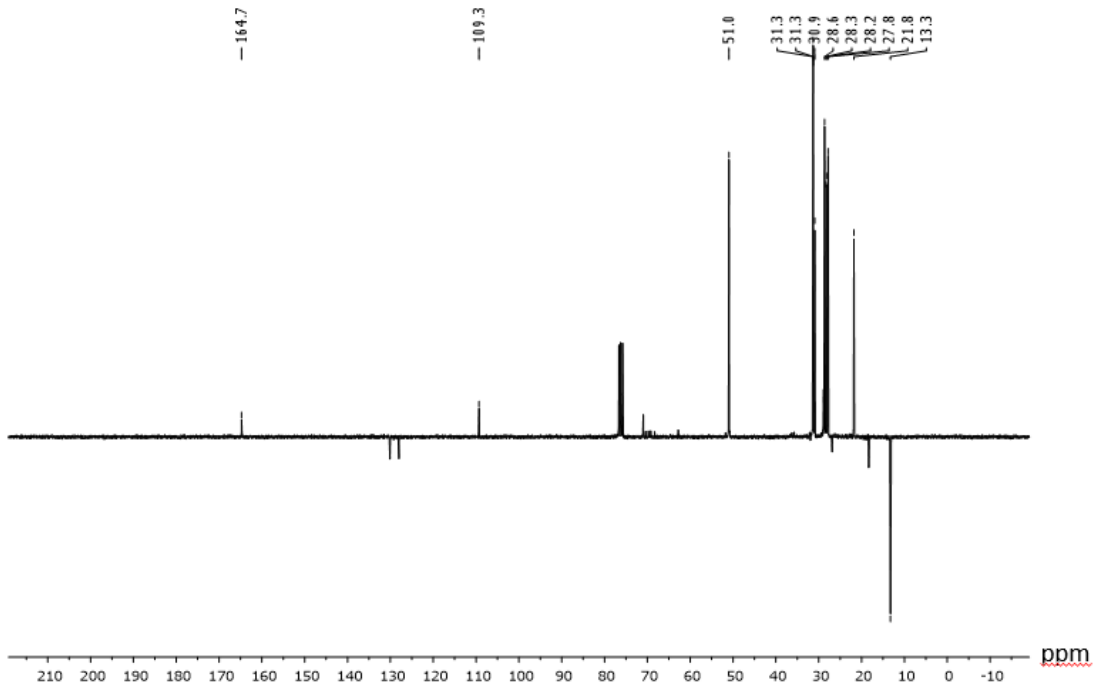

Figure S11 : ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **4a**

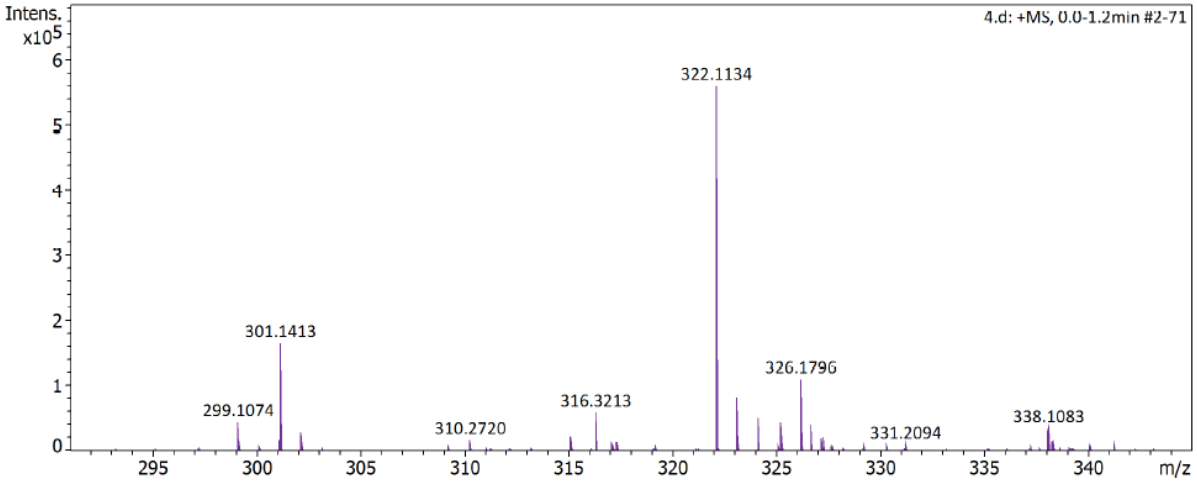

Figure S12: Mass Spectrum of compound **4a**

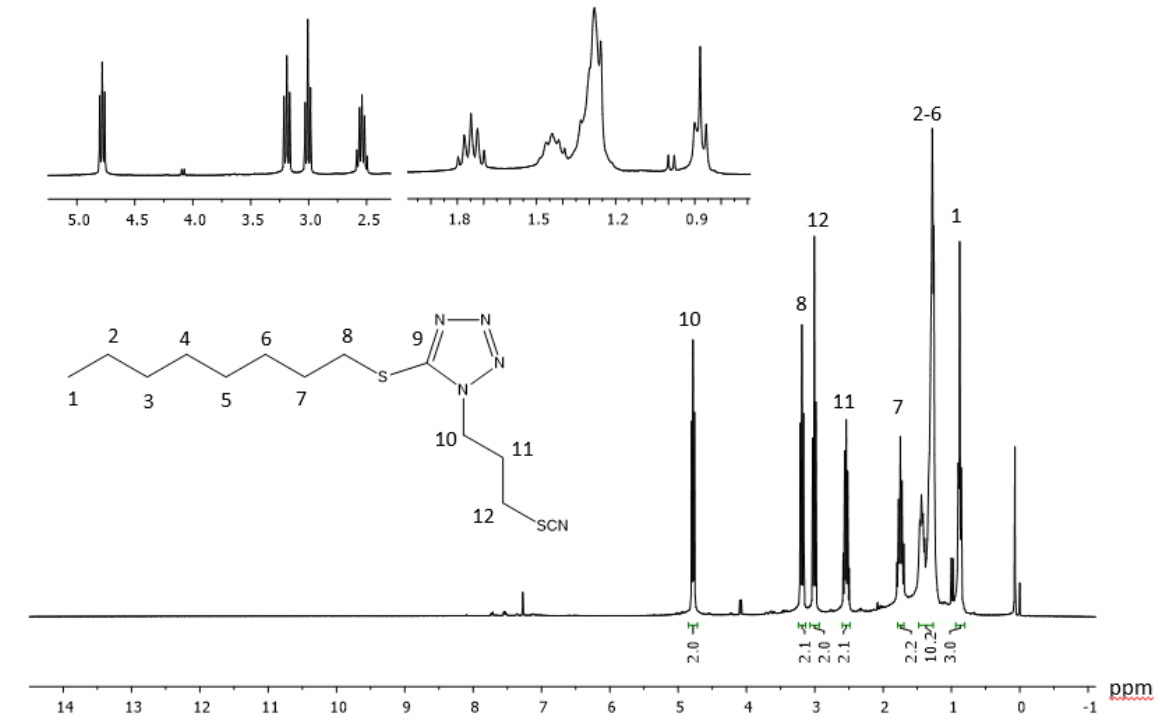

Figure S13: ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **4b**

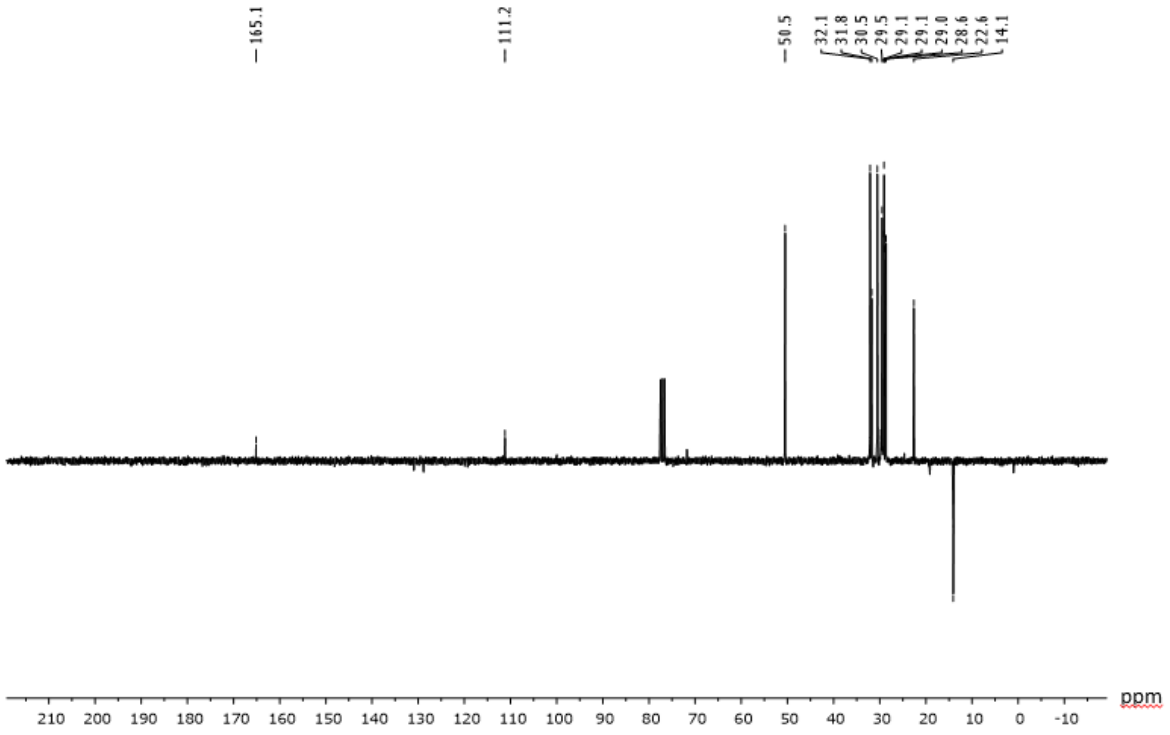

Figure S14 : ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **4b**

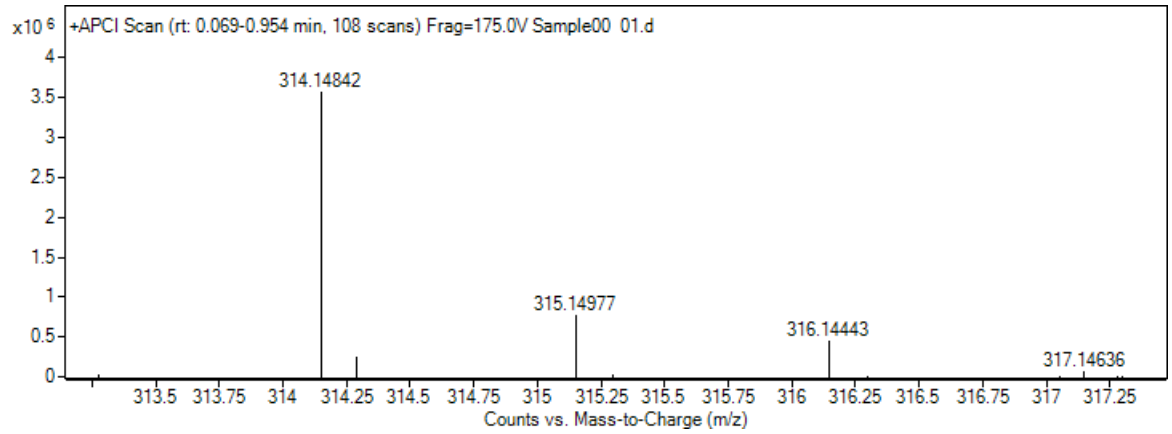

Figure S15: Mass Spectrum of compound **4b**

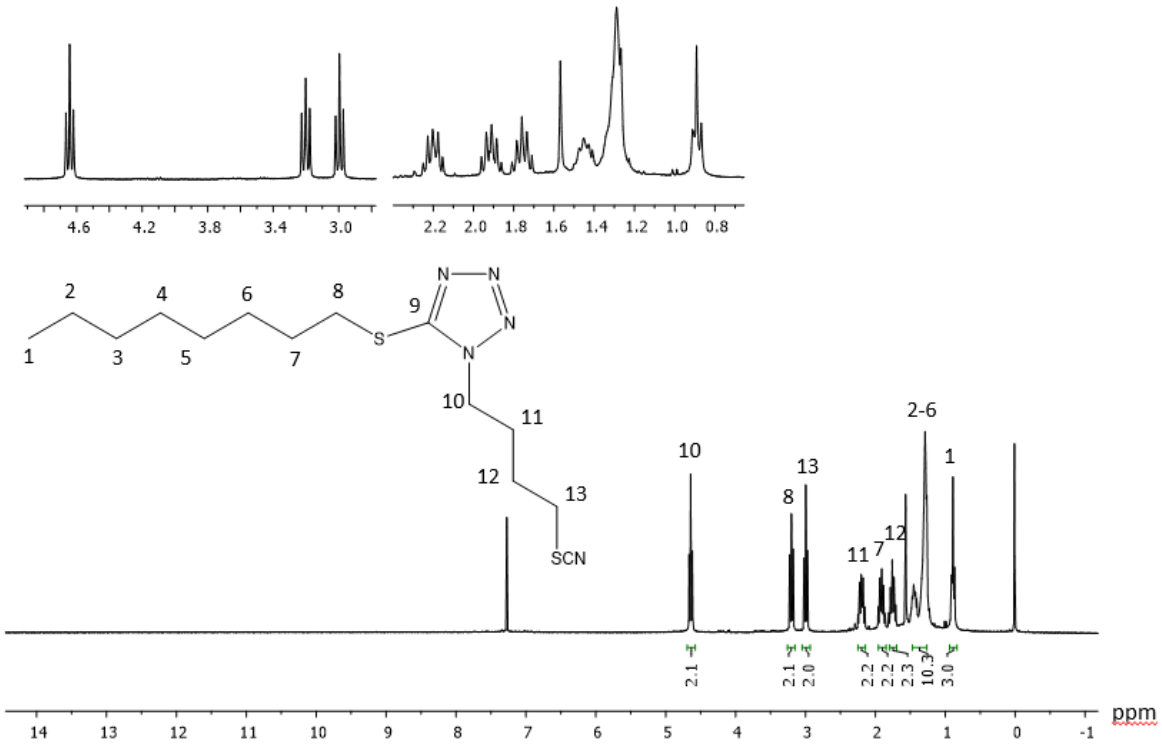

Figure S16: ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **4c**

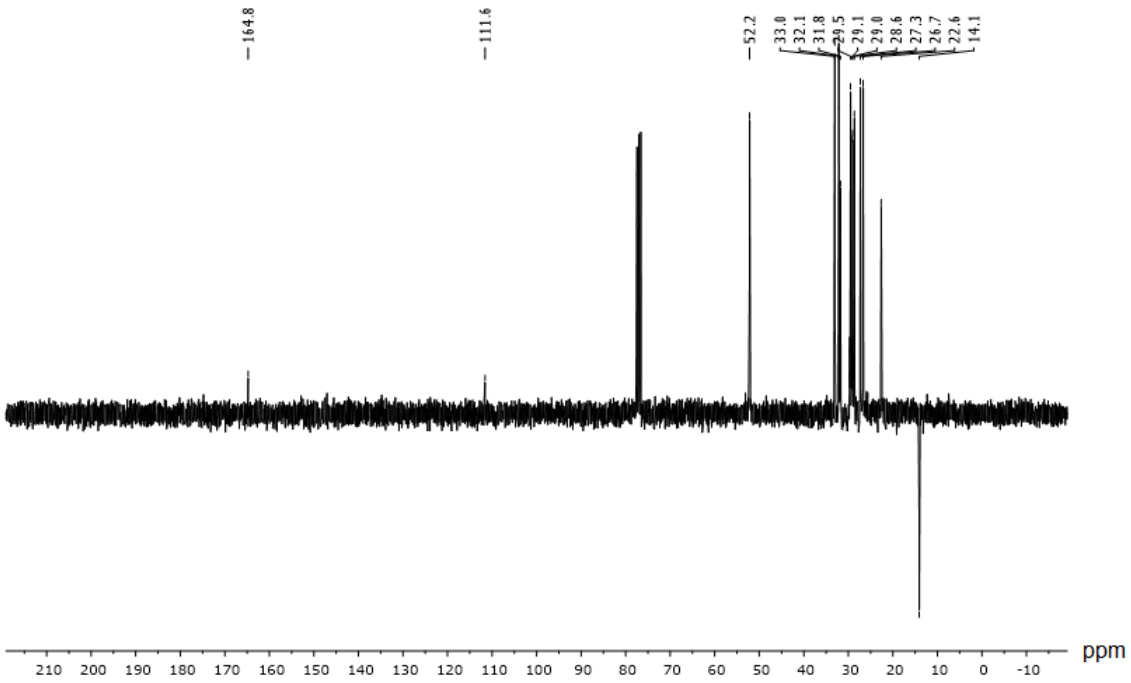

Figure S17: ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **4c**

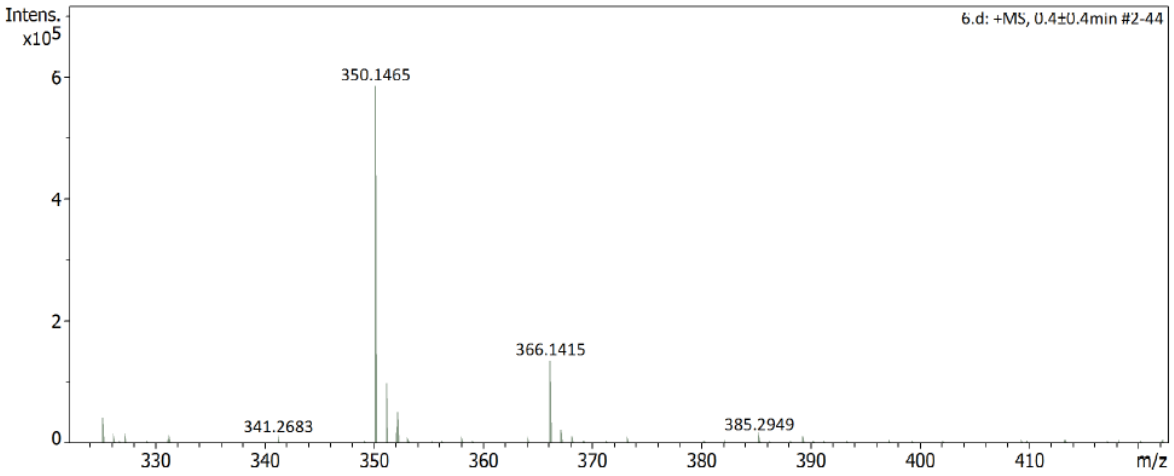

Figure S18: Mass Spectrum of compound **4c**

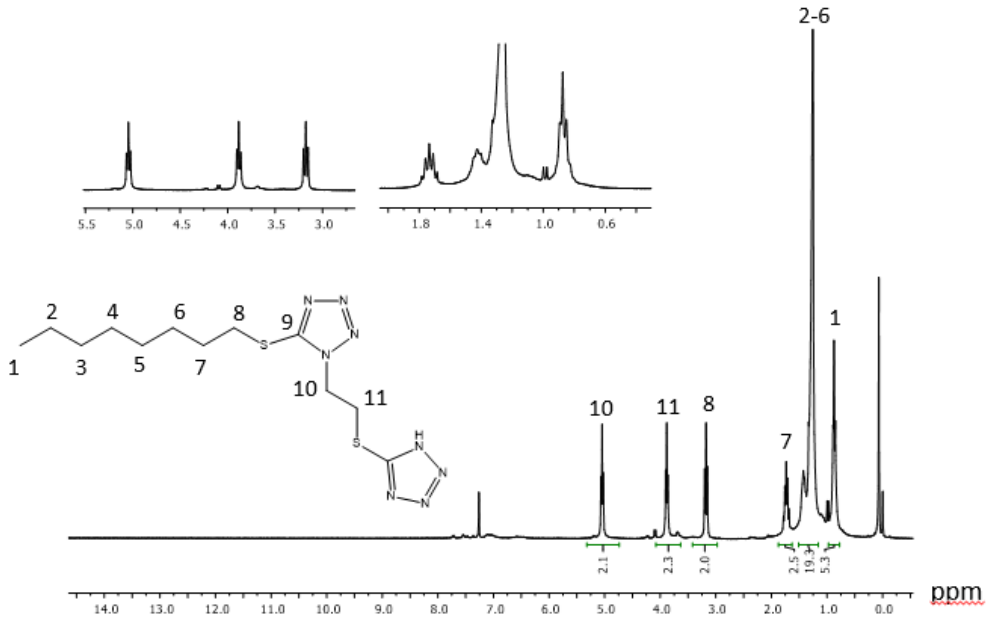

Figure S19: ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **5a**

*Higher integration of the peaks between 0.8-1.5 ppm results from the hexane (column chromatography eluent) residues[1].

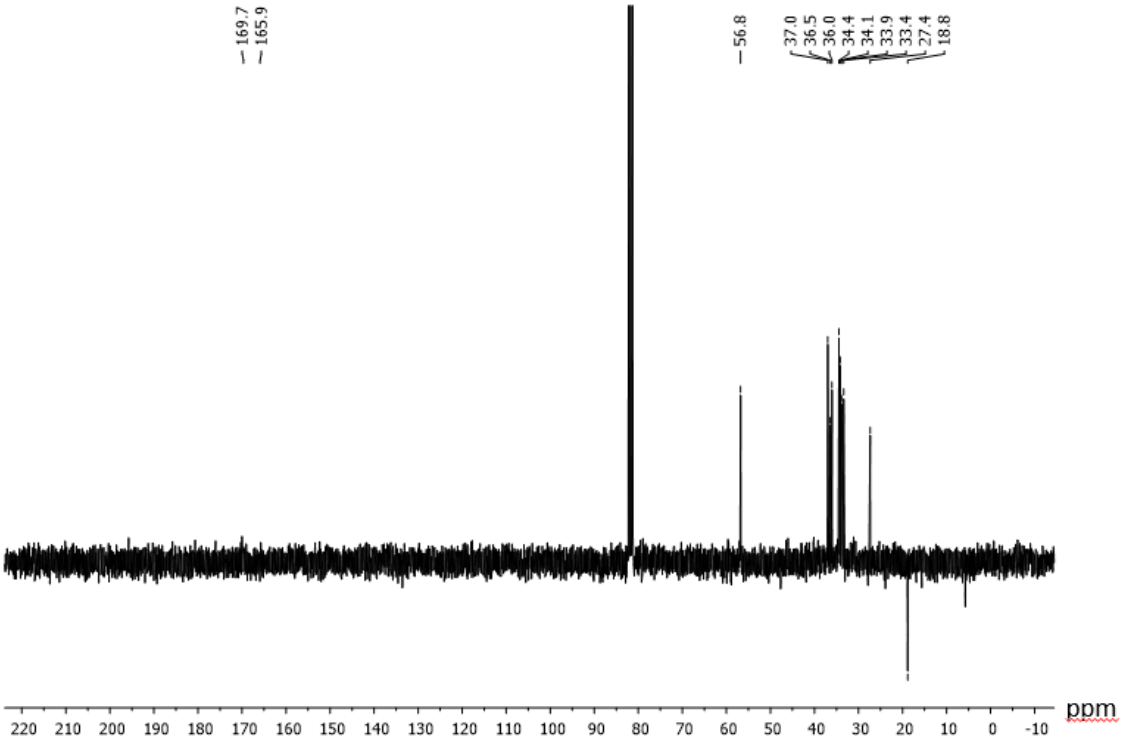

Figure S20: ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **5a**

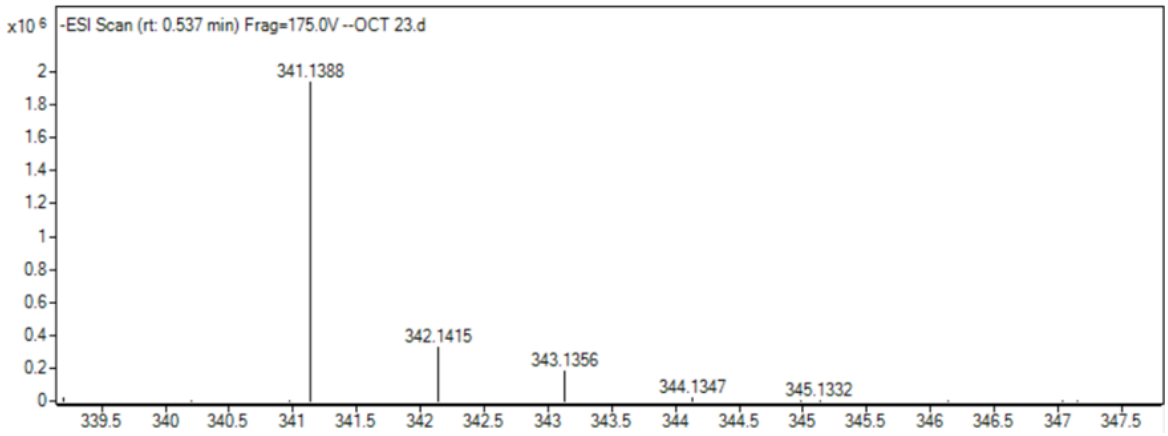

Figure S21: Mass Spectrum of compound **5a**

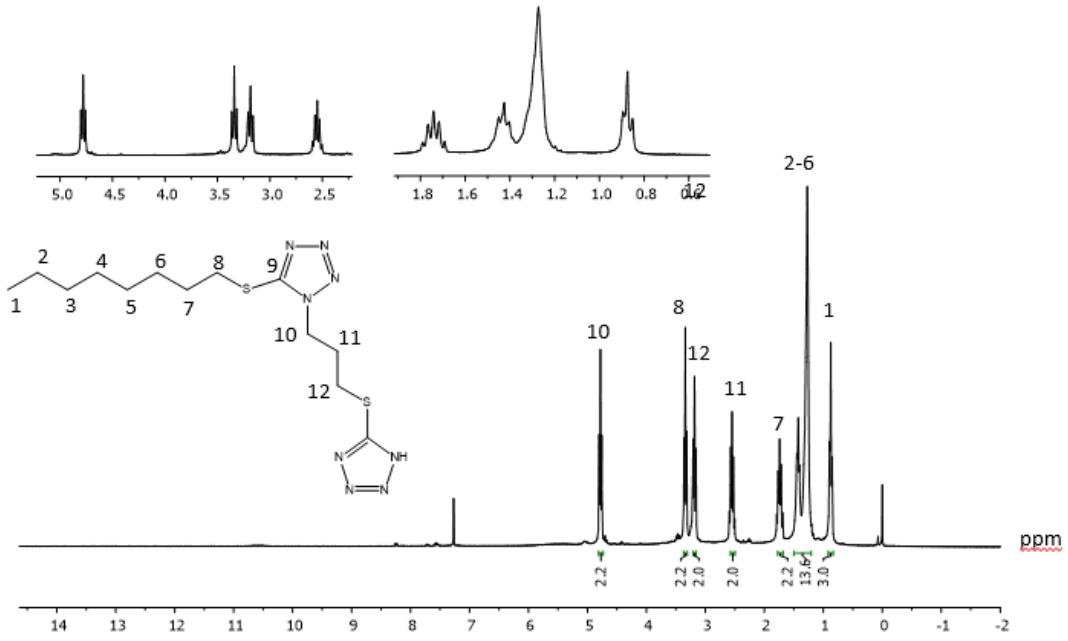

Figure S22: ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **5b**

*Higher integration of the peaks between 0.8-1.5 ppm results from the hexane (column chromatography eluent) residues[1].

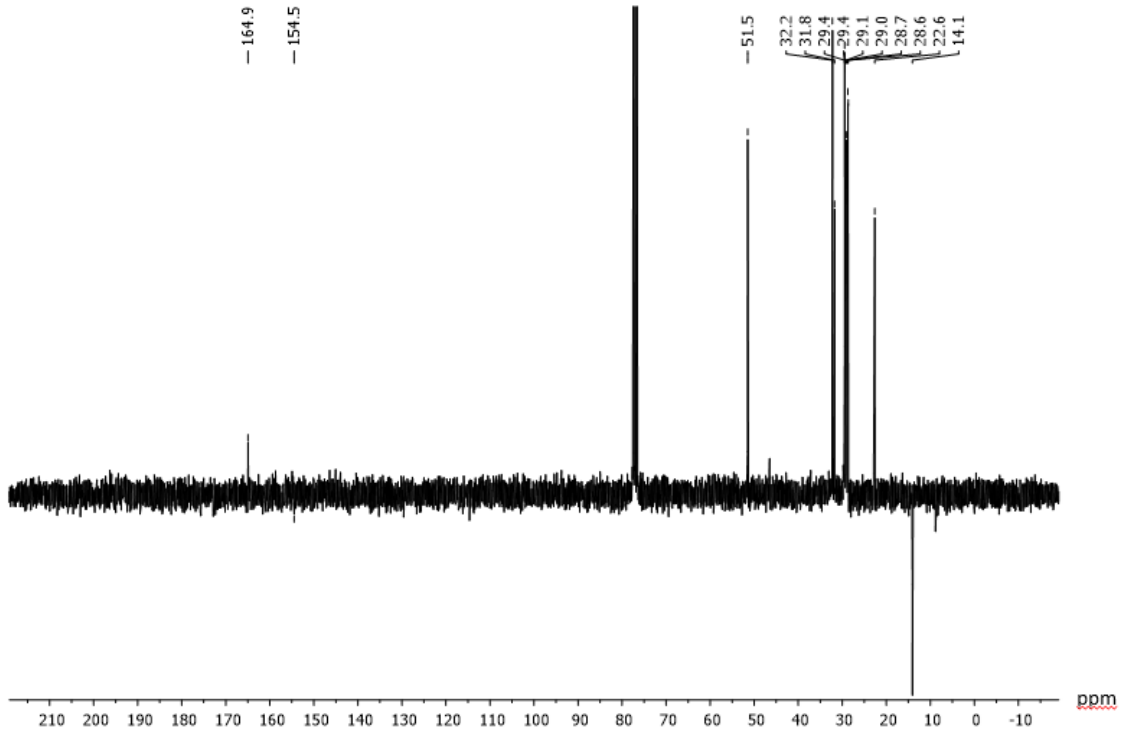

Figure S23: ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **5b**

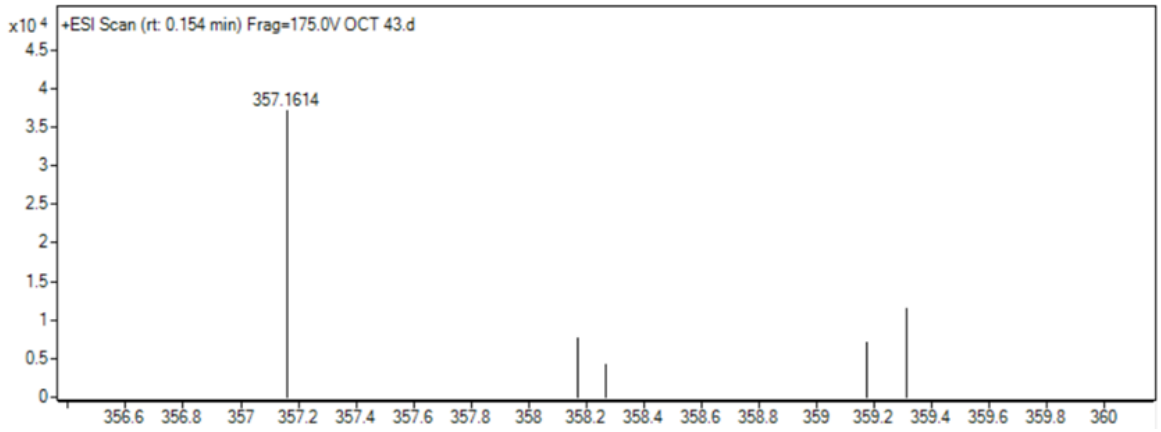

Figure S24: Mass Spectrum of compound **5b**

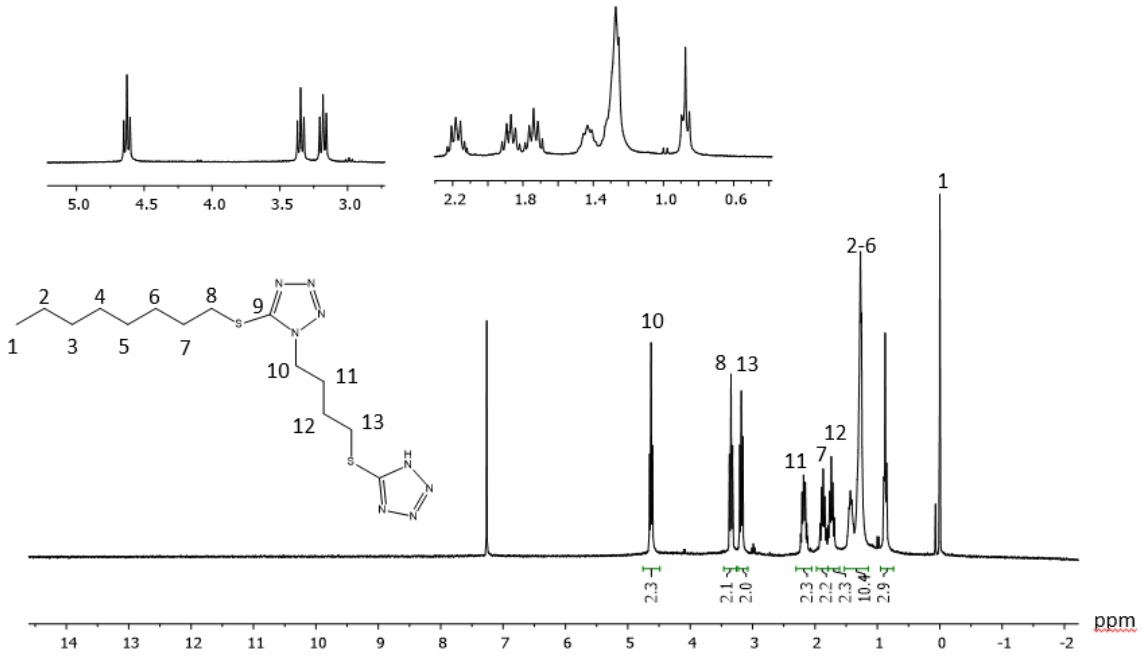

Figure S25: ^{1}H NMR (300 MHz, $CDCl_3$) Spectrum of compound **5c**

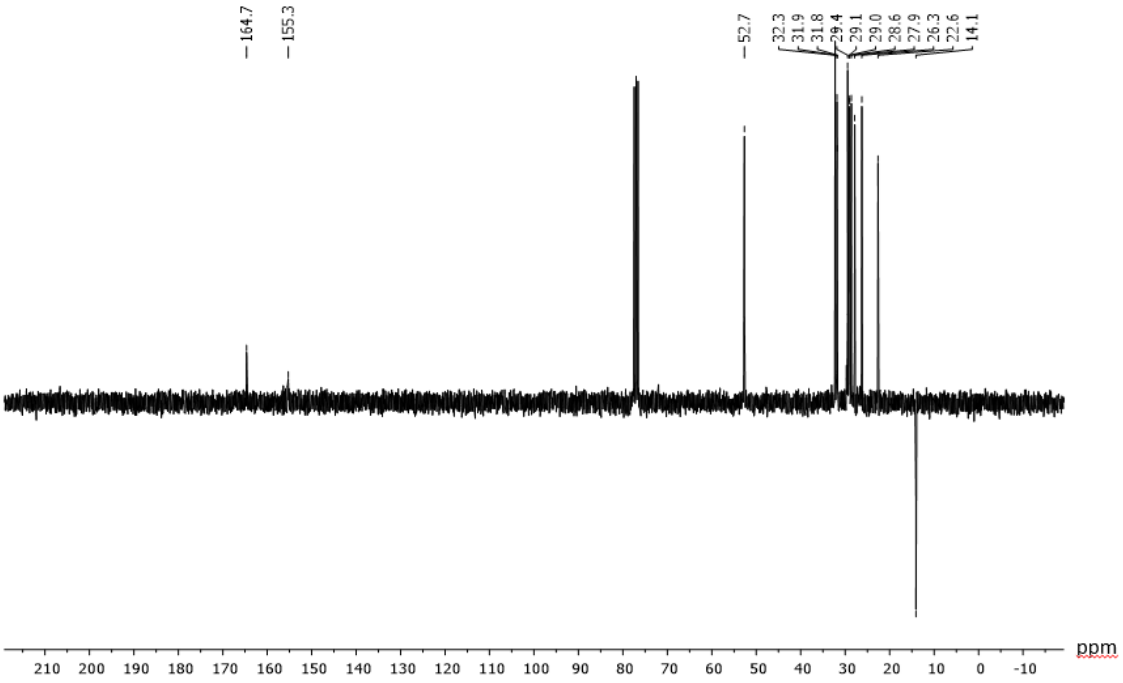

Figure S26: ^{13}C NMR (300 MHz, $CDCl_3$) Spectrum of compound **5c**

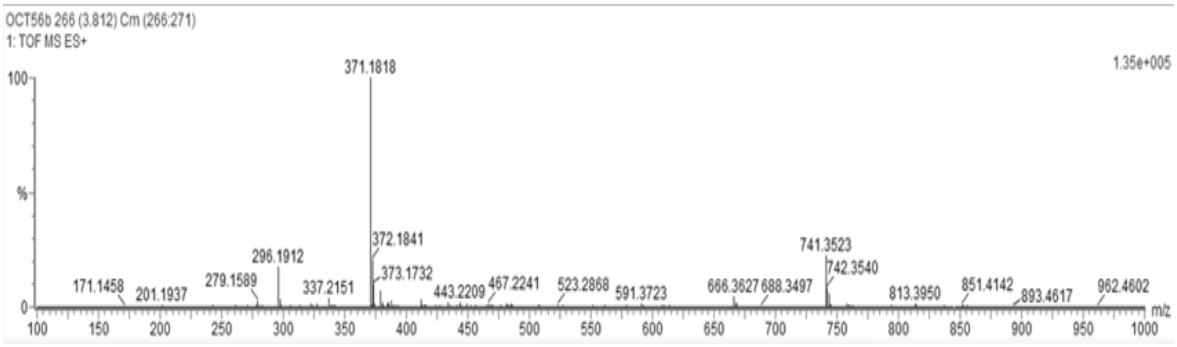

Figure S27: Mass Spectrum of compound **5c**

S1:Antimicrobial Bioassay

The synthesized compounds showed variable activity (11 mm-23 mm) on the growth of the pathogenic bacteria-yeasts used, and the inhibition rates mainly differed between medium and high activities. In addition, compounds were more effective in Gr (-) bacteria than Gr (+) bacteria (Table S1).

The antimicrobial activity data shown in Table S1 are discussed as follows:

1. Compound **3a** showed higher inhibitory activity in *P. aeroginosa* (16 mm) than AMP10 (8 mm), AMC30 (15 mm) and K30 (14 mm). Bacteria of the genus Pseudomonas are widespread in nature and cause opportunistic infections and nosocomial infections. Among them, *P. aeruginosa* ranks first among nosocomial infections and can develop resistance to various antibiotics and cause high mortality and morbidity due to infection[2-4]. In addition, this compound showed the same inhibitory effect as K30 (20 mm) on *S. typhi*, but showed higher activity than SXT25, AMC30, AMP10 (respectively; 17 mm, 19 mm, 11 mm) ().

2. Compound **4a** showed high inhibitory activity in *S. aureus*, *P. aeroginosa*, *S. typhi* and *E. coli* (respectively; 23 mm, 20 mm, 18 mm). It is well known that *S. aureus* is a versatile pathogen, is very diverse in nature and varies in intensity of infection affecting the skin, soft tissue, respiratory system, bone joints and endovascular tissues[5,6]. In addition, this compound showed higher inhibitory activity than all standard antibiotics in *P. aeroginosa* ().

3. Compound **5a** showed higher activity than AMP10 (8 mm) in *P. aeroginosa* (13mm), while *S.typhi* (11 mm) showed the same inhibition activity with this antibiotic ().

4. Compound **3b** showed higher activity in *P. aeroginosa* (20 mm) than all standard antibiotics. Further this compound showed higher inhibitory activity than AMP10 (10 mm) and AMC30 (14 mm) ().

5. Compound **4b** showed a greater inhibitory effect in Gr (-) *S. typhi* (18 mm) and *E. coli* (17 mm) (). Salmonella serovars cause many different clinical symptoms, ranging from asymptomatic infection to severe typhoid-like syndromes in infants or in some high sensitivity in humans[7,8].

6. Compound **5b** showed higher inhibitory activity in *P. aeroginosa* (18mm), *S. typhi* (17 mm) and *E.coli* (21 mm). Further this compound showed the same inhibitory effect as SXT25 (18 mm) on *P.aeroginosa* but showed higher activity than K30, AMC30, AMP10 (respectively; 14 mm, 15 mm, 8 mm) (Figure 1).

7. Compound **3c** showed a greater inhibitor effect in Gr (-) *P. aeroginosa* (20 mm) than all of standard antibiotics. In addition, this compound showed higher inhibitory activity than AMP10 (10 mm) and AMC30 (14 mm) ().

8. Compound **4c** demonstrated higher inhibitory activity in *P.aeroginosa* (15 mm) and *E.coli* (18 mm) ().

9. Compound **5c** showed greater inhibition activity in Gr (-) *P.aeroginosa* (15mm), *S.typhi* (12 mm) and *E.coli* (18 mm) ().

10. All three compounds showed low activity in *C.albicans* than the antifungal. 11. From the interpretation of the data given in Table 1, it was seen that compounds prepared in this work recorded high antimicrobial activity similar to the reference drugs used and could help antimicrobial agents. As a result, it was concluded that these compounds are more effective in Gr (-) bacteria than Gr (+) bacteria (). The potential cause for this may be the presence of the outer impermeable membrane, thin peptidoglycan monolayer, periplasmic space, and cell wall composition in Gram-negative bacteria[9].

		Compounds and Mean[a] of zone diameter(mm)									**Standard Antibiotics (inhibition zone (mm))**				
Microorganisms		**3a**	**4a**	**5a**	**3b**	**4b**	**5b**	**3c**	**4c**	**5c**	**AMP 10***	**SXT 25**	**AMC 30**	**K30**	**NYS 100**
Gr (+)	***M.luteus***	**13 L**	**12 L**	**11 L**	**12 L**	**-**	**11 L**	**-**	**-**	**-**	**22**	**21**	**25**	**23**	**N**
	S.epidermidis	**-**	**16 I**	**-**	**13 L**	**15 I**	**17 I**	**11 L**	**12 L**	**17 I**	**26**	**25**	**27**	**25**	**N**
	S.aureus	**15 I**	**23 H**	**20 H**	**18 H**	**15 I**	**21 H**	**21 H**	**21 H**	**20 H**	**30**	**24**	**30**	**25**	**N**
	B. cereus	**15 I**	**15 I**	**13 L**	**12 L**	**13 L**	**16 I**	**12 L**	**16 I**	**15 I**	**23**	**25**	**20**	**28**	**N**
Gr (-)	***P.aeroginosa***	**16 H**	**20 H**	**13 L**	**20 H**	**-**	**18 H**	**20 H**	**15 I**	**15 I**	**8**	**18**	**15**	**14**	**N**
	K. pneumonia	**-**	**11 L**	**-**	**11 L**	**-**	**11 L**	**-**	**-**	**-**	**21**	**20**	**21**	**23**	**N**
	E. aerogenes	**13 L**	**17 I**	**18 H**	**1 3L**	**12 L**	**13 L**	**-**	**-**	**13 L**	**21**	**19**	**20**	**24**	**N**
	S.typhi	**20 H**	**20 H**	**11 L**	**-**	**18 H**	**17 I**	**-**	**-**	**12 L**	**11**	**17**	**19**	**20**	**N**
	E. coli	**18 H**	**18 H**	**18 H**	**17 I**	**17 I**	**21H**	**15 I**	**18 H**	**18 H**	**10**	**18**	**14**	**25**	**N**
	P. vulgaris	**-**	**11 L**	**-**	**11 L**	**-**	**-**	**11 L**	**11 L**	**-**	**17**	**19**	**20**	**21**	**N**
Yeast	***C. albicans***	**11 L**	**-**	**-**	**12 L**	**-**	**-**	**12 L**	**-**	**-**	**N**	**N**	**N**	**N**	**20**

*Standard reagents (diameter of zone inhibition (mm): SXT25 (Sulfamethoxazole); AMP10 (Ampicillin); NYS100 (Nystatin); K30 (Kanamycin); AMC30 (Amoxycillin); N: not tried. Abbreviations: H, high activity; I, intermediate activity; L, low activity.

Figure S28: Antimicrobial activity of compounds and standard reagents (diameter of inhibition zone (mm))