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Synthesis and antimicrobial and antioxidant activities of hybrid molecules containing benzotriazole and 1,2,4-triazole

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Abstract: Eleven novel 1,2,4-triazolylbenzotriazoles have been prepared using 1-(hydrazinylcarbonylmethyl)-1*H*-benzotriazole (**3**) as a potent intermediate. Compound **3**, however, was obtained from benzotriazole in two steps. All synthesized compounds were characterized by detailed spectral studies like IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. All synthesized compounds were evaluated for their *in vitro* antimicrobial activity against seven strains of bacteria and four strains of fungi. Compounds **13**, **17**, **19**, **20**, and **21** were found to possess antibacterial activity comparable to that of ciprofloxacin against a *Klebsiella pneumoniae* strain. Except for compounds **2** and **13**, all compounds showed good antifungal activity against an *Aspergillus niger* strain as compared to miconazole. The synthesized compounds were also evaluated for their antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay and the results are encouraging, especially for compounds **3**, **20**, and **21**.

Key words: Benzotriazole, 1,2,4-triazole, triazolylbenzotriazole, antimicrobial and antioxidant activities

1. Introduction

Extensive research is going on around the world to discover novel molecules to fight various infections. This is even more relevant to the present-day scenario because of the emergence of antibiotic resistance among various pathogenic bacteria.[1] The demand therefore is to synthesize new bioactive molecules that are more effective and have fewer or no side effects. One way to achieve this is to construct new bioactive molecules using a molecular modification approach or else to synthesize hybrid molecules by tethering various known bioactive molecules together using simple chemistry. Recently hybrid molecules have also emerged as a new strategy in drug design and hence a few small molecules can be put together in the same frame to get a novel hybrid molecule.[2] Traditionally small molecules have also been recognized as a reliable source for discovering novel biologically active compounds.[3] Since we were interested in developing new N-containing heterocycles, we explored benzotriazoles, as they play a unique role in heterocyclic chemistry.[4] 1*H*-Benzotriazole is an intriguing molecule that is present in various medicinal drugs[5] as it possesses diverse and interesting biological and pharmacological activities, namely anticancer,[6–9] antifungal,[10,11] antibacterial,[12,13] antitubercular,[14] antiviral,[15,16] antiparasitic,[17–19] and antioxidant.[20,21]

Besides benzotriazoles, another nitrogen-containing heterocycle, 1,2,4-triazole has also aroused our interest due to its excellent pharmacokinetic characteristics, favorable safety profile, and ability for the formation of hydrogen bonds with other active molecules. Besides these, it possesses a wide spectrum of chemotherapeu-

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tic activities such as antimicrobial,[22–24] anticonvulsant,[25] antitumor,[26,27] antiinflammatory and analgesic,[28] antiviral/anti-HIV,[29] antituberculosis,[30] antioxidant,[31] and antihypertensive.[32] Although the chemistry of benzotriazole has been extensively explored, there is still potential for the development of medicinally important hybrid molecules based on it. Our research group has been working on the chemistry of 1,2,4-triazoles for the last few years.[33–36] Therefore, in continuation of our efforts to develop a new lead hybrid molecule, we planned to synthesize new triazolyl-benzotriazoles, containing benzotriazole and 1,2,4-triazole, in order to enhance the biological activity of the resulting molecule. The results are reported in this communication.

2. Result and discussions

2.1. Chemistry

In continuation to our ongoing research work on triazolyl chemistry we herein report the synthesis of some new 1-(((aryl)-3-yl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazoles **13**–**21**, **24**, and **25**. These were synthesized using hydrazide **3** as a potent intermediate and substituted benzaldehyde **4**–**12** and heterocyclic aldehydes **22** and **23**. These new triazolyl-benzotriazoles were then evaluated for their antimicrobial and antioxidant activities. All the intermediates along with the final compounds have been fully characterized by detailed spectral studies, some of which are discussed in the following text. Please see the Supplementary data for spectra of the compounds.

Alkylation[33–35] of benzotriazole (**1**) with ethyl bromoacetate in the presence of anhyd. potassium carbonate in acetone at room temperature gave a colorless oil labeled as **2**. Its IR spectrum showed an absorption band at 1742 cm^{-1}, characteristic for carbonyl of an ester. Furthermore, its ^{1}H NMR showed a quartet of two protons at δ 4.25 and a triplet for three protons at δ 1.28, typical for ethyl ester. Besides this, it also showed peaks at δ 8.06 as a doublet for one proton, at δ 7.52–7.46 as a multiplet for two protons, and at δ 7.41–7.38 as a multiplet for one proton in the aromatic region in the ^{1}H NMR spectrum for benzotriazole moiety. This indicated that benzotriazole and ethyl bromoacetate reacted with the loss of HBr. The methylene group in **2** appeared at δ 5.43 as a singlet for two protons in ^{1}H NMR and at δ 48.9 in ^{13}C NMR. Finally, the mass spectrum confirmed **2** to be 1-(ethoxycarbonylmethyl)-1*H*-benzotriazole as showed by $M^+ + 1$ at m/z 206 in TOF ES+ corresponding to the molecular formula $C_{10}H_{11}N_3O_2$.

1-(Ethoxycarbonylmethyl)-1*H*-benzotriazole (**2**) was refluxed with hydrazine hydrate in abs. ethanol[33–35] to give white solid **3**, having mp 150–152 °C. It showed an absence of protons for the ester ethyl group and instead displayed a D_2O-exchangeable broad singlet for one proton at δ 9.69 and another broad singlet for two protons at δ 4.29 corresponding to –$NHNH_2$ in its ^{1}H NMR spectrum. This was also supported by its IR spectrum showing absorption bands at 3338 and 3061 cm^{-1} and at 1648 cm^{-1}. The aromatic protons for the benzotriazole ring were observed at δ 7.97 as a doublet for one proton, at δ 7.72 as a doublet for one proton, at δ 7.50 as a triplet for one proton, and at δ 7.39–7.36 as a multiplet for one proton in its ^{1}H NMR spectrum. This indicated **3** to be 1-(hydrazinylcarbonylmethyl)-1*H*-benzotriazole, which was confirmed by its mass spectrum, showing $M^+ + 1$ at m/z 192 in TOF ES+ corresponding to the molecular formula $C_8H_9N_5O$.

In the final step, 1-(hydrazinylcarbonylmethyl)-1*H*-benzotriazole (**3**) was reacted with an equimolar amount of 4-methoxybenzaldehyde (**8**) in the presence of ammonium acetate in acetic acid at room temperature,[33–35] which yielded a white solid having mp 164–166 °C labeled as **17**. Its IR spectrum showed an absence of bands for hydrazidic carbonyl and –$NHNH_2$, indicating that hydrazide reacted to give a triazole ring as indicated by the absorption band at 3282 cm^{-1} corresponding to >NH of the triazole ring. The >NH

was further confirmed by its characteristic D_2O-exchangeable broad singlet at δ 11.57 for one proton in its ^1H NMR. Furthermore, its ^1H NMR showed the usual peaks for a benzotriazole ring and 4-methoxyphenyl ring observed at δ 7.96–7.94 as a multiplet for two protons, at δ 7.45–7.43 as a multiplet for one proton, and at δ 7.34–7.29 as a multiplet for one proton along with a multiplet at δ 7.60–7.55 for two protons and at δ 6.88–6.83 for two protons. The protons of $-OCH_3$ appeared as a singlet at δ 3.77 in its ^1H NMR and in ^{13}C NMR at δ 54.8. A broad singlet at δ 5.92–5.87 for two protons in ^1H NMR corresponded to the methylene flanked between benzotriazole and triazole, which appeared at δ 48.5 in ^{13}C NMR. Its ^{13}C NMR displayed peaks at δ 166.4, 160.6, 145.1, 144.5, 133.6, 126.9, 125.9, 123.3, 118.8, 117.5, 113.7, and 110 in the aromatic region, which indicated the presence of benzotriazole, 4-methoxyphenyl, and triazole moieties. Finally, its TOF ES+ showed $M^+ + 1$ at m/z 307, corresponding to the molecular formula $C_{16}H_{14}N_6O$ and confirming that **3** and 4-methoxybenzaldehyde (**8**) reacted together and underwent intermolecular cyclisation to give **17**, characterized as 1-(3-(4-methoxyphenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole on the basis of above spectral details.

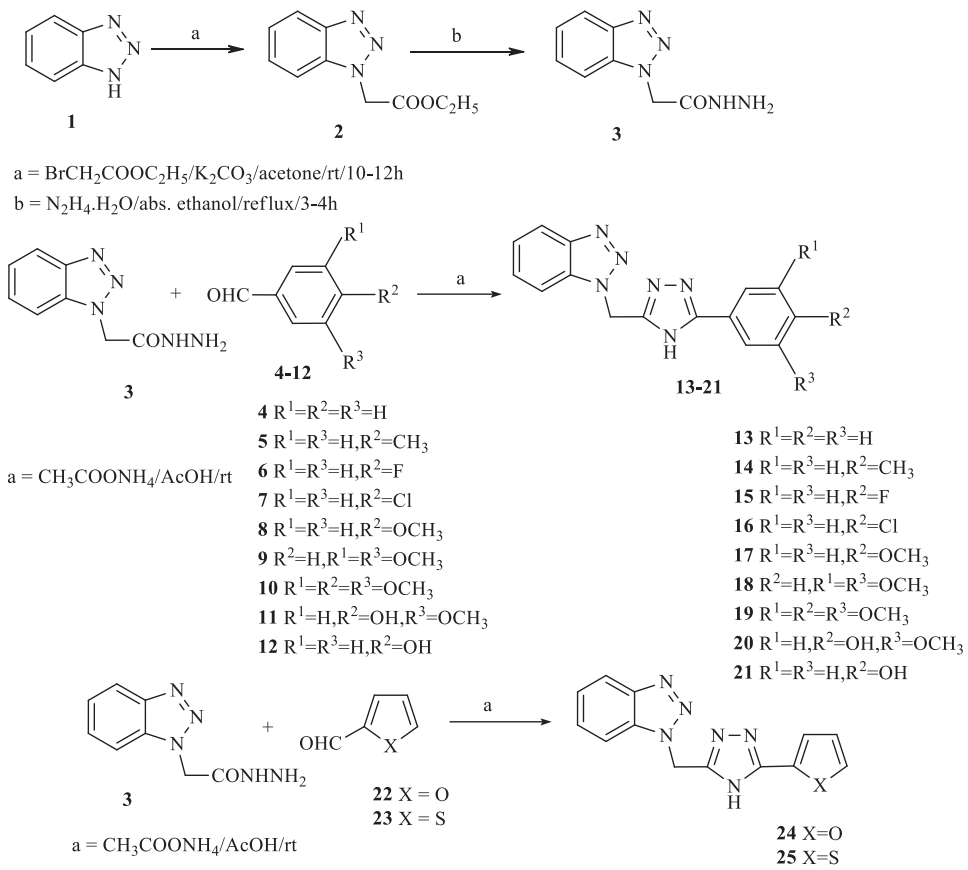
Similarly, the above reaction was carried out using 1-(hydrazinylcarbonylmethyl)-1*H*-benzotriazole (**3**) and different substituted aromatic aldehydes (**4**–**7** and **9**–**12**) to give the corresponding triazolylbenzotriazoles, **13**–**16** and **18**–**21**. All the synthesized compounds were completely characterized on the basis of their detailed spectral data.

The hydrazide 1-(hydrazinylcarbonylmethyl)-1*H*-benzotriazole (**3**) was also made to react with heterocyclic aldehydes **22** and **23** to get corresponding triazolylbenzotriazoles **24** and **25**.

Characterization of 1-(3-(furan-2-yl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (**24**): 1-(Hydrazinylcarbonylmethyl)-1*H*-benzotriazole (**3**), when reacted with furfuraldehyde (**22**) in a 1:1 ratio using ammonium acetate in acetic acid, gave white solid **24**, which has $R_f = 0.48$ in petroleum ether/ethyl acetate (85:15) and mp 190–192 °C. In ^1H NMR a D_2O-exchangeable broad singlet that appeared at δ 11.80–11.73 for one proton indicated the presence of >NH of the triazole ring. This indicated that hydrazide reacted with furfuraldehyde and resulted in a triazole ring formation. The protons in the aromatic region appeared at δ 8.01 as a doublet for one proton, at δ 7.94 as a doublet for one proton, at δ 7.60–7.56 as a multiplet for one proton, at δ 7.50–7.48 as a multiplet for one proton, at δ 7.39–7.36 as a multiplet for one proton, at δ 6.77–6.75 as a multiplet for one proton, and at δ 6.53 as a multiplet for one proton in its ^1H NMR spectrum and peaks at δ 166.4, 148.7, 143.9, 134.6, 133.2, 126.9, 123.3, 118.9, 117.5, 112.6, 111.4, and 109.6 in ^{13}C NMR indicated the presence of benzotriazole, furfural, and triazole moieties. A singlet for two protons at δ 5.87 in ^1H NMR and peak at δ 48.3 in ^{13}C NMR corresponded to methylene flanked between benzotriazole and triazole units. Finally, in its TOF ES+ it showed $M^+ + 1$ at m/z 267 corresponding to the molecular formula $C_{13}H_{10}N_6O$, confirming its structure to be 1-(3-(furan-2-yl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole.

Following the above strategy, **25** was also synthesized by intermolecular cyclization of 1-(hydrazinylcarbonylmethyl)-1*H*-benzotriazole (**3**) with thiophen-2-carboxyaldehyde (**23**). All the synthesized compounds were completely characterized on the basis of their detailed spectral data.

The synthetic schemes are outlined below:



2.2. Antimicrobial activity

All the synthesized compounds, **2**, **3**, **13**–**21**, **24**, and **25**, were evaluated for their in vitro antimicrobial (antibacterial and antifungal) activity using the cup-plate method[36−38] at 100 µg/mL against three gram-positive bacterial strains [*Staphylococcus aureus* (MTCC 096), *Bacillus subtilis* (MTCC 441), and *Staphylococcus epidermis* (MTCC 435)], four gram-negative bacterial strains [*Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 424), *Salmonella typhi* (MTCC 733), and *Klebsiella pneumoniae* (MTCC 432)], and four fungal strains [*Aspergillus niger* (MTCC 282), *Aspergillus fumigates* (MTCC 343), *Aspergillus flavus* (MTCC 277), and *Candida albicans* (MTCC 227)]. Both antibacterial and antifungal activities were assessed by measuring zones of inhibition.[39] Antimicrobial drugs ciprofloxacin and miconazole were used as positive controls and DMSO was used for a blank.[33,34] The experiments were repeated three times and the average values are presented in Table 1. Figures 1 and 2 show the graphical representation. These revealed that all the selected compounds could effectively, to some extent, inhibit the growth of all tested strains in vitro.

All tested compounds showed significant to comparable antibacterial activity against *S. aureus* and compound **16** showed similar antibacterial activity to that shown by the standard. All tested compounds possessed moderate antibacterial activity against *B. subtilis*. All compounds showed some antibacterial activity against *S. epidermis*. All tested compounds showed significant to comparable antibacterial activity against *K. pneumoniae*, except compound **3**. Compounds **13**, **17**, **19**, and **21** were found almost comparable to the standard and compound **20** showed slightly better antibacterial activity than the standard against *P. aeruginosa* and hence can be developed into a lead molecule in future. Compounds **14**, **24**, and **25** showed significant

Table 1. Antibacterial activity against bacterial strains and antifungal activity against fungal strains (zone of inhibition shown numerically in mm).

S. no.	Sample code	Gram-positive bacteria			Gram-negative bacteria				Fungi			
		S. aureus	*B. subtilis*	*S. epidermis*	*K. pneumoniae*	*S. typhi*	*P. aeruginosa*	*E. coli*	*A. niger*	*A. fumigatus*	*A. flavus*	*C. albicans*
1	Std.#	19	20	22	20	22	26	17	16	20	18	20
2	**2**	15	12	12	16	12	13	12	12	12	12	13
3	**3**	14	14	13	13	13	15	13	14	12	12	13
4	**13**	14	14	13	21	13	13	14	12	12	13	12
5	**14**	18	12	13	16	15	14	12	14	12	12	14
6	**15**	16	12	13	18	13	14	12	13	13	13	12
7	**16**	19	12	14	15	12	14	14	14	12	14	13
8	**17**	14	13	13	20	14	15	14	13	14	12	14
9	**18**	12	12	12	18	12	15	13	14	13	13	12
10	**19**	16	12	12	21	12	14	13	14	17	12	13
11	**20**	16	13	14	24	13	15	14	13	12	14	12
12	**21**	16	14	14	20	14	14	15	14	13	12	12
13	**24**	13	14	13	16	15	14	14	13	13	12	13
14	**25**	14	14	12	18	15	16	14	15	14	14	14

#Standard drug for bacteria: ciprofloxacin, # Standard drug for fungi: Miconazole

Zone of inhibition: internal diameter: 6 mm.

antibacterial activities against *S. typhi* and the rest of the compounds showed moderate activity. Compounds **13**, **16**, **20**, **21**, and **24** possessed significant antibacterial activity against *E. coli*.

All tested compounds showed very good antifungal activity against *A. niger*, except **2** and **13**. All compounds showed moderate antifungal activity against *A. fumigatus*, *A. flavus*, and *C. albicans*.

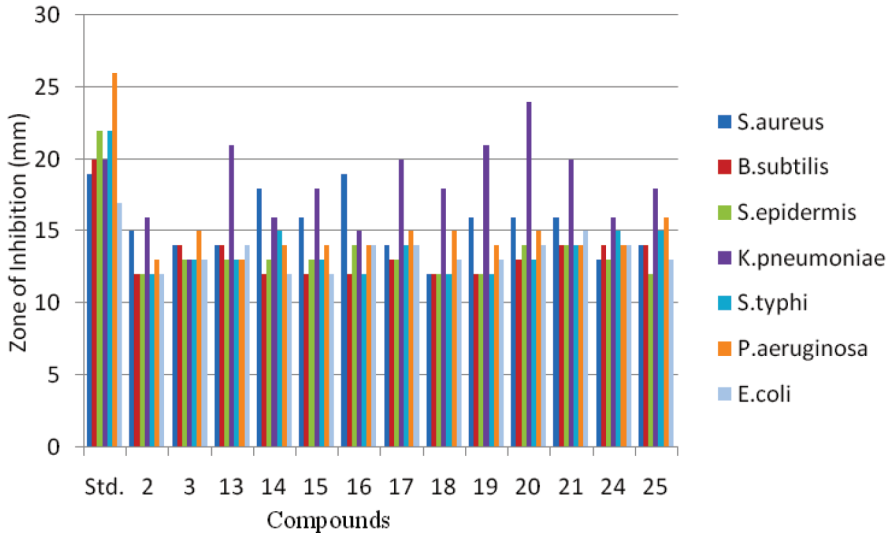


Figure 1. Antibacterial activity against bacterial strains.

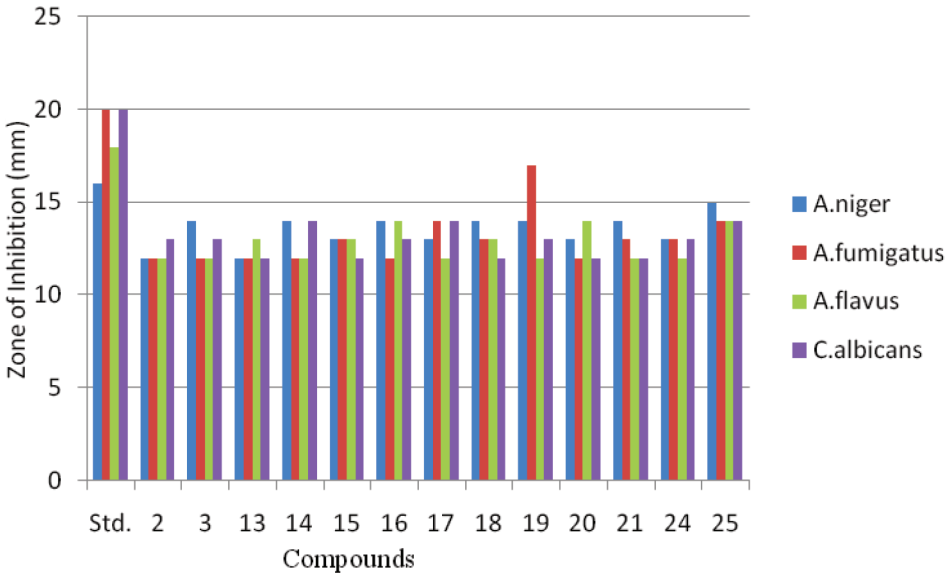


Figure 2. Antifungal activity against fungal strains.

2.3. Calculation of log *P* and molar refractivity (MR)

The lipophilicity of the compounds, expressed as log P, explains the main predictor for the activity.[40] The octanol/water partition coefficient C log P as a measure of hydrophobicity/lipophilicity was calculated using ChemDraw Ultra 13.0 software integrated with Cambridgesoft Software (Cambridgesoft Corporation).

The results obtained are given in Table 2 while Figures 3 and 4 show the graphical representation. The calculated values of log P for 1-(((aryl)-3yl)-4H-(1,2,4)-triazol-5-ylmethyl)-1H-benzotriazoles **2**, **3**, **13**–**21**, **24**, and **25** are included in Table 2. The lipophilic power of compounds increases with increasing log P. The MR,[41,42] which represents the size and polarization ability of a molecule describing steric effects, was also calculated using ChemDraw Ultra 13.0 software to explain the activity behavior of the synthesized compounds.

Table 2. Calculation of log P and molar refractivity (MR).

Compound	Log P	MR
2	1.32	56.61
3	0.18	53.19
13	2.95	83.16
14	3.43	89.05
15	3.10	83.58
16	3.50	87.76
17	2.82	90.41
18	2.69	97.66
19	2.57	104.90
20	2.43	92.22
21	2.56	84.97
24	1.56	75.68
25	2.93	81.15
Ciprofloxacin	1.32	89.39
Miconazole	5.09	102.57

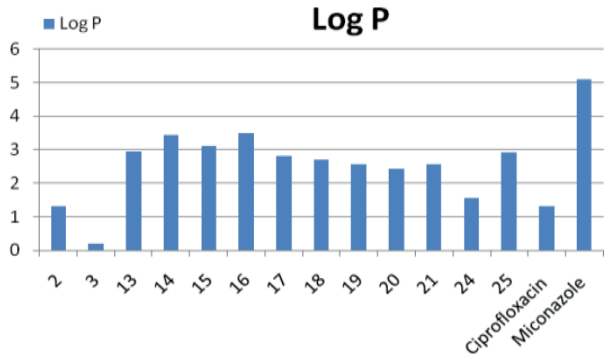


Figure 3. Log P values.

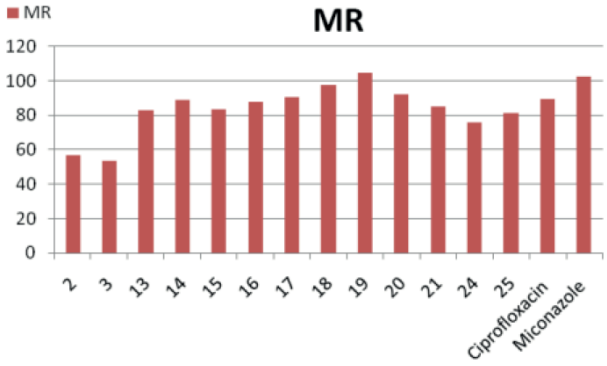


Figure 4. MR values.

2.4. Antioxidative studies

Reactive oxygen species (ROS) such as hydroxyl radicals, superoxide radicals, singlet oxygen, and hydrogen peroxide radicals are constantly formed as a result of normal organ functions or excessive oxidative stress.[43,44] Their presence in the biological system is very harmful as these species are responsible for the damage of biomolecules such as nucleic acid, proteins, lipids, DNA, and carbohydrates[45] and may result in many diseases such as

cancer, atherosclerosis, aging, hair loss, inflammation, immunosuppression, diabetes, and neurodegenerative disorders such as Alzheimer and Parkinson diseases.[46−51] The balance between the production and elimination of ROS is normally controlled by the body's defense mechanisms through the use of different enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. However, when it is disturbed, oxidative stress is generated, leading to oxidative damage of biomolecules. Antioxidants are compounds that slow down or prevent the oxidation of other molecules.[52,53] They interact with free radicals and prevent the damage by ROS. Thus, treatment with antioxidants is potentially a way to overcome oxidative stress. Because of this, there is a great interest in the discovery of natural and synthetic antioxidants that can serve as protective agents against these diseases. Phenolic compounds are known for their antimicrobial and antioxidant properties.[54,55] They act as free radical scavengers and their antioxidant potential depends on the substituent present and the extent of structure conjugation.[56,57]

2.4.1. Method and procedure

We used the 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) assay to determine the antioxidant activity of our synthetic samples.[58] For this, stock solutions of compounds **3**, **13**–**21**, and **24** were prepared in abs. ethanol (solvent) with 1000 µM/mL. This was then diluted with 95% ethanol to obtain 500, 250, 100, 50, 25, 10, 5, 2.5, and 1 µM/mL concentrations. DPPH solution (3.9 mg in 50 mL ethanol) was also prepared. Then, to 0.5 mL of test solution, 0.5 mL of DPPH solution (freshly prepared) was added. DPPH (0.5 mL) and 0.5 mL of ethanol were used as a control. The reaction mixture was allowed to stand for 20 min. UV absorbance at 517 nm was then recorded. The percentage of scavenging was calculated. Ascorbic acid was used as a standard drug.

2.4.2. Calculation of percentage of scavenging by test drug

$$\% \text{ Scavenging of test samples } = \frac{\text{Control abs. } (A_o) - \text{ Test abs. } (A_i)}{\text{Control abs. } (A_o)} \times 100$$

Compounds **3**, **13**–**21**, and **24** were screened for their antioxidant activities at various concentrations of 1000, 500, 250, 100, 50, 25, 10, 5, 2.5, and 1 µM/mL and the results were recorded as % inhibition. The analysis of results, shown in Table 3 (Figures 5 and 6 show the graphical representation), revealed that compound **3** possessed comparable activities at various concentrations to that of the standard and even better at low concentrations in vitro. Compound **20** possessed very good to comparable activities at various concentrations to that of the standard. Compound **21** possessed promising activity at high concentrations compared to the standard. The rest of compounds showed either low or no antioxidant activity even at high concentrations.

2.5. Conclusion

Eleven 1,2,4-triazolylbenzotriazoles have been synthesized using simple methodology in high yields. All synthesized compounds along with intermediates were evaluated for their antibacterial, antifungal, and antioxidant activities. Compounds **13**, **17**, and **19**–**21** and all compounds except **2** and **13** were found to possess good antibacterial and antifungal activities, respectively, while compounds **3**, **20**, and **21** were found to be good antioxidants. Thus, the presence of the –OH and/or $-OCH_3$ group in the phenyl ring increases the antimicrobial activity of these triazolylbenzotriazoles. Besides this, hydrazide **3** and the presence of the –OH group at 4 positions in **20** and **21** make these compounds good antioxidants because of possible extended conjugation after the abstraction of a hydrogen radical. Thus, some of these novel 1,2,4-triazolylbenzotriazoles are promising leads to explore further in order to discover a new antimicrobial or antioxidant for the future.

Table 3. Antioxidant activities at various concentrations in µM/mL.

Compound	% Inhibition at various concentration µM/mL									
	1000	500	250	100	50	25	10	5	2.5	1
Standard#	94.36	94.51	94.59	95.03	79.84	44.71	27.81	16.52	12.64	8.34
3	92.33	92.70	92.85	93.33	92.33	89.53	81.93	54.12	22.85	9.59
13	22.10	7.37	1.92	–	–	–	–	–	–	–
14	10.33	3.36	–	–	–	–	–	–	–	–
15	–	–	–	–	–	–	–	–	–	–
16	17.46	14.00	4.59	–	–	–	–	–	–	–
17	–	–	–	–	–	–	–	–	–	–
18	–	–	–	–	–	–	–	–	–	–
19	3.00	–	–	–	–	–	–	–	–	–
20	83.20	90.91	88.74	84.43	76.47	54.86	46.62	26.90	8.01	2.61
21	84.73	84.20	66.47	55.03	38.43	10.95	9.85	–	–	–
24	8.67	–	–	–	–	–	–	–	–	–

Standard drug: ascorbic acid.

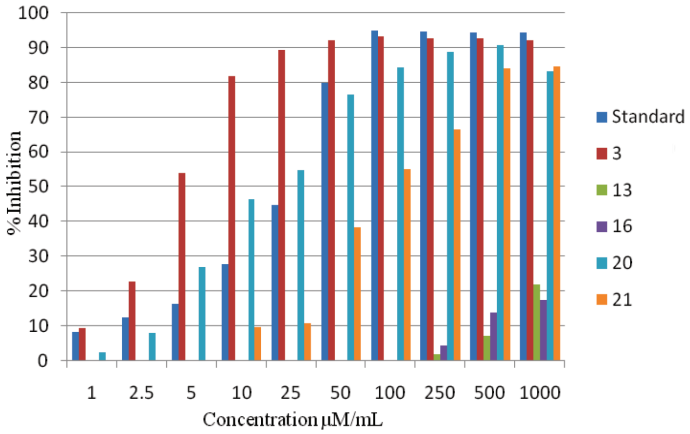


Figure 5. Antioxidant activities.

3. Experimental

3.1. 1-(Ethoxycarbonylmethyl)-1*H*-benzotriazole (2)

To a stirred solution of benzotriazole (**1**) (5.0 g, 42.0 mmol) in acetone (30 mL), anhyd. potassium carbonate (5.80 g, 42.0 mmol) was added. After 30 min, ethylbromoacetate (7.014 g, 42.0 mmol) was added and stirred at room temperature for 12 h. Progress of the reaction was monitored using TLC. On completion of the reaction, the contents were poured over an ice/water mixture and extracted with ethyl acetate three times. Combined organic layers were dried over anhyd. sodium sulfate and the solvent was removed under reduced pressure to give a crude product, which was subjected to column chromatography on silica gel (petroleum ether/ethyl acetate) to give 1-(ethoxycarbonylmethyl)-1*H*-benzotriazole (**2**) as a colorless oil with yield of 76% (6.590 g), R_f = 0.42, in petroleum ether/ethyl acetate (90:10) as a developing solvent system.

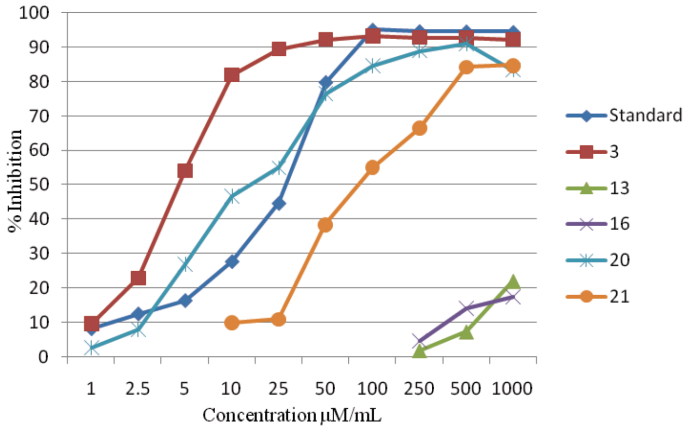


Figure 6. Antioxidant activities.

IR (film) ν_{max}: 2986, 2933, 1742, 1427, 1381, 1271, 1105, 1029, 968, 744 cm^{-1}; ^1H NMR (δ, $CDCl_3$, 400 MHz, ppm): 8.06 (d, 1H, J = 9.5 Hz), 7.52–7.46 (m, 2H), 7.41–7.36 (m, 1H), 5.43 (s, 2H, $-CH_2-$), 4.25 (q, J = 7.3 Hz, 2H, $-OCH_2CH_3$), 1.28 (t, 3H, J = 3.6 Hz, $-OCH_2CH_3$); ^{13}C NMR (δ, $CDCl_3$, 100 MHz, ppm): 166.2 (>C=O), 145.8, 127.7, 123.9, 119.9, 118.0, 109.1, 62.2 ($-CH_2-$), 48.9 ($-OCH_2CH_3$), 13.9($-OCH_2CH_3$); Mass spectral data, TOF ES+m/z (%): 206 ($M^+ + 1$); Molecular formula: $C_{10}H_{11}N_3O_2$.

3.2. 1-(Hydrazinylcarbonylmethyl)-1*H*-benzotriazole (3)

A solution of 1-(ethoxycarbonylmethyl)-1*H*-benzotriazole (**2**) (4.0 g, 19.5 mmol) with hydrazine hydrate (0.980 g, 19.5 mmol) in abs. ethanol was refluxed for 3–4 h. Progress of the reaction was monitored by TLC, and after completion of the reaction, the solid was separated out on cooling. It was filtered to give 1-(hydrazinylcarbonylmethyl)-1*H*-benzotriazole (**3**) as a white solid with yield of 72% (2.680 g), mp 150–152 °C, R_f = 0.38, in petroleum ether/ethyl acetate (80:20) as a developing solvent.

IR (KBr) ν_{max}: 3338, 3061, 2926, 1648, 1604, 1546, 1412, 1339, 1285, 1229, 1166, 1105, 977, 753, 568 cm^{-1}; ^1H NMR (δ,$CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 9.69 (brs, 1H, D_2O-exchangeable for >NH), 7.97 (d, 1H, J = 7.3 Hz), 7.72 (d, 1H, J = 7.3 Hz), 7.50 (t, 1H, J = 8.8 Hz), 7.39–7.36 (m, 1H), 5.35 (s, 2H, $-CH_2-$), 4.29 (brs, 2H, D_2O-exchangeable for -NH_2); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 164.7 (>C=O), 143.5, 126.8, 123.4, 118.7, 117.5, 110.2, 48.6 ($-CH_2-$); Mass spectral data, TOF ES+m/z (%): 192 ($M^+ + 1$); Molecular formula: $C_8H_9N_5O$.

3.3. General procedure for the synthesis of 1,2,4-triazole[33–35,59]

A mixture of acetohydrazide (1 equivalent) and substituted aromatic aldehyde/heteroaromatic aldehyde (1 equivalent) were dissolved in a minimum amount of acetic acid. Ammonium acetate (1.5 equivalents) was added to it and it was stirred at room temperature. Progress of the reaction was monitored using TLC, and on completion of the reaction, the contents were quenched with ice-cold water and that was neutralized with ammonia, and then the solid that separated out was filtered to obtain **13**–**21**, **24**, and **25**. R_f was recorded in petroleum ether/ethyl acetate (85:15) as a developing solvent system.

3.3.1. 1-(3-Phenyl-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (13)

Synthesized as per the general procedure and using benzaldehyde (**4**) to give the title compound (**13**) as a white solid (76%), mp 174–176 °C, $R_f = 0.54$.

IR (KBr) ν_{max}: 3266, 3090, 1677, 1416, 1263, 1070, 957, 869, 768, 662 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 10.91 (brs, 1H, D_2O-exchangeable, >NH), 8.03 (d, 1H, $J = 8.0$ Hz), 7.97 (d, 1H, $J = 8.0$ Hz), 7.88–7.86 (m, 1H), 7.81 (d, 1H, $J = 8.8$ Hz), 7.58 (t, 2H, $J = 7.3$ Hz), 7.45–7.37 (m, 3H), 6.12 (s, 2H, –CH_2–); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 157.2, 145.1, 144.0, 132.4, 127.6, 125.8, 124.1, 123.9, 123.2, 119.1, 117.6, 109.6, 48.1 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 277 ($M^+ + 1$); Molecular formula: $C_{15}H_{12}N_6$.

3.3.2. 1-(3-(4-Methylphenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (14)

As per the general procedure and using 4-methylbenzaldehyde (**5**) to give the title compound (**14**) as a white solid (75%), mp 184–186 °C, $R_f = 0.62$.

IR (KBr) ν_{max}: 3422, 3095, 2954, 1683, 1419, 1388, 1279, 1227, 1162, 1094, 942, 738, 688 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.09 (brs, 1H, D_2O-exchangeable, >NH), 8.04 (d, 2H, $J = 8.7$ Hz), 7.60 (d, 2H, $J = 8.0$ Hz), 7.50 (t, 2H, $J = 8.8$ Hz), 7.38 (t, 2H, $J = 7.4$ Hz), 6.01 (s, 2H, –CH_2–), 2.00 (s, 3H); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 156.1, 151.5, 147.6, 144.4, 131.8, 128.0, 123.7, 122.1, 119.8, 115.5, 113.2, 104.3, 48.3 (–CH_2–), 22.5 (–CH_3); Mass spectral data, TOF ES+m/z (%): 291 ($M^+ + 1$); Molecular formula: $C_{16}H_{14}N_6$.

3.3.3. 1-(3-(4-Florophenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (15)

As per the general procedure and using 4-fluorobenzaldehyde (**6**) to give the title compound (**15**) as a white solid (75%), mp 210–212 °C, $R_f = 0.50$.

IR (KBr) ν_{max}: 3419, 3185, 2966, 1681, 1416, 1280, 1164, 1094, 814, 747 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.83 (brs, 1H, D_2O-exchangeable, >NH), 8.06–8.01 (m, 1H), 7.84 (d, 1H, $J = 8.0$ Hz), 7.66–7.61 (m, 2H), 7.54–7.51 (m, 1H), 7.45–7.40 (m, 1H), 7.27–7.23 (m, 2H), 6.04 (s, 2H, –CH_2–); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 167.3, 144.6, 143.9, 139.7, 134.1, 131.2, 129.4, 127.2, 123.6, 118.7, 117.9, 110.9, 48.6 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 295 ($M^+ + 1$); Molecular formula: $C_{15}H_{11}N_6F$.

3.3.4. 1-(3-(4-Chlorophenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (16)

As per the general procedure and using 4-chlorobenzaldehyde (**7**) to give the title compound (**16**) as a white solid (75%), mp 242–244 °C, $R_f = 0.62$.

IR (KBr) ν_{max}: 3437, 3099, 2954, 1498, 1420, 1281, 1157, 1097, 834, 742, cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.82 (brs, 1H, D_2O-exchangeable, >NH), 8.06–8.01 (m, 1H), 7.87–7.85 (m, 1H), 7.74–7.65 (m, 2H), 7.51 (m, 1H), 7.42–7.39 (m, 1H), 7.16–7.12 (m, 2H), 5.99 (s, 2H, –CH_2–); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 165.6, 144.1, 130.3, 128.6, 127.0, 125.9, 122.7, 121.2, 118.8, 117.5, 115.4, 110.4, 48.5 (–CH_2–); Mass spectral data, TOF ES+ m/z (%): 311 ($M^+ + 1$); Molecular formula: $C_{15}H_{11}N_6Cl$.

3.3.5. 1-(3-(4-Methoxyphenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (17)

As per the general procedure and using 4-methoxybenzaldehyde (**8**) to give the title compound (**17**) as a white solid (75%), mp 164–166 °C, $R_f = 0.56$.

IR (KBr) ν_{max}: 3282, 3076, 1513, 1257, 1166, 1090, 957, 845, 723, 667 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.57 (brs, 1H, D_2O-exchangeable, >NH), 7.96–7.94 (m, 2H), 7.60–7.55 (m, 2H), 7.45–7.43 (m, 1H), 7.34–7.29 (m, 1H), 6.88–6.83 (m, 2H), 5.92–5.87 (m, 2H, –CH_2–), 3.77 (s, 3H, –OCH_3); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 166.4, 160.6, 145.1, 144.5, 133.6, 126.9, 125.9, 123.3, 118.8, 117.5, 113.7, 110.0, 54.8 (–OCH_3), 48.5 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 307 (M^+ + 1); Molecular formula: $C_{16}H_{14}N_6O$.

3.3.6. 1-(3-(3,5-Dimethoxyphenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (18)

As per the general procedure and using 3,5-dimethoxybenzaldehyde (**9**) to give the title compound (**18**) as a white solid (72%), mp 184–186 °C, $R_f = 0.50$.

IR (KBr) ν_{max}: 3432, 3094, 2996, 1517, 1418, 1337, 1267, 1166, 1023, 751 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.67 (brs, 1H, D_2O-exchangeable, >NH), 7.98–7.92 (m, 2H), 7.46–7.43 (m, 1H), 7.34–7.28 (m, 2H), 7.11 (d, 1H, $J = 8.0$ Hz), 6.88 (d, 1H, $J = 8.0$ Hz), 5.95 (s, 2H, –CH_2–), 3.83–3.81 (m, 6H, 2 ×–OCH_3); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 166.5, 150.4, 148.7, 144.7, 144.6, 126.8, 123.3, 121.4, 118.7, 117.5, 110.7, 110.2, 108.1, 55.3 (2 ×–OCH_3), 48.6 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 337 (M^+ + 1); Molecular formula: $C_{17}H_{16}N_6O_2$.

3.3.7. 1-(3-(3,4,5-Trimethoxyphenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (19)

As per the general procedure and using 3,4,5-trimethoxybenzaldehyde (**10**) to give the title compound (**19**) as a white solid (78%), mp 168–170 °C, $R_f = 0.48$.

IR (KBr) ν_{max}: 3447, 3090, 2939, 1583, 1419, 1235, 1133, 1007, 819, 739 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.72 (brs, 1H, D_2O-exchangeable, >NH), 7.95–7.91 (m, 2H), 7.65–7.63 (m, 1H), 7.46–7.42 (m, 1H), 7.34–7.32 (m, 1H), 6.93–6.90 (m, 1H), 5.95–5.91 (m, 2H, –CH_2–), 3.82-3.81 (brs, 6H, 2 ×–OCH_3), 3.73 (s, 3H, –OCH_3); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 165.3, 151.6, 143.9, 142.8, 127.7, 125.3, 124.5, 121.9, 117.8, 116.0, 108.9, 102.6, 58.7 (2 ×–OCH_3), 54.4 (–OCH_3), 47.4 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 367 (M^+ + 1); Molecular formula: $C_{18}H_{18}N_6O_3$.

3.3.8. 1-(3-(4-Hydroxy-3-methoxyphenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (20)

As per the general procedure and using vanillin (**11**) to give the title compound (**20**) as a white solid (76%), mp 198–200 °C, $R_f = 0.40$.

IR (KBr) ν_{max}: 3204, 3079, 2940, 1685, 1601, 1512, 1426, 1288, 1201, 1128, 1033, 816, 740, 621 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.67 (brs, 1H, D_2O-exchangeable, >NH), 9.34 (brs, 1H, D_2O-exchangeable, –OH), 8.00 (d, 1H, $J = 8.8$ Hz), 7.94 (d, 1H, $J = 9.5$ Hz), 7.50 (t, 1H, $J = 7.3$ Hz), 7.42–7.30 (m, 2H), 7.07 (t, 1H, $J = 9.2$ Hz), 6.84 (t, 1H, $J = 8.0$ Hz), 5.97 (s, 2H, –CH_2–), 3.84 (s, 3H, –OCH_3); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 166.4, 148.7, 147.6, 145.0, 144.9, 133.9, 126.8,

125.9, 123.3, 121.5, 118.7, 117.5, 115.0, 110.3, 55.3 (–OCH_3), 48.6 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 323 ($M^+ + 1$); Molecular formula: $C_{16}H_{14}N_6O_2$.

3.3.9. 1-(3-(4-Hydroxyphenyl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (21)

As per the general procedure and using 4-hydroxybenzaldehyde (**12**) to give the title compound (**21**) as a white solid (76%), mp 226–228 °C, $R_f = 0.42$.

IR (KBr) ν_{max}: 3233, 3104, 3069, 2953, 1694, 1609, 1414, 1294, 1224, 1166, 1095, 846, 751, 656 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.78–11.64 (brs, 1H, D_2O-exchangeable, >NH), 9.72 (brs, 1H, D_2O-exchangeable, –OH), 8.02–7.95 (m, 1H), 7.79–7.74 (m, 1H), 7.56–7.48 (m, 2H), 7.38 (d, 2H, J = 8.0 Hz), 6.82 (d, 2H, J = 8.0 Hz), 5.95 (s, 2H, –CH_2–); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 171.8, 166.5, 159.3, 145.0, 133.7, 128.4, 126.0, 124.6, 118.7, 117.6, 115.4, 110.4, 48.5 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 293 ($M^+ + 1$); Molecular formula: $C_{15}H_{12}N_6O$.

3.3.10. 1-(3-(Furan-2-yl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (24)

As per the general procedure and using furfuraldehyde (**22**) to give the title compound (**24**) as a white solid (75%), mp 190–192 °C, $R_f = 0.46$.

IR (KBr) ν_{max}: 3230, 3172, 3057, 2974, 1695, 1671, 1569, 1429, 1335, 1248, 1110, 1019, 743 cm^{-1}; ^{1}H NMR (δ,$CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.80–11.73 (brs, 1H, D_2O-exchangeable, >NH), 8.01 (d, 1H, J = 8.8 Hz), 7.94 (d, 1H, J = 8.8 Hz), 7.60–7.56 (m, 1H), 7.50–7.48 (m, 1H), 7.39–7.36 (m, 1H), 6.77–6.75 (m, 1H), 6.53 (m, 1H), 5.87 (s, 2H, –CH_2–); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 166.4, 148.7, 143.9, 134.6, 133.2, 126.9, 123.3, 118.9, 117.5, 112.6, 111.4, 109.6, 48.3 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 267 ($M^+ + 1$); Molecular formula: $C_{13}H_{10}N_6O$.

3.3.11. 1-(3-(Thiophen-2-yl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazole (25)

As per the general procedure and using thiophenaldehyde (**23**) to give the title compound (**25**) as a white solid (74%), mp 172–174 °C, $R_f = 0.48$.

IR (KBr) ν_{max}: 3432, 3104, 2944, 1680, 1419, 1282, 1226, 1093, 929, 744 cm^{-1}; ^{1}H NMR (δ, $CDCl_3$ & DMSO-d_6, 400 MHz, ppm): 11.80 (brs, 1H, D_2O-exchangeable, >NH), 8.22 (d, 1H, J = 9.5 Hz), 7.99 (d, 1H, J = 8.0 Hz), 7.68 (d, 1H, J = 8.8 Hz), 7.52–7.47 (m, 1H), 7.40–7.33 (m, 2H), 7.10–7.06 (m, 1H), 5.89 (s, 2H, -CH_2-); ^{13}C NMR (δ, $CDCl_3$ & DMSO-d_6, 100 MHz, ppm): 166.3, 145.0, 139.4, 138.3, 133.6, 129.8, 127.2, 125.8, 123.1, 118.7, 117.5, 110.1, 48.3 (–CH_2–); Mass spectral data, TOF ES+m/z (%): 283 ($M^+ + 1$); Molecular formula: $C_{13}H_{10}N_6S$.

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Supplementary data

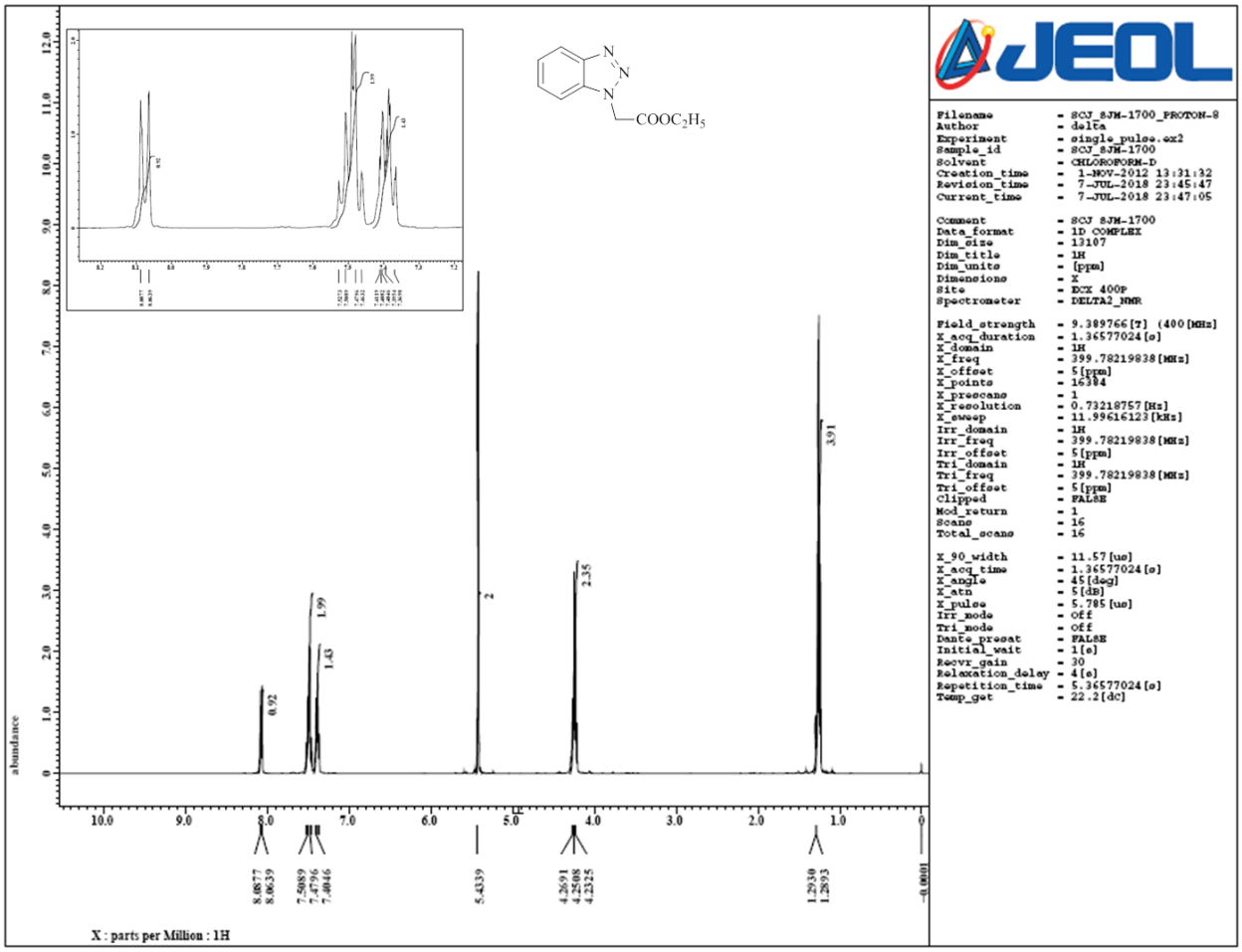

Figure S1. ^{1}H NMR spectra of compound **2**.

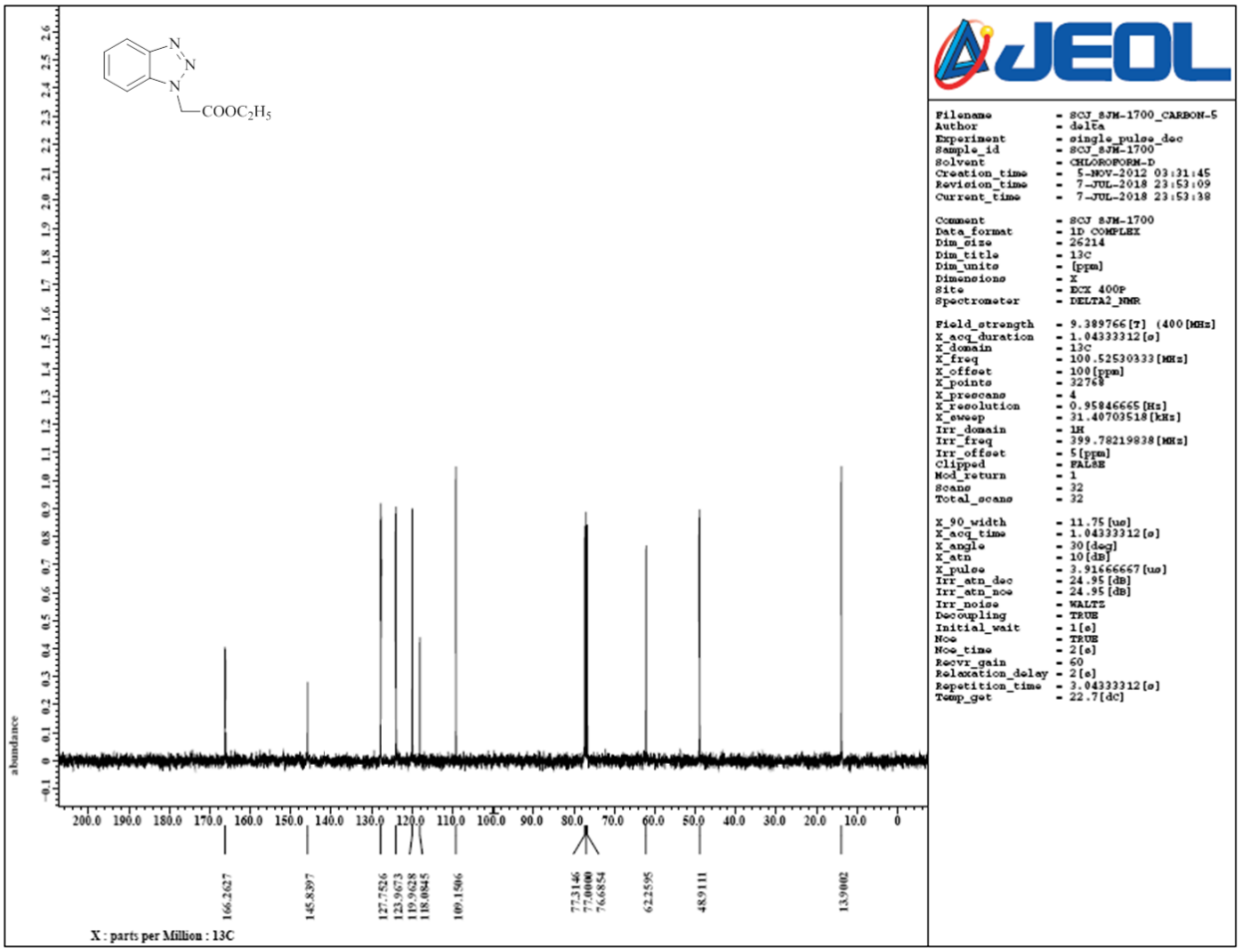

Figure S2. ^{13}C NMR spectra of compound **2**.

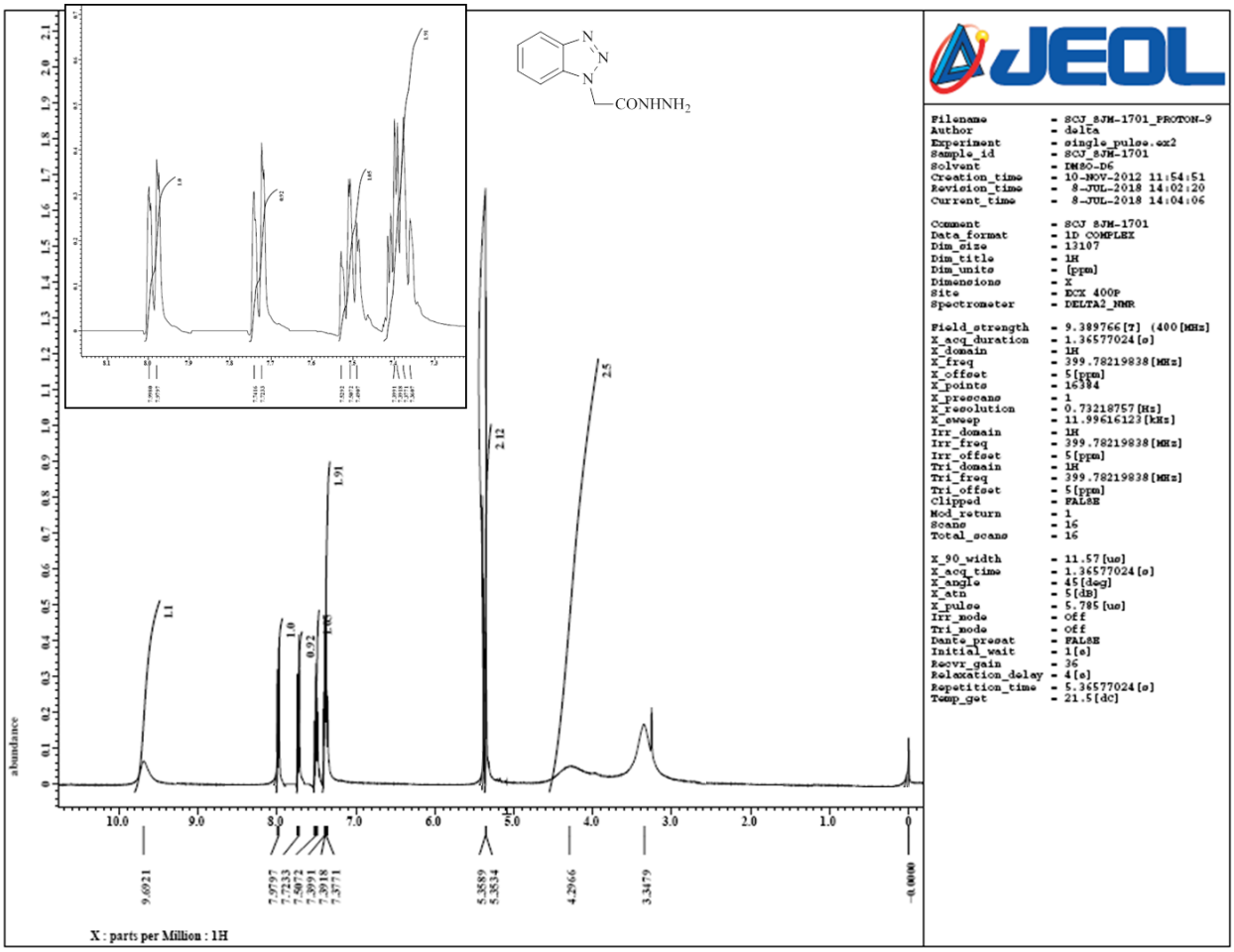

Figure S3. ^{1}H NMR spectra of compound **3**.

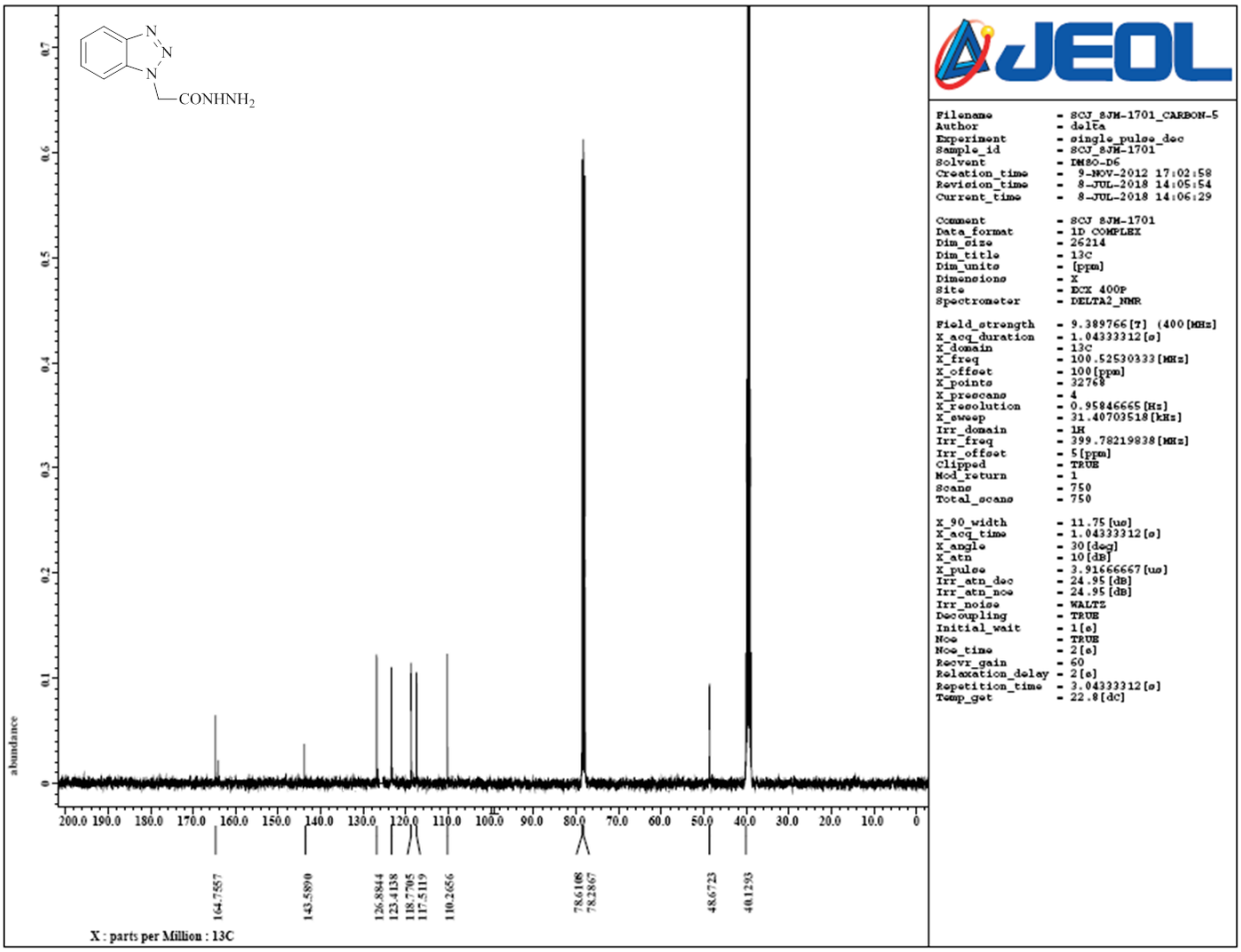

Figure S4. ^{13}C NMR spectra of compound **3**.

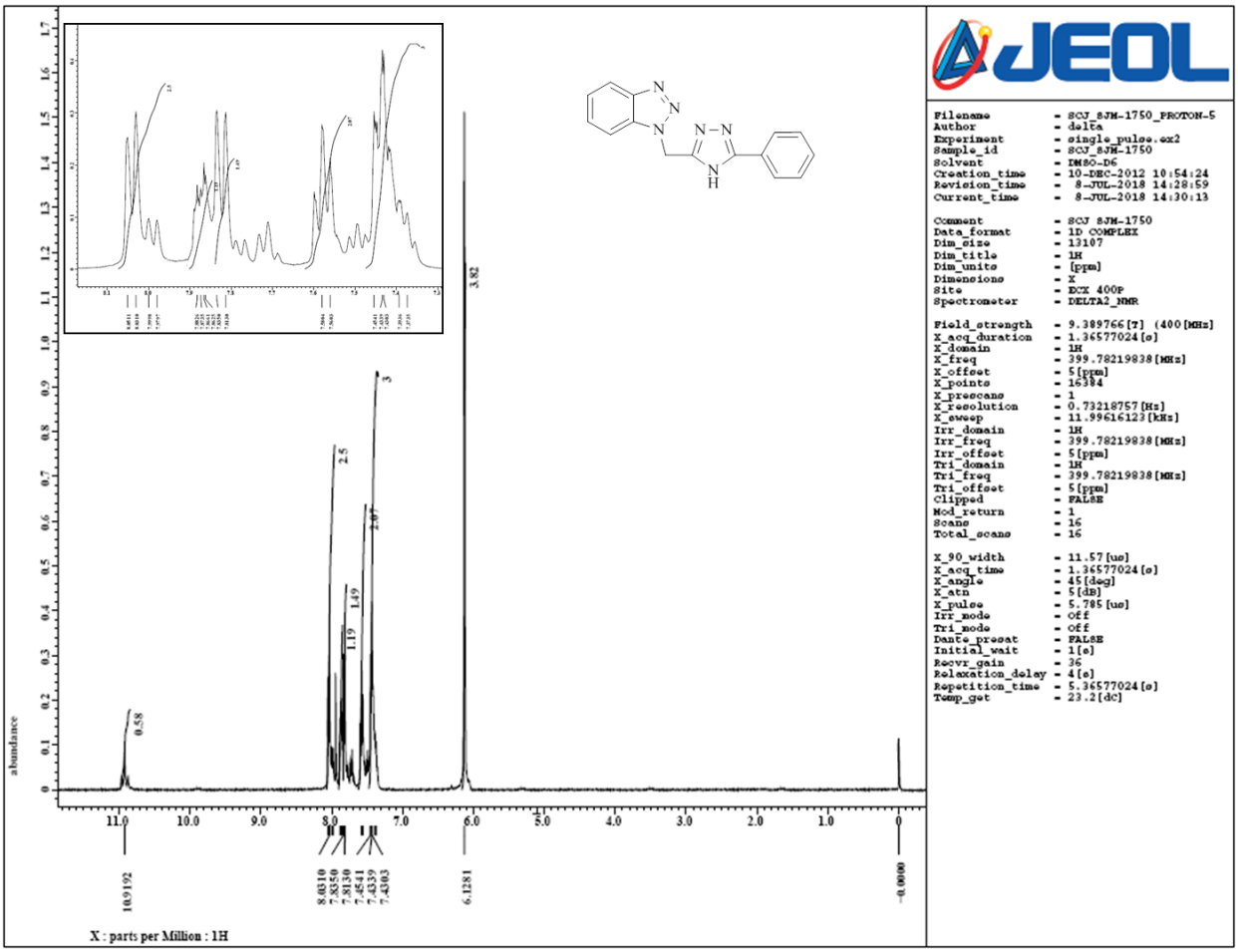

Figure S5. ^{1}H NMR spectra of compound **13**.

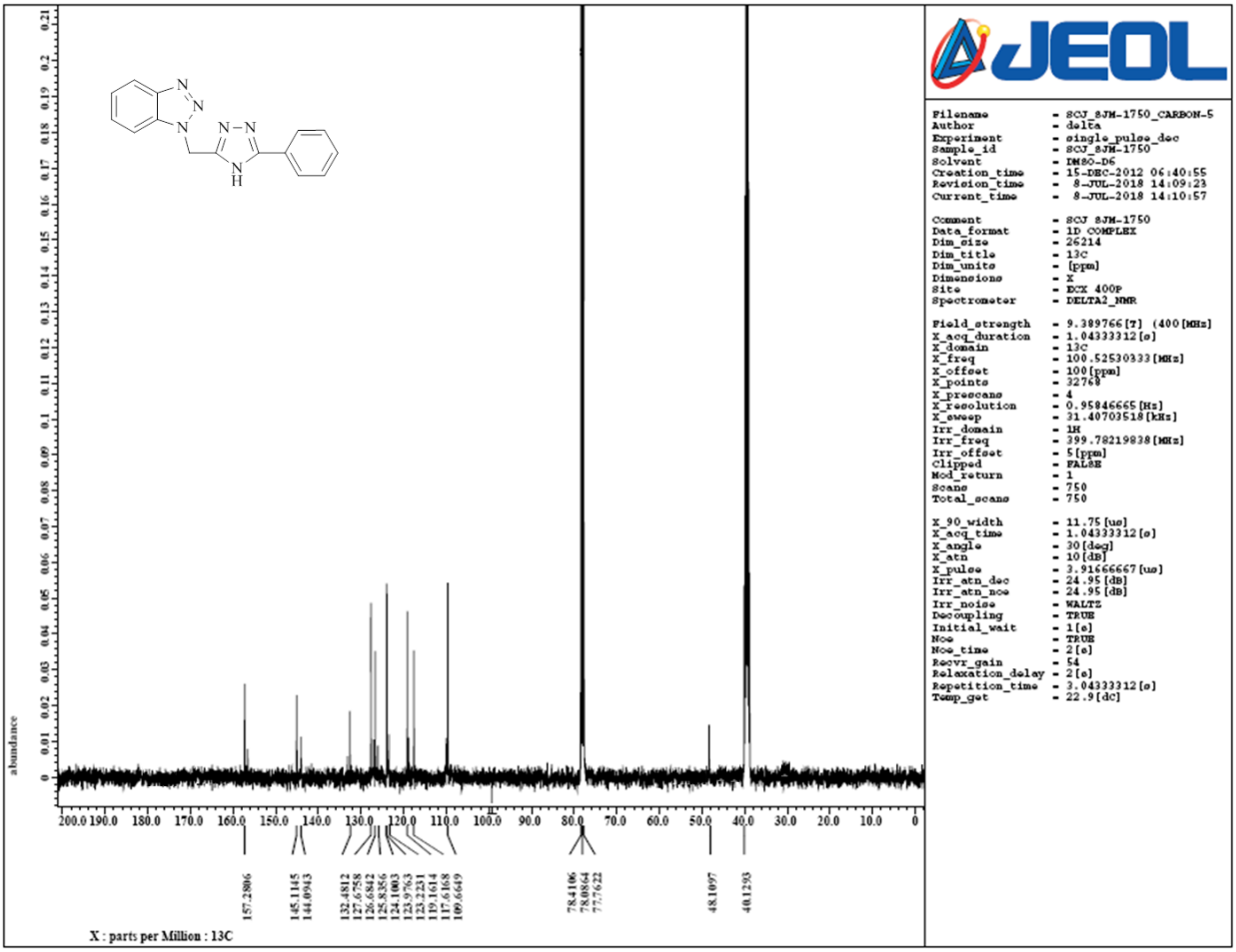

Figure S6. ^{13}C NMR spectra of compound **13**.

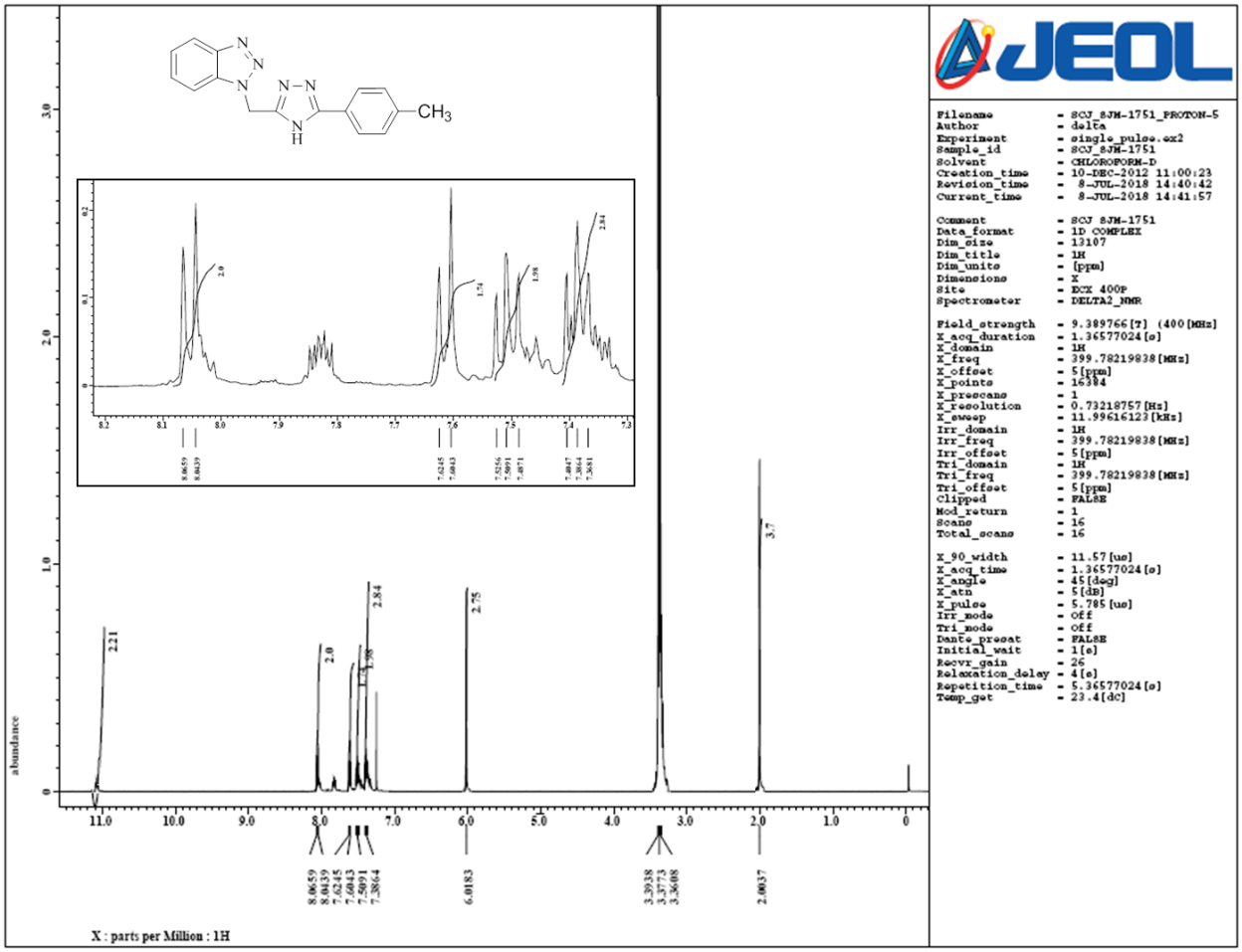

Figure S7. ^{1}H NMR spectra of compound **14**.

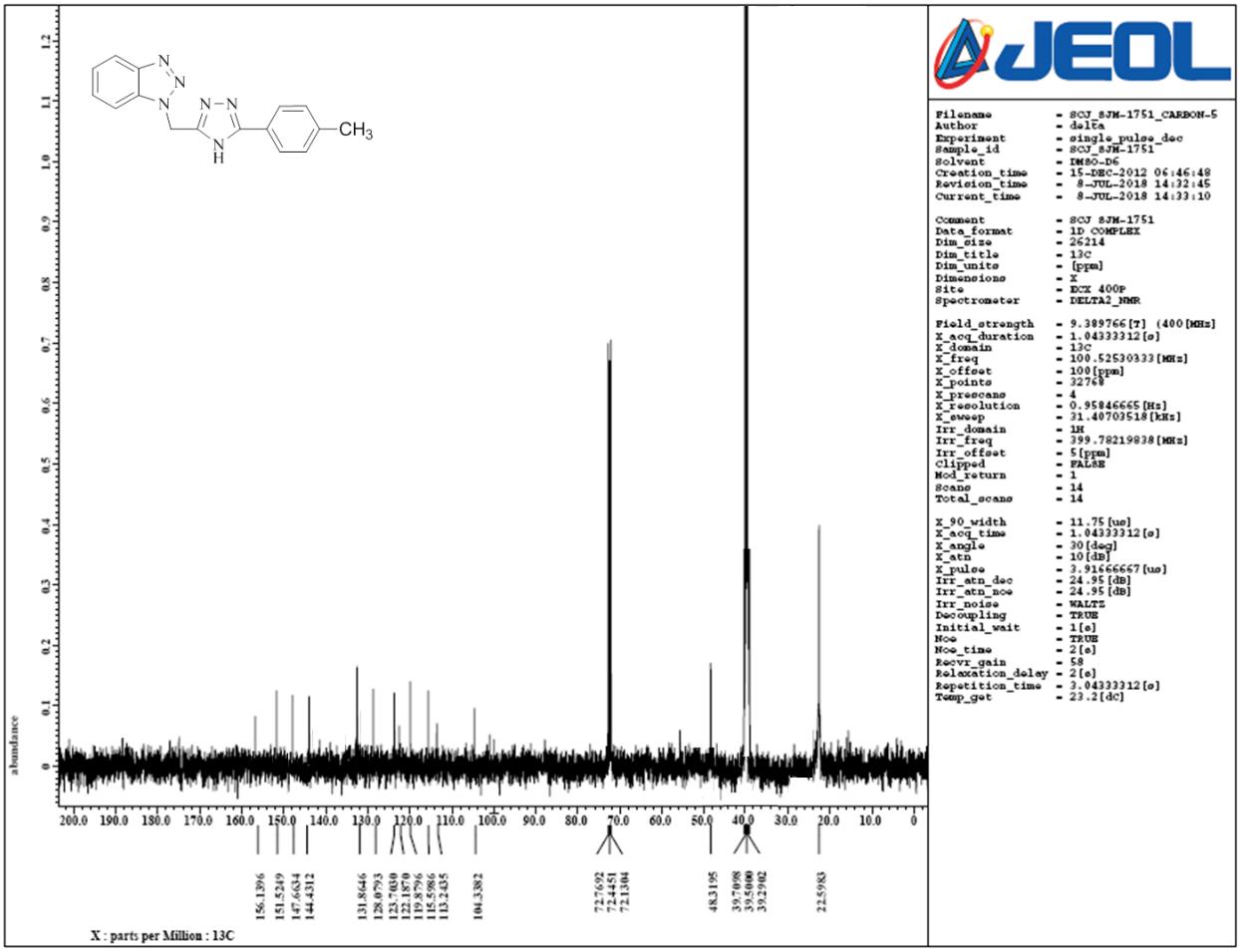

Figure S8. ^{13}C NMR spectra of compound **14**.

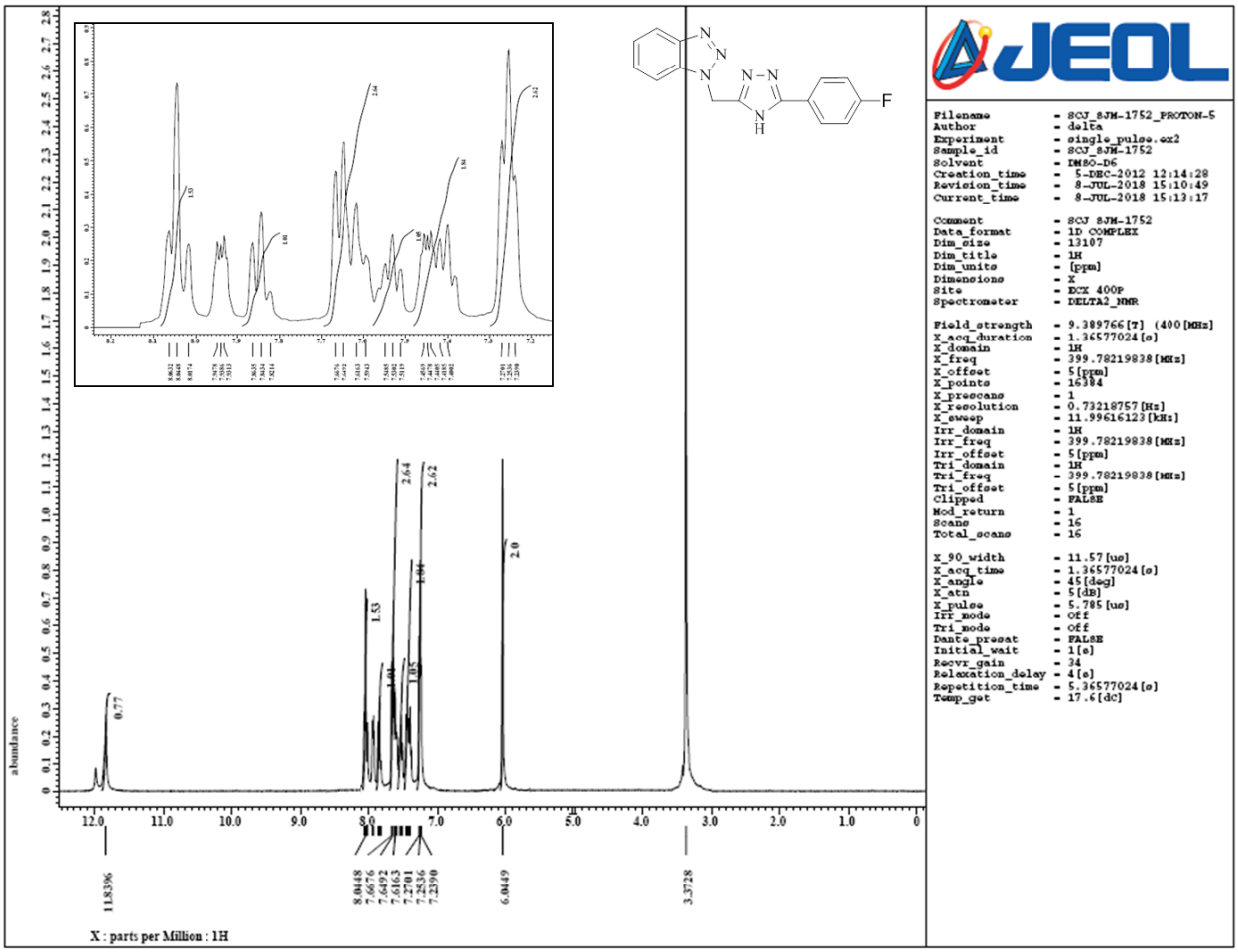

Figure S9. ^{1}H NMR spectra of compound **15**.

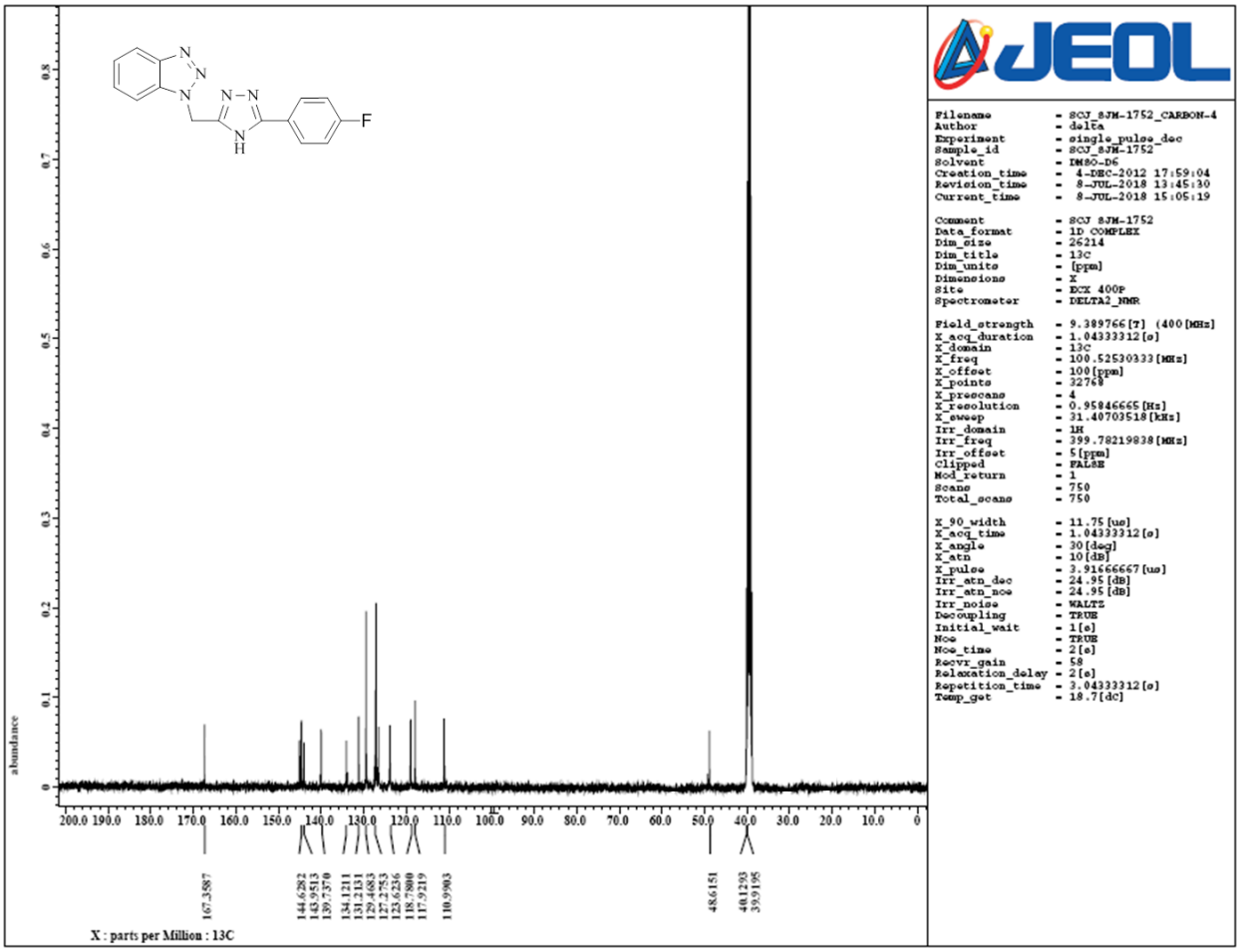

Figure S10. ^{13}C NMR spectra of compound **15**.

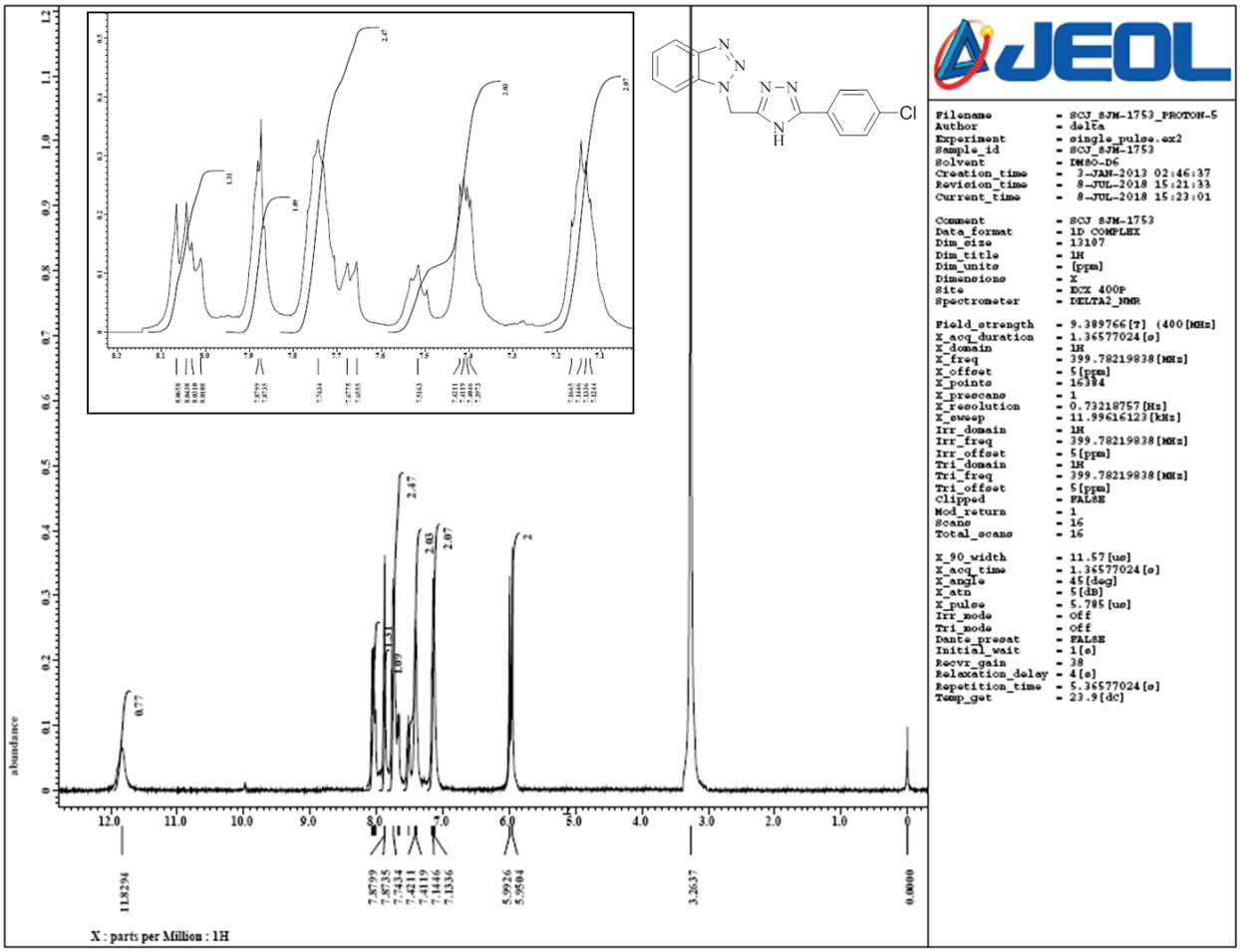

Figure S11. ^{1}H NMR spectra of compound **16**.

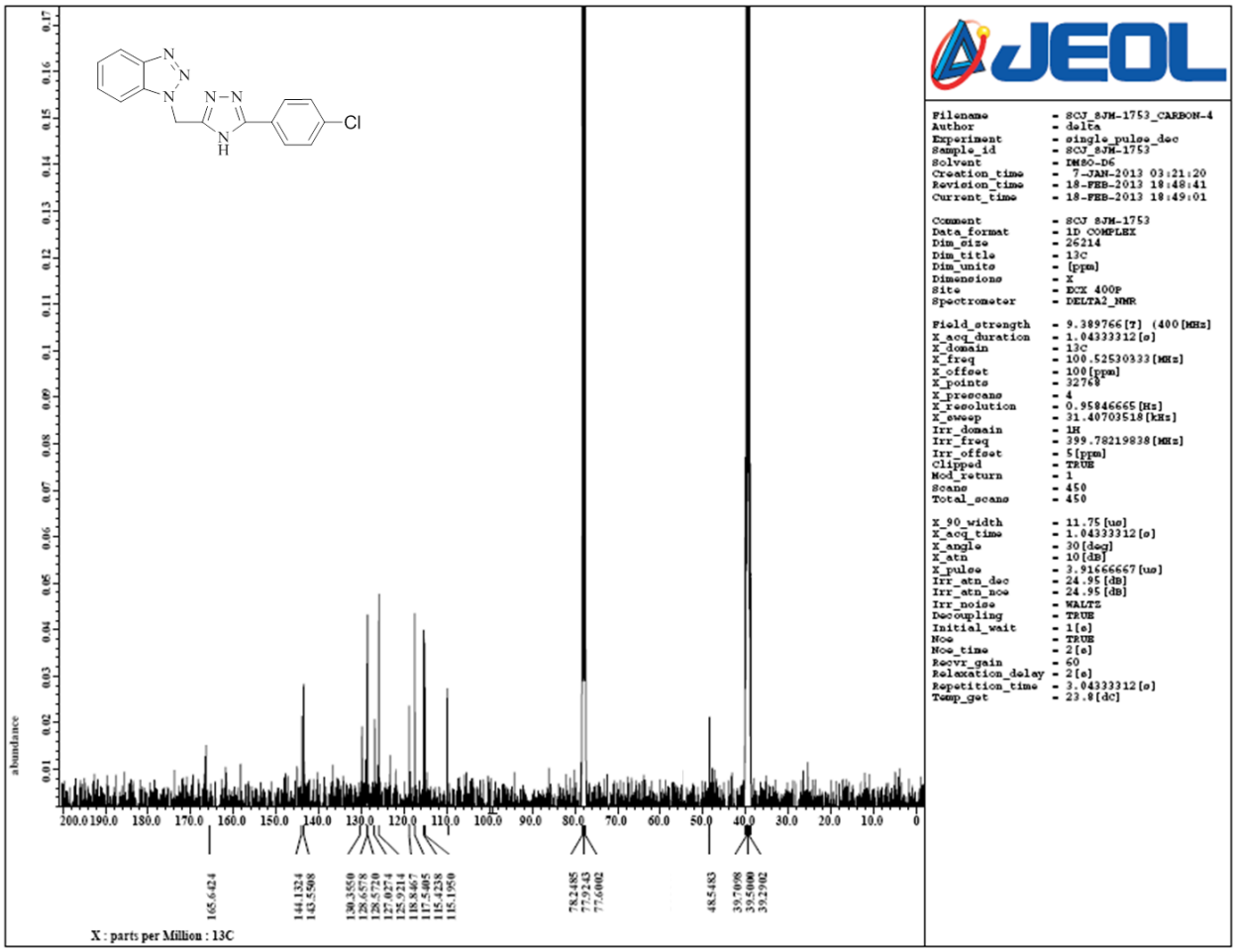

Figure S12. ^{13}C NMR spectra of compound **16**.

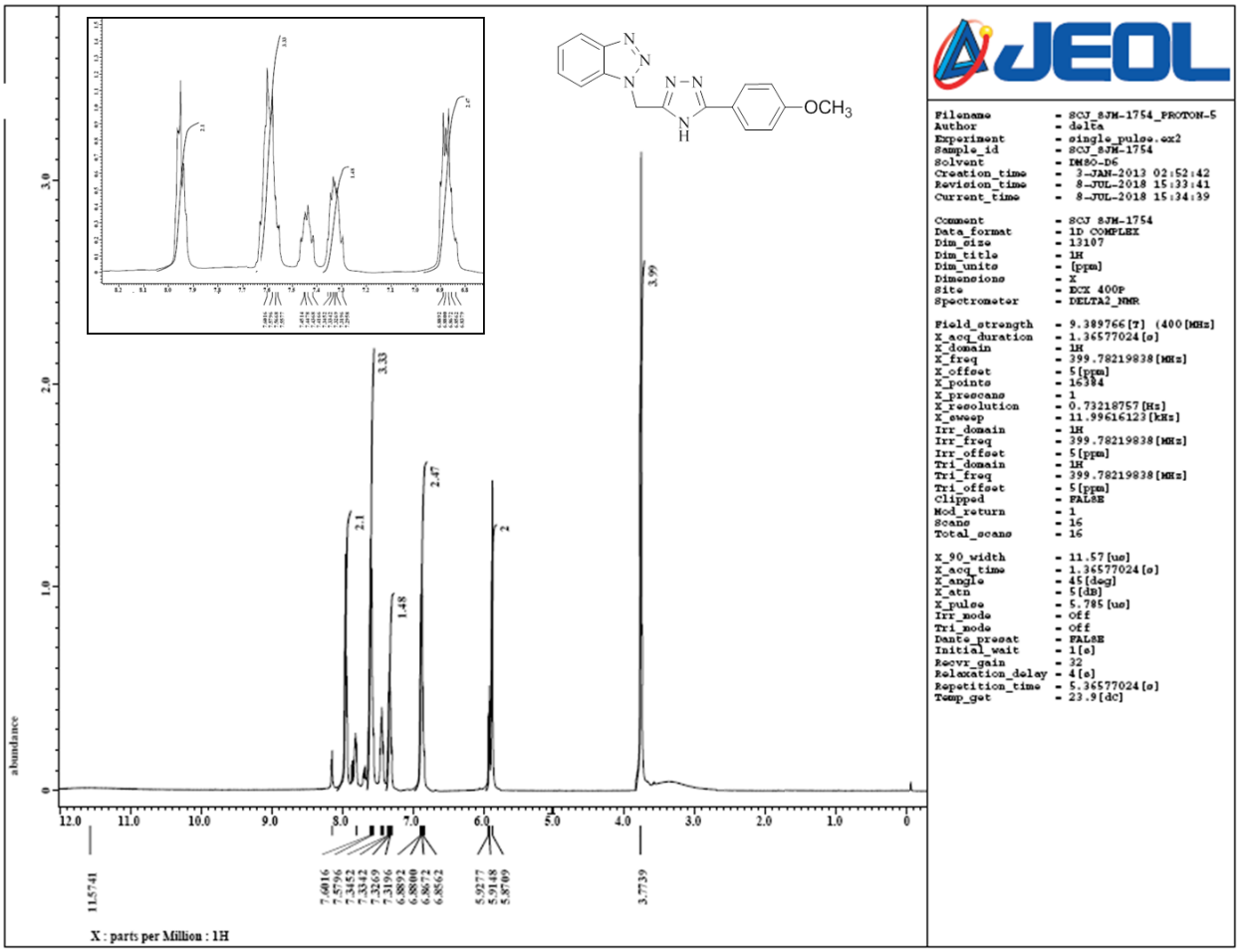

Figure S13. ^{1}H NMR spectra of compound **17**.

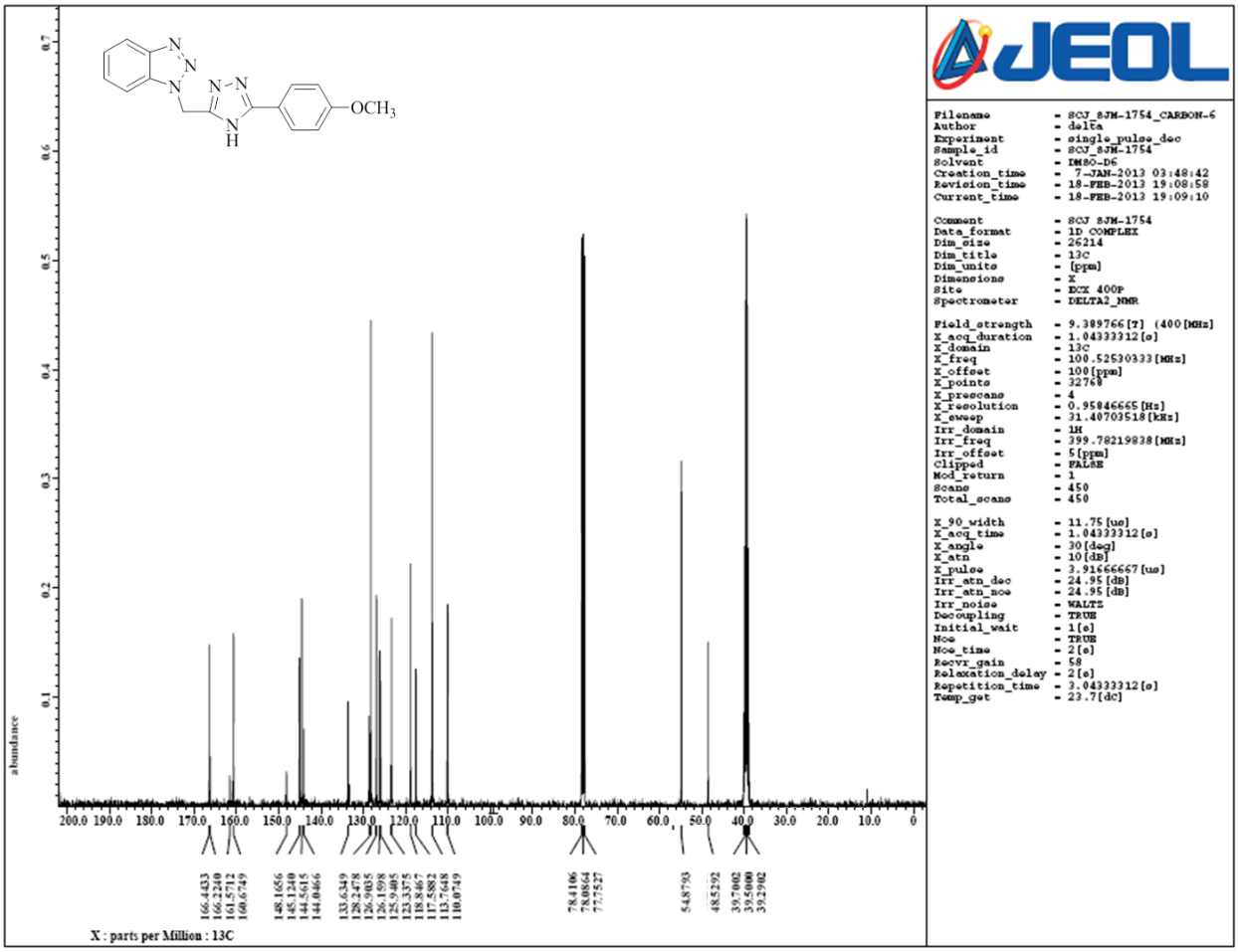

Figure S14. ^{13}C NMR spectra of compound **17**.

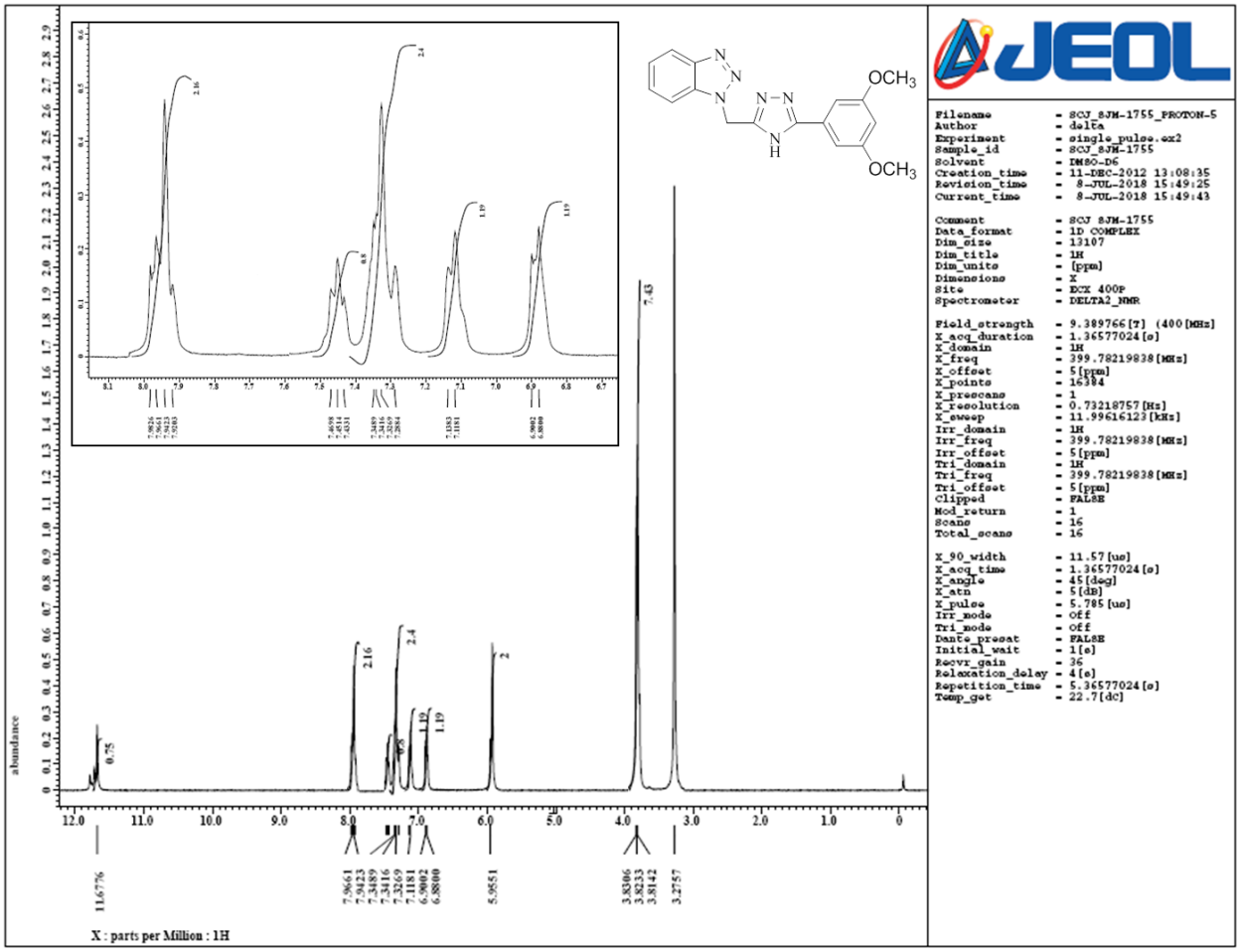

Figure S15. ^{1}H NMR spectra of compound **18**.

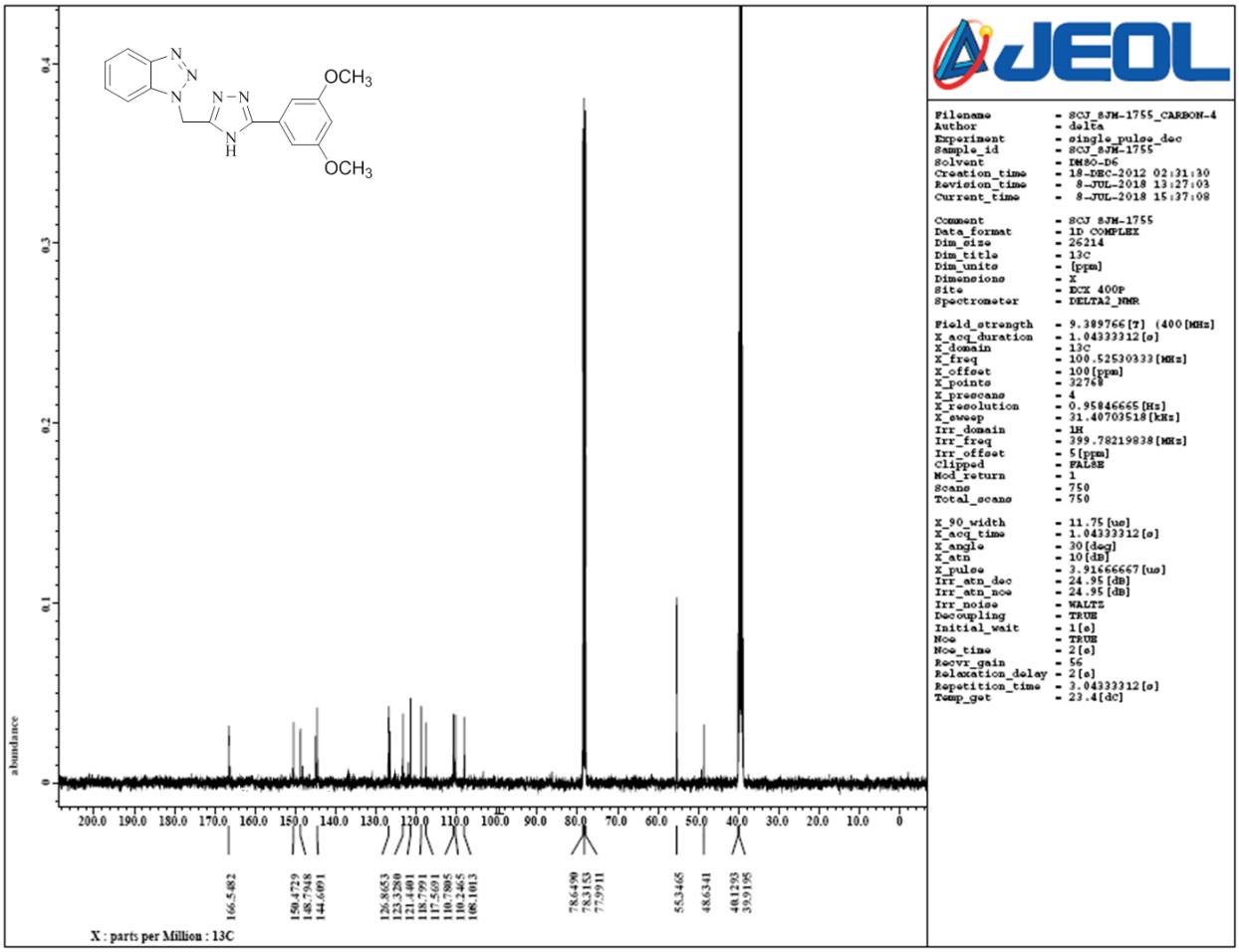

Figure S16. ^{13}C NMR spectra of compound **18**.

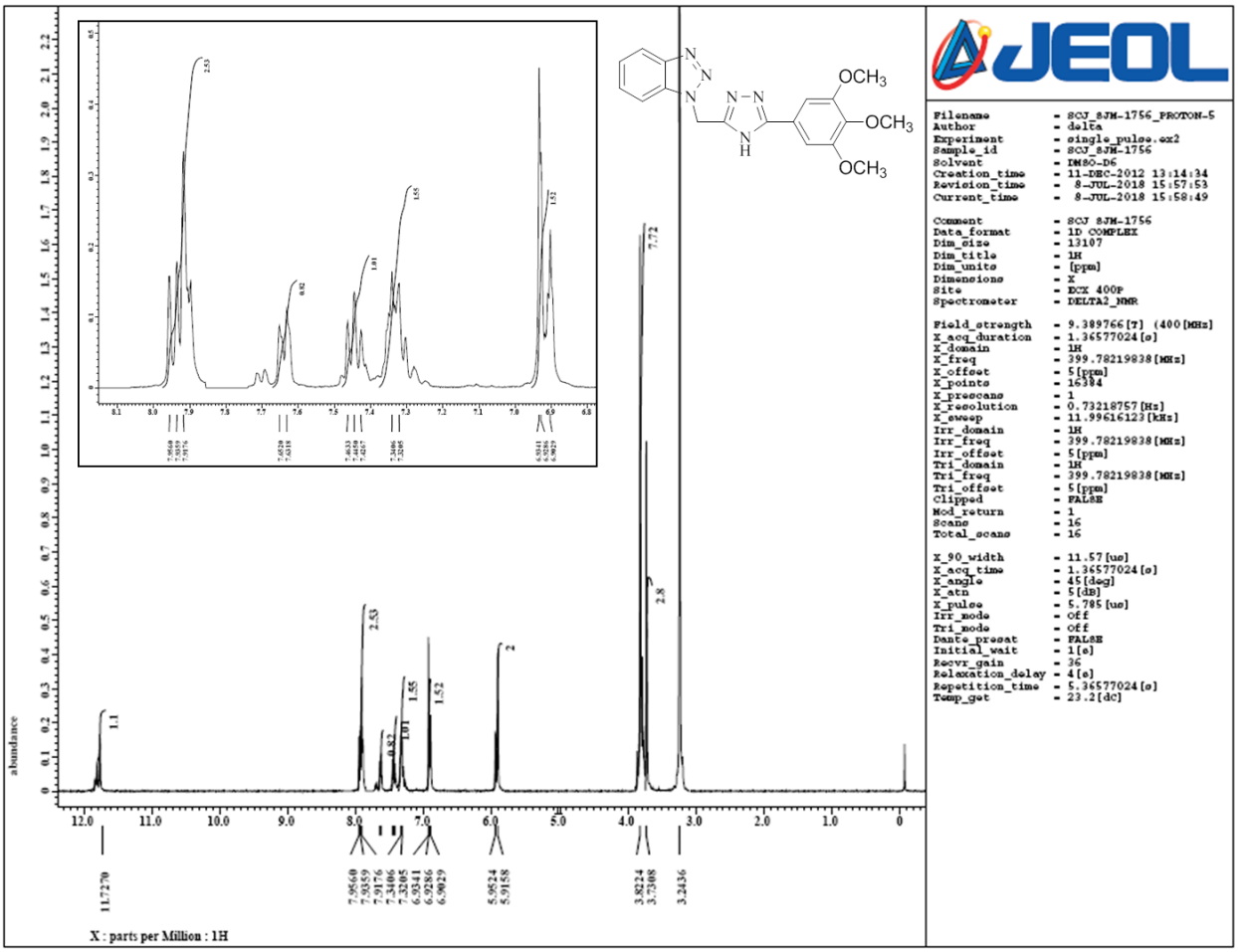

Figure S17. ^{1}H NMR spectra of compound **19**.

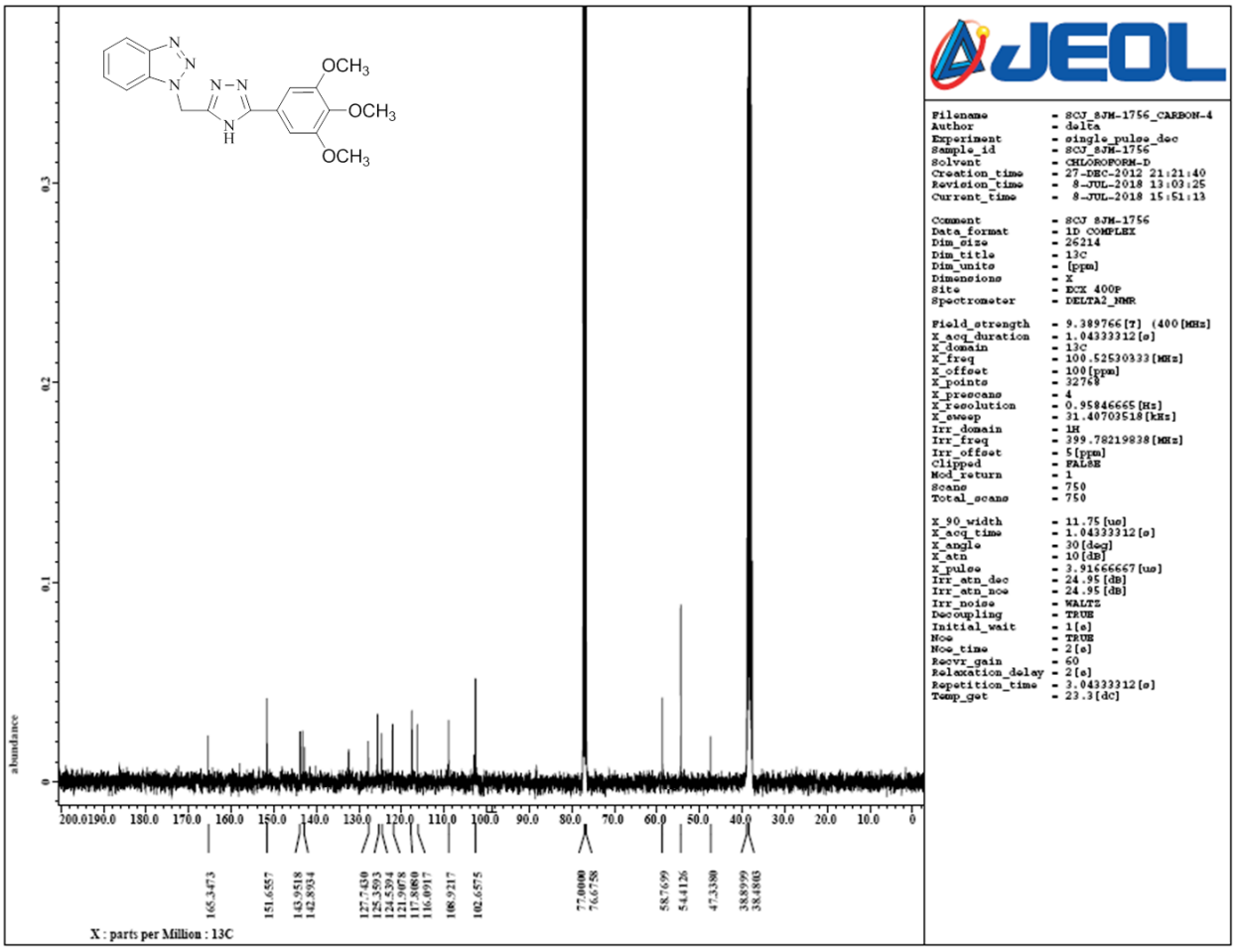

Figure S18. ^{13}C NMR spectra of compound **19**.

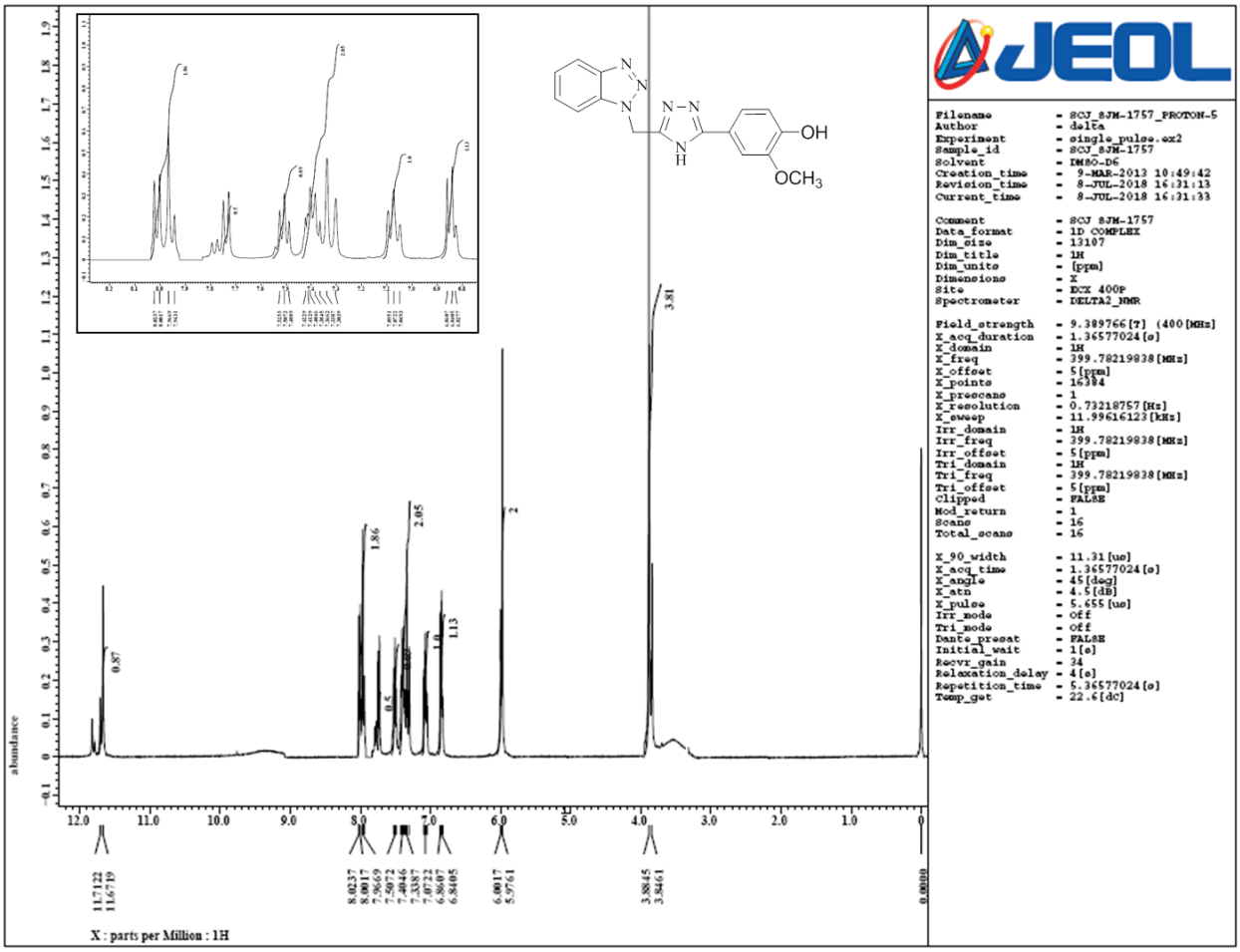

Figure S19. ^{1}H NMR spectra of compound **20**.

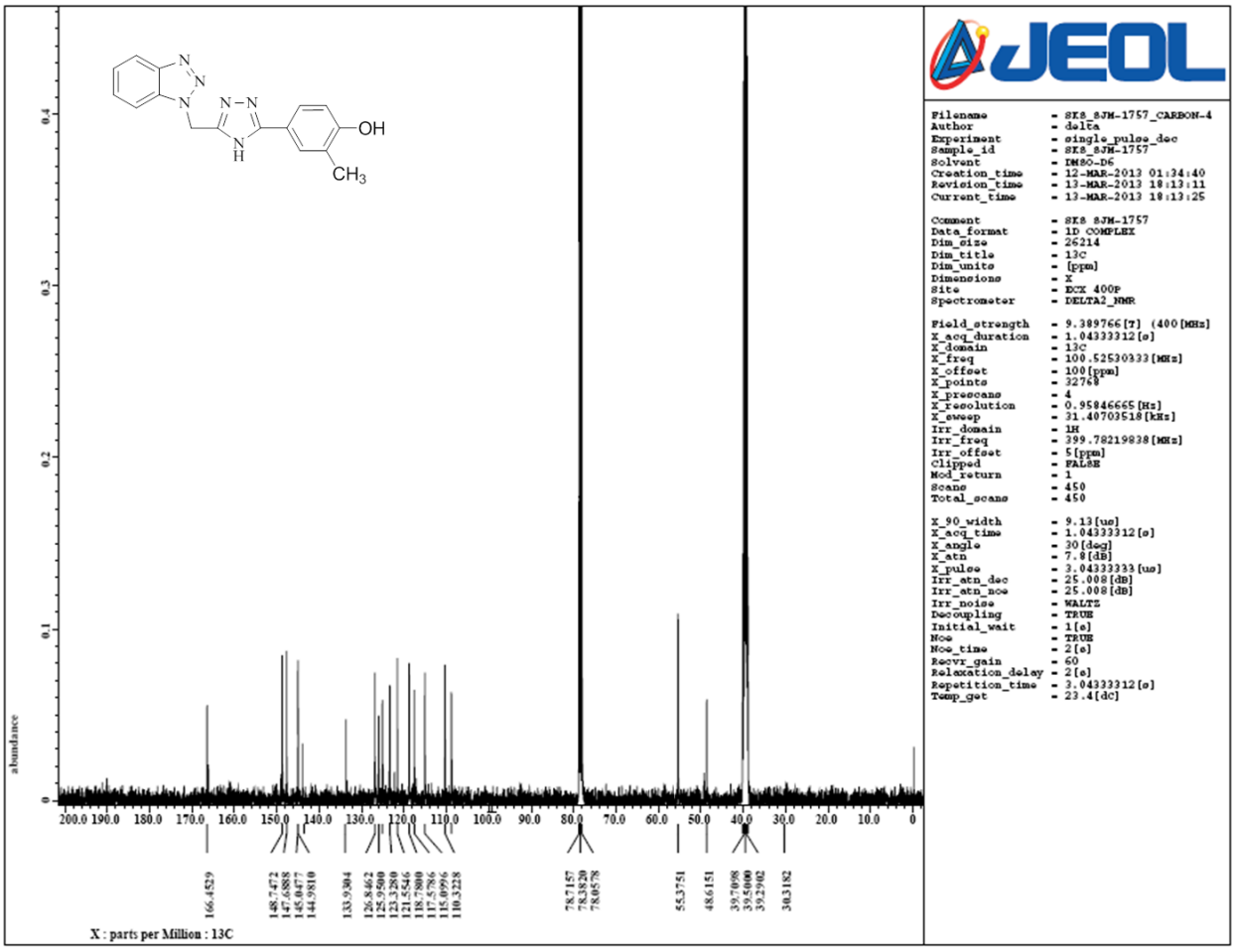

Figure S20. ^{13}C NMR spectra of compound **20**.

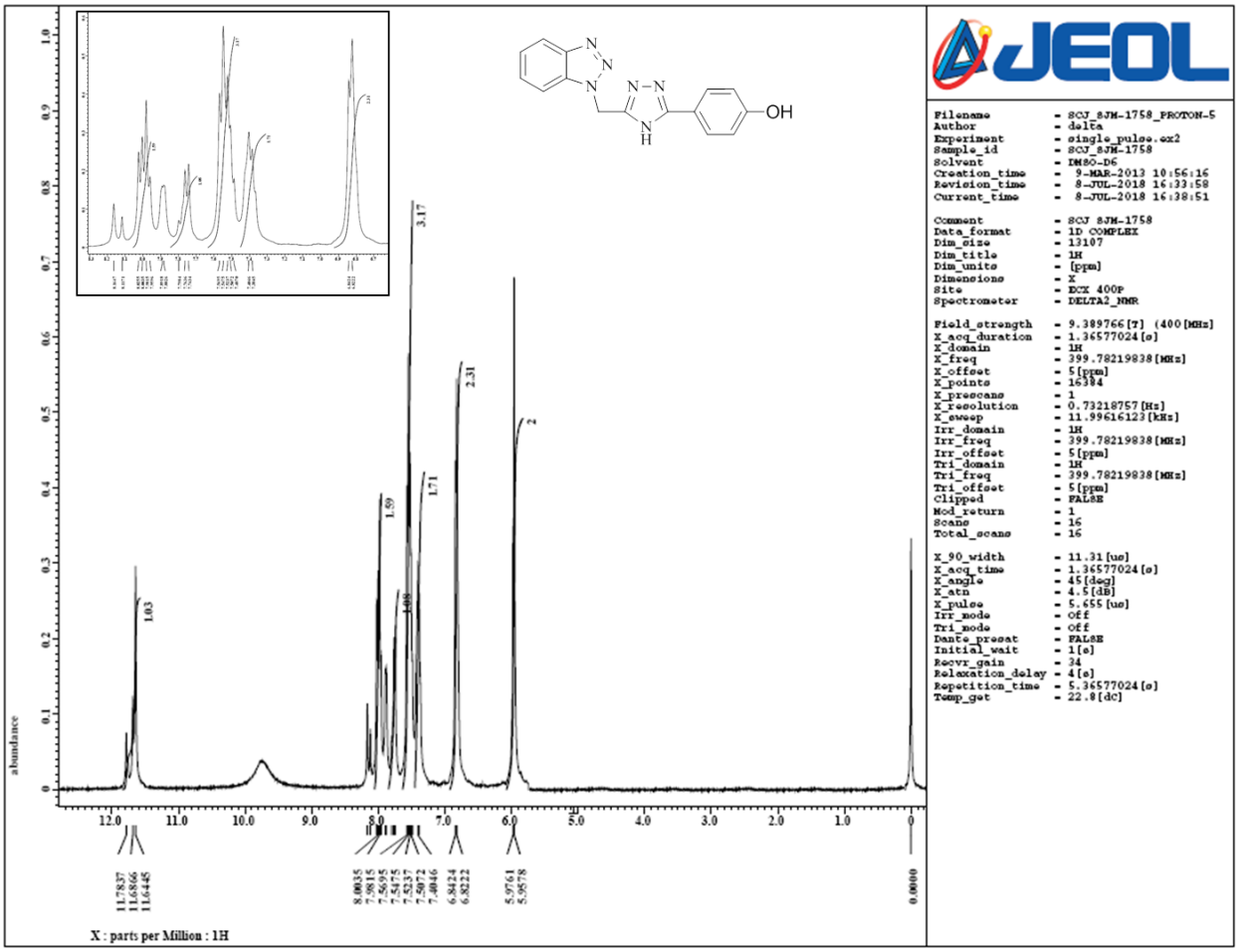

Figure S21. ^{1}H NMR spectra of compound **21**.

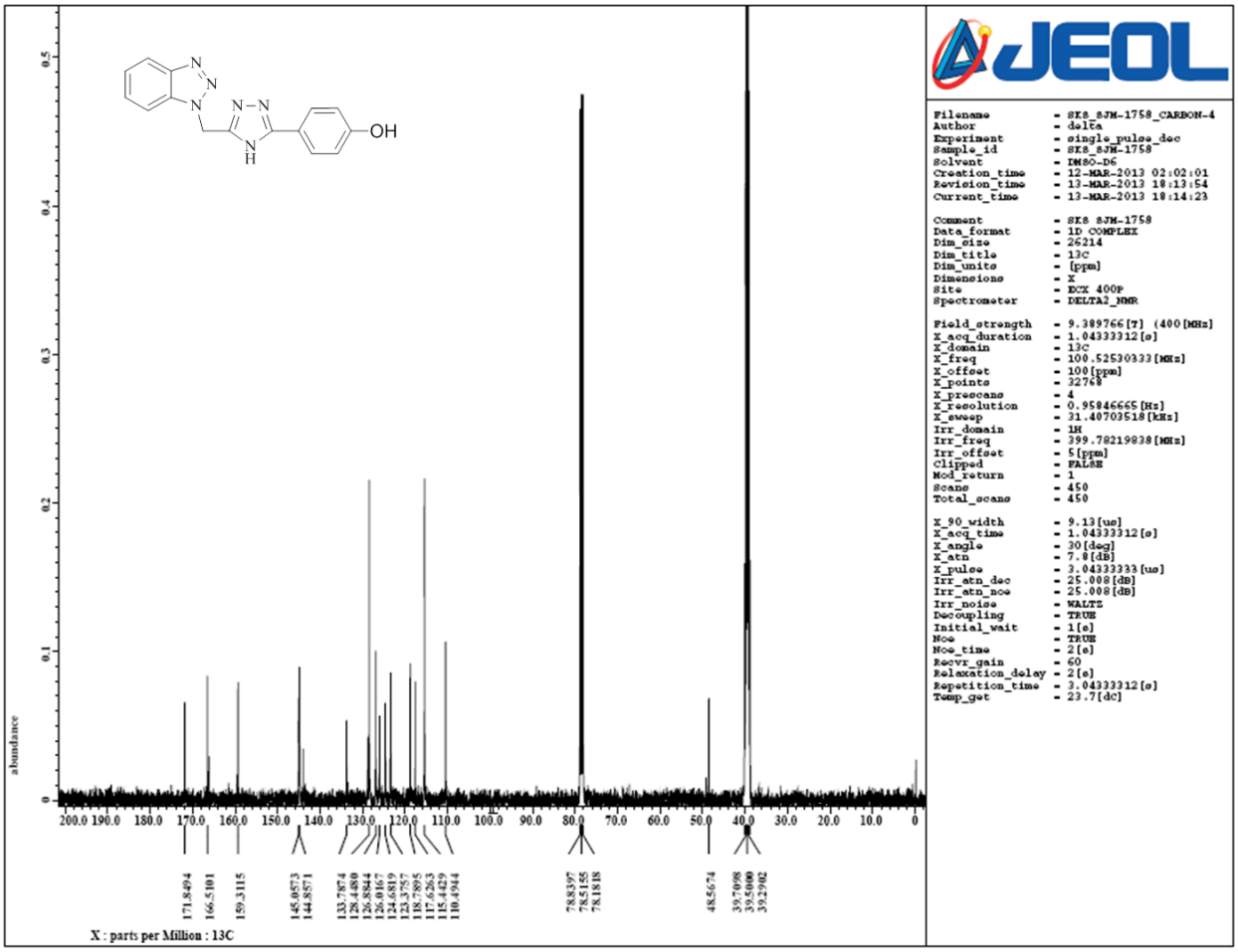

Figure S22. ^{13}C NMR spectra of compound **21**.

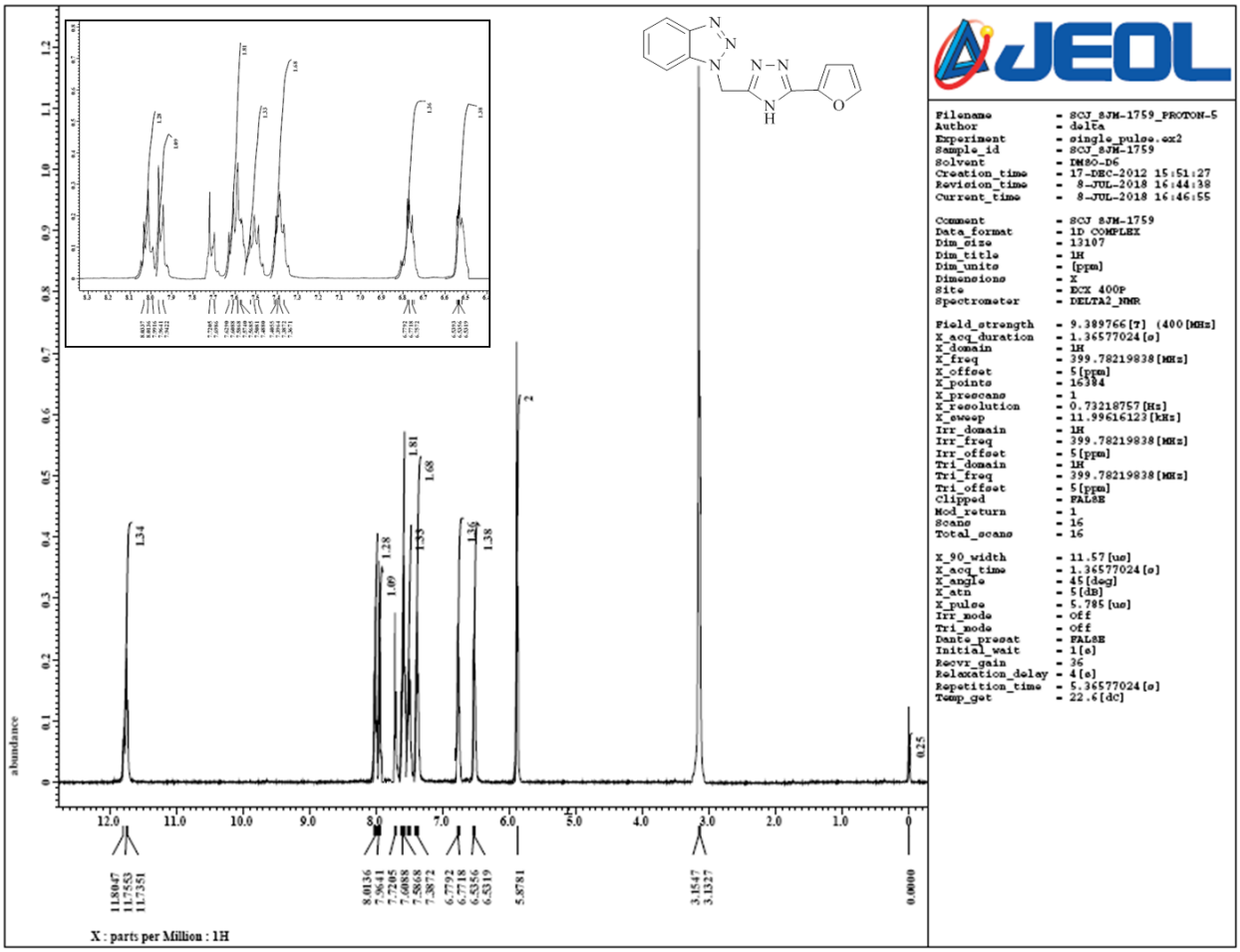

Figure S23. ^{1}H NMR spectra of compound **24**.

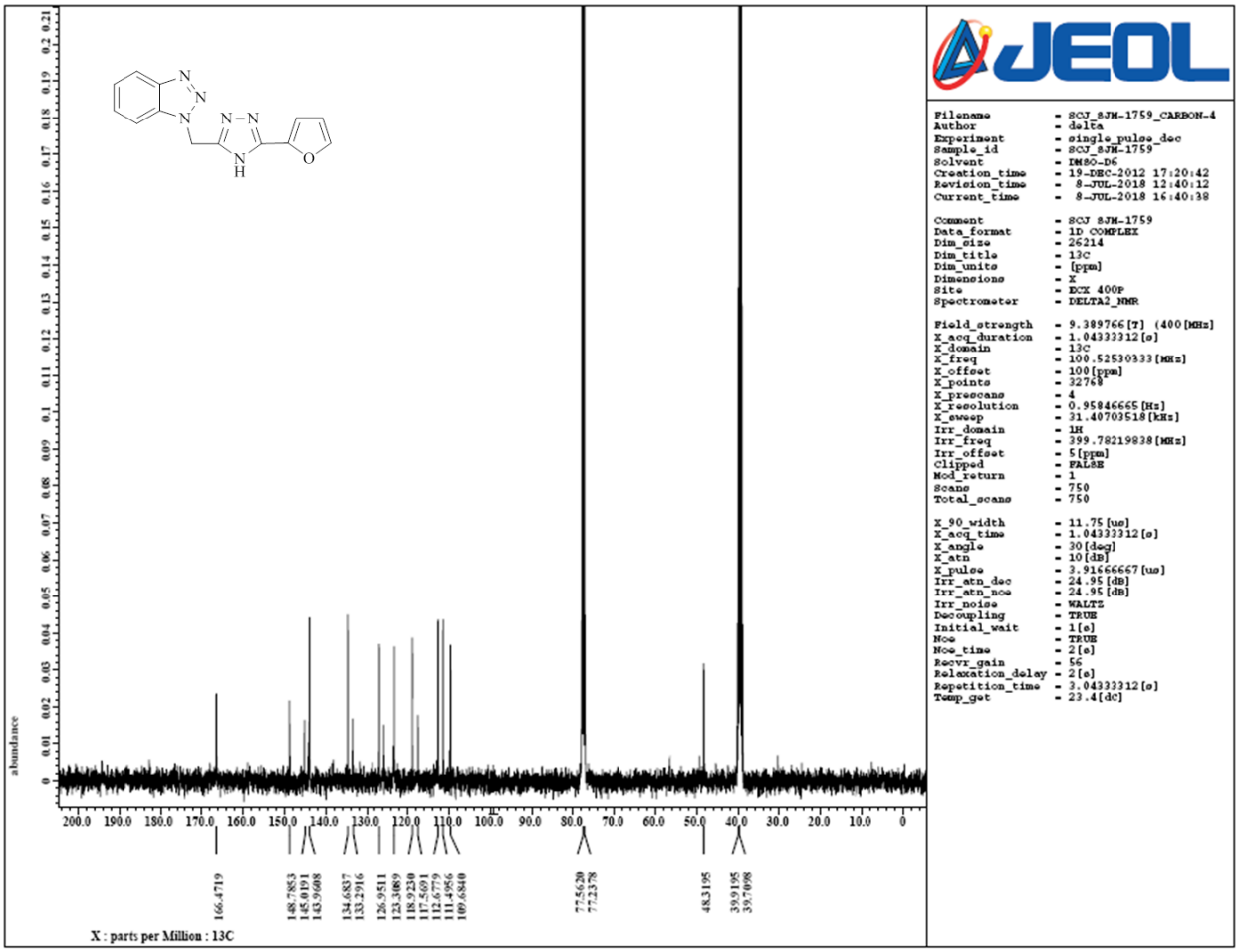

Figure S24. ^{13}C NMR spectra of compound **24**.

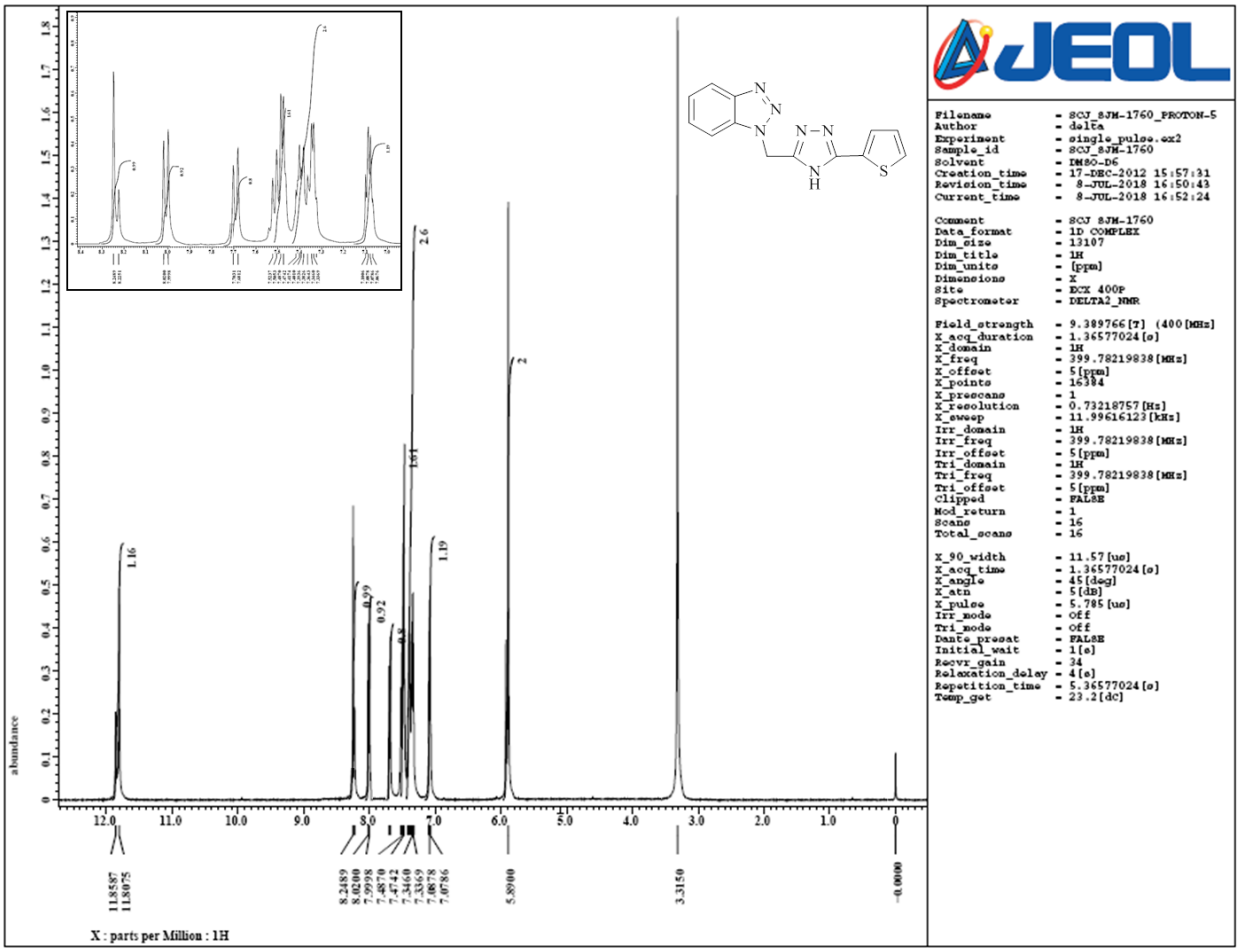

Figure S25. ^{1}H NMR spectra of compound **25**.

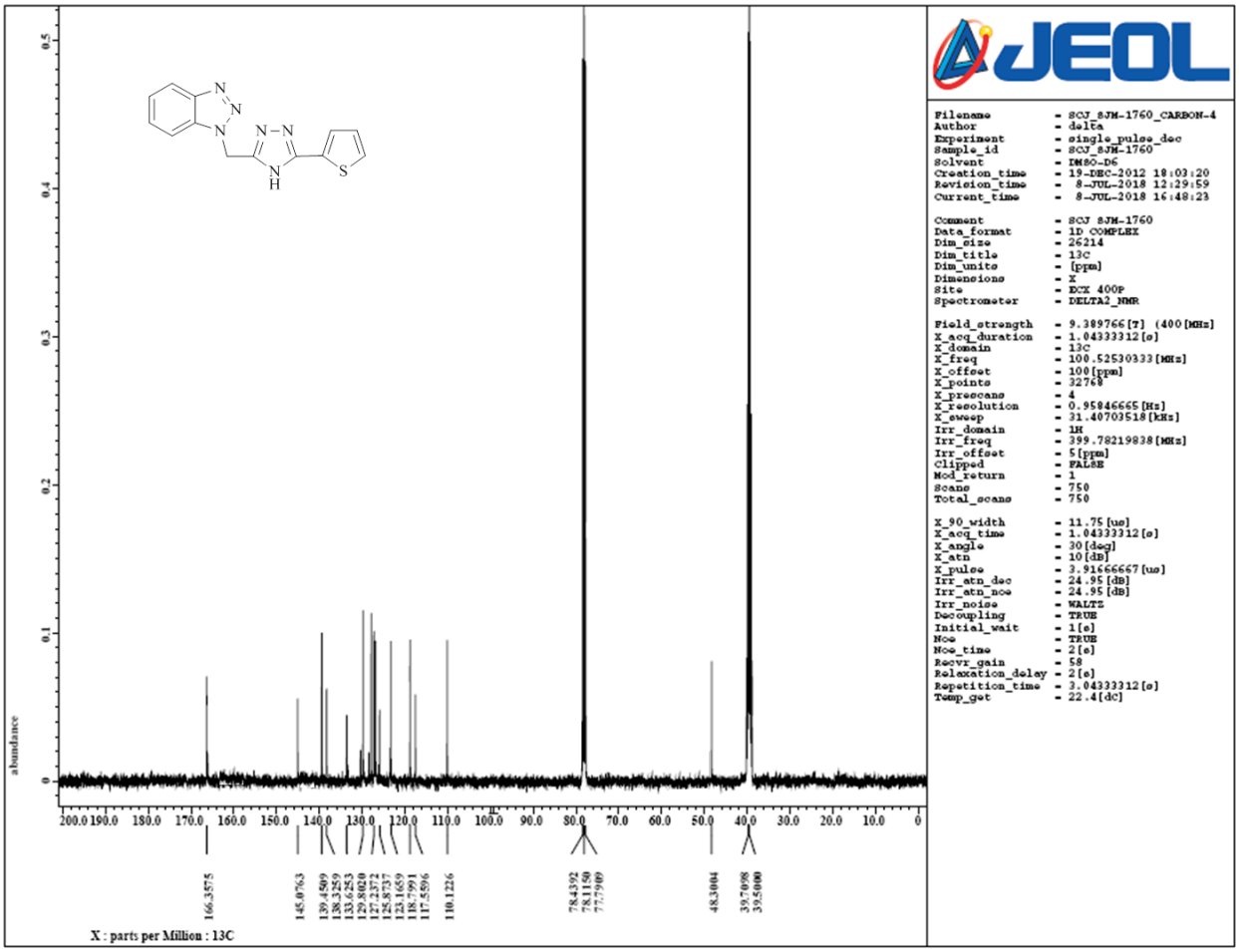

Figure S26. ^{13}C NMR spectra of compound **25**.