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Graphical abstract:

Synthesis and biological screening of 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles as anti-proliferative and anti-inflammatory agents

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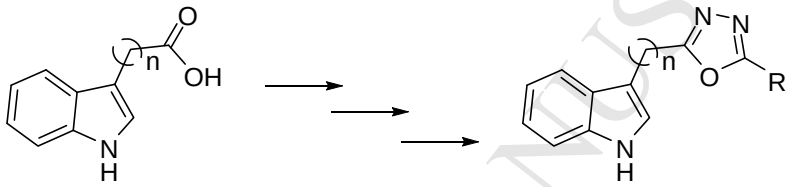
A series of 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles were synthesized and evaluated for anti-proliferative activity against four different cancer cell lines and anti-inflammatory activity. A correlation between the anti-proliferative anti-inflammatory activities has been established.



Highlights

- Titled compounds were synthesized using DIB mediated oxidative cyclisation.
- Anti-inflammatory & anti-proliferative activities screened exhibit correlation.
- Compound **6i** and **6t** showed better inhibition of paw edema compared to standard.
- *In vitro* cytotoxicity evaluated against A-549, HeLa, HepG-2 and Du145 cancer cells.
- **6i**, **6q** and **6t** are identified as good candidates against all the cancer cell lines tested.

Synthesis and biological screening of 5-(alkyl (1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles as antiproliferative and anti-inflammatory agents

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Abstract A series of 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles were efficiently synthesized by oxidative cyclisation of N'-benzylidene-(1H-indol-3-yl)alkane hydrazides using di(acetoxy)iodobenzene. N'-benzylidene-(1H-indol-3-yl)alkane hydrazides themselves were derived from simple indole-3-carboxylic acids. The 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles were evaluated for their anti-inflammatory and anti-proliferative activities. Based on the results obtained structure and activity relationship (SAR) was established and a correlation between the activities was observed. Compound **6i** and **6t** showed best activity against proliferation of human cancer cell lines and as well as inflammation of rat paw edema.

Keywords: Indole-3-carboxlic acids, Indolyl-1,3,4-oxadiazoles, Antiproliferative agents, Anti-inflammatory agents.

1. Introduction

Inflammation is a major cause in chronic illnesses, including diabetes, cardiovascular disease, arthritis, psoriasis, and cancer [1]. Cancer, one of the prime life threat causes in the present society. Chronic inflammation increases the threat of various cancers, indicating that eliminating inflammation may represent a valid strategy for cancer prevention and therapy [2]. Investigation of new therapeutic agents for the treatment of cancer has become a major area of research owing to its resistance to conventional single drug chemotherapeutic agents [3]. Since mono-therapy is generally insufficient for treating cancer, the combined use of anti-inflammatory agents and conventional cancer therapy is gaining attention as a new therapeutic approach. Moreover, non steroidal anti-inflammatory drugs (NSAIDs) are in general recognized as prototypical chemo-preventive agents against many forms of cancers [4].

Indole, the most active pharmacodynamic nucleus in nature [5], has been a major constituent of number of bio-molecules such as a plant growth regulator hormone indole-3-acetic acid, an amino acid tryptophan, the hormones serotonin and melatonin. It is also incorporated in various natural products such as alkaloids [6]. In particular, 3-substituted indole derivatives have been found to play an important role in many biologically active compounds especially with anti-inflammatory, antitumor, hypoglycemic, analgesic and antipyretic activities [7]. Clinically effective agents like anti-inflammatory drug indomethacin, the psychotropic drug LSD and the anti-tumor agent vinblastine are few of the representative compounds possessing 3-substituted indoles nucleus [8]. Recent reports on naturally occurring 5-(3'-indolyl)oxazoles indicate that they are endowed with diverse biological activities [9-10], where Labradorin 1 (**a**) and Labradorin 2 (**b**) (**Figure 1)** were found to exhibit anticancer activity against NCI-H 460 (lung-NSC) with GI_{50} values 9.8 and 9.6 µg/ML, respectively [11]. Among the azoles, 1,3,4-oxadiazoles have received a great deal of attention owing to their simple structure and wide variety of pharmacological activities such as anti-inflammatory and anti-edema [12], anticancer [13], analgesic, antibacterial [14], antifungal, anticonvulsant [15] etc.

Non-steroidal anti-inflammatory drugs like indomethacin (**c**) and tenidap (**d**) have led to exploration of indole ring, especially by modifying it at C-3 position. These modifications mainly include the introduction of alkyl and heterocyclic groups to increasing its pharmacological efficacy [16-17].Encouraged by the above observations and considering the interesting anti-inflammatory and cytotoxic profiles of 3-substituted indoles, a project has been

conceived to synthesize 1,3,4-oxadiazole skeleton appended to the C-3 position of the indole ring with varying alkyl linkers between the two active heterocyclic units. The program also aims to introduce diversity in substitutions at C-2 position of oxadiazole ring with (un)substituted phenyl group to study the synergic effect on the pharmacological profile. These newly synthesized compounds would be evaluated for anti-inflammatory and antiproliferative activities, with a view to study the structure-activity relationship.

Fig. 1 Some of the biologically active 3-substituted indole representatives.

2. Results and Discussion

2.1 Chemistry

Synthesis of the 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles, has been accomplished by the simple chemical reactions outlined in the **Scheme 1** below. Indole-3-carboxylic acids namely, indole-3-propionic and indole-3-butyric acids are selected as starting materials thus fixing the two different alkyl chain linkers for present study. Diversity at C-2 position of oxadiazole ring was envisaged by introducing various aromatic and hetero aromatic aldehydes at an appropriate stage in the synthesis.

Esterification of the indole-3-carboxylic acids **1**(**a-b**) was achieved with ethanol and catalytic amount of con.H_2SO_4, to afford the corresponding esters **2**(**a-b**). The reaction of esters with 99% hydrazine monohydrate in ethanol medium produced the corresponding hydrazides **3**(**a-b**). Refluxing the hydrazides with various aldehydes **4**(**a-r**) in ethanol for 5h resulted in the formation of hydrazone intermediates **5**(**a-v**).Target compounds **6**(**a–v**) (**Table 1**) were accessed by oxidative cyclisation of hydrazones using a benign and non-toxic hypervalent iodine reagent, di(acetoxy)iodobenzene (DIB) [18–20]. All the synthesized compounds were characterized by ^{1}H NMR and MS data.

Scheme 1. Synthesis of compounds **6**(**a-v**), Reagents and conditions: (a) H_2SO_4, reflux, 3-4h (b) $NH_2NH_2.H_2O$ (99%), EtOH, reflux, 5-6h. (c) EtOH, reflux, 4-5h. (d) DIB, DCM, rt, 4-6h.

Table 1 Synthesized 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

Pharmacology

3.1 *In vivo* anti-inflammatory activity

The *in vivo* anti-inflammatory screening of the synthesized compounds was carried out by employing the carrageenan-induced paw edema bioassay in rats [21]. From the results obtained (**Table 2**), it has been noticed that all the tested oxadiazole derivatives exhibit considerable inhibition of inflammation i.e., paw-edema. In addition, it has been noticed that, several synthetic compounds (**6f, 6h, 6i, 6k, 6q, 6t**) reveal remarkable inhibition of paw-edema (61.0-70.9% inhibition of edema) comparable to that of Ibuprofen which is used as a reference standard (72.8% inhibition of edema). Compound **6i** exhibit better inhibition of inflammation (78.3% inhibition of edema) compared to that of the reference standard (Ibuprofen) at the end of 3rd hour (**Table 3**).

Another feature observed during the study is that, the analogues derived from indole-3-propionic acid (n=2), show better anti-inflammatory properties than the analogues derived from indole-3-butyric acid (n=3). Among the substitutions at C-2 position of the oxadiazole ring, **6i** having 4-chlorophenyl and **6t** having *m*-phenoxyphenyl substitution shows inhibition of inflammation comparable to that of the standard employed (**Figure 2**).

Table 2 Anti-inflammatory activity of 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

Table 3 Percentage protection against edema formation

Fig. 2. Graphical representation of the percentage protection of 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles against edema formation.

3.2 *In vitro* anticancer activity

The *in vitro* antiproliferative activity of the synthesized compounds were evaluated against four human cancer cell lines, i.e., human epithelial lung carcinoma (A549), human epithelial cervical cancer (HeLa), human liver carcinoma (HepG2), and human prostate cancer (Du145) cells and the IC_{50} values determined are summarized in table **4**. From the results obtained (**Table 4**), it is clear that, all the 1,3,4-oxadiazoles reduce the cancer cell viability significantly with IC_{50} values ranging from 20µM-100µM. MTT assay reveals that compounds **6a**, **6e**, **6i**, **6m**, **6p, 6r, 6t** and **6u** are potent against all the cell lines at IC_{50} values less than

50µM. Interestingly, majority of these active compounds are derived from indole-3-propionic acid i.e., analogues having two carbon linker between the indole and oxadiazole (n=2).

The SAR study reveals that, alkyl linkers at C-5 position and substitutions on phenyl ring at C-2 of the oxadiazole ring are playing an important role. Comparing the inhibitory concentrations of the pairs (with similar substitution and variation in n) **6e** and **6f, 6i** and **6j, 6u** and **6v** clearly indicate that, a shorter alkyl side chain (n=2) show relatively enhanced activity than longer alkyl side chain (n=3). Compound **6i** having 4-chlorophenyl substitution at C-2 position of the oxadiazole ring exhibited the effective cytotoxicity against all the four cell lines, with the best inhibition concentrations 23.4 µM and 21.2 µM against HeLa and HepG2, respectively. Compound **6q** with 4-methoxyphenyl substitution at C-2 of oxadiazole ring showed IC_{50} values 23.2 µM and 22.2 µM against A549 and HeLa, respectively, while **6t** with C-2 *meta*-phenoxyphenyl group also inhibited the proliferation of A549 (23.3 µM) and HeLa (25.4 µM) cell lines. Comparison of these two compounds indicates that there is no selectivity between 4-methoxyphenyl and 3-phenoxyphenyl groups with respect to bulkiness of the group or substituent position. Compound **6a** with a phenyl group at C-2 showed good activity against all the cell lines. While **6b** having 1-naphthyl ring at C-2 exhibited moderate activity against HepG2 (101.9 µM) and relatively good activity against all other. Introduction of 2,6-dichlorophenyl group at the C-2 position of 1,3,4-oxadiazole ring in **6n** results in reduction of activity against different cancer cell lines except against HeLa (47.5 µM). On the other hand, 3,4-dichlorophenyl group at the C-2 position in **6o** proved to be a better in inhibition of cell proliferation against all cell lines when compared 2,6-dichlorophenyl group. 2,4,6-trimethoxyphenyl group in **6s** displayed moderate activity against HepG2 (366.16 µM) and good with other cell lines (between 26.3-31.5 µM). Comparing the anti-inflammatory and antiproliferative activities reveal that, compounds that inhibit inflammation also exhibit good antiproliferative activity. The best among them are **6i** and **6t** both with n=2 linker.

Table 4 Anti-proliferative activity profile of synthesized 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

3. Conclusion

In conclusion, we have successfully synthesized 22 analogues of 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazole. These analogues were evaluated for their anti-inflammatory and antiproliferative activities. Majority of the compounds showed good inhibition of paw edema and cancer cell line growth. Compound **6i** having 4-chloro phenyl substitution at C-2 position of the oxadiazole ring exhibited better inhibition of inflammation than that of the standard reference Ibuprofen, whereas the anti-inflammatory activity of **6t** is comparable with standard. Similarly, among the oxadiazoles tested for antiproliferative activity **6i** exhibited better inhibition concentration against all the cell lines. Compounds **6q** and **6t** displayed good antiproliferative activity against all the cell lines. A correlation between the anti-inflammatory and anti-proliferative activities among the 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazole analogues was observed. Interestingly, compound **6i** and **6t** proved to be good in both the activities, thus justifying our contention that good anti-inflammatory agents are likely to good antiproliferative agents as well. Studies on mode of action of these 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles, and improvisation of lead molecules as both anti-inflammatory and antiproliferative agents is underway.

Experimental

5.1 Chemistry

All the chemicals used are of synthetic grade procured from Sd-fine, Spectrochem and Aldrich chemicals. Completion of the reactions was monitored by analytical thin layer chromatography (TLC) using E-Merck 0.25 mm silica gel plates using ethyl acetate/hexane (4:6) as eluting medium. Visualization was accomplished with UV light (256 nm) and iodine chamber. Synthesized compounds were purified by column chromatography using a mixture of hexane and ethyl acetate. All the solvents are dried using appropriate drying agents before use. By employing standard laboratory techniques, the reagents are purified. Melting points were determined on ANALAB melting point apparatus and are uncorrected. All the ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ and DMSO-D_6 solvents unless otherwise mentioned. Chemical shifts are reported on AVANCE 300 MHz, INNOVA 500 MHz and JCAMP DX-50 (300 MHz for ^{1}H and 75 MHz for ^{13}C) relative to TMS internal standard on the δ-scale. The IR spectra were recorded on SCHIMADZU FT-IR SPECTROPHOTOMETER by using 1% potassium bromide

discs. The Electron Ionization mass spectra were recorded on Agilent 1100 series & HRMS done on high resolution QSTAR XL Hybrid /MS system.

5.2 General Procedure for Preparation of indole-3-carboxylates (2a-b):

The indole-3-carboxylic acids (**1a-b**) (10 mmol) were esterified in a classical manner with ethanol and catalytic amount of con.H_2SO_4 under reflux for 3 h. After completion, the reaction mixture was cooled and solvent ethanol was removed under reduce pressure, The residue was then poured onto crushed ice and treated with aq. NaOH solution (10%) drop wise till the reaction mixture became slightly basic in nature. The solid product obtained was filtered, washed with water and dried and characterized.

Ethyl-3-(1H-indol-3-yl)propanoate (2a): Yield: 95%; m. p.: 32-35^{0}C; FTIR (KBr) ν (cm-1): 3322 (N-H), 1718 (C=O), 1187 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) : δ 1.23 (t, 3H, *J* = 7.2 Hz, CH_3), 2.69 (t, 2H, *J* = 7.7 Hz, CH_2), 3.07 (t, 2H, *J* = 7.4 Hz, CH_2), 4.12 (q, 2H, *J* = 7.2 & 14.2 Hz, CH_2), 6.93 (s, 1H, ArH), 7.03-7.15 (m, 2H, ArH), 7.27 (d, 1H, *J* = 7.9 Hz, ArH), 7.55 (d, 1H, *J* = 7.7 Hz, ArH), 7.9 (s, 1H, -NH); MS (ESI) m/z : 217 $[M]^+$.

*Ethyl-4-(1H-indol-3-yl)butanoate (2b**):*** Yield: 80%; m. p.: 35-37^{0}C; FTIR (KBr) ν (cm-1): 3334 (N-H), 1720 (C=O), 1185 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) : δ 1.24 (t, 3H, *J* = 7.0 Hz, CH_3), 1.98 -2.07 (m, 2H, CH_2), 2.34 (t, 2H, *J* = 7.4 Hz, CH_2), 2.79 (t, 2H, *J* = 7.4 Hz, CH_2), 4.10 (q, 2H, *J* = 7.2 & 14.2 Hz, CH_2), 6.92 (s, 1H, ArH), 7.02-7.14 (m, 2H, ArH), 7.25 (d, 1H, *J* = 8.1 Hz, ArH), 7.55 (d, 1H, *J* = 7.7 Hz, ArH),7.87 (s, 1H, -NH), MS (EI) m/z: 231 $[M]^+$.

5.3 General procedure for preparation of indole-3-carboxylic acid hydrazides (3a-b):

An aqueous solution of hydrazine hydrate (15 ml, 99%) was added to a solution of appropriate indole-3-carboxylates (**2a-b**) (10 mmol) in ethanol (15 ml). The reaction mixture was refluxed for 5 h. At the end, the reaction mixture was cooled and poured onto crushed ice followed by extraction with ethyl acetate (3x10ml). The organic layer was dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield the product.

3-(1H-Indol-3-yl)propanehydrazide (3a): Yield: 92%; m. p.: 123-126^{0}C; FTIR (KBr) ν (cm-1): 3308 (N-H), 1638 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 2.43 (t, 2H, *J* = 7.5 Hz, CH_2), 2.99 (t, 2H, *J* = 7.5 Hz, CH_2), 3.91 (s, 2H, -NH_2), 6.92-7.04 (m, 3H, ArH), 7.30 (d, 1H *J* = 7.9 Hz, ArH), 7.48 (d, 1H, *J* = 7.7 Hz, ArH), 8.88 (s, 1H, -NH), 10.41 (s, 1H, ArH); MS (EI) m/z: 203 $[M]^+$.

*4-(1H-Indol-3-yl)butanehydrazide (3b**):*** Yield: 93%; m. p.: 102-106^{0}C; FTIR (KBr) ν (cm-1): 3321, 3269 (N-H), 1667 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 1.92-1.99 (m, 2H, CH_2); 2.13 (t, 2H, *J* = 6.8 Hz, CH_2), 2.71 (t, 2H, *J* = 7.8 Hz, CH_2), 3.89 (s, 2H, -NH_2), 6.89-6.96 (m, 2H, ArH), 7.01 (t, 1H, *J* = 6.8 Hz, ArH), 7.27 (d, 1H, *J* = 7.8 Hz, ArH), 7.46 (d, 1H, *J* = 7.8 Hz, ArH), 8.77 (s, 1H, -NH),10.29 (s, 1H, -NH), MS (EI) m/z: 217 $[M]^+$.

5.4 General procedure for preparation of N'-benzylidene-(1H-indol-3-yl)alkane hydrazide *(5a-v):*

A mixture of substituted benzaldehydes (**4a-r**) (1 mmol), indole-3-carboxylic acid hydrazides (**3a-b**) (1 mmol) in ethanol were refluxed for 3-4 h. As the reaction progresses, the N'-benzylidene-(1H-indol-3-yl)alkane hydrazide separates out as a solid product in the reaction mixture and was collected by simple filtration. The product obtained so was dried and purified by recrystallisation from hot ethylacetate/hexane.

N'-benzylidene-4-(1H-indol-3-yl)butanehydrazide (5a): White solid, Yield: 95%; m. p.: 146-148^{0}C; FTIR (KBr) ν (cm-1): 3279 (N-H), 1654 (C=O); ^{1}H NMR (DMSO-d_6, 500 MHz, ppm) : δ 1.99-2.05 (m, 2H, CH_2), 2.70-2.73 (t, 2H, *J* = 7.5 Hz, CH_2), 2.78-2.82 (t, 2H, *J* = 7.5 Hz, CH_2), 6.91-6.95 (q, 1H, *J* = 6.1 Hz, ArH), 7.00-7.04 (t, 2H, *J* = 6.8 Hz, ArH), 7.29-7.35 (m, 5H, ArH), 7.49-7.54 (dd, 2H, *J* = 6.8 & 8.2 Hz, ArH), 7.90 (s, 1H, ArH), 10.42 (brs, 1H, -NH), 11.02 (brs, 1H, -NH); MS (ESI) m/z: 306 $[M+H]^+$; HRMS: m/z Calculated value $C_{19}H_{19}ON_3Na$ = 328.1420, Observed value = 328.1408.

N'-(naphthalen-1-ylmethylene)-4-(1H-indol-3-yl)butanehydrazide (5b): White solid, Yield: 86%; m. p.: 155-157^{0}C; FTIR (KBr) ν (cm-1): 3409 (N-H), 1669 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) : δ 2.03-2.13 (q, 2H, CH_2), 2.77-2.87 (q, 4H, $2CH_2$), 6.90-7.02 (m, 3H, ArH), 7.28-7.31 (d, 1H, *J* = 7.9 Hz, ArH), 7.45-7.57 (m, 4H, ArH), 7.76-7.78 (d, 1H, *J* = 6.9 Hz, ArH), 7.93 (m, 2H, ArH), 8.60-8.79 (m, 2H, ArH), 10.39 (brs, 1H, -NH), 11.14 (brs, 1H, -NH); MS (ESI)

m/z: 356 $[M+H]^+$; HRMS: m/z Calculated value $C_{21}H_{23}ON_3Na$ = 356.1733, Observed value = 356.1751.

N'-(pyridin-2-ylmethylene)-3-(1H-indol-3-yl)propanehydrazide (5c): White solid, Yield : 82%; m.p. 201-202^{0}C; FTIR (KBr) ν (cm-1): 3312 (N-H), 1697 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.59 (s, 4H, $2CH_2$), 6.39-6.52 (m, 3H, ArH), 6.65-6.69 (d, 1H, *J* = 7.7 Hz, ArH), 6.88-6.92 (t, 1H, *J* = 7.3 Hz, ArH), 7.06-7.08 (d, 1H, *J* = 6.7 Hz, ArH), 7.22-7.26 (t, 1H, *J* = 7.5 Hz, ArH), 7.48-7.51 (d, 1H, *J* = 7.3 Hz, ArH), 7.65-7.66 (d, 1H, *J* = 4.3 Hz, ArH), 8.08 (s, 1H, ArH),10.20 (brs, 1H, -NH), 10.99 (brs, 1H, -NH); ESI Mass (m/z) 293 $[M+Na]^+$.

N'-(pyridin-3-ylmethylene)-3-(1H-indol-3-yl)propanehydrazide (5d): White solid, Yield : 84%; m.p. 153-155^{0}C; FTIR (KBr) ν (cm-1): 3285 (N-H), 1616 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.98 (s, 4H, $2CH_2$),6.98-7.14 (m, 3H, ArH), 7.16-7.26 (m, 2H, ArH), 7.23-7.26 (d, 1H, *J* = 8.3 Hz, ArH), 7.38 (d, 1H, *J* = 7.9 Hz, ArH), 7.52-7.59 (d, 1H, *J* = 8.1 Hz, ArH), 7.67-7.69 (dd, 1H, *J* = 1.3 & 5.1 Hz, ArH), 8.06 (s, 1H, ArH),10.33 (brs, 1H, -NH), 11.09 (brs, 1H, -NH); ESI Mass (m/z) 293 $[M+H]^+$.

N'-(thiophen-2-ylmethylene)-3-(1H-indol-3-yl)propanehydrazide (5e): White solid, Yield: 87%; m. p.: 152-154^{0}C; FTIR (KBr) ν (cm-1): 3409 (N-H), 1660 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) : δ 2.94-3.03 (q, 4H, CH_2), 6.94-7.06 (m, 4H, CH_2), 7.18-7.23 (dd, 1H, *J* = 2.6 & 12.0 Hz, ArH), 7.28-7.37 (m, 2H, CH_2), 7.52-7.59 (dd, 1H, *J* = 7.5 & 14.3 Hz, ArH), 8.09 (s, 1H, ArH), 10.32 (brs, 1H, -NH), 11.07 (brs, 1H, -NH); MS (ESI) m/z: 298 $[M+H]^+$.

N'-(thiophen-2-ylmethylene)-4-(1H-indol-3-yl)butanehydrazide (5f): White solid, Yield: 84%; m. p.: 164-166^{0}C; FTIR (KBr) ν (cm-1): 3390 (N-H), 1659 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) : δ 1.98-2.08 (q, 2H, CH_2), 2.67-2.72 (t, 2H, *J* = 7.3 Hz, CH_2), 2.78-2.83 (q, 2H, *J* = 7.3 Hz, CH_2), 6.91-7.04 (m, 4H, ArH), 7.14-7.24 (dd, 1H, *J* = 3.2 &17.1Hz, ArH), 7.28-7.34 (m, 2H, ArH), 7.48-7.52 (t, 1H, *J* = 7.5 Hz, ArH), 8.05 (s, 1H, ArH), 10.20 (brs, 1H, -NH), 10.98 (brs, 1H, -NH); MS (ESI) m/z: 334 $[M+H]^+$; HRMS: m/z Calculated value $C_{18}H_{14}O_3N_4$ = 334.1060, Observed value = 334.0973.

N'-(4-nitrobenzylidene)-3-(1H-indol-3-yl)propanehydrazide (5g): Yellow solid, Yield: 82%; m. p.: 189-192^{0}C; FTIR (KBr) ν (cm-1): 3390 (N-H), 1665 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) : δ 3.05-3.13 (q, 4H, CH_2), 6.95-7.07 (m, 3H, CH_2), 7.29-7.31 (d, 1H, *J* = 7.7 Hz, ArH),

7.54-7.56 (d, 1H, *J* = 7.3 Hz, ArH), 7.73-7.76 (d, 2H, *J* = 8.8 Hz, ArH), 7.96 (s, 1H, ArH), 8.15-8.18 (d, 2H, *J* = 8.6 Hz, ArH), 10.20 (brs, 1H, -NH), 11.39 (brs, 1H, -NH); MS (ESI) m/z: 337 $[M+H]^+$.

N'-(4-Fluorobenzylidene)-4-(1H-indol-3-yl)butanehydrazide (5h): White solid, Yield: 85%; m. p.: 147-150^{0}C; FTIR (KBr) ν (cm-1): 3263 (N-H), 1658 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 1.95 -2.06 (m, 2H, CH_2), 2.26 (t, 1H, *J* = 7.4 Hz, CH_2), 2.71 (t, 1H, *J* = 7.4 Hz, CH_2), 2.81 (t, 2H, *J* = 7.0 Hz, CH_2), 6.91-7.11 (m, 5H, ArH), 7.32 (d, 1H, *J* = 7.9 Hz, ArH), 7.49 -7.54 (m, 2H, Ar-H), 7.67-7.75 (m, 1H, ArH), 7.87 (s, 1H, ArH), 10.31 (s, 1H, -NH), 10.98 (s, 1H, -NH); MS (ESI) m/z: 324 $[M+H]^+$, 346 $[M+Na]^+$.

N'-(4-Chlorobenzylidene)-3-(1H-indol-3-yl)propanehydrazide (5i): White solid, Yield: 87%; m. p.: 190-192^{0}C; FTIR (KBr) ν (cm-1): 3382 (N-H), 1660 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz,) : δ 2.54-2.62 (m, 1H, CH_2), 3.02-3.13 (m, 3H, CH_2), 6.94-7.07- (m, 3H, ArH), 7.29-7.33 (m, 3H, 3 ArH), 7.50-7.59 (m, 2H, ArH), 7.62-7.69 (m, 1H, ArH), 7.87 (s, 1H, ArH), 10.18 (s, 1H, -NH), 11.09 (s, 1H, -NH); MS (ESI) m/z: 326 $[M+H]^+$, 348 $[M+Na]^+$.

N'-(4-Chlorobenzylidene)-4-(1H-indol-3-yl)butanehydrazide (5j): White solid, Yield: 87%; m. p.: 155-160^{0}C; FTIR (KBr) ν (cm-1): 3416 (N-H), 1658 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 1.96-2.08 (m, 2H, CH_2), 2.26 (t, 1H, *J* = 7.2 Hz, CH_2), 2.71 (t, 1H, *J* = 7.4 Hz, CH_2), 2.82 (t, 2H, *J* = 7.2 Hz, CH_2), 6.91-7.06 (m, 3H, ArH), 7.29-7.34 (m, 3H, ArH), 7.46-7.52 (m, 2H, ArH), 7.66 (d, 1H, *J* = 8.3 Hz, ArH), 7.85 (s, 1H, ArH), 10.31 (s, 1H, -NH), 11.06 (s, 1H, -NH); MS (ESI) m/z: 340 $[M+H]^+$, 362 $[M+Na]^+$.

N'-(3-Chlorobenzylidene)-3-(1H-indol-3-yl)propanehydrazide (5k): White solid, Yield: 86%; m. p.: 170-173^{0}C; FTIR (KBr) ν (cm-1): 3449 (N-H), 1667 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 2.53-2.62 (m, 1H, CH_2), 3.03-3.13 (m, 3H, CH_2), 6.95-7.06 (m, 3H, ArH), 7.25-7.35 (m, 3H, ArH), 7.45-7.63 (m, 3H, ArH), 7.88 (s, 1H, ArH), 10.29 (s, 1H, ArH), 11.17 (s, 1H, -NH); MS (ESI) m/z: 326 $[M+H]^+$, 348 $[M+Na]^+$.

N'-(3-Chlorobenzylidene)-4-(1H-indol-3-yl)butanehydrazide (5l): White solid, Yield: 86%; m. p.: 128-132^{0}C; FTIR (KBr) ν (cm-1): 3312 (N-H), 1654 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 1.99-2.16 (m, 2H, CH_2), 2.27 (t, 1H, *J* = 6.4 Hz, CH_2), 2.69-2.87 (m, 3H, CH_2), 6.94-7.07 (m, 3H, ArH), 7.23-7.31 (m, 3H, ArH), 7.36-7.41 (m, 1H, ArH), 7.50-7.59 (m,

2H, ArH), 7.82 (s, 1H, CH), 9.81 (s, 1H, -NH), 10.99 (s, 1H, -NH); MS (ESI) m/z: 340 $[M+H]^+$, 362 $[M+Na]^+$.

N'-(3-bromobenzylidene)-3-(1H-indol-3-yl)propanehydrazide(5m): White solid, Yield: 89%; m. p.: 165-167^{0}C; FTIR (KBr) ν (cm-1): 3438 (N-H), 1664 (C=O); ^{1}H NMR (DMSO-d_6, 500 MHz, ppm) : δ 2.99- 3.02 (q, 4H, $2CH_2$), 6.93-7.03 (m, 3H, ArH), 7.22-7.29 (q, 2H, CH_2), 7.41-7.45 (d, 1H, *J* = 8.9 Hz, ArH), 7.51-7.54 (t, 1H, *J* = 7.5 Hz, ArH), 7.58-7.60 (d, 1H, *J* = 8.2 Hz, ArH), 7.74 (s, 1H, ArH), 7.86 (s, 1H, ArH), 10.35 (brs, 1H, -NH), 11.17 (brs, 1H, -NH); MS (ESI) m/z: 370 $[M+H]^+$; HRMS: m/z Calculated value $C_{18}H_{17}ON_3Br$ = 370.0549, Observed value = 370.0548.

N'-(2,6-dichlorobenzylidene)-3-(1H-indol-3-yl)propanehydrazide(5n): White solid, Yield: 89%; m. p.: 172-174^{0}C; FTIR (KBr) ν (cm-1): 3436 (N-H), 1590 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) : δ 2.5-2.55 (t, 2H, *J* = 1.7 Hz, CH_2), 2.99-3.01 (t, 2H, *J* = 2.0 Hz, CH_2), 6.89-7.04 (m, 3H, ArH), 7.24-7.29 (t, 2H, *J* = 8.3 Hz, ArH), 7.35-7.38 (d, 2H, *J* = 7.3 Hz, ArH), 7.50-7.52 (d, 1H, *J* = 7.3 Hz, ArH), 8.18 (s, 1H, ArH), 10.29 (brs, 1H, -NH), 11.31 (brs, 1H, -NH); MS (ESI) m/z: 360 $[M+H]^+$; HRMS: m/z Calculated value $C_{18}H_{16}ON_3Cl_2$ = 360.0664, Observed value = 360.0665.

N'-(3,4-dichlorobenzylidene)-4-(1H-indol-3-yl)butanehydrazide (5o): White solid, Yield: 88%; m. p.: 166-168^{0}C; FTIR (KBr) ν (cm-1): 3321 (N-H), 1658 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) : δ 1.97- 2.11 (m, 2H, CH_2), 2.69-2.75 (t, 2H, *J* = 7.5 Hz, CH_2), 2.76-2.83 (q, 2H, *J* = 7.1 Hz, CH_2), 6.91-7.04 (m, 3H, ArH), 7.29-7.31 (d, 1H, *J* = 7.9 Hz, ArH), 7.39-7.59 (m, 3H, ArH), 7.67 (s, 1H, ArH), 7.82-7.84 (d, 1H, *J* = 6.4 Hz, ArH), 10.40 (brs, 1H, -NH), 11.21 (brs, 1H, -NH); MS (ESI) m/z: 374 $[M+H]^+$; HRMS: m/z Calculated value $C_{19}H_{17}ON_3Cl_2Na$ = 396.0640, Observed value = 396.0634.

N'-(4-methylbenzylidene)-3-(1H-Indol-3-yl)propanehydrazide (5p): White solid, Yield: 92%; m. p.: 147-150^{0}C; FTIR (KBr) ν (cm-1): 3435 (N-H), 1656 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 2.36 (s, 3H, CH_3), 2.53-2.61 (m, 1H, CH_2), 2.97-3.11 (m, 3H, CH_2), 6.94-7.06- (m, 3H, ArH), 7.15 (t, 2H, *J* = 4.9 Hz, ArH), 7.29 (d, 1H, *J* = 7.7 Hz, ArH), 7.47 (d, 1H, *J* = 7.9 Hz, ArH), 7.57 (d, 2H, *J* = 7.0 Hz, ArH), 7.88 (s, 1H, ArH), 10.33 (s, 1H, -NH), 10.99 (s, 1H, -NH),; MS (ESI) m/z: 306 $[M+H]^+$, 328 $[M+Na]^+$.

N'-(4-methoxybenzylidene)-3-(1H-Indol-3-yl)propanehydrazide (5q): White solid, Yield: 90%; m. p.: 162-164^{0}C; FTIR (KBr) ν (cm-1): 3432 (N-H), 1656 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 2.54-2.62 (m, 1H, CH_2), 2.96-3.13 (m, 3H, CH_2), 3.81 (s, 3H, CH_3), 6.83 (d, 2H, *J* = 8.3 Hz, ArH), 6.94-7.06 (m, 3H, ArH), 7.29 (d, 1H, *J* = 7.9 Hz, ArH), 7.51-7.64 (m, 3H, ArH), 7.85 (s, 1H, ArH), 10.21 (s, 1H, ArH), 10.88 (s, 1H, -NH); MS (ESI) m/z: 322 $[M+H]^+$, 344 $[M+Na]^+$.

N'-(4-methoxybenzylidene)-4-(1H-indol-3-yl)butanehydrazide (5r): White solid, Yield: 83%; m. p.: 156-158^{0}C; FTIR (KBr) ν (cm-1): 3278 (N-H), 1651 (C=O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm) : δ 1.97-2.10 (m, 2H, CH_2), 2.24 (t, 1H, *J* = 7.4 Hz, CH_2), 2.71 (t, 1H, *J* = 7.5 Hz, CH_2), 2.82 (t, 2H, *J* = 7.4 Hz, CH_2), 3.82 (s, 3H, CH_3), 6.80-7.05 (m, 5H, ArH), 7.29 (d, 1H, *J* = 8.1 Hz, ArH), 7.42-7.54 (m, 2H, ArH), 7.62 (d, 1H, *J* = 8.5 Hz, ArH), 7.82 (s, 1H, ArH), 10.29 (s, 1H, -NH), 10.85 (s, 1H, -NH); MS (ESI) m/z: 336 $[M+H]^+$, 358 $[M+Na]^+$.

N'-(2,4,6-trimethoxybenzylidene)-4-(1H-indol-3-yl)butanehydrazide (5s): Yellow solid, Yield : 82%; m.p. 189-191^{0}C; FTIR (KBr) ν (cm-1): 3304 (N-H), 1651 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.27-2.34 (q, 2H, CH_2), 2.94-2.98 (t, 2H, *J* = 7.2 Hz, CH_2), 3.02-3.06 (t, 2H, *J* = 7.3 Hz, CH_2), 3.77-3.81(s, 9H, $3CH_3$), 6.11 (s, 2H, ArH), 6.89-7.04 (s, 3H, ArH), 7.27-7.30 (d, 1H, *J* = 7.9 Hz, ArH), 7.54-7.56 (d, 1H, *J* = 7.7 Hz, ArH), 8.08 (s, 1H, ArH), 10.29 (brs, 1H, -NH) 10.56 (brs, 1H, -NH); ESI Mass (m/z) 396 $[M+H]^+$; HRMS: m/z Calculated value $C_{22}H_{24}N_3O_4$ = 396.1676, Observed value = 396.1653.

N'-(4-(3,5,6-trichloropyridin-2-yloxy)benzylidene)-3-(1H-indol-3-yl)propanehydrazide (5u): White solid, Yield: 91%; m. p.: 169-172^{0}C; FTIR (KBr) ν (cm-1): 3405 (N-H), 1673 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) : δ 3.03-3.13 (q, 4H, $2CH_2$), 6.94-7.06 (m, 3H, ArH), 7.11-7.16 (t, 2H, *J* = 6.6 & 8.4 Hz, ArH), 7.28-7.31 (d, 1H, *J* = 7.9 Hz, ArH), 7.55-7.58 (d, 1H, *J* = 7.5 Hz, ArH), 7.65-7.68 (d, 1H, *J* = 8.6 Hz, ArH),7.73-7.78 (t, 1H, *J* = 8.8 Hz, ArH), 7.94 (s, 1H, ArH), 7.99 (s, 1H, ArH), 10.23 (brs, 1H, -NH), 11.06 (brs, 1H, -NH); MS (ESI) m/z: 489 $[M+H]^+$.

N'-(4-(3,5,6-trichloropyridin-2-yloxy)benzylidene)-4-(1H-indol-3-yl)butanehydrazide (5v): White solid, Yield: 93%; m. p.: 167-168^{0}C; FTIR (KBr) ν (cm-1): 3400 (N-H), 1658 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) : δ 1.99-2.09 (q, 2H, CH_2), 2.70-2.75 (t, 2H, *J* = 7.5 Hz, CH_2),

2.78-2.84 (q, 2H, *J* = 6.9 Hz, CH_2), 6.91-7.04 (m, 3H, ArH), 7.11-7.17 (t, 2H, *J* = 7.9 Hz, ArH), 7.29-7.32 (d, 1H, *J* = 7.9 Hz, ArH), 7.50-7.52 (d, 1H, *J* = 7.7 Hz, ArH), 7.59-7.61 (d, 1H, *J* = 8.4 Hz, ArH), 7.76-7.86 (dd, 1H, *J* = 8.4 Hz, ArH), 7.92 (s, 1H, ArH), 8.04-8.05 (d, 1H, *J* = 5.4 Hz, ArH), 10.35 (brs, 1H, -NH), 11.03 (brs, 1H, -NH); MS (ESI) m/z: 501 $[M+H]^+$, 523 $[M+Na]^+$; HRMS: m/z Calculated value $C_{24}H_{20}O_2N_4Cl_3$ = 501.0646, Observed value = 501.0639.

5.5 General procedure for the synthesis of 5-(alkyl(1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles (6a-6v):

To the solution of N'-benzylidene-(1H-indol-3-yl)alkane hydrazides (**5a-y**) (1 mmol) in DCM was added $PhI(OAc)_2$ (1.2 mmol) and the mixture was allowed to stir at room temperature. Progress of the reaction was monitored by TLC using ethyl acetate/hexane (4:6) as eluting medium. At the end of the reaction, reaction mixture was diluted with water (5 mL) and extracted with DCM (3x5mL). The combined organic layers were dried over sodium sulphate, filtered, concentrated under vacuum and purified by silica gel column chromatography using ethyl acetate:hexane as eluent to afford pure compounds. All the synthesized compounds are characterized by ^{1}H-NMR and mass spectroscopic techniques.

5.6 5-(3-(1H-indol-3-yl)propyl)-2-phenyl-1,3,4-oxadiazole (6a): White solid, Yield : 78%; R_f = 0.31; m.p. 122-124^{0}C; FTIR (KBr) ν (cm-1): 3226 (N-H), 1022 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.19-2.26 (m, 2H, CH_2), 2.84-2.92 (m, 4H, $2CH_2$), 6.93 (s, 1H, ArH), 6.98-7.01 (t, 1H, *J* = 7.3 Hz, ArH), 7.04-7.08 (t, 1H, *J* = 7.3 Hz, ArH), 7.19-7.22 (t, 1H, *J* = 8.0 Hz, ArH), 7.41 (m, 3H, ArH), 7.48-7.50 (d, 1H, *J* = 7.3 Hz, ArH), 7.89-7.91 (d, 2H, *J* = 7.3 Hz, ArH), 7.95 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz, ppm): δ 21.5, 23.3, 25.5, 110.7, 111.8, 117.2, 117.9, 120.5, 121.4, 124.2, 126.0, 127.2, 128.5, 129.1, 135.6, 159.8, 165.1; ESI Mass (m/z) 304 $[M+H]^+$; HRMS: m/z Calculated value $C_{19}H_{17}N_3ONa$ = 326.1269, Observed value = 326.1271.

5.7 5-(3-(1H-indol-3-yl)propyl)-2-(naphthalen-1-yl)-1,3,4-oxadiazole (6b): White solid, Yield : 69%; R_f = 0.37; m.p. 143-146^{0}C; FTIR (KBr) ν (cm-1): 3230 (N-H), 1128 (C-O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 2.29-2.34 (t, 2H, *J* = 7.3 Hz, CH_2), 2.94-2.99 (t, 2H, *J* =7.1 Hz, CH_2), 3.02-3.07 (t, 2H, *J* = 7.5 Hz, CH_2), 7.03-7.17 (m, 3H, ArH), 7.35-7.38 (d, 1H, *J* = 7.9 Hz, ArH), 7.54-7.68 (m, 4H, ArH), 7.92-7.95 (d, 1H, *J* = 7.9 Hz, ArH), 8.02-8.08 (dd, 2H, *J* = 7.3 &

10.3 Hz, ArH), 9.16-9.19 (d, 1H, *J* = 8.4 Hz, ArH), 9.82 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75MHz, ppm): δ 23.1, 23.6, 25.7, 110.2, 112.3, 117.1, 117.3, 119.1, 119.9, 121.1, 123.8, 124.7, 125.4, 125.9, 126.7, 126.9, 127.4, 128.5, 131.0, 132.4, 135.4, 163.0, 165.2; ESI Mass (m/z) 376 $[M+Na]^+$; HRMS: m/z Calculated value $C_{23}H_{19}ON_3Na$ = 376.1420, Observed value = 376.1418.

5.8 5-(3-(1H-indol-3-yl)ethyl)-2-(pyridin-2-yl)-1,3,4-oxadiazole (6c): White solid, Yield : 70%; R_f = 0.33; m.p. 190-193^{0}C; FTIR (KBr) ν (cm-1): 3210 (N-H), 1097 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.83 (s, 4H, $2CH_2$), 6.50-6.63 (m, 3H, ArH), 6.84-6.87 (d, 1H, *J* = 7.9 Hz, ArH), 6.96-7.01 (t, 1H, *J* = 7.5 Hz, ArH), 7.04-7.06 (d, 1H, *J* = 6.6 Hz, ArH), 7.38-7.43 (t, 1H, *J* = 7.7 Hz, ArH), 7.64-7.67 (d, 1H, *J* = 7.7 Hz, ArH), 8.25-8.26 (d, 1H, *J* = 4.5 Hz, ArH), 9.60 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ 22.4, 26.5, 111.1, 114.0, 118.5, 119.5, 121.7, 122.2, 123.0, 125.7, 127.0, 136.2, 137.23, 143.6, 150.1, 163.9, 167.7; ESI Mass (m/z) 313 $[M+Na]^+$; HRMS: m/z Calculated value $C_{17}H_{14}N_4ONa$ = 313.1059, Observed value = 313.10618.

5.9 5-(3-(1H-indol-3-yl)ethyl)-2-(pyridin-3-yl)-1,3,4-oxadiazole (6d): White solid, Yield : 72%; R_f = 0.33; m.p. 140-142^{0}C; FTIR (KBr) ν (cm-1): 3183 (N-H), 1016 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 3.36 (s, 4H, $2CH_2$), 7.08-7.23 (m, 3H, ArH), 7.36-7.46 (m, 2H, ArH), 7.60-7.62 (d, 1H, *J* = 8.3 Hz, ArH), 8.07 (brs, 1H, NH), 8.26-8.29 (d, 1H, *J* = 8.3 Hz, ArH), 8.74-8.76 (dd, 1H, *J* = 1.5 & 5.2 Hz, ArH), 9.18 (d, 1H, *J* = 1.5 Hz, ArH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 125MHz, ppm): δ 21.2, 25.3, 110.5, 116.8, 117.6, 120.2, 121.2, 121.7, 122.8, 124.8, 125.8, 132.8, 135.4, 136.3, 146.2, 149.0, 151.0; ESI Mass (m/z) 291 $[M+H]^+$; HRMS: m/z Calculated value $C_{17}H_{14}N_4O$ = 291.1002, Observed value = 291.1235.

5.10 5-(3-(1H-indol-3-yl)ethyl)-2-(thiophen-2-yl)-1,3,4-oxadiazole (6e): White solid, Yield : 75%; R_f = 0.31; m.p. 132-134^{0}C; FTIR (KBr) ν (cm-1): 3179 (N-H), 1009 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 3.29-3.32 (m, 4H, $2CH_2$), 7.03-7.04 (d, 1H, *J* = 2.6 Hz, ArH), 7.07-7.17 (m, 3H, ArH), 7.28-7.31(d, 1H, *J* = 7.7 Hz, ArH), 7.48-7.49 (d, 1H, *J* = 4.9 Hz, ArH), 7.55-7.57 (d, 1H, *J* = 7.7 Hz, ArH), 7.64-7.65 (d, 1H, *J* = 3.7 HZ, ArH), 7.94 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 75MHz, ppm): δ 22.3, 26.3, 111.2 113.9, 118.4, 119.5, 121.7, 122.2,126.9, 128.0, 129.5, 129.8 136.2; 139.1, 157.5, 167.5; ESI Mass (m/z) 296 $[M+H]^+$; HRMS: m/z Calculated value $C_{16}H_{13}N_3ONaS$ = 318.0677, Observed value = 318.0674.

5.11 5-(3-(1H-indol-3-yl)propyl)-2-(thiophen-2-yl)-1,3,4-oxadiazole (6f): White solid, Yield : 77%; R_f = 0.31; m.p. 114-116^{0}C; FTIR (KBr) ν (cm-1): 3181 (N-H), 1015 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.21-2.31 (m, 2H, $2CH_2$), 2.89-2.95 (m, 4H, $2CH_2$), 6.98-6.99 (d, 1H, *J* = 2.2 Hz, ArH), 7.02-7.14 (m, 3H, ArH), 7.26-7.29 (d, 1H, *J* = 8.3 Hz, ArH), 7.48-7.49 (d, 1H, *J* = 5.2 Hz, ArH), 7.53-7.56 (d, 1H, *J* = 7.5 Hz, ArH), 7.62-7.63 (dd, 1H, *J* = 1.5 & 3.7 Hz, ArH), 8.00 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 75MHz, ppm): δ 24.3, 24.9, 26.8 111.1, 114.8, 118.7, 119.2, 121.7, 121.9, 124.0, 126.7, 127.2, 128.9, 131.4, 136.4, 164.6, 166.8; ESI Mass (m/z) 332 $[M+Na]^+$; HRMS: m/z Calculated value $C_{17}H_{15}N_3ONaS$ = 332.0833, Observed value = 332.0831.

5.12 5-(3-(1H-indol-3-yl)ethyl)-2-(4-nitrophenyl)-1,3,4-oxadiazole (6g): White solid, Yield : 65%; R_f = 0.34; m.p. 160-163^{0}C; FTIR (KBr) ν (cm-1): 3233(N-H), 1098 (C-O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.31 (s, 4H, $2CH_2$), 6.92-7.06 (m, 3H, ArH), 7.31-7.33 (d, 1H, *J* = 7.9 Hz, ArH), 7.45-7.48 (d, 1H, *J* = 7.7 Hz, ArH), 8.15-8.18 (d, 2H, *J* = 8.4 Hz, ArH), 8.34-8.39 (d, 2H, *J* = 8.8 Hz, ArH), 10.52 (brs, 1H, ArH). ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75MHz, ppm): δ 21.2, 25.4, 110.5, 111.3, 116.8, 117.6, 120.2, 121.3, 123.1, 125.7, 126.5 128.3, 135.4, 148.1, 161.7, 166.5; ESI Mass (m/z) 335 $[M+H]^+$; HRMS: m/z Calculated value $C_{18}H_{14}N_4O_3Na$ = 357.0963, Observed value = 357.0957.

5.14 5-(3-(1H-Indol-3-yl)propyl)-2-(4-fluorophenyl)-1,3,4-oxadiazole (6h): White solid, Yield : 67%; R_f = 0.31; m. p. 153-157^{0}C; FTIR (KBr) ν (cm-1): 3216 (N-H), 1089 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.21-2.33 (m, 2H, CH_2), 2.90-2.99 (m, 4H,2 CH_2), 6.99 (s, 1H, ArH), 7.01-7.18 (m, 4H, ArH), 7.23-7.28 (m, 1H, ArH), 7.53 (d, 1H, *J* = 7.5 Hz, ArH), 7.88-7.99 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz, ppm): δ 23.7, 24.2, 26.2, 110.8, 113.2, 115.5,115.8, 117.8, 118.0, 120.7, 121.6, 126.6,128.4, 128.4, 135.9, 162.2, 163.1, 165.5, 166.3; ESI Mass (m/z) 344 $[M+Na]^+$; HRMS: m/z Calculated value $C_{19}H_{16}N_3OFNa$ = 344.1175, Observed value = 344.1180.

5.15 5-(2-(1H-Indol-3-yl)ethyl)-2-(4-chlorophenyl)-1,3,4-oxadiazole (6i): White solid, Yield : 70%; R_f = 0.34; m. p. 160-161^{0}C; FTIR (KBr) ν (cm-1): 3232 (N-H), 1093 (C-O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.29 (s, 4H, $2CH_2$), 6.94-7.08 (m, 3H, ArH), 7.31 (d, 1H, *J* = 7.9 Hz, ArH), 7.5 (dd, 3H, *J* = 2.3, & 1.89 Hz, ArH), 7.93 (d, 2H, *J* = 8.5 Hz, ArH), 10.42 (s, 1H, NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 50 MHz, ppm): δ 21.7, 25.8, 110.8, 112.0, 117.3, 118.1,

120.7, 121.5, 121.7, 126.2, 127.2, 128.6, 135.8, 136.7, 163.0, 166.1; ESI Mass (m/z) 324 $[M+H]^+$; HRMS: m/z Calculated value = $C_{18}H_{14}N_3ONaCl$ = 346.0723, Observed value = 346.0726.

5.16 5-(3-(1H-Indol-3-yl)propyl)-2-(4-chlorophenyl)-1,3,4-oxadiazole (6j): White solid, Yield : 71%; R_f = 0.34; m. p. 149-150^{0}C; FTIR (KBr) ν (cm-1): 3217 (N-H), 1095 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.21-2.33 (m, 2H, CH_2), 2.88-2.98 (m, 4H, $2CH_2$), 6.98 (s, 1H, ArH), 7.01-7.16 (m, 2H, ArH), 7.25-7.28 (m, 1H, ArH), 7.43 (d, 2H, *J* = 8.3 Hz, ArH), 7.53 (d, 1H, *J* = 7.5 Hz, ArH), 7.87-7.92 (m, 3H, 1 ArH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz, ppm): δ 22.7, 23.1, 25.2, 109.9, 111.6, 116.6, 116.7, 119.4, 120.7, 120.9 125.5, 126.4, 127.7, 135.8, 135.5, 161.6, 165.1; ESI Mass (m/z) 338 $[M+H]^+$; HRMS: m/z Calculated value $C_{19}H_{16}N_3ONaCl$ = 360.0879, Observed value = 360.0893.

5.17 5-(2-(1H-Indol-3-yl)ethyl)-2-(3-chlorophenyl)-1,3,4-oxadiazole (6k): White solid, Yield : 63%; R_f = 0.37; m. p. 117-118^{0}C; FTIR (KBr) ν (cm-1): 3287 (N-H), 1077 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 3.32 (s, 4H, $2CH_2$), 7.02-7.17 (m, 3H, ArH), 7.29 (d, 1H, *J* = 8.3 Hz, ArH), 7.37-7.48 (m, 2H, ArH), 7.53 (d, 1H, *J* = 7.5 Hz, ArH), 7.85 (d, 1H, *J* = 6.8 Hz, ArH), 7.92 (s, 1H, ArH), 7.98 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$+DMSO, 75 MHz, ppm): δ 21.4, 25.5, 110.5, 111.6, 117.0, 117.7, 120.4, 121.3, 123.8, 124.5, 125.4, 125.9, 129.5, 130.4, 133.8, 135.5, 162.3, 165.9; ESI Mass (m/z) 324 $[M+H]^+$; HRMS: m/z Calculated value $C_{18}H_{14}N_3ONaCl$ = 346.0723, Observed value = 346.0731.

5.18 5-(3-(1H-Indol-3-yl)propyl)-2-(3-chlorophenyl)-1,3,4-oxadiazole (6l): White solid, Yield : 65%; R_f = 0.37; m. p. 116-117^{0}C; FTIR (KBr) ν (cm-1): 3221 (N-H), 1079 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.24-2.33 (m, 2H, CH_2), 2.90-2.98 (m, 4H, $2CH_2$), 6.97 (s, 1H, ArH), 7.037-14 (m, 2H, ArH), 7.27 (s, 1H, ArH), 7.37-7.47 (m, 2H, ArH), 7.53 (d, 1H, *J* = 7.5 Hz, ArH), 7.84 (d, 1H, *J* = 7.5 Hz, ArH), 7.91 (s, 1H, ArH), 7.96 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz, ppm): δ 24.1, 24.6, 26.5, 111.1, 113.9, 118.2, 118.6, 121.4, 121.8, 124.5, 125.2, 126.3, 126.9, 130.1, 131.2, 134.7, 136.2, 163.2, 167.0; ESI Mass (m/z) 338 $[M+H]^+$; HRMS: m/z Calculated value $C_{19}H_{16}N_3ONaCl$ = 360.0879, Observed value = 360.0892.

5.19 5-(3-(1H-indol-3-yl)ethyl)-2-(3-bromophenyl)-1,3,4-oxadiazole (6m): White solid, Yield : 66%; R_f = 0.34; m.p. 112-114^{0}C; FTIR (KBr) ν (cm-1) : 3167 (N-H), 1117 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 3.30 (s, 4H, $2CH_2$), 6.95-7.09 (m, 3H, ArH), 7.32-7.43 (m, 2H, ArH), 7.47-7.50 (d, 1H, *J* = 7.7 Hz, ArH), 7.62-7.65 (d, 1H, *J* = 7.1 Hz, ArH), 7.89-7.92 (d, 1H, *J* = 7.7 Hz, ArH), 8.06 (s, 1H, ArH), 10.23 (brs, 1H, NH); ESI Mass (m/z) 368 $[M]^+$; HRMS: m/z Calculated value $C_{18}H_{14}N_3ONaBr$ = 390.0217, Observed value = 390.0234.

5.20 5-(3-(1H-indol-3-yl)ethyl)-2-(2,6-dichlorophenyl)-1,3,4-oxadiazole (6n): White solid, Yield : 68%; R_f = 0.34; m.p. 154-156^{0}C; FTIR (KBr) ν (cm-1): 3263 (N-H), 1024 (C-O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.31 (s, 4H, $2CH_2$), 6.98-7.09 (m, 3H, ArH), 7.30-7.33 (d, 1H, *J* = 8.1 Hz, ArH), 7.47-7.56 (m, 4H, ArH), 10.14 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75MHz, ppm): δ 21.8, 25.8, 110.8, 111.9, 117.4, 118.1, 120.8, 121.6, 123.6, 126.2, 127.6, 132.3, 135.5, 135.8, 159.0, 167.1; ESI Mass (m/z) 358 $[M]^+$; HRMS: m/z Calculated value $C_{18}H_{13}N_3ONaCl_2$ = 380.0333, Observed value = 380.0336.

5.21 5-(3-(1H-indol-3-yl)propyl)-2-(3,4-dichlorophenyl)-1,3,4-oxadiazole (6o): White solid, Yield : 69%; R_f = 0.34; m.p. 134-136^{0}C; FTIR (KBr) ν (cm-1): 3249 (N-H), 1035 (C-O); ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 2.22-2.32 (m, 2H, CH_2), 2.89-2.94 (t, 2H, *J* = 7.3Hz, CH_2), 2.96-3.01 (t, 2H, *J* = 7.3Hz, CH_2), 7.03-7.14 (m, 3H, ArH), 7.34-7.36 (d, 1H, *J* = 7.9Hz, ArH), 7.52-7.61 (m, 2H, ArH), 7.80-7.84 (dd, 1H, *J* = 1.8 & 8.3Hz, ArH), 8.05-8.06 (d, 1H, *J* = 1.8 Hz, ArH), 9.87 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75MHz, ppm): δ 23.4, 23.9, 25.8, 110.5, 112.6, 117.4, 117.6, 120.3, 121.3, 124.9, 127.3, 130.3, 132.2, 134.5, 135.6, 161.7, 166.4; ESI Mass (m/z) 372 $[M+H]^+$; HRMS: m/z Calculated value $C_{19}H_{15}N_3ONaCl_2$ = 372.06649, Observed value = 372.06700.

5.22 5-(2-(1H-Indol-3-yl)ethyl)-2-p-tolyl-1,3,4-oxadiazole (6p): White solid, Yield : 55%; R_f = 0.34; m. p. 163-165^{0}C; FTIR (KBr) ν (cm-1): 3215 (N-H), 1090 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.42 (s, 3H, CH_3), 3.31 (t, 4H, *J* = 3.4 Hz, $2CH_2$), 7.18-7.02 (m, 3H, ArH), 7.31-7.24 (m, 3H, ArH), 7.57 (d, 1H, *J* = 7.7 Hz, ArH), 7.84 (d, 2H, *J* = 8.1 Hz, ArH), 7.98 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz, ppm): δ 21.0, 21.8, 25.9, 111.0, 112.4, 117.5, 118.3, 120.5, 120.9, 121.6, 126.0, 126.3, 129.1, 135.9, 141.4, 164.1, 165.8; ESI Mass (m/z) 304 $[M+H]^+$; HRMS: m/z Calculated value $C_{19}H_{18}N_3O$ = 304.1449, Observed value = 304.1461.

5.24 5-(2-(1H-Indol-3-yl)ethyl)-2-(4-methoxyphenyl)-1,3,4-oxadiazole (6q): White solid, Yield : 64%; R_f = 0.31; m. p. 154-157^{0}C; FTIR (KBr) ν (cm-1): 3181 (N-H), 1025 (C-O); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, ppm): δ 3.09-3.27 (m, 4H, $2CH_2$), 3.87 (s, 3H, CH_3), 6.99-7.03 (s, 5H, ArH), 7.31 (s, 1H, ArH), 7.50 (s, 1H, ArH), 7.868 (s, 2H, ArH), 10.53 (brs, 1H, -NH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz, ppm): δ 21.1, 25.1, 54.0, 110.3, 111.3, 113.1, 115.1, 116.7, 117.3, 120.0, 121.0, 125.6, 127.0, 135.2, 160.7, 162.9, 164.6; ESI Mass (m/z) 320 $[M+H]^+$, 342 ($M+Na^+$); HRMS: m/z Calculated value $C_{19}H_{17}N_3O_2Na$ = 342.1218, Observed value = 342.1225.

5.25 5-(3-(1H-indol-3-yl)propyl)-2-(4-methoxyphenyl)-1,3,4-oxadiazole (6r): White solid, Yield : 69%; R_f = 0.31; m. p. 139-142^{0}C; FTIR (KBr) ν (cm-1): 3218 (N-H), 1024 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.22-2.33 (m, 2H, CH_2), 2.88-2.96 (m, 4H, $2CH_2$), 3.87 (s, 3H, CH_3), 7.18-6.91 (m, 5H, ArH), 7.28 (d, *J* = 8.3 Hz, 1H, ArH), 7.54 (d, *J* = 7.5 Hz, 1H, ArH), 7.91-7.85 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz, ppm): δ 23.9, 24.4, 26.4, 54.9, 110.9, 113.4, 113.9, 115.9, 117.9, 118.1, 120.8, 121.6, 126.7, 127.8, 136.1, 161.6, 163.9, 165.8; ESI Mass (m/z) 334 $[M+H]^+$, 356 $[M+Na]^+$; HRMS: m/z Calculated value $C_{20}H_{19}N_3O_2Na$ = 356.1374, Observed value = 356.1383.

5.26 5-(3-(1H-indol-3-yl)propyl)-2-(2,4,6-trimethoxyphenyl)-1,3,4-oxadiazole (6s): Yellow solid, Yield : 50%; R_f = 0.30; m.p. semisolid; FTIR (KBr) ν (cm-1): 3289 (N-H), 1131(C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.18-2.24 (q, 2H, CH_2), 2.84-2.87 (t, 2H, *J* = 7.2 Hz, CH_2), 2.91-2.94 (t, 2H, *J* = 7.2 Hz, CH_2), 3.71 (s, 6H, $2CH_3$), 3.81 (s, 3H, CH_3), 6.51 (s, 2H, ArH), 6.95 (s, 1H, ArH), 7.04-7.07 (t, 1H, *J* = 7.2 Hz, ArH), 7.10-7.14 (t, 1H, *J* = 7.2 Hz, ArH), 7.30-7.31 (t, 1H, *J* = 7.2 Hz, ArH), 7.56-7.57 (d, 1H, *J* = 7.2 Hz, ArH), 8.88 (brs, 1H, -NH); ESI Mass (m/z) 394 $[M+H]^+$; HRMS: m/z Calculated value $C_{22}H_{24}N_3O_4$ = 394.1766, Observed value = 394.1753.

5.27 5-(3-(1H-indol-3-yl)ethyl)-2-(3-phenoxyphenyl)-1,3,4-oxadiazole (6t): White solid, Yield : 69%; R_f = 0.31; m.p. 75-78^{0}C; FTIR (KBr) ν (cm-1): 3221 (N-H), 1231 (C-O); ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 3.31 (s, 4H, $2CH_2$), 7.03-7.04 (m, 3H, ArH), 7.10-7.20 (m, 4H, ArH), 7.33-7.38 (q, 3H, *J* = 7.9 & 15.8 Hz, ArH), 7.41-7.44 (t, 1H, *J* = 7.9 Hz, ArH), 7.59 (s, 2H, ArH), 7.71-7.72 (d, 1H, ArH), 8.00 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.4, 24.5, 109.7, 110.6, 114.1, 116.2, 116.7, 117.4, 119.4, 119.7, 120.7, 122.3, 123.6, 125.1, 126.1, 128.3 129.1, 134.6, 154.3, 155.9, 161.8, 164.9. ESI Mass (m/z) 382 $[M+H]^+$; HRMS: m/z Calculated value $C_{24}H_{20}N_3O_2$ = 382.1550, Observed value = 382.1553.

5.28 5-(2-(1H-indol-3-yl)ethyl)-2-(4-(3,5,6-trichloropyridin-2-yloxy)-1,3,4-oxadiazole (6u): White solid, Yield : 82%; R_f = 0.34; m.p. 158-160^{0}C; FTIR (KBr) ν (cm-1): 3223 (N-H), 1063 (C-O) cm-1; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 3.29 (s, 4H, 2CH_2), 6.94-7.05 (m, 3H, ArH), 7.29-7.31 (t, 3H, ArH), 7.48-7.51 (d, 1H, *J* = 7.5 Hz, ArH), 8.02-8.05 (d, 2H, *J* = 8.3 Hz, ArH), 8.08 (s, 1H, ArH), 10.50 (brs, 1H, -NH); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 21.3, 25.4, 110.5, 111.6, 117.0, 117.2, 117.7, 120.1, 120.3, 120.5 (2C), 121.2, 123.4, 125.8, 127.2 (2C), 135.4, 140.2, 142.3, 154.3, 162.3, 162.7, 165.5; ESI Mass (m/z) 485 $[M+H]^+$; HRMS: m/z Calculated value $C_{23}H_{17}N_4O_2Cl_2$ = 507.0158, Observed value = 507.0158.

5.29 5-(3-(1H-indol-3-yl)propyl)-2-(4-(3,5,6-trichloropyridin-2-yloxy)phenyl)-1,3,4-xadiazole (6v): White solid, Yield : 84%; R_f = 0.34; m.p. 156-158^{0}C; FTIR (KBr) ν (cm-1): 3254 (N-H), 1082 (C-O); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 2.24-2.33 (m, 2H, CH_2), 2.91-2.98 (m, 4H, 2CH_2), 6.98 (s, 1H, ArH), 7.03-7.14 (m, 2H, ArH), 7.25-7.30 (m, 3H, ArH), 7.54-7.56 (d, 1H, *J* = 6.7 Hz, ArH), 7.86 (s, 2H, ArH), 7.98-8.01 (d, 2H, *J* =7.3 Hz, ArH); ^{13}C NMR (DMSO-d_6, 75MHz, ppm): δ 24.3, 25.0, 26.7, 111.2, 114.7, 118.1, 118.7, 119.2, 121.1, 121.5, 121.90, 121.97, 124.5, 127.2, 128.3 136.3, 141.0, 143.7, 155.3, 155.4, 164.0, 166.9; ESI Mass (m/z) 499 $[M+H]^+$; HRMS: m/z Calculated value $C_{24}H_{17}N_4O_2NaCl_3$ = 521.0314, Observed value = 521.0303.

5.31 In vivo Anti-inflammatory activity:

In the present investigation, *in vivo* anti-inflammatory activity of the synthesized compounds were tested by carrageenan induced rat paw edema method **[**22-24] using Ibuprofen as standard. Young adult male Wistar rats weighing 150-200 g were used, which were acclimatized to the laboratory conditions and maintained on standard laboratory rat feed and clean water. Rats were fasted for 12 h prior to the experiment, while allowing free access to water throughout the experiment. The rats were divided into the groups of 6 animals each. A mark was made on the hind paw (left) just beyond the tibio-tarsal junction, so that every time the paw was dipped in the mercury column up to the marked level to ensure constant paw volume.

To each group, except the control group, test and standard drugs were administered orally in a dose of 100 mg/kg of the body weight (0.5 ml of 20 mg/ml drug solutions per 100 g body weight). The control group received an equivalent amount of vehicle (1% carboxy methyl

cellulose (CMC)). After one hour, carrageenan (0.1 ml, 1% w/v solution in saline) was injected into the dorsal region of sub-plantar surface of hind paw of control and drug treated groups subcutaneously with the help of 26G needle. The paw volumes were measured using the plethysmometer at 0 h, 0.5 h, 1 h, 2 h, 3 h and 4 h after the carrageenan challenge.

Inflammation was expressed as the change in paw edema volume.

Edema = $T_t - T_0$ Where T_0 = volume at 0 h, T_t = Volume at t h.

The average value of edema was calculated by taking the average of each group at different hours. Percentage inhibition of edema was calculated for each group with respect to the control group.

Percentage inhibition = $(V_0 - V_t)/V_0 \times 100$. Where, V0 = Volume of the paw of control at time't'

Data are expressed as the mean ± SEM, significant difference between the control and the treated groups was obtained using Student's t-test and *P* values. The difference in results was considered significant when $P < 0.001$, percentage reduction in edema formation was calculated for each compound. The results revealed that of all the tested compounds exhibited significant inhibition of edema (% protection 68.8, 67.4, 78.3, 62.0, 61.0, 70.9 respectively) comparable to that of standard Ibuprofen (% protection 72.8).

5.32 Evaluation of the anti-proliferative activity against A549, HeLa, HepG2 and DU145 cell lines:

(a) Materials and Methods

All cell lines used in this study were purchased from the American Type Culture Collection (ATCC, USA). A549, HepG2, and HeLa cells were grown in Dulbecco's modified Eagle's medium containing fetal bovine serum (FBS, 10%) in a humidified atmosphere of 5% CO_2 at 37^0C. DU145 cells were cultured in Eagle's minimal essential medium containing nonessential amino acids, sodium pyruvate (1 mm), bovine insulin (10 $mgmL^{-1}$), and FBS (10%). Cells were trypsinized when sub-confluent from T75 flasks/90 mm dishes, and seeded in 12-well or 6-well plates at a concentration of $2.5x10^5 cellsmL^{-1}$ in complete medium, and treated with the

test compounds at the desired concentrations for 48 h, then harvested as required. For immunohistochemistry experiments, wells were seeded on cover slips in a 6-well plate [25].

(b) Anti-proliferative Assay

The synthesized compounds were evaluated for their in vitro cytotoxicity. A protocol of 48 h continuous drug exposure was used, and a 3-(4,5 dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) protein assay was used to estimate cell viability or growth. The cell lines were grown in the respective media containing FBS (10%) and 2µmL-glutamine and were inoculated into 96-well micro-titer plates in 200 µL aliquots at plating densities depending on the doubling time of individual cell lines. The micro-titer plates were incubated at 37^0C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of the experimental drugs. Aliquots of 2 µL of the drug dilutions were added to the appropriate micro-titer wells already containing 200 µL of cells, resulting in the required final drug concentrations. For each compound, four concentrations (1, 10, and 100 µm) were evaluated and each was performed in triplicate wells. Plates were incubated further for 48 h, and the assay was terminated by the addition of MTT (5%, 10 µL) and incubated for 60 min at $37\ ^0$C. Later, the plates were air dried. Bound stain was subsequently eluted with DMSO (100 µL), and the absorbance was read on an ELISA plate reader at a wavelength of 560 nm. Percent growth was calculated on a plate-by-plate basis for test wells relative to control wells. The above determinations were repeated three times. The inhibitory effects of the compounds on cell growth were analyzed by generating dose-response curves as a plot of the percentage of surviving cells versus drug concentration. Sensitivity of the cancer cells to the drug treatment was expressed in terms of IC_{50} value, a value defined as the concentration of compound that produced a 50% reduction relative to the control absorbance. The percentage of cells killed was obtained from the formula:

$$\text{Percentage cells killed} = \frac{\text{100-mean OD sample}}{\text{mean OD at day 0}} \times 100$$

Acknowledgement

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Captions:

Fig. 1 Some of the biologically active 3-sustituted indole representatives.

Fig. 2 Graphical representation of the percentage protection of of 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles against edema formation.

Scheme 1: Synthesis of compounds **6(a-v)**, Reagents and conditions: (a) H_2SO_4, reflux, 3-4h (b) $NH_2NH_2.H_2O$ (99%), EtOH, reflux, 5-6h. (c) EtOH, reflux, 4-5h. (d) DIB, DCM, rt, 4-6h.

Table 1 Synthesized 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

Table 2 Anti-inflammatory activity of 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

Table 3 Percentage protection against edema formation

Table 4 Anti-proliferative activity profile of synthesized 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

Table 1 Synthesized 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

Entry	Product	n	R	M. P (^{0}C)
1	**6a**	3	C_6H_5	122-124
2	**6b**	3	1-$C_{10}H_7$	143-146
3	**6c**	2	2-C_5H_4N	190-193
4	**6d**	2	3-C_5H_4N	140-142
5	**6e**	2	2-C_4H_3S	132-134
6	**6f**	3	2-C_4H_3S	114-116
7	**6g**	2	4-NO_2-C_6H_4	160-163
8	**6h**	3	4-F-C_6H_4	153-157
9	**6i**	2	4-Cl-C_6H_4	160-161
10	**6j**	3	4-Cl-C_6H_4	149-150
11	**6k**	2	3-Cl-C_6H_4	117-118
12	**6l**	3	3-Cl-C_6H_4	116-117
13	**6m**	2	3-Br-C_6H_4	112-114
14	**6n**	2	2,6-$C_6H_3Cl_2$	154-156
15	**6o**	3	3,4-$C_6H_3Cl_2$	134-136
16	**6p**	2	4-CH_3-C_6H_4	163-165
17	**6q**	2	4-OCH_3-C_6H_4	154-157
18	**6r**	3	4-OCH_3-C_6H_4	139-142
19	**6s**	3	2,4,6-OCH_3-C_6H_2	Hygroscopic
20	**6t**	2	4-OC_6H_5-C_6H_4	75-78
21	**6u**	2	4-(3,5,6-OC_5HNCl_3)-C_6H_4	136-138
22	**6v**	3	4-(3,5,6-OC_5HNCl_3)-C_6H_4	156-158

Table 2 Anti-inflammatory activity of 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

Treatment	Dose (mg/kg)	Mean paw edema volume in mL±SEM[ab]				
		0.5 h	1 h	2 h	3 h	4 h
Control	100	0.17 ± 0.004	0.36 ± 0.003	0.73 ± 0.003	0.93 ± 0.004	0.91 ± 0.003
6f	100	0.13 ± 0.011	0.27 ± 0.003	0.39 ± 0.008	0.29 ± 0.004	0.48 ± 0.012
6h	100	0.15 ± 0.018	0.21 ± 0.008	0.25 ± 0.018	0.30 ± 0.013	0.39 ± 0.008
6i	100	0.18 ± 0.011	0.19 ± 0.024	0.21 ± 0.008	0.20 ± 0.018	0.40 ± 0.012
6j	100	0.14 ± 0.008	0.19 ± 0.008	0.35 ± 0.022	0.37 ± 0.011	0.40 ± 0.022
6k	100	0.15 ± 0.022	0.25 ± 0.022	0.42 ± 0.011	0.35 ± 0.018	0.50 ± 0.013
6p	100	0.16 ± 0.008	0.20 ± 0.018	0.15 ± 0.018	0.39 ± 0.008	0.60 ± 0.018
6q	100	0.15 ± 0.013	0.17 ± 0.011	0.30 ± 0.022	0.36 ± 0.008	0.38 ± 0.01
6r	100	0.15 ± 0.013	0.20 ± 0.018	0.24 ± 0.008	0.40 ± 0.013	0.40 ± 0.013
6t	100	0.14 ± 0.003	0.24 ± 0.004	0.38 ± 0.005	0.31 ± 0.00	0.35 ± 0.003
Standard (Ibuprofen)	100	0.12 ± 0.011	0.22 ± 0.011	0.32 ± 0.011	0.25 ± 0.018	0.33 ± 0.011

[a]All values are represented as means ± SE 'standard error'. [b]All data significantly different from control value at $p < 0.001$

Table 3 Percentage protection against edema formation

Treatment	Dose (mg/kg)	% protection against edema formation				
		0.5 h	1 h	2 h	3 h	4 h
6f	100	23.5	25.0	46.5	**68.8**	47.2
6h	100	25.0	44.7	65.3	**67.4**	56. 7
6i	100	10.0	50.0	70.8	**78.3**	56.9
6j	100	30.0	50.0	51.4	59.8	55.6
6k	100	25.0	34.2	41. 7	**62.0**	44.4
6p	100	20.0	47.4	79.2	57.6	33.3
6q	100	25.0	55.3	58.3	**61.0**	57.8
6r	100	25.0	47.4	66.7	56.5	55.6
6t	100	23.5	47.2	64.3	**70.9**	53.8
Standard (Ibuprofen)	100	40.0	42.1	55.5	**72.8**	63.3

Table 4 Anti-proliferative activity profiles of synthesized 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles.

Compound	IC_{50}±SD values against cancer cell lines (μM)			
	A549	**HeLa**	**HepG2**	**DU145**
6a	22 ± 4.2	36 ± 5.5	40 ± 5.7	42 ± 6.5
6b	27 ± 3.9	33 ± 5.2	101 ± 9.1	44 ± 3.8
6c	41 ± 5.0	98 ± 8.9	37 ± 5.1	50 ± 4.5
6d	31 ± 4.6	81 ± 7.9	32 ± 4.2	60 ± 6.1
6e	34 ± 5.2	25 ± 2.9	24 ± 3.1	42 ± 3.5
6f	31 ± 5.1	37 ± 4.8	181 ± 12.2	45 ± 3.9
6g	36 ± 6.5	71 ± 8.1	62 ± 7.5	68 ± 6.9
6h	34 ± 5.2	28 ± 3.2	40 ± 4.5	73 ± 6.9
6i	29 ± 4.2	23 ± 4.6	21 ± 2.8	43 ± 4
6j	38 ± 7.1	27 ± 3.6	41 ± 3.8	68 ± 8.8
6l	64 ± 8.6	36 ± 5.2	28 ± 3.2	52 ± 4.6
6m	25 ± 3.5	44 ± 6.5	33 ± 4.5	37 ± 3.8
6n	97 ± 12.2	47 ± 5.9	102 ± 10.9	80 ± 8.6
6o	20 ± 2.5	29 ± 3.8	36 ± 6.2	61 ± 6.7
6p	30 ± 4.6	24 ± 3.2	24 ± 2.2	38 ± 4.6
6q	23 ± 2.8	22 ± 2.9	29 ± 2.6	32 ± 5.1
6s	31 ± 4.6	26 ± 3.7	366 ± 16.5	31 ± 5.2
6t	23 ± 3.9	25 ± 4.1	40 ± 3.9	43 ± 4.1
6u	30 ± 5.2	27 ± 4.2	40 ± 5.1	44 ± 4.5
6v	40 ± 4.8	28 ± 4.9	91 ± 9.5	56 ± 6.9

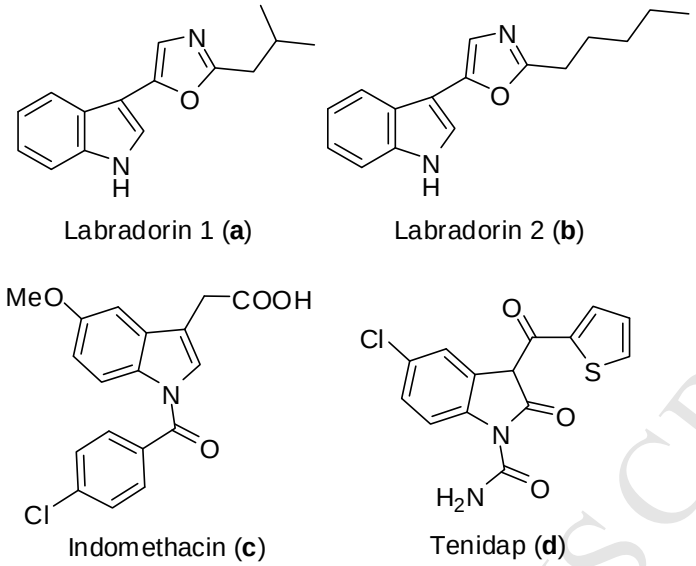


Figure 1. Some of the biologically active 3-sustituted indole representatives.

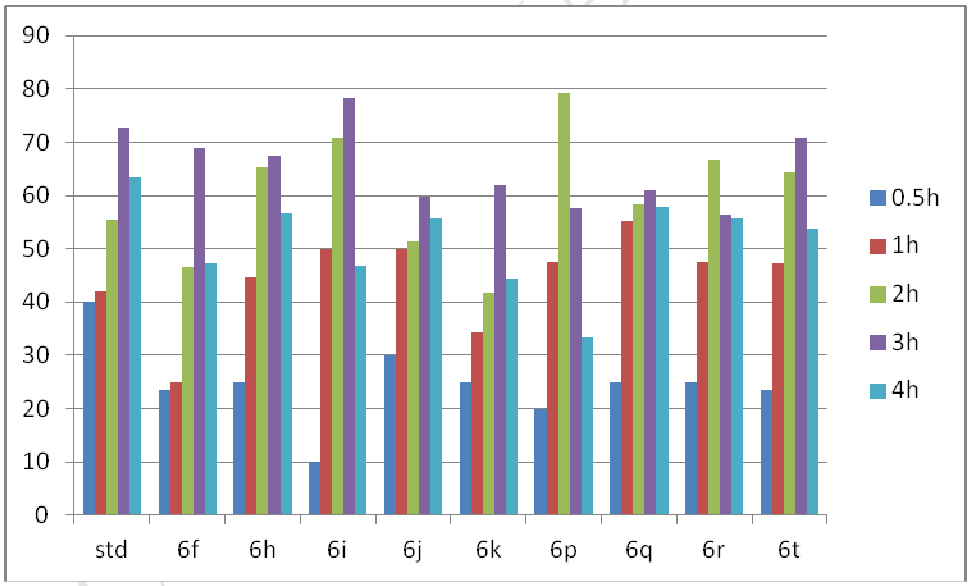
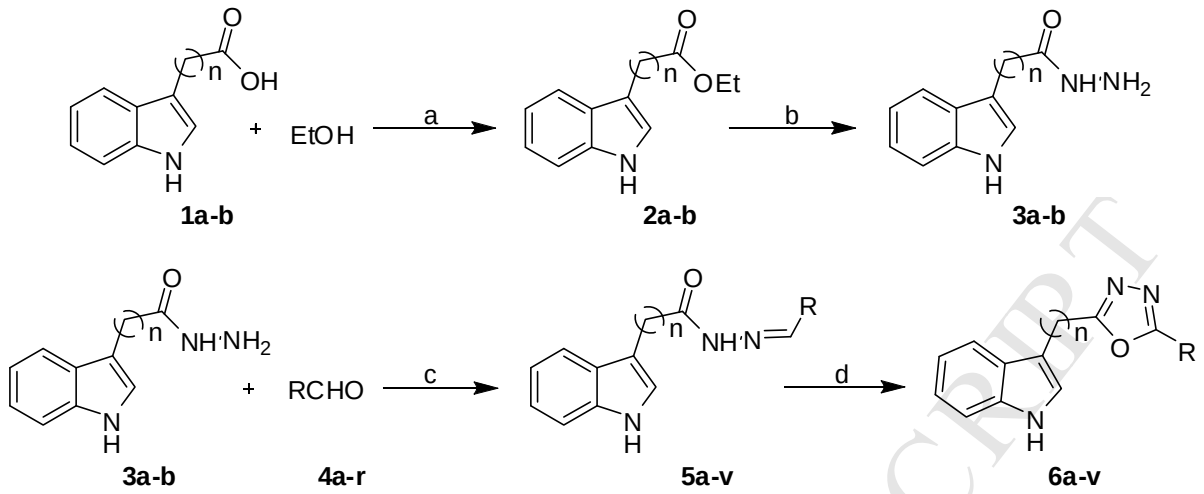


Figure 2. Graphical representation of the percentage protection of 5-(3-(indolyl)alkyl)-2-(substituted)-1,3,4-oxadiazoles against edema formation.



Scheme 1. Synthesis of compounds **6(a-v),** Reagents and conditions: (a) H_2SO_4, reflux, 3-4h (b) $NH_2NH_2.H_2O$ (99%), EtOH, reflux, 5-6h. (c) EtOH, reflux, 4-5h. (d) DIB, DCM, rt, 4-6h.

Supplementary Material:

Synthesis and biological screening of 5-(alkyl (1H-indol-3-yl))-2-(substituted)-1,3,4-oxadiazoles as anti-proliferative and anti-inflammatory agents

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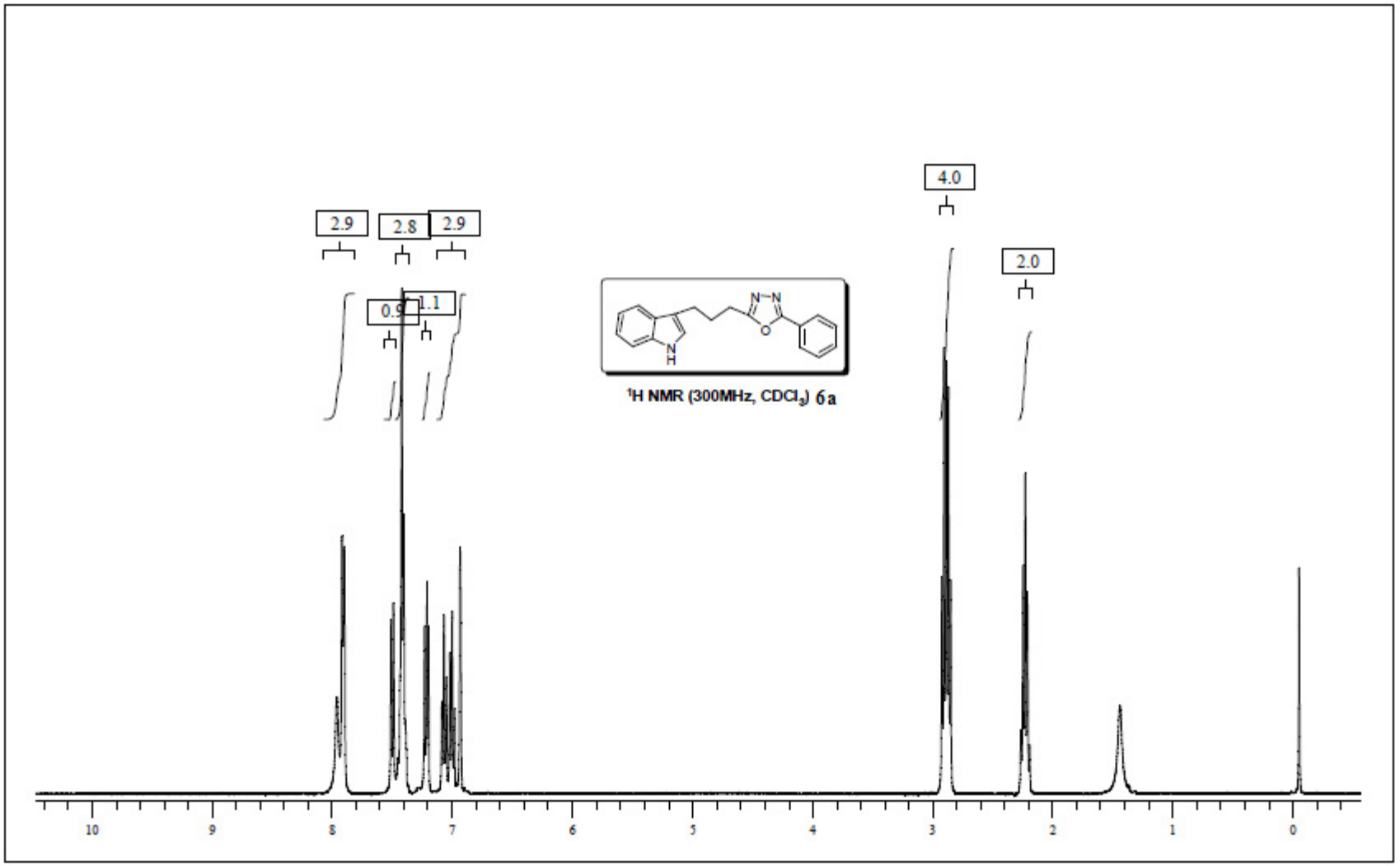
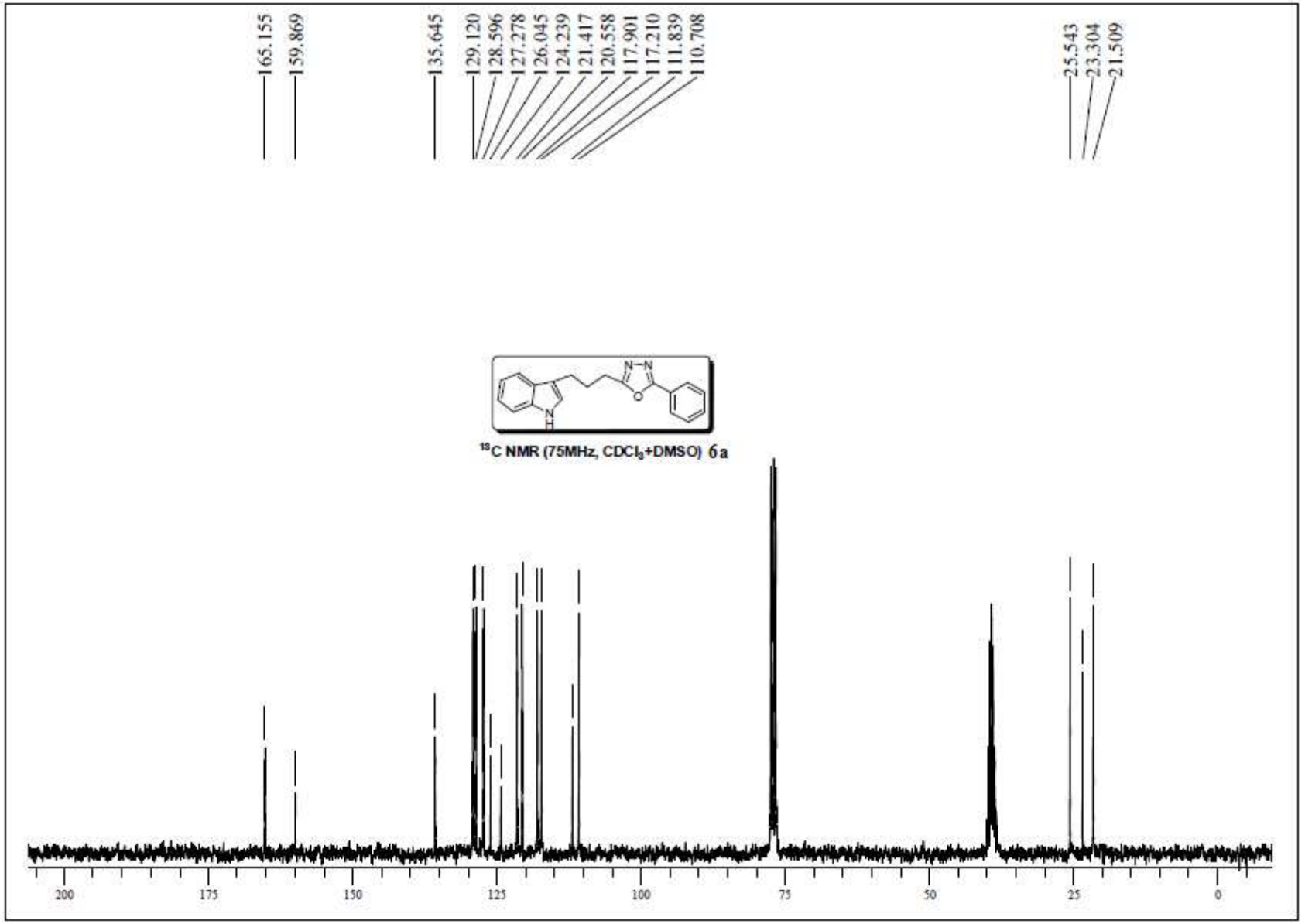
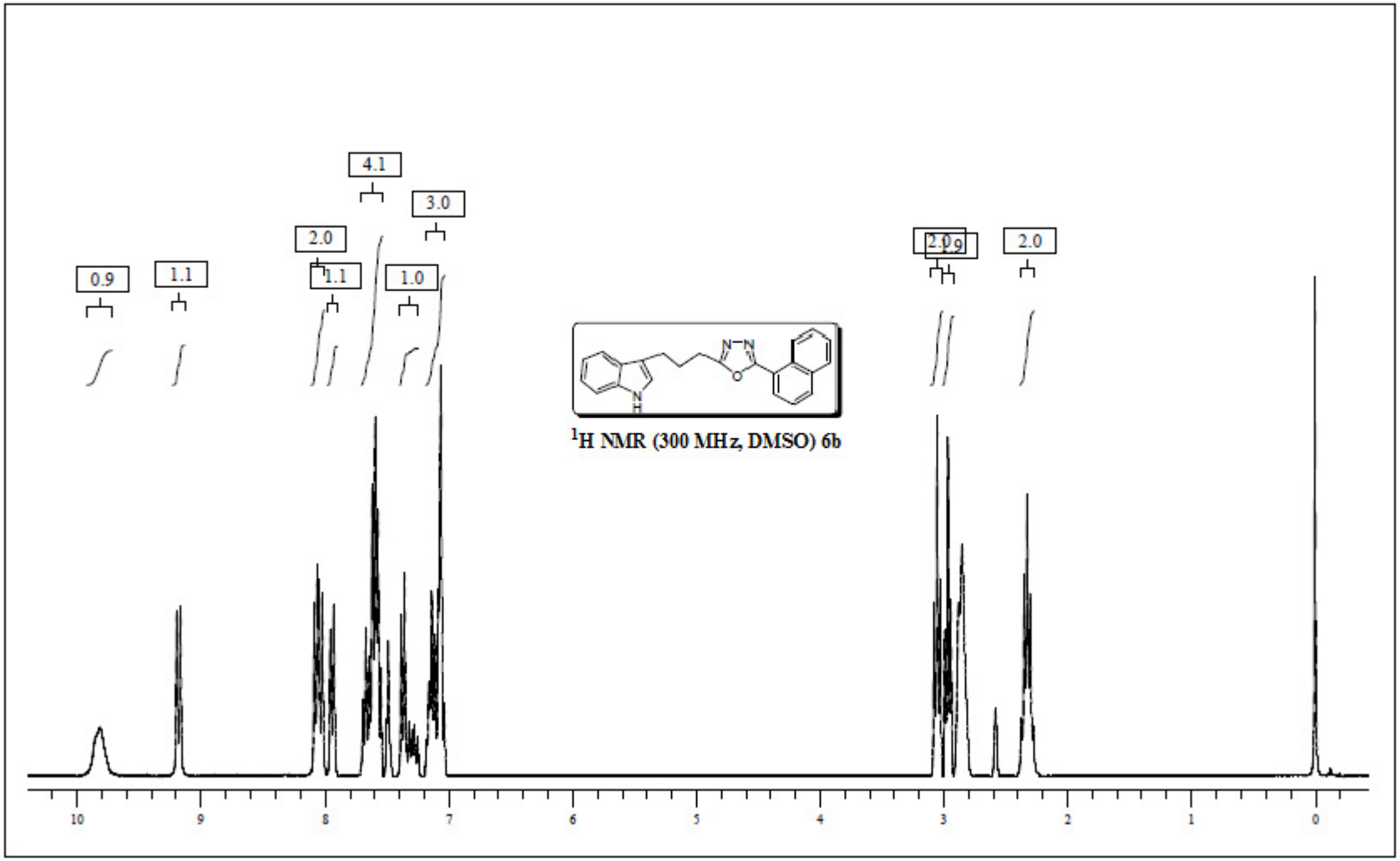


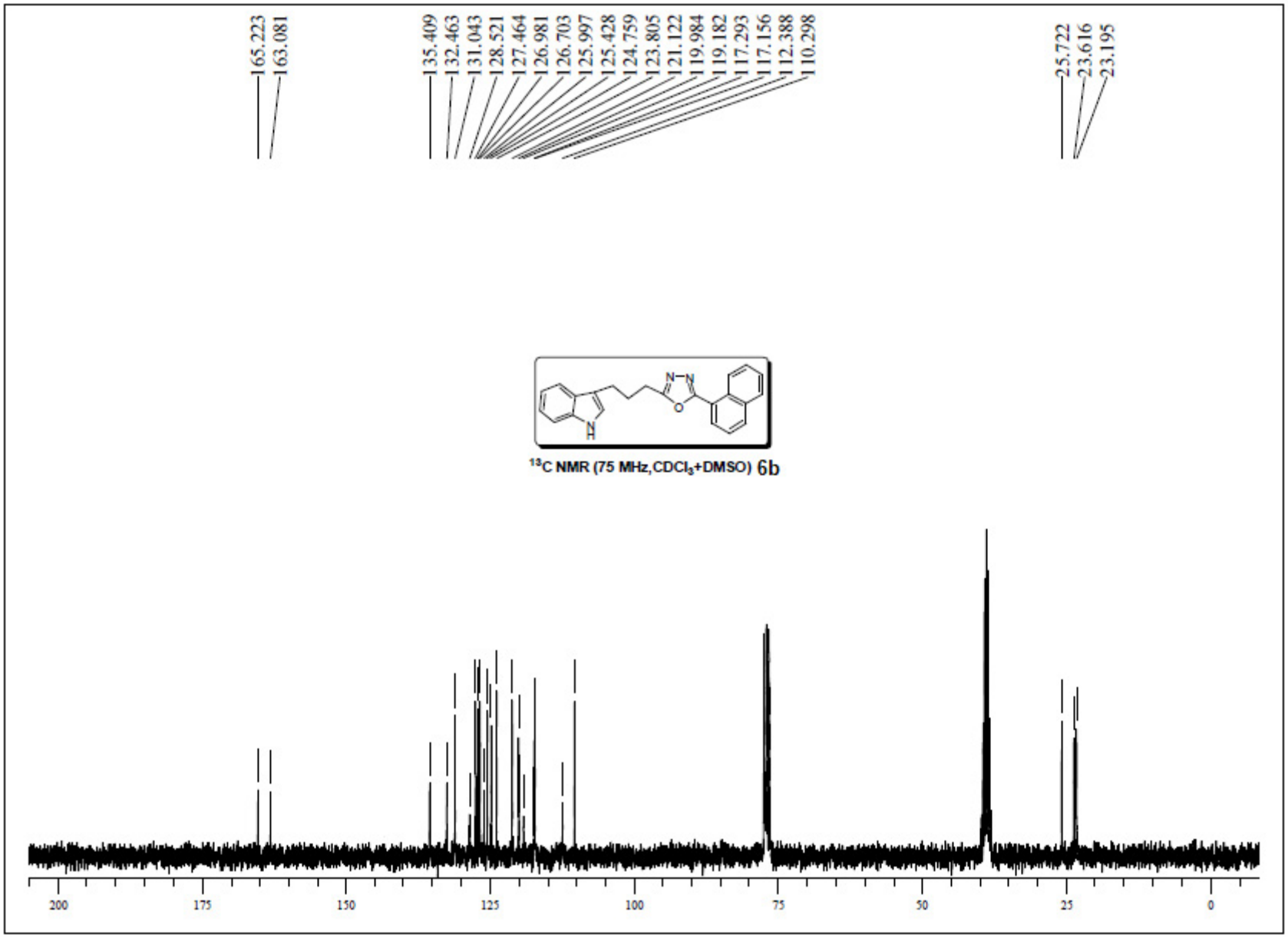
^{1}H NMR (300MHz, $CDCl_3$) **6a**



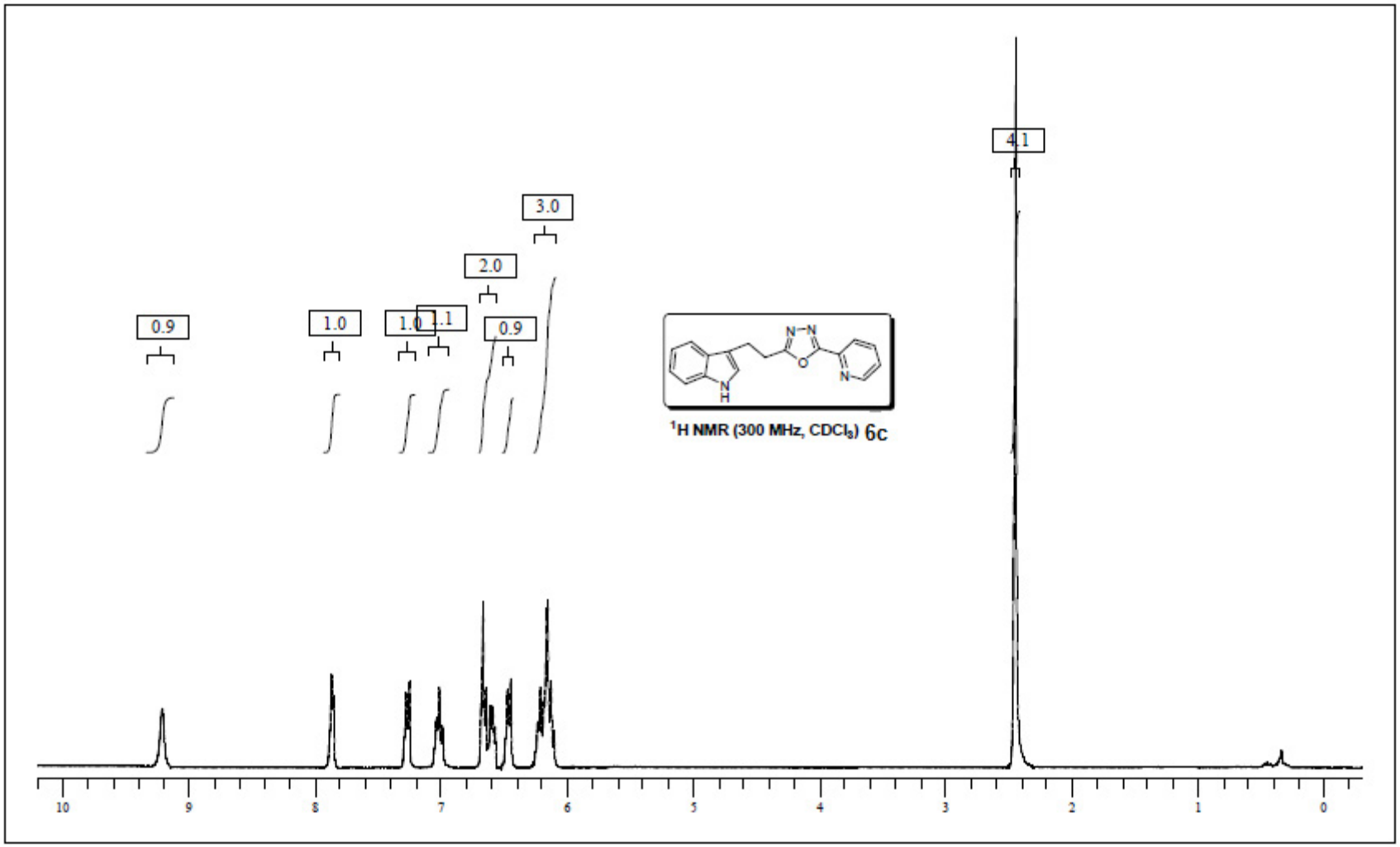
^{13}C NMR (75MHz, $CDCl_3$+DMSO) **6a**



^{1}H NMR (300 MHz, DMSO) 6b



^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6b**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1.0
1.1
2.0
0.9
3.0
4.1
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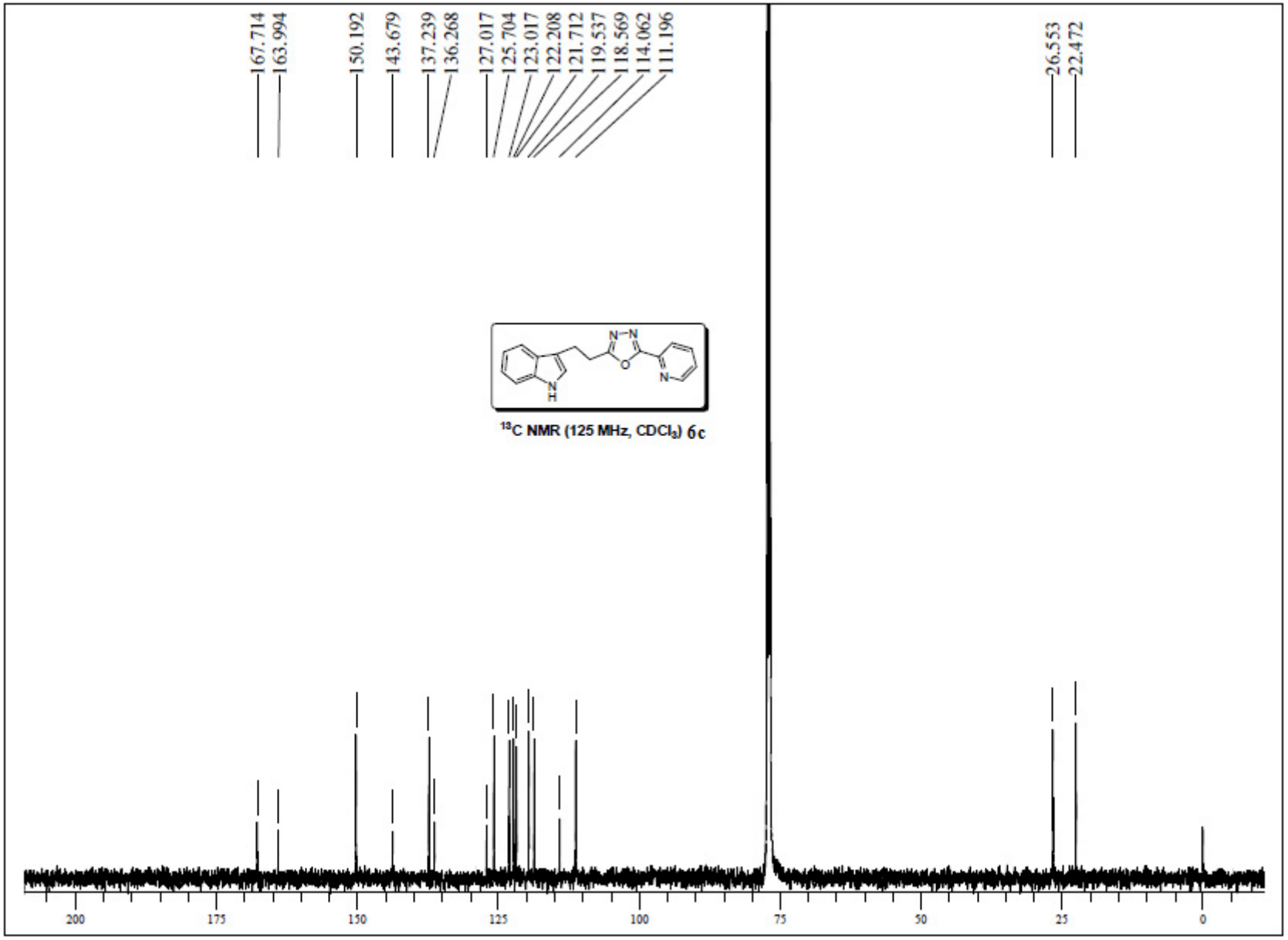
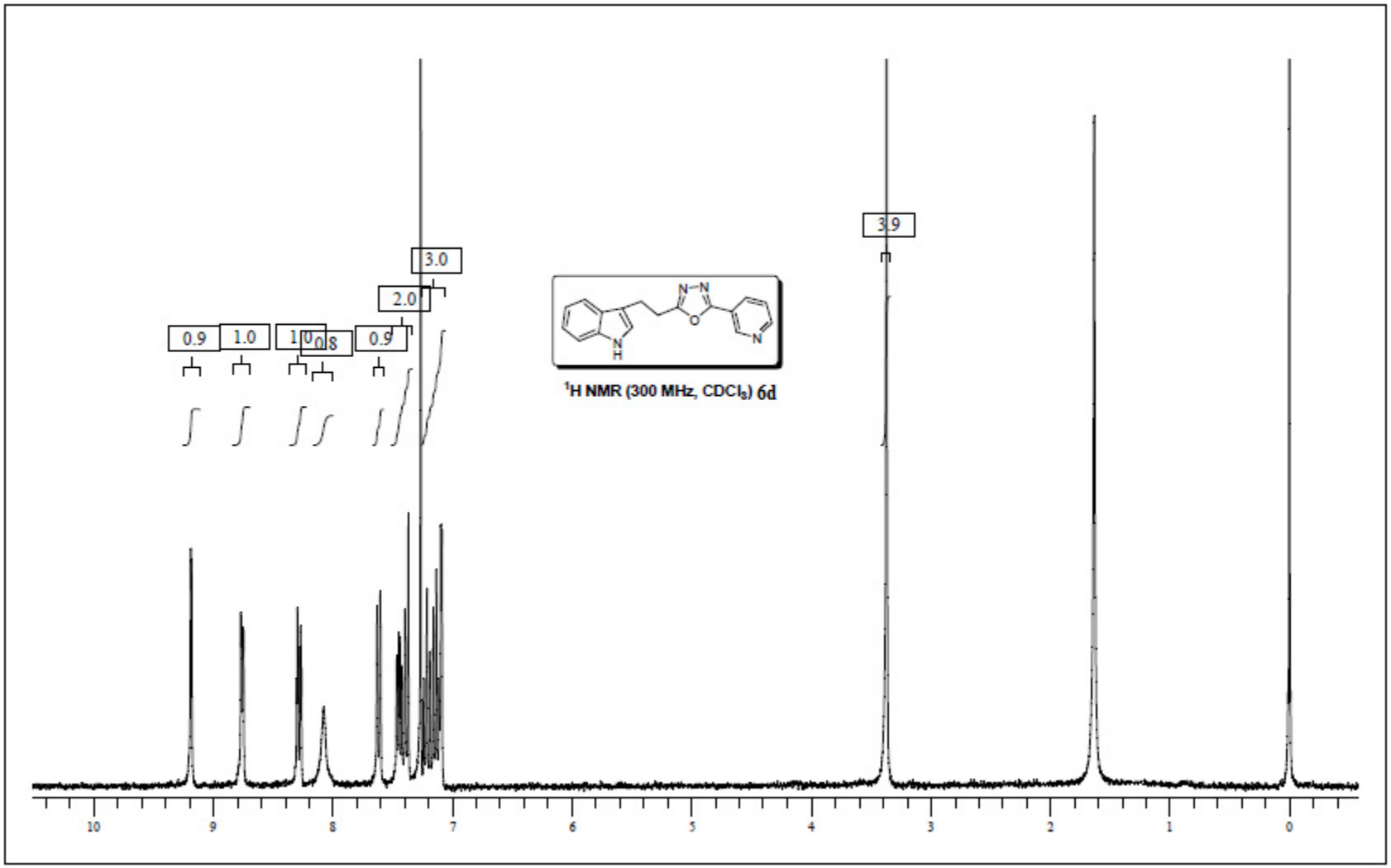
10
9
8
7
6
5
4
3
2
1
0



^{13}C NMR (125 MHz, $CDCl_3$) **6c**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^{1}H NMR (300 MHz, CDCl$_3$) 6d
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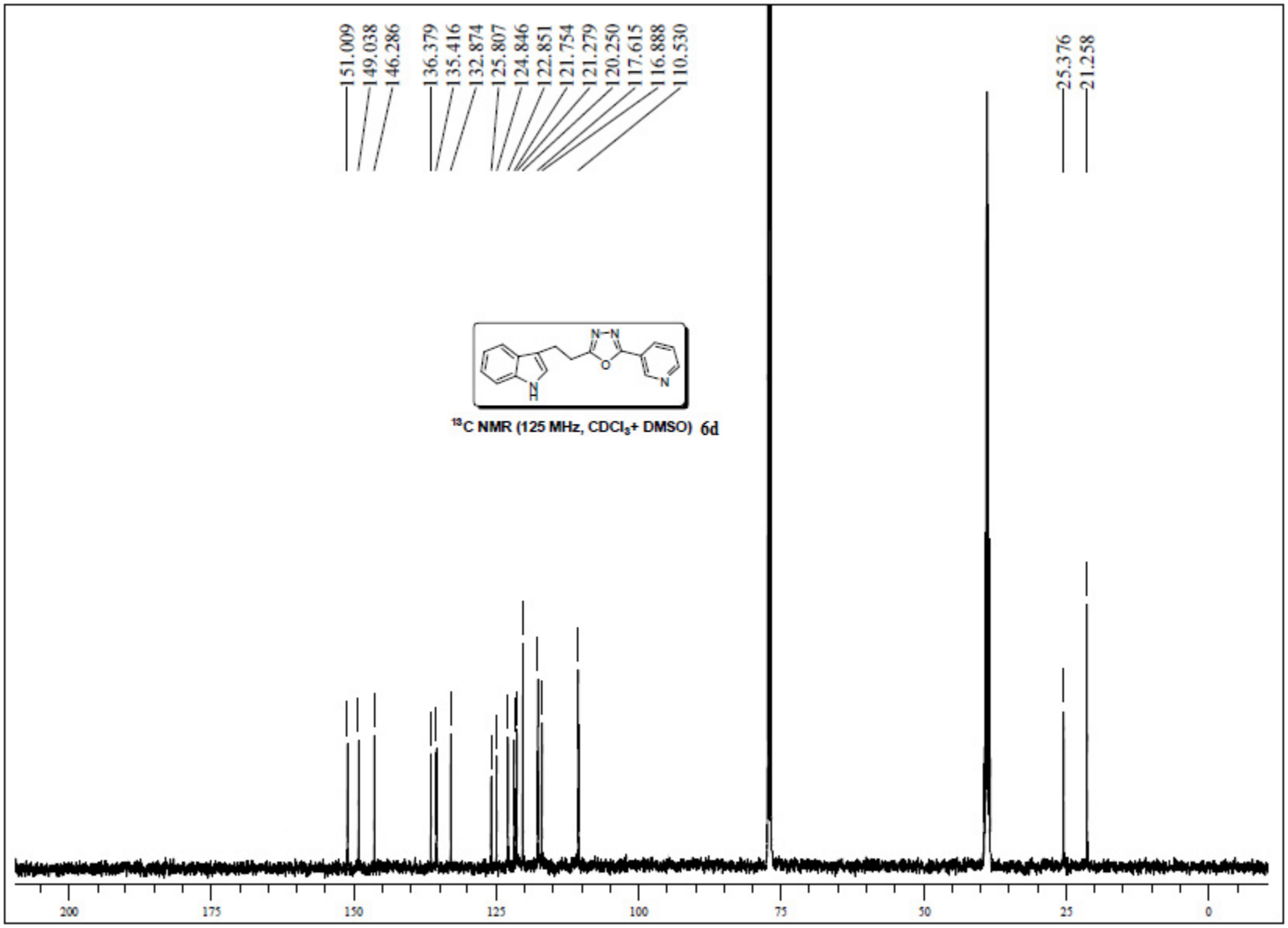
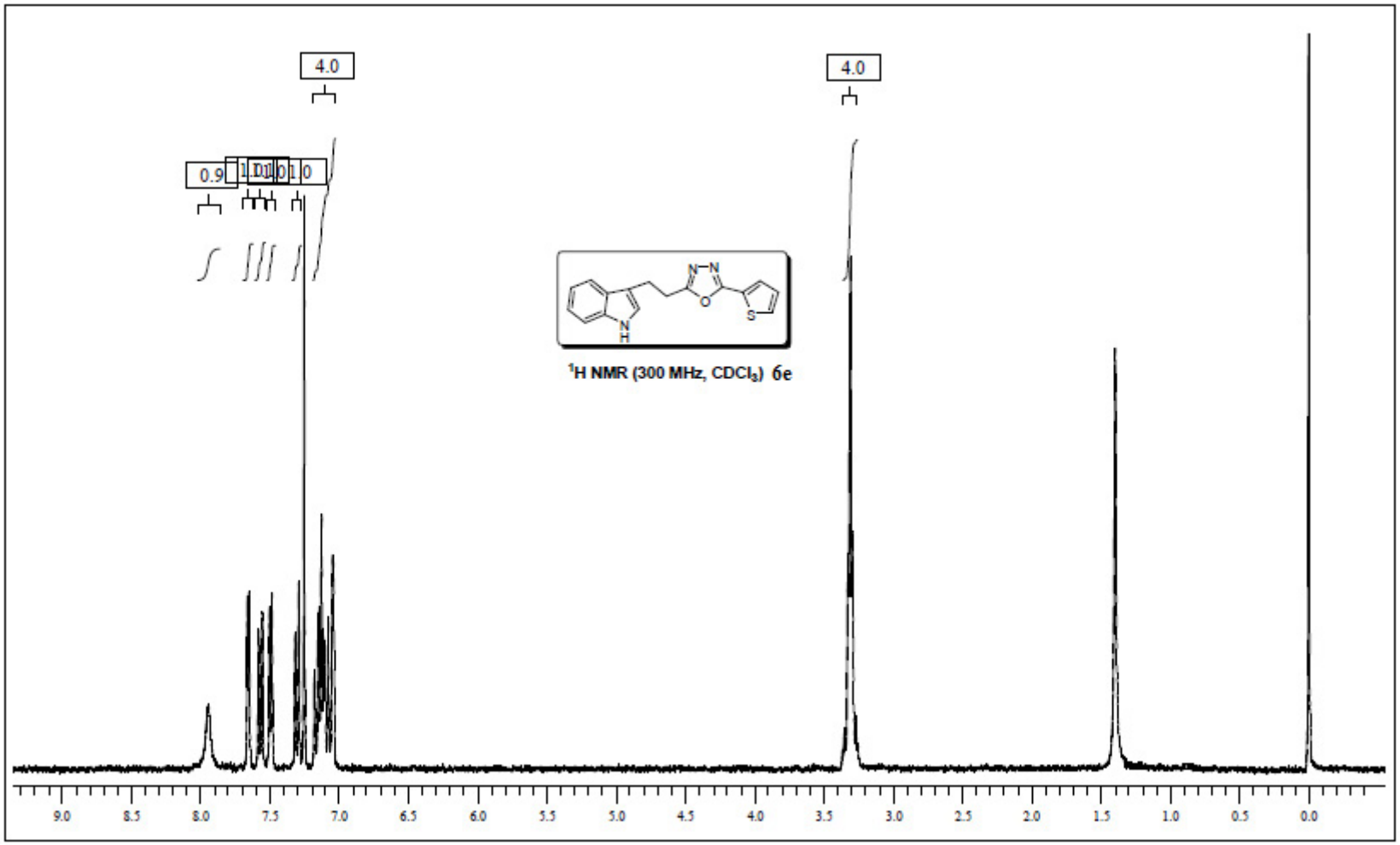


^{13}C NMR (125 MHz, $CDCl_3$+ DMSO) **6d**



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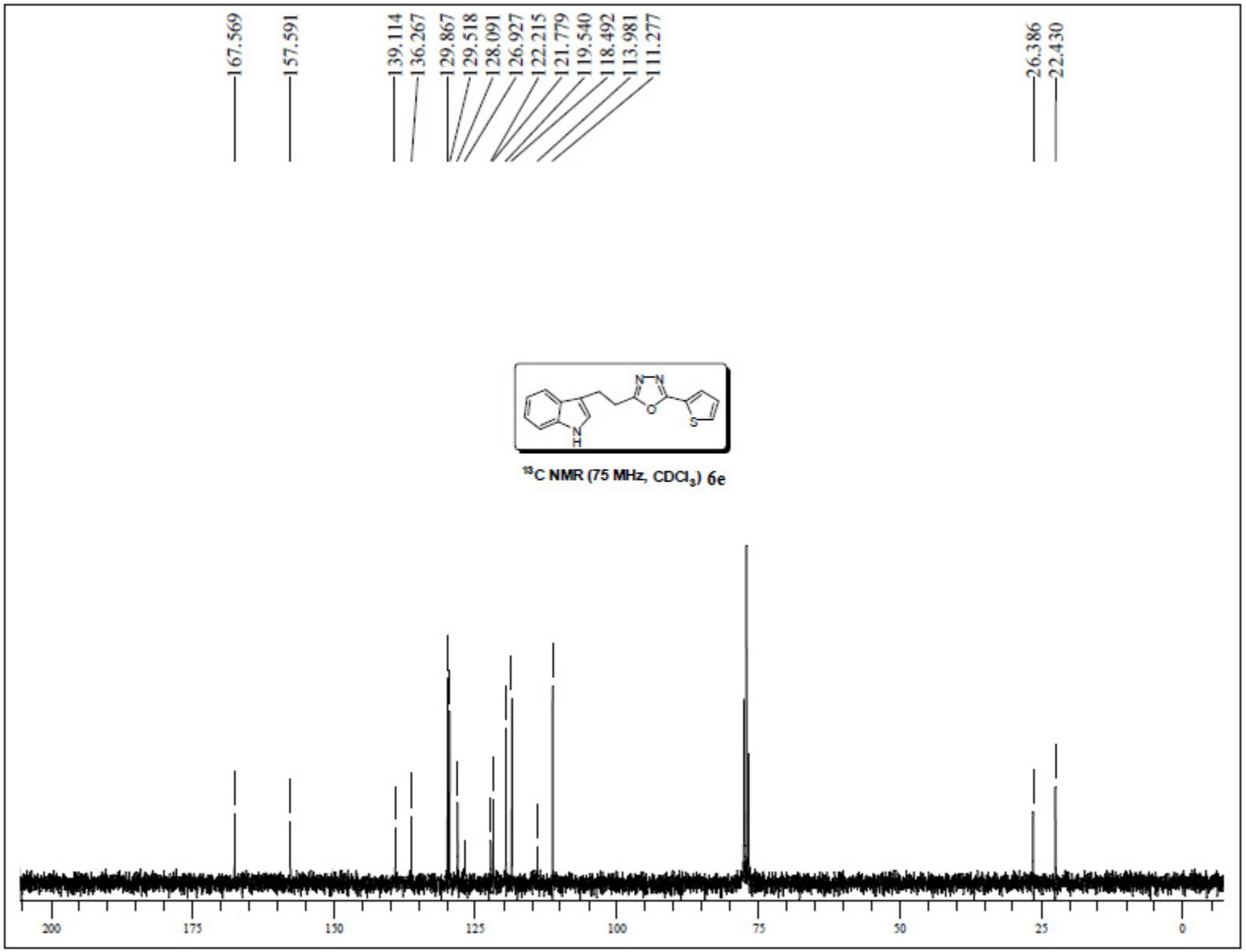
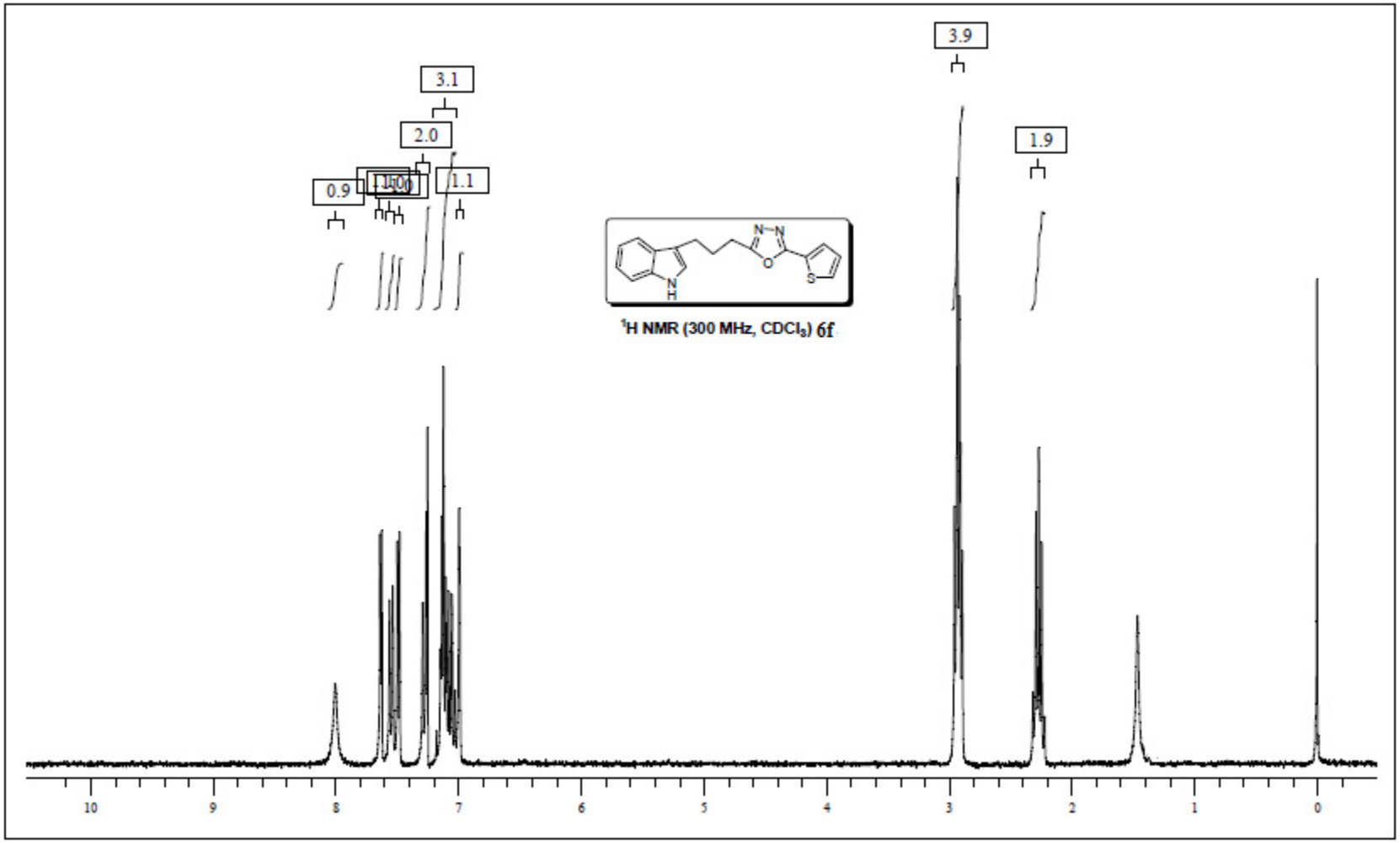
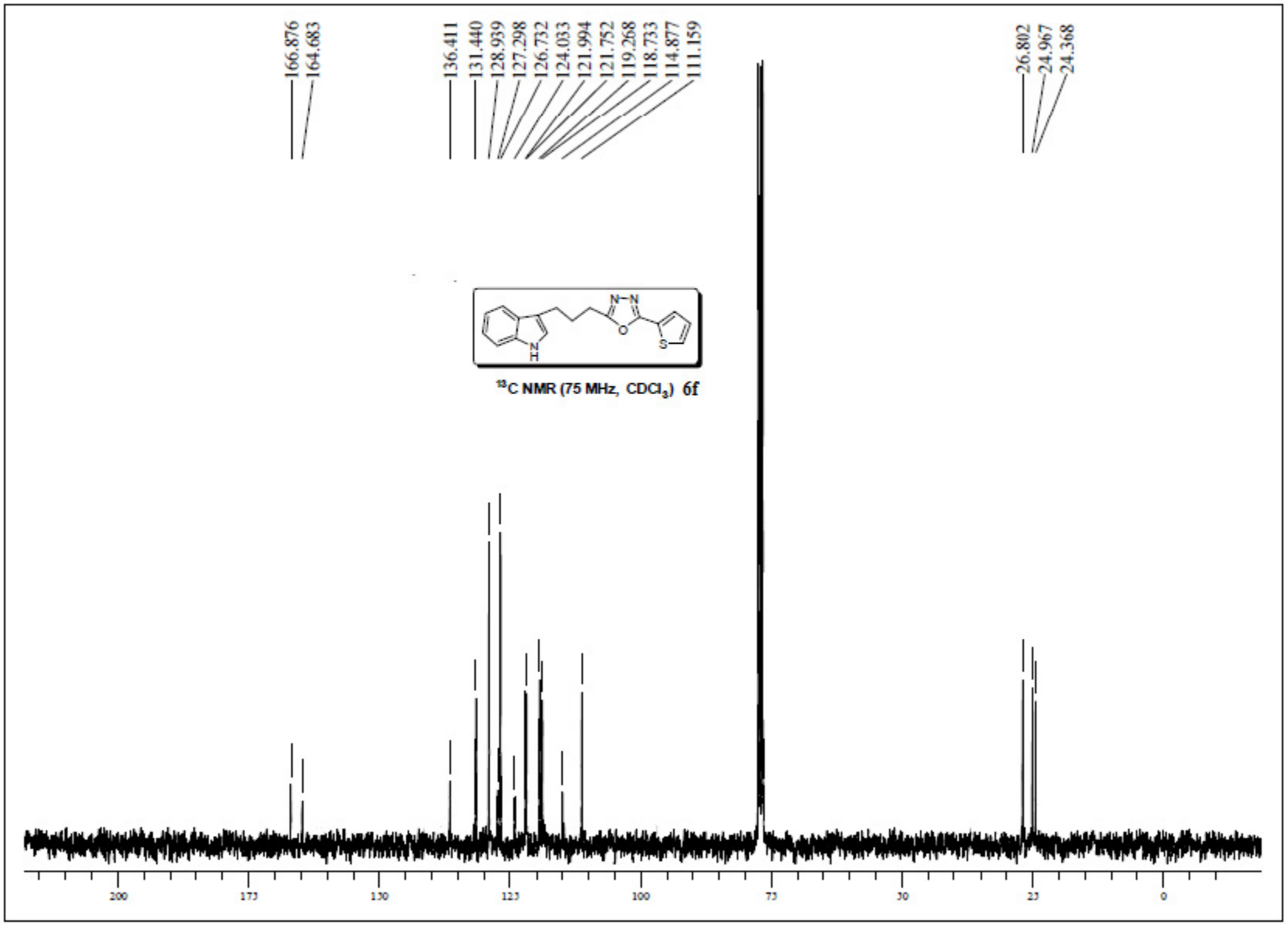


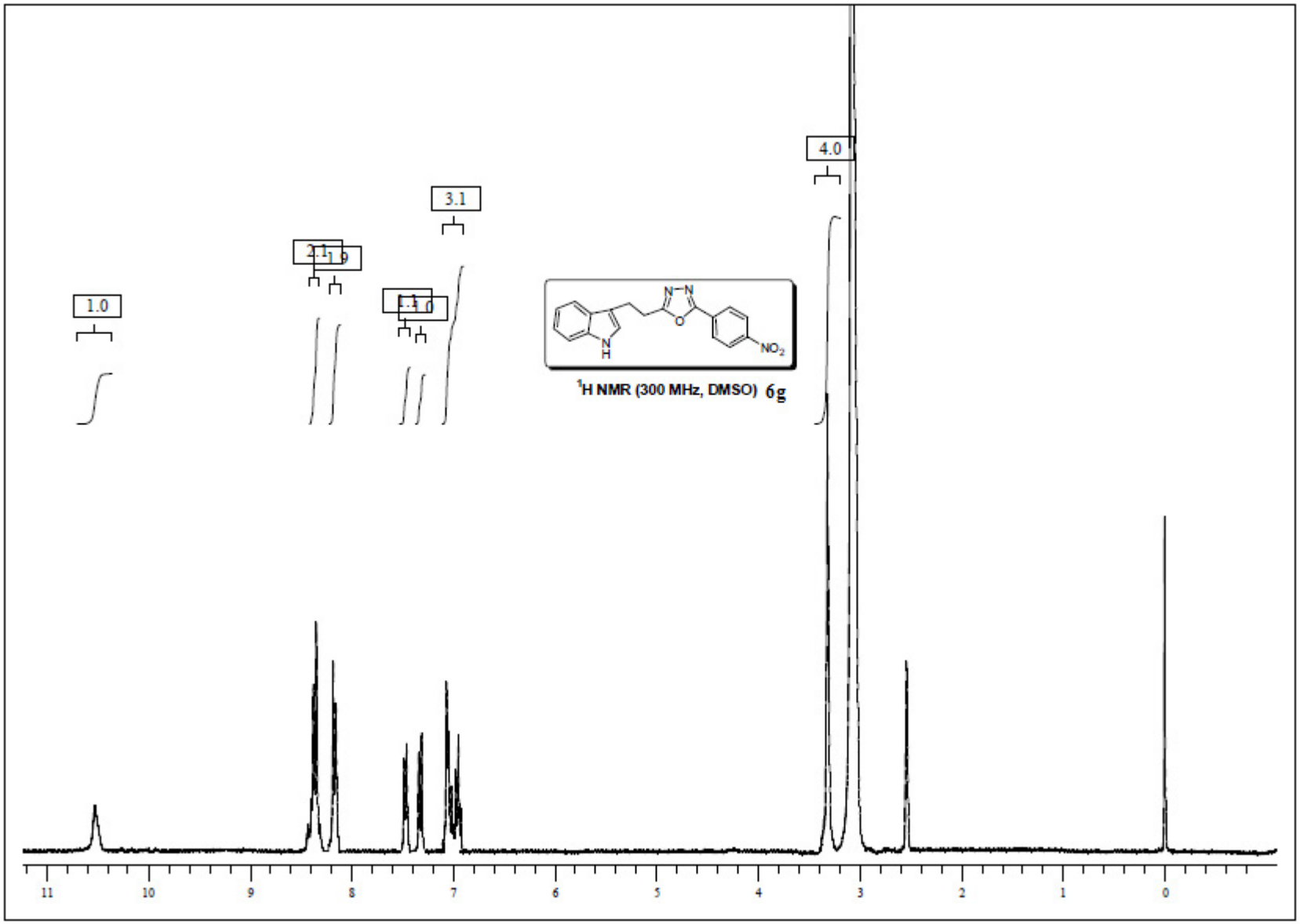
^{13}C NMR (75 MHz, $CDCl_3$) **6e**



^{1}H NMR (300 MHz, $CDCl_3$) **6f**



^{13}C NMR (75 MHz, $CDCl_3$) **6f**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2.1
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1.1
1.0
3.1
4.0
^{1}H NMR (300 MHz, DMSO) 6g
11
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5
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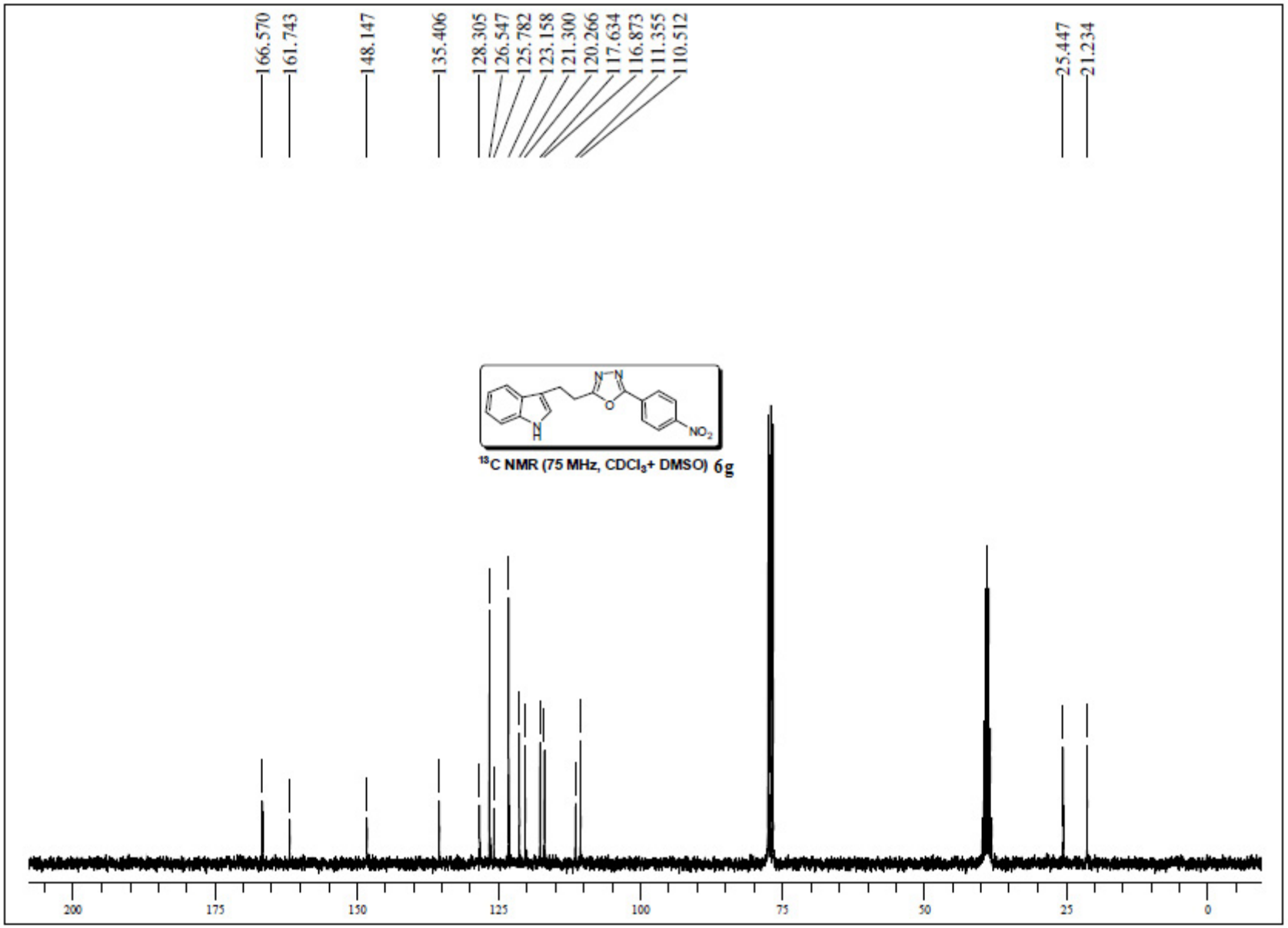
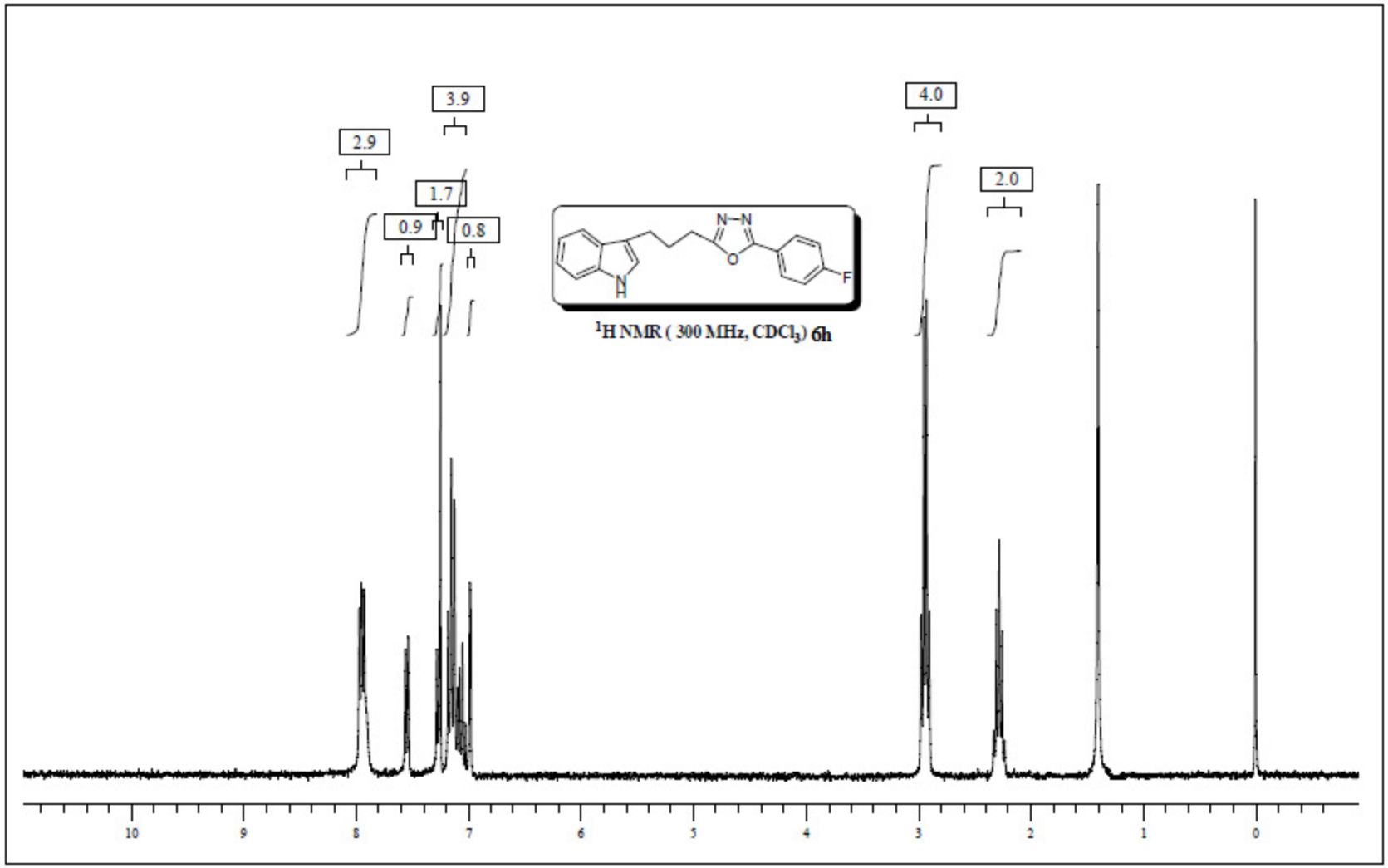
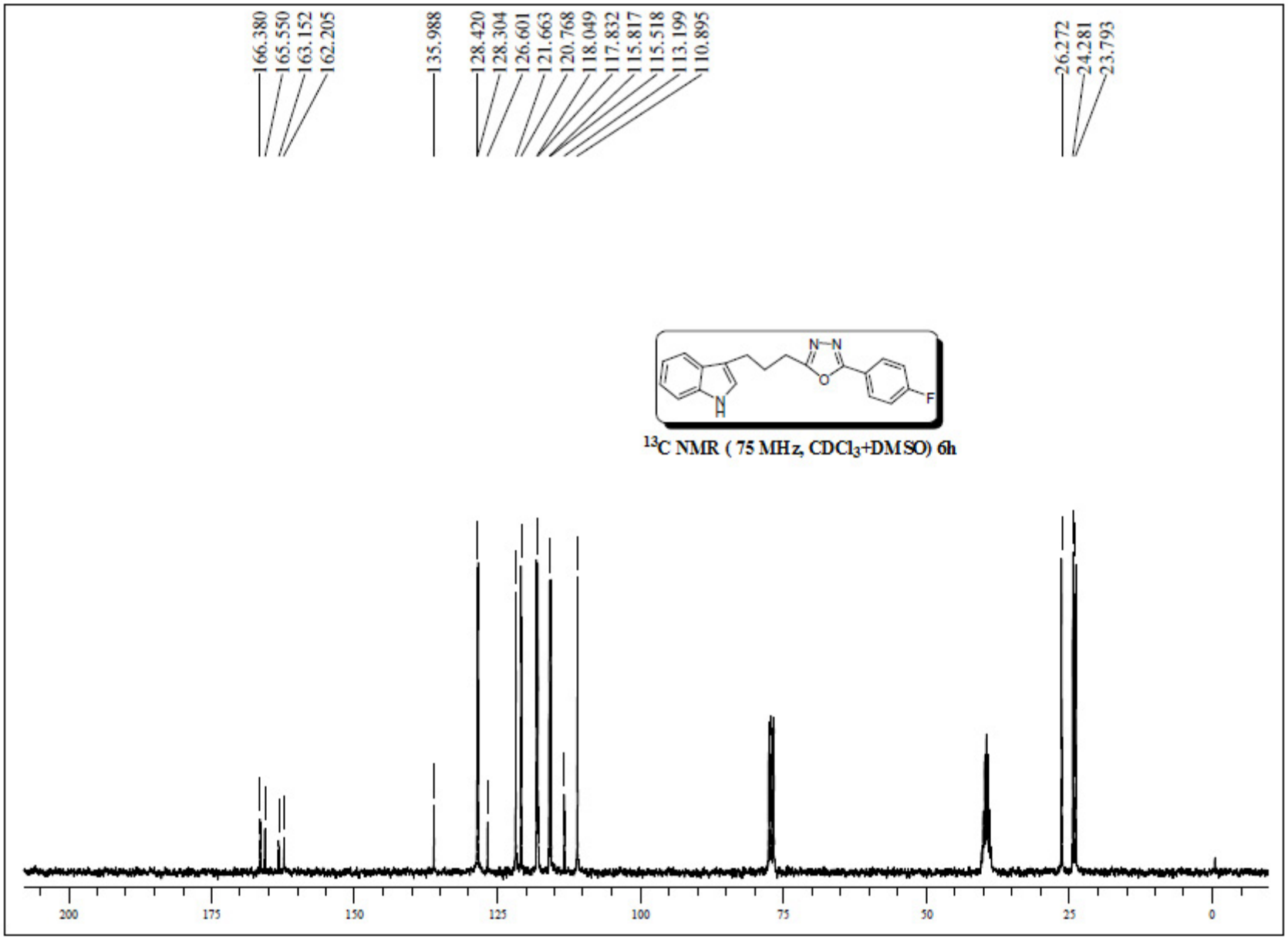
3
2
1
0



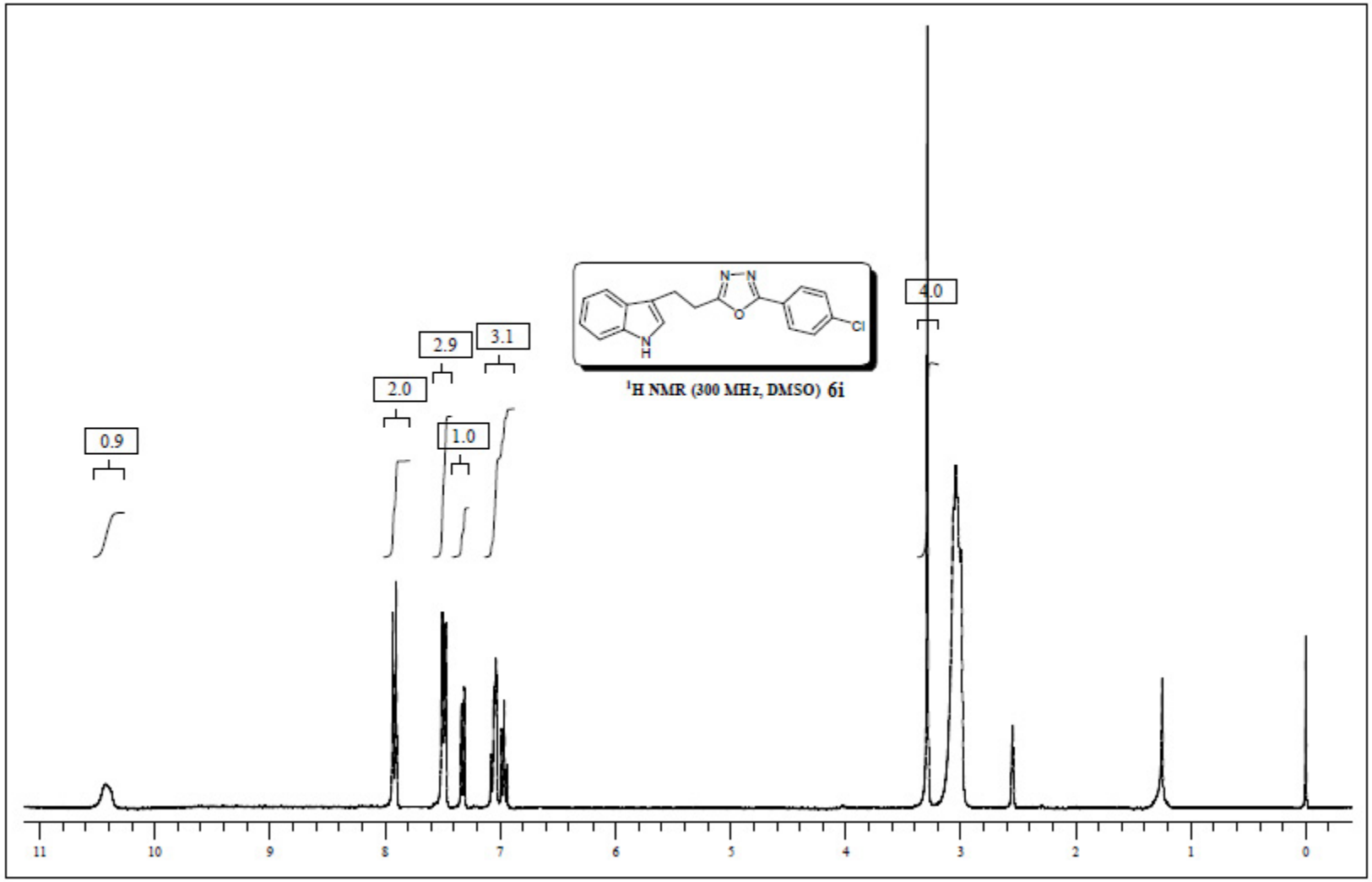
^{13}C NMR (75 MHz, $CDCl_3$+ DMSO) **6g**



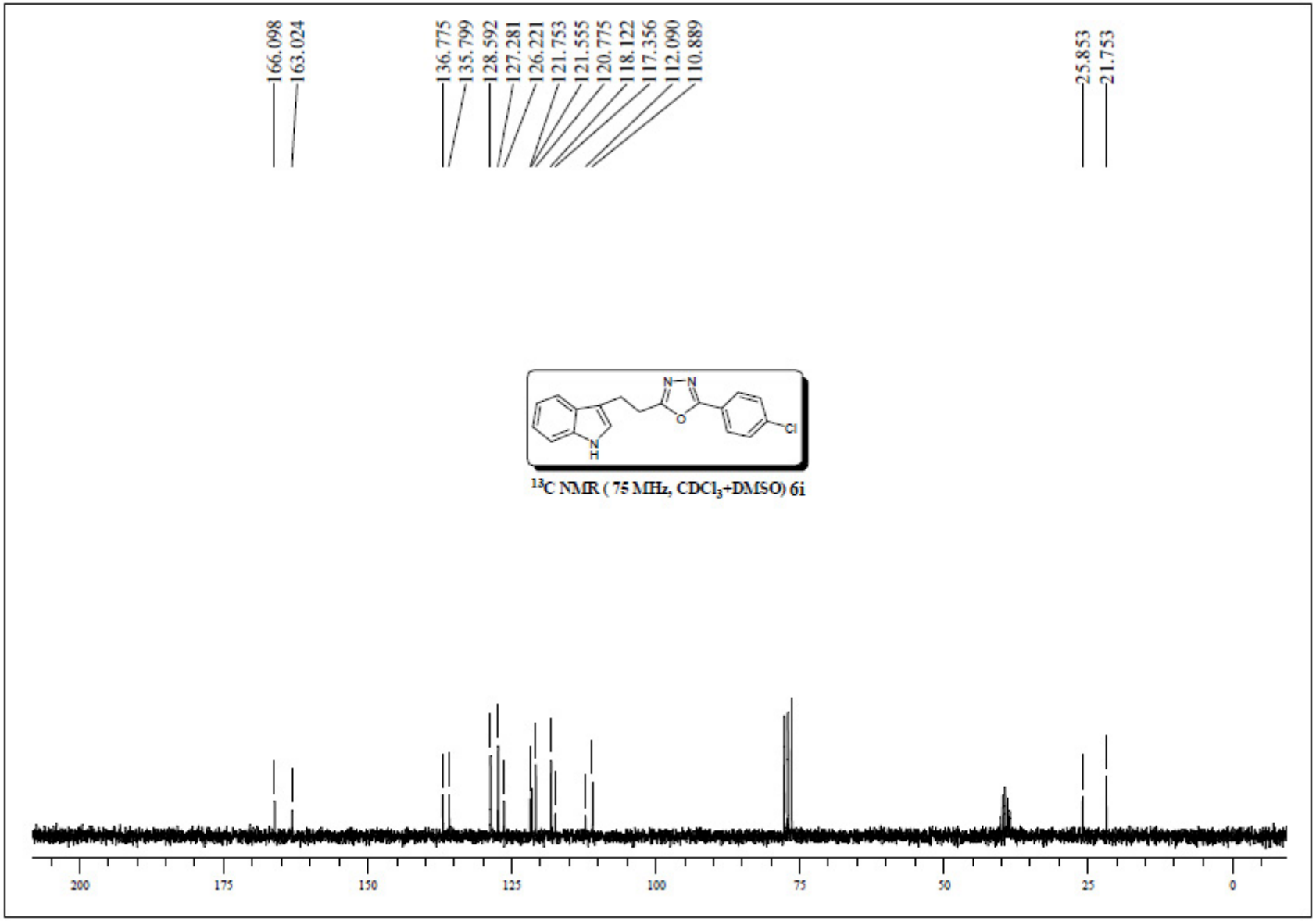
^{1}H NMR (300 MHz, $CDCl_3$) **6h**



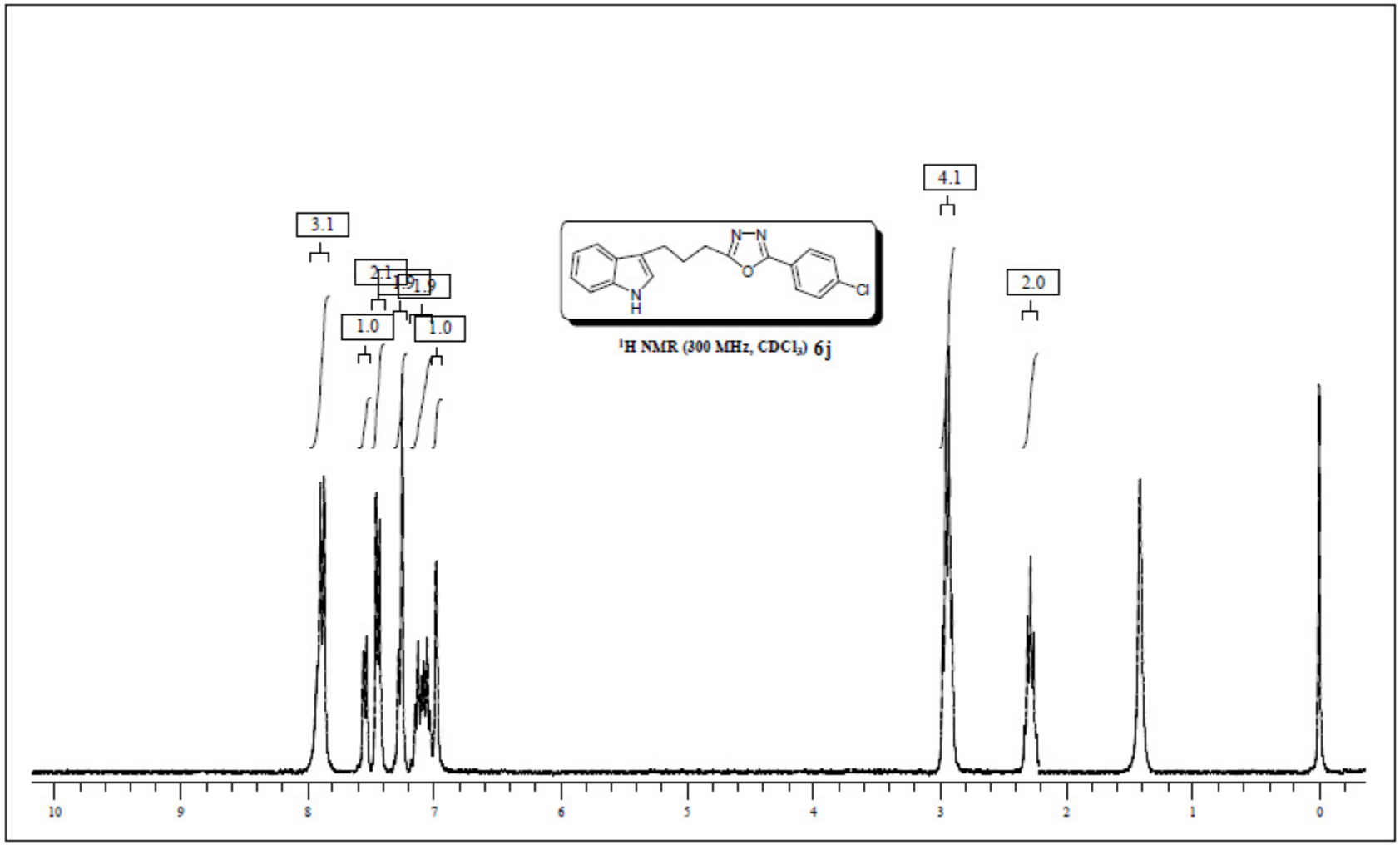
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) 6h



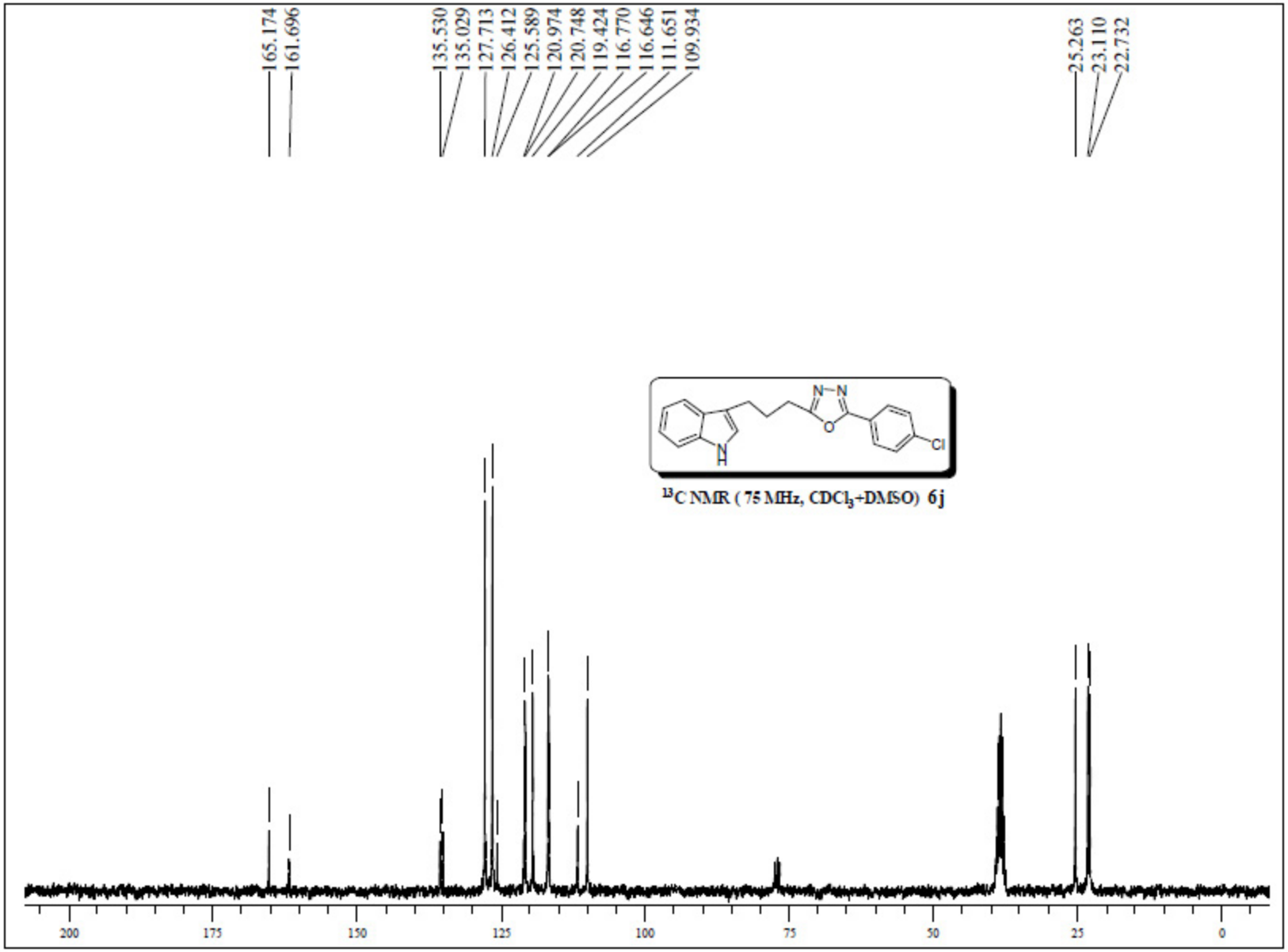
^{1}H NMR (300 MHz, DMSO) **6i**



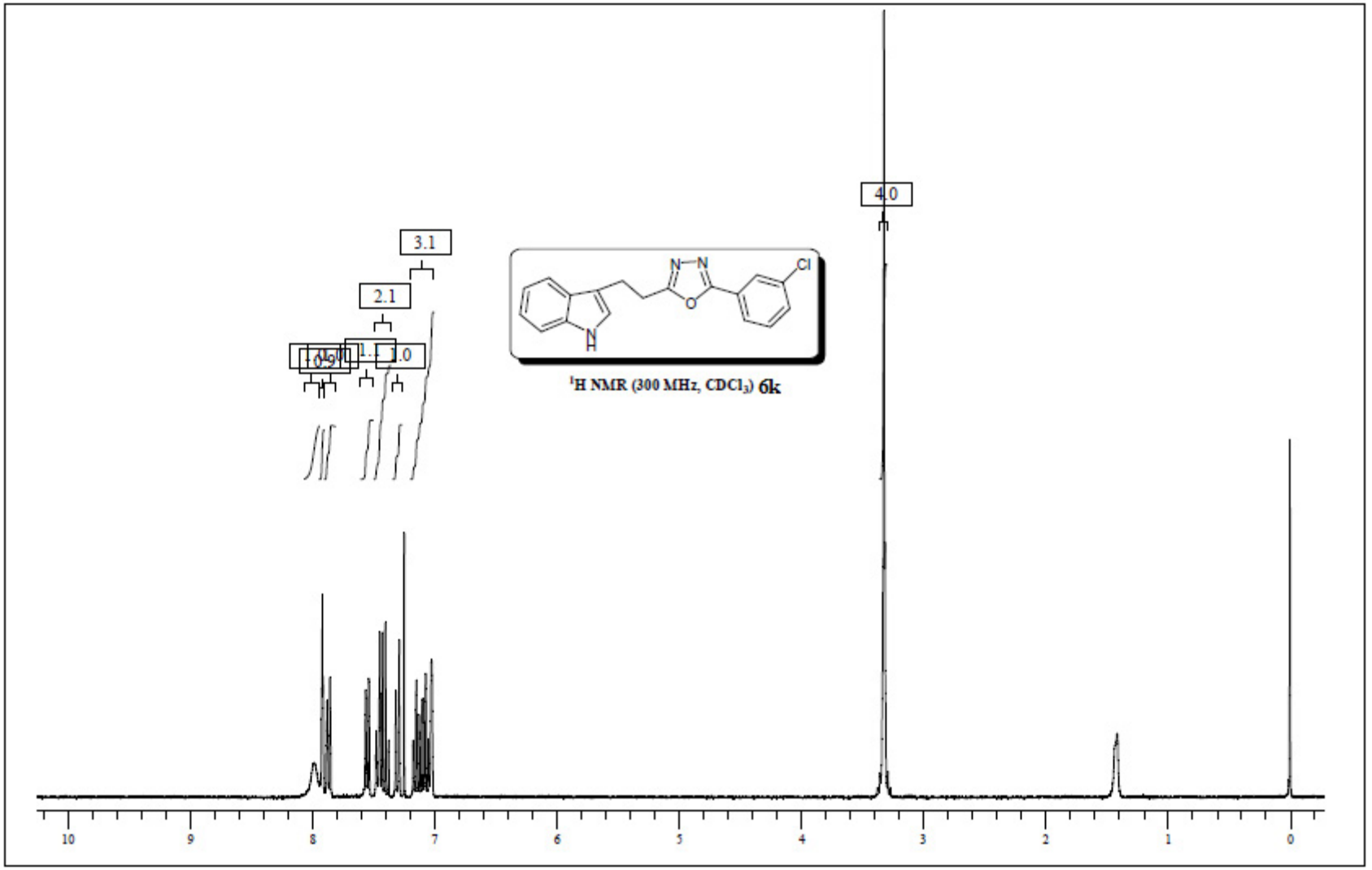
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6i**



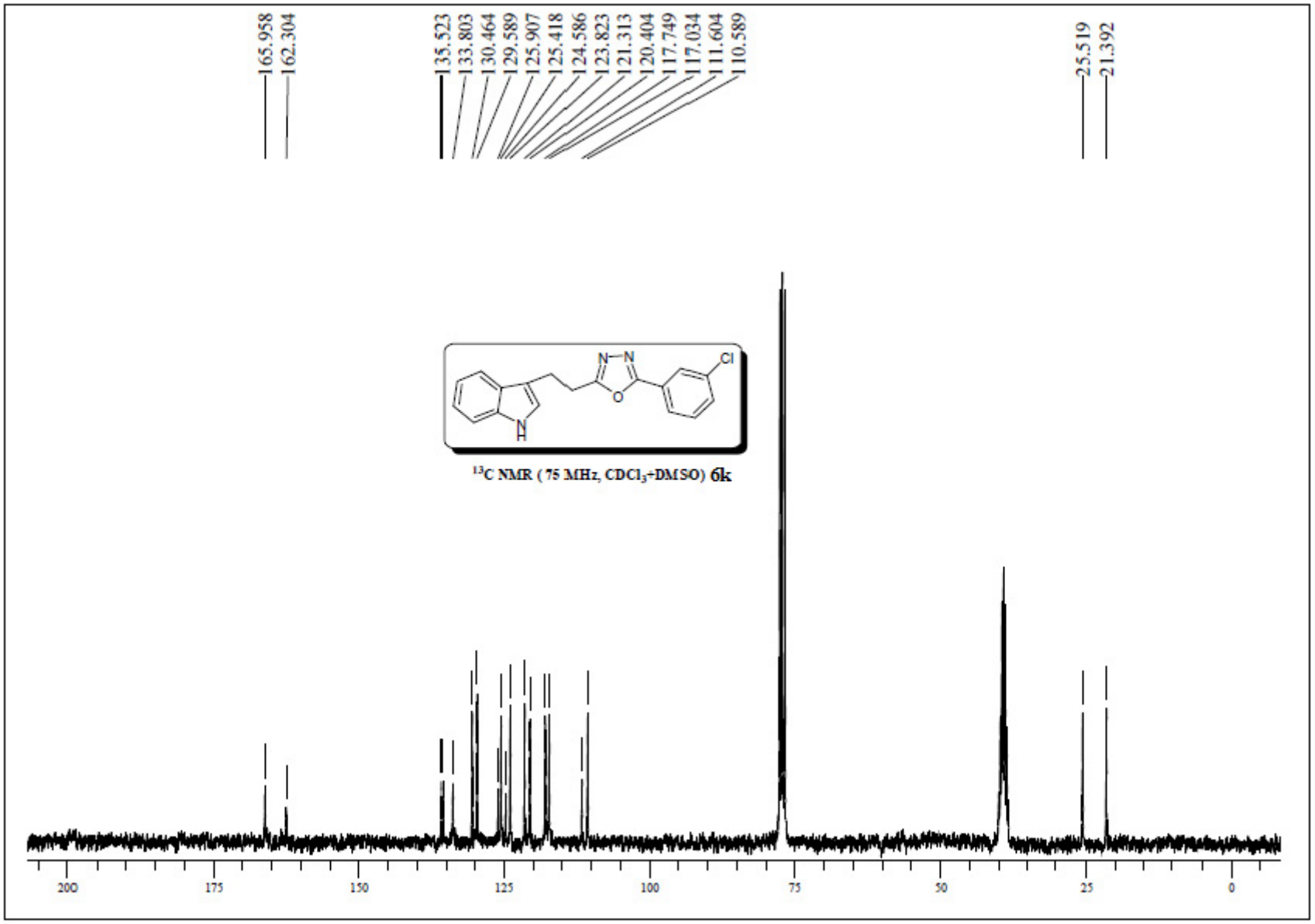
^{1}H NMR (300 MHz, $CDCl_3$) **6j**



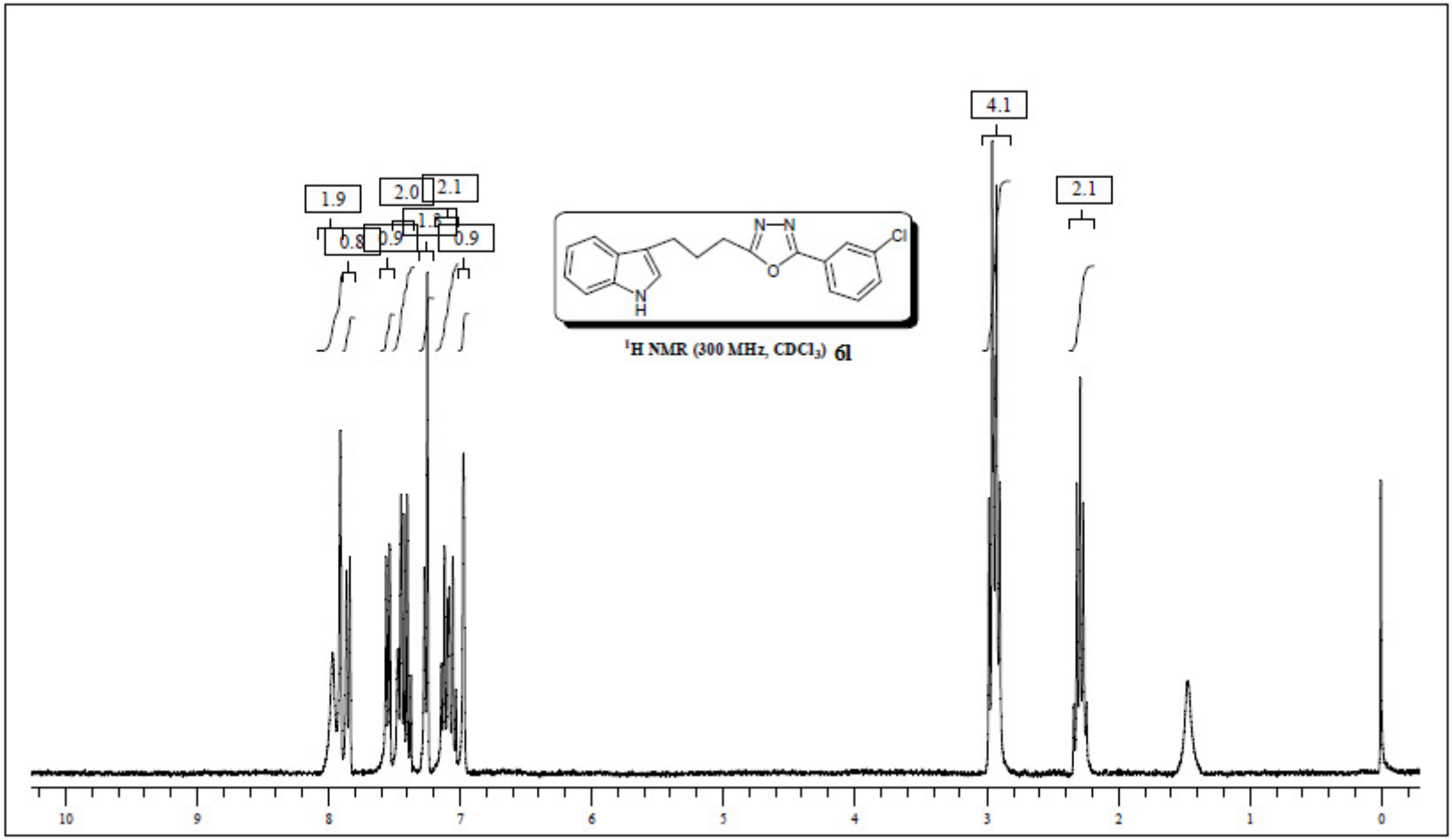
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6j**



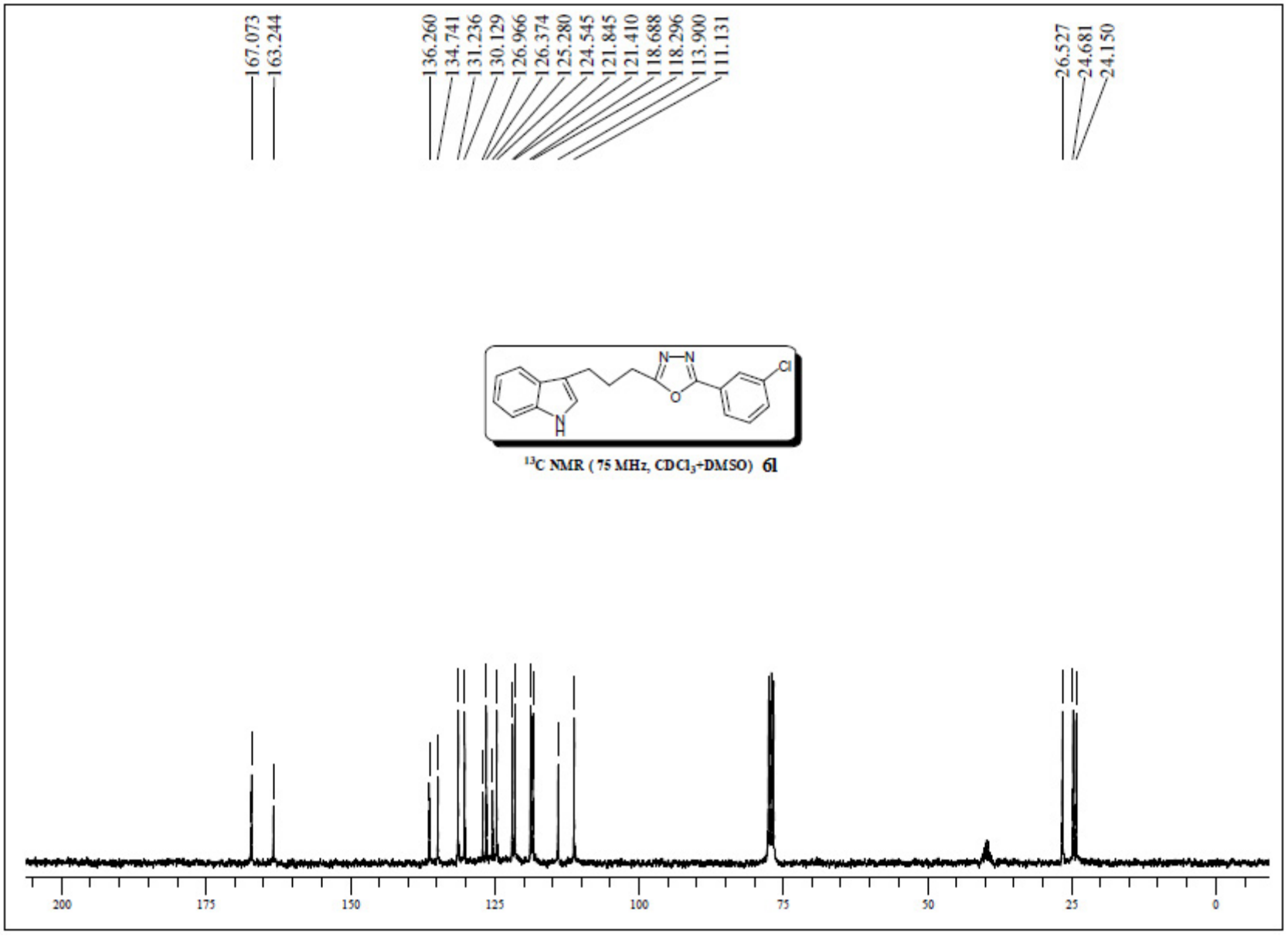
^{1}H NMR (300 MHz, $CDCl_3$) **6k**



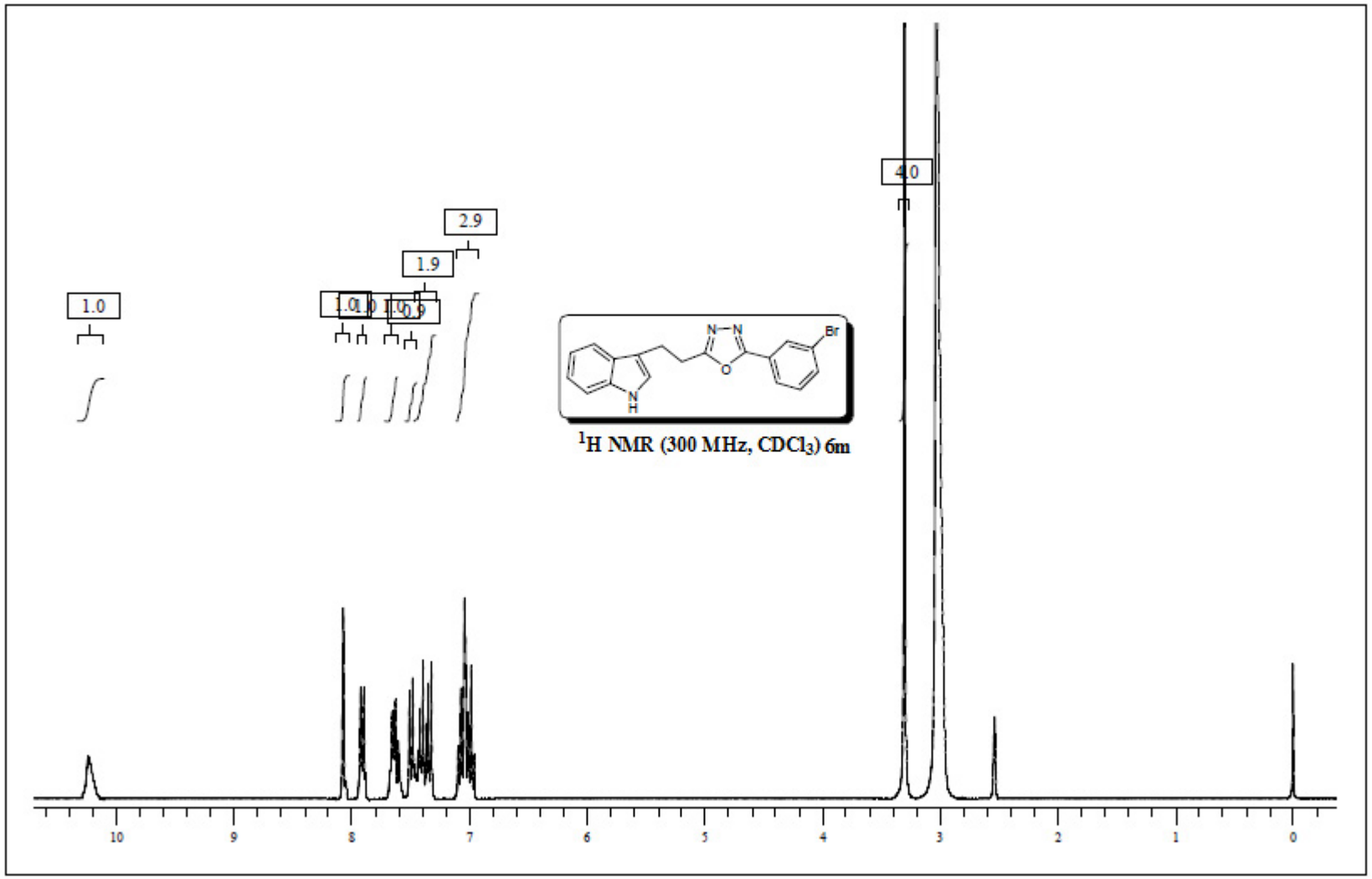
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6k**



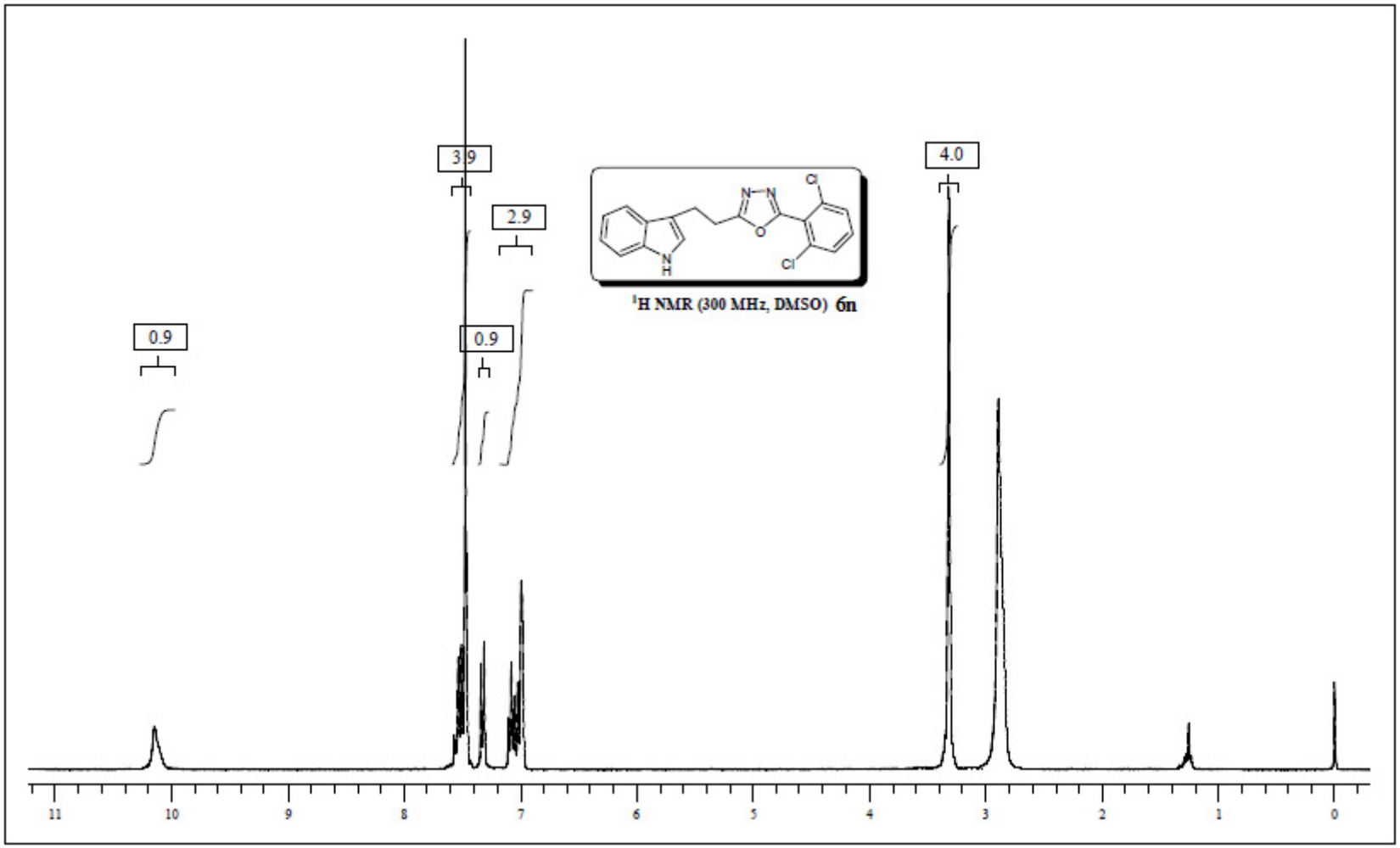
^{1}H NMR (300 MHz, $CDCl_3$) **6l**

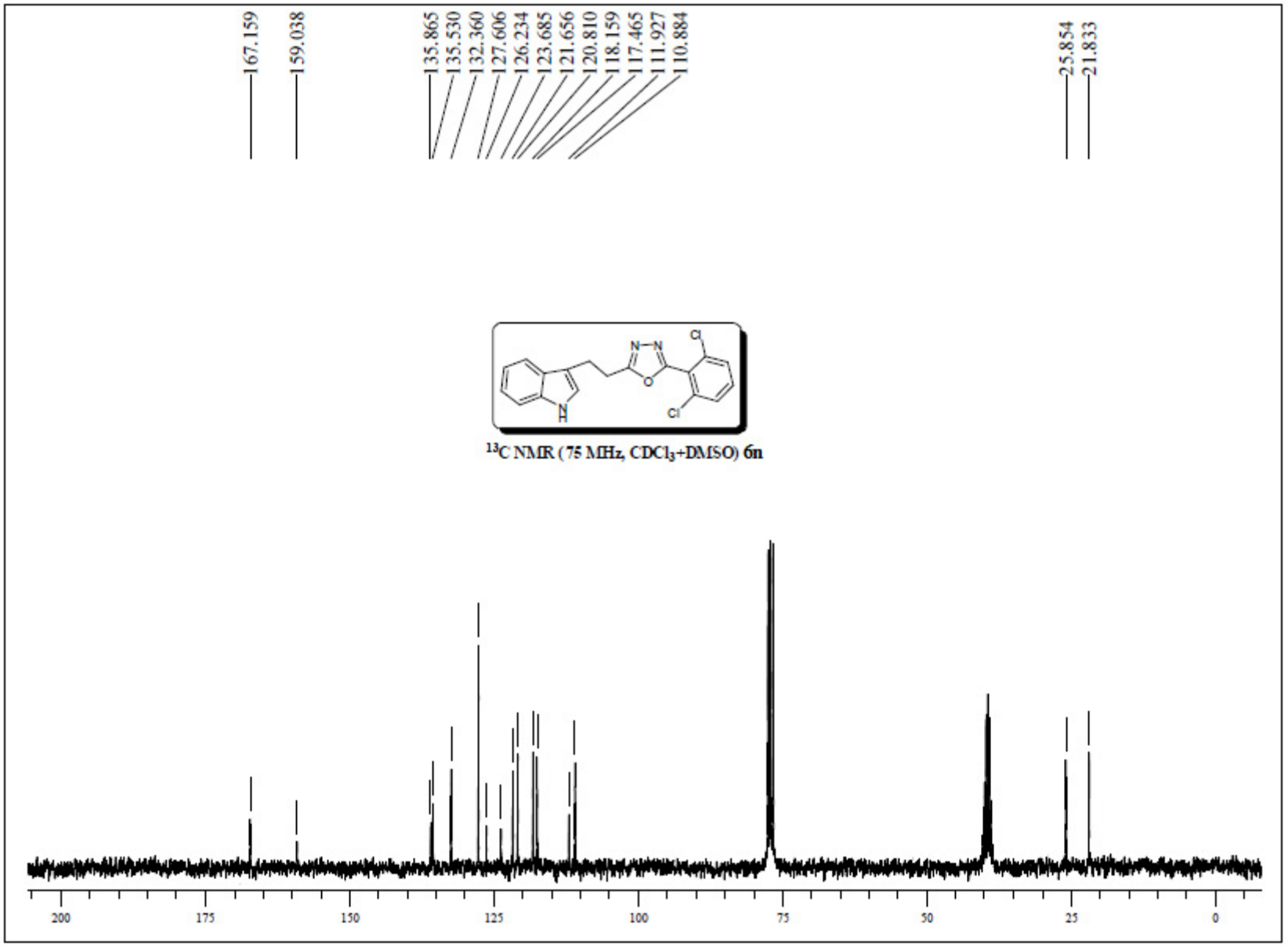


^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6l**

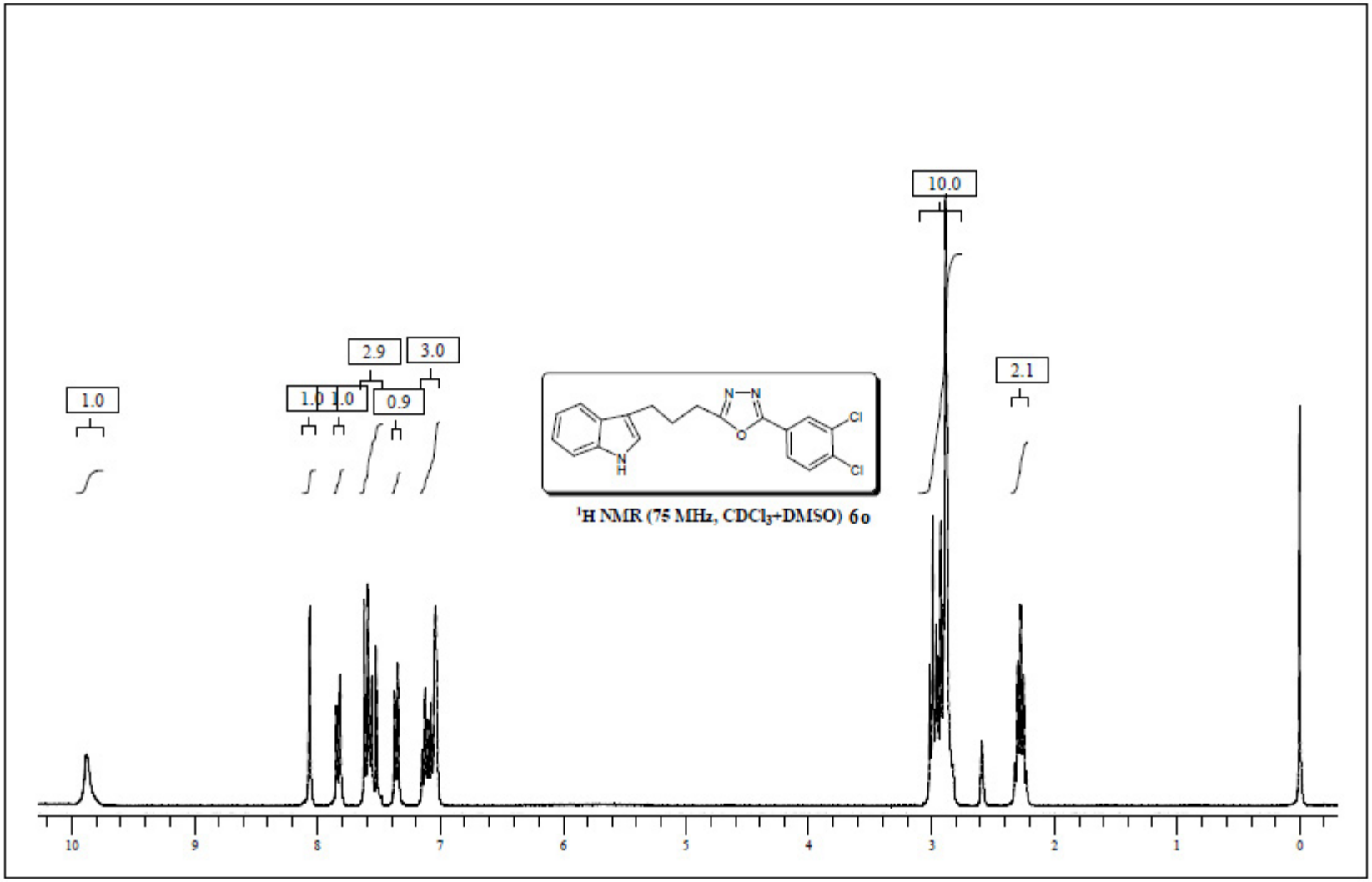


^{1}H NMR (300 MHz, $CDCl_3$) 6m


3.9
2.9
4.0
0.9
0.9
Cl
Cl
N
N
O
N
H
^{1}H NMR (300 MHz, DMSO) 6n
11
10
9
8
7
6
5
4
3
2
1
0

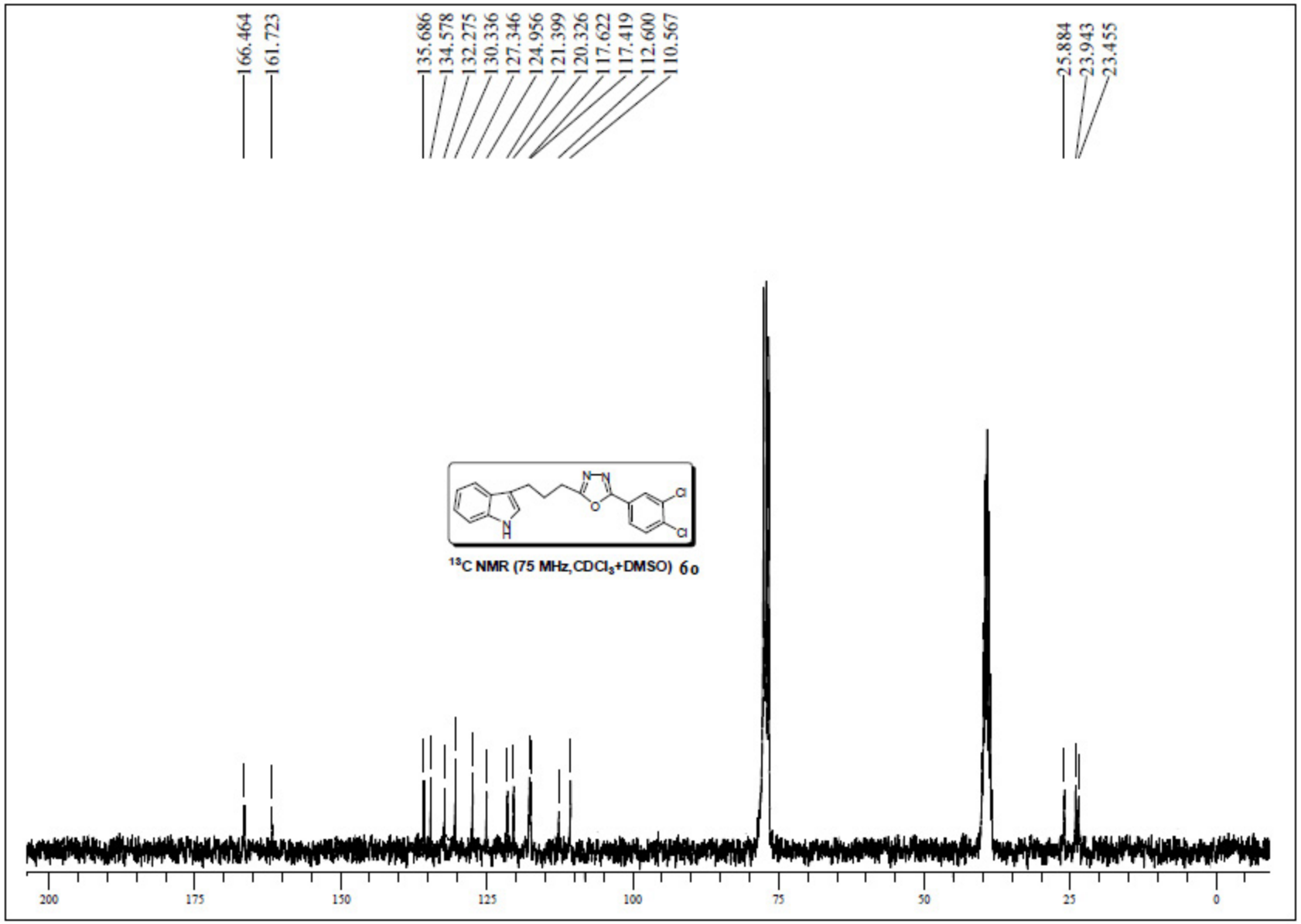


^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6n**

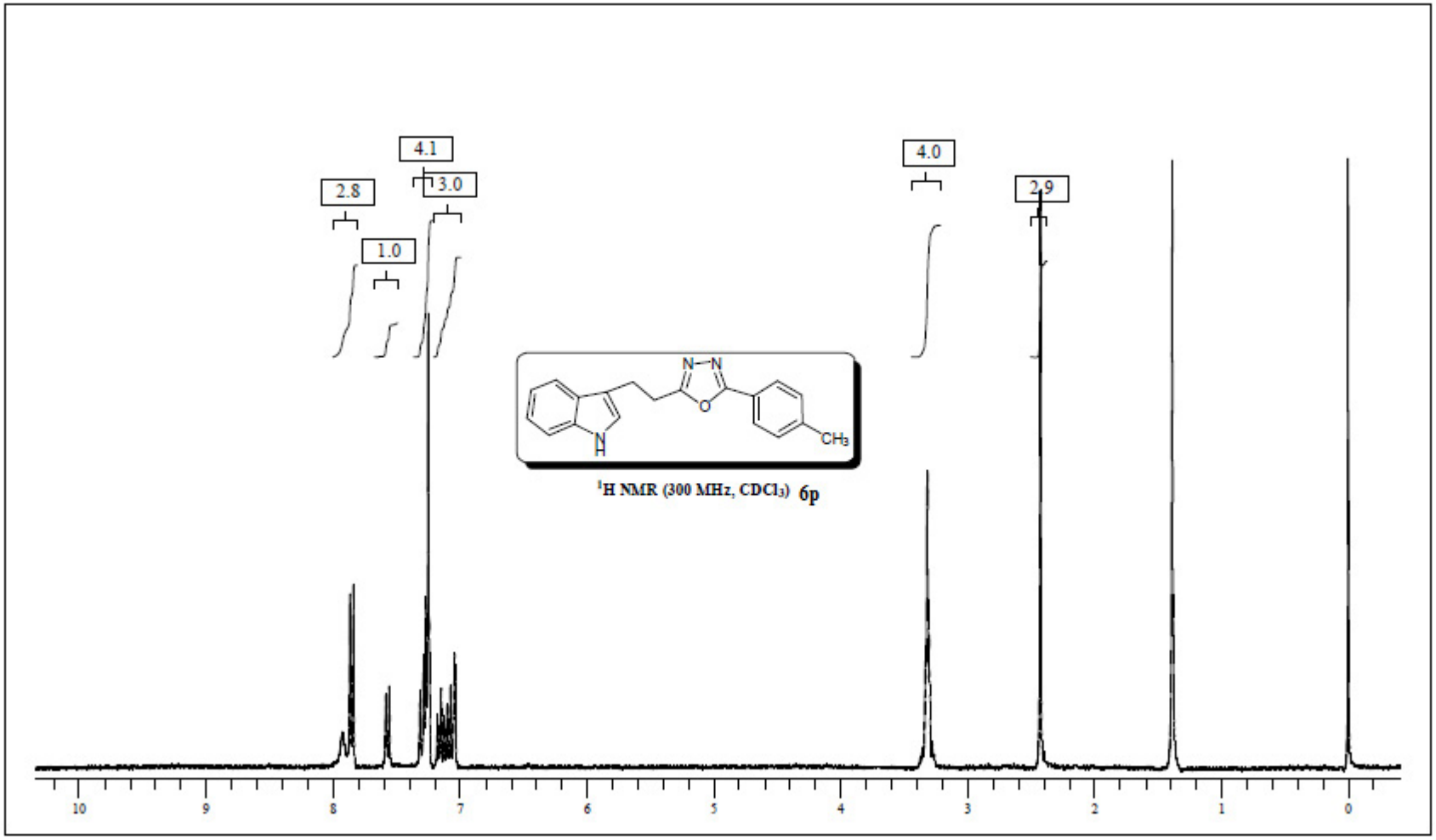


^{1}H NMR (75 MHz, $CDCl_3$+DMSO) **6o**

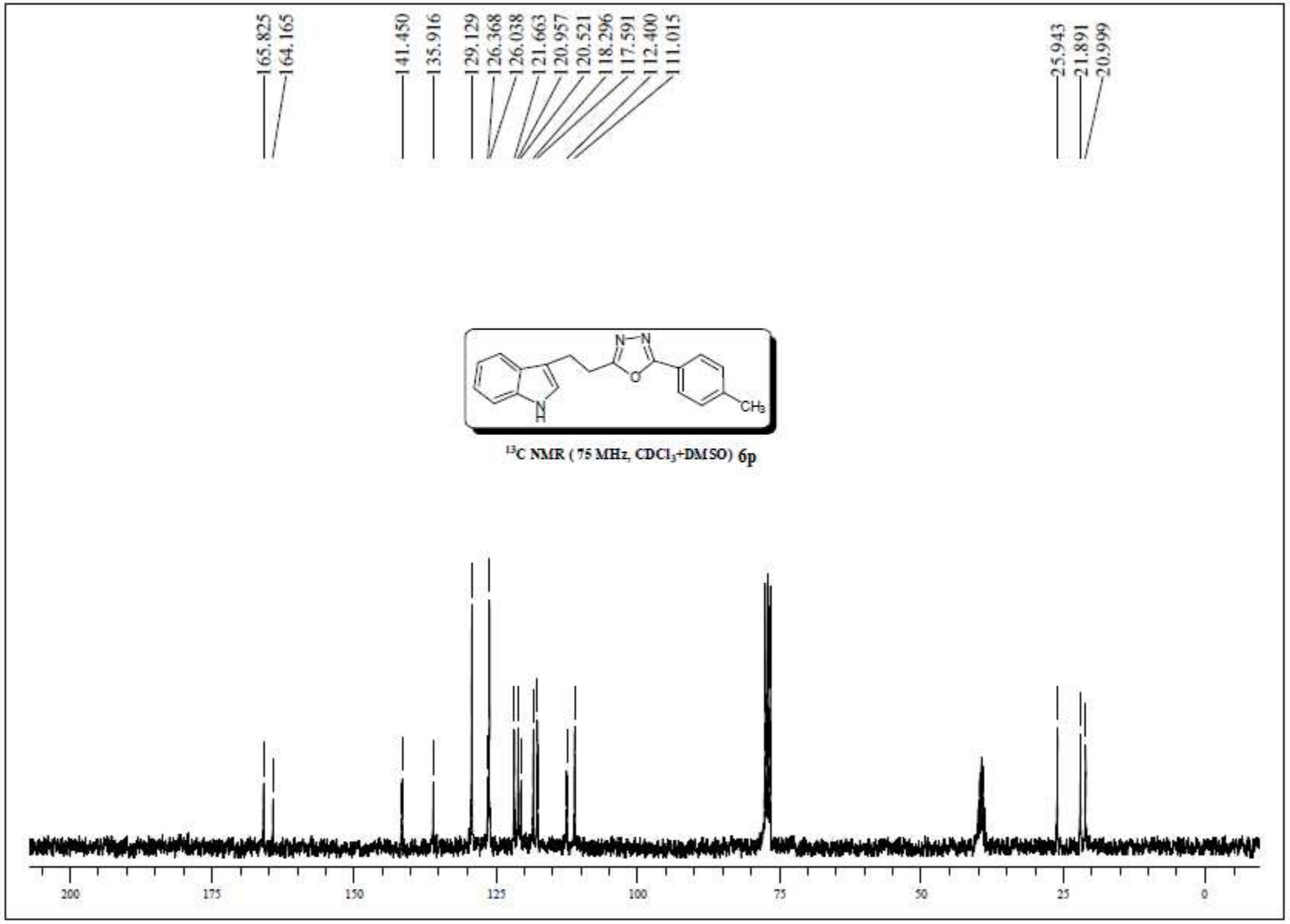
Peck centered at δ 2.9 integrating for 10 protons, consists 6 protons of solvent (DMSO) and 4 protons of aliphatic chain. In aromatic region peak at δ 7.6 integrating for 2.9 protons, contains one proton of solvent ($CDCl_3$).



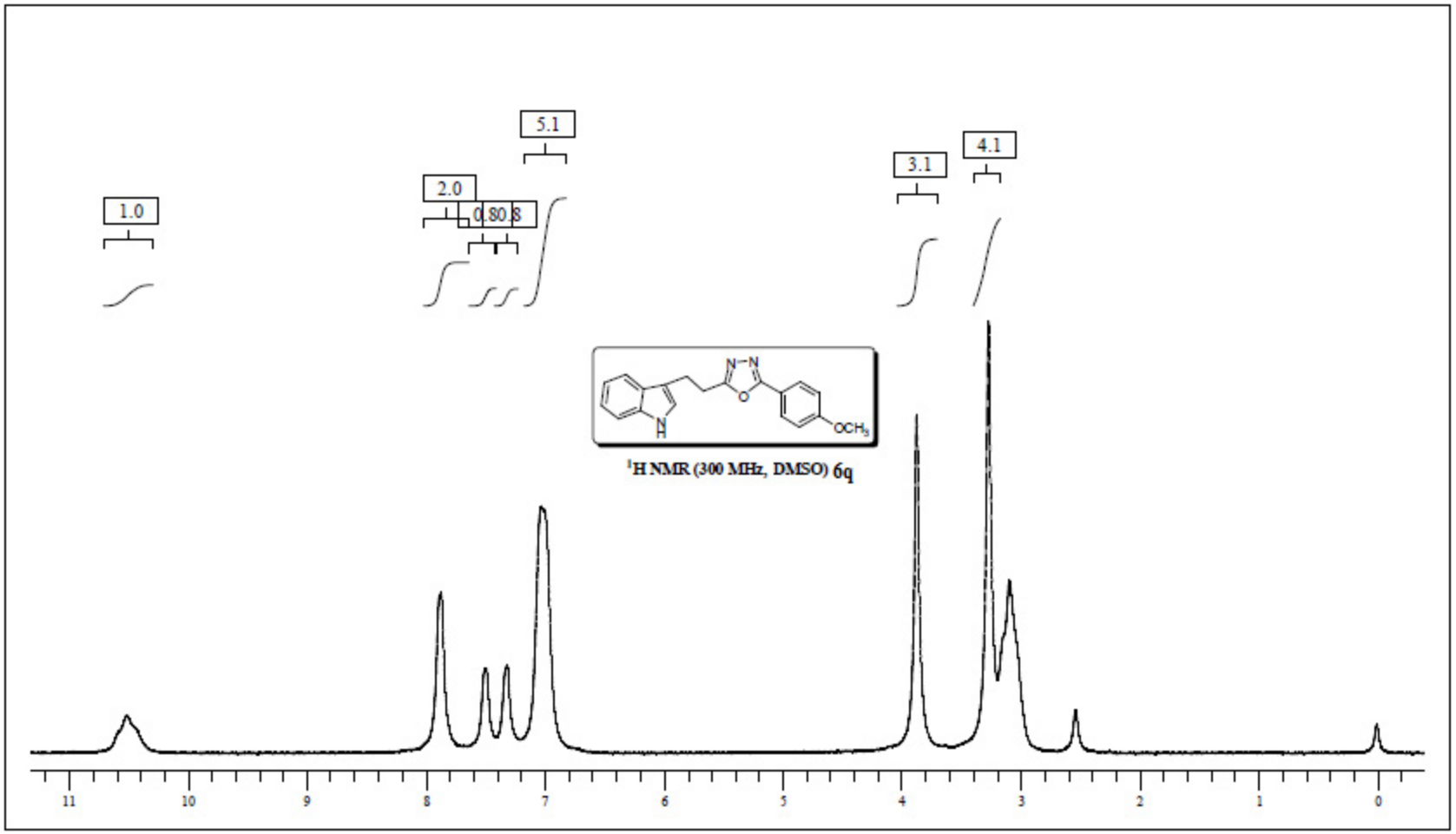
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ_O



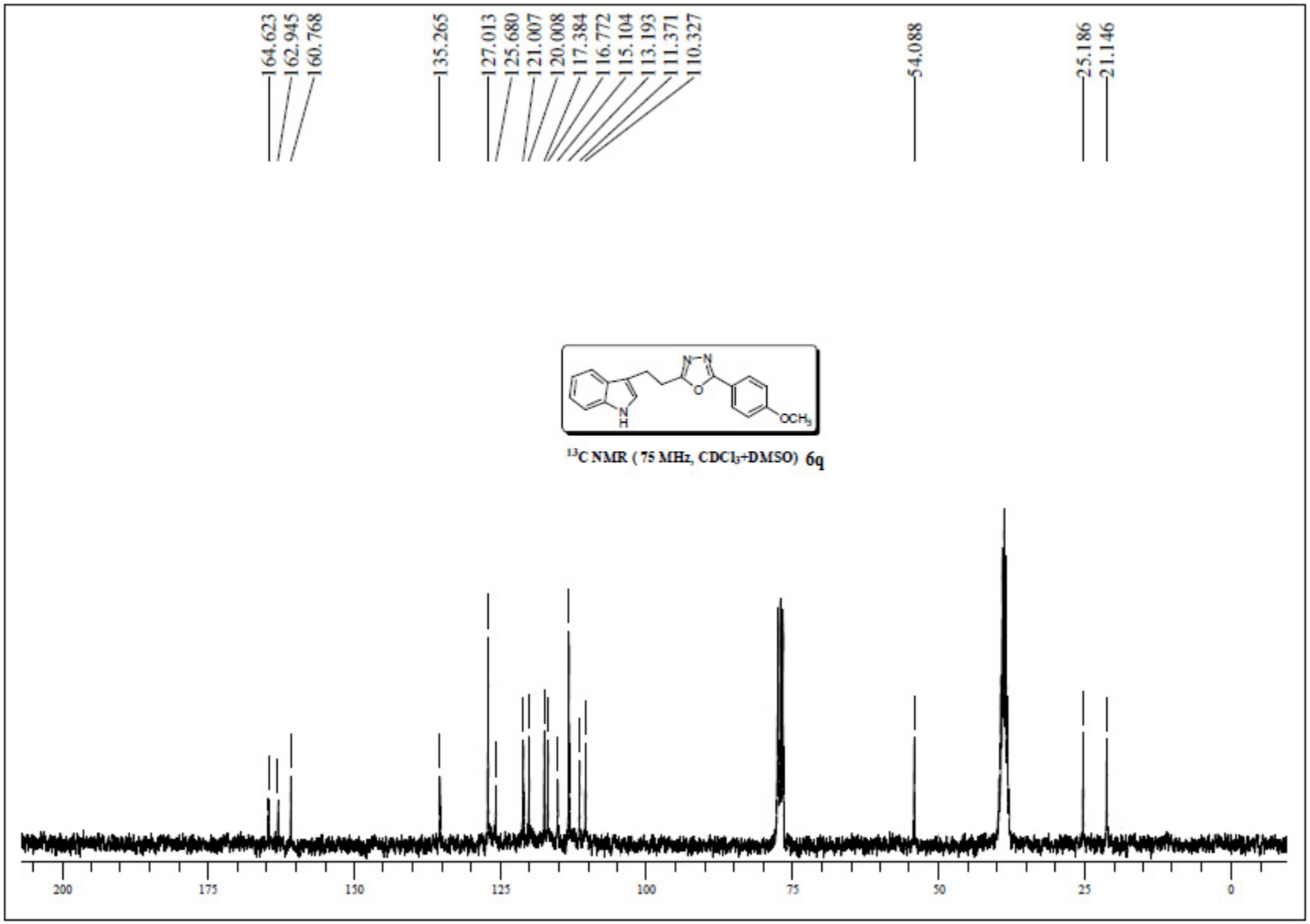
^{1}H NMR (300 MHz, $CDCl_3$) **6p**



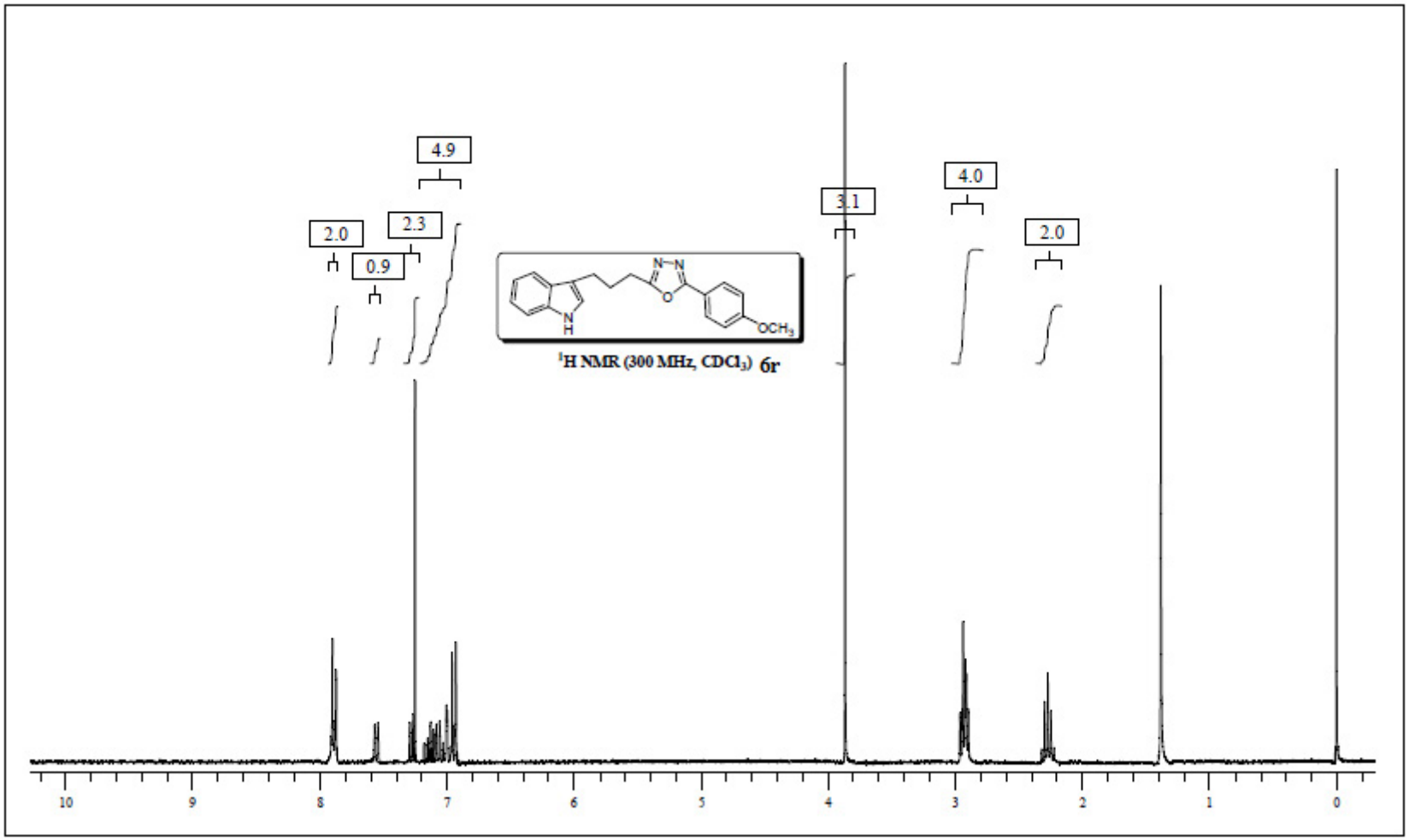
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6p**



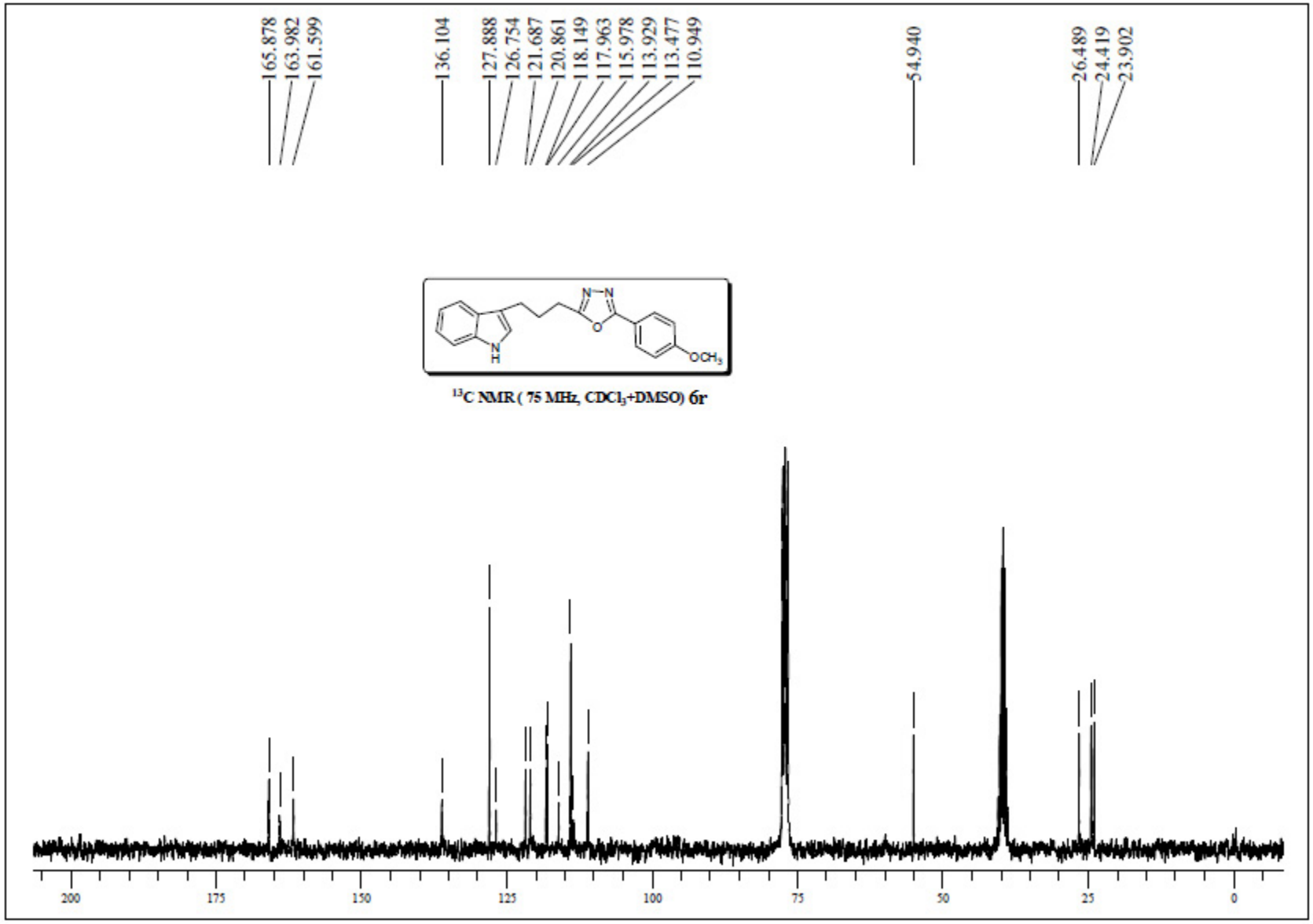
^{1}H NMR (300 MHz, DMSO) 6q



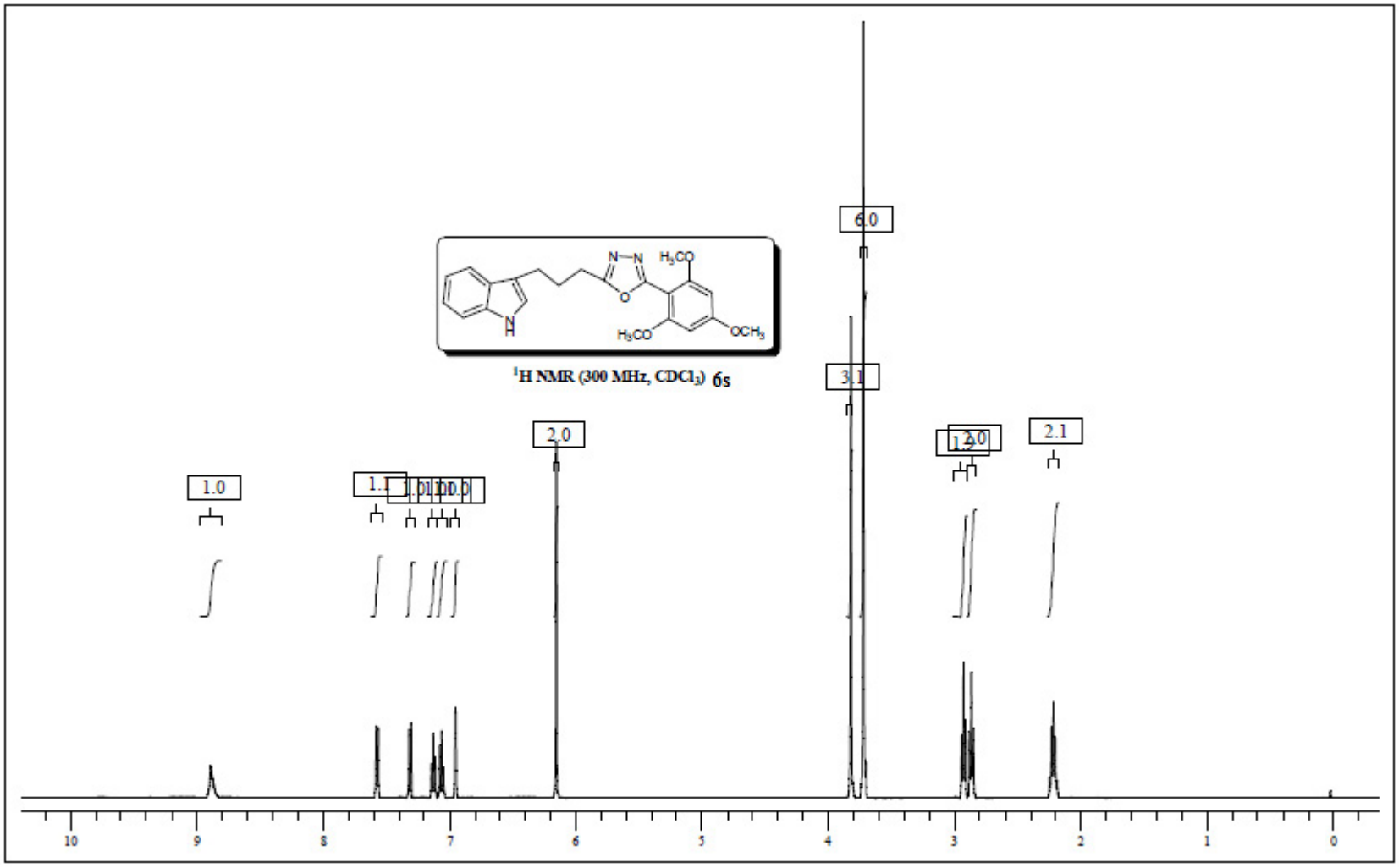
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6q**

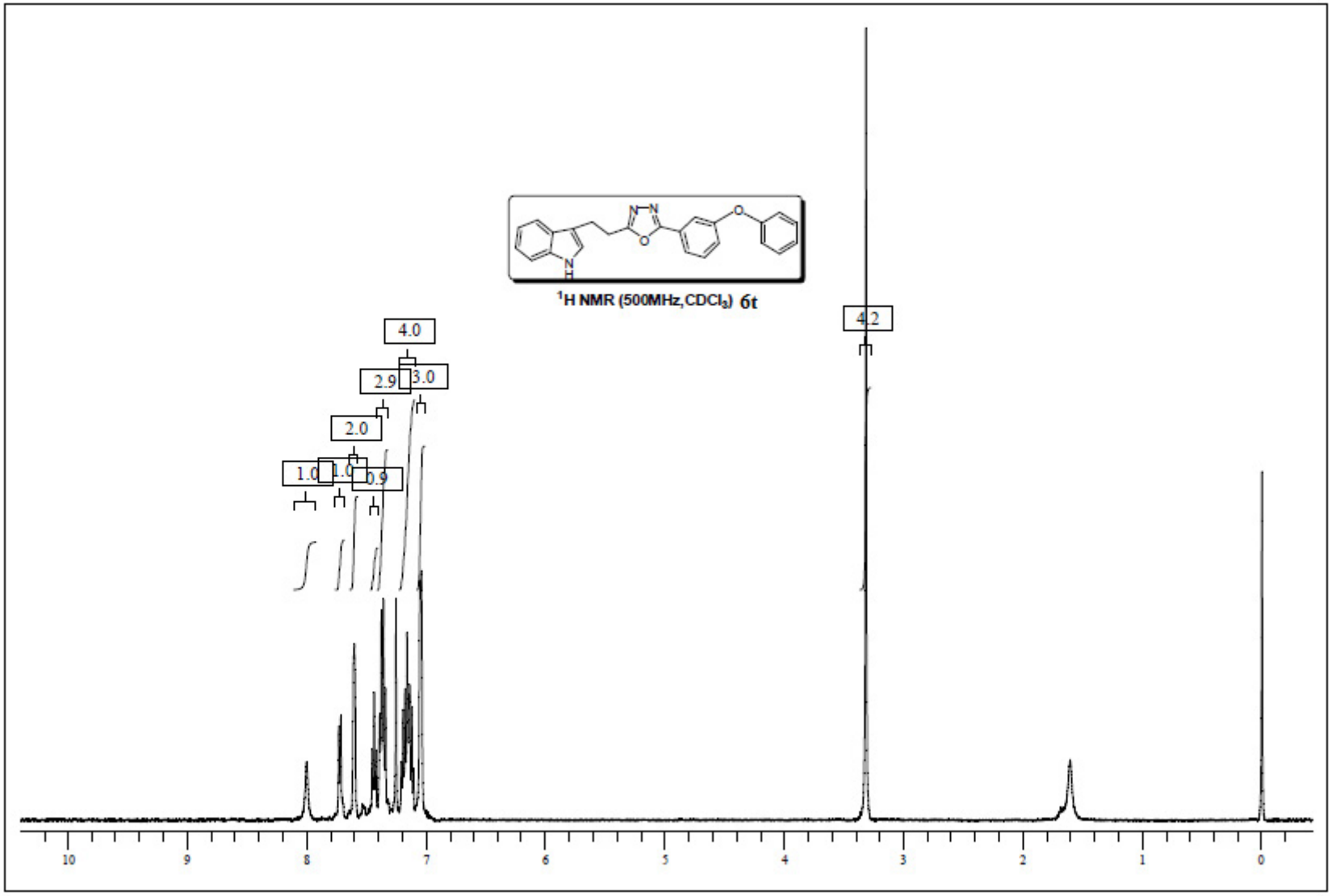


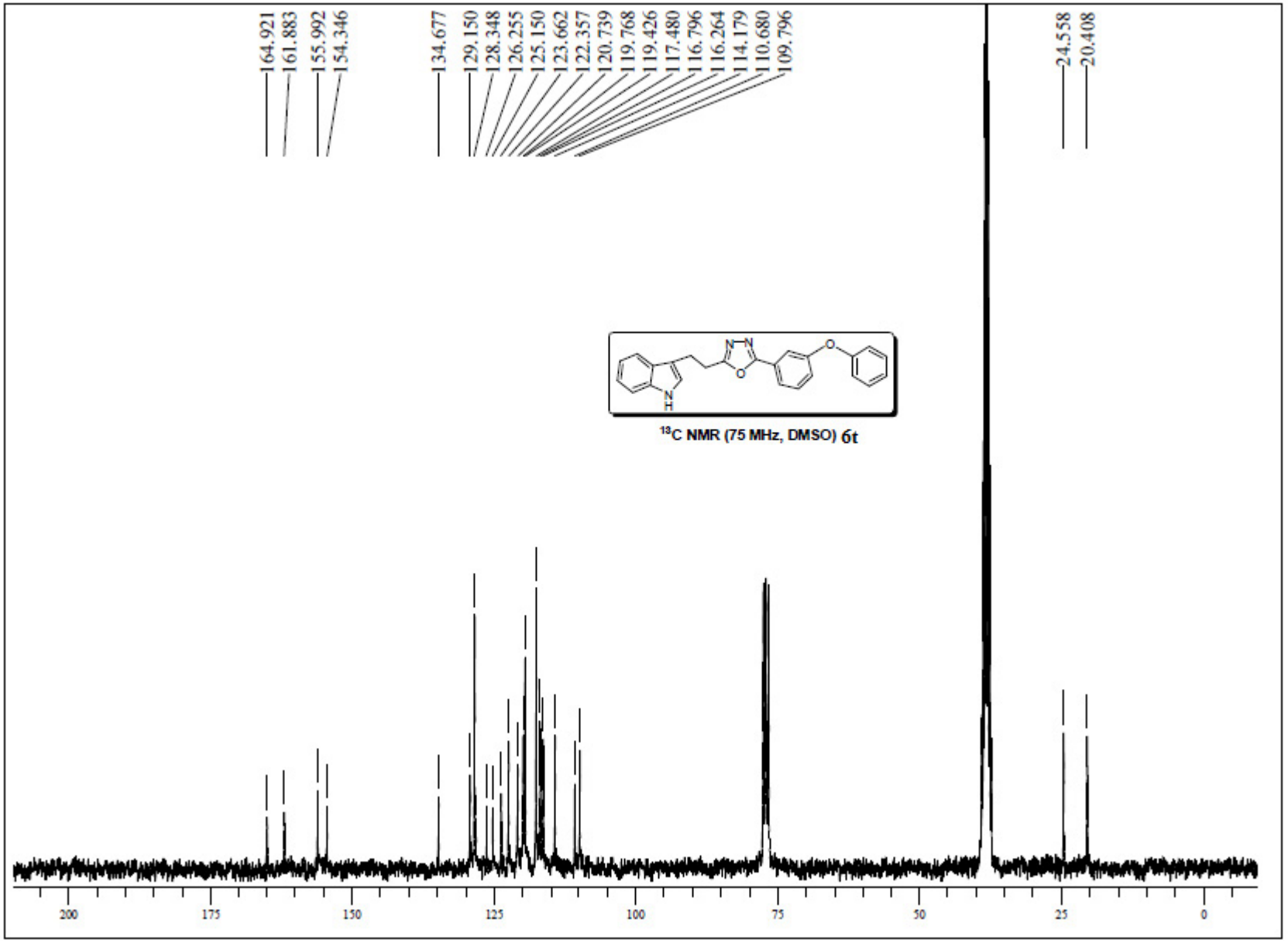
^{1}H NMR (300 MHz, $CDCl_3$) **6r**



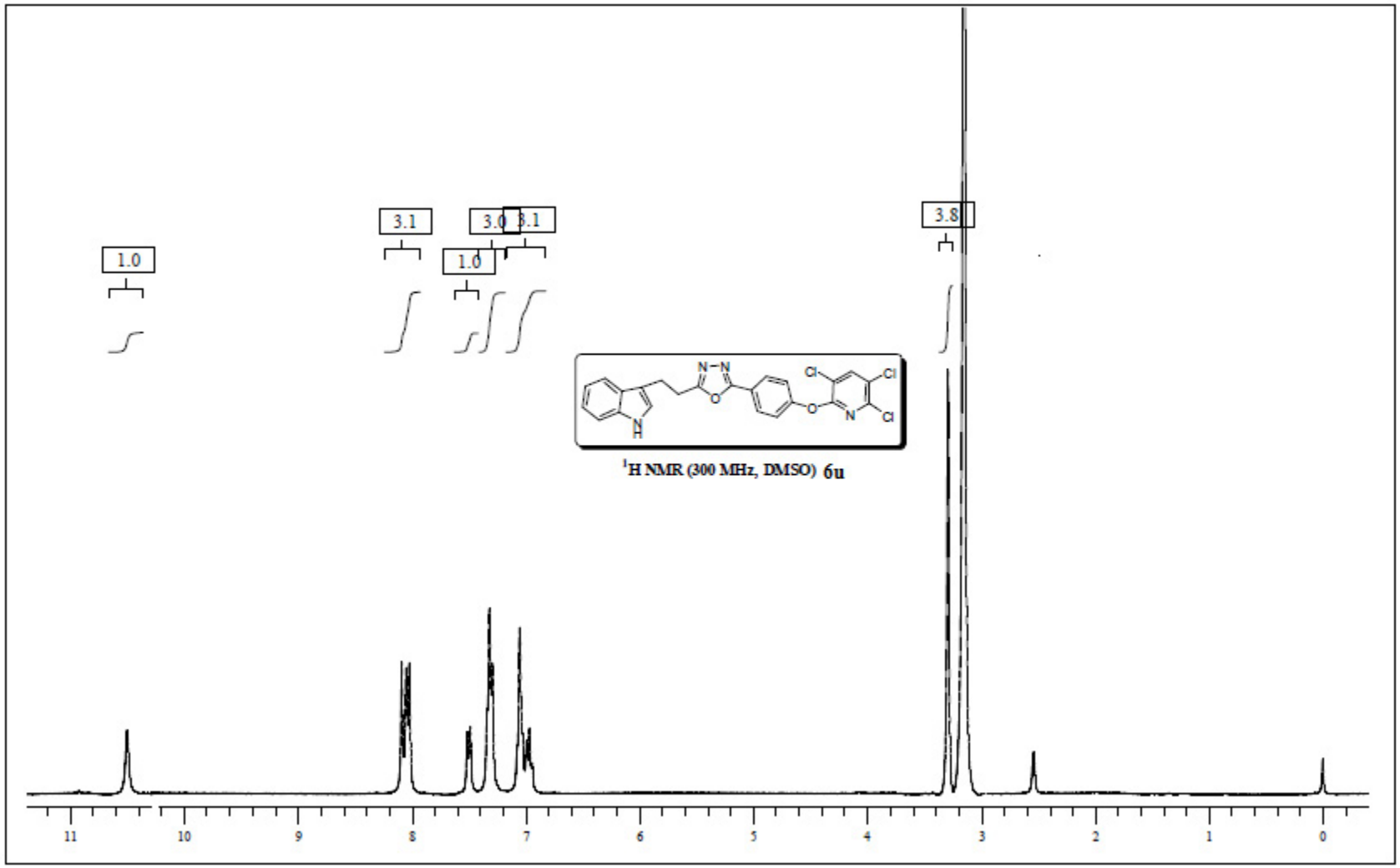
^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6r**


6.0
3.1
2.0
2.1
1.0
1.1
2.0
^{1}H NMR (300 MHz, CDCl$_3$) 6s

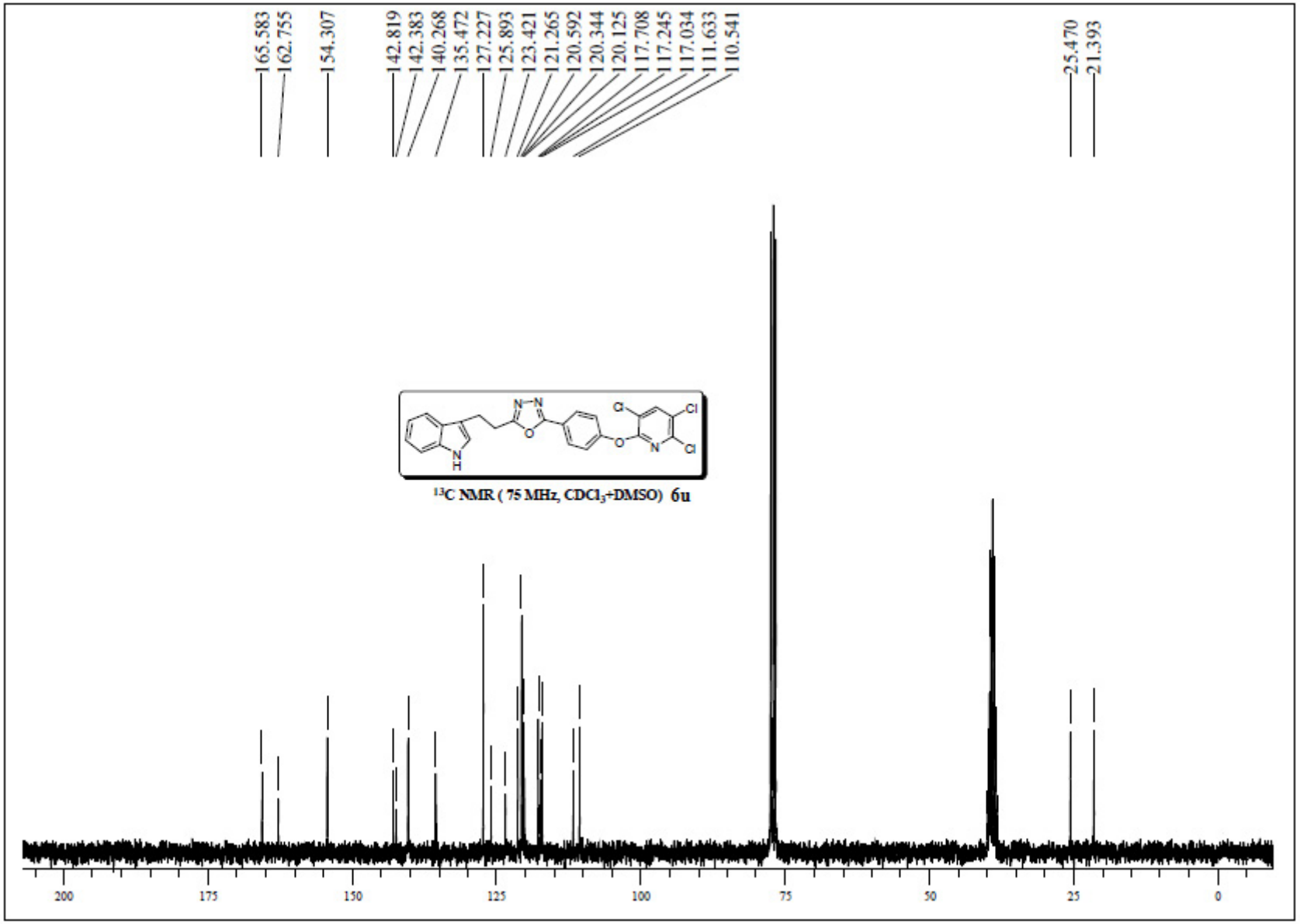

^{1}H NMR (500MHz,CDCl$_3$) 6t
4.0
2.9
3.0
2.0
1.0
1.0
0.9
4.2
10
9
8
7
6
5
4
3
2
1
0



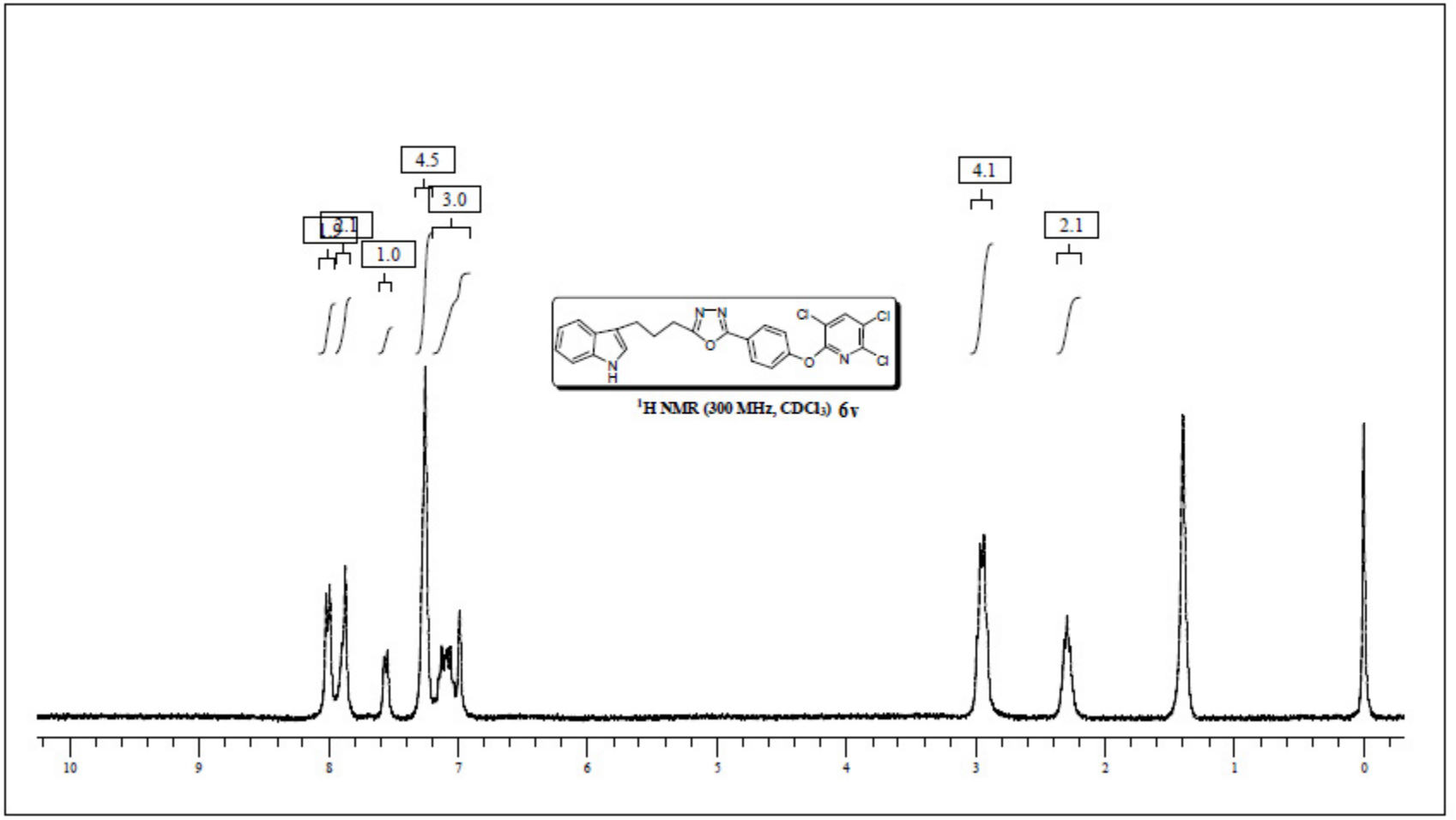
^{13}C NMR (75 MHz, DMSO) **6t**



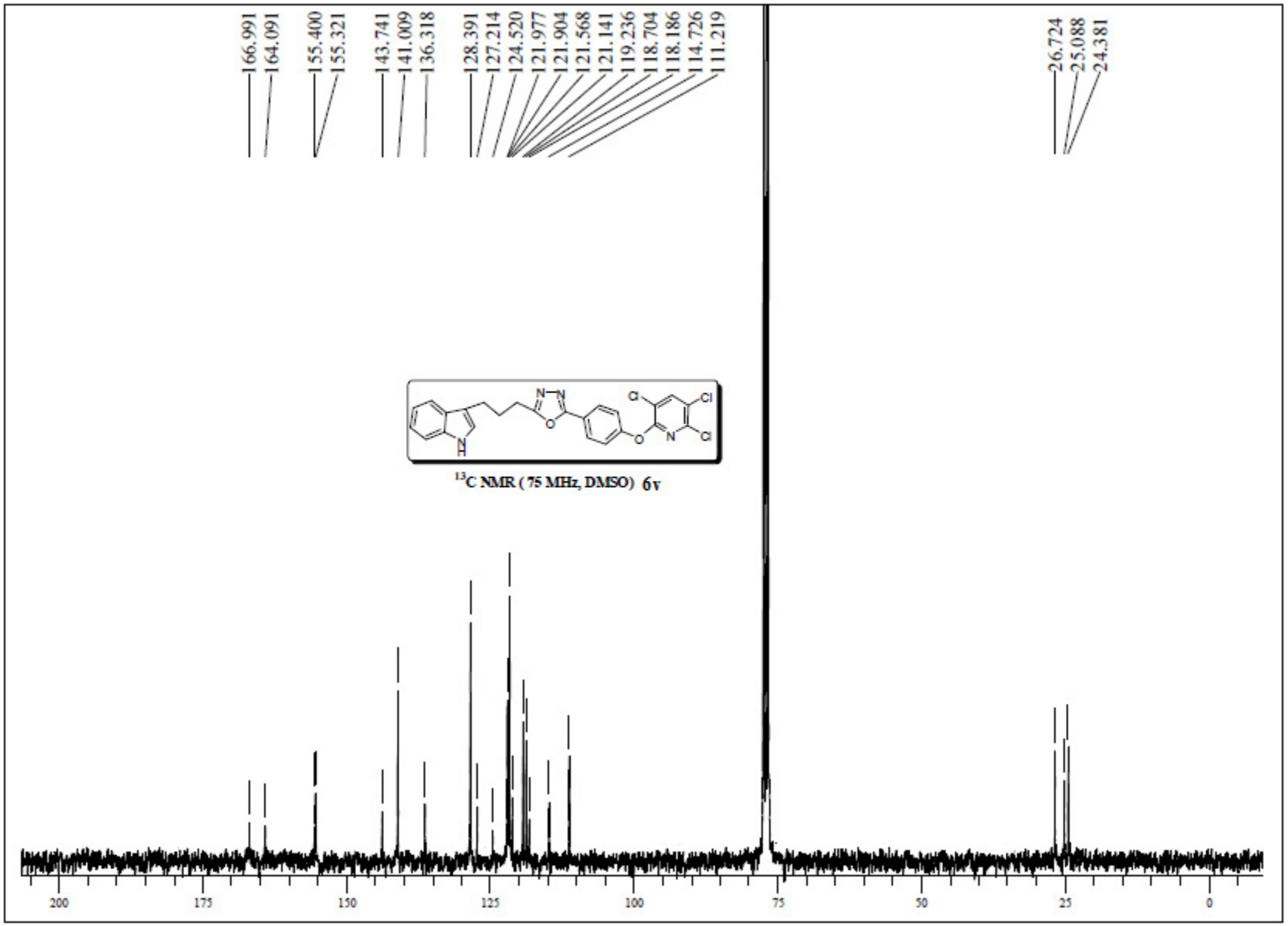
^{1}H NMR (300 MHz, DMSO) **6u**



^{13}C NMR (75 MHz, $CDCl_3$+DMSO) **6u**



^{1}H NMR (300 MHz, $CDCl_3$) **6v**



^{13}C NMR (75 MHz, DMSO) 6v