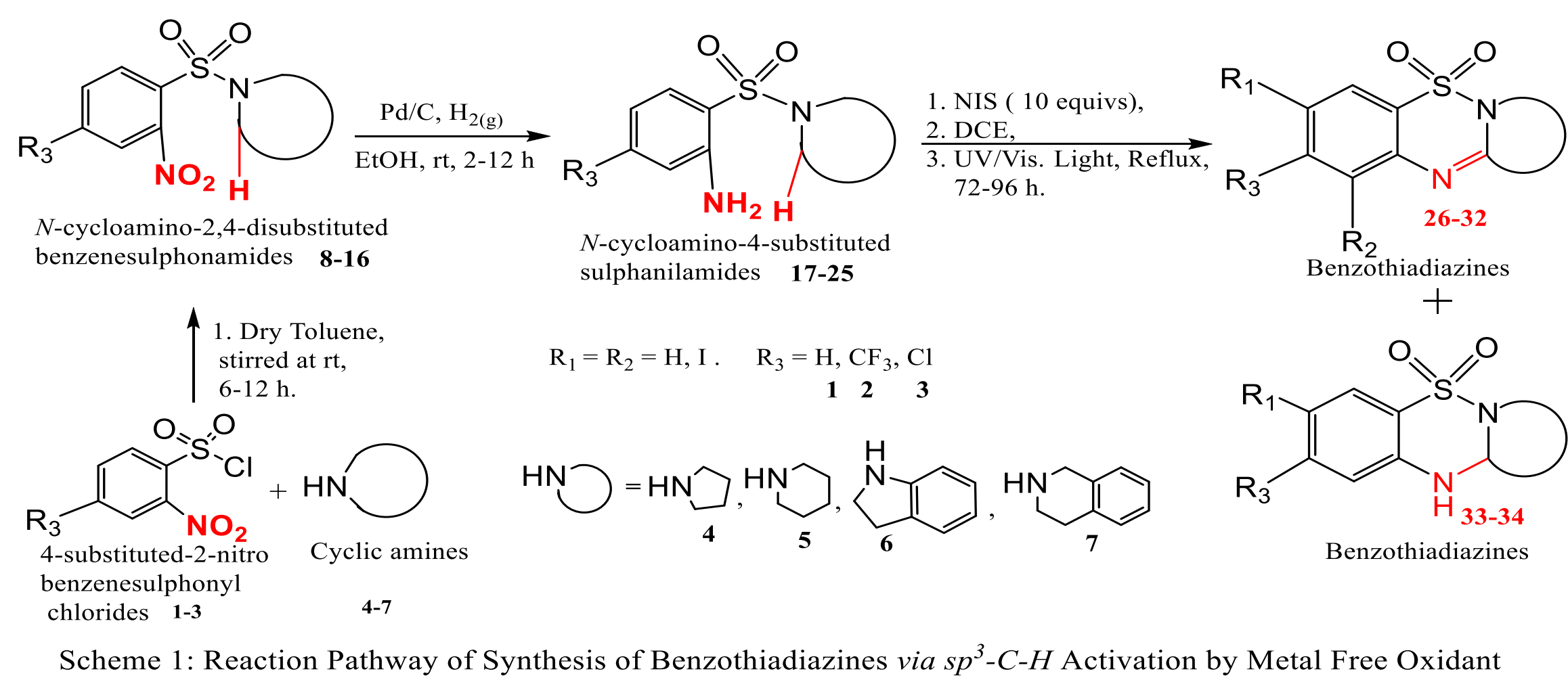


Abstract

The synthesis of tricyclic and angular tetracyclic benzothiadiazines **26-34** was achieved via metal-free intramolecular *N*-iodosuccinimide mediated radical oxidative *sp*³-*C-H* aminative cyclisation of *N*-cycloamino-4-substituted-2-sulphanilamides **17-25**. The precursors **17-25** were obtained from the catalytic hydrogenation of *N*-cycloamino-4-substituted-2-nitrosulphonamides **8-16** and these were prepared by condensation of 4-substituted-2-nitrobenzenesulphonyl chlorides **1-3** and cyclic amines **4-7** at room temperature in dry toluene. From the docking studies, many of the compounds showed significant anti-cancer activity against colon, breast and lung cancer.

Keywords: benzothiadiazines; metal-free; *sp*³-*C-H* activation; docking; anti-cancer. activity.

Graphical Abstract



Introduction

Atom-economy strategies for the construction of C=N bond remains fundamental and of immense importance in organic heterocyclic synthesis because of its prevalence in natural products, pharmaceuticals and materials.¹ Benzothiadiazines have interesting, wide-ranging physiological attributes.² Several synthetic procedures have been reported for benzothiadiazines; including via iminium ion intermediates,³ Fisher indole synthesis,⁴ intramolecular aza-Wittig reaction,⁵ Ullmann-type *N*-arylation² as well as iodine-mediated synthesis.⁶ Herein, this study provides a facile and low-cost access to different tricyclic and angular tetracyclic thiazides of physiological importance.

Ligand's inhibitors against colon cancer cell line (5B6G)

Benzothiadiazines as colon cancer inhibitor	Binding Affinity
5b6g_KS8_uff_E=605.04 27	-7.3
5b6g_KS9_uff_E=691.84 34	-6.8
5b6g_KS5_uff_E=592.02 28	-6.7
5b6g_KS4_uff_E=683.57 33	-6.6
5b6g_KS7_uff_E=574.59 31	-6.4
5b6g_KS3_uff_E=595.09 26	-6.3
5b6g_Trifluridine_uff_E=282.80	-6.2
5b6g_KS6_uff_E=545.36 32	-6.2
5b6g_Capecitabine_uff_E=624.15	-5.9
5b6g_KS2_uff_E=565.70 29	-5.5
5b6g_KS1_uff_E=537.65 30	-5.3
5b6g_5-Fluorouracil_uff_E=45.86	-4.4

Figure 1: Inhibitory results of Ligands' Interaction with the colon cancer protein and that of 2D Structure of Ligand 27 with highest binding energy (-7.3 kcal / mol)



SYNTHESIS AND ANTICANCER ACTIVITIES OF TRICYCLIC AND ANGULAR TETRACYCLIC [1,2,4]-BENZOTHIADIAZINE DIOXIDES via METAL-FREE *sp*³-C-H ACTIVATION

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Results and Discussion

Figure 2 showed 7 aromatic protons of compound **24** resonated downfield between δ 7.79-6.97 ppm. The singlet signal resonated at δ 5.35 ppm was assignable to the aromatic primary amine protons (**H16**) while the

methylene protons (**7**, **15** and **14**) of isoquinoline resonated upfield as singlet and triplet at δ 4.40, δ 3.51 (J = 6.0 Hz) and 2.96 ppm (J = 6.0 Hz) respectively. In Figure 3, there was disappearance of the singlet signals attributed to the amino protons, **H16** and methylene protons, **H7** in the ¹H NMR spectrum of compound **27** with the requisite proximal carbon atom, **C7** resonating downfield in ¹³C NMR spectrum of compound **27** (Figure 5) which changed its signal from δ 47.30 ppm (Figure 4) to 150.26 ppm as a result of successful formation of imine carbon (C=N) of the potentially bioactive angular tetracyclic benzothaidiazine[11-(trifluoromethyl)-5,6-dihydrobenzo[5,6][1,2,4]thiadiazino[3,2-a] isoquinoline **8,8-dioxide** **27**.

Docking studies of the synthesised compounds

Molecular docking study (Figure 1) of all the synthesised compounds was performed using AutoDock vina 1.2.0. software. 5B6G (human adenomatous polyposis-colon cancer), 2XUS (breast cancer metastasis-suppressor 1) and 1GFZ (glycogen phosphorylase-lung cancer) cell lines were used to identify best anticancer target. Out of the nine synthesised benzothiadiazines (26-32) docked on the three cancer cell lines, six of them showed better activities against the colon cancer cell line than the three standard drugs (Capecitabine, Trifluridine and Fluorouracil) with compound **27** being the most potent. It also displayed better inhibitory properties on the breast and lung cancer cell lines when compared with the reference drugs (Abemaciclib 'breast' and Sotorasib 'lung'). Many of the nitro sulphonamides (8-16) and amino sulphonamides (17-25) also displayed better inhibitory activity against colon cancer cell lines than the reference drugs. Interestingly compound (**27**) also showed good cytotoxic activity giving the percentage of Hepatotoxicity (inactive) 70 %, Carcinogenicity (inactive) 58 %, Immunotoxicity (inactive) 98%, Mutagenicity (inactive) 70% and Cytotoxicity (inactive) 77%.

Conclusion

A facile and atom-economy protocol has been developed for the synthesis of tricyclic and angular tetracyclic 1,2,4-benzothiadiazine dioxides. This is the first report for the chemoselective synthesis of these potentially bioactive heterocycles through radical oxidative *sp*³-*C-H* aminative cyclisation under UV-Visible light. The salient features of this approach include milder reaction conditions, inexpensive reagents, high-atom economy, and a clean reaction profile in a single synthetic operation. These compounds especially (**11**, **24** and **27**) may be taken as lead molecules for the discovery of new anticancer agents. This research work agrees with the policy of the United Nation of Sustainable Development Goal (SDG)

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S/N	2	6	Adduct	M. Pt. (°C)	Yield (%)
1	4-Trifluoromethyl-2-nitrobenzene sulphonyl chloride	1,2,3,4-tetrahydroisoquinoline		155.3-156.8	87

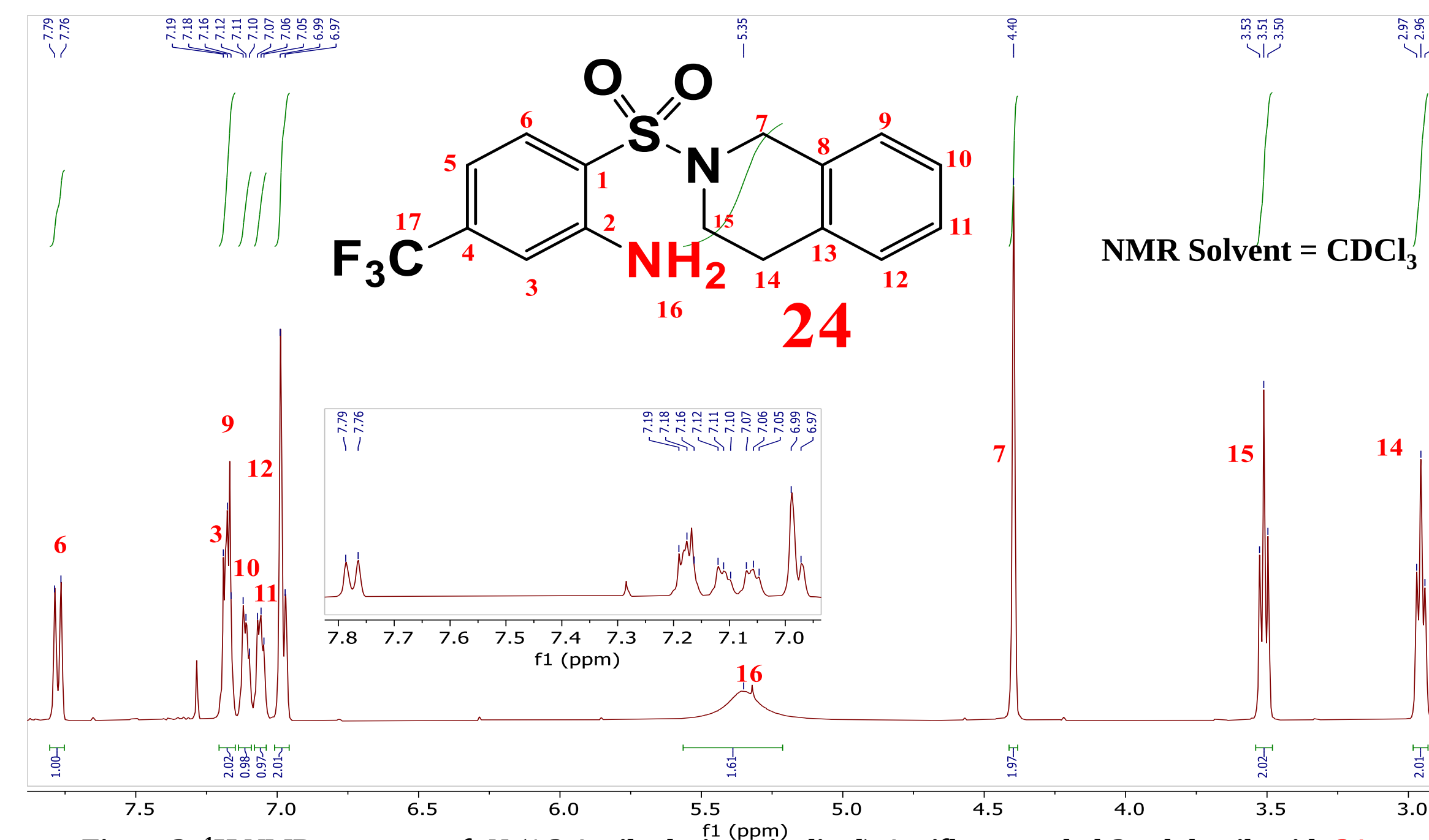


Table 2: Property of Synthesized 11-(trifluoromethyl)-5,6-dihydrobenzo[5,6][1,2,4]thiadiazino[3,2-a] isoquinoline 8,8-dioxide				
S/N	<i>N</i> -(1,3,4-trihydroisoquinolinyl)-4-trifluoromethyl-2-sulphanilamide	11-(trifluoromethyl)-5,6-dihydrobenzo[5,6][1,2,4]thiadiazino[3,2-a] isoquinoline 8,8-dioxide	M. pt. (°C)	Yield (%)
1			181.4-182.2	90

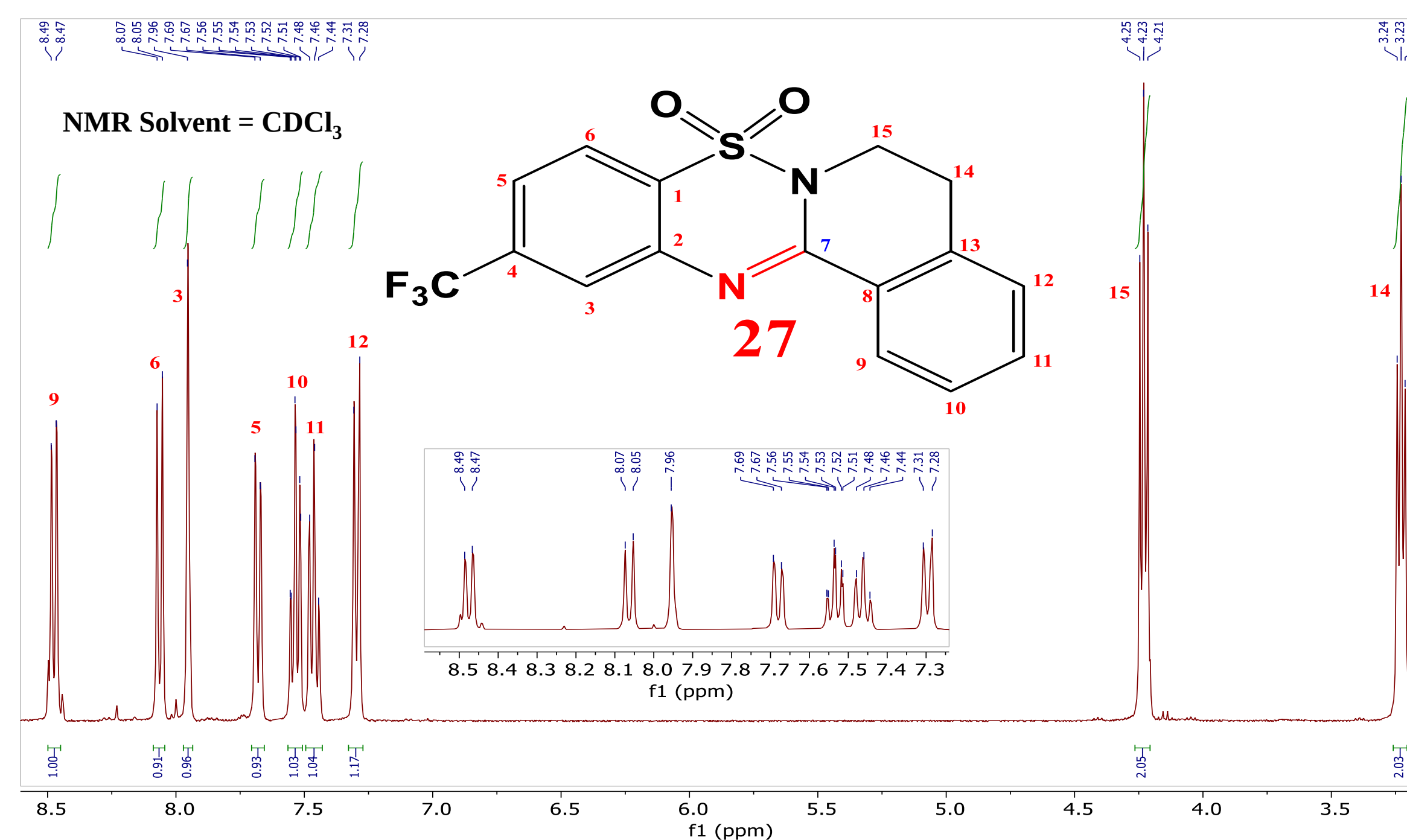
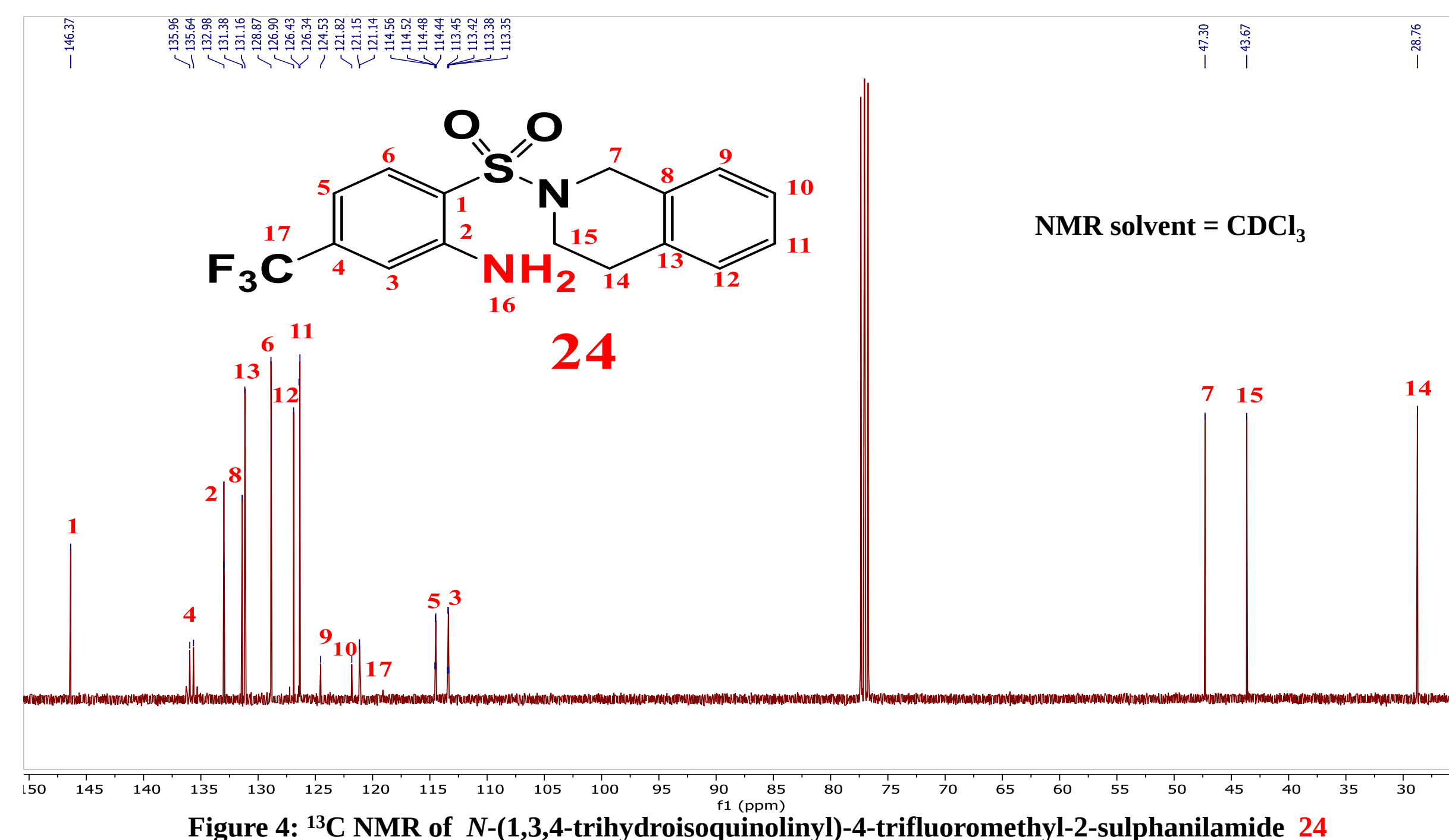
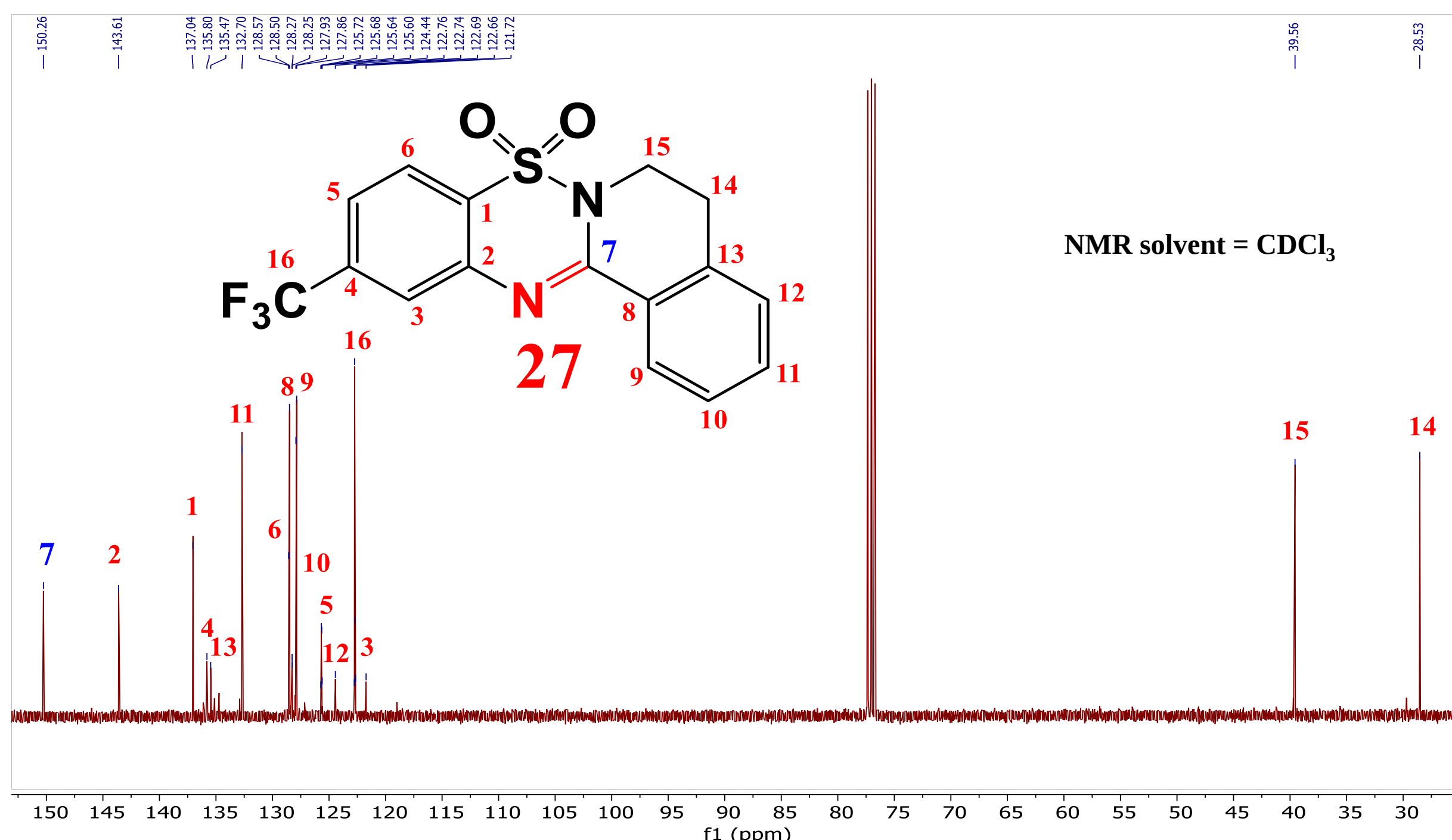


Figure 3: ¹H NMR spectrum of 11-(trifluoromethyl)-5,6-dihydrobenzo[5,6][1,2,4]thiadiazino[3,2-a] isoquinoline **8,8-dioxide** **27**



Representative procedure for the synthesis of Tricyclic and Angular Tetracyclic 1,2,4-Benzothiadiazene dioxides

To a stirring solution of *N*-cycloamino-4-substituted-2-sulphonamides **17-25** (0.5 mmol) in 1,2-dichloroethane (7 ml) was added *N*-iodosuccinimide (5.0 mmol, 10 equivs.) in portions. The resulting solution was refluxed under UV visible-light irradiation for 96h and monitored by thin layer chromatography (TLC). On completion, the reaction mixture was allowed to cool to ambient temperature. The crude product was extracted into ethyl acetate (20 ml), washed with saturated aqueous sodium thiosulphate solution (10 ml x 2) and then with distilled water (10 ml x 2). The organic extract was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated on oil bath to a brown oil, which was purified by preparative TLC (dichloromethane/n-hexane, 2:1 v/v) to give orange crystals (**26-28**) or orange oil (**29-34**) of the desired products.