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Synthesis, Structural Characterization, and Thermal Stability Investigation of Methoxybenzamide Derivatives Containing the 5-Mercapto-1,3,4-Thiadiazol-2-yl Group

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Dursun Ali KÖSE: The investigation of the thermal stability of derivatives and their elemental analysis, writing of the article.

Synthesis, Structural Characterization, and Thermal Stability Investigation of Methoxybenzamide Derivatives Containing the 5-Mercapto-1,3,4-Thiadiazol-2-yl Group

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Abstract
Compounds with a methoxy benzamide structure contain a methoxy group (–OCH_3) and an amide functional group (–$CONH_2$) within a benzene ring. This causes the compound to exhibit a complex structure with polar and nonpolar characteristics. These compounds are significant in pharmaceutical chemistry, biological research, and chemical synthesis. Due to its active properties, the "N–C–S" linkage in the thiadiazole ring can chelate metal ions. The antimicrobial activity of benzamide compounds derived from thiazoles and their wide applications in medicine increases the importance of methoxybenzamide derivatives. In this study, 5-amino-1,3,4-thiadiazole-2-thiol compounds were reacted with 2-methoxy, 3-methoxy, and 4-methoxybenzoyl chloride in toluene under a reflux condenser, resulting in the synthesis of methoxybenzamide derivatives (a, b, c). The structural characterization of the obtained methoxybenzamide (a, b, c) compounds was performed using FTIR, LC/MS-ESI, 1H NMR, 13C APT spectroscopy, and elemental analysis. Additionally, the thermal stability of the synthesized methoxybenzamide compounds was investigated through thermal analysis (TGA/DTA/DTG).

Keywords: Methoxybenzamide, 1,3,4-thiadiazol, Synthesis, Structural Characterization, Thermal Stability,

INTRODUCTION
Nonlinear optical materials containing amides play a significant role in the evolution of modern technology (Figure 1). These compounds notably impact technology and industrial applications [1-5]. Recent studies in nonlinear optics have highlighted the significant potential of second-order organic optical materials. These materials are recognized for their versatility and effectiveness across a range of applications, including photonics, which involves the generation, manipulation, and detection of photons; lasers, where they serve as crucial components for light amplification; and electro-optic switches, which enable rapid control of light signals in communication systems. Additionally, second-order organic materials play a vital role in frequency conversion processes that allow for the generation of new wavelengths of light, essential for telecommunications and data transmission. Their unique properties also make them suitable for advanced data storage solutions, improving the efficiency and capacity of information technology systems. [6-9].

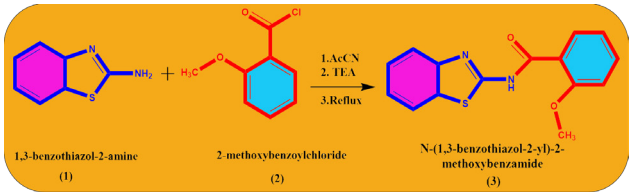

Figure 1. Synthesis of a compound containing methoxybenzamide [4].

Pyrazole is a five-membered ring compound containing two adjacent nitrogen atoms [10,11]. Knorr's 1883 discovery of antipyrine inspired the chemical structure of pyrazole. Since that time, numerous new derivatives have been synthesized. The pyrazole derivative compounds obtained have been found to exhibit a wide range of biological activities, including anticancer [12], anti-inflammatory [13], analgesic [14], antihypertensive [15], antipyretic [16], antimicrobial [17], and antioxidant [18] properties [19]. Among the drugs available on the market, Sildenafil, Celebrex, Zometapin, Fipronil, Rimonabant, and Lonazolac show therapeutic potential [20]. 1,3,4-Thiadiazoles are a crucial class of heterocyclic compounds. The "N–C–S" linkage in 1,3,4-thiadiazole can serve as an active site, demonstrate good tissue permeability, and chelate various metal ions in the body. The aromaticity of thiadiazole significantly influences its lower toxicity and in vivo stability [21]. So far, thiadiazoles have demonstrated impressive antiviral [22], antimicrobial [23], anti-inflammatory [24], antituberculosis [25], and anticancer [26] activities. 1,3,4-Thiadiazole is also found in many drugs, such as ceftazidime, cefazolin, acetazolamide, methazolamide, and megazol [27]. Amid derivatives are widely used in medicinal chemistry, organic compounds, and biomolecules due to the prevalence of amide bonds and their biological activity in living systems [28-31].

To discover and design more effective and cost-efficient drugs for clinical use, hybrid molecules have been created by combining different pharmacophores through a thorough literature review. This approach aims to achieve synergistic chemotherapeutic activity, increased selectivity, and minimized toxicity. As a result, pyrazole-containing thiazole [32], 1,2,4-oxadiazole [33], 1,3,4-oxadiazole [34], 1,2,4-triazoles, and benzoxazoles [35] have been synthesized, and an increase in pharmacological activity has been observed. Additionally, many biologically active pyrazolyl-1,3,4-thiadiazole derivative compounds have been synthesized. Therefore, studies on synthesizing pyrazole-based thiadiazole derivatives have gained importance [36,37].

Problems arise due to the increasing resistance to drugs during the treatment of fungal infections [38-42]. Therefore, the results obtained when synthesizing new antifungal compounds indicate that tetrazole-containing compounds provide more effective outcomes. These azole compounds inhibit the growth of many pathogenic strains. For example, 1-(2,4-dihydroxythiobenzoyl) tetrazoles and tetrazole compounds containing hydrazone groups exhibit high antifungal activity against Candida spp. [43-46]. Tetrazole-based compounds, distinguished by the presence of both hydrazone and thiazoline functional groups, have demonstrated notable antifungal properties. These compounds are particularly effective against a range

of fungal pathogens, including Trichoderma harzianum, Aspergillus ochraceus, and several species of Fusarium such as Fusarium solani, Fusarium moniliforme, and Fusarium culmorum. Additionally, they have shown activity against Candida albicans, making them promising candidates for the development of antifungal treatments [47]. Tetrazoles with a quinolone scaffold are effective against C. albicans and A. niger, while tetrazole derivatives with triazine dendrimeric chalcones show high fungicidal activity against C. albicans, A. niger, A. fumigatus, and Saccharomyces cerevisiae [48-52].

EXPERIMENTAL

Reagents and Instrumentation

All melting points are uncorrected and in °C with a Gallenkamp apparatus. FT-IR spectra were recorded on a Thermo Nicolet 6700 Spectrometer (ATR). NMR spectrometer and chemical shifts are expressed in 6 ppm using TMS as an internal standard. using a Bruker AVANCE III spectrometer. Mass spectra were obtained (LC-MS/MS) method with a Thermo Scientific / TSQ Quantum Access Max Mass Spectrometer. Compounds were thermally analyzed using a Shimadzu DTG-60 and a Perkin Elmer Pyris TGA device. Elemental analyses were conducted using the Leco TruSpec Micro Elemental Device.

General synthesis of N-(5-mercapto-1,3,4-thiadiazol-2-yl)-2/3/4-methoxybenzamide (a-c)

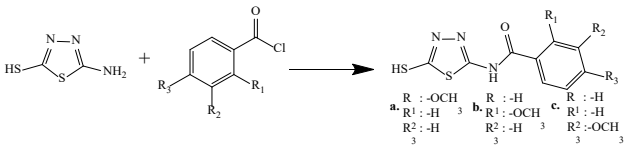

Figure 2. General synthetic procedure of methoxybenzamide derivatives (a-c)

Substances *5-amino-1,3,4-thiadiazole-2-thiol* (1.33 g, 1.0 mmol) and pyridine (1.0 mmol) were placed in toluene (5 mL) a balloon in which nitrogen gas was passed. 2-methoxybenzoyl chloride (a, b, c) was added to this mixture drop by drop within 10 minutes. The mixture was boiled under the back cooler until the reaction was complete. The completion of the reaction was checked by TLC (n-hexane: ethyl acetate, 1:1). After 4 hours, the reaction was completed, and pyridine was extracted with water (3 times 15 mL). Toluene was evaporated under reduced pressure. The resulting precipitate was crystallized in ethanol [53,54].

N-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-methoxybenzamide, (a).

As stated in headline 2.2, it was prepared based on items 5-amino-1,3,4-thiadiazole-2-thiol and 2-methoxybenzoyl chloride. Yield: 0.60 g (75%); white solid. Melting point: 246-247 °C; FT-IR (ATR, cm^{-1}) : 3271 NH, 3124, 3082 aromatic C-H, 2981, 2936, 2835 aliphatic C-H, 1648 CO, 1595 C=C. ^{1}H NMR spectra data (ppm, d_6-DMSO): 7.63-7.61 (d, 1H, Ar-H), 7.53-7.49 (t, 1H, j=7.46 Hz, Ar-H), 7.14-7.11 (d, 1H, Ar-H), 7.01-6.99 (t, 1H, j=7.46 Hz, Ar-H), 3.81 (s, 3H, OCH_3). ^{13}C NMR APT (ppm, d_6-DMSO): Negative amplitude: 167.82 (HS-C), 159.35 (C=O), 158.48 (Ar-C-OCH_3), 157.69 (S-C=N), 121.69 (Ar-C-CO). Positive amplitude: 133.51 (Ar-CH), 131.07 (Ar-CH), 120.47 (Ar-CH), 112.71 (Ar-CH), 56.14 (OCH_3). MS (-ESI): m/z 265.99 ([M-H]$^-$; $C_{10}H_9N_3O_2S_2$ (M=267.32 g/mol).

N-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-methoxybenzamide, (b).

As stated in headline 2.2, it was prepared based on items 5-amino-1,3,4-thiadiazole-2-thiol and 3-methoxybenzoyl chloride. Yield :0.48 g (60%); white solid. Melting point: 245-247 °C; FT-IR (ATR, cm^{-1}) : 3215 NH, 3086 aromatic C-H, 2942, 2847, 2821 aliphatic C-H, 1676, 1642 CO, 1577 C=C. ^{1}H NMR spectra data (ppm, d_6-DMSO): 8.79 (s, 1H, NH), 7.71 (s, 1H, Ar-H), 7.54-7.52 (s, 1H, Ar-H), 7.44-7.42-7.40 (t, 1H, Ar-H), 7.21-7.20-7.19 (d, 1H, Ar-H), 3.86 (s, 3H, OCH_3). ^{13}C NMR APT (ppm, d_6-DMSO): Negative amplitude: 172.75 (HS-C), 167.57 (C=O), 162.84 (Ar-C-OCH_3), 159.75 (S-C=N), 132.71 (Ar-C-CO). Positive amplitude: 130.16 (Ar-CH), 122.00 (Ar-CH), 119.33 (Ar-CH), 114.35 (Ar-CH), 55.93 (OCH_3). MS (-ESI): m/z 266.94 ([M-H]$^-$; $C_{10}H_9N_3O_2S_2$ (M=267.32 g/mol).

N-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-methoxybenzamide, (c).

As started in headline 2.2, it was prepared the basis of items *5-amino-1,3,4-thiadiazole-2-thiol* and 4-methoxybenzoyl chloride. Yield : 0.57 g (71%); white solid. Melting point: 244-246 °C; FT-IR (ATR, cm^{-1}) : 3263 NH, 3057, 3017 aromatic C-H, 2898, 2849 aliphatic C-H, 1666, 1624 CO, 1593, 1565 CC. ^{1}H NMR spectra data (ppm, d_6-DMSO): 8.81 (s, 1H, NH) 7.91, 7.82 (d, 2H, Ar-H), 7.03-7.00 (d, 2H, Ar-H), 3.82 (s, 3H, OCH_3). ^{13}C NMR APT (ppm, DMSO-d_6) (The solvent peak was referenced when giving the APT. The solvent peak here is located on the opposite side compared to the others): Positive amplitude: 172.53 (HS-C), 167.48 (C=O), 163.27 (Ar-C-OCH_3), 123.39 (Ar-CH). Negative amplitude: 131.80 (Ar-CH), 114.51 (Ar-CH), 56.06 (OCH_3). MS (-ESI): m/z 266.93 ([M-H]$^-$; $C_{10}H_9N_3O_2S_2$ (M=267.32 g/mol).

RESULT AND DISCUSSION

Elemental Analysis

CHNS elemental analyses of molecules were performed and when the obtained results were examined, it was determined that the experimental and theoretical element composition percentages were compatible. The values in parentheses were calculated theoretically, while the others are the experimentally found percentage compositions.

N-(5-mercapto-1,3,4-thiadiazol-2-yl)-*2*-methoxybenzamide (a):

C: 44.52% (44.93%); H: 4.12% (3.39%); N: 15.87% (15.72%); S: 23.65% (23.99%)

N-(5-mercapto-1,3,4-thiadiazol-2-yl)-*3*-methoxybenzamide (b):

C: 44.15% (44.93%); H: 4.21% (3.39%); N: 15.63% (15.72%); S: 23.71% (23.99%)

N-(5-mercapto-1,3,4-thiadiazol-2-yl)-*4*-methoxybenzamide (c):

C: 44.33% (44.93%); H: 4.05% (3.39%); N: 15.58% (15.72%); S: 23.81% (23.99%)

FTIR Analysis

Methoxybenzamide derivatives (a, b, c) were obtained from the reaction of 5-amino-1,3,4-thiadiazole-2-thiol with methoxybenzamide compounds (2-methoxy, 3-methoxy, 4-methoxy). FTIR spectroscopy was initially used to characterize the structure of the obtained compounds. In the starting compound, 5-amino-1,3,4-thiadiazole-2-thiol, the -NH_2 group shows a broad stretching band around 3400 cm^{-1}

in the FTIR spectrum. In the synthesized methoxybenzamide compounds, a weak stretching band around 3263 cm^{-1} is observed, indicating the formation of the amide bond and confirming that the reaction has occurred. The C=O stretching bands in the structures of the a, b, and c methoxybenzamide compounds are close at 1648, 1642, and 1624 cm^{-1}, respectively, demonstrating that the obtained compounds are correct.

^{13}C NMR APT and ^{1}H NMR Analysis

In the ^{1}H NMR spectrum of N-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-methoxybenzamide (a), chemical shifts correspond to four different protons in the aromatic region. In the 1H NMR spectrum of N-(5-mercapto-1,3,4-thiadiazol-2-yl)-3-methoxybenzamide (b), five different proton chemical shifts are observed in the aromatic region, while in N-(5-mercapto-1,3,4-thiadiazol-2-yl)-4-methoxybenzamide (c), due to the para position of the methoxy group on the benzene ring, the protons in the benzene ring are symmetric, and two different proton chemical shifts are observed. The different chemical shifts of the aromatic protons indicate that the three compounds are distinct. In compounds b and c, a singlet for the N-H group chemical shift is observed at 8.79 and 8.81, while no chemical shift for the N-H group is observed in compound a. ^{1}H and ^{13}C NMR spectra of the synthesized new compounds were recorded in Dimethyl sulfoxide-d6 (DMSO-d6) as solvent. The chemical shifts of the carbons in the compounds were investigated using ^{13}C-NMR (APT) spectroscopy. By referencing the solvent peak, the chemical shifts of the carbons in the compounds were examined in positive and negative fields. In compounds a and b, the carbon chemical shifts are observed in similar regions. The carbons in the benzene ring and the methoxy group in compounds a and b exhibit chemical shifts in the positive field, while the other carbons in the structure show chemical shifts in the negative field. In compound c, the carbon chemical shifts are observed in the opposite field compared to compounds a and b. The chemical shifts of the carbons in the benzene ring and the methoxy group are observed in the negative field, while the other carbons show chemical shifts in the positive field.

Liquid chromatography-tandem mass spectrometry analysis

The LC/MS (Electrospray Ionisation-ESI) molecular ion peaks for compounds a, b, and c were identified at 265.99 $[M-H]^-$, 266.94 $[M-H]^-$, and 266.93 $[M-H]^-$ respectively, confirming the structures of these compounds. The physical properties of the synthesized compounds include white solids or powders, and they were obtained with high yields. In the mass spectrometry of compound (a), looking at the separated molecular ion peaks, the fragments of 72.99 [CHN_2S^{3-}] and 131.97 [$C_2H_2N_3S^{2\bullet}$] have been released, and the remaining compound has a peak at 135.04 g/mol [$C_8H_7O^{2\bullet}$]. In compound (b), the fragments of 58.98 [$CHNS^{2-}$] and 131.96 [$C_3H_2NOSO_2^{5-}$] are released, and the remaining ion peak is at 107.13 [$C_7H_7O^{3-}$]. Compound (c)'s mass spectrometry has detected no specific fragmentation product similar to the other compounds. In compound (c), the absence of fragmentation in the molecular ion peaks may be due to the methoxy functional group being attached to the phenyl ring in the para position and positioned away from the branched groups with electron density.

Thermal Analysis

Thermal analysis curves recorded because of thermal decomposition carried out in an inert nitrogen atmosphere in the range of 25-1000 °C are shown in Figures 3 and 4 for three samples combined. The decomposition steps of the samples whose weight loss curves are given in Figure 3 were determined to be close to each other. It was observed that the decomposition of the (a) molecule created better observable decomposition steps compared to other samples. The molecule with the most difficult decomposition steps to follow is the (c) derivative molecule, and this can be thought to be due to the methoxy functional group attached to the phenyl ring being attached in the para position and positioned away from the branched groups with electron density. Again, this may be the reason why the stability of the para derivative molecule is higher than the others. In all samples, it is seen that the first decomposition step starts at approximately 140 °C and ends at 200 °C. In this temperature range, the decomposition of the methoxy group attached to the phenyl ring is considered (experimental weight loss: 10.50%, theoretical weight loss: 11.61%). The next decomposition step is observed to start around 230 °C and end at 400 °C. The highest weight loss is observed in this temperature range, which can be interpreted as the decomposition of the thiazole group attached to the phenyl ring with the carbonyl bridge (experimental weight loss: 48.80%, theoretical weight loss: 49.45%). The temperature range that draws attention as the last decomposition step starts at 400 °C and ends in the 780 °C temperature regions. In this temperature range, the decomposition of the remaining phenyl and carbonyl groups of the organic molecule was observed (experimental weight loss: 38.20%, theoretical weight loss: 38.95%). As a result of thermal analysis, it was observed that approximately 1-2% black residues were present in the reaction vessel. Since the structure is completely organic, no residue was expected because of thermal analysis, but the 1-2% residue detected was interpreted as non-burnable carbonized carbon residue because of thermal decomposition carried out in an inert nitrogen atmosphere. It was confirmed by the differential thermal analysis (DTA) curves (Figure 4) that all thermal decomposition steps occurred under endothermic decomposition.

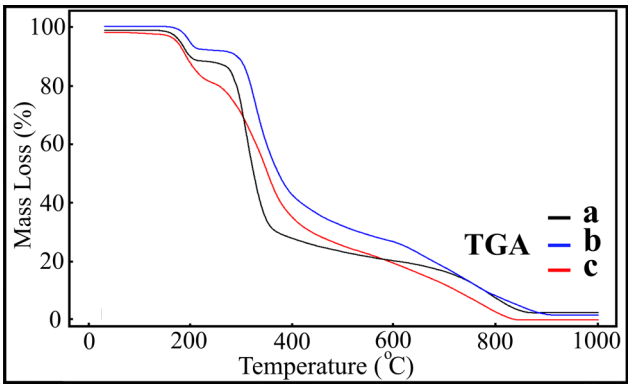

Figure 3. Thermal weight loss curves of o-, m-, p-methoxybenzamide derivative molecules

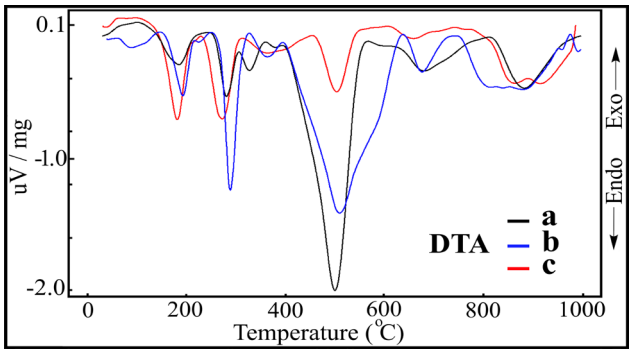

Figure 4. Differential thermal analysis curves of o-, m-, p-methoxybenzamide derivative molecules

CONCLUSION

The compounds N-(5-mercapto-1,3,4-thiadiazol-2-yl)-2-methoxybenzamide (a), N-(5-mercapto-1,3,4-thiadiazol-2-yl)-3-methoxybenzamide (b), and N-(5-mercapto-1,3,4-thiadiazol-2-yl)-4-methoxybenzamide (c) were obtained by the reaction of 5-amino-1,3,4-thiadiazole-2-thiol with 2-methoxybenzoyl chloride (a), 3-methoxybenzoyl chloride (b), and 4-methoxybenzoyl chloride (c), forming an amide bond. The antimicrobial properties of the obtained compounds and their potential as essential drug components in the medical field are attributed to the nature of the amide bond. Furthermore, heterocyclic compounds containing a 1,3,4-thiadiazole structure are essential due to their broad application fields. As a result of this study, methoxybenzamide derivatives containing 1,3,4-thiadiazole and amide bonds were obtained. The structural characterization of the obtained compounds was carried out using FTIR, MS-ESI, 1H NMR, 13C NMR APT spectroscopy, and elemental analysis. Thermal analysis (TGA/DTA/DrTG) examined their thermal stability. In conclusion, new compounds have been introduced to the chemical literature.

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Supplementary Materials

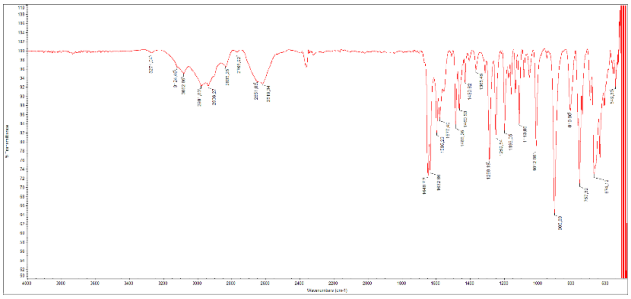

Fig S1. FTIR spectrum of (**a)** compound

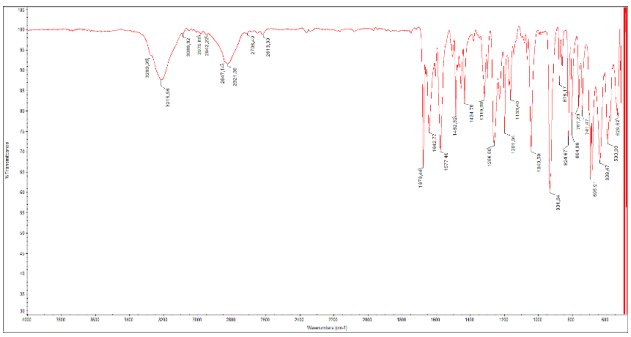

Fig S2. FTIR spectrum of (**b)** compound

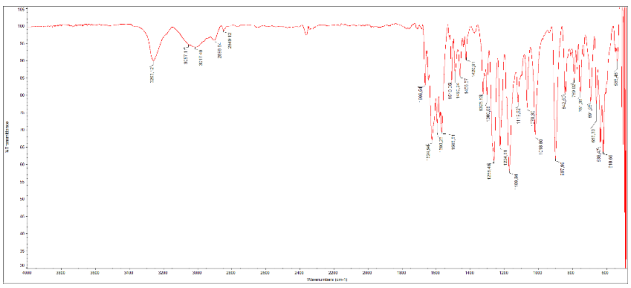

Fig S3. FTIR spectrum of (**c**) compound

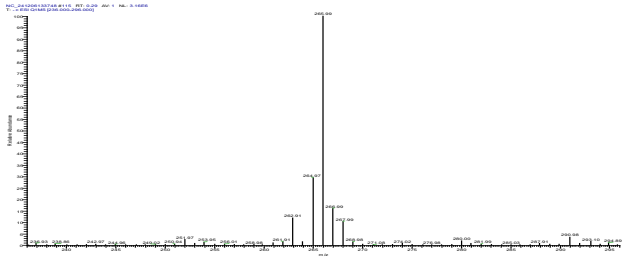

Fig S4. LS/MS (-ESI) spectrum of (**a**) compound

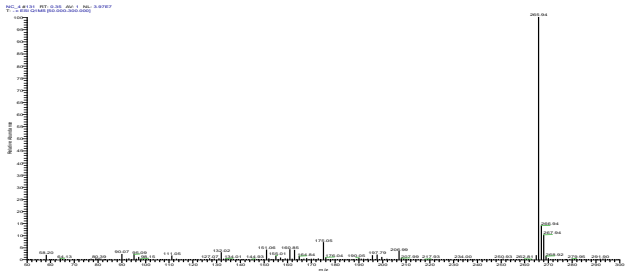

Fig S5. LS/MS (-ESI) spectrum of (**b**) compound

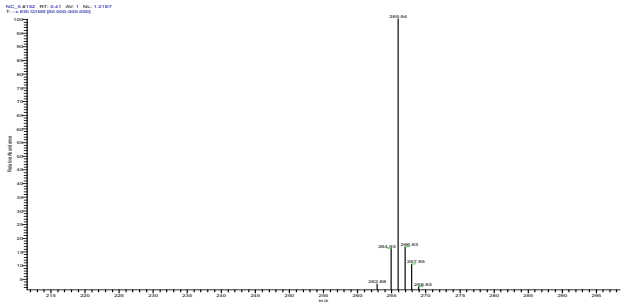

Fig S6. LS/MS (-ESI) spectrum of (**c**) compound

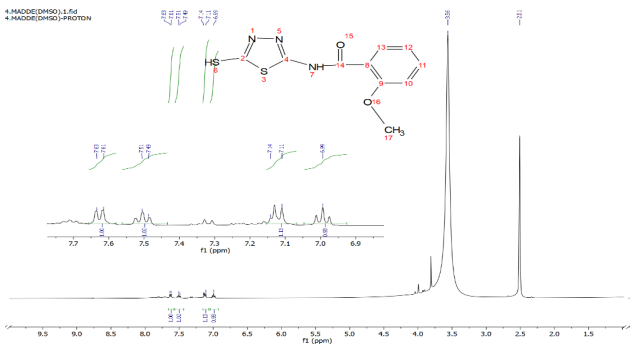

Fig S7. ^{1}H-NMR spectrum of (**a**) compound

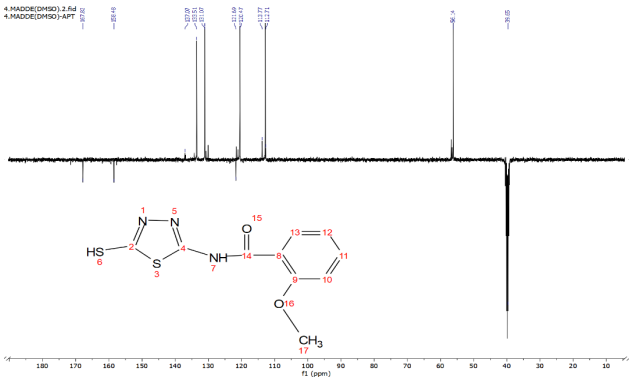

Fig S8. ^{13}C-NMR APT spectrum of (**a**) compound

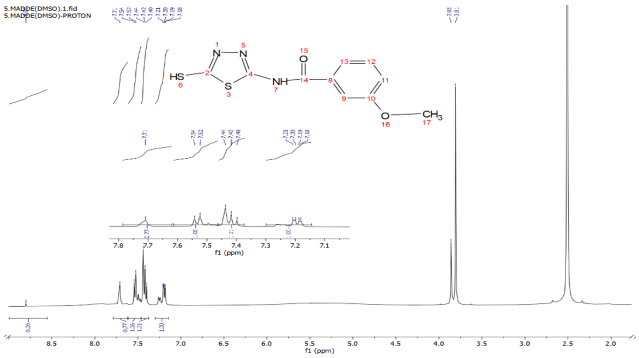

Fig S9. ^{1}H-NMR spectrum of (**b**) compound

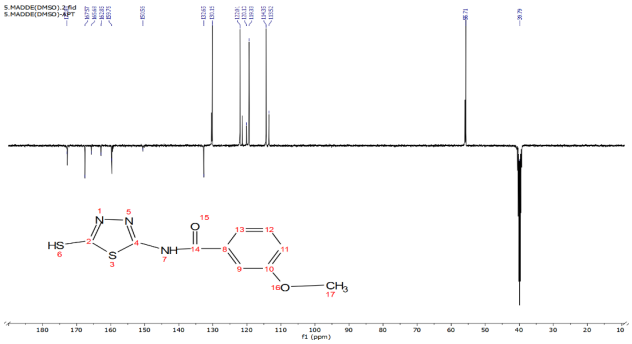

Fig S10. ^{13}C-NMR APT spectrum of (**b**) compound

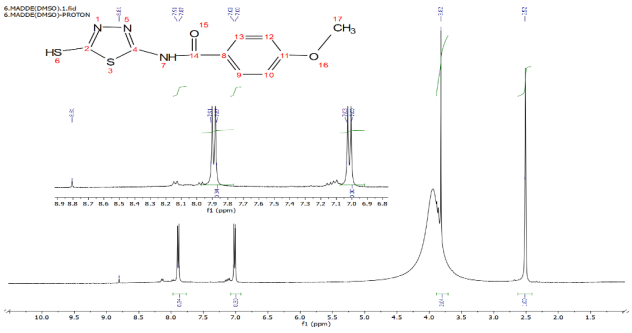

Fig S11. ^{1}H-NMR spectrum of (**c**) compound

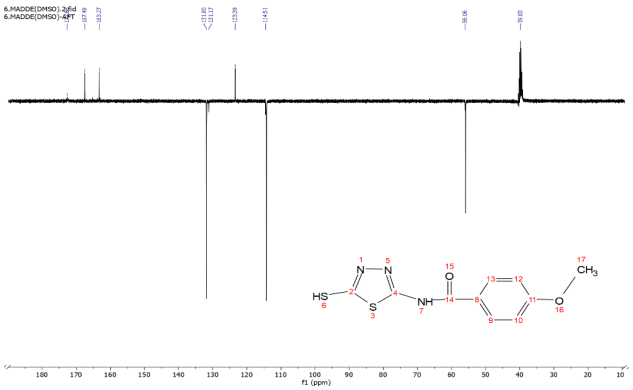

Fig S12. ^{13}C-NMR APT spectrum of (**c**) compound