

## Supplementary Material

# Synthesis, Characterization, and Biological Evaluation of Novel *N*-{4-[(4-Bromophenyl)sulfonyl]benzoyl}-*L*-valine Derivatives

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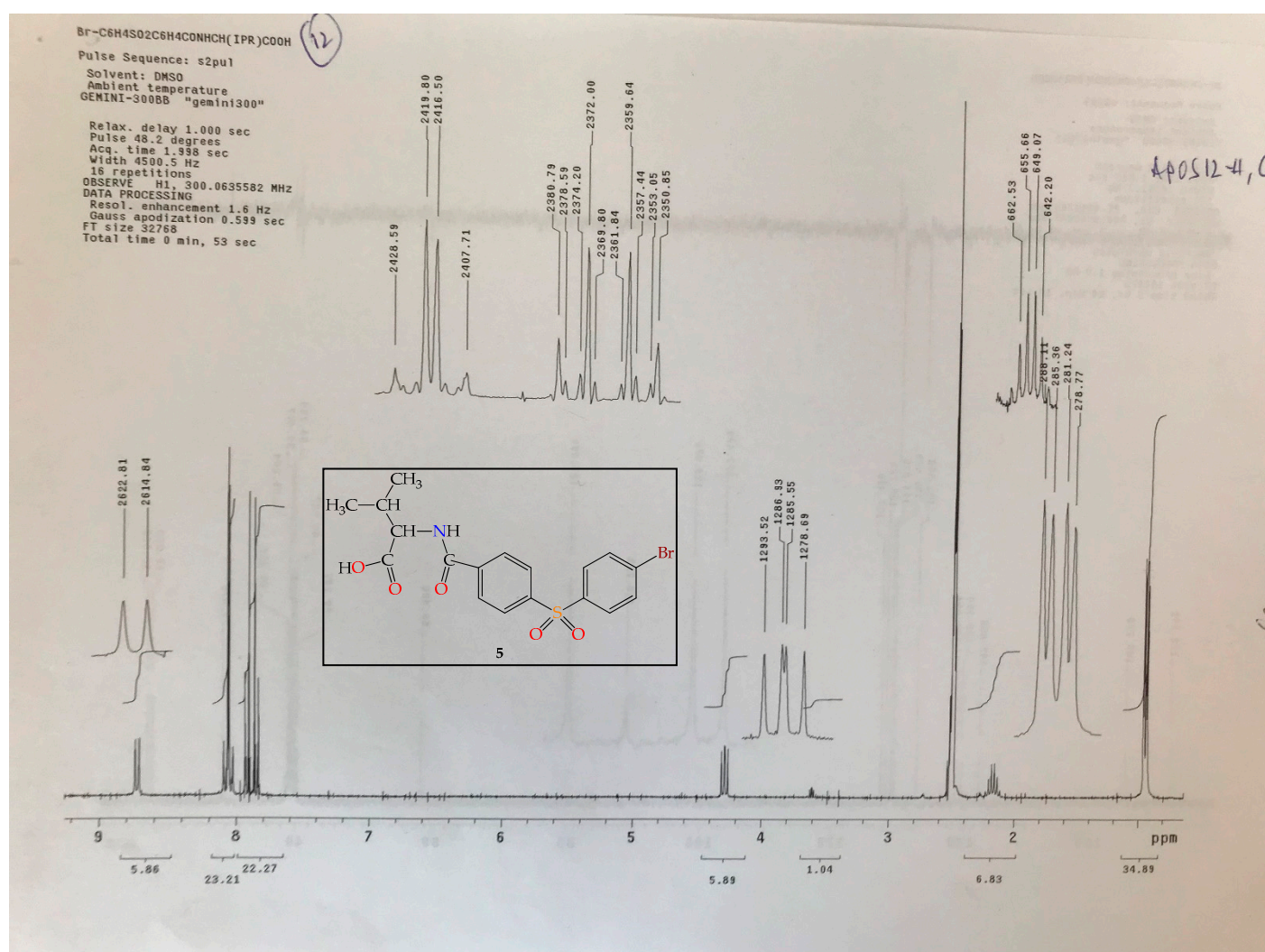


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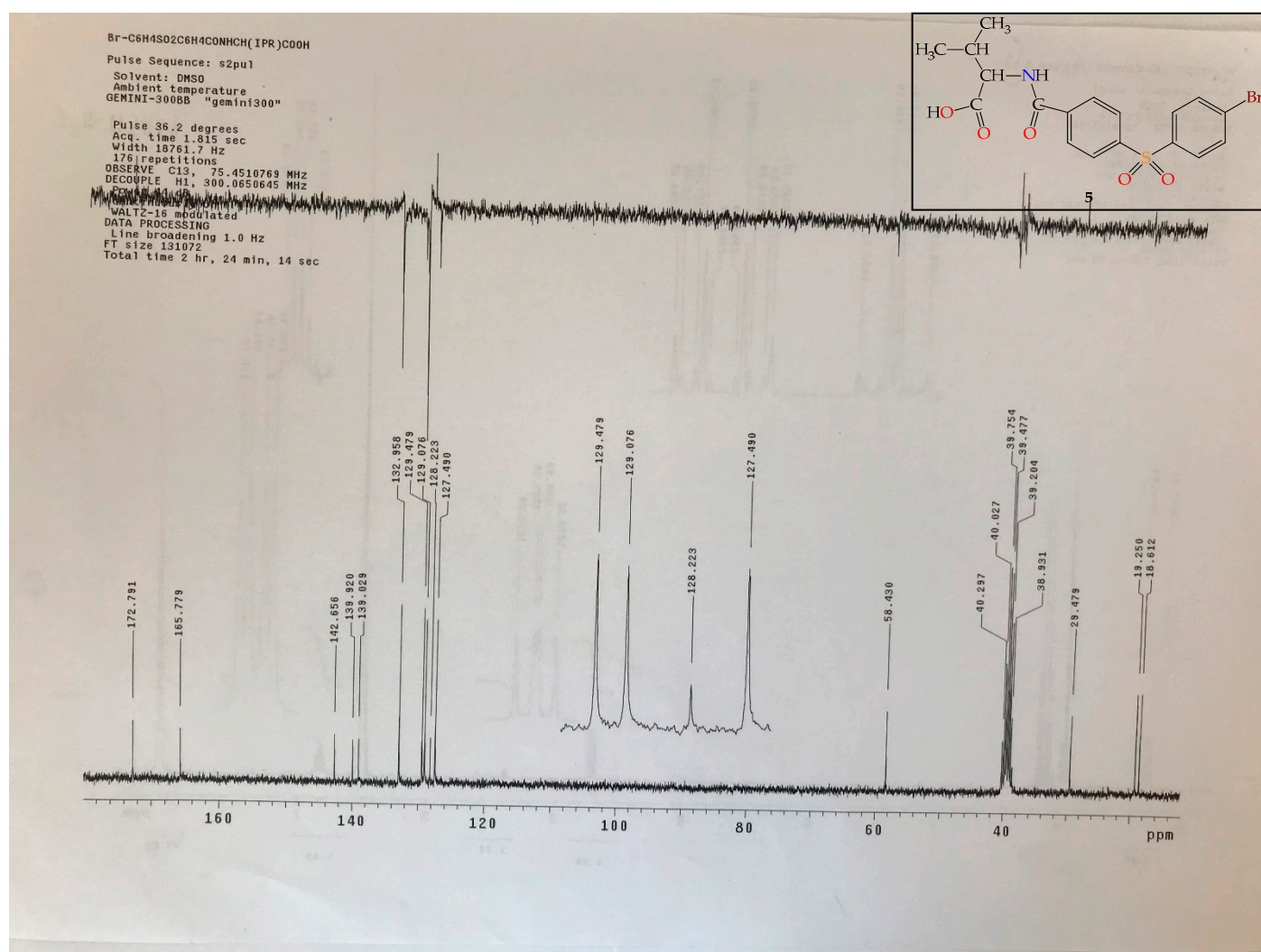
**Abstract:** In this article, we present the design and synthesis of novel compounds, containing in their molecules an *L*-valine residue and a 4-[(4-bromophenyl)sulfonyl]phenyl moiety, which belong to *N*-acyl- $\alpha$ -amino acids, 4*H*-1,3-oxazol-5-ones, 2-acylamino ketones, and 1,3-oxazoles chemotypes. The synthesized compounds were characterized through elemental analysis, MS, NMR, UV/VIS, and FTIR spectroscopic techniques, the data obtained are in accordance with the assigned structures. Their purities were verified by reversed-phase HPLC. The new compounds were tested for antimicrobial action against bacterial and fungal strains for antioxidant activity by DPPH, ABTS, and ferric reducing power assays, and for toxicity on freshwater cladoceran *Daphnia magna* Straus. Furthermore, *in silico* studies were performed concerning the potential antimicrobial effect and toxicity. The results of antimicrobial activity, antioxidant effect, and toxicity assays, as well as of *in silico* analysis revealed a promising potential of *N*-{4-[(4-bromophenyl)sulfonyl]benzoyl}-*L*-valine and 2-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-isopropyl-4*H*-1,3-oxazol-5-one for developing novel antimicrobial agents to fight Gram-positive pathogens, and particularly *Enterococcus faecium* biofilm-associated infections.

**Keywords:** *N*-acyl-*L*-valine; 4*H*-1,3-oxazol-5-one; 2-acylamino ketone; 1,3-oxazole; diphenyl sulfone scaffold; drug design; *in silico* studies; antimicrobial and antibiofilm actions; antioxidant effect; alternative toxicity testing

## Supplementary Material



**Figure S1.** The <sup>1</sup>H NMR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]benzamido]-3-methylbutanoic acid **5**.



**Figure S2.** The  $^{13}\text{C}$  NMR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]benzamido]-3-methylbutanoic acid **5**.



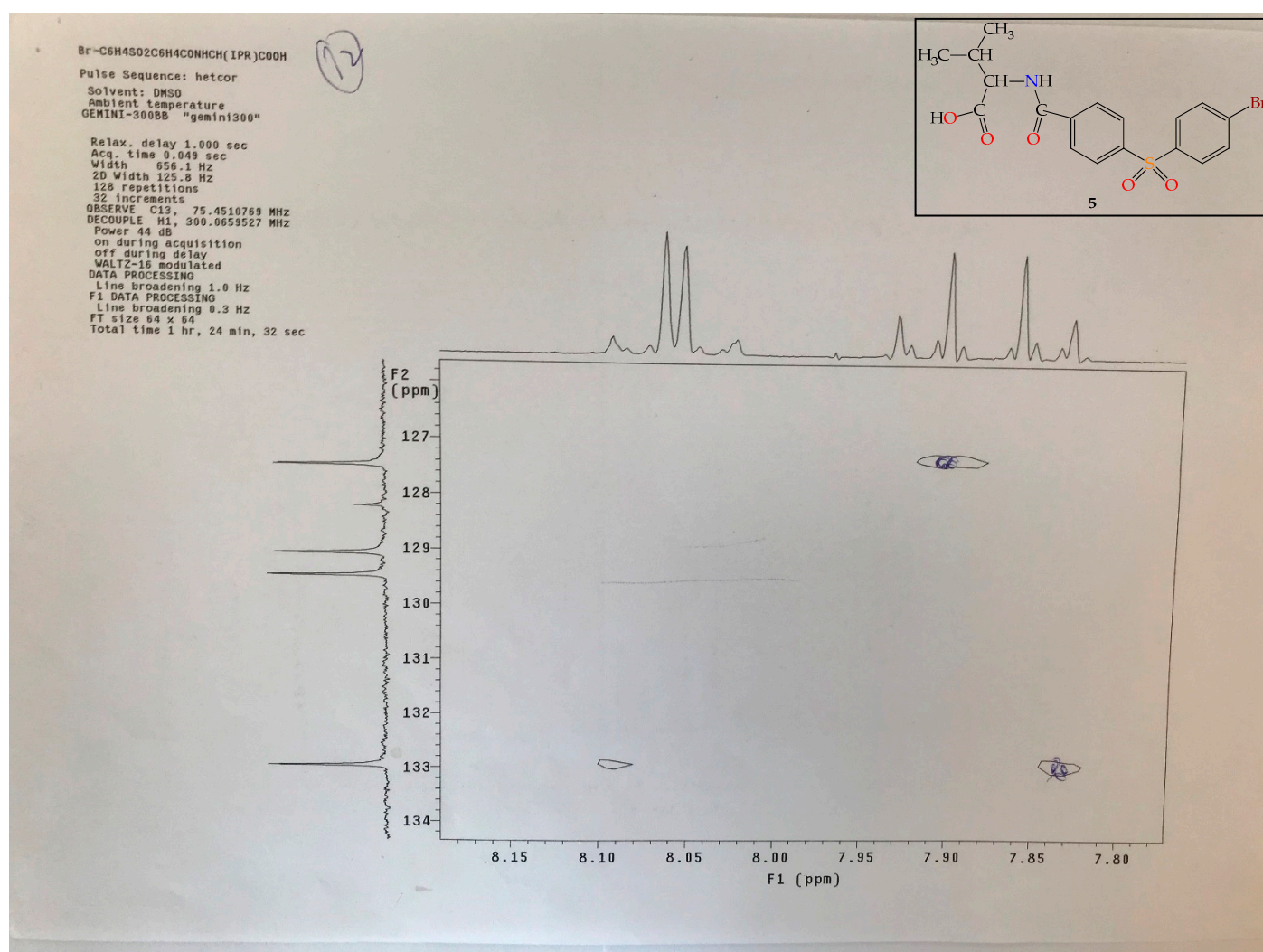
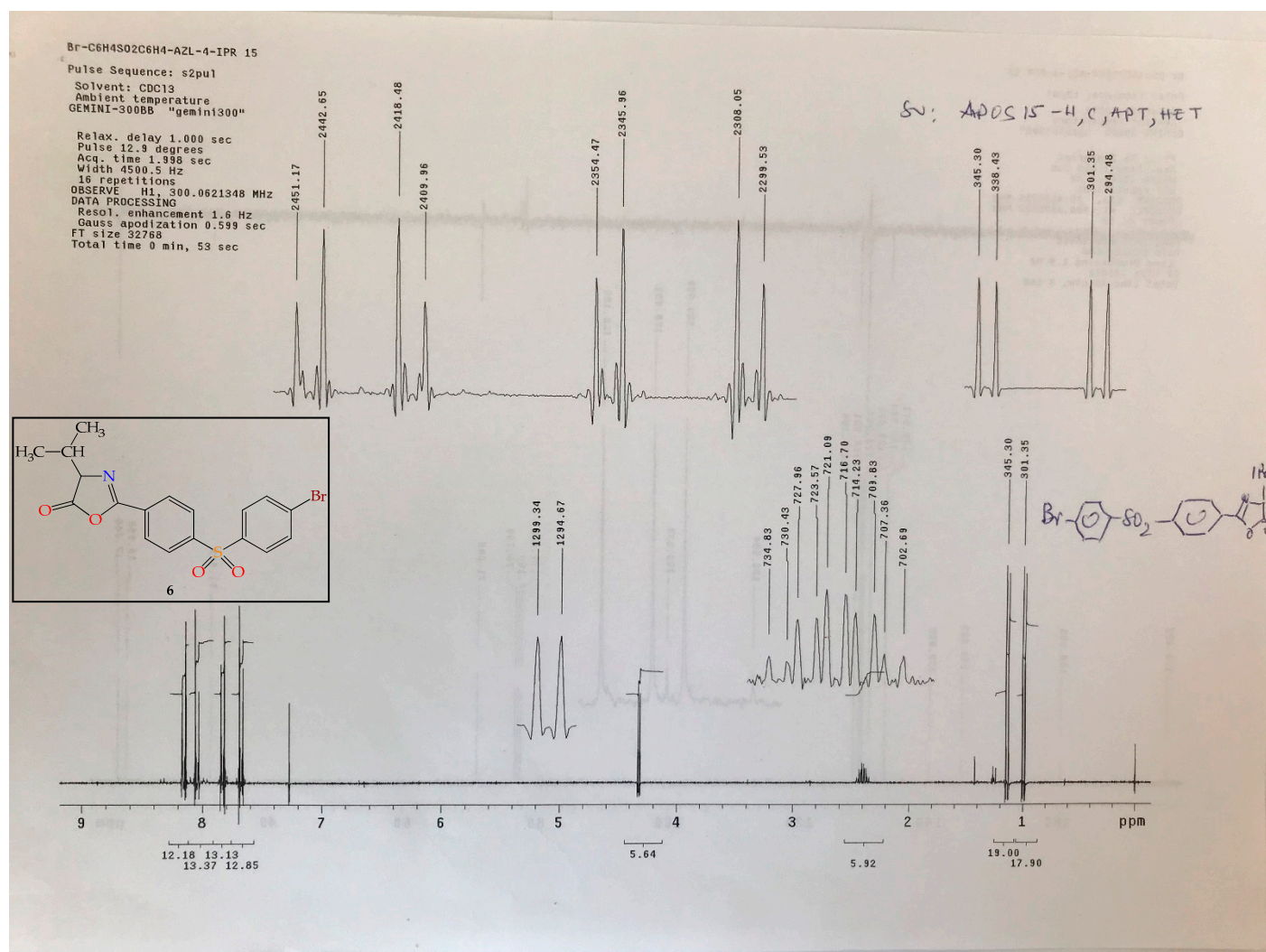


Figure S3. The 2D HETCOR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]benzamido]-3-methylbutanoic acid 5.





**Figure S4.** The  $^1\text{H}$  NMR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-4H-1,3-oxazol-5-one 6.

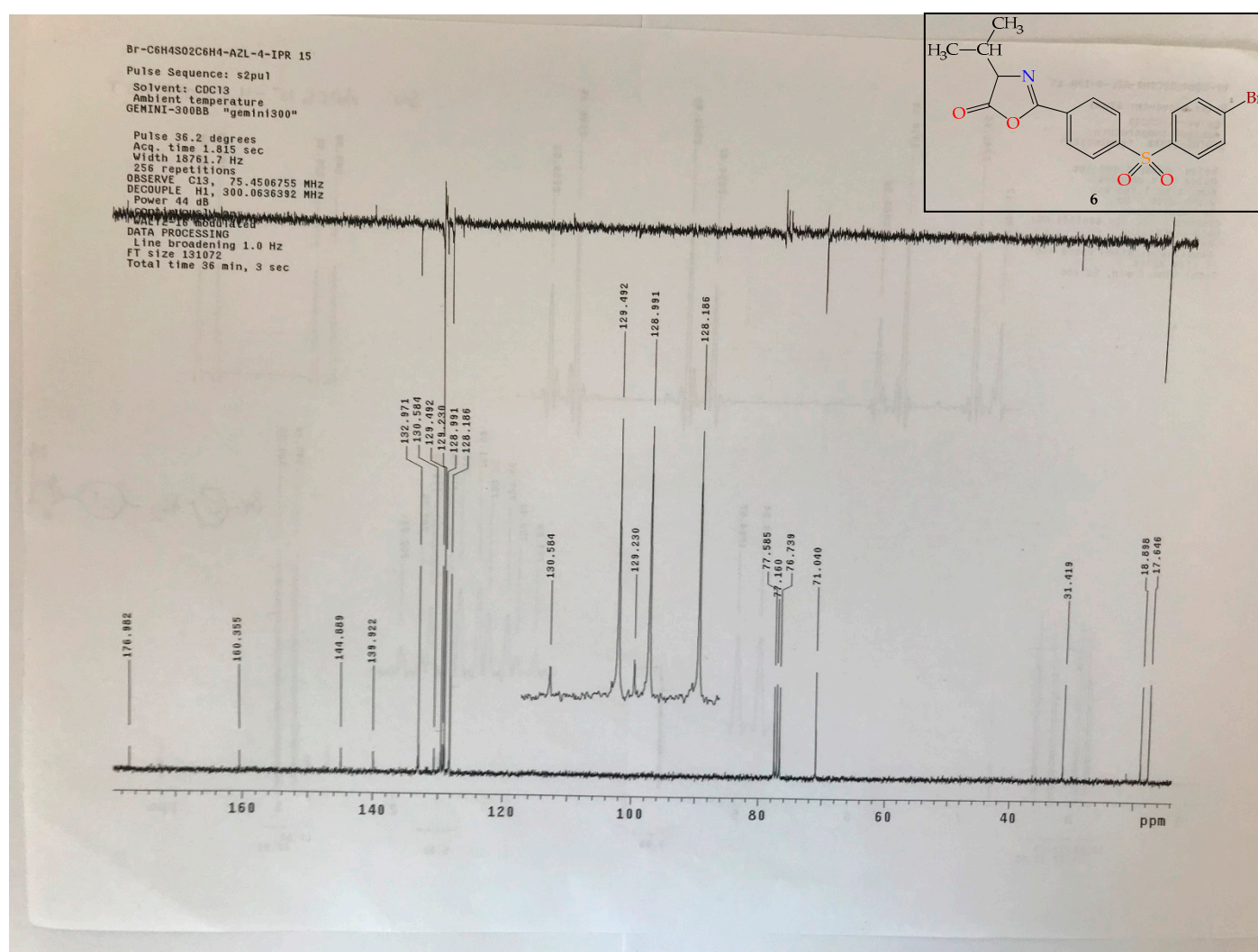
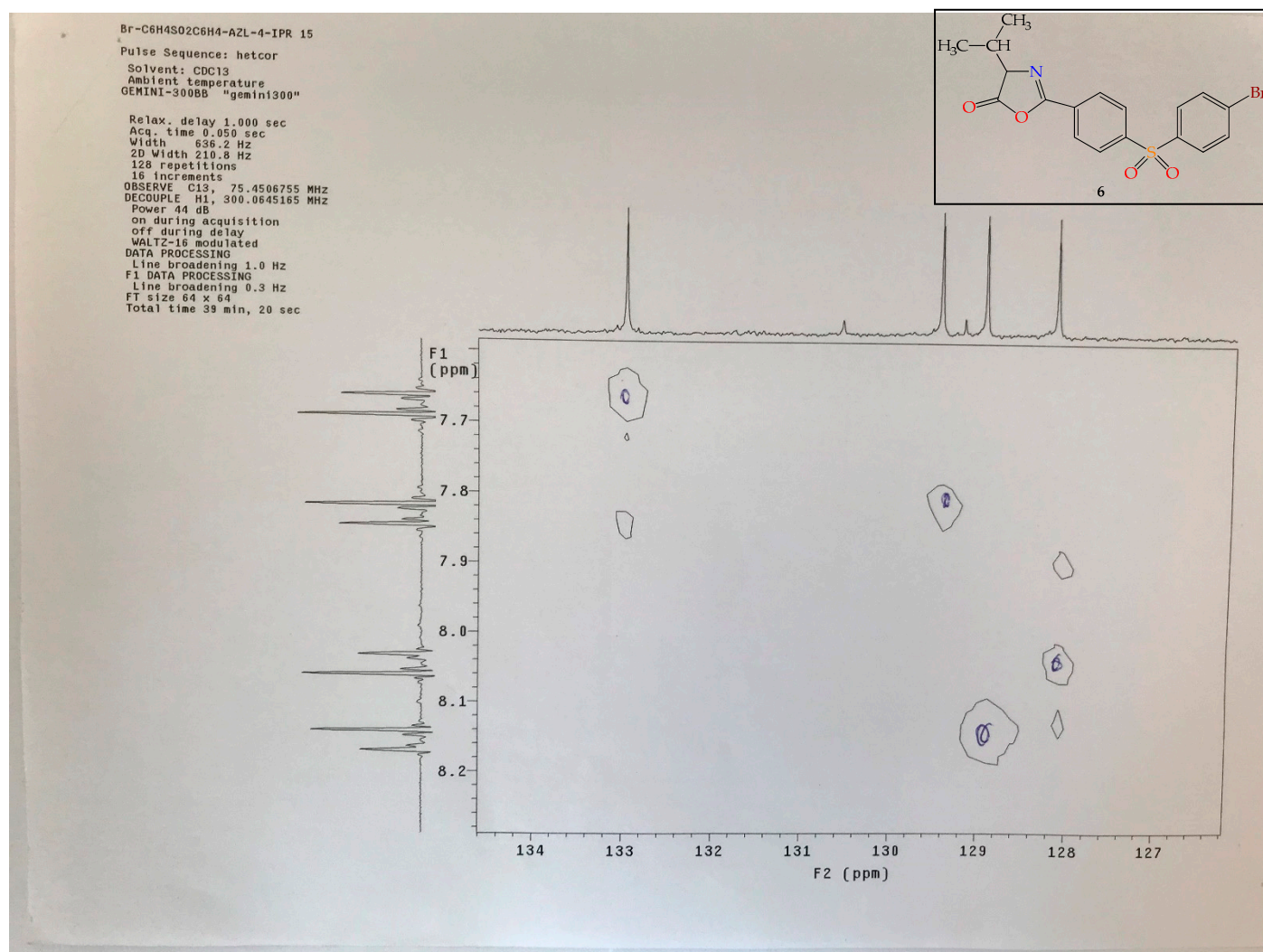
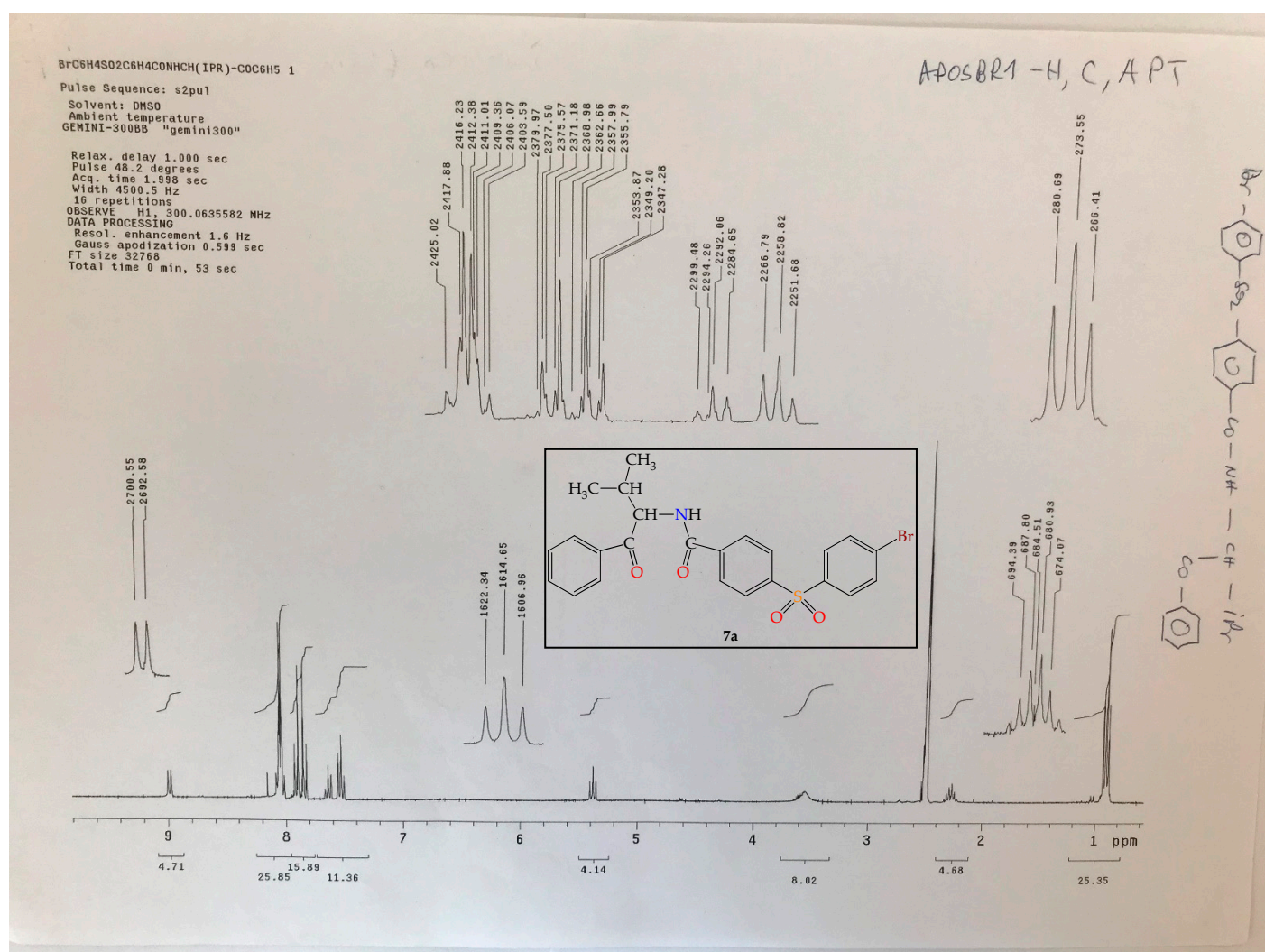


Figure S5. The  $^{13}\text{C}$  NMR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-4H-1,3-oxazol-5-one 6.



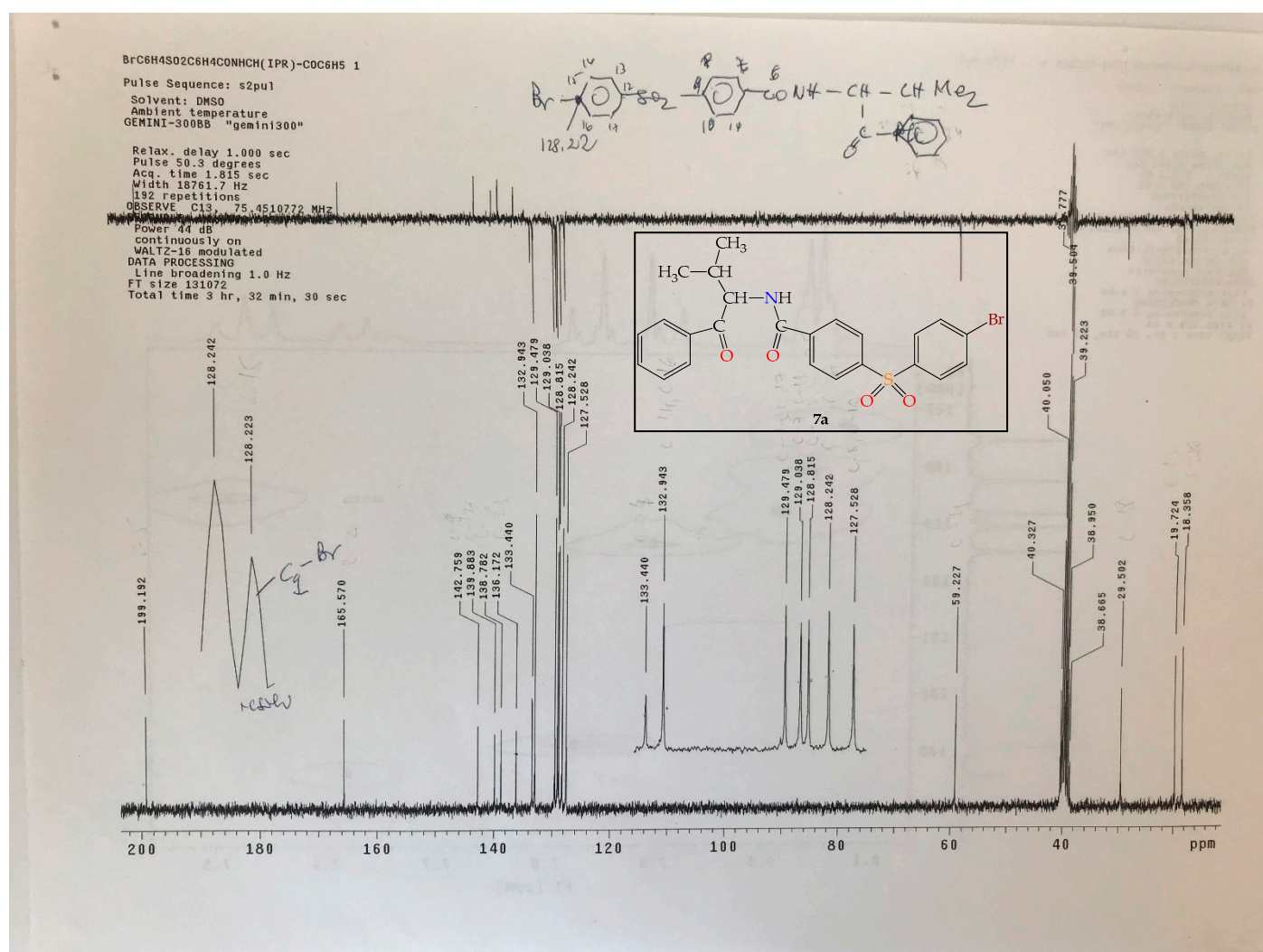


**Figure S6.** The 2D HETCOR spectrum of 2-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-isopropyl-4H-1,3-oxazol-5-one **6**.



**Figure S7.** The  $^1\text{H}$  NMR spectrum of 4-[(4-bromophenyl)sulfonyl]-N-(3-methyl-1-oxo-1-phenylbutan-2-yl)benzamide **7a**.





**Figure S8.** The  $^{13}\text{C}$  NMR spectrum of 4-[(4-bromophenyl)sulfonyl]-N-(3-methyl-1-oxo-1-phenylbutan-2-yl)benzamide **7a**.

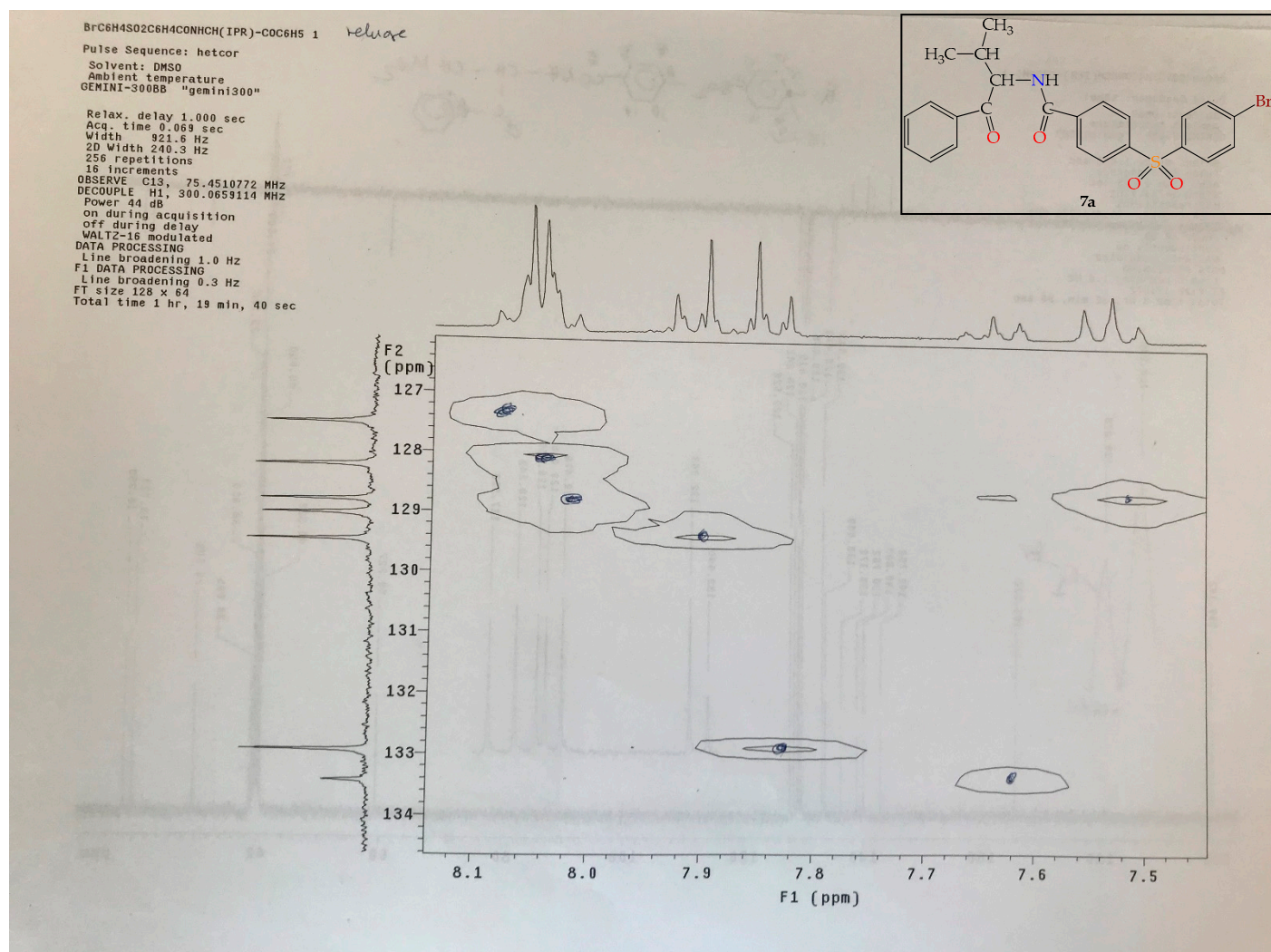


Figure S9. The  $^{13}\text{C}$  NMR spectrum of 4-[(4-bromophenyl)sulfonyl]-N-(3-methyl-1-oxo-1-phenylbutan-2-yl)benzamide **7a**.



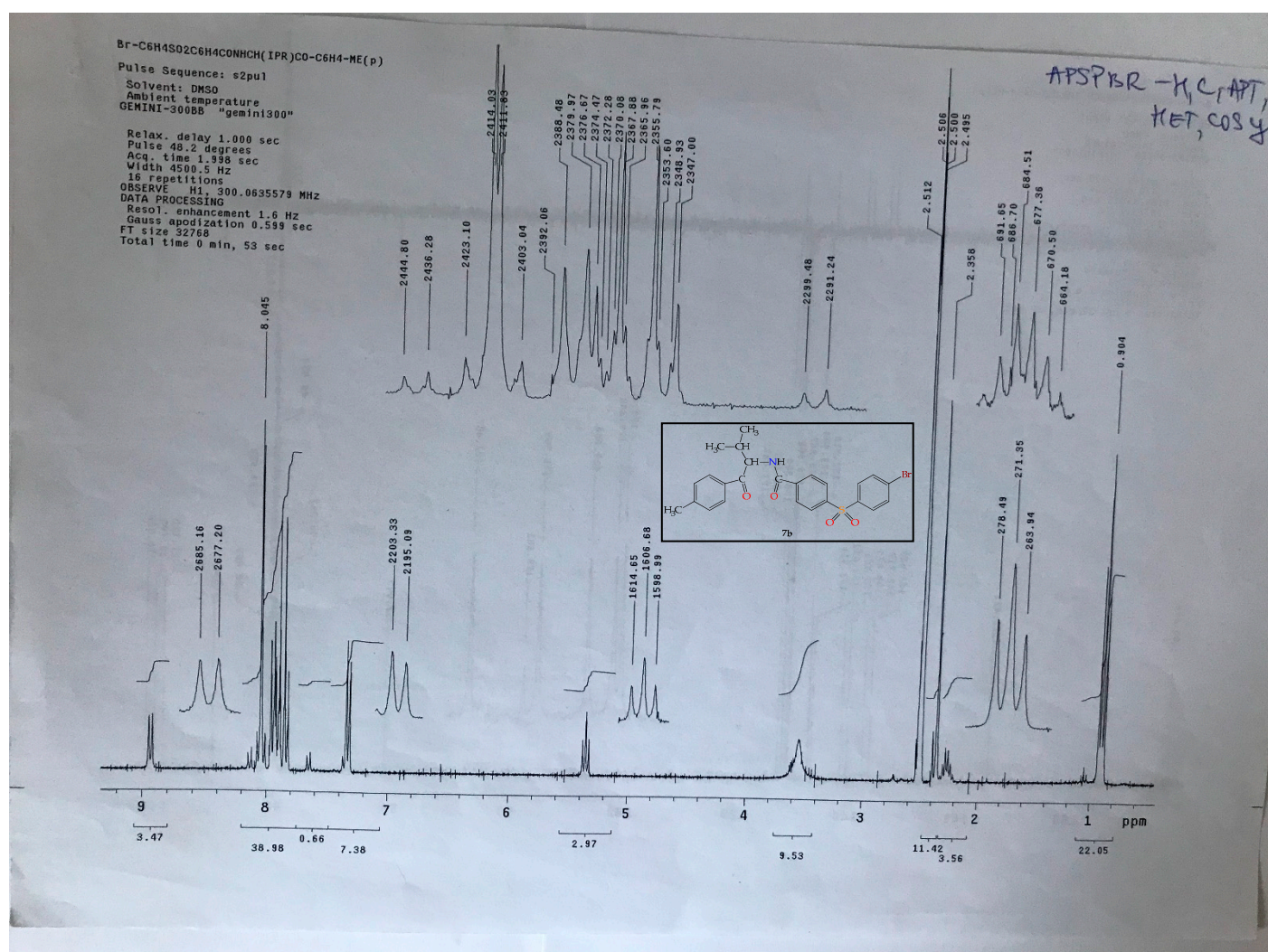


Figure S10. The  $^1\text{H}$  NMR spectrum of 4-[(4-bromophenyl)sulfonyl]-N-[3-methyl-1-oxo-1-(*p*-tolyl)butan-2-yl]benzamide **7b**.



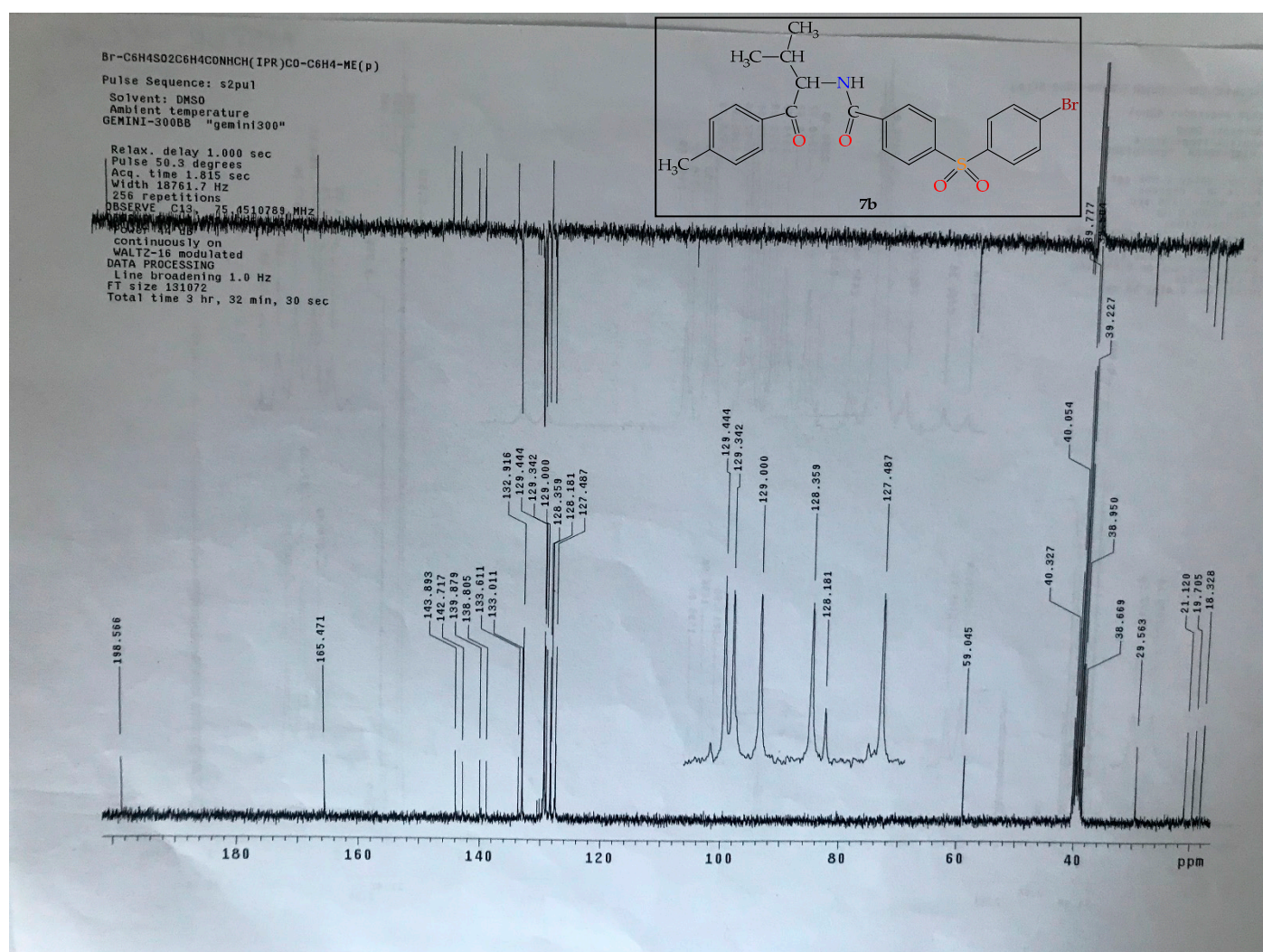
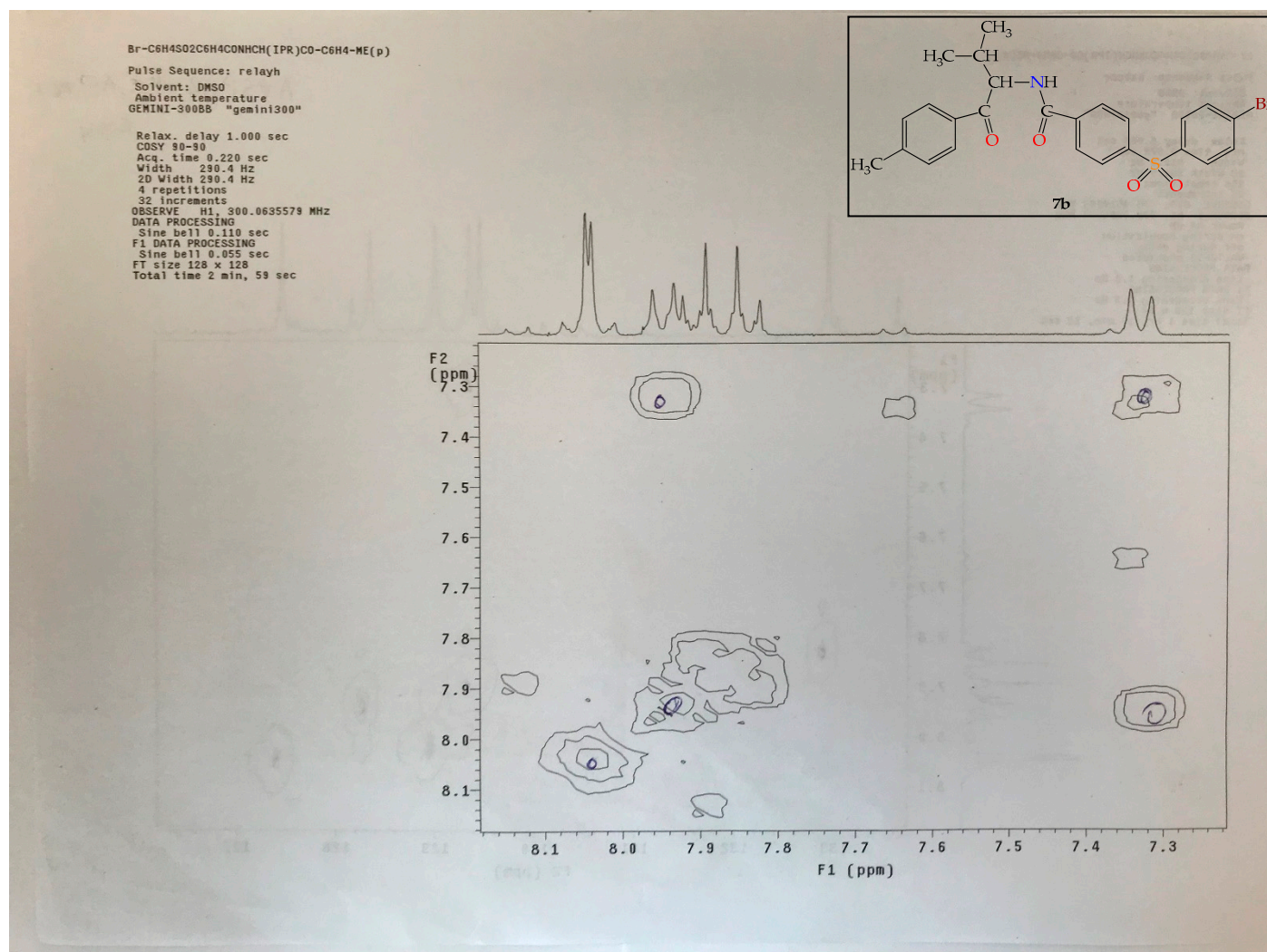


Figure S11. The  $^{13}\text{C}$  NMR spectrum of 4-[(4-bromophenyl)sulfonyl]-N-[3-methyl-1-oxo-1-(*p*-tolyl)butan-2-yl]benzamide **7b**.





**Figure S12.** The 2D COSY spectrum of 4-[(4-bromophenyl)sulfonyl]-N-[3-methyl-1-oxo-1-(*p*-tolyl)butan-2-yl]benzamide **7b**.

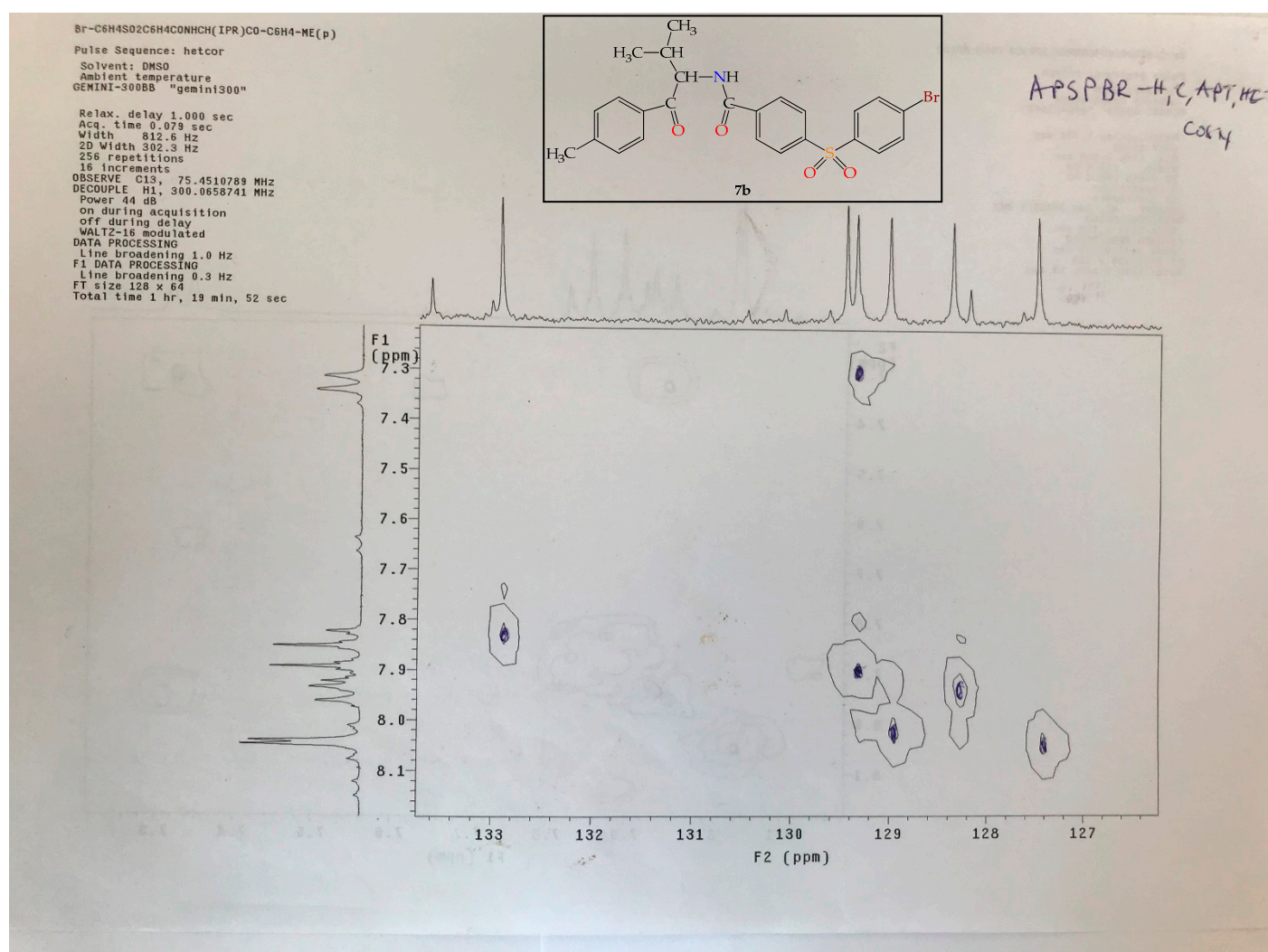


Figure S13. The 2D HETCOR spectrum of 4-[(4-bromophenyl)sulfonyl]-N-[3-methyl-1-oxo-1-(*p*-tolyl)butan-2-yl]benzamide **7b**.



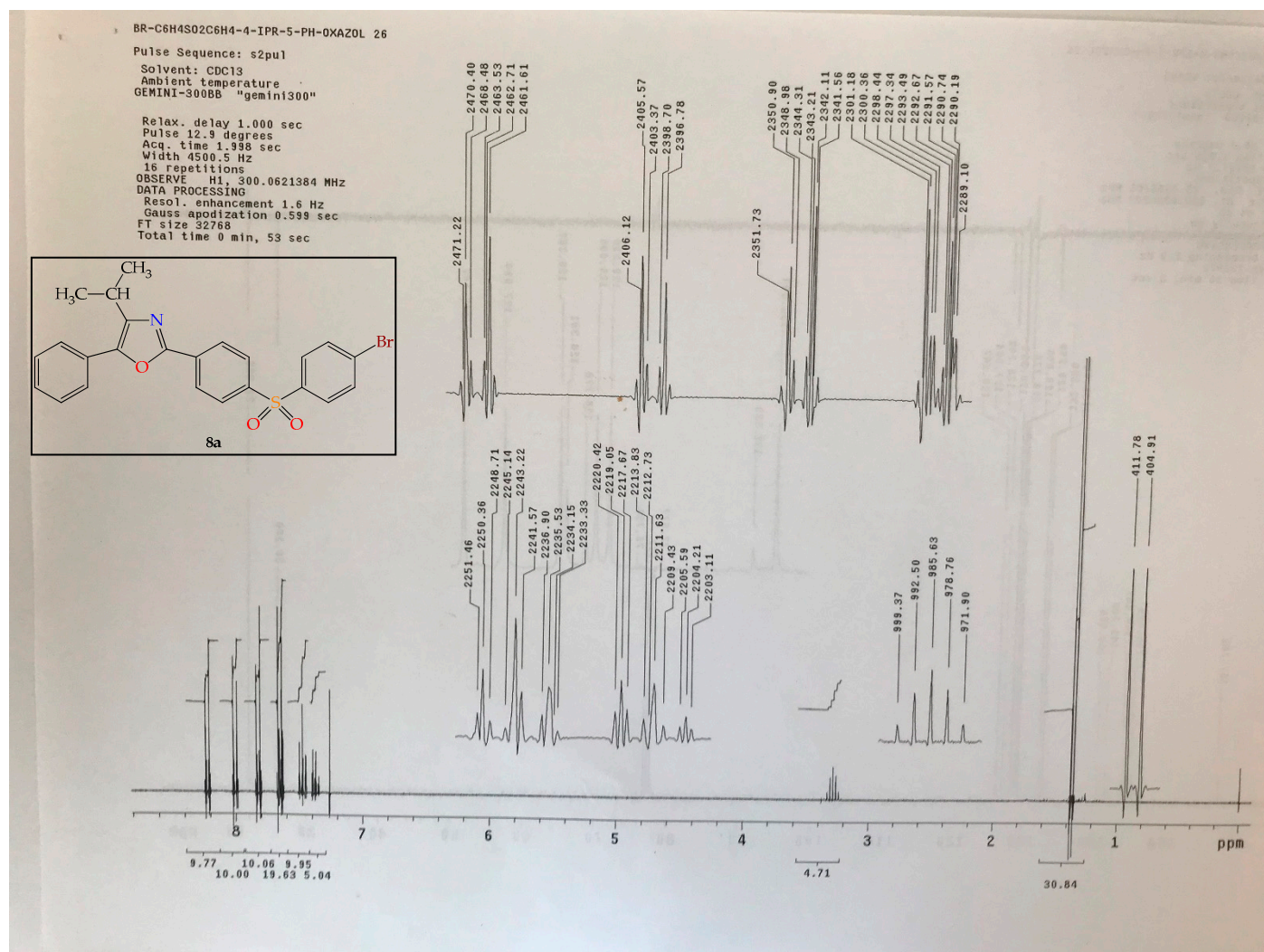
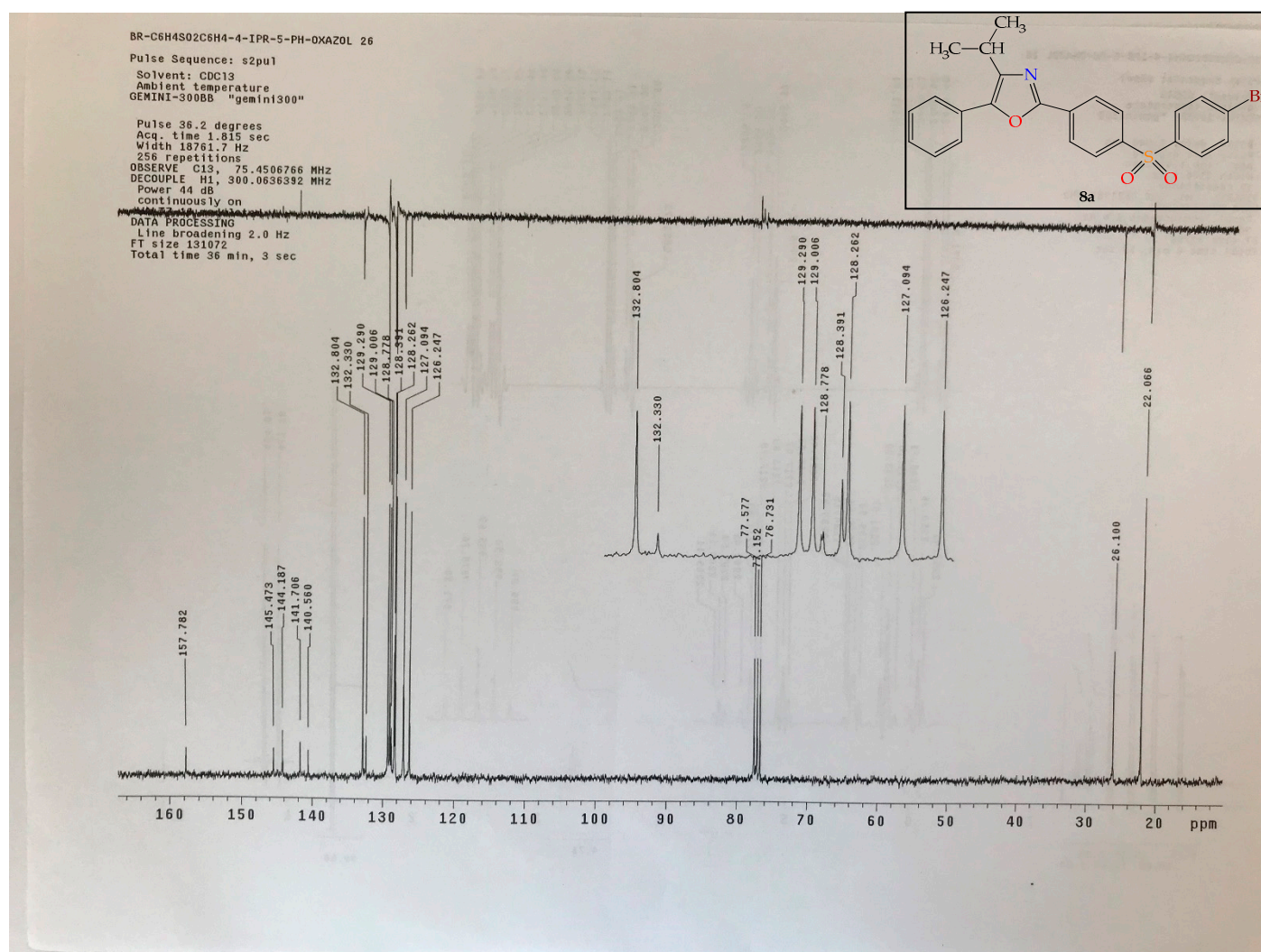


Figure S14. The  $^1\text{H}$  NMR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-phenyl-1,3-oxazole **8a**.



**Figure S15.** The  $^{13}\text{C}$  NMR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-phenyl-1,3-oxazole **8a**.



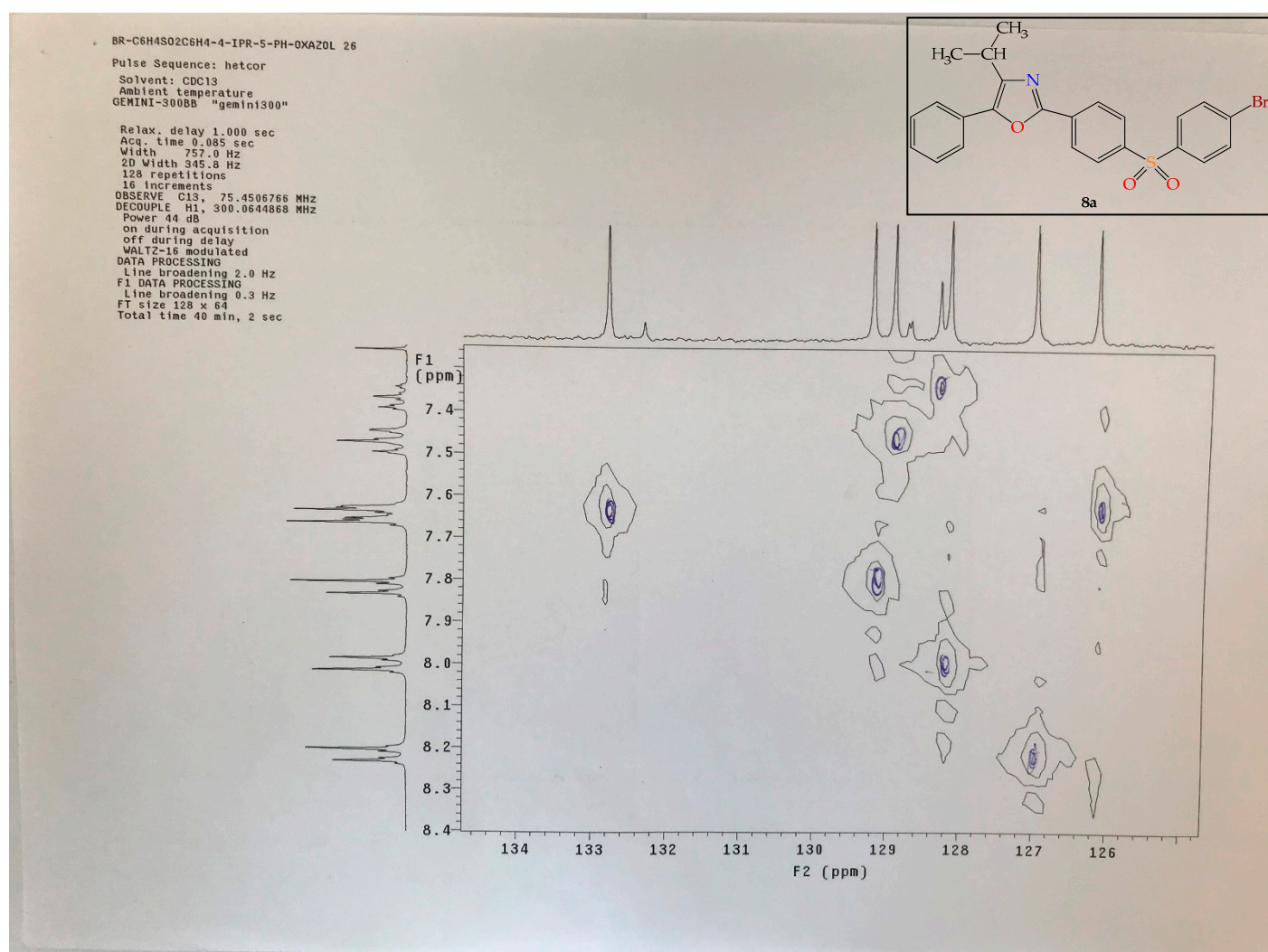
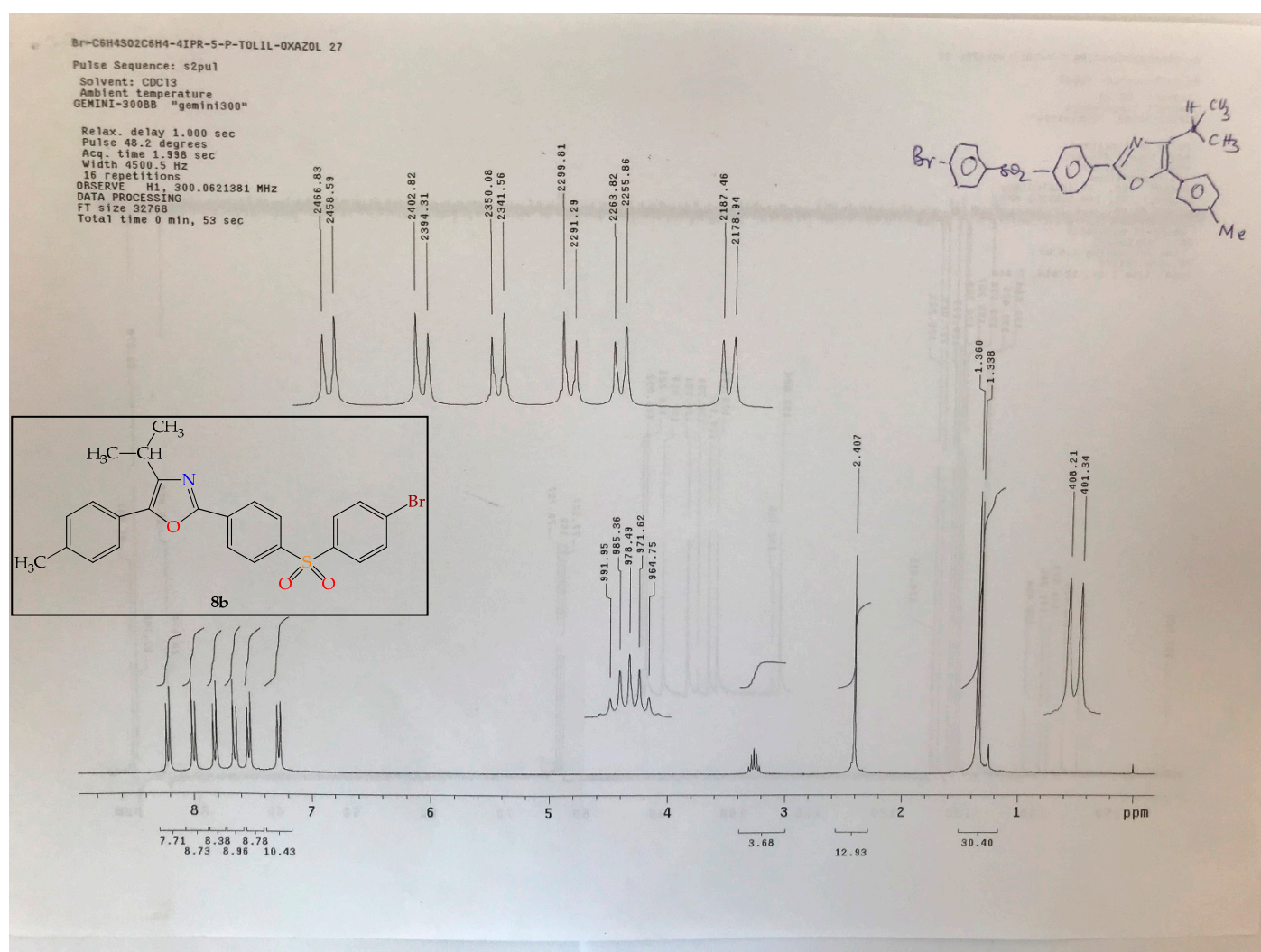


Figure S16. The 2D HETCOR spectrum of 2-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-isopropyl-5-phenyl-1,3-oxazole **8a**.



**Figure S17.** The  $^1\text{H}$  NMR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-(*p*-tolyl)-1,3-oxazole **8b**.



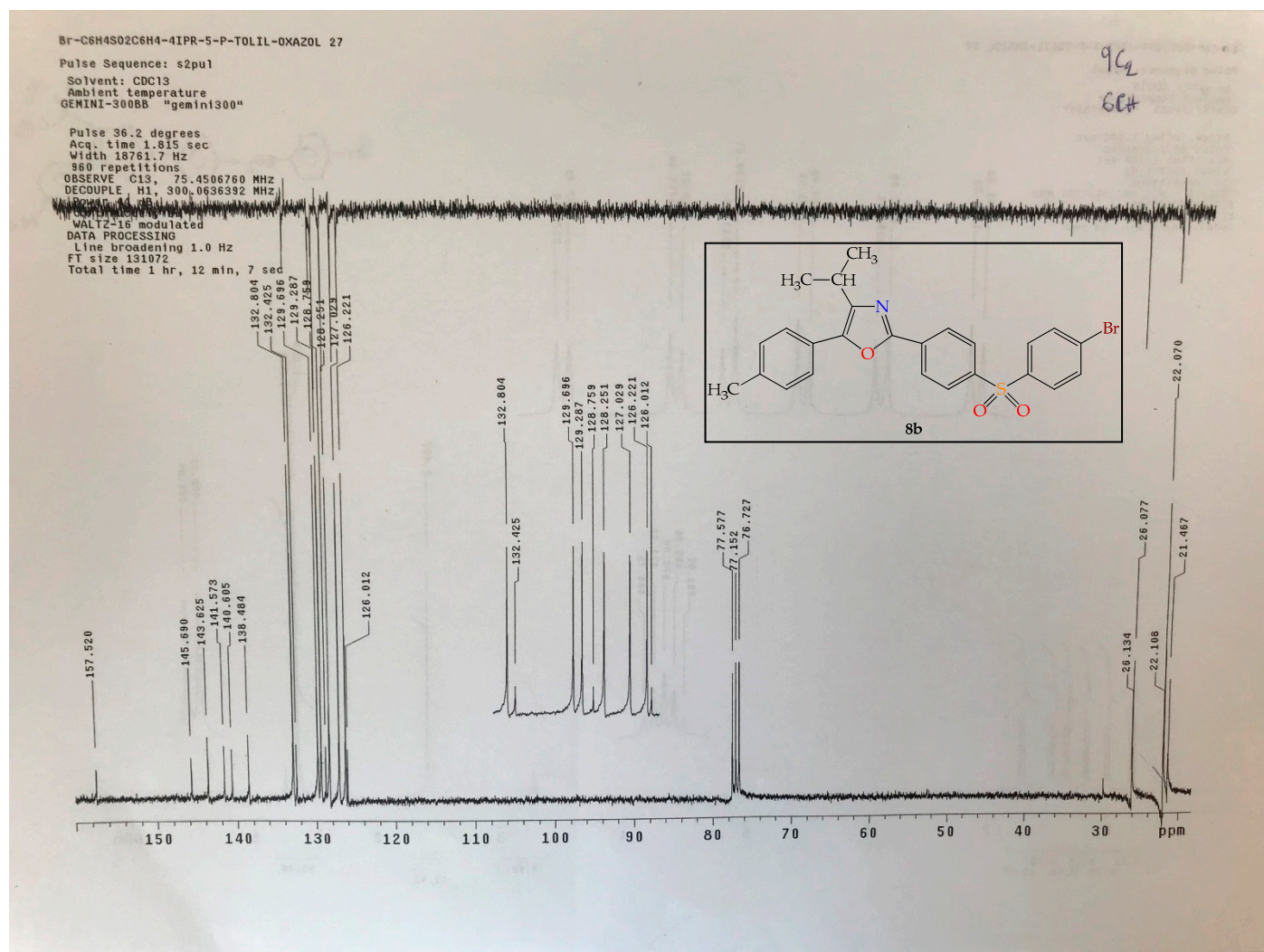
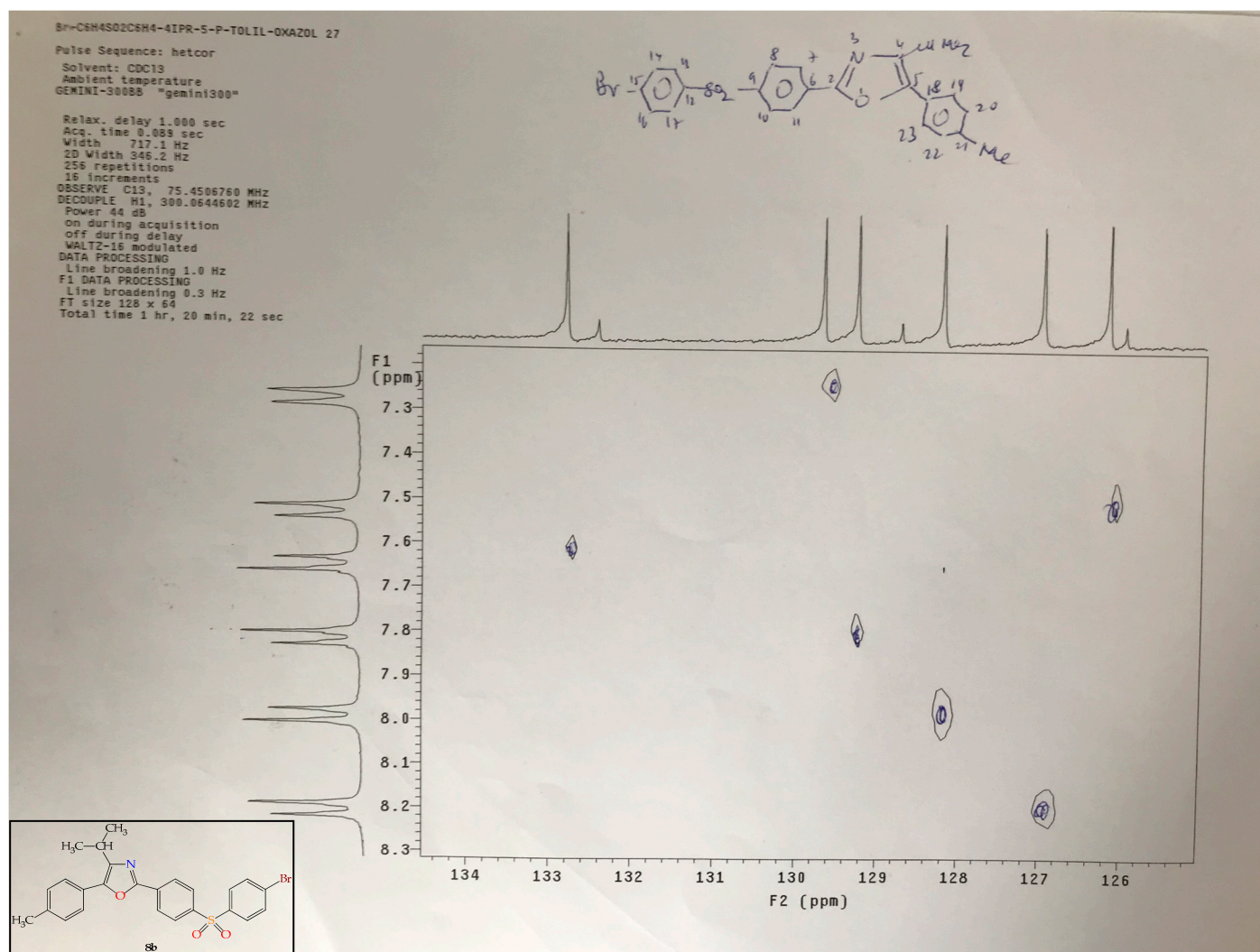
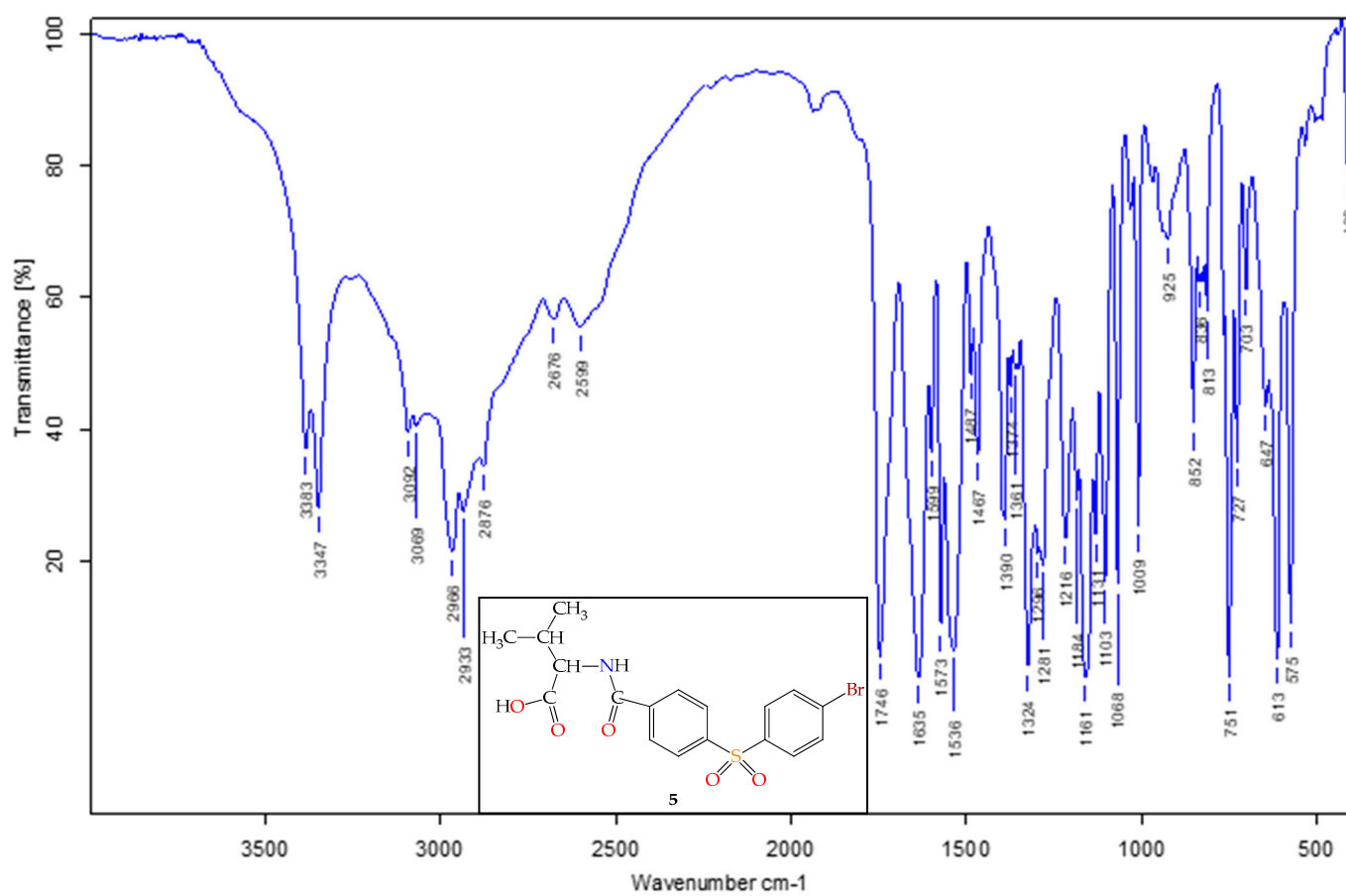


Figure S18. The  $^{13}\text{C}$  NMR spectrum of 2-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-isopropyl-5-(*p*-tolyl)-1,3-oxazole **8b**.

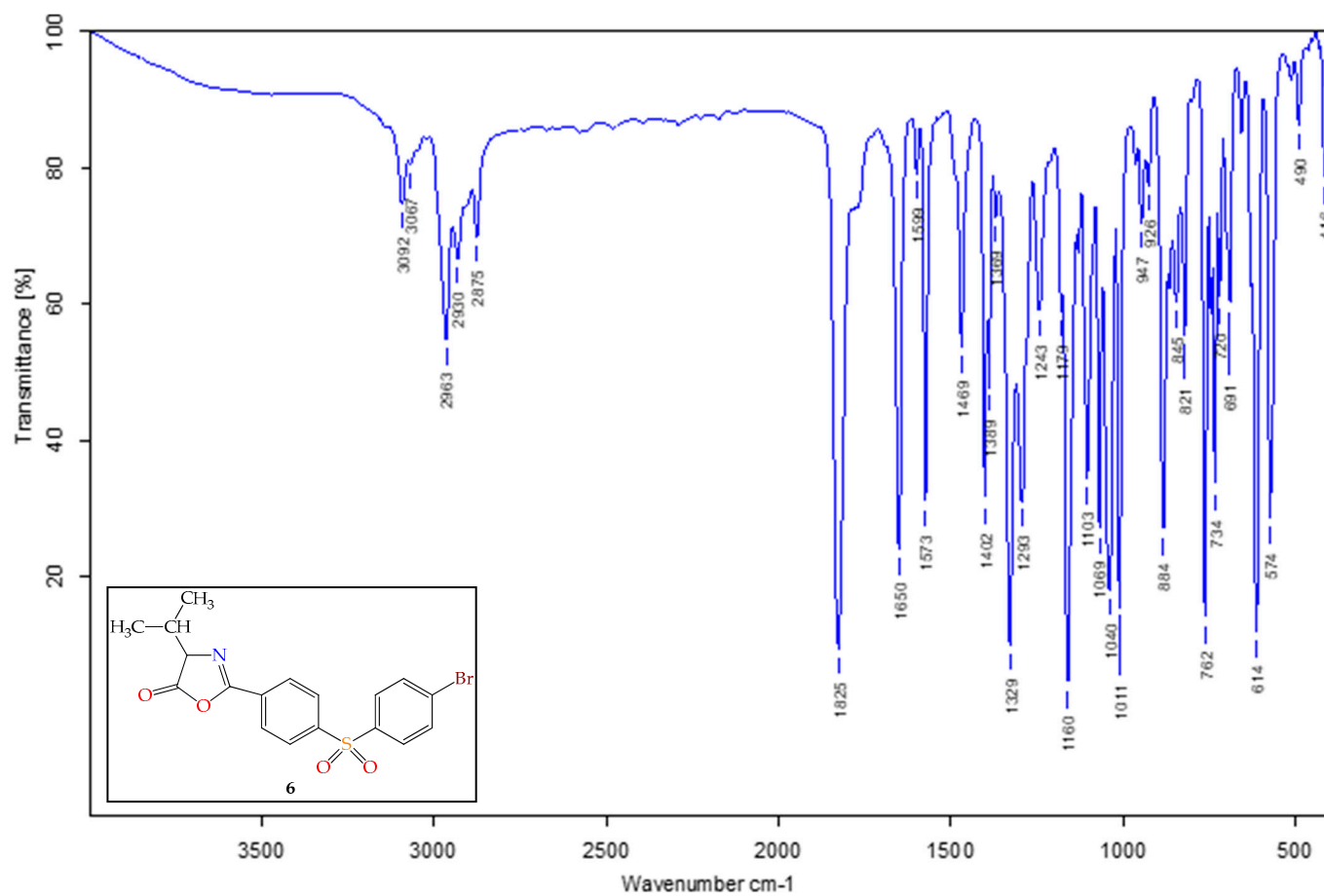


**Figure S19.** The 2D HETCOR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-(*p*-tolyl)-1,3-oxazole **8b**.



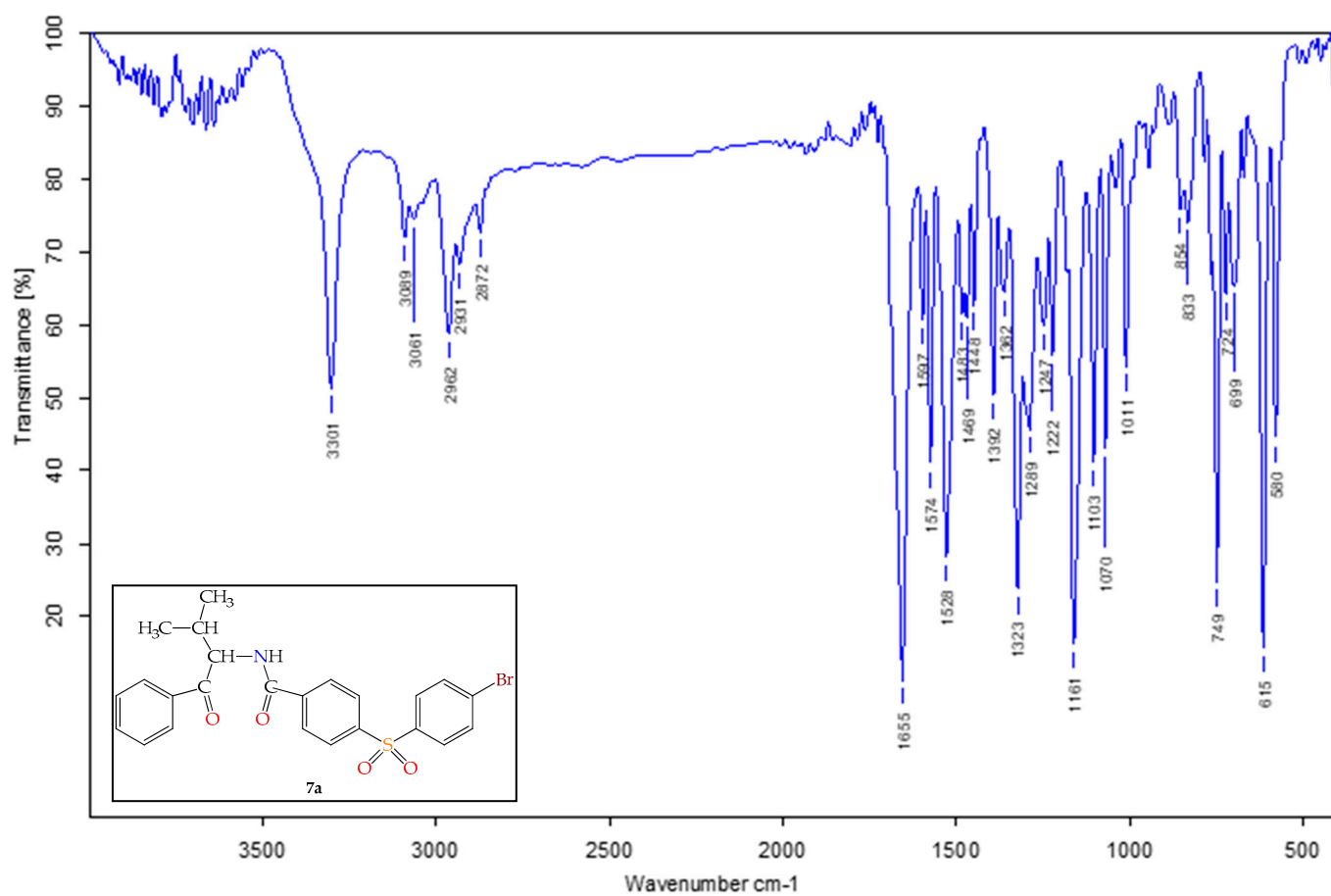


**Figure S20.** The FTIR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]benzamido]-3-methylbutanoic acid 5.

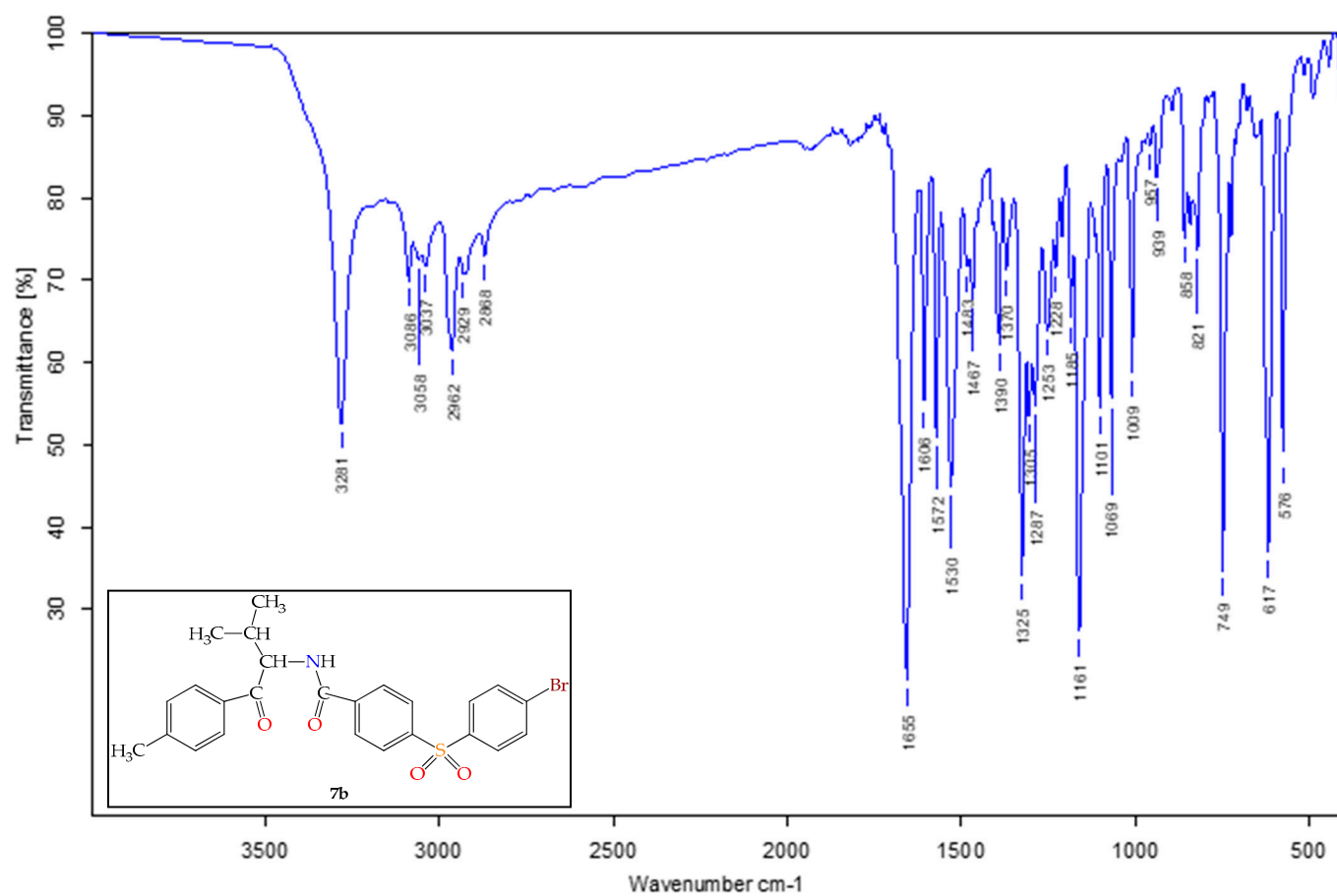


**Figure S21.** The FTIR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-4H-1,3-oxazol-5-one 6.



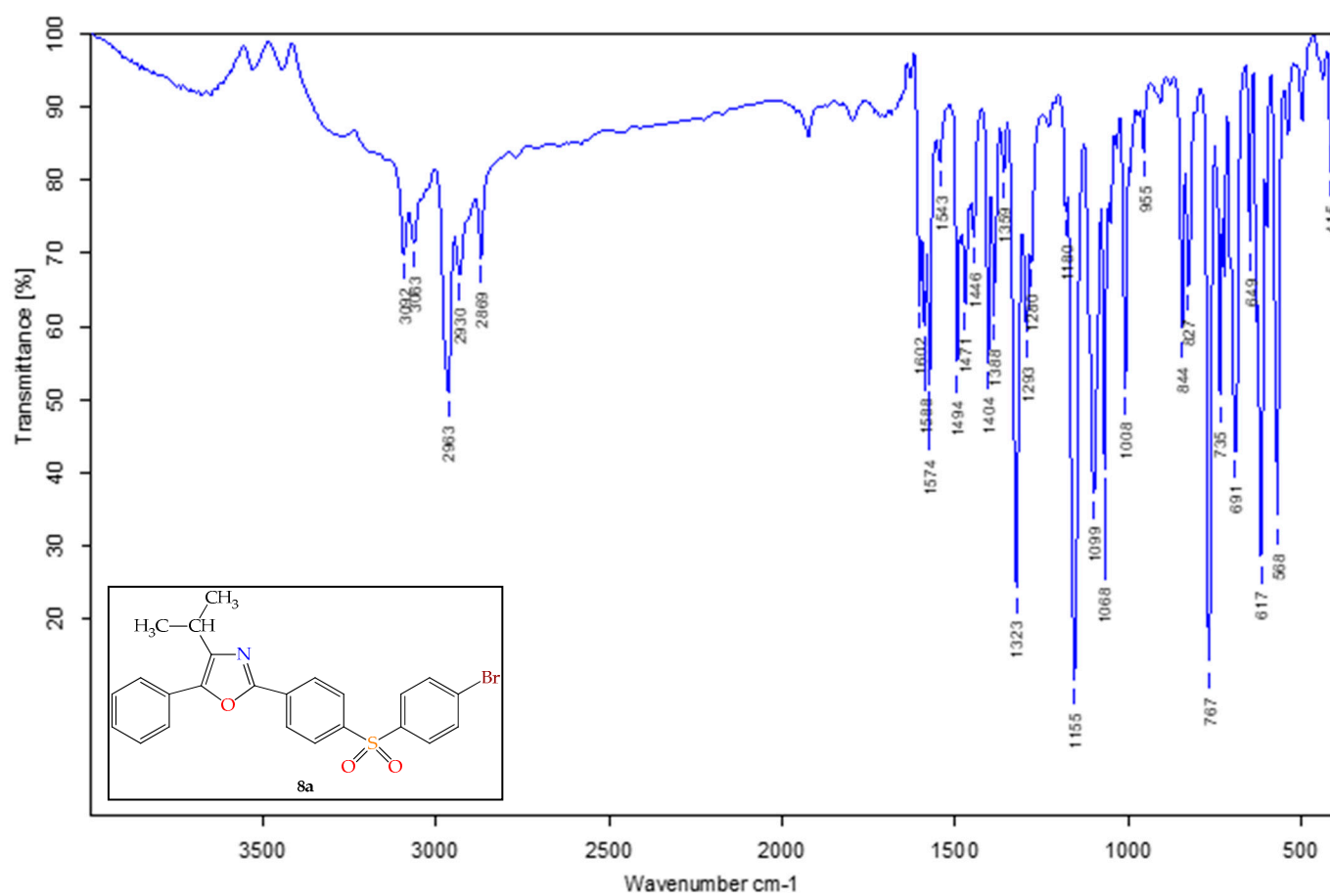


**Figure S22.** The FTIR spectrum of 4-[(4-bromophenyl)sulfonyl]-N-(3-methyl-1-oxo-1-phenylbutan-2-yl)benzamide **7a**.

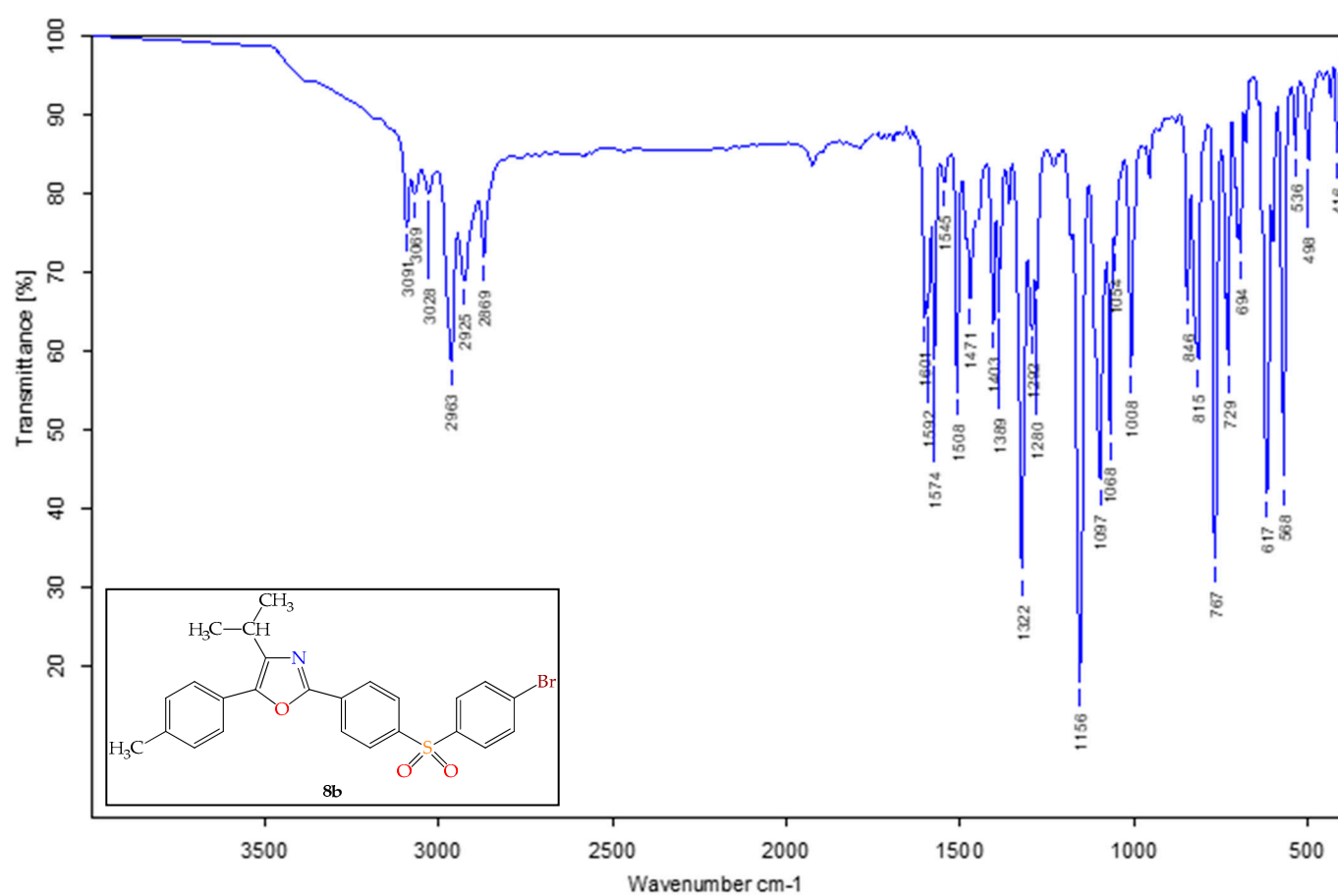


**Figure S23.** The FTIR spectrum of 4-[(4-bromophenyl)sulfonyl]-N-[3-methyl-1-oxo-1-(*p*-tolyl)butan-2-yl]benzamide **7b**.



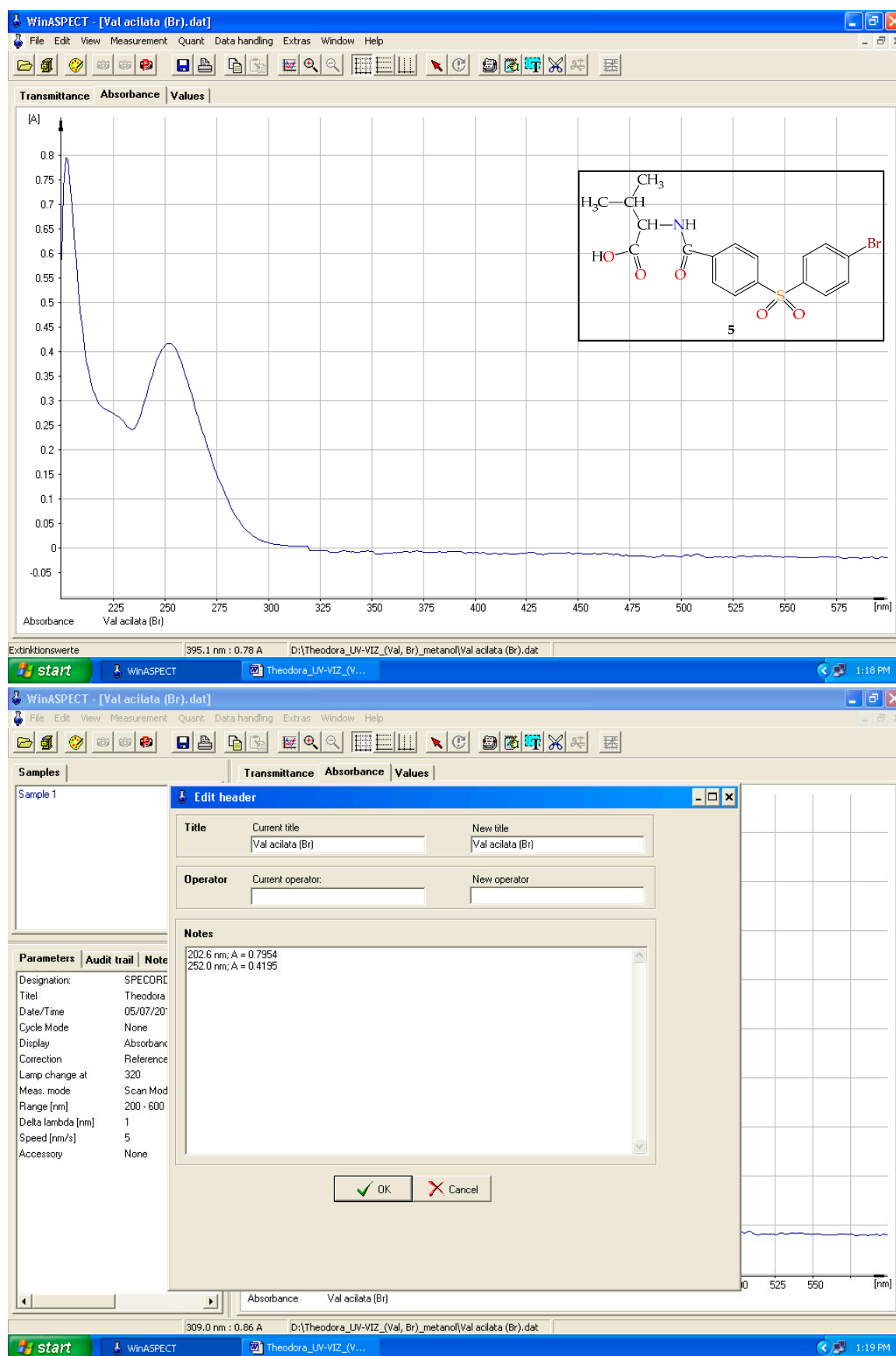


**Figure S24.** The FTIR spectrum of 2-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-isopropyl-5-phenyl-1,3-oxazole **8a**.



**Figure S25.** The FTIR spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-(*p*-tolyl)-1,3-oxazole **8b**.





**Figure S26.** The UV/VIS spectrum of 2-[4-[(4-bromophenyl)sulfonyl]benzamido]-3-methylbutanoic acid **5** dissolved in methanol at  $\approx 0.025$  mM.

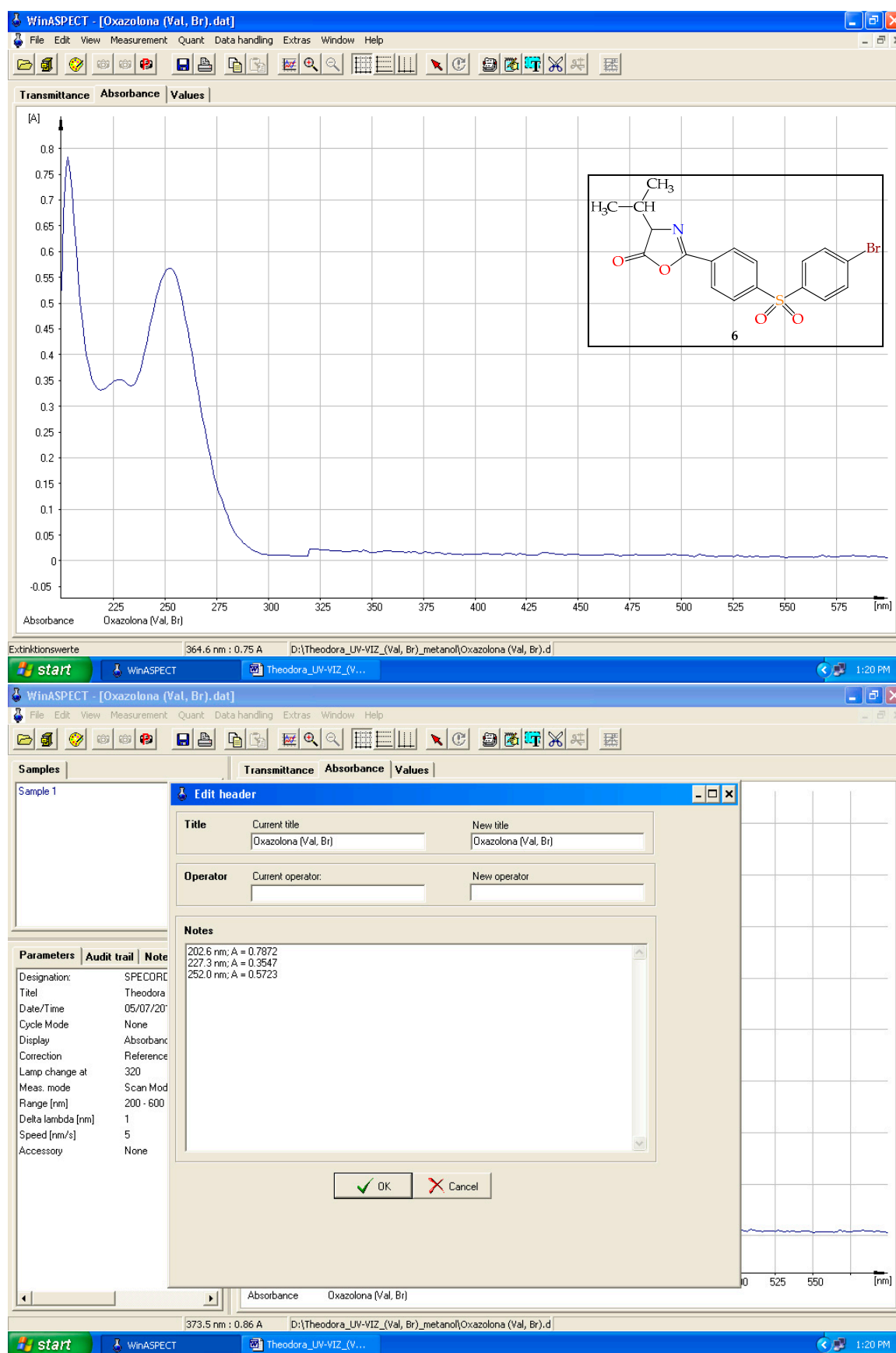
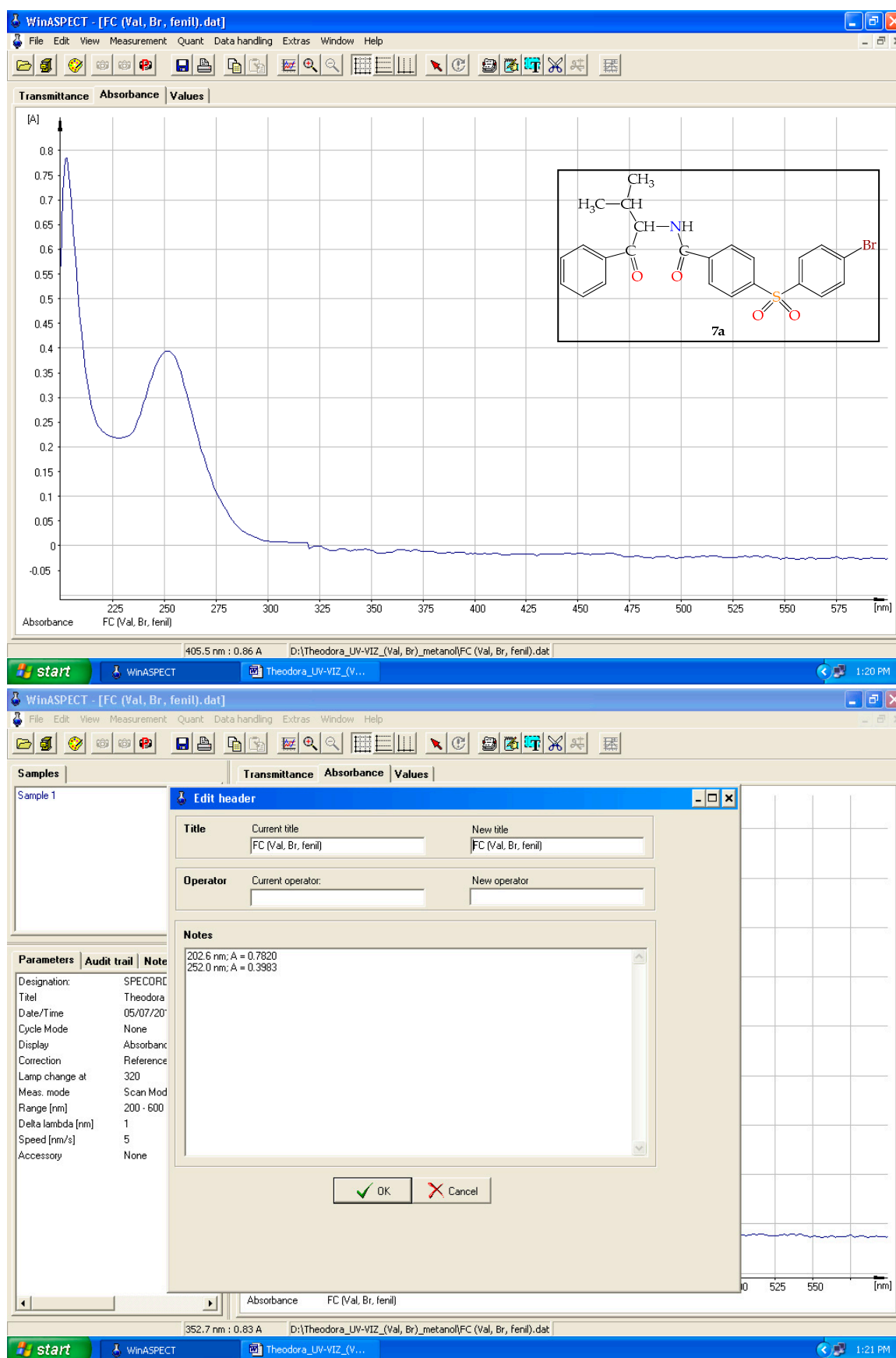


Figure S27. The UV/VIS spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-4*H*-1,3-oxazol-5-one **6** dissolved in methanol at  $\approx 0.025$  mM.



**Figure S28.** The UV/VIS spectrum of 4-[(4-bromophenyl)sulfonyl]-N-(3-methyl-1-oxo-1-phenylbutan-2-yl)benzamide **7a** dissolved in methanol at  $\approx 0.025$  mM.



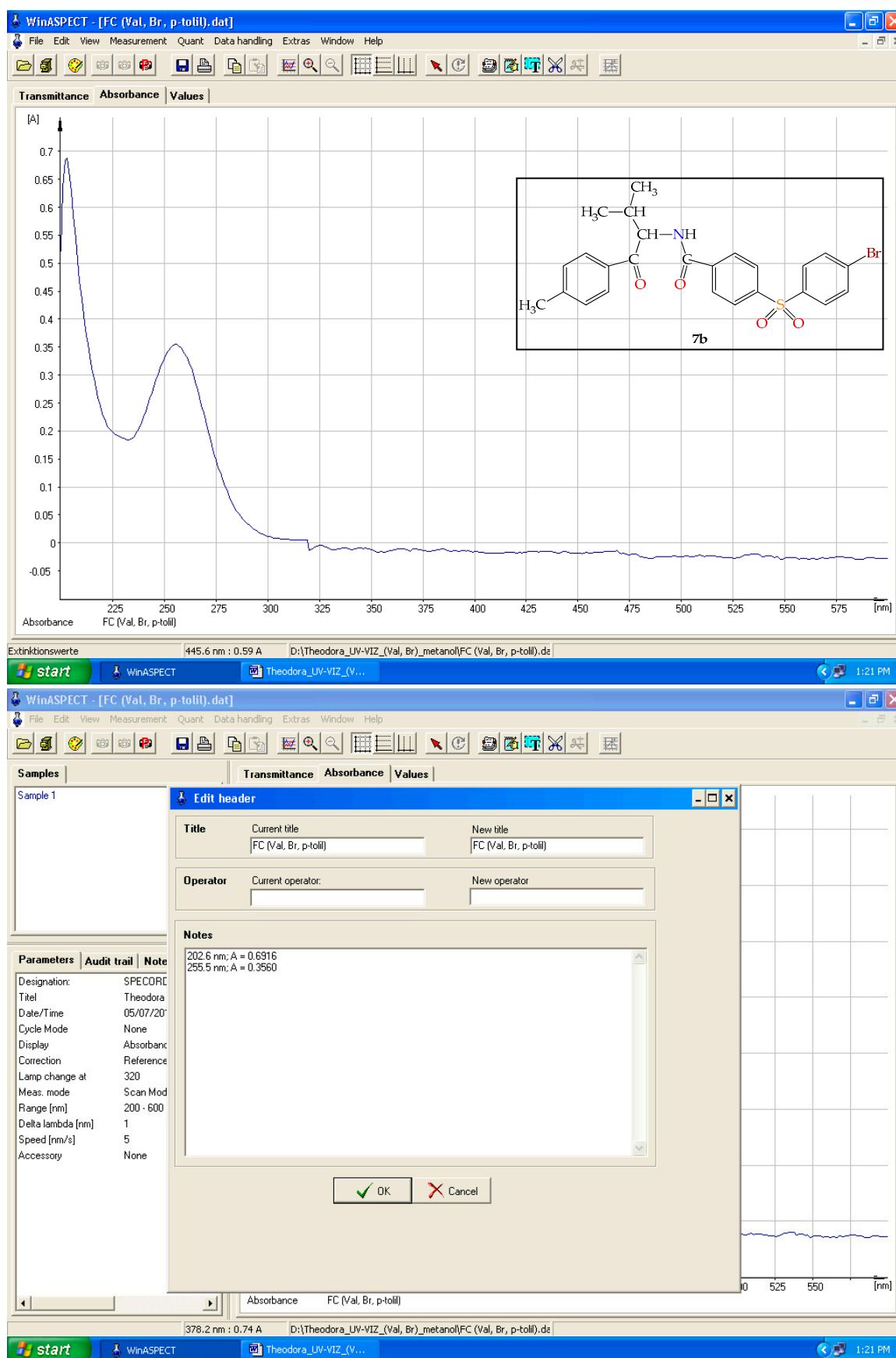
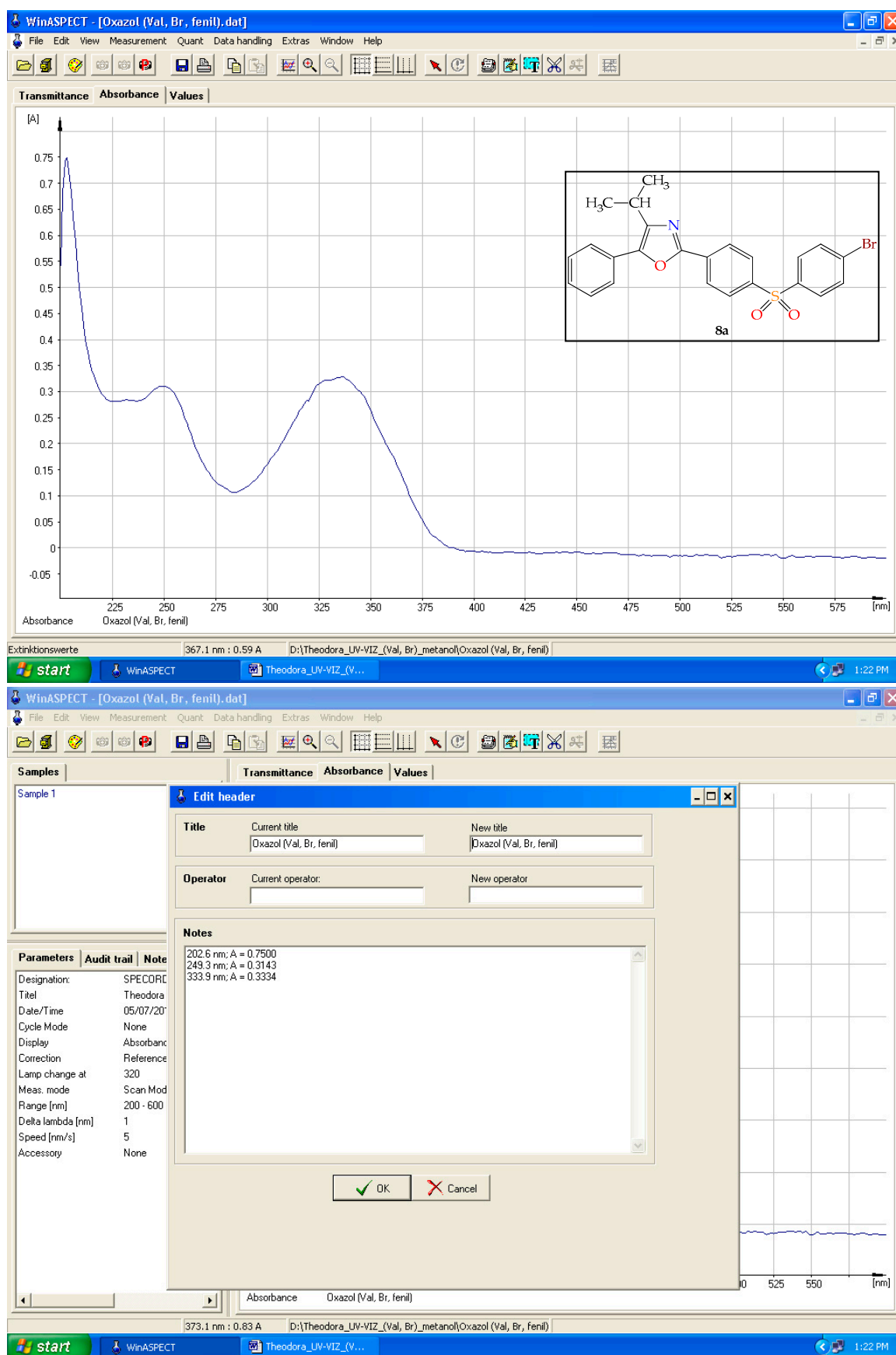
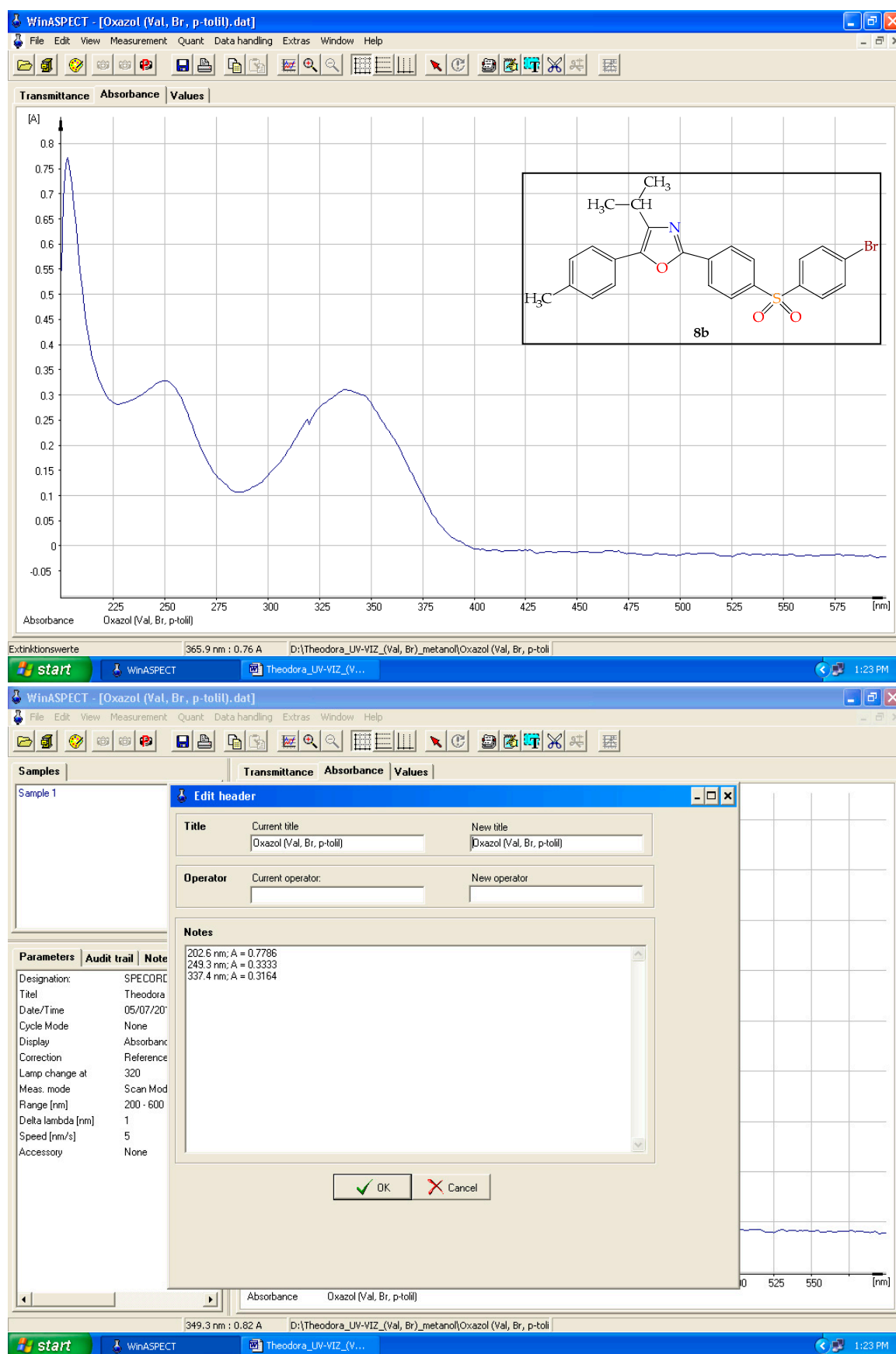


Figure S29. The UV/VIS spectrum of 4-[(4-bromophenyl)sulfonyl]-N-[3-methyl-1-oxo-1-(*p*-tolyl)butan-2-yl]benzamide **7b** dissolved in methanol at  $\approx 0.025$  mM.

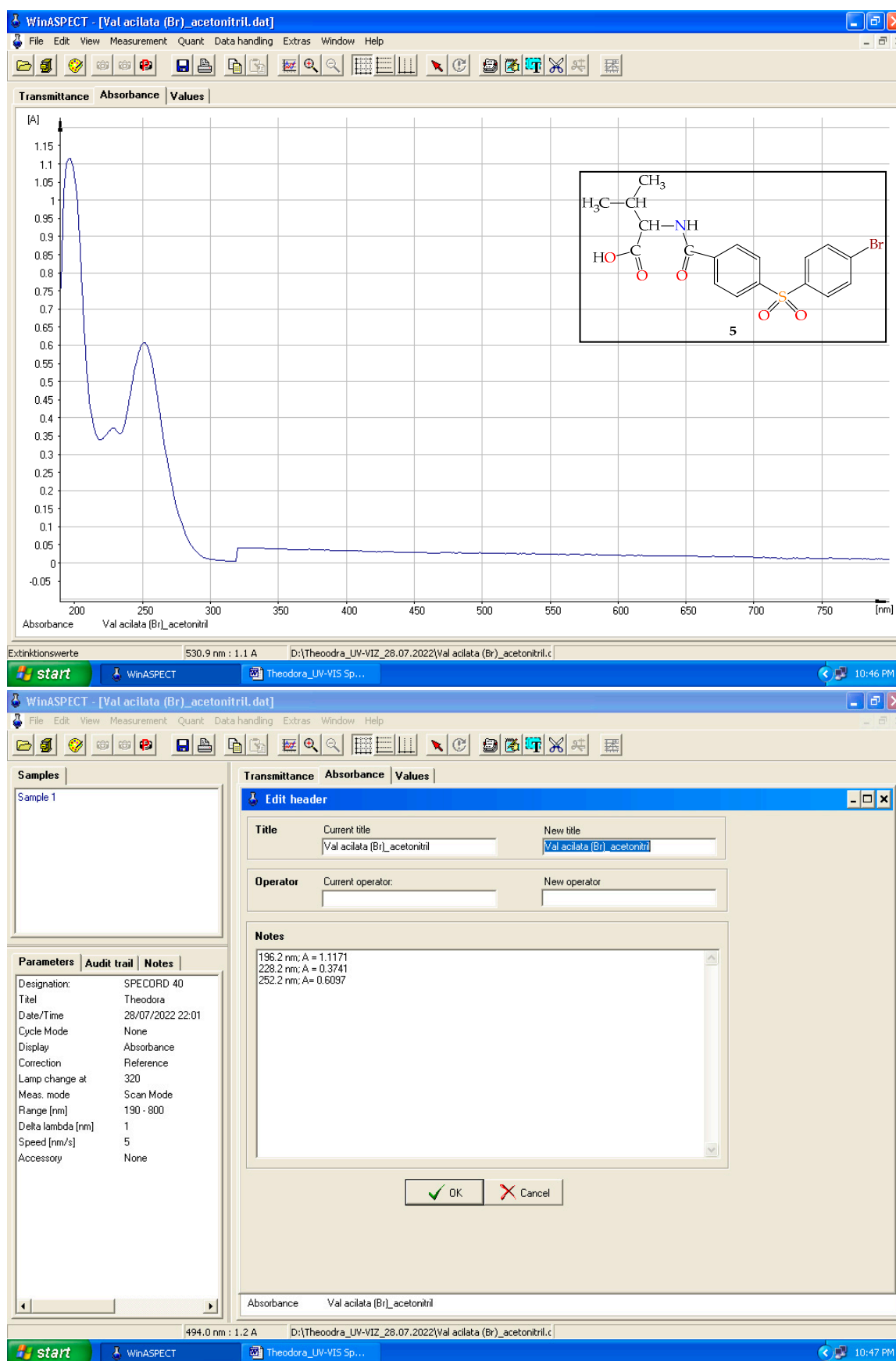


**Figure S30.** The UV/VIS spectrum of 2-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-isopropyl-5-phenyl-1,3-oxazole **8a** dissolved in methanol at  $\approx 0.025$  mM.



**Figure S31.** The UV/VIS spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-(p-tolyl)-1,3-oxazole **8b** dissolved in methanol at  $\approx 0.025$  mM.





**Figure S32.** The UV/VIS spectrum of 2-[4-[(4-bromophenyl)sulfonyl]benzamido]-3-methylbutanoic acid **5** dissolved in acetonitrile at  $\approx 0.015$  mM.

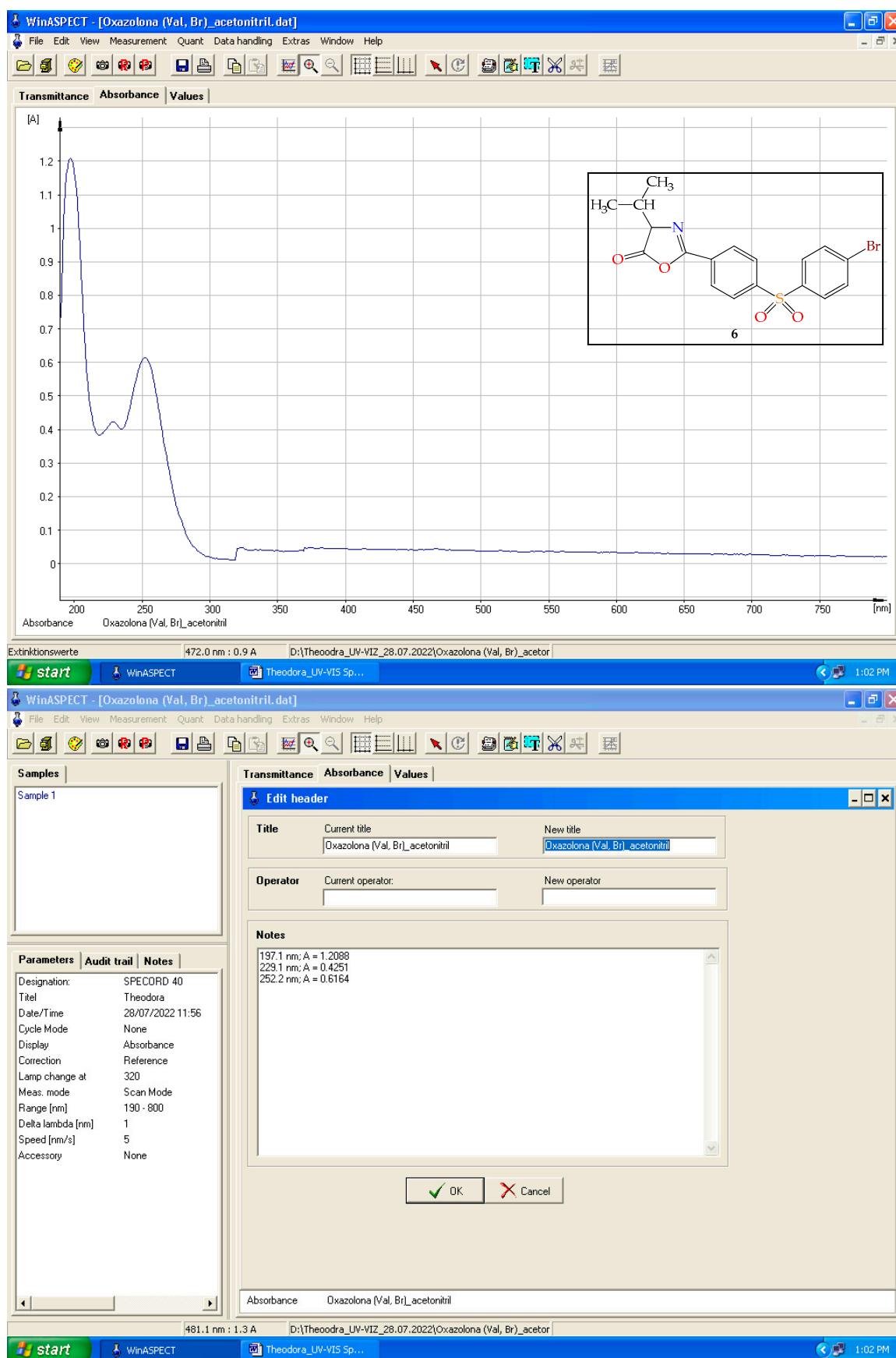
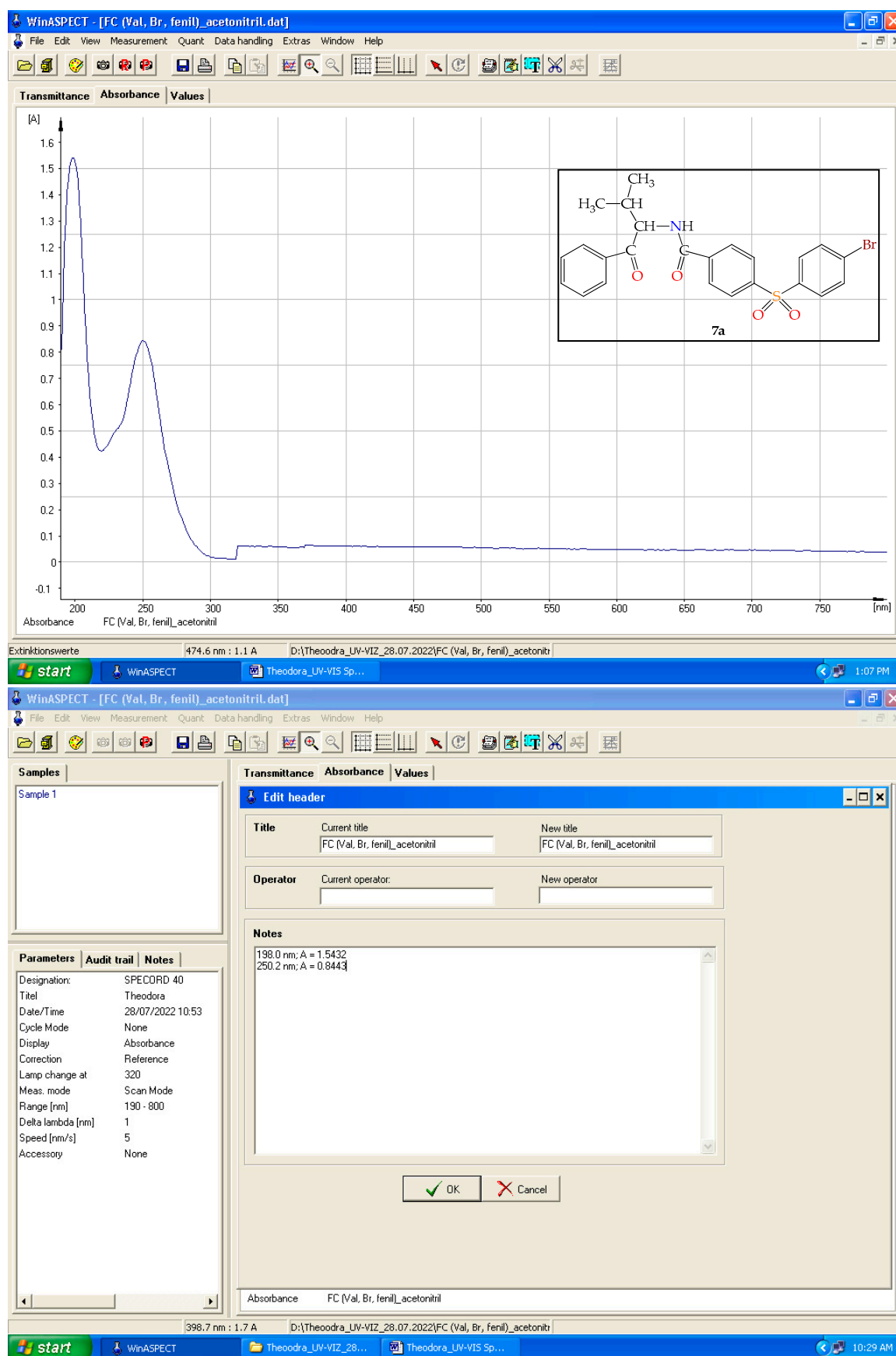


Figure S33. The UV/VIS spectrum of 2-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-isopropyl-4H-1,3-oxazol-5-one **6** dissolved in acetonitrile at  $\approx 0.015$  mM.



**Figure S34.** The UV/VIS spectrum of 4-[(4-bromophenyl)sulfonyl]-N-(3-methyl-1-oxo-1-phenylbutan-2-yl)benzamide **7a** dissolved in acetonitrile at  $\approx 0.015$  mM.



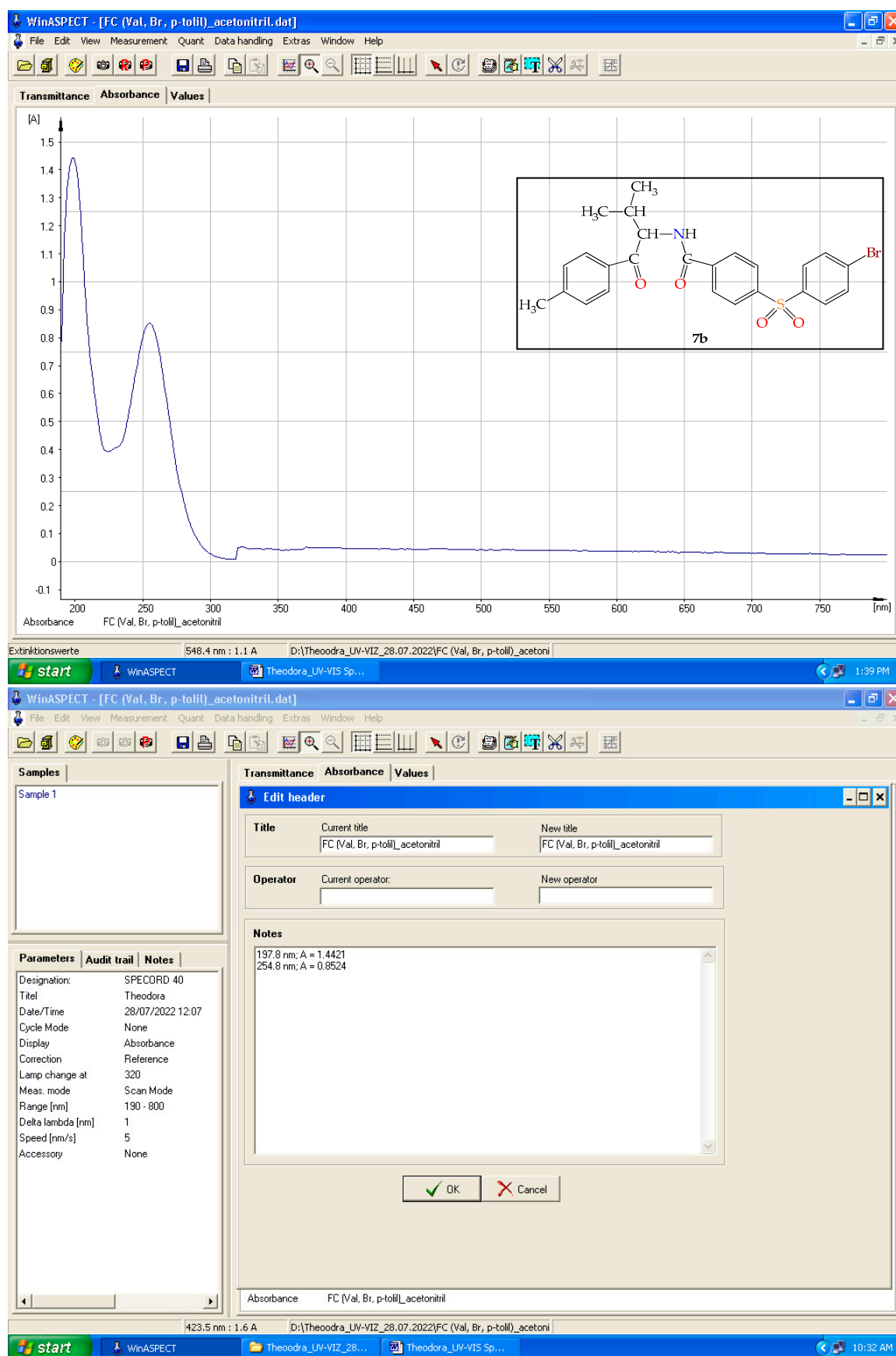
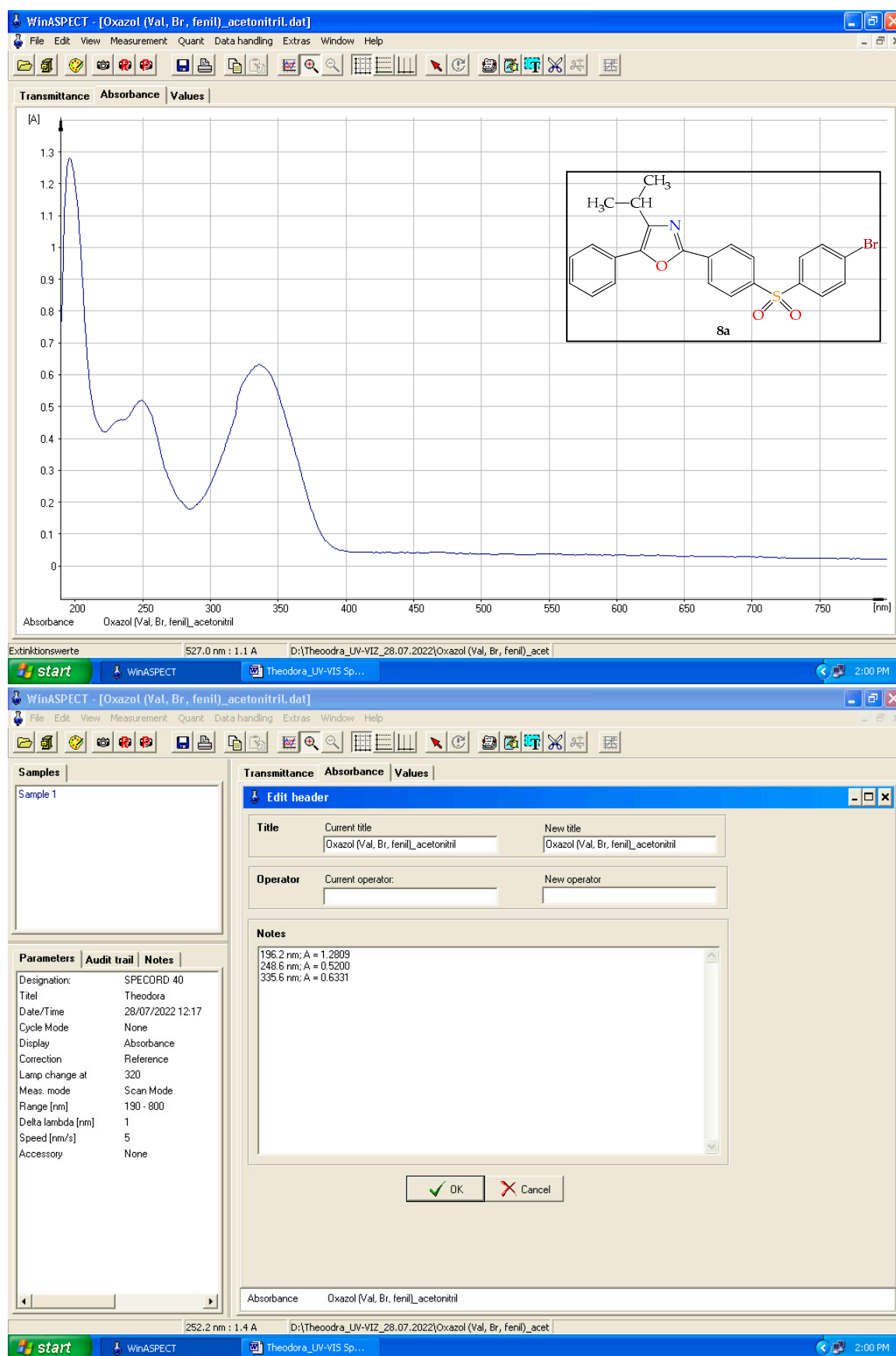
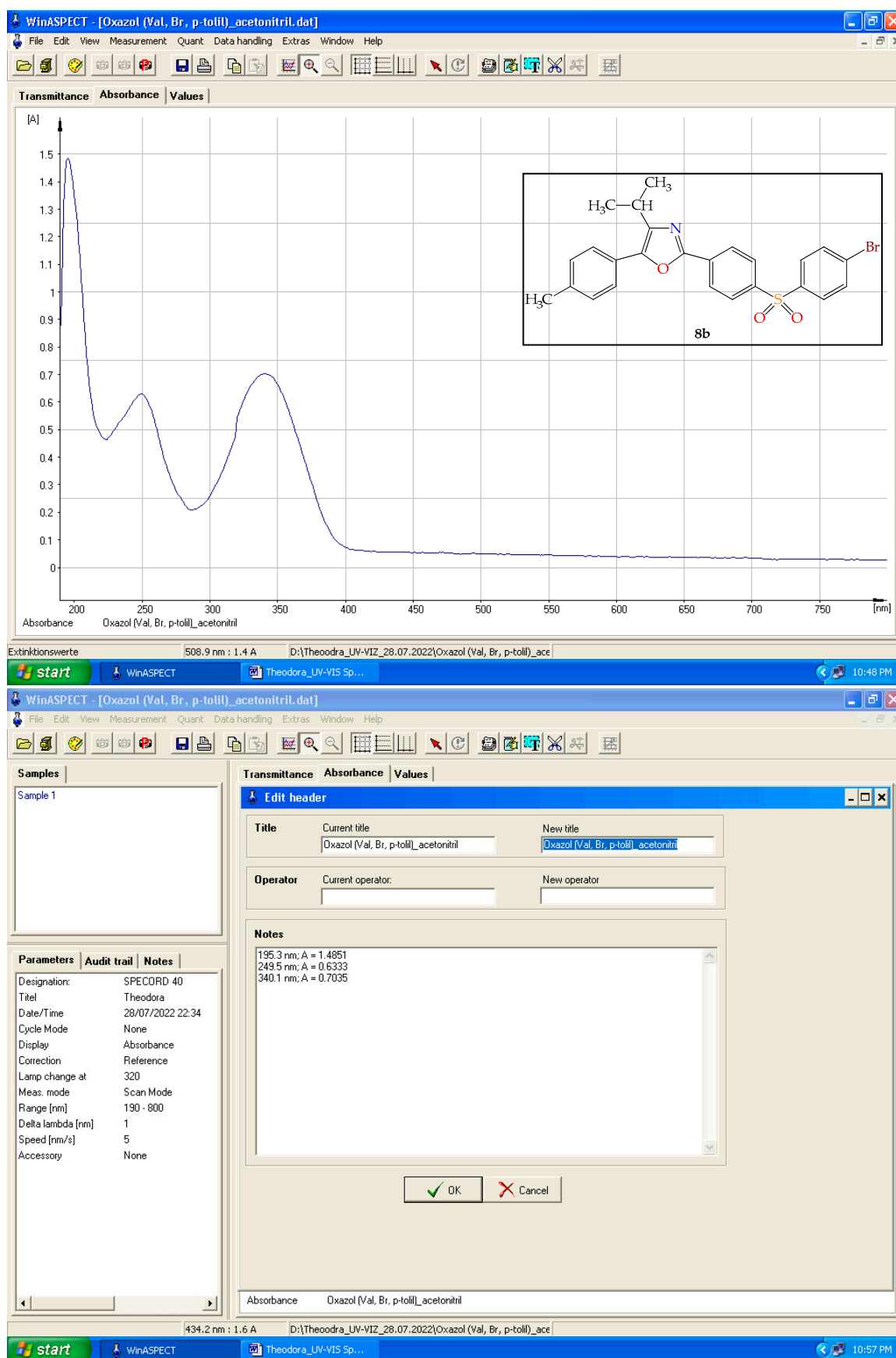


Figure S35. The UV/VIS spectrum of 4-[(4-bromophenyl)sulfonyl]-N-[3-methyl-1-oxo-1-(*p*-tolyl)butan-2-yl]benzamide **7b** dissolved in acetonitrile at  $\approx 0.015$  mM.



**Figure S36.** The UV/VIS spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-phenyl-1,3-oxazole **8a** dissolved in acetonitrile at  $\approx 0.015$  mM.



**Figure S37.** The UV/VIS spectrum of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-(p-tolyl)-1,3-oxazole **8b** dissolved in acetonitrile at  $\approx 0.015$  mM.



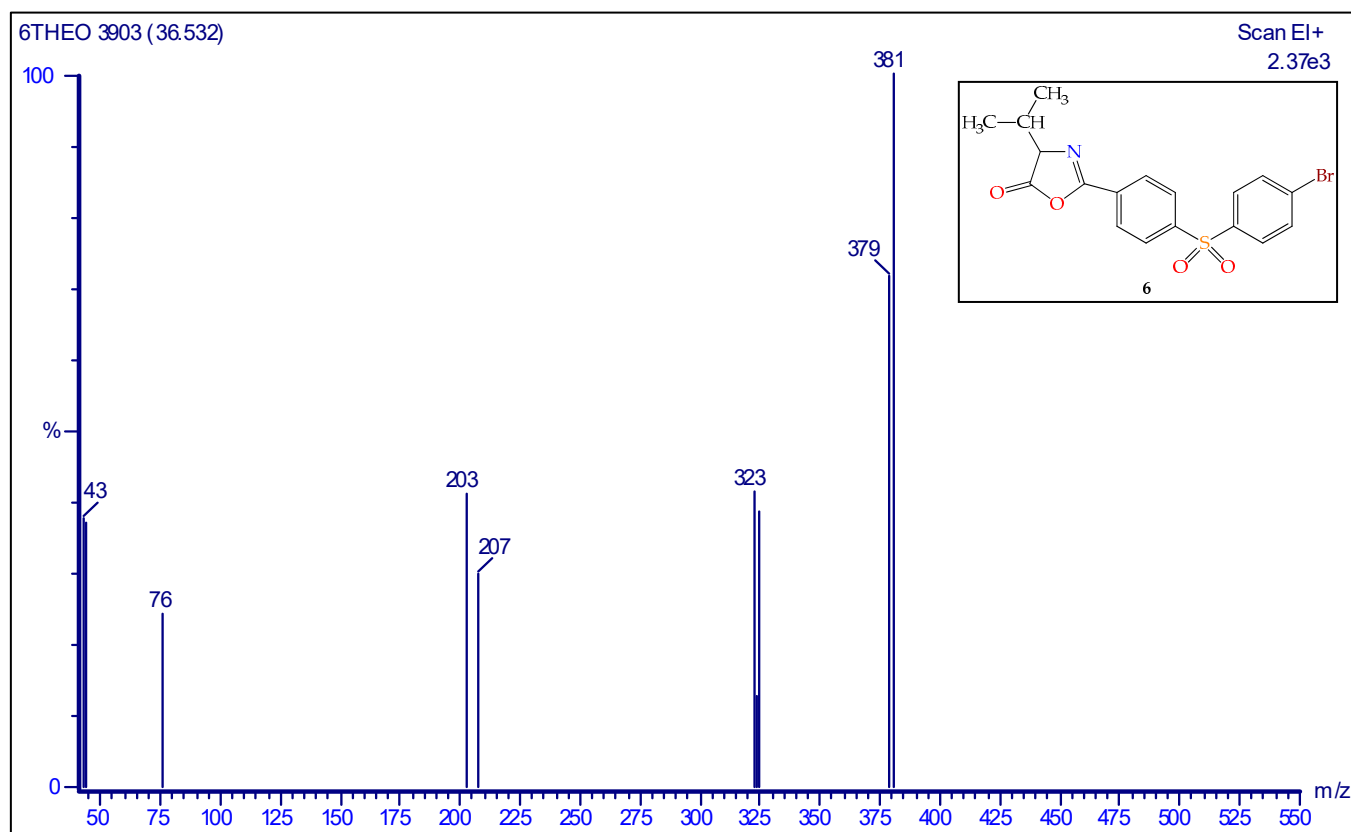


Figure S38. The GC/MS spectrum of 2-{4-[(4-bromophenyl)sulfonyl]phenyl}-4-isopropyl-4H-1,3-oxazol-5-one 6.

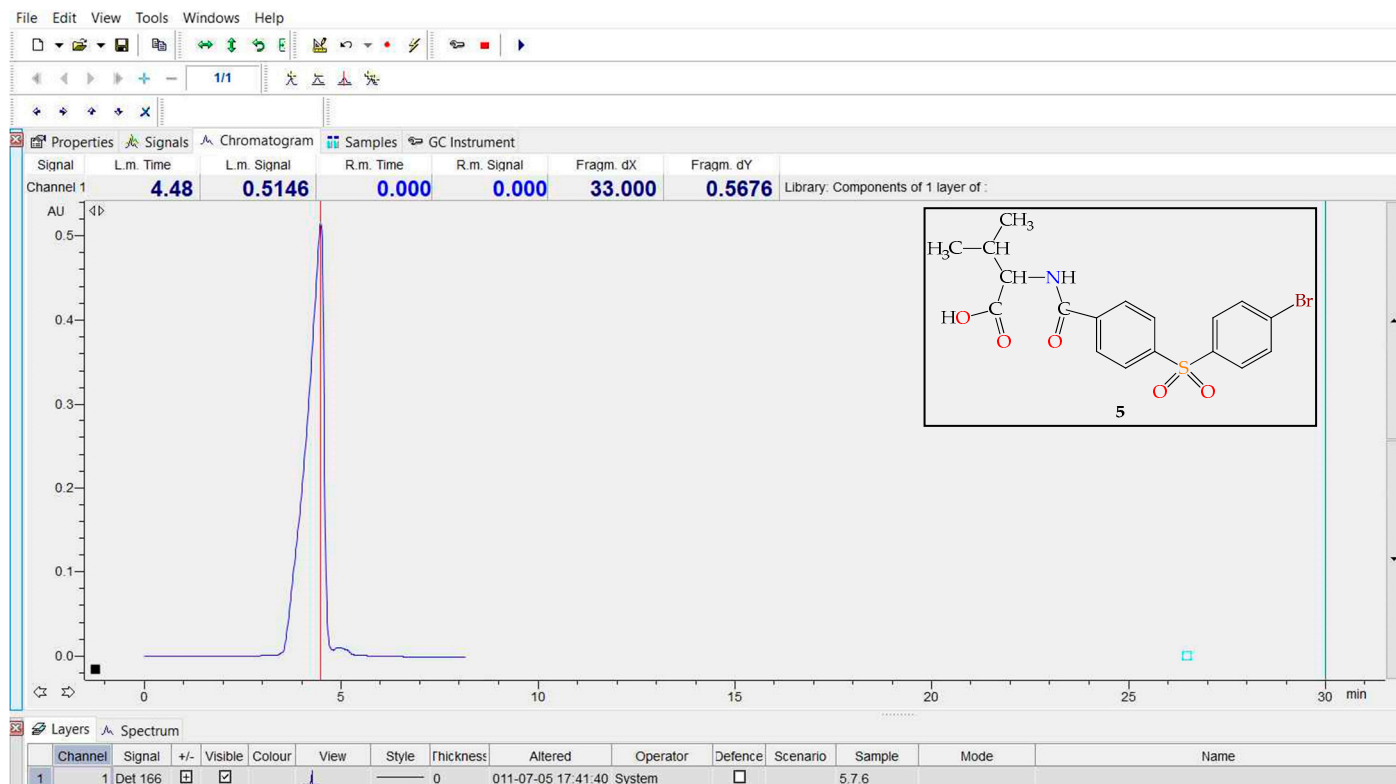


Figure S39. The RP-HPLC chromatogram of 2-{4-[(4-bromophenyl)sulfonyl]benzamido}-3-methylbutanoic acid 5.

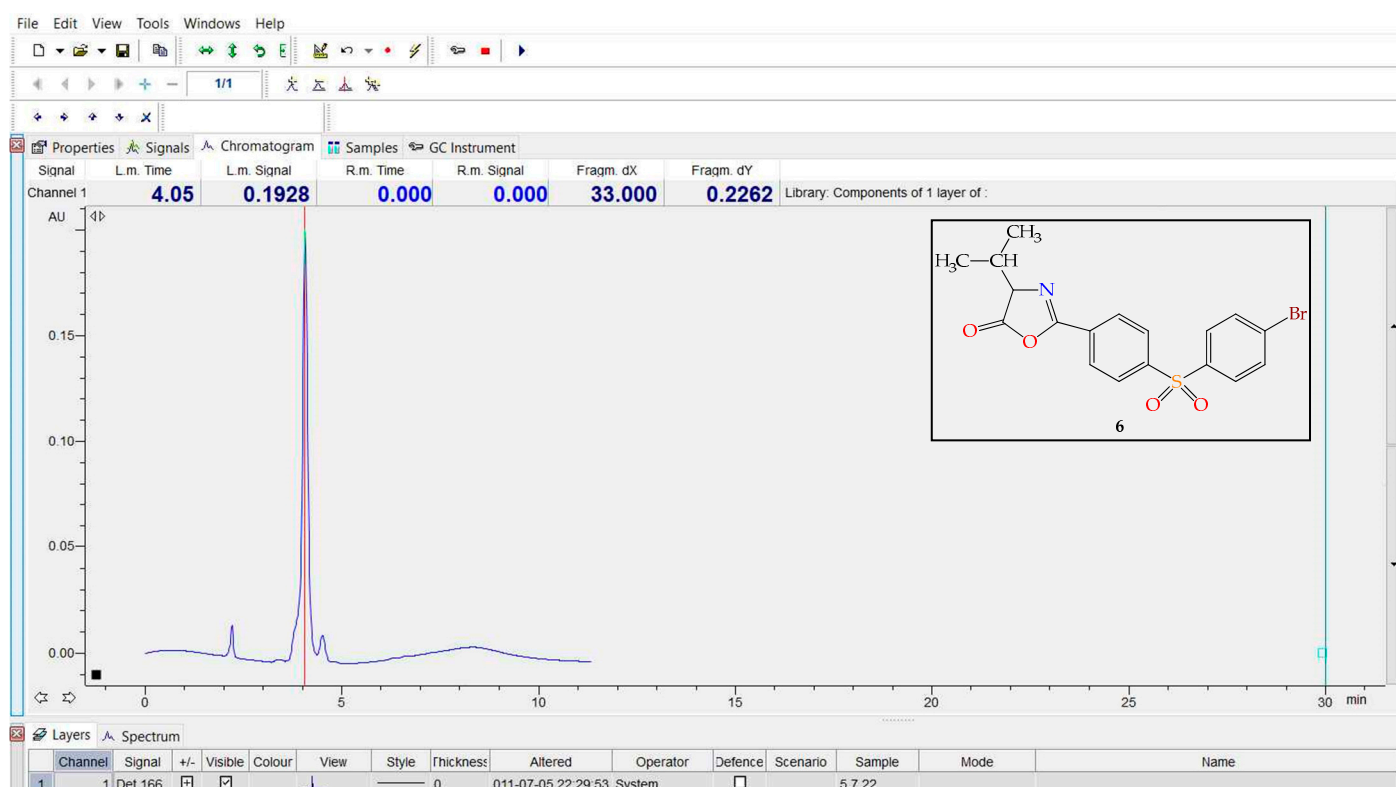


Figure S40. The RP-HPLC chromatogram of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-4H-1,3-oxazol-5-one 6.

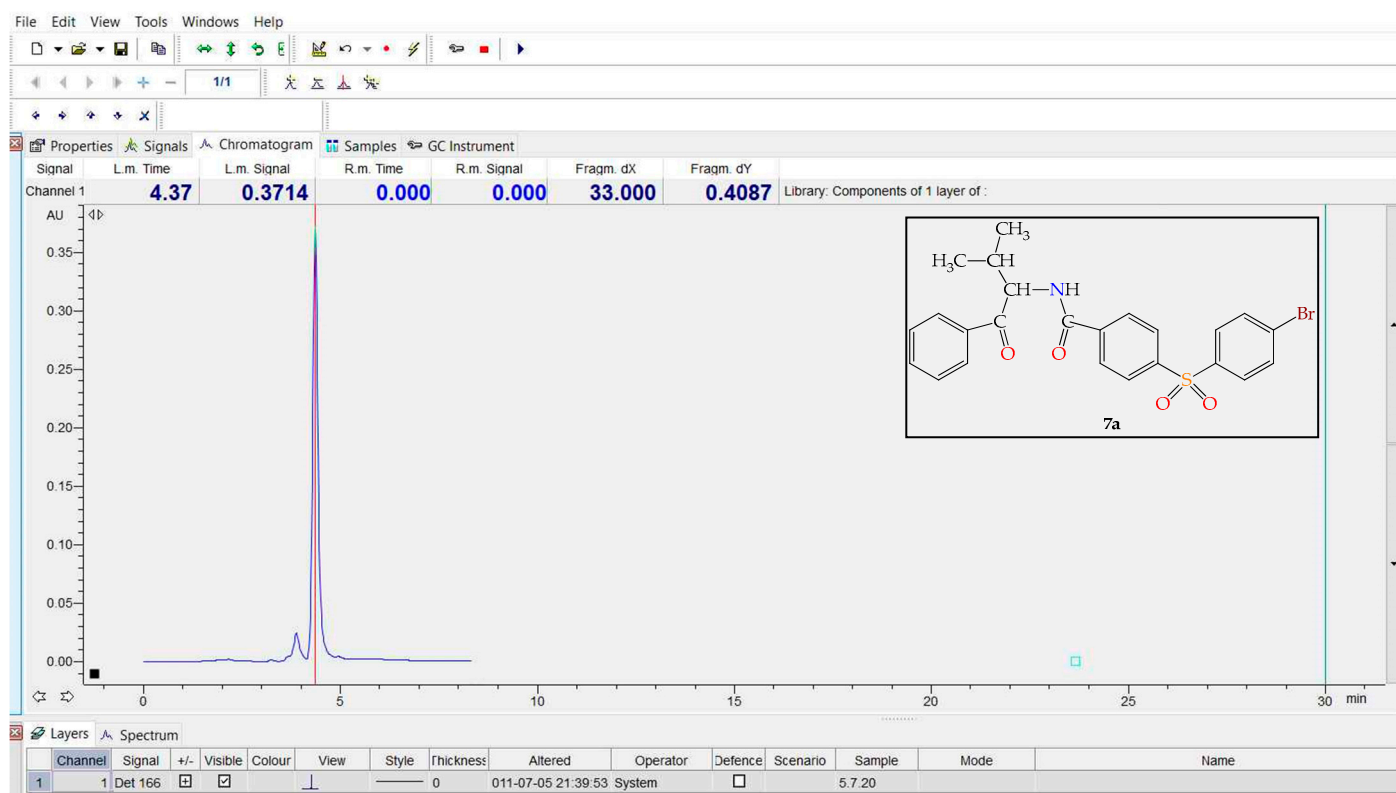
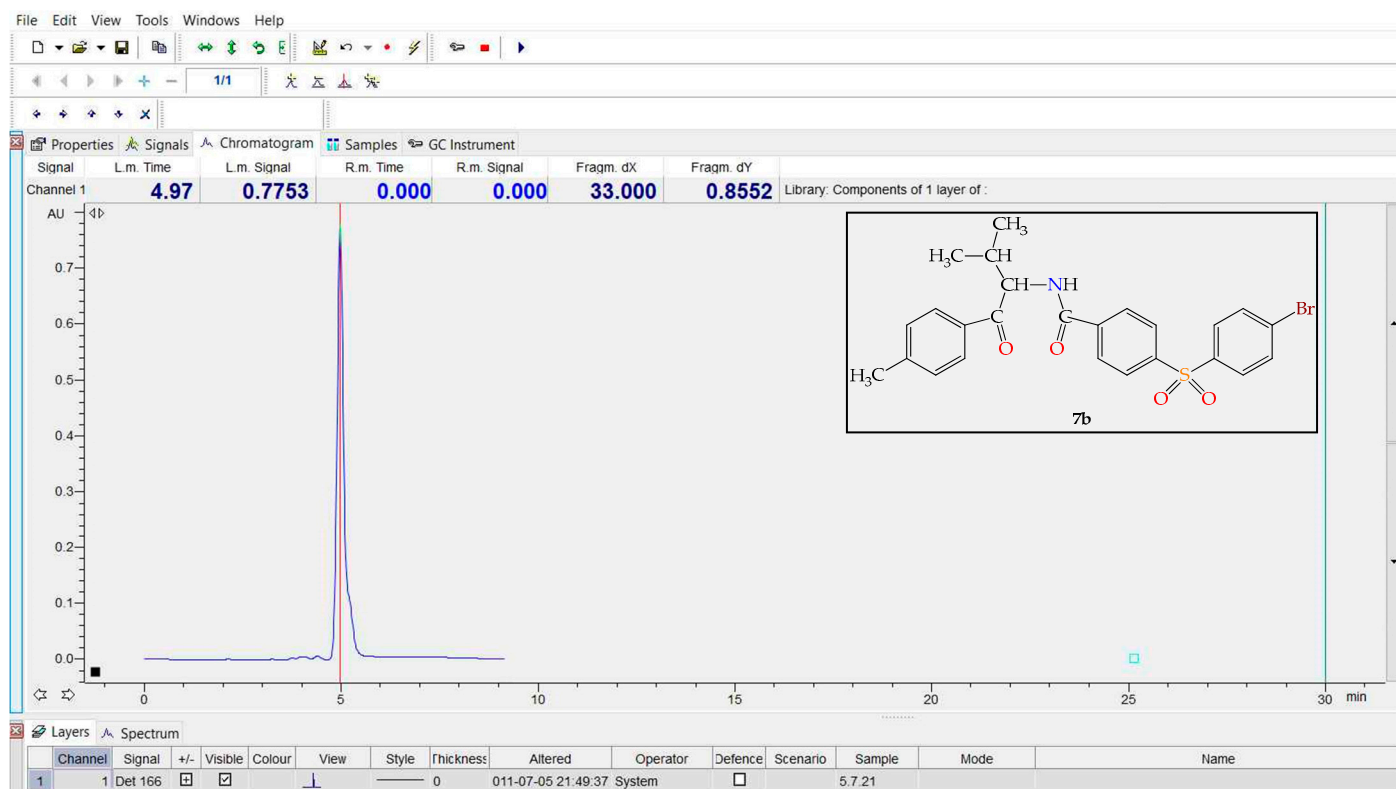
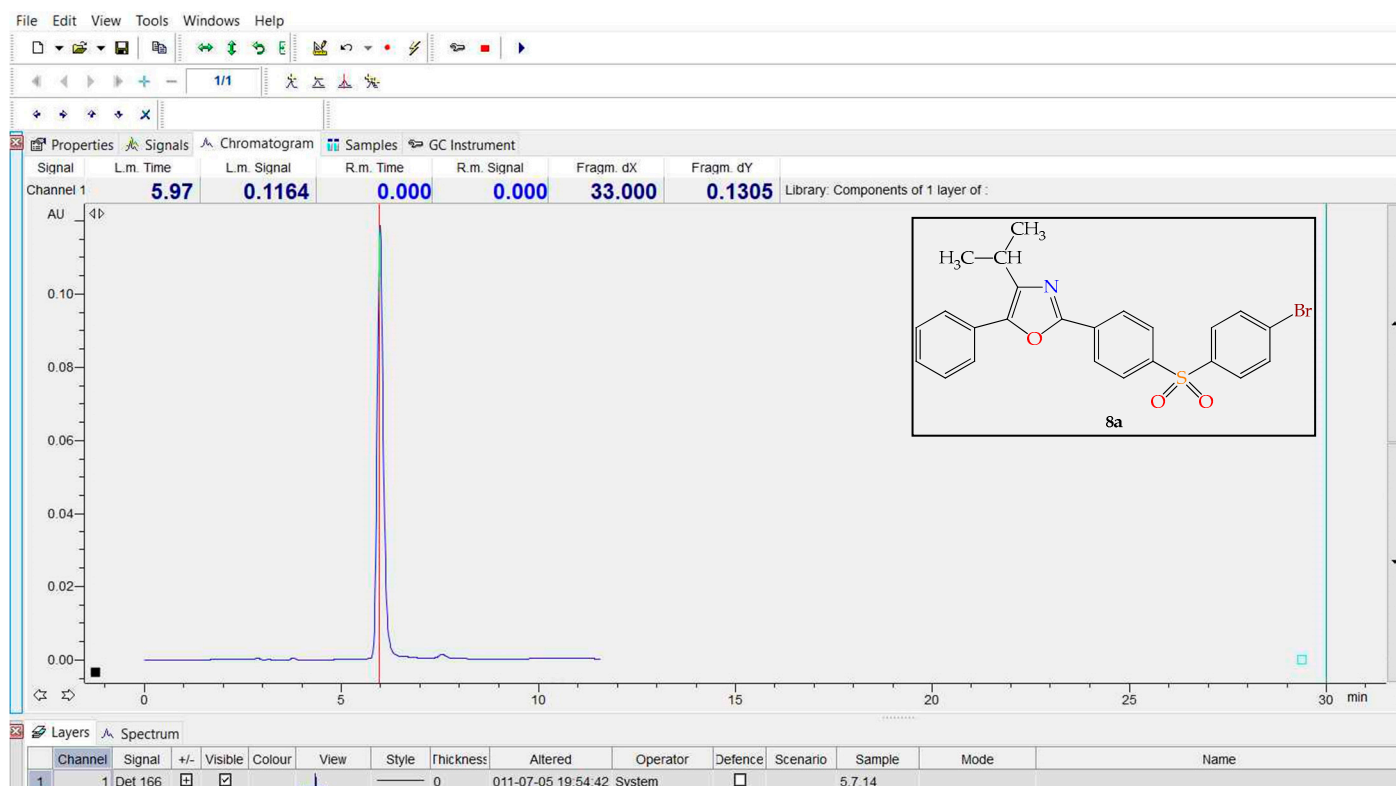


Figure S41. The RP-HPLC chromatogram of 4-[4-(4-bromophenyl)sulfonyl]-N-(3-methyl-1-oxo-1-phenylbutan-2-yl)benzamide 7a.



**Figure S42.** The RP-HPLC chromatogram of 4-[(4-bromophenyl)sulfonyl]-*N*-[3-methyl-1-oxo-1-(*p*-tolyl)butan-2-yl]benzamide **7b**.



**Figure S43.** The RP-HPLC chromatogram of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-phenyl-1,3-oxazole **8a**.



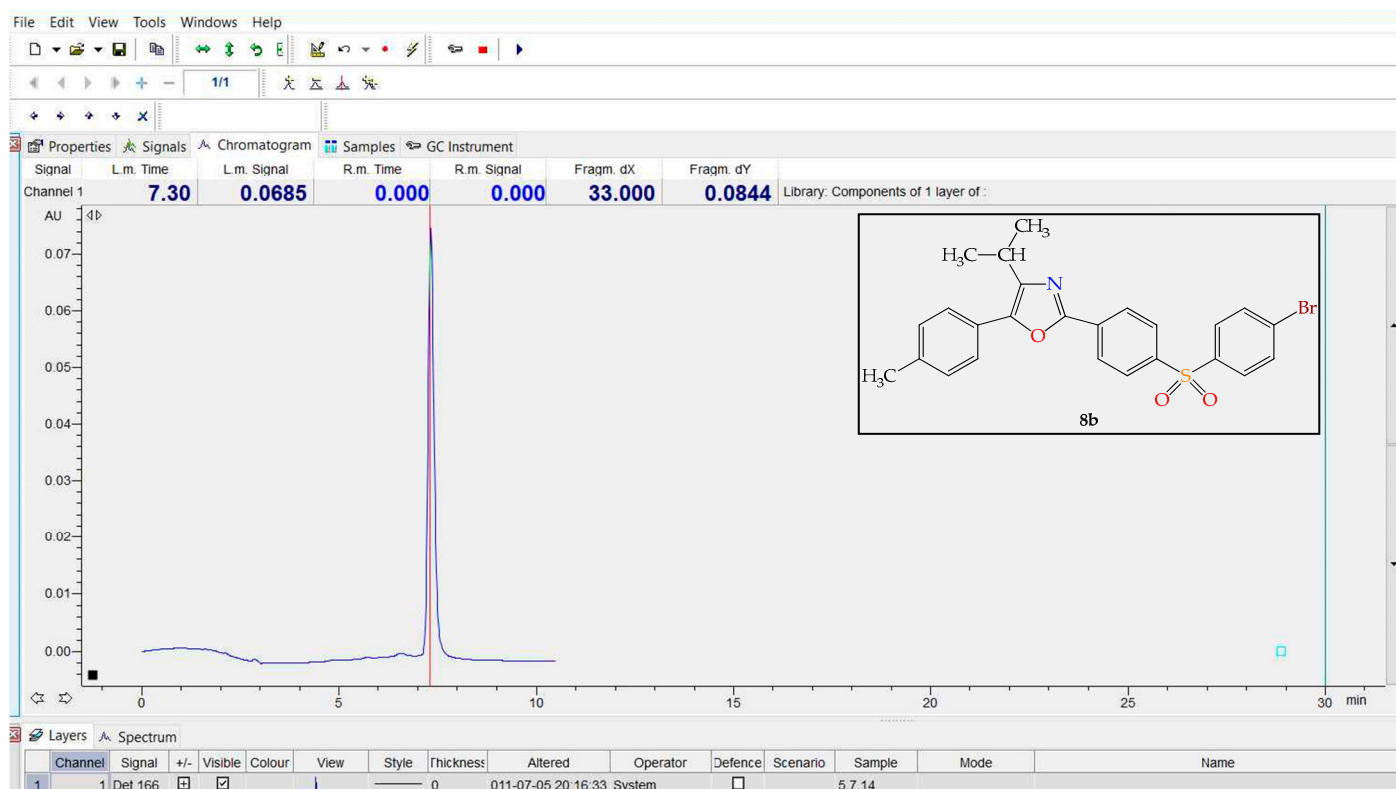


Figure S44. The RP-HPLC chromatogram of 2-[4-[(4-bromophenyl)sulfonyl]phenyl]-4-isopropyl-5-(*p*-tolyl)-1,3-oxazole **8b**.