Design, synthesis and biological evaluation of carbohydrate-based sulfonamide derivatives as topical antiglaucoma agents through selective inhibition of carbonic anhydrase II

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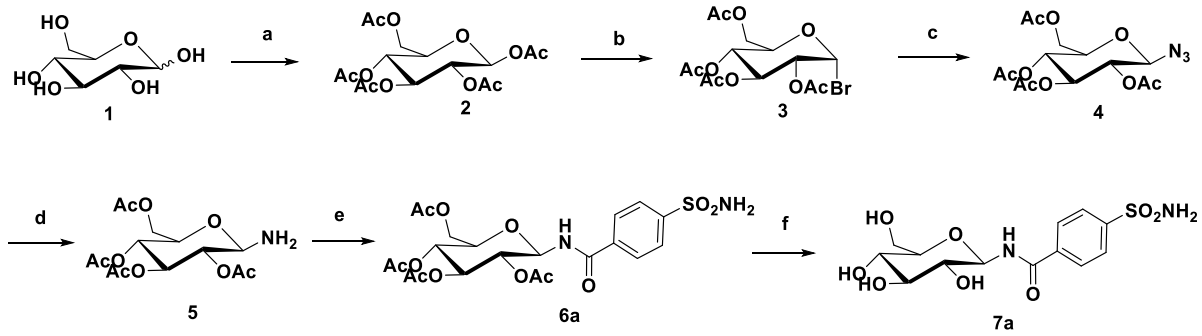
Reagents were used without further purification unless otherwise specified. Solvents were dried and redistilled prior to use in the usual way. Analytical TLC was performed using silica gel HF254. Preparative column chromatography was performed with silica gel H. Melting points were obtained on a Büchi melting point B-540 apparatus.^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 600 MHz spectrometer. ESI-MS were obtained on Agilent ESI-QTOF instrument. HR-MS were obtained on a Bruker micrOTOF_Q spectrometer.

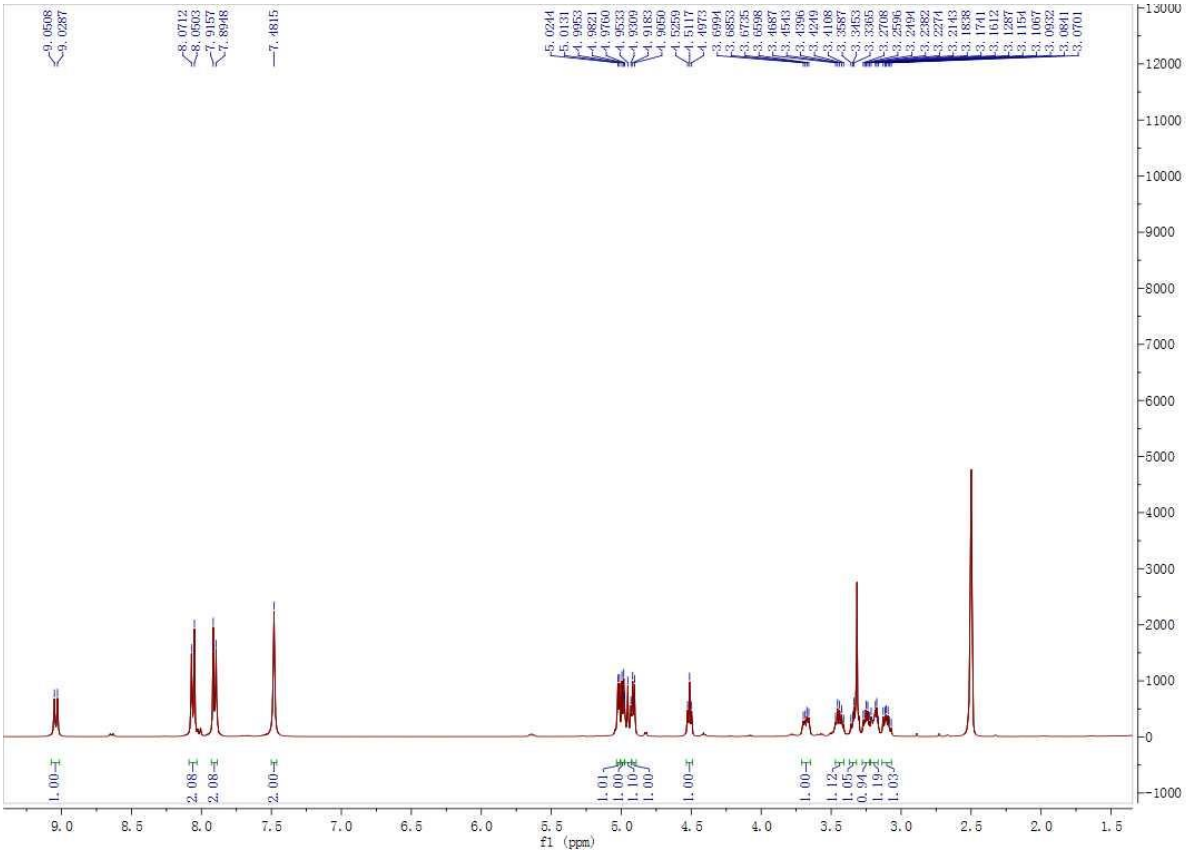
General procedure for the synthesis of compound 7a-7h

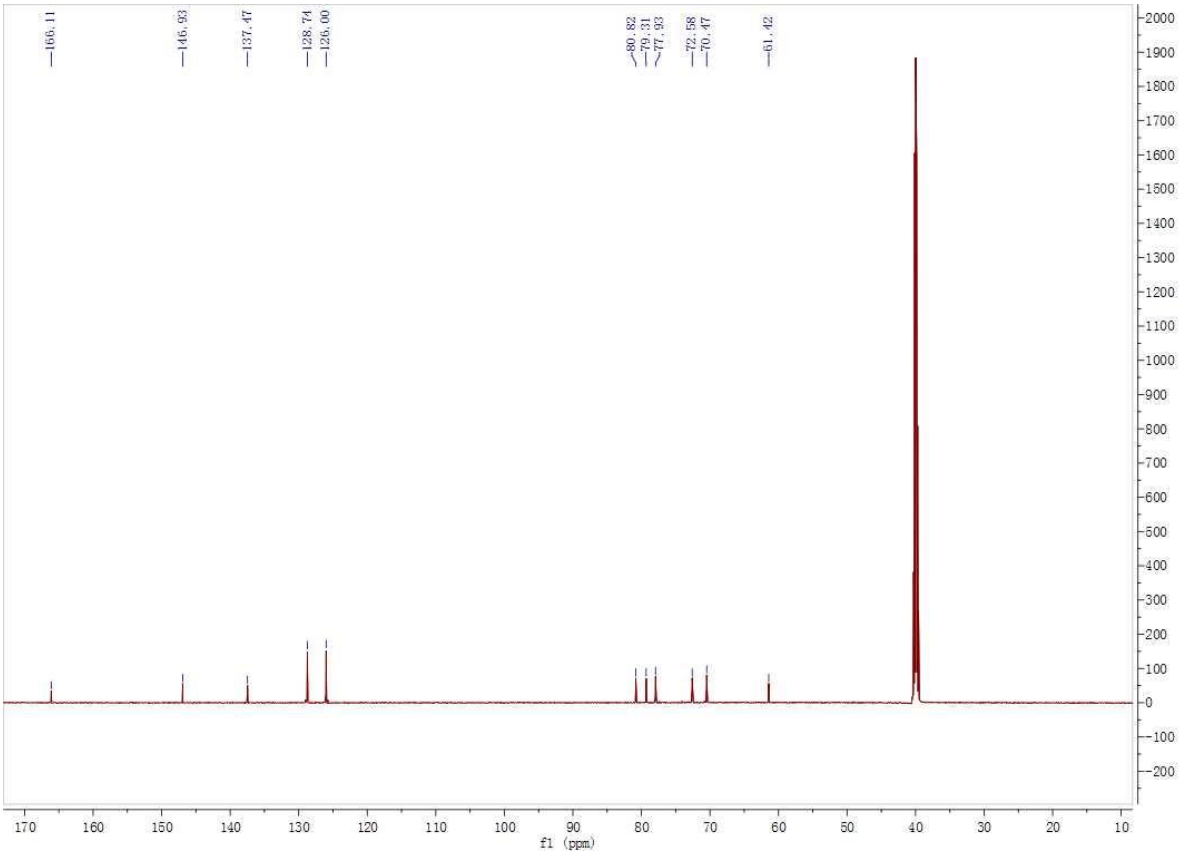


To a solution of **1** (5 g, 27.8 mmol) in pyridine (50 mL) was added acetic anhydride (35 mL). The reaction mixture was stirred for 5 h and then H_2O (100 mL) was added and stirring continued for 20 min. The reaction mixture was washed with 0.1 M HCl (15 mL), satd aq $NaHCO_3$ (15 mL), and dried ($MgSO_4$), Filtration, evaporation of solvent under diminished pressure to dryness to give **2**. To a solution of **2** in dichloromethane (35 mL) was added HBr-HOAc (35 mL). The reaction mixture was stirred for 5 h and then H_2O (50 mL) was added and stirring continued for 20 min. The reaction mixture was washed with satd aq $NaHCO_3$ (25 mL), and dried ($MgSO_4$). Filtration, evaporation of solvent under diminished pressure and chromatography of the residue (EtOAc–petroleum ether, 1:8) gave **3** as a white solid (4.4 g, 65 %). To a solution of **3** (4.4 g, 10.8 mmol) in DMF (30 mL) was added NaN_3 (3.5 g, 53.8 mmol). The reaction mixture was stirred for 4 h. Filtration, evaporation of solvent under diminished pressure and chromatography of the residue (EtOAc–petroleum ether, 1:5) gave **4** as a white solid (2.1 g, 53%). To a solution of **4** (2.1 g, 5.6 mmol) in EtOAc (20 mL) was added Pd/C (1.05 g) and add hydrogen. The reaction mixture was stirred for 2 h. Filtration, evaporation of solvent under diminished pressure to dryness to give **5** (1.6 g, 85%). To a solution of compound **5** (200 mg, 0.58 mmol) in dry CH_2Cl_2 (10 mL), *p*-sulfamoylbenzoic acid (116 mg, 0.58 mmol) and EDCI (111.2 mg,0.58 mmol) were added at room temperature and the reaction mixture was stirred

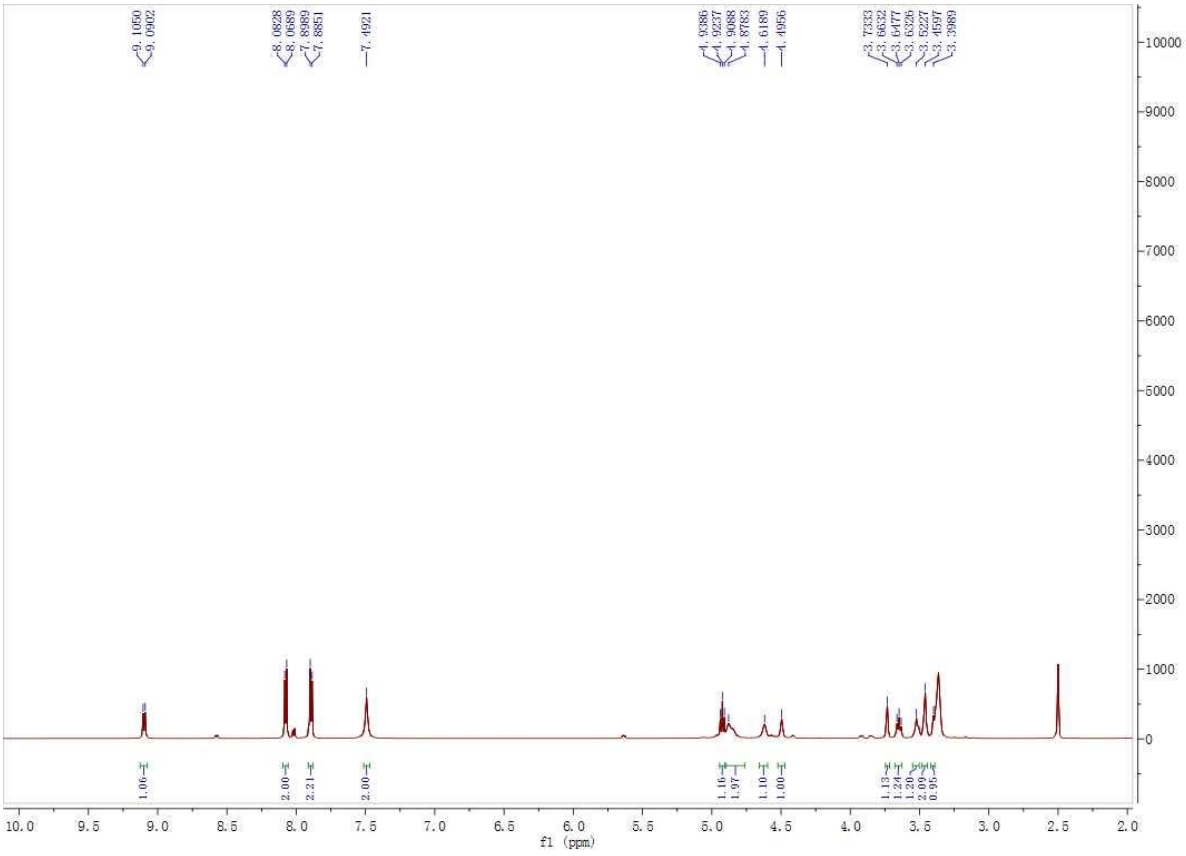
for 0.5 h. The reaction mixture was washed with 0.1 M HCl (5 mL), satd aq $NaHCO_3$ (5 mL), and dried ($MgSO_4$), Filtration, evaporation of solvent under diminished pressure to dryness to give **6a** (162 mg, 53%). To a solution of **6a** (162 mg, 0.31 mmol) in CH_2Cl_2-MeOH (1:1, 5 mL), freshly prepared NaOMe in MeOH solution (1.0 mol/L, 1 mL) was added. After it was stirred overnight, the mixture was neutralized with Dowex H^+ resin to pH 7, then filtered. The filtrate was concentrated and purified by a silica gel column chromatography (5:1, CH_2Cl_2-MeOH) to afford **7a** (52 mg, 47%) as a white solid.

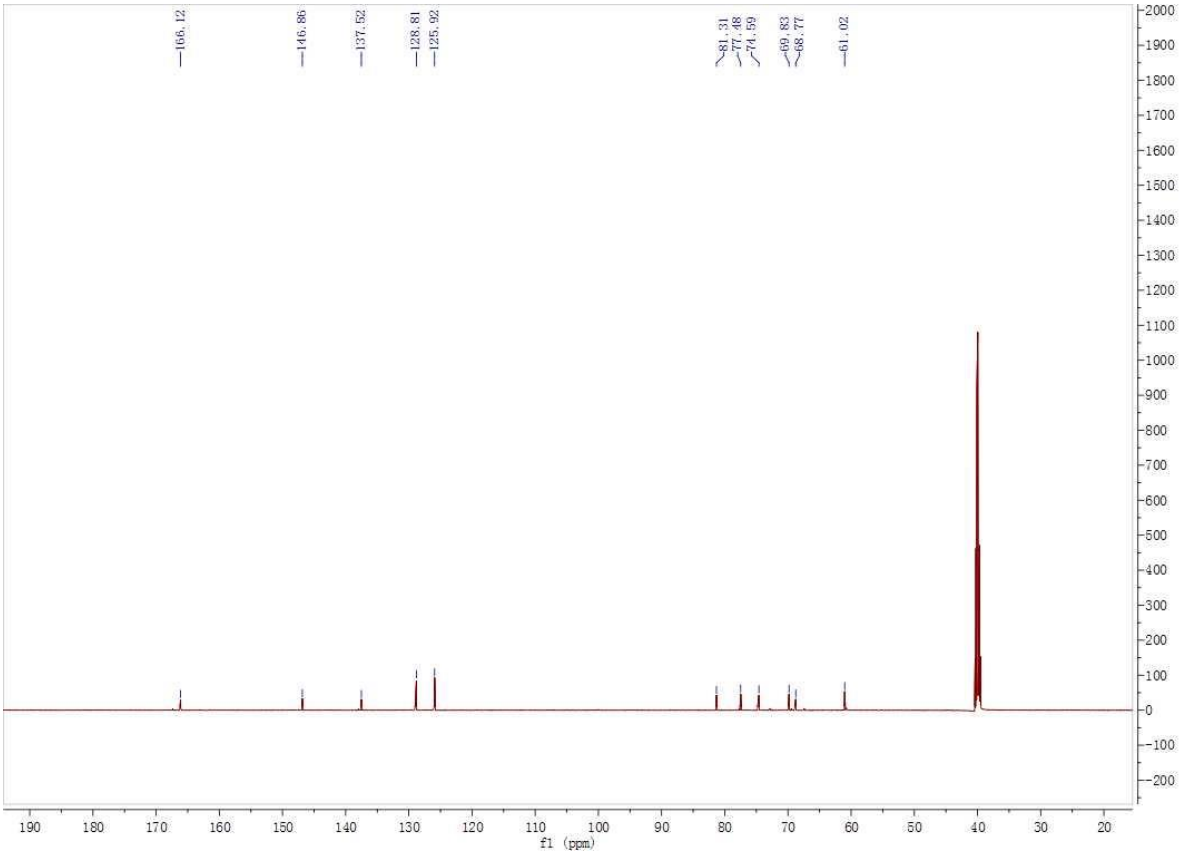
*4-Aminosulfonyl-N- (β-D-glucopyranosyl) benzamide (**7a**)*



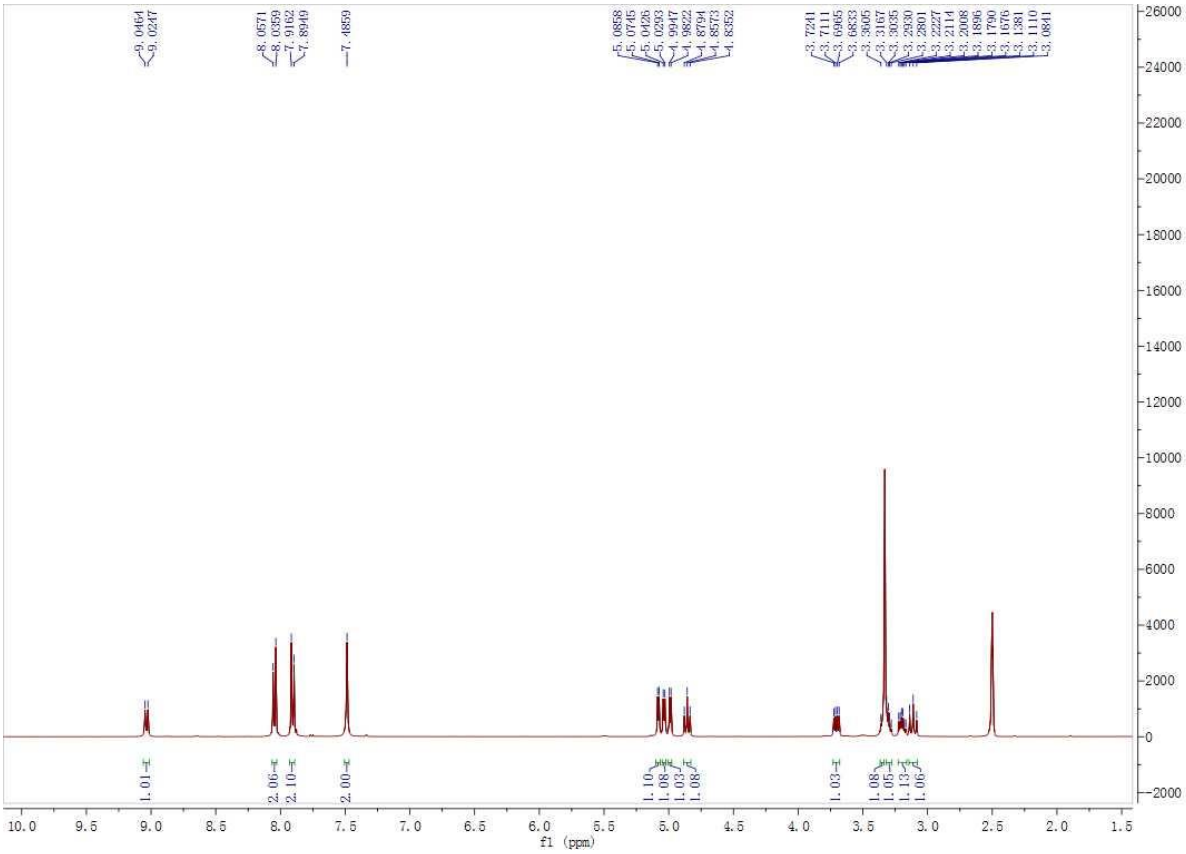


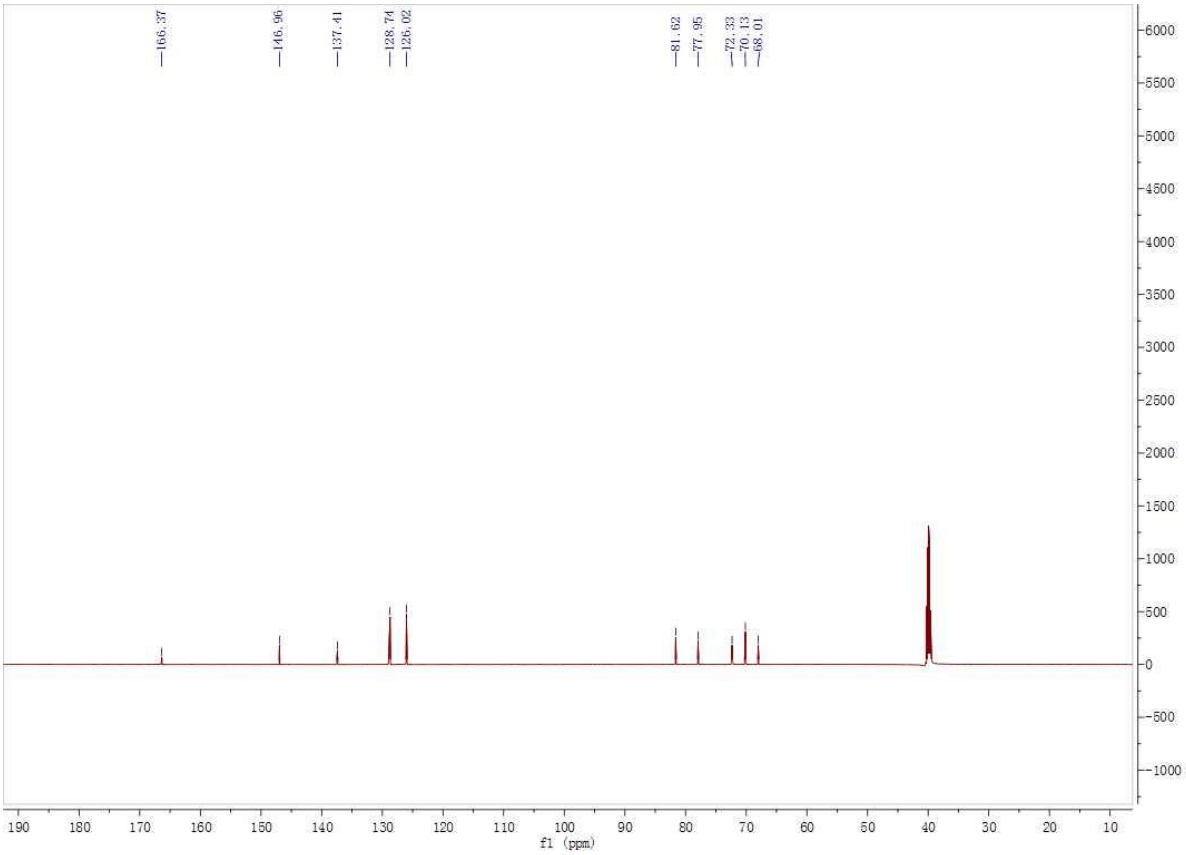
*4-Aminosulfonyl-N-(β-D-galactopyranosyl) benzamide (7**b**)*



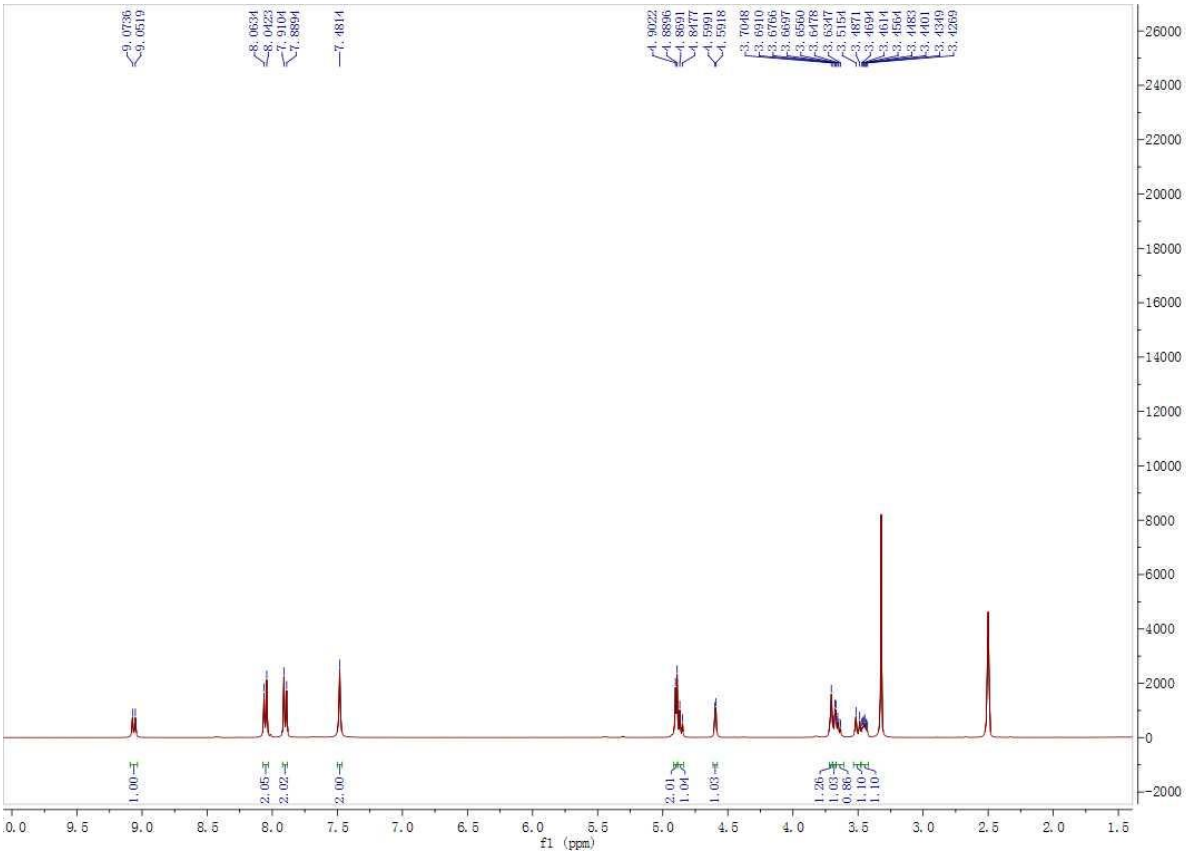


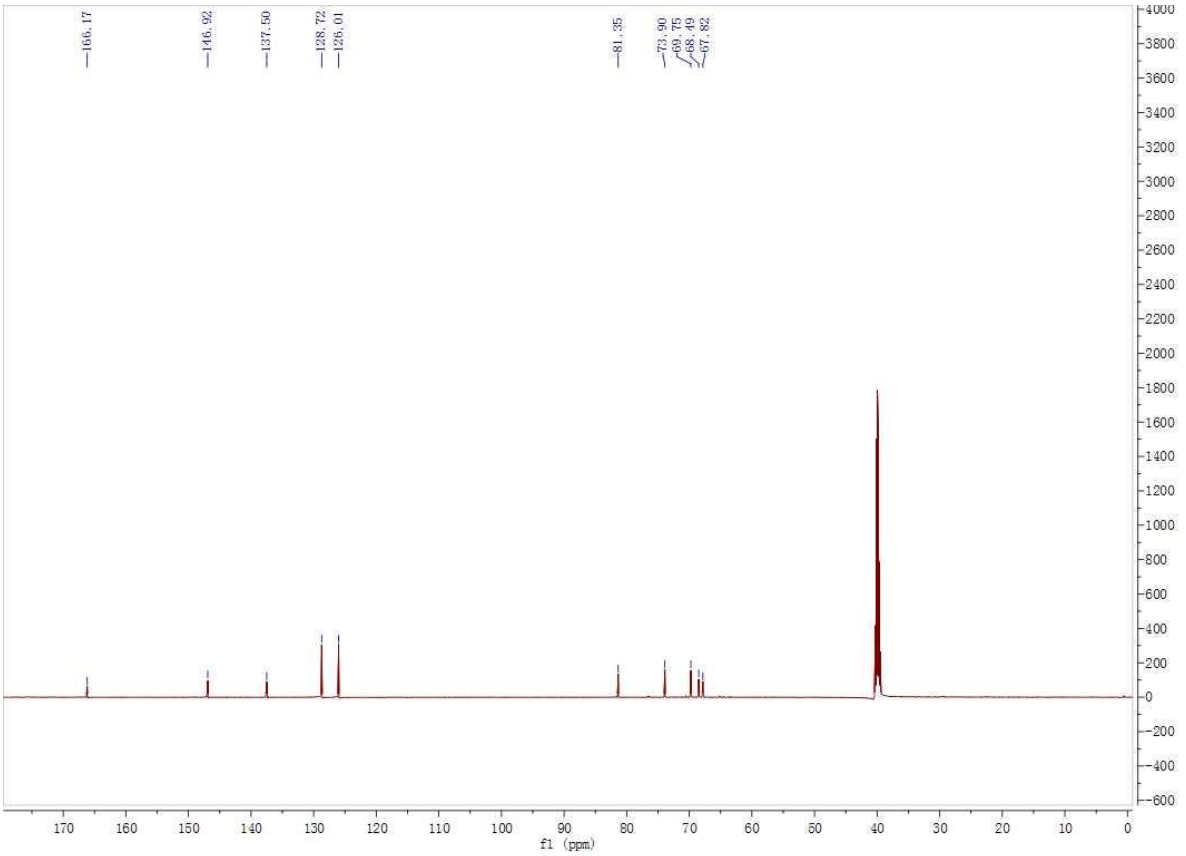
*4-Aminosulfonyl-N-(β-L-arabinopyranosyl) benzamide (7**c**)*



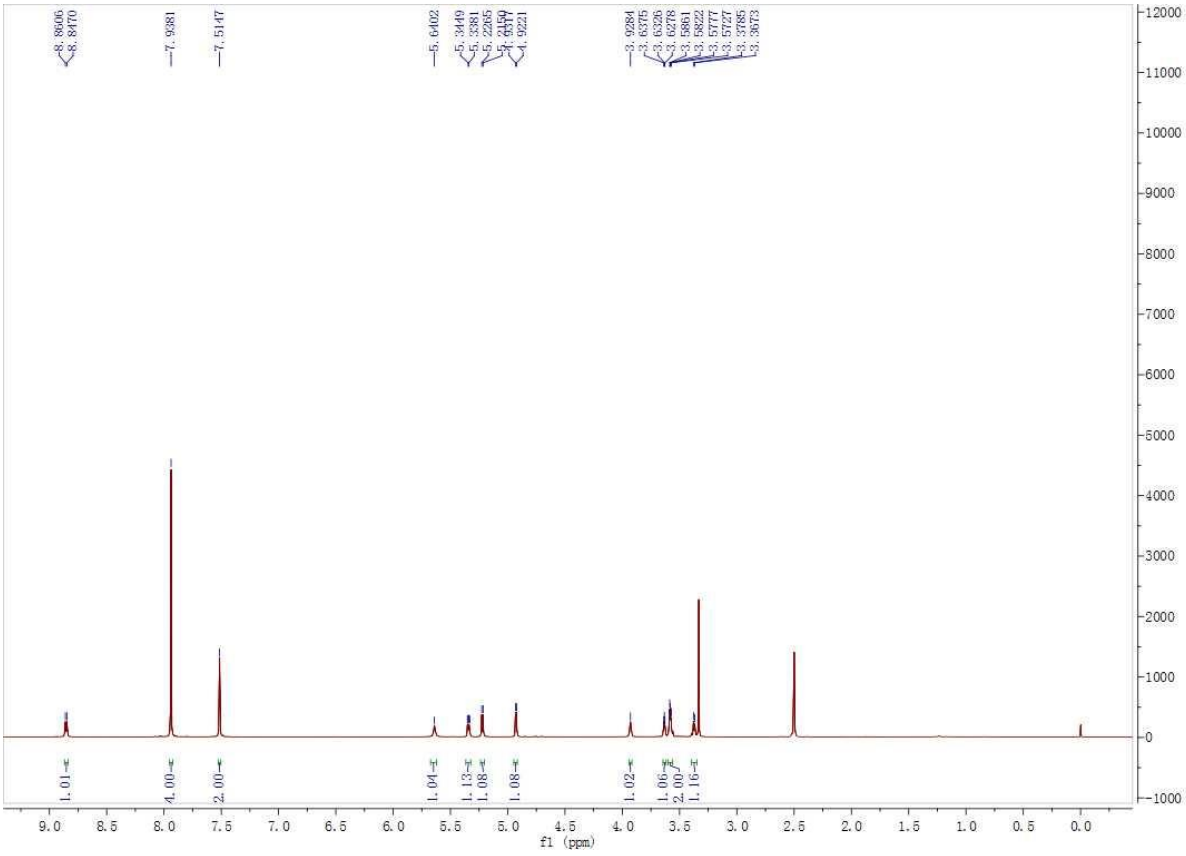


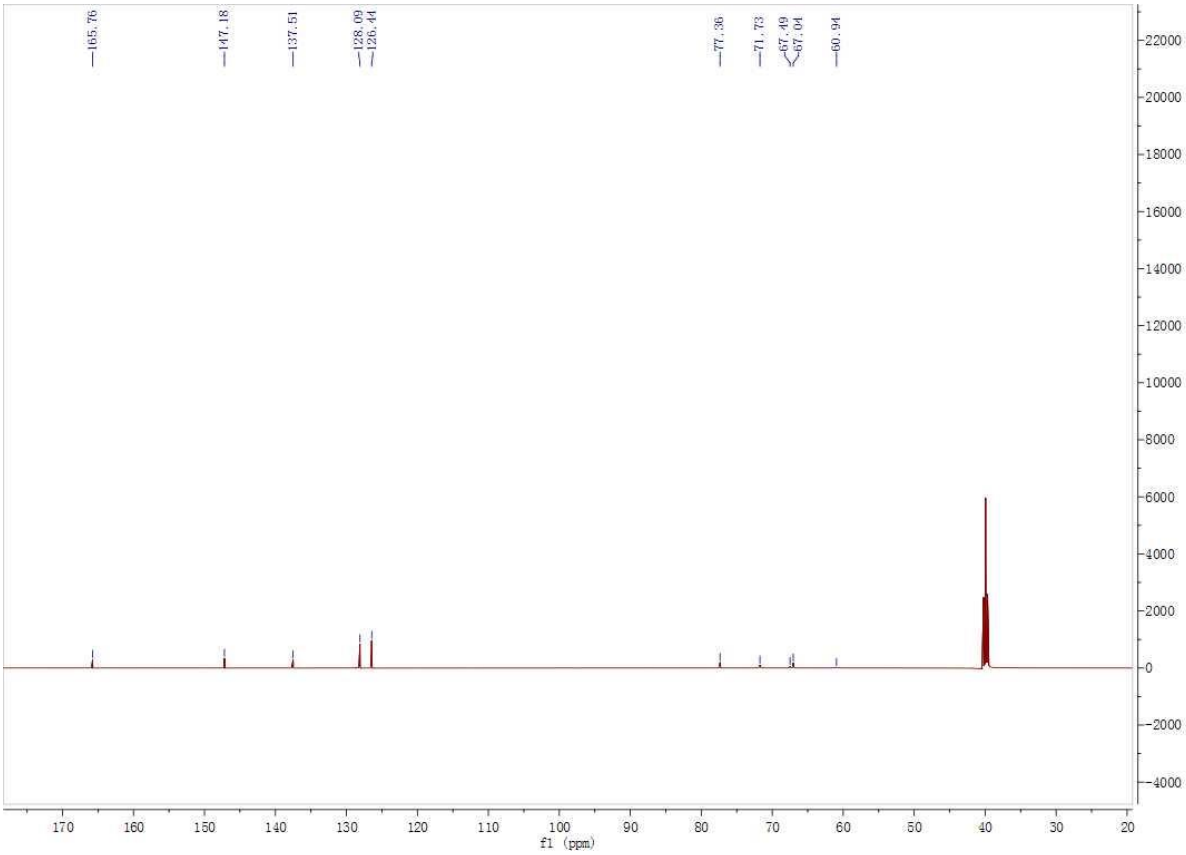
*4-Aminosulfonyl-N-(β-D-xylopyranosyl) benzamide (**7d**)*



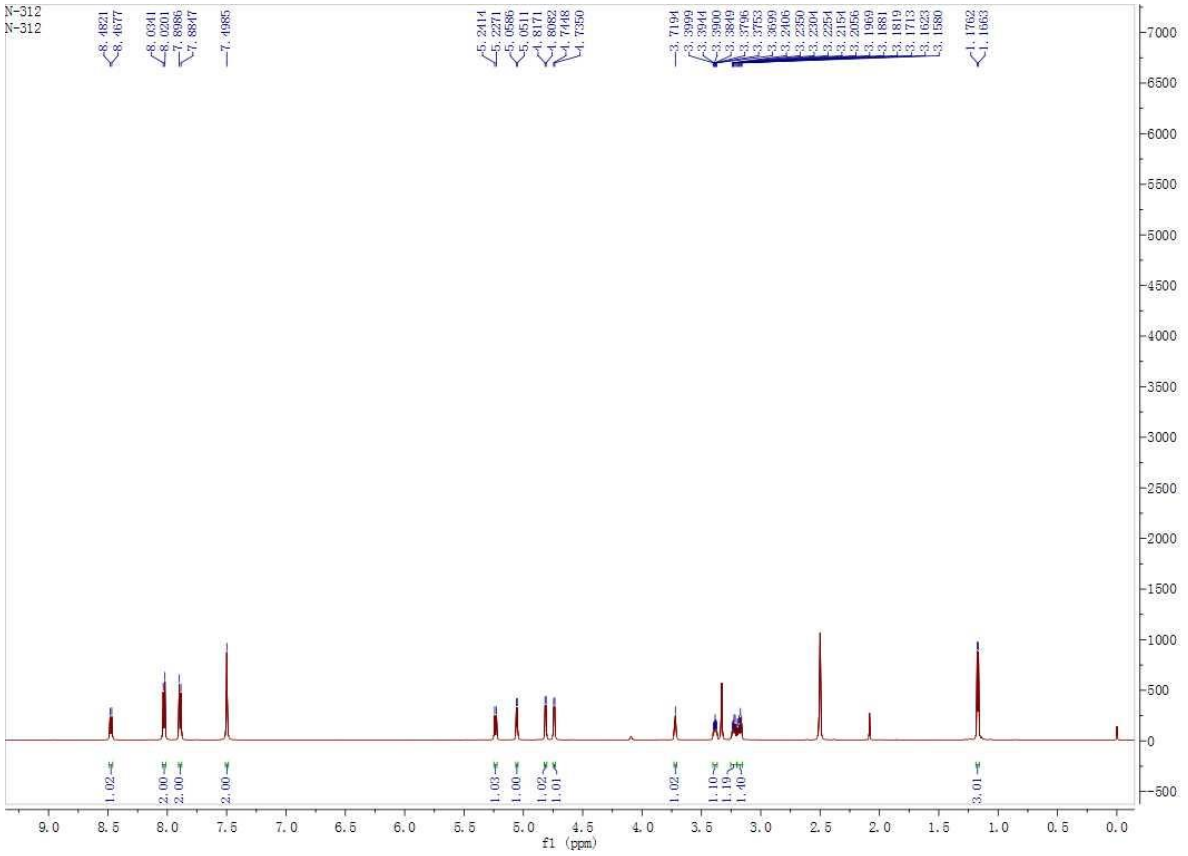


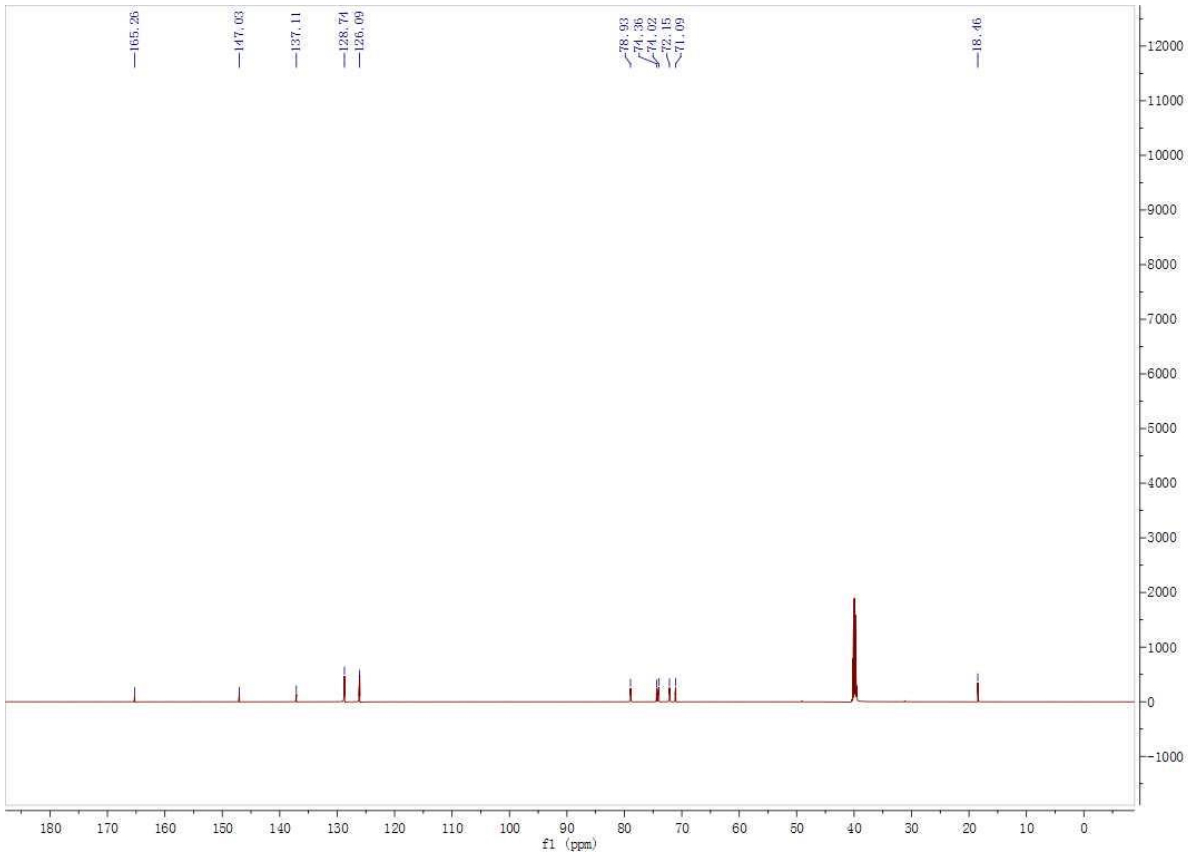
*4-Aminosulfonyl-N-(β-D-ribofuranosyl) benzamide (**7e**)*



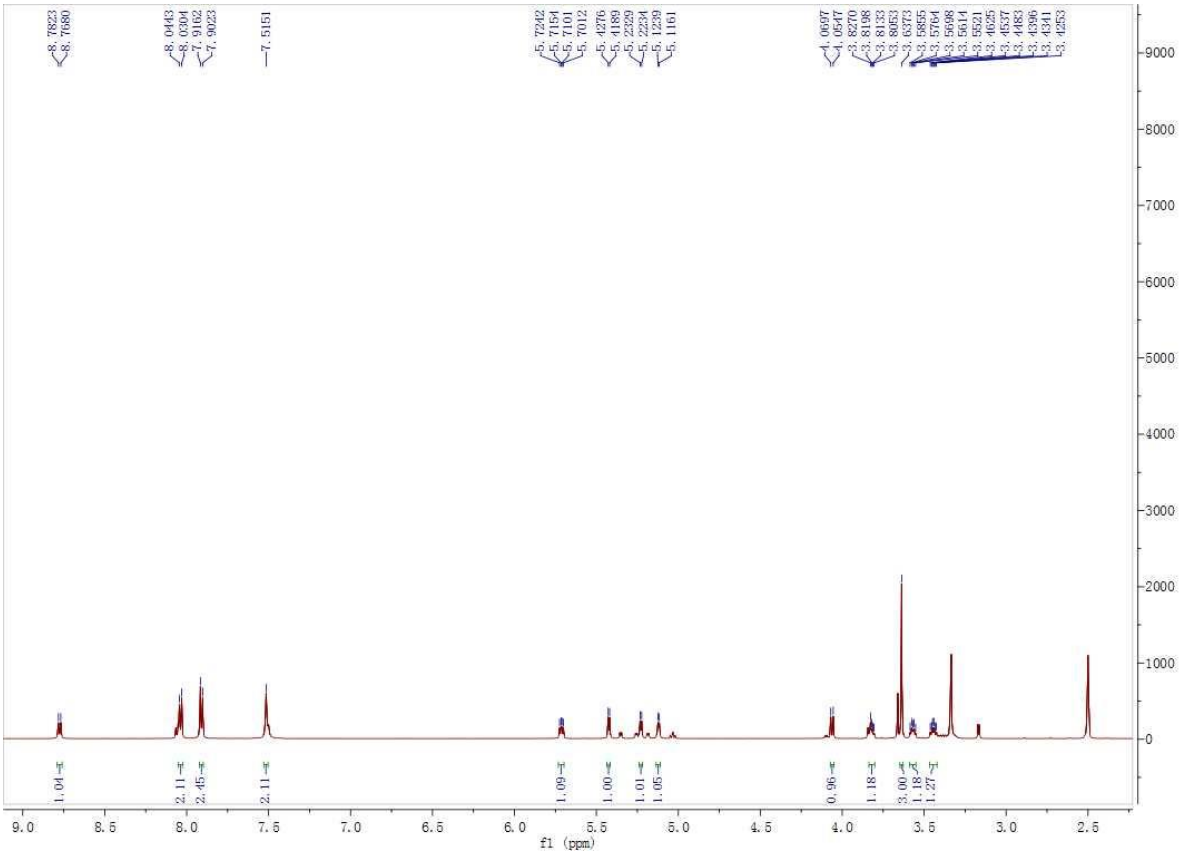


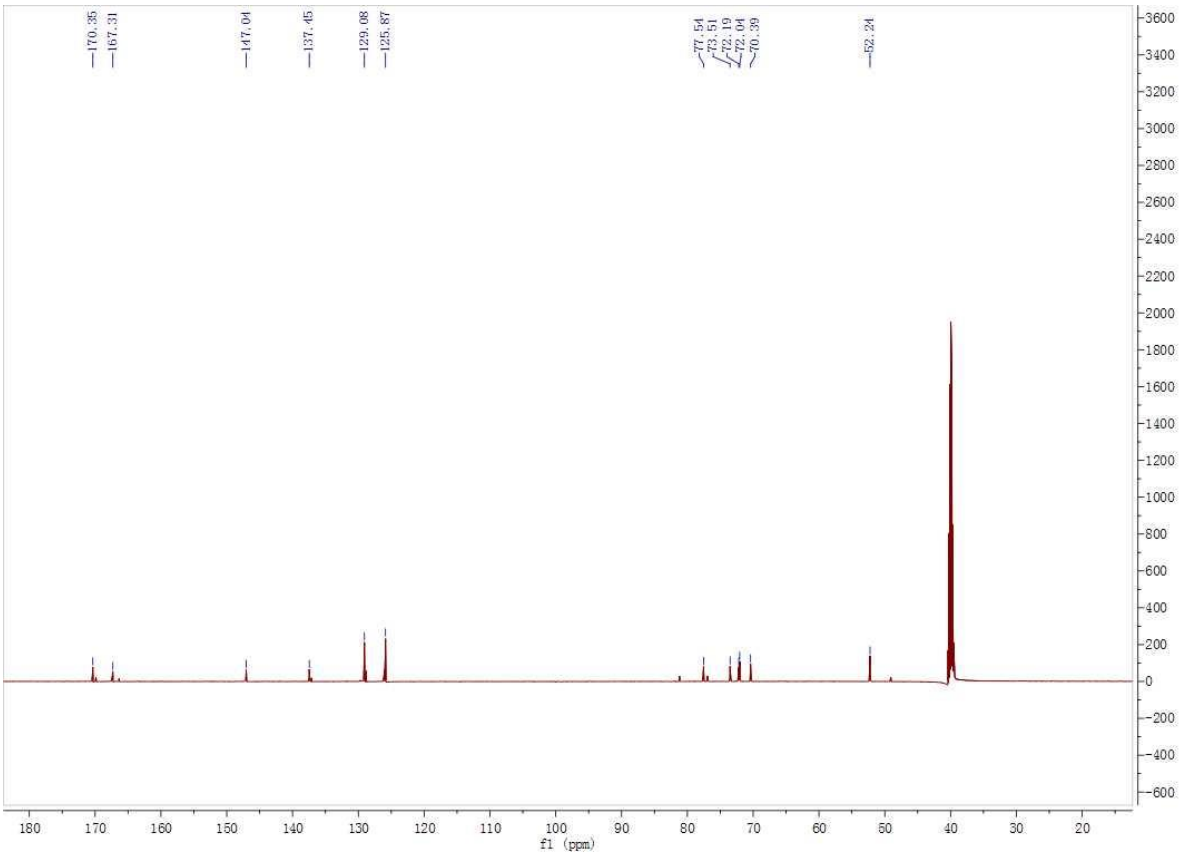
*4-Aminosulfonyl-N-(β-L-rhamnosyl) benzamide (**7f**)*





*4-Aminosulfonyl-N-(β-D-glucuronic acid methyl ester) benzamide (**7g**)*





*4-Aminosulfonyl-N-(β-D-mannopyranosyl) benzamide (**7h**)*