Electronic Supplementary Material (ESI) for RSC Advances.

Synthesis, Biological Activity and Structural Study of New Benzotriazole-Based Protein Kinase CK2 inhibitors

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ELECTRONIC SUPPLEMENTARY INFORMATION

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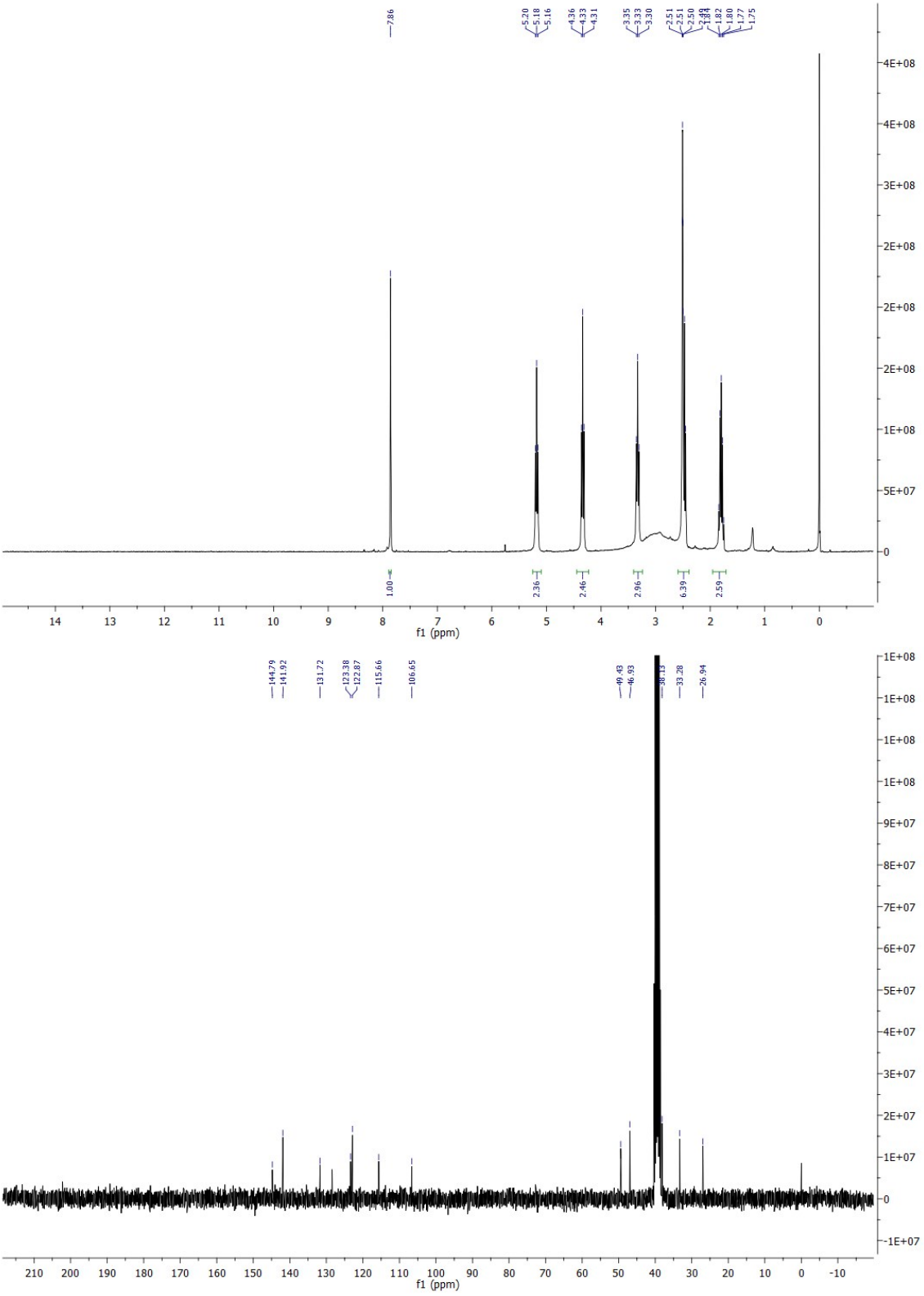
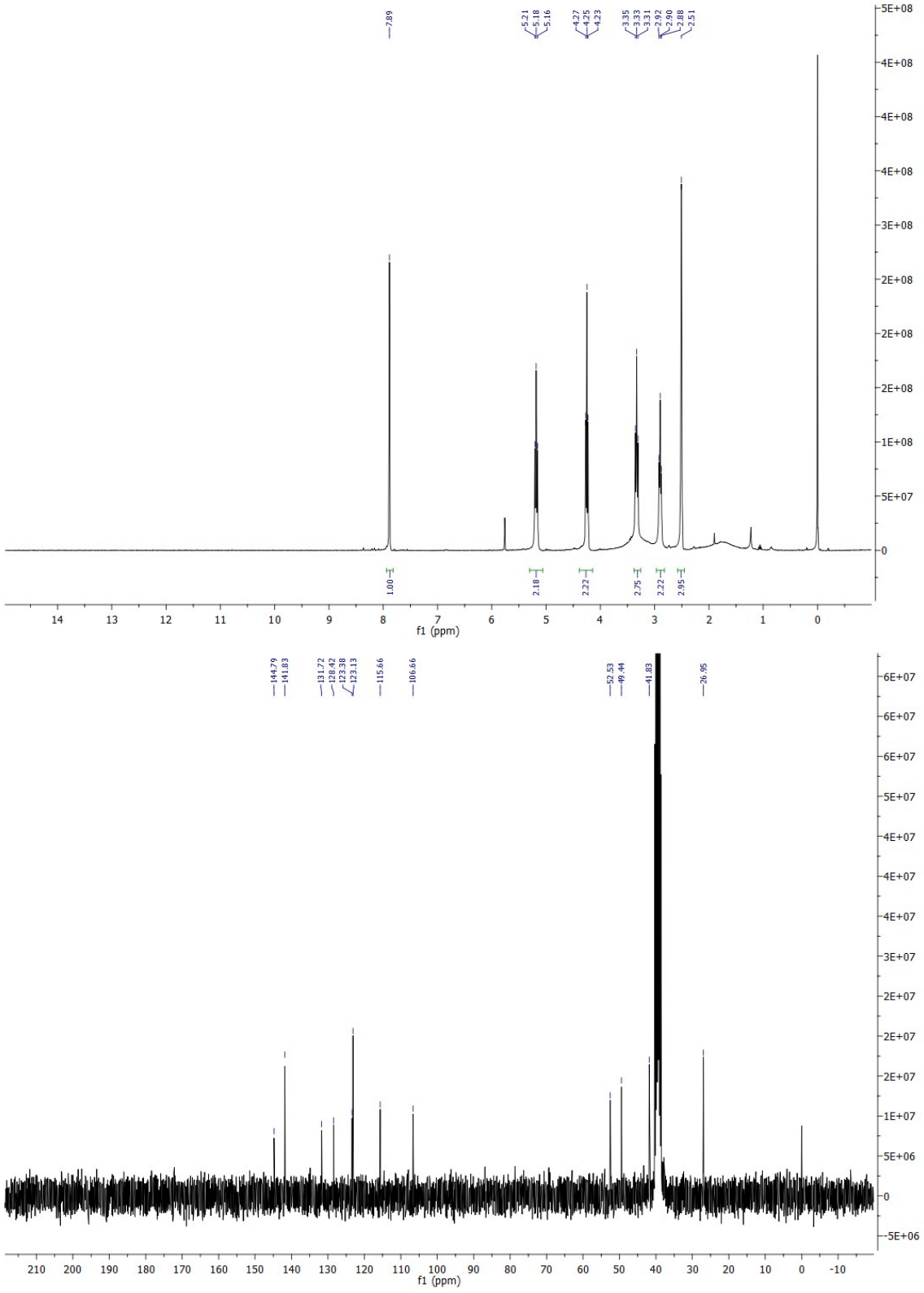
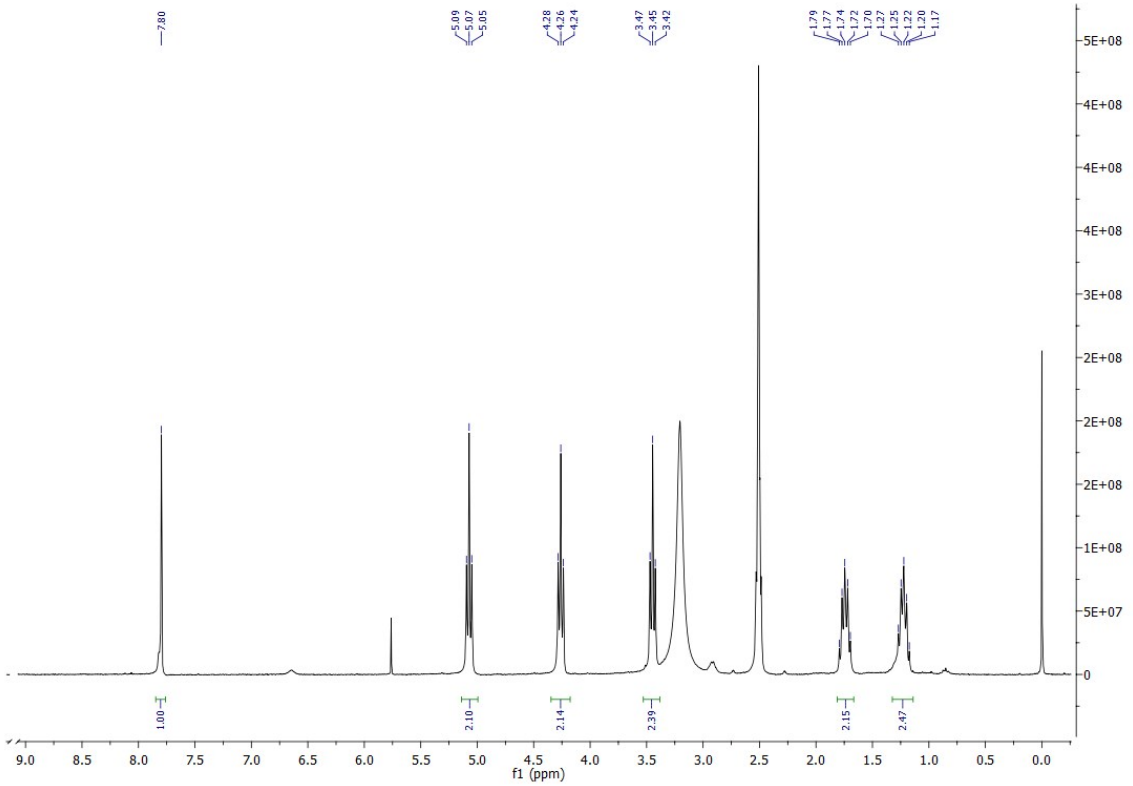
3-(4-(2-(Perbromo-1*H*-benzo[*d*][1,2,3]triazol-1-yl)ethyl)-1*H*-1,2,3-triazol-1-yl)propan-1-amine [9]

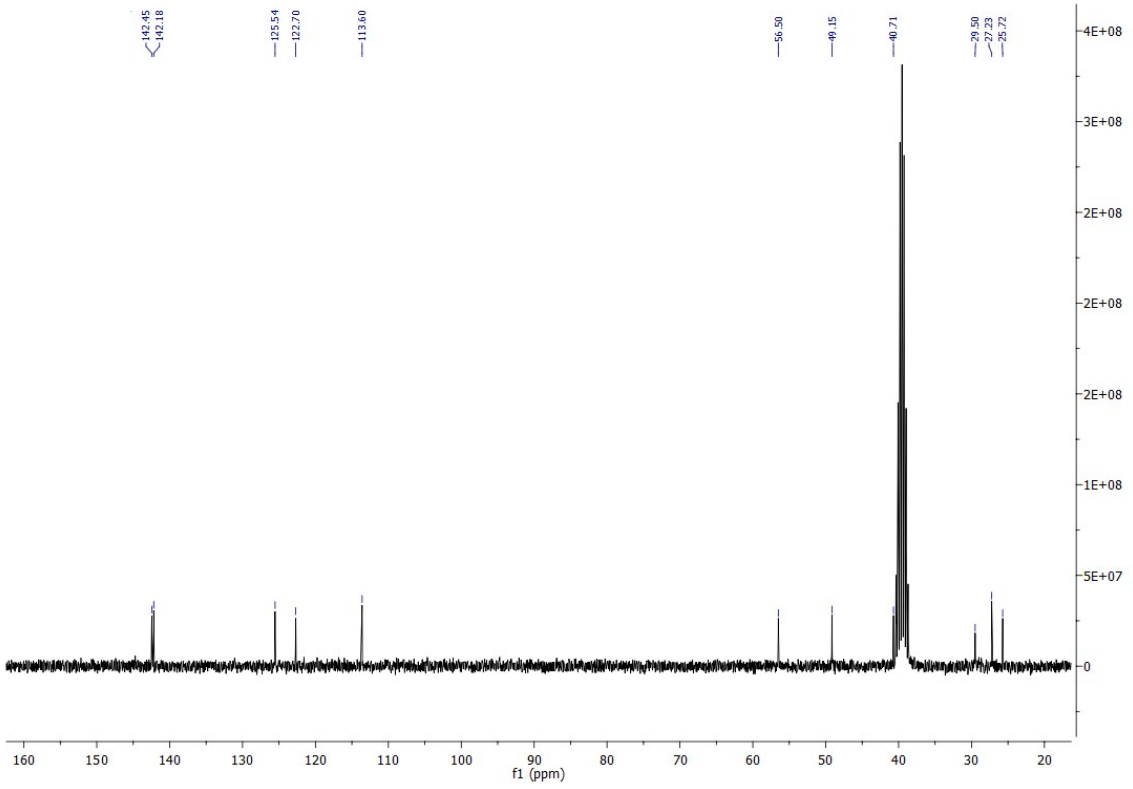


2-(4-(2-(Perbromo-1*H*-benzo[*d*][1,2,3]triazol-1-yl)ethyl)-1*H*-1,2,3-triazol-1-yl)ethanamine [10]

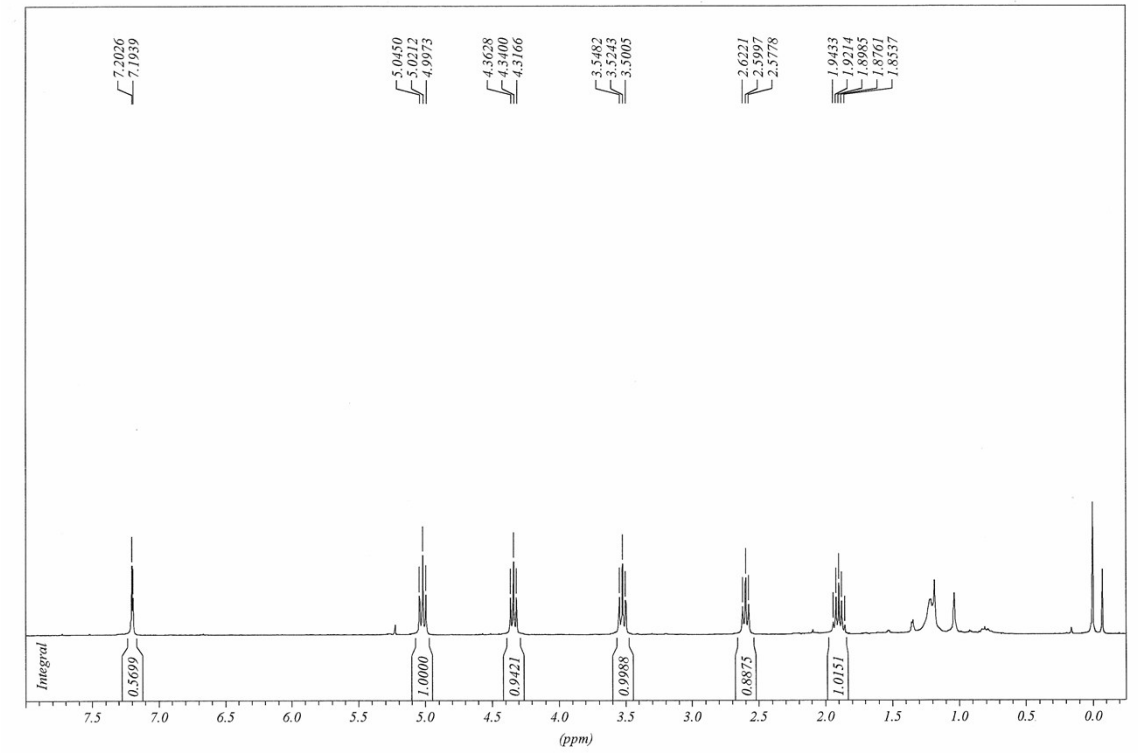


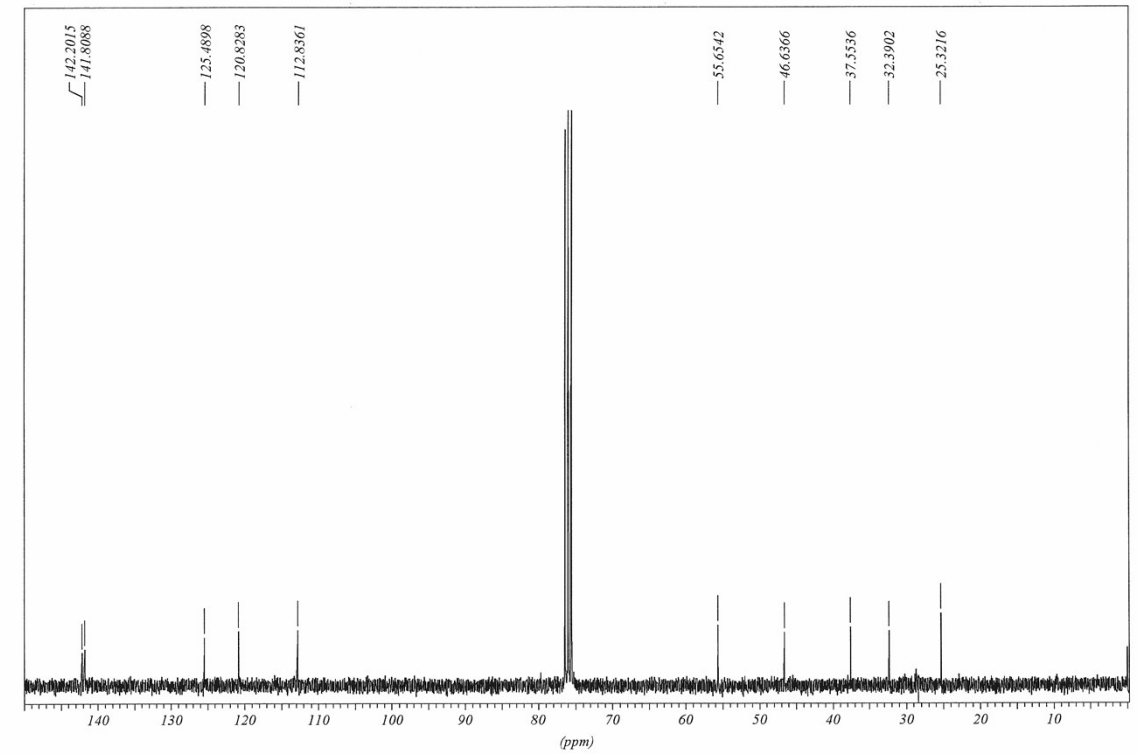
4-(4-(2-(Perbromo-2*H*-benzo[*d*][1,2,3]triazol-2-yl)ethyl)-1*H*-1,2,3-triazol-1-yl)butan-1-amine [14]



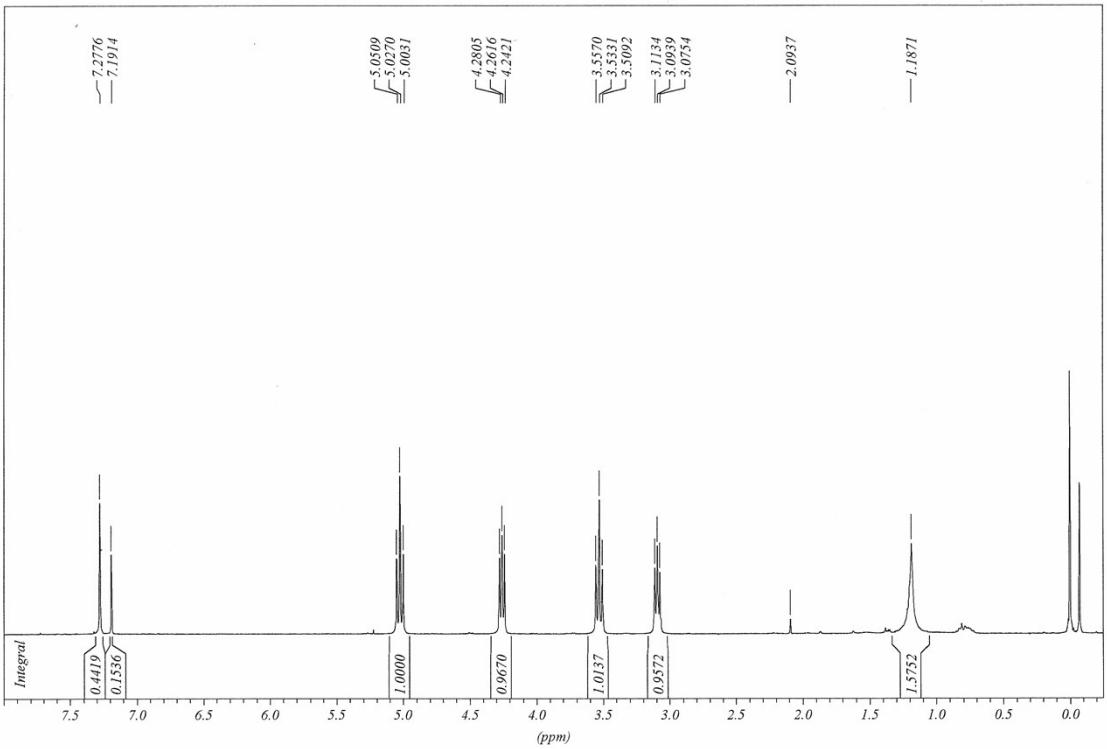


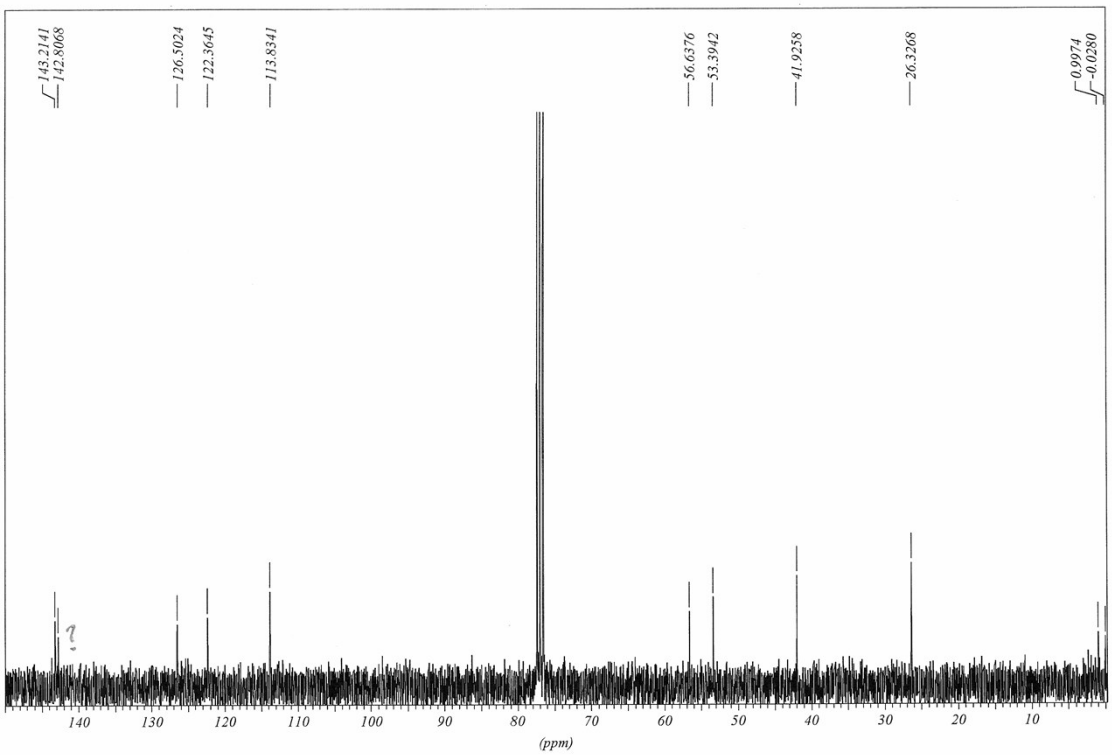
3-(4-(2-(Perbromo-2*H*-benzo[*d*][1,2,3]triazol-2-yl)ethyl)-1*H*-1,2,3-triazol-1-yl)propan-1-amine [15]



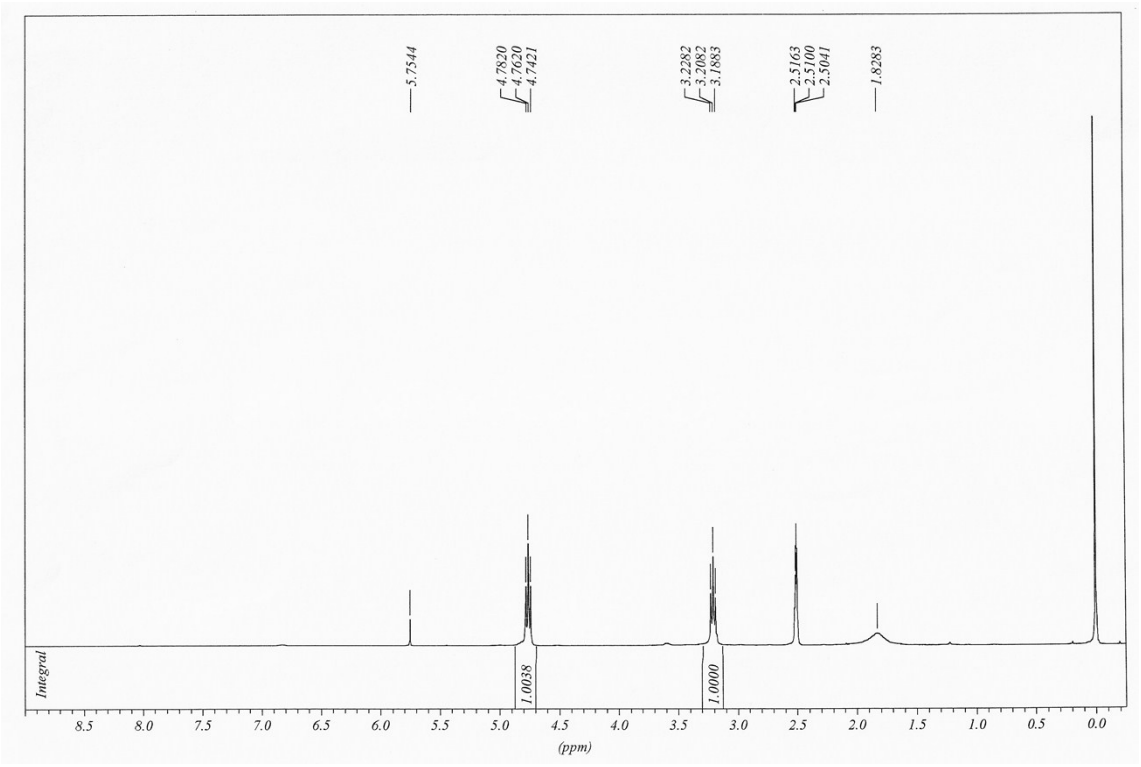


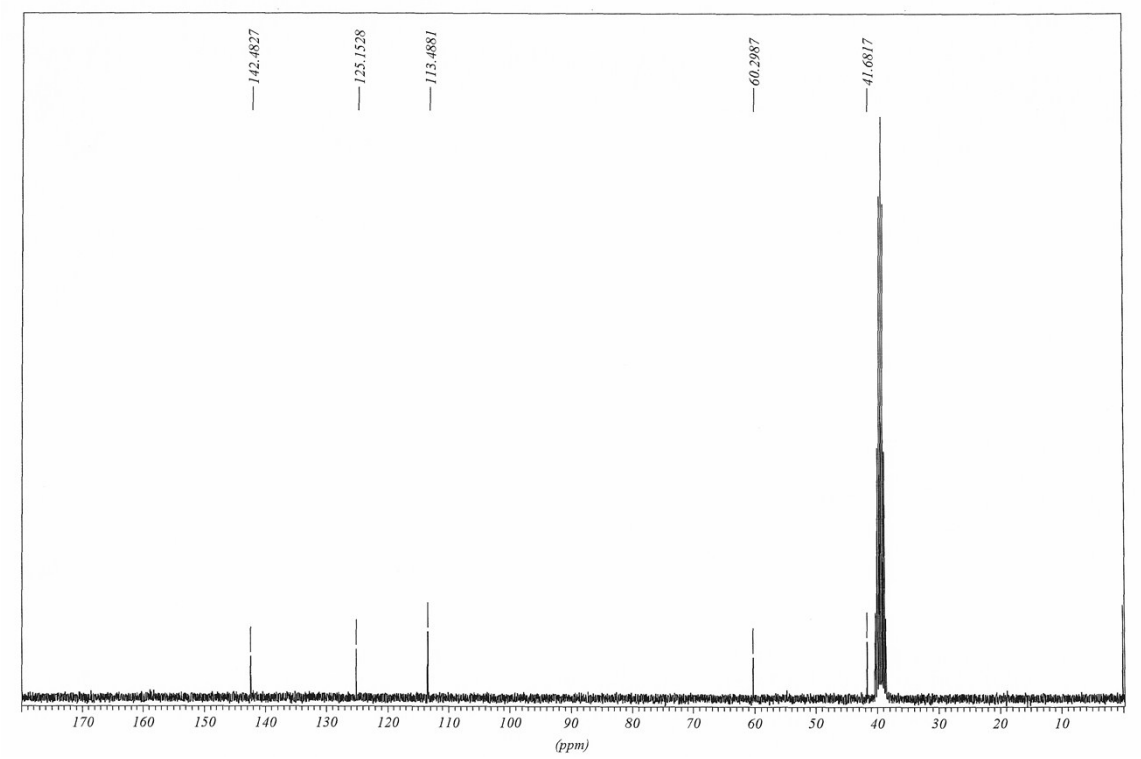
2-(4-(2-(Perbromo-2*H*-benzo[*d*][1,2,3]triazol-2-yl)ethyl)-1*H*-1,2,3-triazol-1-yl)ethanamine [16]



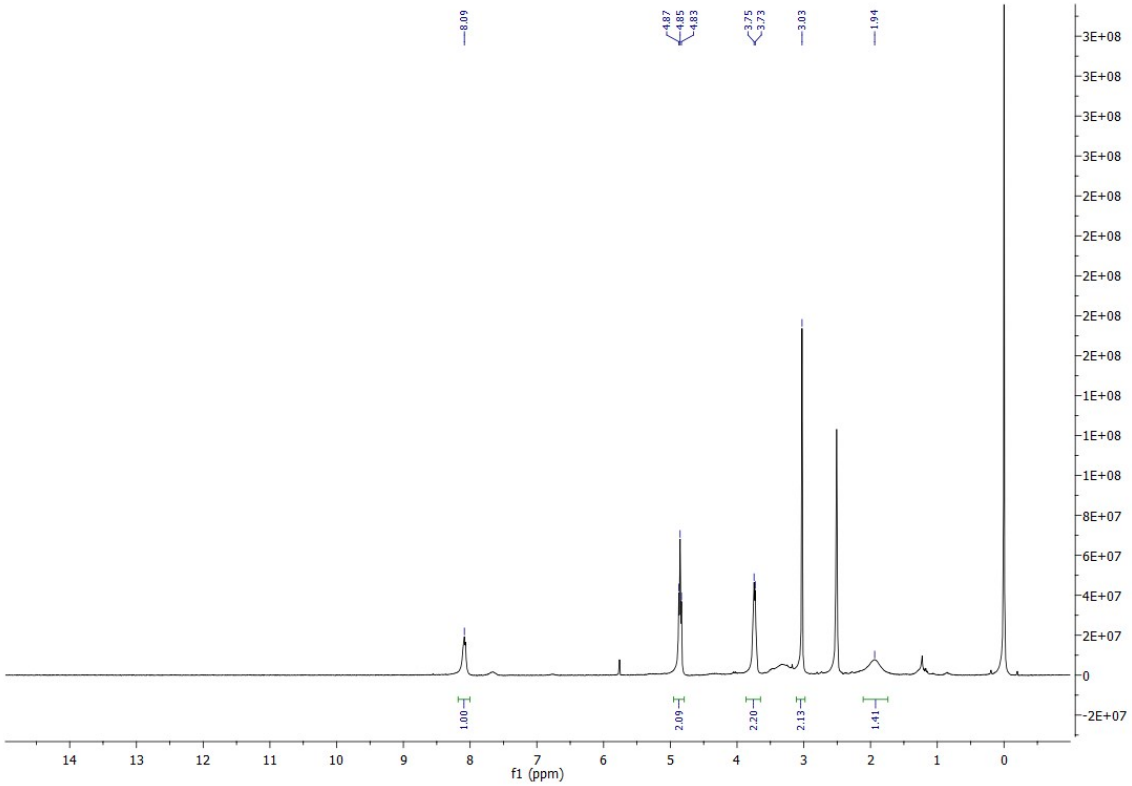


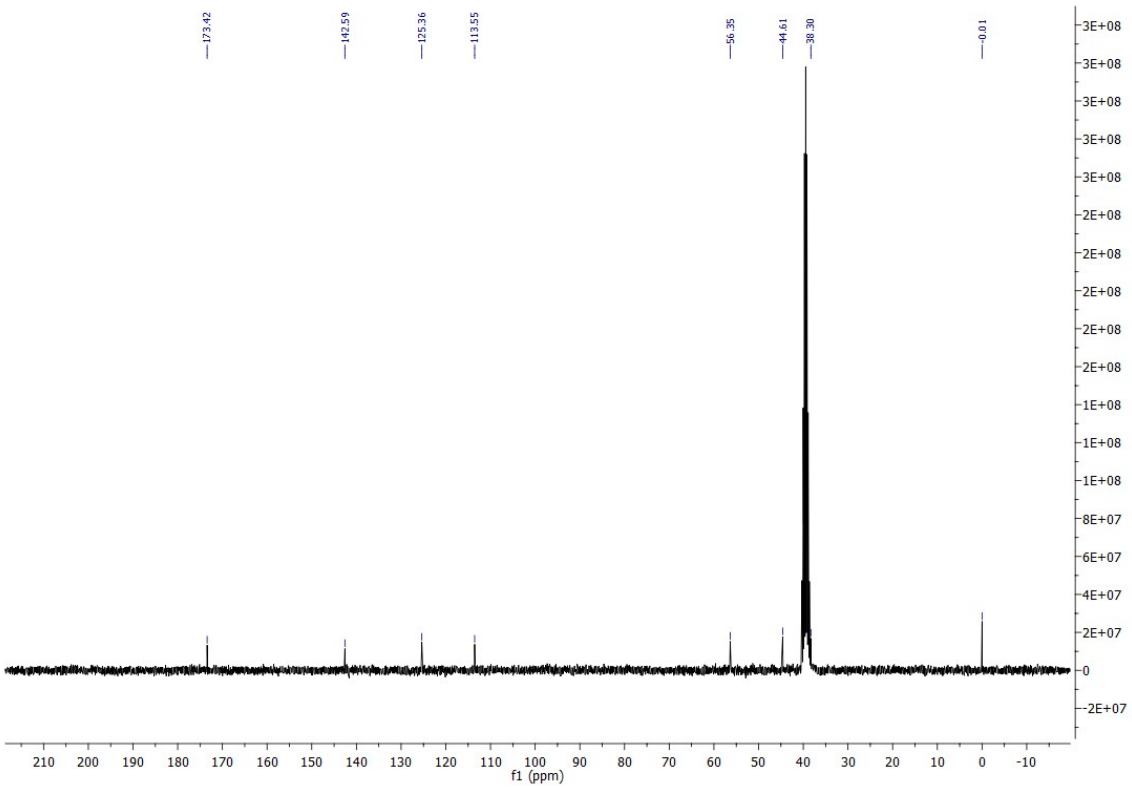
2-(Perbromo-2*H*-benzo[*d*][1,2,3]triazol-2-yl)ethanamine [17]



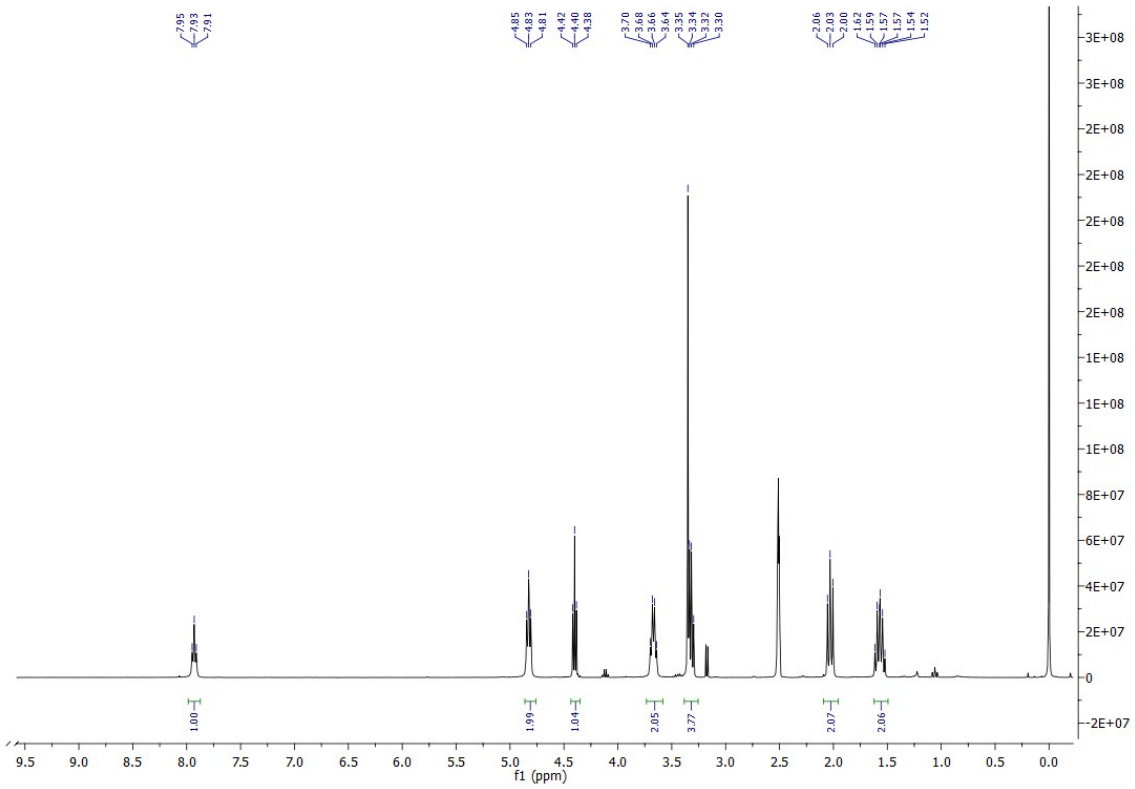


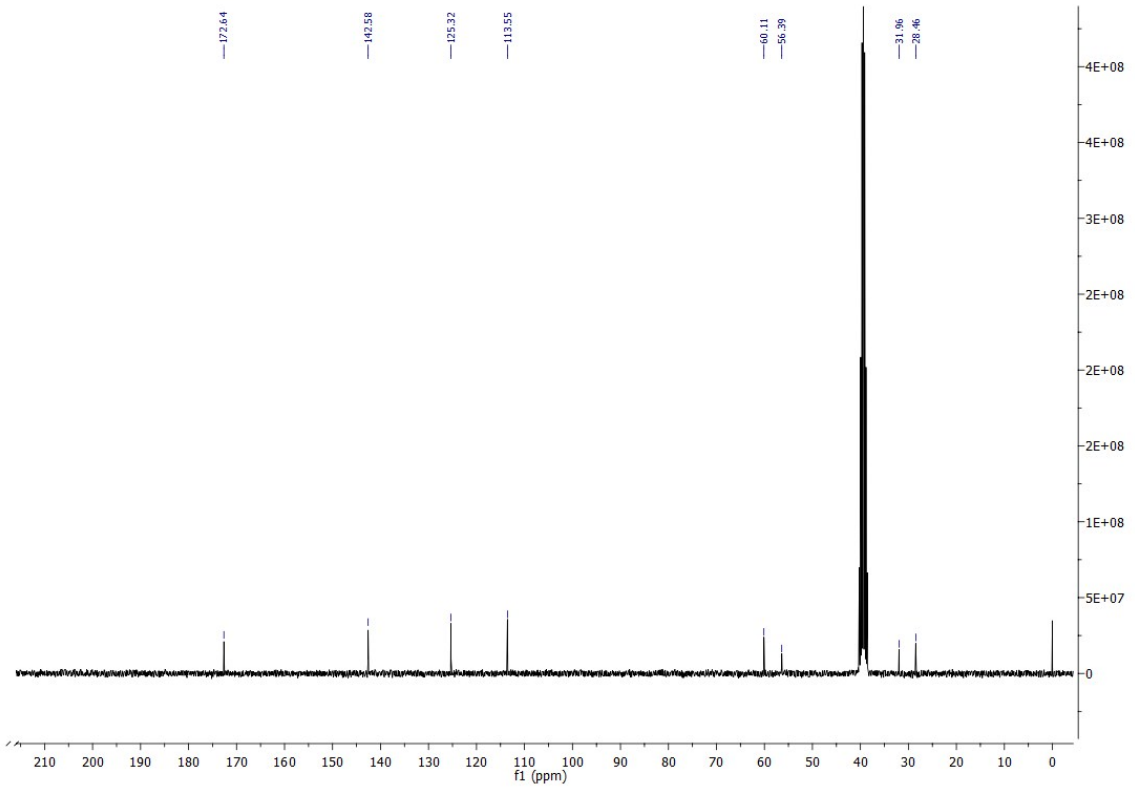
2-Amino-*N*-(2-(perbromo-2*H*-benzo[*d*][1,2,3]triazol-2-yl)ethyl)acetamide [19]



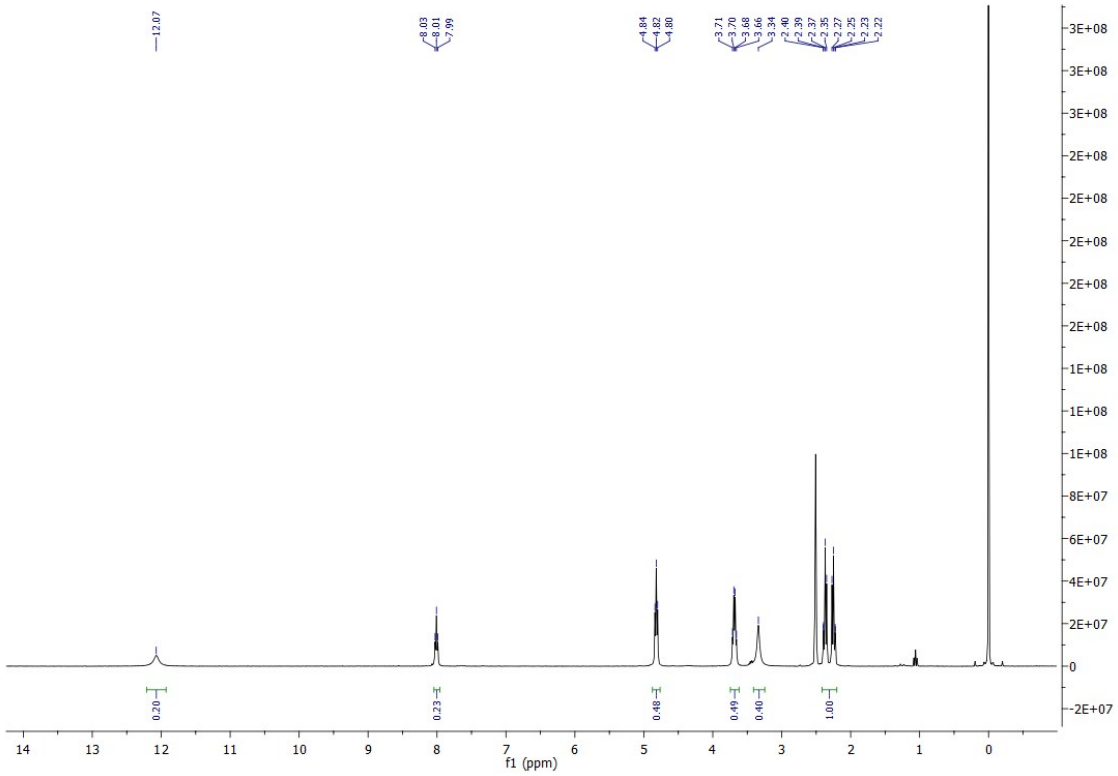


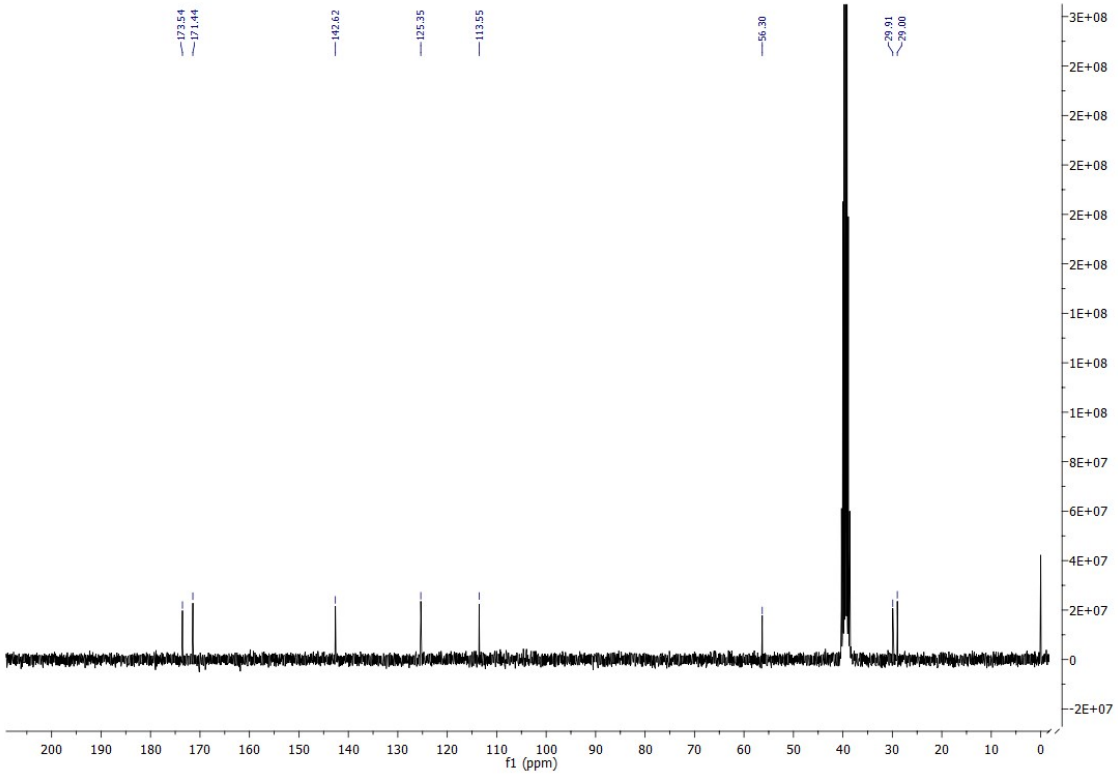
4-Hydroxy-*N*-(2-(perbromo-2*H*-benzo[*d*][1,2,3]triazol-2-yl)ethyl)butanamide [20]



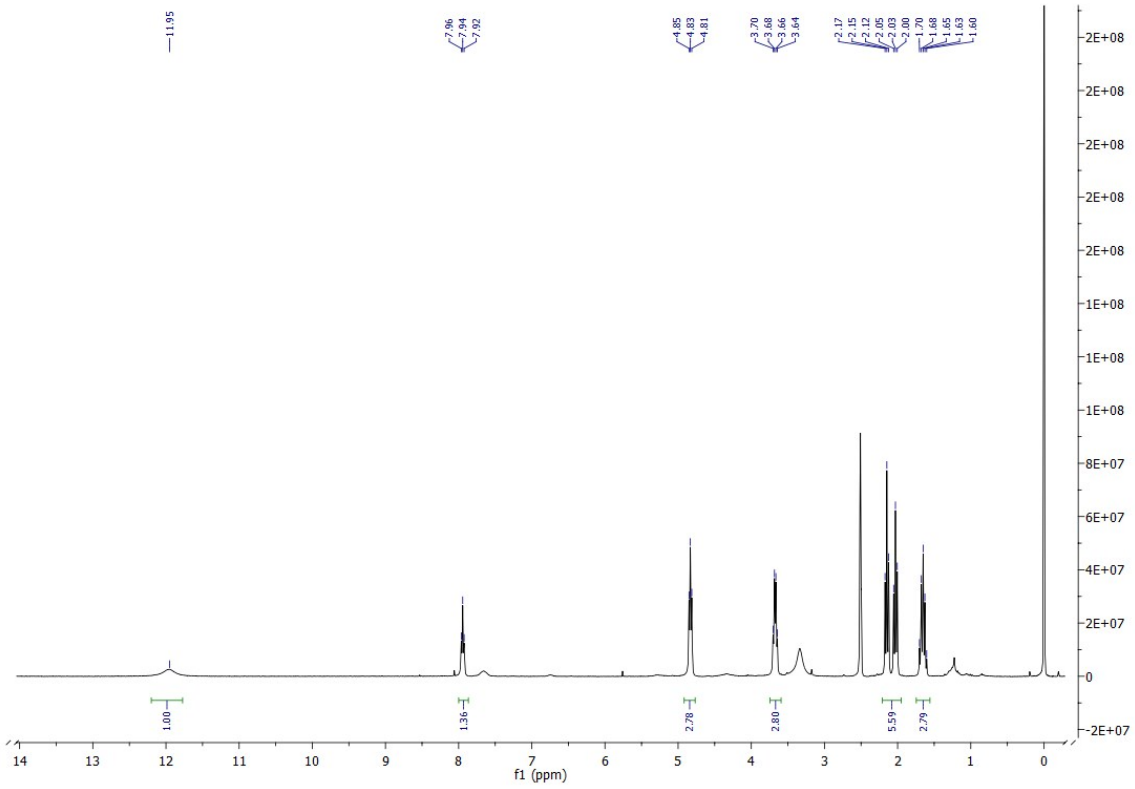


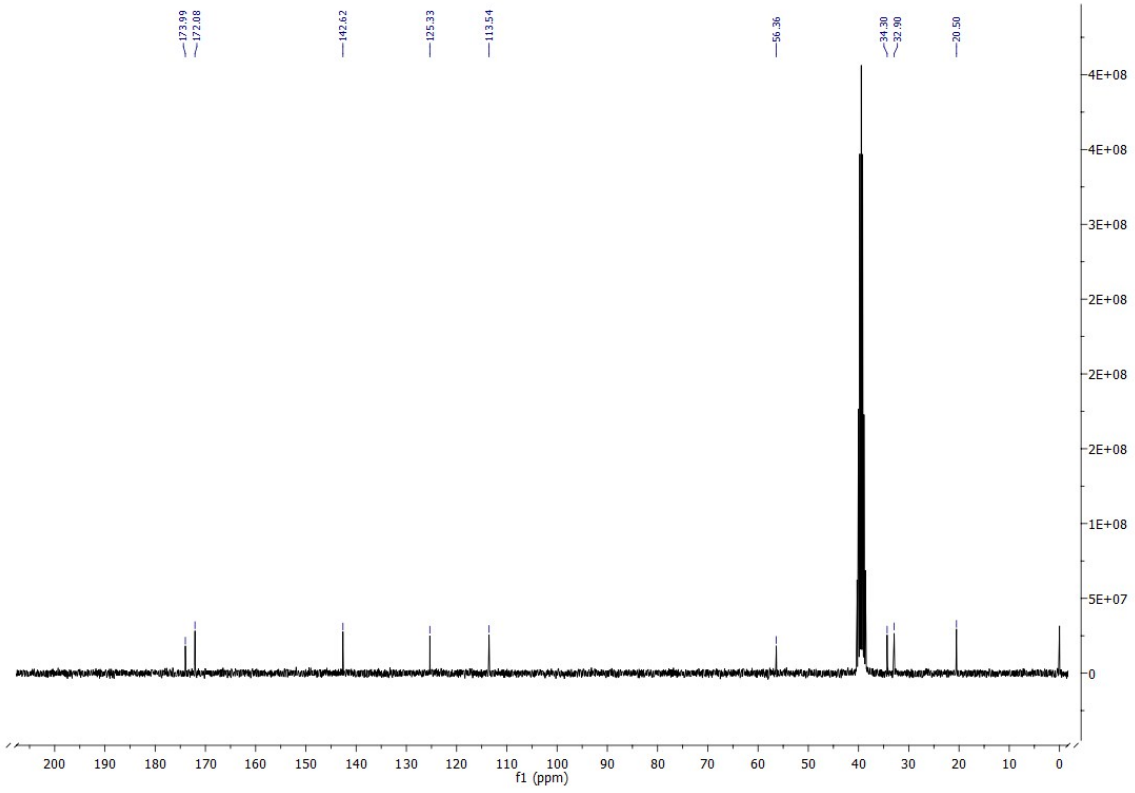
4-Oxo-4-(2-(perbromo-2*H*-benzo[*d*][1,2,3]triazol-2-yl)ethylamino)butanoic acid [21]





5-Oxo-5-(2-(perbromo-2*H*-benzo[d][1,2,3]triazol-2-yl)ethylamino)pentanoic acid [22]





First Docking studies

We chose the crystallographic structure of CK2 in complex with AMP-PNP (a non-hydrolysable ATP-analogue) as starting geometry (PDB code 3NSZ), to ensure the right open conformation of the target protein. The full computational protocol is described in the Experimental Section. All compounds gave good docked poses in CK2, and presented the expected interactions within the ATP binding site. They share a common TBB based scaffold and only differ in the nature and position of the side chain. In all cases the TBB core is placed in the adenine-binding site, and the side chain, containing amine, hydroxyl or acid groups, drives the orientation of the compounds within the ATP binding site.

The amine group present in the side chain of compounds **9-10**, **14-16** establishes polar interactions reinforced by hydrogen bonds with Asp156 and Asp175 (9, 10) or Asp156 (**14, 15, 16**). Additionally, a hydrogen bond between Ser51 in the phosphate interacting loop or Lys68 and one of the nitrogen atoms in the triazole ring of the TBB substructure is found in some cases. However, the terminal amine group of compound **19** adopts different orientation and coordinates Ser51. A similar orientation is observed in the case of **20**, where the hydroxyl group establishes a hydrogen bond with an amine group of Tyr50 backbone On the other hand, carboxyl groups present in the side chains of compounds **21** and **22** are oriented toward a groove formed by His160, Asp120, ASN118 and Met163. All described interactions can account for reasonable predicted binding poses of these inhibitors within the ATP binding site of CK2. Binding modes predicted for **14**, **15** and **16** with CK2α subunit are shown in Figure 1

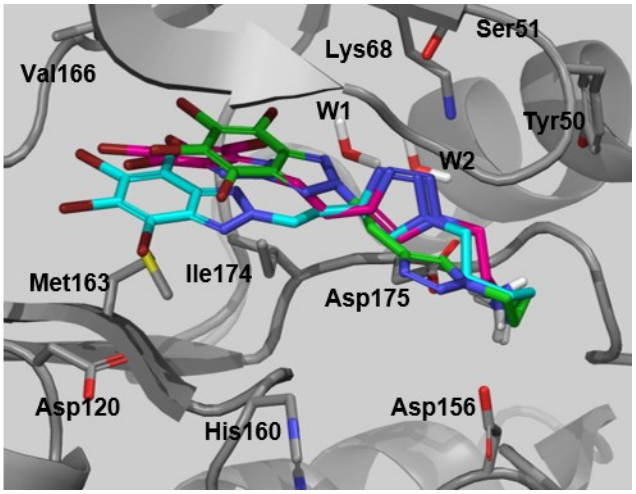


Figure 1. Binding modes of **14**, **15** and **16** obtained from docking studies. Compounds were docked into CK2α subunit using GLIDE software. Compounds are colored as follows: **14** - cyan, **15**- green, **16** – purple.

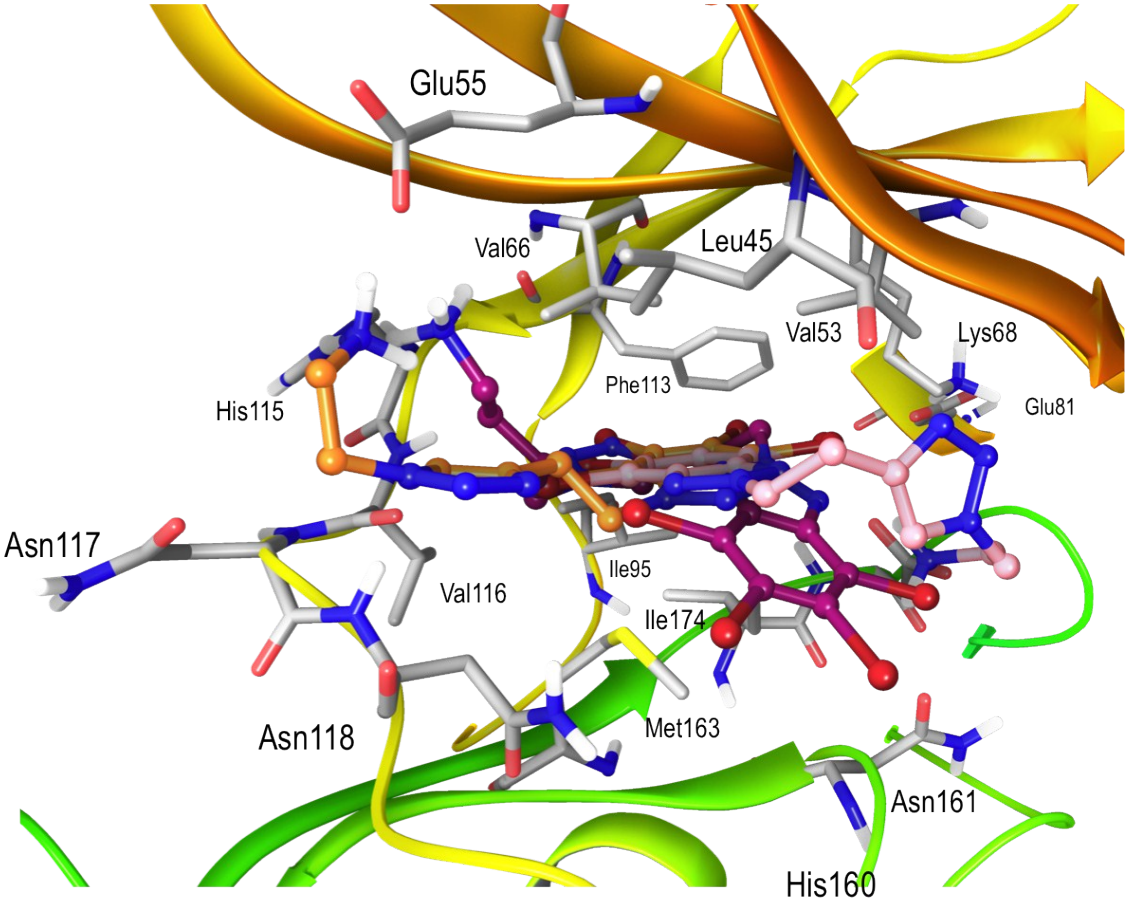


Figure 2. Maestro representation of the structure of human CK2α (PDB: 5CQU) represented as rainbow-colored cartoons in complex with compounds **10**, **14** and **16** represented as orange, maroon and pink balls and sticks. For the sake of clarity only polar hydrogens are displayed; and only the side chains of the amino acids that interact with the compounds are represented as grey sticks. Due to the image orientation the side chain of Asp175 lies hidden behind the amine end of compounds **10** and **16** with which it establishes a hydrogen bond.