## Supporting Information

# Multi-functionalized biologically active isatin-tagged dihydropyrimidine derivatives: Green synthesis by the use of recyclable Fe doped Ce-oxide nanoparticles, computational study and their *ex vivo* anti-breast cancer activity

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## 1. General Information

## (Methods and materials)

All the reagents required for the current study were analytical reagent grade and were used as such without further purification. All the reagents and materials were procured from Sigma Aldrich, Merk, and Spectrochem from commercial suppliers. All the solvents were purchased from Finar Ltd. All the reactions were monitored with thin-layer chromatography silica gel plates (TLC) Kieselgel 60 $F_{254}$ (Merk) using ethyl acetate/petrol or methanol/chloroform as mobile phases and visualised in UV light. The purification of all synthesised molecules was carried out using silica gel 100-200 Mesh (Qualikems). The melting points of all synthesised molecules were determined by the electrothermal melting point apparatus, Buchi instrument (M-560) and were uncorrected. Infrared spectra were recorded using KBr pellets on a SHIMADZU FT-IR Affinity 1s spectrophotometer, and the recordings are expressed as $\upsilon_{max}$ cm$^{-1}$. The formation of the synthesised molecule was confirmed by $^{1}$H NMR and $^{13}$C NMR on a JEOL, ECX-400P spectrometer, USA at 400 MHz and 100 MHz using tetramethylsilane (TMS) as an internal reference standard. The chemical shift (δ), coupling constant, and absorption frequency for the NMR spectra were reported as parts per million, J (Hz), and v (cm$^{-1}$), respectively, in dimethyl sulfoxide (DMSO-$d_6$) as the solvent. All mass spectrometry readings for all synthesised compounds were taken using a 6530 Accurate-Mass Q-TOF LC/MS instrument.

## 2. Experimental Section

### 2.1 Synthesis of ethyl 5-(3-chlorophenyl)-7-((prop-2-yn-1-yloxy)methyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (6)

Target compound **6** was synthesised by taking 1 mmol propargylated ethyl 4-chloroacetoacetate **(2),** 1 mmol 3-chlorobenzaldehyde **(3)** and 1 mmol 2-aminothiazole **(4)** dissolved in $C_2H_5OH$. To this, 0.05 M% Fe-doped Ce oxide nanoparticles were added and refluxed them for 8 hours to get novel starting material **6** via a one-pot cascade reaction**.** TLC was used to monitor the progression of the reaction. The solvent $C_2H_5OH$ was removed from the resulting reaction mixture on vacuum at reduced pressure then extraction of the crude product was done using ethyl acetate (4 × 32 mL). The resulting extracts were washed by using NaCl solution and dried with $Na_2SO_4$ (anhydrous). The dried product was filtered and then concentrated at reduced pressure under vacuum to isolate the crude product. The silica gel chromatography (100-200 mesh size) was used to further purify the crude product to afford the product **6** as pale-yellow solid with 90% yield.

### 2.2 Synthesis of ethyl 4-(3-chlorophenyl)-2-((prop-2-yn-1-yloxy)methyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate (7)

Target compound **7** was synthesised by taking 1 mmol propargylated ethyl 4-chloroacetoacetate **(2),** 1 mmol 3-chlorobenzaldehyde **(3)** and 1 mmol 2-aminobenzothiazole **(5)** dissolved in $C_2H_5OH$. To this, 0.05 M % Fe-doped Ce oxide nanoparticles were added and refluxed it for 8 hr to get novel starting material **7,** via a one-pot cascade reaction. TLC was used to monitor the progression of the reaction. The solvent $C_2H_5OH$ was removed from the resulting reaction mixture on vacuum at reduced pressure then extraction of the crude product was done using ethyl acetate (4 × 32 mL). The resulting extracts were washed by using NaCl solution and dried with $Na_2SO_4$

(anhydrous). The dried product was filtered and then concentrated at reduced pressure under vacuum to isolate the crude product. The silica gel chromatography (100-200 mesh size) was used to further purify the crude product to afford the product **7** as pale-yellow solid with 91% yield.

### 2.3 Synthesis of ethyl 5-(3-chlorophenyl)-7-(((1-(2-(2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14a-d)

Target compound **14a-d** were synthesised by using the well-known alkyne-azide cycloaddition catalysed by the Cu-I (CuAAC) reaction. To a stirred solution of compound **6** (1 mmol) and N-(2-azidoethyl) isatins **10a-d** (1 mmol) in DMF-$H_2O$ (1:1); sodium ascorbate (0.4 mmol) and $CuSO_4.5H_2O$ (0.2 mmol) were added as catalysts and reaction mixture was heated for 12-18 min at 60°C. TLC was used to monitor the progression of the reaction. The resulting crude product was poured into 55 mL ice-cold water then extraction of the crude product was done using ethyl acetate (4 × 32 mL). The resulting extracts were washed by using NaCl solution and dried with $Na_2SO_4$ (anhydrous). The dried product was filtered and then concentrated at reduced pressure under vacuum to isolate the crude product. The silica gel chromatography (100-200 mesh size) was used to further purify the crude products to afford the products **14a-d** as an yellow to orange solid with yields ranging from 85 to 89%.

### 2.4 Synthesis of thiazolo[3,2-a]pyrimidin-7-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl) tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (15)

Target compound **15** was synthesised by using the well-known alkyne-azide cycloaddition catalysed by the Cu-I (CuAAC) reaction. To a stirred solution of compound **6** (1 mmol) and 2-(acetoxymethyl)-6-azidotetrahydro-2H-pyran-3,4,5-triyl triacetate **13** (1 mmol) in DMF-$H_2O$ (1:1); sodium ascorbate (0.4 mmol) and $CuSO_4.5H_2O$ (0.2 mmol) were added as catalysts and reaction

mixture was heated for 12-18 min at 60°C. TLC was used to monitor the progression of the reaction. The resulting crude product was poured into 55 mL ice-cold water then extraction of the crude product was done using ethyl acetate (4 × 32 mL). The resulting extracts were washed by using NaCl solution and dried with $Na_2SO_4$ (anhydrous). The dried product was filtered and then concentrated at reduced pressure under vacuum to isolate the crude product. The silica gel chromatography (100-200 mesh size) was used to further purify the crude product to afford the product **15** as a yellow solid with 85% yield.

### 2.5 Synthesis of ethyl 4-(3-chlorophenyl)-2-(((1-(2-(2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate (16a-d)

Target compound **16a-d** ware synthesised by using the well-known alkyne-azide cycloaddition catalysed by the Cu-I (CuAAC) reaction. To a stirred solution of compound **7** (1 mmol) and N-(2-azidoethyl) isatins **10a-d** (1 mmol) in DMF-$H_2O$ (1:1); sodium ascorbate (0.4 mmol) and $CuSO_4.5H_2O$ (0.2 mmol) were added as catalysts and reaction mixture was heated for 12-18 min at 60°C. TLC was used to monitor the progression of the reaction. The resulting crude product was poured into 55 mL ice-cold water then extraction of the crude product was done using ethyl acetate (4 × 32 mL). The resulting extracts were washed by using NaCl solution and dried with $Na_2SO_4$ (anhydrous). The dried product was filtered and then concentrated at reduced pressure under vacuum to isolate the crude product. The silica gel chromatography (100-200 mesh size) was used to further purify the crude product to afford the product **16a-d** as a yellow-orange solid with yield ranging from 86 to 89%

## 2.6 Synthesis of 2-(Acetoxymethyl)-6-(4-(((4-(3-chlorophenyl)-3-(ethoxycarbonyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-2-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (17)

Target compound **17** was synthesised by using the well-known alkyne-azide cycloaddition catalysed by the Cu-I (CuAAC) reaction. To a stirred solution of compound **7** (1 mmol) and 2-(acetoxymethyl)-6-azidotetrahydro-2*H*-pyran-3,4,5-triyl triacetate **13** (1 mmol) in DMF-$H_2O$ (1:1); sodium ascorbate (0.4 mmol) and $CuSO_4.5H_2O$ (0.2 mmol) were added as catalysts and reaction mixture was heated for 12-18 min at 60°C. TLC was used to monitor the progression of the reaction. The resulting crude product was poured into 55 mL ice-cold water then extraction of the crude product was done using ethyl acetate (4 × 32 mL). The resulting extracts were washed by using NaCl solution and dried with $Na_2SO_4$ (anhydrous). The dried product was filtered and then concentrated at reduced pressure under vacuum to isolate the crude product. The silica gel chromatography (100-200 mesh size) was used to further purify the crude product to afford the product **17** as a yellow solid with 84% yield.

## 3 Figures

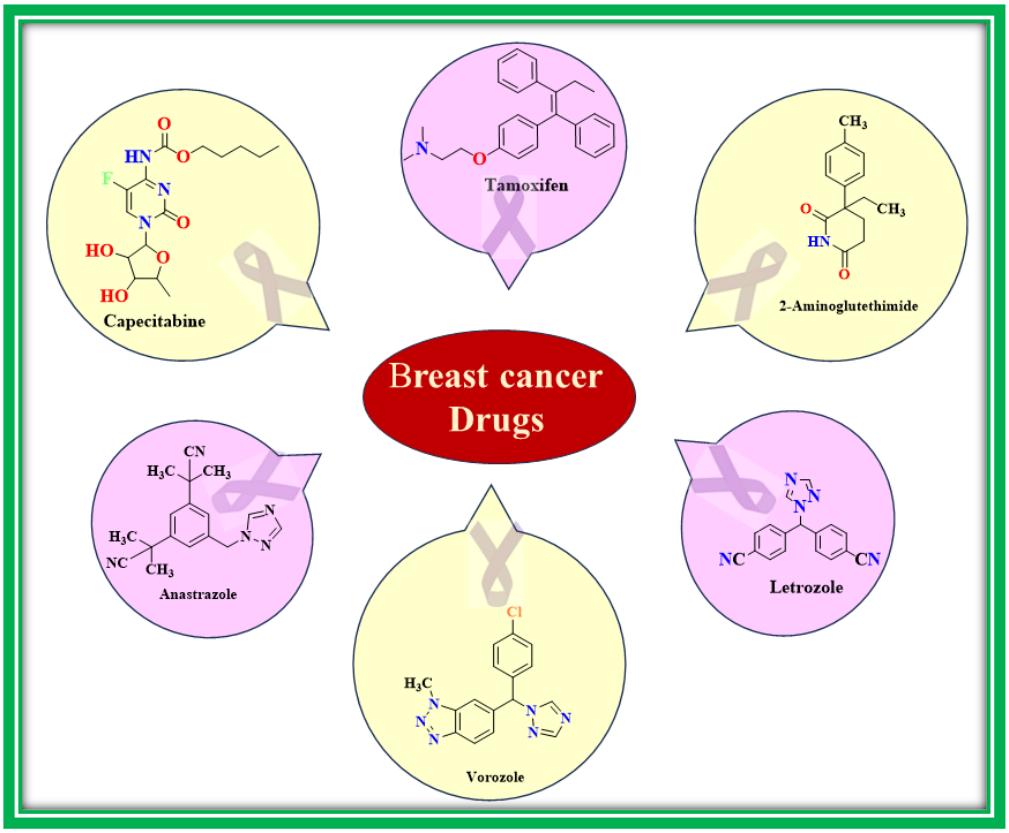
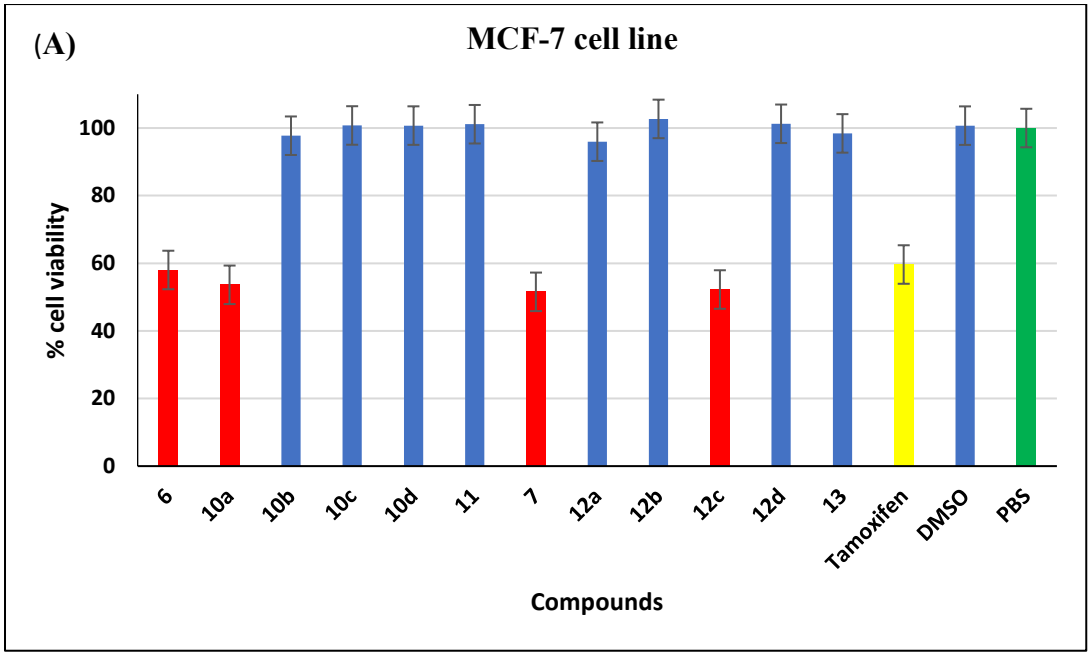
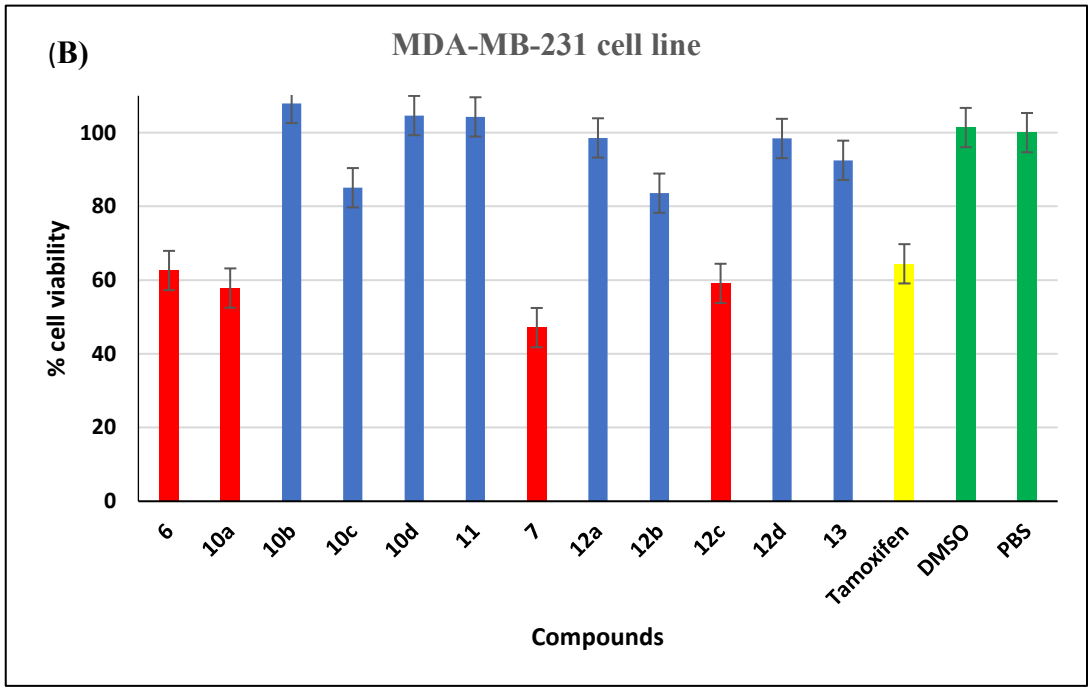



*Figure 1: Structures of some commercially available anti-cancer drugs.*


(A)
MCF-7 cell line
% cell viability
0
20
40
60
80
100
6
10a
10b
10c
10d
11
7
12a
12b
12c
12d
13
Tamoxifen
DMSO
PBS
Compounds


(B)
MDA-MB-231 cell line
% cell viability
0
20
40
60
80
100
6
10a
10b
10c
10d
11
7
12a
12b
12c
12d
13
Tamoxifen
DMSO
PBS
Compounds

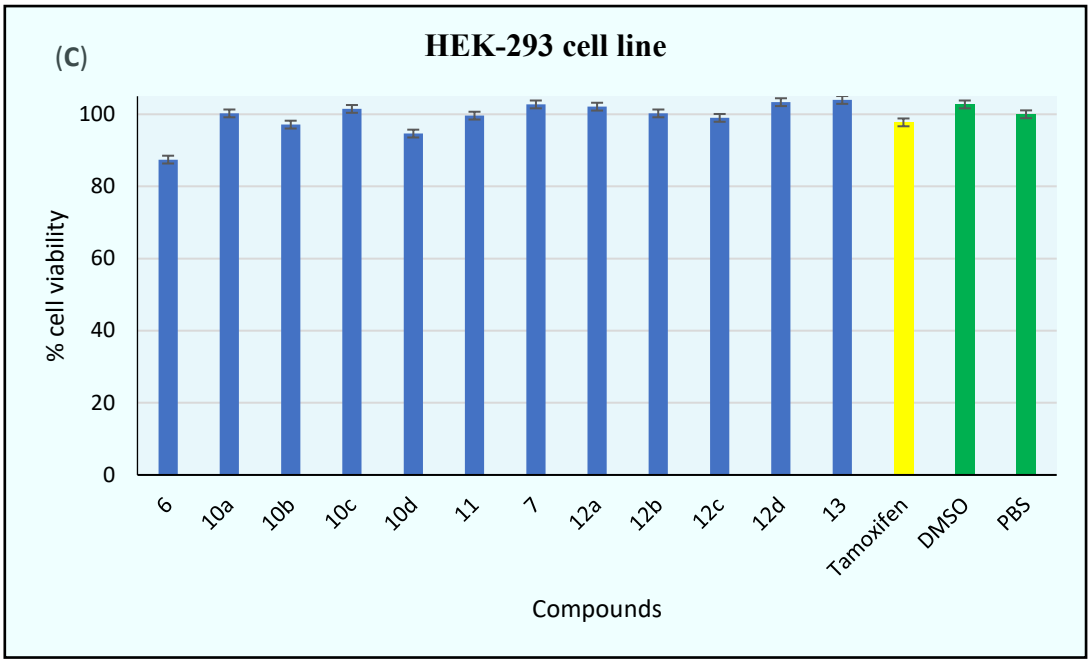
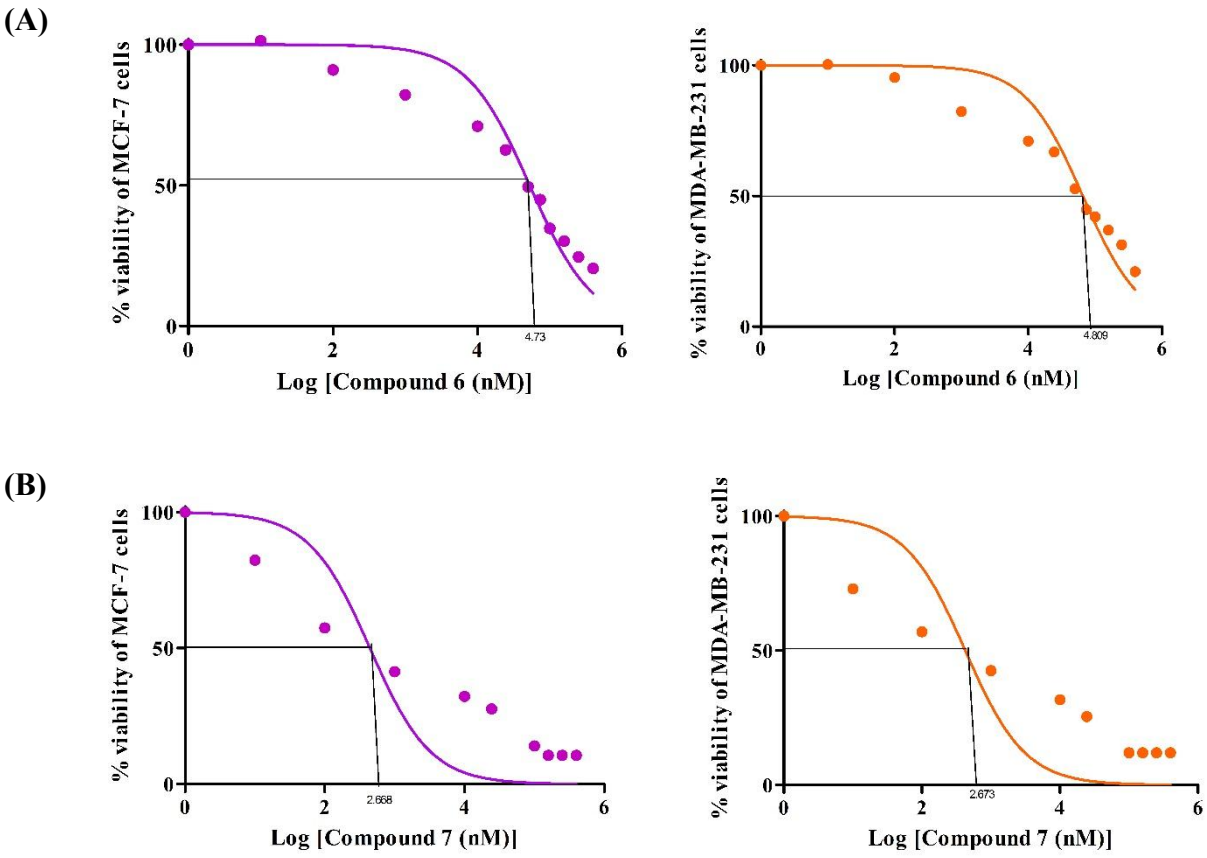



**Figure 2 Cell viability evaluation of cells treated with compounds:** After 48 hours of treatment with 100 µM concentrations of the corresponding compounds, the viability of **(A)** MCF-7 cells, **(B)** MDA-MB-231 cells, and **(C)** HEK-293 cells was assessed using the MTT cell viability test.



(C)

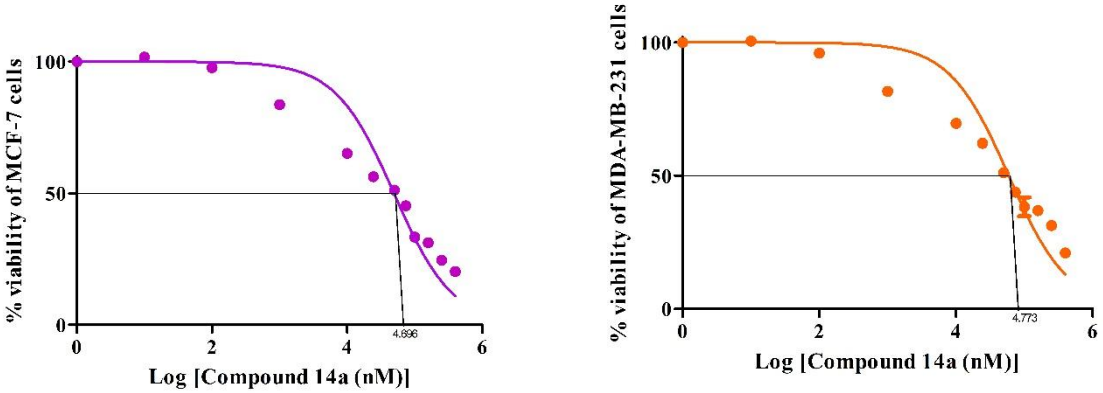



**Figure 3 $IC_{50}$ plots of the best breast cancer cell growth inhibitors compounds 6, 7 and 14a evaluated against MCF- 7 and MDA- MB- 231 cells.** (A) compound 6, (B) compound 7 and (c) compound 14a. Each experiment was repeated thrice and the plots are showing the corresponding SD values. (Compounds **6**, **14a**, and **7** showed $IC_{50}$ values of 52.7 ± 0.73 µM, 42.3 ± 0.83 µM, and 63.7 ± 2.17 nM in MDA-MB-231 cells, and 62.6 ± 0.86 µM, 81.9 ± 2.26 µM, and 55.0 ± 1.19 nM in MCF-**7** cells, respectively.)

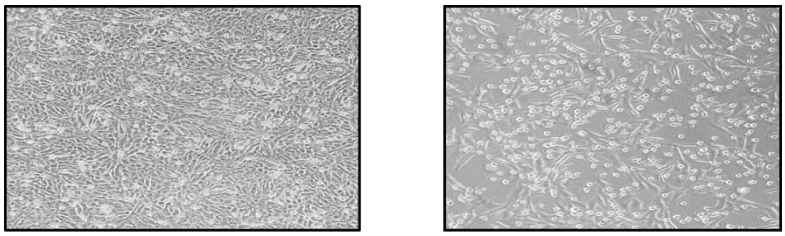



**Figure 4: Cells before compound/drug treatment. (A) MCF-7, a breast cancer cell line; (B) HEK-29, a human embryonic kidney cell line that serves as a non-cancerous control.**

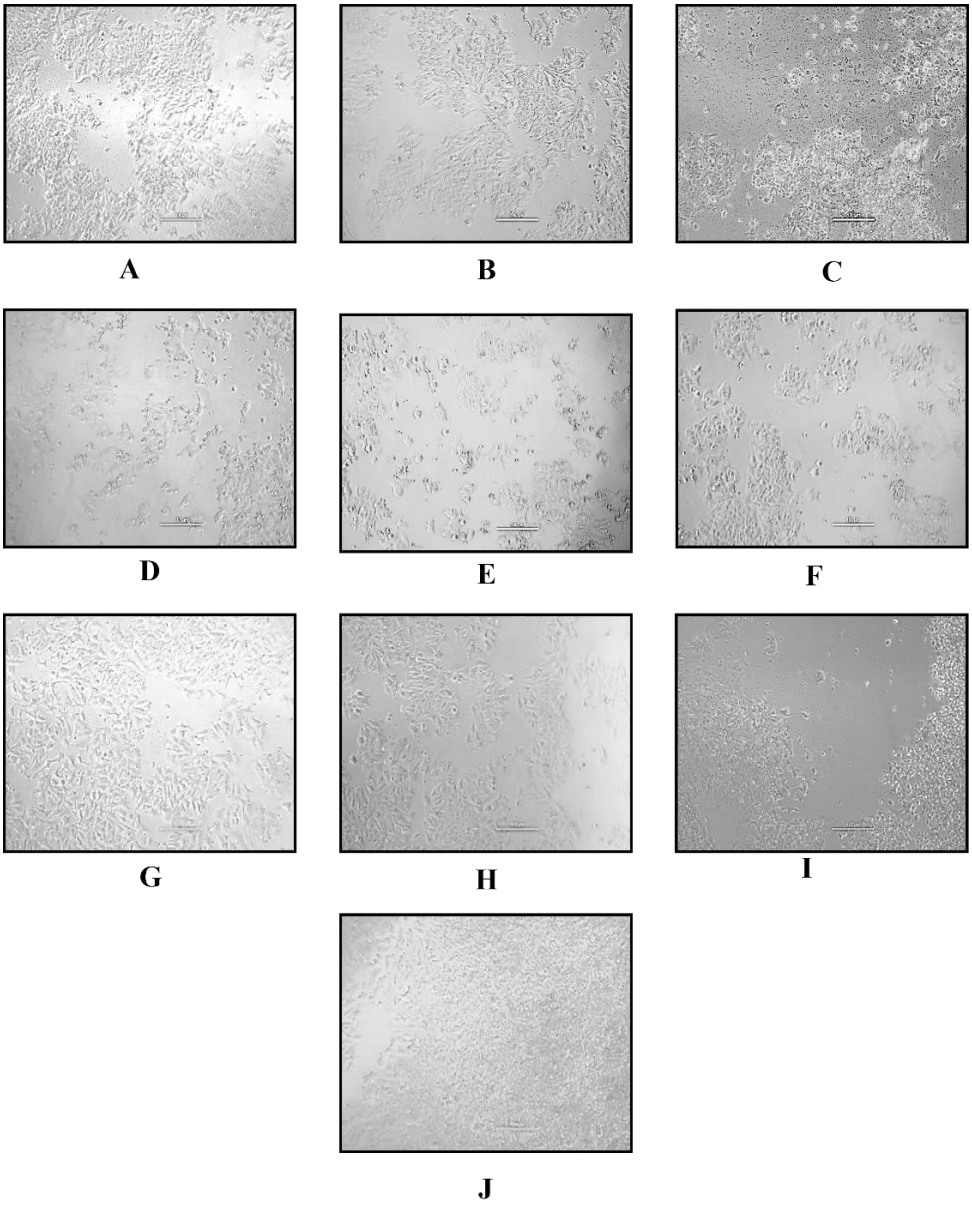



**Figure 5 Compounds inducing the breast cancer cell-selective cytotoxicity: MCF- 7 cell-lines were treated for 48 hours with** (A) **6**, (B) **14a**, (C) **7**, (D) **16c**, (E) **16d**, (F) Tamoxifen (positive control), (G) PBS (solvent control), and (H) DMSO (vehicle control) **(I) 16d (J) 17** and Sections A to J indicative of a minimum of three separate tests.

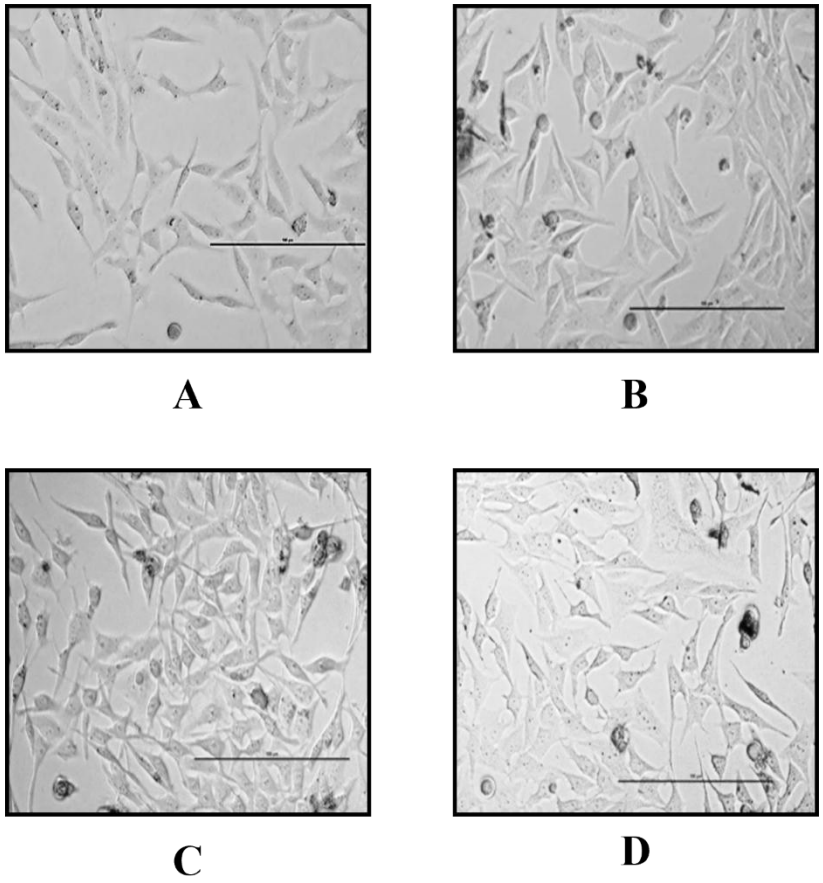



**Figure 6:** MDA-MB-231 cell lines in representative pictures prior to compound/drug treatment.

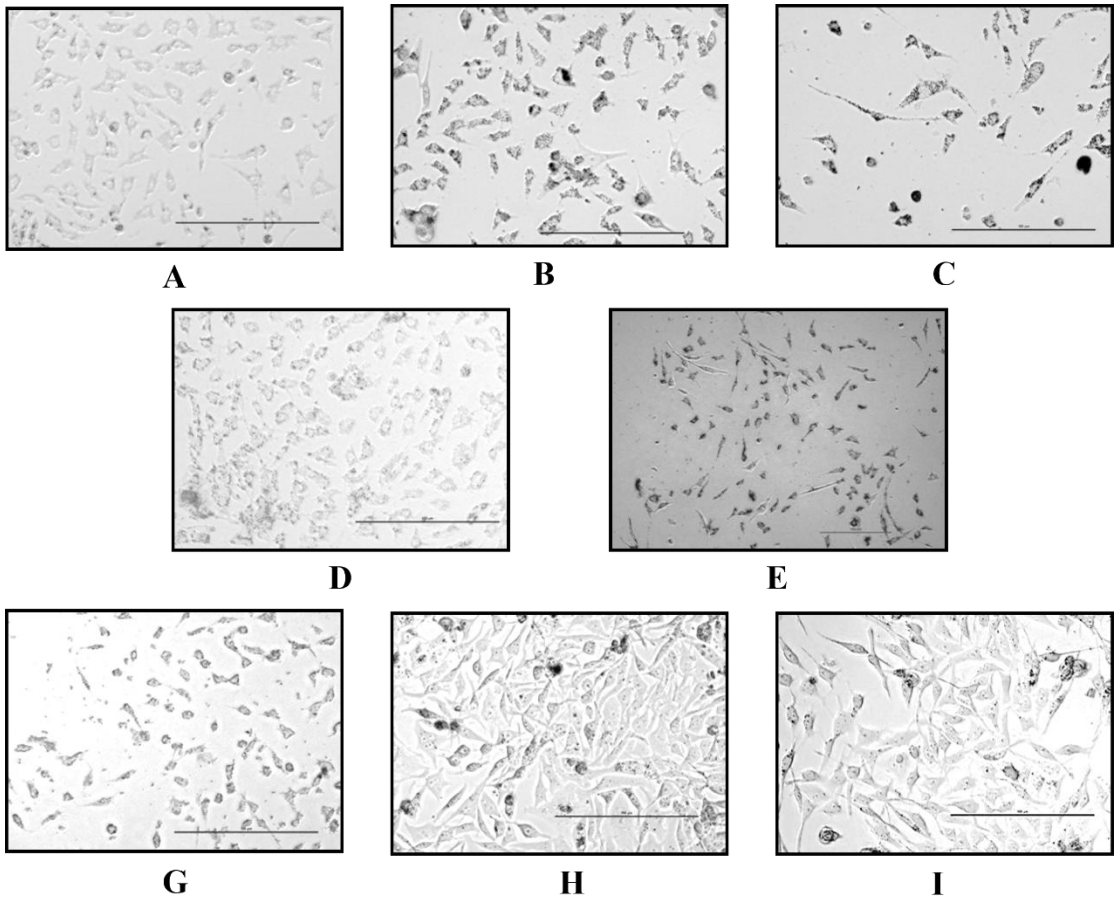



**Figure 7** MDA-MB-231 cells subsequent to compound/drug treatment. The cells MDA-MB-231 were exposed to **(A) 6**, **(B) 14a**, **(C) 7**, **(D) 16c**, **(E) 16d**, **(F)** Tamoxifen (positive control), **(G)** PBS (solvent control), and **(H)** DMSO (vehicle control) for 48 h.

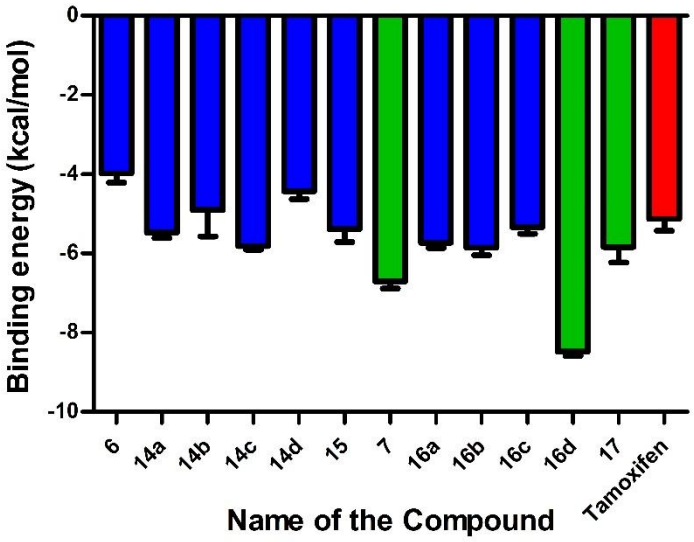


**Figure 8 Graph showing binding energies based on docking scores against Topoisomerase II of 12 compounds (Blue: less negative, Green: more negative), and tamoxifen (Red: negative control).**

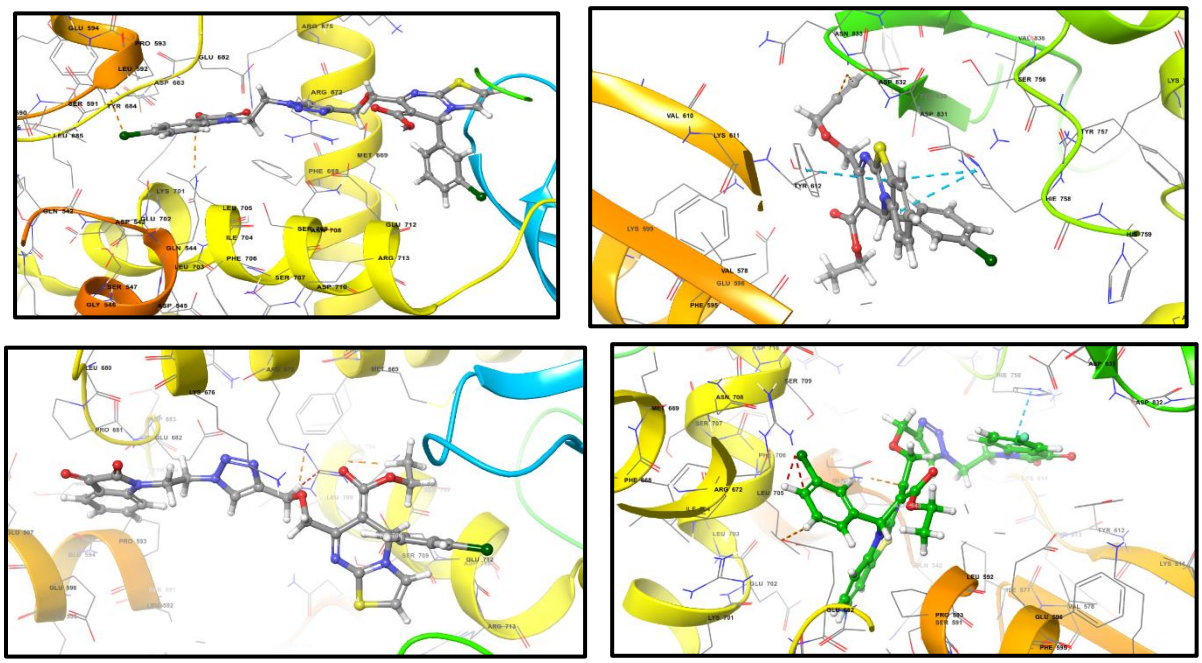


**Figure 9 Three dimensional docked structures of the best four compounds (14c, 7, 16a and 16d) with Topoisomerase (PDB ID: 5GWK) visualized using Maestro visualizer.**

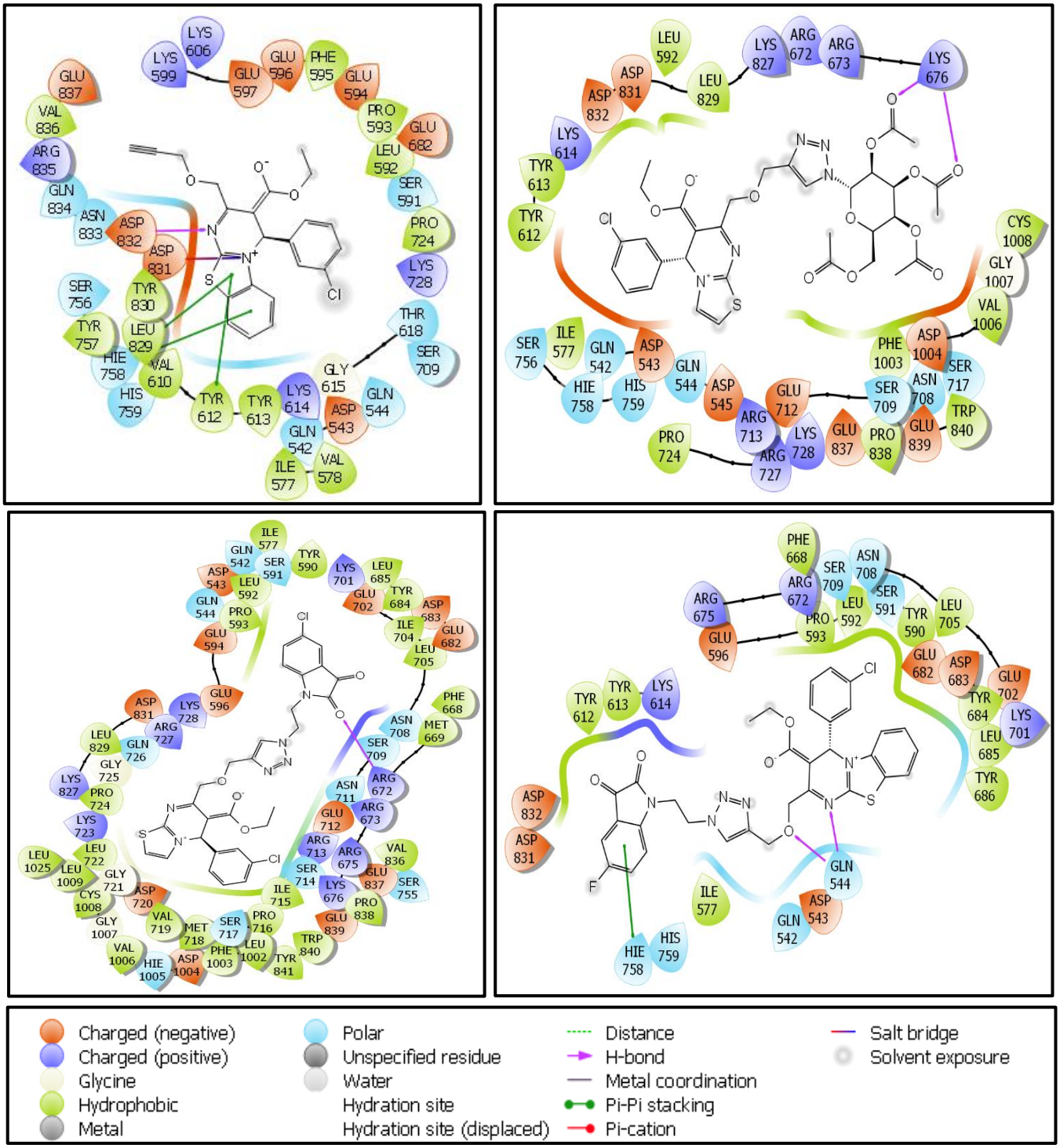



**Figure 10 Two-dimensional docked structures of the best four compounds (14c, 7, 16a and 16d) with Topoisomerase (PDB ID: 5GWK) visualised using Maestro visualizer.**

## 4 Tables

**Table S1** Predicted binding energies of compounds against Topoisomerase II alpha (PDB ID: 5GWK).

| S. No. | Compounds | Docking Score (kcal/mol) | No. of H-Bonds | Interacting residues through H-Bond | Interacting domain of Topoisomerase II (PDB ID: 5GWK) |
|---|---|---|---|---|---|
| 1 | **6** | -3.51 | 1 | GLN544 | GLN542, ASP543, GLN544, SER709, GLU712, ILE577, TYR686, LEU685, TYR684, ASP683, GLU682, PRO681 |
| 2 | **14a** | -6.32 | 1 | ASP832 | ARG835, GLN834, ASN833, ASP832, ASP831, TYR830, SER756, HIE758, TYR612, TYR613, LYS614, ASP543, ILE577, LYS728, LEU592, PRO593, PHE595, GLU596, LYS599 |
| 3 | **14b** | -5.17 | 0 | - | LEU829, PRO724, ARG727, PHE1003, ASP1004, HIE1005, VAL1006, GLY1007, CYS1008, LEU1009 MET669, ARG672, ARG673, ARG675, LYS676, GLY679, LEU680, PRO681, GLU682 |
| 4 | **14c** | -3.58 | 3 | ARG727(2), SER717 | ARG672, ARG673, ARG675, LYS676, LEU680, GLU682, GLN544, LEU705, ASN708, SER709, GLU712, ARG727, PRO724, LEU722, VAL719, MET718, SER717, PRO716, GLY1007, VAL1006, HIE 1005, ASP1004, PHE1003 |

| S. No. | Compounds | Docking Score (kcal/mol) | No. of H-Bonds | Interacting residues through H-Bond | Interacting domain of Topoisomerase II (PDB ID: 5GWK) |
|---|---|---|---|---|---|
| 5 | **14d** | -5.77 | 1 | ARG672 | GLN544, ASP543, GLN542, ILE577, SER591, LEU592, PRO593, GLU682, ASP683, TYR684, PHE668, ARG672, ARG673, LEU829, LYS676, LYS728, ARG727, PRO724, LYS723, LEU722, SER717, PRO716, ILE715, ARG713, GLU712, ASN711, SER709, ASN708, LEU705 |
| 6 | **15** | -4.03 | 1 | ARG673 | GLU682, PRO681, LEU680, GLY679, LYS676, ARG675, ARG673, ARG672, LYS728, ARG727, SER717, PRO716, ILE715, GLU712, ASN711, PHE1003, ASP1004, HIE1005, VAL1006, GLY1007 |
| 7 | **7** | -5.02 | 2 | LYS676 (2) | CYS1008, GLY1007, VAL1006, ASP1004, PHE1003, LYS827, LEU829, ASP831, ASP832, ILE577, LYS614, TYR613, TYR612, GLN542, ASP543, GLN544, ASP545, ARG713, GLU712, SER709, ASN708, ARG672, ARG673, LYS676 |
| 8 | **16a** | -5.67 | 1 | LEU592 | LEU705, GLU702, LYS701, PHE668, TYR830, LYS550, SER547, GLN544, ASP543, GLN542, TYR686,LEU685, TYR684, ASP683, GLU682, PRO681, LEU680, GLY679, |

| S. No. | Compounds | Docking Score (kcal/mol) | No. of H-Bonds | Interacting residues through H-Bond | Interacting domain of Topoisomerase II (PDB ID: 5GWK) |
|---|---|---|---|---|---|
| | | | | | LYS676, ARG675, ARG672, TYR590, SER591, LEU592, PRO593, GLU594, GLU596, GLU597, LYS599, SER600 |
| 9 | **16b** | -5.62 | 1 | ARG672 | HIE758, TYR612, TYR613, LYS614, GLY615, ILE577, GLU682, PRO681, LEU680, LYS599, GLU597, GLU596, LYS676, ARG675, ARG673, ARG672, PRO593, LEU592, SER591, LEU705, GLN542, ASP543, GLN544, ASP831 |
| 10 | **16c** | -5.02 | 1 | GLN544 | LYS827, LEU829, LYS676, ARG673, ARG672, CYS1008, GLY1007, MET669, ARG713, GLU839, PHE1003, GLU712, ARG727, PRO724, SER709, ASN708, LEU705, GLN544, ASP543, GLU702, GLN542, LYS701, PRO593, LEU592, SER591, TYR590, GLU682, ASP683, TYR684, LEU685, TYR686, ILE577 |
| 11 | **16d** | -8.28 | 2 | GLN544 (2) | TYR612, TYR613, LYS614, SER709, ASN708, ILE577, LEU705, GLU702, LYS701, GLN544, ASP543, GLN542, TYR686, LEU685, TYR684, ASP683, GLU682, ARG672, ARG675, PHE668, TYR590, SER591, LEU592, PRO593, |

| S. No. | Compounds | Docking Score (kcal/mol) | No. of H-Bonds | Interacting residues through H-Bond | Interacting domain of Topoisomerase II (PDB ID: 5GWK) |
|---|---|---|---|---|---|
| | | | | | GLU596, HIS759, HIE758, ASP832, ASP831 |
| 12 | **17** | -5.13 | 3 | ARG727 | LYS676, ARG673, ARG672, MET669, SER717, PRO716, ILE715, ARG713, GLU712, ASN711, SER709, ASN708, LEU705, LYS614, TYR613, TYR612, GLN544, ASP543, GLN542, SER591, LEU592, PRO593, ASP832, ASP831, TYR830, LEU829, VAL836, GLU837, GLU839, TRP840, CYS1008, GLY1007, VAL1006, PHE1003, LYS723, PRO724, ARG727, LYS728, SER756, TYR757, HIE759, ILE577 |
| Control | | | | | |
| 13 | Tamoxifen | -5.287 | 0 | - | ARG672, ARG675, GLU682, PHE668, ASP683, TYR684, LEU685, TYR686, LEU705, GLU702, LYS701, LYS550, SER547, ASP545, GLN544, ASP543, GLN542, ILE574, ILE577, PRO593, LEU592, SER591, TYR590, LYS614, HIE758, HIS759 |

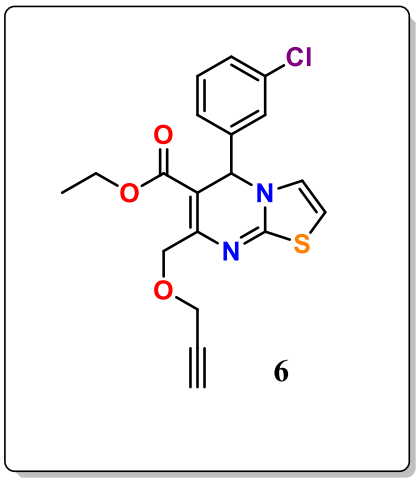
**Table S2** Protein-ligand interacting amino acid residue details of compounds with Topoisomerase II alpha using UCSF Chimera software.

| S. No. | Name of Compound | Interacting Residues and Type of Interaction |
|---|---|---|
| **1** | **7** | ARG835 (**Hydrogen Bond**), GLN834 (**Hydrogen Bond**), ASN833 (**Hydrogen Bond**), ASP832 (**Ionic**), ASP831 (**Ionic**), TYR830 (**Hydrophobic**), SER756 (**Hydrogen Bond**), HIE758 (**Hydrogen Bond**), TYR612 (**Hydrophobic**), TYR613 (**Hydrophobic**), LYS614 (**Ionic**), ASP543 (**Ionic**), ILE577 (**Hydrophobic**), LYS728 (**Ionic**), LEU592 (**Hydrophobic**), PRO593 (**Hydrophobic**), PHE595 (**Hydrophobic**), GLU596 (**Ionic**), LYS599 (**Ionic**) |
| **2** | **14c** | GLN544 (**Hydrogen Bond**), ASP543 (**Ionic**), GLN542 (**Hydrogen Bond**), ILE577 (**Hydrophobic**), SER591 (**Hydrogen Bond**), LEU592 (**Hydrophobic**), PRO593 (**Hydrophobic**), GLU682 (**Ionic**), ASP683 (**Ionic**), TYR684 (**Hydrophobic**), PHE668 (**Hydrophobic**), ARG672 (**Ionic**), ARG673 (**Ionic**), LEU829 (**Hydrophobic**), LYS676 (**Ionic**), LYS728 (**Ionic**), ARG727 (**Ionic**), PRO724 (**Hydrophobic**), LYS723 (**Ionic**), LEU722 (**Hydrophobic**), SER717 (**Hydrogen Bond**), PRO716 (**Hydrophobic**), ILE715 (**Hydrophobic**), ARG713 (**Ionic**), GLU712 (**Ionic**), ASN711 (**Hydrogen Bond**), SER709 (**Hydrogen Bond**), ASN708 (**Hydrogen Bond**), LEU705 (**Hydrophobic**) |
| **3** | **16a** | LEU705 (**Hydrophobic**), GLU702 (**Ionic**), LYS701 (**Ionic**), PHE668 (**Hydrophobic**), TYR830 (**Hydrophobic**), LYS550 (**Ionic**), SER547 (**Hydrogen Bond**), GLN544 (**Hydrogen Bond**), ASP543 (**Ionic**), GLN542 (**Hydrogen Bond**), TYR686 (**Hydrophobic**), LEU685 (**Hydrophobic**), TYR684 (**Hydrophobic**), ASP683 (**Ionic**), GLU682 (**Ionic**), PRO681 (**Hydrophobic**), LEU680 (**Hydrophobic**), GLY679 (**Hydrogen Bond**), LYS676 (**Ionic**), ARG675 (**Ionic**), ARG672 (**Ionic**), TYR590 (**Hydrophobic**), SER591 (**Hydrogen Bond**), LEU592 (**Hydrophobic**), PRO593 (**Hydrophobic**), GLU594 (**Ionic**), GLU596 (**Ionic**), GLU597 (**Ionic**), LYS599 (**Ionic**), SER600 (**Hydrogen Bond**) |
| **4** | **16d** | TYR612 (**Hydrophobic**), TYR613 (**Hydrophobic**), LYS614 (**Ionic**), SER709 (**Hydrogen Bond**), ASN708 (**Hydrogen Bond**), ILE577 (**Hydrophobic**), |

| | | |
|---|---|---|
| | | LEU705 (**Hydrophobic**), GLU702 (**Ionic**), LYS701 (**Ionic**), GLN544 (**Hydrogen Bond**), ASP543 (**Ionic**), GLN542 (**Hydrogen Bond**), TYR686 (**Hydrophobic**), LEU685 (**Hydrophobic**), TYR684 (**Hydrophobic**), ASP683 (**Ionic**), GLU682 (**Ionic**), ARG672 (**Ionic**), ARG675 (**Ionic**), PHE668 (**Hydrophobic**), TYR590 (**Hydrophobic**), SER591 (**Hydrogen Bond**), LEU592 (**Hydrophobic**), PRO593 (**Hydrophobic**), GLU596 (**Ionic**), HIS759 (**Hydrogen Bond**), HIE758 (**Hydrogen Bond**), ASP832 (**Ionic**), ASP831 (**Ionic**) |
| **5** | Tamoxifen | ARG835 (**Hydrogen Bond**), TRP1036 (**Hydrophobic**), TYR830 (**Hydrophobic**), PHE828 (**Hydrophobic**) |

## 5. Characterisation data of products

### 5.1 Ethyl 5-(3-chlorophenyl)-7-((prop-2-yn-1-yloxy)methyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (6)




6

The pale yellow solid was obtained with 90% yield.

**Melting point:** 114-115°C.

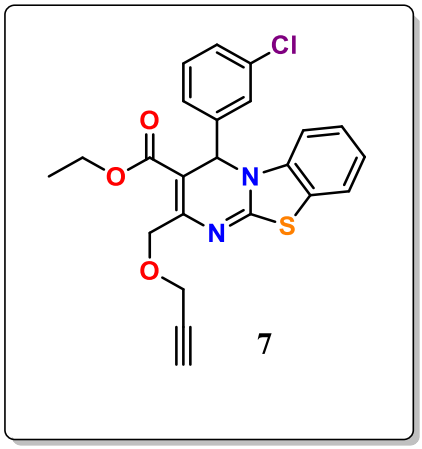
**IR** (KBr, $cm^{-1}$) 3348, 1747, 1681, 1210, 775.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 7.39 (dd, J = 11.8, 7.8 Hz, 3H), 7.27 (dd, J = 13.6, 6.0 Hz, 2H), 6.83 (d, J = 4.7 Hz, 1H), 6.36 (s, 1H), 4.56 (s, 2H), 4.20 (d, J = 2.3 Hz, 2H), 4.03 – 3.96 (m, 2H), 3.41 (t, J = 2.3 Hz, 1H), 1.10 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 165.37, 164.89, 155.01, 144.74, 133.24, 130.88, 128.34, 127.68, 126.50, 125.27, 107.25, 99.06, 80.44, 79.15, 77.08, 69.45, 59.46, 57.98, 57.49, 14.00.

**HRMS data**: Calculated mass for $C_{19}H_{17}ClN_2O_3S$ $(M+H)^+$, 389.0649, found, 389.0721.

### 5.2 Ethyl 4-(3-chlorophenyl)-2-((prop-2-yn-1-yloxy)methyl)-4*H*-benzo[4,5] thiazolo[3,2-a]pyrimidine-3-carboxylate (7)




7

The pale yellow solid was obtained with 91% yield.

**Melting point:** 117-118$^o$C.

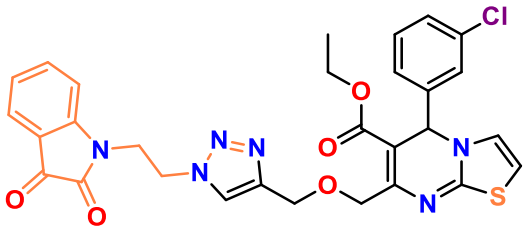
**IR** (KBr, cm$^{-1}$) 3340, 1742, 1676, 1201, 776.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 7.78 (d, J = 7.4 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.39 – 7.30 (m, 4H), 7.22 (t, J = 7.6 Hz, 1H), 6.56 (s, 1H), 4.56 (s, 2H), 4.21 (s, 2H), 4.09 (dd, J = 16.8, 7.1 Hz, 2H), 3.43 (t, J = 2.3 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 164.77, 163.41, 152.74, 143.40, 137.21, 133.12, 130.84, 128.49, 127.04, 125.61, 124.36, 123.00, 112.46, 104.09, 80.36, 77.25, 69.06, 60.05, 57.49, 56.10, 13.98.

**HRMS data**: Calculated mass for $C_{23}H_{17}ClN_2O_3S$ $(M+H)^+$, 439.0805, found, 439.0942.

### 5.3 Ethyl 5-(3-chlorophenyl)-7-(((1-(2-(2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14a)




**14a**

The orange solid was obtained with 88% yield.

**Melting point:** 141-142°C.

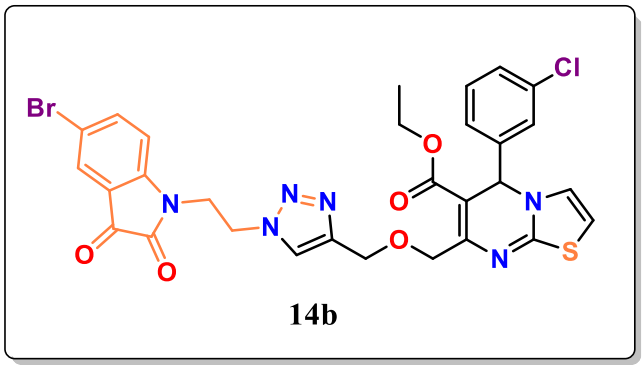
**IR** (KBr, $cm^{-1}$) 3064, 1740, 1673, 1199, 775.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.19 (s, 1H), 7.59 – 7.51 (m, 2H), 7.38 (dd, J = 10.7, 6.6 Hz, 3H), 7.31 – 7.25 (m, 2H), 7.07 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 4.7 Hz, 1H), 6.37 (s, 1H), 4.65 (t, J = 5.8 Hz, 2H), 4.53 (s, 2H), 4.47 (d, J = 4.5 Hz, 2H), 4.13 (t, J = 5.8 Hz, 2H), 4.02 – 3.93 (m, 2H), 1.08 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 182.93, 165.26, 164.91, 162.30, 158.13, 155.19, 150.23, 144.76, 144.18, 138.13, 133.26, 130.93, 128.37, 127.72, 126.54, 125.31, 124.73, 124.48, 123.24, 117.38, 110.26, 107.33, 99.15, 69.93, 63.55, 59.48, 57.99, 46.82, 13.99.

**HRMS data**: Calculated mass for $C_{29}H_{25}ClN_6O_5S$ $(M+H)^+$, 605.1283, found, 605.1353.

### 5.4 Ethyl 7-(((1-(2-(5-bromo-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-5-(3-chlorophenyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14b)




**14b**

The orange solid was obtained with 89% yield.

**Melting point 145-146**ºC.

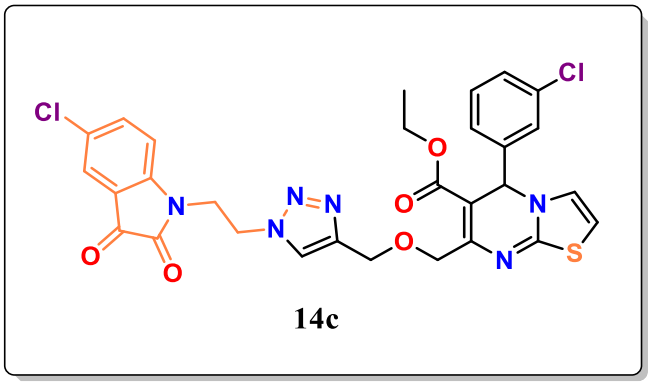
**IR** (KBr, $cm^{-1}$) 3076, 1745, 1683, 1203, 776.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.19 (s, 1H), 7.75 (dd, J = 8.4, 2.1 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.31 – 7.25 (m, 2H), 6.87 – 6.79 (m, 2H), 6.37 (s, 1H), 4.63 (t, J = 5.8 Hz, 2H), 4.53 (s, 2H), 4.49 – 4.41 (m, 2H), 4.13 (t, J = 5.7 Hz, 2H), 4.02 – 3.94 (m, 2H), 1.09 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 181.71, 165.23, 164.90, 157.77, 149.15, 144.74, 144.18, 139.81, 133.26, 130.93, 128.39, 127.74, 126.65, 125.34, 124.83, 119.11, 115.04, 112.40, 107.42, 99.17, 69.86, 63.53, 59.51, 58.03, 46.84, 14.01.

**HRMS data**: Calculated mass for $C_{29}H_{24}BrClN_6O_5S$ $(M+H)^+$, 683.0388, found, 683.0459.

### 5.5 Ethyl-7-(((1-(2-(5-chloro-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-5-(3-chlorophenyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14c).




**14c**

The yellow orange solid was obtained with 85% yield.

**Melting point:** 148-149ºC.

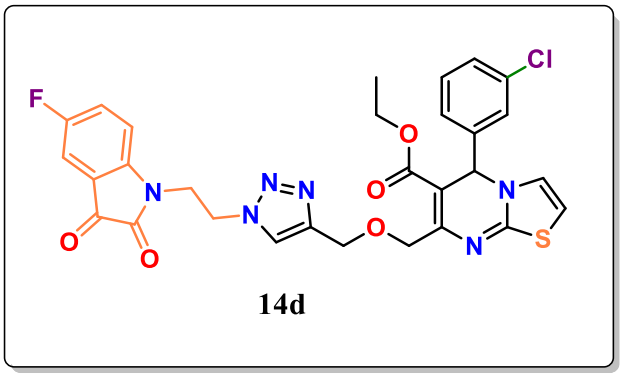
**IR** (KBr, $cm^{-1}$) 3074, 1744, 1686, 1202, 779.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.19 (s, 1H), 7.64 – 7.56 (m, 2H), 7.41 – 7.35 (m, 3H), 7.27 (dd, J = 12.8, 5.7 Hz, 2H), 6.88 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 4.6 Hz, 1H), 6.36 (s, 1H), 4.63 (t, J = 5.5 Hz, 2H), 4.49 (d, J = 32.9 Hz, 4H), 4.13 (t, J = 5.6 Hz, 2H), 4.02 – 3.94 (m, 2H), 1.09 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 181.83, 157.91, 148.77, 144.78, 136.98, 133.24, 130.89, 128.34, 127.60, 126.52, 125.29, 123.96, 118.71, 111.95, 107.24, 79.15, 59.45, 57.98, 46.84, 13.98.

**HRMS data**: Calculated mass for $C_{29}H_{24}Cl_2N_6O_5S$ $(M+H)^+$, 639.00896, found, 639.0996.

### 5.6 Ethyl 5-(3-chlorophenyl)-7-(((1-(2-(5-fluoro-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14d)



**14d**

The orange solid was obtained with 87% yield.

**Melting point:** 146-147°C.

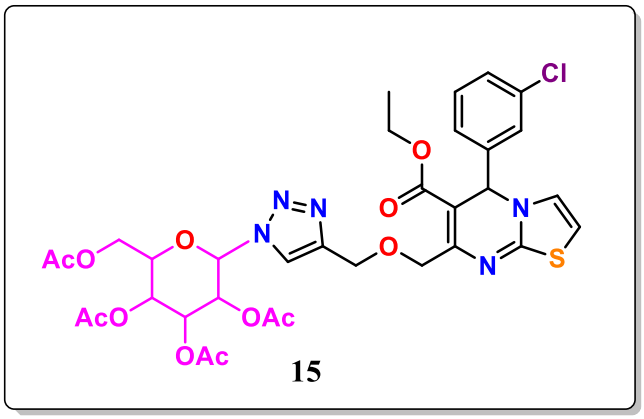
**IR** (KBr, $cm^{-1}$) 3075, 1747, 1685, 1198, 785.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.19 (s, 1H), 7.49 – 7.35 (m, 5H), 7.27 (dd, J = 10.7, 5.9 Hz, 2H), 6.91 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 4.4 Hz, 1H), 6.36 (s, 1H), 4.63 (t, 2H), 4.53 (s, 2H), 4.46 (s, 2H), 4.13 (t, 2H), 4.03 – 3.92 (m, 2H), 1.08 (t, J = 6.9 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 182.38, 165.36, 164.95, 159.67, 158.21, 157.27, 155.36, 146.50, 144.83, 144.21, 133.27, 130.95, 128.39, 127.74, 126.56, 125.33, 124.84, 124.23, 123.99, 118.28, 111.96, 111.35, 107.29, 99.16, 79.20, 70.01, 63.55, 59.50, 58.00, 46.85, 14.02.

**HRMS data**: Calculated mass for $C_{29}H_{24}ClFN_6O_5S$ $(M+H)^+$, 623.1194, found, 623.1262.

### 5.7 2-(Acetoxymethyl)-6-(4-(((5-(3-chlorophenyl)-6-(ethoxycarbonyl)-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (15)




**15**

The yellow solid was obtained with 85% yield.

**Melting point:** 139-140°C.

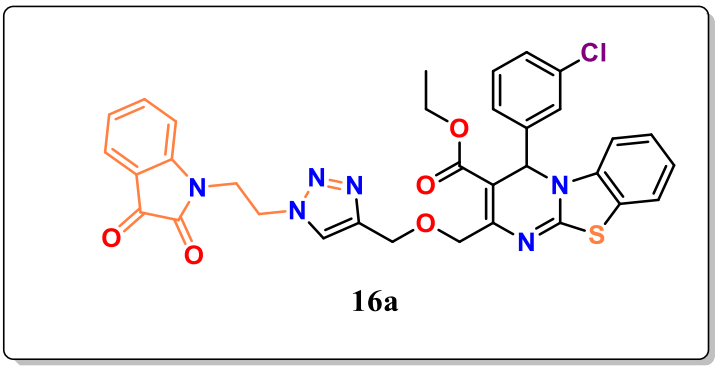
**IR** (KBr, $cm^{-1}$) 3100, 1740, 1689, 1205, 789.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 7.95 (s, 1H), 7.41 – 7.36 (m, 3H), 7.31 – 7.24 (m, 2H), 6.86 (d, J = 3.0 Hz, 1H), 6.39 – 6.34 (m, 2H), 5.67 (t, J = 9.4 Hz, 1H), 5.57 (d, J = 9.5 Hz, 1H), 5.18 (t, J = 9.8 Hz, 1H), 4.61 (s, 2H), 4.53 (d, J = 14.0 Hz, 2H), 4.37 (dd, J = 8.8, 4.2 Hz, 1H), 4.13 – 4.05 (m, 2H), 4.02 – 3.91 (m, 2H), 2.03 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.80 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 170.06, 169.59, 169.41, 168.53, 162.33, 144.75, 133.28, 130.97, 128.44, 127.80, 126.61, 125.42, 123.05, 99.20, 83.81, 73.21, 72.18, 70.19, 67.55, 63.47, 61.87, 59.56, 58.04, 20.52, 19.94, 14.00.

**HRMS data**: Calculated mass for $C_{33}H_{36}ClN_5O_{12}S$ $(M+H)^+$, 762.1747, found, 762.1817.

## 5.8 Ethyl 4-(3-chlorophenyl)-2-(((1-(2-(2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate (16a)




**16a**

The yellow orange solid was obtained with 87% yield.

**Melting point:** 144-145°C.

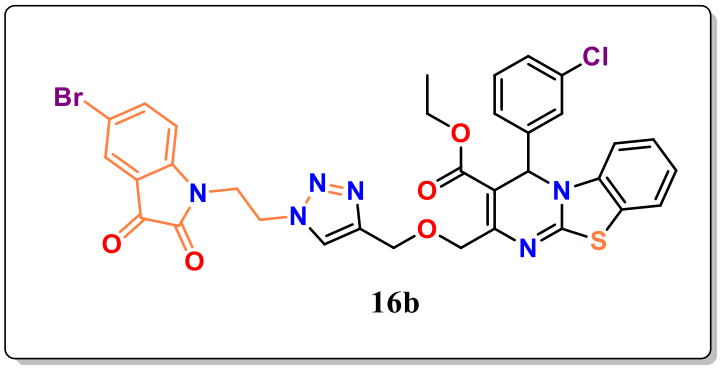
**IR** (KBr, $cm^{-1}$) 3094, 1742, 1682, 1197, 769.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 1H), 7.78 (d, J = 7.4 Hz, 1H), 7.54 (dt, J = 7.3, 5.7 Hz, 4H), 7.40 – 7.30 (m, 4H), 7.22 (t, J = 7.6 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.56 (s, 1H), 4.65 (t, J = 5.8 Hz, 2H), 4.52 (s, 2H), 4.45 (t, J = 8.7 Hz, 2H), 4.13 (t, J = 5.8 Hz, 2H), 4.06 (dt, J = 10.8, 3.8 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 182.93, 164.79, 163.32, 158.13, 153.07, 150.23, 144.08, 143.44, 138.13, 137.22, 133.11, 130.84, 128.48, 127.04, 125.60, 124.78, 124.41, 123.24, 122.99, 117.37, 112.45, 110.25, 104.09, 69.58, 63.49, 60.03, 56.09, 46.83, 13.95.

**HRMS data**: Calculated mass for $C_{33}H_{27}ClN_6O_5S$ $(M+H)^+$, 655.1436, found, 655.1507.

## 5.9 ethyl 2-(((1-(2-(5-bromo-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl) methoxy)methyl)-4-(3-chlorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate (16b)




**16b**

The orange solid was obtained with 89% yield.

**Melting point:** 147-148°C.

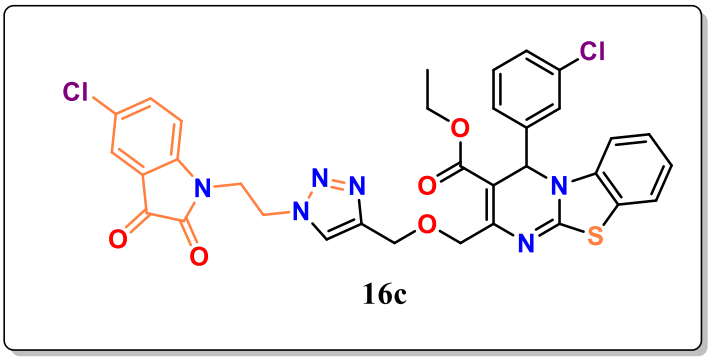
**IR** (KBr, $cm^{-1}$) 3084, 1744, 1686, 1190, 773.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.19 (s, 1H), 7.76 (dd, J = 16.1, 9.1 Hz, 2H), 7.67 (d, J = 1.8 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.41 – 7.29 (m, 4H), 7.22 (t, J = 7.6 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 6.56 (s, 1H), 4.63 (t, J = 5.6 Hz, 2H), 4.53 (s, 2H), 4.51 – 4.41 (m, 2H), 4.13 (t, J = 5.7 Hz, 2H), 4.11 – 3.98 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 181.70, 164.78, 163.30, 157.76, 149.14, 144.08, 143.41, 139.78, 137.21, 133.12, 130.82, 128.49, 127.05, 126.71, 125.62, 124.89, 124.37, 123.01, 119.10, 115.03, 112.42, 69.53, 63.48, 60.04, 56.12, 46.85, 13.95.

**HRMS data**: Calculated mass for $C_{33}H_{26}BrClN_6O_5S$ $(M+H)^+$, 733.0557, found, 733.1011.

**5.10 Ethyl 2-(((1-(2-(5-chloro-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl) methoxy)methyl)-4-(3-chlorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-a] pyrimidine-3-carboxylate (16c)**




**16c**

The yellow orange solid was obtained with 86% yield.

**Melting point:** 150-151°C.

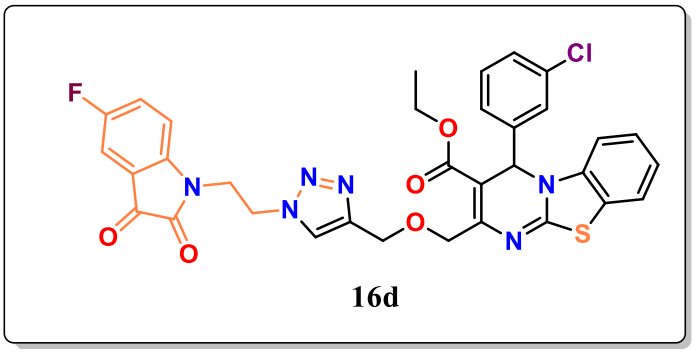
**IR** (KBr, $cm^{-1}$) 3078, 1742, 1681, 1201, 763.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.19 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.63 (s, 1H), 7.58 – 7.50 (m, 3H), 7.38 – 7.30 (m, 4H), 7.22 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.56 (s, 1H), 4.63 (t, J = 5.5 Hz, 2H), 4.53 (s, 2H), 4.45 (q, J = 11.8 Hz, 2H), 4.16 – 4.12 (m, 2H), 4.05 (dd, J = 17.3, 10.3 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 181.84, 164.77, 163.31, 157.92, 148.76, 144.08, 143.41, 137.21, 136.97, 133.11, 130.81, 128.48, 127.51, 127.04, 125.61, 124.88, 124.35, 123.97, 123.00, 118.72, 112.45, 111.94, 69.55, 63.48, 60.03, 56.10, 46.86, 13.94.

**HRMS data**: Calculated mass for $C_{33}H_{26}Cl_2N_6O_5S$ $(M+H)^+$, 689.1052, found, 689.0996.

### 5.11 Ethyl 4-(3-chlorophenyl)-2-(((1-(2-(5-fluoro-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate (16d)




**16d**

The orange solid was obtained with 88% yield.

**Melting point:** 149-150°C.

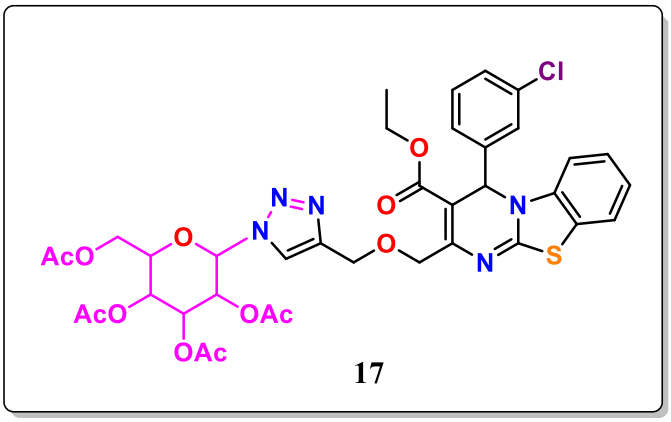
**IR** (KBr, $cm^{-1}$) 3065, 1747, 1685, 1206, 781.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.20 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.49 – 7.41 (m, 2H), 7.40 – 7.28 (m, 4H), 7.22 (t, J = 7.6 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.56 (s, 1H), 4.64 (t, J = 5.6 Hz, 2H), 4.54 (s, 2H), 4.47 (q, J = 12.3 Hz, 2H), 4.13 (t, J = 5.6 Hz, 2H), 4.11 – 3.95 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 182.35, 164.81, 163.36, 159.67, 158.18, 157.25, 153.03, 146.48, 143.44, 137.22, 133.11, 130.82, 127.04, 125.60, 124.89, 124.27, 123.95, 122.99, 118.25, 112.45, 111.84, 111.32, 69.60, 63.48, 60.02, 56.09, 46.83, 13.94.

**HRMS data**: Calculated mass for $C_{33}H_{26}ClFN_6O_5S$ $(M+H)^+$, 673.1358, found, 673.1416.

### 5.12 2-(Acetoxymethyl)-6-(4-(((4-(3-chlorophenyl)-3-(ethoxycarbonyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-2-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (17)




**17**

The yellow solid was obtained with 84% yield.

**Melting point:** 143-144°C.

**IR** (KBr, $cm^{-1}$) 3083, 1756, 1678, 1207, 794.

**$^1$H NMR** (400 MHz, DMSO-$d_6$) $\delta$ 8.43 (s, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.39 – 7.31 (m, 3H), 7.22 (t, J = 7.6 Hz, 1H), 6.57 (s, 1H), 6.36 (d, J = 9.2 Hz, 1H), 5.67 (td, J = 9.4, 2.8 Hz, 1H), 5.56 (t, J = 9.5 Hz, 1H), 5.18 (t, J = 9.7 Hz, 1H), 4.59 (d, J = 30.4 Hz, 3H), 4.37 (dd, J = 10.0, 3.0 Hz, 1H), 4.10 (dd, J = 9.6, 6.5 Hz, 4H), 2.03 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.80 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H).

**$^{13}$C NMR** (100 MHz, DMSO-$d_6$) $\delta$ 170.02, 169.55, 169.36, 168.49, 143.43, 137.24, 133.09, 130.81, 128.46, 127.03, 125.59, 124.3, 122.98, 112.47, 83.82, 73.19, 72.15, 70.13, 67.53, 61.83, 60.02, 56.08, 20.57, 19.89, 13.91.

**HRMS data**: Calculated mass for $C_{37}H_{38}ClN_5O_{12}S$ $(M+H)^+$, 812.1898, found, 812.1973.

## 6 $^{1}$H and $^{13}$C NMR spectra of products

### 6.1 Ethyl 5-(3-chlorophenyl)-7-((prop-2-yn-1-yloxy)methyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (6)

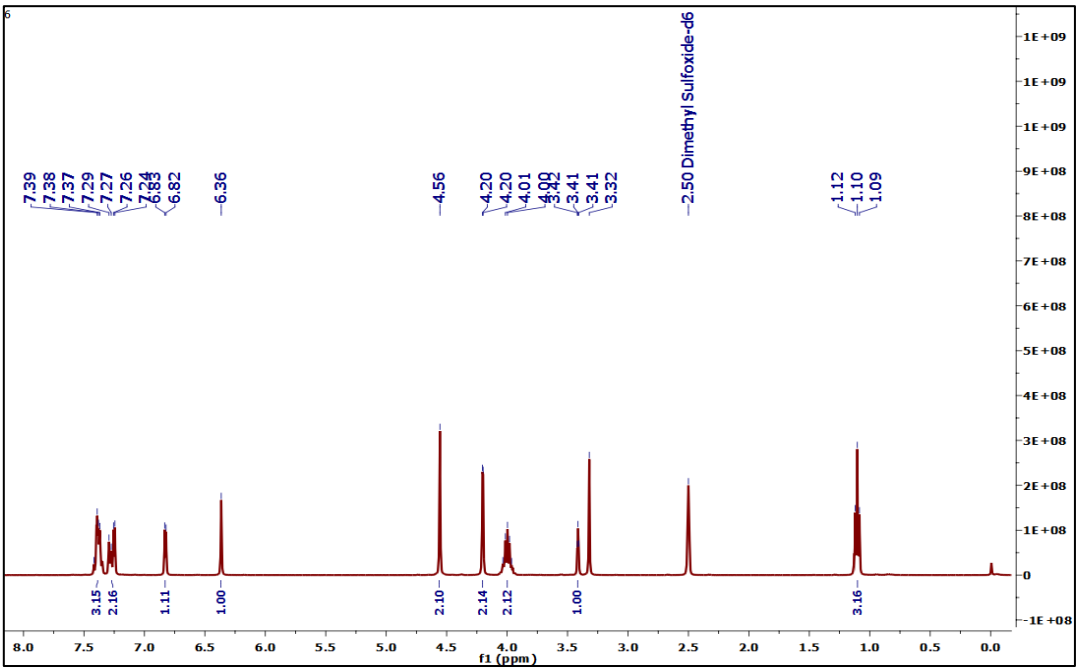



**Figure 2.7** $^{1}$H NMR spectrum of the compound **6** (400 MHz DMSO-$d_6$).

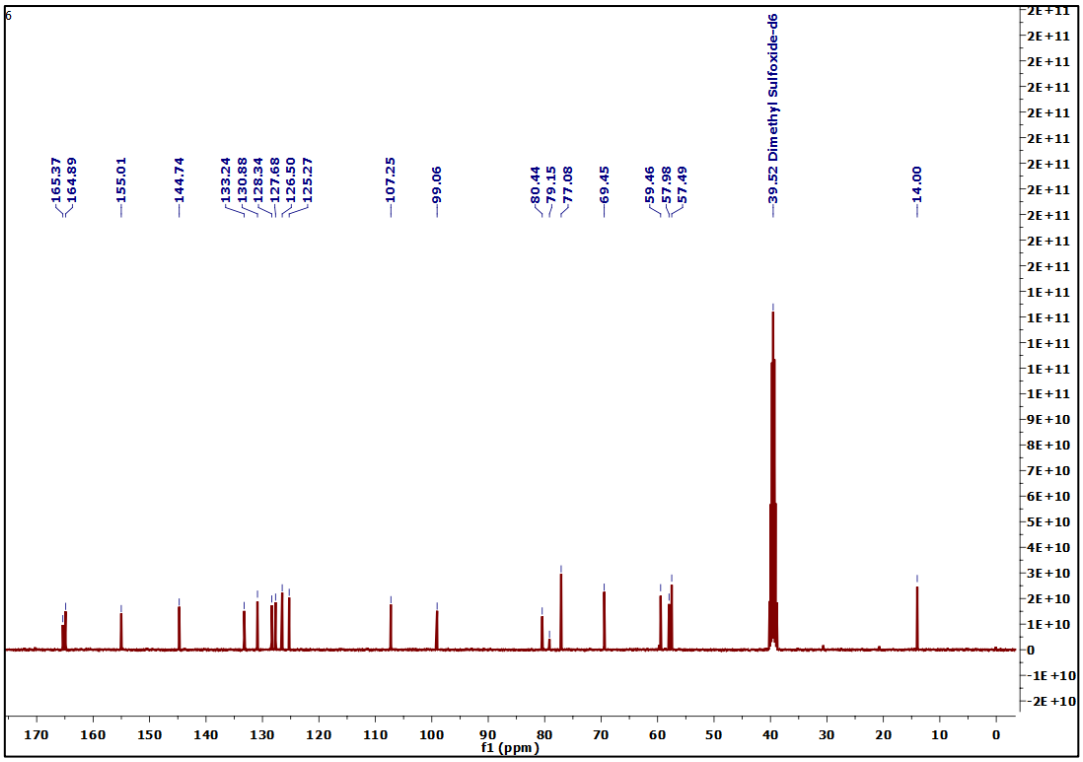



**Figure 2.8** $^{13}$C NMR spectrum of the compound **6** (100 MHz, DMSO-$d_6$).

## 6.2 Ethyl 4-(3-chlorophenyl)-2-((prop-2-yn-1-yloxy)methyl)-4*H*-benzo[4,5] thiazolo[3,2-a] pyrimidine-3-carboxylate (7)

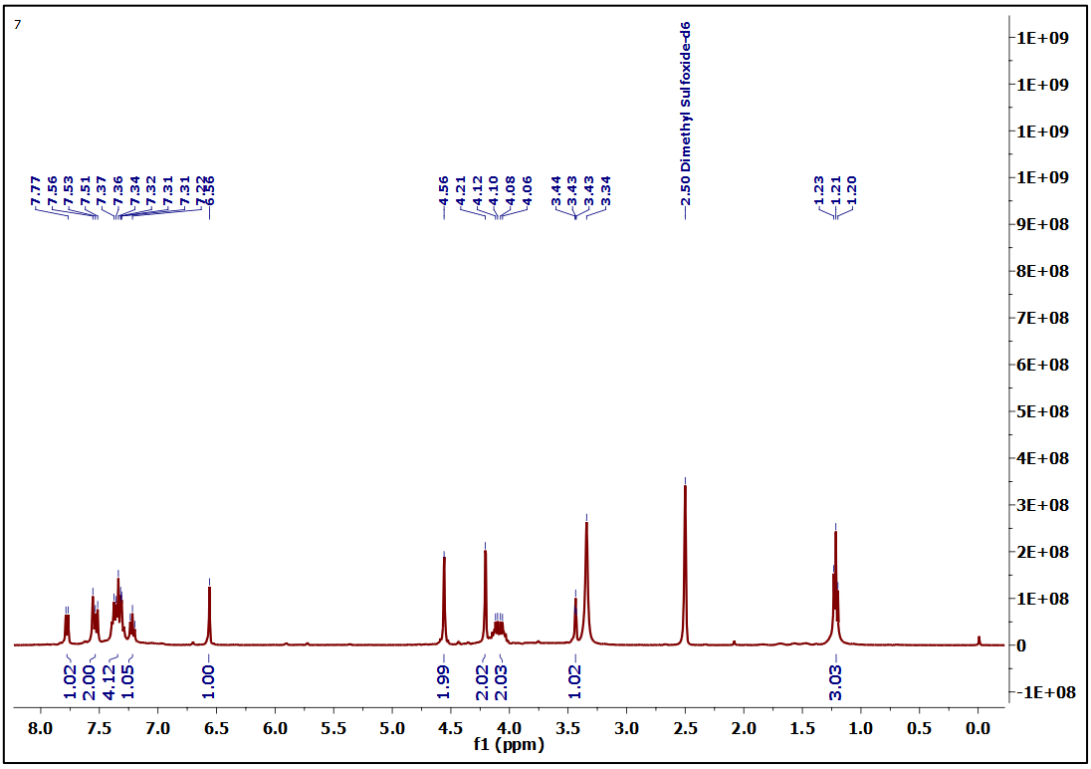



**Figure 3** $^{1}$H NMR spectrum of the compound **7** (400 MHz DMSO-$d_6$).

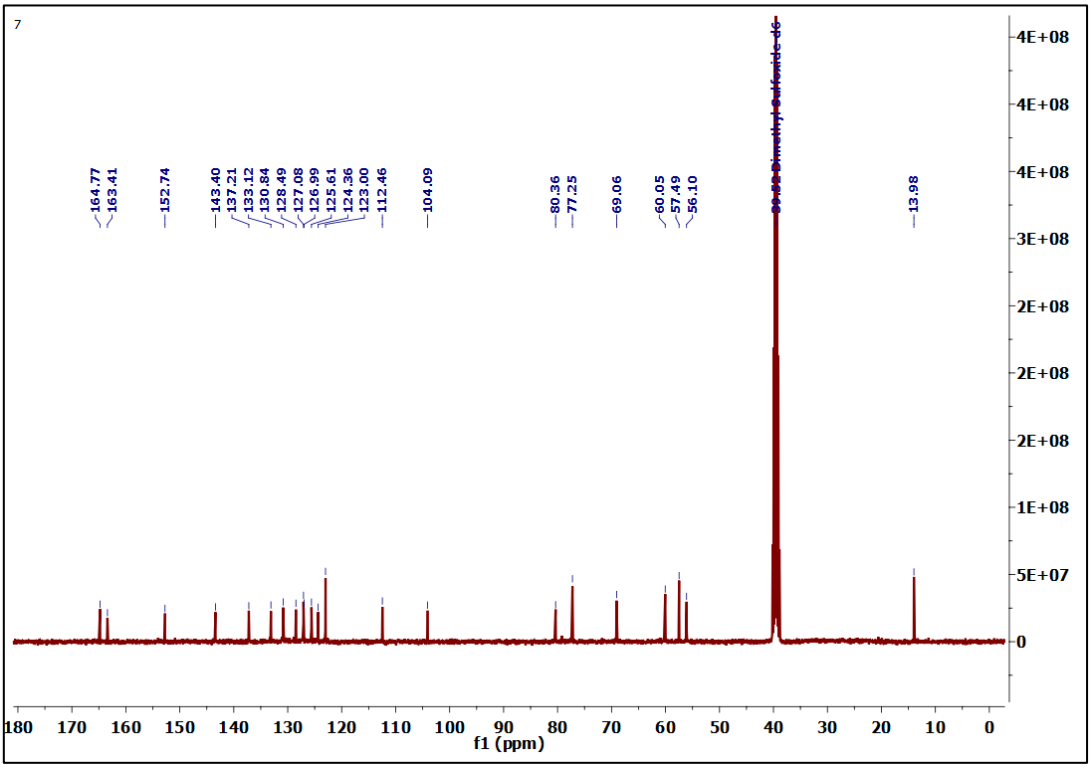



**Figure 4** $^{13}$C NMR spectrum of the compound **7** (100 MHz, DMSO-$d_6$).

**6.3 Ethyl 5-(3-chlorophenyl)-7-(((1-(2-(2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14a)**

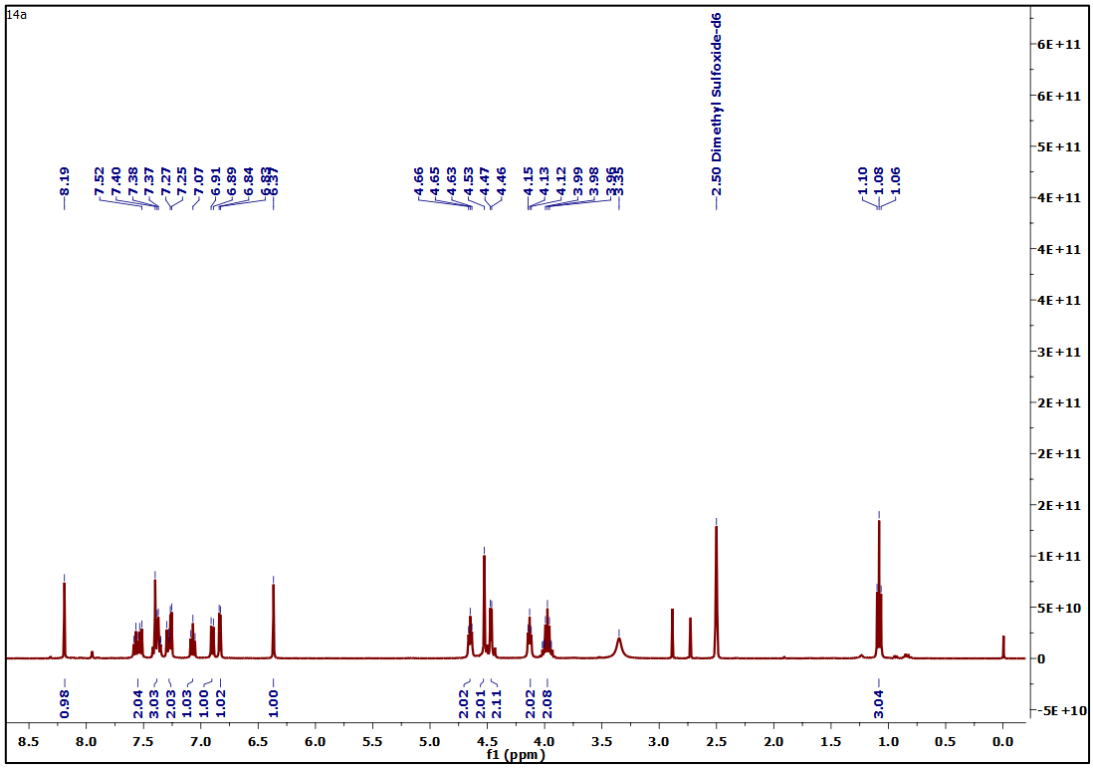



**Figure 5** $^{1}$H NMR spectrum of the compound **14a** (400 MHz DMSO-$d_6$).

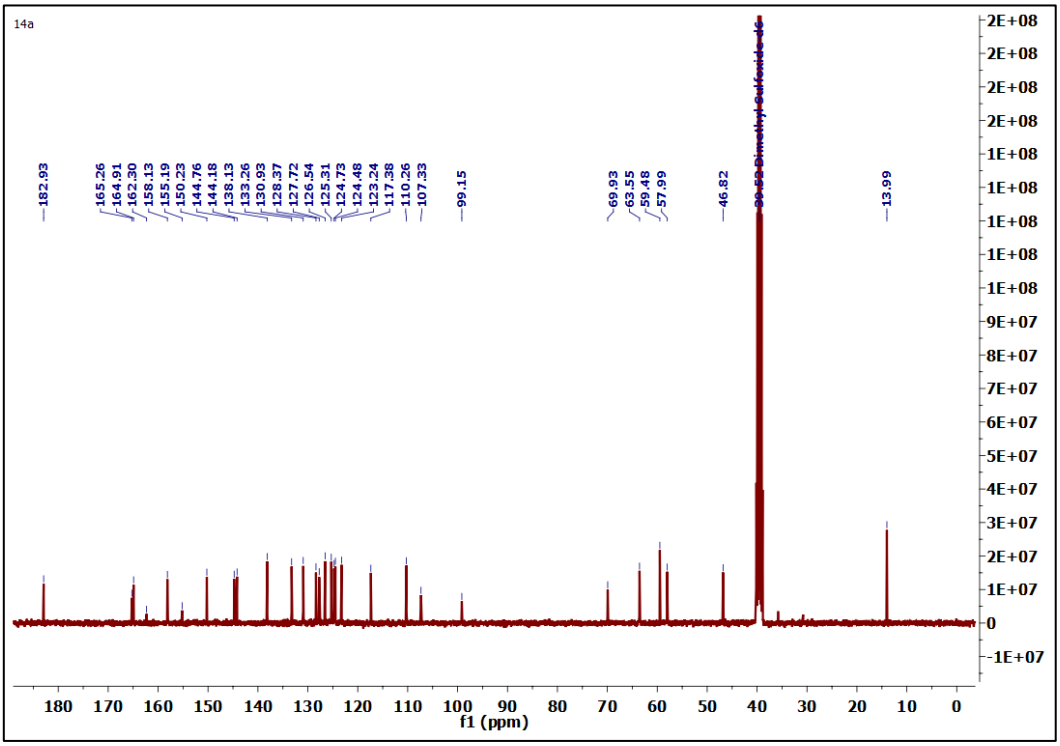



**Figure 6** $^{13}$C NMR spectrum of the compound **14a** (100 MHz, DMSO-$d_6$).

**6.4 Ethyl 7-(((1-(2-(5-bromo-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-5-(3-chlorophenyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14b)**

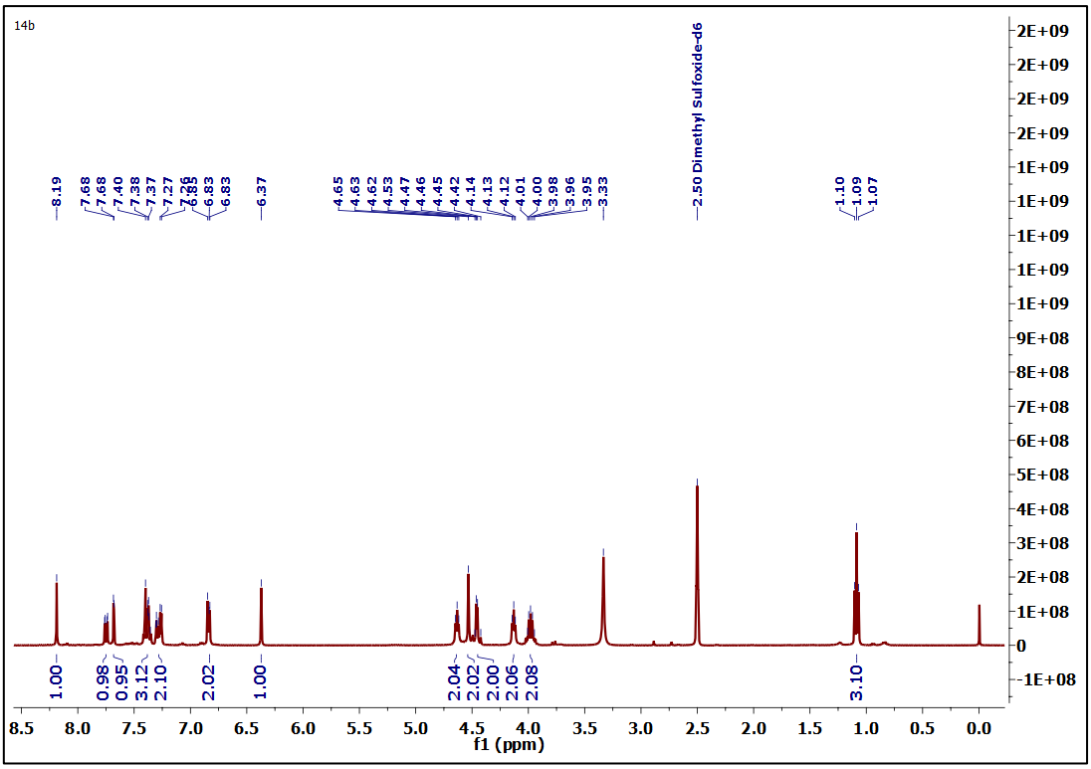



**Figure 7** $^{1}$H NMR spectrum of the compound **14b** (400 MHz DMSO-$d_6$).

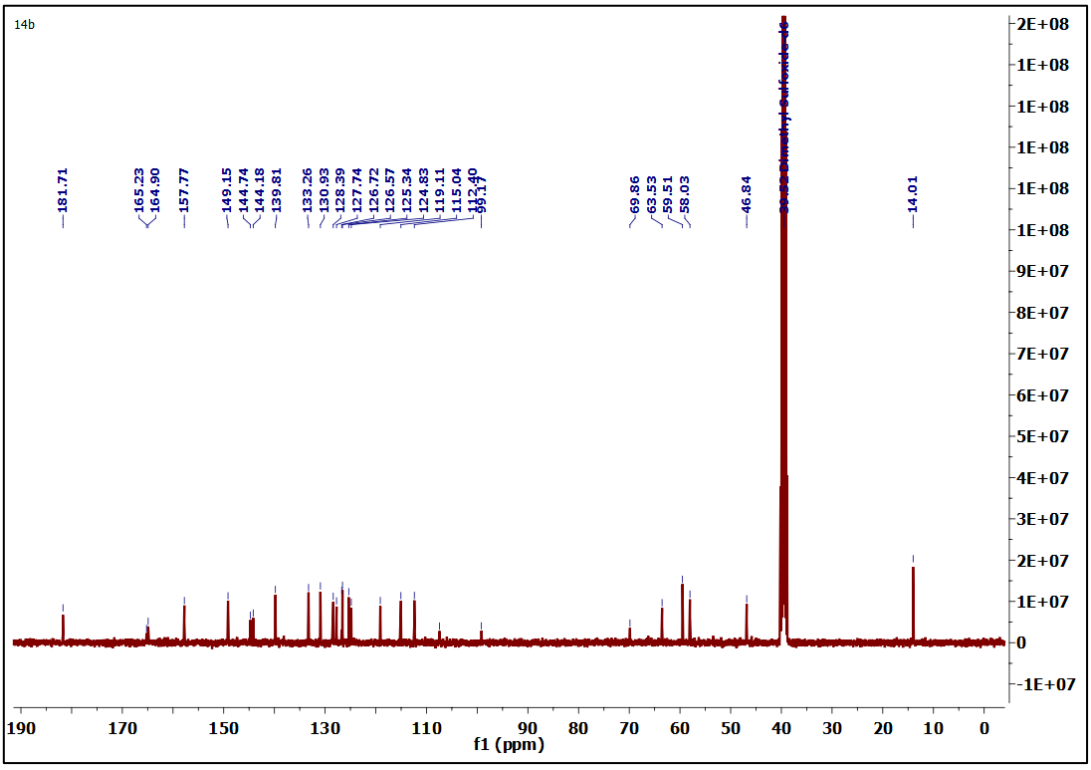



**Figure 8** $^{13}$C NMR spectrum of the compound **14b** (100 MHz, DMSO-$d_6$).

## 6.5 Ethyl-7-(((1-(2-(5-chloro-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl) methoxy)methyl)-5-(3-chlorophenyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14c)

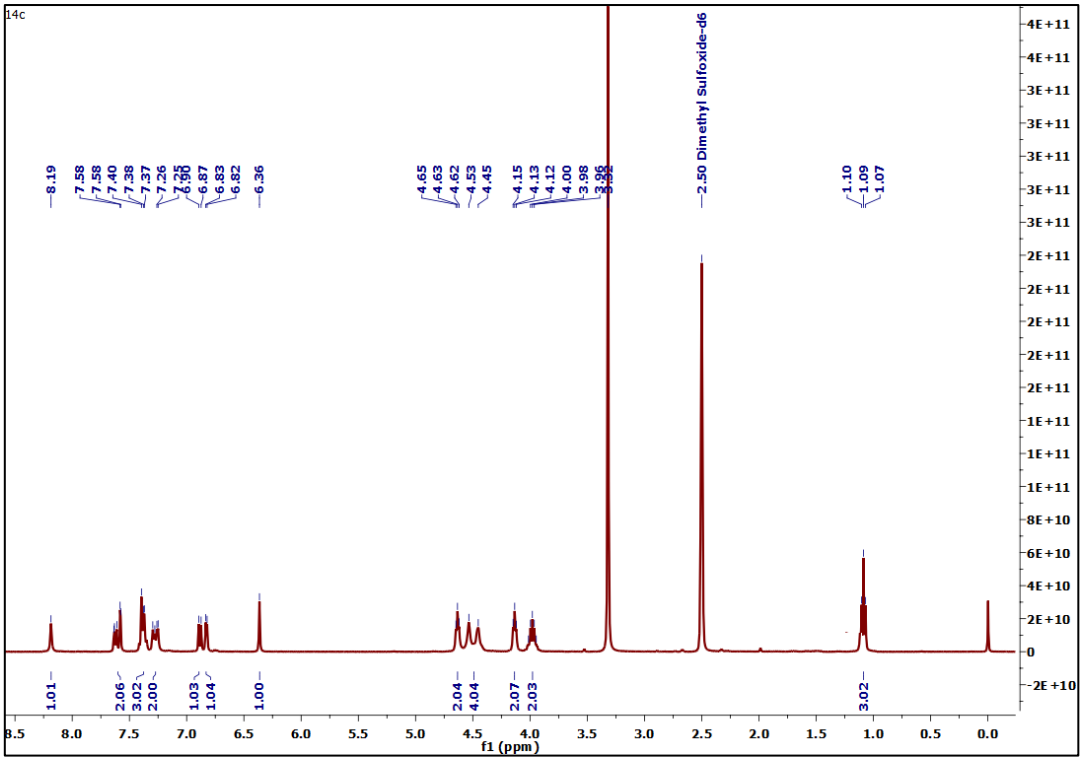



**Figure 9** $^{1}$H NMR spectrum of the compound **14c** (400 MHz DMSO-$d_6$).

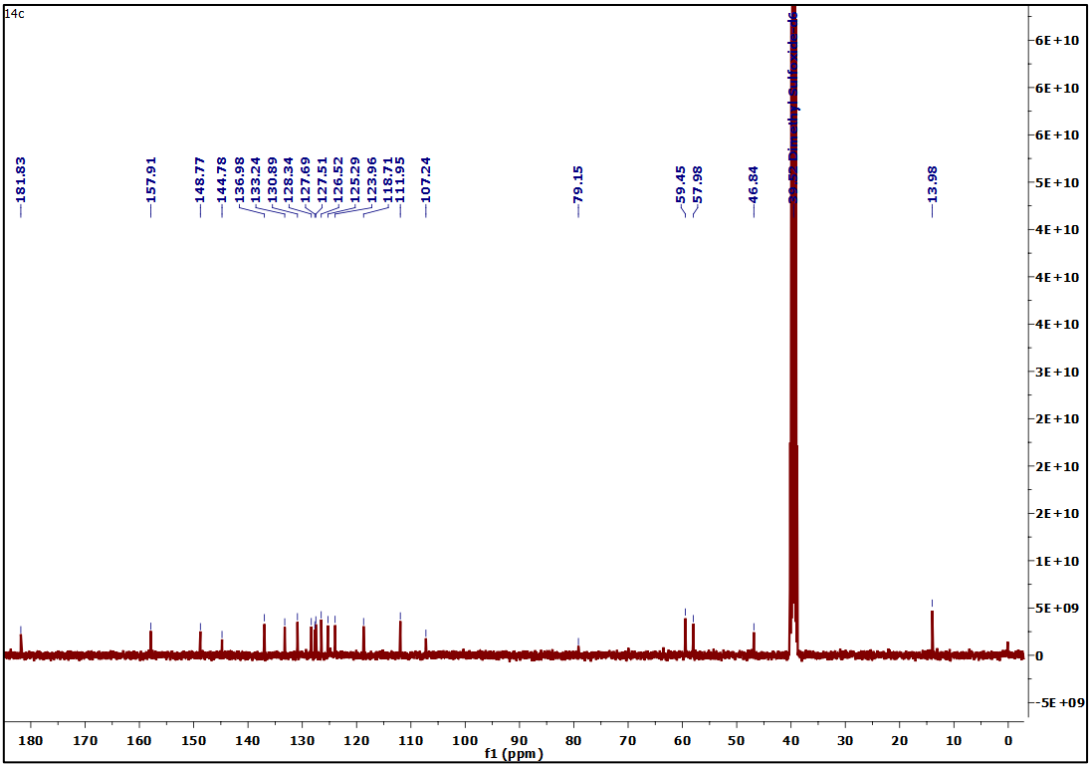



**Figure 10** $^{13}$C NMR spectrum of the compound **14c** (100 MHz, DMSO-$d_6$).

## 6.6 Ethyl 5-(3-chlorophenyl)-7-(((1-(2-(5-fluoro-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate (14d)

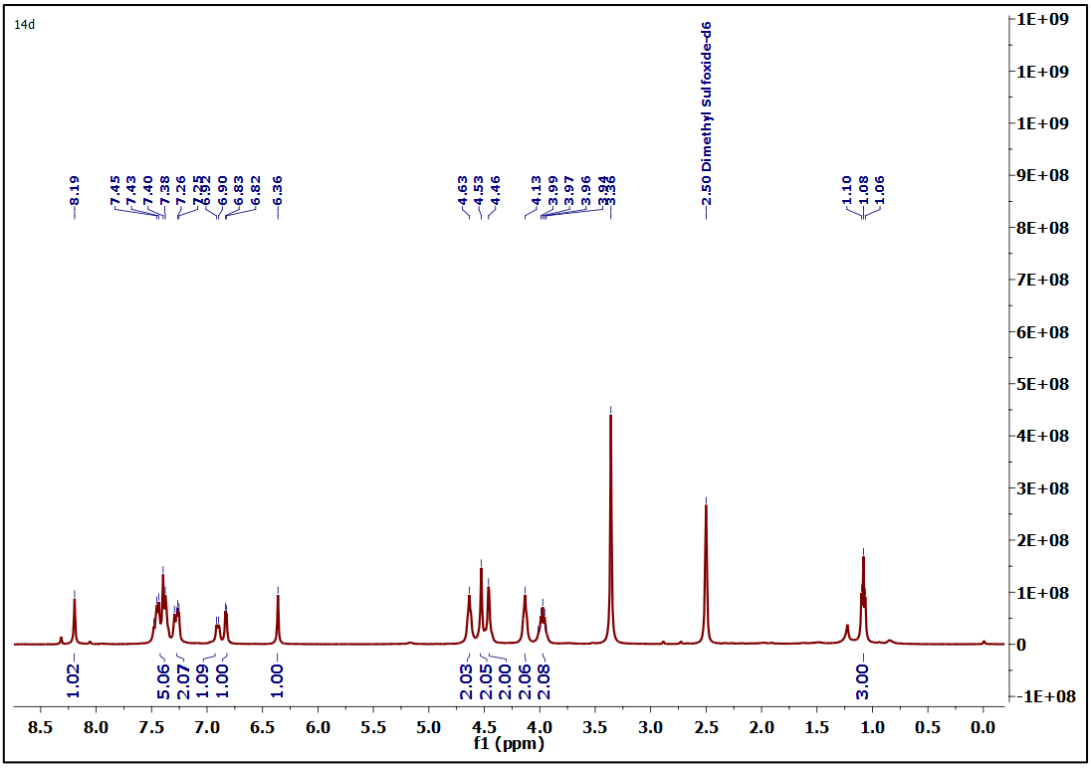



**Figure 11** $^{1}$H NMR spectrum of the compound **14d** (400 DMSO-$d_6$).

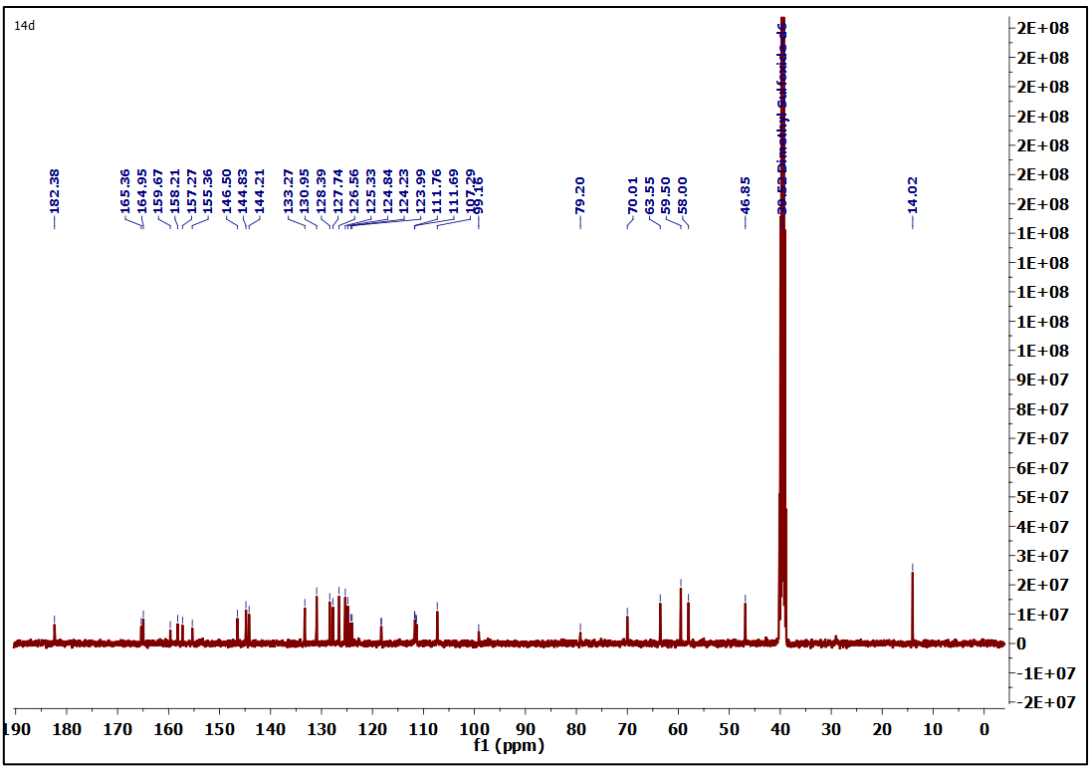



**Figure 12** $^{13}$C NMR spectrum of the compound **14d** (100 MHz, DMSO-$d_6$).

## 6.7 2-(Acetoxymethyl)-6-(4-(((5-(3-chlorophenyl)-6-(ethoxycarbonyl)-5*H*-thiazolo[3,2-a]pyrimidin-7-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl) tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (15)

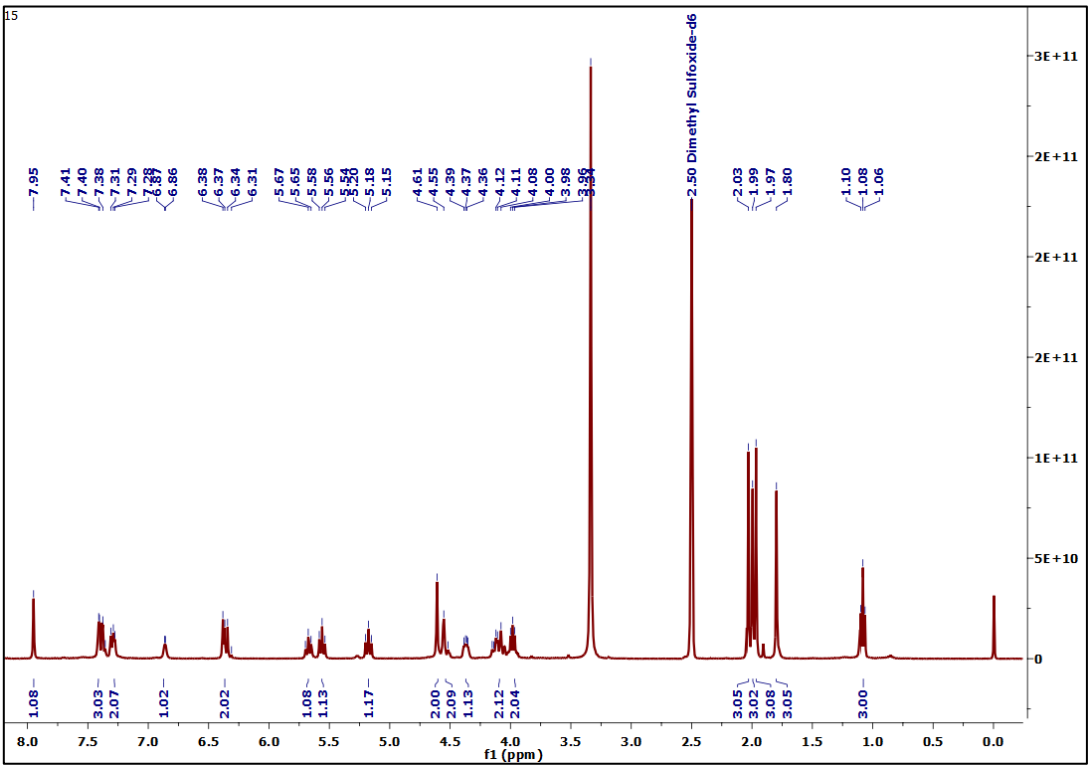



**Figure 13** $^{1}$H NMR spectrum of the compound **15** (400 MHz DMSO-$d_6$).

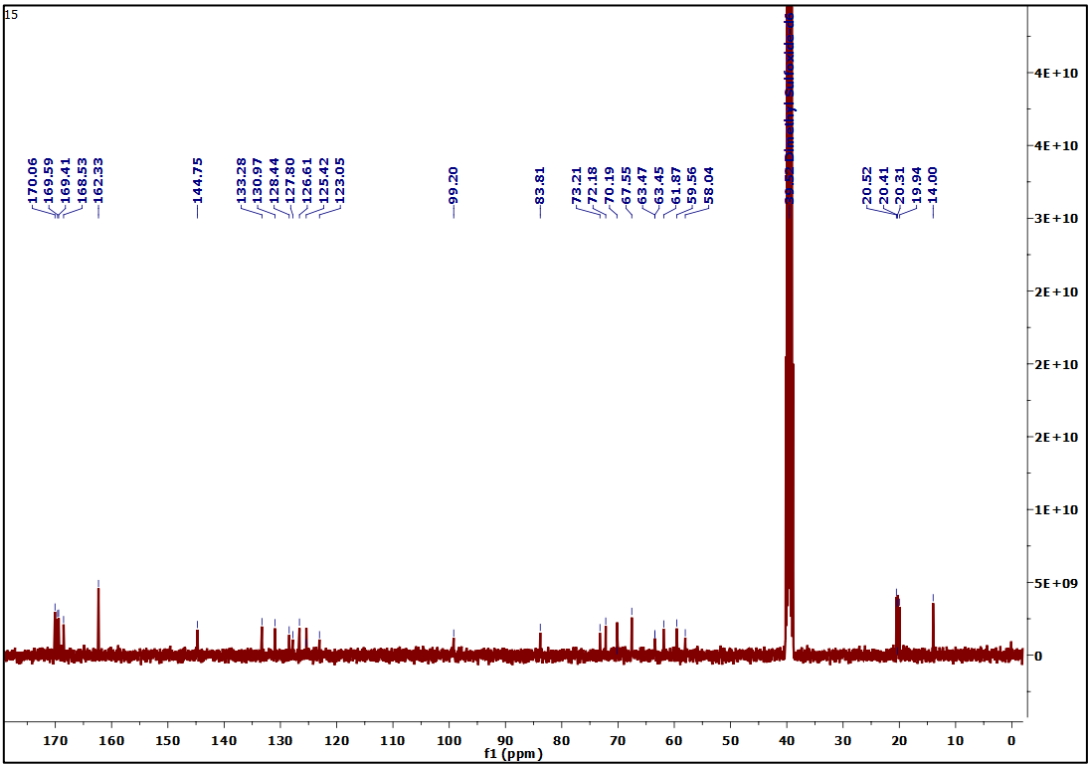



**Figure 14** $^{13}$C NMR spectrum of the compound **15** (100 MHz, DMSO-$d_6$).

## 6.8 Ethyl 4-(3-chlorophenyl)-2-(((1-(2-(2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxylate (16a)

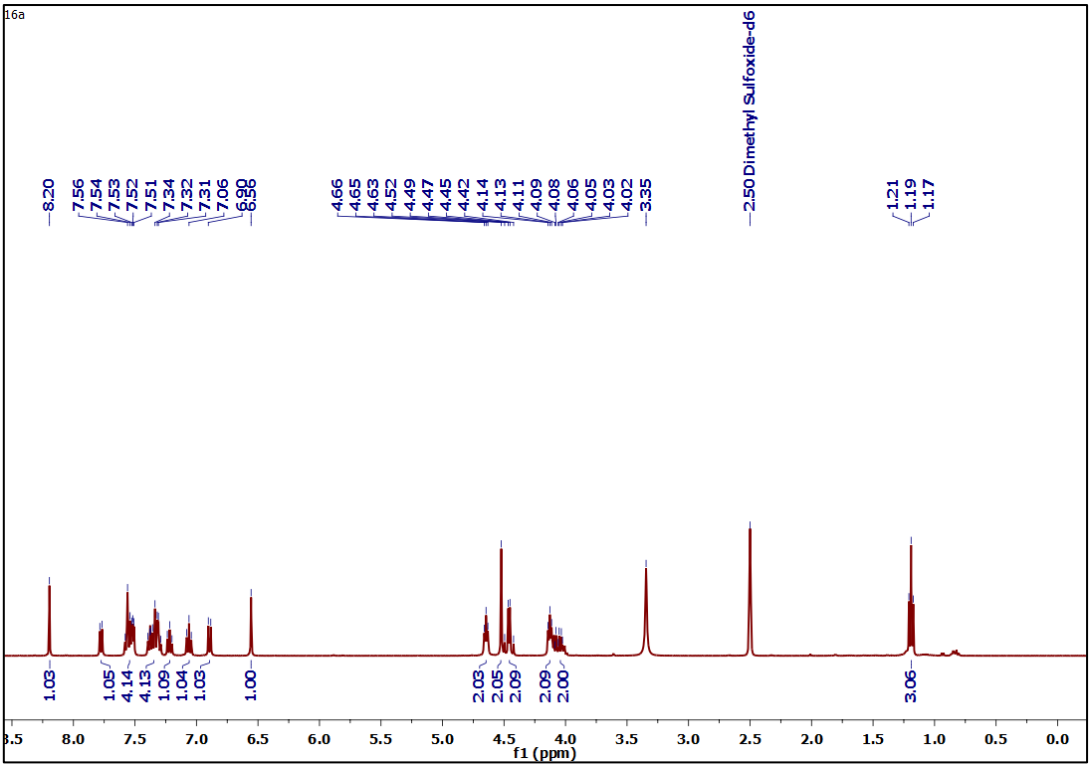



**Figure 15** $^{1}$H NMR spectrum of the compound **16a** (400 MHz DMSO-$d_6$).

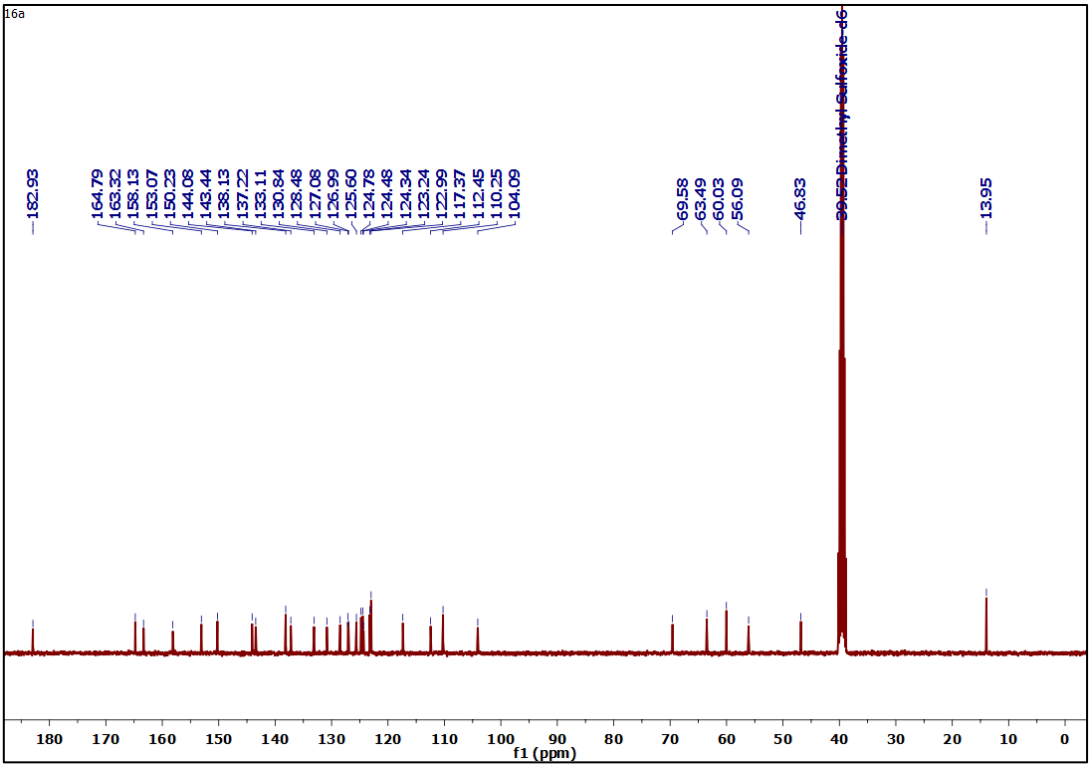



**Figure 16** $^{13}$C NMR spectrum of the compound **16a** (100 MHz, DMSO-$d_6$).

### 6.9 Ethyl 2-(((1-(2-(5-bromo-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl) methoxy)methyl)-4-(3-chlorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-a] pyrimidine-3-carboxylate (16b)

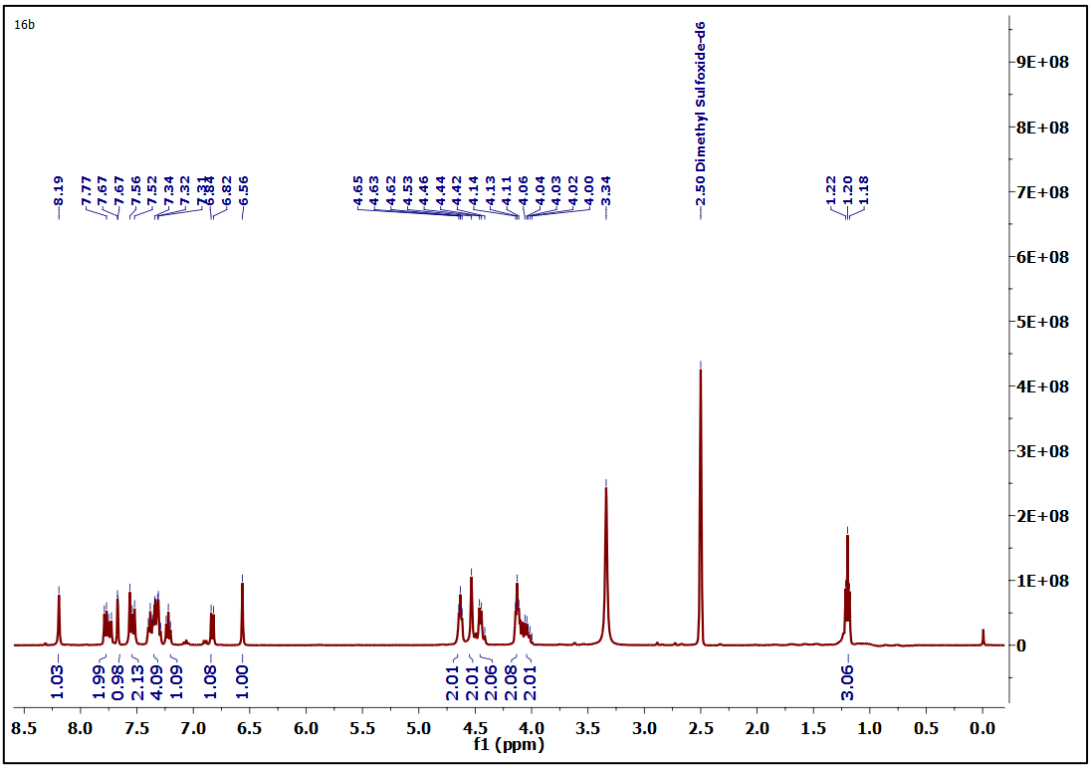



**Figure 17** $^{1}$H NMR spectrum of the compound **16b** (400 MHz DMSO-$d_6$).

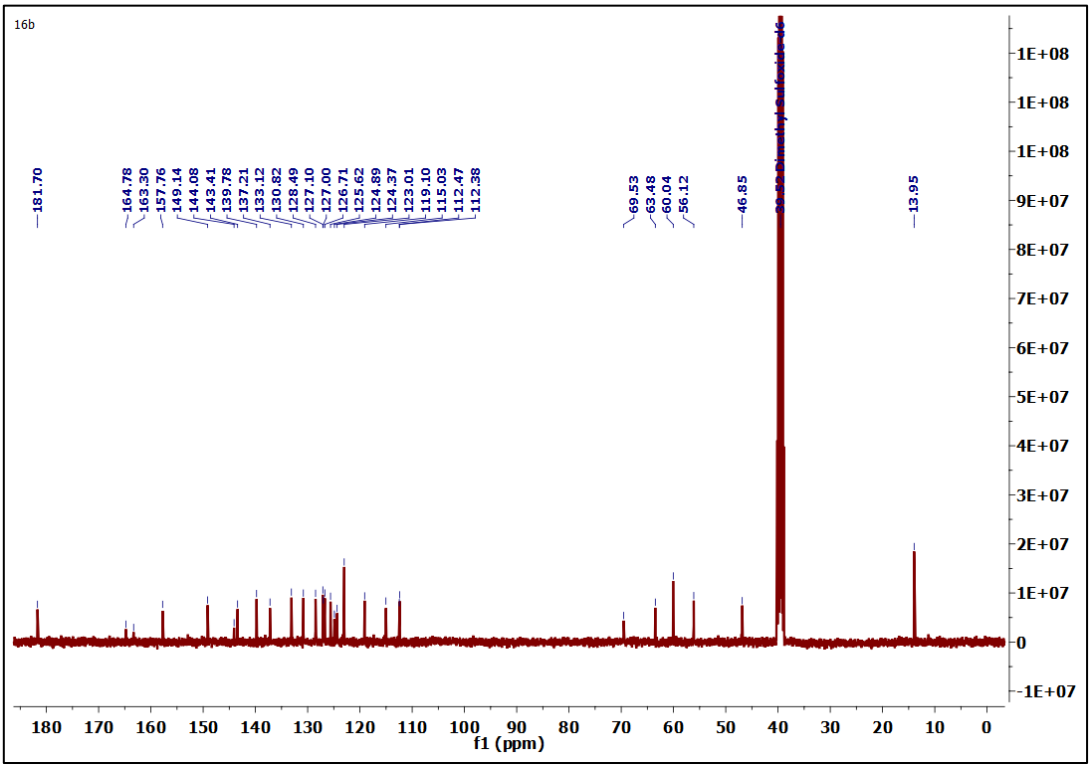



**Figure 18** $^{13}$C NMR spectrum of the compound **16b** (100 MHz, DMSO-$d_6$).

## 6.10 Ethyl 2-(((1-(2-(5-chloro-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-4-(3-chlorophenyl)-4*H*-benzo[4,5]thiazolo[3,2-a] pyrimidine-3-carboxylate (16c)

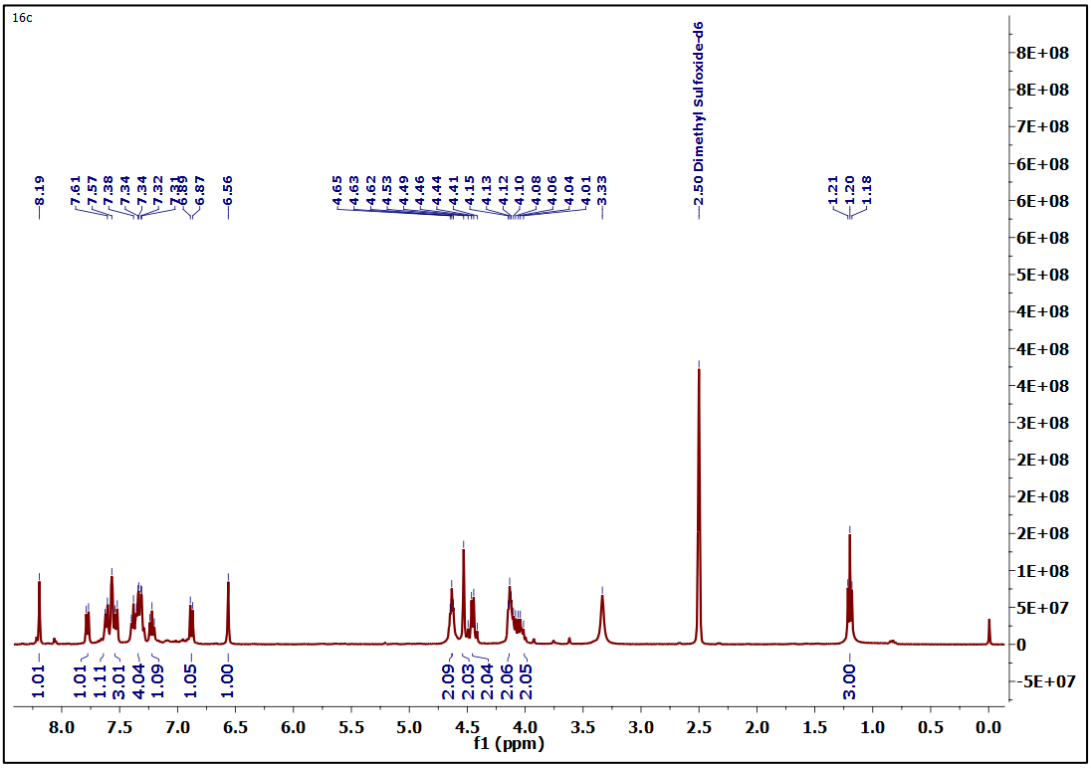



**Figure 19** $^{1}$H NMR spectrum of the compound **16c** (400 MHz DMSO-$d_6$).

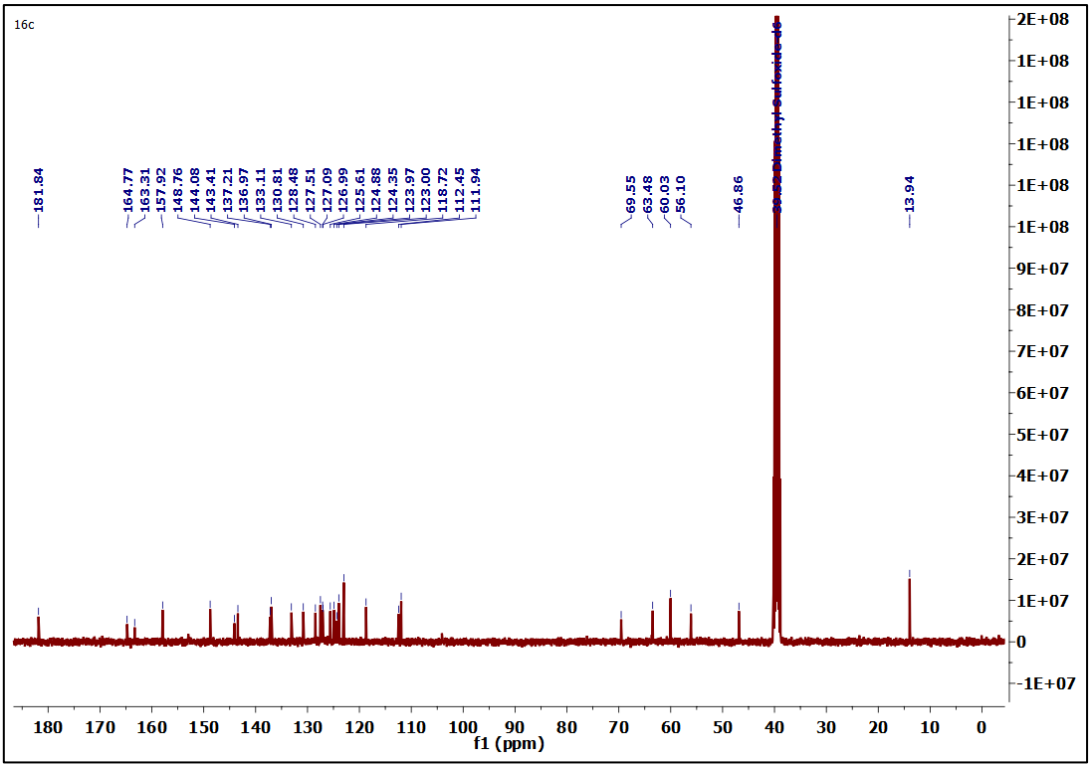



**Figure 20** $^{13}$C NMR spectrum of the compound **16c** (100 MHz, DMSO-$d_6$).

## 6.11 Ethyl 4-(3-chlorophenyl)-2-(((1-(2-(5-fluoro-2,3-dioxoindolin-1-yl)ethyl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-4*H*-benzo[4,5]thiazolo[3,2-a] pyrimidine-3-carboxylate (16d)

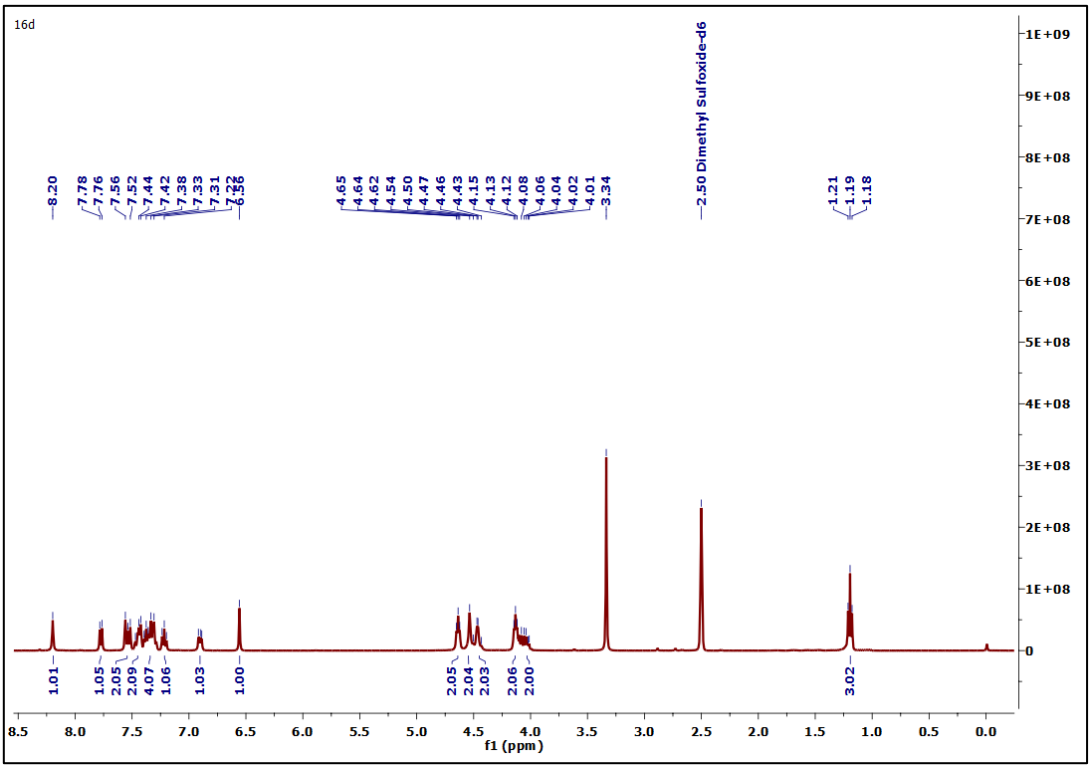



**Figure 21** $^{1}$H NMR spectrum of the compound **16d** (400 MHz DMSO-$d_6$).

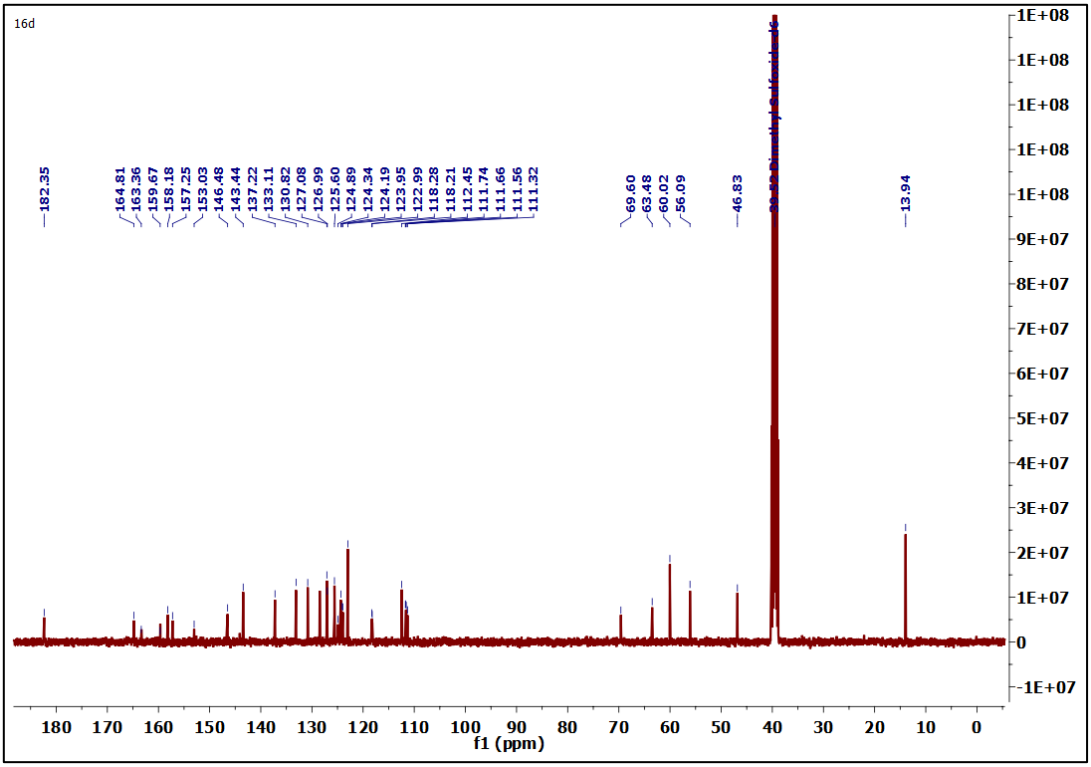



**Figure 22** $^{13}$C NMR spectrum of the compound **16d** (100 MHz, DMSO-$d_6$).

**6.12 2-(Acetoxymethyl)-6-(4-(((4-(3-chlorophenyl)-3-(ethoxycarbonyl)-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-2-yl)methoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (17).**

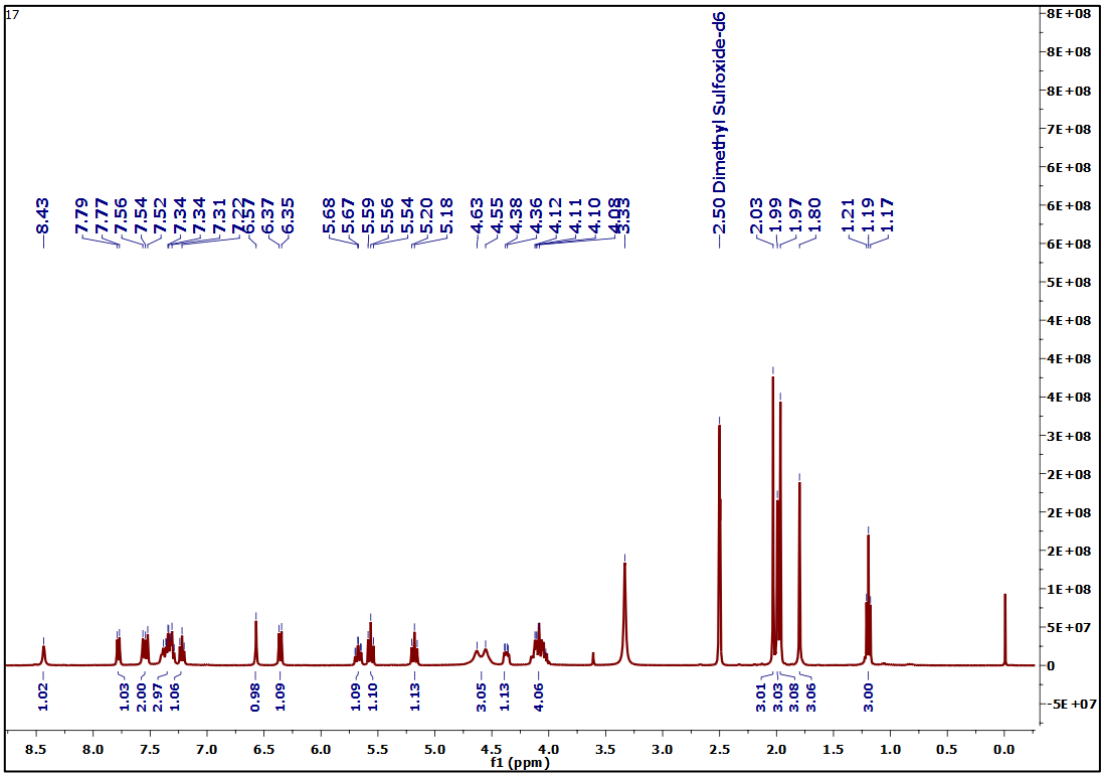



**Figure 23** $^{1}$H NMR spectrum of the compound **17** (400 MHz DMSO-$d_6$).

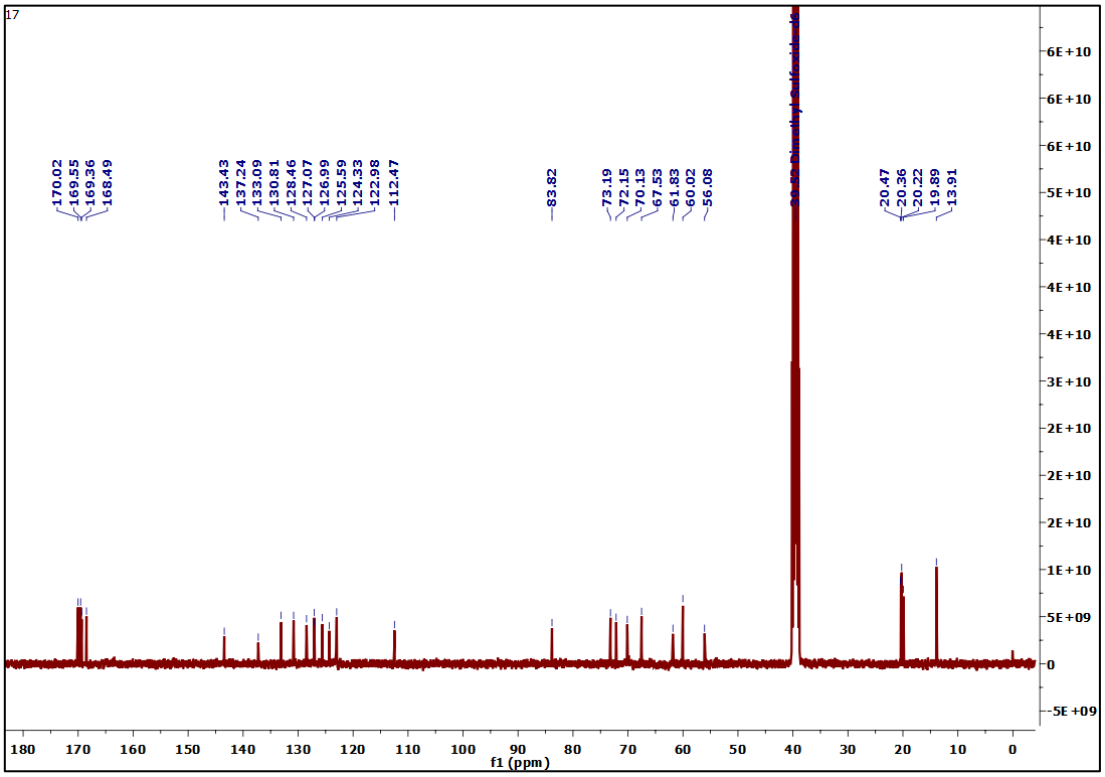



**Figure 24** $^{13}$C NMR spectrum of the compound **17** (100 MHz, DMSO-$d_6$).