Supplementary Material

Novel benzenesulfonamides containing dual triazole moiety with selective carbonic anhydrase inhibition and anticancer activity

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Fig. S56. Lineweaver-Burk plots of compound **7k** (4-{4-[1-({[1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

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Fig. S61. Lineweaver-Burk plots of compound **7l** (2-hydroxy-4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

Fig. S62. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

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Fig. S64. IR spectrum of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

Fig. S65. Mass spectrum of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

Fig. S66. Lineweaver-Burk plots of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

Fig. S67. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

Fig. S68. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

Fig. S69. IR spectrum of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

Fig. S70. Mass spectrum of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

Fig. S71. Lineweaver-Burk plots of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

Fig. S72. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

Fig. S73. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

Fig. S74. IR spectrum of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

Fig. S75. Mass spectrum of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

Fig. S76. Lineweaver-Burk plots of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

Table S1. ADME-related parameters [a] of the novel 1,2,3-triazolyloxime substituted-1,2,3-triazolyl sulfonamide derivatives (**7a-o**) and clinically used reference inhibitor acetazolamide.

Compound ID	#stars	#rtvFG	CNS	MW	Dipole	SASA	Volume	donorHB	accptHB	QPlogPC16	QPlogPoct	QPlogPw	QPlogPo/w	QPlogS	QPPCaco	QPlogBB	QPPMDCK	QPlogKp	#metab	QPlogKhsa	HOA	PSA	Rule of Five	Rule of Three
7a	0	0	–2	452.5	9.8	797.1	1385.9	2.0	11.2	16.2	26.5	18.3	1.9	–5.5	42	–2.8	16	–4.2	3	–0.2	54	148.2	1	0
7b	0	0	–2	466.5	9.9	700.5	1322.7	2.0	11.7	14.5	25.2	17.3	1.3	–3.5	48	–2.3	19	–4.2	4	–0.4	52	148.9	1	0
7c	0	0	–2	466.5	6.0	810.1	1430.9	2.0	11.2	16.2	26.2	17.9	2.2	–5.7	52	–2.6	21	–4.1	4	–0.4	57	145.7	1	1
7d	1	0	–2	468.5	6.5	798.1	1400.1	3.0	12.0	16.6	27.8	20.3	1.1	–5.2	13	–3.4	5	–5.2	4	–0.3	41	170.3	1	1
7e	1	0	–2	578.4	8.4	831.8	1448.8	2.0	11.2	17.1	27.2	18.1	2.5	–6.4	42	–2.7	47	–4.3	3	–0.1	45	148.2	2	1
7f	1	0	–2	531.4	6.7	827.0	1440.4	2.0	11.2	17.0	26.8	18.0	2.4	–6.3	42	–2.7	44	–4.3	3	–0.3	44	148.5	2	1
7g	1	0	–2	486.9	7.9	820.4	1429.9	2.0	11.2	16.9	26.8	18.0	2.4	–6.2	43	–2.6	42	–4.3	3	–0.6	57	148.0	1	1
7h	0	0	–2	470.5	5.4	775.5	1380.6	2.0	11.2	15.5	25.7	17.9	1.9	–5.3	43	–2.6	26	–4.3	3	–0.2	55	147.3	1	0
7i	0	0	–2	470.5	8.3	806.9	1402.8	2.0	11.2	15.8	26.5	18.1	2.1	–5.9	42	–2.7	30	–4.3	3	–0.1	55	148.2	1	1
7j	2	0	–2	477.5	8.3	837.3	1453.7	2.0	12.7	17.2	27.8	19.9	1.1	–6.5	9	–3.8	3	–5.5	3	–0.3	37	174.5	1	2
7k	4	0	–2	513.9	5.3	858.7	1502.8	2.0	12.2	17.9	27.9	19.2	1.6	–6.3	6	–4.0	4	–6.1	4	–0.1	24	192.6	2	2
7l	4	0	–2	512.5	6.5	854.3	1493.5	3.0	13.0	18.0	29.5	21.5	1.1	–5.6	0	–4.8	0	–7.0	4	–0.5	1	218.9	2	1
7m	7	0	–2	531.6	12.9	869.7	1524.1	4.0	15.7	18.7	34.1	25.9	–0.3	–5.0	2	–4.8	1	–6.8	3	–0.7	4	214.0	2	1
7n	2	0	–2	496.5	5.5	827.7	1459.0	3.0	13.2	17.4	29.3	21.8	1.1	–5.3	1	–4.1	0	–6.2	3	–0.5	21	197.5	1	1
7o	2	0	–2	494.5	10.7	862.1	1510.3	2.0	13.2	17.4	29.0	20.1	1.3	–5.7	13	–3.6	5	–5.3	3	–0.3	42	177.5	1	2
AAZ [b]	0	0	–2	222.2	10.9	412.9	634.3	3.0	9.0	6.8	17.6	15.2	–1.8	–1.6	36	–1.8	24	–5.9	1	–1.0	44	133.3	0	0

[a] Various computational pharmacodynamic and pharmacokinetic parameters of synthesized compounds in this research were predicted such as number of property or descriptor values that fall outside the 95% range of similar values for known drugs. (#stars; 0 - 5), number of reactive functional groups (#rtvFG; 0 - 2), central nervous system activity (CNS; –2 inactive, +2 active), molecular weight of the compound (MW; 130.0 - 725.0), computed dipole moment of the compound (Dipole; 1.0 - 12.5), total solvent accessible surface area (SASA; 300.0 - 1000.0), total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å Radius (Volume; 500.0 - 2000.0), number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution (donorHB; 0.0 - 6.0), number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution (accptHB; 2.0 - 20.0), hexadecane/gas partition coefficient (QPlogPC16; 4.0 - 18.0), octanol/gas partition coefficient (QPlogPoct; 8.0 - 35.0), water/gas partition coefficient (QPlogPw; 4.0 - 45.0), octanol/water partition coefficient (QPlogPo/w; –2.0 - 6.5), aqueous solubility (QPlogS; –6.5 - 0.5), apparent Caco-2 cell permeability in nm/sec (QPPCaco; <25 poor, great>500), brain/blood partition coefficient (QPlogBB; –3.0 - 1.2), apparent MDCK cell permeability in nm/sec (QPPMDCK; <25 poor, great>500), skin permeability (QPlogKp; –8.0 - –1.0), number of likely metabolic reactions (#metab; 1 - 8),prediction of binding to human serum albumin (QPlogKhsa; –1.5 - 1.5), human oral absorption (HOA; <25% poor, high>80%), van der Waals surface area of polar nitrogen and oxygen atoms (PSA; 7.0 - 200.0), number of violations of Lipinski's rule of five (max. 4), and number of violations of Jorgensen's rule of three (max. 3).

[b] Acetazolamide.

Table S2. Pharmacokinetic properties [a] of the novel 1,2,3-triazolyloxime substituted-1,2,3-triazolyl sulfonamide derivatives (**7a-o**) and clinically used reference inhibitor acetazolamide.

Compounds ID	GI absorption	BBB permeant	P-gp substrate	CYP inhibitor				
				CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
7a	Low	No	Yes	No	No	No	No	Yes
7b	Low	No	Yes	No	No	No	No	Yes
7c	Low	No	No	No	No	Yes	No	Yes
7d	Low	No	Yes	No	No	No	No	Yes
7e	Low	No	No	No	No	No	No	Yes
7f	Low	No	No	No	No	Yes	No	Yes
7g	Low	No	No	No	No	Yes	No	Yes
7h	Low	No	No	No	No	No	No	Yes
7i	Low	No	Yes	No	No	No	No	Yes
7j	Low	No	Yes	No	No	Yes	No	Yes
7k	Low	No	Yes	No	No	No	No	Yes
7l	Low	No	Yes	No	No	No	No	Yes
7m	Low	No	Yes	No	No	No	No	Yes
7n	Low	No	Yes	No	No	No	No	Yes
7o	Low	No	Yes	No	No	Yes	No	Yes
AAZ [b]	Low	No	No	No	No	No	No	No

[a] Various pharmacokinetic parameters, such as the GI absorption, human gastrointestinal absorption; BBB permeant, blood-brain barrier permeation; P-gp substrate, prediction of being substrate or non-substrate of P-glycoprotein; CYP inhibitor, prediction of being inhibitor or non-inhibitor of cytochromes P450 (CYP) five major isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4); and log K_p, prediction of the skin permeability coefficient of targeted compounds in this research, were predicted using SwissADME platform.

[b] Acetazolamide.

Table S3. Drug-likeness descriptors [a] of the novel 1,2,3-triazolyloxime substituted-1,2,3-triazolyl sulfonamide derivatives (**7a-o**) and clinically used reference inhibitor acetazolamide.

Compounds ID	Ghose	Veber	Egan	Muegge	Bioavailability Score
7a	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
7b	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
7c	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
7d	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
7e	No; 1 violation: MW>480	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.17
7f	No; 1 violation: MW>480	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.17
7g	No; 1 violation: MW>480	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
7h	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
7i	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
7j	Yes	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
7k	No; 1 violation: MW>480	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violation: TPSA>150, H-acc>10	0.17
7l	No; 1 violation: MW>480	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violation: TPSA>150, H-acc>10	0.55
7m	No; 1 violation: MW>480	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violation: TPSA>150, H-acc>10	0.17
7n	No; 1 violation: MW>480	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violation: TPSA>150, H-acc>10	0.11
7o	No; 1 violation: MW>480	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150	0.55
AAZ [b]	No; 1 violation: #atoms<20	No; 1 violation: TPSA>140	No; 1 violation: TPSA>131.6	No; 2 violations: TPSA>150, #C<5	0.55

[a] Drug-likeness parameters, such as the Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) methods and bioavailability score (Abbot) of targeted compounds in this research, were predicted using SwissADME platform.

[b] Acetazolamide.

Table S4. Medicinal Chemistry pattern recognition methods [a] of the novel 1,2,3-triazolyloxime substituted-1,2,3-triazolyl sulfonamide derivatives (**7a-o**) and clinically used reference inhibitor acetazolamide.

Compounds ID	PAINS	Brenk	Lead-likeness	SA score
7a	0 alert	2 alert	No; 1 violation: MW>350	3.89
7b	0 alert	2 alert	No; 2 violation: MW>350, Rotors>7	3.99
7c	0 alert	2 alert	No; 1 violation: MW>350	3.99
7d	0 alert	2 alert	No; 1 violation: MW>350	3.90
7e	0 alert	3 alert	No; 1 violation: MW>350	3.98
7f	0 alert	2 alert	No; 1 violation: MW>350	3.89
7g	0 alert	2 alert	No; 1 violation: MW>350	3.89
7h	0 alert	2 alert	No; 1 violation: MW>350	3.83
7i	0 alert	2 alert	No; 1 violation: MW>350	3.84
7j	0 alert	2 alert	No; 1 violation: MW>350	3.96
7k	0 alert	3 alert	No; 2 violation: MW>350, Rotors>7	3.99
7l	0 alert	3 alert	No; 2 violation: MW>350, Rotors>7	3.98
7m	0 alert	2 alert	No; 2 violation: MW>350, Rotors>7	4.08
7n	0 alert	2 alert	No; 2 violation: MW>350, Rotors>7	3.94
7o	0 alert	2 alert	No; 2 violation: MW>350, Rotors>7	4.00
AAZ [b]	0 alert	1 alert	No; 1 violation: MW<250	3.00

[a] Medicinal Chemistry pattern recognition method, such as the PAINS, pan assay interference structure alert filter; Brenk, structural alert filter; Lead-likeness, lead-likeness criteria; and SA score, synthetic accessibility score (ranges from 1, very easy, to 10, very difficult) of targeted compounds in this research, were predicted using SwissADME platform.

[b] Acetazolamide.

[c] Tacrine.

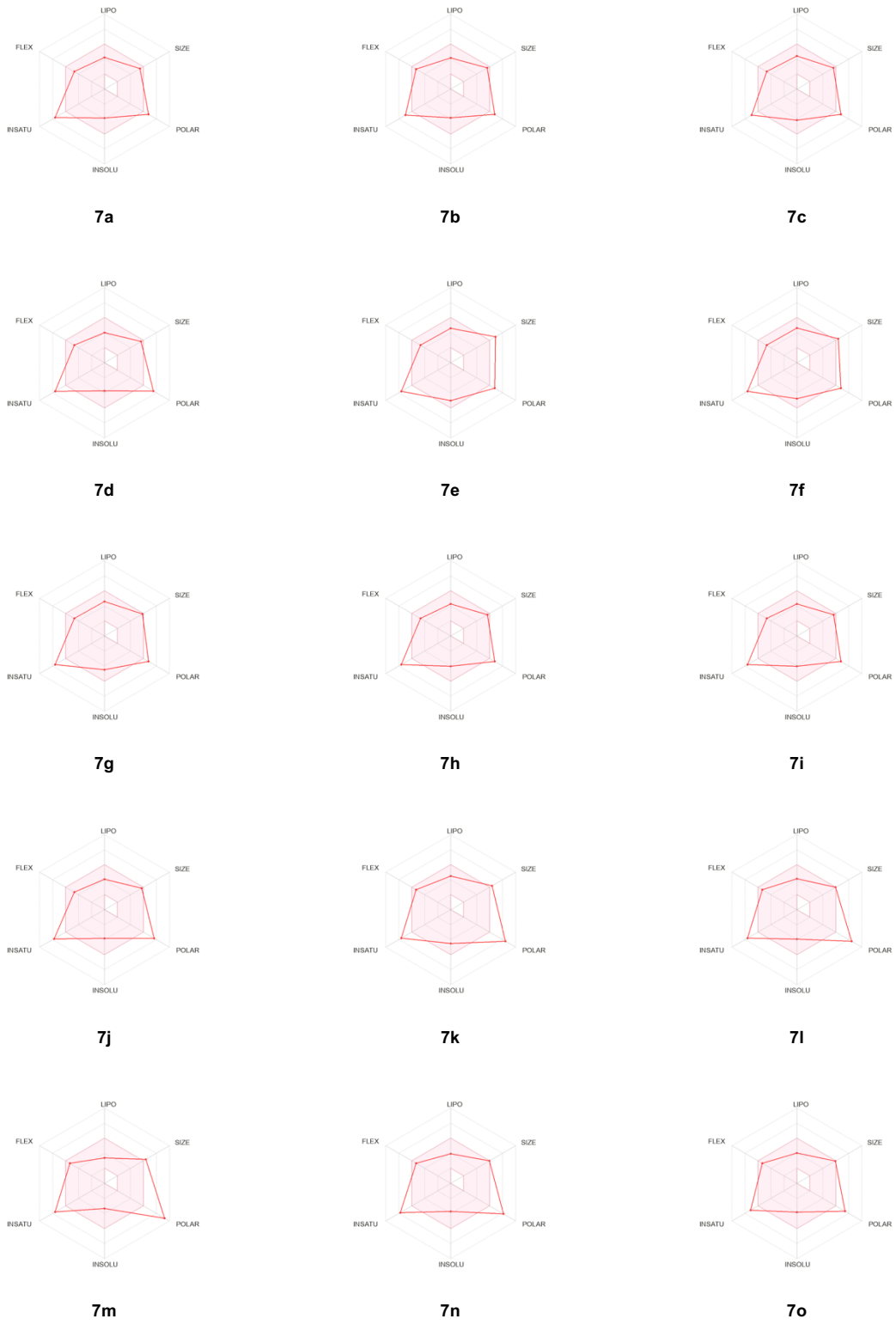

Fig. S1. Diagrams showing 'drug-likeness' descriptors for the novel 1,2,3-triazolyloxime substituted-1,2,3-triazolyl sulfonamide derivatives (**7a-o**). The red-colored zone has been identified as a feasible physicochemical domain to enhance oral bioavailability. LIPO, lipophilicity; SIZE, molecular weight; POLAR, polarity; INSOLU, insolubility; INSATU, saturation; and FLEX, flexibility.

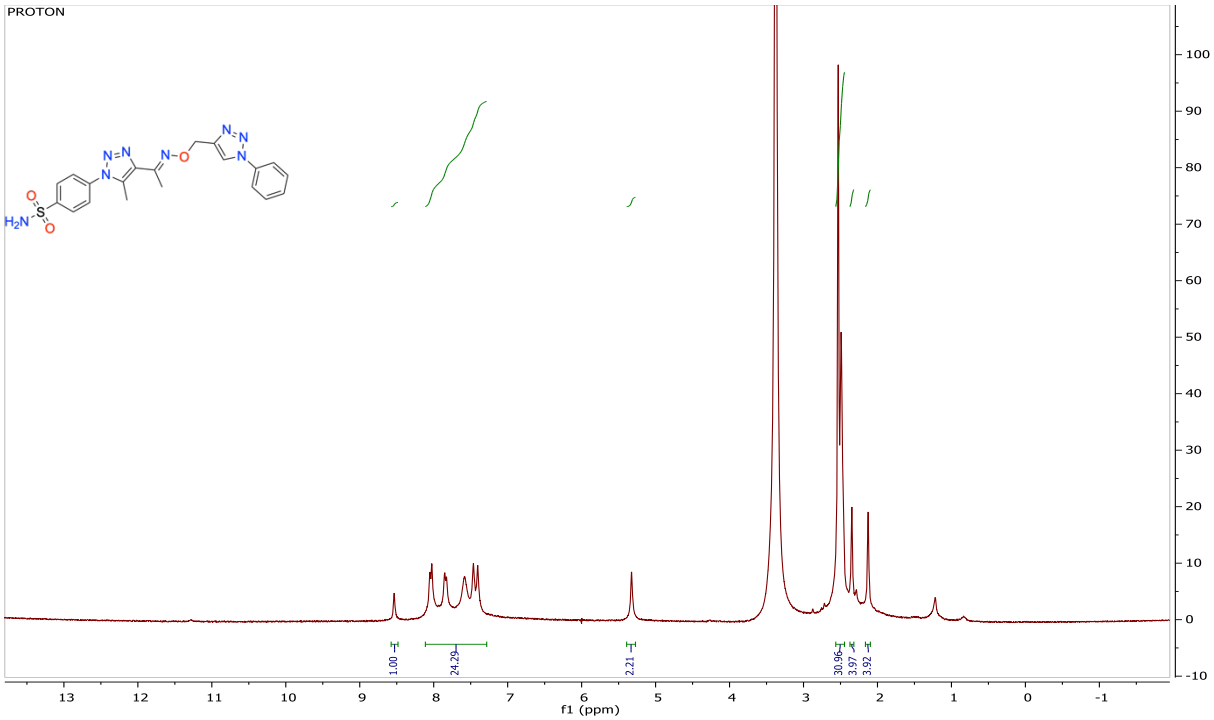

Fig. S2. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7a** (4-[5-methyl-4-(1-{[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

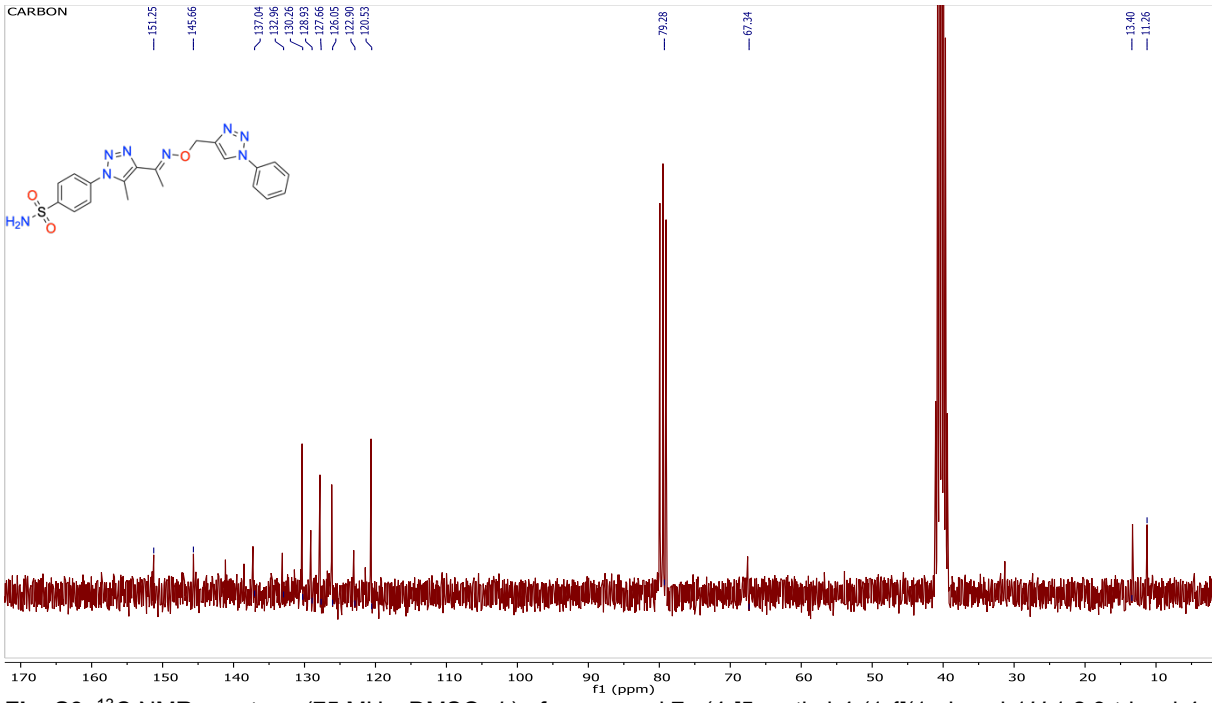

Fig. S3. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7a** (4-[5-methyl-4-(1-{[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

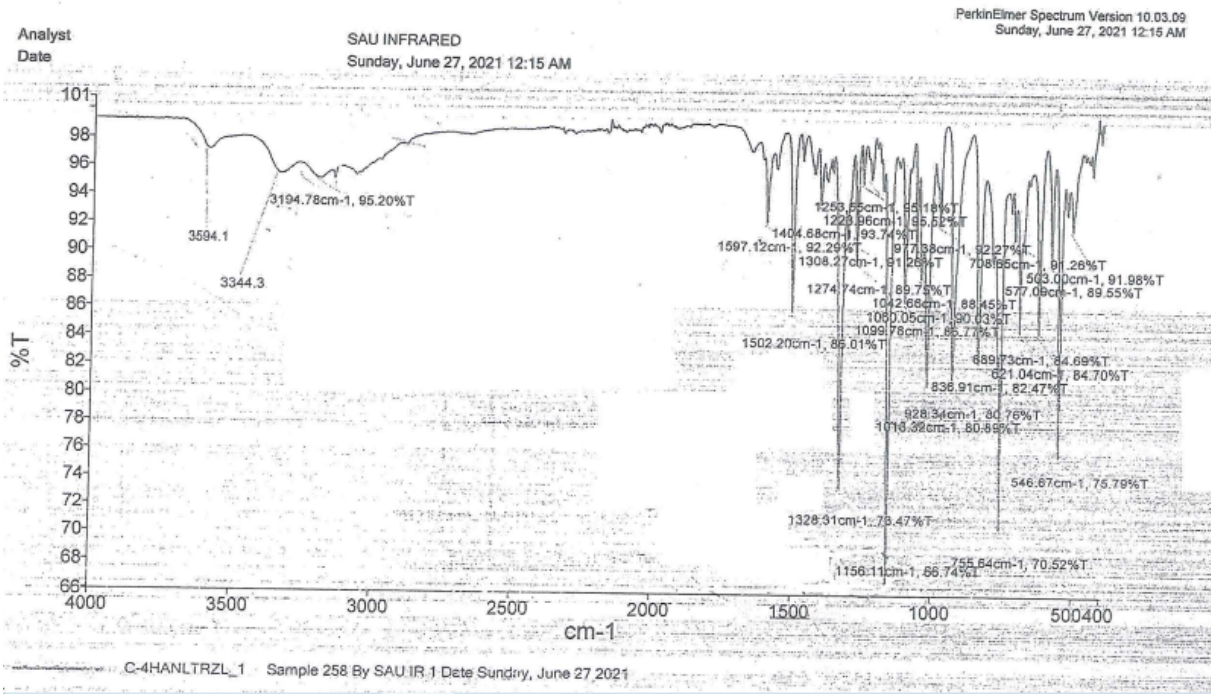

Fig. S4. IR spectrum of compound **7a** (4-[5-methyl-4-(1-{[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

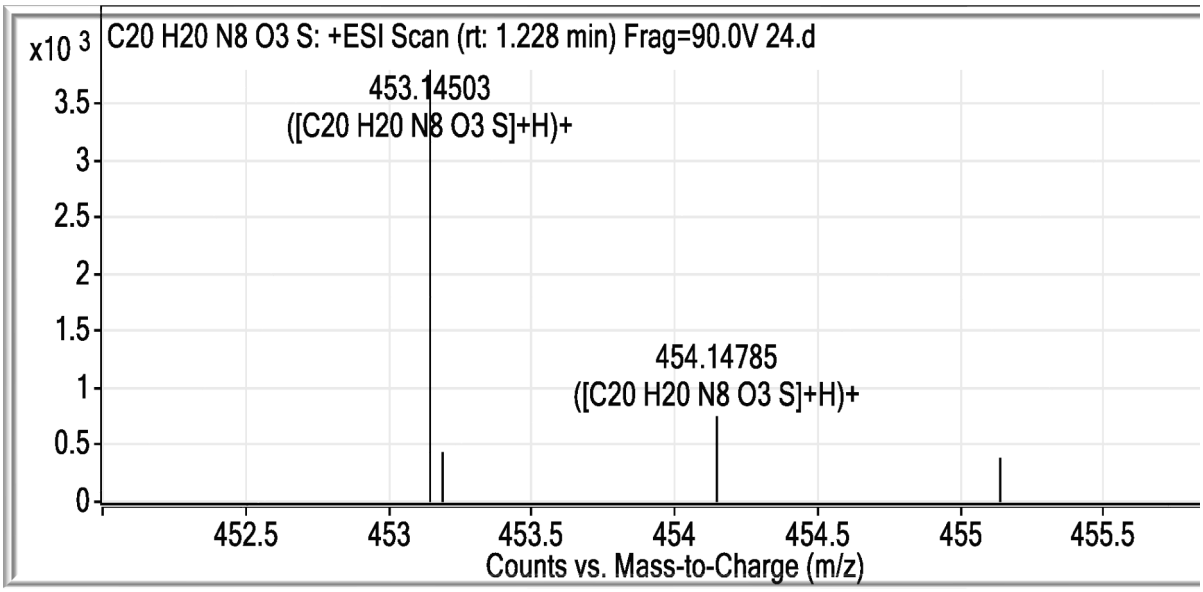

Fig. S5. Mass spectrum of compound **7a** (4-[5-methyl-4-(1-{[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

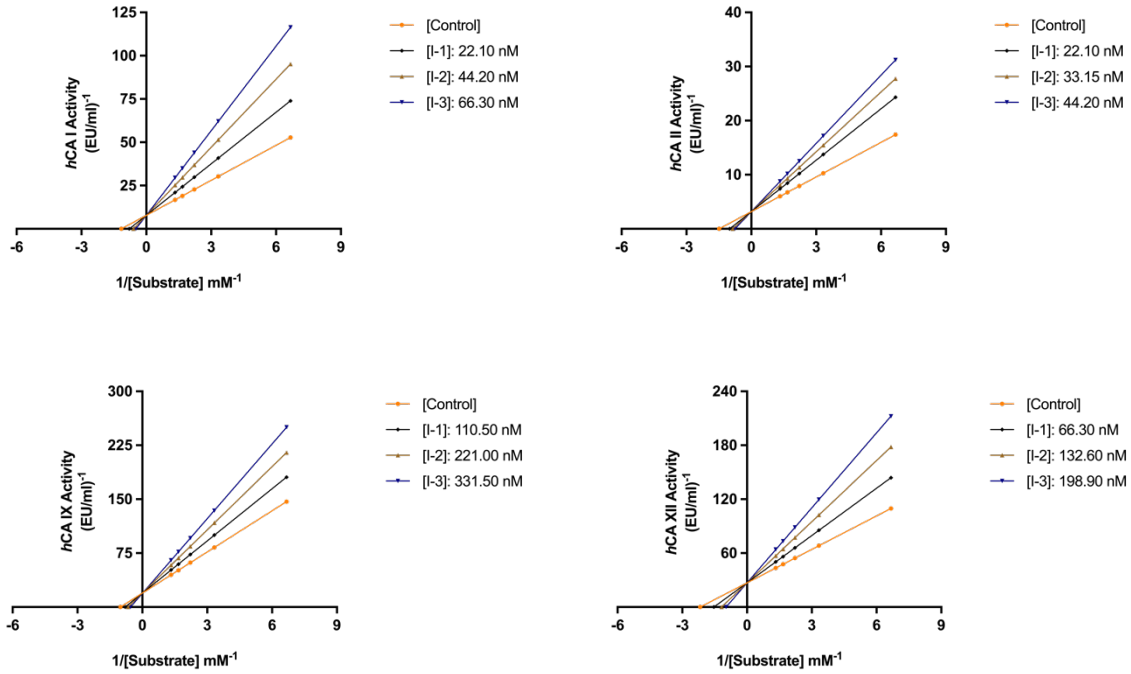

Fig. S6. Lineweaver-Burk plots of compound **7a** (4-[5-methyl-4-(1-{[(1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

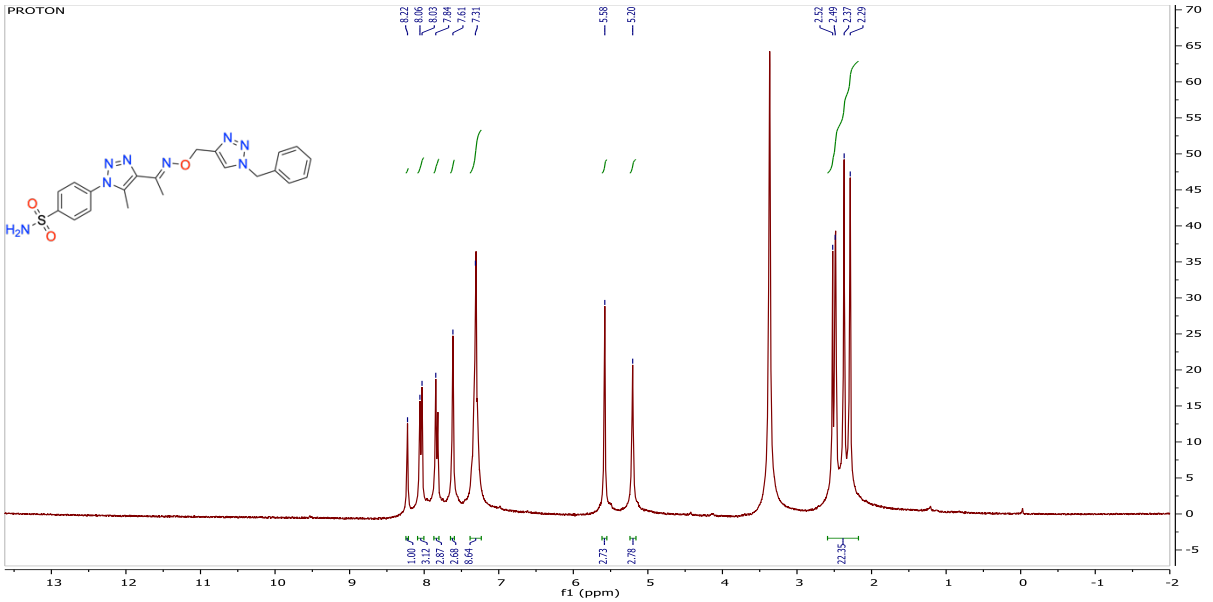

Fig. S7. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7b** (4-[4-(1-{[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

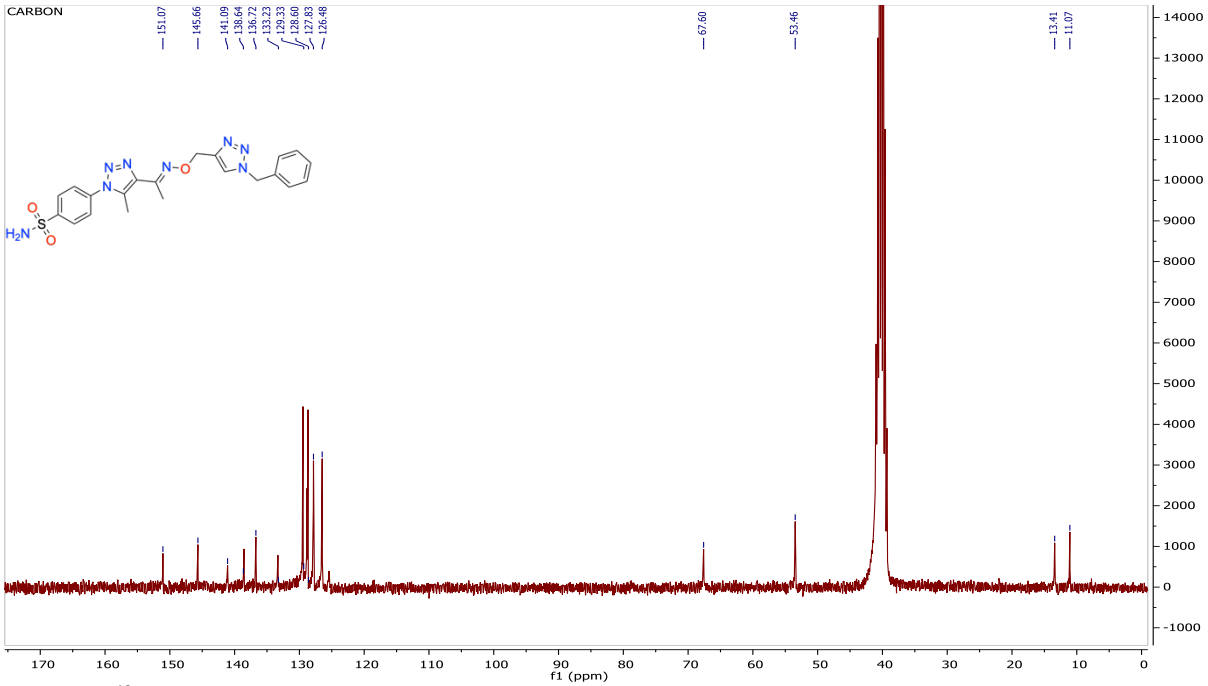

Fig. S8. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7b** (4-[4-(1-{[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

Fig. S9. IR spectrum of compound **7b** (4-[4-(1-{[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

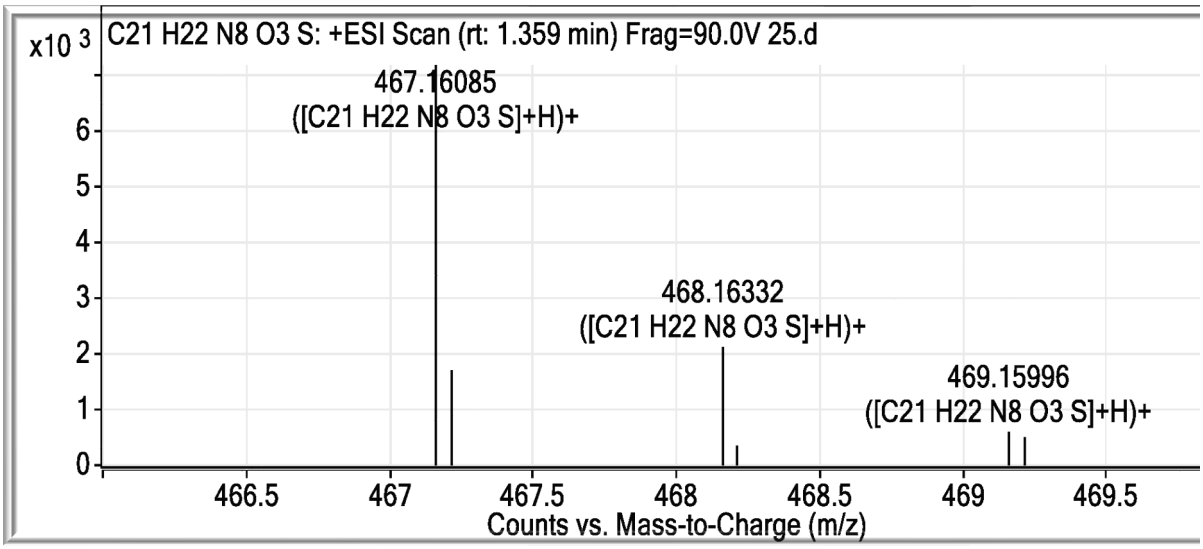

Fig. S10. Mass spectrum of compound **7b** (4-[4-(1-{[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

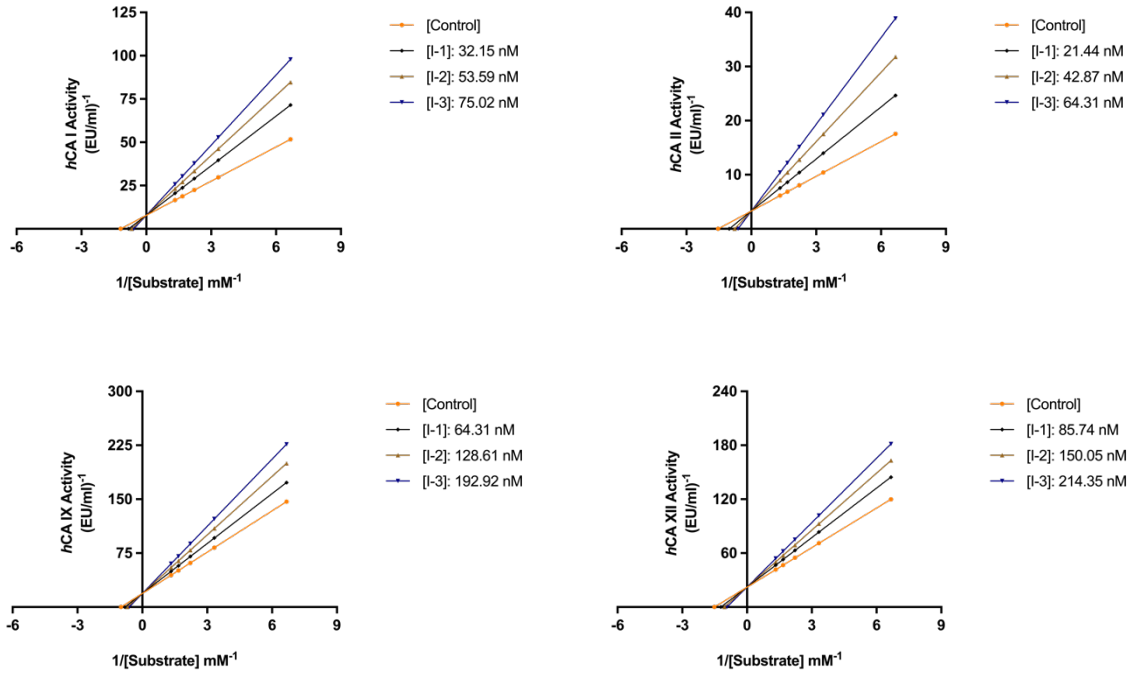

Fig. S11. Lineweaver-Burk plots of compound **7b** (4-[4-(1-{[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]imino}ethyl)-5-methyl-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide).

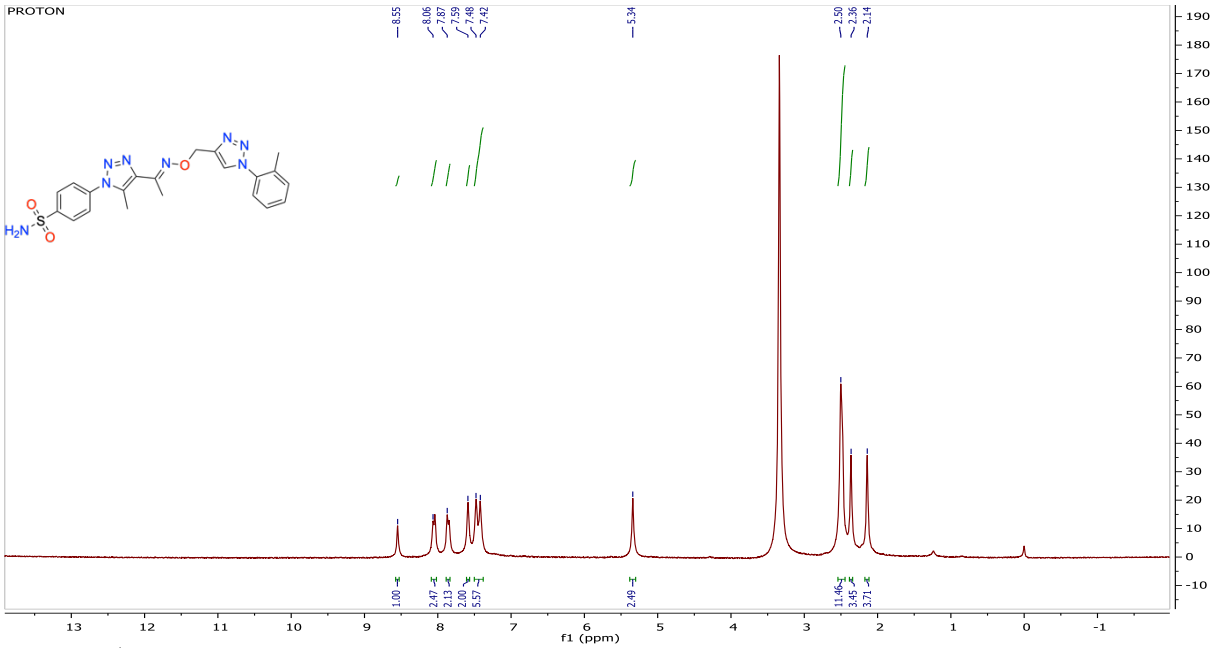

Fig. S12. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7c** ((*E*)-4-{5-methyl-4-[1-({[1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

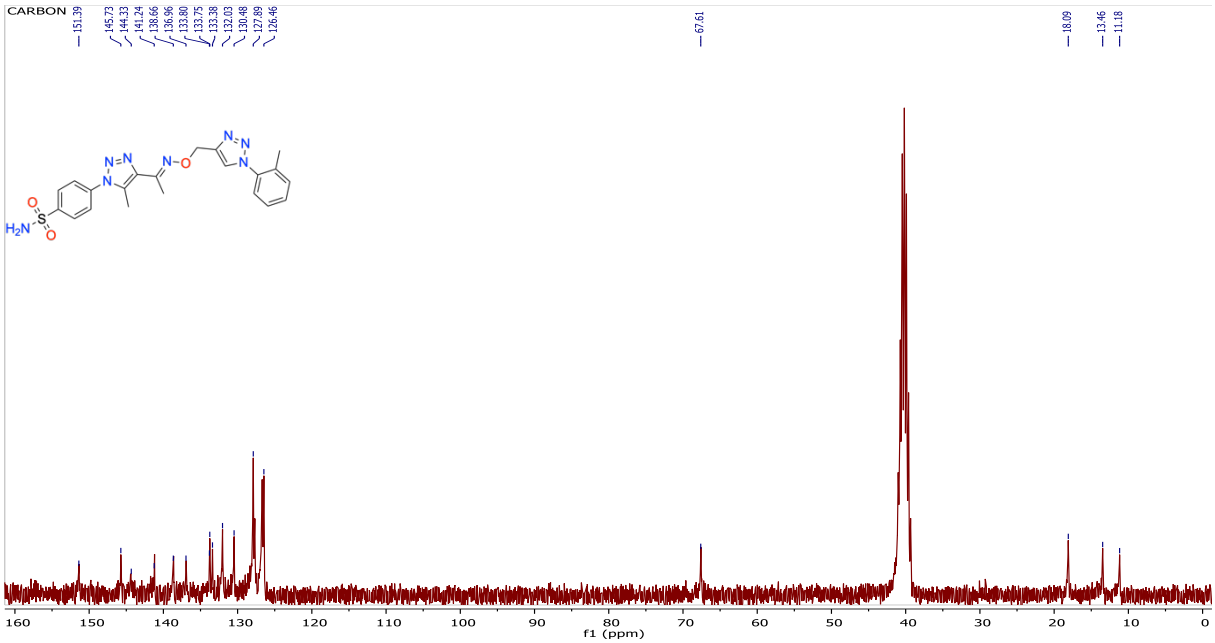

Fig. S13. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7c** ((*E*)-4-{5-methyl-4-[1-({[1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

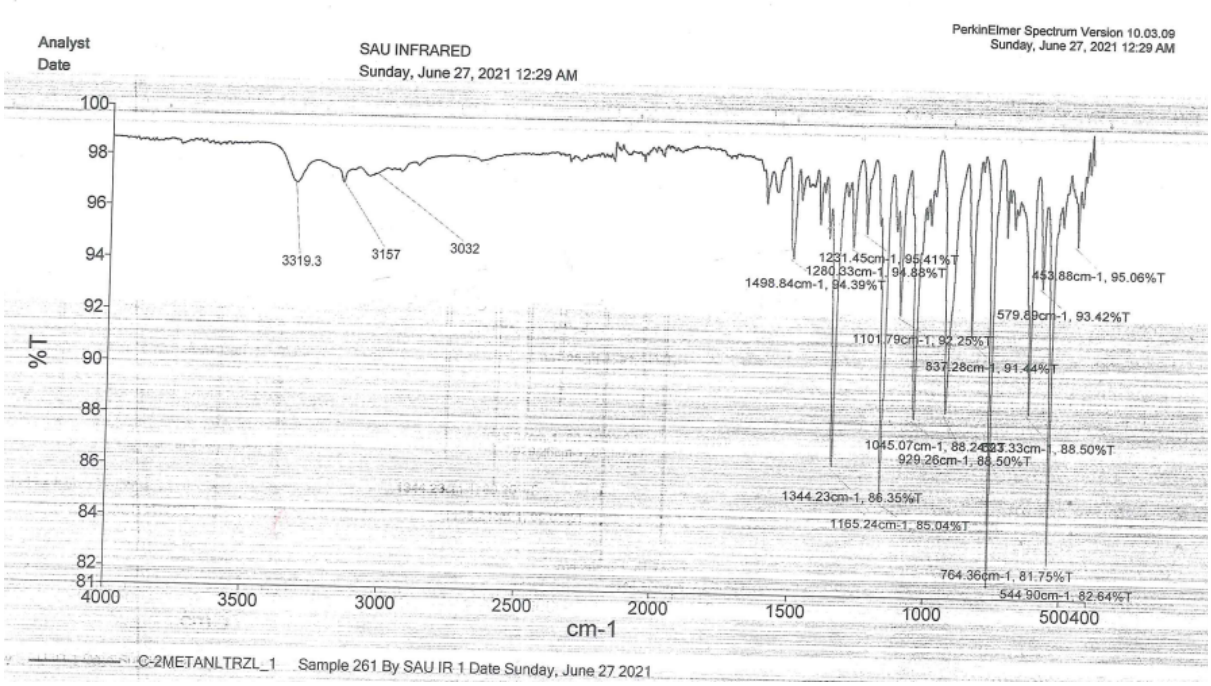

Fig. S14. IR spectrum of compound **7c** ((*E*)-4-{5-methyl-4-[1-({[1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

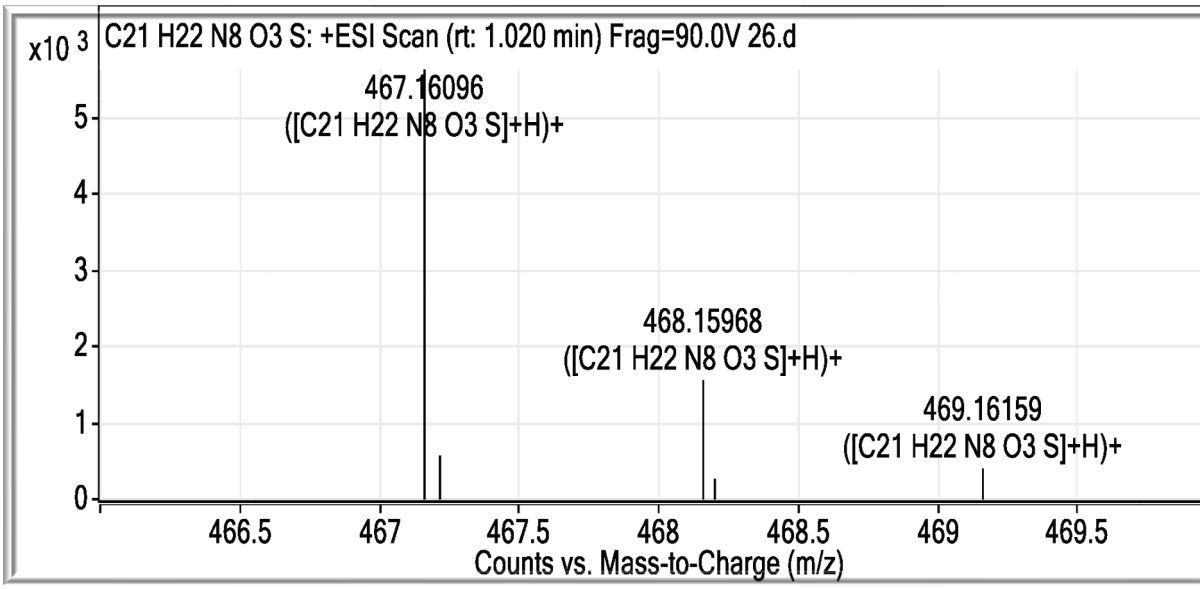

Fig. S15. Mass spectrum of compound **7c** ((*E*)-4-{5-methyl-4-[1-({[1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

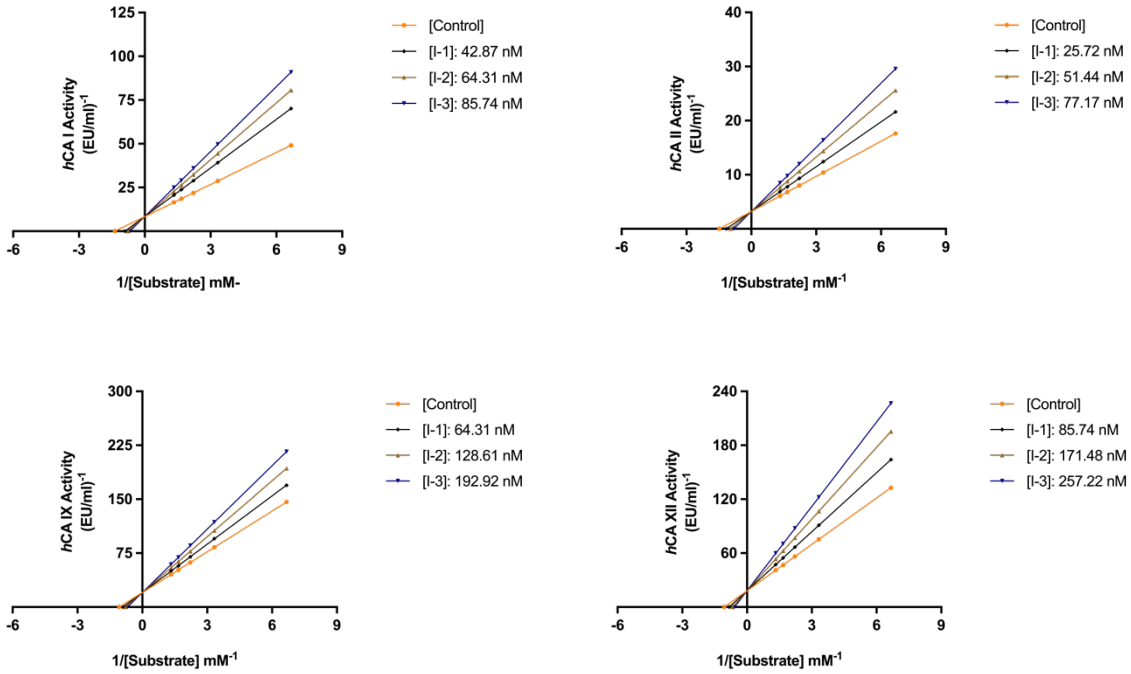

Fig. S16. Lineweaver-Burk plots of compound **7c** ((*E*)-4-{5-methyl-4-[1-({[1-(o-tolyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

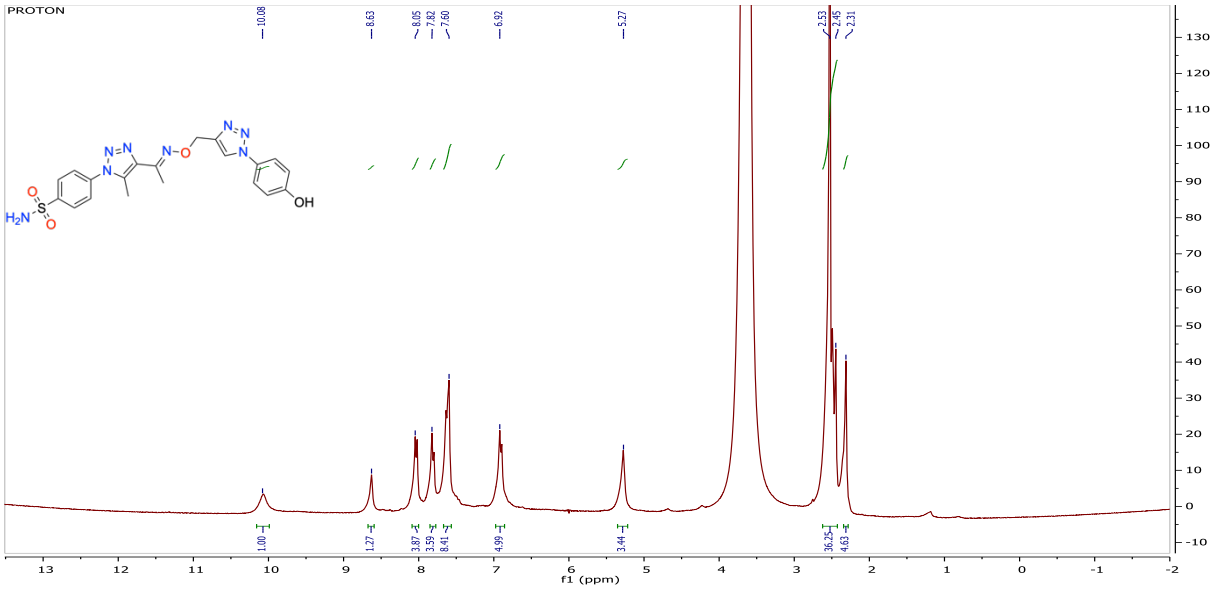

Fig. S17. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7d** (4-{4-[1-{[(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

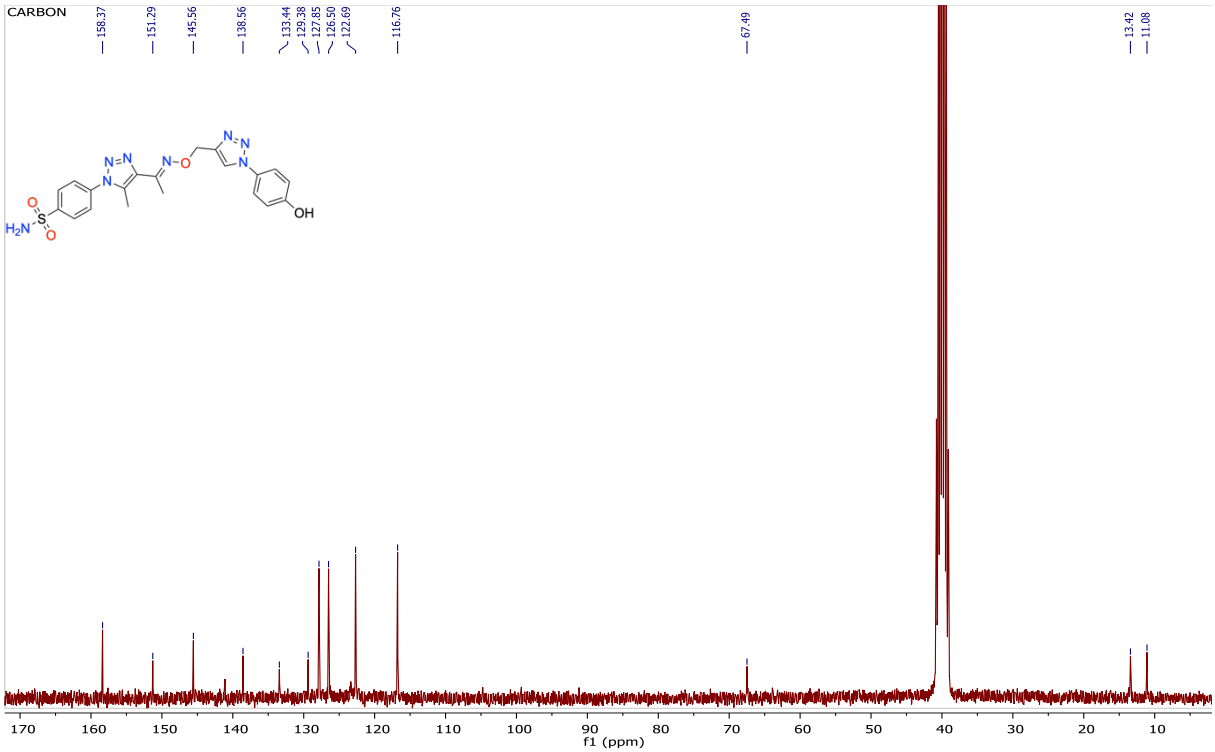

Fig. S18. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7d** (4-{4-[1-{[(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

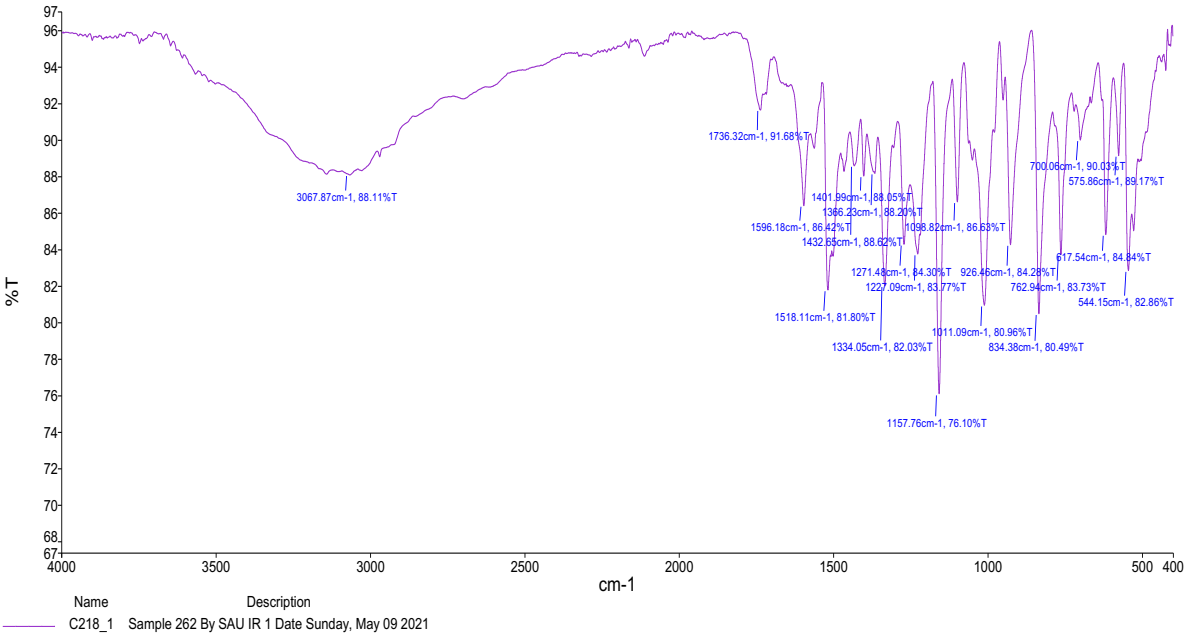

Fig. S19. IR spectrum of compound **7d** (4-{4-[1-{[(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

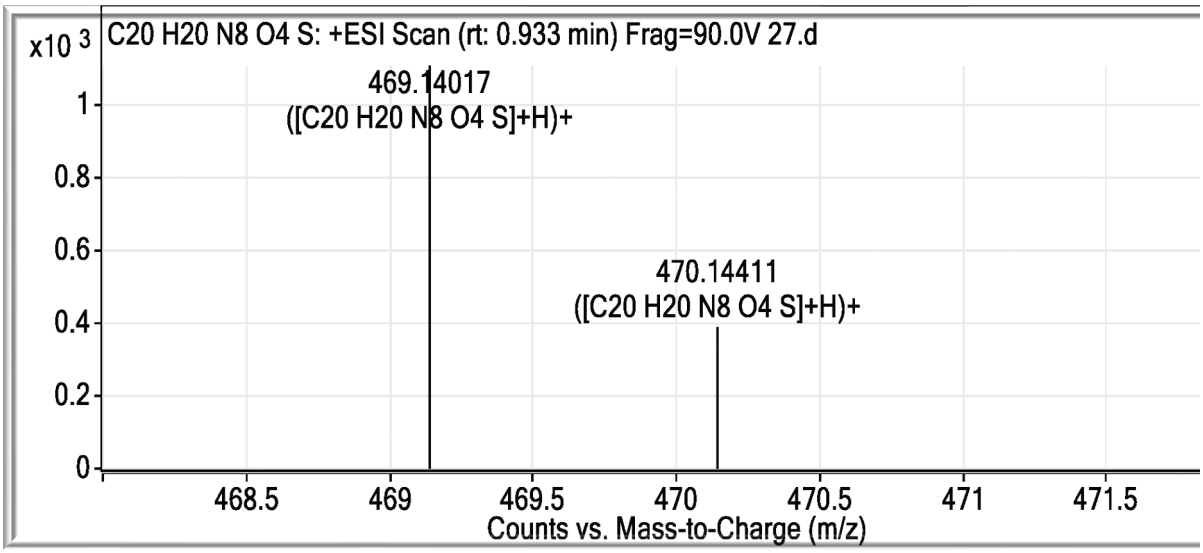

Fig. S20. Mass spectrum of compound **7d** (4-{4-[1-{[(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

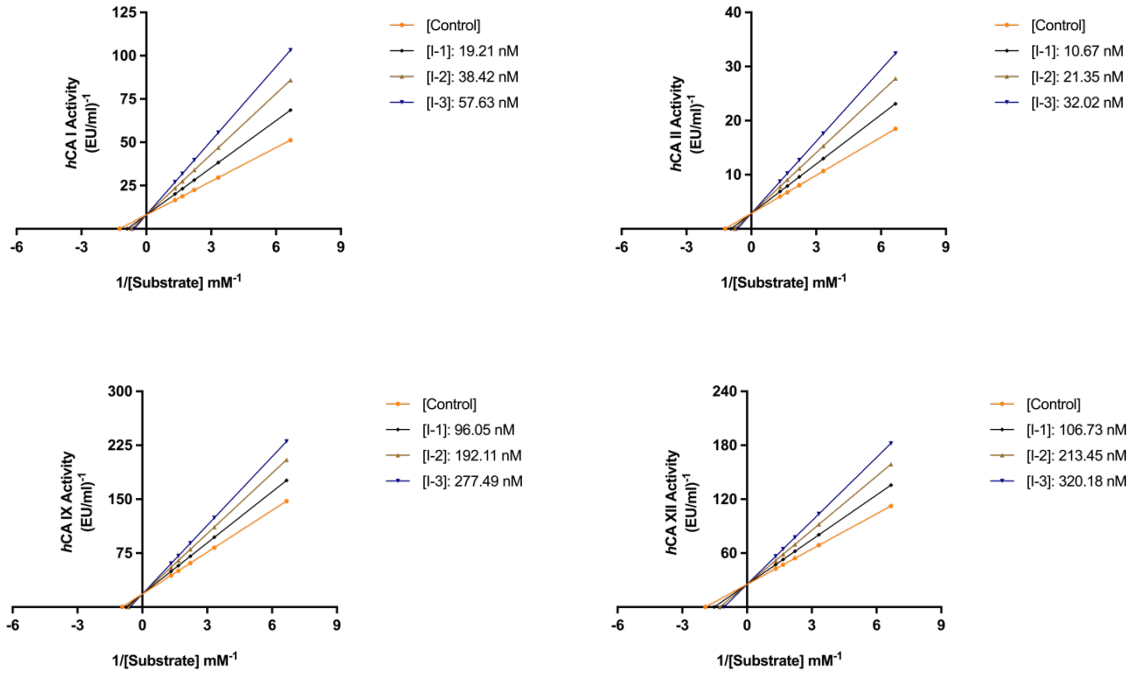

Fig. S21. Lineweaver-Burk plots of compound **7d** (4-{4-[1-{[(1-(4-hydroxyphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

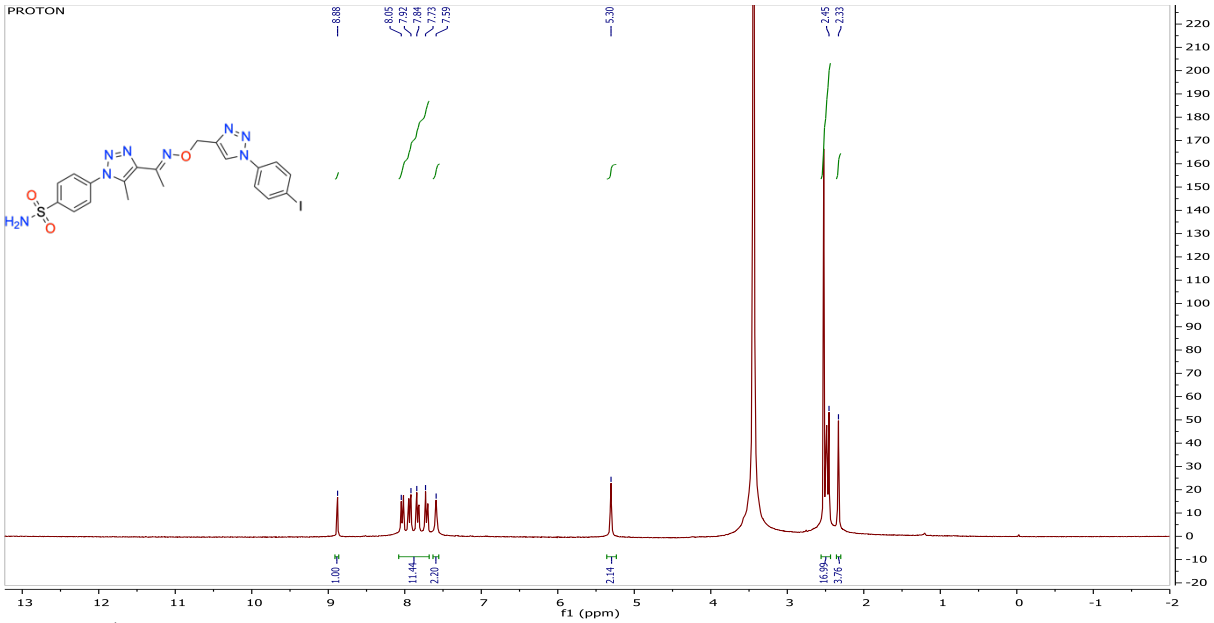

Fig. S22. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7e** (4-{4-[1-({[1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

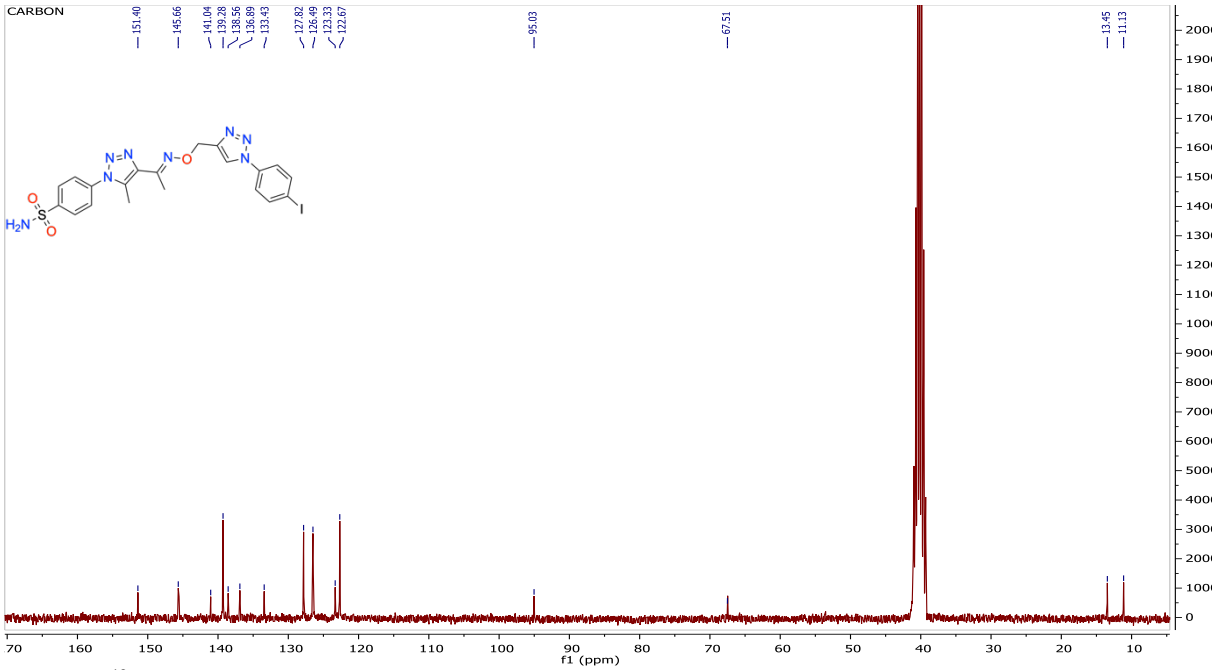

Fig. S23. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7e** (4-{4-[1-({[1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

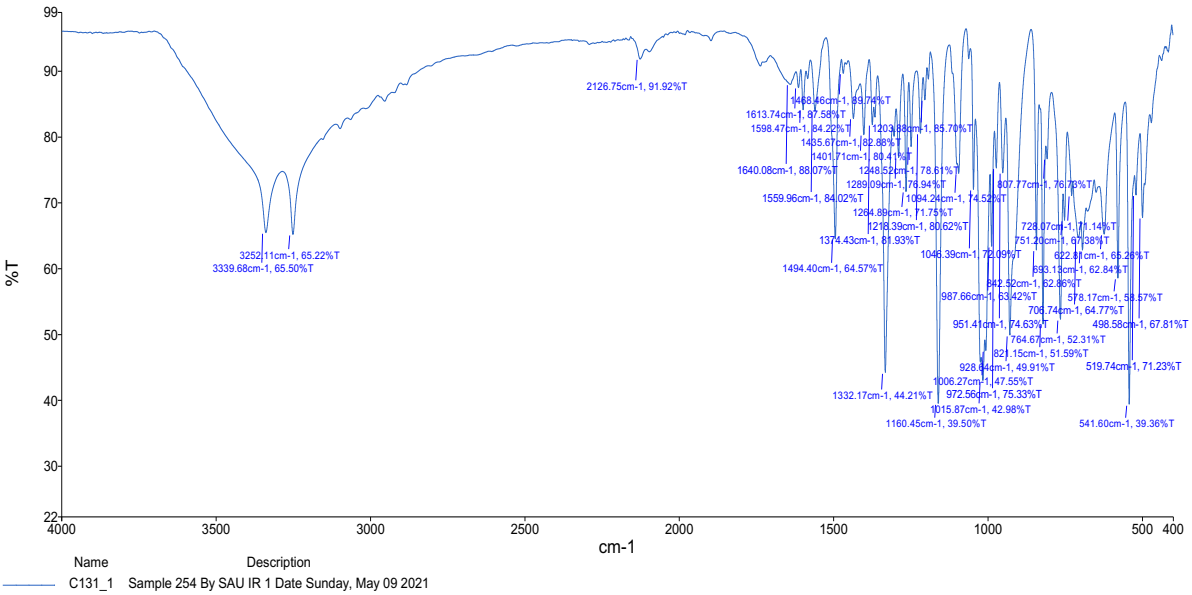

Fig. S24. IR spectrum of compound **7e** (4-{4-[1-({[1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

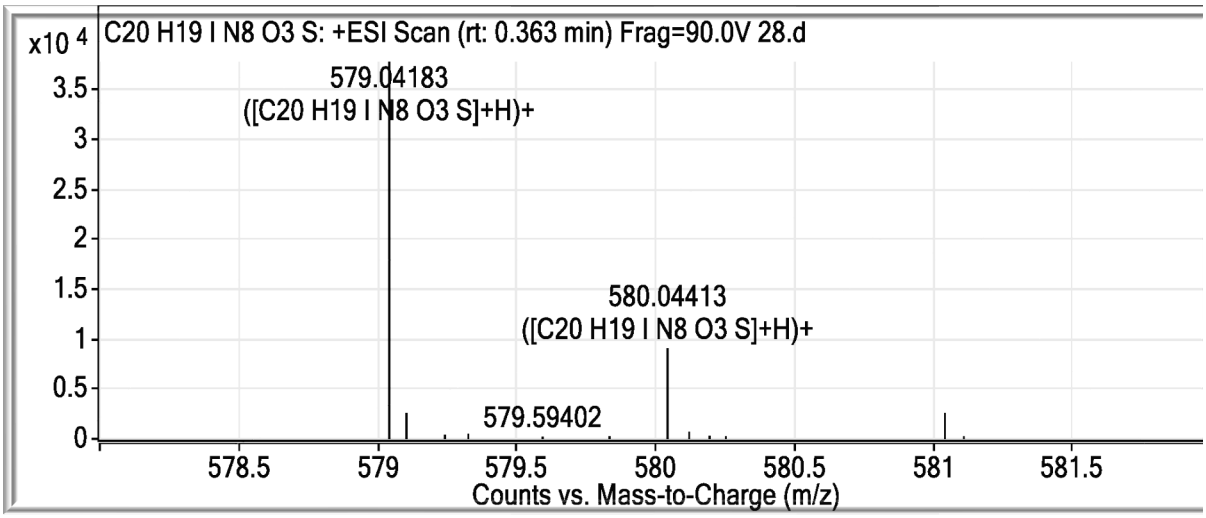

Fig. S25. Mass spectrum of compound **7e** (4-{4-[1-({[1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

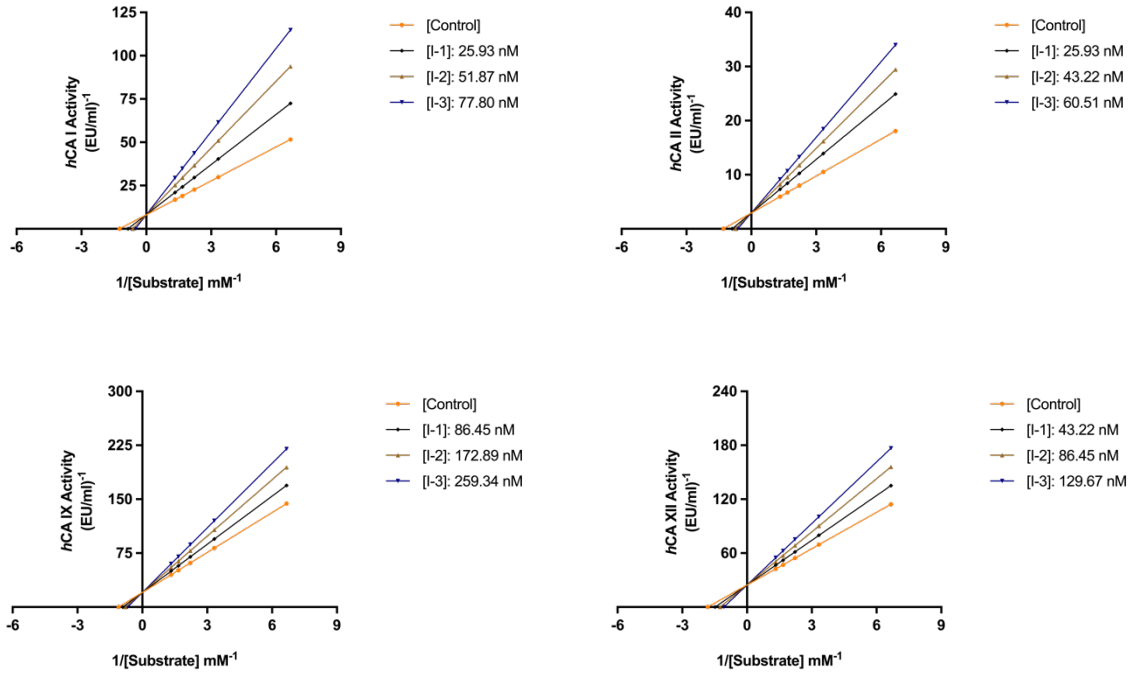

Fig. S26. Lineweaver-Burk plots of compound **7e** (4-{4-[1-({[1-(4-iodophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

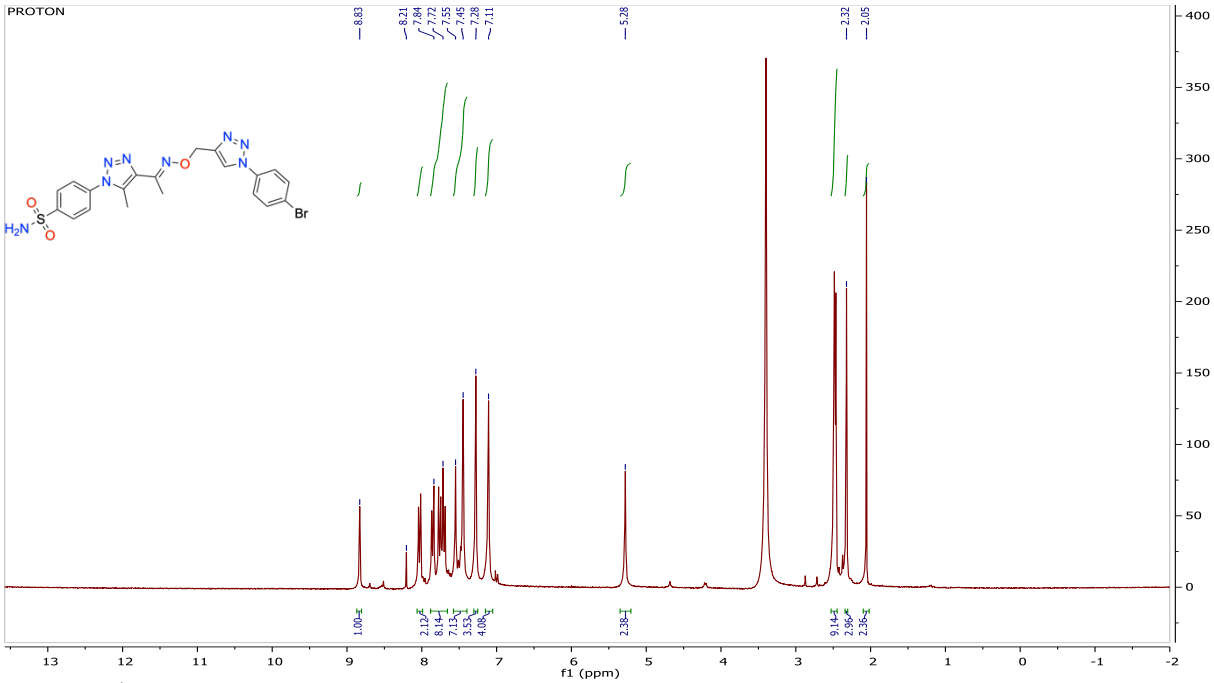

Fig. S27. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7f** ((*E*)-4-{4-[1-({[1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

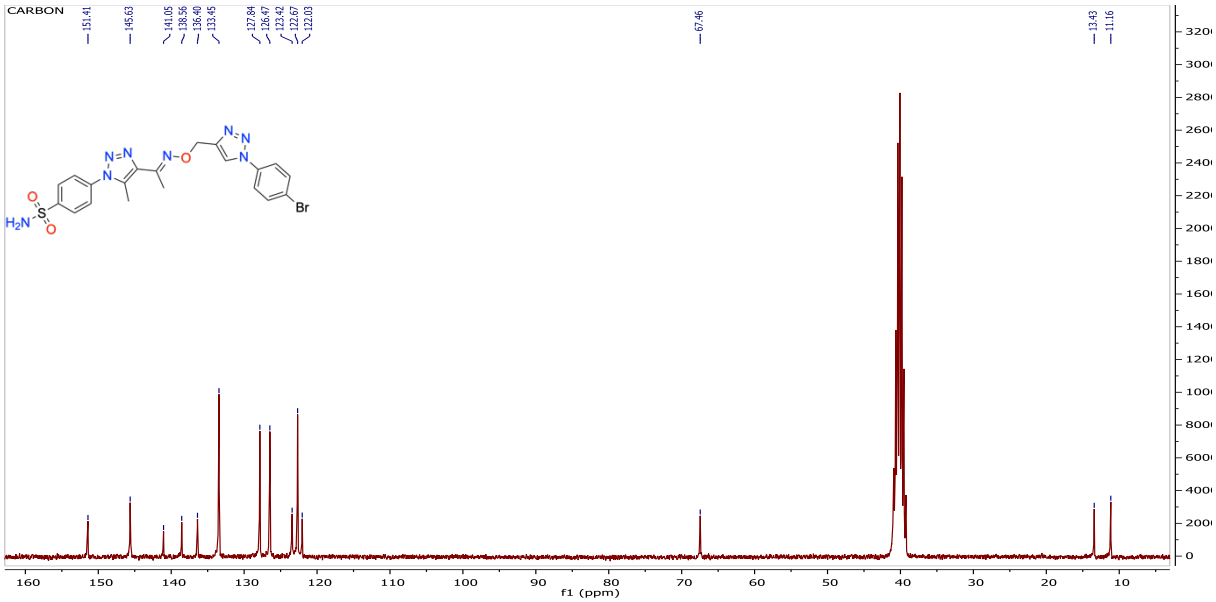

Fig. S28. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7f** ((*E*)-4-{4-[1-({[1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

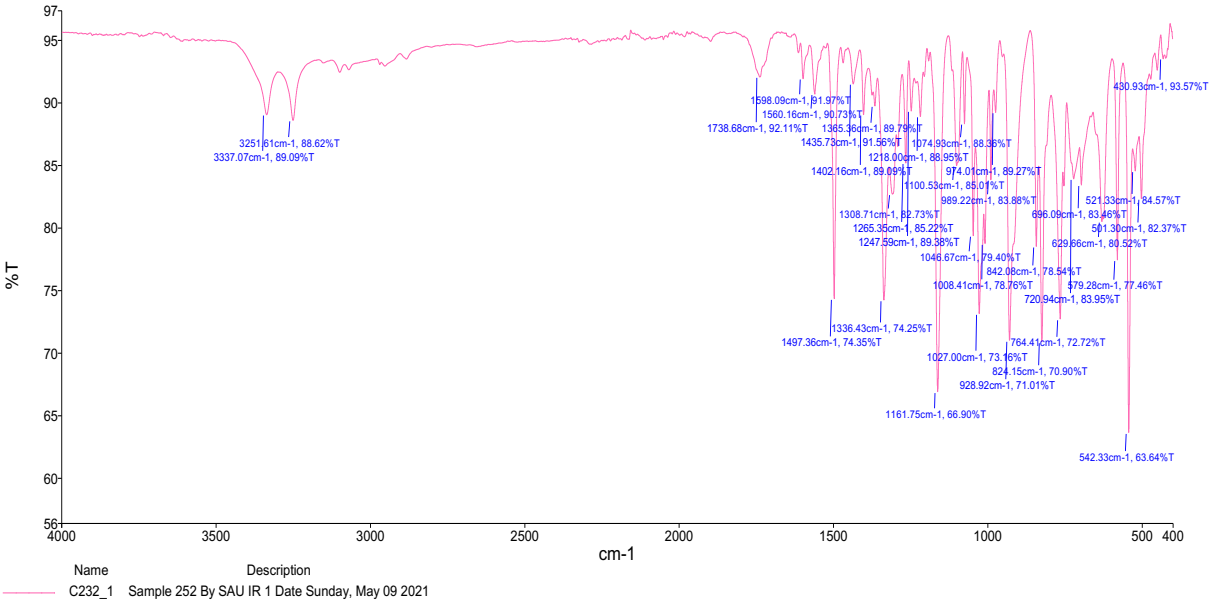

Fig. S29. IR spectrum of compound **7f** ((*E*)-4-{4-[1-({[1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

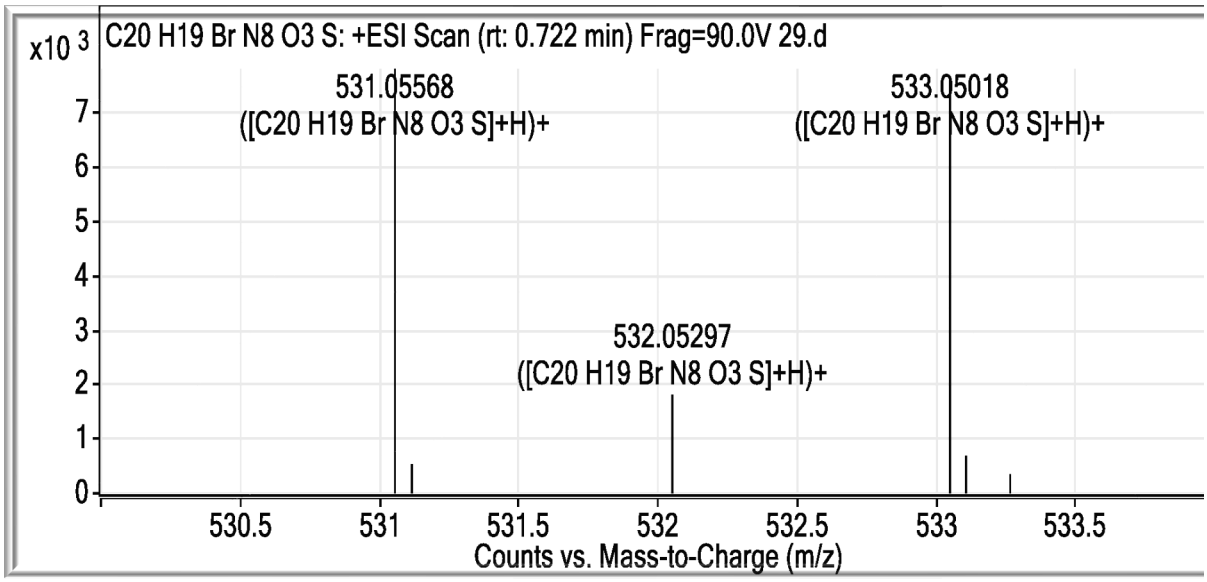

Fig. S30. Mass spectrum of compound **7f** ((*E*)-4-{4-[1-({[1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

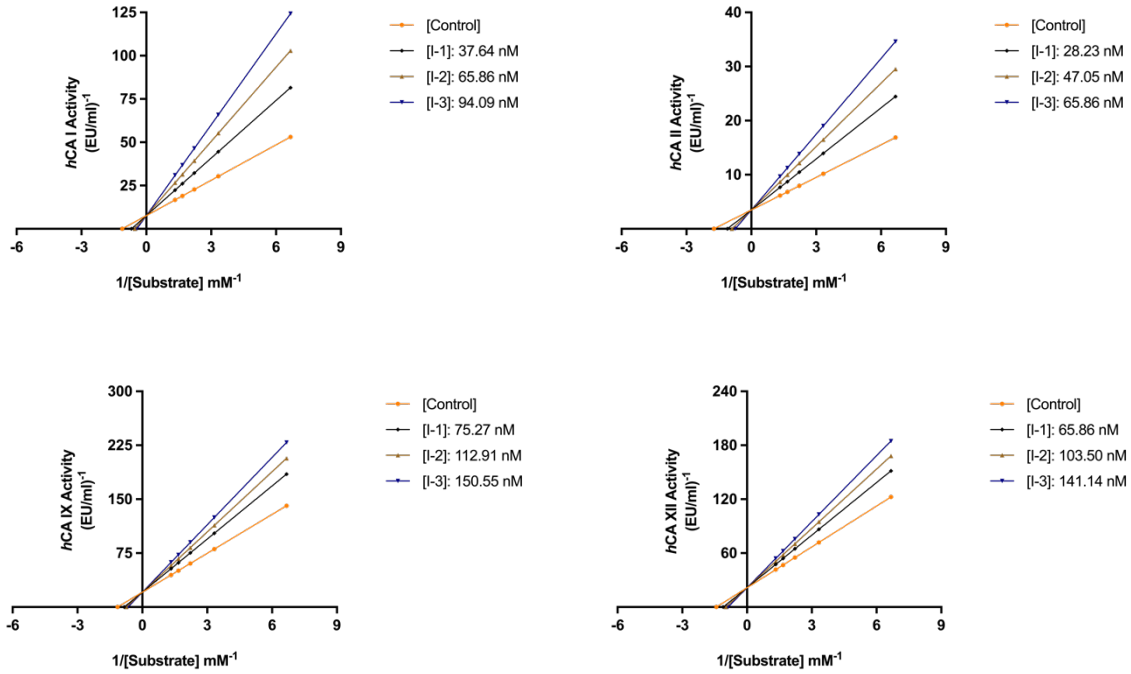

Fig. S31. Lineweaver-Burk plots of compound **7f** ((*E*)-4-{4-[1-({[1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

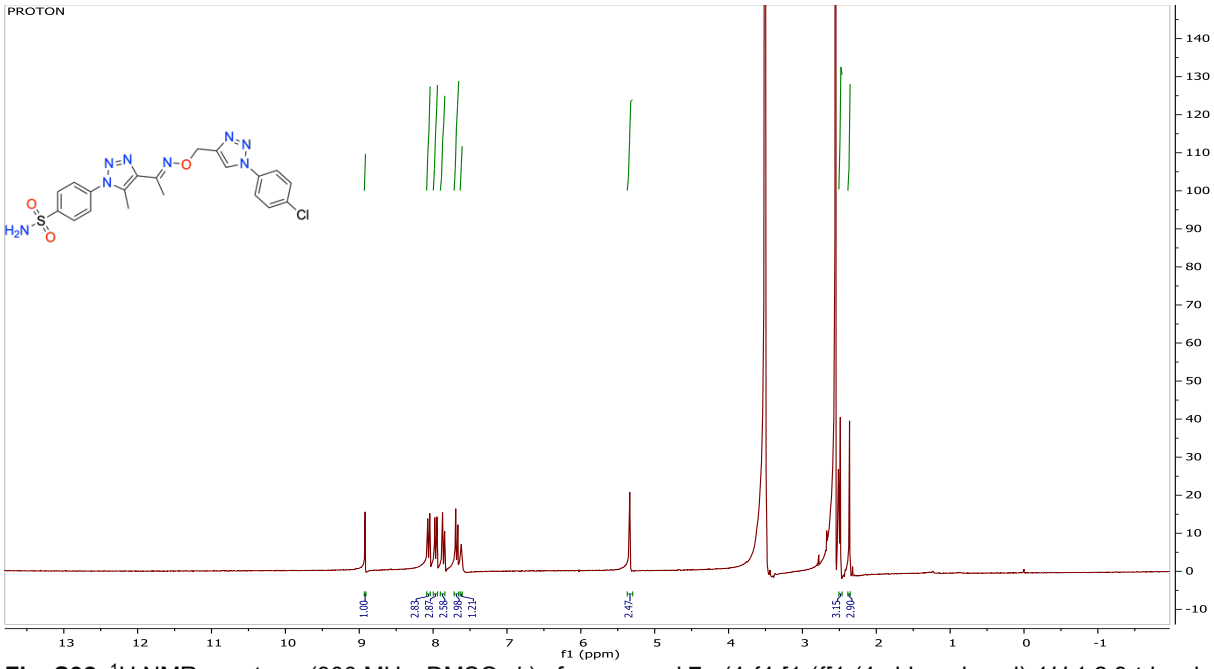

Fig. S32. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7g** (4-{4-[1-({[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

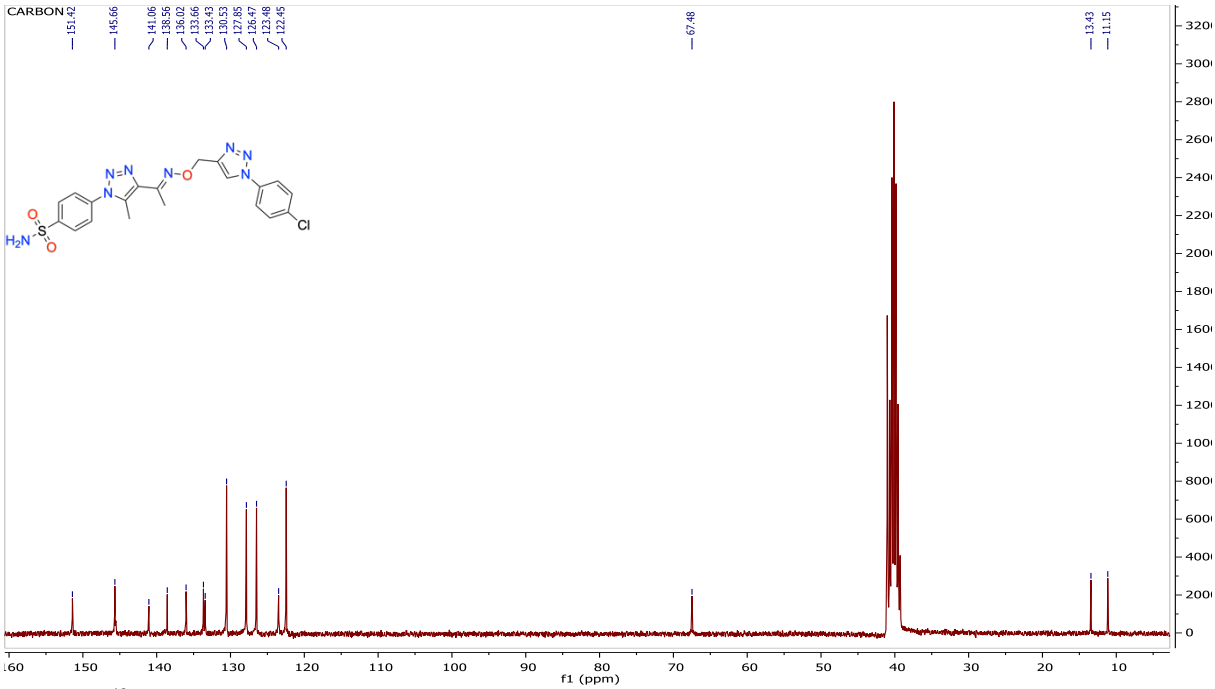

Fig. S33. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7g** (4-{4-[1-({[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

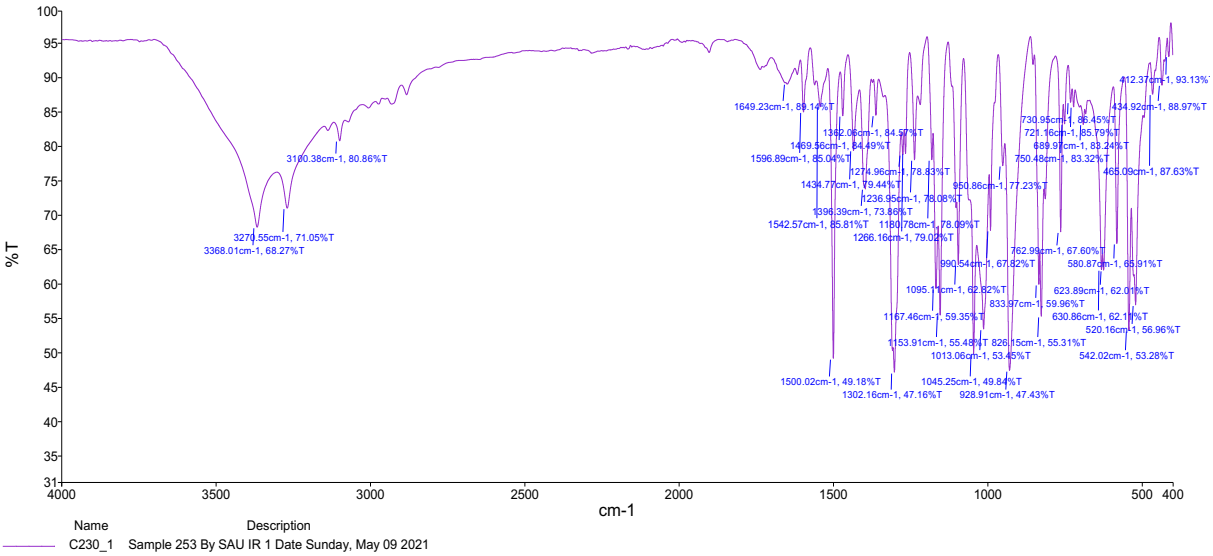

Fig. S34. IR spectrum of compound **7g** (4-{4-[1-({[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

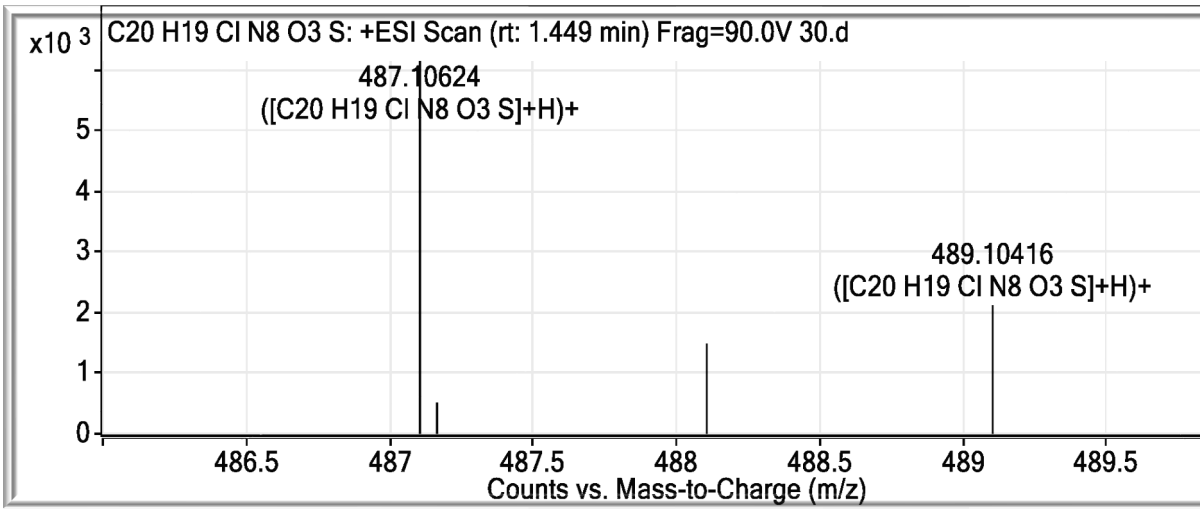

Fig. S35. Mass spectrum of compound **7g** (4-{4-[1-({[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

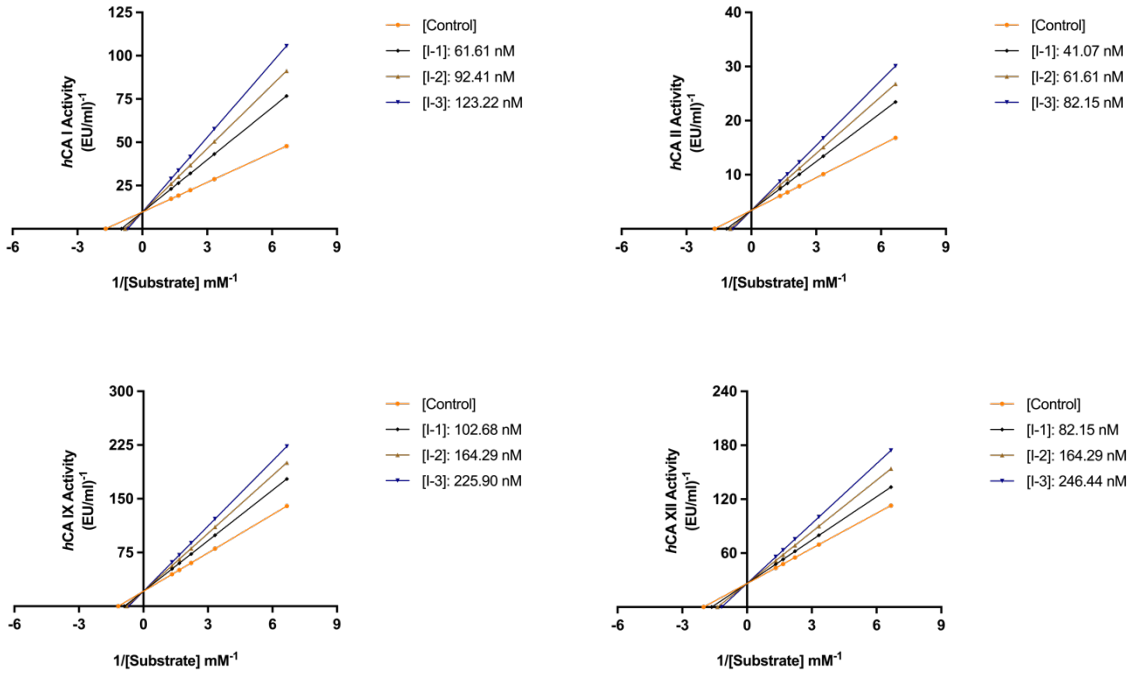

Fig. S36. Lineweaver-Burk plots of compound **7g** (4-{4-[1-({[1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

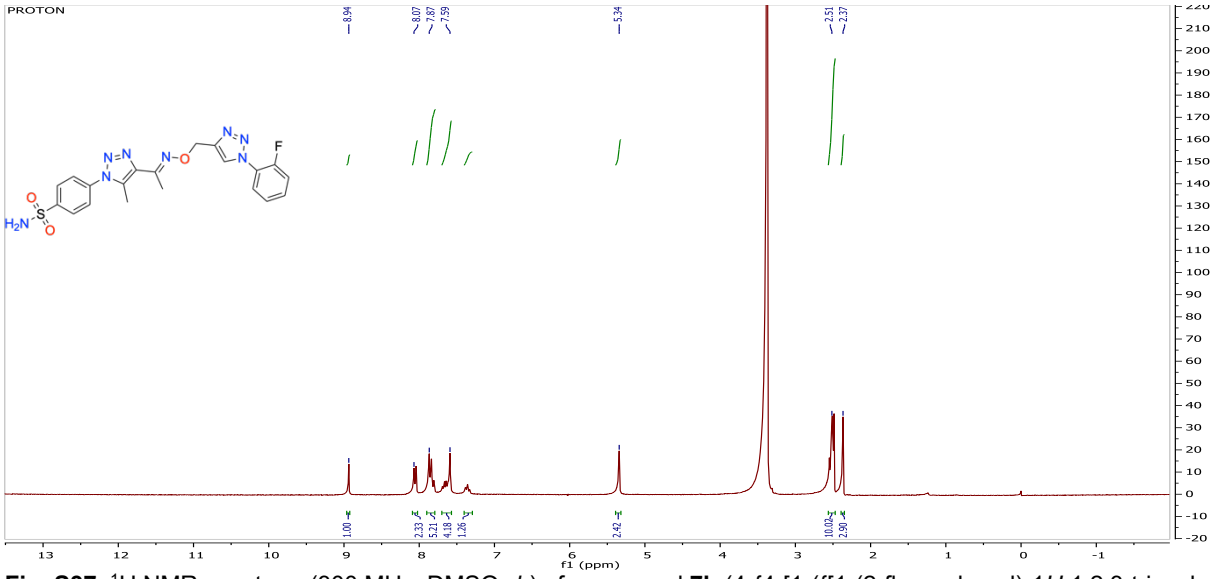

Fig. S37. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7h** (4-{4-[1-({[1-(2-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

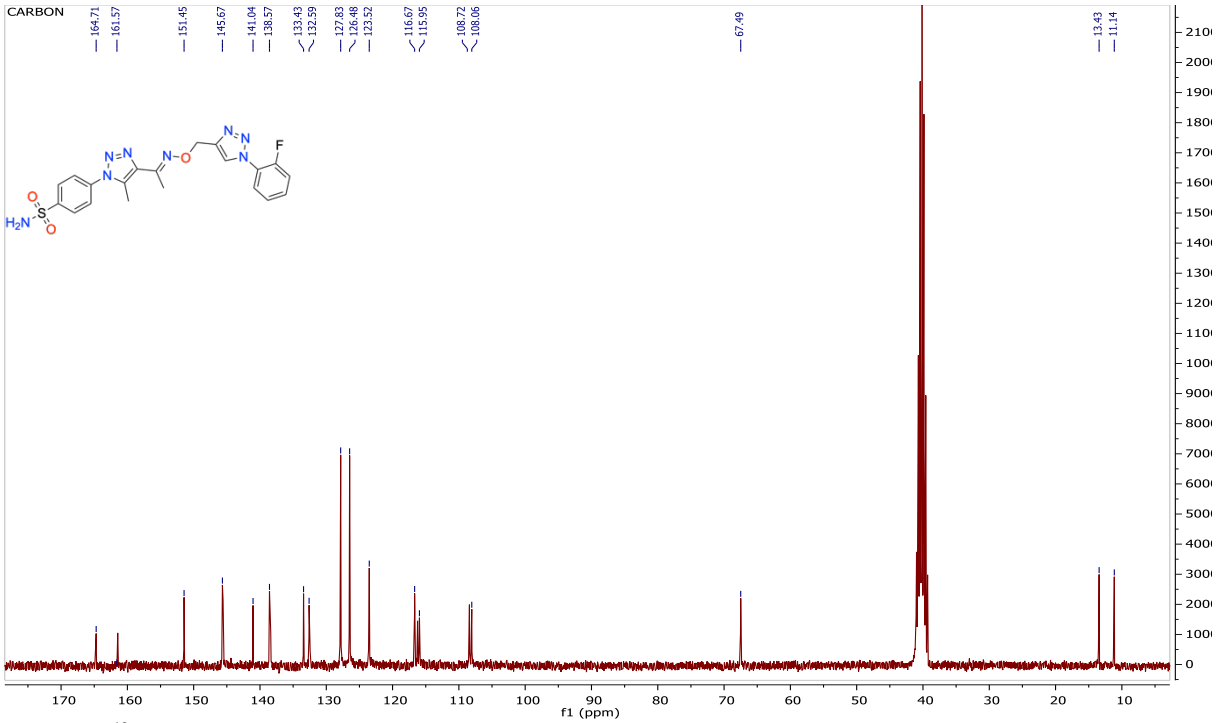

Fig. S38. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7h** (4-{4-[1-({[1-(2-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

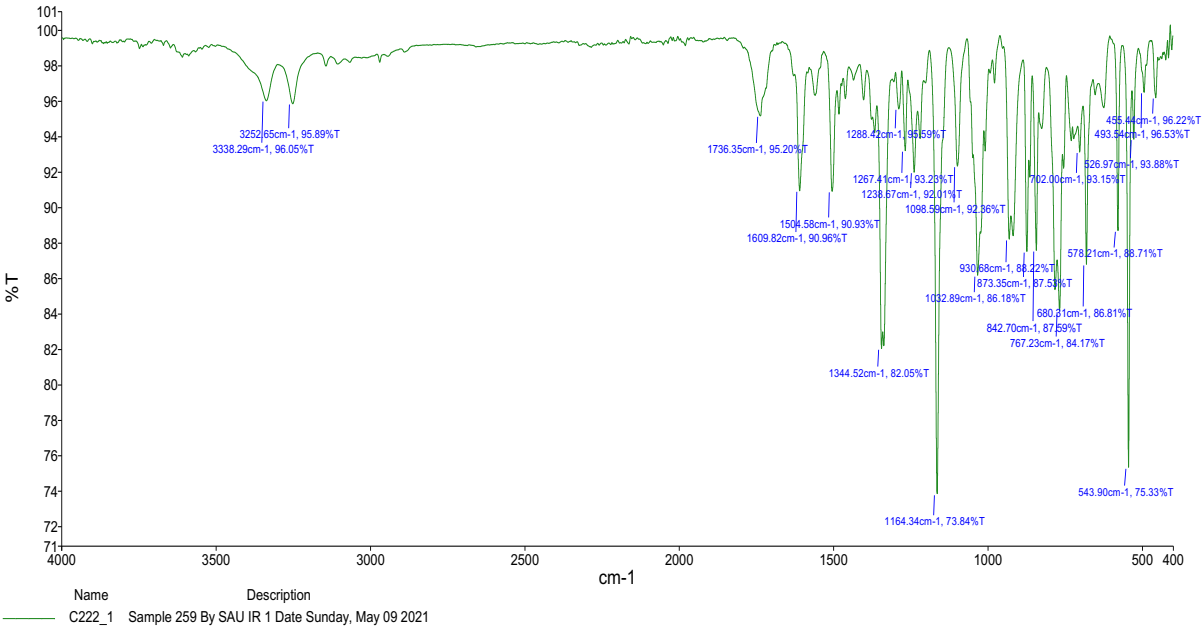

Fig. S39. IR spectrum of compound **7h** (4-{4-[1-({[1-(2-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

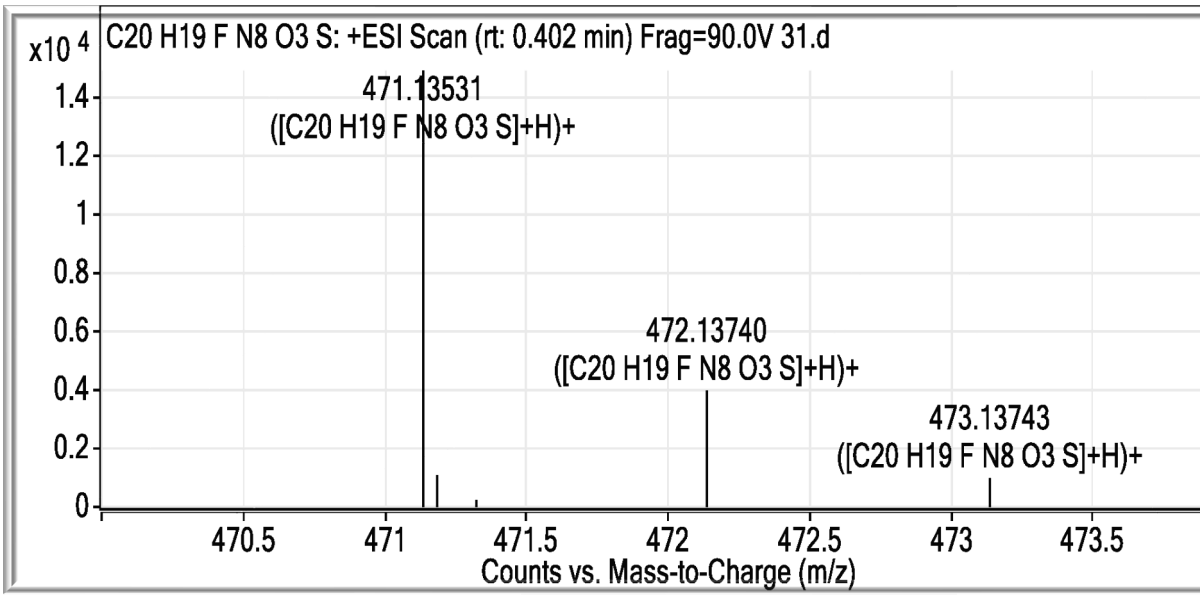

Fig. S40. Mass spectrum of compound **7h** (4-{4-[1-({[1-(2-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

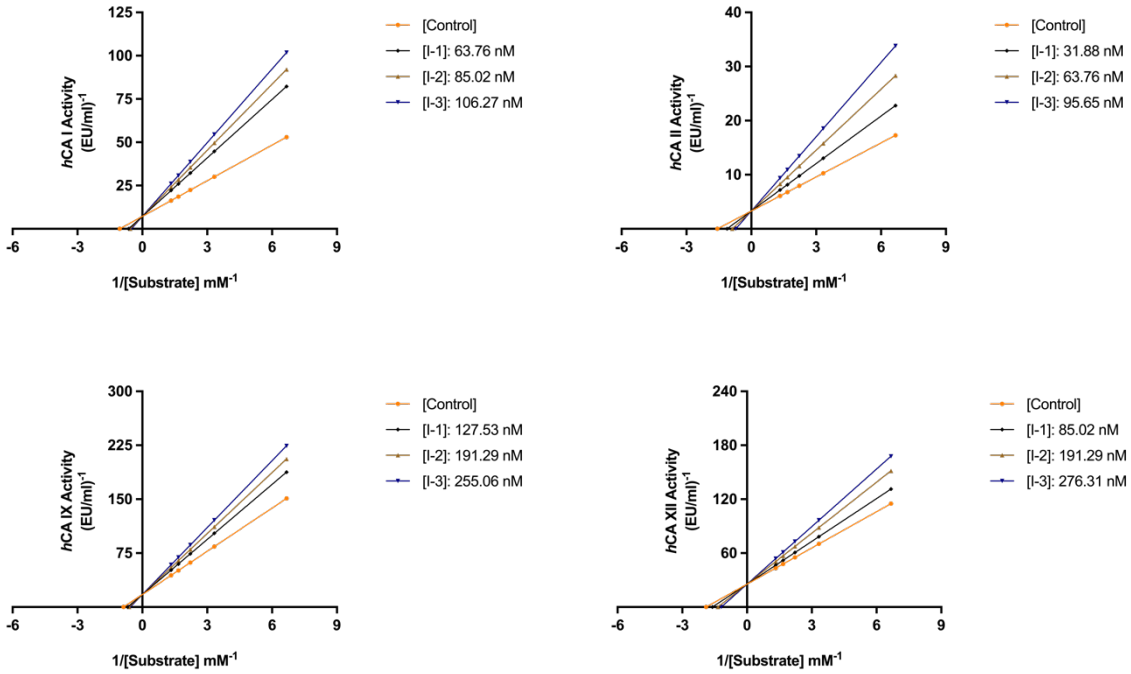

Fig. S41. Lineweaver-Burk plots of compound **7h** (4-{4-[1-({[1-(2-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

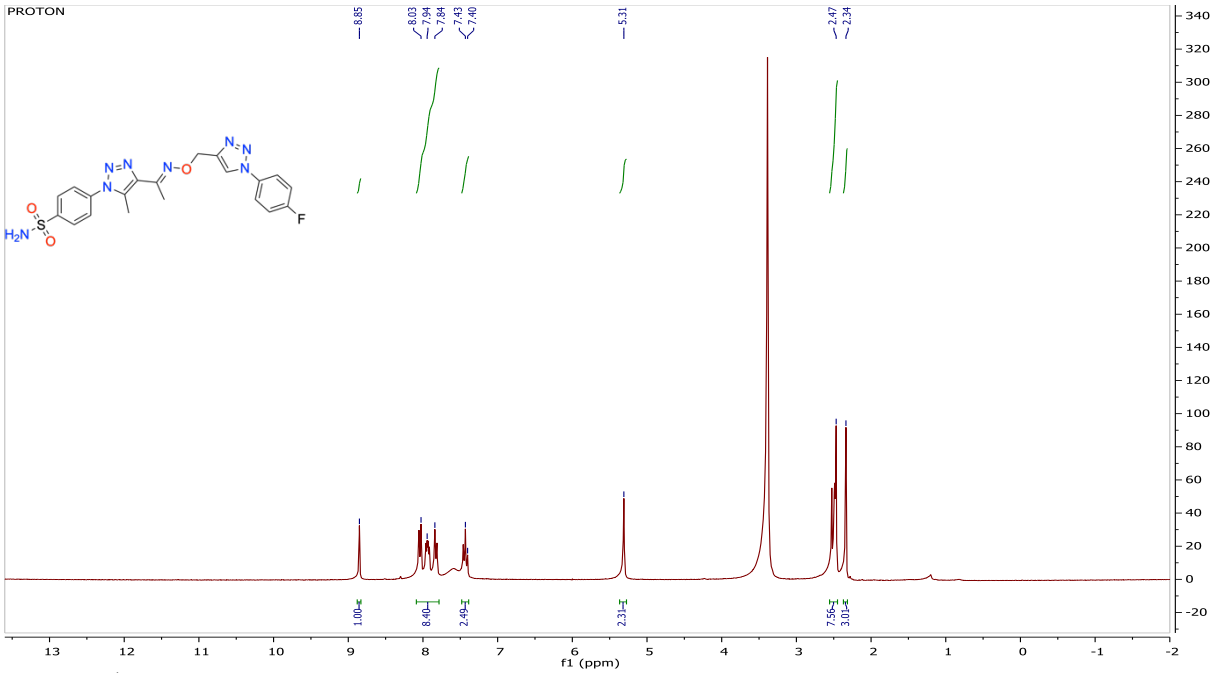

Fig. S42. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7i** (4-{4-[1-({[1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

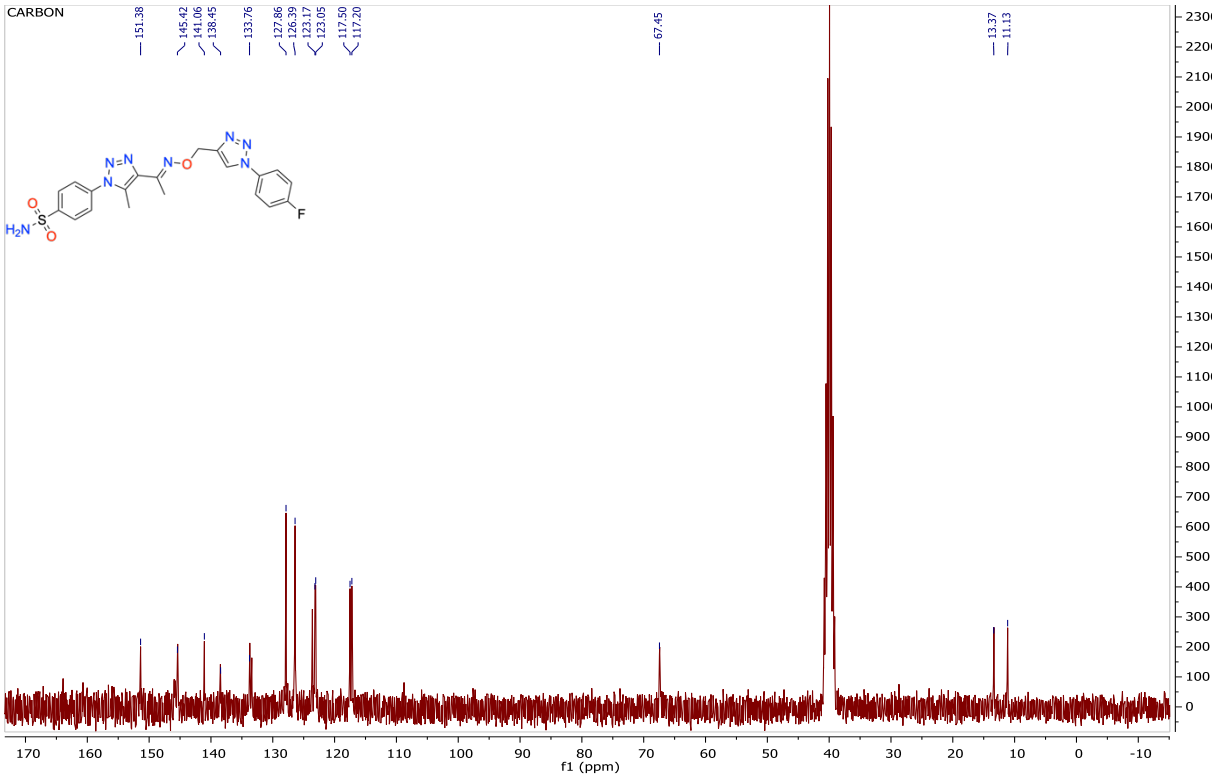

Fig. S43. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7i** (4-{4-[1-({[1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

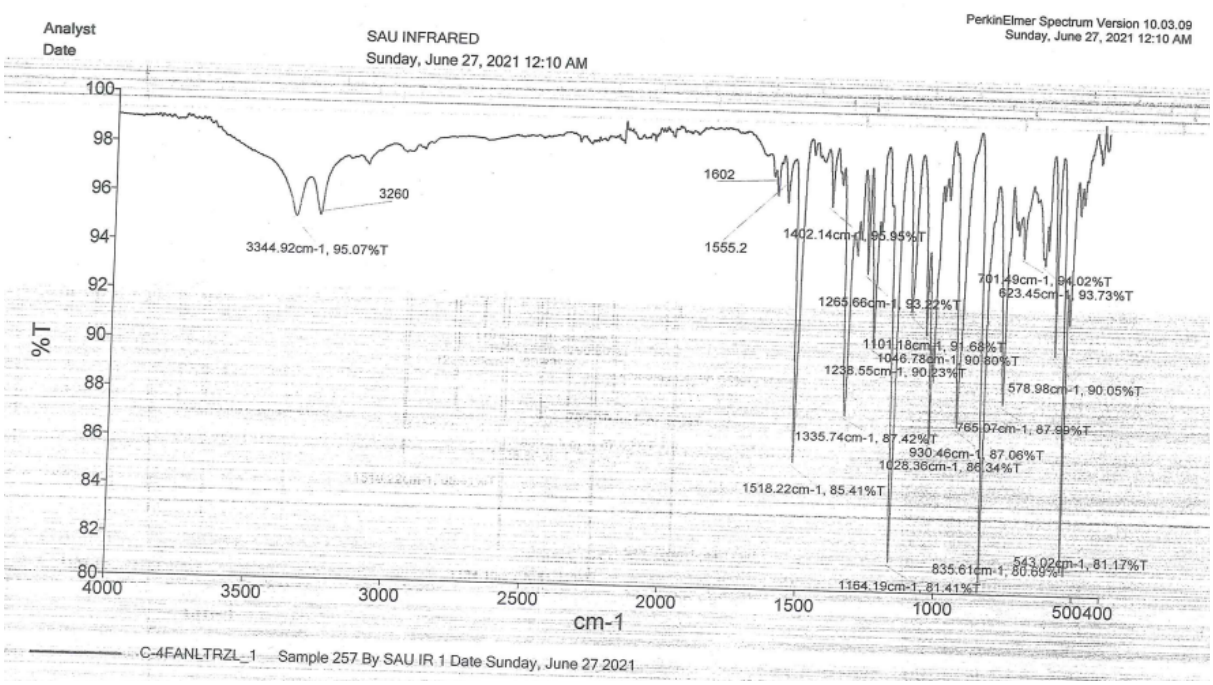

Fig. S44. IR spectrum of compound **7i** (4-{4-[1-({[1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

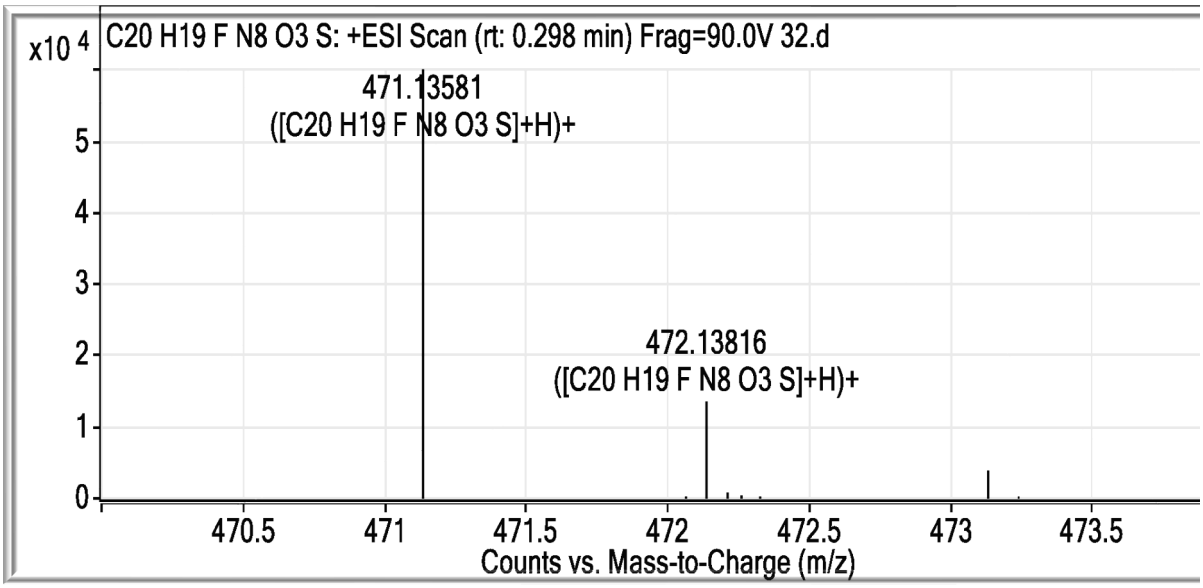

Fig. S45. Mass spectrum of compound **7i** (4-{4-[1-({[1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

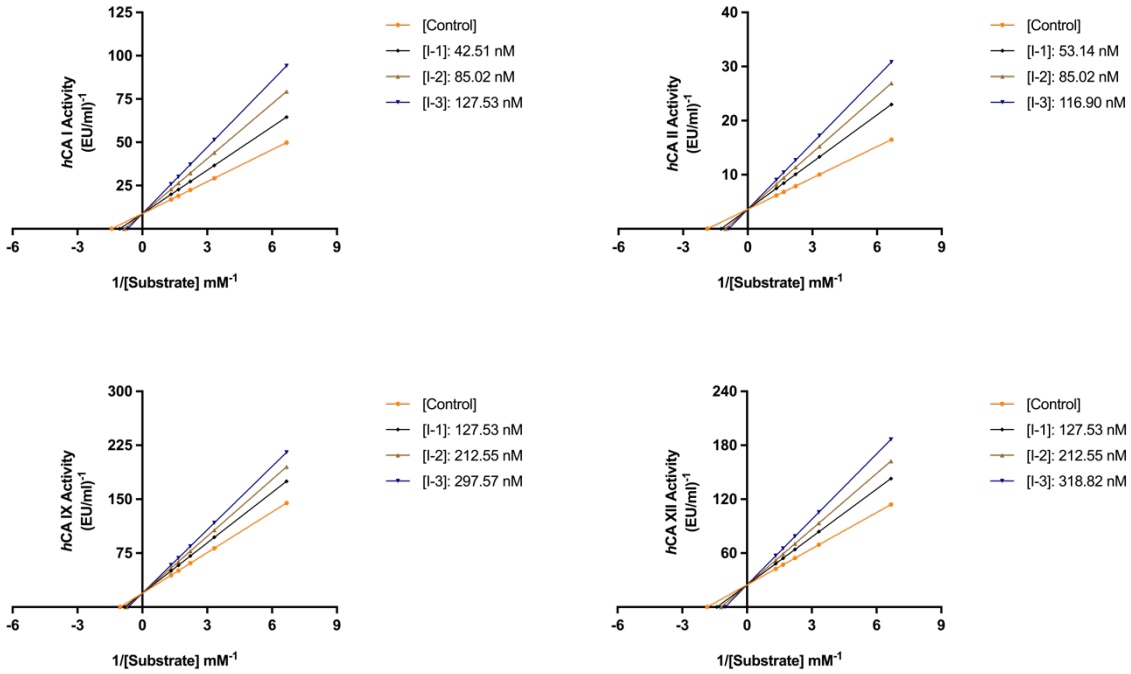

Fig. S46. Lineweaver-Burk plots of compound **7i** (4-{4-[1-({[1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

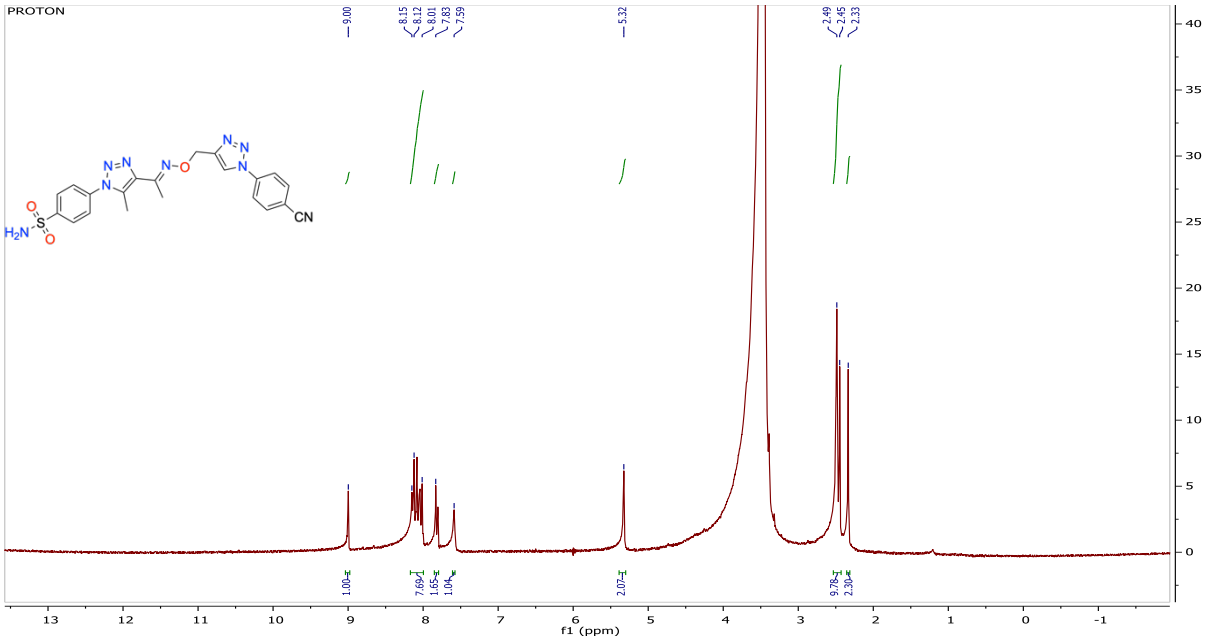

Fig. S47. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7j** (4-{4-[1-({[1-(4-cyanophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

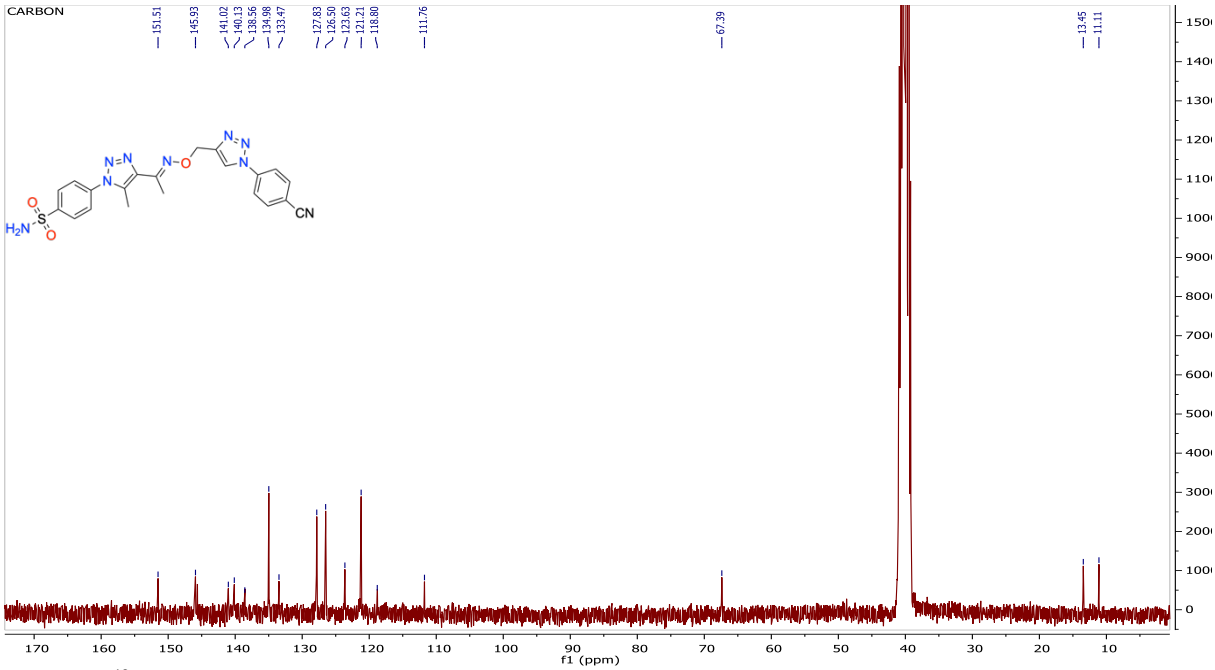

Fig. S48. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7j** (4-{4-[1-({[1-(4-cyanophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

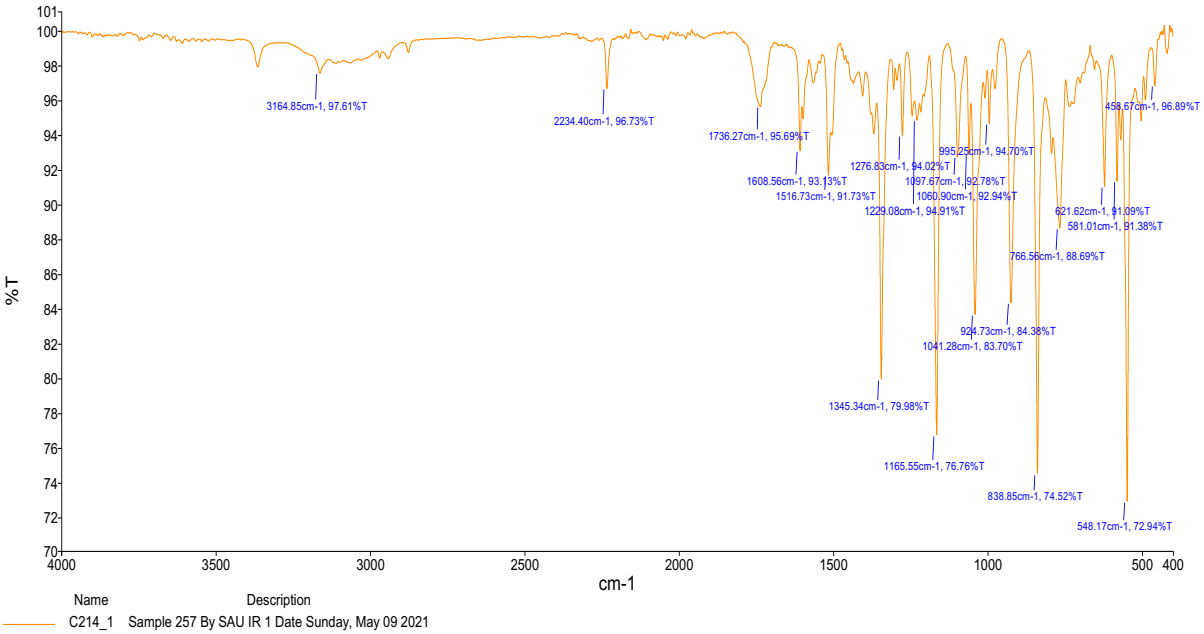

Fig. S49. IR spectrum of compound **7j** (4-{4-[1-({[1-(4-cyanophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

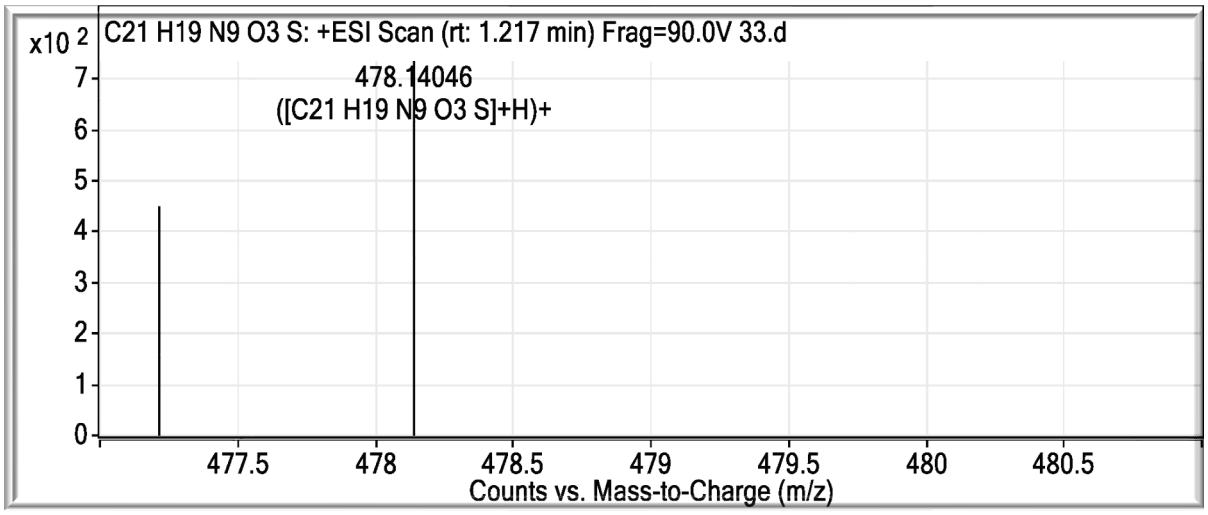

Fig. S50. Mass spectrum of compound **7j** (4-{4-[1-({[1-(4-cyanophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

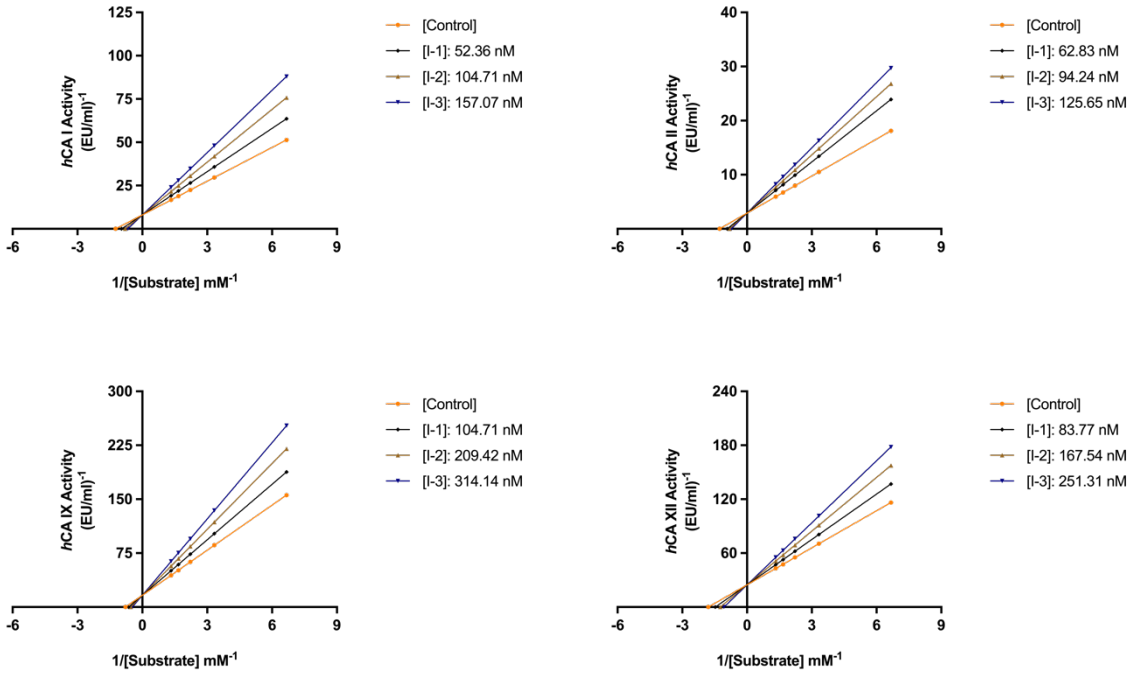

Fig. S51. Lineweaver-Burk plots of compound **7j** (4-{4-[1-({[1-(4-cyanophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

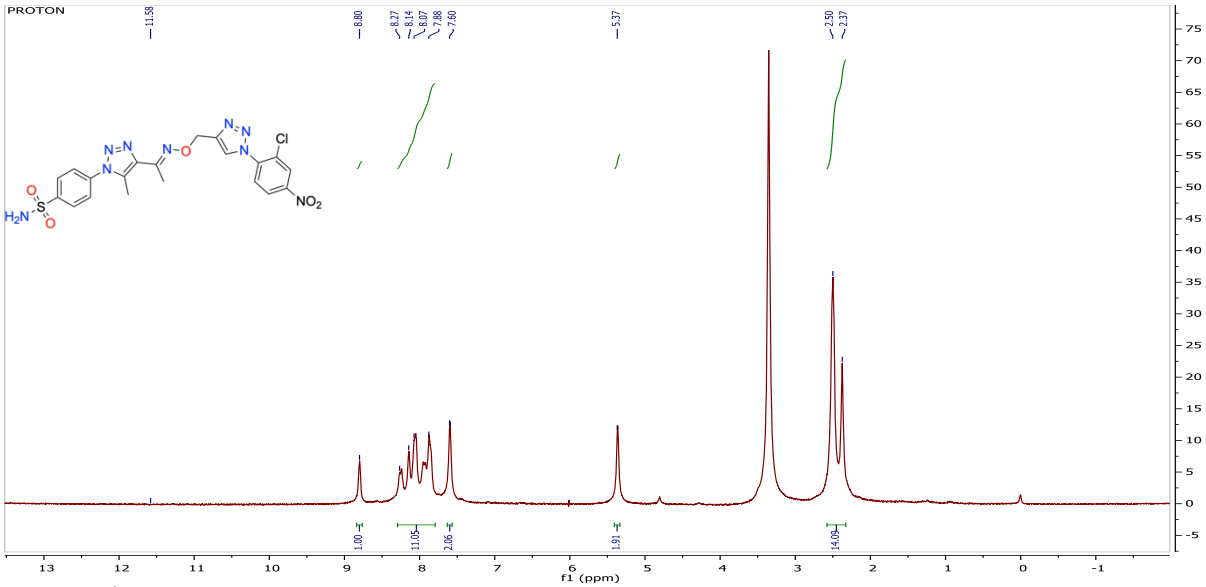

Fig. S52. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7k** (4-{4-[1-({[1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

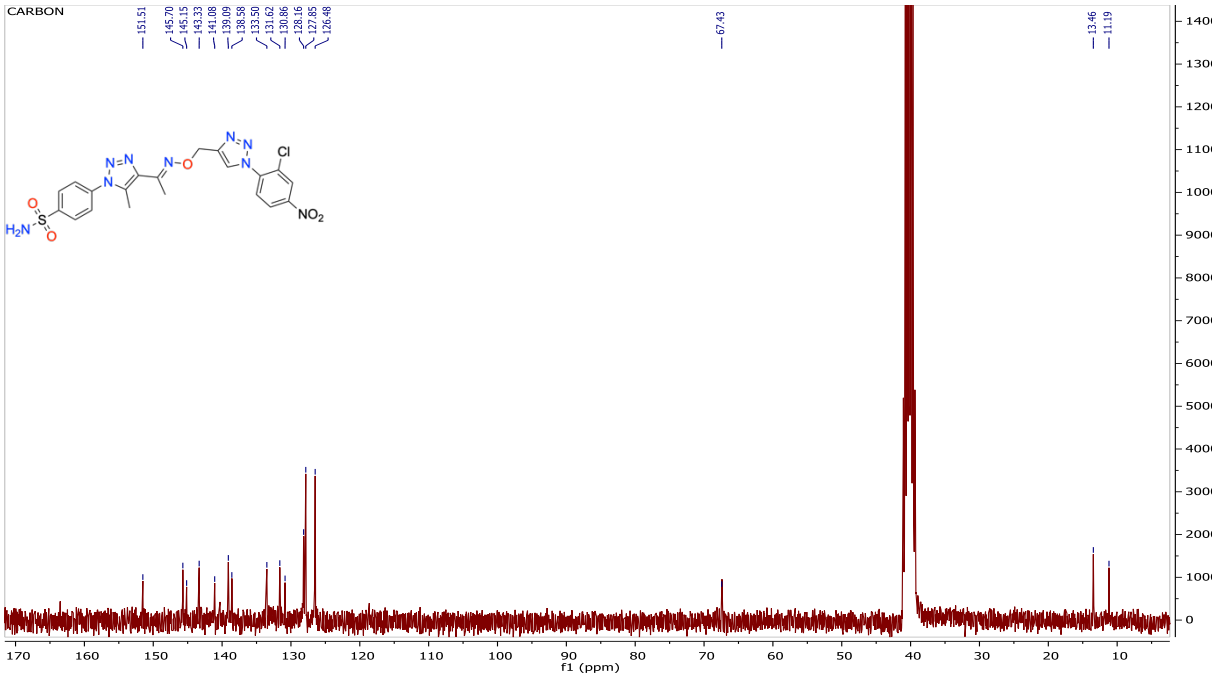

Fig. S53. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7k** (4-{4-[1-({[1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

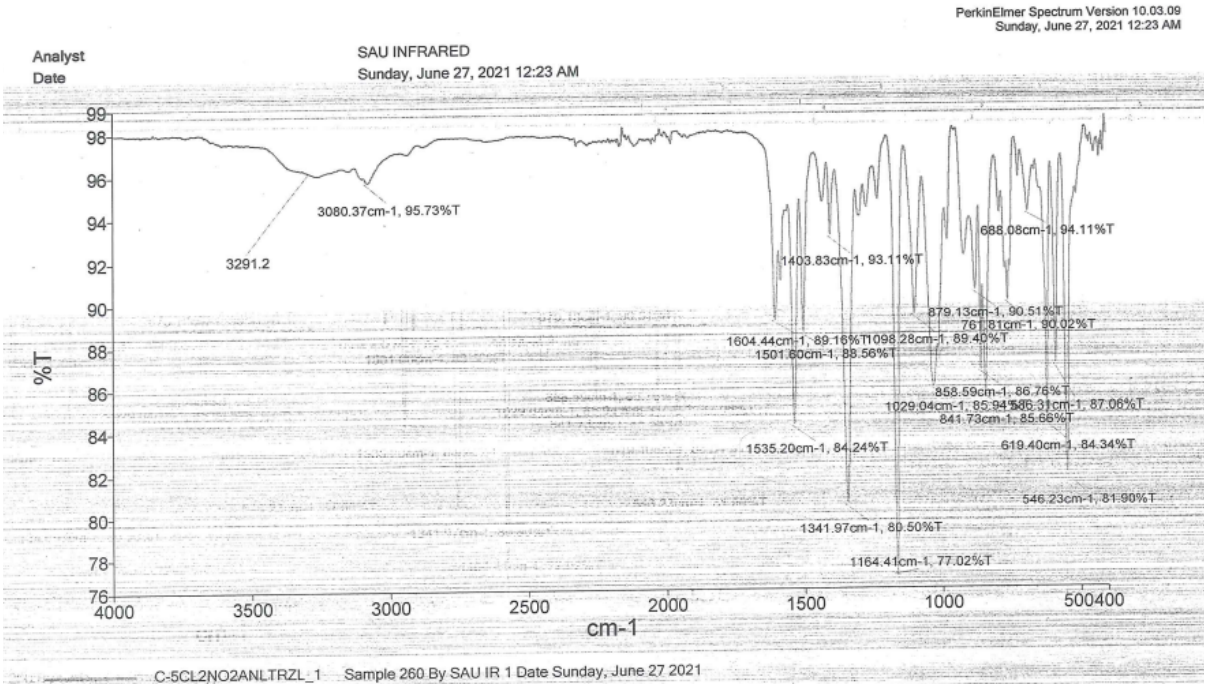

Fig. S54. IR spectrum of compound **7k** (4-{4-[1-({[1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

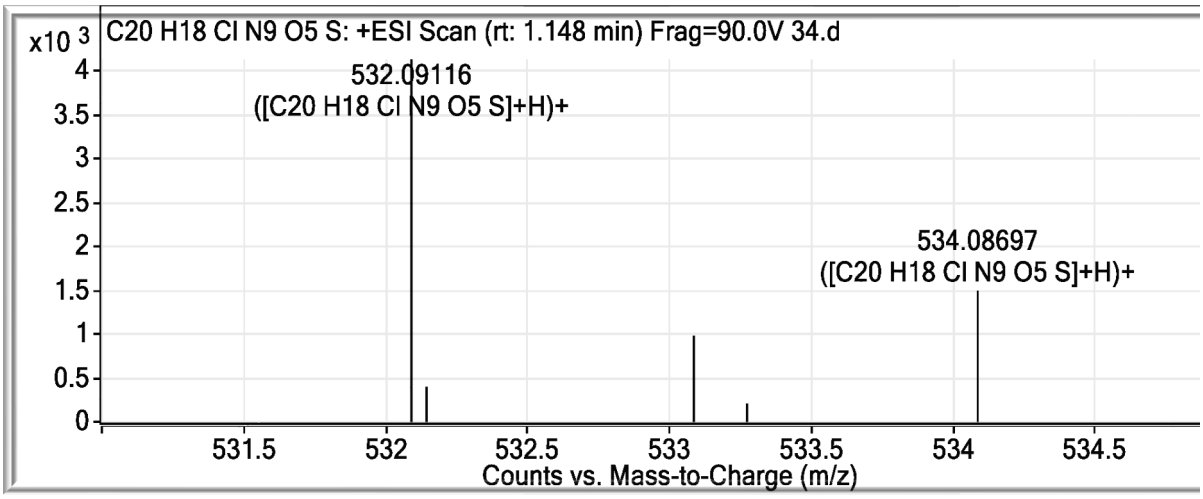

Fig. S55. Mass spectrum of compound **7k** (4-{4-[1-({[1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

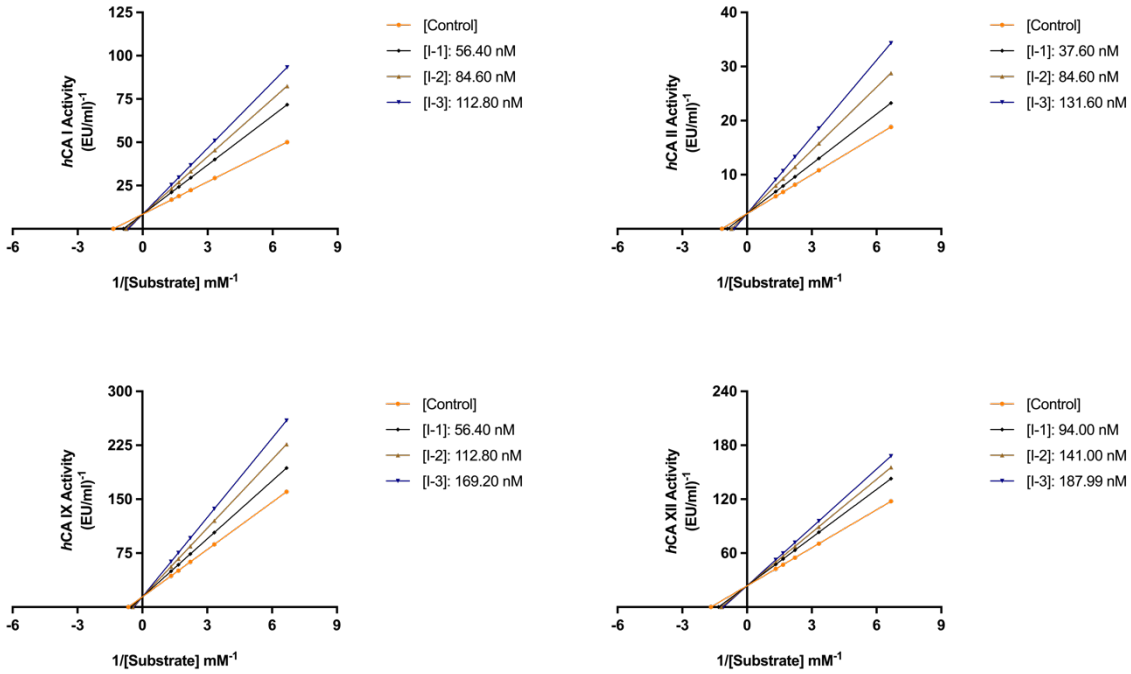

Fig. S56. Lineweaver-Burk plots of compound **7k** (4-{4-[1-({[1-(2-chloro-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

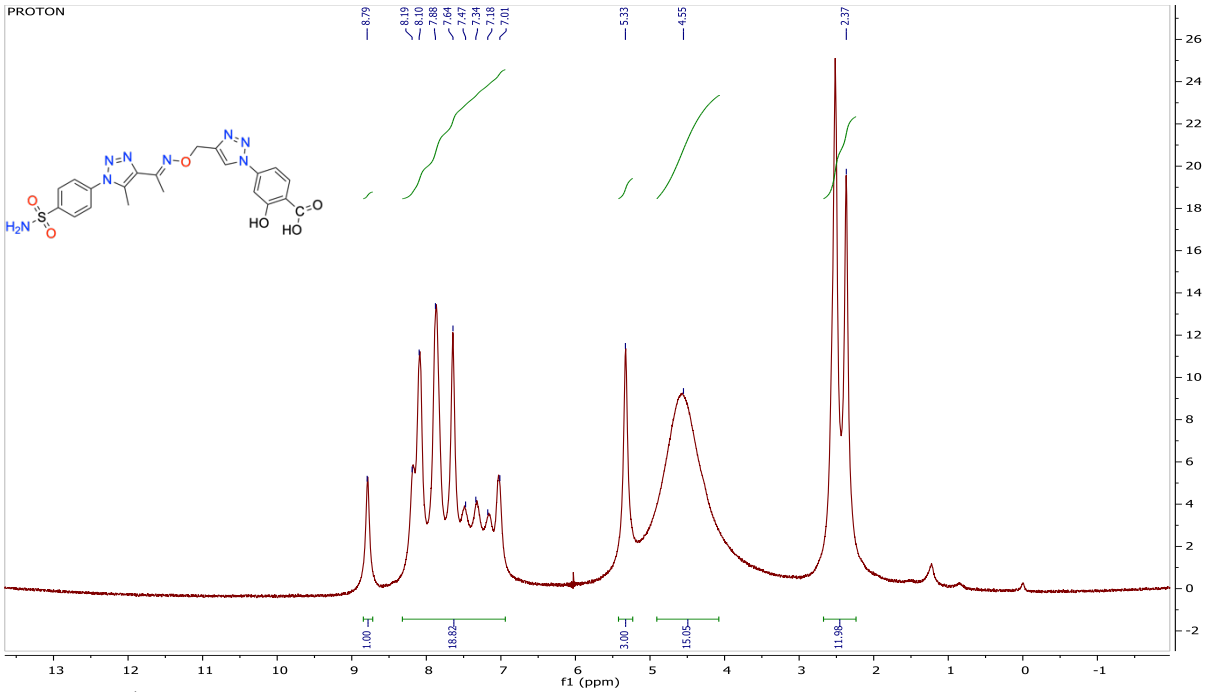

Fig. S57. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7l** (2-hydroxy-4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

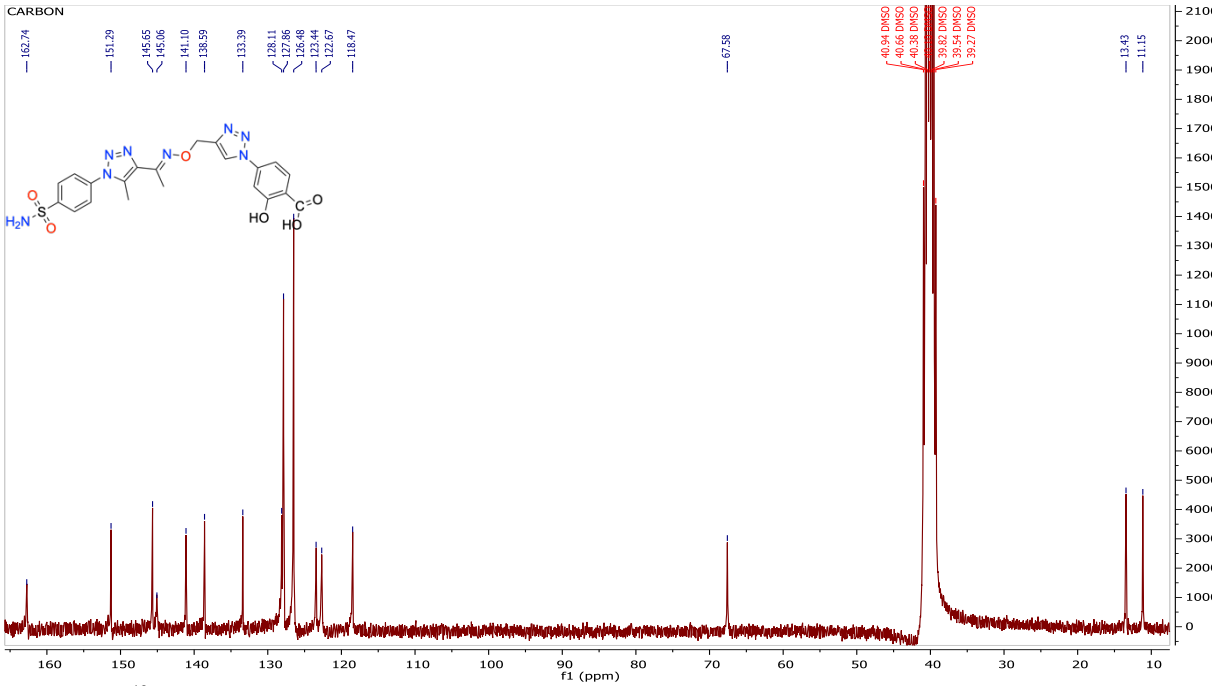

Fig. S58. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7l** (2-hydroxy-4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

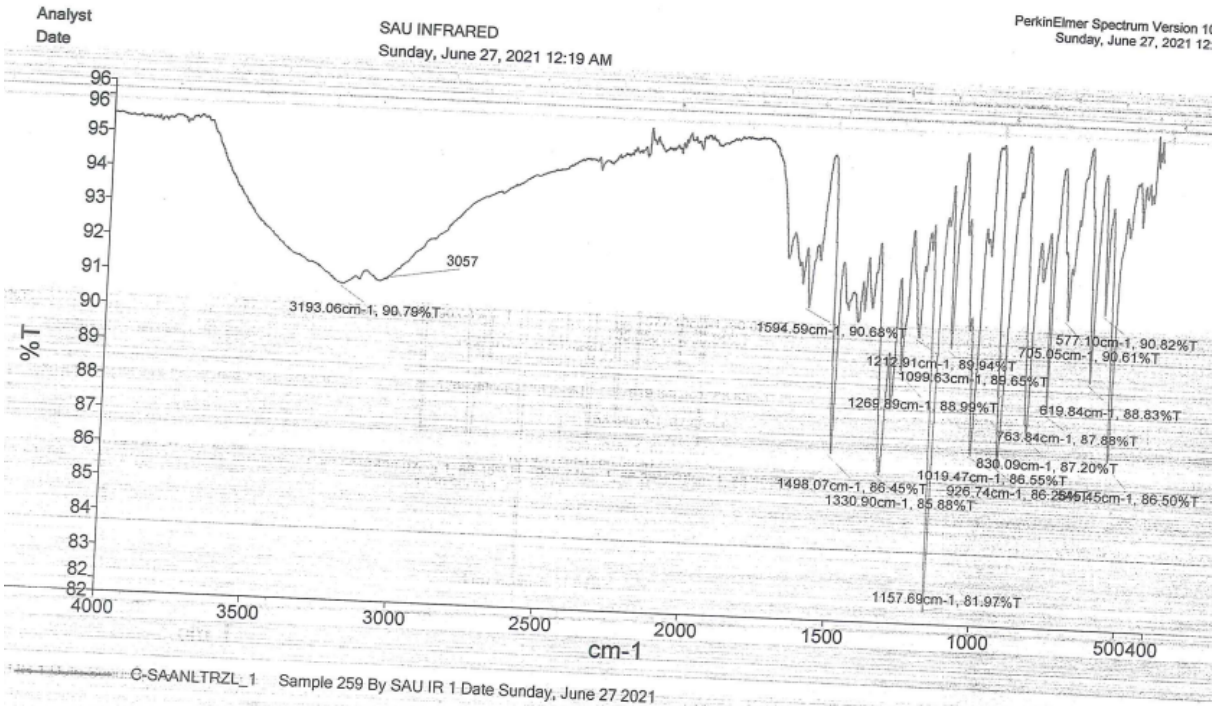

Fig. S59. IR spectrum of compound **7l** (2-hydroxy-4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

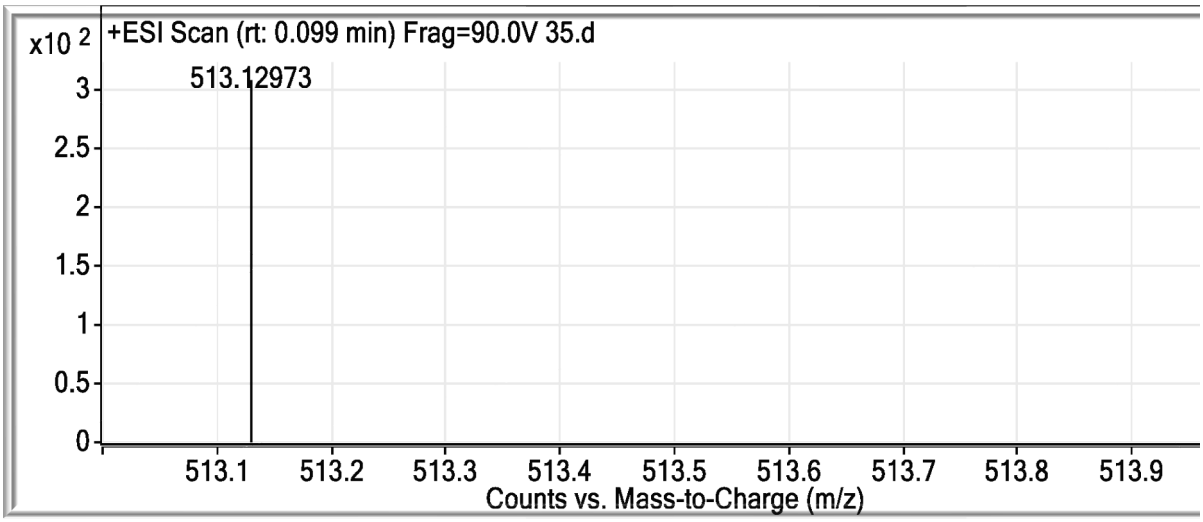

Fig. S60. Mass spectrum of compound **7l** (2-hydroxy-4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

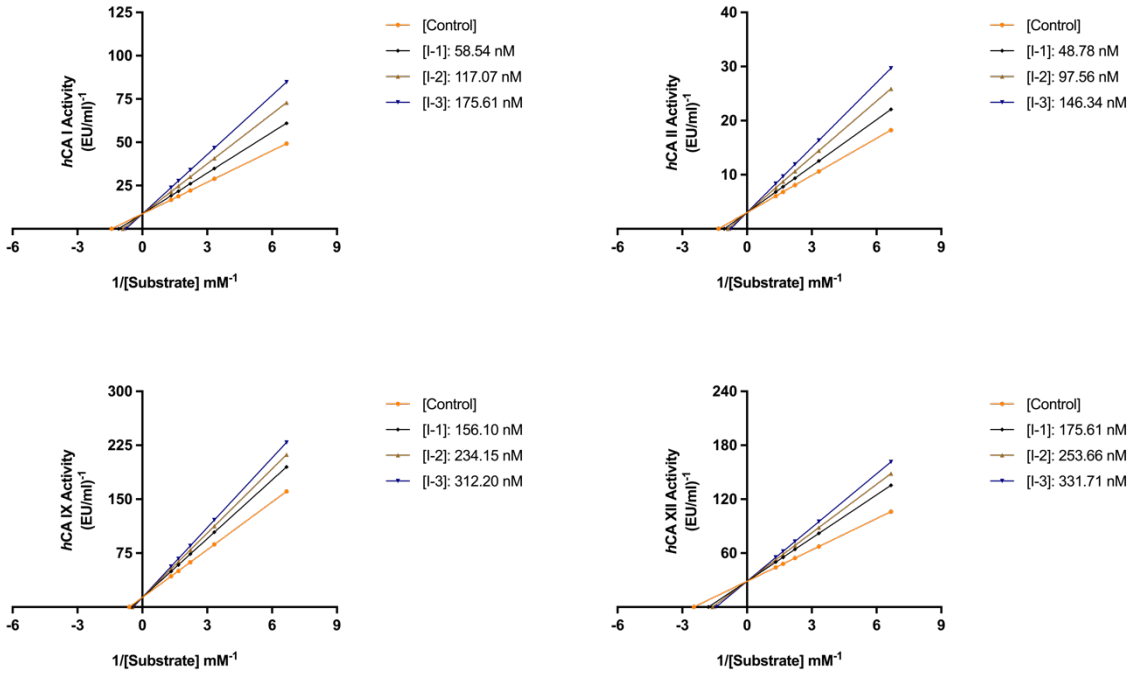

Fig. S61. Lineweaver-Burk plots of compound **7l** (2-hydroxy-4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

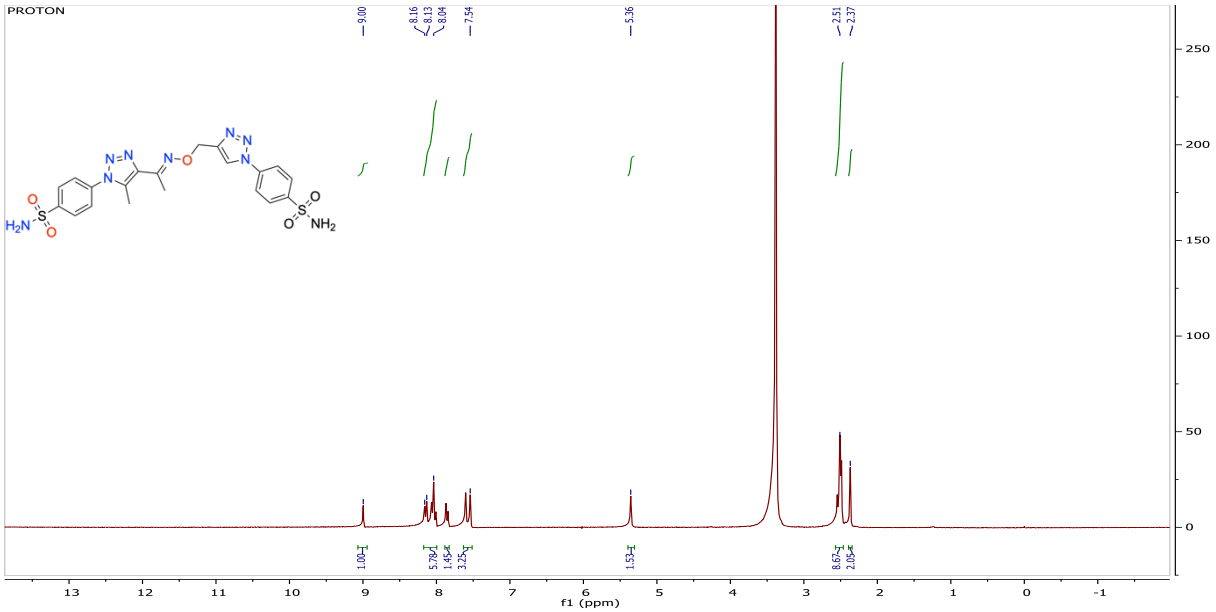

Fig. S62. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

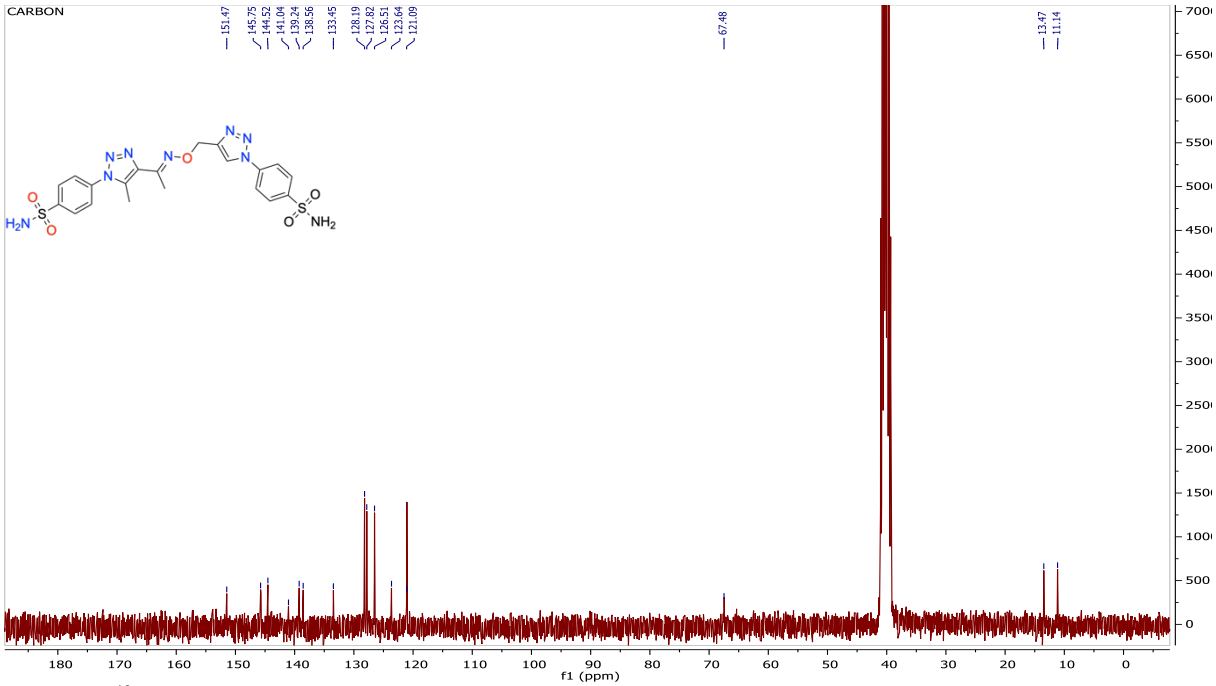

Fig. S63. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

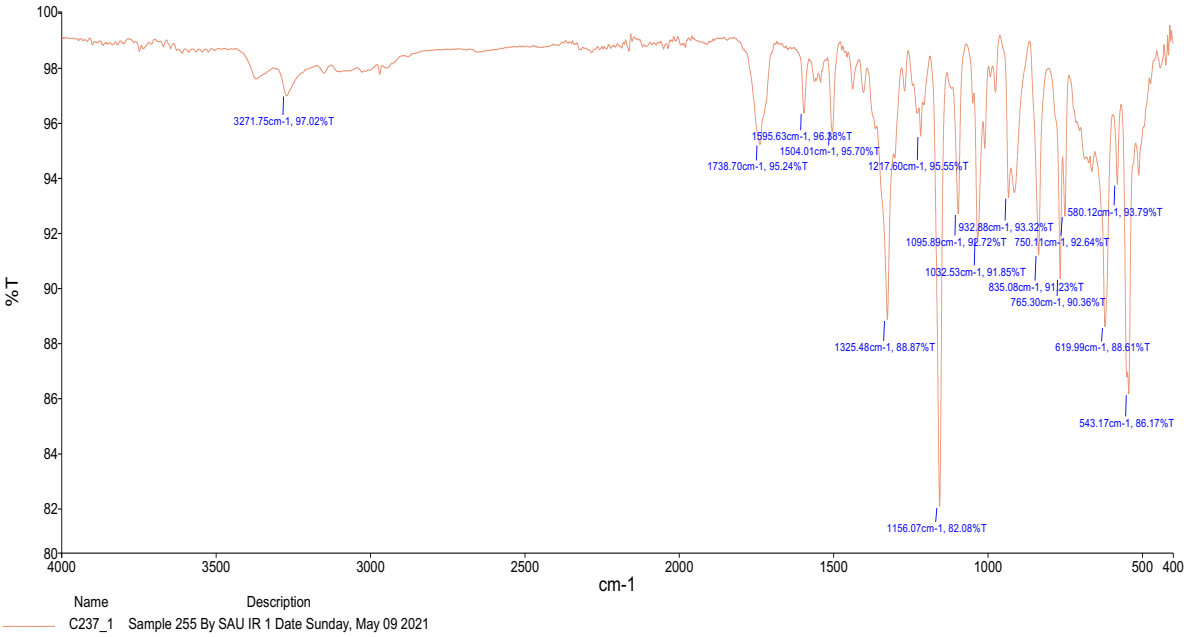

Fig. S64. IR spectrum of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

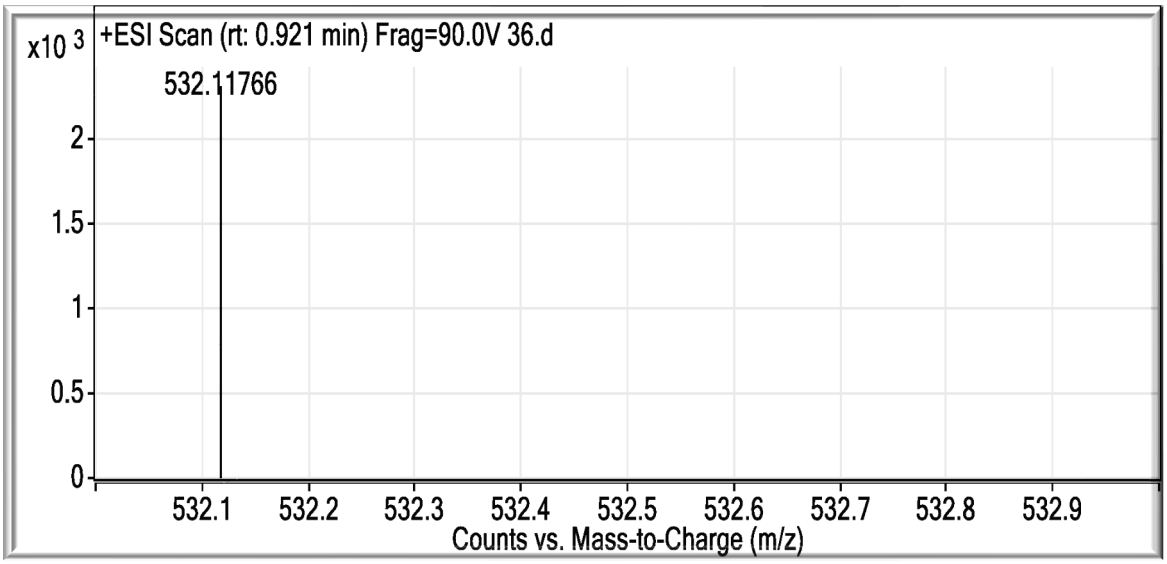

Fig. S65. Mass spectrum of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

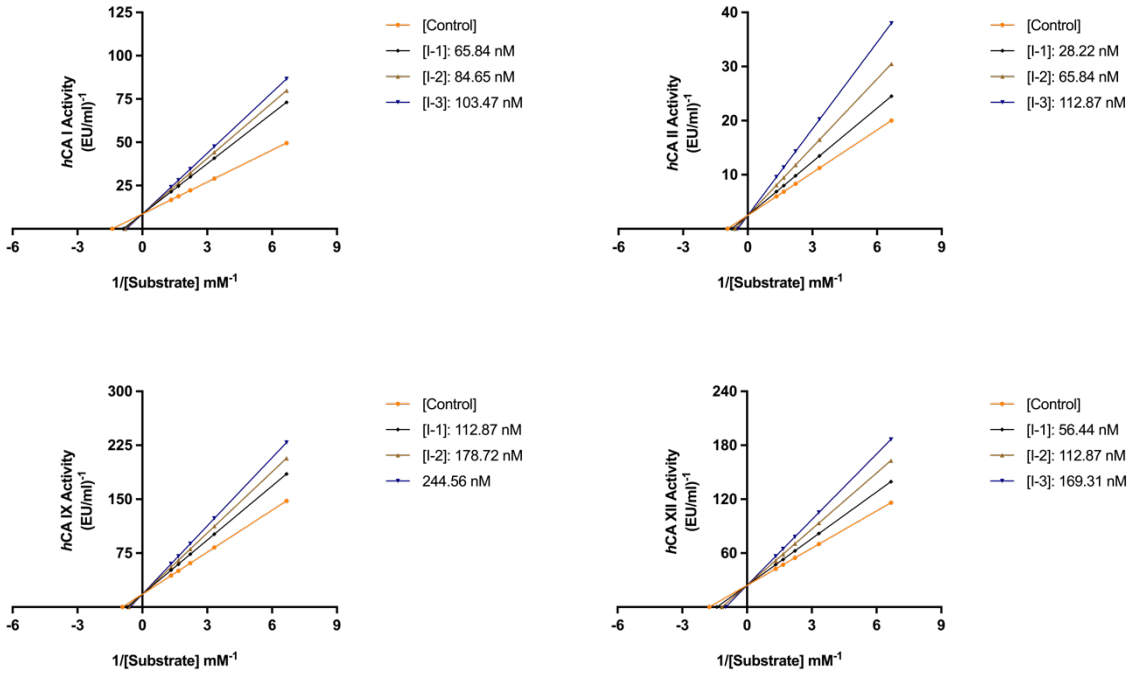

Fig. S66. Lineweaver-Burk plots of compound **7m** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide).

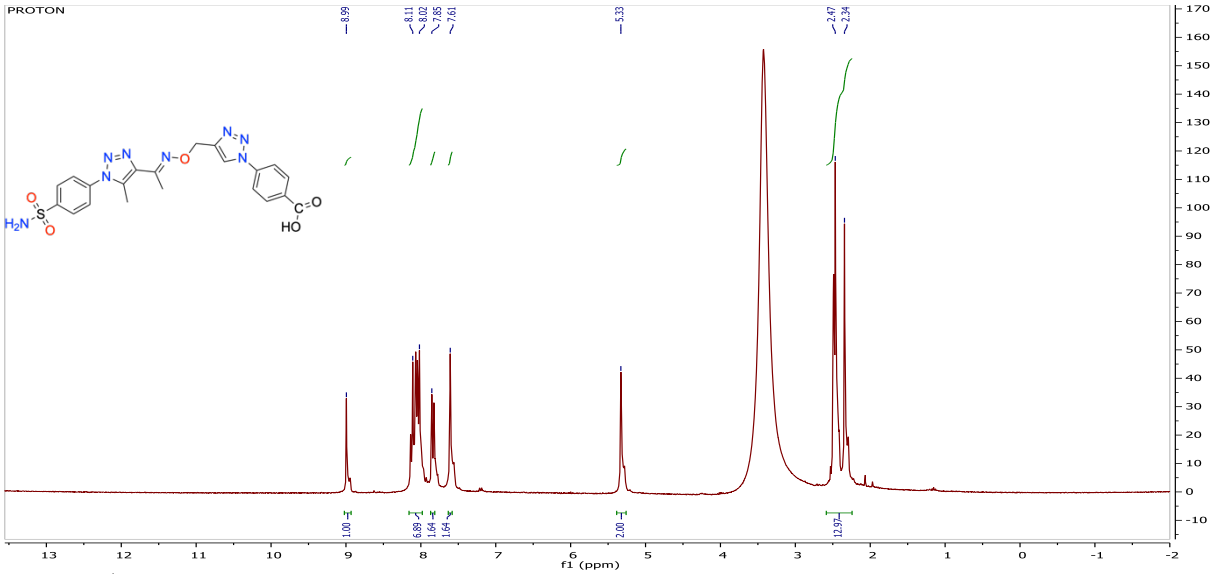

Fig. S67. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

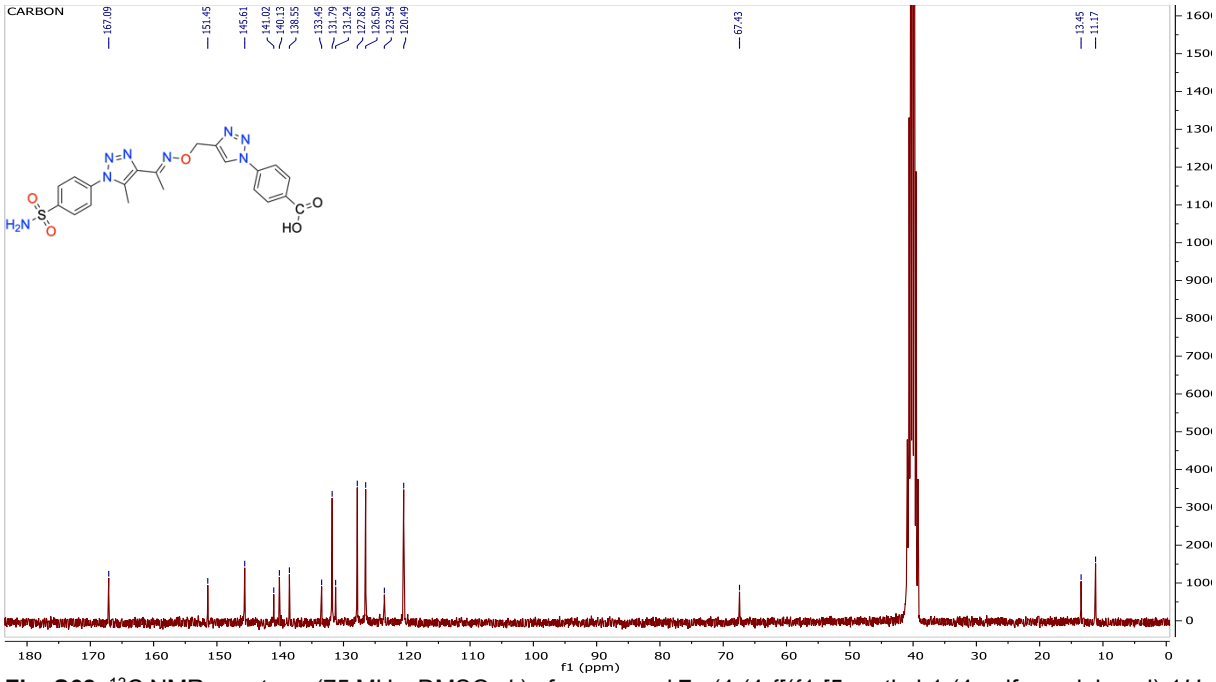

Fig. S68. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

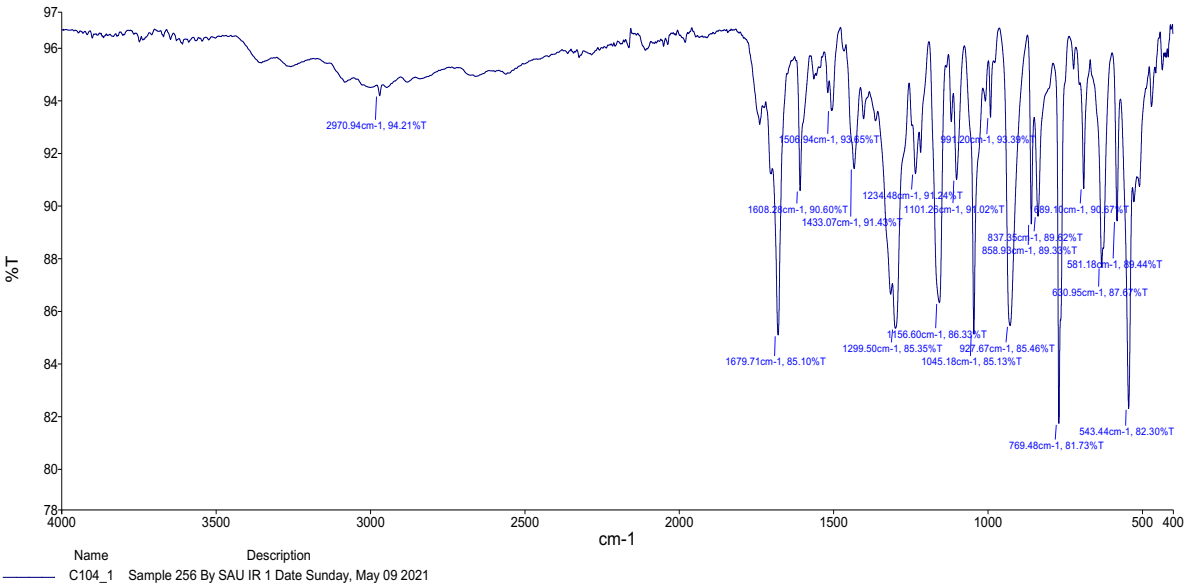

Fig. S69. IR spectrum of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

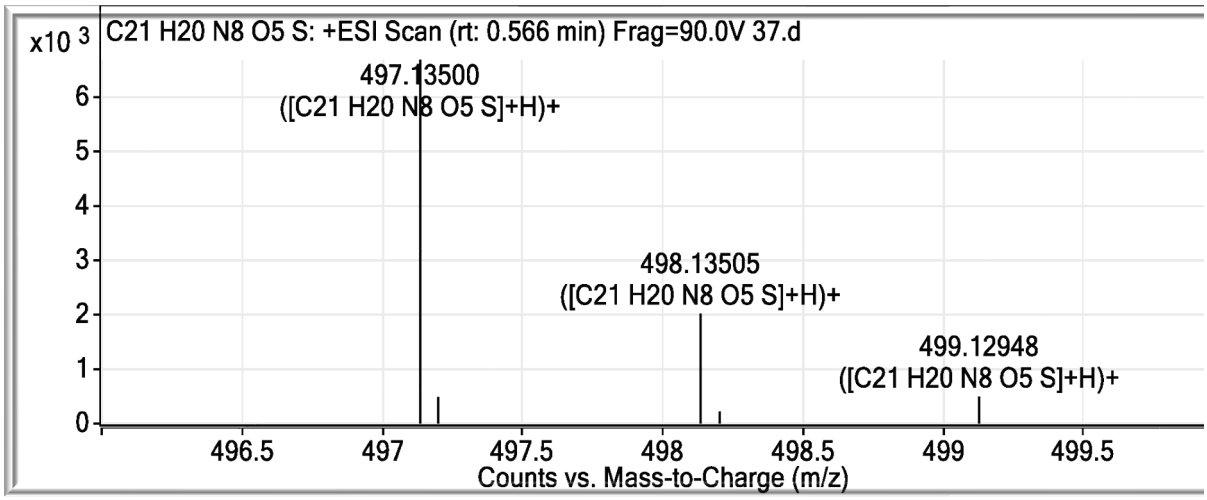

Fig. S70. Mass spectrum of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

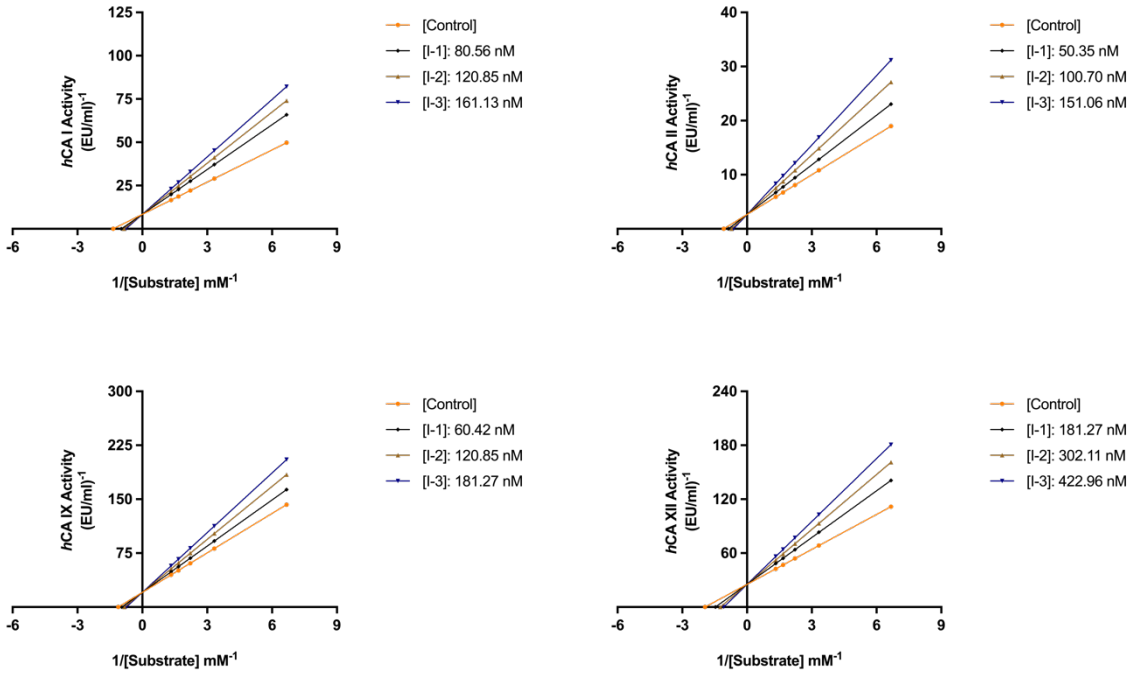

Fig. S71. Lineweaver-Burk plots of compound **7n** (4-(4-{[({1-[5-methyl-1-(4-sulfamoylphenyl)-1*H*-1,2,3-triazol-4-yl]ethylidene}amino)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)benzoic acid).

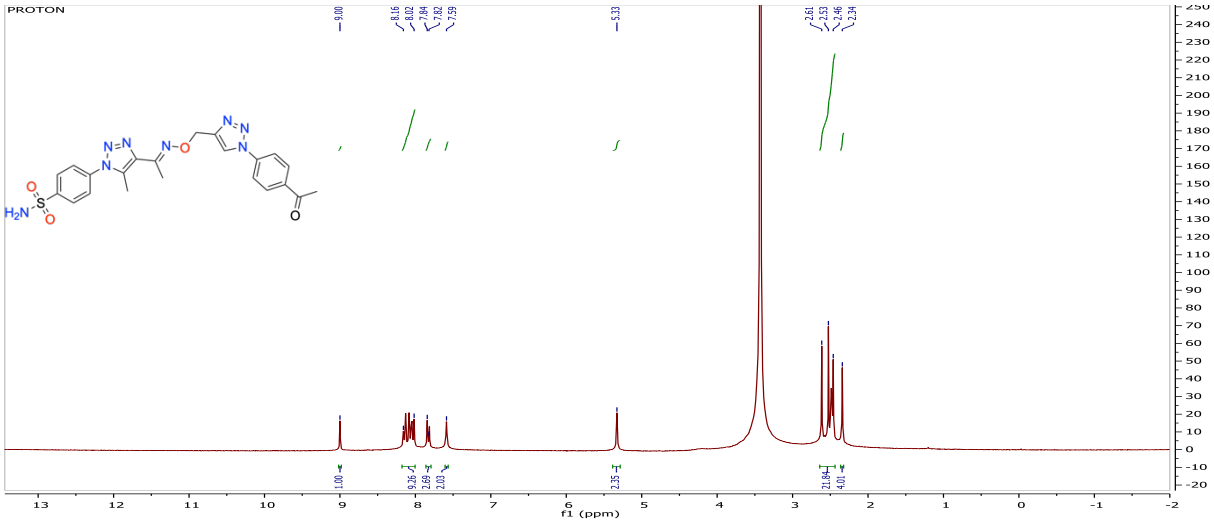

Fig. S72. ^{1}H NMR spectrum (300 MHz, DMSO-d_6) of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

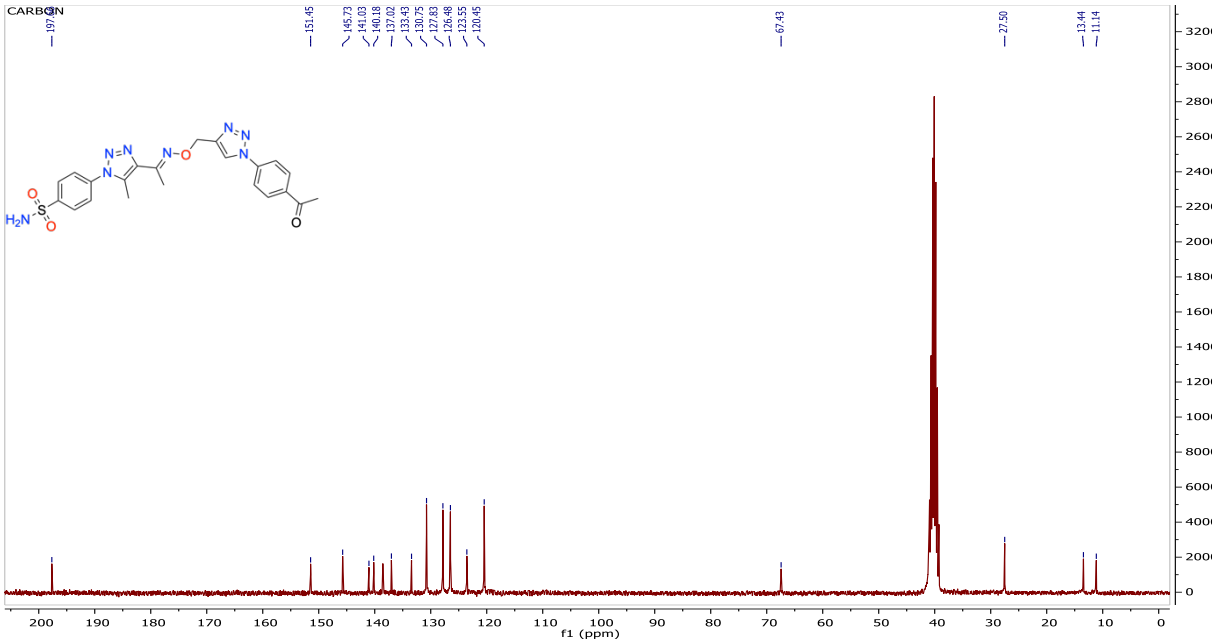

Fig. S73. ^{13}C NMR spectrum (75 MHz, DMSO-d_6) of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

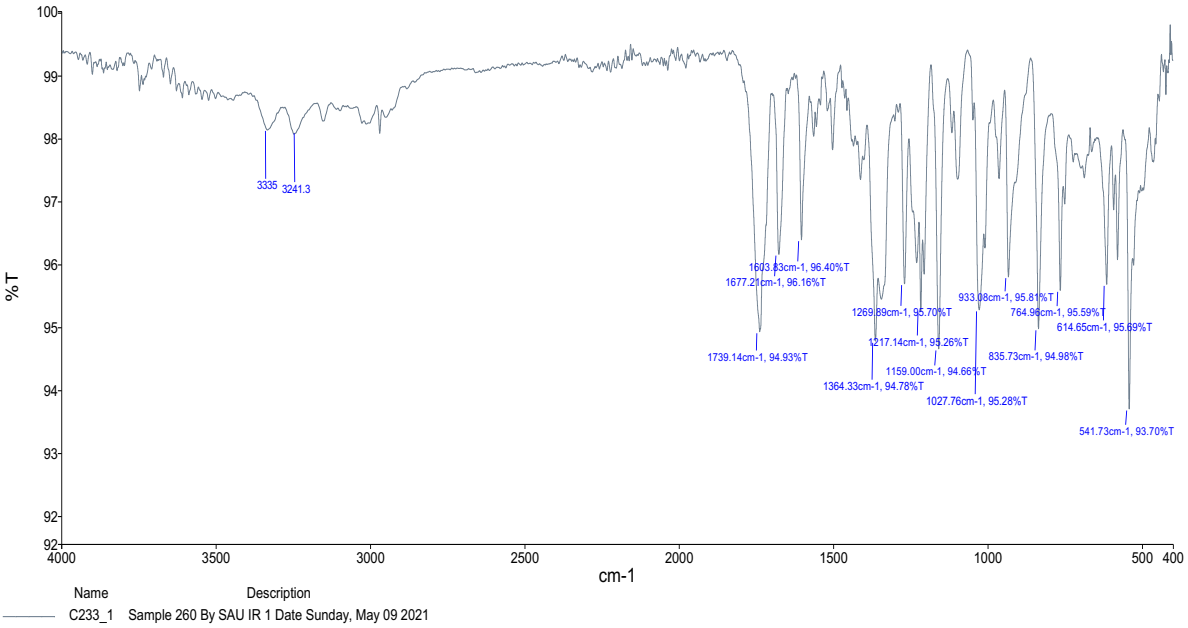

Fig. S74. IR spectrum of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

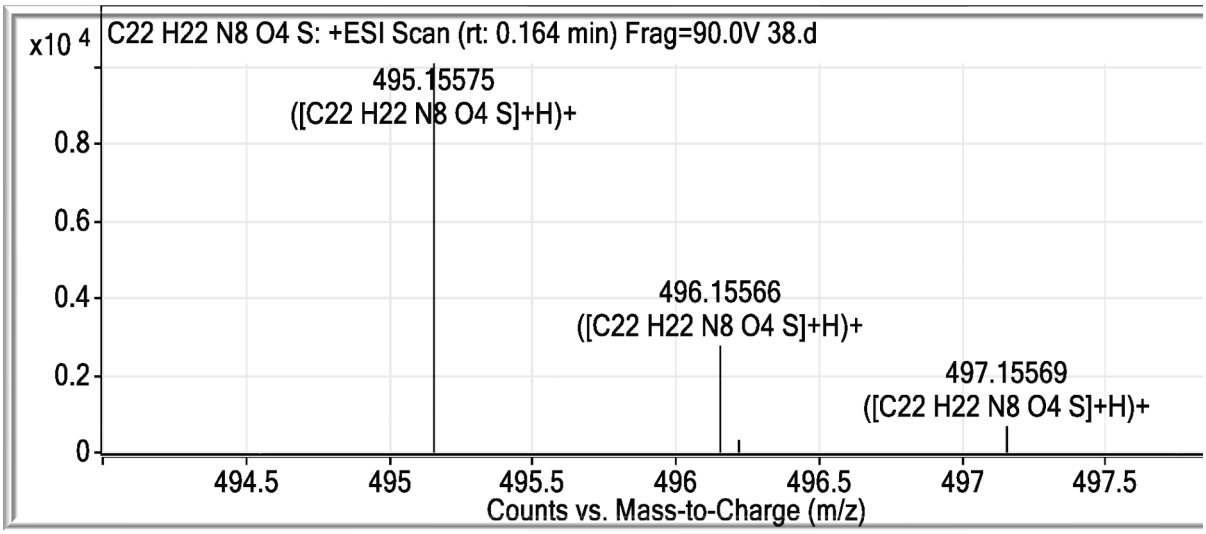

Fig. S75. Mass spectrum of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).

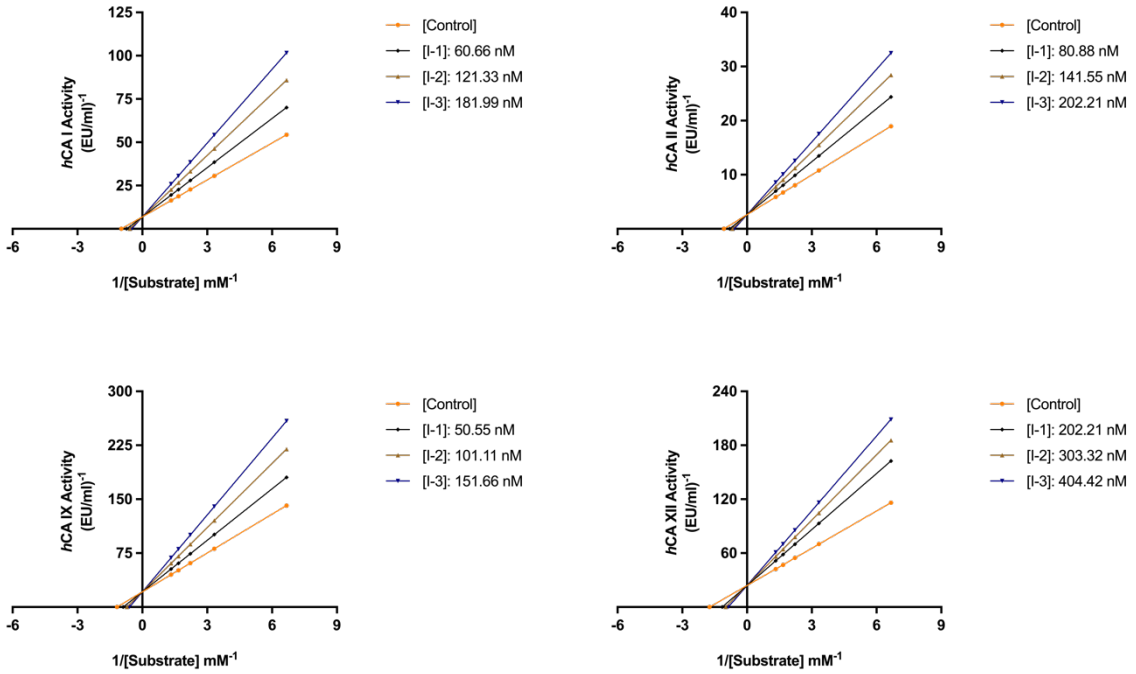

Fig. S76. Lineweaver-Burk plots of compound **7o** (4-{4-[1-({[1-(4-acetylphenyl)-1*H*-1,2,3-triazol-4-yl]methoxy}imino)ethyl]-5-methyl-1*H*-1,2,3-triazol-1-yl}benzenesulfonamide).