Electronic Supplementary Information

Novel stereoselective 2,3-disubstituted quinazoline-4(3*H*)-one derivatives derived from glycine as a potent antimalarial lead

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1. Material and Methods

This includes all the experimental aspects for synthesis of entitled desired compounds. Unless and otherwise indicated, all common reagents (Synthesis grade) were used as obtained from commercial suppliers without further purification; and all solvents (AR grade) were purified by the recommended purification procedures [1]. All the conventional reactions were carried out at atmospheric pressure with constant stirring in the appropriate glass vessel fitted with reflux condenser, whereby heating was provided using the routine instruments (magnetic stirrer with hot plate, overhead stirrer, heating mental or rota mental, etc.) available in the laboratory. All the microwave assisted reactions were carried out at atmospheric pressure using a microwave reactor (Microwave Synthesis System, Model: Cata-R, Catalyst^{TM} Systems, Pune-India) with attachment of glass vessel prolonged by a reflux condenser with constant stirring, whereby microwave irradiations are generated by magnetron at a frequency of 2450 MHz having an output energy range of 140 to 700 Watts, and the temperature was monitored with an external flexible probe. Alumina supported pre coated silica gel 60 F_{254} thin layer chromatography (TLC) plates (E. Merck Limited, Mumbai-India) were used to check purity of compounds and, to study and to monitor the progress of the reaction, whereby TLC plates were illuminated under Ultraviolet light (254 nm), evaluated in I_2 vapours and visualized by spraying with *Draggendorff's* reagent. Column chromatographic separations were carried out on silica gel (60-120 mesh). Melting points were measured by the open capillary method and are uncorrected. Micro analytical data (C, H, N) were obtained by using a Perkin-Elmer 2400 CHN elemental analyzer. Infrared spectra (FT-IR) were obtained in the range of 4000-400 cm^{-1} with a Perkin Elmer spectrum GX spectrophotometer (FT-IR) instrument using KBr pellets. ^{1}H, ^{13}C (APT), HMQC, HMBC and NOESY NMR spectra were recorded on a Bruker AVANCE II 400-MHz NMR spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), with chemical shift in ppm downfield from TMS as an internal reference and DMSO-d_6 (residual peak at δ ~2.5, 3.4 and ~ 39.5 ppm respectively, at 300 K) used as solvent as well as an external reference standard. Protons were assigned according to HMQC and/or 1D ^{1}H-NMR experiments; carbons were assigned according to APT, HMQC and/or HMBC experiments. NOESY experiments allowed the assignation of the *E*- and *Z*- diastereoisomers. Optical properties were measured on a polarimeter, Optical rotation values were determined in an Equip-Tronics EQ-801 digital polarimeter equipped with a 10 mL cell measuring 10 cm at 25 °C, using the emission wavelength of a sodium lamp; concentrations are given in g/100 mL. The electro-spray ionization mass spectra (ESI-MS) were recorded on a Shimadzu LC-MS 2010 eV mass spectrophotometer using methanol or acetonitrile as a solvent, and *m/z* values of ionization peak (+ve mode) corresponding to either exact mass or molecular weight of compound were represented. HPLC was performed on Varian Prostar instrumental setup having U.V. visible detector. The column used was BDS hypersil C18 with length 250 mm, 4.6 mm internal diameter and particle size 5 μm. The flow rate adjusted was 0.7 ml/minute with injected volume 20 μl of sample. The mobile phase used for the required separation was 100% acetonitrile. Crystallographic data were obtained by analyzing the single crystal of the **5** heterocyclic molecule by single crystal *X*-ray diffractometer (Kappa Apex-II). A suitable sample of single crystal of size (0.6 × 0.4 × 0.1) mm^3 was selected for the crystallographic study. All diffraction measurements were performed at room temperature (296 K) using

graphite monochromatic MoK*α* radiation of wavelength 0.71073 Å. The crystal structure was solved by direct methods and refined by full matrix least square technique on *F*2, using SHELX-97 set of program.

2. Results and Discussion of Synthetic Methodologies

2.1. Synthetic approchies

2.1.1. Multi step approach *via* hetero cyclization of *N*-acylanthranilic acids

To establish a more general, efficient and convenient synthetic method, our efforts begins with the hetero cyclization approach to derive desired quinazolinone-sulfonamide derivatives **(5)** under milder reaction conditions and to obtain high isolated yield. We recently have been engaged for the reinvestigation of this heterocyclization approach, and the successful modifications is reported in our article describing the synthesis of various 2-(alkyl- or aryl-substituted)-3-(4-substituted benzenesulfonamido) yl-4(3*H*)-quinazolinone derivatives.[44] With these results in hand, various attempts have been made to modify further this approach, and are disclosed herein. In continuation of previous efforts, the first approach applied in our laboratory for synthesis of quinazolinone-sulfonamide hybrid molecule **5** commence with some older reaction method for dehydrative cyclization by the interaction of *N*-acylanthranilic acids with hydrazines in the presence of PCl₃ as a condensing agent.
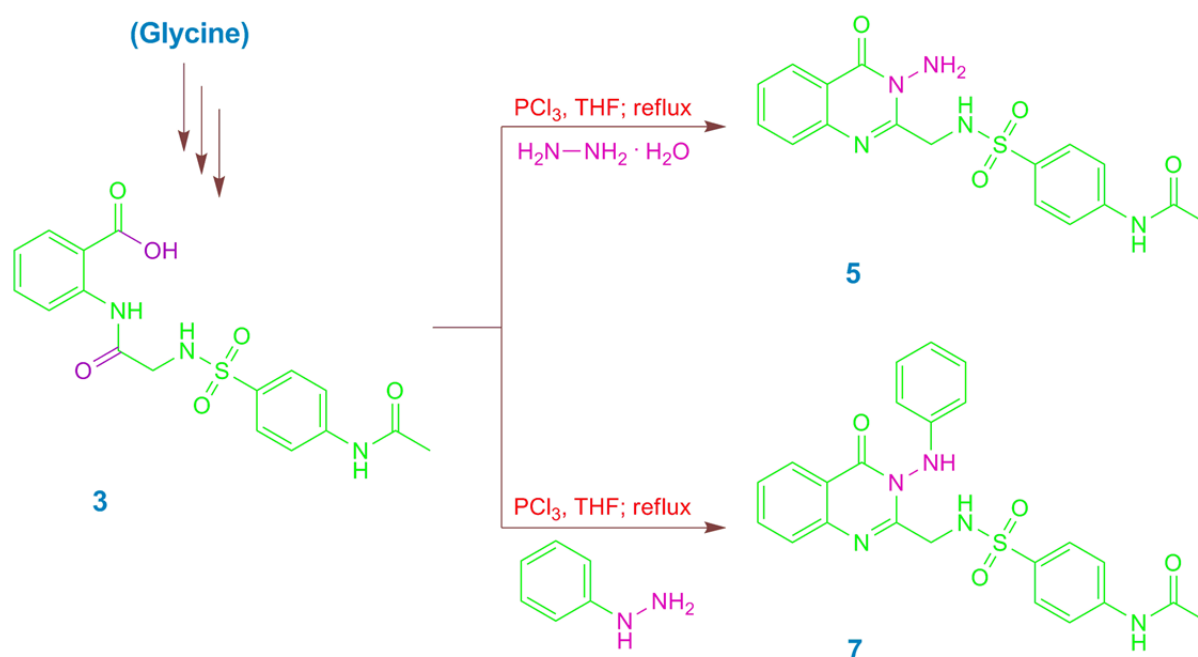
Scheme S1 Synthesis of various quinazolinone-sulfonamide hybrid derivatives via heterocyclization of *N*-acyanthranilic acids using Grimmel's method **Reagents & Conditions:** (i) Method-I: Conventional method of synthesis – hydrazines, PCl₃, THF, Δ. (ii) Method-II: Microwave Irradiation method of synthesis – hydrazines, PCl₃, THF, MWI (280 W).

Moreover, the satisfactory results achieved for the several reactions including the condensation reaction to prepare some amides (**2**) by the phosphazo method in earlier step and fewer similar cyclization reactions under Grimmel's conditions [2], where PCl_3 has been employed as an appropriate reagent has encouraged us to explore this approach further. Consequently, to probe the scope and limitations of newly developed protocol for the synthesis of desired quinazolone-sulfonamide derivatives **5** under classical heating conditions (Scheme S1), it was planned to employ optimized conditions for the several hetero cyclization of *N*-acylanthranilic acid (**3**) with a variety of (un)substituted-hydrazine hydrates respectively. Therefore, it was decided to reinvestigate again the solvent and temperature effects on the efficiency of cyclization reactions with the hope to identify an ideal combination that could improve reaction duration and contribute eventually the higher conversion to quinazolinone-sulfonamide hybrids in the ring formation step. Hence, the effect of various solvents, temperature and amounts of PCl_3 on the reaction time and yield were examined as shown in Table S1. An excellent conversion of **3** to **5** was achieved (entry 6-8) within short reaction span (25-30 min.) as indicated by isolated yield (91-96 %). Under the optimized condition (1 equiv. of PCl_3, in THF), **5** was isolated in high yield (91 %).

Table S1 Optimization of reaction conditions for the hetero cyclization step to prepare Quinazolinone-Sulfonamide Hybrid (**5**) by classical method

Entry	Solvent	PCl_3 [equiv.]	Conventional Method		
			Temp. [°C]	Time [min.]	Yield [%]
1	Toluene	2.00	110	120	61
2	Xylene	2.00	130	120	64
3	CH_2Cl_2	2.00	40	180	42
4	CH_3CN	2.00	50	120	66
5	THF	0.50	65	30	84
6	THF	1.00	60	30	93
7	THF	2.00	60	25	96
8	THF	1.00	50	25	91
9	Pyridine	1.00	80	30	65
10	Pyridine	1.00	50	30	62

In addition to this, the feasibility of Grimmel's method under microwave irradiation was reported for the first time to synthesize a series of 4-amino-*N*-(4-oxo-2-substituted-4*H*-quinazolin-3-yl)benzenesulfonamide derivatives in good yields. However, there are no any other reports, which employ the microwave irradiation conditions for this approach. Hence, it was decided further to investigate the effect of microwave irradiation on the yield and the

reaction time. The optimization of reaction between **3** with appropriate (un)substituted-hydrazine hydrates compounds were examined under microwave irradiation conditions for the formation of **5** was achieved by considering the effect of change of power levels, solvents and amount of PCl_3 (Table S2). Amongst the solvents examined, good results were observed, when the THF was employed as a solvent (Entry 3-8). Further, the conditions which employ 1 equivalent of PCl_3 in THF was consider to optimize. Under the optimized condition (Entry 6), reaction under microwave irradiation (280 W) has afforded desired **5** in excellent yield (95 %).

Table S2 Optimization of reaction conditions for the hetero cyclization step to prepare Quinazolinone-Sulfonamide Hybrid (**5**) utilizing microwave irradiation method

Entry	Solvent	PCl_3 [equiv.]	Microwave Irradiation Method		
			Power (Watt)	Time (min.)	Yield
1	CH_2Cl_2	2.00	210	10	51 %
2	CH_3CN	2.00	245	8	65 %
3	THF	0.50	245	8	84 %
4	THF	1.00	245	5	91 %
5	THF	2.00	245	3	97 %
6	THF	1.00	280	3	95 %
7	THF	1.00	350	3	89 %
8	THF	1.00	420	2	81 %
9	Pyridine	1.00	350	4	56 %
10	Pyridine	1.00	420	4	52 %

With these exciting results in hands, it was thought that the synthesis of 3-aminophenyl-4-quinazolinones would be possible using phenyl hydrazine instead of hydrazine under the previously optimized conditions. However, when the reaction were conducted, we found contradicting results which showed poor yield of **7** as compared to that obtained using hydrazine. In an earlier condensation step, pyridine was found to be better solvent, but came out with little poor results in the cyclization step. It was our observation for the several condensation or cylization reactions which utilize PCl_3 as a reagent, that it was presumably proceeds in suspension phase (particles starts suspending immediately addition of PCl_3, or within few minute when pyridine was used as a solvent). It might be due to presence of various acids (employed PCl_3, generated H_3PO_4, HCl) in the reaction. Hence, we rule out the earlier suggestion that low solubility of intermediates (*N*-acylanthranilic acid or amines) may not be one of the factor contributing low yield [3]. It has also been renowned that one-third

mole of it can accomplish condensation to amide, whereas the employment of two moles of this condensing agent might normally have been expected.

2.1.2. Multi step cyclo condensation approach *via* 3,1-benzoxazin-4-ones

Recently, we have reported the synthesis of various 2,3-disubstitituded-4(3*H*)-quinazolinones by the reaction of 4-acetamidobenzenesulfonyl hydrazide [4] and 2-aminobenzothiazoles or 2-aminoisoxazoles [5] with appropriate (*E*)-2-styryl-4-benzoxazinones using DMF-pyridine mixture under the microwave conditions [4,5]. With these results in our hands, we envisaged further that these conditions could be employed in the synthesis of desired quinazolinone-sulfonamide derivatives with improved yields *via* cyclo condensation of benzoxazinones in a shorter reaction time (Scheme S2).
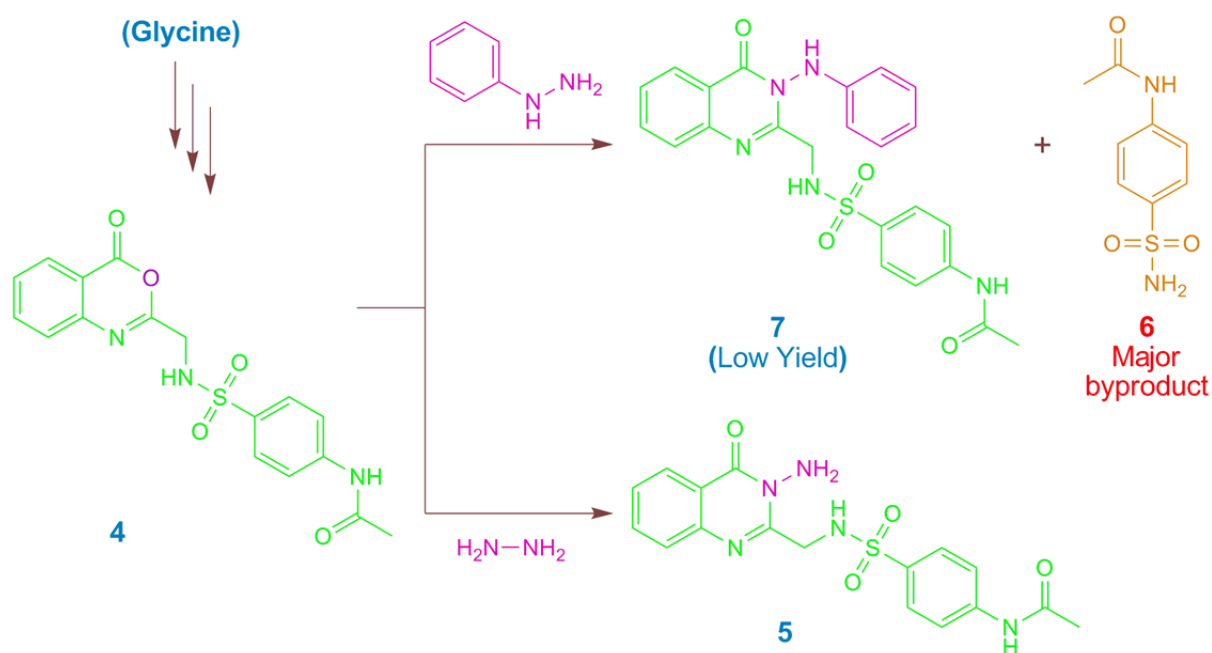
Scheme S2 Synthesis of quinazolinone-sulfonamide derivatives (**5**) **Reagents & Conditions:** Conventional or Microwave Irradiation method (i) DMF/Py/DMF-Py/AcOH/neat, Δ.

The cyclo condensation and subsequent ring closure reaction of appropriate **4** with reactive amines was examined as shown in Scheme S2. However, in initial attempt, the reaction of **4** with amines (phenyl hydrazine) in pyridine even under refluxing conditions (2-5 hr.) resulted in the formation of complex reaction mixture, and **7** was isolated in low yield (38%) along with unreacted **4** and side product (**6**) using column chromatography. In addition, the use of solvents like Py or DMF or Py-DMF or AcOH failed to gave the higher yield of **7**. Further, when a higher equivalent of phenyl hydrazine (5 equiv.) was employed in the reaction, it was found to be insufficient to show efficient and complete conversion, and no major improvement in the yield was measured. However, in all attempts with the selected active aromatic-amines employed in this reaction, the low isolated yield (highest 42 %) was measured as shown in the Table S3.

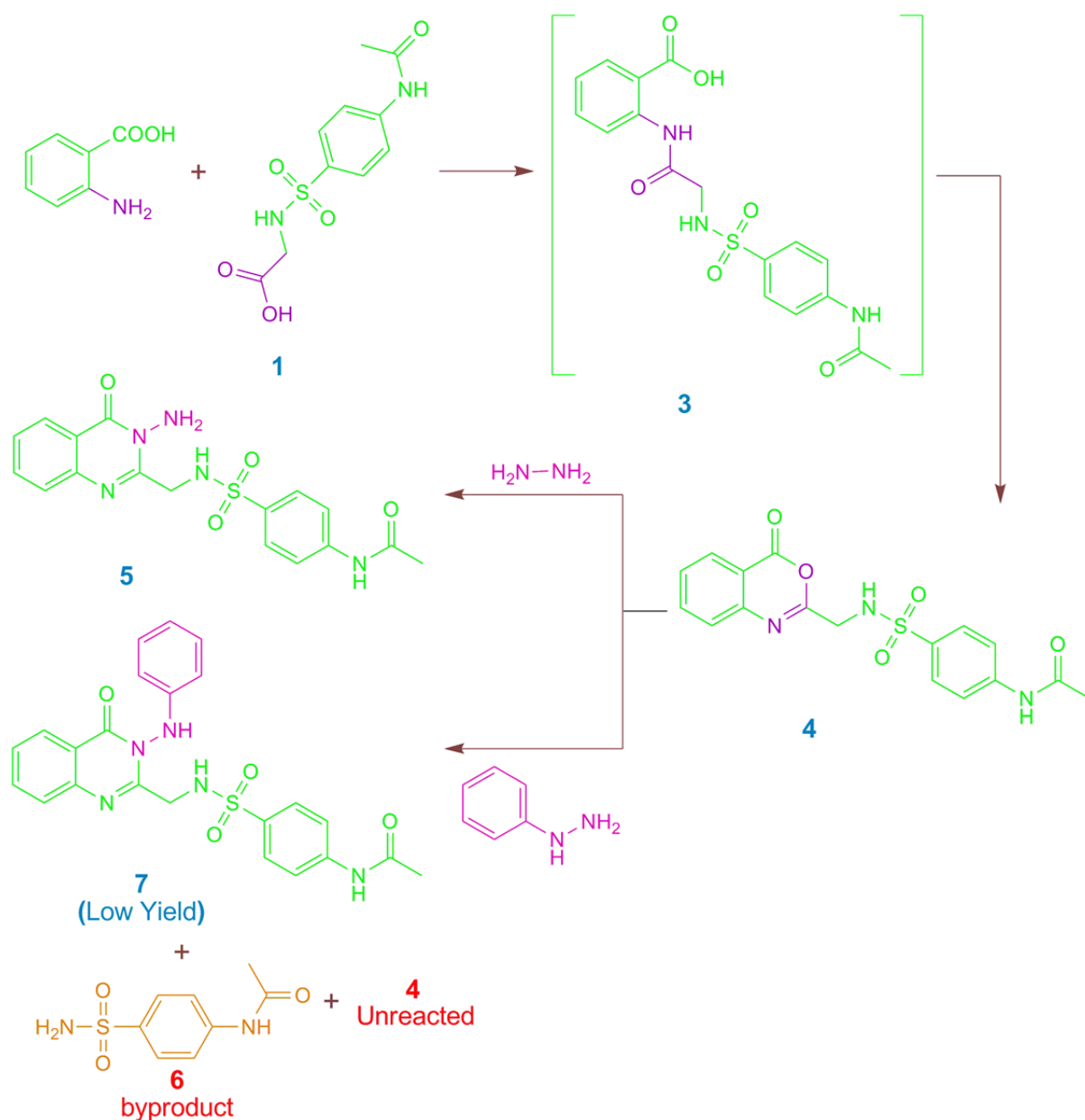**Table S3** Synthesis of Quinazolinone-Sulfonamide hybrids **7** & **5**

Entry	Comp	Amine [equiv.]	Group (R'$_3$)	Method-I CH		Method-II MI	
				Time	Yield	Time	Yield
1	7	1.2	–NHC$_6$H$_5$	2.5 hr.	38 %	7 min.	39 %
2	7	5.0	–NHC$_6$H$_5$	2.5 hr.	41 %	5 min.	42 %
3	5	1.1	–NH$_2$	1.5 hr.	80 %	2 min.	89 %

Therefore, it was decided to use some more reactive amine like hydrazine hydrate instead of aryl or heteroaryl amines to react with benzoxazinones. For that, the treatment of appropriate **4** with hydrazine hydrate in pyridine under the refluxing conditions was examined. In almost all the case, complete conversion was observed for the corresponding 3-amino-2-substitituted-4-quinazolinones. However, under the similar reaction condition, when guanidine was used in the reaction, again the low yields to corresponding quinazolinone derivatives by the incomplete conversion of corresponding **4** were measured, along with same side product was observed. All the above mentioned efforts led to unsatisfactory results in this approach, it might be due to the limited nucleophilicity owing to phenyl hydrazine, which becomes more problematic in case of heterocyclic amines, and it might be considered as a primary reason. Further, the steric hindrances at position-2 of benzoxazinones and their relative stable nature with respect to 2-(methyl or phenyl or styryl)-4-benzoxazinones might be considered as another reasons for lower yields. These unsatisfactory results prompted us to search for a new facile and convergent method for the synthesis of quinazolinone-sulfonamide derivatives, which could tolerate the desired substitution pattern at 2nd & 3rd positions respectively.

2.1.3. One pot sequential domino reaction approach

With aforesaid results in hands, a new route has been sought, which employs a single reagent to proceed efficiently the reaction without isolation of 3,1-benzoxazinone to provide the higher conversion to facilitate the synthesis of desired quinazolinones and to reduce the formation of undesired product as well. The recent work published with modifications of Silion's approach by several investigators involved a multi-component one-pot reaction for the synthesis of quinazolinones under conventional or microwave assisted heating conditions [6-8]. Hence, we become interested to use a one pot sequential domino reaction approach to establish a more general, convenient and convergent method for the synthesis of desired quinazolinone-sulfonamide derivatives by using such a single suitable reagent efficient for three consecutive condensations and a subsequent cyclization reaction (Scheme S3). It was further envisioned that desired 2,3-disubstituted (3*H*)-quinazolin-4-one derivatives (**5**) could be synthesized by using this approach by reacting anthranilic acid and *N*-(4-acetamidobenzenesulfonyl)amino acids (**1**) and subsequent ring closure with hydrazine or phenyl hydrazine of *in situ* generated benzoxazinones (**4**). Accordingly, the treatment of

appropriate **1** with anthranilic acid (equi-molar) and P(OPh)₃ (1.1 or 1.2 equiv.) in pyridine under reflux afforded corresponding 4-benzoxazinones (**4**) in nearly quantitative yield (as described earlier and as shown in Scheme S3).

Scheme S3 Efficient and convergent one-pot sequential domino reaction approach for the synthesis of desired quinazolinone-sulfonamide hybrid system via *N*-acylanthranilic acids followed by 3,1-benzoxazin-4-ones **Reagents & Conditions:** (i) Method-I: Conventional method of synthesis – amines, P(OPh)₃, Py, Δ; (ii) Method-II: Microwave Irradiation method of synthesis – amines, P(OPh)₃, Py, MWI (420 W).

The complete conversion of **1** to **4** encouraged us to explore further this approach for the synthesis of desired quinazolinone-sulfonamide hybrid molecules. Hence, it was envisaged that condensation of *in situ* generated 4-benzoxazinones with active amines (hydrazines)

followed by ring closure reaction could afford desired quinazolinone-sulfonamide derivatives (Scheme S3).

Therefore, it was decided to examine the reaction conditions for the condensation of **4** with the hydrazines to lead the formation of corresponding entitled products. In an initial effort, synthesis of **7** was attempted by addition of phenyl hydrazine (1 equiv.) to *in situ* generated **4**. But the reaction resulted with incomplete conversion again even under refluxing conditions for a longer time (12 hr.; shorter than earlier cyclo condensation) and from the resulting complex reaction mixture **7** was isolated in 31 % yield along with same by product **6** (23 %) and unreacted **4** (18 %) using column chromatography. In the preparations of **7**, optimization of reaction conditions appropriate for the cyclo condensation step was achieved by varying the amount of P(OPh)$_3$ and phenyl hydrazines (Table S4).

Table S4 Optimization of reaction conditions under classical heating to prepare **7** & **5**

Entry	Product	Amine [equiv.]	P(OPh)$_3$ [equiv.]	Conventional Method	
				Time	Yield[a]
1	7	1.00	1.20	8 hr.	29 %
2	7	1.10	1.20	8 hr.	31 %
3	5	1.10	1.20	6 hr.	77 %

[a] *Isolated yields of **5** from **1** for combined three steps after chromatographic purifications.*

The results for initial attempts have encouraged us to optimize the conditions to prepare desired quinazolinone-sulfonamide derivatives **5** under conventional heating conditions. However, a hurdle while working with the reactions involving P(OPh)$_3$ was: it usually requires a chromatographic separations and it might be very difficult to isolate possible products in the pure form due to the large presence of several other side products which might have been formed probably due to the prolonged reaction time or the reagent itself. Therefore, there was a further requirement to establish an easy experimental procedure to improve the yields and work up procedure as well. For achievement of the same, we employed the utilization of hydrazine hydrate substituting phenyl hydrazine with same reaction conditions. Surprisingly, we obtained positive results with better yield as compared to earlier step. Thus, we discovered further scope to establish an easy experimental methodology using this pathway.

The modifications applied in reaction, gave better results in terms of improved yield of desired products in little shorter time. Hence, under the optimized conditions (Entry 2; Table S4) desired quinazolinone-sulfonamide hybrids **(7)** were synthesized in satisfactory yields by employing appropriate hydrazine hydrate.

It was intended to synthesize desired quinazolinone-sulfonamide linked hybrid derivatives **5** and **7** under the microwave mediated heating conditions. Further, the

satisfactory yields observed under classical heating in aforesaid attempts encouraged us to optimize the conditions under the microwave irradiation to prepare **5** and **7**. It was further envisioned that the use of microwave irradiation could further improve the yield and reduce the reaction time (as observed in conventional method). Therefore, it was decided to optimize previously established conventional reaction conditions under microwave irradiation by changing power levels for the formation of **5**. Subsequently to optimize the conditions, we investigated the effect of microwave irradiation on the reaction rate as well as yield of the cyclized product as shown in Table S5.

Table S5 Optimization of reaction conditions for the hetero cyclization step to prepare Quinazolinone-Sulfonamide Hybrids (**5**) [a] under microwave irradiation

Entry	Product	Amine [equiv.]	P(OPh)$_3$ [equiv.]	Microwave Irradiation Method		
				Power	Time	Yield
1	5	1.10	1.20	350 W	11 min.	51 %
2	5	1.10	1.20	420 W	8 min.	86 %
3	5	1.10	1.20	700 W	6 min.	57 %
4	5	1.10	1.20	560 W	7 min.	66 %
5	5	1.10	1.20	490 W	8 min.	69 %
6	5	1.10	1.20	455 W	8 min.	72 %
7	5	1.10	1.20	280 W	17 min.	46 %

[a] *Isolated yields of **5** from **1** for combined three steps after chromatographic purifications.*

To optimize the conditions, appropriate **4** and hydrazines (1.1 equiv.) in pyridine and 1.2 equivalent of P(OPh)$_3$ was experimented under the microwave irradiation (at 350 W), and in pilot experimentations (Table S5, Entry 1), improvement in the yield of cyclized product was observed. The more better results were obtained upon heating the reaction mixture under the microwave irradiation (at 420 W or 455 W), when higher equivalent of hydrazines (1.1 equiv.) and P(OPh)$_3$ (1.2 equiv.) were employed in the reaction. Under the optimized condition involving the use of hydrazines (1.1 equiv.) and P(OPh)$_3$ (1.2 equiv.), the reaction resulted with higher isolated yield of **5**.

2.2. Structural confirmations

The structures of all the synthesized compounds were confirmed using various physicochemical methods and spectroscopic investigations, and the relevant analytical data have been given in experimental section.

Mass spectra and elemental analysis of compounds reveals that they are consistent with the proposed structures. Further, the results of elemental analysis of all compounds were

in good agreement (± 0.4 %) with their predicted molecular formula. All the ESI-MS (positive mode) spectra of synthesized compounds showed molecular ion peak [M+H]$^+$ corresponding to either exact mass or molecular weight of respective compound [9, 10]. The mass spectrum of compound **5** exhibited a parent peak at *m/z* 388.0 [M+H]$^+$ and compound **8a** exhibited a parent peak at *m/z* 520.8[M+H]$^+$, which confirms the proposed formula. The MS spectra of halogenated derivatives (except fluorine compounds), **8m-8u** showed molecular ion peak in characteristic two peak pattern [M+H]$^+$ and [M+H]$^{+2}$ (in almost 1:1 and 3:1 ratio due to the isotopic abundance nature of Br/Cl atoms respectively, demonstrated the proposed molecular formula of respective halo compounds. Compounds, **8o** (chloro-derivative) and **8r** (bromo-derivative) exhibited ionization peaks ([M+H]$^+$ and [M+H]$^{+2}$) at *m/z* (509.9, 511.9) and at *m/z* (555.8, 557.8) respectively.

The FT-IR spectra represent an obvious tool for initial identification of the presence of various functional groups in the moiety [9, 10]. In IR spectra of all the compounds, presence of –SO$_2$NH– group was evidenced by the two strong bands appeared at 1318-1340 and 1144-1165 cm^{-1} due to asymmetric and symmetric S=O stretching vibrations respectively, and further absorption band at ~3250 cm^{-1}assigned to –SO$_2$N–H stretching. For the quinazolinone derivatives (**5**), strong intensity bands appeared in the IR spectra at 1690-1670, 1610-1650 and at ~1495 cm^{-1} attributed to C=O, C=N and C=C stretching vibrations respectively, provides a strong evidence for the parent heterocyclic ring skeleton vibrations. The spectrum of benzoxazinone show a sharp band at ~1750 cm^{-1} for the C=O group of semi-anhydride type lactone ring. However, the overlapping of absorption bands due to amine, acetamido and sulphonamide in the region ~3100-3400 and ~1600-1650 cm^{-1}, had generated a little difficulty in assignment of N-H starching bands.

The ^{1}H-NMR spectra of synthesized compounds supported the proposed structures by the assignments of NMR resonances rested on chemical shifts, signal intensity, multiplicities, and are in comparison with structurally related compounds [9-11]. In the ^{1}H-NMR spectra of **(8a-v)**, proton of –N=C**H**– group resonated variably between 8.5-9.4 ppm and appeared as a singlet, while proton of –SO$_2$N**H**– group resonated variably between 7.8-8.1 ppm and appeared as a triplet (*J*= 4.8-6.0 Hz) for the compounds **8a-v, 5**. The protons attached to –SO$_2$NH–, –SO$_2$NH–C**H$_2$** group in **8a-v, 5** appeared as a singlet or doublet (*J*=4.8-6.0) or multiplet in the aliphatic region (at δ 3.7-4.5 ppm). The protons of Ph–SO$_2$NH–CH(R)–Q exhibited absorption at slight higher frequency than such normal protons –NH–CH(R)– might be due to deshielding effect of –SO$_2$NH– and quinazolinone ring. Further, in the ^{1}H NMR spectra, the two-bond geminal (H–C–H) coupling for protons of –CH$_2$–NH– (in **8c, 8f, 8i, 8l, 8o, 8r, 8u**) were exhibited in DMSO-*d$_6$* solution. The geminal protons (H-C-H) of– C**H$_2$**–NH– group resonated with considerable difference of frequency (δ 0.2-0.4 ppm), as a result two separate signals (dd; *J*=14-18, 4-6.8 Hz) were appeared corresponding to each proton. In ^{1}H-NMR spectra of compounds **8a-v, 5** with acetamido group (Ar–NHCOCH$_3$), protons of –COCH$_3$ and –NHCO were appeard as a singlet at δ >10.0 ppm due to –N**H**CO and between δ 2.0-2.3 ppm due to –COC**H$_3$** respectively. In addition to this, the aromatic protons of benzenesulfonyl ring protons **(Ar–NHAc group in 8a-v, 5)** appeared as broad multiplet (at δ 7.5-7.8 ppm) due to the symmetry might have been influenced by acetamido

group. The proton at C_5 of quinazolinone ring appeared as a doublet around $\delta > 8$ ppm. All the other protons of aromatic and heteroaromatic ring resonated in aromatic region (δ 6.2-8.6 ppm).

^{13}C-(APT) NMR experiment was used to prove interpretation of carbon resonances in acceptable patterns (positive/negative peak) i.e. signals of primary-ternary and secondary-quaternary carbons observed on the opposite amplitude [9-11]. All ^{13}C-NMR spectra of **8a-v, 5** were characterized by two signals (quaternary carbons) at low frequencies (δ 150-157 and 160-162 ppm) associated with a cyclic amide or lactam ring of quinazolinone carbon (with a cyclic –N=C=N carbon conjugated with **C=O** group), while acyclic carbon of –N=CH– group resonated variably between 161-169 ppm. In **8a-v, 5**, signal due to –CH$_2$ (secondary carbon) attached to sulphonamide group observed at little higher frequency (δ ~45 ppm). All the other carbons (–CH, –C) of aryl and quinazolinone ring were resonated in expected region (δ 112-150 ppm). ^{13}C-NMR spectra of synthesized compounds were also consistent with the anticipated structures.

2.3. *X*-ray crystallographic outcomes of major intermediate 5

The intermediate molecule, *N*-(4-((3-amino-4-oxo-3,4-dihydroquinazolin-2-yl)methylsulfonamido)phenyl)acetamide, monohydrate crystallizes in triclinic $P\bar{1}$ space group with one water molecule in the asymmetric unit (Fig. S1). The fused quinazoline ring system of the molecule is very much planer with a dihedral angle of 2.63(9) between the fused system. An U shape twisting of the molecule about S1-N14 (C4-S1-N14-C15 = 69.48(14)°) and N14-C15 bonds (S1-N14-C15-C16 = -71.67(18)°) brings the two terminals very close to each other. The folding of the molecule not only helps to accommodate the long molecule in a comparatively small unit cell but also facilitates in formation of half a dozen strong intra and inter molecular hydrogen bond interactions with a maximum donor acceptor distance of 2.51 Å resulting in strong molecular packing. Oxygen of the solvent water actively contributes in intra and inter-molecular interactions. Sulfamido nitrogen N14 acts as a donor to sulfonyl oxygen O3 from an inversely related molecule forming N14-H14…O3 (-x,-y,-z) dimmer at each inversion center of unit cell of R_2^2 (8) graph set motif (Fig. S2). A π-π interaction of Cg-Cg separation distance of 3.52 Å involving the centroids of pyrimidine ring from symmetry related molecule further strengthen the molecular packing.

Molecular packing is due to C-H⋯O, C-H⋯π and π-π intramolecular hydrogen bond interactions in the structure (Table S6), while the crystallographic data and details of the data collection and structure refinements are enumerated in Table S7.

Table S6 Selected bond lengths, bond angles, torsional angles and dihedral angles of the molecule 5

Bond lengths (Å)			
O2- S1	1.4348(14)	C15- N14	1.457(2)
C7 -N10	1.405(2)	C16 -N25	1.376(2)
C11- N10	1.358(2)	C18 -N17	1.392(2)
C11 -O12	1.210(2)	N14 -S1	1.6207(16)

Bond Angles (°)			
O12- C11- N10	123.88(17)	O3- S1 -O2	118.50(8)
N10 -C11- C13	114.13(16)	O3- S1 -N14	105.85(8)
N25- C24- C23	113.61(15)	O2 -S1 -N14	107.90(9)
O2-S1- C4	107.27(8)	N14 -S1 -C4	107.81(7)
Torsional angles (°)			
C5 -C4 -S1- O3	120.00(16)	C9- C4 -S1 -O3	61.87(16)
N25- C16 -N17- C18	2.8(2)	O12- C11 -N10 -C7	2.8(4)
C4-S1-N14-C15	69.48(14)	S1-N14-C15-C16	-71.67(18)

Table S7 Crystal data and structure refinement parameters of molecule 5

Crystal data and structure refinement parameters	
Empirical formula	$C_{17} H_{19} N_5 O_5 S$
Formula weight	405.43
Temperature (K)	293 (2) K
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
Crystal size (mm^3)	1.2 × 0.4 × 0.1
a (Å)	8.8900(2)
b (Å)	10.3346(2)
c (Å)	11.2245(2)
α (°)	115.313(1)
β (°)	95.614(1)
γ (°)	93.303(1)
Volume (Å^3)	922.07(3)
Z	2
Calculated density (Mg m^{-3}),	1.460
Absorption coefficient (mm^{-1})	0.217
F(000)	424
Crystal size (mm)	0.2 × 0.2× 0.1
θ range for data collection (°)	2.03 to 27.51
Limiting indices	$-11 \leq h \leq 11$; $-13 \leq k \leq 13$; $-13 \leq l \leq 14$
Reflections collected/unique [R(int)]	15472/ 4260 [0.0373]
Completeness to θ = 27.51 (%)	99.8
Absorption correction	N.A.
Refinement method	Full Matrix Least Square of $|F|^2$
Data/restrains/parameters	4260 /3/255
Goodness-of-fit on F^2	1.044
Final R indices	R_1 = 0.0469, wR_2 = 0.1361
R indices (all data)	R_1 = 0.0523, wR_2 = 0.1432
Largest diff. peak and hole (e Å^{-3})	0.549 and -0.541

[a] $w=1/[\sigma^2(Fo^2)+(0.0842P)^2+0.3601P]$ where $P=(Fo^2+2Fc^2)/3$.

Fig. S1. The ORTEP view of the title molecule shows atomic labelling scheme and 50% probability level displacement ellipsoids
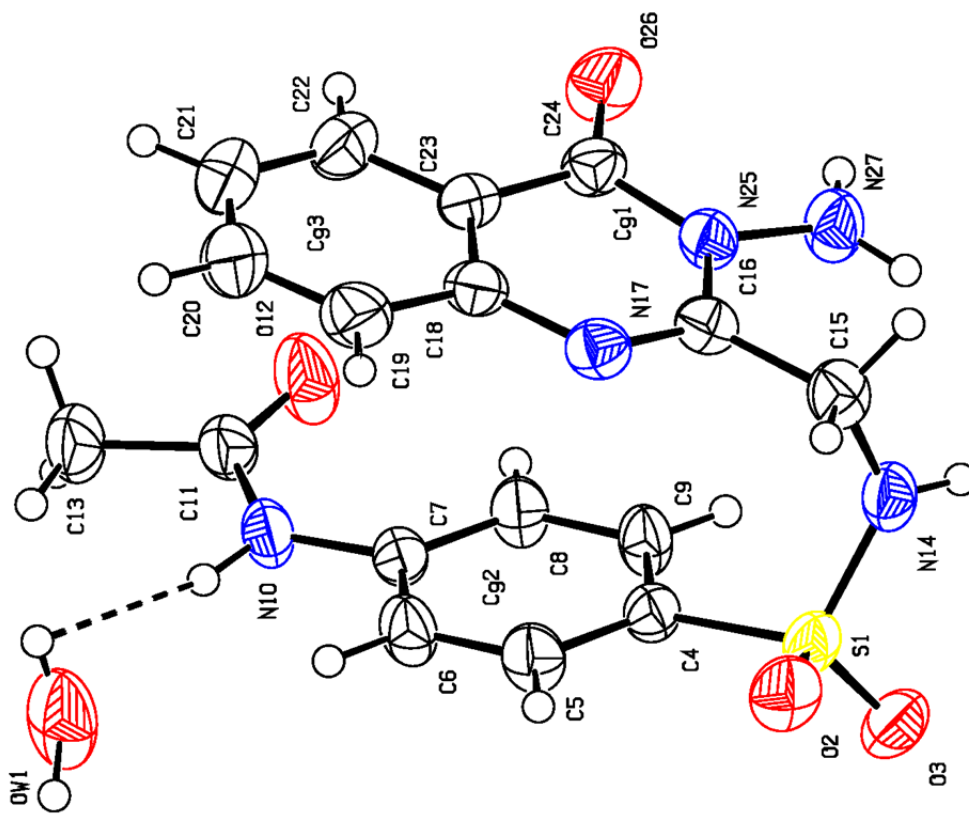
Fig. S2. Molecular packing diagram
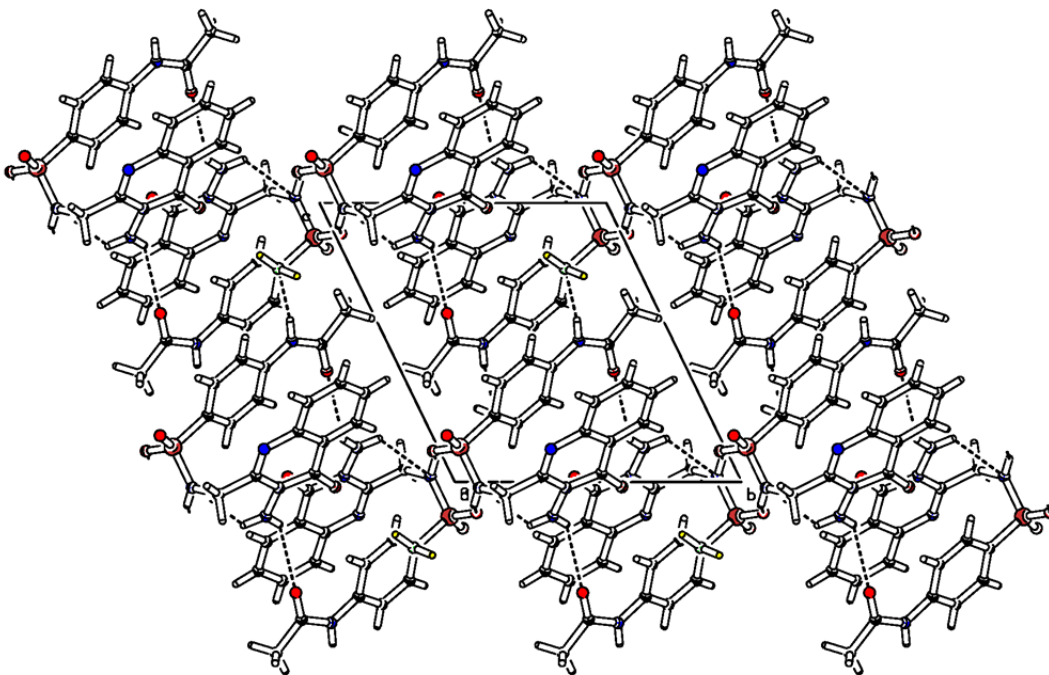
3. Experimental Section

3.1. Synthesis of *N*-(4-(*N*-((3-amino-4-oxo-3,4-dihydroquinazolin-2-yl)methyl) sulfamoyl)phenyl) acetamide 5

Method-I: To a mixture of *N*-acylanthranilic acid (**3**) (0.783 g, 0.002 mol) and appropriate hydrazines (0.0022 mol) [for instance, hydrazine hydrates respectively] in THF (25 mL), a solution of phosphorus trichloride (PCl₃, 0.275 g, 0.002 mol) in THF (5 mL) was added slowly with continuous stirring over a period of 5-10 min. The resulting mixture was allowed to warm at appropriate temperature (40-70 °C) for 25-35 min, after completion of the reaction as indicated by TLC, the mixture was allowed to cool at room temperature, poured into 100 mL icecold water and neutralized with 10% NaHCO₃ solution. The solid product thus separated was filtered off, washed with distilled water and recrystallized from *R*-spirit to give appropriate 4-quinazolone derivatives in excellent yields (Table S1). Also similar protocol was followed with the same reactants in their mole ratio under microwave irradiation methodology for an appropriate time with a power of 280 W leading to desired compounds (Table S2).

Method-II: An appropriate quantity of benzoxazinones (**4**) (0.002 mol) and hydrazines (0.0022 mol) were taken in a solution of pyridine (2-3 mL). The mixture was then heated under refluxing temperature for an appropriate time (Table S3) and monitored for the formation of desired products. For microwave assisted synthesis, the mixture was heated under microwave irradiation at 455 W for an appropriate time (Table S3) and monitored for the formation of desired products. After cooling to room temperature, reaction mixture was diluted with in ethyl acetate (40 mL) and washed with distilled water (2 × 20 mL), dil. acid (2 × 10 mL), aqueous base (2 × 20 mL) and distilled water (20 mL) sequentially by liquid-liquid extraction. The organic layer was dried and the resulting crude product was further purified by column chromatography.

Method-III: An anthranilic acid (0.002 mol), *N*-(4-acetamidobenzenesulfonyl)amino acids (**1**) (0.002 mol), and triphenyl phosphite (0.63 mL, 0.75 g, 0.0024 mol) in 2-3 mL of dry pyridine were charged in a round bottom flask fitted with a reflux condenser. The resulting clear solution was heated to reflux with constant stirring till completion of the reaction as indicated by TLC. Upon consumption of anthranilic acid, appropriate hydrazine hydrate (0.002 mol) was added and the resulting mixture was heated again to reflux for appropriate time (Table S4). After completion of the reaction as per TLC evaluations, the reaction mixture was concentrated *in vacuo*, and the residues were purified by column chromatography (chloroform/methanol) to afford the desired products. Similarly, the same reaction was carried out under microwave irradiation at 455 W for appropriate time (Table S5) leading to desired product.

3.2. Synthesis of *N*-(4-(*N*-((3-(substituted benzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)alkyl)sulfamoyl)phenyl)acetamide derivatives 8a-v

Method-I: To a mixture of 3-amino quinazolinone (0.002 mol) and appropriate aromatic aldehydes (0.0022 mol) in ethanol (25 mL) and catalytic amount of acetic acid was added

with continuous stirring. The resulting mixture was heated under classical as well as microwave irradiation to reflux for appropriate time, after completion of the reaction as indicated by TLC, the mixture was allowed to cool at room temperature, poured into 100 mL icecold water and neutralized with 10% $NaHCO_3$ solution. The solid product thus separated was filtered off, washed with distilled water and dried in *vacuo* to afford the desired products.

Method-II: To a mixture of 3-amino quinazolinone (0.002 mol) and appropriate aromatic aldehydes (0.0022 mol) in ethanol (25 mL) and catalytic amount of mineral acid (H_2SO_4) was added with continuous stirring. The resulting mixture was heated under conventional as well as microwave irradiation to reflux for appropriate time span, after completion of the reaction as indicated by TLC, the mixture was allowed to cool at room temperature, poured into 100 mL icecold water and neutralized with 10% Na_2CO_3 solution. The solid product thus separated was filtered off, washed with distilled water and dried in *vacuo* to afford the desired products.

Method-III: To a mixture of 3-amino quinazolinone (0.002 mol) and appropriate aromatic aldehydes (0.0022 mol) in DMF (30 mL). The resulting reaction mass was heated under conventional as well as microwave irradiation to reflux for appropriate time span, after completion of the reaction as indicated by TLC, the mixture was allowed to cool at room temperature, poured into 100 mL icecold water and neutralized with 10% Na_2CO_3/ $NaHCO_3$ solution. The solid product thus separated was filtered off, washed with distilled water and dried in *vacuo* to afford the desired products.

4. Spectral Data (8a-8v)

4.1. (E)-N-(4-(N-((3-(4-nitrobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8a). White solid; mp: 176-178 °C; $[\alpha]_D^{25}$ -97.8 (*c* 0.75 in $CHCl_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3268, 3189 (N–H str.), 3061, 2929 (C–H str.), 1685 (C=O str.), 1611, 1592, 1493 (C=N, C=C str.), 1329, 1156 (S=O str.), 1530, 1349 (N=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.18 (s, 1H, Ar–N$\underline{H}$Ac), 9.28 (s, 1H, –N=C$\underline{H}$–), 8.39 (d, *J*= 8.8 Hz, 2H, Ar$\underline{H}$), 8.19 (d, *J*= 8.8 Hz, 2H, Ar$\underline{H}$), 8.14 (dd, *J*= 8.0, 1.2 Hz, 2H, Ar$\underline{H}$), 8.09 (t, *J*= 6 Hz, 1H, SO_2N$\underline{H}$–CH_2), 7.84 (dt, *J*= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.71 (d, *J*= 8.8 Hz, 2H, Ar$\underline{H}$), 7.60 (d, *J*= 7.6 Hz, 1H, Ar$\underline{H}$), 7.58-7.54 (m, 2H, Ar$\underline{H}$), 4.32 (d, *J*= 6 Hz, 2H, NH–C$\underline{H_2}$), 2.04 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.8, 165.6, 157.4, 150.8, 149.5, 145.3, 142.7, 138.6, 134.7, 134.0, 129.9, 127.7, 127.2, 126.7, 124.1, 121.0, 118.2, 44.9, 24.0; MS (ESI) *m/z*: 520.8 $[M+H]^+$; Anal. Calcd. for $C_{24}H_{20}N_6O_6S$: C, 55.38; H, 3.87; N, 16.15. Found: C, 55.25; H, 3.90; N, 16.25 %.

4.2. (E)-N-(4-(N-((3-(3-nitrobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8b). White solid; mp: 166-169 °C; $[\alpha]_D^{25}$ -103.2 (*c* 0.75 in $CHCl_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3241, 3180 (N–H str.), 3061, 2930 (C–H str.), 1689 (C=O str.), 1605, 1594, 1493 (C=N, C=C str.), 1320, 1159 (S=O str.), 1533, 1351 (N=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.25 (s, 1H, Ar–N$\underline{H}$Ac), 8.64 (s, 1H, –N=C$\underline{H}$–), 8.34 (dd, *J*= 8, 1.2 Hz, 1H, Ar$\underline{H}$), 8.29 (s, 1H, Ar$\underline{H}$), 7.99 (t, *J*= 5.6 Hz, 1H, SO_2N$\underline{H}$–CH_2), 7.91-7.80 (m, 3H, Ar$\underline{H}$), 7.68 (dt, *J*= 8, 1.2 Hz, 1H, Ar$\underline{H}$), 7.60-7.54 (m, 5H,

Ar$\underline{H}$), 7.44 (dt, *J*= 8, 1.6 Hz, 1H, Ar$\underline{H}$), 4.06 (d, *J*= 5.6 Hz, 2H, NH–C$\underline{H_2}$), 2.01 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.2, 162.6, 161.7, 151.8, 147.4, 146.2, 142.5, 138.2, 134.7, 134.1, 132.5, 131.3, 127.6, 127.1, 126.8, 126.2, 122.4, 120.7, 118.3, 118.1, 45.2, 24.2; MS (ESI) *m/z*: 520.8 [M+H]$^+$; Anal. Calcd. for C$_{24}$H$_{20}$N$_6$O$_6$S: C, 55.38; H, 3.87; N, 16.15. Found: C, 55.21; H, 3.89; N, 16.23%.

4.3. *(E)-N-(4-(N-((3-(2-nitrobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8c).* White solid; mp: 229-231 °C; [*α*]$_D^{25}$ -62.7 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3249, 3190 (N–H str.), 3073, 2926 (C–H str.), 1690 (C=O str.), 1619, 1595, 1493 (C=N, C=C str.), 1327, 1160 (S=O str.), 1532, 1345 (N=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.17 (s, 1H, Ar–N$\underline{H}$Ac), 8.46 (s, 1H, –N=C$\underline{H}$–), 8.38 (dd, *J*= 8.4, 1.6 Hz, 1H, Ar$\underline{H}$), 8.10 (d, *J*= 8 Hz, 1H, Ar$\underline{H}$), 8.05 (d, *J*= 8 Hz, 1H, Ar$\underline{H}$), 7.92 (t, *J*= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.85 (d, *J*= 8.4 Hz, 1H, Ar$\underline{H}$), 7.78-7.75 (m, 3H, Ar$\underline{H}$), 7.62-7.57 (m, 5H, Ar$\underline{H}$), 3.96 (dd, *J*= 17.2, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 3.76 (dd, *J*= 17.2, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 2.02 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.4, 161.7, 160.3, 151.0, 146.8, 142.3, 139.1, 136.4, 135.2, 134.6, 129.5, 127.7, 127.5, 127.1, 126.3, 126.1, 125.7, 121.8, 120.7, 118.6, 45.3, 24.5; MS (ESI) *m/z*: 520.7 [M+H]$^+$; Anal. Calcd. for C$_{24}$H$_{20}$N$_6$O$_6$S: C, 55.38; H, 3.87; N, 16.15. Found: C, 55.19; H, 3.84; N, 16.07 %.

4.4. *(E)-N-(4-(N-((3-(4-hydroxybenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8d).* White solid; mp: 153-156 °C; [*α*]$_D^{25}$ -38.4 (*c* 0.75 in CHCl$_3$); **FT-IR** (KBr, v_{max}, cm^{-1}): 3265, 3180 (N–H str.), 3063, 2930 (C–H str.), 1685 (C=O str.), 1612, 1594, 1511 (C=N, C=C str.), 1325, 1157 (S=O str.), 1254 (C–O–C str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.18 (s, 1H, Ar–N$\underline{H}$Ac), 9.16 (s, 1H, –N=C$\underline{H}$–), 8.14 (dd, *J*= 7.6,1.2 Hz, 1H, Ar$\underline{H}$), 7.86 (t, *J*= 5.2 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.79 (dt, *J*= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.67 (d, *J*= 7.6 Hz, 1H, Ar$\underline{H}$), 7.61 (m, 4H, Ar$\underline{H}$), 7.51 (t, *J*= 7.6 Hz, 1H, Ar$\underline{H}$), 7.37 (d, *J*= 8.8 Hz, 2H, Ar$\underline{H}$), 6.87 (d, *J*= 8.8 Hz, 2H, Ar$\underline{H}$), 5.68 (s, 1H, Ar–O$\underline{H}$), 4.21 (d, *J*= 5.2 Hz, 2H, NH–C$\underline{H_2}$), 2.10 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.4, 162.1, 161.1, 155.5, 151.0, 146.2, 142.4, 134.9, 134.3, 133.3, 131.6, 127.7, 127.2, 126.6, 126.2, 121.5, 118.9, 116.4, 45.8, 24.2; MS (ESI) *m/z*: 491.8 [M+H]$^+$; Anal. Calcd. for C$_{24}$H$_{21}$N$_5$O$_5$S: C, 58.65; H, 4.31; N, 14.25. Found: C, 58.58; H, 4.27; N, 14.31 %.

4.5. *(E)-N-(4-(N-((3-(3-hydroxybenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8e).* White solid; mp: 150-152 °C; [*α*]$_D^{25}$ +04.9 (*c* 0.75 in CHCl$_3$); **FT-IR** (KBr, v_{max}, cm^{-1}): 3271, 3189 (N–H str.), 3061, 2932 (C–H str.), 1666 (C=O str.), 1610, 1592, 1494 (C=N, C=C str.), 1328, 1158 (S=O str.), 1268 (C–O–C str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.26 (s, 1H, Ar–N$\underline{H}$Ac), 8.89 (s, 1H, –N=C$\underline{H}$–), 8.12 (dd, *J*= 8, 1.2 Hz, 1H, Ar$\underline{H}$), 7.94 (t, *J*= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.82 (dt, *J*= 8, 1.2 Hz, 1H, Ar$\underline{H}$), 7.75-7.63 (m, 2H, Ar$\underline{H}$), 7.59 (m, 4H, Ar$\underline{H}$), 7.46-7.34 (m, 2H, Ar$\underline{H}$), 7.19-7.06 (m, 2H, Ar$\underline{H}$), 5.78 (s, 1H, Ar–O$\underline{H}$), 4.10 (d, *J*= 5.6 Hz, 2H, NH–C$\underline{H_2}$), 2.03 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.6, 162.2, 161.1, 154.5, 151.3, 146.6, 142.7, 136.1, 134.5, 134.1, 132.4, 127.8, 127.4, 126.5, 126.2, 126.1, 120.5, 118.6, 116.3, 110.9, 45.3, 24.2; MS (ESI) *m/z*: 491.9 [M+H]$^+$; Anal. Calcd. for C$_{24}$H$_{21}$N$_5$O$_5$S: C, 58.65; H, 4.31; N, 14.25. Found: C, 58.60; H, 4.25; N, 14.19 %.

4.6. *(E)-N-(4-(N-((3-(2-hydroxybenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8f).* White solid; mp: 210-213 °C; $[\alpha]_D^{25}$ -20.6 (*c* 0.75 in CHCl₃); FT-IR (KBr, v_{max}, cm⁻¹): 3277, 3188 (N–H str.), 3064, 2939 (C–H str.), 1665 (C=O str.), 1612, 1593, 1498 (C=N, C=C str.), 1327, 1161 (S=O str.), 1264 (C–O–C str.); ¹H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.15 (s, 1H, Ar–N*H*Ac), 8.74 (s, 1H, –N=C*H*–), 8.12 (dd, *J*= 7.6, 1.2 Hz, 1H, Ar*H*), 7.92 (t, *J*= 5.6 Hz, 1H, SO₂N*H*–CH₂), 7.82 (dt, *J*= 7.6, 1.2 Hz, 1H, Ar*H*), 7.75 (dt, *J*= 7.6, 1.2 Hz, 1H, Ar*H*), 7.60-7.56 (m, 5H, Ar*H*), 7.49-7.35 (m, 2H, Ar*H*), 7.10-6.95 (m, 2H, Ar*H*), 5.71 (s, 1H, Ar–O*H*), 3.78 (dd, *J*= 17.0, 5.6 Hz, 1H, NH–C*H*(H)–), 3.69 (dd, *J*= 17.0, 5.6 Hz, 1H, NH–C*H*(H)–), 2.07 (s, 3H, Ar–NHCOC*H₃*); ¹³C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.4, 164.8, 160.2, 155.8, 150.3, 146.6, 142.5, 135.1, 133.5, 134.3, 132.2, 127.7, 127.4, 127.2, 126.7, 126.3, 123.3, 120.7, 118.1, 117.6, 45.4, 24.1; MS (ESI) *m/z*: 491.8 [M+H]⁺; Anal. Calcd. for C₂₄H₂₁N₅O₅S: C, 58.65; H, 4.31; N, 14.25. Found: C, 58.53; H, 4.29; N, 14.20 %.

4.7. *(E)-N-(4-(N-((3-(4-methoxybenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8g).* White solid; mp: 158-162 °C; $[\alpha]_D^{25}$ +29.5 (*c* 0.75 in CHCl₃); FT-IR (KBr, v_{max}, cm⁻¹): 3265, 3180 (N–H str.), 3063, 2930 (C–H str.), 1685 (C=O str.), 1612, 1594, 1511 (C=N, C=C str.), 1325, 1157 (S=O str.), 1254 (C–O–C str.); ¹H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.19 (s, 1H, Ar–N*H*Ac), 8.83 (s, 1H, –N=C*H*–), 8.11 (d, *J*= 7.6 Hz, 1H, Ar*H*), 7.99 (s, 1H, SO₂N*H*–CH₂), 7.88 (d, *J*= 8.4 Hz, 2H, Ar*H*), 7.81 (t, *J*= 8.4 Hz, 1H, Ar*H*), 7.73 (d, *J*= 8.8 Hz, 2H, Ar*H*), 7.64 (d, *J*= 8.8 Hz, 2H, Ar*H*), 7.57 (d, *J*= 8.0 Hz, 1H, Ar*H*), 7.53 (t, *J*= 8.4 Hz, 1H, Ar*H*), 7.12 (d, *J*= 8.4 Hz, 2H, Ar*H*), 4.26 (d, *J*= 3.2 Hz, 2H, NH–C*H₂*), 3.87 (s, 3H, Ar–OC*H₃*), 2.05 (s, 3H, Ar–NHCOC*H₃*); ¹³C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.8, 168.5, 162.9, 157.4, 150.8, 145.5, 142.7, 134.3, 134.0, 130.9, 127.8, 127.1, 126.8, 126.5, 124.7, 121.1, 118.2, 113.6, 55.5, 44.5, 24.1; MS (ESI) *m/z*: 505.9 [M+H]⁺; Anal. Calcd. for C₂₅H₂₃N₅O₅S: C, 59.39; H, 4.59; N, 13.85. Found: C, 59.31; H, 4.54; N, 13.79 %.

4.8. *(E)-N-(4-(N-((3-(3-methoxybenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8h).* White solid; mp: 152-155 °C; $[\alpha]_D^{25}$ -73.3 (*c* 0.75 in CHCl₃); FT-IR (KBr, v_{max}, cm⁻¹): 3271, 3189 (N–H str.), 3061, 2932 (C–H str.), 1666 (C=O str.), 1610, 1592, 1494 (C=N, C=C str.), 1328, 1158 (S=O str.), 1268 (C–O–C str.); ¹H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.19 (s, 1H, Ar–N*H*Ac), 9.09 (s, 1H, –N=C*H*–), 8.15 (dd, *J*= 8, 1.2 Hz, 1H, Ar*H*), 7.87 (t, *J*= 5.6 Hz, 1H, SO₂N*H*–CH₂), 7.79 (dt, *J*= 8, 1.2 Hz, 1H, Ar*H*), 7.72-7.60 (m, 2H, Ar*H*), 7.59 (m, 4H, Ar*H*), 7.45-7.37 (m, 2H, Ar*H*), 7.13-7.10 (m, 2H, Ar*H*), 4.12 (d, *J*= 5.6 Hz, 2H, NH–C*H₂*), 3.84 (s, 3H, Ar–OC*H₃*), 2.04 (s, 3H, Ar–NHCOC*H₃*); ¹³C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.7, 165.4, 161.1, 154.3, 151.7, 146.2, 142.9, 136.5, 134.6, 134.2, 132.3, 127.8, 127.5, 126.7, 126.2, 126.1, 120.3, 118.6, 116.8, 110.9, 55.3, 45.5, 24.2; MS (ESI) *m/z*: 505.8 [M+H]⁺; Anal. Calcd. for C₂₅H₂₃N₅O₅S: C, 59.39; H, 4.59; N, 13.85. Found: C, 59.27; H, 4.65; N, 13.80 %.

4.9. *(E)-N-(4-(N-((3-(2-methoxybenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8i).* White solid; mp: 209-213 °C; $[\alpha]_D^{25}$ -56.1 (*c* 0.75 in CHCl₃); FT-IR (KBr, v_{max}, cm⁻¹): 3277, 3188 (N–H str.), 3064, 2939 (C–H str.), 1665 (C=O str.), 1612, 1593, 1498 (C=N, C=C str.), 1327, 1161 (S=O str.), 1264 (C–O–C str.);

^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.15 (s, 1H, Ar–N$\underline{H}$Ac), 9.17 (s, 1H, –N=C$\underline{H}$–), 8.13 (dd, J= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.85 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.80 (dt, J= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.69 (dt, J= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.63-7.54 (m, 5H, Ar$\underline{H}$), 7.40-7.31 (m, 2H, Ar$\underline{H}$), 7.09-6.95 (m, 2H, Ar$\underline{H}$), 3.81 (dd, J= 17.0, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 3.73 (dd, J= 17.0, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 3.85 (s, 3H, Ar–OC$\underline{H_3}$), 2.07 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.7, 164.2, 160.1, 155.7, 150.9, 146.5, 142.8, 135.4, 133.5, 134.2, 132.4, 127.9, 127.4, 127.1, 126.6, 126.2, 123.9, 120.4, 118.6, 117.7, 55.3, 45.3, 24.1; MS (ESI) m/z: 505.9 [M+H]$^+$; Anal. Calcd. for C$_{25}$H$_{23}$N$_5$O$_5$S: C, 59.39; H, 4.59; N, 13.85. Found: C, 59.25; H, 4.51; N, 13.89 %.

4.10.   (E)-N-(4-(N-((3-(4-methylbenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide **(8j).** White solid; mp: 193-196 °C; $[\alpha]_D^{25}$ +49.7 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3281, 3180 (N–H str.), 3051, 2926 (C–H str.), 1688 (C=O str.), 1605, 1593, 1509 (C=N, C=C str.), 1325, 1159 (S=O str.), 1374 (C–H def.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.25 (s, 1H, Ar–N$\underline{H}$Ac), 8.92 (s, 1H, –N=C$\underline{H}$–), 8.15 (dd, J= 7.6,1.2 Hz, 1H, Ar$\underline{H}$), 7.83 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.78 (dt, J= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.65 (m, 4H, Ar$\underline{H}$), 7.57 (d, J= 7.6 Hz, 1H, Ar$\underline{H}$), 7.51 (t, J= 7.6 Hz, 1H, Ar$\underline{H}$), 7.39 (d, J= 8.8 Hz, 2H, Ar$\underline{H}$), 7.21 (d, J= 8.8 Hz, 2H, Ar$\underline{H}$), 4.19 (d, J= 5.2 Hz, 2H, NH–C$\underline{H_2}$), 2.17 (s, 3H, Ar–C$\underline{H_3}$), 2.01 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.8, 168.4, 161.7, 151.5, 146.5, 142.5, 138.3, 134.7, 134.3, 133.9, 128.2, 127.8, 127.6, 127.2, 126.7, 121.9, 118.5, 45.1, 24.1, 21.3, 12.4; MS (ESI) m/z: 489.8 [M+H]$^+$; Anal. Calcd. for C$_{25}$H$_{23}$N$_5$O$_4$S: C, 61.34; H, 4.74; N, 14.31. Found: C, 61.22; H, 4.76; N, 14.35 %.

4.11.   (E)-N-(4-(N-((3-(3-methylbenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide **(8k).** White solid; mp: 203-205 °C; $[\alpha]_D^{25}$ +07.5 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3231, 3173 (N–H str.), 3050, 2928 (C–H str.), 1677 (C=O str.), 1604, 1591, 1487 (C=N, C=C str.), 1323, 1159 (S=O str.), 1381 (C–H def.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.20 (s, 1H, Ar–N$\underline{H}$Ac), 8.77 (s, 1H, –N=C$\underline{H}$–), 8.05 (dd, J= 8, 1.2 Hz, 1H, Ar$\underline{H}$), 7.93 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.87 (dt, J= 7.6, 1.6 Hz, 1H, Ar$\underline{H}$), 7.71-7.65 (m, 3H, Ar$\underline{H}$), 7.61 (m, 4H, Ar$\underline{H}$), 7.34 (dt, J= 8, 1.6 Hz, 1H, Ar$\underline{H}$), 7.32-7.27 (m, 2H, Ar$\underline{H}$), 4.09 (d, J= 5.6 Hz, 2H, NH–C$\underline{H_2}$), 2.21 (s, 3H, Ar–C$\underline{H_3}$), 2.09 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.7, 167.0, 161.3, 151.3, 146.7, 142.9, 137.3, 134.5, 133.6, 132.4, 128.5, 128.8, 127.9, 127.5, 127.1, 126.6, 126.2, 122.6, 120.2, 118.7, 44.7, 24.1, 21.6; MS (ESI) m/z: 489.9 [M+H]$^+$; Anal. Calcd. for C$_{25}$H$_{23}$N$_5$O$_4$S: C, 61.34; H, 4.74; N, 14.31. Found: C, 61.31; H, 4.69; N, 14.24 %.

4.12.   (E)-N-(4-(N-((3-(2-methylbenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide **(8l).** White solid; mp: 177-179 °C; $[\alpha]_D^{25}$ -26.2 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3280, 3190 (N–H str.), 3063, 2924 (C–H str.), 1664 (C=O str.), 1612, 1594, 1492 (C=N, C=C str.), 1332, 1162 (S=O str.), 1362 (C–H def.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.23 (s, 1H, Ar–N$\underline{H}$Ac), 8.59 (s, 1H, –N=C$\underline{H}$–), 8.13 (dd, J= 8.4, 1.6 Hz, 1H, Ar$\underline{H}$), 7.96 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.81 (dt, J= 7.6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.54 (dt, J= 7.6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.59 (m, 4H, Ar$\underline{H}$), 7.52-7.48 (m, 3H, Ar$\underline{H}$), 7.42-7.33 (m, 2H, Ar$\underline{H}$), 3.82 (dd, J= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 3.77 (dd, J= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 2.18 (s, 3H, Ar–C$\underline{H_3}$), 2.07 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100

MHz, DMSO-d_6, δ_C, ppm): 168.6, 166.2, 160.1, 150.7, 146.3, 142.4, 136.5, 135.0, 134.1, 133.4, 130.4, 128.5, 127.7, 127.2, 126.6, 126.3, 126.0, 125.4, 120.3, 118.1, 45.5, 24.1, 19.5; MS (ESI) m/z: 489.9 [M+H]$^+$; Anal. Calcd. for $C_{25}H_{23}N_5O_4S$: C, 61.34; H, 4.74; N, 14.31. Found: C, 61.28; H, 4.70; N, 14.25 %.

3.13. *(E)-N-(4-(N-((3-(4-chlorobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8m).* White solid; mp: 168-170 °C; $[\alpha]_D^{25}$ -187.9 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3260, 3189 (N–H str.), 3065, 2927 (C–H str.), 1675 (C=O str.), 1604, 1591, 1492 (C=N, C=C str.), 1338, 1155 (S=O str.), 725 (C–Cl str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.22 (s, 1H, Ar–N$\underline{H}$Ac), 9.12 (s, 1H, –N=C$\underline{H}$–), 8.01 (dd, J= 7.6,1.2 Hz, 1H, Ar$\underline{H}$), 7.95 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.87 (dt, J= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.73 (d, J= 8.8 Hz, 2H, Ar$\underline{H}$), 7.67 (m, 4H, Ar$\underline{H}$), 7.61 (d, J= 7.6 Hz, 1H, Ar$\underline{H}$), 7.55 (t, J= 7.6 Hz, 1H, Ar$\underline{H}$), 7.40 (d, J= 8.8 Hz, 2H, Ar$\underline{H}$), 4.31 (d, J= 5.2 Hz, 2H, NH–C$\underline{H_2}$), 2.10 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.7, 164.6, 161.4, 151.9, 146.6, 142.4, 135.7, 134.9, 132.4, 130.3, 128.2, 127.8, 127.5, 127.0, 126.7, 126.4, 120.9, 118.3, 44.5, 24.1; MS (ESI) m/z: 509.8 [M+H]$^+$, 511.8 [(M+H)+2]$^+$; Anal. Calcd. for $C_{24}H_{20}ClN_5O_4S$: C, 56.52; H, 3.95; N, 13.73. Found: C, 56.39; H, 3.89; N, 13.75 %.

4.14. *(E)-N-(4-(N-((3-(3-chlorobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8n).* White solid; mp: 199-203 °C; $[\alpha]_D^{25}$ -156.8 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3241, 3182 (N–H str.), 3062, 2931 (C–H str.), 1683 (C=O str.), 1609, 1590, 1492 (C=N, C=C str.), 1322, 1159 (S=O str.), 729 (C–Cl str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.16 (s, 1H, Ar–N$\underline{H}$Ac), 8.93 (s, 1H, –N=C$\underline{H}$–), 8.12 (dd, J= 8, 1.2 Hz, 1H, Ar$\underline{H}$), 7.90 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.79 (dt, J= 7.6, 1.6 Hz, 1H, Ar$\underline{H}$), 7.75-7.69 (m, 2H, Ar$\underline{H}$), 7.60 (m, 4H, Ar$\underline{H}$), 7.56-7.50 (m, 3H, Ar$\underline{H}$), 7.43 (dt, J= 8, 1.6 Hz, 1H, Ar$\underline{H}$), 4.02 (d, J= 5.6 Hz, 2H, NH–C$\underline{H_2}$), 2.03 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.9, 163.8, 161.5, 151.9, 146.7, 142.5, 137.4, 134.8, 133.4, 131.7, 130.7, 130.5, 127.9, 127.6, 127.3, 126.7, 126.4, 125.8, 120.7, 118.8, 45.2, 24.1; MS (ESI) m/z: 509.8 [M+H]$^+$, 511.8 [(M+H)+2]$^+$; Anal. Calcd. for $C_{24}H_{20}ClN_5O_4S$: C, 56.52; H, 3.95; N, 13.73. Found: C, 56.46; H, 3.91; N, 13.80 %.
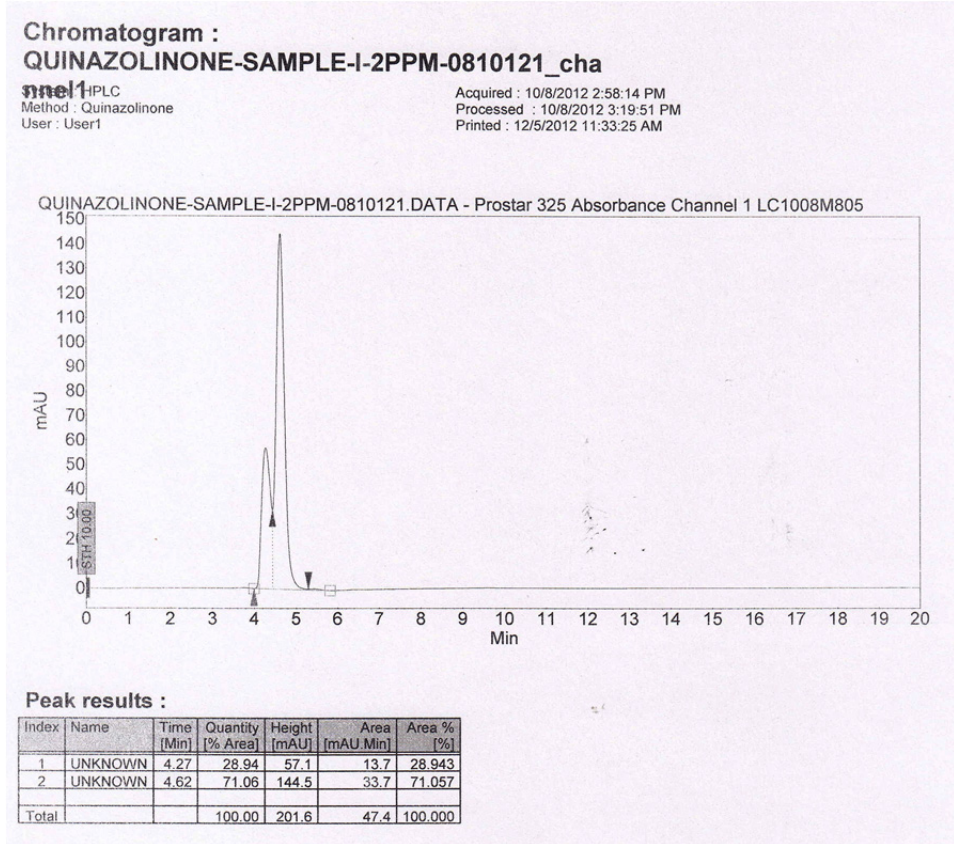
4.15. *(E)-N-(4-(N-((3-(2-chlorobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8o).* White solid; mp: 195-198 °C; $[\alpha]_D^{25}$ -84.3 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3281, 3190 (N–H str.), 3069, 2935 (C–H str.), 1689 (C=O str.), 1610, 1593, 1492 (C=N, C=C str.), 1331, 1161 (S=O str.), 722 (C–Cl str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.14 (s, 1H, Ar–N$\underline{H}$Ac), 8.77 (s, 1H, –N=C$\underline{H}$–), 8.04 (dd, J= 8.4, 1.6 Hz, 1H, Ar$\underline{H}$), 8.01 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.82 (dt, J= 6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.79 (dt, J= 6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.65-7.58 (m, 6H, Ar$\underline{H}$), 7.56-7.45 (m, 3H, Ar$\underline{H}$), 3.78 (dd, J= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 3.72 (dd, J= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 2.11 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.6, 163.5, 161.2, 150.7, 146.9, 142.9, 135.3, 134.8, 133.6, 130.4, 129.7, 129.4, 127.7, 127.5, 127.1, 126.6, 126.3, 125.4, 120.6, 118.7, 44.9, 24.1; MS (ESI) m/z: 509.9 [M+H]$^+$, 511.9 [(M+H)+2]$^+$; Anal. Calcd. for $C_{24}H_{20}ClN_5O_4S$: C, 56.52; H, 3.95; N, 13.73. Found: C, 56.47; H, 3.92; N, 13.77 %.

4.16. *(E)-N-(4-(N-((3-(4-bromobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide **(8p).*** White solid; mp: 169-173 °C; $[\alpha]_D^{25}$ -77.6 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3262, 3183 (N–H str.), 3050, 2929 (C–H str.), 1680 (C=O str.), 1612, 1593, 1492 (C=N, C=C str.), 1325, 1155 (S=O str.), 618(C–Br str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.22 (s, 1H, Ar–N$\underline{H}$Ac), 9.39 (s, 1H, –N=C$\underline{H}$–), 8.07 (dd, *J*= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.94 (t, *J*= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.84 (dt, *J*= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.75 (d, *J*= 8.8 Hz, 2H, Ar$\underline{H}$), 7.64 (m, 4H, Ar$\underline{H}$), 7.59 (d, *J*= 7.6 Hz, 1H, Ar$\underline{H}$), 7.54 (t, *J*= 7.6 Hz, 1H, Ar$\underline{H}$), 7.39 (d, *J*= 8.8 Hz, 2H, Ar$\underline{H}$), 4.42 (d, *J*= 5.6 Hz, 2H, NH–C$\underline{H}_2$), 2.04 (s, 3H, Ar–NHCOC$\underline{H}_3$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.8, 165.0, 161.0, 151.3, 146.4, 142.8, 135.2, 134.7, 132.5, 133.0, 130.8, 127.3, 127.1, 127.0, 126.3, 123.0, 120.4, 118.3, 45.4, 24.1; MS (ESI) *m/z*: 555.9 [M+H]$^+$, 557.9 [(M+H)+2]$^+$; Anal. Calcd. for C$_{24}$H$_{20}$BrN$_5$O$_4$S: C, 51.99; H, 3.64; N, 12.63. Found: C, 51.96; H, 3.60; N, 12.67 %.

4.17. *(E)-N-(4-(N-((3-(3-bromobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide **(8q).*** White solid; mp: 161-164 °C; $[\alpha]_D^{25}$+29.8 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3240, 3179 (N–H str.), 3057, 2930 (C–H str.), 1680 (C=O str.), 1610, 1590, 1493 (C=N, C=C str.), 1322, 1158 (S=O str.), 617 (C–Br str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.23 (s, 1H, Ar–N$\underline{H}$Ac), 9.11 (s, 1H, –N=C$\underline{H}$–), 8.07 (dd, *J*= 8, 1.2 Hz, 1H, Ar$\underline{H}$), 7.97 (t, *J*= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.85 (dt, *J*= 7.6, 1.6 Hz, 1H, Ar$\underline{H}$), 7.79-7.74 (m, 2H, Ar$\underline{H}$), 7.59 (m, 5H, Ar$\underline{H}$), 7.55-7.50 (m, 3H, Ar$\underline{H}$), 7.40 (dt, *J*= 8, 1.6 Hz, 1H, Ar$\underline{H}$), 4.15 (d, *J*= 5.6 Hz, 1H, NH–C$\underline{H}_2$), 2.11 (s, 3H, Ar–NHCOC$\underline{H}_3$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.7, 164.3, 161.7, 151.0, 146.3, 142.0, 137.7, 134.9, 133.3, 132.5, 131.2, 130.8, 127.8, 127.5, 127.0, 126.5, 126.1, 121.9, 120.9, 118.7, 45.6, 24.1; MS (ESI) *m/z*: 555.9 [M+H]$^+$, 557.9 [(M+H)+2]$^+$; Anal. Calcd. for C$_{24}$H$_{20}$BrN$_5$O$_4$S: C, 51.99; H, 3.64; N, 12.63. Found: C, 51.90; H, 3.62; N, 12.60 %.

4.18. *(E)-N-(4-(N-((3-(2-bromobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide **(8r).*** White solid; mp: 182-187 °C; $[\alpha]_D^{25}$ +103.2 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3234, 3183 (N–H str.), 3053, 2922 (C–H str.), 1675 (C=O str.), 1612, 1592, 1493 (C=N, C=C str.), 1323, 1161 (S=O str.), 616 (C–Br str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.18 (s, 1H, Ar–N$\underline{H}$Ac), 8.90 (s, 1H, –N=C$\underline{H}$–), 8.16 (dd, *J*= 8.4, 1.6 Hz, 1H, Ar$\underline{H}$), 8.07 (t, *J*= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.91 (dt, *J*= 6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.80 (dt, *J*= 6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.61-7.57 (m, 6H, Ar$\underline{H}$), 7.51-7.44 (m, 3H, Ar$\underline{H}$), 3.79 (dd, *J*= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 3.71 (dd, *J*= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 2.00 (s, 3H, Ar–NHCOC$\underline{H}_3$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.8, 163.1, 160.3, 150.5, 146.7, 142.9, 135.6, 134.8, 133.4, 133.1, 131.0, 130.3, 129.5, 127.9, 127.7, 127.3, 126.6, 122.1, 120.6, 118.4, 44.7, 24.1; MS (ESI) *m/z*: 555.8 [M+H]$^+$, 557.8 [(M+H)+2]$^+$; Anal. Calcd. for C$_{24}$H$_{20}$BrN$_5$O$_4$S: C, 51.99; H, 3.64; N, 12.63. Found: C, 51.88; H, 3.67; N, 13.57 %.

4.19. *(E)-N-(4-(N-((3-(4-fluorobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide **(8s).*** White solid; mp: 201-205 °C; $[\alpha]_D^{25}$ -21.7 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3262, 3184 (N–H str.), 3049, 2928 (C–H str.), 1676 (C=O str.), 1591, 1504 (C=N, C=C str.), 1334, 1157 (S=O str.), 1222 (C–F str.); ^{1}H-NMR

(400 MHz, DMSO-d_6, δ_H, ppm): 10.20 (s, 1H, Ar–N$\underline{H}$Ac), 9.18 (s, 1H, –N=C$\underline{H}$–), 8.06 (dd, J= 7.6,1.2 Hz, 1H, Ar$\underline{H}$), 7.81 (t, J= 5.2 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.74 (dt, J= 7.6, 1.2 Hz, 1H, Ar$\underline{H}$), 7.68 (d, J= 8.8 Hz, 2H, Ar$\underline{H}$), 7.63 (m, 4H, Ar$\underline{H}$), 7.55 (d, J= 7.6 Hz, 1H, Ar$\underline{H}$), 7.51 (t, J= 7.6 Hz, 1H, Ar$\underline{H}$), 7.34 (d, J= 8.8 Hz, 2H, Ar$\underline{H}$), 4.22 (d, J= 5.2 Hz, 2H, NH–C$\underline{H_2}$), 2.13 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.9, 164.7, 161.1, 153.5, 151.9, 146.5, 142.6, 136.3, 134.9, 133.4, 127.5, 127.0, 126.4, 126.1, 125.4, 121.6, 118.5, 116.9, 44.9, 24.1; MS (ESI) *m/z*: 493.9 [M+H]$^+$; Anal. Calcd. for C$_{24}$H$_{20}$FN$_5$O$_4$S: C, 58.41; H, 4.08; N, 14.19. Found: C, 58.38; H, 4.05; N, 14.14 %.

4.20.   (E)-N-(4-(N-((3-(3-fluorobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8t). White solid; mp: 150-153 °C; $[\alpha]_D^{25}$ -42.2 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3261, 3181 (N–H str.), 3053, 2930 (C–H str.), 1680 (C=O str.), 1605, 1609, 1594, 1501 (C=N, C=C str.), 1326, 1155 (S=O str.), 1219 (C–F str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.24 (s, 1H, Ar–N$\underline{H}$Ac), 9.02 (s, 1H, –N=C$\underline{H}$–), 8.12 (dd, J= 8.4, 1.6 Hz, 1H, Ar$\underline{H}$), 7.92 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.88 (dt, J= 6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.78 (dt, J= 6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.68-7.60 (m, 6H, Ar$\underline{H}$), 7.20-7.07 (m, 3H, Ar$\underline{H}$), 4.02 (dd, J= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 3.89 (dd, J= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 2.08 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.7, 163.9, 160.4, 151.6, 151.3, 146.4, 142.0, 135.5, 135.0, 134.6, 130.9, 129.5, 128.1, 127.7, 127.2, 126.7, 126.3, 120.7, 118.5, 113.8, 44.7, 24.1; MS (ESI) *m/z*: 493.8 [M+H]$^+$; Anal. Calcd. for C$_{24}$H$_{20}$FN$_5$O$_4$S: C, 58.41; H, 4.08; N, 14.19. Found: C, 58.35; H, 4.02; N, 14.16 %.

4.21.   (E)-N-(4-(N-((3-(2-fluorobenzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8u). White solid; mp: 152-154 °C; $[\alpha]_D^{25}$ -16.9 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3261, 3181 (N–H str.), 3053, 2930 (C–H str.), 1680 (C=O str.), 1605, 1609, 1594, 1501 (C=N, C=C str.), 1326, 1155 (S=O str.), 1219 (C–F str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.18 (s, 1H, Ar–N$\underline{H}$Ac), 8.78 (s, 1H, –N=C$\underline{H}$–), 8.05 (dd, J= 8.4, 1.6 Hz, 1H, Ar$\underline{H}$), 7.93 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.80 (dt, J= 6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.74 (dt, J= 6, 0.8 Hz, 1H, Ar$\underline{H}$), 7.63-7.57 (m, 6H, Ar$\underline{H}$), 7.15-7.02 (m, 3H, Ar$\underline{H}$), 3.76 (dd, J= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 3.70 (dd, J= 16.8, 5.6 Hz, 1H, NH–C$\underline{H}$(H)–), 2.03 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.9, 163.0, 160.3, 151.8, 151.4, 146.6, 142.3, 135.6, 135.0, 134.0, 130.1, 129.7, 128.5, 127.4, 127.6, 127.3, 126.0, 120.3, 118.8, 113.7, 45.2, 24.1; MS (ESI) *m/z*: 493.9 [M+H]$^+$; Anal. Calcd. for C$_{24}$H$_{20}$FN$_5$O$_4$S: C, 58.41; H, 4.08; N, 14.19. Found: C, 58.29; H, 4.10; N, 14.15 %.

4.22.   (E)-N-(4-(N-((3-(benzylideneamino)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)sulfamoyl)phenyl)acetamide (8v). White solid; mp: 175-177 °C; $[\alpha]_D^{25}$ +124.7 (*c* 0.75 in CHCl$_3$); FT-IR (KBr, v_{max}, cm^{-1}): 3358, 3223 (N–H str.), 3062, 2924 (C–H str.), 1676 (C=O str.), 1612, 1595, 1492 (C=N, C=C str.), 1316, 1154 (S=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6, δ_H, ppm): 10.17 (s, 1H, Ar–N$\underline{H}$Ac), 8.50 (s, 1H, –N=C$\underline{H}$–), 8.16 (dd, J= 8, 1.2 Hz, 1H, , Ar$\underline{H}$), 7.97 (t, J= 5.6 Hz, 1H, SO$_2$N$\underline{H}$–CH$_2$), 7.84 (dt, J= 8, 1.2 Hz, 1H, Ar$\underline{H}$), 7.64 (s, 4H, Ar$\underline{H}$), 7.60-7.54 (m, 5H, Ar$\underline{H}$), 7.46 (dd, J= 8.8, 1.6 Hz, 2H, Ar$\underline{H}$), 4.16 (d, J= 5.6 Hz, 2H, NH–C$\underline{H_2}$), 2.01 (s, 3H, Ar–NHCOC$\underline{H_3}$); ^{13}C-NMR (100 MHz, DMSO-d_6, δ_C, ppm): 168.8, 161.4, 153.2, 151.0, 146.6, 142.3, 135.3, 134.2, 133.6, 129.0, 128.8, 128.6, 127.9,

127.3, 126.5, 126.1, 120.6, 118.4, 45.4, 24.1; MS (ESI) *m/z*: 475.9 [M+H]$^+$; Anal. Calcd. for C$_{24}$H$_{21}$N$_5$O$_4$S: C, 60.62; H, 4.45; N, 14.73. Found: C, 60.59; H, 4.49; N, 14.69 %.

5. Spectral Copies

Fig. S3. HPLC Chromatogram of *E/Z* conformers of 8a molecule having ratio of 71:29

Chromatogram :
QUINAZOLINONE-SAMPLE-I-2PPM-0810121_cha

nnel 1 HPLC
Method : Quinazolinone
User : User1

Acquired : 10/8/2012 2:58:14 PM
Processed : 10/8/2012 3:19:51 PM
Printed : 12/5/2012 11:33:25 AM

QUINAZOLINONE-SAMPLE-I-2PPM-0810121.DATA - Prostar 325 Absorbance Channel 1 LC1008M805

Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	4.27	28.94	57.1	13.7	28.943
2	UNKNOWN	4.62	71.06	144.5	33.7	71.057
Total			100.00	201.6	47.4	100.000

Fig. S4. HPLC Chromatogram of *E*/*Z* conformers of 8a molecule having ratio of 98.88:1.11

Chromatogram :
Quinazolinopne-sample-2-90872ppm-0512121_c
hannel1
Method : Quinazolinone
User : User1

Acquired : 12/5/2012 10:46:49 AM
Processed : 12/5/2012 11:18:56 AM
Printed : 12/5/2012 11:43:51 AM

Quinazolinopne-sample-2-90872ppm-0512121.DATA - Prostar 325 Absorbance Channel 1 LC1008M805

Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	2.47	1.11	0.1	0.0	1.113
2	UNKNOWN	3.12	98.89	3.1	1.3	98.887
Total			100.00	3.1	1.3	100.000

Fig. S5. HPLC Chromatogram of *E*/*Z* conformers of 8a molecule having ratio of 99.98:0.02

Chromatogram :
quinazolinone-sample-2-ppm-r-ii-0910121_chan
nel1 : HPLC
Method : Quinazolinone
User : User1

Acquired : 10/9/2012 11:35:02 AM
Processed : 10/9/2012 11:56:37 AM
Printed : 12/5/2012 11:37:22 AM

quinazolinone-sample-2-ppm-r-ii-0910121.DATA - Prostar 325 Absorbance Channel 1 LC1008M805

Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	1.91	0.02	0.0	0.0	0.022
2	UNKNOWN	4.25	99.98	85.8	20.9	99.978
Total			100.00	85.9	20.9	100.000

Fig. S6. ^{1}H-NMR Spectra of 5

3-NH Quina-Gly
AAA_1H DMSO {D:\Sept09} SICART 1

3-NH Quina-Gly
AAA_1H DMSO {D:\Sept09} SICART 1

3-NH Quina-Gly
AAA_1H DMSO {D:\Sept09} SICART 1

10.171

8.082
8.079
8.062
8.059
7.792
7.789
7.770
7.753
7.748
7.742
7.648
7.630
7.626
7.551
7.531
7.513
7.493
7.475
7.473

10.0   9.5   9.0   8.5   8.0   7.5   ppm

1.00   1.02 4.07 2.04 2.09

Fig. S7. ^{13}C-NMR (APT) Spectra of 5

3-NH Quina-Gly
C13APT DMSO {D:\Sept09} SICART 1

168.79
160.36
153.09
145.96
142.69
134.04
133.78
126.92
126.49
125.82
119.98
118.24

44.31
40.09
39.93
39.73
39.46
39.25
39.04
38.83
24.04

180 160 140 120 100 80   60   40   20   ppm

3-NH Quina-Gly
C13APT DMSO {D:\Sept09} SICART 1

Fig. S8. Mass Spectra of 5

Fig. S9. ^{1}H-NMR Spectra of 8a ii

UNO2
AAA_1H DMSO {D:\Sept09} SICART 1

UNO2
AAA_1H DMSO {D:\Sept09} SICART 1
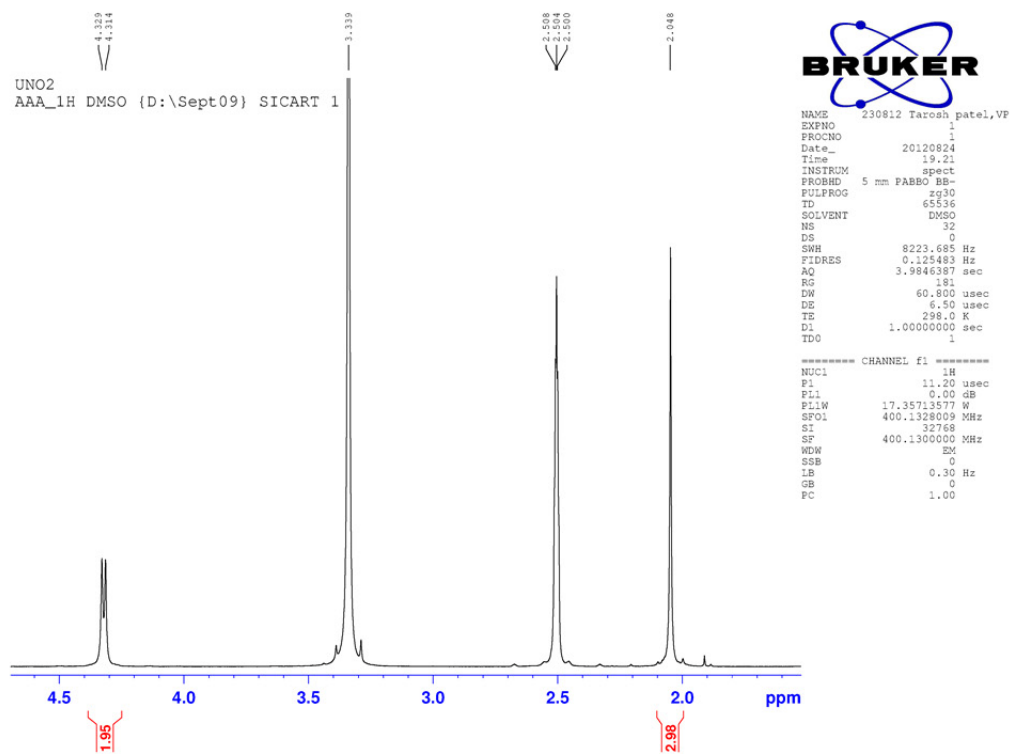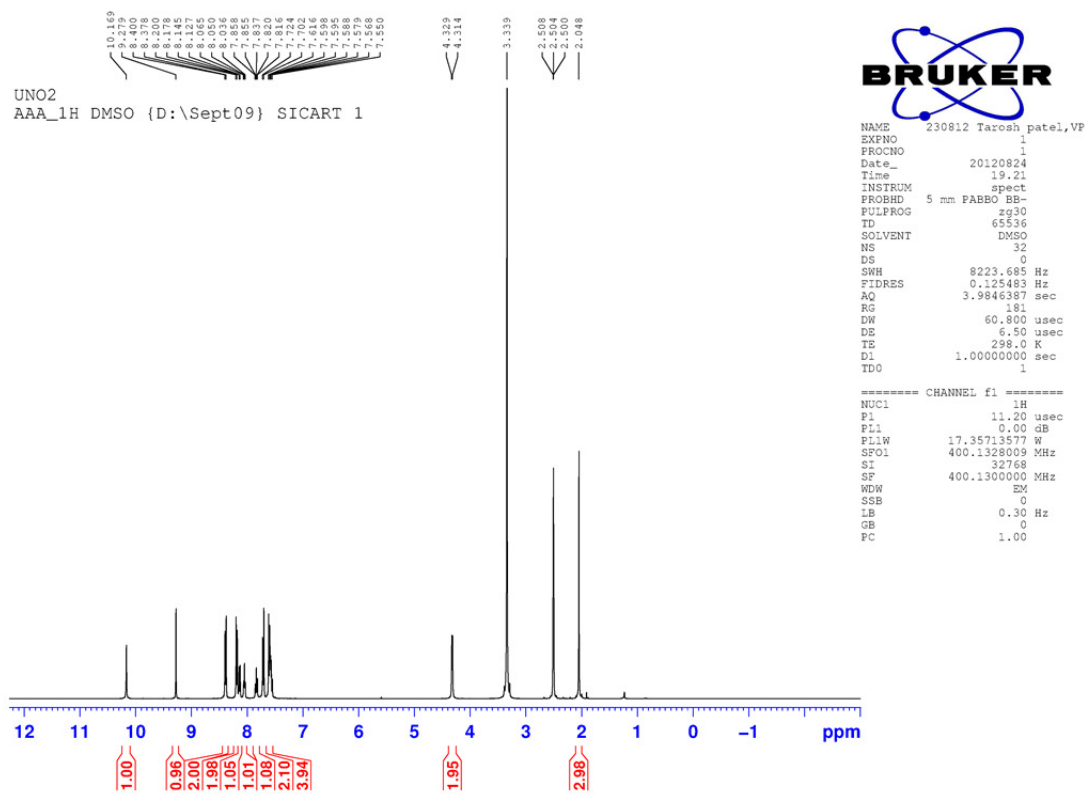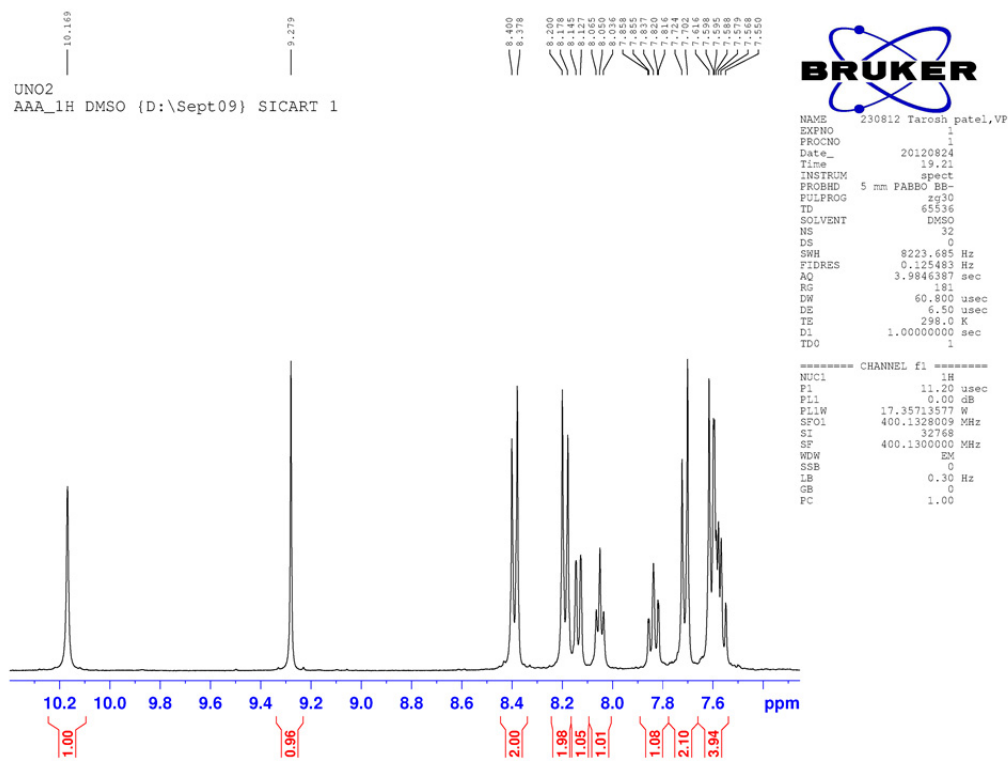
Fig. S10. ^{13}C-NMR Spectra of 8a ii

168.77
165.59
157.44
150.79
149.52
145.25
142.68
138.25
134.67
134.02
129.89
127.70
127.18
126.73
124.06
121.01
118.20

170 165 160 155 150 145 140 135 130 125 120 115 ppm

Fig. S11. ¹³C-NMR (APT) Spectra of 8a ii

168.78
165.66
157.42
150.78
149.52
145.25
145.68
142.68
134.00
134.68
129.90
127.71
127.18
126.73
124.07
124.00
121.00
118.19

44.85
40.09
39.88
39.68
39.47
39.26
39.05
38.84
24.04

180 160 140 120 100 80 60 40 20 ppm

Fig. S12. ^{1}H-^{13}C HMBC Spectra of 8a ii
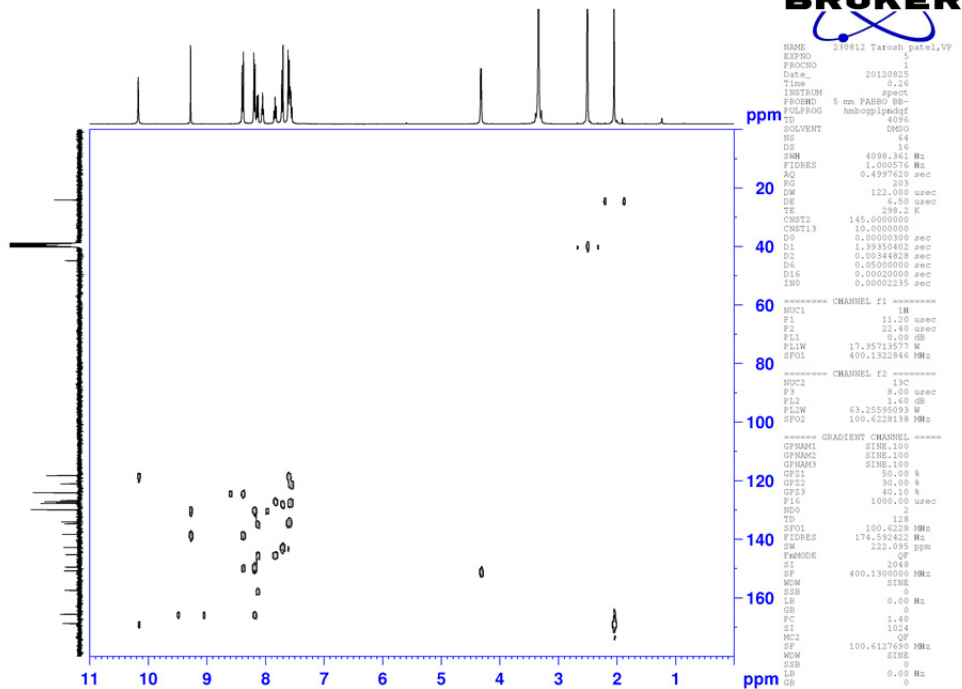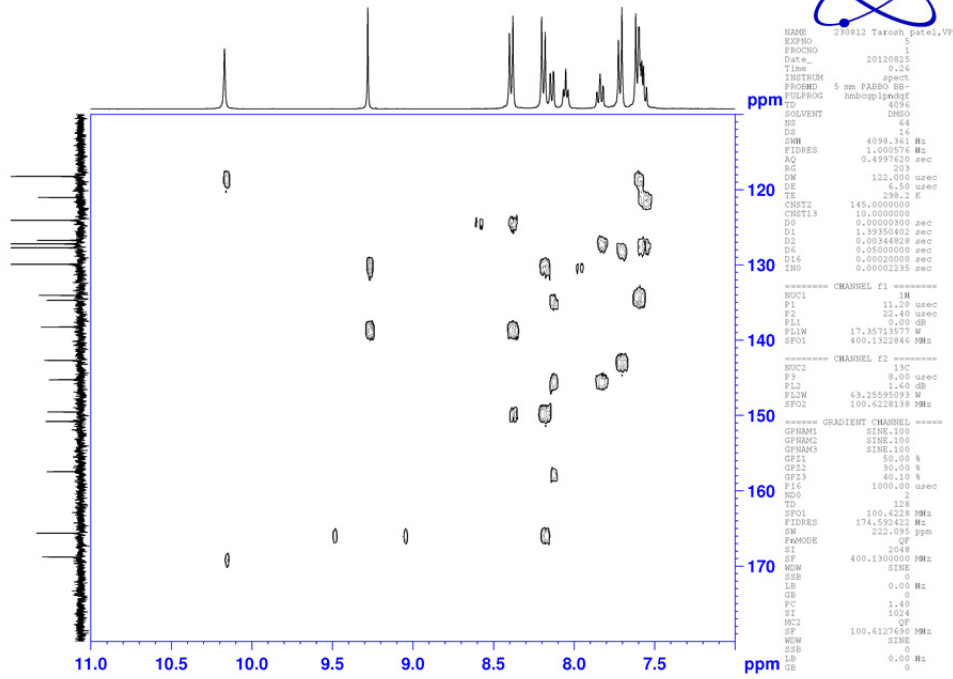
Fig. S13. ^{1}H-^{13}C HMQC Spectra of 8a ii
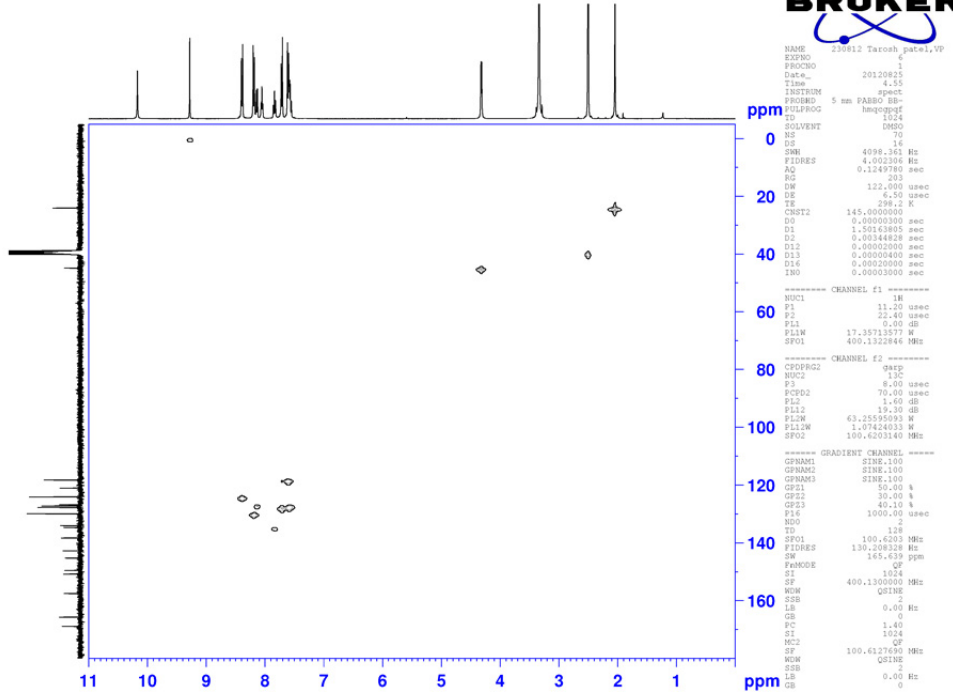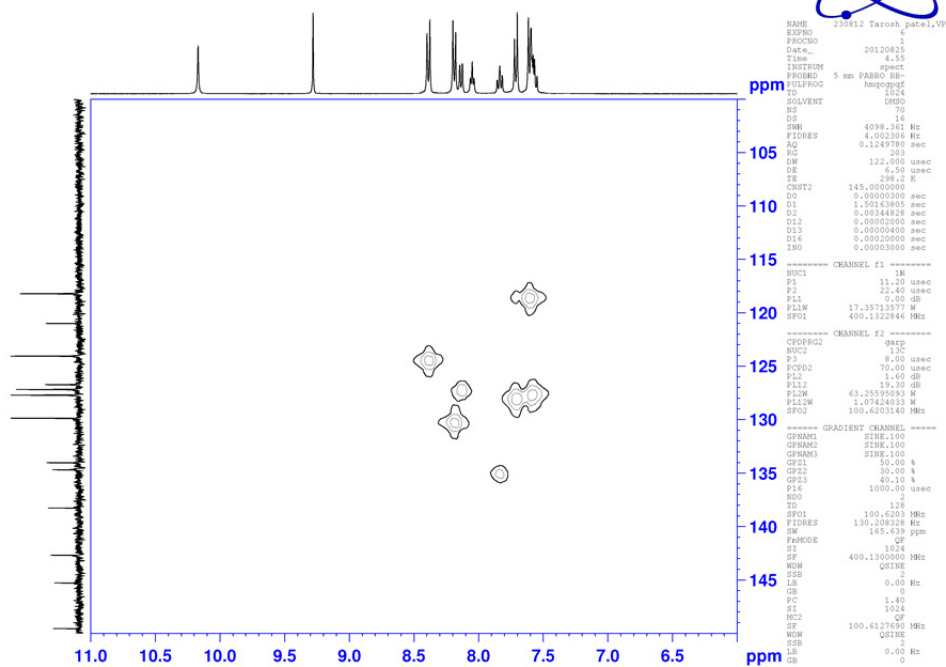
Fig. S14. ^{1}H-^{1}H NOESY Spectra of 8a ii

BRUKER
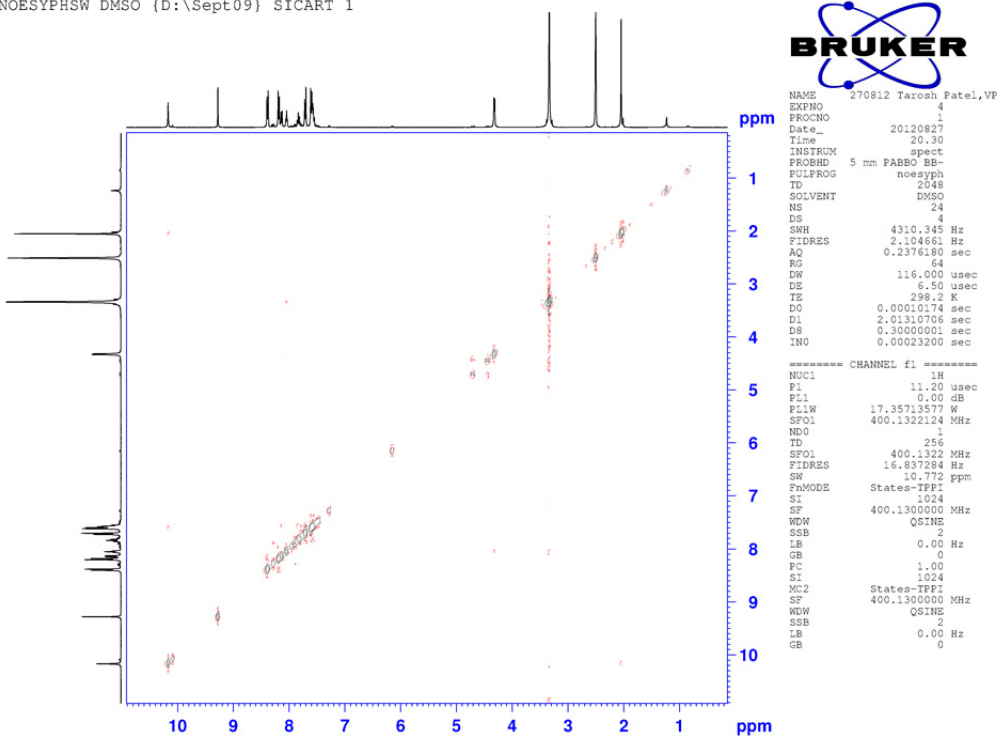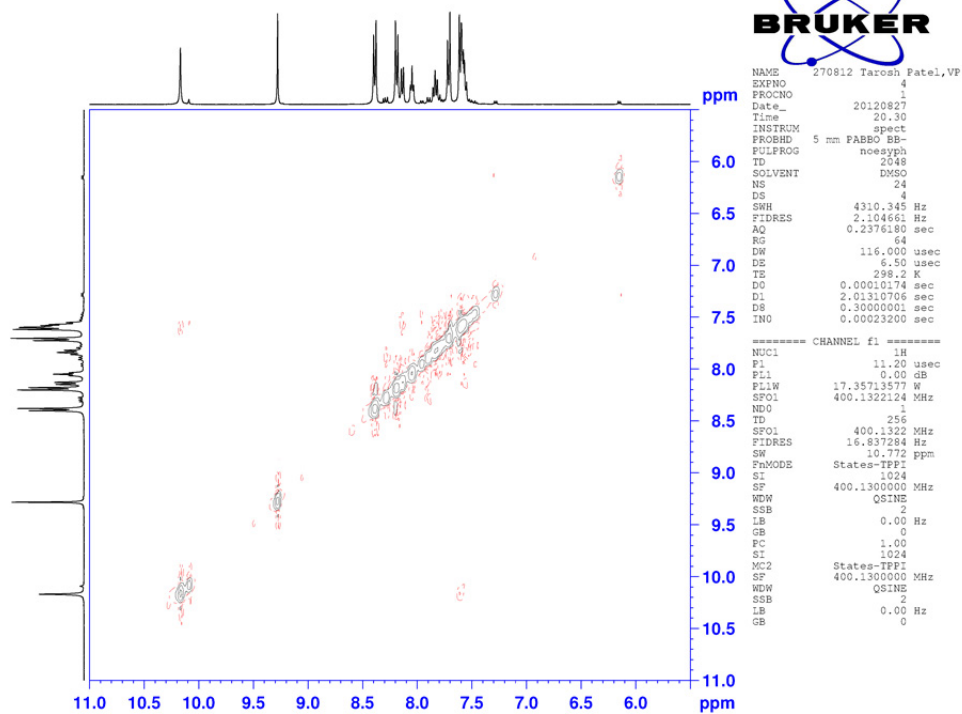
Fig. S15. Mass Spectra of 8a ii
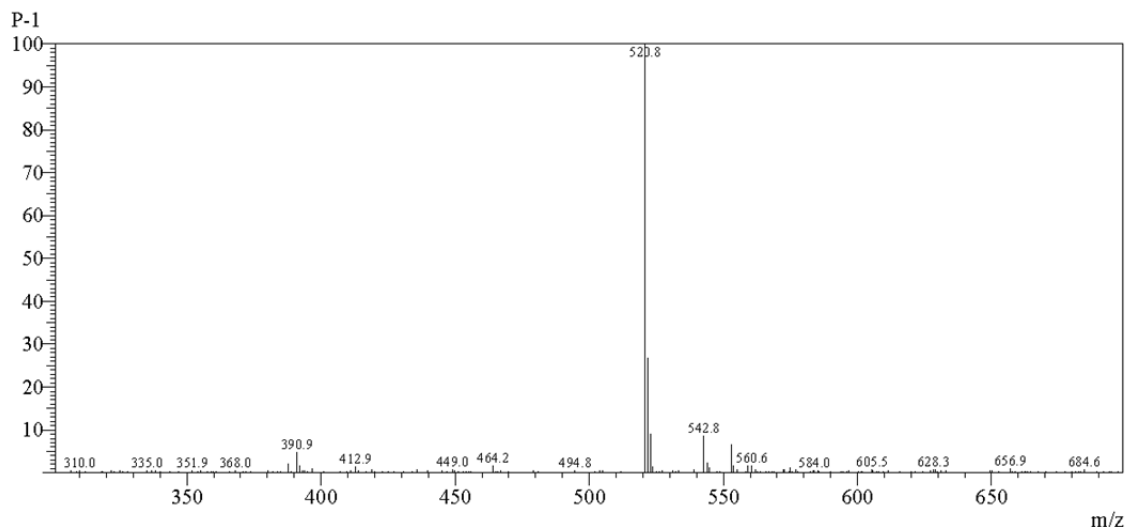
Fig. S16. [1]H-MMR Spectra of 8a i

LNo2
AAA_1H DMSO {D:\Sept09} SICART 1

NAME   270812 Tarosh Patel,VP
EXPNO   1
PROCNO   1
Date_   20120827
Time   19.27
INSTRUM   spect
PROBHD   5 mm PABBO BB-
PULPROG   zg30
TD   65536
SOLVENT   DMSO
NS   32
DS   0
SWH   8223.685 Hz
FIDRES   0.125483 Hz
AQ   3.9846387 sec
RG   203
DW   60.800 usec
DE   6.50 usec
TE   298.2 K
D1   1.00000000 sec
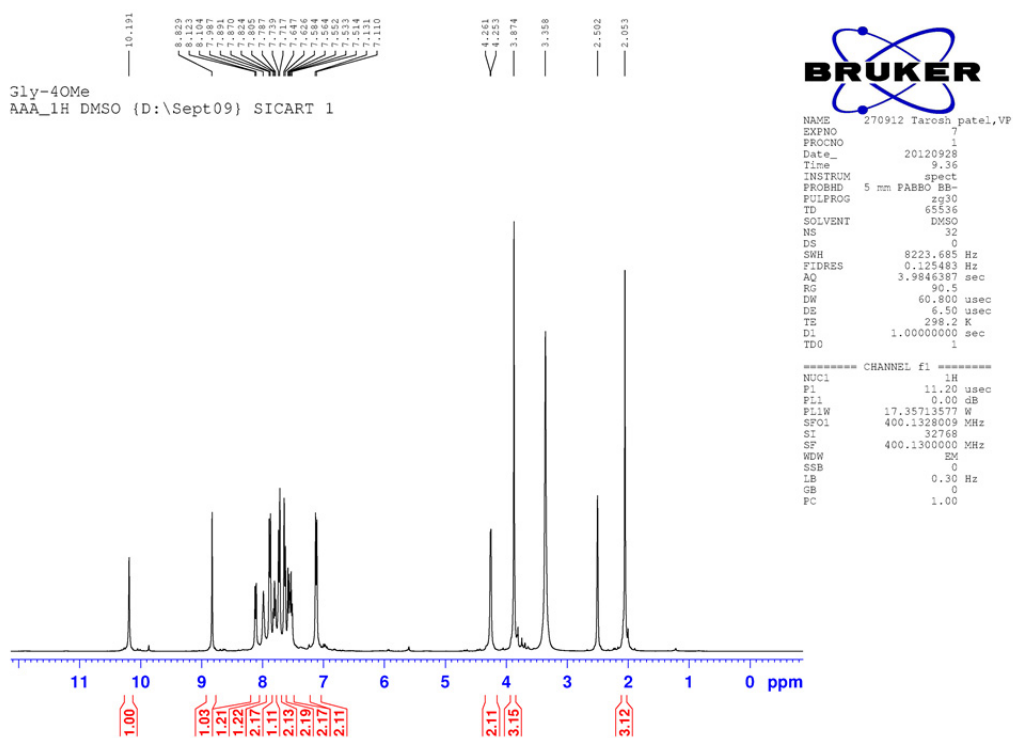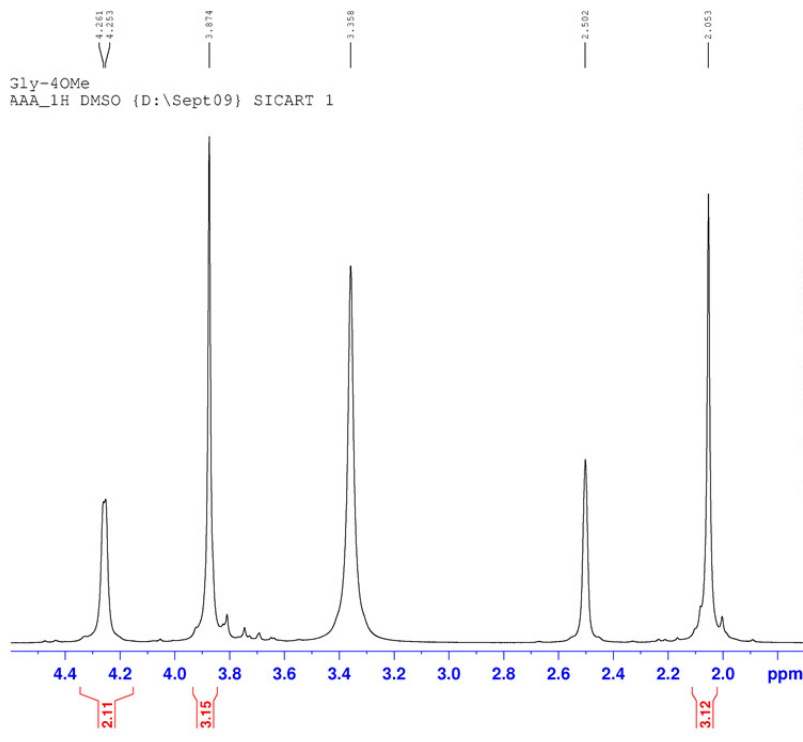TD0   1

======== CHANNEL f1 ========
NUC1   1H
P1   11.20 usec
PL1   0.00 dB
PL1W   17.35713577 W
SFO1   400.1328009 MHz
SI   32768
SF   400.1300000 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   1.00

LNo2
AAA_1H DMSO {D:\Sept09} SICART 1

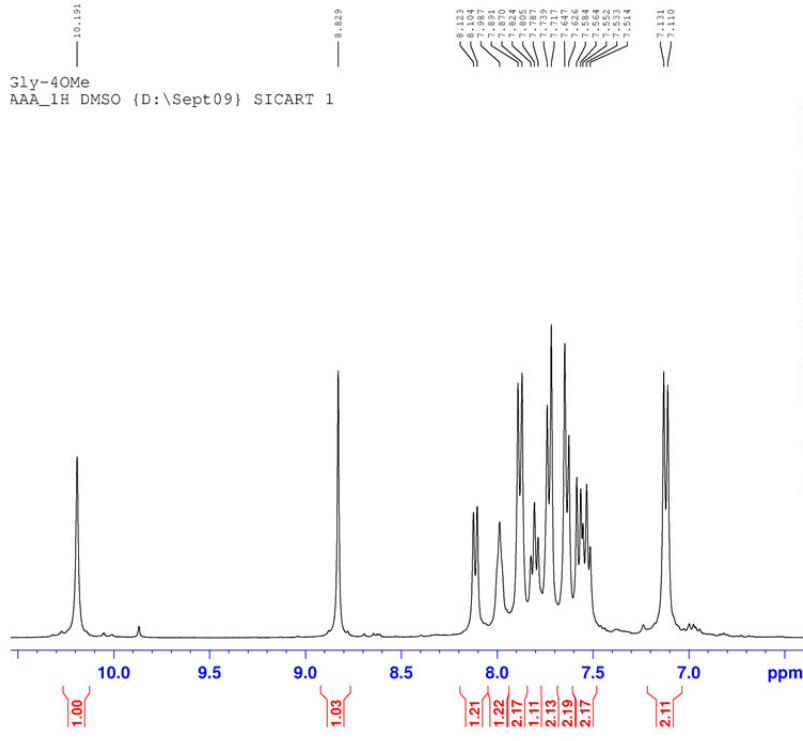NAME   270812 Tarosh Patel,VP
EXPNO   1
PROCNO   1
Date_   20120827
Time   19.27
INSTRUM   spect
PROBHD   5 mm PABBO BB-
PULPROG   zg30
TD   65536
SOLVENT   DMSO
NS   32
DS   0
SWH   8223.685 Hz
FIDRES   0.125483 Hz
AQ   3.9846387 sec
RG   203
DW   60.800 usec
DE   6.50 usec
TE   298.2 K
D1   1.00000000 sec
TD0   1

======== CHANNEL f1 ========
NUC1   1H
P1   11.20 usec
PL1   0.00 dB
PL1W   17.35713577 W
SFO1   400.1328009 MHz
SI   32768
SF   400.1300000 MHz
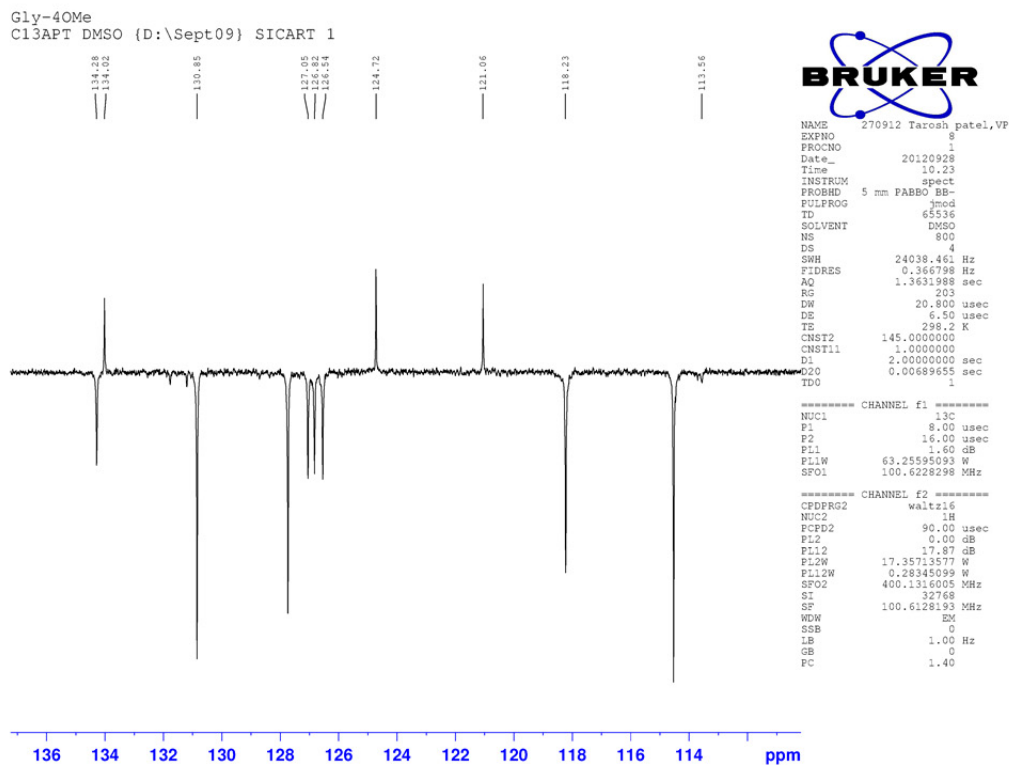WDW   EM
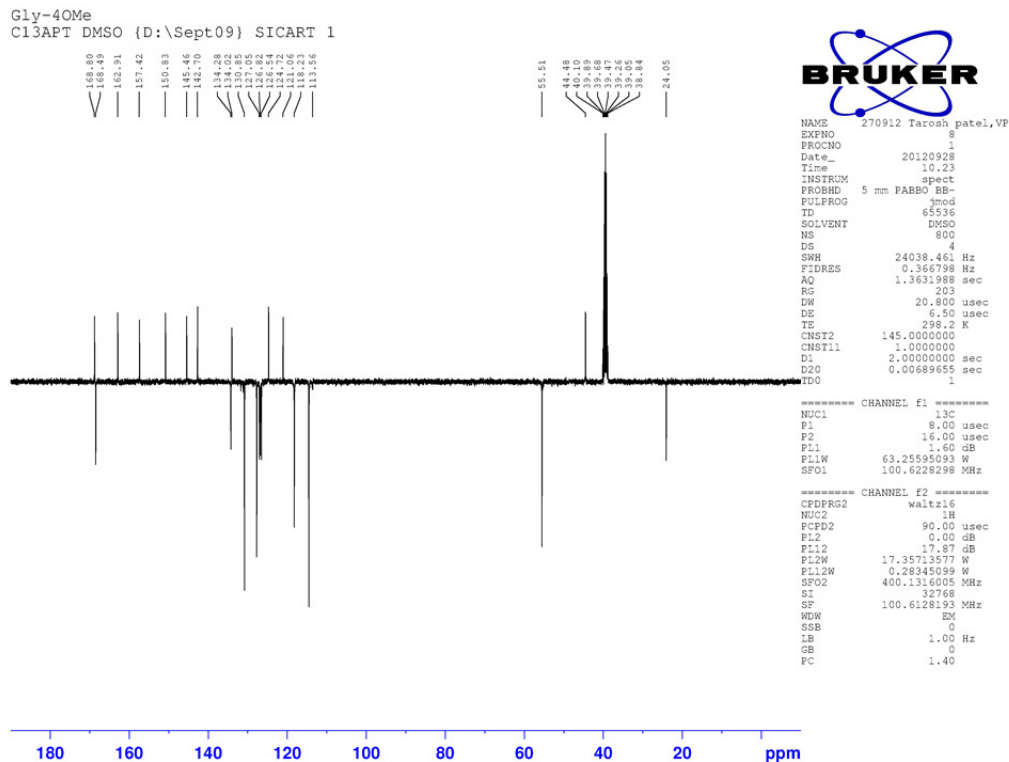SSB   0
LB   0.30 Hz
GB   0
PC   1.00

LNo2
AAA_1H DMSO {D:\Sept09} SICART 1

Fig. S17. ^{13}C-NMR Spectra of 8a i
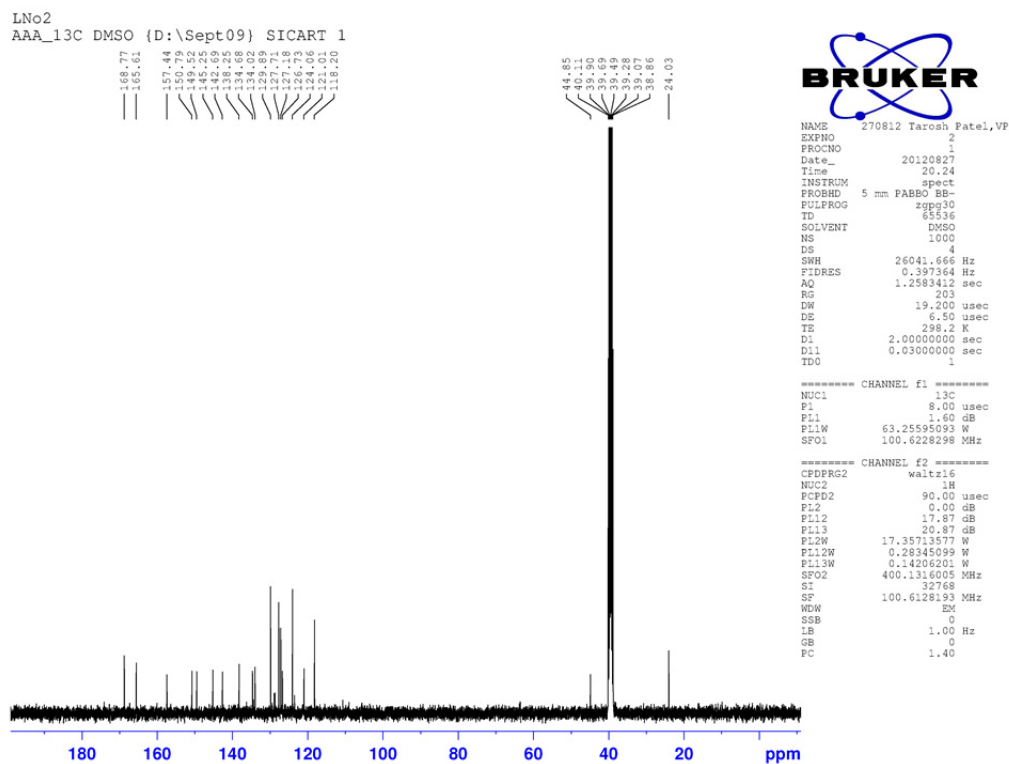
LNo2
AAA_13C DMSO {D:\Sept09} SICART 1

Fig. S18. ^{13}C-NMR (APT) Spectra of 8a i

Fig. S19. ^{1}H-^{13}C HMBC Spectra of 8a i
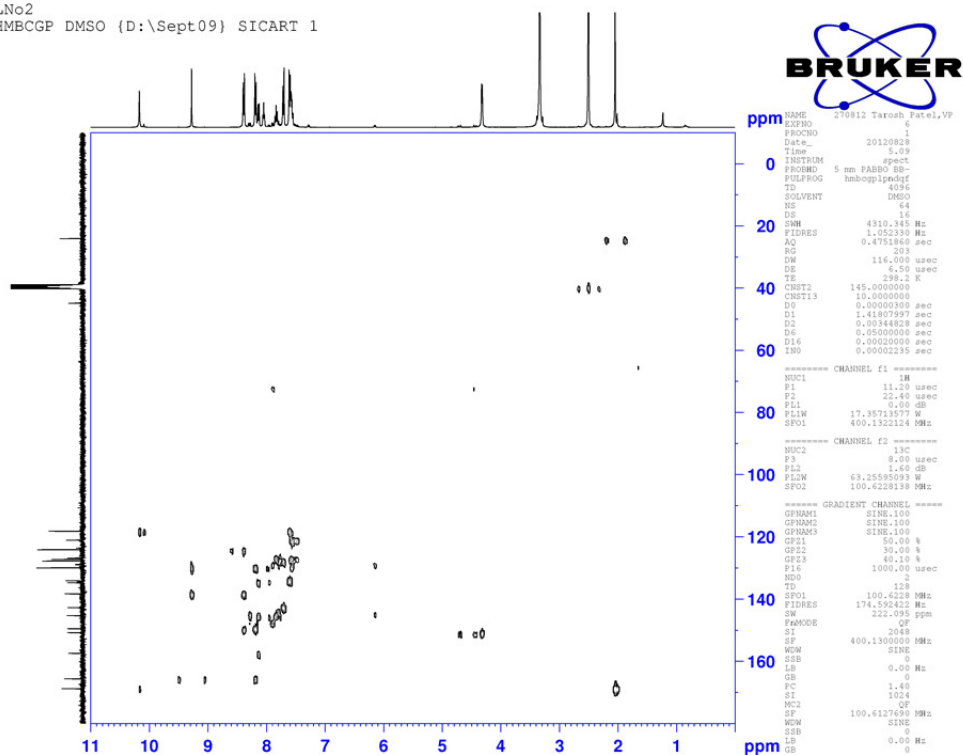
Fig. S20. ^{1}H-^{13}C HMQC Spectra of 8a i

LNo2
HMQCGP DMSO {D:\Sept09} SICART 1
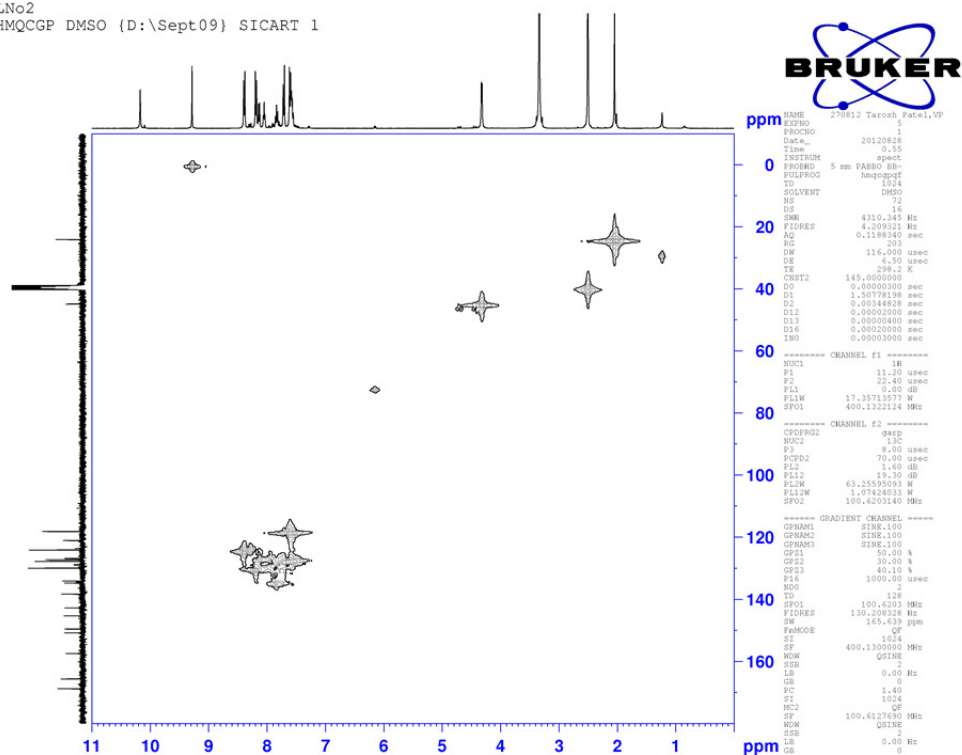
LNo2
HMQCGP DMSO {D:\Sept09} SICART 1
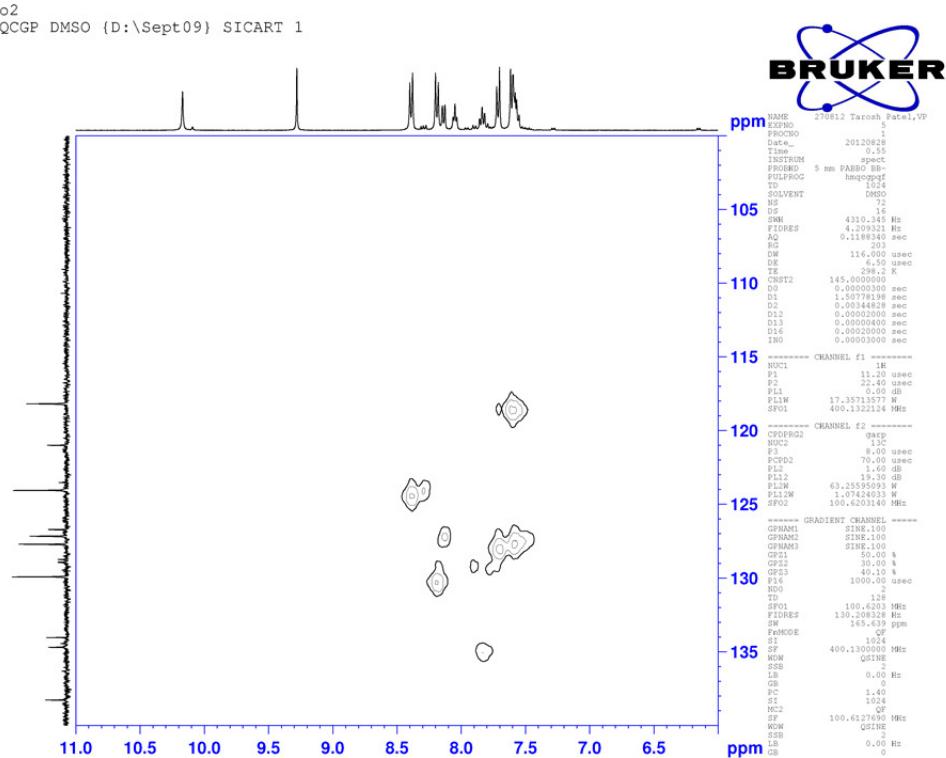
Fig. S21. ^{1}H-^{1}H NOESY Spectra of 8a i

LNo2
NOESYPHSW DMSO {D:\Sept09} SICART 1

LNo2
NOESYPHSW DMSO {D:\Sept09} SICART 1

Fig. S22. Mass Spectra of 8a i
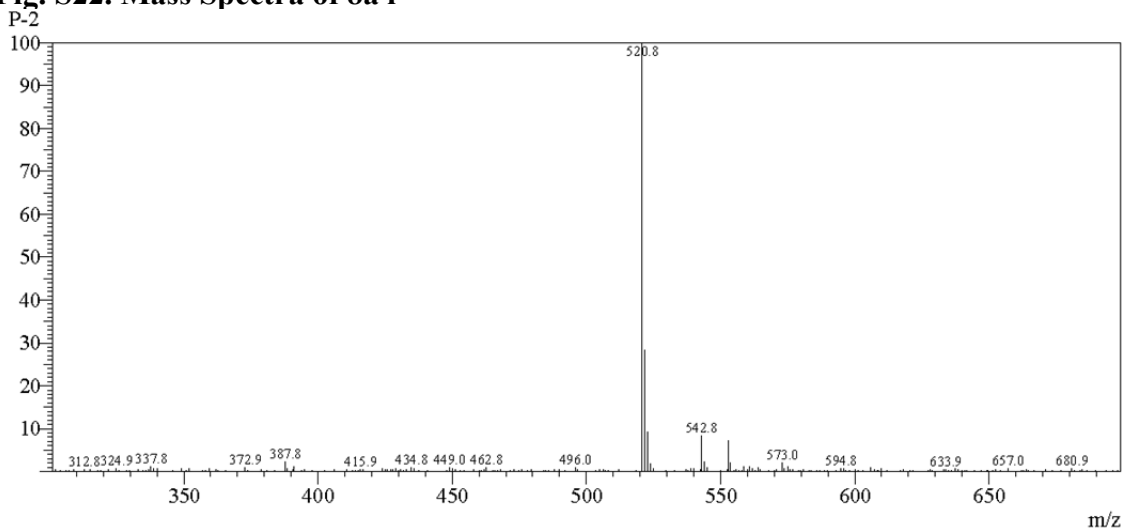
Fig. S23. ^{1}H-NMR Spectra of 8g

Gly-4OMe
AAA_1H DMSO {D:\Sept09} SICART 1

Gly-4OMe
AAA_1H DMSO {D:\Sept09} SICART 1

Fig. S24. ^{13}C-NMR (APT) Spectra of 8g

Gly-4OMe
C13APT DMSO {D:\Sept09} SICART 1

Gly-4OMe
C13APT DMSO {D:\Sept09} SICART 1

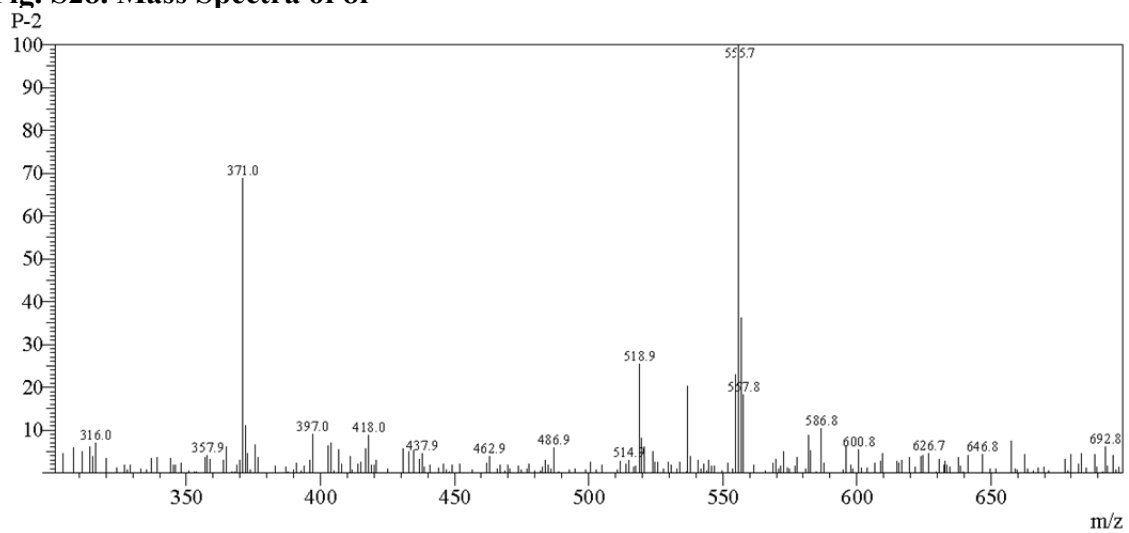**Fig. S25. Mass Spectra of 8g**
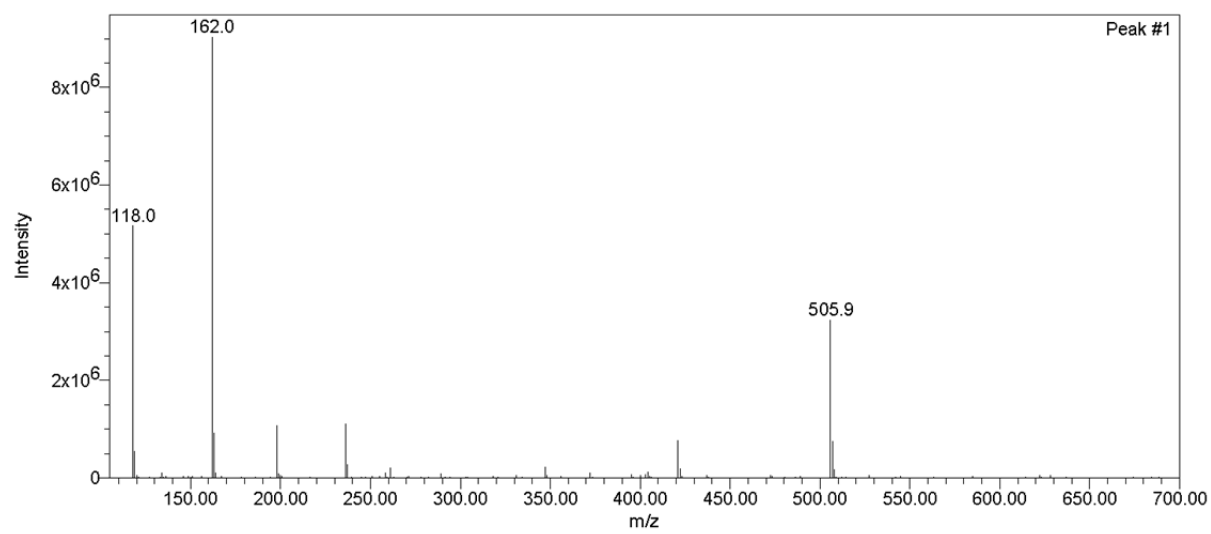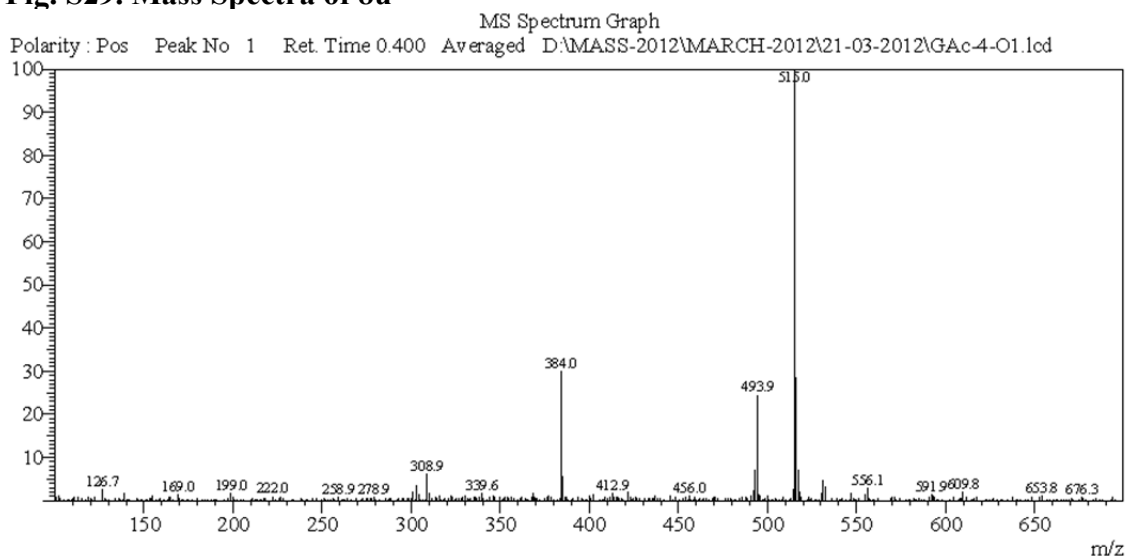

Fig. S26. ¹H-NMR Spectra of 8p

Fig. S27. ¹³C-NMR (APT) Spectra of 8p

Fig. S28. Mass Spectra of 8r

Fig. S29. Mass Spectra of 8u

MS Spectrum Graph
Polarity : Pos   Peak No   1   Ret. Time 0.400   Averaged   D:\MASS-2012\MARCH-2012\21-03-2012\GAc-4-O1.lcd

Fig. S30. Mass Spectra of 8v

MS Spectrum Graph
Polarity : Pos   Peak No   1   Ret. Time 0.367   Averaged   D:\MASS-2012\MARCH-2012\21-03-2012\GAc-4-M1.lcd
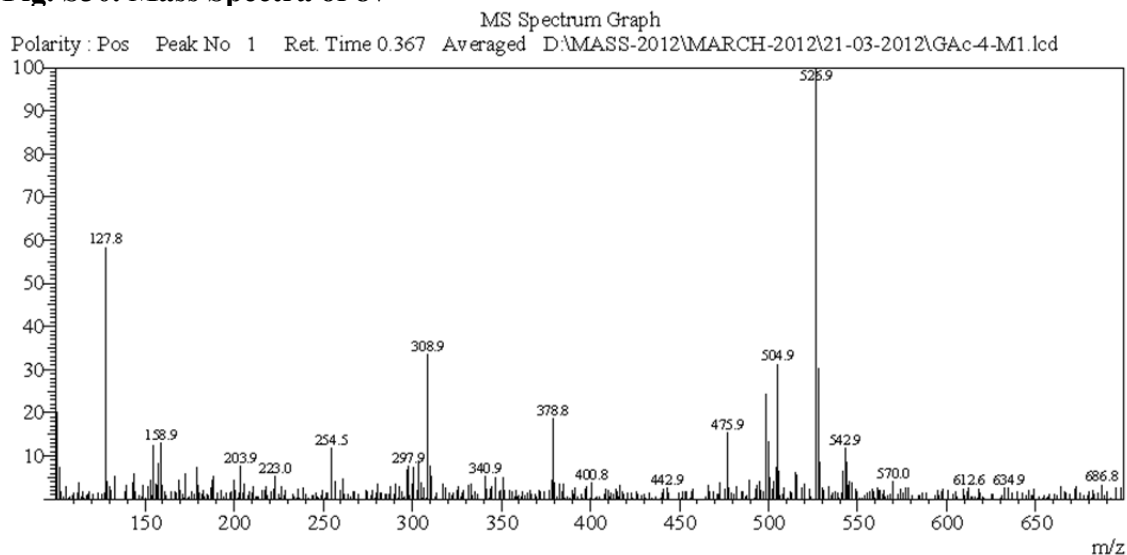
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