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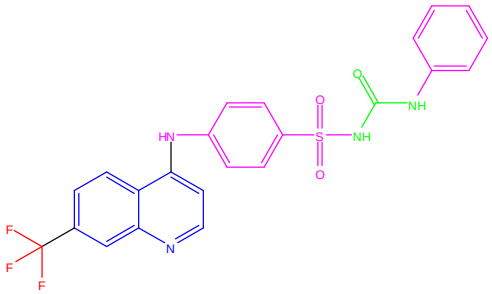

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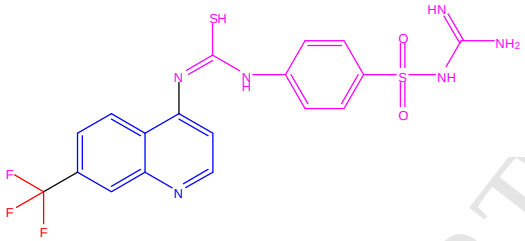

21

IC_{50} = 18.39 µM (MDA-MB231)
17.89 µM (HT 1080)
27.62 µM (HepG2)
19.65 µM (Lovo)
18.42 µM (AS49-Raw)
35.29 µM (Hela)

IC_{50} =
24.29µM (HT 1080)
33.48µM (HepG2)
23.91µM (Lovo)
23.91µM (AS49-Raw)
23.91µM (Hela)

Most of the synthesized compounds showed good cytotoxic activity especially compounds **15** and **21** on breast, lung, liver, colorectal, lung and Hela cancer cell lines

Synthesis and Anticancer Activity Of Some Novel Trifluoromethylquinolines Carrying A Biologically Active Benzenesulfonamide Moiety

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Abstract

Several trifluoromethylquinoline derivatives containing a biologically active benzenesulfonamide moiety **2-14**, **16**, urea derivatives **15, 17**, 4-isothiocyanate **18** and the corresponding carbamimidothioic acid derivatives **19- 30**, were synthesized from the strategic starting material 4-chloro-7-trifluoromethylquinoline **1**. The structures of the newly synthesized compounds were elucidated on the basis of elemental and spectral analyses. All the prepared compounds were evaluated for their *in vitro* anticancer activity against various cancer cell lines. Most of the synthesized compounds showed good activity, especially compound **15** which exhibited higher activity than the reference drug doxorubicin. In order to suggest the mechanism of action for their cytotoxic activity, molecular docking for all synthesized compounds was done on the active site of PI3K and good results were obtained.

Keywords: trifluoromethylquinoline, sulfonamide, carbamimidothioic acid, anticancer activity.

1. Introduction

It is observed from the literature that many quinoline derivatives posses a wide range of biological activities including anti-inflammatory [1], antileshmanial [2], antifungal [3], antituberclosis [4], antimalarial [5,6] and anticancer activity [7-9]. On the other hand, quinoline containing compounds have only been used for the treatment of malaria [10], beginning with quinine, which is a 4,6-substitued quinoline. Recently, the antitumor activity of quinolines as anticancer agents [11] and specially against breast cancer cell lines, with chloroquinoline being the most apoptosis-inducing agent, has been reported [12]. All differentiation-inducing quinolines caused growth suppression in MCF-7 and MCF 10 A cells. The mechanism of action of the differentiation-inducing quinolines has been proposed to involve strong suppression of E2F1 that inhibits growth by preventing cell cycle progression and fasters differentiation by creating a permissive environment for cell differentiation [13]. It has been known that aryl/heteroaryl sulfonamides may act as antitumor agents through a variety of mechanisms such as cell cycle perturbation in the G1 phase, disruption of microtubule assembly, angiogenesis inhibition, and functional suppression of the transcriptional activator NF-Y. Moreover, following an extensive evaluation, numerous sulfonamides were found to act as carbonic anhydrase (CA)

inhibitors[14-16]. Recently, combination of quinoline nuclues with sulfonamide moieties has received a great attention in seeking for novel anticancer agents [17]. Several quinoline sulfonamide derivatives showed potent anticancer activity as phosphoinisitol kinase (PI3K) inhibitors [17]. In addition, the special properties of the fluorine atom, such as a strong electronegativity, small size and the low polariazability of the C-F bond, can have a considerable impact on the behavior of a molecule in a biological environment [18-20]. The incorporation of electronic, lipophilic and steric parameters , all of which can critically influence both the pharmacodynamic and pharmacokinetics properties of drugs. Bioisosteric substitution for hydrogens by fluorines is therefore, an important strategy for incorporation of a group capable of reinforcing drug-receptor interactions (electronic modulation), aiding translocation across lipid bilayers or absorption (lipophilic modulation) and inducing conformational changes/ blocking metabolism (steric parameters) [21]. On the basis of these reports and in continuation of our research program [22-35] on the synthesis of novel heterocyclic compounds exhibiting anticancer activity, we reported here the synthesis of novel compounds containing quinoline derivatives carrying a biologically active benzenesulfonamide moiety **2- 30** to evaluate their anticancer activity hoping to discover a new series of anticancer agent that may add to the continuous search for better anticancer agents with less side effects.

2. Results and discussion

2.1.Chemistry

The aim of the this work was to design and synthesize a new series of trifluoromethylquinoline derivatives carrying a biologically active benzenesulfonamide and to evaluate their anticancer activity. Thus, the interaction of 4-chloro-7-trifluoromethylquinoline **1** with several sulfa drugs in dry N,N'-dimethylformamide afforded the corresponding 7-trifluoromethylquinoline sulfonamide derivatives **2-14**. The structures of the formed compounds were confirmed on the basis of elemental analysis and spectral data. In addition the structure compound **2** was confirmed through x-ray crystallography [36] (Figure 1).

IR spectra for compounds **2-14** showed absorption bands for (NH), (CH aromatic) and (SO_2). ^{1}H-NMR spectra exhibited a doublet signals at 6.6 - 8.6 ppm corresponding to (2CH) of quinoline

and singlet signals at 8.5-9.7 ppm corresponding to (NH) which were exchanged upon deuteration.

Interaction of compound **2** with phenyl isocyanate in dry N,N'-dimethylformamide in the prescence of anhydrous potassium carbonate furnished the corresponding phenyl urea derivative **15** in good yeild. IR spectrum of compound **15** revealed bands at 3200, 3163 and 3123cm^{-1} (NH), 1664 cm^{-1} (C=O) and 1379, 1163 cm^{-1} (SO_2). ^{1}H-NMR spectrum of **15** showed two doublets at 6.9, 8.6 ppm for 2CH of quinoline and a singlet at 8.5 ppm due to 2NH of urea group. On the other hand, when compound **1** was reacted with sulfanilamide in dry DMF in the prescence of anhydrous potassium carbonate [37], the corresponding 4-amino-*N*-(7-(trifluoromethyl)quinolin-4-yl)benzenesulfonamide **16** was obtained. The structure of compound **16** was proved based on analytical and spectral data. IR spectrum of compound 16 revealed bands at 3483, 3355 and 3222 cm^{-1} (NH,NH_2), 1596 cm^{-1} (C=N), 1372 and 1177 cm^{-1} (SO_2). ^{1}H-NMR spectrum exhibited a singlet at 6.7 ppm due to NH_2 group and two doublets at 6.8 and 8.5 ppm corresponding to 2CH of quinoline. Interaction of compound **16** with phenyl isocyanate in dry DMF gave the coressponding ureido derivative **17**. IR spectrum of 17 exhibited bands at 3420, 3386 and 3210 cm^{-1} (NH), 1668 cm^{-1} (C=O), 1625 cm^{-1} (C=N), 1398 and 1155 cm^{-1}(SO_2). ^{1}H-NMR spectrum of **17** showed a singlet at 8.8 ppm for 2NH of urea moiety. In addition, it was aimed to prepare the isothiocyanato intermediate **18** as isothiocyante derivatives are useful and widely used building blocks in the synthesis of nitrogen, sulfur and oxygen heterocylic compounds and organometallics of academic and pharmaceutical and industrial interest. Thus, interaction of compound **1** with ammonium thiocyanate in dry acetone under reflux for 1hr gave the corresponding 4-isothiocyanato derivative **18**.This method led to a higher overall yield and shorter working time compared to the reported method that was using silver thiocyanate in dry toulene [38]. IR spectrum of **18** revealed a new band at 2059 cm^{-1} for (N=C=S). ^{1}H-NMR spectrum of **18** revealed two doublets at 7.8 and 9.1 ppm for 2CH of quinoline.

Finally, the carbamimidothioic acid derivatives **19- 30** were achieved by treatment of isothiocyanato quinoline derivative **18** with several sulfa drugs in dry DMF containing a catalytic amount of triethylamine. The structures of the synthesized compounds **19-30** were confirmed on the basis of analytical and spectral data. IR spectra of these compounds revealed the abscence of

(N=C=S) band and the appearance of new bands corresponding to (NH) and (C=N). ^{1}H-NMR spectra for these compounds showed singlet signals at 2.5-2.7 ppm corresponding to SH group.

2.2. Molecular docking

Almost 20 years of cancer biology and genomic studies have identified phosphoinositide 3-kinase (PI3K) and the PI3K pathway as important players in tumor onset and maintenance. PI3K is therefore considered a well-validated target for cancer treatment, and hence the demand for inhibitors with drug-like properties was highly anticipated 5 years ago [39].

Based on the previous findings and as a trial to suggest the mechanism of action of the cytotoxic activity for the synthesized compounds docking of all newly synthesized compounds was done on the active site of PI3K.

The protein data bank file (PDB: 3S2A) was selected for this purpose. The file contains PI3K enzyme co-crystallized with a quinoline ligand. All docking procedures were achieved by MOE (Molecular Operating Environment) software 10.2008 provided by chemical computing group, Canada. Docking on the active site of PI3K enzyme was performed for all synthesized compounds.

Docking protocol was verified by redocking of the co-crystallized ligand in the vicinity of the active site of the enzyme with energy score (S) = -29.8249 Kcal/mol and root mean standard deviation (RMSD) = 1.9094 (Figure 2). The quinoline ligand interacts with the active site of PI3K by six interactions: Val 882 with a hydrogen bond of 2.90 A^{o}, Tyr 867 with a hydrogen bond of 3.33 A^{o}, Asp 864 with a hydrogen bond of 3.33 A^{o}, Lys 833 with a hydrogen bond of 3.33 A^{o}, Ser 806 with a hydrogen bond of 3.74 A^{o} and Asp 841 with a hydrogen bond of 2.79 A^{o} through a water molecule. All synthesized compounds were fit to the active site of PI3K enzyme with good energy scores (S) suggesting activity as PI3K inhibitors. Energy scores (S) and amino acid interactions for the synthesized compounds were listed in (Table 1). Compound **29** gave the best energy score (S) = -27.2076 and interacted with Lys 808 with a hydrogen bond of 3.65 A^{o}, Lys 890 with a hydrogen bond of 2.92 A^{o} and Asp 841(through a water molecule) with a hydrogen bond of 3.08 A^{o} (Figure 3).

2.3. In vitro antitumor activity

The newly synthesized compounds were evaluated for their *in vitro* cytotoxic activity against human breast cancer cell line (MDA-MB231), lung cancer cell line (AS49- Raw), Hela cancer cell line, colorectal cell line (Lovo), skin cancer cell line (HT-1080) and liver cancer cell line ($HepG_2$). Doxorubicin which is a known and effective anticancer agent was used as the reference drug in this study. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of cancer cell lines. The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. Table 2 shows the *in vitro* cytotoxic activity of the newly synthesized compounds where all compounds exhibited good activity compared to the reference drugs in case of human breast cancer cell line (MDA-MB231) except compounds **11, 13** and **21.** On the other hand, all the synthesized compounds exhibited good activity on skin cancer cell line (HT-1080), while only compound **12** was inactive on lung cancer cell line (AS49-Raw lung). The cytotoxic activity on Hela cell line was moderate for most of the synthesized compounds except for compounds **3, 6, 11, 14, 23, 26** and **30** which were inactive. In case of colorectal cell line (Lovo), all compounds showed good to moderate activity except for compounds **8, 11** and **22**. Finally, the activity on liver cell lines ($HepG_2$) was moderate except for compounds **4, 8, 10, 11, 12, 17** and **27**.

Compound **15** which is the phenylureido derivative was the most active compound on breast cell line cancer (MDA-MB231) with IC_{50} value of 18.39 µM. The sulfapyridine derivative **9** exhibited a nearly similar IC_{50} value of 18.40 µM while compounds **24, 23, 4, 27, 16** showed IC_{50} values of 24.39, 27.94, 28.83, 29.78 and 30.95 µM, respectively better than that of Doxorubicin on the same cell line with IC_{50} value of 33.98 µM. Also compound **15** was the most active compound on colorectal cell line cancer (Lovo) with IC_{50} value of 19.65 µM, while compounds **9** and **21** showed IC_{50} values of 20.22 and 23.91 µM, respectively, which were better than that of Doxorubicin on the same cell line with IC_{50} value of 24.33 µM. Compound **15** continues to be the most active compound on liver cancer cell line ($HepG_2$) with IC_{50} value of 27.62 µM close to that of Doxorubicin on the same cell line with Ic50 value of 27.11 µM. On lung cancer cell line (AS49- Raw), also compound **15** was the most active compound with IC_{50} value of 18.42 µM while compounds **21, 17, 24, 16, 9** and **27** exhibited IC_{50} values of 23.91, 24.50, 27.15, 29.23, 30.38 and 31.03 µM, respectively, which were better of that of Doxorubicin on the same cell line with IC_{50} value of 32.78 µM. Compound **15** was still the most active

compound on skin cancer cell line (HT-1080) with IC_{50} value of 17.89 µM which was better than that of Doxorubicin with IC_{50} value of 19.22 µM. The cytotoxic activity on Hela cell line revealed that compound **21** showed IC_{50} value of 23.01 µM, while, compound **15** exhibited IC_{50} value of 35.29 µM while Doxorubicin showed IC_{50} value of 30.21 µM.

It was obvious from the aforementioned results that the phenylureido derivative **15** was in general the best compound on most cell lines except for Hela cell line. Figure 4 illustrate the 3D interaction of compound **15** on the active site of (PI3K) enzyme. Neither the subtituted or unsubstituted sulfonamide derivatives **2- 14, 16** and **17** nor the carbamimidothioic acid derivatives **19-30** showed better activity except for compound **21** on Hela cell line.

Conclusion

Quinolinesulfonamide derivatives could represent a promising new class for anticancer agents as illustrated in this research for its promising cytotoxic activity on breast, skin, colorectal, liver , Hela and lung cancer cell lines. Compound **15** was the most active compound, which showed higher activity than the reference drug Doxorubicin as positive control. The mechanism of action of this cytotoxic activity could be suggested to be PI3K inhibitors due to the promising results from molecular docking on the active site of this enzyme. Further investigation to the mechanism of action should be conducted on next researches to confirm this mechanism of action urged by the promising *in vitro* antitumor activity.

3.Experimental

3.1. Chemistry

The starting material 4-chloro-7-trifluoromethylquinoline **1** and all sulfa- drugs were purchased from Sigma-Aldrich. Melting points were determined on an electrothermal melting point apparatus (BUCHI melting point B-545- Switzerland) and were uncorrected. Precoated Silica gel plates (Kiesel gel 0.25 mm, 60 G F 254, Merck) were used for thin layer chromatography (TLC). The developing solvent system was chloroform/ methanol (10:3) and the spot were detected by ultraviolet light. Infrared (IR) spectra (KBr disc) were recorded on FT-IR spectrophotometer (Perkin Elmer) at the research Centre, College of Pharmacy, King Saud University, Saudi Arabia. ^{1}H-NMR spectra were scanned in dimethylsulfoxide (DMSO-D_6) on NMR spectrophotometer (Bruker AXS Inc.) operating at 500 MHz for ^{1}H and 125.76 MHz for ^{13}C at

the aforementioned Research Center. Chemical shifts are expressed in δ values (ppm) relative to tetramethylsilane (TMS) as an internal standard. Exchangeable protons were confirmed by addition of drop of D_2O. Elemental analyses were done on model 2400 CHNSO analyzer (Perkin Elmer).

3.1.1. General procedure for the synthesis of compounds ***2-14***

A mixture of **1** (2.31 g, 0.01 mol.) and the corresponding sulfa drugs (0.012 mol.) in dry DMF (20 mL) was refluxed for 12h. The solid obtained after concentration was filtered and crystallized from dioxane to give **2-14,** respectively.

3.1.1.2. 4-(7-(Trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide ***2***

Yellow crystals, Yield 89 %, melting point 272.4 ^oC. IR: $\upsilon_{max}./cm^{-1}$ 3317, 3300, 3290 (NH, NH_2), 3071(CH arom.), 1585 (C=N) and 1381, 1157 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O) δ: 7.3, 8.6 (2d, 2H, 2CH quinoline, *J*= 7.2 Hz), 7.5-8.5 (m, 9H, Ar-H + SO_2NH_2), 9.5(s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 120.1, 120.7 (2), 122.3, 122.9, 124.5, 125.1, 127.2(2), 129.5, 129.7, 138.0, 143.8, 146.3, 148.0, 151.8. Anal. Calcd. for $C_{16}H_{12}F_3N_3O_2S$ (367.35): C, 52.31; H, 3.29; N, 11.44. Found: C, 53.59; H, 3.61; N, 11.11.

3.1.1.3. N-(4-(7-(trifluoromethyl)quinolin-4-ylamino)phenylsulfonyl)acetamide ***3***

Yellow powder, Yield 82 %, melting point >350 ^oC. IR: $\upsilon_{max}./cm^{-1}$ 3280, 3176 (2NH), 3067 (CH arom.), 2970, 2836 (CH aliph.), 1696 (C=O), 1610 (C=N), 1396, 1155 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 3.0(s, 3H, $COCH_3$), 6.9, 8.6 (2d, 2H, 2CH quinoline, *J*= 7.3 Hz), 7.0-8.2 (m, 8H, Ar-H+ SO_2NH), 8.5 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 22.0, 119.3, 120.7 (2), 123.9, 125.1, 126.7, 127.7, 128.7 (2), 129.0, 129.2, 130.0, 148.3(3), 151.8, 156.4. Anal. Calcd. for $C_{18}H_{14}F_3N_3O_3S$ (409.38): C, 52.81; H, 3.45; N, 10.26. Found: C, 52.62; H, 3.19; N, 10.58.

3.1.1.4. N-carbamimidoyl-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide ***4***

Yellow powder, Yield 79 %, melting point 304.0 ^oC. IR: $\upsilon_{max}./cm^{-1}$ 3454, 3440, 3344 (NH, NH_2), 3056 (CH arom.), 1635 (C=N), 1382, 1138 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O) δ: 6.5 (s, 2H, NH_2, D_2O-exchangeable), 7.2, 8.6 (2d, 2H, 2CH quinoline, *J*= 7.1 Hz), 7.4-8.2 (m, 8H, Ar-H+

SO_2NH_2), 9.5 (s, 1H, NHPh, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 116.6, 118.6(2), 120.7, 122.1, 122.8, 124.5, 128.0(2), 129.6, 129.8, 130.1, 146.8, 147.4, 151.9. 152.3, 159.9. Anal. Calcd. for $C_{17}H_{14}F_3N_5O_2S$ (409.39): C, 49.88; H, 3.45; N, 17.11. Found: C, 49.59; H, 3.19; N, 17.39.

3.1.1.5. N-(3-methylisoxazol-5-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide ***5***

Yellow powder, Yield 91 %, melting point 161.6 ^{o}C. IR: υ_{max}./cm^{-1} 3292, 3190 (NH), 3077 (CH arom.), 2960, 2840 (CH aliph.), 1616 (C=N), 1381, 1155 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 2.2 (s, 3H, CH_3), 6.9 (s, 1H, CH isoxazole), 7.2, 6.8 (2d, 2H, 2CH quinoline, *J*= 7.4 Hz), 7.3-8.3 (m, 8H, Ar-H + SO_2NH), 9.7 (s, 1H, NHPh, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 12.0, 104.7, 119.8, 120.9 (2), 121.1, 122.5, 122.8, 125.8, 128.5 (2), 129.9, 130.2, 132.6, 146.4, 147.4, 151.2, 151.7, 162.2, 170.2. Anal. Calcd. for $C_{20}H_{15}F_3N_4O_3S$ (448.42): C, 53.57; H, 3.37; N, 12.49. Found: C, 53.21; H, 3.09; N, 12.72.

3.1.1.6. N-(3,4-dimethylisoxazol-5-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide ***6***

Orange powder, Yield 89 %, melting point 157.5 ^{o}C. IR: υ_{max}./cm^{-1} 3372, 3280 (2NH), 3061 (CH arom.), 2940, 2860 (CH aliph.), 1629 (C=N), 1381, 1157 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O) δ: 2.4 (s, 6H, $2CH_3$), 7.3, 8. 6 (2d, 2H, 2CH quinoline, *J*= 7.0 Hz), 7.4-8.5 (m, 8H, Ar-H + SO_2NH), 9.5 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 8.6, 10.3, 104.7, 119.9, 120.6 (2), 122.5, 122.8, 124.9, 125.6, 129.6 (2), 129.8, 130.3, 137.2, 145.3, 146.9, 147.2, 151.5, 159.6, 162.2. Anal. Calcd. for $C_{21}H_{17}F_3N_4O_3S$ (462.44): C, 54.54; H, 3.71; N, 12.12. Found: C, 54.81; H, 3.47; N, 12.41.

3.1.1.7. N-(1-phenyl-1H-pyrazol-5-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide ***7***

Orange powder, Yield 76 %, melting point 153.6 ^{o}C. IR: υ_{max}./cm^{-1} 3481, 3210 (NH), 3046 (CH arom.), 1624 (C=N), 1381, 1153 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 6.5 (d, 2H, 2CH pyrazole, *J*= 7.8 Hz), 7.3, 8.6 (2d, 2H, 2CH quinoline, *J*= 7.4 Hz), 7.4-8.5 (m, 13H, Ar-H + SO_2NH), 8.7 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 102.5, 119.3, 120.8 (2), 123.8 (2),

124.1 (2), 125.1, 126.3, 126.5, 127.3 (2), 128.8, 129.3 (2), 129.6, 130.2, 135.1, 135.2, 147.4, 149.6, 152.0, 153.5, 162.0. Anal. Calcd. for $C_{25}H_{18}F_3IN_5O_2S$ (509.50): C, 58.93; H, 3.56; N, 13.75. Found: C, 58.69; H, 3.29; N, 13.99.

3.1.1.8. N-(thiazol-2-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide ***8***

Yellow powder, Yield 79 %, melting point 169.8 ^{o}C. IR: υ_{max}./cm^{-1} 3410, 3260 (NH), 3100 (CH arom.), 1577 (C=N), 1381, 1141 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 6.8, 8.6 (2d, 2H, 2CH quinoline, *J*= 7.1 Hz), 7.2-8.3 (m, 10H, Ar-H + SO_2NH), 8.7 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 116.7, 118.7(2), 121.0, 121.8, 122.7, 124.2, 124.6, 127.7(2), 129.9, 130.4, 136.7, 143.3, 145.7, 147.9, 150.6, 160.0, 168.7. Anal. Calcd. for $C_{19}H_{13}F_3N_4O_2S_2$ (450.46): C, 50.66; H, 2.91; N, 12.44. Found: C, 50.36; H, 3.19; N, 12.13.

3.1.1.9. N-(pyridin-2-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide ***9***

Yellow powder, Yield 84 %, melting point 166.5 ^{o}C. IR: υ_{max}./cm^{-1} 3340, 3210 (NH), 3078 (CH arom.), 1635 (C=N), 1381, 1138 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 6.5-7.0 (m, 2CH, pyridine), 7.1, 8.1 (2d, 2CH, pyridine, *J*= 7.6, 8.1 Hz), 7.2, 8.6 (2d, 2H, 2CH quinoline, J= 7.8 Hz), 7.3-8.3 (m, 8H, Ar-H+ SO_2NH), 8.7 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 112.0, 113.6, 115.6, 118.7(2), 121.8, 122.7, 124.7, 124.9, 128.8(2), 129.9, 130.7, 136.3, 140.2, 141.4, 143.5, 145.6, 147.9, 150.5, 153.0. Anal. Calcd. for $C_{21}H_{15}F_3N_4O_2S$ (444.43): C, 56.75; H, 3.40; N, 12.61. Found: C, 56.48; H, 3.17; N, 12.97.

3.1.1.10. N-(pyrimidin-2-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide ***10***

Orange powder, Yield 77 %, melting point 271.9 ^{o}C. IR: υ_{max}./cm^{-1} 3462, 3228 (NH), 3058 (CH arom.), 1577 (C=N), 1381, 1161 (SO_2). ^{1}H-NMR (DMSO-d_6, D_2O) δ: 6.9, 8.6 (2d, 2H, 2CH quinoline, *J*= 7.7 Hz), 7.0- 8.4 (m, 9H, Ar-H + CH pyrimidine + SO_2NH), 8.5,8.7 (2d, 2H, 2CH pyrimidine, *J*= 7.5 Hz), 8.8 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 105.8, 115.7, 118.5(2), 122.4, 122.8, 124.8, 127.1, 129.7(2), 129.9, 130.2, 134.5, 147.5, 152.0, 153.0, 156.9, 158.3, 160.2, 162.2. Anal. Calcd. for $C_{20}H_{14}F_3N_5O_2S$ (445.42): C, 53.93; H, 3.17; N, 15.72. Found: C, 53.58; H, 3.49; N, 15.44.

*3.1.1.11. N-(4-methylpyrimidin-2-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide **11***

Brown powder, Yield 69 %, melting point 154.1 ^{o}C. IR: υ_{max}./cm^{-1} 3387, 3294 (2NH), 3081 (CH arom.), 2930, 2883 (CH aliph.), 1585 (C=N), 1381, 1157 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 2.3 (s, 3H, CH_3), 6.8, 8.2 (2d, 2H, 2CH pyrimidine, *J*= 7.7, 7.8 Hz), 6.9, 8.6 (2d, 2H, 2CH quinoline, *J*=7.5 Hz), 7.3-8.3 (m, 8H, Ar-H+ SO_2NH), 8.7 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 23.2, 111.9, 114.7, 119.6 (2), 122.8, 124.7, 125.6, 127.1, 129.1(2), 129.9, 130.1, 134.0, 144.5, 146.8, 151.5, 156.5, 157.5, 162.2, 168.2. Anal. Calcd. for $C_{21}H_{16}F_3N_5O_2S$ (459.44): C, 54.90; H, 3.51; N, 15.24. Found: C, 54.66; H, 3.27; N, 15.52.

*3.1.1.12. N-(4,6-dimethylpyrimidin-2-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide **12***

Brown powder, Yield 80 %, melting point 153.9 ^{o}C. IR: υ_{max}./cm^{-1} 3420, 3260 (NH), 3091 (CH arom.), 2946, 2830 (CH aliph.), 1598 (C=N), 1381, 1159 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 2.4 (s, 6H, $2CH_3$), 6.7 (s, 1H, CH pyrimidine), 7.3, 8.6 (2d, 2H, 2CH quinoline, *J*=7.9 Hz) 7.4-8.5 (m, 8H, Ar-H + SO_2NH), 8.7 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 22.8 (2), 105.4, 113.4, 119.5 (2), 122.2, 122.8, 124.5, 125.6, 129.8 (2), 130.1, 130.2, 134.3, 146.8, 149.9, 151.6, 156.2, 162.2 (2), 167.3. Anal. Calcd. for $C_{22}H_{18}F_3N_5O_2S$ (473.47): C, 55.81; H, 3.83; N, 14.79. Found: C, 55.54; H, 3.59; N, 14.44.

*3.1.1.13. N-(2,6-dimethoxypyrimidin-4-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzene-esulfonamide **13***

Brown powder, Yield 76 %, melting point 204.9 ^{o}C. IR: υ_{max}./cm^{-1} 3253, 3221 (NH), 3074 (CH arom.), 2946, 2862 (CH aliph.), 1581 (C=N), 1381, 1147 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 3.8 (s, 6H, $2OCH_3$), 5.8 (s, 1H, CH pyrimidine), 6.6, 8.6 (2d, 2H, 2CH quinoline, *J*= 7.7 Hz), 7.3-8.4 (m, 8H, Ar-H + SO_2NH), 8.9 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 54.3(2), 89.6, 122.4, 120.1(2), 122.0, 124.9, 126.3, 127.3, 128.6 (2), 128.9, 129.3, 130.4, 146.7, 149.4, 152.6, 157.9, 162.2, 163.3, 171.8. Anal. Calcd. for $C_{22}H_{18}F_3N_5O_4S$ (505.47): C, 52.28; H, 3.59; N, 13.86. Found: C, 52.49; H, 3.26; N, 13.49.

*3.1.1.14. N-(5,6-dimethoxypyrimidin-4-yl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzene-sulfonamide **14***

Brown powder, Yield 69 %, melting point >350 ^{o}C. IR: υ_{max}./cm^{-1} 3406, 3240 (NH), 3091 (CH arom.), 2920, 2860 (CH aliph.), 1622 (C=N), 1381, 1156 (SO_2).^{1}H-NMR (DMSO-d_6, D_2O) δ: 3.6 (s, 6H, 2OCH_3), 6.6, 8.6 (2d, 2H, 2CH quinoline, *J*= 7.1 Hz), 7.0-8.3 (m, 9H, Ar-H + CH pyrimidine + SO_2NH), 8.7 (s, 1H, NH, D_2O-exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 58.1(2), 116.0, 118.3(2), 122.8, 123.6, 124.0, 125.6, 127.6 (2), 129.8, 130.1, 132.6, 134.3, 143.2, 145.7, 148.3, 150.0, 152.9, 158.6, 169.2. Anal. Calcd. for $C_{22}H_{18}F_3N_5O_4S$ (505.47): C, 52.28; H, 3.59; N, 13.86. Found: C, 52.48; H, 3.23; N, 13.60.

*3.1.1.15. N-(phenylcarbamoyl)-4-(7-(trifluoromethyl)quinolin-4-ylamino)benzenesulfonamide **15***

Dark brown powder, A mixture of **2** (3.6 g, 0.01 mol.) and phenyl isocyanate (1.21 g, 0.01 mol.) in dry DMF (30 mL) containing anhydrous K_2CO_3 (1 g) was refluxed for 17h. The reaction mixture was cooled and poured onto ice/ water. The obtained solid was filtered and crystallized from acetic acid to give **15**. Yield 84%, melting point 254.5 ^{o}C, IR: ν_{max}/cm^{-1} 3200, 3163, 3123 (NH), 3064 (CH arom.), 1664 (C=O), 1575 (C=N), 1379, 1163 (SO_2). ^{1}H-NMR (DMSO-d_6 D_2O) δ: 6.9, 8.6 (2d, 2H, 2CH quinoline, *J*=7.5 Hz), 7.0-8.4 (m, 12 H, Ar-H), 8.5 (s, 2H, 2NHCO, D_2O exchangeable), 8.7 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 119.5, 120.1(2), 121.7, 122.7 (2), 124.3, 125.1, 126.0, 126.8,127.4 (2), 129.0, 129.4 (2), 129.5, 129.8, 140.0, 147.9, 148.0, 148.3, 152.3, 162.2. Anal. Calcd. for $C_{23}H_{17}F_3N_4O_3S$ (486.47): C, 56.79; H, 3.52; N, 11.52. Found: C, 56.44; H, 3.76; N, 11.29.

*3.1.2. 4-Amino-N-(7-(trifluoromethyl)quinolin-4-yl)benzenesulfonamide **16***

A mixture of **1** (2.31 g, 0.01 mol.) and sulfanilamide (1.72 g, 0.01 mol.) in dry DMF (30 mL) containing anhydrous K_2CO_3 (1 g) was refluxed for 10h. The reaction mixture was poured onto ice/water and the obtained solid was crystallized from dioxane to give **16**. Yellow powder, Yield 88%, melting point 211.0 ^{o}C, IR: ν_{max}/cm^{-1} 3483, 3355, 3222 (NH, NH_2), 3100 (CH arom.), 1596 (C=N), 1372, 1177 (SO_2). ^{1}H-NMR (DMSO-d_6 D_2O) δ: 6.7 (s, 2H, NH_2, D_2O exchangeable), 6.8, 8.5 (2d, 2H, 2CH quinoline, *J*=7.7 Hz), 7.0-8.3 (m, 8 H, Ar-H + SO_2NH). ^{13}C-NMR (DMSO-d_6) δ: 116.5, 118.8 (2), 122.2, 124.4, 125.2, 126.6, 128.0 (2), 130.0, 131.3, 132.1, 141.8,

150.1, 154.0, 158.8. Anal. Calcd. for $C_{16}H_{12}F_3N_3O_2S$ (367.35): C, 52.31; H, 3.29; N, 11.44. Found: C, 52.55; H, 3.05; N, 11.18.

*3.1.3. 4-(3-Phenylureido)-N-(7-(trifluoromethyl)quinolin-4-yl)benzenesulfonamide **17***

A mixture of **16** (3.67 g, 0.01 mol.) and phenyl isocyanate (1.21 g, 0.01 mol.) in dry DMF (30 mL) was heated under reflux for 12h. The reaction mixture was cooled and poured onto ice/water. The obtained solid was crystallized from ethanol to give **17**. Yellow powder, Yield 81%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3420, 3386, 3210 (NH), 1668 (C=O), 1625 (C=N), 1389, 1155 (SO_2). ^{1}H-NMR (DMSO-d_6 D_2O) δ: 6.7, 8.6 (2d, 2H, 2CH quinoline, *J*=7.5 Hz), 7.0-8.3 (m, 13 H, Ar-H + SO_2NH), 8.8 (s, 2H, 2NHCO, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 118.0, 120.2, 121.7 (2), 122.3 (2), 123.0, 124.5, 125.2, 126.9, 128.7(2), 129.7, 131.9 (2), 135.7, 138.0, 139.3, 141.4, 142.8, 149.7, 152.2, 152.5. Anal. Calcd. for $C_{23}H_{17}F_3N_4O_3S$ (486.47): C, 56.79; H, 3.52; N, 11.52. Found: C, 56.98; H, 3.77; N, 11.21.

*3.1.4. 4-Isothiocyanato- 7-(triflouromethyl) quinoline **18***

A mixture of **1** (2.31 g, 0.01 mol.) and ammonium thiocyanate (1.52 g, 0.02 mol.) in dry acetone (30 mL) was refluxed for 1h. The reaction mixture was cooled, poured onto ice/ water and the obtained solid was crystallized from dioxane to give **18**.Yellow crystals, Yield 96%, melting point 79.4 ^{o}C, IR: ν_{max}/cm^{-1} 3100 (CH arom.), 2059 (N=C=S), 1600 (C=N). ^{1}H-NMR (DMSO-d_6 D_2O) δ: 7.8, 9.1 (2d, 2H, 2CH quinoline, *J*=7.8 Hz), 7.1-8.3 (m, 3 H, Ar-H). ^{13}C-NMR (DMSO-d_6) δ: 120.6, 121.7, 124.1, 126.2, 126.8, 129.8, 130.1, 135.4, 137.6, 147.1, 152.6. Anal. Calcd. for $C_{11}H_5F_3N_2S$ (254.23): C, 51.97; H, 1.98; N, 11.02. Found: C, 51.68; H, 2.22; N, 11.31.

*3.1.5 General procedure for the synthesis of carbamimidothoic acid derivatives **19- 30.***

A mixture of **18** (0.43 g, 0.001 mol.) and the appropriate sulfa drugs (0.0012 mol.) in dry DMF (30 mL) containing a catalytic amount of triethylamine was heated under reflux for 24h. The obtained solid was filtered and crystallized from dioxane to give **19**- **30**, respectively.

*3.1.5.1.(E)-N-(4-sulfamoylphenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid **19***

Brown powder, Yield 76%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3489, 3414, 3320 (NH, NH_2), 1625 (C=N), 1381, 1128 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.5 (s, 1H, SH, D_2O exchangeable), 6.6, 8.5 (2d, 2H, 2CH quinoline, *J*=7.3 Hz), 6.8- 8.4 (m, 9H, Ar-H + SO_2NH_2), 9.1 (s, 1H, NH, D_2O exchangeable) ^{13}C-NMR (DMSO-d_6) δ: 116.9(2), 117.7, 122.9, 123.0, 123.6, 127.9(2), 128.3, 129.0, 129.3, 132.7, 143.0, 146.9, 153.0, 154.6, 164.2. Anal. Calcd. for $C_{17}H_{13}F_3N_4O_2S_2$ (426.44): C, 47.88; H, 3.07; N, 13.14. Found: C, 47.56; H, 3.28; N, 13.45.

3.1.5.2. (E)-N-(4-(N-acetylsulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid ***20***

Brown powder, Yield 71%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3489, 3400 (NH), 1685 (C=O), 1616 (C=N), 1327, 1114 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.4 (s, 3H, $COCH_3$), 2.6 (s, 1H, SH, D_2O exchangeable), 6.7, 8.9 (2d, 2H, 2CH quinoline, *J*=7.1 Hz), 7.5-8.4 (m, 8 H, Ar-H + SO_2NH), 11.7 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 19.8, 113.7(2), 117.6, 123.7, 125.8(2), 127.6(2), 127.8, 128.0, 128.8, 132.0, 143.2, 148.7, 153.7, 155.9, 168.7, 188.2. Anal. Calcd. for $C_{19}H_{15}F_3N_4O_3S_2$ (468.47): C, 48.71; H, 3.23; N, 11.96. Found: C, 48.45; H, 3.50; N, 11.66.

3.1.5.3. (E)-N-(4-(N-carbamimidoylsulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid ***21***

Brown powder, Yield 81%, melting point 332.8 ^{o}C, IR: ν_{max}/cm^{-1} 3429, 3373, 3330, 3221 (NH, NH_2), 1627 (C=N), 1398, 1130 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.5 (s, 1H, SH, D_2O exchangeable), 5.6 (s, 2H, NH_2, D_2O exchangeable), 6.5, 8.8 (2d, 2H, 2CH quinoline, *J*=7.4 Hz), 6.7-7.9 (m, 8 H, Ar-H + SO_2NH), 8.2 (s, 1H, NH imino, D_2O exchangeable), 10.5 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 112.2(2), 116.6, 118.5, 126.7(2), 127.2 (2), 127.4, 130.7(2), 139.1, 140.4, 151.3, 157.7, 158.0, 160.0 (2). Anal. Calcd. for $C_{18}H_{15}F_3N_6O_2S_2$ (468.48): C, 46.15; H, 3.23; N, 17.94. Found: C, 46.44; H, 3.52; N, 17.69.

3.1.5.4. (E)-N-(4-(N-(3-methylisoxazol-5-yl)sulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid ***22***

Brown powder, Yield 72%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3487, 3406 (NH), 1620 (C=N), 1381, 1138 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.3 (s, 3H, CH_3), 2.6 (s, 1H, SH, D_2O exchangeable), 6.0 (s, 1H, CH isoxazole), 6.6, 8.9 (2d, 2H, 2CH quinoline, J=7.0 Hz), 7.4-8.4 (m, 8 H, Ar-H + SO_2NH), 9.1 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 18.2, 100.7, 116.6 (2), 117.8, 122.3, 124.0, 124.9, 128.6 (2), 128.7, 129.8, 132.0, 132.9, 142.8, 143.7, 152.6, 155.8, 160.0, 161.8, 162.1. Anal. Calcd. for $C_{21}H_{16}F_3N_5O_3S_2$ (507.51): C, 49.70; H, 3.18; N, 13.80. Found: C, 49.39; H, 3.38; N, 13.46.

3.1.5.5. ***(****E)-N-(4-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid* ***23***

Brown powder, Yield 82%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3491, 3404 (NH), 1620 (C=N), 1381, 1138 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.4 (s, 6H, $2CH_3$), 2.6 (s, 1H, SH, D_2O exchangeable), 6.5, 8.5 (2d, 2H, 2CH quinoline, *J*=7.2 Hz), 6.9-8.3 (m, 8H, Ar-H + SO_2NH), 9.0 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 9.9, 16.2, 101.2, 115.7(2), 118.6, 121.3, 124.0, 125.6, 128.7(2), 128.9, 129.2, 129.8, 132.5, 142.8, 144.9, 153.6, 156.0, 156.7, 158.2, 163.1. Anal. Calcd. for $C_{22}H_{18}F_3N_5O_3S_2$ (521.54): C, 50.66; H, 3.48; N, 13.43. Found: C, 50.31; H, 3.19; N, 13.71.

3.1.5.6. (E)-N-(4-(N-thiazol-2-ylsulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimido-thioic acid ***24***

Brown powder, Yield 78%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3404, 3329 (NH), 3100 (CH arom.), 1614 (C=N), 1379, 1130 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.6 (s, 1H, SH, D_2O exchangeable), 6.7, 8.5 (2d, 2H, 2CH quinoline, *J*=6.8 Hz), 7.1-8.4 (m, 10H, Ar-H + SO_2NH), 10.6 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 116.0 (2), 116.3, 119.4, 119.9, 122.4, 125.1, 128.6 (2), 128.9, 129.0, 129.8, 133.1, 143.6, 146.2, 146.8, 152.6, 153.9, 155.0, 162.2. Anal. Calcd. for $C_{20}H_{14}F_3N_5O_2S_3$ (509.55): C, 47.14; H, 2.77; N, 13.74. Found: C, 47.49; H, 2.41; N, 13.98.

3.1.5.7. (E)-N-(4-(N-pyridin-2-ylsulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimido-thioic acid ***25***

Brown powder, Yield 81%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3362, 3278 (NH), 3079 (CH arom.), 1627 (C=N), 1381, 1158 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.6 (s, 1H, SH, D_2O exchangeable), 6.7, 8.5 (2d, 2H, 2CH quinoline, *J*=6.8 Hz), 7.5-8.4 (m, 12H, Ar-H + SO_2NH), 9.9 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 108.9, 112.8, 117.2 (2), 118.0, 122.6, 124.4, 125.1, 128.7(2), 128.9, 129.2, 129.9, 131.0, 136.7, 145.8, 148.6, 151.6, 152.1, 153.4, 158.2, 162.2 . Anal. Calcd. for $C_{22}H_{16}F_3N_5O_2S_2$ (503.52): C, 52.48; H, 3.20; N, 13.91. Found: C, 52.77; H, 3.02; N, 13.59.

3.1.5.8. (E)-N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carba-mimidothioic acid ***26***

Brown powder, Yield 69%, melting point 194.7 ^{o}C, IR: ν_{max}/cm^{-1} 3427, 3360 (NH), 3068 (CH arom.), 1581 (C=N), 1325, 1155 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.7 (s, 1H, SH, D_2O exchangeable), 6.5, 8.5 (2d, 2H, 2CH quinoline, *J*=6.9 Hz), 7.0-8.5 (m, 11H, Ar-H + SO_2NH), 11.4 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 112.1, 116.4 (2), 118.5, 121.4, 124.7, 126.1, 128.9 (2), 129.0, 129.3, 129.7, 134.4, 142.0, 142.8, 153.0, 157.1, 158.2 (2), 162.3, 162.6. Anal. Calcd. for $C_{21}H_{15}F_3N_6O_2S_2$ (504.51): C, 49.99; H, 3.00; N, 16.66. Found: C, 49.68; H, 2.79; N, 16.96.

3.1.5.9. ((E)-N-(4-(N-(4-methylpyrimidin-2-yl)sulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid ***27***

Brown powder, Yield 65%, melting point 256.9 ^{o}C, IR: ν_{max}/cm^{-1} 3379, 3251 (NH), 3093 (CH arom.), 2934, 2861(CH aliph.), 1631 (C=N), 1381, 1151 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.1 (s, 3H, CH_3), 2.7 (s, 1H, SH, D_2O exchangeable), 6.5, 8.6 (2d, 2H, 2CH quinoline, *J*=7.0 Hz), 7.1-8.6 (m, 10H, Ar-H + SO_2NH), 10.7 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 23.4, 109.2, 115.6(2), 117.6, 120.6, 124.0, 124.6, 128.1(2), 128.4, 128.6, 129.3, 129.5, 141.1, 151.1, 151.8, 157.0, 162.3, 163.7, 165.9, 166.6. Anal. Calcd. for $C_{22}H_{17}F_3N_6O_2S_2$ (518.53): C, 50.96; H, 3.30; N, 16.21. Found: C, 51.26; H, 3.56; N, 16.03.

3.1.5.10. (E)-N-(4-(N-(4,6-dimethylpyrimidin-2-yl)sulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid ***28***

Brown powder, Yield 62%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3367, 3242 (NH), 3082 (CH arom.), 2931, 2860(CH aliph.), 1597 (C=N), 1379, 1151 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.2 (s, 6H, 2CH_3), 2.7 (s, 1H, SH, D_2O exchangeable), 6.0 (s, 1H, CH pyrimidine), 6.5, 8.4 (2d, 2H, 2CH quinoline, *J*=7.1 Hz), 7.1-8.6 (m, 8H, Ar-H + SO_2NH), 10.6 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 23.0(2), 103.7, 118.1(2), 118.5, 120.3, 124.5, 124.9, 126.0(2), 126.1, 129.0, 129.3, 130.2, 147.6, 151.7, 152.8, 156.6, 160.1, 162.2(2), 167.2. Anal. Calcd. for $C_{23}H_{19}F_3N_6O_2S_2$ (532.56): C, 51.87; H, 3.60; N, 15.78. Found: C, 51.51; H, 3.39; N, 15.43.

3.1.5.11. (E)-N-(4-(N-(2,6-dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid ***29***

Brown powder, Yield 73%, melting point 331.3 ^{o}C, IR: ν_{max}/cm^{-1} 3350, 3234 (NH), 3100 (CH arom.), 2953, 2846(CH aliph.), 1593 (C=N), 1381, 1145 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.6 (s, 1H, SH, D_2O exchangeable), 3.7, 3.8 (2s, 6H, 2OCH_3), 5.9 (s, 1H, CH pyrimidine), 6.6, 8.6 (2d, 2H, 2CH quinoline, *J*=7.0 Hz), 7.4-8.7 (m, 8H, Ar-H + SO_2NH), 10.9 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 54.3, 54.8, 84.1, 116.7(2), 117.3, 122.5, 123.6, 124.1, 128.7(2), 128.8, 129.1, 129.3, 135.6, 150.5, 151.3, 156.8, 158.1, 160.1, 164.3, 171.5, 173.2. Anal. Calcd. for $C_{23}H_{19}F_3N_6O_4S_2$ (564.56): C, 48.93; H, 3.39; N, 14.89. Found: C, 48.59; H, 3.12; N, 14.60.

3.1.5.12. (E)-N-(4-(N-(5,6-dimethoxypyrimidin-4-yl)sulfamoyl)phenyl)-N'-(7-(trifluoromethyl)quinolin-4-yl)carbamimidothioic acid ***30***

Brown powder, Yield 61%, melting point >350 ^{o}C, IR: ν_{max}/cm^{-1} 3442, 3380 (NH), 2978, 2871 (CH aliph.), 1591 (C=N), 1379, 1151 (SO_2).^{1}H-NMR (DMSO-d_6 D_2O) δ: 2.7 (s, 1H, SH, D_2O exchangeable), 3.8 (s, 6H, 2OCH_3), 6.5, 8.6 (2d, 2H, 2CH quinoline, *J*=6.8 Hz), 7.0-8.5 (m, 9H, Ar-H + SO_2NH], 8.7[s,1H, CH pyrimidine), 10.8 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ: 54.0(2), 117.7(2), 118.5, 122.1, 124.2, 125.9, 127.1(2), 127.2, 128.8, 129.7, 132.4, 132.7, 142.8, 150.5, 150.7, 153.0, 157.9, 160.2, 161.5, 167.1. Anal. Calcd. for $C_{23}H_{19}F_3N_6O_4S_2$ (564.56): C, 48.93; H, 3.39; N, 14.89. Found: C, 49.26; H, 3.64; N, 15.28.

3.2. Molecular docking

All the molecular modeling studies were carried out on an Intel Pentium 1.6 GHz processor, 512 MB memory with Windows XP operating system using Molecular Operating Environment (MOE, 10.2008) software. All the minimizations were performed with MOE until a RMSD gradient of 0.05 kcal $mol^{-1}A^{o-1}$with MMFF94X force field and the partial charges were automatically calculated. The X-ray crystallographic structure of franesyltransferase and arginine methyltransferase (PRMT1) complexes with their ligands (PDB ID: 3E30, 3Q7E) were obtained from the protein data bank. The enzymes were prepared for docking studies where: (i) Ligand molecule was removed from the enzyme active site. (ii) Hydrogen atoms were added to the structure with their standard geometry. (iii) MOE Alpha Site Finder was used for the active sites search in the enzyme structure and dummy atoms were created from the obtained alpha spheres. (iv) The obtained model was then used in predicting the ligand enzymes interactions at the active site

3.3. In vitro antitumor activity

The cytotoxic activity was measured *in vitro* for the newly synthesized compounds using the Sulfo-Rhodamine-B stain (SRB) assay using the method of Skehan et al. [40]. The *in vitro* anticancer screening was done by the pharmacology unit at Pharmacognosy Department, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

Cells were plated in 96-multiwell plate (104 cells/well) for 24 h before treatment with the compound(s) to allow attachment of cell to the wall of the plate. The tested compounds were dissolved in dimethyl sulfoxide. Different concentrations of the compound under test (10, 25, 50, and 100 µM) were added to the cell monolayer. Triplicate wells were prepared for each individual concentration. Monolayer cells were incubated with the compound(s) for 48 h at 37 ^{o}C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained for 30 min with 0.4% (wt/vol) SRB dissolved in 1% acetic acid. Excess unbound dye was removed by four washes with 1% acetic acid and attached stain was recovered with Trise-EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve for breast tumor cell line after the specified

time. The molar concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and compared to the reference drug Doxorubicin (CAS, 25316-40-9).

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Figure 1: X-ray crystallography of compound 2 with ethanol and methanol
Figure 2: Co-crystallized quinoline ligand on the active site of phosphoinisitol kinase (PI3K)
Figure 3: Compound **29** on the active site of phosphoinisitol kinase (PI3K)
Figure 4: 3D interactions of compound **15** on the active site of PI3K enzyme

Table 1
Binding scores and amino acid interactions of the docked compounds on the active site of phosphoinisitol kinase (PI3K).

Compound No.	S Kcal/Mol	Amino acid interactions	Interacting groups	H bond length A^o
2	-14.5528	Lys 890	N-quinoline	2.58
3	-18.1977	Lys 833, Lys 890	N-quinoline, NHCO	2.57, 2.46
4	-26.4252	Asp 841(water), His 957 Lys 833	N-quinoline, NH NH	3.05, 2.48 2.78
5	-18.2927	Lys 833, Lys 890 Ser 836, Lys 808	SO_2, N-quinoline SO_2, N oxazole	2.35, 2.64 2.79, 3.03
6	-19.4952	Asp 841(water), Lys 867 Lys 808, His 848(water)	N-quinoline, SO_2 SO_2, N-isoxazole	3.06, 2.60 3.29, 2.70
7	-19.6350	Lys 890	N-quinoline	2.70
8	-18.4821	Asp 841(water), His 867 Lys 808, His 848	N-quinoline, SO_2 SO_2, N-thiazole	3.01, 2.04 2.70, 3.06
9	-22.4510	Asp 841(water), Lys 808 Asn 861, His 867	N-quinoline, SO_2 SO_2, N-pyridine	3.24, 2.07 3.06, 2.72

10	-19.4511	Asn 861, Lys 833	N-pyrimidine, SO_2	2.90, 2.56
11	-22.7769	Lys 890, Lys 808 Lys 833, Ser 836	N-quinoline, SO_2 SO_2, NH	2.95, 3.15 2.83, 2.83
12	-23.1235	Asp 841 (water), Lys 808, His 807	N-quinoline SO_2, N-pyrimidine	3.01 2.58, 3.08
13	-25.7419	Asp 841 (water) Lys 890, Lys 890	N-quinoline SO_2, N-pyrimidine	3.12 3.10, 2.61
14	-18.0536	Lys 890 Ser 806	N-quinoline N-pyrimidine	2.59 2.53
15	-23.7148	Lys 890, Lys 833	N-quinoline, SO_2	2.74, 2.77
16	-18.2562	Ser 836, Asp 841 Lys 833	SO_2, NH SO_2	3.00, 1.34 2.33
17	-19.3946	Ser 836, Val 802 Val 802	N-quinoline, NH C=O	2.82, 3.01 3.78, 3.60
19	-21.1616	Asp 841(water), Asp 864	N-quinoline, NH	2.93,1.31
20	-14.8902	Asp 841(water), Asp 954	SO_2, C=O	2.41, 2.60
21	-20.3150	Lys 833, Glu 889	N-quinoline, NH	2.87, 2.41
22	-16.7515	Ser 836, Lys 833	SO_2, SO_2	2.44, 2.96
23	-24.8105	Ser 836, Lys 833	SO_2, SO_2	2.76, 2.40
24	-21.9811	Ser 836, Lys 890	N-quinoline, N-thiazole	3.05, 2.74
25	-22.1491	Ser 836, Lys 890	SO_2, SO_2	3.03, 2.66
26	-20.1491	Lys 890	N-quinoline	2.95
27	-22.3484	Lys 890, Lys 890	N-pyrimidine, SO_2	2.77, 2.40
28	-22.4054	Lys 890, Ser 808 Lys 833, Asp 864	N-quinoline, SO_2 SO_2, NH	2.74, 2.89 2.37, 1.39
29	-27.2076	Lys 808, Lys 890 Asp 841(water)	N-quinoline, C=N N-pyrimidine	2.65, 2.92 3.08

30	-19.0437	Asp 841(water), Lys 833 Lys 890	N-quinoline, C=N SO_2	2.46, 2.66 3.24

Table 2
In vitro anticancer screening of the synthesized compounds against six cell lines

Compound No.	MDA-MB231 (breast cancer cells)	HT 1080 (skin cancer cells)	HepG2 (liver cancer cells)	Lovo (colorectal cancer cells)	AS49-Raw (lung cancer cells)	Hela cells
			IC_{50} (μM)			
2	34.40	56.06	50.76	26.56	79.01	61.17
3	75.58	41.55	45.99	51.47	64.18	NA
4	28.83	49.81	NA	24.65	55.25	41.26
5	74.76	33.55	33.55	33.56	74.76	97.59
6	39.31	31.88	40.80	36.02	53.08	NA
7	52.82	25.81	82.60	56.77	52.82	34.10
8	90.78	40.34	NA	NA	66.08	70.75
9	18.40	41.80	46.10	20.22	30.38	44.76
10	54.73	27.16	NA	27.41	34.23	78.06
11	NA	32.50	NA	NA	62.52	NA
12	36.18	32.77	NA	44.33	NA	32.01
13	NA	39.19	83.82	50.41	37.91	83.23
14	49.41	25.96	66.06	39.85	36.86	NA
15	18.39	17.89	27.62	19.65	18.42	35.29
16	30.95	29.57	93.11	53.65	29.23	45.98
17	52.93	25.44	NA	30.23	24.50	40.96
19	52.87	31.02	52.17	34.53	36.55	36.55
20	58.64	28.32	28.41	30.03	37.60	37.60
21	NA	24.29	33.48	23.91	23.91	23.91
22	80.26	27.34	28.49	NA	60.16	60.16
23	27.94	27.74	36.76	67.05	34.01	NA
24	24.39	27.31	28.16	67.08	27.15	95.18

25	49.30	28.04	28.04	87.50	33.51	68.78
26	45.16	29.12	42.08	34.72	37.75	NA
27	29.78	28.67	NA	31.03	31.03	31.03
28	52.91	29.48	72.15	40.21	43.41	32.98
29	52.09	29.48	76.66	76.65	64.45	53.79
30	82.99	22.76	77.25	28.39	81.76	NA
Doxorubicin	33.98	19.22	27.11	24.33	32.78	30.21

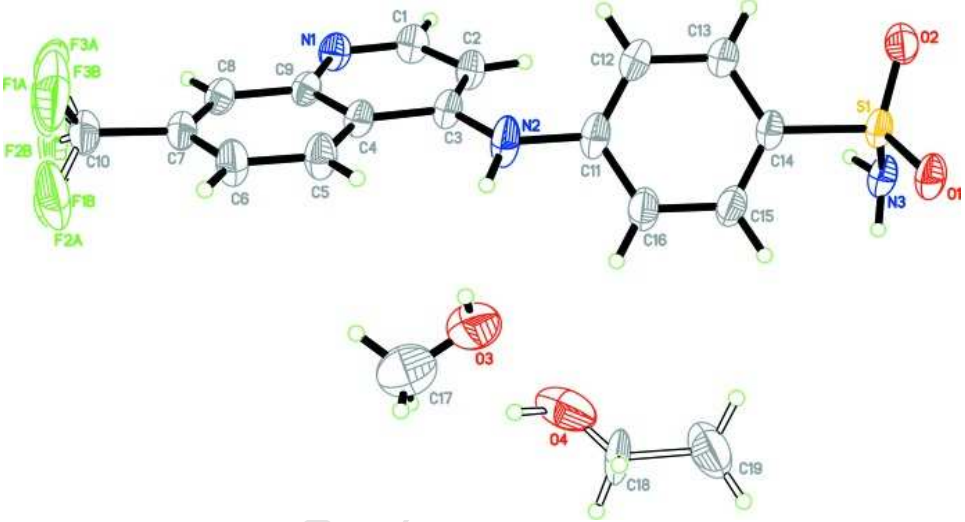


Figure 1: X-ray crystallography of compound 2 with ethanol and methanol

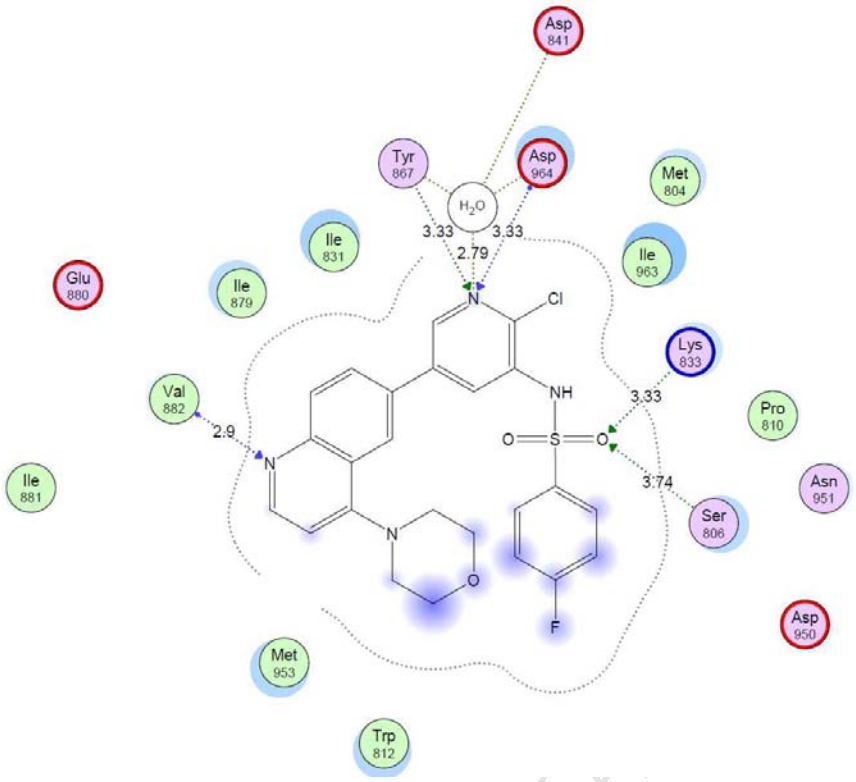


Figure 2: Co-crystallized quinoline ligand on the active site of phosphoinisitol kinase (PI3K)

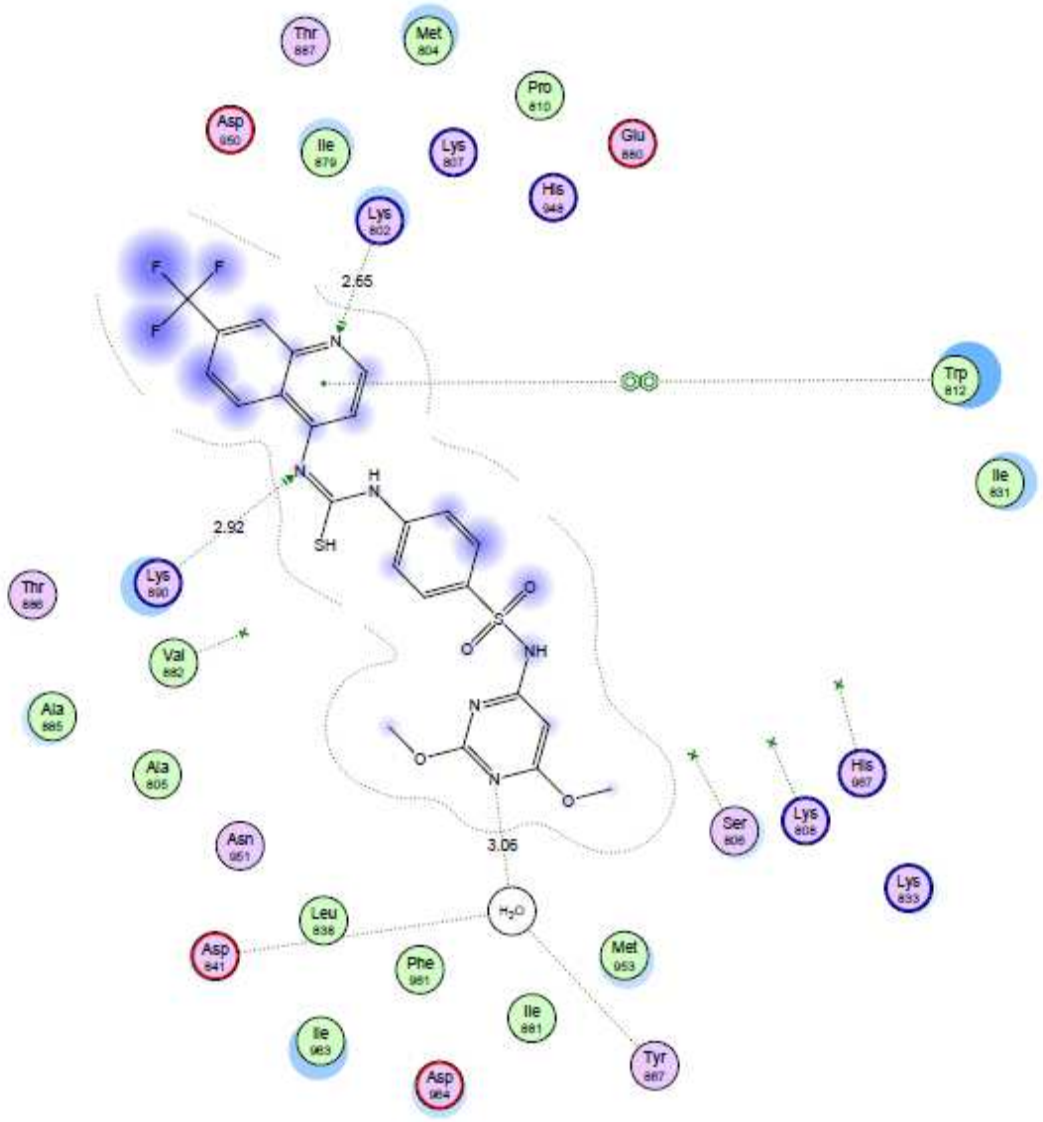


Figure 3: Compound **29** on the active site of phosphoinisitol kinase (PI3K)

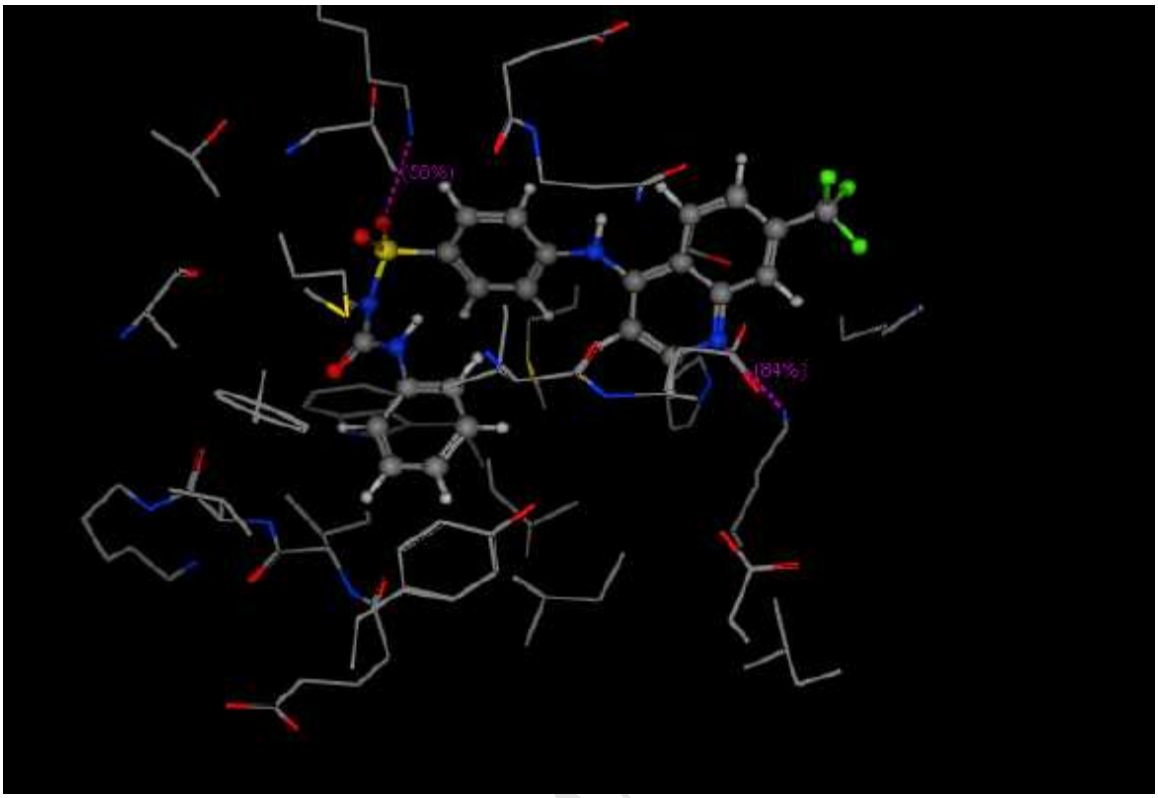
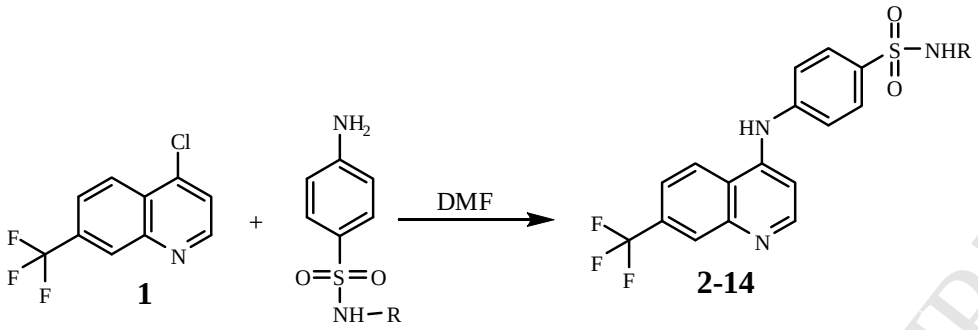


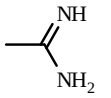
Figure 4: 3D interactions of compound **15** on the active site of PI3K enzyme



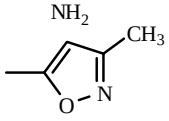
2: R = H

3: R = $COCH_3$

4: R =



5: R =



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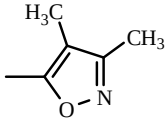

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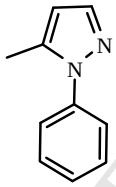
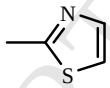
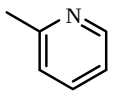


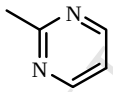
8: R =



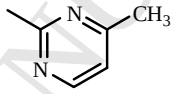
9: R =



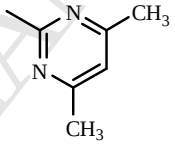
10: R =



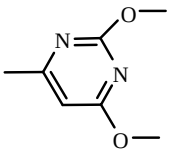
11: R =



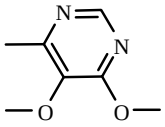
12: R =



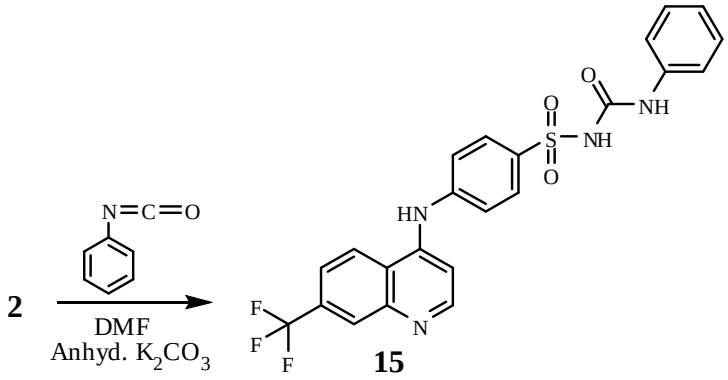
13: R =



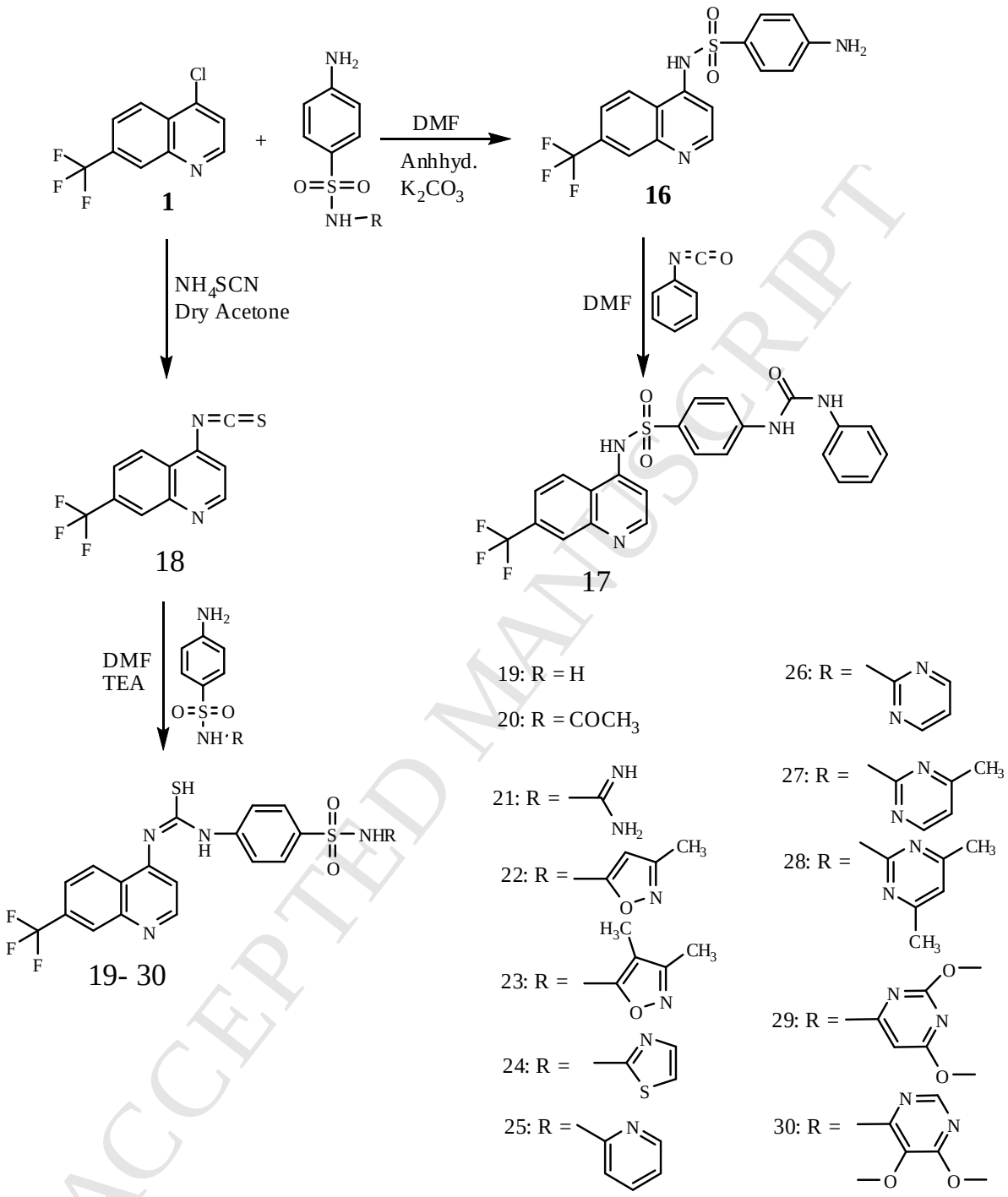
14: R =



Scheme 1: Synthesis of compounds **2-14**



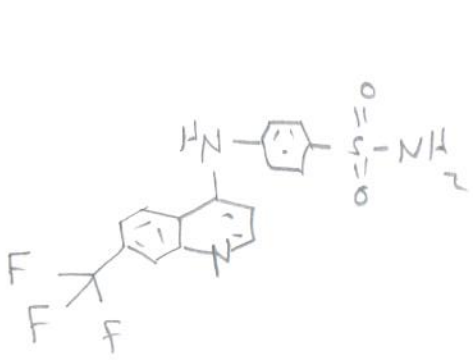
Scheme 2: Synthesis of compound **15**



Scheme 3: Synthesis of compounds **16-30**

- Novel trifluoroquinoline derivatives.
- Molecular docking on the active site of PI3K.
- *In vitro* anticancer activity.
- Most of the compounds showed good anticancer activity.

-BBO DMSO D:\\ m



compound (2)

7.3, 8.6 [2d, 2H, 2CH pyridine, J = 7.2 Hz], 7.5 - 8.5 [m, 9H, Ar-H + SO_2NH_2], 9.5 [s, 1H, NH, D_2O exchangable].

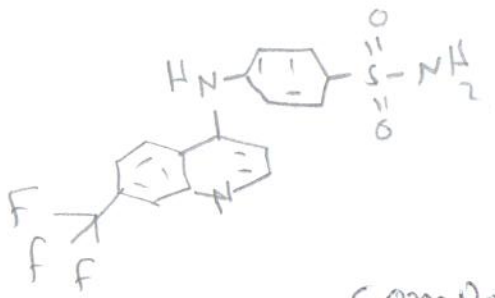
BRUKER

NAME	drdosari-2
EXPNO	10
PROCNO	1
Date_	20120407
Time	4.11
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1720407 sec
RG	114
DW	48.400 usec
DE	6.50 usec
TE	296.6 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

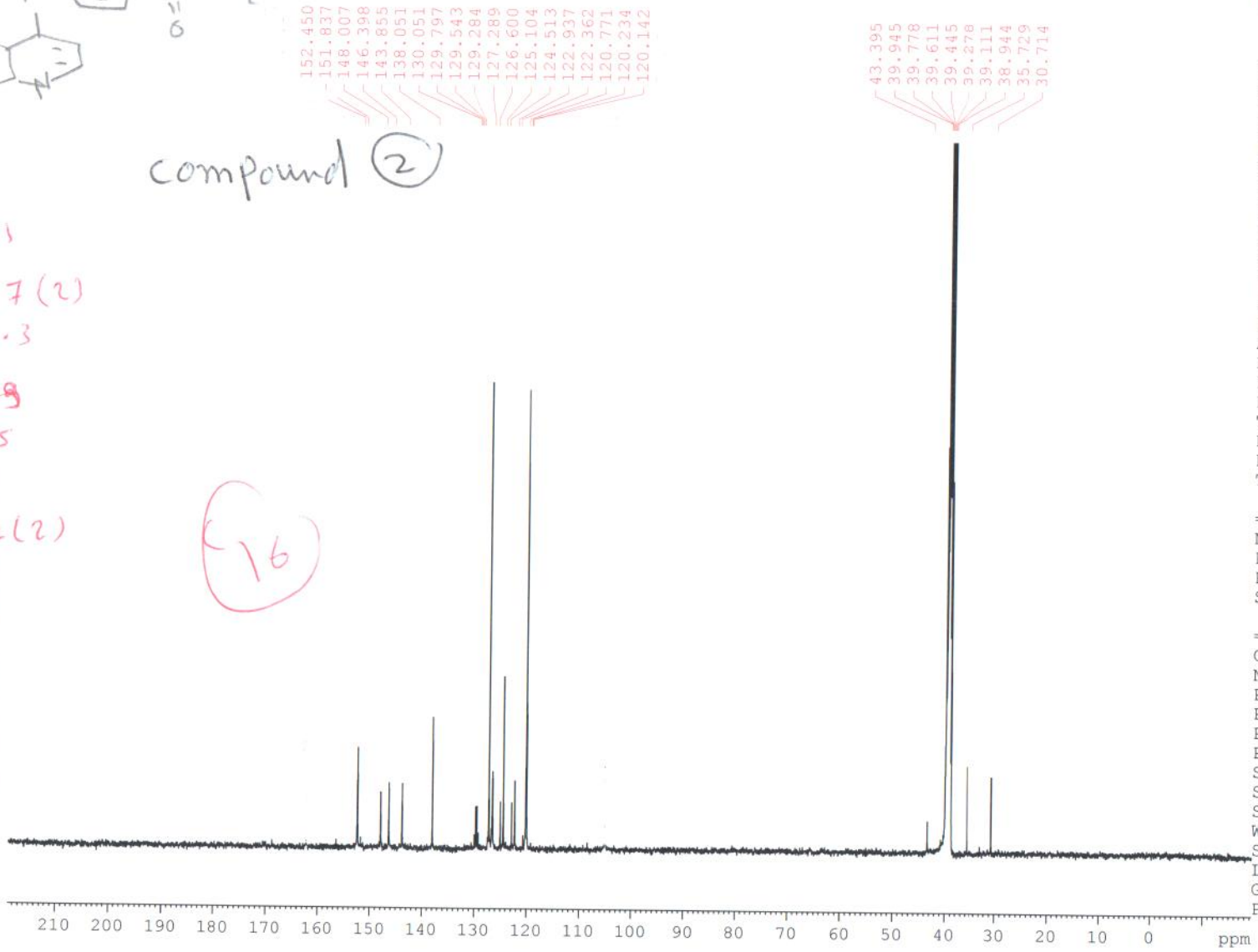
3BO DMSO D:\\ mmj



compound (2)

120.1
120.7 (2)
122.3
122.9
124.5
125.1
127.2 (2)
129.5
129.7
138.0
143.8
146.3
148.0
151.8

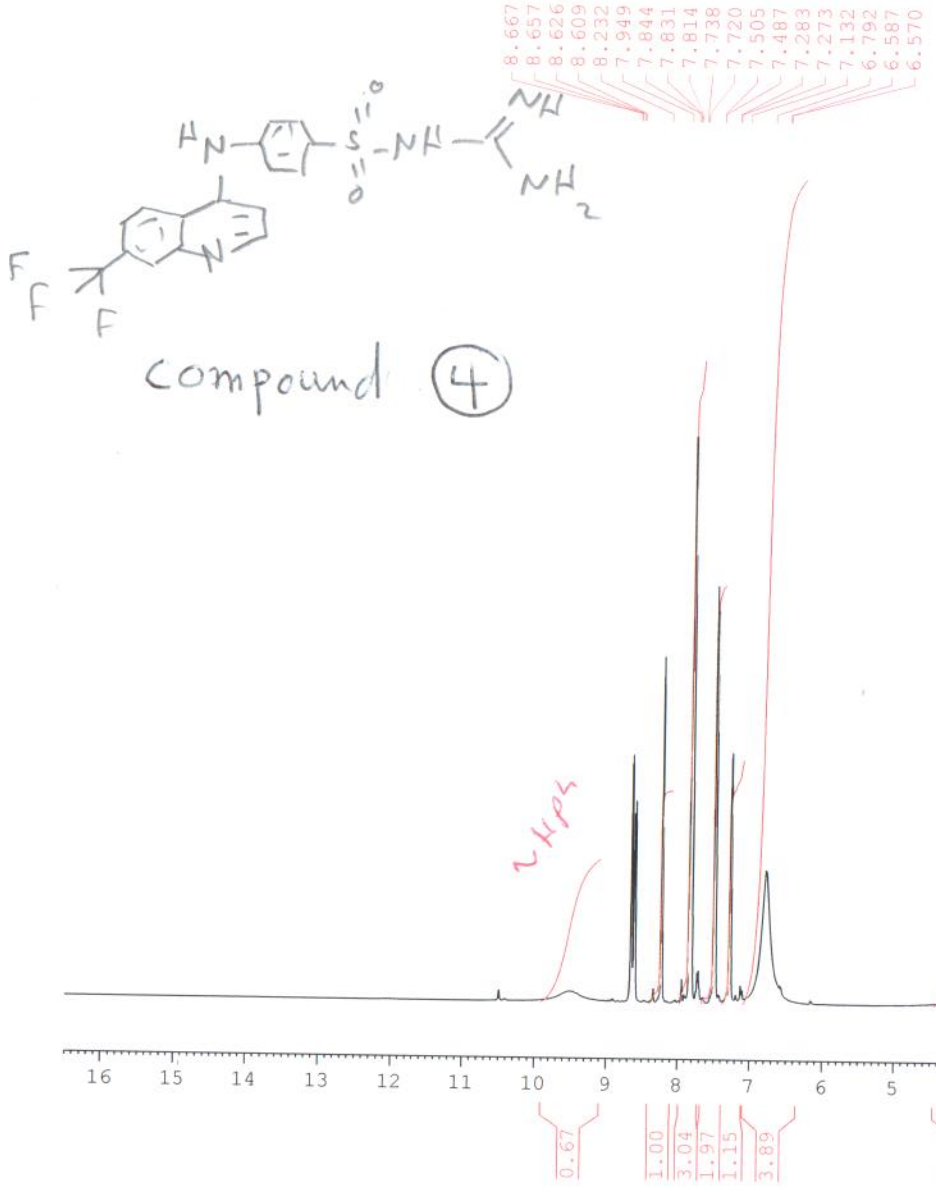
(16)



BRUKER

NAME	drdosari-2
EXPNO	11
PROCNO	1
Date_	20120407
Time	6.00
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	1625.5
DW	16.650 usec
DE	6.50 usec
TE	297.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

-BBO DMSO D:\\ m



6.5 [s, 2H, NH2, D2O-exc]
7.2, 8.6 [2d, 2H, 2CH, Pyridine, J = 7.1 Hz]
7.4-8.2 [m, 8H, Ar-H + SO2NH], 8.62 [s, 1H, NH imine, D2O-exch]
9.5 [s, 1H, NHph, D2O-exchg. (6)]

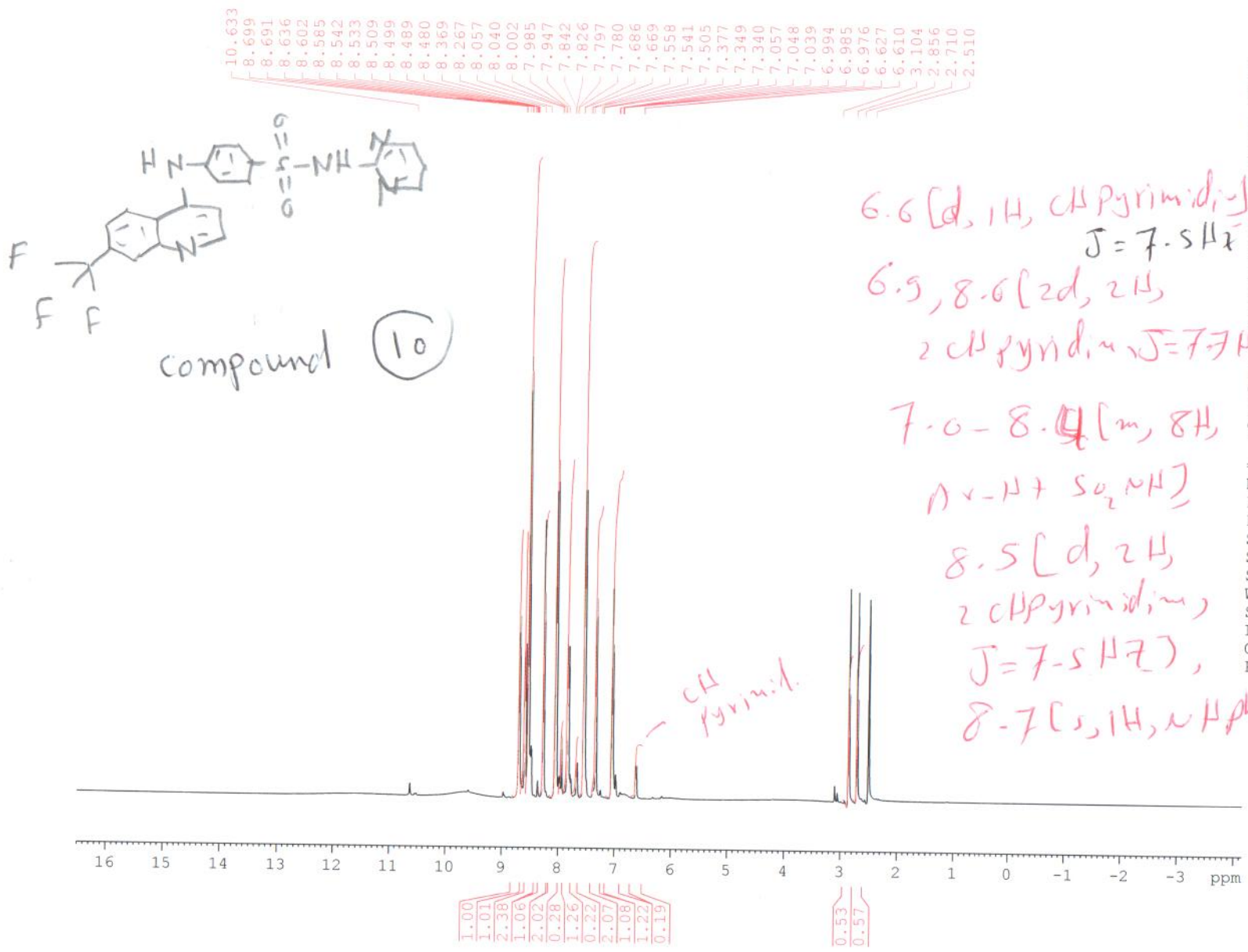
BRUKER

NAME	drdosari-4
EXPNO	20
PROCNO	1
Date_	20120407
Time	2.19
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1720407 sec
RG	71.8
DW	48.400 usec
DE	6.50 usec
TE	296.6 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

-BBO DMSO D:\\ m

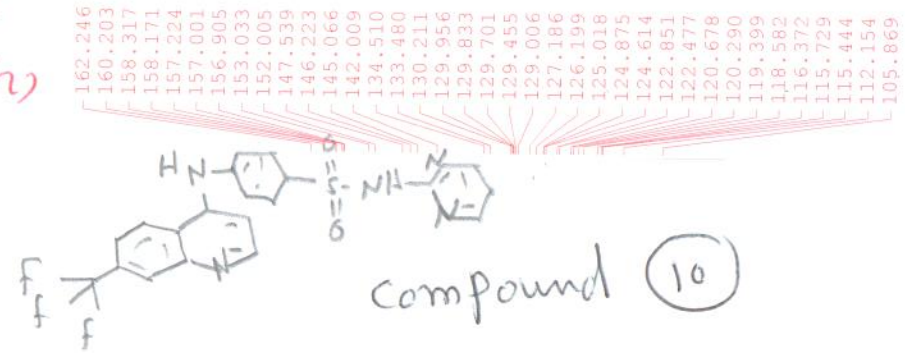


BRUKER

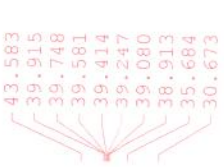
NAME	drdosari-10
EXPNO	20
PROCNO	1
Date_	20120406
Time	15.04
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1720407 sec
RG	57
DW	48.400 usec
DE	6.50 usec
TE	296.7 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

3BO DMSO D:\\ mmj

105.8
115.7
118.5 (2)
122.4
122.8
124.8
127.1
129.7 (2)
129.9
130.2
134.5
147.5
152.0
153.0
156.9
158.3
160.2 (2)
162.2

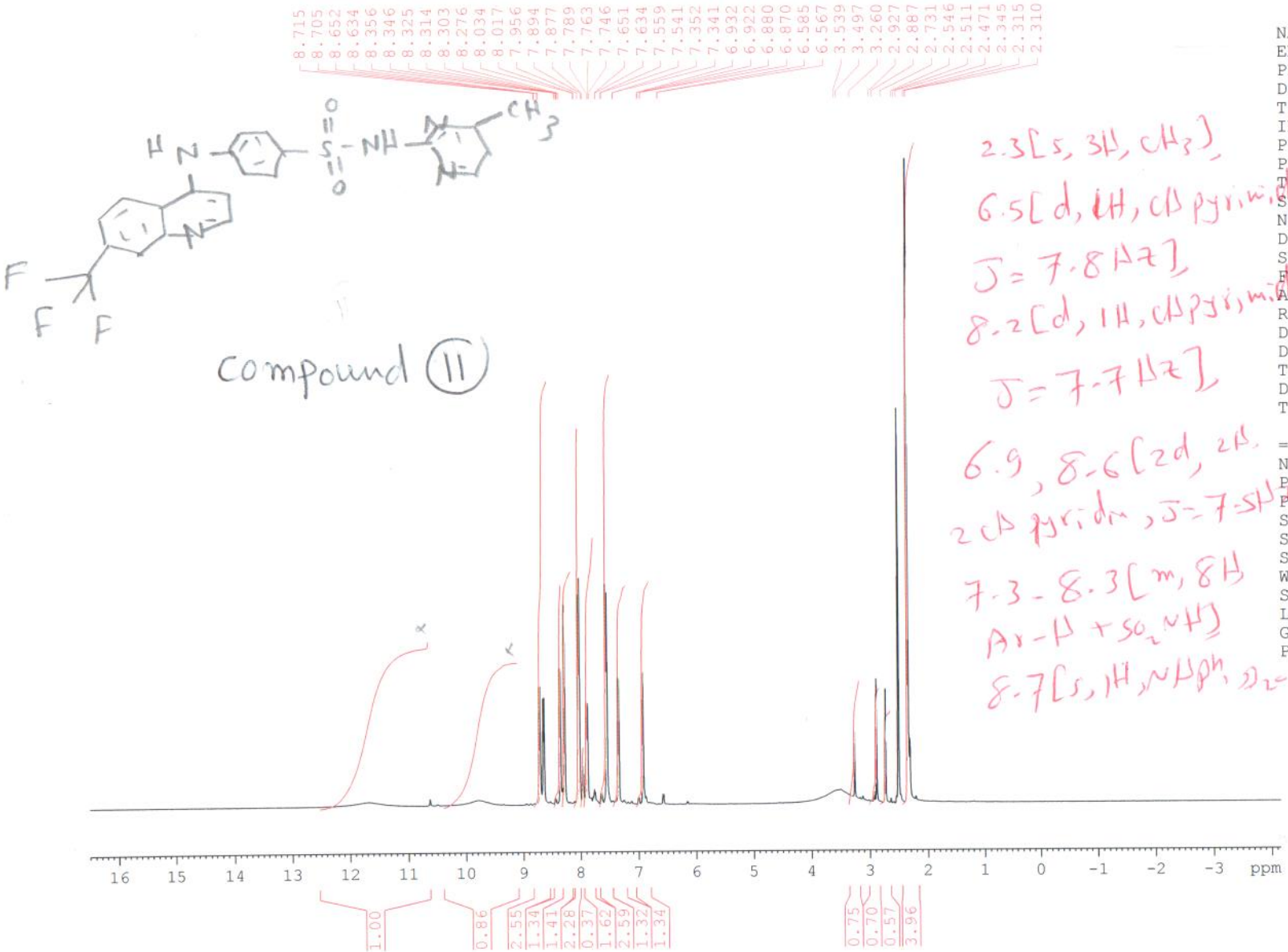


compound (10)



NAME	drdosari-10
EXPNO	21
PROCNO	1
Date_	20120406
Time	16.52
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	1625.5
DW	16.650 usec
DE	6.50 usec
TE	297.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

-BBO DMSO D:\\ m



2.3[s, 3H, CH_3]

6.5[d, 1H, Ch pyridine, J = 7.8 Hz]

8.2[d, 1H, Ch pyridine, J = 7.7 Hz]

6.9, 8.6[2d, 2H, 2 Ch pyridine, J = 7.5 Hz]

7.3 - 8.3[m, 8H Ar-H + SO_2NH]

8.7[s, 1H, NHph, D2O - exch.]

BRUKER

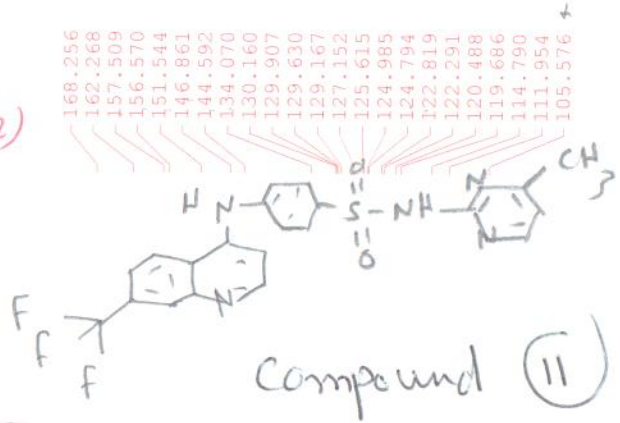
NAME	drdosari-11
EXPNO	20
PROCNO	1
Date_	20120406
Time	13.11
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1720407 sec
RG	128
DW	48.400 usec
DE	6.50 usec
TE	296.8 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

3BO DMSO D:\\ mmj

23.2
111.9
114.7
119.6 (2)
122.8
124.7
125.6
127.1
129.1(2)
129.9
130.1
134.0
~~144.9~~ 144.5
146.8
151.5
156.5
157.5
162.2
168.2

168.256 162.268 157.509 156.570 151.544 146.861 144.592 134.070 130.160 129.907 129.630 129.167 127.152 125.615 124.985 124.794 122.819 122.291 120.488 119.686 114.790 111.954 105.576

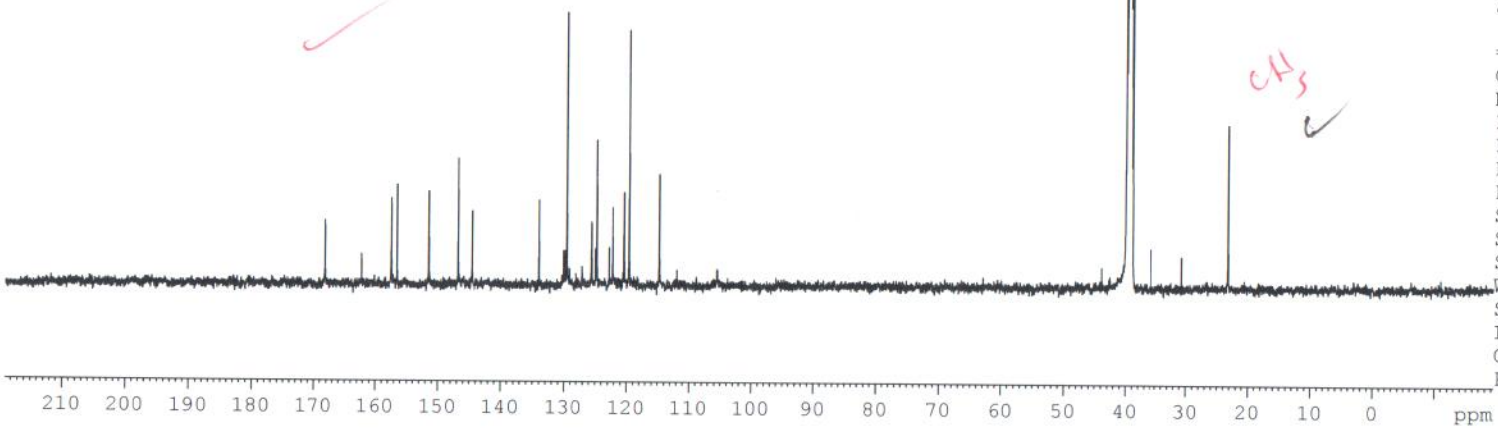
43.904 39.967 39.800 39.633 39.466 39.299 39.132 38.965 35.733 30.721 23.240



Compound (11)

C21

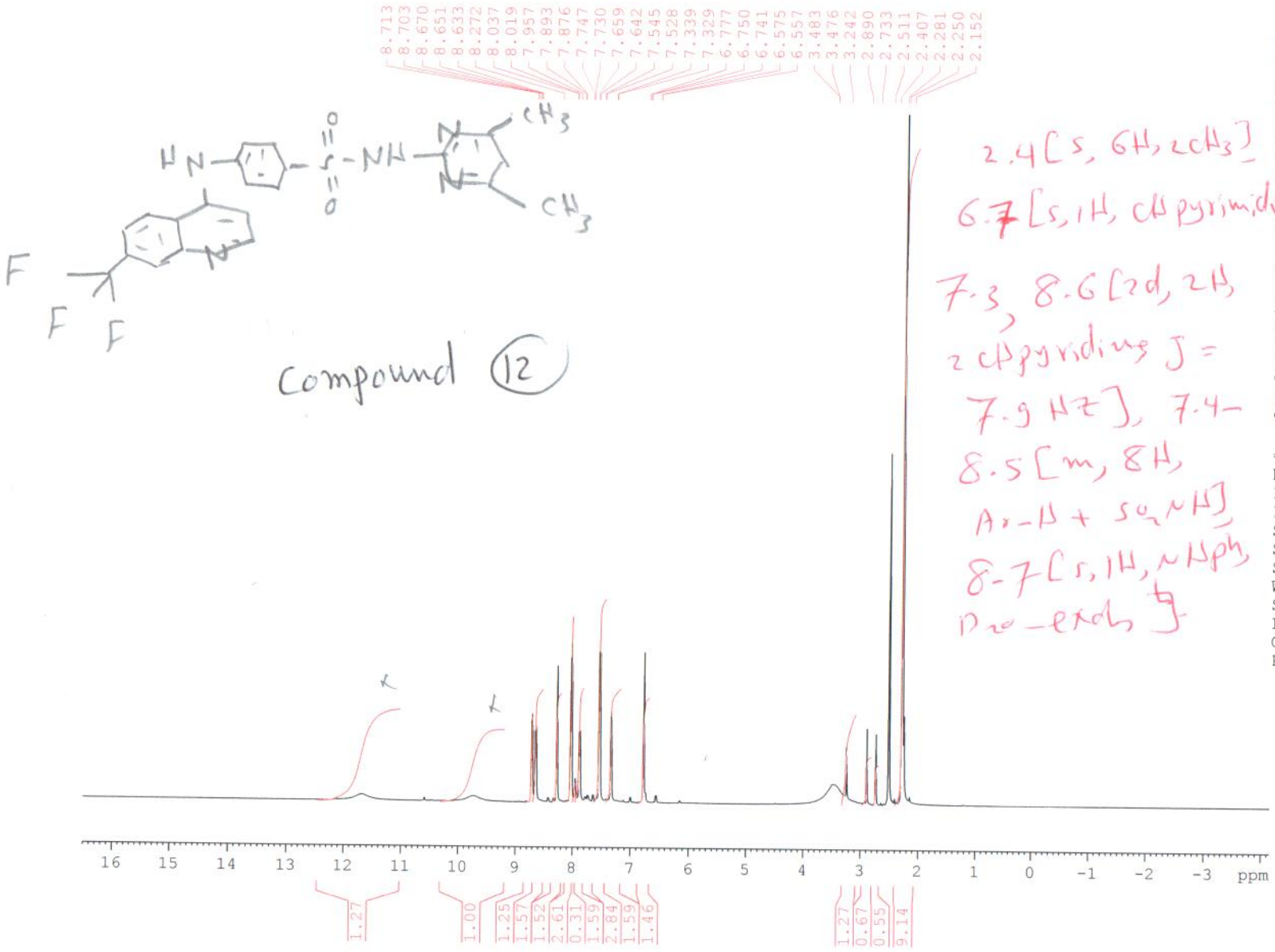
CH3



BRUKER

NAME	drdosari-11
EXPNO	21
PROCNO	1
Date_	20120406
Time	15.00
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	1625.5
DW	16.650 usec
DE	6.50 usec
TE	297.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

-BBO DMSO D:\\ mu



Compound (12)

2.4 [s, 6H, 2CH3]
6.7 [s, 1H, CH pyrimidine]
7.3, 8.6 [2d, 2H, 2 CH pyridine J = 7.9 Hz], 7.4–8.5 [m, 8H, Ar-H + SO2NH]
8.7 [s, 1H, NHph, D2O exch]

BRUKER

NAME	drdosari-12
EXPNO	30
PROCNO	1
Date_	20120406
Time	11.19
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1720407 sec
RG	161.3
DW	48.400 usec
DE	6.50 usec
TE	296.7 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

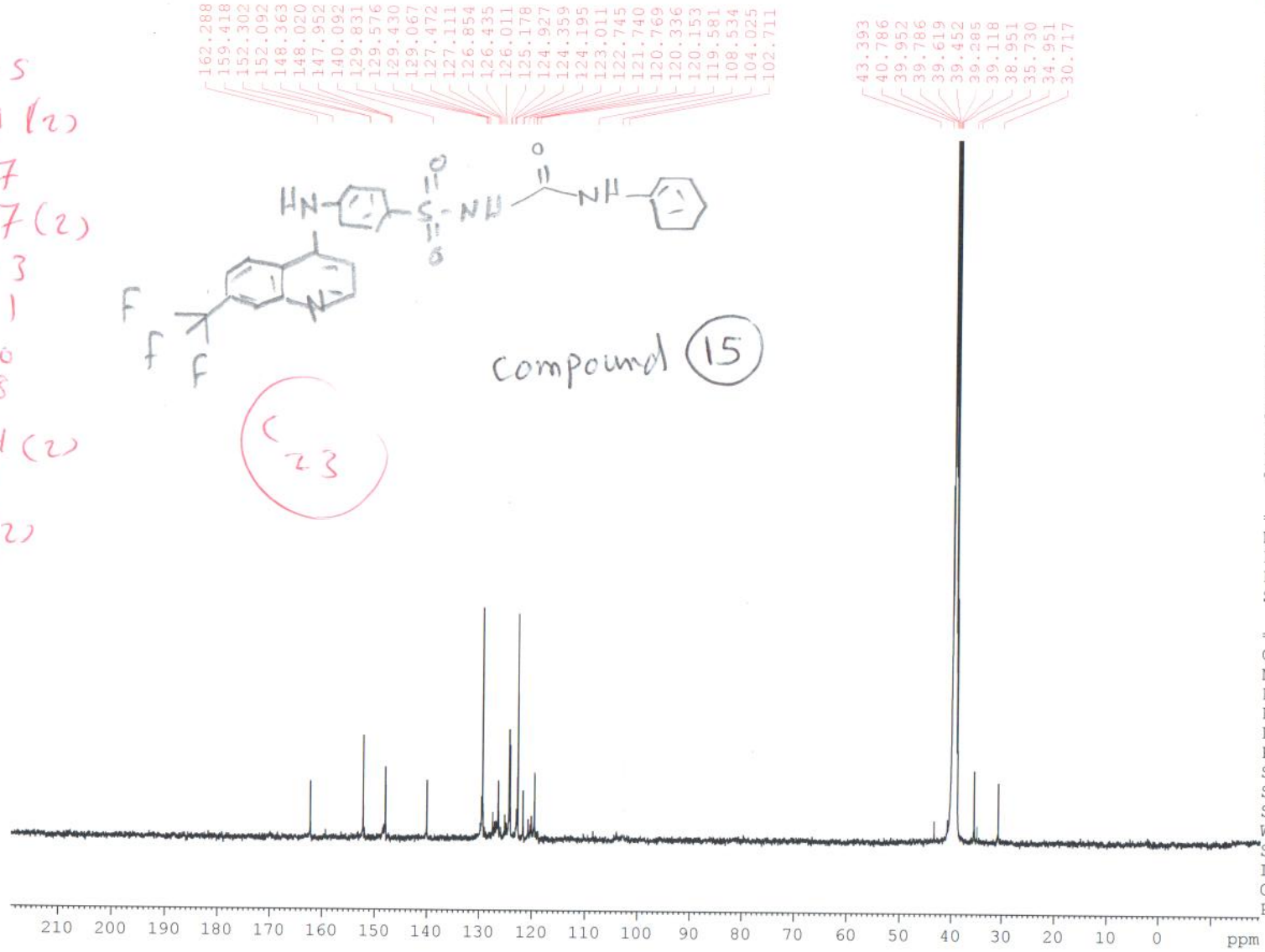
3BO DMSO D:\\ mmj

22.8(2)
105.4
113.4
119.5(2)
122.2
122.8
124.9
125.6
129.8(2)
130.1
130.2
134.3
146.8
146.9
151.6
156.2
162.2(2)
167.3

BRUKER

NAME	drdosari-12
EXPNO	31
PROCNO	1
Date_	20120406
Time	13.07
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	1625.5
DW	16.650 usec
DE	6.50 usec
TE	297.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

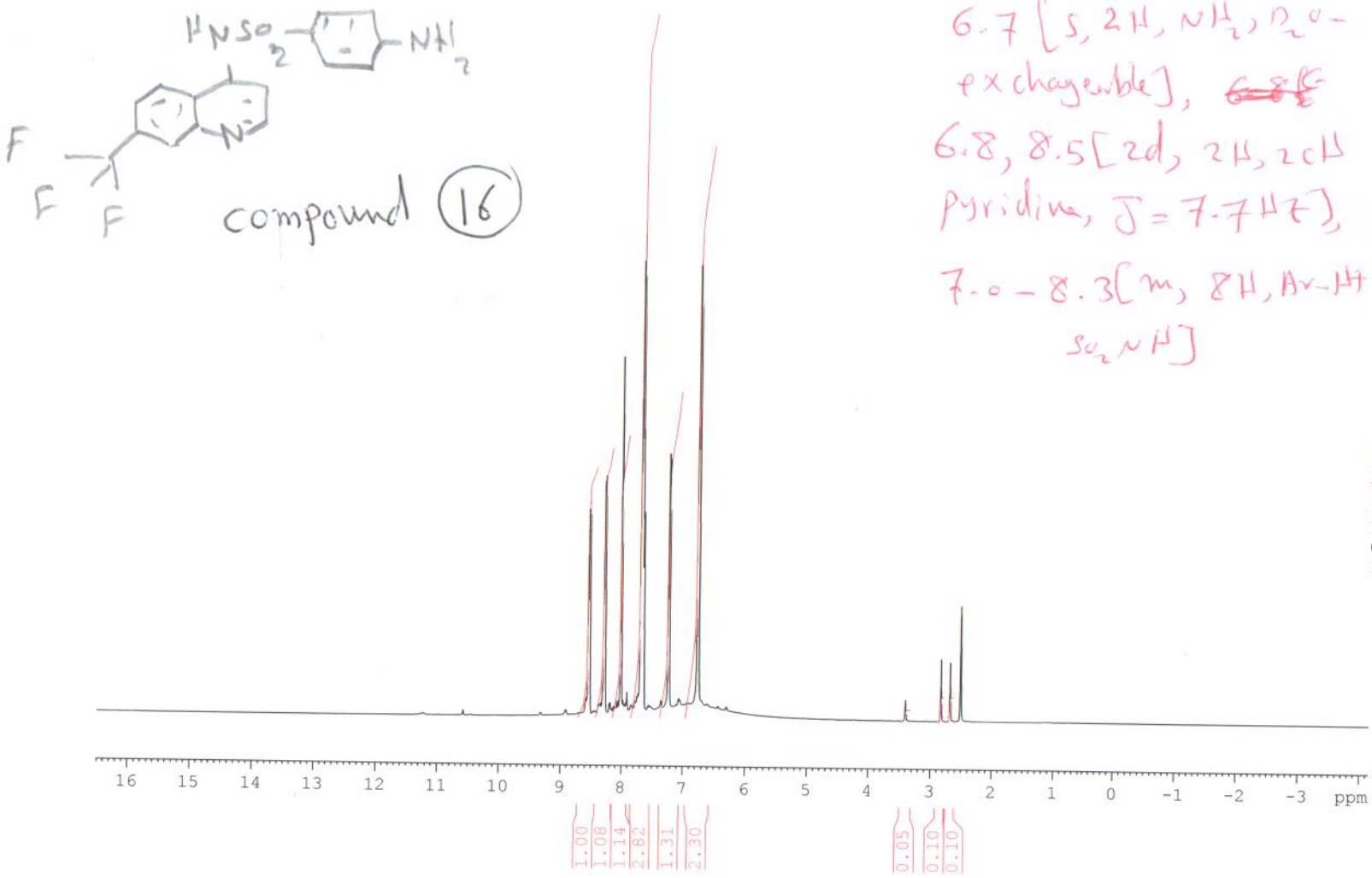
3BO DMSO D:\\ mmj



119.5
120.1 (2)
121.7
122.7 (2)
124.3
125.1
126.0
126.8
127.4 (2)
129.0
129.4 (2)
129.5
129.8
140.0
147.9
148.0
148.3
152.3
162.2

NAME	drdosari-15
EXPNO	21
PROCNO	1
Date_	20120406
Time_	7.30
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	1625.5
DW	16.650 usec
DE	6.50 usec
TE	298.9 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

-BBO DMSO D:\\ m



compound (16)

6.7 [s, 2H, NH_2, D_2O-exchangeable], ~~6.8F~~
6.8, 8.5 [2d, 2H, 2CH pyridine, J = 7.7 Hz],
7.0 – 8.3 [m, 8H, Ar-H SO_2NH]

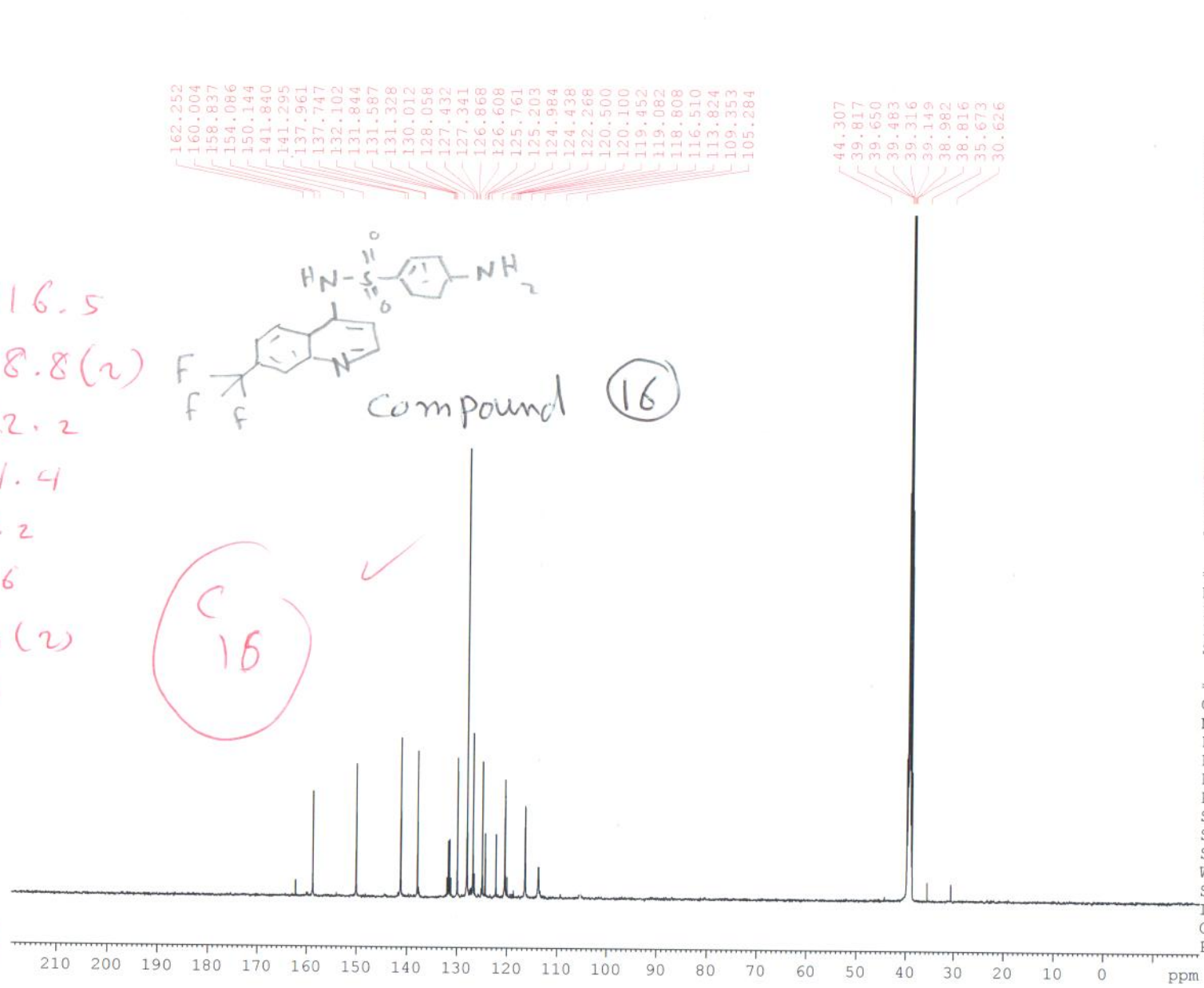
BRUKER

NAME	drdosari-16
EXPNO	30
PROCNO	1
Date_	20120406
Time	3.49
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1720407 sec
RG	35.9
DW	48.400 usec
DE	6.50 usec
TE	296.7 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

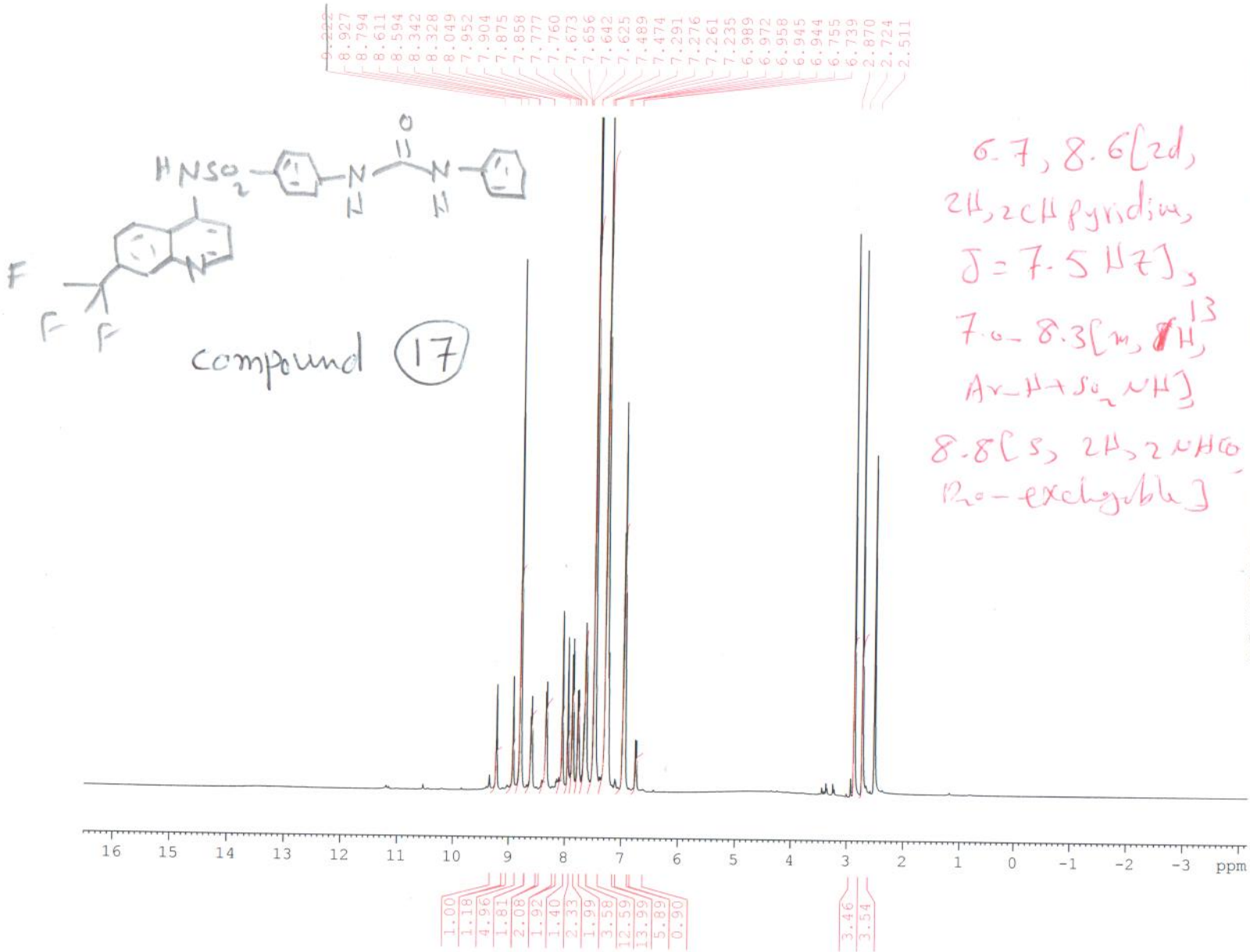
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

3BO DMSO D:\\ mmj



NAME	drdosari-16
EXPNO	31
PROCNO	1
Date_	20120406
Time	5.37
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	3251
DW	16.650 usec
DE	6.50 usec
TE	297.2 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

-BBO DMSO D:\\ mu



compound (17)

6.7, 8.6[2d, 2H, 2CH pyridine, J = 7.5 Hz],
7.0 - 8.3[m, 8H, Ar-H + SO2NH]
8.8[s, 2H, 2NHCO, D2O-exchgable]

BRUKER

NAME	drdosari-17
EXPNO	20
PROCNO	1
Date_	20120406
Time	1.56
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1720407 sec
RG	57
DW	48.400 usec
DE	6.50 usec
TE	296.9 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

3BO DMSO D:\\ mmj

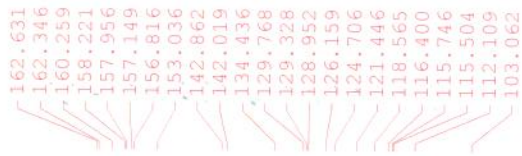
118.0
120.2
121.7(2)
122.3(2)
123.0
124.5
125.2
126.9
128.7(2)
129.7
131.9(2)
135.7
138.0
139.3
141.4
142.8
149.7
152.2
152.5

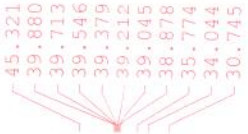
BRUKER

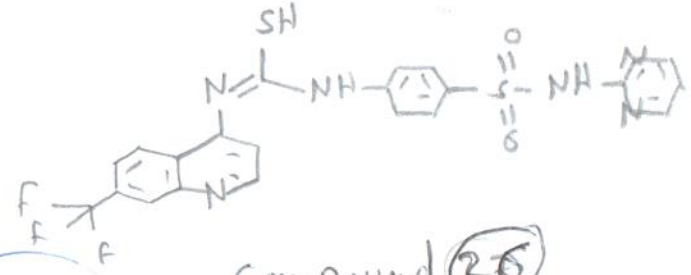
NAME	drdosari-17
EXPNO	21
PROCNO	1
Date_	20120406
Time	3.44
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	1625.5
DW	16.650 usec
DE	6.50 usec
TE	297.3 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

3BO DMSO D:\\ mmj

112.1
116.4 (2)
118.5
121.4
124.7
126.1
128.9 (3)
129.3
129.7
134.4
142.0
142.8
153.0
157.1
158.2 (2)
162.3
162.6

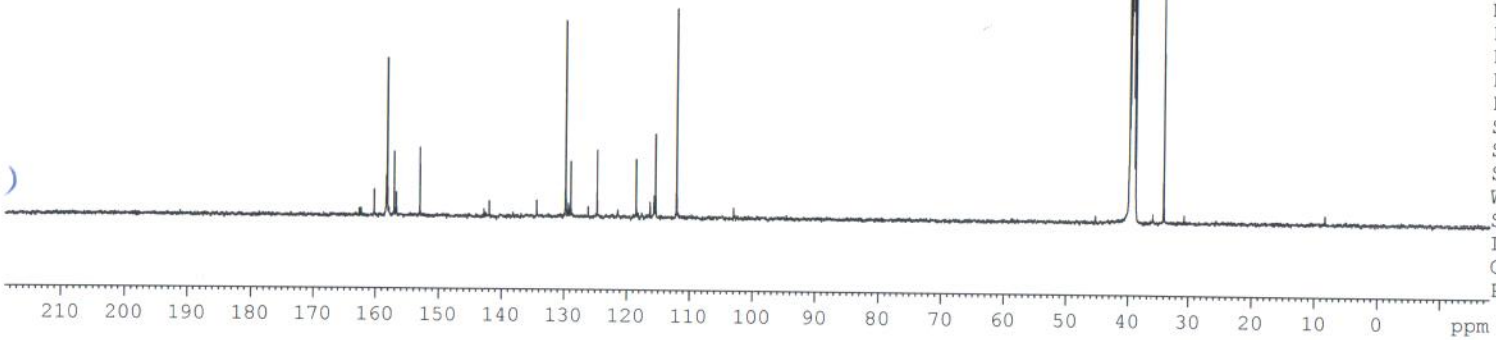






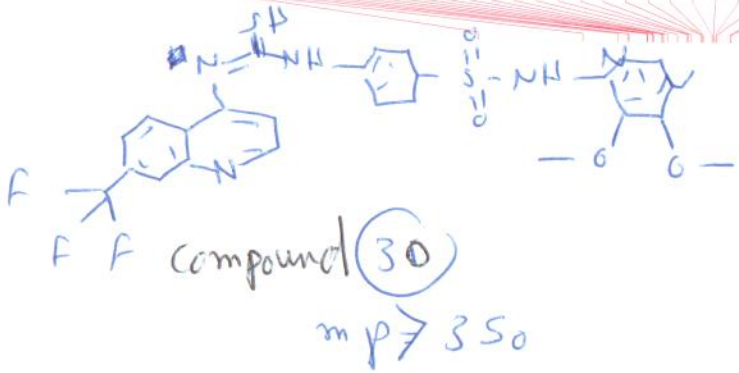
Compound (26)

C 21



NAME	drghorab-27
EXPNO	31
PROCNO	1
Date_	20120421
Time	0.42
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	2580.3
DW	16.650 usec
DE	6.50 usec
TE	295.0 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40

-BBO DMSO D:\\ mu



compound (30)

mp > 350

2.7 [s, 1H, SH, D_2O-exchangeable], 3.8 [s, 6H, $2OCH_3$], 6.5, 8.6 [2d, 2H, 2CH pyridine, δ=6.8 Hz], 7.0-8.3 [m, 8H, Ar-H + CH Pyrimidine], 9.4 [s, 1H, SO_2NH, D_2O-exchangeable], 10.8 [s, 1H, NH, D_2O-exchangeable.

BRUKER

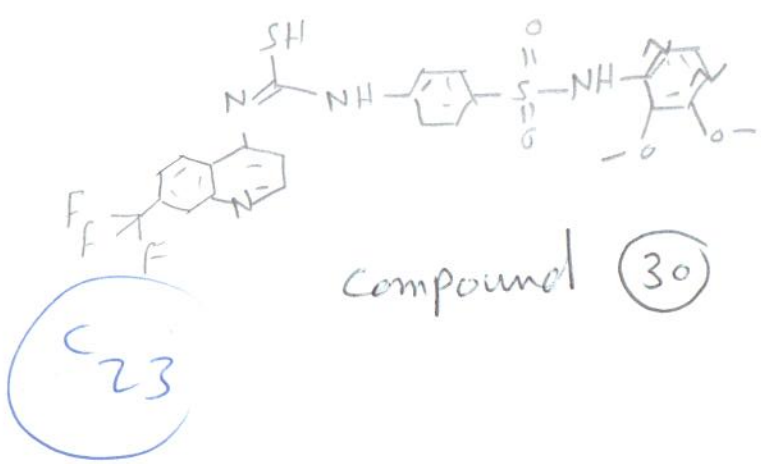
NAME	drghorab-31
EXPNO	30
PROCNO	1
Date_	20120420
Time	15.24
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	10330.578 Hz
FIDRES	0.157632 Hz
AQ	3.1720407 sec
RG	114
DW	48.400 usec
DE	6.50 usec
TE	294.5 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.50 usec
PL1	-3.00 dB
SFO1	500.1330885 MHz
SI	32768
SF	500.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

3BO DMSO D:\\ mmj

54.0(2)
117.7(2)
118.5
122.1
124.2
125.9
127.1(3)
128.8
129.7
132.4
132.7
142.8
150.5
150.7
153.0
157.9
160.2
161.5
167.1

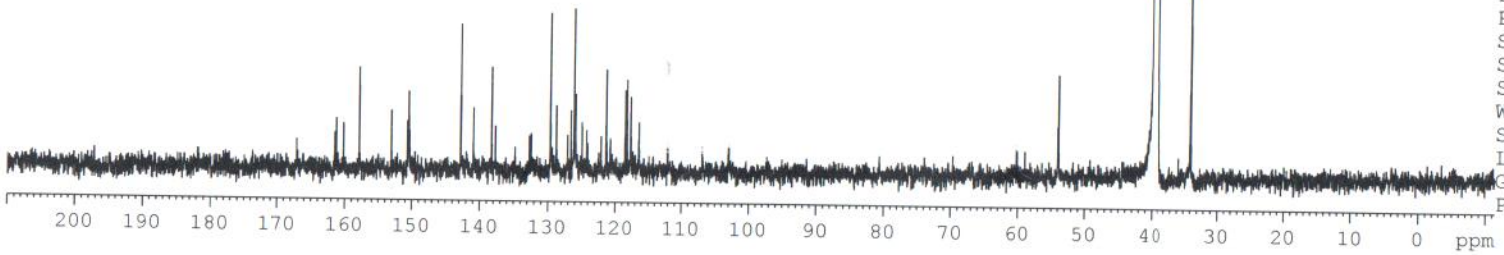
167.151 161.542 161.314 160.237 157.910 153.087 150.722 150.510 142.840 140.986 138.326 137.772 132.749 132.489 129.723 128.821 127.159 126.652 126.199 125.949 124.976 124.274 124.120 122.105 121.353 120.743 118.545 118.276 117.719 116.391 112.077 106.919 103.036

60.149 54.025 53.915 39.922 39.756 39.589 39.422 39.255 39.088 38.921 33.976



C_{23}

Compound (30)



BRUKER

NAME	drghorab-31
EXPNO	31
PROCNO	1
Date_	20120420
Time	17.12
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	30030.029 Hz
FIDRES	0.458222 Hz
AQ	1.0912410 sec
RG	2580.3
DW	16.650 usec
DE	6.50 usec
TE	294.7 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	5.80 usec
PL1	-2.00 dB
SFO1	125.7703643 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	14.64 dB
PL13	17.64 dB
SFO2	500.1320005 MHz
SI	32768
SF	125.7578519 MHz
WDW	EM
SSB	0
LB	3.00 Hz
GB	0
PC	1.40