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Graphic Abstract

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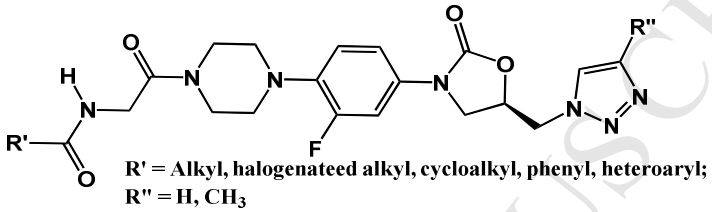

R' = Alkyl, halogenateed alkyl, cycloalkyl, phenyl, heteroaryl;
R" = H, CH_3

A series of N-substituedglycinyl-1*H*-1,2,3-triazolyl oxazolidinone derivatives were synthesized and evaluated for antibacterial activities against Gram-positive and Gram-negative susceptible and resistant clinical isolates.

Synthesis and antibacterial activities of *N*-substituted-glycinyl 1*H*-1,2,3-triazolyl oxazolidinones

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Running Title Head

Antibacterial Activity of Glycinyl Triazolyl Oxazolidinones.

Key Words: Antibacterial activity, Gram-positive bacteria, Linezolid, Substituted-glycinyl oxazolidinone, Triazolyl-oxazolidinone.

Abstract

A series of 1*H*-1,2,3-triazolyl piperazino oxazolidinone analogs with optionally varied glycinyl substitutions were synthesized and their antibacterial activity assessed against a panel of susceptible and resistant Gram-positive and selected Gram-negative bacteria including clinical isolates. The N-aroyl- and N-heteroaroyl-glycinyl (MIC: 0.06-4 µg /ml) derivatives were more potent than the N-acylglycinyl (2-8 µg/ml) derivatives against all Gram-positive bacteria tested. Nitro substitution on aryl and heteroaryl rings significantly enhanced activity against Gram-positive bacteria, as noted with the 3,5-dinitrobenzoyl (**6m** and **6n**) and 5-nitro-2-furoyl (**6u** and **6v**) derivatives with MIC ranges of and 0.25-0.5 and 0.06-0.5 µg /ml, respectively. These nitro analogs also showed more potent extended activity against *M. catarrhalis*, with MICs ranges of 0.25-1 µg /ml, compared to linezolid (MIC: 8 µg /ml). Hence, the presence of the N-aroyl and / or N-heteroaroyl glycinyl structural motifs as spacer group could significantly enhance the antibacterial activities of 1*H*-1,2,3-triazolyl oxazolidinone class of compounds.

1.0 Introduction

The increasing frequency of bacterial infections with antibiotic-resistant strains, particularly the Gram-positive organisms both in the community and hospital settings world-wide continue to serve as impetus for search for new, more effective and safer antibacterial agents. Oxazolidinones, exemplified by Linezolid (**Lzd**, **1**; Fig. 1), represent a relatively new class of antibacterial agents with potent activity against Gram-positive bacteria pathogens, including multidrug-resistant strains namely, methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin-resistant enteroccoci (VRE) [1]. These Gram-positive bacteria are frequent causes of serious infection among patients in the hospital and community [2]. The emergence of bacterial resistance to known antibacterial agents continue to be a major health problem world-wide and thus provides an impetus for the efforts directed towards the discovery of novel, more efficacious and safer antibacterial agents [2-3].

Oxazolidinone class of compounds have been extensively studied and shown to inhibit bacterial protein biosynthesis by binding to sites on the bacterial ribosomes, thus preventing formation of the functional 70S initiation complex [4-5]. However, the most recent studies by Duffy et.al. [6] divulged that linezolid binds to the A-site of the 50S subunit, thus preventing binding of the aminoacyl-tRNA to this site. Extensive structural modifications around the phenyl-oxazolidinone moiety have been performed with the aim of identifying novel derivatives with extended antibacterial spectrum and decreased side-effects [7-8]. Other studies have shown that incorporation of diverse substituents such as the 3-aryl or heteroaryl ring at the 4-position of the 3-phenyloxazolidinone moiety significantly enhanced antibacterial potency, even when the C-5 position contains an acetamidomethyl or hydroxymethyl

group (**4a-b**; Fig 1) [8]. Furthermore, these substituent groups have been demonstrated to extend antibacterial potency against linezolid-resistant MRSA ribosomal mutants, with MIC ranges of 0.5 to 1 µg/ml in comparison to **Lzd** with MIC ranges of 2-32 µg/ml. We have been interested in the triazolyl-oxazolidinone derivatives and have reported the potent activities for the several triazolyl oxazolidinone derivatives bearing the morpholino group, general structure **2** (**PH027**, **PH084**; Fig 1) and N-substitutedpiperazino (**3**, Fig 1) moieties at the position 4 of the phenyl ring [9-11]. In addition, structure-activity relationships studies from others [8] have yielded other derivatives (**4a-b**, Fig 1) having the biheteroaryl or heteroaryl-substitutedphenyl groups at the position 4 of the phenyl-oxazolidinone. These derivatives showed improved antibacterial activities coupled with significantly improved binding at the bacterial ribosomal site. The introduction of "spacer groups" containing hydrogen bond donor and / or acceptor groups on the terminal substituent moiety at the C-4 position of the phenyl-oxazolidinone pharmacophore have been implicated in the potent antibacterial activities due to enhanced interactions at the bacterial 50S ribosomal binding sites [8, 12-14]. Recently, introduction of substituted-glycinyl moieties as spacer on the 4N-piperazinyl position of eperezolid yielded compounds with the general structure **5** (Fig 1). Computational structural analysis studies of the binding of these compounds at the bacterial ribosomal active site revealed that a H-bond acceptor and / or donor group is an essential structural motif that would fit a potential pocket identified at the bacterial ribosomal receptor site [12]. Based on these observations we synthesized the substituted-glycinyl derivatives of general structure (**6a-x**, Fig 1) containing varied H-bond donor and acceptor groups at the terminal N-glycinyl position. We herein report the synthesis of a series of new 5-(4-methyl-1H-1,2,3-triazole)methyl and 5-(4-methyl-1H-1,2,3-triazole)

oxazolidinones, which are expected to exhibit enhanced binding at the active site and improve antibacterial activity against susceptible and multidrug-resistant Gram-positive bacteria.

Insert: Figure 1.

2.0 Chemistry

The synthesis of the final piperazine oxazolidinone derivatives **16a-x** is illustrated in Scheme 1. Starting from the readily available piperazine **7** and 3,4-difluoroaniline **8** the intermediate trifluoroacetic acid salt derivatives **13** and **14** were obtained in quantitative yields, respectively, in multi-step reactions according to previously published procedures [11, 15-16]. Further chemical transformation of **13** and **14** were by reacting with N-tert-butoxycarbonylglycine activated with DCC and 1-HOBT as coupling reagents gave the boc-protected glycinyl-derivatives **6a-b** in very good yields. Deprotection of the boc-protected glycinyl-oxazolidinones **6a-b** with trifluoroacetic acid in CH_2Cl_2 at 0 ^oC to room temperature gave the key-intermediate N-glycinyl-oxazolidinones derivatives **15** and **16** as the trifluoroacetic acid salts in quantitative yields. To obtain the target compounds (**6c-x**), further derivatization of the intermediate oxazolidinone derivatives **15** and **16** were performed by subsequent reactions with appropriate acid chlorides or anhydrides and arylsulfonyl chlorides in CH_2Cl_2/CH_3CN and triethylamine in moderate to excellent yields.

Insert: Scheme 1.

3.0 Results and Discussion

The synthesized N-substitutedglycinyl oxazolidinones **6a-x** were evaluated for *in vitro* antibacterial activity against selected antibiotic-susceptible and -resistant clinical isolates, and standard strains of Gram-positive and Gram-negative bacteria. Gram-positive strains tested included MRSA, methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant coagulase-negative staphylococci (MR-CNS), methicillin-sensitive coagulase-negative staphylococci (MS-CNS), PRSP, VRE, and vancomycin-sensitive (VSE) enterococci. The selected Gram-negative organisms were limited to *E. coli* ATCC 25922, *H. influenzae* ATCC 49247 and *M. catarrhalis* ATCC 8176 and clinical strains of *M. catarrhalis*. The standard agar dilution method according to the National Committee for Clinical Laboratory [17] was employed to determine the minimum inhibitory concentration (MIC, µg/ml) values *in vitro*. The results of *in vitro* antibacterial activity against several bacterial strains are summarized in Table 1. Overall, most of the compounds showed potent to moderate (MIC range < 0.25 to 8 µg/ml) antibacterial activity against staphylococcal and enterococcal strains with the exception of the tetrahydrofuran-2-carbonyl (**6j**) and thiophene-2-sulfonamide (**6x**) derivatives with MIC ranges of ≥ 8-32 µg/ml. Both of these compounds contain a methyl group at the C-5 position of the triazole ring. All the tested compounds exhibited potent antibacterial activity against *S. pneumoniae* (MIC ranges of < 0.25 - 4 µg/ml), with the exception of the tert-butoxycarbonyl derivative **6b**. The substitution of an aroyl and / or heteroaroyl moieties on the N-glycine enhanced antibacterial activity against Gram-positive bacterial strains. While the nitro substitution on the furan ring resulted in compounds **6u-v**, which are found to be 4-8 -fold more active than linezolid and other reference compounds evaluated in this study.

Insert: Table 1.

From the antibacterial evaluation results (Table 1), none of the compounds showed activity against *E. coli* and only selected compounds, namely, the nicotinoyl (**6o**), 2-furoyl (**6t**), and the 5-nitro-2-furoyl (**6u-v**) derivatives showed comparable activity to linezolid (MIC = 8 µg/ml) against the *H. influenzae* reference strain ATCC49247 with MIC value ranges of ≥ 2-8 µg/ml. A number of the benzoyl (**6l**) and heteroaroyl (**6o-r** and **6t**) derivatives exhibited antibacterial activity comparable to that of linezolid (MIC = 8 µg/ml) against a standard strain of *M. catarrhalis.* While the 3,5-dinitro-benzoyl (**6m-n**, MIC = 0.5 and 1 µg/ml) and 5-nitro-2-furoyl (**6u-v**, MIC = 1 and 0.5 µg/ml) derivatives were 8-10 -fold more active than linezolid (MIC = 8 µg/ml) against the same strain. Based on this activity, a total of 10 compounds were selected and further evaluated against *M. catarrhalis* clinical isolates (n=8). The results are presented in Table 2. The superior antibacterial activities of the 3,5-dinitrobenzoyl (**6m-n**) and 5-nitro-2-furoyl (**6u-v**) derivatives compared to linezolid were obvious in all the strains.

These nitroaroyl and nitroheteroaroyl substituted compounds demonstrate more potent antibacterial activities against Gram-positive bacterial and *M. catarrhalis* strains compared to linezolid and the eperezolid analogs with glycinyl substitutions of general structure **5** reported by Wang et al. [13]. Although Wang et al.[13] did not report any activity against *M. catarrhalis* strains they suggested that N-acyl-, N-aroyl- or N-heteroaroyl-glycinyl structural motif plays a key role in enhancing antibacterial activity. In addition, a recently published study from our laboratory have shown that incorporation of the 5-nitro-2-furoyl and dinitrobenzoyl groups selectively enhanced

antibacterial activity of some piperazinyl triazolyl-oxazolidinones against Gram-positive bacterial strains [16]. However, the results from our presence study showed that the combined presence of N-(3,5-dinitrobenzoyl)- or N-(5-nitro-2-furoyl)-glycinyl structural motif and a 5-triazolyl or 5-(4-methyltriazolyl) groups resulted in more potent triazolyl-oxazolidinone analogs with extended antibacterial activity against *M. catarrhalis* strains.

Insert: Table 2.

In order to assess the extent of plasma binding and / or plasma instability, test compounds were evaluated against *S. aureus* ATTC 25923 in Mueller-Hinton (MH) broth supplemented with 50% human plasma, and the results are presented in Table 3. In general, only a few of the compounds showed a fourfold or higher MIC values in the presence of 50% human plasma, which indicated potential significant plasma protein binding. Of the most active derivatives in this series of compounds, the of N-(3,5-dinitrobenzoyl)- glycinyl derivatives **6n-m** exhibited 16 and 4-fold increases in MIC in the presence of 50% plasma. On the other hand, the N-(5-nitro-2-furoyl)-glycinyl derivatives retained their activity in 50% human plasma. Overall, no direct correlations could be established between antibacterial activity or plasma protein binding and the calculated log of partition coefficient (C log P) values.

Insert: Table 3.

4.0 Conclusions

The synthesis and antibacterial activities of a number of new 1*H*-1,2,3-triazolyl piperazino oxazolidinone analogs bearing optionally substituted N-glycinyl groups have been reported. These compounds showed moderate to strong antibacterial activities against standard reference strains and clinical isolates of streptococci, enterococci and staphylococci. While the nitrofuran-2-carbonyl analogs **6u-v**, showed antibacterial activity that is 4-8 -fold more active than linezolid and other reference compounds used. Furthermore, the N-(3,5-dinitrobenzoyl)- (**6m-n**) and N-(5-nitro-2-furoyl)- (**6u-v**) derivatives were also 8-10 -fold more active than linezolid against the fastidious Gram-negative bacteria *M. catarrahlis* strains. This study highlighted the presence of the N-aroyl and / or N-heteroaroyl glycinyl structural motifs as potential spacer group that could significantly enhance both the antibacterial activities of the 1*H*-1,2,3-triazolyl oxazolidinone class of compounds and their affinity at the bacterial ribosomal binding site.

5.0 Experimental

5.1 Characterization

Column chromatography was carried out with silica gel (Kieselgel 60, 70-230 mesh; Aldrich) and TLC conducted on 0.25 mm pre-coated silica gel plates ($60F_{254}$, Merck). Melting points were determined on a Stuart Scientific melting point apparatus (SMP1, UK) and were uncorrected. ^{1}H-NMR spectra were recorded on Bruker Avance II 600 NMR spectrometer. In addition, the ^{13}C-NMR spectrum of representative compounds **6k**, **6q**, **6u**, **6v**, **6w** and **6x**, were recorded on Bruker Avance II 600 NMR spectrometer. The ^{13}C-NMR experiments performed included ^{13}C-NMR decoupled,

^{13}C-DEPT-135 (Distortionless Enhancement by Polarization Transfer-139) and ^{13}C-APT (Attached Proton Test). Chemical shifts of protons are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal reference or DMSO-d_6 (δ=2.5; 39.7) as solvent. Mass spectra were recorded on a Thermo Scientific DFS High Resolution Gas Chromatography / Mass Spectrometer (DFS GC-MS) and Quattro LC (Micro Mass, UK) Mass Spectrometer. Infrared (IR) spectra were recorded on JASCO FT-IR-6300 (JASCO, Japan) spectrometer. Elemental analyses were performed on an Elementar Vario Micro Cube CHN Analyzer apparatus (Elementar, Germany), and analyses indicated by the symbols of the elements were within ± 0.4% of the theoretical values. Analyses were performed at the Science Analytical Facilities (SAF), Faculty of Science, and Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kuwait University, Kuwait. The structures of the oxazolidinones were sketched and the Clog P values estimated using PerkinElmer, ChemDraw Ultra 13.0 (CambridgeSoft, USA, 2012).

5.2. Syntheses

*5.2.1. (R)-2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-yl)-2-oxoethanaminium 2,2,2-trifluoroacetate **(15)***

A solution of N-tert-butoxycarbonylglycine (1.52 g, 8.69 mmol) in anhydrous DCM (15 mL) under N_2 was treated with DCC (2.24 gm, 10.86 mmol) and 1-hydroxy-benzotriazole (1.47 g, 10.86 mmol) and the mixture stirred for 2 hrs at r.t. under N_2. The reaction mixture was filtered directly into a round bottom flask containing (*R*)-4-(4-(5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl) piperazin-1-ium 2,2,2-trifluoroacetate (**13**; 4.0 g, 8.69 mmol) and triethylamine (3.51 mL) in anhydrous CH_3CN (60 mL). The reaction mixture was stirred overnight at r.t.

under N_2 and concentrated under vacuum to give a gum, which was dissolved in ethyl acetate (40 mL), washed with 10% Na_2CO_3, water, brine, dried (Na_2SO_4) and concentrated on rotovap to afford a white solid. Recrystallization (Ethyl acetate – hexane) gave **6a** as a solid (3.20 g, yield, 80%), mp- 150-152 ^oC. ^1H-NMR (DMSO-d_6, 600 MHz): δ 8.16 (s, 1H, NH), 7.76 (s, 1H, triazolyl H), 7.42 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.12 (dd, 1H J=2.5 Hz, 8.8 Hz, phenyl H), 7.05 (t, 1H, J=9.0 Hz, phenyl H), 6.77 (br. t, 1H, NH), 5.10-5.13 (m, 1H, oxazolidinone H), 4.81 (d, 2H, J=5.2 Hz, CH_2), 4.20 (t, 1H, J=9.0 Hz, oxazolidinone H), 3.85 (dd, 1H, J=5.8 Hz, 9.4 Hz, oxazolidinone H), 3.81 (d, 1H, J=5.9 Hz, CH_2), 3.55-3.59 (m, 4H, piperazinyl H), 2.92-2.96 (m, 4H, piperazinyl H), 1.38 (s, 9H, $C(CH_3)_3$). IR (KBr pellet, cm^{-1}): ν 3437, 2987, 2928, 1744, 1683, 1657, 1521, 1446, 1417, 1455, 1368, 1317, 1290, 1227, 1190, 1063, 1029. MS 503.2 (M^+). Anal calcd for $C_{23}H_{30}FN_7O_5$: C: 54.86, H: 6.01, N: 19.47 found C: 54.85, H: 6.16, N: 19.19.

A mixture of **6a** (3.40 g, 6.75 mmol) in DCM (7 mL) and TFA (7 mL) at 0 ^oC was stirred to r.t. overnight. The reaction mixture was concentrated on a rotavap to give a semisolid **6g**, which was triturated with a mixture of THF-Et_2O 1:1 ratio to give **15** as a white solid (3.49 g, quant yield). ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 8.16 (s,1H, triazolyl H), 8.03 (br. d, 2H, NH, exchangeable with D_2O), 7.76 (s,1H, triazolyl H), 7.42 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.14 (dd,1H, J=2.3 Hz, 8.8 Hz, phenyl H), 7.06 (t, 1H, J=9.4 Hz, phenyl H), 5.11-5.15 (m, 1H, oxazolidinone H), 4.83 (d , 2H, J=5.0 Hz, CH_2), 4.20 (t, 1H, J=9.2 Hz, oxazolidinone H), 3.92-3.94 (m, 2H, piperazinyl H), 3.86 (dd, 1H, J=5.7 Hz, 9.3 Hz, oxazolidinone H), 3.66 (m, 2H , piperazinyl H), 2.95-3.00 (br. d, 4H, piperazinyl H). IR (KBr pellet, cm^{-1}): ν 3425, 2975, 2930, 1760, 1678, 1521, 1486, 1430, 1204, 1136, 1024. MS 405.01 (M^+ + H

minus CF_3CO_2). This product was used for subsequent reactions without further purification.

*5.2.2. (R)-2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo-oxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethanaminium 2,2,2-trifluoroacetate **(16)***

In a similar manner, compound **6b** was prepared from 4-(2-fluoro-4-(5-((4-methyl-1*H*-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-ium 2,2,2-trifluoroacetate (**14**; 1.0 gm, 2.12 mmol) as reported for **6a**. Recrystallization (ethyl acetate - hexane) gave **6b** as a white solid (900 mg, yield, 83 %), mp- 175-177 ^oC. ^1H-NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H, triazolyl H), 7.43 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H J=2.5 Hz, 9.0 Hz, phenyl H), 7.06 (t, 1H, J=9.0, Hz, phenyl H), 6.77 (br. t, 1H, NH, exchangeable with D_2O), 5.07-5.10 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J=5.2 Hz, CH_2), 4.19 (t, 1H, J=9.0 Hz, oxazolidinone H), 3.82-3.85 (m, 3H, CH_2 and oxazolidinone H), 3.55-3.59 (m, 4H, piperazinyl H), 2.92-2.97 (m, 4H, piperazinyl H) 2.22 (s, 3H, triazolyl CH_3), 1.39 (s, 9H, $C(CH_3)_3$). IR (KBr pellet, cm^{-1}): ν 3444, 2977, 2932, 1741, 1708, 1668, 1517, 1427, 1440, 1455, 1367, 1339, 1283, 1230, 1165, 1049, 1034. MS 517.4 (M^+). Anal calcd for $C_{24}H_{32}FN_7O_5$: C: 55.70, H: 6.23, N: 18.94 found C: 55.74, H: 6.52, N: 18.74.

Compound **6b** (2.77 g, 5.22 mmol) was then converted to **16** by a similar procedure reported for **15** to give the title compound **16** as a solid (2.68 g, quant yield). ^1H-NMR (DMSO-d_6, 600 MHz): δ 7.70-7.82 (m, 3H, amine $+NH_3$, exchangeable with D_2O), 7.64 (s, 1H, triazolyl H), 7.21 (dd, 1H, J=2.6 Hz, 14.7 Hz, phenyl H), 6.93 (dd, 1H, J=2.1 Hz, 8.6 Hz, phenyl H), 6.84 (t, 1H, J=9.5 Hz, phenyl H), 4.86-4.88 (m, 1H, oxazolidinone H), 4.52 (d, 2H, J=5.2 Hz, CH_2), 3.97 (t, 1H, J=9.2 Hz, oxazolidinone H), 3.71 (q, 2H, J=5.7 Hz, 11.4 Hz, CH_2), 3.61 (dd, 1H, J=5.9 Hz, 9.3 Hz, oxazolidinone H), 3.4-3.5 (m, 4H, piperazinyl H), 2.7-2.8 (m, 4H, piperazinyl H),

2.00 (s, 3H, triazolyl CH_3). Full MS 418.75 (M^++H). IR (KBr pellet, cm^{-1}): ν 3444, 2977, 2932, 1760, 1678, 1521, 1486, 1430, 1204, 1136, 1024. MS 419.06 (M^+ + H minus CF_3CO_2). This product was used for subsequent reactions without further purification.

5.2.3. General procedure for the synthesis of the N-substitued-glycinyl derivatives **(6c-x)**

The final compounds **6c-x** were prepared from a solution of compound **15** or **16** in DCM and / or CH_3CN and TEA (1.5 mL) treated with 1.1 eq. of suitable acid anhydride or acid chloride or an activated acid (activated by reaction with DCC or 1-[3-(diethylamine)propyl]-3-ethyl carbodiimide hydrochloride and 1-hydroxy-benzotriazole or by oxalyl chloride) or the arylsulfonyl chloride under stirring at 0 ^oC. Stirring was continued to r.t. overnight and the reaction mixture was concentrated on a rotovap to give a crude, which was dissolved in DCM (60 mL), washed successively with water, dilute aq. Na_2CO_3 solution, water, dried (anhydrous Na_2SO_4), filtered and concentrated to obtain a crude product. The purification of the crude was performed either by silica gel column chromatography and/or recrystallized from suitable organic solvents to give the final products.

5.2.3.1. (R)-N-(2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluoro-phenyl piperazin-1-yl)-2-oxoethyl)acetamide ***(6c)***

Compound **6c** was prepared via the general procedure from **15** (500 mg, 0.97 mmol) and acetic anhydride (200 mg, 0.18 mL, 1.94 mmol) in TEA, DCM (5 mL) and CH_3CN (5 mL) to give a crude gum. Purification by silica gel column chromatography (EtOAc-MeOH 9:1) afforded the title compound **6c** as a white solid

(210 mg, yield, 49%), mp- 205-207 °C. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 8.16 (s, 1H, triazolyl H), 7.99 (t, 1H, J=5.5 Hz, NH, exchangeable with D_2O), 7.76 (s, 1H, triazolyl H), 7.42 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd, 1H, J=2.3 Hz, 8.8 Hz, phenyl H), 7.06 (t, 1H, J=9.3 Hz, phenyl H), 5.09-5.14 (m, 1H, oxazolidinone H), 4.82 (d, 2H, J=5.1 Hz, CH_2), 4.20 (t, 1H, J= 9.2 Hz, oxazolidinone H), 3.97 (d, 2H, J=5.5 Hz, CH_2), 3.85 (dd, 1H, J=5.7 Hz, 9.3 Hz oxazolidione H), 3.56-3.61 (br. d, 4H, piperazinyl H), 2.92-2.98 (m, 4H, piperazinyl H), 1.87 (s, 3H, CH_3CO). IR (KBr pellet, cm^{-1}): ν 3370, 2916, 2840, 1763, 1746, 1633, 1517, 1435, 1328, 1234, 1163, 1113, 1034. MS 445.2 (M^+). Anal calcd for $C_{20}H_{24}FN_7O_4$: C: 53.93, H: 5.43, N: 22.01 found C: 53.96, H: 5.08, N: 21.97

5.2.3.2. ***(****R)-N-(2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo-oxazolidin -3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)acetamide* ***(6d)***

Compound **6d** was prepared via the general procedure from **16** (500 mg, 0.94 mmol) and acetic anhydride (190 mg, 0.18 mL, 1.88 mmol) in TEA and DCM (5 mL) and CH_3CN (5 mL) to give the crude solid (470 mg). Purification by silica gel column chromatography (EtOAc → EtOAc-methanol 9:1) gave **6d** as a white solid (370 mg, yield, 86%), mp- 215-217°C. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 7.99 (t, 1H, J= 6.0 Hz, NH, exchangeable with D_2O), 7.86 (s, 1H, triazolyl), 7.43 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl), 7.14 (dd, 1H, J=2.7 Hz, 10.3 Hz, phenyl), 7.06 (t, 1H, J= 9.6, phenyl), 5.05-5.10 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J= 5.2 Hz, CH_2), 4.19 (t, 1H, J= 9.3 Hz, oxazolidinone H), 3.97 (d, 2H, J=5.5 Hz, CH_2), 3.83 (dd, 1H, J=5.9 Hz, 9.6 Hz oxazolidione H), 3.56-3.61 (m, 4H, piperazinyl H), 2.92-2.98 (m, 4H, piperazinyl H), 2.22 (s, 3H, triazolyl CH_3), 1.87 (s, 3H, CH_3CO). IR (KBr pellet, cm^{-1}): ν 3364, 3341, 2976, 2896, 2857, 1749, 1640, 1518, 1475, 1442, 1415, 1327, 1232, 1211, 1161,

1136, 1111, 1054. MS 459.4 (M^+). Anal calcd for $C_{21}H_{26}FN_7O_4$: C: 54.89, H: 5.70, N: 21.34 found C: 54.99, H: 6.00, N: 20.99

5.2.3.3. (R)-2,2,2-Trifluoro-N-(2-(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)acetamide ***(6e)***

Compound **6e** was prepared via the general procedure from **16** (400 mg, 0.75 mmoL) and trifluoroacetic anhydride (236 mg, 159 µL, 1.125 mmol) in TEA and CH_3CN (10 mL) to give a crude solid (330 mg). Purification by silica gel column chromatography (EtOAc → EtOAc-methanol 10:1) gave **6e** as a white powder (50 mg, yield 13%), mp- 205-207 ^oC. ^1H-NMR (DMSO-d_6, 600 MHz): δ 9.54 (br. s, 1H, NH, exchangeable with D_2O), 7.86 (s, 1H, triazolyl H), 7.43 (dd, 1H, J=2.4 Hz, 14.3 Hz, phenyl H), 7.14 (dd, 1H, J=2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, J=8.8 Hz, phenyl H), 5.06-5.09 (m, 1H, oxazolidinone H), 4.64-4.74 (m, 2H, CH_2), 4.18 (t, 1H, J=10.7 Hz, oxazolidinone H) 4.11 (s, 2H, $CF_3CONHCH_2$), 3.80-3.90 (m, 5H, oxazolidinone & piperazinyl H), 2.94-3.00 (br, 4H, piperazinyl H), 2.20 (s, 3H, triazolyl CH_3). IR (KBr pellet, cm^{-1}): ν 3524, 2919, 1741, 1724, 1653, 1518, 1517, 1436, 1336, 1228, 1185, 1162, 1035. MS 513.2 (M^+). Anal calcd for $C_{21}H_{23}F_4N_7O_4$: C: 49.12, H: 4.52, N: 19.10; found C: 48.92, H: 4.62, N: 19.20.

5.2.3.4. (R)-2,2-Dichloro-N-(2-(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)acetamide ***(6f)***

Compound **6f** was prepared via the general procedure from **16** (400 mg, 0.75 mmol) and dichloroacetyl chloride (160 mg, 1.28 mmol) in TEA and CH_3CN (20 mL) to give a crude solid (350 mg). Recrystallization (THF) gave **6f** as a white solid (190 mg, yield 48%), mp- 206-208 ^oC. ^1H-NMR (DMSO-d_6, 600 MHz): δ 8.67 (t, 1H,

J=5.4 Hz, NH, exchangeable with D_2O), 7.56 (s, 1H, triazolyl H), 7.43 (dd, 1H, J=3.2 Hz, 15.6 Hz, phenyl H), 7.14 (dd, 1H, J=3.2 Hz, 10.6 Hz, phenyl H), 7.07 (t, 1H, J=10.5 Hz, phenyl H), 6.68 (s, 1H, Cl_2CH), 5.06-5.09 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J=5.5 Hz, CH_2), 4.19 (t, 1H, J=10.5 Hz, oxazolidinone H) 4.12 (d, 2H, J=5.2 Hz, $Cl_2CONHCH_2$), 3.83 (dd, 1H, J=5.9 Hz, 9.2 Hz, oxazolidinone H), 3.56-3.63 (br. 4H, piperazinyl H), 2.94-3.00 (br, 4H, piperazinyl H), 2.22 (s, 3H, triazolyl CH_3). IR (KBr pellet, cm^{-1}): ν 3389, 3281, 2919, 1745, 1704, 1627, 1516, 1445, 1418, 1327, 1233, 1107, 1031. MS 528.96 (M^+ + H). Anal calcd for $C_{21}H_{24}Cl_2FN_7O_4$: C: 47.74, H: 4.58, N: 18.56; found C: 47.88, H: 4.78, N: 18.80.

5.2.3.5. (R)-Ethyl 3-((2-(4-(4-(5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2-oxoethyl)amino)-3-oxopropanoate ***(6g)***

Compound **6g** was prepared via the general procedure from 15 (700 mg,1.35 mmol) and mono ethyl malonate (270 mg, 240 µL, 2.02 mmol) activated by oxalyl chloride (1.33 g, 910 µL, 10.50 mmol), in TEA, DCM (5 mL) and CH_3CN (25 mL) to give a crude solid (750 mg). Purification by silica gel column chromatography (EtOAc-MeOH 10:1 → 9:2), gave the title compound as white powder (210 mg, yield 30%), mp- 198-200 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 8.26 (t, 1H, J=5.2 Hz, NH, exchangeable with D_2O), 8.16 (s, 1H, triazolyl H), 7.76 (s, 1H, triazolyl H), 7.42 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.13 (dd,1H ,J=2.3 Hz, 8.8 Hz, phenyl H), 7.06 (t, 1H, J=9.3 Hz, phenyl H), 5.10-5.14 (m, 1H, oxazolidinone H), 4.82 (d, 2H, J=5.1 Hz, CH_2), 4.20 (t, 1H, J=9.2 Hz, oxazolidinone H), 4.07 (q, 2H, J=7.1 Hz, CH_2), 4.03 (d, 2H, J=5.3 Hz, CH_2), 3.86 (dd, 1H, J=5.9 Hz, 9.4 Hz, oxazolidinone H), 3.58-3.64 (br. t, 2H, piperazinyl H), 3.55-3.58 (br. t, 2H, piperazinyl H), 2.96-3.00 (br. t, 2H, piperazinyl H), 2.93-2.96 (br. t, 2H, piperazinyl H), 1.17 (t, 3H, J=7.1 Hz, CH_3). IR

(KBr pellet, cm^{-1}): ν 3429, 2911, 2859, 1753, 1638, 1518, 1473, 1442, 1417, 1329, 1282, 1225, 1192, 1163, 1111, 1034. MS 517.2 (M^+). Anal calcd for $C_{23}H_{28}FN_7O_6$: C: 53.38, H: 5.45, N: 18.95; found C: 53.20, H: 5.12, N: 18.68.

5.2.3.6. (R)-Ethyl 3-((2-(4-(2-fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo oxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)amino)-3-oxopropanoate ***(6h)***

Compound **6h** was prepared via the general procedure from **16** (500 mg, 0.94 mmol) and mono ethyl malonate (190 mg, 170 µL, 1.41 mmol) activated by oxalyl chloride (930 mg, 640 µL, 7.3 mmol), in TEA, DCM (5 mL) and CH_3CN (20 mL) to give a crude solid (560 mg). Purification by silica gel column chromatography (EtOAc-MeOH 10:1) gave the title compound as white powder (130mg, yield 26%), mp- 205-207 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 8.27 (t, 1H, J=5.2 Hz, NH, exchangeable with D_2O), 7.86 (s, 1H, triazolyl H), 7.44 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.14 (dd,1H ,J=2.3 Hz, 8.8 Hz, phenyl H), 7.06 (t, 1H, J=9.3 Hz, phenyl H), 5.07-5.09 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J=5.3 Hz, CH_2), 4.19 (t, 1H, J=9.1 Hz, oxazolidinone H), 4.07 (q, 2H, J=7.1 Hz, CH_2), 4.04 (d, 2H, J=5.2 Hz, CH_2), 3.83 (dd, 1H, J=5.9 Hz, 9.3 Hz, oxazolidinone H), 3.60-3.64 (br. t, 2H, piperazinyl H), 3.56-3.60 (br. t, 2H, piperazinyl H), 2.96-3.00 (br. t, 2H, piperazinyl H), 2.93-2.96 (br. t, 2H, piperazinyl H), 2.22(s, 3H, CH_3), 1.18 (t, 3H, J=7.1 Hz, CH_3). IR (KBr pellet, cm^{-1}): ν 3429, 2911, 2859, 1753, 1638, 1518, 1473, 1442, 1417, 1329, 1282, 1225, 1192, 1163, 1111, 1034. MS 531.3 (M^+). Anal calcd for $C_{24}H_{30}FN_7O_6$: C: 54.23, H: 5.69, N: 18.45; found C: 53.98, H: 5.72, N: 18.15.

5.2.3.7. N-(2-(4-(4-((R)-5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluoro- phenyl)piperazin-1-yl)-2-oxoethyl)tetrahydrofuran-2-carboxamide ***(6i)***

Compound **6i** was prepared via the general procedure from **15** (500 mg,0.97 mmol) and tetrahydrofuran-2-carboxylic acid (340 mg, 280 µL, 2.91 mmol) activated by oxalyl chloride (3.69 mg, 2.54 mL, 29.1 mmol), in TEA, DCM (5 mL) and CH_3CN (10 mL) to give a crude solid (400 mg). Recrystallization (CH_3CN-Et_2O) gave **6i** as a solid (150 mg, yield 31%), mp- 198-200 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 8.16 (s, 1H, triazolyl H), 7.76 (s, 1H, triazolyl H), 7.74 (t, 1H, J=5.3 Hz, NH, exchangeable with D_2O), 7.42 (dd, 1H ,J=3.74 Hz, 15.66 Hz, phenyl H), 7.13 (dd, 1H,J=3.24 Hz, 9.96 Hz, phenyl H), 7.06 (t, 1H, J=9.72 Hz, phenyl H), 5.12-5.13 (m, 1H, oxazolidinone H), 4.82 (d, 2H, J=4.0 Hz, CH_2), 4.26 (dd, 1H, J=5.3 Hz, 9.0 Hz, tetrahydrofuran H), 4.19 (t, 1H, J=8.9 Hz, oxazolidinone H), 4.00 (dd, 2H, J=4.9 Hz, 16.7 Hz, CH_2), 3.91 (q, 1H, J=8.9 Hz, tetrahydrofuran H), 3.86 (dd, 1H, J=6.3 Hz, 9.8 Hz, oxazolidinone H), 3.79 (q, 1H, J=6.6 Hz, tetrahydrofuran H), 3.56-3.62 (br. d, 4H, piperazinyl H), 2.92-2.99 (br. d, 4H, piperazinyl H), 2.11-2.12 (m, 1H, tetrahydrofuran H), 1.82-1.90 (m, 3H, tetrahydrofuran H). IR (KBr pellet, cm^{-1}): ν 3408, 2871, 1747, 1649, 1518, 1437, 1330, 1279, 1232, 1164, 1111, 1075, 1032. MS 501.2 (M^+). Anal calcd for $C_{23}H_{28}FN_7O_5$: C: 55.08, H: 5.63, N: 19.55; found C: 54.94, H: 5.47, N: 19.25.

5.2.3.8. N-(2-(4-(2-Fluoro-4-((R)-5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo-oxazolidin -3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)tetrahydrofuran-2-carboxamide

(6j)

Compound **6j** was prepared via the general procedure from **16** (800 mg, 1.50 mmol) and tetrahydrofuran-2-carboxylic acid (200 mg, 1.80 mmol) activated by 1-hydroxy-benzotriazole (300 mg, 2.16 mmol) and 1-[3-(diethylamine) propyl)3-ethyl carbodimide hydrochloride (680 mg, 3.6 mmol), in TEA, DCM / CH_3CN (25-25 mL)

to give a crude solid (280 mg). Purification by silica gel column (EtOAc-MeOH 10:1), gave the title compound as a white powder (60 mg, yield 8%), mp- 100-102 ^{o}C. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 7.86 (s, 1H, triazolyl H), 7.74 (t, 1H, J=5.4 Hz, NH, exchangeable with D_2O), 7.43 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 1H, J=2.5 Hz, 9.6 Hz, phenyl H), 7.06 (t, 1H, J=9.4 Hz, phenyl H), 5.05-5.12 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J=5.0 Hz, CH_2), 4.18-4.28 (m, 2H), 3.78-4.04 (m, 5H), 3.55-3.62 (br, 4H, piperazinyl H), 2.94-3.00 (br, 4H, piperazinyl H), 2.20 (s, 3H, CH_3), 2.08-2.13 (m, 1H), 1.81-1.87 (m, 3H). IR (KBr pellet, cm^{-1}): ν 3524, 2923, 1745, 1654, 1517, 1444, 1331, 1332, 1233, 1133, 1039. MS 517.02 (M^+ + H). Anal calcd for $C_{24}H_{30}FN_7O_5$: C: 55.91, H: 5.87, N: 19.02; found C: 55.71, H: 5.78, N: 18.91.

5.2.3.9. (R)-N-(2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2-oxoethyl)benzamide ***(6k)***

Compound **6k** was prepared via the general procedure from **15** (500 mg, 0.97 mmol) and benzoyl chloride (200 mg, 0.17 mL, 1.46 mmol) in TEA and CH_3CN (5 mL) to give a crude solid (580 mg). Purification by silica gel column chromatography (EtOAc-MeOH 10: 0.5) afforded **6k** as a white solid (390 mg, yield 79%), mp- 228-230 °C. ^{1}H-NMR (DMSO-d_6,600 MHz): 8.59 (t, 1H, J=5.2 Hz, NH, exchangeable with D_2O), (s, 1H, triazolyl H), 7.87-7.89 (m, 2H, phenyl H), 7.77 (s, 1H, triazolyl H), 7.53-7.56 (m, 1 H, phenyl H), 7.48-7.50 (m, 2H, phenyl H), 7.43 (dd, 1H, J= 2.5 Hz, 14.6 Hz, phenyl H), 7.14 (dd, 1H, J=2.4 Hz, 8.8 Hz, phenyl H), 7.08 (t, 1H, J=9.4 Hz, phenyl H), 5.10-5.14 (m, 1H, oxazolidinone H), 4.83 (d, 2H, J=5.1 Hz , CH_2), 4.21 (t, 1H, J=9.2, oxazolidinone H), 4.18 (d, 2H, J=5.7 Hz, CH_2), 3.86 (dd, 1H, J=5.7 Hz, 9.3 Hz, oxazolidinone H), 3.65 (br d, 4H, piperazinyl H), 2.98 (br d, 4H, piperazinyl H).

^{13}C-NMR (DMSO-d_6): δ 167.08, 166.36, 155.80, 153.50, 153.37, 135.51, 134.13, 133.42, 133.35, 131.33, 128.35, 127.25, 125.90, 119.81, 119.77, 114.29, 106.88, 106.62, 70.81, 54.93, 51.73, 50.62, 50.26, 47.09, 44.18. IR (KBr pellet, cm^{-1}): ν 3357, 2992, 2898, 1731, 1650, 1516, 1429, 1328, 1232, 1114, 1031. MS 507.5 (M^+). Anal calcd for $C_{25}H_{26}FN_7O4$: C: 59.16, H: 5.16, N: 19.32 found C: 58.90, H: 4.98, N: 18.98.

5.2.3.10. (R)-N-(2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo-oxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)benzamide ***(6l)***

Compound **6l** was prepared via the general procedure from **16** (500 mg, 0.94 mmol) and benzoyl chloride (200 mg, 0.17 mL, 1.41 mmol) in TEA and CH_3CN (5 mL) to give a crude solid (580 mg). Purification by silica gel chromatography (EtOAc-MeOH 10:0.5 → EtOAc-MeOH 10:1) gave **6l** as a white solid (400 mg, yield 82%), mp- 205-207 °C. ^{1}H-NMR (DMSO-d_6, 600 MHz): δ 8.60 (t, 1H, J=5.8, NH, exchangeable with D_2O), 7.86-7.88 (m, 3H, phenyl H, triazolyl H), 7.53-7.56 (m, 1H, phenyl H), 7.47-7.50 (m, 2H, phenyl H), 7.44 (dd, 1H, J=2.6 Hz, 14.9 Hz, phenyl H), 7.15 (dd, 2H, J=2.4 Hz, 9.5 Hz, phenyl H), 7.08 (t, 1H, J=9.5 Hz, phenyl), 5.06-5.11 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J=5.4 Hz, CH_2), 44.18-4.21 (m, 3H, oxazolidinone H, CH_2), 3.84 (dd, 4H, J=5.1 Hz, 9.6 Hz oxazolidinone H), 3.62-3.67 (br d, 4H, piperazinyl H), 2.94-2.95 (br d, 4H, piperazinyl H), 2.22 (s,3H, triazolyl CH_3). IR (KBr pellet, cm^{-1}): ν 3428, 2918, 1745, 1636, 1517, 1465, 1425, 1337, 1224, 1135, 1041. MS 521.1 (M^+). Anal calcd for $C_{26}H_{28}FN_7O_4$: C: 59.88, H: 5.41, N: 18.80 found C: 59.64, H: 5.40, N: 18.83.

5.2.3.11. (R)-N-(2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2-oxoethyl)-3,5-dinitrobenzamide ***(6m)***

Compound **6m** was prepared via the general procedure from **15** (500 mg, 0.97 mmol) and 3,5-dinitrobenzoyl chloride (666 mg, 2.89 mmol) in TEA and CH_3CN (25 mL) to give a yellow solid. Recrystallization (CH_3CN) gave the title compound as a yellow solid (290 mg, yield 50%), mp- 199-201 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 9.46 (t, 1H, J=6.8 Hz, NH, exchangeable with D_2O), 9.08 (d,2H, J=2.1 Hz, nitrophenyl H), 8.98 (t, 1H, J=2.2 Hz, nitrophenyl H), 8.17 (s, 1H, triazolyl H), 7.77 (s, 1H, triazolyl H), 7.43 (dd,1H, J=2.6 Hz,15.0 Hz, phenyl H), 7.14 (dd, 1H,J=3.0 Hz,8.2 Hz, phenyl H),7.08 (t, 1H, J=8.8 Hz, Phenyl H), 5.11-5.14 (m, 1H, oxazolidinone H), 4.83 (d, 2H, J=5.1Hz, CH_2), 4.28 (d, 2H, J=5.2 Hz , CH_2), 4.21 (t, 1H, J=9.2 Hz, oxazolidinone H),3.86 (dd, 1H, J=5.4 Hz, 8.7 Hz, oxazolidinone H), 3.64-3.69 (br. d, 4H, piperazinyl H), 2.95-3.04 (br. d, 4H, piperazinyl H). IR (KBr pellet, cm^{-1}): ν 3389, 2918, 1750, 1678, 1651, 1539, 1428, 1338, 1299, 1234, 1200, 1176, 1105, 1076, 1031. MS 597.3 (M^+). Anal calcd for $C_{25}H_{24}FN_9O_8$: C: 50.25, H: 4.05, N: 21.10; found C: 50.17, H: 4.02, N: 20.96.

5.2.3.12. (R)-N-(2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo-oxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)-3,5-dinitrobenzamide ***(6n)***

Compound **6n** was prepared via the general procedure from **16** (450 mg, 0.85 mmol) and 3,5-dinitrobenzoyl chloride (290 mg, 1.28 mmol) in TEA and CH_3CN (10 mL) to give a reddish-yellow gum (620 mg). Purification by silica gel column chromatography (EtOAc → EtOAc-MeOH 10:1) gave **6n** as a solid (260 mg, yield 52%), mp- 234-236 ^oC. ^1H-NMR (DMSO-d_6, 600 MHz): δ 9.46 (t, 1H, J=6.0 Hz, NH, exchangeable with D_2O), 9.08 (s, 2H, J=2.2 Hz, phenyl H), 8.98 (t, 1H, J=2.1 Hz,

phenyl H), 7.86 (s, 1H, triazolyl H), 7.44 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.15 (dd, 1H, J=2.7 Hz, 8.7 Hz, phenyl H), 7.09 (t, 1H, J=9.3 Hz, phenyl H), 5.08-5.10 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J=5.02 Hz, CH_2), 4.29 (d, 2H, J=5.7 Hz, CH_2), 4.20 (t, 1H, J=9.1 Hz, oxazolidinone H), 3.84 (dd, 1H, J=5.9 Hz, 9.3 Hz, oxazolidinone H), 3.65-3.68 (two br t, 4H, J=5.3 Hz, piperazine H), 2.95-3.04 (two br t, 4H, J=5.3 Hz, piperazine H), 2.23 (s, 3H, triazolyl CH_3). IR (KBr pellet, cm^{-1}): ν 3401, 3089, 2821, 1750, 1655, 1535, 1525, 1443, 1344, 1300, 1236, 1103, 1033. MS 612.2 (M^+ + H). Anal calcd for $C_{26}H_{26}FN_9O_8$: C: 51.06, H: 4.29, N: 20.61; found C: 50.80, H: 4.62, N: 20.08.

5.2.3.13. (R)-N-(2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2-oxoethyl)nicotinamide ***(6o)***

Compound **6o** was prepared via the general procedure from **15** (500 mg,0.97 mmol) and nicotinoyl chloride (515 mg, 2.89 mmol) in TEA and CH_3CN (10 mL) to give a crude solid (580 mg). Recrystallization (MeOH-Et_2O) gave **6o** as a solid (60 mg, yield 29%), mp- 198-200 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 9.04 (d, 1H, J=1.8 Hz, nicotinoyl H), 8.85 (br. t, 1H, NH, exchangeable with D_2O), 8.73 (d, 1H, J=4.8 Hz, nicotinoyl H), 8.22 (d, 1H, J=7.9 Hz, nicotinoyl H), 8.17 (s, 1H, triazolyl H), 7.77 (s, 1H, triazolyl H), 7.53 (dd,1H, J=4.1 Hz, 8.3 Hz, nicotinoyl H), 7.43 (dd, 1H, J=2.8 Hz, 14.6 Hz , phenyl H), 7.14 (dd, 1H, J=2.7 Hz, 9.1 Hz, phenyl H), 7.08 (t, 1H, J=8.7 Hz, phenyl H), 5.11-5.14 (m, 1H, oxazolidinone H), 4.83 (d, 2H, J=5.0 Hz , CH_2), 4.20-4.25 (m, 3H, CH_2 & oxazolidinone H), 3.86 (dd, 1H, J=6.7 Hz, 9.0 Hz, oxazolidinone H), 3.63-3.67 (br. d, 4H, piperazinyl H), 2.95-3.03 (br. d, 4H, piperazinyl H). IR (KBr pellet, cm^{-1}): ν 3370, 2942, 1743, 1639, 1588, 1518, 1465, 1444, 1420, 1335, 1284, 1230, 1201, 1162, 1107, 1078, 1026. MS 509.99 (M^+ + H).

Anal calcd for $C_{24}H_{25}FN_8O_4$: C: 56.69, H: 4.96, N: 22.04; found C: 56.78, H: 4.85, N: 22.21.

5.2.3.14. (R)-N-(2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo-oxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)nicotinamide ***(6p)***

Compound **6p** was prepared via the general procedure from **16** (400 mg, 0.75 mmol) and nicotinoyl chloride (200 mg, 2.25 mmol) in TEA and CH_3CN (10 mL) to give a crude solid (190 mg). Purification by silica gel column chromatography (EtOAc → EtOAc-MeOH 10:1 → 10:2) afforded **6p** as a while solid (110 mg, yield 28%), mp-185-187 ^oC. ^1H-NMR (DMSO-d_6, 600 MHz): δ 8.99 (s, 1H, triazolyl), 8.88 (t, 1H, J=5.9 Hz, NH, exchangeable with D_2O), 8.70 (d, 1H, J=5.9 Hz, pyridyl H), 8.19-8.21 (m 1H, pyridyl H), 7.83 (s, 1H, pyridyl H), 7.53 (dd, 1H, 7.5 Hz, 15.1 Hz, pyridyl H), 7.44 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.10 (dd, 1H, J=2.7 Hz, 8.8 Hz, phenyl H), 7.05-7.11 (m, 2H, phenyl H), 5.08-5.10 (m, 1H, oxazolidinone H), 4.70-4.72 (m, 2H, CH_2), 4.18-4.24 (m, 3H, oxazolidinone H,), 3.80-3.85 (m, 1H, oxazolidinone H), 3.59-3.66 (br, 4H, piperazinyl H), 2.95-3.04 (two br s, 4H, piperazinyl H), 2.20 (s, 3H, triazolyl CH_3). IR (KBr pellet, cm^{-1}): ν 3392, 2921, 1745, 1649, 1518, 1472, 1420, 1334, 1228, 1033. MS 523.98 (M^+ + H). Anal calcd for $C_{25}H_{27}FN_8O_4$: C: 57.46, H: 5.21, N: 21.44; found C: 57.12, H: 5.40, N: 21.04.

5.2.3.15. (R)-N-(2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2-oxoethyl)thiophene-2-carboxamide ***(6q)***

Compound **6q** was prepared via the general procedure from **15** (500 mg,0.97 mmol) and 2-thiophene- carbonyl chloride (424 mg, 2.89 mmol) in TEA and CH_3CN (10 mL) to give a crude solid. Recrystallization (CH_3CN) gave **6q** as a crystalline solid

(320 mg, yield 61%), mp- 230-232 ^{o}C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.62 (t, 1H, J=5.7 Hz, NH, exchangeable with D_2O), 8.16 (s, 1H, triazolyl H), 7.62-7.82 (m, 3H, triazolyl H & thiophene H), 7.43 (dd, 1H, J=2.5 Hz,14.7 Hz, phenyl H), 7.16 (dd, 1H, J=3.8 Hz, 4.9 Hz, thiophene H), 7.13 (dd, 1H, J=2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, J=9.4, Hz, phenyl H), 5.11-5.13 (m, 1H, oxazolidinone H), 4.83 (d, 2H, J=5.1 Hz, CH_2), 4.21 (t, 1H, J=9.2 Hz, oxazolidinone H), 4.15 (d, 2H, J=5.6 Hz, CH_2), 3.86,(dd, 1H, J=5.7 Hz, 9.3 Hz, oxazolidinone H), 3.63-3.65 (m, 4H, piperazinyl H), 2.94-3.01 (br. d, 4H, piperazinyl H). ^{13}C-NMR (DMSO-d_6): δ 166.98, 161.34, 155.80, 153.50, 139.64, 135.50, 133.40, 133.35, 130.89, 128.36, 127.98, 125.90, 119.81, 114.27, 106.88, 106.62, 70.81, 51.74, 50.62, 50.27, 47.10, 44.21. IR (KBr pellet, cm^{-1}): ν 3422, 3368, 2915, 1735, 1635, 1518, 1441, 1335, 1281, 1227, 1200, 1164, 1104, 1024. MS 513.2 (M^+). Anal calcd for $C_{23}H_{24}FN_7O_4S$: C: 53.79, H: 4.71, N: 19.09; found C: 53.57, H: 4.64, N: 18.86.

5.2.3.16. (R)-N-(2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)thiophene-2-carboxamide ***(6r)***

Compound **6r** was prepared via the general procedure from **16** (400 mg, 0.75 mmol) and 2-thiophene carbonyl chloride (330 mg, 2.25 mmol) in TEA and CH_3CN (10 mL) to give a crude light yellow solid (580 mg). Recrystallization (CH_3CN) gave **6r** as an off-white solid (150 mg, yield, 37%), m.p. 212-215 ^{o}C. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.62 (t, 1H, J=6.8 Hz , NH, exchangeable with D_2O), 7.86 (s, 1H, triazolyl H), 7.81 (dd, 1H, J=1.1 Hz, 3.7 Hz, thiophene H), 7.77 (dd, 1H, J=1.1 Hz, 5.0 Hz, thiophene H), 7.44 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.13-7.17 (m, 2H, phenyl H, thiophene H), 7.07 (t, 1H, J=9.3 Hz, phenyl H), 5.07-5.09 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J=5.0 Hz, CH_2), 4.19 (t, 1H, J=9.1 Hz, oxazolidinone H), 4.15 (d, 2H,

J=5.7 Hz, CH_2), 3.84 (dd, 1H, J=5.9 Hz, 9.3 Hz, oxazolidinone H), 3.63-3.65 (dd, 4H, piperazinyl H), 3.32 (dd, 1H, oxazolidinone H overlapping partly with D_2O signal), 2.94-3.01 (br. d, 4H, piperazinyl H), 2.23 (s, 3H, triazolyl H). IR (KBr pellet, cm^{-1}): ν 3428, 2920, 1740, 1633, 1523, 1475, 1429, 1338, 1232, 1204, 1051. MS 527.3 (M^+). Anal calcd for $C_{24}H_{26}FN_7O_4S$: C: 54.64, H: 4.97,N: 18.58, found C: 54.49, H: 4.90, N: 18.35.

5.2.3.17. (R)-N-(2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2-oxoethyl)furan-2-carboxamide ***(6s)***

Compound **6s** was prepared via the general procedure from **15** (500 mg,0.97 mmol) and 2-furoyl chloride (377 mg, 2.89 mmol) in TEA and CH_3CN (10 mL) to give a crude solid. Recrystallization (CH_3CN) gave **6s** as a crystalline solid (230mg, yield 50%), mp- 198-200 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 8.30 (t, 1H, J=5.6 Hz, NH, exchangeable with D_2O), 8.16(s, 1H, triazolyl H), 7.86 (s, 1H , thiophene H), 7.76 (s, 1H, triazolyl H), 7.43 (dd, 1H, J=2.5 Hz, 14.6 Hz, phenyl H), 7.12-7.14 (m, 2H, furan H & phenyl H), 7.07 (t, 1H, J=9.3 Hz, phenyl H), 6.64 (dd, 1H, J=1.7 Hz, 3.4 Hz, furan H), 5.10-5.14 (m, 1H, oxazolidinone H), 4.83 (d, 2H, J=5.1 Hz, CH_2), 4.21(t, 1H, J=9.2 Hz , oxazolidinone H), 4.13 (d,1H, J=5.4 Hz , CH_2), 3.86 (dd, 1H, J=5.7 Hz, 9.3 Hz, oxazolidinone H), 3.60-3.63 br. s, 4H, piperazinyl H), 2.94-3.00 (br. s, 4H, piperazinyl H). IR (KBr pellet, cm^{-1}): ν 3422, 3362, 2918, 1735, 1643, 1592, 1516, 1440, 1337, 1225, 1200, 1166, 1105, 1068, 1026. MS 497.2 (M^+). Anal calcd for $C_{23}H_{24}FN_7O_5$: C: 55.53, H: 4.86, N: 19.71; found C: 55.34, H: 4.89, N: 19.51.

5.2.3.18. (R)-N-(2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)furan-2-carboxamide ***(6t)***

Compound **6t** was prepared via the general procedure from **16** (400 mg, 0.75 mmol) and 2-furoyl chloride (290 mg, 2.25 mmol) in TEA and CH_3CN (10 mL) to give a crude solid (620 mg). Recrystallization (CH_3CN) gave the title compound as a with powder (220 mg, yield 58%), mp- 206-208 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 8.29 (t,1H, J=6.8 Hz , NH, exchangeable with D_2O) , 7.86 (d, 2H , triazolyl, furan H), 7.44 (dd, 1H, J=3.8 H_Z, 13.7 H_Z, phenyl H), 7.14 (dd, 2H, J=3.1, Hz, 10.5 Hz, phenyl H, furan H), 7.08 (t, 1H, J=10.4 Hz, phenyl H), 6.64 (dd, 1H, J=1.8 Hz, 3.4 Hz, furan H), 5.07-5.09 (m, 1H, oxazolidinone H), 4.74 (d, 2H, J=5.1 Hz, oxazolidinone H), 4.19 (t, 1H, J=9.6 H_Z, oxazolidinone H), 4.14 (d, 2H, J=5.4 Hz, CH_2), 3.84 (dd, 1H, J=6.0 Hz, 13.1 Hz, oxazolidinione H), 3.63 (br, 4H, piperazinyl H), 2.94-3.00 (br. d, 4H, piperazinyl H), 2.23 (s, 3H, triazolyl H). IR (KBr pellet, cm^{-1}): ν 3371, 2921, 1741, 1642, 1596, 1518, 1469, 1429, 1339, 1232, 1203, 1022. MS 511.51 (M^+). Anal calcd for $C_{24}H_{26}FN_7O_5$: C: 56.36, H: 5.12, N: 19.17; found C: 56.20, H: 5.02, N: 18.90.

5.2.3.19. (R)-N-(2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2-oxoethyl)-5-nitrofuran-2-carboxamide ***(6u)***

Compound **6u** was prepared via the general procedure from **15** (600 mg,1.16 mmol) 5-nitrofuran-2-carboxylic acid (360 mg, 2.32 mmol) activated by oxalyl chloride; in TEA and CH_3CN (20 mL) to give a crude yellow solid (1.60 g). Recrystallization (DCM) gave **6u** as a yellow solid (620 mg, yield 35%), mp- 210-213 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 8.93 (t,1H, J=5.8 Hz, NH, exchangeable with D_2O), 8.17 (s, 1H, triazolyl H), 7.76 (d, 2H, J=3.4 Hz, furan H, triazolyl H), 7.47 (d, 1H, J=3.9 Hz, furan H), 7.43 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.14 (dd, 1H, J=2.3 Hz, 8.8 Hz, phenyl H), 7.07 (t, 1H, J=9.3 Hz, phenyl H), 5.11-5.13 (m, 1H, oxazolidinone H),

4.83 (d, 2H, J=5.1 Hz, CH_2), 4.20 (m, 3H, CH_2, oxazolidinone H), 3.85 (dd, 1H, J=5.7 Hz, 9.3 Hz, oxazolidinone H), 3.63 (br. s, 4H, piperazinyl H), 2.98 (br. d, 4H, piperazinyl H). ^{13}C-NMR (DMSO-d_6): δ 166.23, 156.25, 155.34, 153.73, 153.45, 147.96, 135.42, 133.31, 125.38, 119.76, 115.78, 114.25, 113.41, 106.81, 106.64, 70.75, 51.69, 51.69, 50.53, 50.16, 47.06, 45.48, 44.14. IR (KBr pellet, cm^{-1}): ν 3422, 2928, 1742, 1665, 1520, 1446, 1407, 1348, 1292, 1239, 1135, 1033. MS 542.2 (M^+). Anal calcd for $C_{23}H_{23}FN_8O_7$: C: 50.92, H: 4.27, N: 20.66; found C: 50.55, H: 4.55, N: 20.46.

5.2.3.20. (R)-N-(2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo-oxazolidin-3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)-5-nitrofuran-2-carboxamide ***(6v)***

Compound **6v** was prepared via the general procedure from **16** (500 mg,0.94 mmol) and 5-nitrofuran carboxylic acid (290 mg, 1.88 mmol) activated by oxalyl chloride, in TEA and CH_3CN (10 mL) to give a crude yellow solid (500 mg). Purification by silica gel column chromatography (EtOAc, →EtOAc-MeOH 10:1) gave **6v** as a yellow solid (240 mg, yield 48%), mp- 160-162 ^oC. ^{1}H-NMR (DMSO-d_6, 600 MH_Z): δ 8.94 (t,1H J=5.6 Hz, NH, exchangeable with D_2O), 7.86 (s, 1H, triazolyl H), 7.77 (d, 1H, J=3.9 Hz, furan H), 7.47(d, 1H J=3.9 Hz, furan H), 7.44 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.15 (dd, 1H, J=2.3 Hz, 8.8 Hz, phenyl H), 7.08 (t, 1H, J=9.5 Hz, phenyl H), 5.07-5.10 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J=5.3 Hz, CH_2), 4.18-4.21 (m, 3H, CH_2, oxazolidinone H), 3.84 (dd, 1H, J=5.9 Hz, 9.5 Hz, oxazolidinone H), 3.62-3.64 (m, 4H, piperazinyl H), 3.01(dd, J=4.9 Hz, piperazinyl H), 2.95 (dd, J=4.9 Hz, piperazinyl H), 2.22 (s, 3H, triazolyl CH_3). **).** ^{13}C-NMR (DMSO-d_6): δ 166.23, 156.25, 155.35, 153.74, 153.47, 147.96, 135.40, 133.30, 123.19, 119.76, 115.78, 114.26, 113.40, 106.81, 106.65, 70.85, 51.66, 50.54, 50.17, 47.10, 44.14,

10.36. IR (KBr pellet, cm^{-1}): ν 3429, 2925, 2855, 1751, 1655, 1519, 1449, 1350, 1291, 1235, 1136, 1108, 1037. MS 556.2 (M^+). Anal calcd for $C_{24}H_{25}FN_8O_7$: C: 51.80, H: 4.53, N: 20.14 found C: 51.72, H: 4.29, N: 19.89.

5.2.3.21. (R)-N-(2-(4-(4-(5-((1H-1,2,3-Triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)piperazin-1-yl)-2-oxoethyl)thiophene-2-sulfonamide ***(6w)***

Compound **6w** was prepared via the general procedure from **15** (500 mg, 0.97 mmol) 2-thiophenesulfonyl chloride (529 mg, 2.89 mmol), in TEA and CH_3CN (10 ml) to give a crude solid. Recrystallized (CH_3CN) gave the title compound as brown crystals (320 mg, yield 60%), mp- 195-197 ^oC. ^1H-NMR (DMSO-d_6, 600 MH_Z): δ 8.16 (s, 1H, triazolyl H), 7.93 (br., 1H, NH, exchangeable with D_2O, overlaps partly with thipohene H), 7.92 (dd, 1H, J=1.1 Hz, 4.9 Hz, thiophene H), 7.76 (s, 1H, triazolyl H), 7.64 (dd, 1H, J=1.2 Hz, 3.7 Hz, thiophene H), 7.41 (dd, 1H, J=2.4 Hz, 14.7 Hz, phenyl H), 7.18 (dd, 1H, J=3.9 H_Z, 4.8 Hz, thiophene H), 7.13 (dd, 1H, J=2.2 Hz, 8.8 Hz, phenyl H), 7.04 (t, 1H, J=9.3 Hz, phenyl H), 5.10-5.14 (m,1H, oxazolidinone H), 4.82 (d, 2H, J=5.1 Hz, CH_2), 4.20 (t, 1H, J=9.2 Hz, oxazolidinone H), 3.86 (m, 3H, oxazolidinone H, CH_2), 3.51-3.54 (m, 4H, piperazinyl H), 2.91 (br. d, 4H, piperazinyl H). **).** ^{13}C-NMR (DMSO-d_6): δ 164.38, 154.20, 152.58, 139.92, 134.24, 132.10, 131.34, 130.65, 126.47, 124.71, 118.61, 113.14, 106.82, 69.53, 50.56, 49.19, 48.92, 45.94, 43.10, 41.43. IR (KBr pellet, cm^{-1}): ν 3437, 2912, 1743, 1642, 1520, 1484, 1412, 1396, 1346, 1286, 1226, 1158, 1109, 1031. MS 549.2 (M^+). Anal calcd for $C_{22}H_{24}FN_7O_5S_2$: C: 48.08, H: 4.40, N: 17.84; found C: 48.01, H: 4.31, N: 17.70.

5.2.3.22. (R)-N-(2-(4-(2-Fluoro-4-(5-((4-methyl-1H-1,2,3-triazol-1-yl)methyl)-2-oxo-oxazolidin -3-yl)phenyl)piperazin-1-yl)-2-oxoethyl)thiophene-2-sulfonamide ***(6x)***

Compound 6x was prepared via the general procedure from 16 (400 mg,0.75 mmol) and 2-thiophenesulfonyl chloride (410 mg, 2.25 mmol) in TEA and CH_3CN (10 mL) to give a semi-solid crude (650 mg). Purification by silica gel column chromatography (EtOAc → EtoAc-MeOH 10:1) afforded **6x** as a white solid (100 gm, yield 24%), mp- 160-162 ^oC. ^1H-NMR (DMSO-d_6, 600 MHz): δ 7.93-7.96 (br, 1H, NH, exchangeable with D_2O), 7.92 (dd, 1H, J=1.2 Hz, 5.0 Hz, thiophene H), 7.85 (s, 1H, triazolyl H), 7.64 (dd, 1H, J=1.3 Hz, 3.7 Hz, thiophene H), 7.43 (dd, 1H, J=2.5 Hz, 14.7 Hz, phenyl H), 7.17 (dd, 1H, J=3.8 Hz, 4.9 Hz, thiphene H), 7.14 (dd, 1H, J=2.3 Hz, 8.8 Hz, phenyl H), 7.05 (t, 1H, J=9.4 Hz, phenyl H), 5.06-5.09 (m, 1H, oxazolidinone H), 4.73 (d, 2H, J=5 Hz, CH_2), 4.19 (t, 1H, J=9.2 Hz, oxazolidinone H), 3.8 (s, 2H, CH_2), 3.83 (dd, 1H, J=5.9 Hz, 9.3 Hz, oxazolidinone H), 3.52-3.54 (br, 4H, piperazinyl H), 2.88-2.95 (br, 4H, piperazinyl H), 2.20 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6): δ 165.50, 155.33, 153.71, 153.48, 142.01, 141.04, 135.36, 133.31, 132.45, 131.76, 127.58, 123.19, 119.72, 114.27, 106.82, 69.72, 50.53, 49.20, 48.91, 45.97, 43.15, 40.31, 9.25. IR (KBr pellet, cm^{-1}): ν 3425, 2916, 1743, 1644, 1521, 1485, 1417, 1337, 1227, 1160, 1106, 1033. MS 563.2 (M^+). Anal calcd for $C_{23}H_{26}FN_7O_5S_2$: C: 49.01, H: 4.65, N: 17.40; found C: 48.90, H: 4.48, N: 17.27.

5.3 Antibacterial susceptibility testing.

The minimum inhibitory concentrations (MIC's, μg/ml), defined as the lowest concentration of a drug that inhibits visible bacterial growth were determined on Mueller-Hinton (MH) agar [17] with medium containing dilutions of antibacterial agents ranging from 0.12 to 64 μg/ml. Linezolid and vancomycin were dissolved in 40% water in ethanol and water, respectively, and test compounds in 80% DMSO in

water. MH agar plates were used for all staphylococci and enterococci, and on MH agar plates supplemented with 5% sheep blood to facilitate the growth of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis.* The Gram-positive clinical isolates at the MRSA Reference Laboratory, Faculty of Medicine, Kuwait University utilized in this study consisted of methicillin-resistant *S. aureus* (MRSA, n=9), methicillin-susceptible *S. aureus* (MSSA, n=11), methicillin-resistant coagulase-negative staphylococci (MR-CNS, n=4), methicillin-sensitive coagulase-negative staphylococci (MS-CNS, n=6), Penicillin-resistant *S. pneumoniae* (n=3), vancomycin-sensitive (VSE, n=7) and vancomycin-resistant (VRE, n=3) enterococci. Reference strains *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228 and *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, *H. influenzae* ATCC 49247 and *M. catarrhalis* ATCC8176 were used. The final bacterial concentration for inocula was 10^7 CFU/ml, and was incubated at 35 ^{o}C for 18 h. To assess the extent of plasma binding and / or plasma instability, test compounds were evaluated against *S. aureus* ATTC 25923 in MH broth supplemented with 50% human plasma. Linezolid, **PH-027** and **PH-084** were used as reference antibacterial agents.

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Conflict of Interest

The authors declare no conflict of interest.

Submission declaration and verification

The authors declare that this work has not been published previously (except in the form of an abstract) , that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tactitly or explicitly by the responsible authorities where the work was carried out. Also, that if accepted, it will not be published anywhere else.

Contributors

We also declare that all contributing authors approved the final article for publication.

Role of the funding source

We also declare that the funding source had no involvement in study design, in collection, analysis and interpretation of data, in witing of the report; and in the decision to submit the article for publication.

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All Legends:-

Figure 1. Chemical structures of oxazolidinone antibacterial agents and proposed derivatives

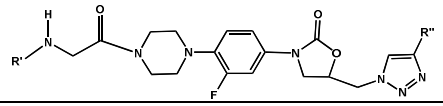
Scheme 1. Synthetic route for the N-substitutedglycinyl triazolyl oxazolidinone derivatives. (i) THF, H_2O, PPh_3, 90 ^oC; (ii) DME, acetylene, 90 ^oC; or MeOH / DIPEA, 2-(1,1-dichloropropan-2-ylidene)-1-tosylhydrazine, r.t.-0 ^oC; (iii) DCM, TFA, 0 ^oC to r.t.; (iv) DCM/CH_3CN/DCC/1-HBT/N-tert-butoxycarbonylglycine; (v) DCM, TFA, 0 ^oC to r.t. (vi) RCOCl/CH_3CN/DCM/TEA 0 ^oC to r.t. or DCM/CH_3CN/ DCC/1-HBT/RCO_2H or $R(CO)_2O$/DCM/TEA, 0 ^oC to r.t. or $ArylSO_2Cl$/DCM/TEA, 0 ^oC to r.t.

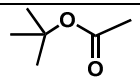
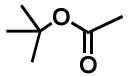
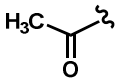
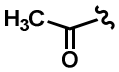
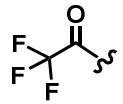
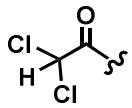
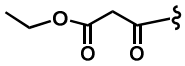
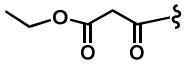
Table 1. Antibacterial activity (MIC, μg/ml) of N-substituted-glycinyl triazolyl oxazolidinones

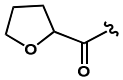
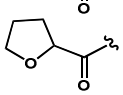
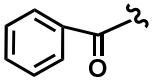
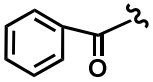
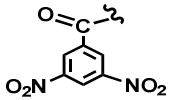
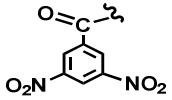
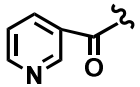
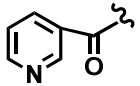
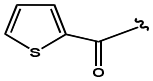
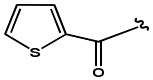
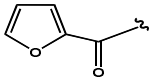
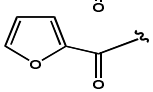
Table 2. Antibacterial activity of N-substituted-glycinyl triazolyl oxazolidinones against clinical isolates of *M. catarrhalis* (n=8)

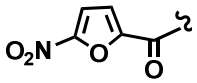
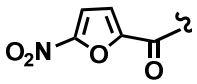
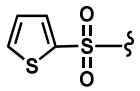
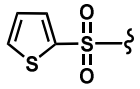
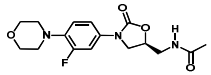
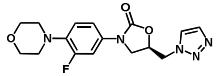
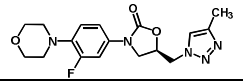
Table 3. Antibacterial activity (MIC, μg/ml) and Clog P values of N-substituted-glycinyl triazolyl oxazolidinones

Table 1. Antibacterial activity (MIC, μg/ml) of N-substituted-glycinyl triazolyl oxazolidinones



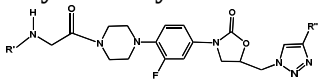
Compd. code	Structure		Staphylococcus aureus			Enterococci			*E coli*[g] ATCC 25922	*H. influ*[h] (n=5)	*S. pn.*[i] (n=4)	*M. cat.*[j] (n=1)
	R'	R"	MRSA[a] (n=10)	MSSA[b] (n=10)	MR CNS[c] (n=3)	MS CNS[d] (n=6)	VSE[e] (n=6)	VRE[f] (n=4)				
6a		H	2-4	2-4	2	2-4	2	2	>64	>64	2	32
b		CH_3	8	4-8	4-8	4-8	4-8	8	>64	64->64	4-8	16
c		H	4	2-4	2-4	2-4	2-4	2-4	>64	64	1	32
d		CH_3	2-4	2-4	2-4	2-4	2-4	4	>64	32	1	16
e		CH_3	4-8	4-8	4-8	4-8	4-8	4-8	>646	32-64	1-2	16
f		CH_3	4-8	4-8	4	4	4-8	4-8	>64	32->64	2	16
g		H	4-8	4-8	4	4-8	4-8	8	>64	64	2	32
h		CH_3	4-8	4-8	4-8	4-8	4	4	>64	>64	4	>64

i		H	4-8	4-8	4-8	4-8	4-8	8	>64	32-64	1-2	16
j		CH_3	16-32	16-32	16	16	16-32	16	>64	32-64	0.5-2	32
k		H	0.5-1	0.5-1	0.5-1	0.5-1	1	0.5	>64	32	1	32
l		CH_3	0.5-2	0.5-1	0.5	0.5	0.5	0.5	>64	32-64	2	8
m		H	0.5-1	0.5-1	0.5	0.5	0.5-1	1	>64	16	0.25	0.5
n		CH_3	1-2	1-2	1	1	1-2	2	>64	16->64	0.25	1
o		H	1-2	1-2	1-2	1-2	2	2	>64	8	0.25	8
p		CH_3	1-2	1-2	1-2	1-2	1-2	1-2	>64	8-16	0.25-0.5	8
q		H	0.5-1	0.5-1	0.5-1	0.5-1	1	1	>64	16	0.5	8
r		CH_3	1-2	1-2	1	1-2	1	1	>64	16	0.5-1	8
s		H	1-2	1-2	1-2	1-2	1	1	>64	16	0.25-0.5	16
t		CH_3	2-4	2-4	2	2	2-4	2-4	>64	4-8	0.5	8

u		H	0.06-0.25	0.06-0.25	0.06-0.25	0.06-0.25	0.25	0.25	>64	8	<0.25	1
v		CH_3	0.06-0.25	0.06-0. 5	0.06-0. 5	0.06-0.25	0.25-0.5	0.5	16	2-8	<0.25	0.5
w		H	2-4	2-4	2-4	2-4	2	2	>64	64->64	1	32
x		CH_3	8-16	8-16	8-16	8-16	8	8	>64	64	2	32
Lzd			0.5-1	0.5-1	0.5-1	0.5-1	0.5-1	0.5-1	>64	8	0.5	8
PH027[ref.9]			0.5-1	0.5-1	0.5-1	0.5-1	0.5-1	1	>64	32	0.5	>16
PH084[ref.11]			0.5-2	1-2	1-2	1-2	1-2	1	>64	64	1-2	8

[a]Methicillin-resistant *Staphylococcus aureus.*
[b]Methicillin-susceptible *S. aureus.*
[c]Methicillin-resistant coagulase-negative staphylococci.
[d]Methicillin-susceptible coagulase-negative staphylococci.
[e]Vancomycin-susceptible enterococci.
[f]Vancomycin-resistant enterococci.
[g]*Escherichia coli*.
[h]*Heamophilus influenzae*.
[i]*Streptococcus pneumoniae*.
[j]*Moraxella catarrhalis*.

Table 2. Antibacterial activity of N-substituted-glycinyl triazolyl oxazolidinones against clinical isolates of *M. catarrhalis* (n=8)



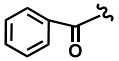
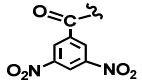
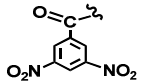
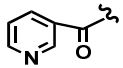
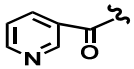
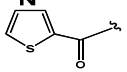
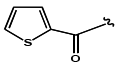
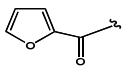
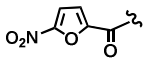
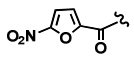
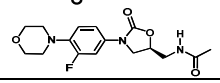
Compd. code	Structure R'	Structure R"	*M. cat* 1	*M. cat* 36	*M. cat* 112	*M. cat* 125	*M. cat* 138	*M. cat* 255	*M. cat* 2824	*M. cat* 3447	*M. cat* (n=8)
6l		CH_3	4-8	4	4-8	4-8	4-8	4-8	4-8	4-8	4-8
m		H	0.25-0.5	0.25-0.5	0.25-0.5	0.25	0.25-0.5	0.25-0.5	0.25-0.5	0.25	0.25-0.5
n		CH_3	1	1	0.5-1	0.5-1	1	0.5-1	1	0.5-1	0.5-1
o		H	8	8	8	8	8	8	8	8	8
p		CH_3	4->8	4->8	4	4	4	4	8	8	4->8
q		H	8	8	8	8	8	8	8	8	8
r		CH_3	8->8	8	8	8	8	8	8	8->8	8->8
t		CH_3	>8	>8	>8	>8	>8	>8	>8	>8	>8
u		H	1	1	1	1	1	1	1	1	1
v		CH_3	1	1	1	1	1	1	1	1	1
Lzd			8	8	8	8	8	8	8	8	8

Table 3. Antibacterial activity (MIC, μg/ml) and Clog P values of N-substituted-glycinyl triazolyl oxazolidinones

Compd Code	Clog P values	MIC μg/ml against *S. aureus* (ATCC 25923)	
		without plasma	with 50% human plasma
6a	1.4286	4	8
b	1.6976	4	16
c	-0.4340	4	8
d	-0.1650	4	8
e	0.9440	8	16
f	2.2640	8	16
g	0.3852	8	16
h	0.6542	8	16
i	0.1962	8	16
j	0.4652	32	32
k	1.2170	1	>64
l	1.4860	1	16

m	1.2862	1	16
n	1.5552	2	8
o	0.4640	2	8
p	0.7330	2	4
q	1.0550	1	8
r	1.5540	2	8
s	0.3930	2	2
t	0.6620	2	4
u	0.5680	<0.25	<0.25
v	0.8370	<0.25	<0.25
w	1.1723	4	32
x	1.6713	16	32
Lzd	0.1681	2	2
PH027[ref.9]	0.2668	1	1
PH084[ref.11]	0.5358	2	4

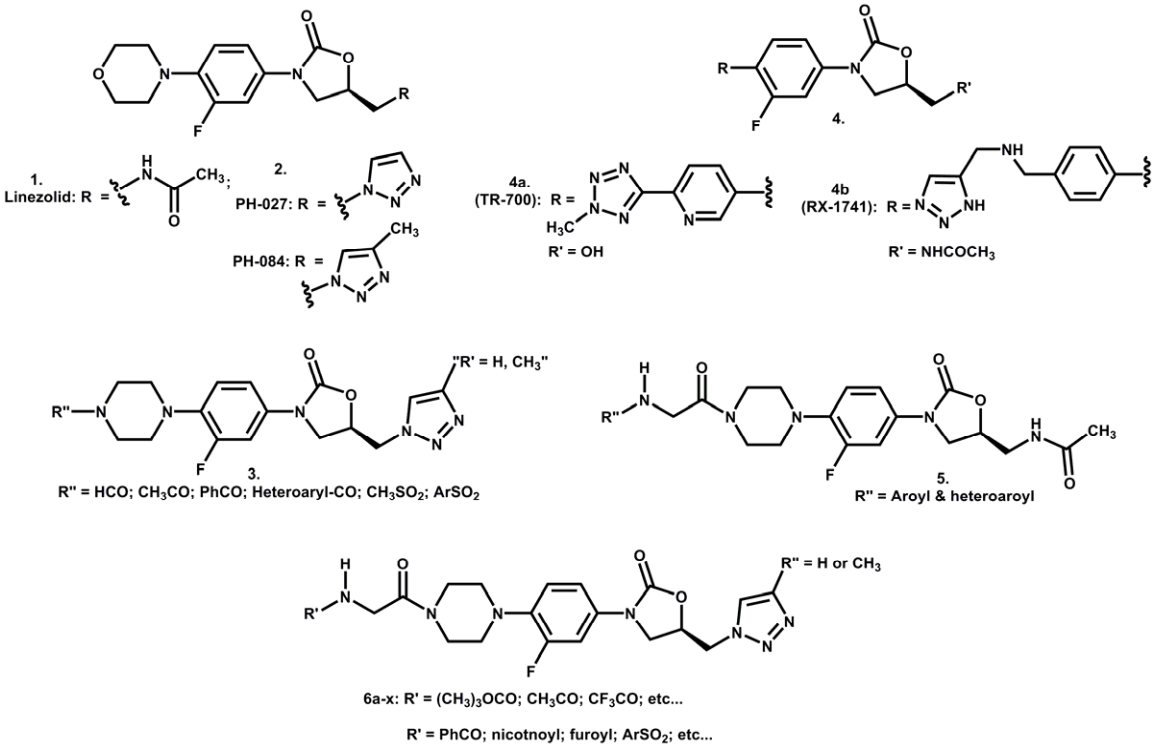
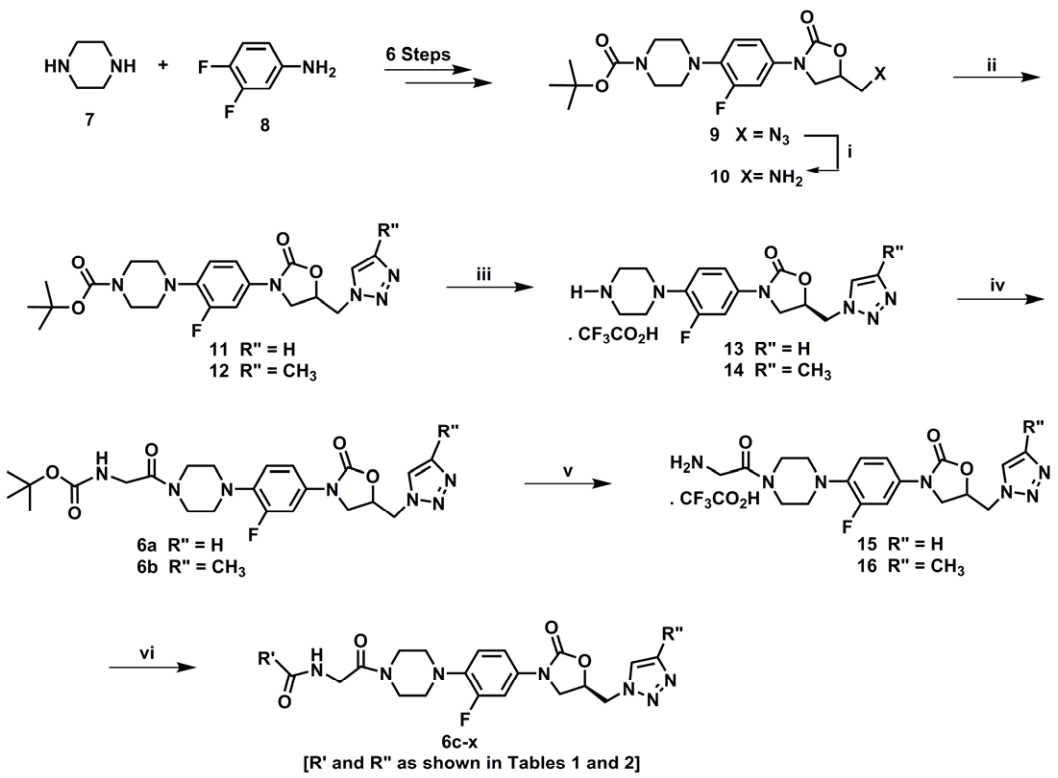


Figure 1:

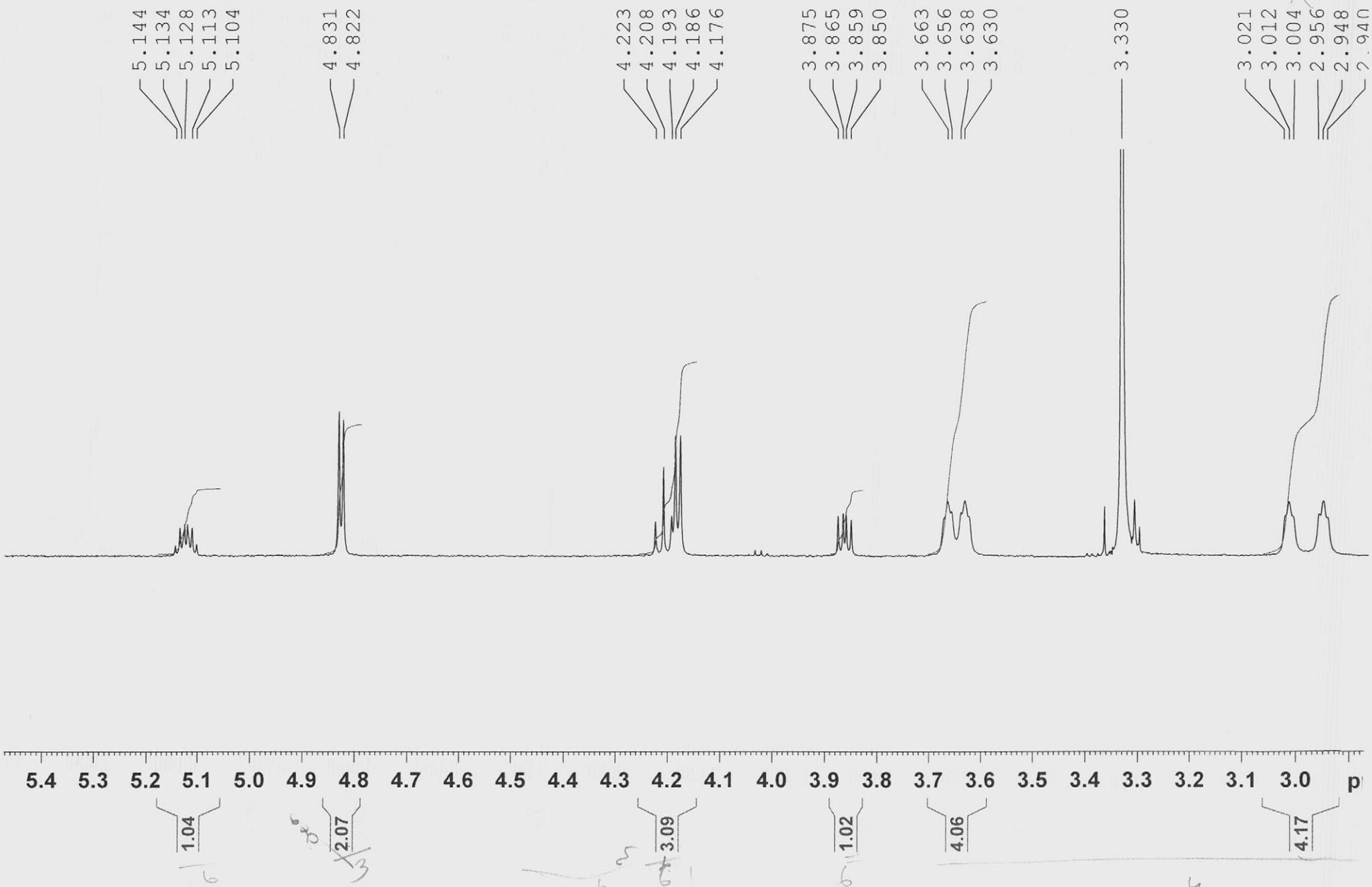
PROF. OLUDOTUN ADEBAYO PHILLIPS



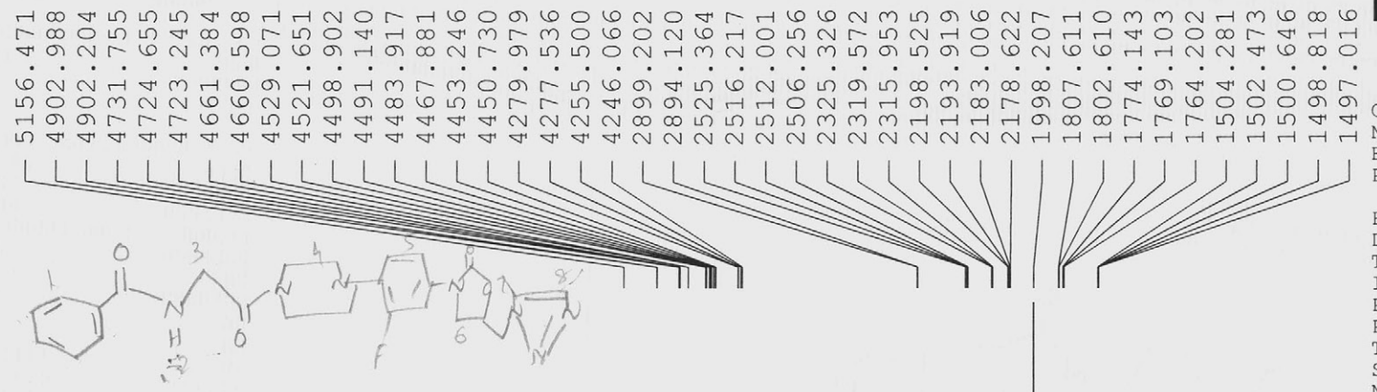
Scheme 1:

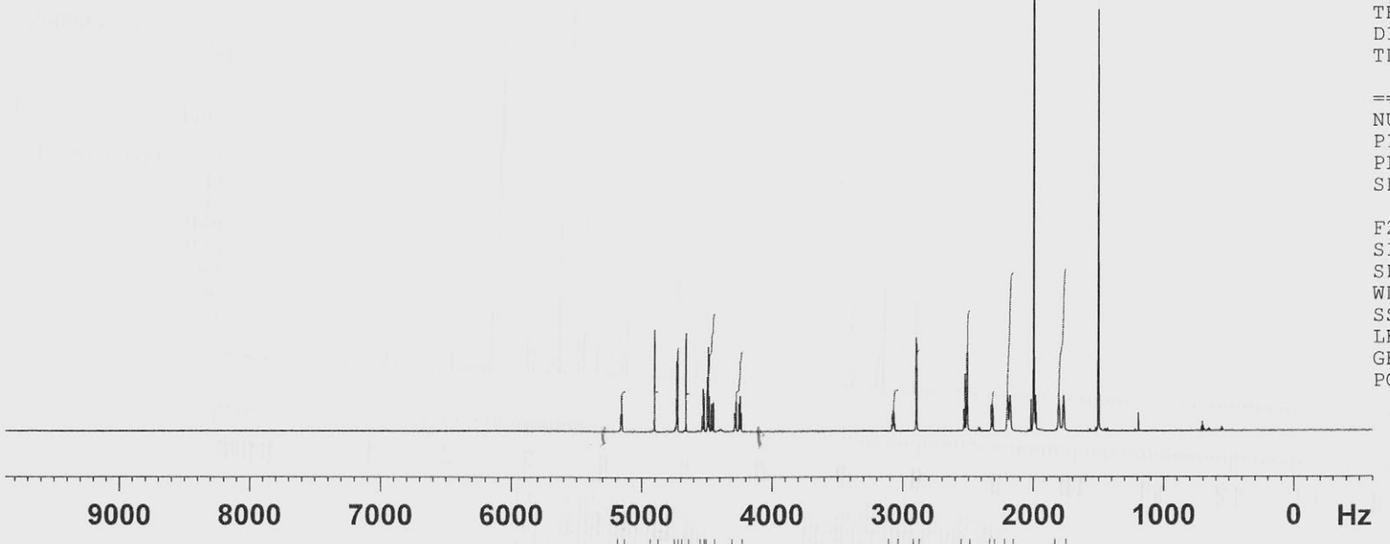
PROF. OLUDOTUN ADEBAYO PHILLIPS

1H spectra Dr.PHILLIPS RV-619 in DMSO



1H spectra Dr.PHILLIPS RV-619 in DMSO





BRUKER

Current Data Parameters

NAME	RV619
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20090125
Time	12.24
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	203
DW	40.533 usec
DE	6.50 usec
TE	296.4 K
D1	1.00000000 sec
TD0	1

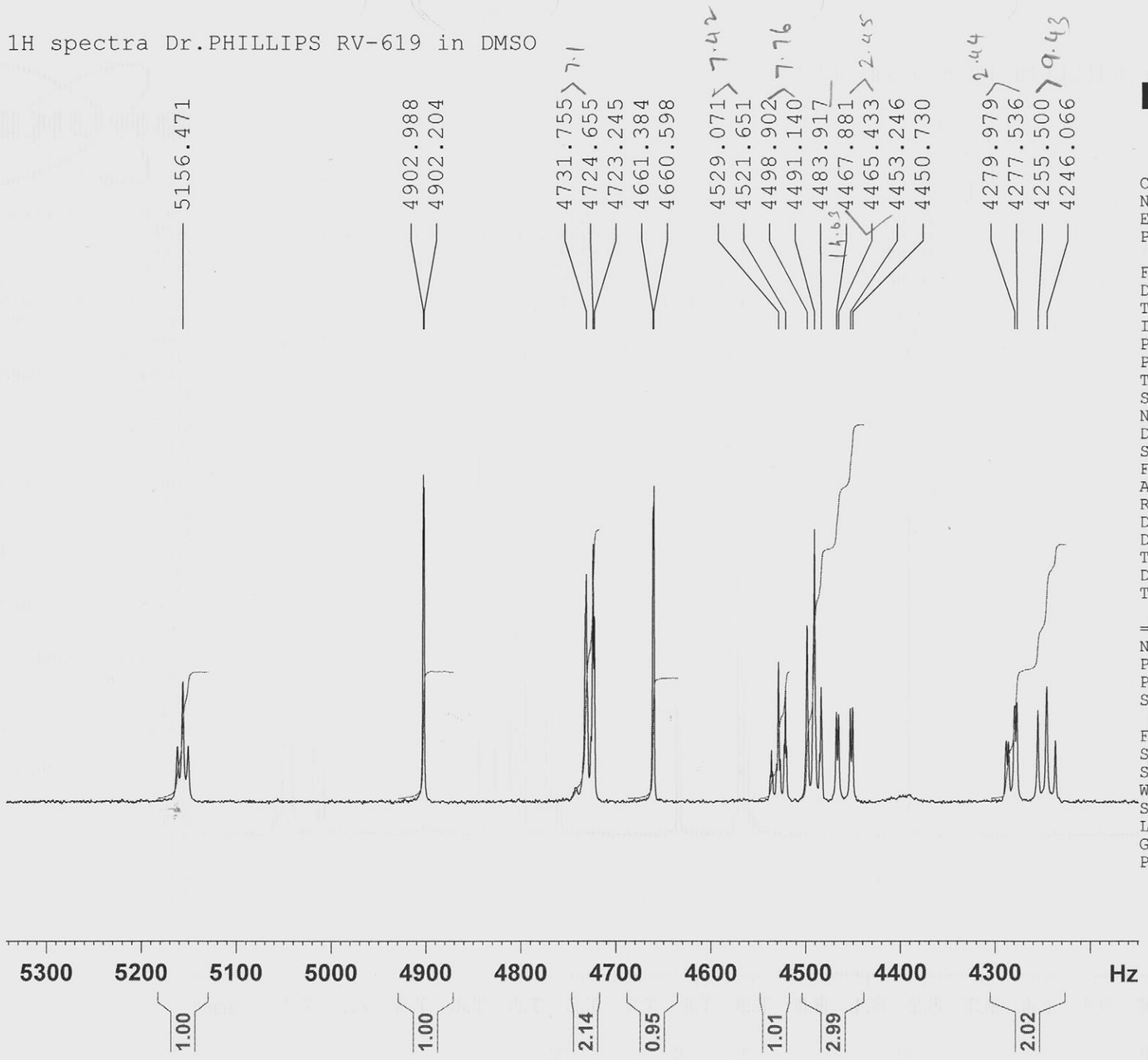
======== CHANNEL f1 ========

NUC1	1H
P1	10.50 usec
PL1	-4.00 dB
SFO1	600.1337060 MHz

F2 - Processing parameters

SI	32768
SF	600.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1H spectra Dr.PHILLIPS RV-619 in DMSO



BRUKER

Current Data Parameters

NAME	RV619
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20090125
Time	12.24
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	2
SWH	12335.526 Hz
FIDRES	0.188225 Hz
AQ	2.6564426 sec
RG	203
DW	40.533 usec
DE	6.50 usec
TE	296.4 K
D1	1.00000000 sec
TD0	1

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

NUC1	1H
P1	10.50 usec
PL1	-4.00 dB
SFO1	600.1337060 MHz

F2 - Processing parameters

SI	32768
SF	600.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1H spectra Dr.PHILLIPS RV-619 in DMSO

3086.889
3081.307
3077.287
3068.465
3062.883

2899.202
2894.120

2534.596
2525.364
2516.217
2512.001
2506.256

2325.326
2319.572
2315.953
2310.318

2198.525
2193.919
2183.006
2178.622

1998.207

1813.053
1807.611
1802.610
1774.143
1769.103
1764.202

3200 3100 3000 2900 2800 2700 2600 2500 2400 2300 2200 2100 2000 1900 1800

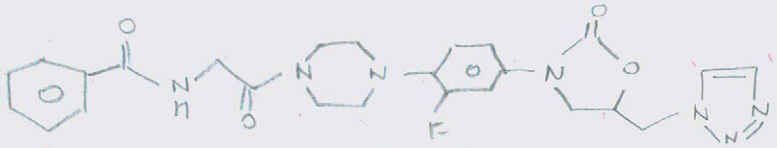
1.04 2.07 3.09 1.02 4.06 4.17

(2)

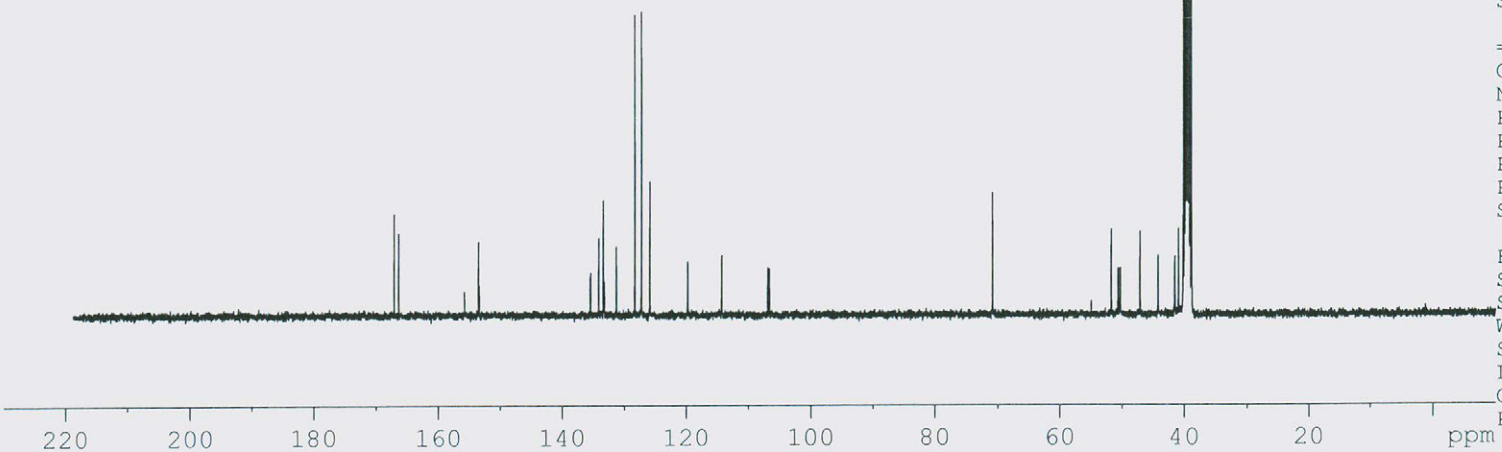
13C decoupled spectra Dr.Phillips 807 in DMSO (PH 166)

167.08 166.36 155.80 153.50 153.37 135.51 135.42 134.13 133.42 133.35 133.25 131.33 128.35 127.25 125.90 119.81 119.77 114.29 114.26 106.88 106.62 70.81 54.93 51.73 50.62 50.26 47.09 44.18 41.49 40.90 40.13 39.92 39.71 39.50 39.29 39.08 38.87

Compd 6K.



$C_{25}H_{30}FN_7O_5$



BRUKER

Current Data Parameters
NAME 807-1H
EXPNO 3
PROCNO 1

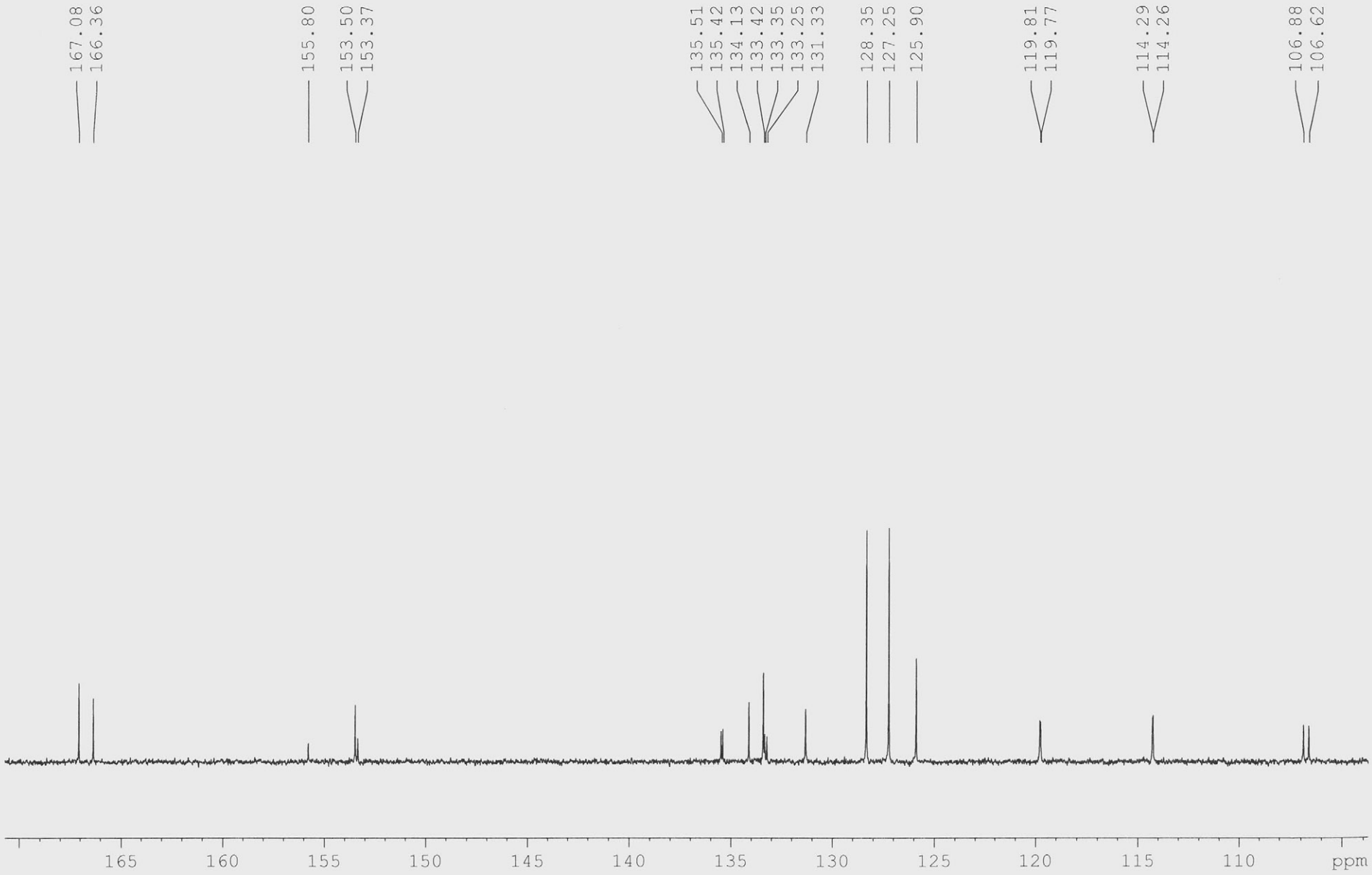
F2 - Acquisition Parameters
Date_ 20110126
Time 0.20
INSTRUM spect
PROBHD 5 mm DUL 13C-1
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 4096
DW 20.850 usec
DE 6.00 usec
TE 673.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 7.20 usec
PL1 -6.00 dB
SFO1 100.6228298 MHz

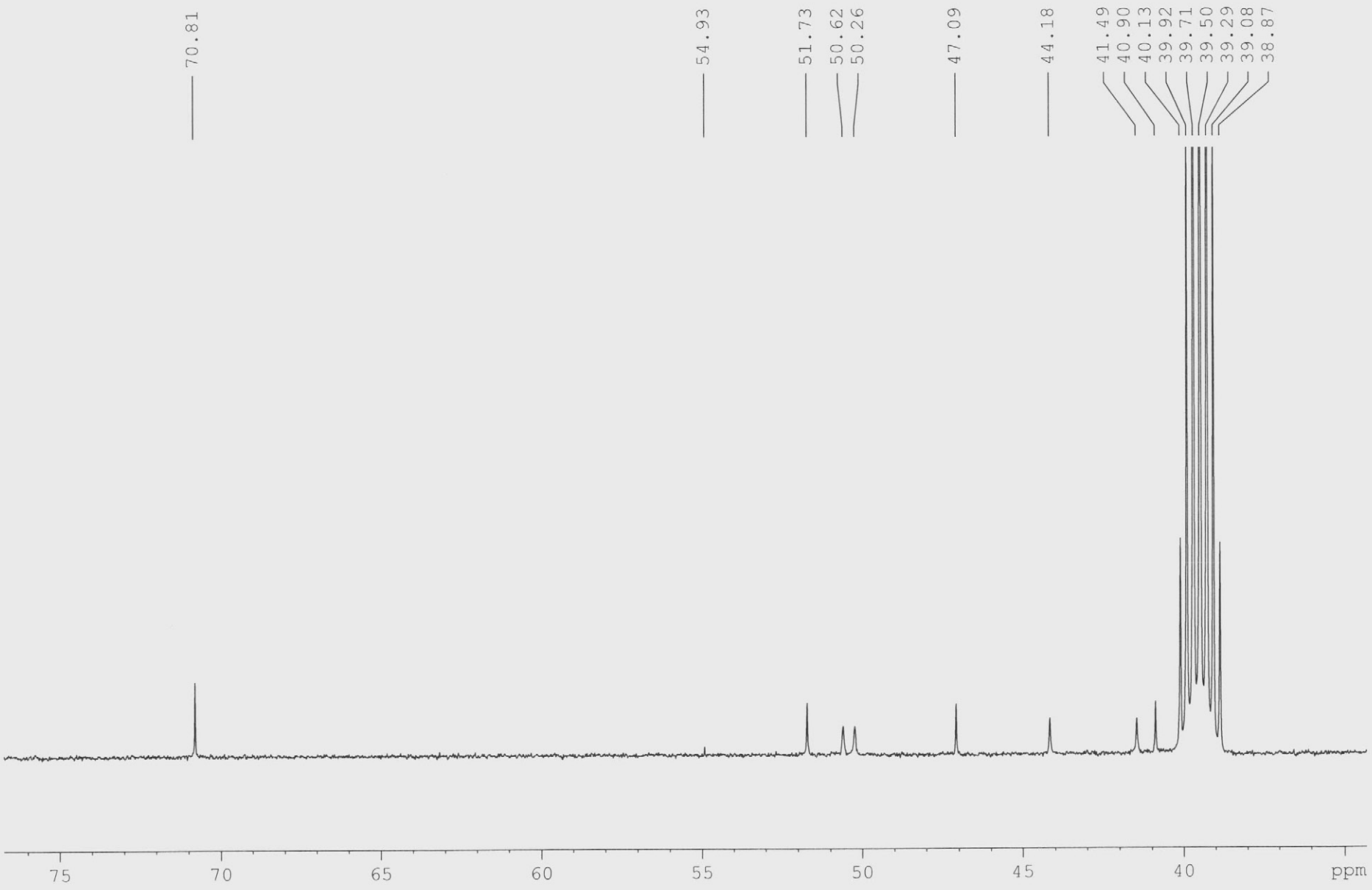
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 15.06 dB
PL13 18.00 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6128151 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

13C decoupled spectra Dr.Phillips 807 in DMSO

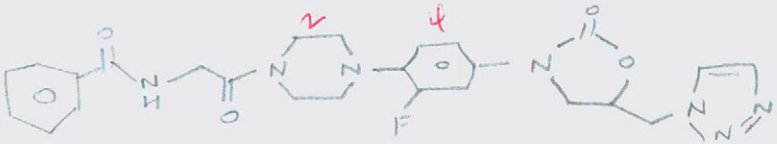


13C decoupled spectra Dr.Phillips 807 in DMSO



(3)

13C DEPT 135 spectra Dr.Phillips 807 in DMSO (PH 166)



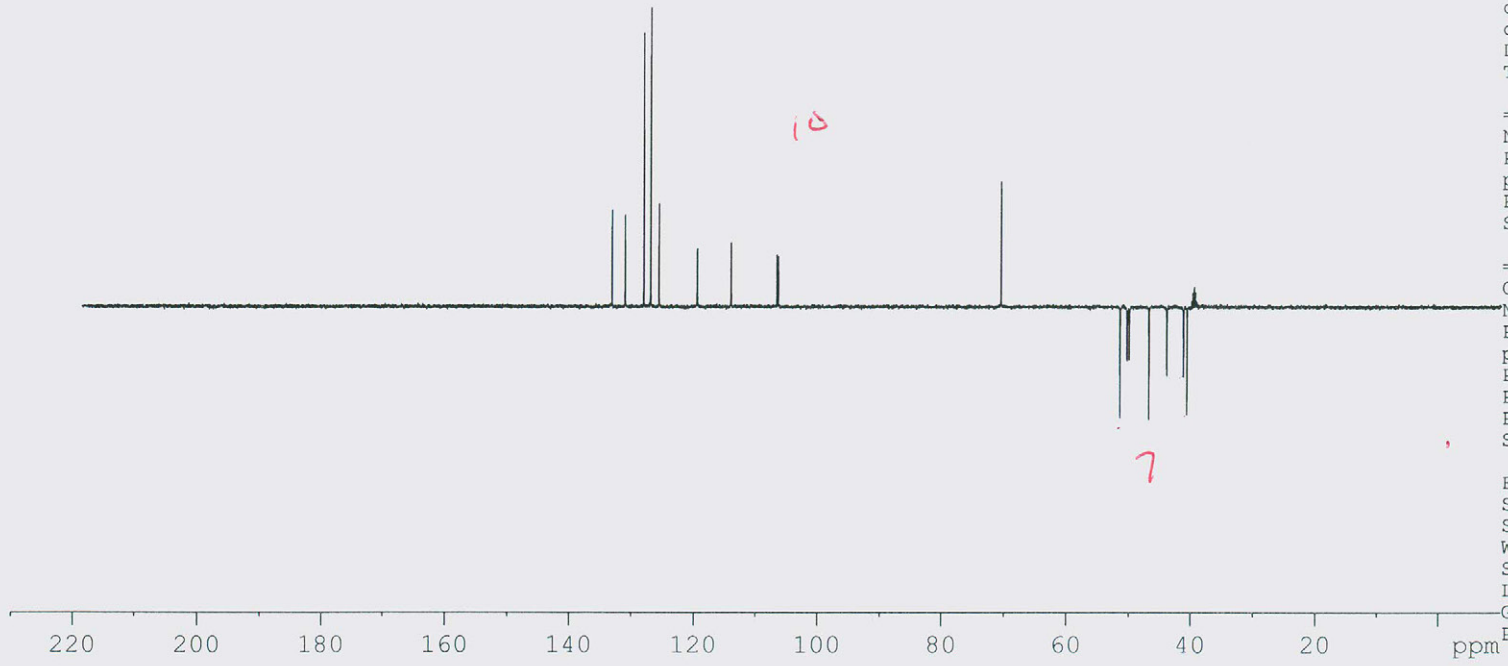
3

$C_{25}H_{30}FN_7O_5$

complex 6K.

133.17
131.07
128.09
126.99
125.64
119.55
119.51
114.03
114.00
106.62
106.36

70.55
51.48
50.36
50.00
46.83
43.92
41.22
40.64
39.70
39.49
39.28



BRUKER

Current Data Parameters
NAME 807-1H
EXPNO 4
PROCNO 1

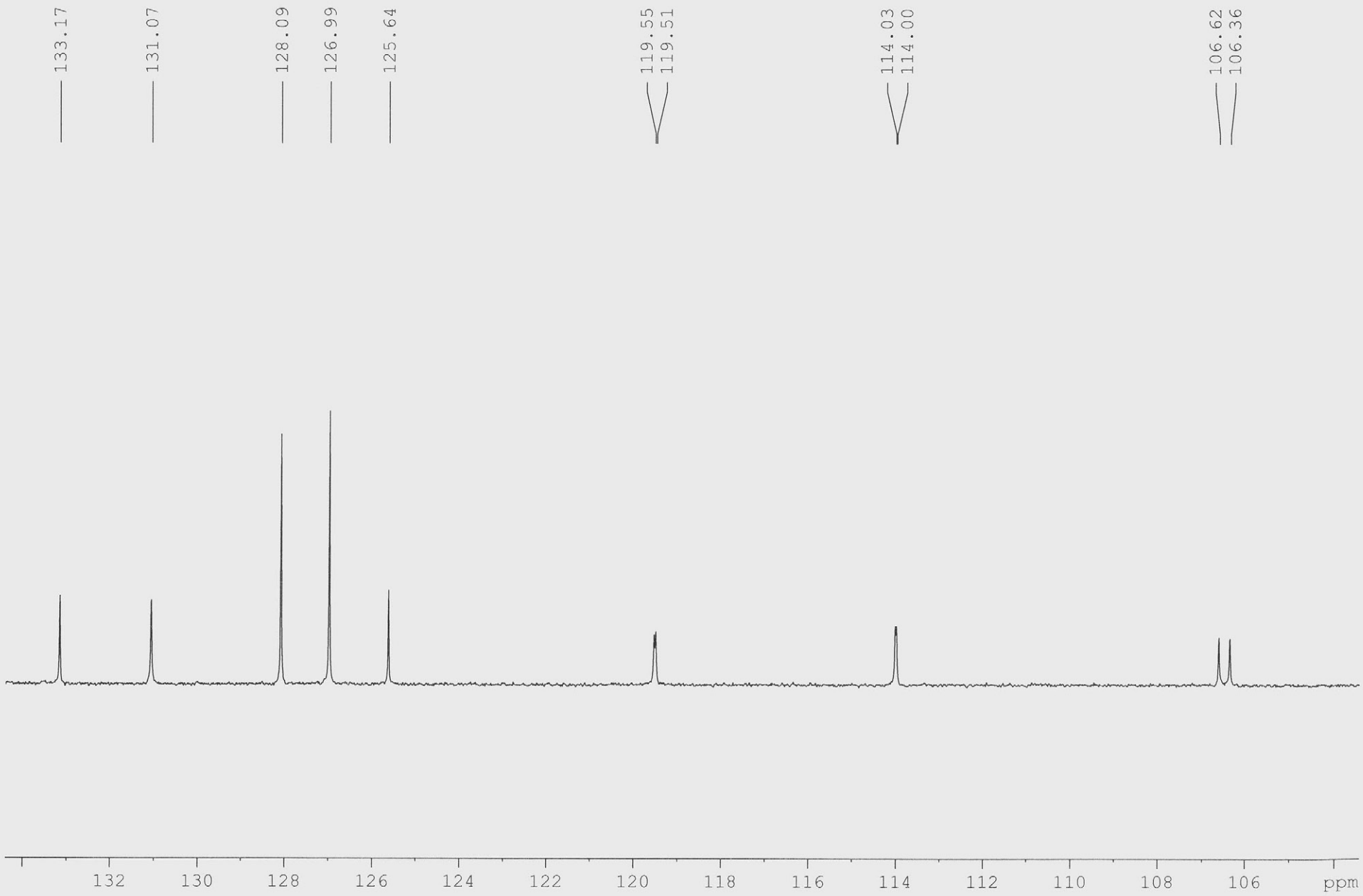
F2 - Acquisition Parameters
Date_ 20110126
Time 2.17
INSTRUM spect
PROBHD 5 mm DUL 13C-1
PULPROG dept135
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 16384
DW 20.850 usec
DE 6.00 usec
TE 673.2 K
CNST2 145.0000000
D1 2.00000000 sec
d2 0.00344828 sec
d12 0.00002000 sec
DELTA 0.00000917 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 7.20 usec
p2 14.40 usec
PL1 -6.00 dB
SFO1 100.6228298 MHz

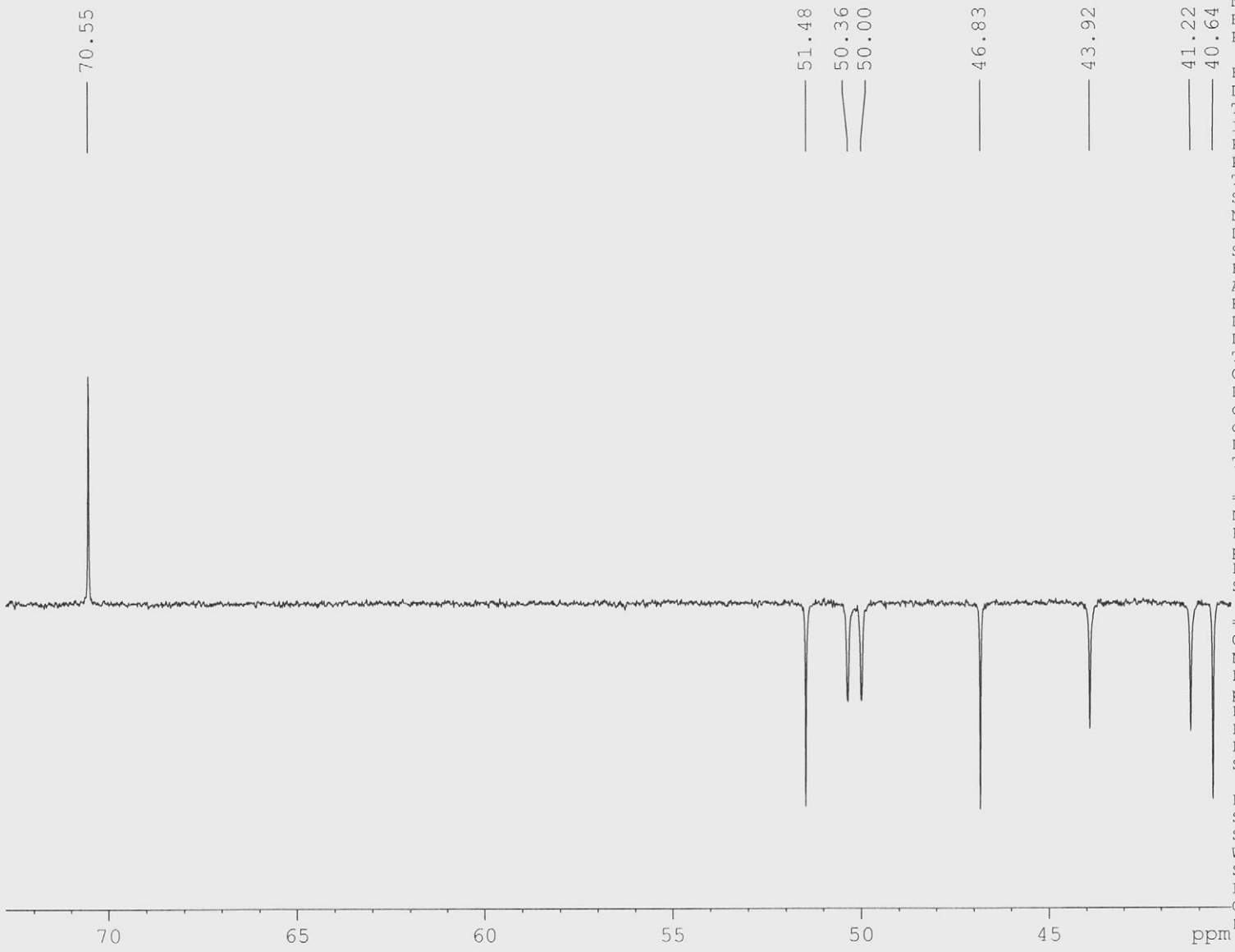
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
P3 10.00 usec
p4 20.00 usec
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 15.06 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6128411 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

13C DEPT 135 spectra Dr.Phillips 807 in DMSO



13C DEPT 135 spectra Dr.Phillips 807 in DMSO



Current Data Parameters

NAME	807-1H
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20110126
Time	2.17
INSTRUM	spect
PROBHD	5 mm DUL 13C-1
PULPROG	dept135
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	16384
DW	20.850 usec
DE	6.00 usec
TE	673.2 K
CNST2	145.0000000
D1	2.00000000 sec
d2	0.00344828 sec
d12	0.00002000 sec
DELTA	0.00000917 sec
TD0	1

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

NUC1	13C
P1	7.20 usec
p2	14.40 usec
PL1	-6.00 dB
SFO1	100.6228298 MHz

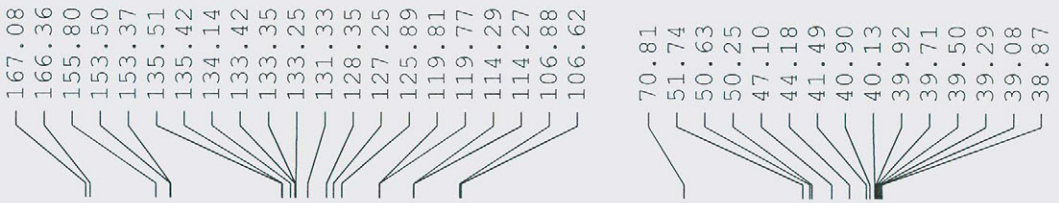
======== CHANNEL f2 ========

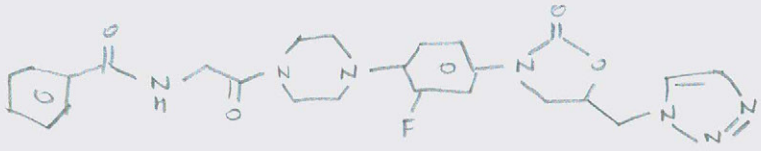
CPDPRG2	waltz16
NUC2	1H
P3	10.00 usec
p4	20.00 usec
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	15.06 dB
SFO2	400.1316005 MHz

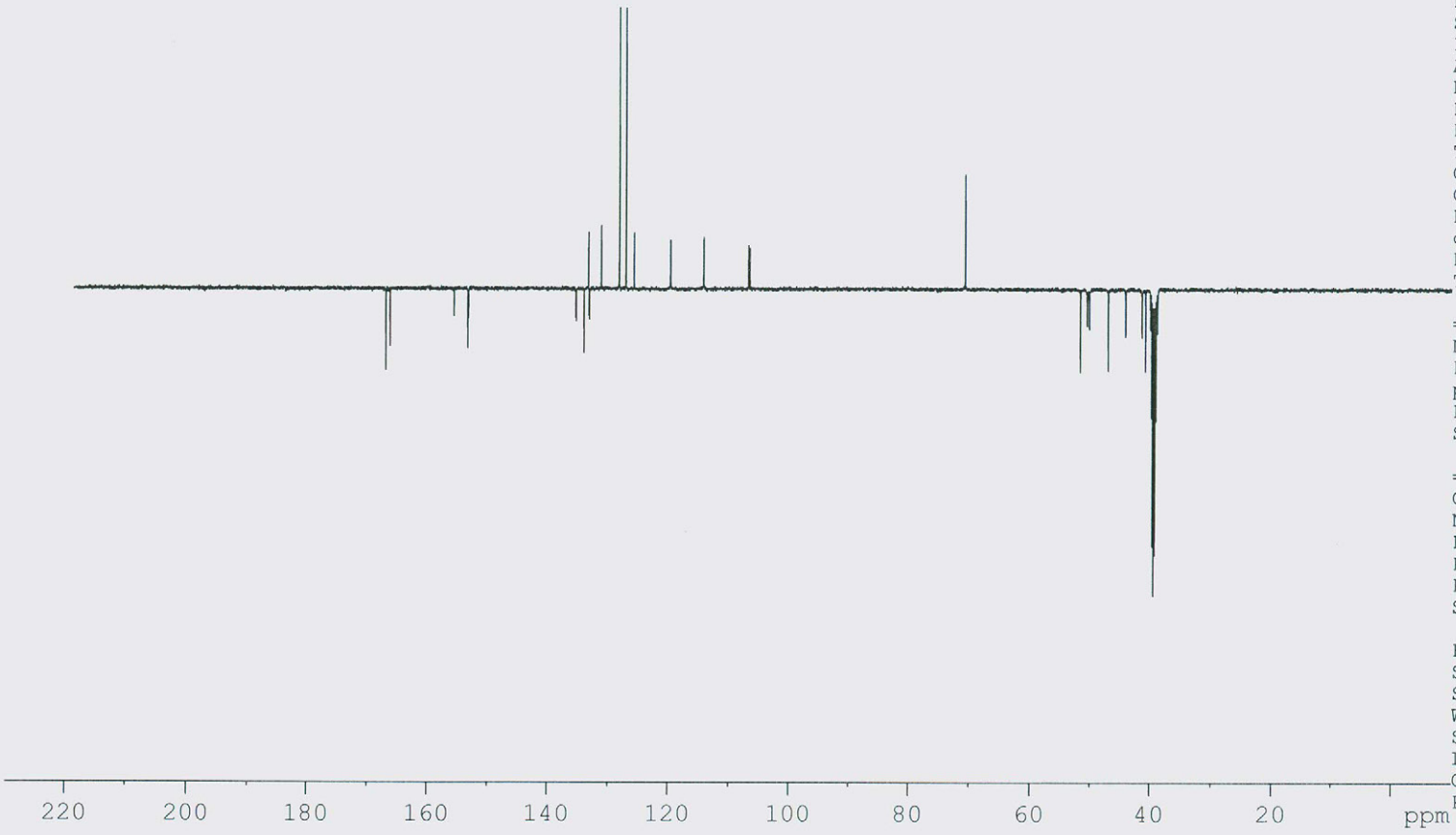
F2 - Processing parameters

SI	32768
SF	100.6128411 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

13C APT spectra Dr.Phillips 807 in DMSO (PH 166)







BRUKER

Current Data Parameters

NAME	807-1H
EXPNO	5
PROCNO	1

F2 - Acquisition Parameters

Date_	20110126
Time	4.14
INSTRUM	spect
PROBHD	5 mm DUL 13C-1
PULPROG	jmod
TD	65536
SOLVENT	DMSO
NS	2048
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	16384
DW	20.850 usec
DE	6.00 usec
TE	673.2 K
CNST2	145.0000000
CNST11	1.0000000
D1	2.00000000 sec
d20	0.00689655 sec
DELTA	0.00000917 sec
TD0	1

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

NUC1	13C
P1	7.20 usec
p2	14.40 usec
PL1	-6.00 dB
SFO1	100.6228298 MHz

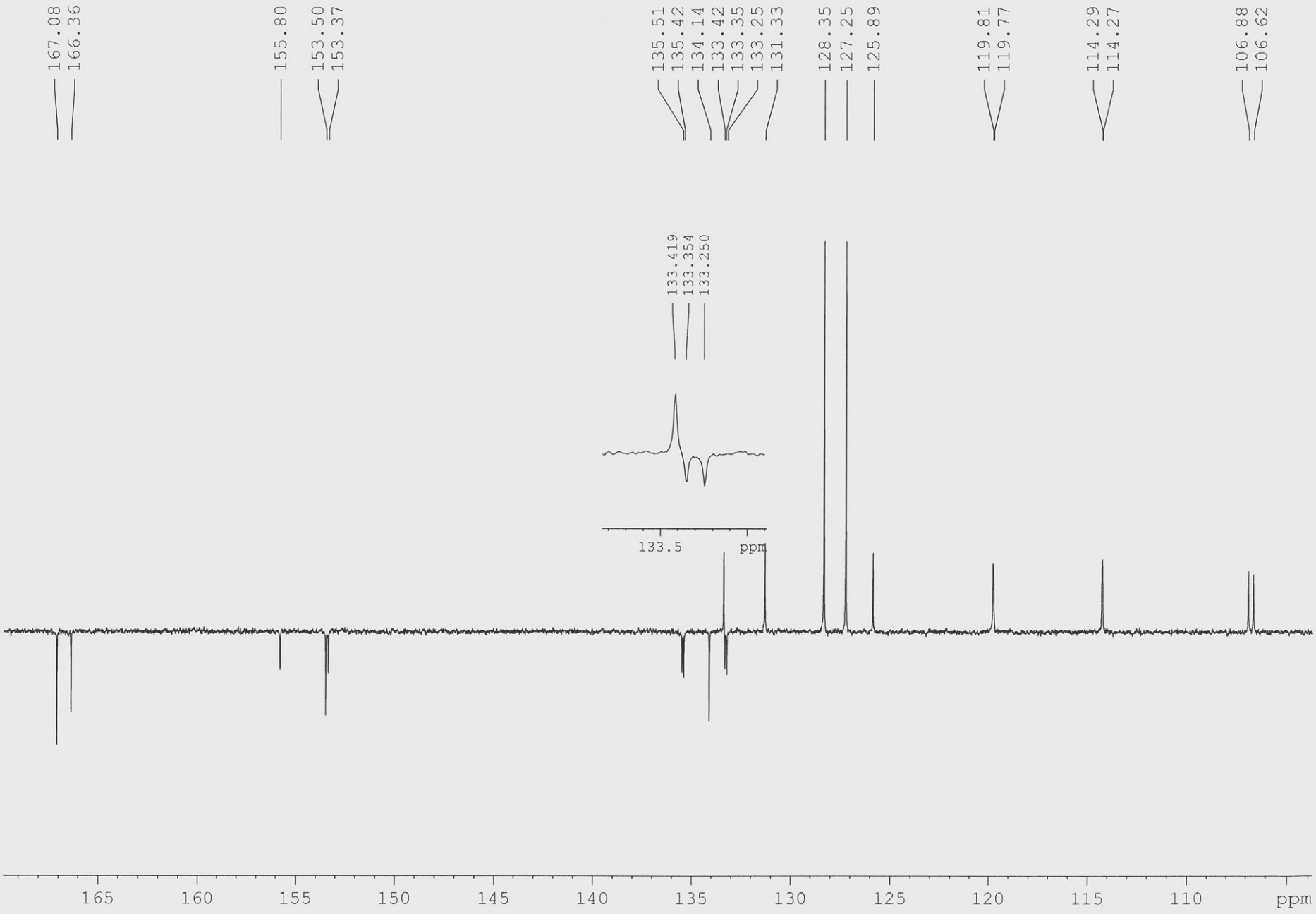
======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	15.06 dB
SFO2	400.1316005 MHz

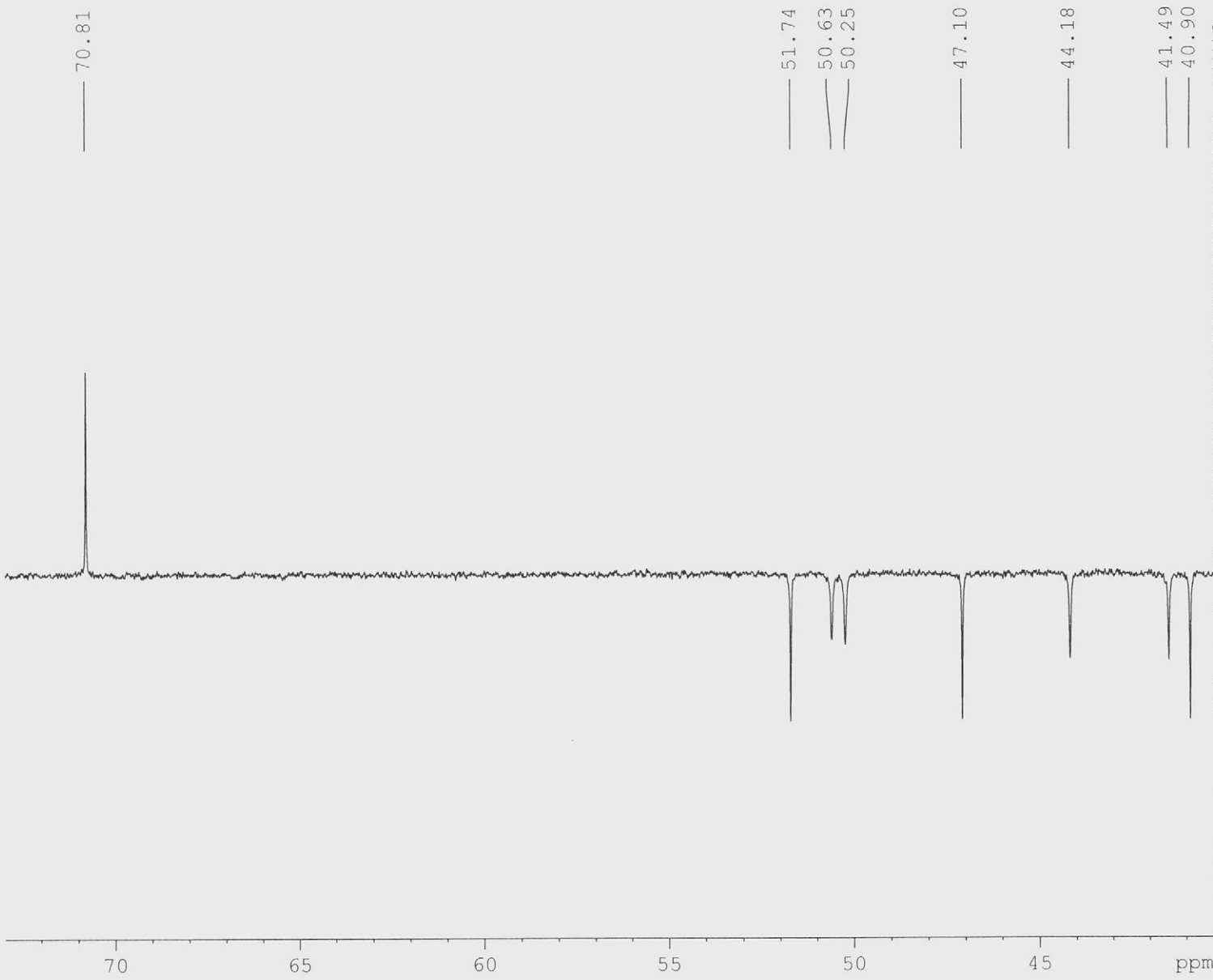
F2 - Processing parameters

SI	32768
SF	100.6128152 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

13C APT spectra Dr.Phillips 807 in DMSO



13C APT spectra Dr.Phillips 807 in DMSO



Current Data Parameters
NAME 807-1H
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110126
Time 4.14
INSTRUM spect
PROBHD 5 mm DUL 13C-1
PULPROG jmod
TD 65536
SOLVENT DMSO
NS 2048
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 16384
DW 20.850 usec
DE 6.00 usec
TE 673.2 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
d20 0.00689655 sec
DELTA 0.00000917 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 7.20 usec
p2 14.40 usec
PL1 -6.00 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 15.06 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6128152 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

Highlights

- We synthesized N-substitutedglycinyl 1*H*-1,2,3-triazolyl oxazolidinones.
- Compounds demonstrated moderate to strong Gram-positive antibacterial activities.
- Compounds **6u** and **6v** showed excellent Gram-positive antibacterial activity.
- Compounds **6m** and **6n** showed remarkable antibacterial activity against *M. catarrhalis*.
- Compounds **6m**, **6n**, **6u** and **6v** demonstrated superior antibacterial activities compared to linezolid.