Supporting Information

Discovery of Proline Sulfonamides as Potent and Selective Hepatitis C Virus NS5b Polymerase Inhibitors. Evidence for a New NS5b Polymerase Binding Site.

Ariamala Gopalsamy, Rajiv Chopra, Kitae Lim, Gregory Ciszewski, Mengxiao Shi, Kevin J. Curran, Steven F. Sukits, Kristine Svenson, Joel Bard, John W. Ellingboe, Atul Agarwal, Girija Krishnamurthy, Anita Y.M. Howe[†], Mark Orlowski[†], Boris Feld[†] John O'Connell[†] and Tarek S. Mansour

Chemical and Screening Sciences and [†]Infectious Diseases,Wyeth Research, Pearl River, New York 10965, USA

General Experimental Details

NMR spectra were recorded on Bruker AM-400 (400 MHz). NMR data are reported in parts per million (d) and are referenced to the deuterium lock signal from the sample solvent. EI mass spectra were obtained on an Agilant SL MSD. LCMS were run on an Agilant 1100 LCMS system. RP preparative HPLC was carried out on Gilson semi-prep HPLC system consisting of a 215 autosampler, 322 solvent pump, 307 make-up pump and 155 UV/VIS detector. Chiral analyses were run on either an Agilant 1100 HPLC or a Berger SFC system. Melting points were measured on Buchi B-545. HRMS was carried out on a Bruker APEX II 9.4 T mass spectrometer.

NS5B RdRp Assay. The RdRp assay was performed in a final volume of 50 µl per reaction. Twenty microliters of the NS5B enzyme mix containing 24 nM of NS5B, 20 mM HEPES (pH 7.5), 5 mM $MgCl_2$, 1 mM DTT, 0.05 mg/ml BSA, 0.5 µM UTP, 1 µM ATP, 0.08 µM CTP and 0.025 µM GTP was incubated in the presence of 10 µl of compounds dissolved in DMSO for 15 min at room temperature. Concentrations of RNA and NTPs were kept at apparent K_m levels. The final concentration of DMSO present in the reaction was 3%. The reaction was initiated by adding 3 nM of pOF transcribed RNA substrate, 0.4 U/µl of RNasin and 0.125 µCi of [α–^{33}P]GTP and incubated at room temperature for 2 h. The reaction was terminated by the addition of 50 µl of 150 mM EDTA and products containing incorporated radioactive nucleotides were collected by filtering through the Millipore Multiscreen plates and washing three times with 200 µl of 0.5 M sodium phosphate buffer (pH 7.0) using a Millipore Manifold. The filters containing the reaction products were allowed to dry at room temperature and counted in a Wallac MicroBeta after an addition of 50 µl of Optiphase^{TM} scintillant.

(S)-1-(2-amino-4-chloro-5-methylphenylsulfonyl)pyrrolidine-2-carboxylic acid (6).

Method A: Solid phase synthesis

4-Chloro-2-(9H-fluoren-9-ylmethoxycarbonylamino)-5-methyl-benzenesulfonic acid (13).

To a solution of 2-amino-4-chloro-5-methyl-benzenesulfonic acid **12** (3.3 g; 15.13 mmol) in water (40 mL) and sodium bicarbonate (2.8 g) was added a solution of 9-fluorenylmethoxycarbonyl chloride (4.3 g; 16.7 mmol) in dioxane (40 mL) at 0 ^{o}C. The reaction mixture was stirred overnight and the volatiles were removed under reduced pressure. The aqueous layer was acidified with 2 N HCl and extracted with ethyl acetate, dried and concentrated. The residue was purified by flash column on silica gel (10% MeOH in EtOAc) to give **13** as a white solid (89%). ^{1}H NMR (DMSO-d_6) δ 9.9 (s, 1H), 8.0 (s, 1H), 7.9 (d, *J* = 7.6 Hz, 2H), 7.7 (d, *J* = 7.6 Hz, 2H), 7.6 (s, 1H), 7.4 (t, J = 7.6 Hz, 2H), 7.3 (t, J = 7.6 Hz, 2H), 4.4 (d, *J* = 6.8 Hz, 2H), 4.0(t, *J* = 6.8 Hz 1H), 2.3 (s, 3H).

(5-Chloro-2-chlorosulfonyl-4-methyl-phenyl)-carbamic acid 9H-fluoren-9-ylmethyl ester (10).

Sulfonic acid **13** (3.0 g; 6.7 mmol) was dissolved in 3 mL of DMF and 2.5 mL of thionyl chloride was added dropwise at room temperature. The resulting solution was stirred at room temperature for additional 4 h and quenched with ice and water to give **10** as white solid which was filtered, dried and used without further purification.

Synthesis of (8):
Wang Resin (Ana Spec 100-200 mesh, 1% crosslinked; loading: 1.1 mmol/g; 5 g, 5.5 mmol) was swollen in anhydrous DMF (20 ml). A solution of N-fmoc-L-proline **7** (7.4 g, 22 mmol), HOBT (3.37 g, 22 mmol), DMAP (268.8 mg, 2.2 mmol) and DIC (3.4 ml, 22 mmol) in anhydrous DMF (30 ml) was added to the resin. The mixture was shaken at room temperature on an orbital shaker overnight. The mixture was filtered and the resin was washed with DMF (3 x 50 ml), MeOH (3 x 50ml), CH_2Cl_2 (3 x 50ml), and dried.

Synthesis of (9):
The resin **8** (5.5 mmol), prepared as described above, was treated with a solution of 20% piperidine in DMF (2 x 50 ml, 10 min for the first time and 30 min for the second time) to remove the Fmoc protecting group from the resin. The mixture was filtered and the resin was washed with DMF (3 x 50 ml), MeOH (3 x 50ml), and CH_2Cl_2 (3 x 50ml).

Synthesis of (11):
To resin **9** (5.5 mmol) was added a solution of (5-Chloro-2-chlorosulfonyl-4-methyl-phenyl)-carbamic acid 9H-fluoren-9-ylmethyl ester **10** (5.1 g, 11 mmol) in 1:1 anhydrous CH_2Cl_2 and pyridine (50 ml). After shaking at room temperature overnight, the mixture was filtered, washed with MeOH (3 x 50ml) and CH_2Cl_2 (5 x 50ml).

Synthesis of (S)-1-(2-amino-4-chloro-5-methylphenylsulfonyl)pyrrolidine-2-carboxylic acid (6):
The resin **11** (5.5 mmol) was reacted with a solution of 20% piperidine in DMF (2 x 50 ml, 10 min for the first time and 30 min for the second time). The mixture was filtered and the resin was washed with DMF (3 x 50 ml), MeOH (3 x 50ml), CH_2Cl_2 (3 x 50ml), and dried. The dry resin was treated with 1:1 TFA:CH_2Cl_2 (50ml) and was shaken at room temperature for 4 h. The mixture was filtered and the resin was washed with CH_2Cl_2 (3 x 10ml). The combined CH_2Cl_2 was concentrated and purified by HPLC to give **6**. ^{1}H NMR (DMSO-d_6) δ 7.5 (s, 1H), 6.9 (s, 1H), 6.2 (s, 2H), 4.3 (dd, J_1 = 8.6 Hz, J_2 = 4.6 Hz 1H), 3.2 (t, J =6.8 Hz, 2H), 2.2 (s, 3H), 2.1 (m, 1H), 1.9 (m, 1H), 1.65-1.8 (m, 2H).

Method B: Solution phase synthesis

2-Amino-4-chloro-5-methylbenzenesulfonyl chloride (15) (R = 2-NH_2, 4-Cl, 5-CH_3): To a solution of 2-Amino-4-chloro-5-methylbenzenesulfonic acid (3.0 g; 1.35 mmol) in dichloromethane (10 mL) was added sulfuryl chloride (4.4 mL; 3.83 mmol) and stirred at 60 ^{o}C. After one hour, thionyl chloride (1.3 mL) was added and the mixture was further stirred for 7 h at 100 ^{o}C. The mixture was poured into ice water and extracted with ether three times. The organic layer was washed with water and then brine and dried over

sodium sulfate and concentrated under reduced pressure to give 2.2 g of **15**. ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 1H), 6.68 (s, 1H), 2.35 (s, 3H).

(S)-methyl 1-(2-amino-4-chloro-5-methylphenylsulfonyl)pyrrolidine-2-carboxylate (16) (R = 2-NH_2, 4-Cl, 5-CH_3):
To a solution of L-proline methyl ester hydrochloride **14** (0.8 g; 5 mmol) in pyridine (100 mL) was added 2-Amino-4-chloro-5-methylbenzenesulfonyl chloride **15** (1.32 g; 5.5 mmol) at 0 ^{o}C. The reaction mixture was warmed to room temperature and stirred for additional 4 h. The mixture was concentrated and purified by flash chromatography on silica gel (25% ethyl acetate in hexane) to yield **16** (1.2g; 75%).

(S)-1-(2-amino-4-chloro-5-methylphenylsulfonyl)pyrrolidine-2-carboxylic acid (6):
The ester **16** was taken up in ethanol (15 mL) and 1 N sodium hydroxide was added and stirred overnight. The reaction mixture was then concentrated, diluted with water and extracted with ethyl acetate. The aqueous layer was acidified with 2N HCl to yield the desired compound **6** as white solid (1.0g; 88%). mp 168-170 °C; ^{1}H NMR (DMSO-d_6) δ 7.5 (s, 1H), 6.9 (s, 1H), 6.2 (s, 2H), 4.3 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz 1H), 3.2 (t, J =6.8 Hz, 2H), 2.2 (s, 3H), 2.1 (m, 1H), 1.9 (m, 1H), 1.65-1.8 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 173.44, 146.26, 139.12, 131.26, 121.57, 116.56, 59.21, 48.13, 30.38, 42.40, 18.17. HRMS: calcd for $C_{12}H_{15}ClN_2O_4S$, 319.05138; found (ESI-FTMS, [M+H]), 319.05198.

(S)-1-(2-aminophenylsulfonyl)pyrrolidine-2-carboxylic acid (17).
Compound was prepared as described for **6** (Method B) using 2-aminobenzenesulfonyl chloride. ^{1}H NMR (DMSO-d_6) δ 7.5 (dd, Jo = 8.0 Hz, Jm = 1.2 Hz, 1H), 7.3 (t, J = 8.0Hz , 1H), 6.9 (Jo = 8.0 Hz, Jm = 1.2 Hz, 1H), 6.6 (t, J = 8.0 Hz, 1H), 6.2 (br, 2H), 4.3 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz 1H), 3.2 (t, J = 7.0 Hz, 2H), 2.1 (m, 1H), 1.9 (m, 1H), 1.65-1.8 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 174.08, 147.81, 134.59, 129.96, 117.66, 117.58, 115.35, 59.75, 53.14, 30.91, 24.90. HRMS: calcd for $C_{12}H_{15}ClN_2O_4S$, 319.05138; found (ESI-FTMS, [M+H]), 319.05198.

(S)-1-(2-amino-5-chloro-4-methylphenylsulfonyl)pyrrolidine-2-carboxylic acid (18).
Prepared as described for compound **6** using Method A. ^{1}H NMR (DMSO-d_6) δ 7.4 (s, 1H), 6.8 (s, 1H), 6.3 (br, 2H), 4.2 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz 1H), 3.1 (t, J = 7.0 Hz, 2H), 2.5 (s, 3H), 2.1 (m, 1H), 1.9 (m, 1H), 1.65-1.8 (m, 2H). HRMS: calcd for $C_{12}H_{15}ClN_2O_4S$, 319.05139; found (ESI-FTMS, [M+H]), 319.05179.

(S)-1-(2-acetamido-5-chloro-4-methylphenylsulfonyl)pyrrolidine-2-carboxylic acid (19).
The compound was prepared as described above for compound **6** (Method A), but the resin **11** was deprotected with piperidine and treated with acetyl chloride in 1:1 anhydrous CH_2Cl_2 and pyridine(10 ml). After shaking at room temperature overnight, the mixture was filtered, washed with MeOH (3 x 50ml) and CH_2Cl_2 (5 x 50ml). The dried resin was subjected to cleavage.

(S)-1-(2-benzamido-5-chloro-4-methylphenylsulfonyl)pyrrolidine-2-carboxylic acid (20).
The compound was prepared as described above for compound **19**, but acetyl chloride was replaced with benzoyl chloride in 1:1 anhydrous CH_2Cl_2 and pyridine(10 ml). After shaking at room temperature overnight, the mixture was filtered, washed with MeOH (3 x 50ml) and CH_2Cl_2 (5 x 50ml). The dried resin was subjected to cleavage as described for compound **6**. ^{1}H NMR (DMSO-d6) δ 8.1(d, J =8.0 Hz, 1H), 7.9 (d, J = 8.0 Hz 1H), 7.9 (s, 1H), 7.8 (t, J = 8.0 Hz, 1H), 7.58(m, 2H), 7.43 (t, J = 8.0 Hz, 1H), 4.2 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz 1H), 3.3 (m, 2H), 2.5 (s, 3H), 2.1 (m, 1H), 1.9 (m, 1H), 1.7 (m, 2H). HRMS: calcd for $C_{19}H_{19}ClN_2O_5S$, 423.07760; found (ESI-FTMS, [M+H]), 423.07785

(S)-1-(3,5-dichloro-2-hydroxyphenylsulfonyl)pyrrolidine-2-carboxylic acid (21).
The compound was synthesized as described for **6** using Method B and using 3, 5 dichloro-2-hydroxybenzene sulfonyl chloride yield: 89%. mp 107.4 °C; ^{1}H NMR ($CDCl_3$) δ 7.6 (d, 1H), 7.5 (d, 1H), 4.5 (dd, 1H), 3.4(m, 2H), 2.3 (m, 2H), 2.0 (m, 2H); MS (ESI) m/z 337.82; HRMS: calcd for $C_{11}H_{11}C_{12}NO_5S$, 337.96622; found (ESI-, [M-H]), 337.96619;

(S)-1-(3,5-dichlorophenylsulfonyl)pyrrolidine-2-carboxylic acid (22).
The compound was prepared as described above for compound **21** using 3,5-dichlorobenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ 7.95 (s, 2H), 7.90 (s, 1H), 4.5 (dd, J_1 = 7.8 Hz, J_2 = 3.0 Hz 1H), 3.3 (m, 1H), 3.2 (m, 1H), 1.86-1.70 (m, 3H). 1.60 (m,1H); HRMS: calcd for $C_{11}H_{11}C_{12}NO_4S$, 323.98586; found (ESI-, [M-H]), 323.98597

(S)-1-(3-chloro-5-fluoro-2-hydroxyphenylsulfonyl)pyrrolidine-2-carboxylic acid (23).
The compound was prepared as described above for compound **21** using 3-chloro,5-fluoro-2-hydroxybenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ 7.7 (s, 1H), 7.4 (s, 1H), 4.5 (dd, J_1 = 8.4 Hz, J_2 = 3.6 Hz, 1H), 3.3 (m, 1H), 3.2 (m, 1H), 2.2 (m, 1H). 1.9 (m, 1H), 1.8 (m, 2H); HRMS: calcd for $C_{11}H_{11}ClFNO_5S$, 324.01032; found (ESI-FTMS, [M+H]), 324.01065.

(S)-1-(3-bromo-5-chloro-2-hydroxyphenylsulfonyl)pyrrolidine-2-carboxylic acid (24).
The compound was prepared as described above for compound **21** using 3-bromo,5-chloro-2-hydroxybenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ 7.9 (s, 1H), 7.6 (s, 1H), 4.5 (dd, J_1 = 8.8 Hz, J_2 = 4.0 Hz, 1H), 3.3 (m, 1H), 3.2 (m, 1H), 2.2 (m, 1H). 1.9 (m, 1H), 1.8 (m, 2H); HRMS: calcd for $C_{11}H_{11}BrClNO_5S$, 383.93026; found (ESI-FTMS, [M+H]), 383.9306.

(S)-1-(3,4,5-trichloro-2-hydroxyphenylsulfonyl)pyrrolidine-2-carboxylic acid (25).
The compound was prepared as described above for compound **21** using 3,4,5-trichloro-2-hydroxybenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ7.7 (s, 1H), 4.5 (dd, J_1 = 8.8 Hz, J_2 = 4.0 Hz, 1H), 3.3 (m, 1H), 3.2 (m, 1H), 2.2 (m, 1H). 1.9 (m, 1H), 1.8 (m, 2H); HRMS: calcd for $C_{11}H_{10}Cl_3NO_5S$, 373.94180; found (ESI-FTMS, [M+H]), 373.94216.

(R)-1-(3,5-dichloro-2-hydroxyphenylsulfonyl)pyrrolidine-2-carboxylic acid (26).
The compound was prepared as described above for compound **21** using D-Proline methyl ester and 3,5-dichloro-2-hydroxybenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ7.8 (s, 1H), 7.6 (s, 1H), 4.5 (dd, J_1 = 8.8 Hz, J_2 = 4.0 Hz, 1H), 3.3 (m, 1H), 3.2 (m, 1H), 2.2 (m, 1H). 1.9 (m, 1H), 1.8 (m, 2H); HRMS: calcd for $C_{11}H_{11}Cl_2NO_5S$, 339.98078; found (ESI-, [M-H]), 339.98082

(S)-methyl 1-(3,5-dichloro-2-hydroxyphenylsulfonyl)pyrrolidine-2-carboxylate (27).
The compound was prepared as described above for compound **21** using 3,5-dichloro-2-hydroxybenzene sulfonyl chloride, but the last step of ester hydrolysis was avoided. ^{1}H NMR (DMSO-d6) δ7.85 (s, 1H), 7.6 (s, 1H), 4.6 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H), 3.6 (s, 3H), 3.4 (m, 1H), 3.2 (m, 1H), 2.2 (m, 1H). 1.8 (m, 3H); HRMS: calcd for $C_{12}H_{13}Cl_2NO_5S$, 353.99643; found (ESI-, [M-H]), 353.99656

(2S)-1-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]pyrrolidine-2-carbonitrile (28).
A mixture of (2S)-pyrolidine-2-carbonitrile hydrochloride (34mg, 0.2 mmol) and 3,5-dichloro-2-hydroxy-benzenesulfonyl chloride (57mg, 0.22mmol) in 2 mL of CH_2Cl_2/pyridine (1:1) was stirred at room temperature for 16 hours. . Then the reaction mixture was concentrated and purified by reverse phase chromatography to give (2S)-1-(3,5-Dichloro-2-hydroxy-benzenesulfonyl)-pyrrolidine-2-carbonitrile (37mg, 58% yield). ^{1}H NMR (DMSO-d6) δ 7.86 (d, J=2.8 Hz, 1H), 7.63 (d, J=2.8 Hz, 1H), 5.08 (br., 1H), 3.44(m, 1H), 3.18 (m, 1H), 2.54(m, 1H), 2.17 (m, 2H), 1.93 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 156.00, 133.49, 129.28, 126.08, 125.8, 120.72,53.93, 49.55, 31.40, 25.14. HRMS: calcd for $C_{11}H_{10}Cl_2N_2O_3S$, 320.9862; found (ESI-, [M-H]), 320.98639.

2,4-dichloro-6-{[(2S)-2-(2H-tetrazol-5-yl)pyrrolidin-1-yl]sulfonyl}phenol (29).
A mixture of (2S)-1-[(3,5-dichloro-2-hydroxyphenyl) sulfonyl] pyrrolidine-2-carbonitrile (37mg, 0.12mmol), sodium azide (24mg, 0.36mmol) and triethylamine hydrochloride (25mg, 0.18 mmol) in 1.5 mL of DMF was stirred at 120 ^{o}C for 6 hours. Then the reaction was cooled to room temperature and acidified by adding 2mL of 1N HCl and concentrated. 2,4-dichloro-6- {[(2S)-2-(2H-tetrazol-5-yl) pyrrolidin-1-yl] sulfonyl} phenol (31mg, 71% yield) was obtained after reverse phase chromatography. ^{1}H NMR (DMSO-d6) δ 7.89 (d, J=3.5 Hz, 1H), 7.60 (d, J=3.5 Hz, 1H), 5.46 (dd, J_1 = 8.4 Hz, J_2 = 3.2 Hz, 1H), 3.56 (m, 1H), 3.33 (m, 1H), 2.30(m, 1H), 1.96 (m, 3H). HRMS: calcd for $C_{11}H_{11}Cl_2N_5O_3S$, 364.00325; found (ESI-, [M-H]), 364.00349.

2,4-dichloro-6-(pyrrolidin-1-ylsulfonyl)phenol (30).
A mixture of (pyrrolidine (21mg, 0.3 mmol) and 3,5-Dichloro-2-hydroxy-benzenesulfonyl chloride (52mg, 0.2mmol) in 2 mL of CH_2Cl_2/pyridine (1:1) was stirred at 40 ^{o}C for 16 hours. Then the reaction mixture was concentrated and purified by reverse phase chromatography to give 2,4-dichloro-6- (pyrrolidin-1-ylsulfonyl) phenol (34mg, 57% yield). ^{1}H NMR ($CDCl_3$) δ 9.29 (br., 1H), 7.57 (d, J=5 Hz, 1H), 7.53 (d, J=5 Hz, 1H), 3.32 (m, 4H), 1.88 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 151.1, 133.19, 128.73, 128.12, 124.25, 121.3, 47.61, 25.09. HRMS: calcd for $C_{10}H_{11}Cl_2NO_3S$, 295.99095; found (ESI-, [M-H]), 295.99111.

(2S)-1-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]piperidine-2-carboxylic acid (31).
The compound was prepared as described above for compound **21** using (S)-piperidine-2-carboxylic acid methyl ester and 3,5-dichloro-2-hydroxybenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ7.7 (s, 1H), 7.58 (s, 1H), 4.6 (m, 1H), 3.6 (m, 1H), 3.1 (m, 1H). 2.1 (m, 1H). 1.6 (m, 3H), 1.3(m, 2H); HRMS: calcd for $C_{12}H_{13}Cl_2NO_5S$, 353.99643; found (ESI-, [M-H]), 353.99682

(2R)-1-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]piperidine-2-carboxylic acid (32).
The compound was prepared as described above for compound **21** using (R)-piperidine-2-carboxylic acid methyl ester and 3,5-dichloro-2-hydroxybenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ7.7 (s, 1H), 7.56 (s, 1H), 4.6 (m, 1H), 3.6 (m, 1H), 3.1 (m, 1H). 2.1 (m, 1H). 1.6 (m, 3H), 1.3 (m, 2H); HRMS: calcd for $C_{12}H_{13}Cl_2NO_5S$, 353.99643; found (ESI-, [M-H]), 353.99661.

(4S)-3-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]-1,3-thiazolidine-4-carboxylic acid (33).
The compound was prepared as described above for compound **21** using (S)-thiazolidine-4-carboxylic acid methyl ester and 3,5-dichloro-2-hydroxybenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ7.8 (s, 1H), 7.6 (s, 1H), 5.0 (t, J =5.4 Hz, 1H), 4.58 (d, J= 9.2 Hz, 1H), 4.25 (d, J = 9.2 Hz, 1H), 3.22(d, J = 5.4 Hz, 2H); HRMS: calcd for $C_{10}H_9Cl_2NO_5S_2$, 357.9372; found (ESI-, [M-H]), 357.93735

(4R)-3-[(3,5-dichloro-2-hydroxyphenyl)sulfonyl]-1,3-thiazolidine-4-carboxylic acid (34).
The compound was prepared as described above for compound **21** using (R)-thiazolidine-4-carboxylic acid methyl ester and 3,5-dichloro-2-hydroxybenzene sulfonyl chloride. ^{1}H NMR (DMSO-d6) δ7.8 (s, 1H), 7.6 (s, 1H), 5.0 (t, J =5.4 Hz, 1H), 4.58 (d, J= 9.2 Hz, 1H), 4.25 (d, J = 9.2 Hz, 1H), 3.22(d, J = 5.4 Hz, 2H); HRMS: calcd for $C_{10}H_9Cl_2NO_5S_2$, 357.9372; found (ESI-, [M-H]), 357.9374.

Compounds Characterization:

Compd	Formula	HRMS adduct	Found	Calcd	Error (mAmu)
1	$C_{12}H_{15}ClN_2O_4S$	M+H	319.05138	319.05198	0.59
17	$C_{12}H_{15}ClN_2O_4S$	M+H	271.07486	271.07471	0.15
18	$C_{12}H_{15}ClN_2O_4S$	M+H	319.05179	319.05139	0.4
20	$C_{19}H_{19}ClN_2O_5S$	M+H	423.07785	423.0776	0.25
21	$C_{11}H_{11}C_{12}NO_5S$	M-H	337.96622	337.96619	0.3
22	$C_{11}H_{11}C_{12}NO_4S$	M-H	323.98597	323.98586	0.11
23	$C_{11}H_{11}ClFNO_5S$	M+H	324.01065	324.01033	0.32
24	$C_{11}H_{11}BrClNO_5S$	M+H	383.9306	383.93026	0.34
25	$C_{11}H_{10}Cl_3NO_5S$	M+H	373.94216	373.94181	0.35
26	$C_{11}H_{11}Cl_2NO_5S$	M-H	339.98082	339.98078	0.04
27	$C_{12}H_{13}Cl_2NO_5S$	M-H	353.99656	353.99643	0.13
28	$C_{11}H_{10}Cl_2N_2O_3S$	M-H	320.98639	320.9862	0.19
29	$C_{11}H_{11}Cl_2N_5O_3S$	M-H	364.00349	364.00325	0.24
30	$C_{10}H_{11}Cl_2NO_3S$	M-H	295.99111	295.99095	0.16
31	$C_{12}H_{13}Cl_2NO_5S$	M-H	353.99682	353.99643	0.39

32	$C_{12}H_{13}Cl_2NO_5S$	M-H	353.99661	353.99643	0.18
33	$C_{10}H_9Cl_2NO_5S_2$	M-H	357.93735	357.9372	0.15
34	$C_{10}H_9Cl_2NO_5S_2$	M-H	357.9374	357.9372	0.2