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Design, synthesis and docking studies of C_2-symmetric 1,4-bis sulphonamido diamino 2, 3- diolderivatives and hydrogen bond interactions with hydrolase

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ABSTRACT

The syntheses of new C_2Symmetric N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-(2-chloro-3-(trifluoromethyl) benzyl) benzenesulfonamide) from N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-(2-chloro-3 (trifluorom ethyl)benz yl)benzenesulfonamide)derivatives aredescribedC_2 Symmetric N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-(2-chloro-3 (trifluo romethyl)benzyl)benzene sulfonamide) derivatives fromN,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl) bis (meth ylene)bis(benzenesulfonamide) derivatives are described. C2-symmetrical diamines were prepared via direct ((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine sinthesized by using(4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide this is followed from the (4S,5S)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate molecule. For C2-symmetrical compounds, for the above targeted molecule reaction used to form the key intermediate, is a corboxamide from corboxilate. Some of the new chiral compounds, produced in good to high yields, potentially useful as asymmetric sterio chemical chemotherapeutic HIV agents. Thus, a bisulphonamido diamino 1, 3- dioxolane derivatives, used in substoichiometric amounts, was found to their broad spectrum of antibacterial activity. A series of novel sulfonamide derivatives were screened in hydrogen bond interactions with hydrolase. The results showed that the derivatives exhibited moderate hydrogen bond interactions against human hydrolase activity. The structure—activity relationships were also briefly discussed.

Keywords: Corboxamide, sulphonamids, HIV agents, chemotherapautic, hydrolase, hydrogen bond.

INTRODUCTION

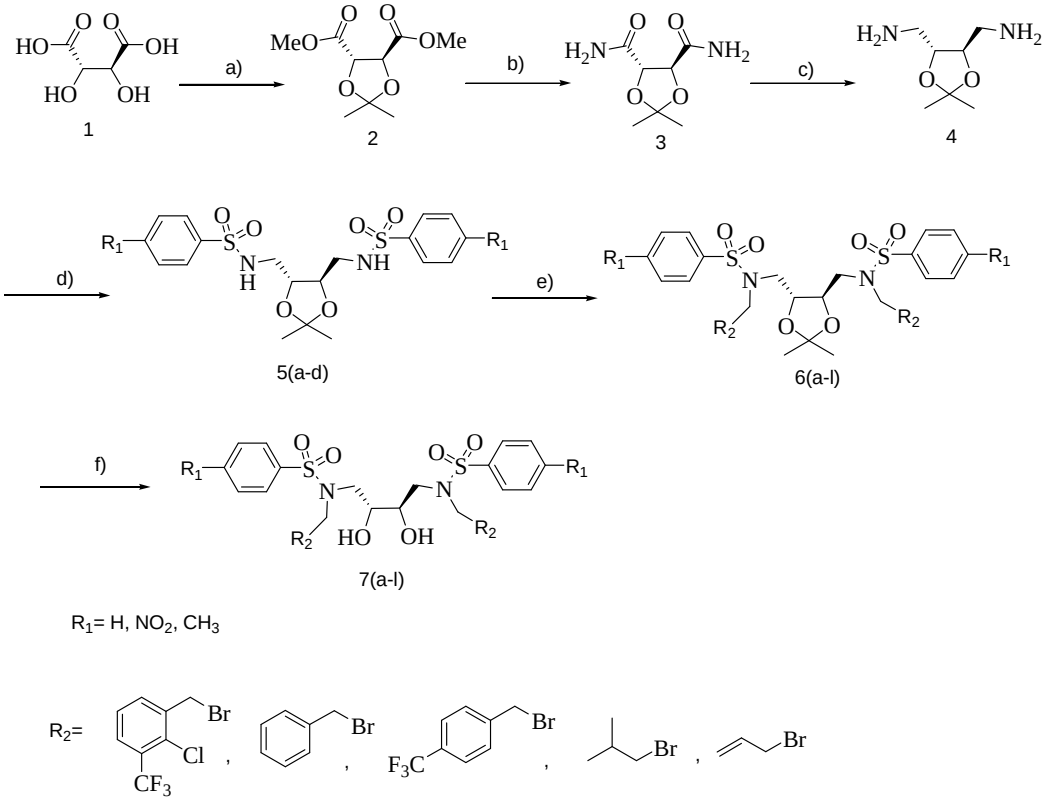
Chiral sulphonamides are important organic compounds. The oxalane ,amine functionality is present in many natural products and due to its interesting physiological activity it is an extremely important pharmacophore in many biologically active compounds [1]. Chiral amines chelated to metals are also used in medicines (e.g. cisplatin), they are used as chiral auxiliaries in stereoselective synthesis and as asymmetric synthesis [2]. We are interested in using inexpensive and readily demand for novel chemotherapeutic antibacterial remains attractive in the field of medicinal chemistry. The discovery of sulfonamides as antibacterial in the early 30s was the beginning of the most fascinating era of chemotherapeutic agents [1-4]. Since the introduction of prontosil over 70 years ago, sulfa drugs have been widely used to treat a broad spectrum of microbial diseases [5]. However, due to the rapid emergence of sulfonamide resistance organisms and the development of more potent drugs have limited their clinical use. The sulphonamide group is considered as a pharmacophore which is present in a number of biologically active molecules, particularly in antimicrobial agents [6-10]. In addition, numerous sulphonamide derivatives have been reported as carbonic anhydrase inhibitors [11-15], anticancer [16], and anti-inflammatory agents [17]. Some organisms are resistant to all approved antibiotics and can only be treated with experimental and potentially toxic drugs. Therefore, there is an overwhelming need to develop more effective antibacterial agents to treat infections caused by antibiotic resistant bacterial pathogens. Sulfonamides exert their effect by targeting on dihydropteroate

synthase (DHPS) enzyme, which catalyzes folic acid pathway in bacteria and some eukaryotic cells [18] but is not present in human cells [19]. This is basis for the selective effect of sulfonamides on bacteria and for their broad spectrum of antibacterial activity. Since sulfanilamide first came into use, different derivatives have appeared on the market. Chemically modified sulfanilamide is prepared to achieve more effective antibacterial activity, wider spectrum of microorganisms affected, or more prolonged action. Because of their low cost they are still used in many parts of the world. The substances are still used to treat some urinary tract infections, leprosy, and in combination with other drugs, fungal diseases such as toxoplasmosis. The pharmaceutical industry has responded with new classes of drugs, thus a great insight to search for potential pharmacologically active sulfanilamide and its derivatives is still of interesting. This study deals with the synthesis of N-substituted sulphonamide derivatives. The structure was established and confirmed using elemental analysis and spectral data e.g. IR, 1 H NMR, 13C NMR and MS spectra. Docking studies of the synthesized compounds has been investigated.

The demand for novel chemotherapeutic antibacterial remains attractive in the field of medicinal chemistry.

The discovery of sulfonamides as antibacterial in the early 30s was the beginning of the most fascinating era of chemotherapeutic agents [1-4]. Since the introduction of prontosil over 70 years ago, sulfa drugs have been widely used to treat a broad spectrum of microbial diseases [5]. However, due to the rapid emergence of sulphonamide resistance organisms and the development of more potent drugs have limited their clinical use. The sulfonamide group is considered as a pharmacophore which is present in a number of biologically active molecules, particularly in antimicrobial agents [6-10]. In addition, numerous sulfonamide derivatives have been reported as carbonic anhydrase inhibitors [11-15], anti- cancer [16], and anti-inflammatory agents [17]. Some organisms are resistant to all approved antibiotics and can only be treated with experimental and potentially toxic drugs. Therefore, there is an overwhelming need to develop more effective antibacterial agents to treat infections caused by antibiotic resistant bacterial pathogens. Sulfonamides exert their effect by targeting on dihydropteroate synthase (DHPS) enzyme, which catalyzes folic acid pathway in bacteria and some eukaryotic cells [18] but is not present in human cells [19].

Schemes:



Reagents and Conditions: a)p-TSA, Dimethoxy propane, Methanol, reflux, 14h; b)NH_3, Methanol, RT, 16h; c)$LiAlH_4$,DryTHF, RT,5h; d)substituted sulphonyl chloride,TEA,MDC,RT,2h; e) substituted aryl/alkyl bromide,K_2CO_3,Acetonitrile, reflux,5h; f)TFA, Dioxane – water,50^oC,6h;

MATERIALS AND METHODS

All compound All Melting points were determined using X-6 digital display binocular microscope. Infrared spectra were taken on a nico-let nexus 470 FT-IR spectrometer using smear KBr crystal or KBr plate.1H NMR spectra were recorded on a Bruker Avance (300 MHz) spectrometer. The reaction progress wasmonitored by TLC using cyclohexane and ethylacetate(9:1) mixture as an elutent. Flash column chromatographywas performed using 300 mesh silica gel.

Docking method :Docking was carried out using Genetic Optimization of Ligand Docking (GOLD) software based on genetic algorithm(GA). The compounds were docked to the active site of the HMGcoA reductase. The interaction of these compounds with the active site residues were thoroughly studied using molecular mechanics calculations. The parameters pertain-ing to GA were population size (100), selection pressure(1.1), number of operations (10,000), number of island (1)and niche size (2). Operator parameters for crossover, mutation and migration were set to 100, 100 and 10 respectively. Default cut off values for hydrogen bonds and wondarwals interactions were 3.0 A◦(dH-X) and 6.0 A^o respectively

(4S,5S)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 2:
To a suspension of L-(+)-tartaric acid (20.0 g, 133 mmol) in a mixture of anhydrous Methanol (10 mL) and cyclohexane (15 mL) was added 2,2-dimethoxypropane(38 mL, 306 mmol) followed by catalytic p-TSA (260 mg, 1.33 mmol). The reaction mixture was refluxed for 12 h, allowed to cool to room temperature and then quenched with solid K_2CO_3 (600 mg, 3.99 mmol). The resulting reaction mixture was filtered through celite pad. Solvents were removed and the residue was distilled under reduced pressure to afford (4*S*, 5*S*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate2 as a colorless oil (23.2 g) in 82% yield. b.p. 110-112 ^oC (2 mm).

^{1}H-NMR :(300MHz, $CDCl_3$) δ, ppm:4.76(s, 2H,O-CH), 3.78(s, 6H, O-CH_3), 1.44(s, 6H, C-CH_3).^{13}C- NMR (75 MHz, $CDCl_3$) δ, ppm: 170.1, 113.8, 76.9, 52.7, 26.2.; IR(KBrCm^{-1}):3023(C-H), 2789(C-H), 1725(C=O), 1200(C-O-C), 1089(C-O-C), 966(C-O).; MS (ESI): 219.21 $[M+H]^{+;}$ Anal. Calcd. For $C_9H_{14}O_6$: C, 49.54%; H, 6.47%: Found: C, 49.28%; H, 6.62%.

(4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide 3:
A solution of (4*S*, 5*S*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate2 (21 g, 96.2 mmol)and methanol (50 ml) were cooled to 5 ^0C and methanolic ammonia solution (20%, 70ml) was slowly added. The mixture was slowly warmed to room temperature and stirred continuously for 12h at room temperature. Reaction monitored by TLC, after completion of reaction, the mixture was concentrated in vacuum to give a white solid. This crude product was recrystallized from ethanol to afford (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide 3 aswhite solid(16.3 g)with 90.1% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 7.78(d, 4H,CO-NH_2), 4.8(s, 2H, O-CH), 1.81 (s, 6H, C-CH_3).^{13}C- NMR (75MHz, DMSO-d_6) δ, ppm: 173.9, 112.8, 88.4, 25.8. IR(KBr Cm^{-1}):3360(NH), 1688(C=O), 1598(NH), 1404(C-N), 1260(C-O-C), 1150(C-O-C), 754(C-O). MS (ESI): 211.12 $[M+Na]^+$ Anal. Calcd. For $C_7H_{12}O_4$: C, 44.68%; H, 6.43%; N, 14.89% Found: C, 44.53%; H, 6.49%; N, 14.92%

((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine 4:
A suspension of $LiAlH_4$ (9.0 g, 239 mmol) in anhydrous THF (150ml) was stirred for 30 min, (4*S*, 5*S*)-2, 2-dimethyl-1, 3-dioxolane-4, 5-dicarboxamide 3 in anhydrous THF (20ml)was slowly added at10^oC. After completion of addition the mixture was warmed to room temperature and continuously stirred for 6h. The reaction monitored by TLC after completion of reaction, the mixture was cooled to 0^oC then quenched with water (9 ml), 15%NaOH (9 ml) and water (27 ml). Then solids were filtered and washed with THF. The filtrate dried over sodium sulphate and evaporated on a rotary evaporator to afford ((4*R*, 5*R*)-2, 2-dimethyl-1, 3-dioxolane-4, 5-diyl) dimethanamine 4 as colourless oil 9.6 g, with 75% Yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm 3.77 (m, 2H, O-CH), 2.89 (d.m, 2H, N-CH), 2.82 (m, 2H, N-CH), 1.55(br s, 2H, NH_2), 1.40(s, 6H, C-CH_3).^{13}C- NMR (75 MHz, DMSO-d_6) δ, ppm: 121.3, 80.34, 44.32, 27.4. IR(KBr Cm^{-1}): 3400(NH),3030(Ar-H), 2789(C-H), 1649(N-H), 1580(NH), 1324(C-N),1211(C-O),1200(C-C), 830(C-N), 675(N-H). MS (ESI): 183.2 $[M+Na]^+$ Anal. Calcd. For $C_7H_{16}O_2$: C, 52.48%; H, 10.07%; N, 17.48%
Found: C, 52.51%; H, 10.01%; N, 17.32%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5 diyl)bis(methylene)bis (benzenesulfonamide) 5a:
To a solution of ((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine 4 (1.0 g, 6.2 mmol)in anhydrous dichloromethane (15 ml), triethyl amine (2.1 ml, 14.9 mmol) was added at 10 ^oC and stirred for 5 mins then

benzene sulfonyl Chloride (1.73 mL, 13.6 mmol) was added slowly at 10^{o}C. The reaction mixture was allowed to warm to room temperature and stirred for 12h at same temperature. Reaction monitored by TLC. After completion of reaction the mixture was poured into saturated aqueous ammonium chloride solution (10 ml). The aqueous phase was separated and extracted with dichloromethane (2x10 mL). The combined organic phases were washed with water (15 mL), brine (15 mL), dried over Na_2SO_4, filtered, and evaporated. The residual oil was purified by silicagel column chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis (benzenesulfonamide) 5a (1.7 g) with 63%yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 7.84(m, 4H, Ar-H), 7.7(m, 2H, Ar-H), 7.63(m,4H, Ar-H), 4.81(t, 2H, O-CH),4.32(br s,-NH),3.14(m,4H,N-CH_2), 1.31(s, 6H, C-CH_3).^{13}C- NMR (75 MHz, DMSO-d_6) δ, ppm: 144.8, 132.4, 129.8, 128.5, 118.9, 76.8, 43.5, 26.8. IR(KBr Cm^{-1}):3340(NH), 3030(Ar-H),2789(C-H), 1648(NH), 1530(C=C), 1356(O=S=O), 1322(C-N),1350(C-N),1211(C-O-C), 1200(C-0-C), 830(C-N),690, 678(N-S). MS (ESI): 441.5 $[M+H]^+$ Anal. Calcd. For $C_{19}H_{24}O_6S_2$: C, 51.80%; H, 5.49%; N, 6.36% Found: C, 51.71%; H, 5.59%; N, 6.28%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(4-methylbenzenesul fonamide)5b:
To a solution of ((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine 4 (1.0 g, 6.2 mmol)in anhydrous dichloromethane (15 ml), triethylamine (2.1 ml, 14.9 mmol) was added at 10 ^{o}C and stirred for 5 mins then 4-methyl benzene sulfonyl Chloride (2.6 g, 13.6 mmol) was added slowly at 10^{o}C. The reaction mixture was allowed to warm to room temperature and stirred for 3h at same temperature. Reaction monitored by TLC. After completion of reaction the mixture was poured into saturated aqueous ammonium chloride solution (10 ml). The aqueous phase was separated and extracted with dichloromethane (2x10 mL). The combined organic phases were washed with water (15 mL), brine (15 mL), dried over Na_2SO_4, filtered, and evaporated. The residual oil was purified by silicagel column chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(4-methylbenzenesulfonamide) 5b (2.2 g)with 78%yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 7.74 (dd, 4H, Ar-H), 7.32 (dd, 4H, Ar-H) ,4.8(t, 2H,O-CH),4.0(br s,-NH),3.1(m,4H,N-CH_2),2.43(s,6H,Ar-CH_3), 1.33(s, 6H, C-CH_3).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm: 143.7, 136.4, 129.4, 121.0,118.4, 75.9, 43.5,26.9, 21.5. IR(KBr Cm^{-1}):3350(NH), 3030(Ar-H), 2889(C-H), 1652(N-H), 1530(C=C),1450(CH3) 1376(O=S=O), 1350(C-N),1211(C-O), 1287(C-O-C), 897(NH), 860(C-N). MS (ESI): 469.6 $[M+H]^+$ Anal. Calcd. For $C_{21}H_{28}O_6S_2$: C, 53.83%; H, 6.02%; N, 5.98% Found: C, 53.71%; H, 6.09%; N, 5.82%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(4-nitrobenzene sulfon amide) 5c:
To a solution of ((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine 4 (1.0 g, 6.2 mmol)in anhydrous dichloromethane (15 ml), triethylamine (2.1 ml, 14.9 mmol) was added at 10^{o}C and stirred for 5 mins then 4-nitrobenzene sulfonyl Chloride (3.0 g, 13.6 mmol) was added slowly at 10^{o}C. The reaction mixture was allowed to warm to room temperature and stirred for 4h at same temperature. Reaction monitored by TLC. After completion of reaction the mixture was poured into saturated aqueous ammonium chloride solution (10 ml). The aqueous phase was separated and extracted with dichloromethane (2x10 mL). The combined organic phases were washed with water (15 mL), brine (15 mL), dried over Na_2SO_4, filtered, and evaporated. The residual oil was purified by silica gel column chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(4-nitrobenzenesulfonamide) 5c (2.7 g)with 81%yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 8.42 (m, 4H, Ar-H), 8.15 (m, 4H, Ar-H),4.81(t, 2H,O-CH),4.23(br s,-NH), 3.21(m,4H,N-CH_2), 1.32(s, 6H, C-CH_3).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm: 152.8, 150.5, 128.5, 124.5, 118.5, 76.1, 43.5,26.9. IR(KBr Cm^{-1}):3360(NH), 1656(N-H), 1498(NH),1531(C=C), 1501(NO2), 1375(O=S=O), 1333(C-N),1210(C-O), 1289(C-O-C), 862(C-N). MS (ESI): 531.52 $[M+H]^+$ Anal. Calcd. For $C_{19}H_{22}N_4O_{10}S_2$: C, 43.01%; H, 4.18%; N, 10.56% Found: C, 43.21%; H, 4.26%; N, 10.62%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-(2-chloro-3-(trifle oromethyl)benzyl) benz enesulfonamide) 6a:
To a stirred solution of N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(benzene sulfonamide)5a (500 mg, 1.13 mmol) anhydrous K_2CO_3(470 mg, 3.4 mmol) in dry acetonitrile (12 mL) was slowly added 1-(bromomethyl)-2-chloro-3-(trifluoromethyl)benzene (740 mg, 2.71 mmol) at room temperature. Then heated to reflux for 5h. Reaction monitored by TLC, after completion of reaction, reaction mixture was allowed to cool down to room temperature and filtered. Filtrate was concentrated under vacuum and purified by silica gel chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-(2-chloro-3-(trifluorom ethyl)benz yl)benze nesulfon amide)6a740 mgwith 79% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm:7.92(m,4H, Ar-H), 7.74(m, 4H, Ar-H), 7.68(m, 4H, Ar-H), 7.46(m, 4H,Ar-H), 7.28(m, 4H, Ar-H), 4.46(dd, 4H, -CH_2-Ph), 3.84(m, 2H, -OCH), 3.52(m,2H, N-CH), 3.21(m, 2H,-NCH), 1.38(s,

6H, - C-CH_3).^{13}CNMR (75 MHz, DMSO-d_6), ppm:140.6, 138.2, 133.3, 131.3, 130.9, 129.2, 128.0, 127.1, 125.1, 124.5, 123.9, 121.4, 80.7, 54.2,48.5, 26.5. IR(KBr Cm^{-1}): 3042(Ar-H),1356(O=S=O), 1344(C-N),1301(C-N),1288(CF_3), 1260(C-F),1211(C-O), 1202(C-O-C), 1160(SO_2), 830(C-N), 808(N-O), 769(C-Cl),678 (C-S). MS (ESI): 826.6 $[M+H]^+$ Anal. Calcd. For $C_{35}H_{32}Cl_2F_6N_2O_6S_2$: C, 50.91%; H, 3.91%; N, 3.39% Found: C, 50.83%; H, 3.82%; N, 3.45%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-(2-chloro-3-(trifle oromethyl)benzyl)-4-methylbenzene sulfonamide) 6b:
To a stirred solution of N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl) bis (methy lene)bis(4-methylbenzenesulfonamide)5b (500 mg, 1.06 mmol) anhydrous K_2CO_3 (442 mg, 3.2 mmol) in dry acetonitrile (12 mL) was slowly added 1-(bromomethyl)-2-chloro-3-(trifluoromethyl)benzene (695 mg, 2.5 mmol) at room temperature. Then heated to reflux for 5h. Reaction monitored by TLC, after completion of reaction, reaction mixture was allowed to cool down to room temperature and filtered. Filtrate was concentrated under vacuum and purified by silica gel chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-(2-chloro-3-(trifluoromethyl)benzyl)-4-methylbenzene sulfonamide) 6b720 mgwith 80%.

^{1}H-NMR: (300MHz, DMSO-d_6) δ, ppm7.81-7.67(m, 6H, Ar-H), 7.63(m, 4H, Ar-H), 7.56(m, 4H, Ar-H), 7.28(m, 4H, Ar-H), 4.46(dd, 4H,-CH_2-Ph), 3.8(m, 2H, O-CH), 3.5(m, 2H, N-CH_2), 3.21(m, 2H, N-CH_2), 2.48(s, 6H,CH_3-Ph), 1.38(s, 6H, ,-C-CH_3).^{13}C NMR: (75 MHz, DMSO-d_6) δ, ppm 143.6, 138.5, 137.3, 132.8, 131.0, 129.7, 128.0, 127.5, 126.3, 124.5, 123.9, 121.2, 80.7, 50.2,46.5, 26.5, 21.4. IR(KBr Cm^{-1}): 3088(Ar-H), 1567(C=C), 1387(O=S=O), 1329(C-N),1244(C-N), 1253(CF_3), 1249(C-F),1225(C-O),1195(C-O-C), 847(C-N), 803(N-O), 765(C-Cl),685(C-S). MS (ESI): 854.72 $[M+H]^+$ Anal. Calcd. For $C_{37}H_{36}Cl_2F_6N_2O_6S_2$: C, 52.05%; H, 4.25%; N, 3.28% Found: C, 52.99%; H, 4.29; N, 3.31%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-isobutyl-4-methy lbenzenesulfonamide) 6c:
To a stirred solution of N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl) bis (met hyl ene) bis(4-methylbenzenesulfonamide) 5b (500 mg, 1.07 mmol) anhydrous K_2CO_3 (442 mg, 3.2 mmol) in dry acetonitrile (12 mL) was slowly added 1-bromo-2-methylpropane (342 mg, 2.5 mmol) at room temperature. Then heated to reflux for 3h. Reaction monitored by TLC, after completion of reaction, reaction mixture was allowed to cool down to room temperature and filtered. Filtrate was concentrated under vacuum and purified by silica gel chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-isobutyl-4-methylbenzene sulfonamide) 6c 421 mgwith 68% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm7.75(m, 4H, Ar-H), 7.46(m, 4H, Ar-H), 3.8(m, 2H, O-CH), 3.5(m, 2H, N-CH_2), 3.21(m, 4H, N-CH_2), 3.17(m, 4H, N-CH_2), 2.46(s,6H, CH_3-Ph), 1.70(m, 2H, -CH(CH_3)$_2$), 1.38(s, 6H, ,-C-CH_3), 0.93(d, 12H, -CH(CH_3)$_2$).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm 144.2, 138.5, 129.3, 127.5, 121.4, 80.5, 50.3, 47.5, 26.4, 25.3, 21.4, 20.9. IR(KBr Cm^{-1}): 3088(Ar-H), 1567(C=C),1387(O=S=O), 1335(C-N),1244(C-O),1195(C-O-C), 1144(SO2),1001(C-N), 806(N-O), 745(C-Cl),686(C-S). MS (ESI): 581.7 $[M+H]^+$ Anal. Calcd. For $C_{29}H_{44}N_2O_6S_2$: C, 59.97%; H, 7.64%; N, 4.84% Found: C, 59.99%; H, 7.53%; N, 4.92%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-allyl-4-methy lbenzenesulfonamide) 6d:
To a stirred solution of N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis (meth ylene)bis(4-methylbenzenesulfonamide) 5b (500 mg, 1.06 mmol) anhydrous K_2CO_3 (442 mg, 3.2 mmol) in dry acetonitrile (12 mL) was slowly added 3-bromoprop-1-ene (303 mg, 2.5 mmol) at room temperature. Then heated to reflux for 3h. Reaction monitored by TLC, after completion of reaction, reaction mixture was allowed to cool down to room temperature and filtered. Filtrate was concentrated under vacuum and purified by silica gel chromatography to N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-allyl-4-methylb enzenesulfonamide)6d497 mgwith 85% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 7.75(m, 4H, Ar-H), 7.46(m, 4H, Ar-H), 5.86(m, 2H, -CH-CH_2), 5.23(m, 2H, -CH=CH_2), 5.17(m, 2H, -CH=CH_2), 3.8(m, 2H, O-CH), 3.5(2H, N-CH_2), 3.21(m, 2H, N-CH_2), 2.48(s, 6H, CH_3-Ph),1.3(s, 6H,-CH_3).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm 138.2, 137.1, 129.3, 126.4,127.5, 121.4, 118.1, 80.5, 50.5, 47.4, 26.4, 21.4. IR(KBr Cm^{-1}): 3024(Ar-H), 1663(C=C), 1399(CH3,CH2), 1345(SO2), 1220(C-O-C), 1197(C-N), 1153(SO2), 678(C-S) MS (ESI): 549.7 $[M+H]^+$ Anal. Calcd. For $C_{27}H_{36}N_2O_6S_2$: C, 59.10%; H, 6.61%; N, 5.11% Found: C, 59.19%; H, 6.52; N, 5.23%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-benzyl-4-methylbenzenesulfonamide) 6e:
To a stirred solution of N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl) bis (meth ylene)bis(4-methylbenzenesulfonamide) 5b (500 mg, 1.06 mmol) anhydrous K_2CO_3 (442 mg, 3.2 mmol) in dry acetonitrile (12 mL) was slowly added 1-(bromomethyl)benzene (427 mg, 2.5 mmol) at room temperature. Then heated to reflux for

7h. Reaction monitored by TLC, after completion of reaction, reaction mixture was allowed to cool down to room temperature and filtered. Filtrate was concentrated under vacuum and purified by silica gel chromatography to N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-benzyl-4-methylbenzenesulfonamide) 6e561 mgwith 81% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 7.75(m, 4H, Ar-H), 7.46(m, 4H, Ar-H), 7.38(m, 4H, Ar-H), 7.24-7.20(m, 6H, Ar-H), 4.46(dd, 2H, -CH_2-Ph), 3.8(m, 2H, O-CH), 3.5(m, 2H, N-CH_2), 3.21(m, 2H, N-CH_2), 2.48(s, 6H, CH_3-Ph), 1.38(s, 6H, ,-C-CH_3).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm 144.2, 138.5, 137.9, 129.4, 128.5, 127.5, 127.0, 126.5, 121.3, 80.5, 50.4, 47.5, 26.4, 21.4. IR(KBr Cm^{-1}): 3101(Ar-H), 2944(C-H), 1521(C=C),1386(O=S=O), 1365(C-N), 1245(C-N), 1323(SO_2), 1225(C-O), 1196(C-O-C), 849(C-N), 685(C-S).MS (ESI): 649.8 $[M+H]^+$
Anal. Calcd. For $C_{35}H_{40}N_2O_6S_2$: C, 64.79%; H, 6.21%; N, 4.32% Found: C, 64.85%; H, 6.80%; N, 4.43%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(4-methyl-N-(4-(trifluoromethyl)benzyl) benzenesulfonamide)6f:
To a stirred solution of N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis (methyl ene)bis(4-methylbenzenesulfonamide) 5b(500 mg, 1.06 mmol) anhydrous K_2CO_3 (442 mg, 3.2 mmol) in dry acetonitrile (12 mL) was slowly added 1-(bromomethyl)-4-(trifluoromethyl)benzene (598 mg, 2.5 mmol) at room temperature. Then heated to reflux for 6h. Reaction monitored by TLC, after completion of reaction, reaction mixture was allowed to cool down to room temperature and filtered. Filtrate was concentrated under vacuum and purified by silica gel chromatography to N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(4-methyl-N-(4-(trifluoromethyl) benzyl) benzene sulfonamide) 6f531mgwith 64% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 7.73(m, 4H, Ar-H), 7.63(m, 4H, Ar-H), 7.56(m, 4H, Ar-H), 7.28(m, 4H, Ar-H), 4.46(dd, 2H, -CH_2-Ph), 3.8(m, 2H, O-CH), 3.5(m, 2H, N-CH_2), 3.21(m, 2H, N-CH_2), 2.48(s, 6H, CH_3-Ph), 1.38(s, 6H, -C-CH_3).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm 144.1, 141.2, 137.1, 130.1, 129.5, 129, 127.7,125.2, 124.3, 121.3, 80.5, 50.4, 47.5, 26.4, 21.4. IR(KBr Cm^{-1}):3030(Ar-H), 1530(C=C), 1356(O=S=O),1344 (CF3), 1350(C-N), 1260(C-F), 1200(C-C), 830(C-N), 678 (C-S). MS (ESI): 785.8 $[M+H]^+$ Anal. Calcd. For $C_{35}H_{38}N_2O_6S_2$: C, 56.62%; H, 4.88%; N,3.57% Found: C, 56.79%; H, 4.91%; N, 3.43%

N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-allyl-4-nitrobenzen esulfonamide) 6g:
To a stirred solution of N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis (methylene) bis(4-nitrobenzene sulfonamide)5c(500 mg, 0.94 mmol) anhydrous K_2CO_3 (391 mg, 2.83 mmol) in dry acetonitrile (12 mL) was slowly added 3-bromoprop-1-ene (273 mg, 2.4 mmol) at room temperature. Then heated to reflux for 3h. Reaction monitored by TLC, after completion of reaction, reaction mixture was allowed to cool down to room temperature and filtered. Filtrate was concentrated under vacuum and purified by silica gel chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-allyl-4-nitro be zenesulfonamide) 6g483 mgwith 84%.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm:8.4(m,4H, Ar-H), 8.21(m, 4H, Ar-H), 5.9(d, 2H, -CH-CH2), 5.24(d, 2H, CH=CH2), 5.2(m, 2H, CH=CH2), 3.82(m, 2H, O-CH), 3.5(m, 2H, N-CH2), 3.21(m, 2H, N-CH2), 1.38(s, 6H, ,-C-CH3).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm:152.0, 146.9, 129.3, 128.1, 125.5, 121.4, 118.1, 80.5, 53.5, 47.4, 26.4. IR(KBr, Cm^{-1}):3024(Ar-H), 1679(NO2), 1663(C=C), 1345(SO2), 1220(C-O-C), 1197(C-N), 1153(SO2), 678(C-S). MS (ESI): 611.7 $[M+H]^+$ Anal. Calcd. For $C_{25}H_{30}N_4O_{10}S_2$: C, 49.17%; H, 4.95%; N, 9.17% Found: C, 49.29%; H, 4.87%; N, 9.31%

N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-(2-chloro-3-(trifluoromethyl) benzyl) ben zeneesulfonamide) 7a:
To a dioxane (10ml) solution of N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis (methylene)bis(N-(2-chloro-3-(trifluoromethyl) benzyl) benzene sulfonamide) 6a (500 mg, 0.6 mmol),trifluoroacetic acid (1ml) was added at room temperature and stirred for 5 mins then water was added (1ml) at same temperature and heated to 60^o C. It was stirred for 6h at same temperature, reaction monitored by TLC, after completion of reaction solvents removed under vacuum and diluted with dichloromethane and water. Dichloromethane layer was washed with water, sodium bicarbonate and brine solutions dried over anhydrous sodium sulfate and concentrated to afford the residue which was purified by silica gel chromatography to afford N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-(2-chloro-3-(trifluoromethyl) benzyl)benzenesulfonamide) 7a 320 mgwith 68%.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 7.84(m, 4H, Ar-H), 7.74(m, 2H, Ar-H), 7.62(m, 4H, Ar-H), 7.18(m, 2H,Ar-H), 4.5(dd, 4H, -CH2-Ph), 3.4(m, 2H, -OCH), 3.15(m,2H, N-CH), 3.1(m, 2H,-NCH), 2.6(d, 2H,-OH).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm:139.9, 138.2, 132.1, 132.3, 130.0, 129.4, 128.3, 127.1, 126.4, 124.1, 123.2, 72.9 ,50.7, 48.5. IR(KBr Cm^{-1}):3455(OH), 3015(Ar-H), 1555,1543(C=C), 1365(SO2),1284(C-F),1244(C-N),

777(C-Cl), 735(C-S) MS (ESI): 786.7 $[M+H]^+$ Anal. Calcd. For $C_{32}H_{28}Cl_2F_6N_2O_6S_2$: C, 48.92%; H, 3.59%; N, 3.57% Found: C, 48.79%; H, 3.77%; N, 3.68%

N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-(2-chloro-3-(trifluoromethyl)benzyl)-4-methylbenzene sulfonamide) 7b:

To a dioxane (10ml) solution of N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl) bis (methylene)bis(N-(2-chloro-3-(trifluoromethyl)benzyl)-4-methylbenzenesulfonamide)6b (500 mg, 0.6 mmol),trifluoroacetic acid (1ml) was added at room temperature and stirred for 5 mins then water was added (1ml) at same temperature and heated to 60^o C. It was stirred for 6h at same temperature, reaction monitored by TLC, after completion of reaction solvents removed under vacuum and diluted with dichloromethane and water. Dichloromethane layer was washed with water, sodium bicarbonate and brine solutions dried over anhydrous sodium sulfate and concentrated to afford the residue which was purified by silica gel chromatography to afford N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-(2-chloro-3-(trifluoromethyl) benzyl)-4-methylbenzenesulfonamide) 7b3 10mg with 65% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm: 7.18(m, 2H, Ar-H), 4.46(dd, 4H,-CH2-Ph), 3.42 (m, 2H, O-CH), 3.18(m,2H, N-CH2), 3.1(m, 2H, N-CH2), 2.57(d,2H,-OH), 2.45(s, 6H,CH3-Ph). ^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm:143.8, 138.2, 137.1, 132.8, 130.3, 129.7, 128.2, 127.5, 26.3, 124.8, 123.5, 72.9, 50.2, 48.5, 21.5. MS (ESI): 814.5 $[M+H]^+$ Anal. Calcd. For $C_{34}H_{32}Cl_2F_6N_2O_6S_2$: C, 50.19%; H, 3.96%; N, 3.44% Found: C, 50.27%; H, 3.77%; N, 3.31%

N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-isobutyl-4-methylbenzene sulfonamide) 7c:

To a dioxane (10ml) solution of N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-isobutyl-4-methylbenzenesulfonamide)6c(500 mg, 0.6 mmol), trifluoroacetic acid (1ml) was added at room temperature and stirred for 5 mins then water was added (1ml) at same temperature and heated to 60^o C. It was stirred for 6h at same temperature, reaction monitored by TLC, after completion of reaction solvents removed under vacuum and diluted with dichloromethane and water. Dichloromethane layer was washed with water, sodium bicarbonate and brine solutions dried over anhydrous sodium sulfate and concentrated to afford the residue which was purified by silica gel chromatography to afford N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-isobutyl-4-methylbenzene sulfonamide) 7c 280 mg with 60% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm:7.74(m, 4H, Ar-H), 7.43(m, 4H, Ar-H), 3.42 (m, 2H, O-CH), 3.18(m,2H, N-CH_2), 3.12(d, 4H, N-CH_2), 3.0(m, 2H, N-CH_2), 2.6(d,2H, -OH) 2.45(s, 6H,CH_3-Ph), 1.7(m, 2H, -CH-$(CH_3)_2$) 0.92(d, 12H, -$(CH_3)_2$). ^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm:143.5, 136.7, 128.7, 127.5, 72.8, 57.9, 48.7, 25.7, 21.5, 20.3. IR(KBr Cm^{-1}):3555(OH), 3015(Ar-H),1689(N02) 1555,1543(C=C), 1488(CH3) 1365(SO2),1284(C-F3), 1246(C-F) 1244(C-N),809(N-O), 777(C-Cl), 735(C-S) MS (ESI): 541.7 $[M+H]^+$ Anal. Calcd. For $C_{26}H_{40}N_2O_6S_2$: C, 57.75%; H, 7.46%; N, 5.18% Found: C, 57.59%; H, 7.70; N, 5.31%

N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-allyl-4-methylbenzene sulfonamide) 7d:

To a dioxane (10ml) solution of of N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-allyl-4-methylbenzenesulfonamide) 6d (500 mg, 0.93 mmol),trifluoroacetic acid (1ml) was added at room temperature and stirred for 5 mins then water was added (1ml) at same temperature and heated to 60^o C. It was stirred for 6h at same temperature, reaction monitored by TLC, after completion of reaction solvents removed under vacuum and diluted with dichloromethane and water. Dichloromethane layer was washed with water, sodium bicarbonate and brine solutions dried over anhydrous sodium sulfate and concentrated to afford the residue which was purified by silica gel chromatography to afford N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-allyl-4-methylbenzene sulfonamide) 7d 300 mgwith 63%.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm:7.84(m, 4H, Ar-H), 7.42(m, 4H, Ar-H), 5.86(m, 2H, -CH-CH_2), 5.21(m, 2H, -CH=CH_2) 5.1(m, 2H, -CH=CH_2), 3.84(d, 4H, -N-CH_2), 3.5(m, 2H, -CH-OH), 3.21(m, 2H, N-CH_2), 3.12(m, 2H, N-CH_2), 2.6(d,2H, -OH), 2.48(s, 6H, CH_3-Ph).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm:137.9, 136.7, 128.8, 127.4, 127.1, 117.9, 72.9, 53.9, 48.7, 21.5. IR(KBr Cm^{-1}):3545(OH), 3017(Ar-H), 1545,1539(C=C), 1488(CH3)1478(CH3) 1369(SO2), 1281(C-F3), 1244(C-F) 1240(C-N),735(C-S) MS (ESI): 509.5 $[M+H]^+$ Anal. Calcd. For $C_{24}H_{32}N_2O_6S_2$: C, 56.67%; H, 6.34%; N, 5.51% Found: C, 56.71%; H, 6.47%; N, 5.58%

N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-benzyl-4-methylbenzene sulfonamide) 7e:

To a dioxane (10ml) solution of N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl) bis (methylene)bis(N-benzyl-4-methylbenzenesulfonamide) 6e (500 mg, 0.77 mmol),trifluo roa cetic acid (1ml) was added at room temperature and stirred for 5 mins then water was added (1ml) at same temperature and heated to 60^o C. It was stirred for 6h at same temperature, reaction monitored by TLC, after completion of reaction solvents removed under vacuum and diluted with dichloromethane and water. Dichloromethane layer was washed with water, sodium bicarbonate and

brine solutions dried over anhydrous sodium sulfate and concentrated to afford the residue which was purified by silica gel chromatography to afford N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-benzyl-4-methylbenzene sulfonamide) 7e 281 mgwith 60% yield.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm:7.74(m, 4H, Ar-H), 7.42(m, 4H, Ar-H), 7.36 – 7.20 (m, 10H, Ar-H), 4.50(dd, 2H, -CH_2-Ph), 3.51 (m, 2H, O-CH), 3.21(m, 2H, N-CH_2), 3.12(m, 2H, N-CH_2), 2.6(d,2H, -OH), 2.48(s, 6H, CH_3-Ph). ^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm:143.5, 136.7, 135.9, 128.8, 128.1, 127.5, 127.0, 126.3, 72.5, 53.5, 48.4, 21.4. IR(KBr Cm^{-1}):3557(OH), 3043(Ar-H), 1544, 1478(C=C)1466(CH3) 1385(SO2), 1266(C-N), 1146(SO2)746(C-S) MS (ESI): 609.7 $[M+H]^+$ Anal. Calcd. For $C_{32}H_{36}N_2O_6S_2$: C, 63.13%; H, 5.96%; N, 4.60% Found: C, 63.24%; H, 5.79%; N, 4.71%.

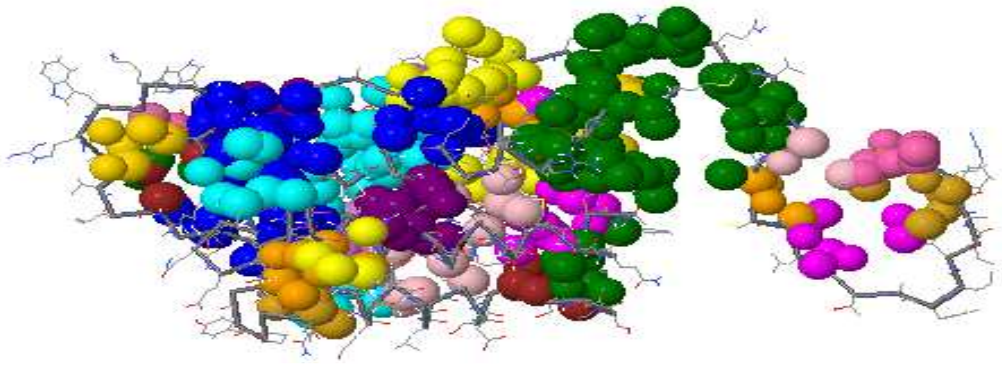
N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(4-methyl-N-(4-(trifluoromethyl) benzyl) benzeneesulfonamide) 7f:
To a dioxane (10ml) solution of N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(4-methyl-N-(4-(trifluoromethyl)benzyl)benzene sulfonamide)6f(500 mg, 0.3 mmol),trifluoroacetic acid (1ml) was added at room temperature and stirred for 5 mins then water was added (1ml) at same temperature and heated to 60^o C. It was stirred for 7h at same temperature, reaction monitored by TLC, after completion of reaction solvents removed under vacuum and diluted with dichloromethane and water. Dichloromethane layer was washed with water, sodium bicarbonate and brine solutions dried over anhydrous sodium sulfate and concentrated to afford the residue which was purified by silica gel chromatography to afford N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(4-methyl-N-(4-(trifluoromethyl) benzyl)benzenesulfonamide)7f 280 mgwith 60%.

^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm:7.75(m, 4H, Ar-H), 7.51(m, 4H, Ar-H), 7.42(m, 4H, Ar-H), 7.18(m, 4H, Ar-H), 4.46(dd, 2H, -CH2-Ph), 3.52(m, 2H, O-CH), 3.21(m, 2H, N-CH_2), 3.12(m, 2H, N-CH_2), 2.6(d,2H, -OH), 2.48(s, 6H, CH_3-Ph).^{13}CNMR (75 MHz, DMSO-d_6) δ, ppm143.2, 140.2, 136.3, 128.7, 129.2, 129.6,127.6,124.2, 123.5, 72.5, 53.5, 48.4, 21.5. IR(KBr Cm^{-1}):3447(OH), 3125(Ar-H), 1544, 1499, 1488(C=C)1476(CH3), 1462(CH3) 1395(SO2), 1286(C-N), 1136(SO2)646(C-S) MS (ESI): 745.7 $[M+H]^+$ Anal. Calcd. For $C_{34}H_{34}F_6N_2O_6S_2$: C, 54.83%; H, 4.60%; N, 3.76% Found: C, 54.72%; H, 4.49%; N, 3.57%

N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-allyl-4-nitrobenzenesulfonamide) 7g:
To a dioxane (10ml) solution of N,N'-((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(N-isobutyl-4-nitrobenzenesulfonamide)6f(500 mg, 0.81 mmol),trifluoroacetic acid (1ml) was added at room temperature and stirred for 5 mins then water was added (1ml) at same temperature and heated to 60^o C. It was stirred for 5h at same temperature, reaction monitored by TLC, after completion of reaction solvents removed under vacuum and diluted with dichloromethane and water. Dichloromethane layer was washed with water, sodium bicarbonate and brine solutions dried over anhydrous sodium sulfate and concentrated to afford the residue which was purified by silica gel chromatography to afford N,N'-((2R,3R)-2,3-dihydroxybutane-1,4-diyl)bis(N-allyl-4-nitrobenzene sulfonamide)7g 337 mgwith 72% yield.

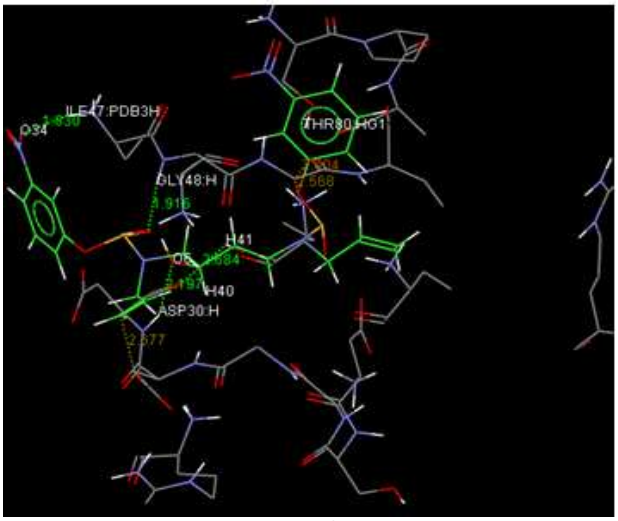
^{1}H-NMR (300MHz, DMSO-d_6) δ, ppm8.41(m, 4H, Ar-H), 8.12(m, 4H, Ar-H), 7.36-7.25(m, 10H, Ar-H), 4.5(dd, 4H, -CH_2-Ph), 3.51(m, 2H, O-CH), 3.23(m, 2H, N-CH_2), 3.12(m, 2H, N-CH_2), 2.6(d,2H, -OH).^{13}CNMR (75MHz, DMSO-d_6) δ, ppm:152.3, 140.5, 128.5, 127.3,124.5, 117.9, 73.2, 53.7, 48.9. IR(KBr Cm^{-1}):3457(OH), 3023(Ar-H), 1546, 1488(C=C)1476(CH3) 1375(SO2), 1256(C-N), 1156(SO2)756(C-S), MS (ESI): 571.6 $[M+H]^+$ Anal. Calcd. For $C_{22}H_{26}N_4O_{10}S_2$: C, 46.31%; H, 4.59%; N, 9.82% Found: C, 47.68%; H, 5.62%; N, 9.39%.

Docking studies of synthesised compounds:
Discussion: In silico pharmacological methods have been developed and widely applied to pharmacology hypothesis development and testing. However, it is well aware that it is impossible to fully model the complex biological systems. These methods comprise databases, structure—activity relationships, pharmacophores, homology models, molecular modelling etc. This information proffers to the creation of computational models or simulations that can be used to make predictions, optimize novel molecules with affinity to target, computational estimates for the bioactivity of molecules and thus to the discoveries in pharmacology(23-27) in the present studies, molecular docking was performed using the Gold version 3.0.1 program to study the binding affinities of synthesized molecules with the active sites Identification of Ribonuclease (RNase) H domain of HIV-1 reverse transcriptase. After the final model was built, the possible binding sites of Ribonuclease (RNase) H domain of HIV-1 reverse transcriptase was searched based on the structural comparison of template and the model build and also with CASTP server and was shown in Figure. In fact from the final refined model of Ribonuclease (RNase) H domain of HIV-1 reverse transcriptase domain using SPDBV program. It was found that secondary structures are highly conserved and the residues, GLY48:H,ASP30:H,ASP30:O,ILE47:H, GLY48:H ,ASP30 :H,ASP30:O ,ASP20:H, ASP30:H, ILE47:H,GLY48:H,GLY48:O,THR80:H,THR80:H,ASP30:H.

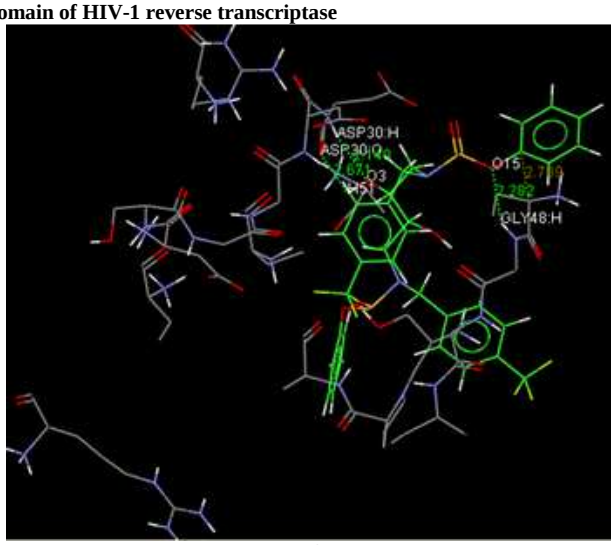


Graphical representation of of Ribonuclease (RNase) H domain of HIV-1 reverse transcriptase

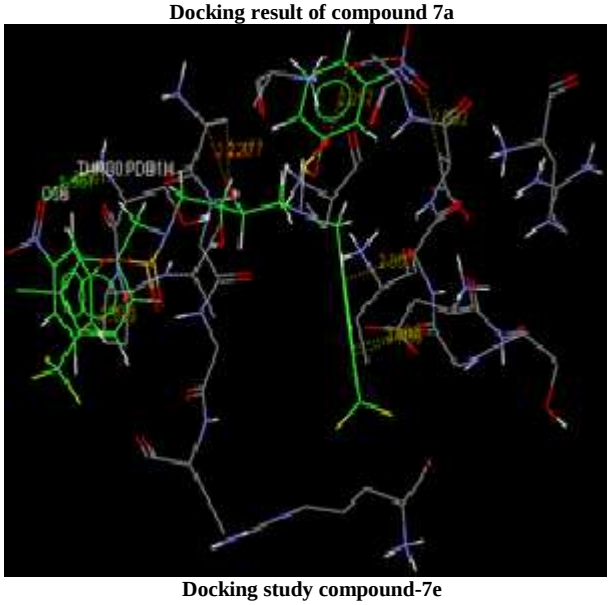
Active site of Ribonuclease (RNase) H domain of HIV-1 reverse transcriptase



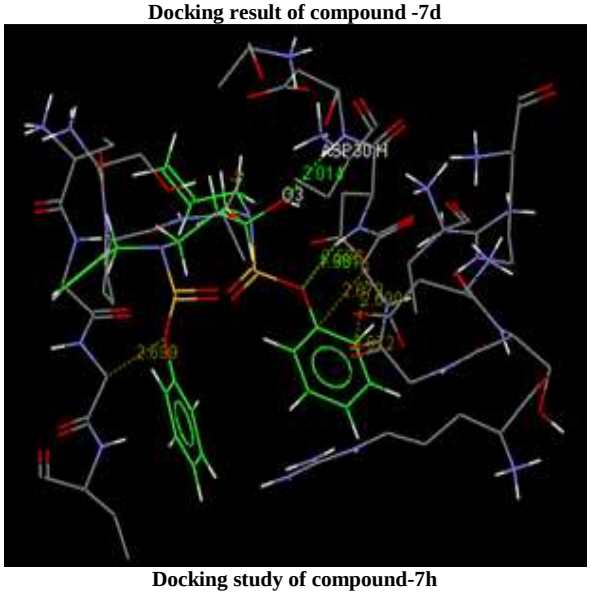
Docking result of compound 7a



Docking result of compound -7d



Docking study compound-7e



Docking study of compound-7h

Hydrogen bonding interactions of compounds 7(a-g) with Ribonuclease

Compound No	No of hydrogen bonds	Atoms		Bond length(A^0)	Fitness
		Protein	Atom		
7a	4	GLY 48H	O34	1.91	39.8
		ASP30 H	O6	2.19	
		ASP30 O	H40	2.68	
		ILE47H	O34	1.83	
7b	2	GLY48 H	O14	1.69	30.5
		GLY48 O	H49	2.63	
7c	1	THR80 H	O56	1.57	38.6
7d	3	ASP29 H	O15	2.67	36.6
		ASP30 H	O13	1.74	
		ILE47 H	O50	2.15	
7e	1	THR80 H	O56	1.56	38.6
7f	1	ASP30 H	O3	2.01	36.1
7g	3	GLY48 H	O15	2.28	40.7
		ASP30 H	O3	2.14	
		ASP30 O	H51	2.67	

The docking studies of 7(a-g) were carried out on sortase A staphylococcus (PDB ID: 1HRH). The docking ligands were found to have some interactions between an oxygen atom of the ligands and sortase A staphylococcus protein. Moreover, these docked conformations formed hydrogen bond interactions with the active site of the protein. Bind pocket, common hydrogen bonding interactions were for formed between all the docked ligands and GLY48:H, ASP30:H, ASP30:O, ILE47:H, GLY48:H, ASP30:H, ASP30:O, ASP20:H, ASP30:H, ILE47:H, GLY48:H, GLY48:O, THR80:H, THR80:H, ASP30:H. The order of protein-ligand hydrogen bond score is 7a>7g>7d>7b>7c>7e>7f.

Besides hydrogen bonding interaction between ligand-protein, the Vander walls interactions between ligand-protein were also noticed. The order of protein-ligand Vander walls score of interaction with the protein. However the ligand fails to exhibit intramolecular hydrogen bonding with the ligand. The ligands exhibit minimum intramolecular strain. Finally, all the ligands exhibit moderate to good antimicrobial activity with sortase. A staphylococcus protein. The order of gold score fitness value of the ligands is 7g>7a>7c>7e>7d>7f>7b. According to gold score fitness value ligand 7g exhibits high binding activity with the protein and ligand 7a showed leads binding activity with the protein.

RESULTS AND DISCUSSION

To a suspension of L-(+)-tartaric acid was added 2,2-dimethoxypropane The reaction mixture was refluxed for 12 h, allowed to cool to room temperature and then quenched with solid K_2CO_3. The resulting reaction mixture was filtered through celite pad. Solvents were removed and the residue was distilled under reduced pressure to afford (4*S*, 5*S*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate2 (82%) A solution of (4*S*, 5*S*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate and methanolic ammonia solution in presence of methanol was slowly added. The mixture was slowly warmed to room temperature Reaction monitored by TLC, after completion of reaction, the mixture was concentrated in vacuum to give a white solid. This crude product was recrystallized from ethanol to afford (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide 3 90.1% yield. A suspension of $LiAlH_4$ in anhydrous THF (150ml) was stirred for 3hours add then (4*S*, 5*S*)-2, 2-dimethyl-1, 3-dioxolane-4, 5-dicarboxamide in anhydrous THF was slowly added. After completion of addition the mixture was warmed to room temperature and continuously stirred. The reaction monitored by TLC after completion of reaction to afford ((4*R*, 5*R*)-2, 2-dimethyl-1, 3-dioxolane-4, 5-diyl) dimethanamine (4) Yield: 75%).To a solution of ((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine in anhydrous dichloromethane (15 ml), triethyl amine was added at 10 ^oC and stirred and then benzene sulfonyl Chloride was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for at same temperature. Reaction monitored by TLC. After completion of reaction the mixture was poured into saturated aqueous ammonium chloride solution (10 ml). The aqueous phase was separated and extracted with dichloromethane. The combined organic phases were washed with water, brine, dried over Na_2SO_4, filtered, and evaporated. The residual oil was purified by silicagel column chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(benzenesulfonamide) (5)63%yield. To a stirred solution of N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(benzenesulfonamide) anhydrous K_2CO_3in dry aceto nitrile was slowly added 1-(bromomethyl)-2-chloro-3-(trifluoromethyl)benzene at room temperature. Then heated to reflux for 6h. Reaction monitored by TLC, after completion of reaction, reaction mixture was allowed to cool down to room temperature and filtered. Filtrate was concentrated under vacuum and purified by silica gel chromatography to afford N,N'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene) bis(N-(2-chloro-3- (trifluoromethyl) benzyl) benzene sulfonamide) (6) derivatives with trifluoroacetic acid was

added at room temperature, the reaction monitored by TLC, after completion of reaction to afford the residue which was purified by silica gel chromatography to afford N,N'-((2*R*,3*R*)-2,3-dihydroxybutane-1,4-diyl)bis(N-(2-chloro-3(trifluoromethyl) benzyl) benzenesulfonamide) derivatives(7a-g).

CONCLUSION

We have developed methodology to synthesize new C_2-symmetric 1,4-bis sulphonamido 2, 3- diol derivatives in good to high yields. To our knowledge compounds 7a-ghave not been described before. They have C_2 symmetry and studied by docking applications the compounds were screened in hydrogen bond interactions with Ribonuclease activity. While all the sulphonamide derivatives demonstrated inhibitory activity against RiboNuclease , the structure-activity studies signified that the hydroxyl sulphonamide moieties in the drug has significantly enhanced the inhibitory activity against the target enzyme.

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