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Synthesis and Characterization of Some New Sulfadiazine derivatives

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Abstract

A series of three and four member rings has been synthesized by N-substituted for 4- (1,3dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl) benzenesulfonamide (sulfadaizine). The nitrogen atoms have been alkylated first to form N-carboxymethyl followed by cyclization reactions to form heterocyclic/substituted aryl group (diaziridine, diazirine and diazetidin derivatives). All the synthesized compounds have been identified using FT-IR, ^{1}H NMR, C^{13}-NMR.

Keywords: **4- (**1,3dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide**)**, 1,2-Diazetidine, 1 ,2-diaziridin, 1,2-diazrine.

INTRODUCTION:

The molecular structures of sulfa drugs that containing the 4-aminobenzenesulfonamide moiety play important roles as a chemotherapeutic agent (1). The biological activity of these drugs is thought to come from the structural similarity between sulfanilamide group and p-amino benzoic acid where the sulpha drug simulators this metabolite and blocks folic acid synthesis in bacteria, thereby causing cell death(2). The SO_2NH moiety as a toxophoric function in many sulfa drugs like sulfadiazine, sulfamethoxa-zole, and sulfamerazine play important roles in its antimicrobial activity (3). Sulfadiazine exhibits in vitro inhibitory activity against several aerobic gram-positive and gram-negative bacteria (4), Sulfadiazine is one of the medication populace of barbituric acids has concern. Azirine a small heterocyclic ring system are of largest importance in theoretical, synthetic organic, bio organic and medicinal chemistry, and in particular aziridines are very useful and interesting systems as they occur in a sum of accepted and biologically lively substances (5-13). 1,2-Diazetidine and 1 ,2-diaziridin constituents founds an useful biological active compounds (13-14) Aziridines are highly appreciated heterocyclic compounds and are widely used through the synthesis of rich medicines and biologically strong natural products (14–16). Apart of our interest in the field of the Biological active compounds (17-22) we decided to examine some of three and four membered heterocyclic/substituted sulfadiazine.

MATERIALS AND METHODS:

The entire chemicals were purchased from Sigma Aldrich, BDH, CDH and Merck. Melting point determinations were performed by the open capillary method using a SMP30 melting point apparatus and are reported uncorrected. The F T - IR spectra (KBr-discs) were recorded with a IRAFFINITY-1CE Shimadzu spectrometer. ^{1}H NMR spectra were recorded on a Jeol-300HZ-NMR spectrophotometer operating at 300 MHz for ^{1}H measurements. C^{13}-NMR spectra were recorded on a Jeol-300HZ-NMR spectrophotometer operating at 300 MHz for C^{13} measurements, thin layer chromatography was performed on pre-coated sheets with a 0.25 mm layer of Silica Gel GF254 of the Merck Company.

Synthesis of: 4-(1,3dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide) (N1)

Compound (N) 4-amino-N-(pyridin-2-yl) benzenesulfonamid (0.01mol, 2.5gm) Phthalicanhydrad (0.01mol, 1.48gm) were heated under reflex in glacial acetic acid (20ml) for 3 h (bath temperature at 118 C^0).this reaction monitored by TLC. The acetic acid was evaporated under vacuum .Water (14ml) was added to the residue and the mixture was refluxed for 1 hour. The reaction monitored by TLC. After cooling, the resulting mixture was extracted with ether:water (1:4). Then it was filtered and dried under vacuum to give white crystal. The precipitate was recrystallized from ethanol.

Color: Crystalline white; Yield: 86%; m.p. 318-320 °C ; IR (v, cm^{-1}):, 3116 cm^{-1} (N-$H_{secondary}$), 3078 cm^{-1}(C-H_{ar}),1242-1338cm^{-1}(C-N), 1635cm^{-1} (C=N);2870-2939(CH_{aliph}) ,1720cm^{-1}(C=O_{amid}) H^1-NMR (300 MHz, DMSO-*d*^{6}) δ (ppm): 3.43 (S , 1H, NH), 7.08(d, 1H, =CHpyrmiden),8.55(d,2H,=CHpyrmiden), 7.56-8.01cm^{-1}(d, 10H , CHar), . TLC R*f* =0.8 (DCM: n-hexane).

Synthesis of:2-(4-(1,3dioxoisoindolin-2-yl)-N-(pyrimidn-2-yl) benzenesulfonamide acetic acid (N2)

Chloroacetic acid (0.05mol, 4.72gm) was dissolved in (20 ml) of dry chloroform and (4ml) pyridine. To which an equimolar amount of (1,3dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl) benzenesulfonamide) was added and reaction mixture was refluxed for 4h. The reaction monitored by TLC. After cooling the residue obtained was washed with DCM/acetone and. The precipitate was recrystallized from ethanol

Color: Crystalline plat brown; Yield: 86%; m.p. 295-298 °C ; IR (v, cm^{-1}): 2493-3419 brod ($OH_{carboxyl}$), 1724(C=$O_{carboxyl}$,1597(C=O_{amid}),1240-1330(C-O), 2860-2939 (C-H_{aliph}), 3047 (C-H_{ar}), 1159(C-N); H^1-NMR (300 MHz, DMSO-*d*6) δ(ppm): 4.44 (S, 2H,N–CH_2), 7.08(d, 1H, =$CH_{pyrmidine}$), 8.54(d, 2H , =$CH)_{pyrmidine}$), 7.56-7.99 (d, 10H, CHar). TLC R*f* = 0.62 (DCM: n-hexane).

Synthesis of: N-(1H-diazirin-3-yl)-4-(1,3-dioxoisoindolin-2-yl)-N-(pyridin-2-yl)benzenesulfonamide (N3)

In a round bottom flask containing (0.01mol, 4.38 gm) of compound (N2), a mixture of hydrazine (0.01 mol, 0.32gm), (20ml) concentrated HCl (4N) have been added. The mixture has been refluxed with stirring for5- 6 hrs. The reaction monitored by TLC. The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol

Color: Crystalline brown; Yield: 86%; m.p. 307-309 °C ; IR (v, cm- 1):3169(NH), 1660 (C=N), 3026 (C-H_{ar}), 2854-2891(C-H_{alph}), 1714(C=O_{amid}); H^1-NMR (300 MHz, DMSO-d6) δ(ppm): 7.10 (S , 1H, NH), 7.30 (d, 1H, CHpyrmidine), 3.52(S, 2H , -N-CH_2-C), 7.87-8.10 (d, 10H, CHar),. C^{13}-NMR :57(N-CH_2), 116($CH_{pyrmidin}$), 155 ($C_{triangl}$),122,133,128,129,158 (C_{ar}),168 (),167(C=O), TLC Rf = 0.62 (DCM: n-hexane).

Synthesis of: 4-(1,3-dioxoisoindolin-2-yl)-N-(2-hydrazinyl-2-oxoethyl)-N-(pyrimidin-2-yl)benzenesulfonamide (N4)

In around bottom flask containing (0.01mol, 4.38 gm) of compound (N2), a mixture of hydrazine (0.01mol, 0.32 gm) and

ethanol (20 ml) and two drop of glacial acetic acid have been added. The mixture refluxed for 8 hrs. The reaction monitored by TLC .The precipitate was filtered of and dried. The precipitate was recrystallized from absolute ethanol. Color: Crystalline plate brown; Yield: 78%; m.p. 293-295 °C; IR (v, cm^{-1}):, 1720 (C=O $_{amid}$),3282 (NH), 3354-3421(NH_2) ,2868-2935 (C-H $_{aliph}$), 3076 (C-H_{ar}); H^1-NMR (300 MHz, DMSO-d_6) δ(ppm): 4.37 (S , 2H, -N-CH_2-C=O), 1.82 (S, 2H, NH2),8.93 (S, 1H, NH), 6.87(d, 1H, $CH_{pyrmidine}$), 7.39-8.11 (d, 10H, CHar). TLC R*f* = 0.62 (DCM: n-hexane). TLC R*f* = 0.62 (DCM: n-hexane).

Synthesis of: 4-amino-N-(2-hydrazinyl-2-oxoethyl)-N-(pyrimidin-2-yl) benzenesulfonamide (N5)

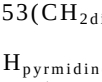
Compound (N4) (0.001mol, 0.5gm) dissolved in hexane (15 ml) and aqueous hydrazine (0.044mol, 1.28gm) was added slowly .the mixture was stirred for 4h at room temperature. The reaction monitored by TLC. The solvent was evaporated and water was added. The aqueous phase was extracted three times with chloroform and the combined organic layer was dried with magnesium sulfate .further evaporation under reduced pressure. The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol. Color: Crystalline plate oily; Yield: 66%; IR (v, cm^{-1}):, 1633 (C=O $_{amid}$), 3155 (NH), 3327-3427 (NH_2) ,2943-2987 (C-H $_{aliph}$), 3084 (C-H_{ar}); H^1-NMR (300 MHz, DMSO-d_6) δ(ppm): 4.73 (S , 2H, -CH_2-C=O), 2.03 (S, 2H, NH2),6.26 (S, 2H, NH_2),8.06 (S, 1H, NH),7.03(d, 1H,$CH_{pyrmidine}$),7.09-8.19(d,6H,CH_{ar}) TLC R*f* = 0.62 (DCM: n-hexane).

Synthesis of: N-(2-(3,4-dioxo-1,2-diazetidin-1-yl)-2-oxoethyl)-4-(1,3-dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(N6)

In around bottom flask containing (0.01mol, 4.52 gm) of compound (N4), a mixture of oxalic acid (0.015 mol, 1.35gm) and ethanol (20 ml) have been added. The mixture refluxed for 5-6 hrs. The reaction monitored by TLC. The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol.

Color: Crystalline brown; Yield: 71%; m.p. 306-308 °C; IR (v, cm^{-1}): 1718 (C=O $_{amid}$), 3321 (NH $_{diazetidin}$), 2866-2931 (C-H $_{aliph.}$), 3076 (C-H_{ar}); H^1-NMR (300 MHz, DMSO-d_6) δ(ppm): 4.38 (S , 2H,N-CH_2-C=O), 8.00 (S, 1H, NH $_{diazetidin}$), 7.04 (d,1H, $CH_{pyrmidine}$) , 7.06-8.50(d, 10H,CH_{ar}), TLC R*f* =0.6(DCM: n-hexane).

Synthesis of: N-(2-(1,2-diazetidin-1-yl)-2-oxoethyl)-4-(1,3-dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (N7)

In around bottom flask containing (0.01mol, 4.52 gm) of compound (N4), a mixture of dichloroethane (0.015 mol, 1.48 gm) and ethanol (20 ml) have been added. The mixture refluxed for 5-6 hrs. The reaction monitored by TLC .The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol. Color: Crystalline brown; Yield: 75%; m.p. 325-328 °C; IR (v, cm^{-1}): 1718 (C=O $_{amid}$), 3290 (NH $_{diazetidin}$), 2854-2924 (C-H $_{aliph.}$), 3078 (C-Har); ^{1}HNMR (300 MHz, DMSO-d_6) δ (ppm): 4.32(S, 2H,N-CH2-C=O), 2.05(S, 1H, -NH). 7.05(d, 1H, $CH_{pyrmidine}$), 7.55, 8.57 (d, 10H, CH_{ar}), 3.44, 3.56(M, 4H,CH_{ar}). C^{13}-NMR: 43, 46(CH_2-CH_2), 53(CH_2-C=O),167(C=O), 168(),115($CH_{pyrmdine}$),119,125,129,132,158(CH_{ar})TLC R*f* = 0.65 (DCM: n-hexane).

Synthesis of: N-(2-(1,2-diazetidin-1-yl)-2-oxoethyl)-4-(1,3-dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (N8)

In around bottom flask containing (0.01mol, 4.52gm) of compound N4, a mixture of dichloromethane (0.015 mol, 1.27 gm) and ethanol (20mL) have been added. The mixture refluxed for 5-6 hrs. The reaction monitored by TLC .The precipitate was filtered of and dried. The precipitate was recrystallized from ethanol.

Color: Crystalline brown; Yield: 75%; m.p. 321-322 °C ; IR (v, cm^{-1}): 1714 (C=O amid), 3286 (NH), 2870-2937 (C-H $_{aliph.}$), 3076 (C-H_{ar}); ^{1}HNMR (300 MHz, DMSO-d_6) δ(ppm): 4.07 (S , 2H, N-CH_2-C=O), 7.02(d, 1H, $CH_{pyrmidine}$), 4.91(d, 2H , -CH_2),2.00 (S , 1H, -NH), 7.56-8.57 (d, 10H, Char).C^{13}-NMR:53($CH_{2diazirine}$),55(CH-C=O),167(C=O), 116($CH_{pyrmidine}$),168(), 119,129, 132,157, 125(CHar) TLC R*f* = 0.62 (DCM: n-hexane).

RESULTS AND DISCUSSION

The designated compounds were synthesized according to the Scheme in Figure 1. The reaction of 4-amino-N-(pyridin-2-yl) benzenesulfonamid (N) and phthalic anhydride gave 4-(1,3dioxoisoindolin-2-yl)-N-(pyrimidin-2-yl) benzenesulfonamide**)** (N1)compound. The IR spectrum of the product was indicated by the disappearance of band (3500-3400) cm^{-1} due to primary amine group. The ^{1}H-NMR spectrum of compound N1, shows the proton signals at 3.43ppm due(S,1H,NH) group ,7.08(d,1H,CHpyrmidin),8.55(d,2H,Chpyrmidine),7.56-8.01(d,8H,CH ar). The IR spectrum of compound(N2) has shown the appearance of broad absorption band due to carboxyl group at(2493-342319) cm^{-1} and new bound due to the carbonyl group at(1597)cm^{-1} ,The ^{1}H-NMR spectrum of compound N2,show new signal at 4.44(S,2H,N-CH2) ,7.08(d,1H,CH pyrimidn),8.45 ppm (d,2H,CHpyrimidn),7.56-7.99ppm(d,8H,CHar). The IR spectrum of compound (N3) has shown the disappearance of absorption band due to Carboxyl group but appearance of absorption band at (3167) cm^{-1} due to presence of NH group. The ^{1}H-NMR has shown singlet peak resonated at (7.10) ppm due to NH group and singlet peak at(3.52) ppm due to(N-CH_2-C)group . The C^{13}-NMR has shown number of peaks due (N-CH_2) at 57ppm, 116 ppm due to(C-$H_{pyrmidin}$), 155 ppm(C azirine), 168 ppm (N-CN=N) group. (Compound (N4) has been identified by IR spectrum through the appearance of absorption band at (3354-3421) cm^{-1} due to the primery amine and absorption band at (1720 cm^{-1}) due to amide group. Also the appearance of NH absorption bands at (3282 cm^{-1}).

The ^{1}H-NMR spectra of compound N4 has shown singlet peak resonated at 1.82 ppm due to NH_2 group and peak singlet resonate at 8.93 ppm due to NH group. Compound (N5) have been identified by IR spectrum through the appearance of absorption band at 3327-3427 cm^{-1} due to the primary amine and absorption band at 1633cm^{-1}due to the amide carbonyl group. Also the appearance of NH absorption bands at(3155 cm^{-1} was a good indication for the formation of compound N5.The H^1-NMR spectra of compound N5 has shown singlet peak resonated at (4.73)ppm due to (-CH_2-C=O)group,(NH_2)groups appearance at (2.03,6.26)ppm . The compound N6 have been identified by IR spectrum through the appearance of absorption band at (1718 cm^{-1}) due to the amide carbonyl group. Beside the appearance of NH absorption bands at 3321 and the disappearance of the NH_2 absorption band was a good in at (3327-3427 cm^{-1}) indication for the formation of compound N6. .

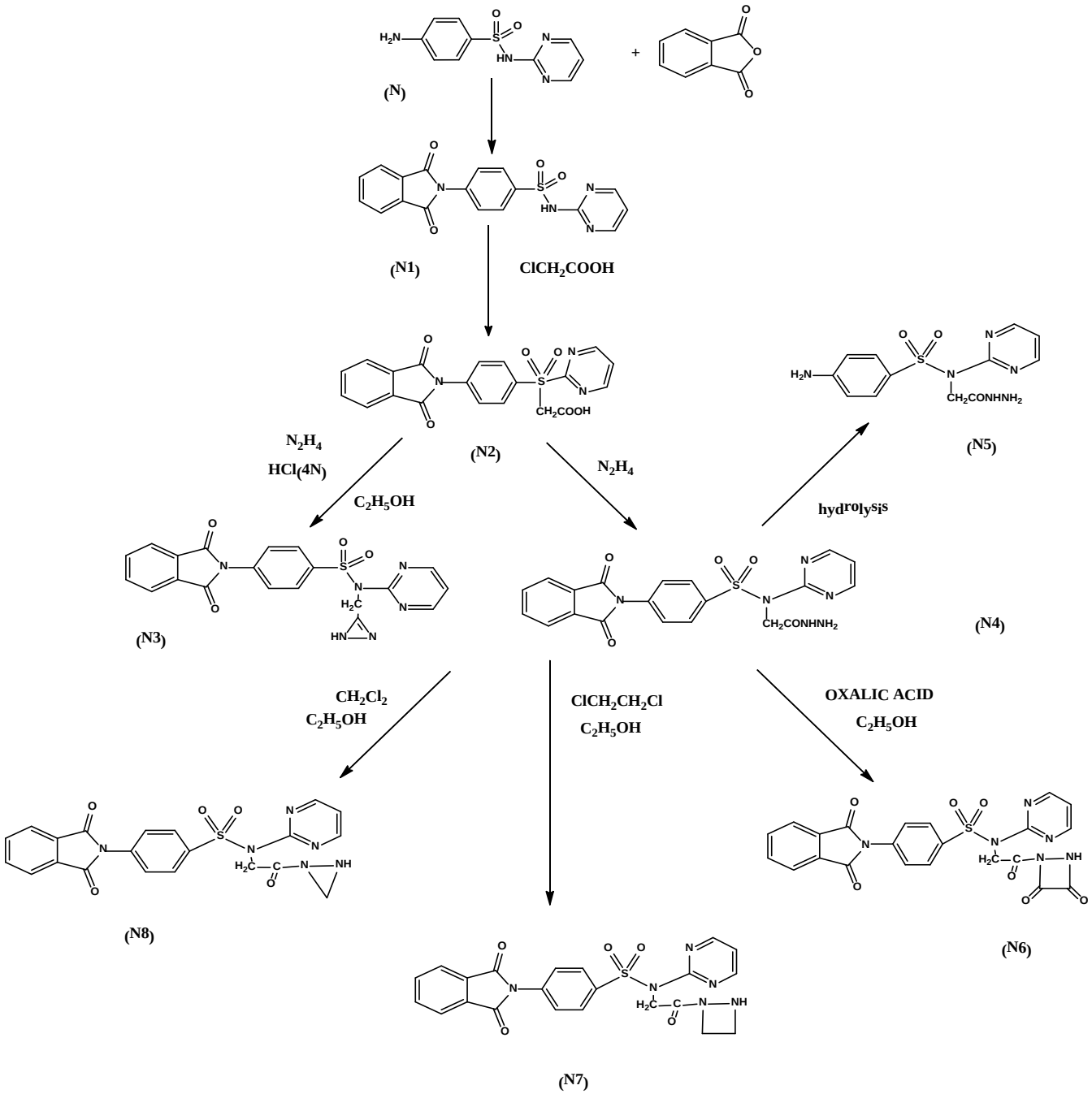


Figure 1 – Synthesis Scheme

The ^{1}H-NMR spectra of compound N6 has shown the disappearance of the singlet peak resonated at (1.82) ppm due to NH_2 group and remaining the single peak resonates at (8.00) ppm due to NH group and appearance of the singlet peak resonated at (4.38) ppm due and (N-CH_2-C=O)group was a good indication for the formation of compound N6. Compound N7 have been identified by IR spectrum through the appearance of absorption band at (1720 cm^{-1}) due to the amide carbonyl group. Beside the appearance of NH absorption bands at (3290 cm^{-1}) was a good indication for the formation of compound N7. The ^{1}H-NMR spectra of compound N7 has shown the disappearance of the singlet peak resonated at (1.82) ppm due to NH_2 group and remaining the single peak resonates at (2.05) ppm due to NH group and appearance of the singlet peak resonated at (3.44) ppm due and (CH_2-CH_2)group.) was a good indication for the formation of compound N7. The C^{13}-NMR spectra of compound N7 has shown the appearance of the number peaks due to the groups .43,46 ppm(CH2-CH_2),53 ppm (CH_2-C=O),167 ppm (C=O). Compound N8 have been identified by IR spectrum through the appearance of absorption band at (1714) cm^{-1} due to the amide carbonyl group. Beside the appearance of NH absorption bands at 3286 cm^{-1} was a good indication for the formation of compound N8. The ^{1}H-NMR spectra of compound N8 has shown the disappearance of the singlet peak resonated at 1.82 ppm due to NH_2 group and remaining the single peak resonates at 2.00 due to NH group. The C^{13}-NMR spectra of compound N8 has shown the appearance of the number peaks due to the groups, 53ppm(CH_2azrdine),55ppm(CH_2-C=O),167(C=O),168ppm(N—C=N).

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