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Synthesis of some new sulfonamide derivatives based on 1,3,4-oxadiazole

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ABSTRACT

In the present work a variety of new heterocyclic compounds namely hydrazide, oxadizole, β-lactam, aza-β-lactam were synthesized by Sequential reactions started from alkylation of Sodium saccharin salt by different alkyl halides namely benzyl chloride, n-propyl bromide and sec-butyl bromide than hydrolysis the N-alkyl saccharin derivatives(1a-c)using 10% NaOH to give the N-alkyl sulfamidobenzoic acid derivatives(2a-c).Reaction (2a-c) with ethyl alcohol in presence Conc. sulfuric acid give the corresponding ester derivatives (3a-c). The benzohydrazide derivatives (4a-c) were obtained via reaction of ester derivative with 80% hydrazine hydrate. The cyclization of (4a-c) with carbondisulfide in presence potassium hydroxide gave the corresponding 2-mercapto-1,3,4-oxdiazol derivatives(5a-c). Reaction of (5a-c) with 80% hydrazine hydrate gave 5-hydrazido 1,3,4-oxadiazol derivatives(6a-c). The Schiff bases(7a-f) were obtained by condensation of (6a-c) with 2,4-dimethoxybenzaldehyde and p-dimethylaminobenzaldehyde. The cyclization of (7a-f) with chloroacetyl chloride and phenylisocynate gave the corresponding β-lactam (8a-f) and aza-B-lactam(9a-f) derivatives. F.T.IR and ^{1}-HNMR were used to characterize the target compounds.

Keywords: benzohydrazide, oxadizole, beta-lactam, aza-beta-lactam

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INTRODUCTION

Saccharin compounds have been intensively investigated due to its suspected cancer genic nature [1]. Many biological activities have been attributed to this group, which are known as inhibitors of serine proteases[2].It`s importance has increased over the years and it can be viewed as a privileged scaffold in the field of medicinal chemistry. This particular heterocyclic can either be a substituent of a larger compound that assumes the role of a frame work, or it can play the role of the pharmacophore of bioactive molecules [3]. Hydrazide derivatives attracted a lot of attention because they are considered as intermediates to synthesize several compounds such as Schiff bases, thiadiazole [4], oxadiazole[5] and triazole[6]. Oxadiazole derivatives belong to an important group of heterocyclic compounds and have been the subject of extensive studies in the past years. Numerous reports have highlighted their chemistry and use diver's biological activities such as anti-tuberculostatic, anti-inflammatory, analgesic, antipyretic and anti-convulsing [7]Schiff bases exhibit good antimicrobial activity and pharmacological applications. These compounds show good fungicidal activity [8] and antiviral[9],antimicrobial[10] and anti-inflammatory activities and play as antioxidant[11],anticancer[12] ,antibacterial[13] antifungal[14] and herbicidal[15].β- Lactams, being a structural unit found in the most widely used antibiotics [16, 17]. β -Lactams have been found to act as cholesterol acyltransferase inhibitors [18], thrombin inhibitors [19] and cysteine protease[20]. Aza-β-lactams have attracted interest because of their biological activity and their utility as intermediates in organic chemistry (e.g., for the generation of a-amino acids and hydantoins) [21-23].

EXPERIMENTAL SECTION

Melting points were recorder using electro thermal melting point apparatus and were uncorrected. FTIR spectra were run on a Shimadzu FTIR-8400S spectrophotometer. ^{1}H-NMR was recorder on Bruker Ultra Shield, 400MHz,

using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. Thin-layer chromatography was performed glass plats coated with 0.25 mm layer of silica-gel (Fluka).

Preparation of *o*-(N-alkylsulfamido)benzohydrazide) (4a-c):
To solution of ester derivatives[24] (3a-c) (0.04 mole) in absolute ethanol (15ml) hydrazine hydrate (80%) (0.08mole) was added and the reaction mixture was refluxed for 5h. After cooling, the formed precipitate was filtered and recrystallized from ethyl acetate to give compounds (4a-c) respectively.

***o*-[N-benzyl sulfamido]benzohydrazide(4a)**
Yield 95%, m.p. 100-103^{0}C, Rf (0.435), IR(KBr) cm^{-1}: 3205(NH), 1633(C=O), 1542(amide II), 1371(C-N). H-NMR (DMSO d_6) δ: (s, 3.3, 2H, -NH_2), (s, 3.9, 2H, CH_2 benzylic), (m, 7-7.9, 10H, Ar-H and $NHSO_2$), (d, 10.6-10.8, 1H, NH-amide).

***o*-[N-(n-propyl)sulfamido]benzohydrazide(4b)**
Yield 90%, m.p. 107-110^{0}C, R_f (0.531), IR(KBr) cm^{-1}: 3236(NH), 1645(C=O), 1541(amide II), 1338(C-N). H-NMR (DMSO d_6) δ: (t, 0.5-0.8, 3H, CH_3), (m, 1.3-2, 2H, $\underline{CH_2}$-CH_3), (t, 2.5, 2H, -NH-$\underline{CH_2}$-), (s, 3.3, 2H, NH_2), (m, 6.8-7.9, 5H, Ar-H and SO_2-NH), (d, 10.7, 1H, NH amide).

***o*-[N-(sec-butyl)sulfamido]benzohydrazide(4c)**
Yield 88%. m.p. 105-107^{0}C. R_f (0.473), IR(KBr) cm^{-1} : 3205(NH), 1633(C=O), 1542(amide II), 1371(C-N). H-NMR (DMSO d_6) δ: (t, 0.5-1.0, 3H, $\underline{CH_3}$-CH), (m, 1.2-2, 5H, $\underline{CH_2}$-CH, $\underline{CH_3}$-CH), (s, 3.3, 2H, NH_2), (m, 3.3-3.6, 1H, CH-N), (m, 7-8, 5H, Ar-H and–NH-SO_2), (d, 10.7, 1H, NH amide).

Preparation of N-[alkyl-*o*-(2-mercapto-1, 3, 4-oxadiazol-5-yl)]benzene sulfonamide(5a-c):
A mixture of compounds (4a-c)(0.04mole) with (0.04mole) carbon disulfide and potassium hydroxide (0.04mole,1.44g)was refluxed for 24h, then the solvent was evaporated and the residue was dissolved in water and acidified by dilute hydrochloric acid, the precipitate was filtered ,wash with water and recrystallized from ethanol to give compounds (5a-c) respectively.

N-benzyl-*o*-(2-mercapto-1, 3, 4-oxadiazol-5-yl) benzene sulfonamide(5a)
Yield 95%, m.p. 100-103^{0}C, R_f (0.435), IR(KBr) cm^{-1}: 3083(Ar-H), 2559(S-H), 1600(C=N), 1081(C-O-C). H-NMR (DMSO d_6) δ: (s, 3.5, 1H, SH), (s, 4.1, 2H, CH_2 benzylic) (m, 7-8.3, 10H, Ar-H and –NH-SO_2).

N- (n-propyl)-*o*-(2-mercapto-1, 3, 4-oxadiazol-5-yl) benzene sulfonamide(5b)
Yield 90%, m.p. 99-102^{0}C, R_f (0.342), IR(KBr) cm^{-1}: 3068(Ar-H), 2595(S-H), 1596(C=N), 1074(C-O-C). H-NMR (DMSO d_6) δ: (t, 0.5-0.8, 3H, CH_3), (m, 1.3-2, 2H, $\underline{CH_2}$-CH_3), (t, 2.5-2, 2H, -NH-$\underline{CH_2}$-), (s, 3.5, 1H, SH), (m, 6.8-7.9, 5H, Ar-H and SO_2-NH).

N- (sec-butyl)-*o*-(2-mercapto-1, 3, 4-oxadiazol-5-yl) benzene sulfonamide(5c)
Yield 88%, m.p. 90-93^{0}C, R_f (0.437), IR(KBr) cm^{-1}: 3066(Ar-H), 2555(S-H), 1604(C=N), 1085(C-O-C). ^{1}H-NMR (DMSO d_0) δ: (t, 0.5-1.0, 3H, $\underline{CH_3}$-CH), (m, 1.2-2, 5H, $\underline{CH_2}$-CH, $\underline{CH_3}$-CH) (m, 3.3-3.6, 1H, CH-N), (s, 3.8, 1H, SH) (m, 7-8, 5H, Ar-H and–NH-SO_2).

Preparation of N-[alkyl-o-(5-hydrazido-1,3,4-oxadiazol-5-yl)]benzene sulfonamide(6a-c):
A mixture of compounds (5a-c) (0.04 mole) with hydrazine hydrate (0.08 mole) and 10ml absolute ethanol was refluxed for 5h.After that the solvent was removed and the formed precipitate was filter and recrystallized from ethanol to give compounds (6a-c) respectively.

N-[benzyl-*o*-(5-hydrazido-1,3,4-oxadiazol-5-yl)]benzene sulfonamide(6a)
Yield 95%, m.p. 72-75^{0}C, R_f (0.576), IR(KBr) cm^{-1}: 3242(NH), 3031(C-H Ar), 1645(δ NH_2), 1645(C=N), 1261(C-N). ^{1}H-NMR (DMSO d_6) δ: (s, 4.1, 2H, CH_2 benzylic), (s, 4, 2H, $\underline{NH_2}$), (s, 6.7, 1H, $\underline{NH}$-NH_2), (m, 7-8.3, 10H, Ar-H and –NH-SO_2).

N-[n-propyl-*o*-(5-hydrazido-1,3,4-oxadiazol-5-yl)]benzene sulfonamide(6b)
Yield 90%, m.p. 67-69^{0}C, R_f (0.511), IR (KBr)cm^{-1}: 3209(NH), 3070(C-H Ar), 1639(δ NH_2), 1597(C=N), 1259(C-N). ^{1}H-NMR (DMSO d_6) δ: (t, 0.5-0.8, 3H, CH_3), (m, 1.3-2, 2H, $\underline{CH_2}$-CH_3), (t, 2.5-2, 2H, -NH-$\underline{CH_2}$-), (s, 4, 2H, NH_2), (s, 6.7, 1H, $\underline{NH}$-NH_2), (m, 6.8-7.9, 5H, Ar-H and SO_2-NH).

N-[sec-butyl-*o*-(5-hydrazido-1,3,4-oxadiazol-5-yl)]benzene sulfonamide(6c)
Yield 88%, m.p. 64-66^{0}C, R_f(0.479), IR(KBr)cm^{-1}: 3200(NH), 3060(C-H Ar), 1631(δ NH_2), 1593(C=N), 1259(C-N). ^{1}H-NMR (DMSO d_6) δ: (t, 0.5-1.0, 3H, $\underline{CH_3}$-CH), (m, 1.2-2, 5H, $\underline{CH_2}$-CH, $\underline{CH_3}$-CH), (m, 3.3-3.6, 1H, CH), (s, 4, 2H, NH_2), (s, 6.7, 1H, $\underline{NH}$-NH_2), (m, 7-8, 5H, Ar-H and –NH-SO_2).

Preparation of Schiff Bases Derivatives (7a-f) :
General procedure: A mixture of compounds (6a-c) (1.9mmol), appropriate aromatic aldehydes namely p-dimethylaminobenzaldehyde, 2, 4-dimethoxybenzaldehyde and few drops of glacial acetic acid in (20ml) absolute ethanol were refluxed for (6 hrs). The formed precipitate after cooling was filtered, dried and recrystallized from ethanol to give compounds 7(a-f) respectively.

N-(p-dimethylbenzylidene)-N$^{\backslash}$-[5-(*o*-N$^{\backslash\backslash}$-benzylphenylsulfamido)1,3,4-oxadiazol-2-yl]hydrozide(7a)
Yield 95%, m.p. 170-172^{0}C, R_f (0.452), IR(KBr) cm^{-1}: 3284(NH), 3072(C-H Ar), 2926(C-Hal ph.), 1649(C=N). ^{1}H-NMR (DMSO d_6) δ: s, 3, 6H, N(CH_3)$_2$), (s, 3.4, 2H, CH_2 benzylic) (s, 6.8, 1H, NH-N), (m, 7.2-7.8, 14H, Ar-H and –NH-SO_2), (s, 8.4, 1H, N=CH-)

N-(2,4- dimethoxy phenyl)-N$^{\backslash}$-[5-(*o*-N$^{\backslash\backslash}$-benzyl phenyl sulfamido)1,3,4-oxadiazol-2-yl]hydrozide(7b)
Yield 80%, m.p. 165-168^{0}C, R_f (0.344), IR(KBr) cm^{-1}: 3290(NH), 3064(C-H Ar), 2964(C-Hal ph.), 1641(C=N). ^{1}H-NMR (DMSO d_6) δ: (s, 3.4, 2H, CH_2 benzylic), (s, 3.8, 6H, (-OCH_3)$_2$), (s, 6.8, 1H, NH-N), (m, 7.2-7.8, 14H, Ar-H and –NH-SO_2), (s, 8.4, 1H, N=CH-)

N-(p- dimethyl benzylidene)-N$^{\backslash}$- [5-(*o*-N$^{\backslash\backslash}$-n-propyl phenyl sulfamido)1,3,4-oxadiazol-2-yl]hydrozide(7c)
Yield 85%, m.p. 120-122^{0}C, R_f (0.344), IR(KBr) cm^{-1}: 3284(NH), 3060(C-H Ar), 2972(C-Hal ph.), 1645(C=N). ^{1}H-NMR (DMSO d_6) δ: (t, 0.7-0.9, 3H, CH_3), (m, 1.3-1.6, 2H $\underline{CH_2}$-CH_3), (t, 2.9-3.2, 2H, N-CH_2), (s, 3.4, 6H, N(CH_3)$_2$), (s, 6.8, 1H, NH-N), (m, 7.2-8, 9H, Ar-H and SO_2-NH), (s, 8.5, 1H, N=CH-).

N-(2,4-dimethoxyphenyl)-N$^{\backslash}$-[5-(*o*-N$^{\backslash\backslash}$-n-propylphenylsulfamido)1,3,4-oxadiazol-2-yl]hydrozide(7d)
Yield 90%, m.p. 110-112, R_f (0.632), IR(KBr) cm^{-1}: 3286(NH), 3090(C-H Ar), 2937(C-Hal ph.), 1677(C=N). ^{1}H-NMR (DMSO d_6) δ: (t, 0.7-0.9, 3H, CH=), (m, 1.3-1.6, 2H $\underline{CH_2}$-CH_3), (t, 2.9-3.2, 2H, N-CH_2), (s, 3.8, 6H, (-OCH_3)$_2$), (s, 6.8, 1H, NH-N), (m, 7.2-8, 9H, Ar-H and SO_2-NH), (s, 8.5, 1H, N=CH-).

N-(p-dimethylbenzylidene)-N$^{\backslash}$-[5-(*o*-N$^{\backslash\backslash}$-sec-butyl phenyl sulfamido)1,3,4-oxadiazol-2-yl]hydrozide(7e)
Yield 88%, m.p. 100-103^{0}C, R_f (0.343), IR(KBr) cm^{-1}: 3261(NH), 3089(C-H Ar), 2927(C-Hal ph.), 1649(C=N). ^{1}H-NMR (DMSO d_6) δ: (t, 0.6-0.9, 3H, $\underline{CH_2}$-CH_3), (m, 1.2-2, 5H, CH-$\underline{CH_3}$, CH-$\underline{CH_2}$), (m, 3-3.5, 1H, CH), (s, 3.7, 6H, N(CH_3)$_2$), (s, 6.6, 1H, NH-N=), (m, 7.4-8.4, 8H, Ar-H and NH-SO_2), (s, 8.7-8.95, 1H, CH=N).

N-(2,4- dimethoxy phenyl)- N$^{\backslash}$- [5-(*o*-N$^{\backslash\backslash}$-sec-butyl phenyl sulfamido)1,3,4-oxadiazol-2-yl]hydrozide(7f)
Yield 78%, m.p. 108-110^{0}C, R_f (0.533), IR(KBr) cm^{-1}: 3263(NH), 3006(C-H Ar), 2970(C-Hal ph.), 1679(C=N). ^{1}H-NMR (DMSO d_6) δ: (t, 0.6-0.9, 3H, CH_2-$\underline{CH_3}$), (m, 1.2-2, 5H, CH-$\underline{CH_3}$, CH-$\underline{CH_2}$), (m, 3-3.5, 1H, CH), (s, 3.8, 6H, (-OCH_3)$_2$), (s, 6.6, 1H, NH-N=), (m, 7.4-8.4, 8H, Ar-H and NH-SO_2), (s, 8.7-8.95, 1H, CH=N).

Preparation of azetidinone derivatives (8a-f):
A solution of chloroacetyl chloride(0.122 gm, 1 mmol.) in dry dioxane(10ml) was slowly added to a solution of Schiff- bases (7a-f) (0.5 mmol.) and triethyl amine(1mmol.) in (10ml) dry dioxane at (0 – 5)°C. The mixture was stirred for 3 h at (0 - 5) °C and set aside to room temperature and stirred for (15h). The precipitate obtained was filtered and recrystallized from hexane: ethylacetate(1:1) to give compounds (8a-f) respectively.

5-[*o*-(N-benzyl) phenyl sulfamido]-2-[3-chloro-4-(*p*-dimethylamino) phenyl-2-oxo-azetine-1-yl] amino-1,3,4-oxadizole (8a)
Yield 94%, m.p. 230^{0}C, R_f (0.566), IR(KBr) cm^{-1}: 3200(NH), 2978(C-H alph.), 1745(C=O lactam.), 850(C-Cl). ^{1}H-NMR (DMSO d_6) δ: (s, 3, 6H, N(CH_3)$_2$), (s, 3.4, 2H, CH_2, benzylic), (d, 5, 2H, N-CH), (d, 5.7, 2H, CH-Cl), (s, 6.9, 1H, NH-N), (m, 7.2-7.9, 14H, Ar-H and –NH-SO_2).

5-[*o*-(N-benzyl) phenyl sulfamido]-2-[3-chloro-4-(2,4-dimethoxy) phenyl-2-oxo-azetine-1-yl]amino-1,3,4-oxadizole (8b)
Yield 83%, m.p. 200^{0}C, R_f (0.544), IR(KBr) cm^{-1}: 3255(NH), 2977(C-H alph.), 1740(C=O lactam.), 850(C-Cl). ^{1}H-NMR (DMSO d_6) δ: (s, 3.4, 2H, CH_2, benzylic), (s, 3.8, 6H, (-OCH_3)$_2$), (d, 5, 2H, N-CH), (d, 5.6, 2H, CH-Cl), (s, 6.9, 1H, NH-N), (m, 7.2-7.9, 14H, Ar-H and –NH-SO_2).

5-[*o*-N-(n-propyl)phenylsulfamido]-2-[3-chloro-4-(*p*-dimethylamino) phenyl-2-oxo-azetine-1-yl] amino-1,3,4-oxadizole (8c)
Yield 84%, m.p. 205^{0}C, R_f (0.343), IR(KBr) cm^{-1}: 3255(NH), 2975(C-H alph.), 1719(C=O lactam.), 850(C-Cl). ^{1}H-NMR (DMSO d_6) δ: (t, 0.7-0.9, 3H, CH_3), (m, 1.3-1.6, 2H, $\underline{CH_2}$-CH_3), (t, 2.9-3.2, 2H, N-CH_2), (s, 3.4, 6H, $N(CH_3)_2$), (d, 5, 2H, N-CH), (d, 5.7, 2H, CH-Cl), (s, 6.8, 1H, NH-N), (m, 7.2-8, 9H, Ar-H and SO_2-NH), (s, 8.5, 1H, N=CH-).

5-[*o*-N-(n-propyl)phenyl sulfamido]-2-[3-chloro-4-(2,4-dimethoxy) phenyl-2-oxo-azetine-1-yl] amino-1,3,4-oxadizole (8d)
Yield 89%, m.p. 210^{0}C, R_f (0.321), IR(KBr) cm^{-1}: 3250(NH), 2977(C-H alph.), 1760(C=O lactam.), 850(C-Cl). ^{1}H-NMR (DMSO d_6) δ: (t, 0.7-0.9, 3H, CH_3), (m, 1.3-1.6, 2H $\underline{CH_2}$-CH_3), (t, 2.9-3.2, 2H, N-CH_2), (s, 3.8, 6H, (-$OCH_3)_2$), (d, 5, 2H, N-CH), (d, 5.7, 2H, CH-Cl), (s, 6.8, 1H, NH-N), (m, 7.2-8, 9H, Ar-H and SO_2-NH), (s, 8.5, 1H, N=CH-).

5-[*o*-N(sec-butyl)phenyl sulfamido]-2-[3-chloro-4-(*p*-dimethylamino) phenyl-2- oxo-azetine-1-yl] amino-1,3,4-oxadizole (8e)
Yield 86%, m.p. 215^{0}C, R_f (0.663), IR(KBr) cm^{-1}: 3250(NH), 2977(C-H alph.), 1720(C=O lactam.), 850(C-Cl). ^{1}H-NMR (DMSO d_6) δ: (t, 0.6-0.9, 3H, CH_2-$\underline{CH_3}$), (m, 1.2-2, 5H, CH-$\underline{CH_3}$, CH-$\underline{CH_2}$), (m, 3-3.5, 1H, CH), (s, 3.7, 6H, $N(CH_3)_2$), (d, 5, 2H, N-CH), (d, 5.7, 2H, CH-Cl), (s, 6.6, 1H, NH-N=), (m, 7.4-8.4, 8H, Ar-H and NH-SO_2), (s, 8.7-8.95, 1H, CH=N).

5-[*o*-N-(sec-butyl) phenyl sulfamido]-2-[3-chloro-4-(*p*-dimethoxy) phenyl-2-oxo-azetine-1-yl] amino-1,3,4-oxadizole (8f)
Yield 80%, m.p. 220^{0}C, R_f (0.433), IR(KBr) cm^{-1}: 3255(NH), 2977(C-H alph.), 1722(C=O lactam.), 850(C-Cl). ^{1}H-NMR (DMSO d_6) δ: (t, 0.6-0.9, 3H, CH_2-CH_3), (m, 1.2-2, 5H, CH-CH_3, CH-CH_2), (m, 3-3.5, 1H, CH), (s, 3.8, 6H, (-$OCH_3)_2$), (d, 4.9-5.1, 2H, N-CH), (d, 5.6-5.9, 2H, CH-Cl), (s, 6.6, 1H, NH-N=), (m, 7.4-8.4, 8H, Ar-H and NH-SO_2), (s, 8.7-8.95, 1H, CH=N).

Preparation of 1,3-diazetidine-4-one(Aza-B-Lactam)derivatives (9a-f):
A mixture of Schiff bases (7a-f) (0.01mole)and phenyl isocyanate (0.01mole,1.2g) in toluene (25ml) was refluxed for 6h. The solvent was removed and the residue treaded with a mixture of (1:1) ethyl acetate and petroleum ether. The resultant precipitate was filtered and dried to give compounds (9a-f) respectively.

5-[*o*-(N-benzyl) phenyl sulfamido]-2-[3-phenyl-4-(*p*-dimethylamino) phenyl-2-oxo-1,3diazetidin-1-yl] amino-1,3,4-oxadizole (9a)
Yield 90%, m.p. 220^{0}C, R_f (0.331), IR(KBr) cm^{-1}: 3269(NH), 2946(C-H alph.), 1747(C=O aza-lactam). ^{1}H-NMR (DMSO d_6) δ: (s, 3, 6H, $N(CH_3)_2$), (s, 3.4, 2H, CH_2, benzylic), (s, 5, 2H, N-CH), (s, 6.9, 1H, NH-N), (m, 7.2-7.9, 14H, Ar-H and –NH-SO_2).

5-[*o*-(N-benzyl) phenyl sulfamido]-2-[3-phenyl-4-(2,4-dimethoxy) phenyl-2-oxo-1,3diazetidin-1-yl] amino-1,3,4-oxadizole (9b)
Yield 88%, m.p. 230^{0}C, R_f (0.342), IR(KBr) cm^{-1}: 3277(NH), 2960(C-H alph.), 1732(C=O aza-lactam). ^{1}H-NMR (DMSO d_6) δ: (s, 3.4, 2H, CH_2, benzylic), (s, 3.8, 6H, (-$OCH_3)_2$), (s, 5, 2H, N-CH), (s, 6.9, 1H, NH-N), (m, 7.2-7.9, 14H, Ar-H and –NH-SO_2).

5-[*o*-N-(n-propyl) phenyl sulfamido]-2-[3-phenyl-4-(*p*-dimethylamino) phenyl-2-oxo-1,3diazetidin-1-yl] amino-1,3,4-oxadizole (9c)
Yield 85%, m.p. 200^{0}C, R_f (0.546), IR(KBr) cm^{-1}: 3267(NH), 2946(C-H alph.), 1716(C=O aza-lactam). ^{1}H-NMR (DMSO d_6) δ: (t, 0.7-0.9, 3H, CH_3), (m, 1.3-1.6, 2H$\underline{CH_2}$-CH_3), (t, 2.9-3.2, 2H, N-CH_2), (s, 3.4, 6H, $N(CH_3)_2$), (s, 5, 2H, N-CH), (s, 6.8, 1H, NH-N), (m, 7.2-8, 9H, Ar-H and SO_2-NH), (s, 8.5, 1H, N=CH-).

5-[*o*-N-(n-propyl) phenyl sulfamido]-2-[3-phenyl-4-(2,4-dimethoxy) phenyl-2-oxo-1,3diazetidin-1-yl] amino-1,3,4-oxadizole (9d)
Yield 86%, m.p. 240^{0}C, R_f (0.433), IR(KBr) cm^{-1}: 3272(NH), 2964(C-H alph.), 1714(C=O aza-lactam). ^{1}H-NMR (DMSO d_6) δ: (t, 0.7-0.9, 3H, CH_3), (m, 1.3-1.6, 2H$\underline{CH_2}$-CH_3), (t, 2.9-3.2, 2H, N-CH_2), (s, 3.8, 6H, (-$OCH_3)_2$), (s, 5, 2H, N-CH), (s, 6.8, 1H, NH-N), (m, 7.2-8, 9H, Ar-H and SO_2-NH), (s, 8.5, 1H, N=CH-).

5-[*o*-N(sec-butyl)phenyl sulfamido]-2-[3-phenyl-4-(*p*-dimethylamino) phenyl-2-Oxo-1,3diazetidin-1-yl] amino-1,3,4-oxadizole (9e)

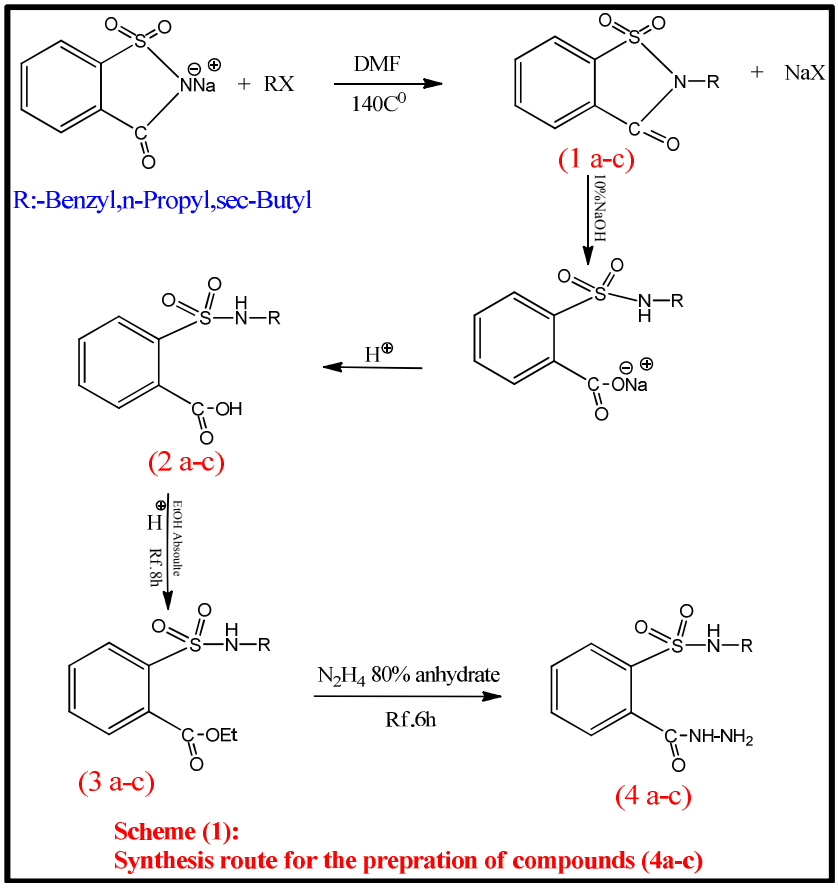
Yield 82%, m.p. 235^{0}C, R_f (0.331), IR(KBr) cm^{-1}: 3261(NH), 2966(C-H alph.), 1720(C=Oaza-lactam). ^{1}H-NMR (DMSO d_6) δ: (t, 0.6-0.9, 3H, CH_2-$\underline{CH_3}$), (m, 1.2-2, 5H, CH-$\underline{CH_3}$, CH-$\underline{CH_2}$), (m, 3-3.5, 1H, CH), (s, 3.7, 6H, $N(CH_3)_2$), (s, 5, 2H, N-CH), (s, 6.6, 1H, NH-N=), (m, 7.4-8.4, 8H, Ar-H and NH-SO_2), (s, 8.7-8.95, 1H, CH=N).

5-[*o*-N-(sec-butyl) phenyl sulfamido]-2-[3-phenyl-4-(2,4-dimethoxy) phenyl-2-oxo-1,3diazetidin-1-yl] amino-1,3,4-oxadizole (9f)

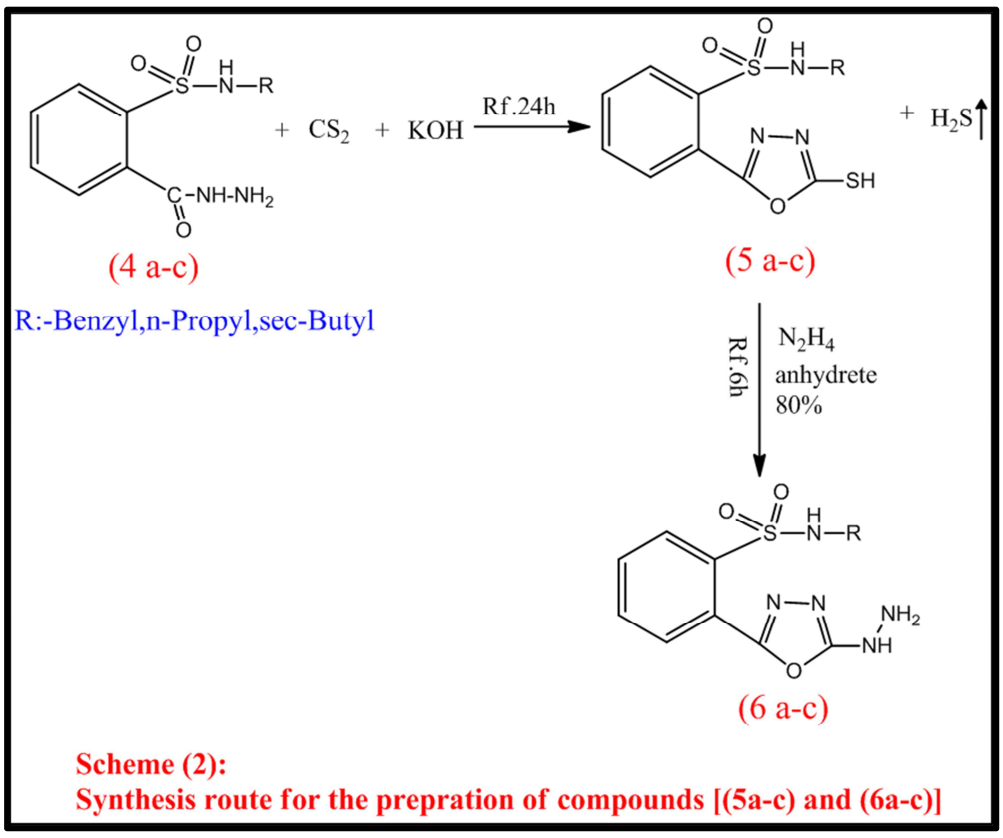
Yield 79%, m.p. 225^{0}C, R_f (0.653), IR(KBr) cm^{-1}: 3269(NH), 2968(C-H alph.), 1710(C=O aza-lactam). ^{1}H-NMR (DMSO d_6) δ: (t, 0.6-0.9, 3H, CH_2-CH_3), (m, 1.2-2, 5H, CH-CH_3, CH-CH_2), (m, 3-3.5, 1H, CH), (s, 3.8, 6H, (-$OCH_3)_2$), (d, 4.9-5.1, 2H, N-CH), (s, 6.6, 1H, NH-N=), (m, 7.4-8.4, 8H, Ar-H and NH-SO_2), (s, 8.7-8.95, 1H, CH=N).

RESULTS AND DISCUSSION

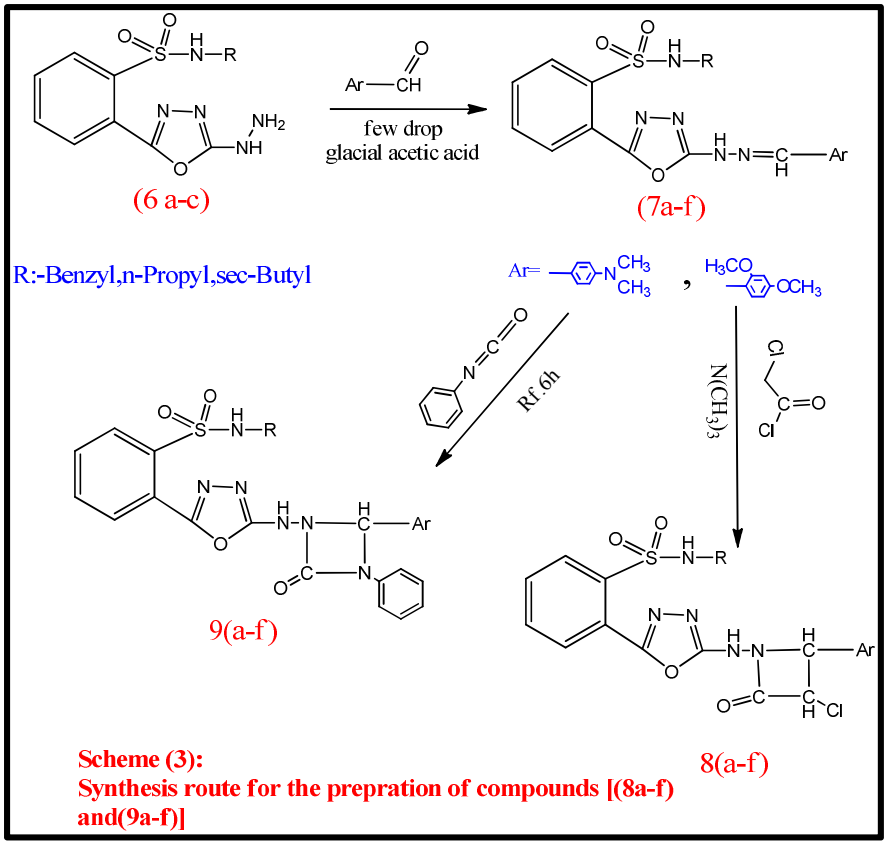
Sodium saccharin salt was chosen as a starting material for the synthesis of all derivatives (1a-c) - (9a-f).It was reacted with different alkyl halide namely benzyl chloride, n-propyl bromide and sec-butyl bromide to get N-alkyl Saccharin(1a-c).Then it was hydrolysis to give N-alkylsulfamidobenzoic acid derivatives (2a-c). To synthesis benzohydrazide compounds (4a-c), the compounds (2a-c) was first converted to ethyl-o-(N-alkylsulfamideo) benzoate (3a-c) by the reaction with absolute ethyl alcohol in presence H_2SO_4 The reaction of hydrazine hydrate with ester in absolute ethylalcohol is one of the most common reactions to synthesize the acid hydride[26] (4a-c). The disappearance of (C=O ester) stretching band at (1737-1716) cm^{-1} and the appearance of stretching bands (NH-NH2) at (3236-3201)cm-1, (C=O amid) at (1645-1633)cm^{-1},and showed^{-1}H-NMR spectrum of compounds characteristic signals:(d, 3.2-3.5, 2H, -NH_2), (d, 10.6-10.8, 1H, NH-amide)are attributed to the formation of acid hydrazide derivatives(Scheme 1). Cyclization of (4a-c) with carbondisulfide in presence potassium hydroxide (Scheme 2) gave the corresponding 2-mercapto-1,3,4-oxadiazole derivatives (5a-c).The disappearance of the absorption bands at (3236-3201)cm^{-1} (NH-NH_2), (1645-1633)cm^{-1} (C=O amide) and appearance absorption bands of SH at (2590-2555) cm^{-1} and (1604-1596) cm^{-1} for C=N were confirm the structures of the compound (5a-c) the ^{1}H.NMR spectrum showed the following signals: singled at 13ppm, 1H, assigned to thiol group(SH).The refluxing of (5a-c) with 80% hydrazide hydrate in absolute ethyl alcohol gave 5-hydrazido-1,3,4-oxdiazole derivatives(6a-c). The absence of a stretching thiol group absorption band at (2590-2555)cm^{-1} and the appearance of absorption band which is due to starching NH2 at (3325-3251)cm^{-1} and vibration bending NH_2 at(1645-1631), were attributed to the formation 5-hydrazido derivatives (6a-c), ^{1}HNMR of these derivatives showed the following characteristic signals:(s, 4, 2H, NH-NH_2), (s, 6.7, 1H, NH-NH_2) (Scheme 2). Schiff-bases (7a-f) (Scheme 3) were prepared by condensation of (6a-c) with some aromatic aldehydes namely 2,4-dimethoxy benzaldehyde and p-dimethyloxybenzaldehyde with few drops of glacial acidic acid. The I. R. and ^{1}H-NMR spectrum of formed Schiff bases showed the presence of(C=N) band at 1677-1645cm^{-1} and a singlet signal for azomethine (CH=N) at 8.7 ppm. Imines (7a-f) that reacted with chloroacetyl chloride in dry dioxane in the presence of trimethyl amine via a [2+2] cycloaddition reaction[25] to give corresponding β-lactam derivatives (8a-f). The I.R. spectrum of formed azetidineones showed the presence of β-lactam carbonyl absorption at 1745-1718 cm^{-1} while the ^{1}H-NMR spectrum showed doublet signal at 4.9 and doublet signal at 5.1 ppm assigned to (CH) protons of β-lactam ring at positions 3 and 4. Also cyclization of imines (7a-f) with phenyl isocyanide gave the corresponding aza-B-lactam derivatives(9a-f) respectively. The I.R spectrum of formed aza-B-lactam showed the presence carbonyl group (C=O aza-β-lactam) at (1745-1710) cm^{-1} while the ^{1}H-NMR spectrum showed singlet signal at 5.2 ppm give a good evidence for the formation of the aza-β-lactam derivatives(9a-f)(Scheme 3).



Scheme (1):
Synthesis route for the prepration of compounds (4a-c)



Scheme (2):
Synthesis route for the prepration of compounds [(5a-c) and (6a-c)]



Scheme (3):
Synthesis route for the prepration of compounds [(8a-f) and(9a-f)]

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