Synthesis, Characterization and Antibacterial Activity of Some New Five-Seven Membered Rings Attached to Sulfonamide Compounds

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Abstract

This work includes the synthesis of some new five- seven heterocyclic rings derived from benzenesulfonylhydrazide as starting material. Its condensation with 4-methoxy and 4-nitro benzaldehyde gives the Schiff bases (1a,b). Schiff bases were reacted with cyclic anhydrides given Oxazepine, Thiazepine derivatives(2,3,4 a,b)(seven membered ring) and with 2-mercapto benzoic acid gives thiazine derivatives (6a,b)(six membered ring) finally with thioglycolic acid give thiazolidine ring(five membered ring) scheme(3). The synthesized compounds have been characterized by melting points,FT-IR, ^{1}H-NMR spectroscopy ,^{13}C-NMR and Elemental analysis. some of synthesized compounds were tested for their antibacterial activity against *staphylococcus aureus*, *pseudomonous aureous* and *Escherichia coli* .The results showed good efficacy against these types of bacteria.

Keywords: sulfonamide, Oxazepine, Thiazepine, Thiazine, Thiazolidine, Schiff bases, Antibacterial activity.

Introducion

Sulfonamide compounds or sulfonamide drugs have brought about an antibiotic revolution in medicinal chemistry are associated with a high range of biological activities [1-3] .Oxygen, Nitrogen; Sulfur heterocycles fused with sulfonamide compounds have a wide amount of attention the literature .heterocyclic compounds attached with sulfonamides were used as carbonic anhydrase inhibitors[4,5],Antimicrobial activity[6,7] γ-secretase inhibitors[8] ,anti-inflammatory[9],Aniticancer[10]. Thiazolidine is a type of heterocyclic compound contains five membered ring with a sulfur, nitrogen atoms. It is an important compound in medicinal chemistry because it has a wide spectrum in biological activity [11] .The thiazine nucleus has been incorporated into a wide variety of therapeutically agents such as antimicrobial[12],antibacterial[13] and cannabinoid[14].oxazepine compounds are seven membered ring contain oxygen and nitrogen. It has documented that oxazepines are important in the diverse fields of heteroatom chemistry and biochemistry owing to its high range of biological activities[15].These compounds are important in medicinal chemistry because they are used as starting material for synthesis of diazepam(valum), it is a class of drug used as relaxant and muscle relaxant because it is often seen in forensic and clinical cases[16].Heterocycles containing thiazepine fragment are a key moiety in a large number of

natural and synthetic bio-active molecules. Thiazepine compounds are used as exhibited angiotensin-converting enzyme inhibition [17], Antiviral [18] and anticancer[19].

Experimental

Whilst p-nitro benzaldehyde, p-methoxybenzaldehyde, maleic anhydride ,phthalic anhydride,o-sulfobenzoicacid cyclic anhydride, 2-mercapto benzoic acid,thioglycolic acid were obtained from Sigma-Aldrich.All solvents were purchased from Fluka used as received. Melting points were determined on digital stuart SMP-3 apparatus. Fourier transform Infrared spectra were measured on Schimadzu 8300 spectrophotometer using KBr disks. ^{1}H-NMR, ^{13C}-NMR spectra were measured in DMSO solutions on a Bruker Av spectrophotometer (300 MHz) using TMS as an internal reference (chemical shifts in δ ppm). All synthesized compounds were elemental analysis C,H,N and S on a European Elemental analyzer.Thin layer chromatography was performed on silica gel as a stationary phase ,ethyl acetate as eluent.

Synthesis of benzenesulfonylhydrazide

A benzenesulfonylchloride (0.01 mol)in dry benzene and hydrazine hydrate (2 ml) were added . the mixture was stirred and heated at reflux for 3h .the reaction mixture was poured with good stirring into 100 ml ice-cold water and kept at room temperature until the reaction product separated as asolid,which was filtered off and recrystallized from ethanol, m.p= 104-1-6 ^{0}C as literature.

Synthesis of N'-(4-substitutedbenzylidene)benzenesulfonylhydrazide(1a,b)

A solution of benzenesulfonohydrazide (0.01mol)on ethanol absolute (15ml),the appropriate aldehyde (0.01mol) and 2-3 drops of glacial acetic acid was refluxed for 3h. The result was allowed to cool at room temperature. The solid was collected by filtration and recrystallized from ethanol absolute to give the pure Schiff bases. The FT-IR of these compounds showed disappearance bands of (-NH_2) group and appearance bands at (1633-1639)$^{cm-1}$ due to of (C=N)moiety.

Synthesis of N-(3-(4-substitutedphenyl)-1,5-dioxobenzo[e][1,3]oxazepin-4(1H,3H,5H)-yl)benzenesulfonamide(2a,b).

Into a dry 50 ml round bottom flask , introduce (0.01mol) of Schiff bases in 20 ml of dry benzene and stirred the reaction mixture for 15min then refluxed at 60^{0C} for 2h. The mixture was allowed to stand overnight and solid separated out was filtered and washed with dioxane. The compound so obtained was dried and recrystallized from appropriate solvents. Recrystallized from ethanol.

Compound 2a

Yield 75%,m.p=215^0C: FT-IR(KBr) ν cm^{-1}:3205(N-H), 2850-2900(C-H),1722(C=O) lactone,1666(C=O)lactam,1170 and 1334(SO_2);H-NMRδ ppm: ^{1}H-NMR (DMSO 300MHz) 9.81 (s,1H, CH) in oxazepine ring, 7.3(s,1H,NH), 6.8-7.18(m,aromatic rings),3.8ppm(s,3H,OCH_3);Anal.calc.for $C_{22}H_{18}N_2O_6S$:found:C, 61.10; H, 4.3: N,6.45: S,7.33 calc: C, 60.27; H, 4.14: N,6.39: S,7.31.

Compound 2b

Yield 79%, m.p=225^0C: FT-IR(KBr) ν cm^{-1}:3219(N-H), 2833-2910(C-H),1720(C=O) lactone,1660(C=O)lactam,1358 and 1551(NO_2),1172 and 1349(SO_2); Anal.calc.for $C_{21}H_{15}N_3O_7S$:found:C, 56.11; H, 3.12: N,9.43: S,7.15 calc: C, 55.63; H, 3.33: N,9.27: S,7.07.

Synthesis of N-(3-(4-substitutedphenyl)-1,5-dioxobenzo[e][1,3]thiazepin-4(1H,3H,5H)-yl)benzenesulfonamide(3a,b)

Equimolar amounts of schiff bases (1a,b) and 2-sulfobenzoic anhydride in 20 mol of dioxane were heated under reflux for 6h. the solid product so obtained on cooling was collected by filtration and crystallized from toluene.

Compound 3a

Yield 55%, m.p=248^0C: FT-IR(KBr) ν cm^{-1}:3203(N-H), 2800-2907(C-H),1726(C=O) lactone,1174 and 1348 (SO_2,sulfonamide), 1141 and 1319 (SO_2,in ring); Anal.calc.for $C_{22}H_{18}N_2O_5S_2$:found:C, 54.00; H, 3.76: N,5.16: S,13.09 calc: C, 53.16; H, 3.82: N,5.90: S,13.52.

Compound 3b

Yield 65%,m.p=224^0C: FT-IR(KBr) ν cm^{-1}:3212(N-H), 2843-2897(C-H),1729(C=O) lactone,1172 and 1330(SO_2),1151 and 1329(SO_2),1345 and 1567(NO_2);H-NMR δ ppm: ^{1}H-NMR (DMSO 300MHz) 9.63 (s,1H, CH), 7.12(s,1H,NH), 6.87-7.77(m,aromatic rings);Anal.calc.for $C_{21}H_{15}N_3O_6S_2$:found:C, 50.05; H, 3.13: N,8.41: S,13.23 calc: C, 49.08; H, 3.09: N,8.58: S,13.10.

synthesis of (Z)-N-(2-(4-substitutedphenyl)-4,7-dioxo-1,3-oxazepin-3(2H,4H,7H)-yl)benzenesulfonamide(4a,b)

To dry benzene (30 ml) maleic anhydride(0.01 mol) and Schiff bases(0.01 mol) were added. The mixture was refluxed under 60 ^{0}C for 3h ., left to cool at room temperature. The solid product so formed was filtered off and crystallized from appropriate solvents.

Compound 4a

Yield 77%,m.p=192^0C: FT-IR(KBr) ν cm^{-1}:3203(N-H), 2833-2902(C-H),1734(C=O) lactone,1654 (C=O) lactam,1170 and 1334(SO_2); Anal.calc.for $C_{18}H_{16}N_2O_6S$:found:C, 56.11; H, 4.32: N,7.56: S,8.13 calc: C, 55.66; H, 4.15: N,7.21: S,8.26.

Compound 4b

Yield 56%,m.p=237^{0}C: FT-IR(KBr) ν cm^{-1}:3210(N-H), 2830-2907(C-H),1730(C=O) lactone,1663 (C=O) lactam,1343 and 1561(NO_2),1169 and 1330(SO_2); Anal.calc.for $C_{17}H_{13}N_3O_7S$:found:C, 51.22; H, .33: N,10.76: S,8.08 calc: C, 50.62; H, 3.25: N,10.42: S,7.95.

synthesis of N-(2-(4-substitutedphenyl)-4-oxothiazolidin-3-yl)benzenesulfonamide(5a,b).

Schiff bases (0.01mol) was added portion wise in 5 ml of dry benzene with thioglycolic acid(0.01mol). the mixture was refluxed for 4h.the reaction mixture was poured into crushed ice and treated with sodium bicarbonate. The precipitate washed with ice water ,dried and recrystalized from appropriate solvents.

Compound 5a

Yield 48%,m.p=148^{0}C: FT-IR(KBr) ν cm^{-1}:3205(N-H), 2833-2889(C-H),1645(C=O),1170 and 1334(SO_2);H-NMR δ ppm: ^{1}H-NMR (DMSO 300MHz) 9.05 (s,1H, CH), 7.90(s,1H,NH), 7.07-7.27(m,aromatic rings);^{13}C-NMR ppm 197(C=O),176(CH,thiazolidine ring),70.16(CH_2); Anal.calc.for $C_{16}H_{16}N_2O_4S_2$:found:C, 52.99; H, 4.64: N,7.89: S,17.17 calc: C, 52.73; H, 4.43: N,7.69: S,17.60.

Compound 5b

Yield 51%,m.p=258^{0}C: FT-IR(KBr) ν cm^{-1}:3203(N-H), 2843-2897(C-H),1646(C=O),1173 and 1325(SO_2),1358 and 1556 (NO_2);Anal.calc.for $C_{15}H_{13}N_3O_5S_2$:found:C, 48.08; H, 3.66: N,11.17: S,17.10 calc: C, 47.48; H, 3.45: N,11.08: S,16.90.

synthesis of N-(3-(4-methoxyphenyl)-4-oxo-3,4-dihydro-2H-benzo[e][1,2]thiazin-2-yl)benzenesulfonamide(6a,b)

A mixture of compounds (1,2) (0.01 mol) ,2-mercapto benzoic acid (0.01 mol) in 30 ml of dioxane. The mixture was refluxed for 4h . the reaction mixture was poured inth crushed ice ,stirred 3 minutes and resulting solid was filtered ,dried and recrystalized from dioxan.

Compound 6a

Yield 63%,m.p=125^{0}C: FT-IR(KBr) ν cm^{-1}:3201(N-H), 2829-2880(C-H),1680(C=O) lactam,1170 and 1338(SO_2); H-NMR δ ppm (DMSO 300MHz) 9.39 (s,1H, CH), 7.78(s,1H,NH), 7.3-7.7(m,aromatic rings),4.01(s,3H,OCH_3);Anal.calc.for $C_{21}H_{18}N_2O_4S_2$:found:C, 60.01; H, 4.10: N,6.34: S,15.24 calc: C, 59.14; H, 4.25: N,6.57: S,15.04.

Compound 6b

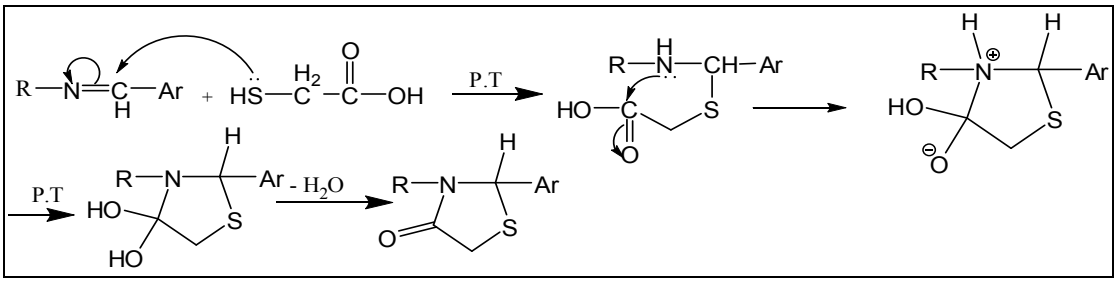
Yield 51%,m.p=242^{0}C: FT-IR(KBr) ν cm^{-1}:3216(N-H), 2830-2881(C-H),1676(C=O) lactam,1173 and 1341(SO_2),1356 and 1557(NO_2);^{13}C-NMR ppm 192(C=O),156(C-NO_2); Anal.calc.for $C_{20}H_{15}N_3O_5S_2$:found:C, 55.65; H, 3.82: N,9.79: S,14.88 calc: C, 54.41; H, 3.42: N,9.52: S,14.53.

Result and Discussion

In this work , many compounds were synthesized by coupling of different compounds with Schiff bases afforded oxazepine,thiazepine,thiazine,thiazolidine. these compounds were prepared by the addition reactions between cyclic anhydride such as phthalic,maleic,o-sulfobenzoicacid with imine group in Schiff bases, seven membered rings are obtained The FT-IR of these compounds (2,4a,b) showed disappearance of (C=N) stretching band at (1639-1643)cm^{-1} and appearance of bands in region (1720-1734) cm^{-1} due to stretching vibration of(C=O)(lactone),(1654-1666) cm^{-1} (C=O)(lactam)[20] . ^{1}H-NMR of compound (2a) showed peaks at 9.81 (s,1H, CH) in oxazepine ring, 7.3(s,1H,NH), 6.8-7.18(m,aromatic

rings),3.8ppm(s,3H,OCH_3).the FT-IR of compound (3a,b) showed disappearance band of (C=N) in Schiff bases and appearance of bands in (1723-1726) cm^{-1} due to strtching vibration of (C=O) in ring and another bands at (1141-1151) cm^{-1} and (1319-1329) cm^{-1} due to (-SO_2) group. : ^{1}H-NMR of compound (3a) showed peaks at 9.63 ppm (s,1H, CH) in seven membered ring, 7.12ppm(s,1H,NH), 6.87-7.77ppm(m,aromatic rings).

The thiazolidinone derivatives (5a,b) were synthesized by refluxing mercapto aceticacid with Schiff bases in dry benzene for 4 hrs. The suggested mechanism of thiazolidinone (5a,b) were obtained as following in scheme 1.



Scheme(1): Mechanism for the synthesis of thiazolidinone compounds

The FT-IR of these compounds(5a,b) showed disappearance of imine group and appearanceof new bands at (1646-1646) cm^{-1} for(C=O) in thiazolidinone ring.

Thiazine derivatives (6a,b) prepared by the heating of 2-mercaptobenzoic acid with shiff bases in dioxane the mechanism of the reaction systematically investigated as [4+2] cyclo addition. FT-IR spectrum showed the disappearance of bands of imine group ,attributed to (C=N) (imine group) a stretching frequency is good evidence of this step of reaction. and appeared a new bands at(1680-1676) cm^{-1} due to of (C=O) in thiazine ring.

Antibacterial activity

The novel synthesized representative compounds were tested for their antibacterial activity against the following *staphylococcus aureus* , *pseudomonas aureous, Escherichia coli* .The preliminary screening of the investigated compounds were performed using the filter paper disc-diffusion method. The compounds were tested at concentration of 100µg/ml. the zone of inhibition was measured in mm (table1).

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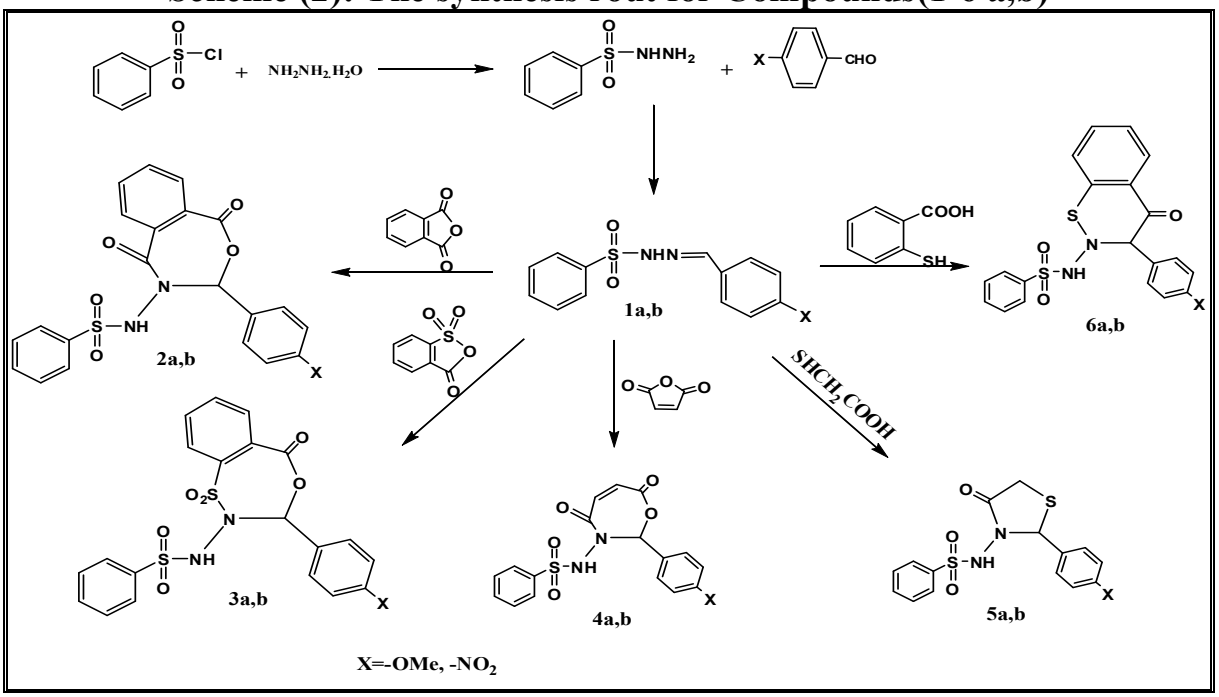
Table(1): Antibacterial activity of synthesized compounds 2a-6b

compounds	Zone inhibition in mm		
	Staphylococcus aureus	***Pseudomonas aureous***	***Escherichia coli***
2a	12	9	5
2b	7	12	11
3a	21	19	12
3b	24	17	18
4a	13	11	6
4b	22	18	17
5a	21	13	12
5b	10	9	9
6a	13	11	6
6b	14	9	3

Scheme (2): The synthesis rout for Compounds(1-6 a,b)



تحضير ، تشخيص ودراسة الفعالية المضادة للبكتريا لبعض الخماسية- سباعية الحلقة الجديدة المرتبطة مع مركبات السلفون امايد

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استلم البحث في : 25 آذار 2014 ، قبل البحث في :2 حزيران 2014

الخلاصة

هذا البحث يتضمن تحضير وتشخيص مركبات حلقية غير متجانسة خماسية وسداسية وسباعية الحلقة من خلال المركب بنزين سلفونيل هيدرازايد. تم مفاعلته مع مشتقات البنزالديهايد لتحضير قواعد شف (1a,b)التي تحتوي على مجموعة السلفون امايد. تم تفاعل قواعد شف مع الانهيدريدات الحلقية لتحضير كل من مشتقات الاوكسازبين والثايازبين (2,3,4a,b) ذات الحلقات السباعية. وتم مفاعلة مركبات قواعد شف مع مركب 2-مركبتوحامض البنزويك لتحضير مشتقات الثايازين (6a,b) ذي الحلقة السداسية بعدها حضرت مشتقات للمركب ثايازولدين (5a,b) من خلال تفاعل قواعد شف مع مركب مركبتو حامض الخليك وكما موضح في المخطط (3).شخصت المركبات المحضرة من خلال بعض الطرائق الفيزيائية والطيفية مثل درجة الانصهار، وطيف الاشعة تحت الحمراء، وطيف الرنين النووي المغناطيسي، وجهاز تحليل العناصر الدقيق. درست الفعالية البايولوجية للمركبات المحضرة ضد بعض انواع البكتريا اذ اعطت الدراسة نتائجا جيدة ضد بعض الانواع من البكتريا .

الكلمات المفتاحية: السلفون امايد، الاوكسازبين، ثايازبين، ثايازين ،ثايازولدين،قواعد شف، الفعالية المضادة للبكتريا