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Studies on post reaction products of novel spiro indoline-thiazolidine derivatives

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ABSTRACT

*In this study, 3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione **5** was synthesized by facile and fast procedure, which further underwent condensation with glucose and p-chlorobenzaldehyde to afford **6** and **7**, respectively. Compound **7** was used as precursor for the preparation of some fused heterocyclic compounds **8-11**. Among them, compound **8** was alkylated using chloroacetic acid and dichloroacetone to afford **12** and **13**, respectively. Also, it reacted with acrylonitrile and hydrazine hydrate to afford **14** and **15**, respectively. Compound **12** was condensed with p-chlorobenzaldehyde and glucose to afford **16** and **17**, respectively. Selected members of the synthesized compounds were screened for antimicrobial activity.*

Keywords: Spiro compound of isatin, thiazolopyrimidine, pyrazolothiazole, thiazolopyridine, bis-thiazolopyrimidine, antimicrobial activities.

INTRODUCTION

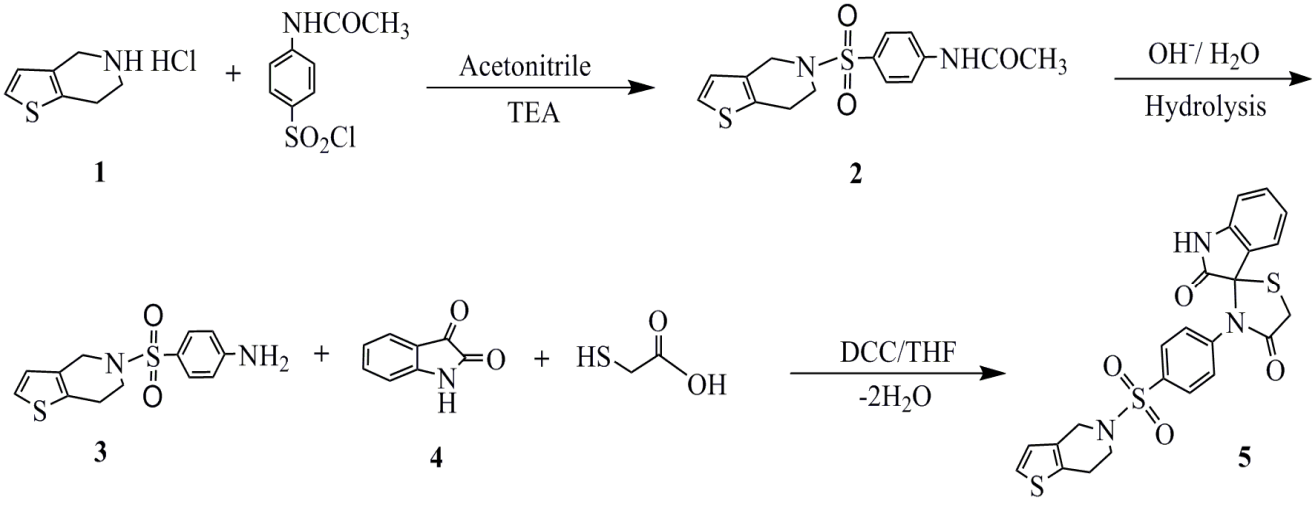
Small ring heterocycles containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties and also contributed to the society from biological and industrial point which helps to understand life processes [1]. Among these types of heterocyclic molecules, 4-thiazolidinones have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, antiinflammatory and analgesic properties [2-4]. 4-Thiazolidinone derivatives exhibit high activity in vitro against mycobacterium tuberculosis (TB) and as drugs to treat HIV and cancer [4-6]. They were also reported as novel inhibitors of the MurB enzyme, integral component in bacterial peptidoglycan biosynthesis, at the low micro molar level [7]. Recently, 2-aryl-4-thiazolidinone has been synthesized and found to exhibit potent selective antiplatelet activating factors both in vitro and in vivo and anti-inflammatory [8],

antibacterial [9], anticancer [10], and anti-HIV-1 activities [11]. Spiro heterocyclic compounds including thiazolidine moiety have antimicrobial activity [12]. Both pyrazolothiazole and thiazolopyrimidine moieties have potent kinase modulators [13] and are used in pharmaceutical compositions [14]. The latter compound has analgesic and anti-Parkinson activities [15] and inhibits the growth of parasite *Trypanosoma cruzi* [16]. Therefore, such medicinal properties associated with these heterocyclic molecules render them as useful structural units in drug research. These findings prompted us to synthesize various spiro heterocyclic derivatives of 4-thiazolidinone, for the investigation of an antimicrobial activity profile. From this point of view, the objective of the present communication comprises the synthesis of series of new compounds having novel spiro indoline-thiazolidine system. The synthetic approach is shown in Schemes-1, 2, 3 and 4.

MATERIALS AND METHODS

General

All melting points were determined on an Electro-thermal IA 9100 apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra (δ, ppm) were recorded in DMSO-*d6* or $CDCl_3$ solutions on a BRUKER 400-MHz spectrometer, and chemical shifts were expressed as part per million (ppm; δ values) against tetramethylsilane as internal reference (TMS) . The Infrared spectra (υ, cm^{-1}) were obtained with a Perkin-Elmer 1650 FTIR spectrometer in KBr pellets. Mass spectra (MS) were recorded on EI +Q1 MSLMR UPLR. Elemental analyses were performed on a ECS 4010 Elemental Combustion System, and the results were within the accepted range (±0.30) of the calculated values. The starting compounds, THTP hydrochlorides and Isatine were synthesized by previously reported routes [17,18]. All other necessary chemicals were purchased from Merck, Fluka and localize companies.



Scheme- 1. Syntetic route for 4-thiazolidinone derivatives

N-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)acetamide. **2**

An equimolecular mixture of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride (THTP) **1** [0.01 mole, 1.755 gm] and 4-acetamidobenzene-1-sulfonylchloride [0.01 mole, 2.335 gm] was dissolved in anhydrous acetonitrile (20 ml) using try ethyl amine[0.01 mole/0.730gm] as base under constant stirring, then the reaction mixture was refluxed for 5 hours. After

completion of reaction, it was poured in ice-cold water to obtain light yellow colored product **2**, which was filtered and dried. It was purified by column chromatographic technique (pet-ether : chloroform; 40:60; v/v) and recrystallized from ethanol to give light yellow colored crystalline compound. Yield 84.5%, m.p. 180-182ºC; IR (KBr, ν, cm^{-1}) : 3084(C-H, aromatic), 1546.7,1469.3(C=C, aromatic), 1224(C-N, THTP), 1356-1148(SO_2), 721(C-S-C, thiophene), 3328 (-NH, amide, D_2O exchangeable), 1665 (>C=O, amide); ^{1}H-NMR δ (ppm): 2.42(t, 2H, THTP), 3.07(t, 2H, THTP), 3.64(s, 2H, THTP), 6.48(s, 1H, -CONH), 2.45(s, 3H, -$COCH_3$), 7.46-6.20(m, 6H, Ar-H); ^{13}C-NMR δ (ppm) : 117-146(aromatic carbon), 22-47(aliphatic carbon), 172.46(-CO-, acetyle); MS, m/z (%): 336.46; Calculated (%) for $C_{15}H_{16}O_3N_2S_2$ (336.46); C : 53.57, H : 4.76, N : 8.33, S : 19.02, found; C : 53.56, H : 4.74, N : 8.32, S : 19.00.

4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)aniline. **3**

Compound **3** was prepared by base catalyzed hydrolysis of 0.01 mole (3.36 gm) N-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)acetamide **2**, using (25 ml) 10% sodium hydroxide solution. The reaction mixture was refluxed for 2 hr. The solid separated was filtred, dried, and recrystallized from ethanol to give white crystalline compound. Yield 68.7%, m.p. 172-174ºC; IR (KBr, ν, cm^{-1}) : 3079(C-H, aromatic), 1542.5,1473.5(C=C, aromatic), 1220(C-N, THHP), 718(C-S-C, thiophene), 3448(N-H, amine); ^{1}H-NMR δ (ppm): 2.47(t, 2H, THTP), 3.09(t, 2H, THTP), 3.68(s, 2H, THTP), 7.56-6.28(m, 6H, Ar-H), 11.24 (s, 2H, -NH_2, D_2O exchangeable); ^{13}C-NMR δ (ppm): 116-142(aromatic carbone), 27-48 (aliphatic carbon); MS, m/z (%): 294.00; Calculated (%) for $C_{13}H_{14}O_2N_2S_2$ (294); C : 53.06, H : 4.76, N : 9.52, S : 21.77, found; C : 53.04, H : 4.75, N : 9.49, S : 21.74.

Indoline-2,3-dione (*Isatine*). **4**

Isatine were synthesized, purified and characterized by previously reported routes. [20]

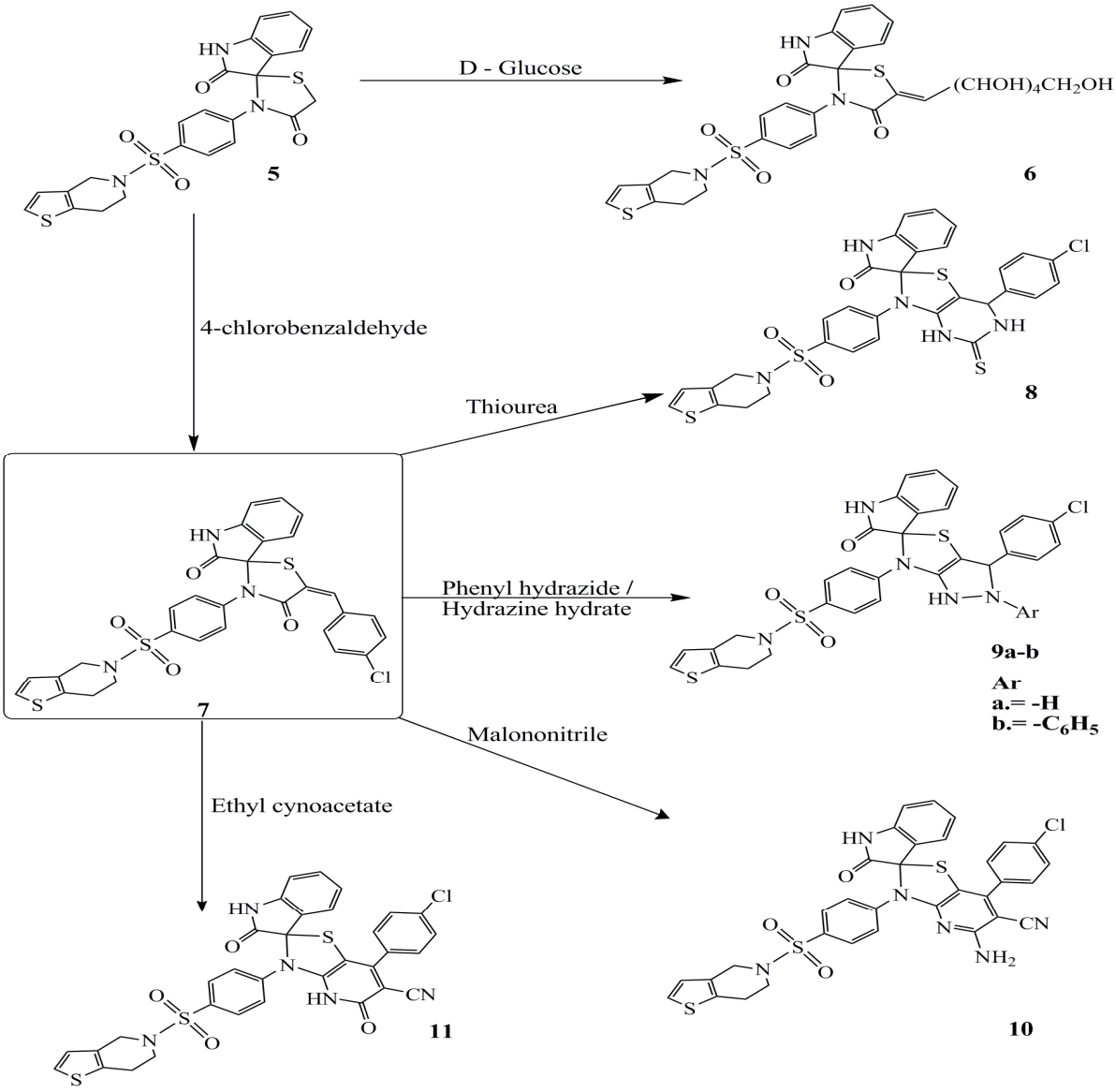
Synthesis of 3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione. **5**

A mixture of 4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)aniline (5.88 gm, 20 mmol), Indoline-2,3-dione (2.94 gm, 20 mmol), and 2-mercaptoacetic acid (1.84 gm, 20 mmol) in 50 mL dry benzene was refluxed for 8 h. The solvent was evaporated under reduced pressure. The formed solid was filtered off, dried, and recrystallized from ethanol to afford compound **5**. Yield 76.1%, m.p. 166–167 ºC; IR (KBr, ν, cm^{-1}): 1695(CO, thiazolidinone), 1742(CO, spiro indole), 3412(NH, spiro indole); ^{1}H-NMR δ (ppm): 8.23(s, 1H, -NH broad, D_2O exchangeable), 3.62(s, 2H, thiazole), 7.28-6.88(m,4H,Ar-H 2-oxo indole), 7.78(d, 2H, Ar-H), 7.48(d, 2H, Ar-H), 2.58(t, 2H, THTP), 3.47(t, 2H, THTP), 4.26(s, 2H, THTP), 7.39(d, 2H, THTP); ^{13}C-NMRδ (ppm): 81.8(spiro carbon), 112.6-148(aromatic carbons), 160.8,175.6(both C=O), 32.6(S-CH_2), 24.6, 44.7, 46.2 (aliphatic carbon); MS, m/z (%):497.05; Calculated (%) for $C_{23}H_{19}N_3O_4S_3$ (497.05); C: 55.51, H: 3.85, N: 8.44, S: 19.33, found (%); C: 55.49, H: 3.86, N: 8.45, S: 19.35.

3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-5'-(2,3,4,5,6-pentahydroxyhexylidene)spiro [indoline-3,2'-thiazolidine]-2,4'-dione. **6**

Compound **5** (2.48 gm, 5 mmol) in absolute ethanol (30 mL) and few drops of acetic acid were added to a solution of D-glucose (0.83 g, 5 mmol) in water (0.5 mL) with stirring at 60 ºC for 5 h. The product that separated out of cooling was filtered off, washed with water followed by ethanol, and dried to afford compound **6**. Yield 60.2%, m.p. 149-150 ºC; IR (KBr, ν, cm^{-1}): 3382-3428 (OH), 1695(CO, thiazolidinone), 1736(CO, spiro indole), 3409(NH, spiro indole); ^{1}H-NMR δ(ppm): 3.34–3.98(m, 6H, glucose), 4.62–4.96(m, 5H, OH,

D_2O exchangeable), 6.58(d, 1H, methylene), 8.25(s, 1H, -NH broad, D_2O exchangeable), 7.30-6.76(m, 4H, Ar-H 2-oxo indole), 7.87(d, 2H, Ar-H), 7.46(d, 2H, Ar-H), 2.49(t, 2H, THTP), 3.12(t, 2H, THTP), 3.67(s, 2H, THTP), 7.37(d, 2H, THTP); ^{13}C-NMR δ (ppm):62.5-74.8(glucose carbon), 81.6(spiro carbon), 116.2-145.6(aromatic & alkenes carbons), 164.3,174.7(both C=O), 24.6, 44.7, 46.2(aliphatic carbon); Calculated (%) for $C_{29}H_{29}N_3O_9S_3$ (659.11); C: 52.79, H: 4.43, N: 6.37, S: 14.58, found (%);C: 52.81, H: 4.42, N: 6.38, S: 14.57.



Scheme- 2. Condensation and michael reaction of thiazolidinone with different reagents

5'-(4-chlorobenzylidene)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)spiro-[indoline-3,2'-thiazolidine]-2,4'-dione. **7**

A mixture of compound **5** (2.48 gm, 5 mmol) and 4-chlorobenzaldehyde (0.7 ml, 5 mmol) was refluxed in a mixture of glacial acetic acid and acetic anhydride (3:1) containing anhydrous sodium acetate (0.36 g, 5 mmol) for 3 h. The reaction mixture was cooled and poured gradually with stirring into cool water (100mL). The formed solid was filtered off, dried, and recrystallized from methanol to give compound **7**. Yield 65%, m.p. 189-190 ºC; IR

(KBr, ν, cm^{-1}): 1697(CO, thiazolidinone), 1739(CO, spiro indole), 3416(NH, spiro indole), 1078 & 1263(C-Cl); ^{1}H-NMR δ (ppm): 6.72(d, 1H, methylene), 8.47(s, 1H, -NH broad, D_2O exchangeable), 7.42-6.92(m, 4H, Ar-H 2-oxo indole), 7.87(d, 2H, Ar), 7.41(d, 2H, Ar-H), 6.87(d, 2H, Ar-Cl), 7.14(d, 2H, Ar-Cl), 2.47(t, 2H, THTP), 3.15(t, 2H, THTP), 3.65(s, 2H, THTP), 7.26 (d, 2H, THTP); ^{13}C-NMR δ (ppm): 81.4(spiro carbon), 113.3-157.2(aromatic & alkenes carbons), 165.1, 173.6(both C=O), 24.4, 44.8, 46.6(aliphatic carbon); MS, m/z (%):619.05; Calculated (%) for $C_{30}H_{22}ClN_3O_4S_3$ (619.05); C: 58.10, H: 3.58, N: 6.78, S: 15.51, found (%);C: 58.12, H: 3.57, N: 6.76, S: 15.52.

7'-(4-chlorophenyl)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-5'-thioxo-4',5',6',7'-tetrahydro-3'H-spiro[indoline-3,2'-thiazolo[4,5-d]pyrimidin]-2-one. **8**

A equimolar mixture of **7** (3.09 gm, 5 mmol) in absolute ethanol (25 ml) / anhyd. pyridine (25 ml) was refluxed for 9 hrs. On cooling, the crude solid appeared which was filtered, washed with ice cold water containing dil. HCl with constant stirring. The formed solid was filtered off, dried and recrystallized from dioxane to give compound **8**. Yield 56%, m.p. 273-274 ºC; IR (KBr, ν, cm^{-1}): 3142, 3120(2NH, pyrimidine), 1218(CS), 1742(CO, spiro indole), 3420 (NH, spiro indole), 1064 & 1273(C-Cl); ^{1}H-NMR δ (ppm): 4.48(d, 1H, methylene), 8.48(s, 1H, -NH broad, D_2O exchangeable), 2.47(t, 2H, THTP), 3.15(t, 2H, THTP), 3.65(s, 2H, THTP), 6.50-7.20(m, 14H, Ar-H), 9.24(s, 1H, NH, D_2O exchangeable), 11.20(s, 1H, NH, D_2O exchangeable); ^{13}C-NMR δ (ppm): 81.9(spiro carbon), 116.8-152.8(aromatic & alkenes carbons), 163.5(C=O), 178.2(C=S), 24.6, 44.7, 46.2(aliphatic carbon), 52.3(methylene carbon); MS, m/z (%):677.05; Calculated (%) for $C_{31}H_{24}ClN_5O_3S_4$ (677.05); C: 54.89, H: 3.57, N: 10.33, S: 18.91, found (%);C: 54.87, H: 3.58, N: 10.31, S: 18.93.

3'-(4-chlorophenyl)-6'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-1',2',3',6'-tetra- hydrospiro[indoline-3,5'-pyrazolo[3,4-d]thiazol]-2-one. **9a**

A mixture of compound **7** (3.09 gm, 5 mmol) and hydrazine hydrate (0.40 mL, 10 mmol) was refluxed in absolute ethanol (30 ml) for 4 h. The solid substance was filtered off, dried, and recrystallized from dioxane to give compound **9a**. Yield 80%, m.p. 209-210 ºC; IR (KBr, ν, cm^{-1}): 3218(NH, pyrazole), 1742(C=O, spiro indole), 3420(NH, spiro indole), 1064 & 1273(C-Cl); ^{1}H-NMR δ (ppm): 8.52(s, 1H, -NH broad, D_2O exchangeable), 4.78(s, 1H, methylene), 2.43(t, 2H, THTP), 3.17(t, 2H, THTP), 3.62(s, 2H, THTP), 6.58-7.48(m, 14H, Ar-H), 9.24(s, 1H, NH, D_2O exchangeable), 10.47(s, 1H, NH, D_2O exchangeable); ^{13}C-NMR δ (ppm): 81.3(spiro carbon), 114.2-150.6(aromatic & alkenes carbons), 164.7(C=O), 24.7, 44.3, 46.5 (aliphatic carbon), 49.7(methylene carbon); MS, m/z (%):633.07; Calculated (%) for $C_{30}H_{24}ClN_5O_3S_3$ (633.07); C: 56.82, H: 3.81, N: 11.04, S: 15.17, found (%);C: 56.82, H: 3.83, N: 10.05, S: 15.18.

3'-(4-chlorophenyl)-6'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-2'-phenyl-1',2',3',6'- tetrahydrospiro[indoline-3,5'-pyrazolo[3,4-d]thiazol]-2-one. **9b**

A mixture of compound **7** (3.09 gm, 5 mmol) and phenyl hydrazine (1.06 mL, 10 mmol) was refluxed in absolute ethanol (50 ml) for 4 h. The reaction mixture was cooled, and the solid substance was filtered off, dried and recrystallized from dioxane to give compound **9b**.Yield 80%, m.p. 263-264 ºC; IR (KBr, ν, cm^{-1}): 3226(NH, pyrazole), 1734(C=O, spiro indole), 3418(NH, spiro indole) ,1061 & 1276(C-Cl); ^{1}H-NMRδ (ppm): 8.64(s, 1H, -NH broad, D_2O exchangeable), 4.86(s, 1H, methylene), 2.45(t, 2H, THTP), 3.16(t, 2H, THTP), 3.61(s, 2H, THTP), 6.40-7.62(m, 19H, Ar-H), 9.43(s, 1H, NH, D_2O exchangeable); ^{13}H-NMR δ (ppm): 81.5(spiro carbon), 114.8-151.4 (aromatic & alkenes carbons), 164.4(C=O), 24.6, 44.1, 46.7(aliphatic carbon), 49.7(methylene carbon); MS, m/z (%):709.10; Calculated (%) for

$C_{36}H_{28}ClN_5O_3S_3$ (709.10); C: 60.87, H: 3.97, N: 9.86, S: 13.54, found (%);C: 60.85, H: 3.98, N: 9.84, S: 13.55.

5'-amino-7'-(4-chlorophenyl)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-2-oxo-3'H-spiro [indoline-3,2'-thiazolo[4,5-b]pyridine]-6'-carbonitrile. **10**

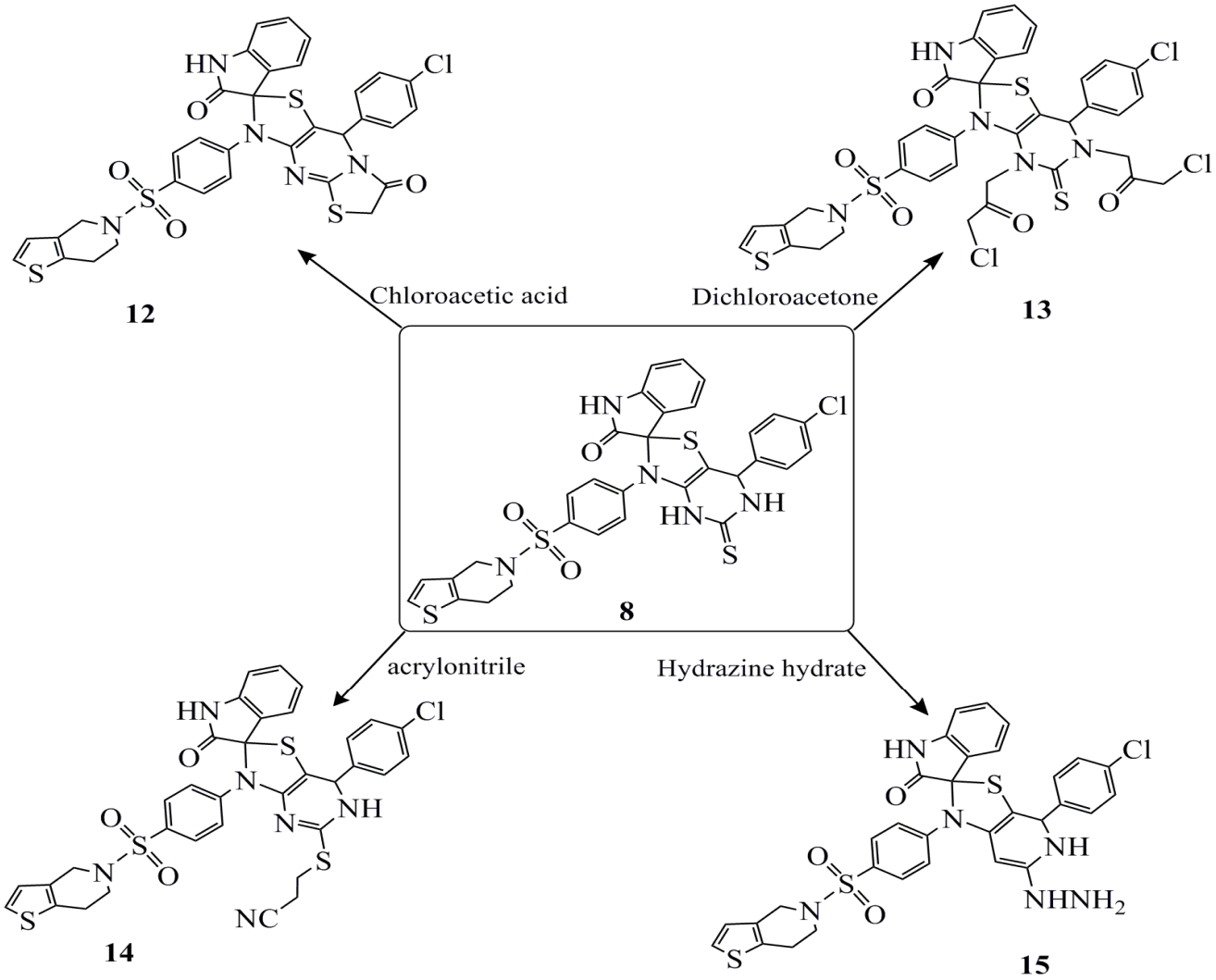
A mixture of compound **7** (3.09 gm, 5 mmol), malononitrile (0.66 gm, 10 mmol) and ammonium acetate (1.53 gm, 20 mmol) was refluxed in glacial acetic acid (40 ml) for 30 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from methanol to give compound **10**. Yield 50%, m.p. 222-223 ºC; IR (KBr, ν, cm^{-1}) : 1730(C=O, spiro indole), 3417(NH, spiro indole), 1058 & 1275 (C-Cl), 3428-3218(NH_2), 2219(CN); ^{1}H-NMR δ (ppm): 6.73-7.65(m, 14H, Ar-H), 7.80(s, 2H, NH_2, D_2O exchangeable), 2.48(t, 2H, THTP), 3.19(t, 2H, THTP), 3.65(s, 2H, THTP), 8.50(s, 1H, -NH broad, D_2O exchangeable); ^{13}C-NMR δ (ppm): 81.7(spiro carbon), 117.4-153.2(aromatic & alkenes carbons), 163.2(C=O), 24.8, 44.1, 46.7 (aliphatic carbon), 119.8(CN carbon); MS, m/z (%):682.07; Calculated (%) for $C_{33}H_{23}ClN_6O_3S_3$ (682.07); C: 58.01, H: 3.39, N: 12.30, S: 14.08, found (%);C: 58.03, H: 3.37, N: 12.33, S: 14.10.

7'-(4-chlorophenyl)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-2,5'-dioxo-4',5'-dihydro-3'H-spiro[indoline-3,2'-thiazolo[4,5-b]pyridine]-6'-carbonitrile. **11**

A mixture of compound **7** (3.09 gm, 5 mmol), ethyl cyanoacetate (1.13 gm, 10 mmol), and anhydrous ammonium acetate (1.60 gm, 20 mmol) was refluxed in glacial acetic acid (40 ml) for 20 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from acetic acid to give compound **11**. Yield 55%, m.p. 251-252 ºC; IR (KBr, ν, cm^{-1}): 1730(C=O, spiro indole), 3421(NH, spiro indole), 1060 & 1279(C-Cl), 3250(NH), 2224(CN), 1686(CO); ^{1}H-NMR δ (ppm): 6.60-7.58(m, 14H, Ar-H), 10.20(s, 1H, NH, D_2O exchangeable), 2.47(t, 2H, THTP), 3.20 (t, 2H, THTP), 3.67(s, 2H, THTP), 8.42(s, 1H, -NH broad, D_2O exchangeable); ^{13}C-NMR δ (ppm): 80.8(spiro carbon), 114.7-158.4(aromatic & alkenes carbons), 164.6, 173.2(both C=O), 23.5, 42.8, 45.7(aliphatic carbon), 121.3(CN carbon); MS, m/z (%):683.05; Calculated (%) for $C_{33}H_{22}ClN_5O_4S_3$ (683.05); C: 57.93, H: 3.24, N: 10.24, S: 14.06, found (%);C: 57.90, H: 3.26, N: 10.23, S: 14.08.

9-(4-chlorophenyl)-3-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-6,9-dihydrospiro- [dithiazolo[3,2-a:4',5'-d]pyrimidine-2,3'-indoline]-2',7(3H)-dione. **12**

A mixture of compound **8** (1.69 gm, 2.5 mmol) and chloroacetic acid (0.26 gm, 2.5 mmol) was refluxed in a mixture of glacial acetic acid and acetic anhydride (3:1) containing anhydrous sodium acetate (0.18 g, 2.5 mmol) for 3 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from methanol to give compound **12**. Yield 75%, m.p. 182-183 ºCl; IR (KBr, ν, cm^{-1}): 1737(CO, spiro indole), 3412(NH, spiro indole), 1698(CO, 4-thiazolidinone), 1064 & 1273(C-Cl); ^{1}H-NMR δ (ppm): 3.38(s, 2H, thiazolone), 5.57(s, 1H, methylene), 6.50-7.42(m, 14H, Ar-H), 8.32(s, 1H, -NH broad, D_2O exchangeable), 2.45(t, 2H, THTP), 3.17(t, 2H, THTP), 3.62(s, 2H, THTP); ^{13}C-NMR δ (ppm): 82.2(spiro carbon), 115.3-154.2(aromatic & alkenes carbons), 163.5, 173.2(both C=O), 24.4, 44.9, 46.8(aliphatic carbon), 52.3(methylene carbon), 34,2(S-CH_2); MS, m/z (%):717.04; Calculated (%) for $C_{33}H_{24}ClN_5O_4S_4$ (717.04); C: 55.18, H: 3.37, N: 9.75, S: 17.86, found (%);C: 55.17, H: 3.39, N: 9.73, S: 17.88.



Scheme- 3. Alkylation and disulfurization of thiazolopyrimidine

3,3'-(7'-(4-chlorophenyl)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-2-oxo-5'-thioxo-3'H-spiro[indoline-3,2'-thiazolo[4,5-d]pyrimidine]-4',6'(5'H,7'H)-diyl)bis(1-chloropropan-2-one).
13

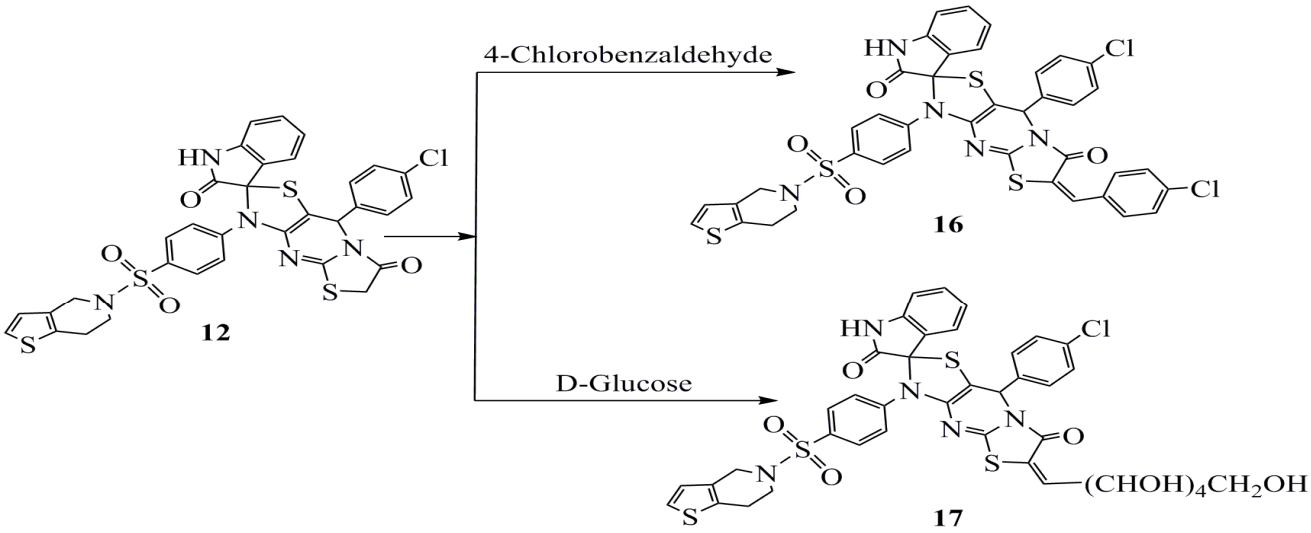
A mixture of compound **8** (1.69 gm, 2.5 mmol) and dichloroacetone (0.73 gm, 50 mmol) was refluxed in ethanolic sodium hydroxide (0.4 g, 30 ml) for 3 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from ethanol to give compound **13**. Yield 70%, m.p. 182-183 ºC; IR (KBr, ν, cm^{-1}): 1703,1709(CO), 1218(CS), 1728(CO, spiro indole), 3408(NH, spiro indole); ^{1}H-NMR δ (ppm): 4.53(s, 4H, $2CH_2$), 4.56(s, 1H, metylene), 6.32 (s, 4H, $2CH_2$), 8.52(s, 1H, -NH broad, D_2O exchangeable), 2.46(t, 2H, THTP), 3.18(t, 2H, THTP), 3.67(s, 2H, THTP), 6.63-7.48(m, 14H, Ar-H); ^{13}C-NMR δ (ppm): 82.2(spiro carbon), 112.7-153.4(aromatic & alkenes carbons), 163.5, 184.2, 182.7(C=O), 178.2(C=S), 24.1-63.4(aliphatic carbon), 52.8(methylene carbon); MS, m/z (%): 857.02; Calculated (%) for $C_{37}H_{30}Cl_3N_5O_5S_4$ (857.02); C: 51.72, H: 3.52, N: 8.15, S: 14.93, found (%);C: 51.73, H: 3.51, N: 8.17, S: 14.95.

3-(7'-(4-chlorophenyl)-3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-2-oxo-6',7'-dihydro-3'H-spiro[indoline-3,2'-thiazolo[4,5-d]pyrimidine]-5'-ylthio)propanenitrile. **14**

A mixture of compound **8** (1.69 gm, 2.5 mmol) and acrylonitrile (0.13 mL, 2.5 mmol) was refluxed in absolute ethanol (30 mL) for 3 h. The formed solid was filtered off, dried, and recrystallized from ethanol to give compound **14**. Yield 70%, m.p. 172-173 ºC; IR (KBr, ν, cm^{-1}): 3196(NH), 2219(CN), 1719(CO, spiro indole), 3372(NH, spiro indole); ^{1}H-NMR δ (ppm): 2.73(t, 2H, CH_2), 3.20(t, 2H, CH_2), 4.60(s, 1H, methylene), 6.67-7.52(m, 14H, Ar-H), 9.60(s, 1H, NH, D_2O exchangeable), 8.32(s, 1H, -NH broad, D_2O exchangeable), 2.43(t, 2H, THTP), 3.14(t, 2H, THTP), 3.61(s, 2H, THTP); ^{13}C-NMR δ (ppm): 82.3(spiro carbon), 111.7-160.2 (aromatic & alkenes carbons), 163.5(C=O), 26.7-64.6(aliphatic carbon), 52.7(methylene carbon), 119.5(CN); MS, m/z (%): 730.07 ; Calculated (%) for $C_{34}H_{27}ClN_6O_3S_4$ (730.07); C: 55.84, H: 3.72, N: 11.49, S: 17.54, found (%);C: 55.82, H: 3.75, N: 11.47, S: 17.53.

4'-(4-chlorophenyl)-1'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-6'-hydrazinyl-4',5'-dihydro-1'H-spiro[indoline-3,2'-thiazolo[5,4-c]pyridin]-2-one. **15**

A mixture of compound **8** (1.69 gm, 2.5 mmol) and hydrazine hydrate 80% (20 mL) was refluxed for 8 h. The reaction mixture was cooled and poured into water. The formed solid was filtered off, dried, and recrystallized from methanol to give compound **15**. Yield 65%, m.p. 167-168 ºC; IR (KBr, ν, cm^{-1}): 3315-3318(NH_2), 3158,3172(NH), 1724(CO, spiro indole), 3382(NH, spiro indole); ^{1}H-NMR δ (ppm): 4.25(s, 2H, NH_2, D_2O exchangeable), 4.74(s, 1H, methylene), 5.64(s, 1H, NH, D_2O exchangeable), 6.40-7.46(m, 15H, Ar-H), 9.61(s, 1H, NH, D_2O exchangeable), 8.39(s, 1H, -NH broad, D_2O exchangeable), 2.44(t, 2H, THTP), 3.16(t, 2H, THTP), 3.64(s, 2H, THTP); ^{13}C-NMR δ (ppm): 82.3(spiro carbon), 112.7-158.0(aromatic & alkenes carbons), 164.8(C=O), 24.4-48.2(aliphatic carbon), 53.7(methylene carbon); MS, m/z (%):674.10; Calculated (%) for $C_{32}H_{27}ClN_6O_3S_3$ (674.10); C: 56.92, H: 4.03, N: 12.45, S: 14.25, found (%);C: 56.90, H: 4.04, N: 12.46, S: 14.23.



Scheme- 4. Condensation of bis-thiazolopyrimidine with aldehyde and glucose

6-(4-chlorobenzylidene)-9-(4-chlorophenyl)-3-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl) phenyl)-6,9-dihydrospiro[dithiazolo[3,2-a:4',5'-d]pyrimidine-2,3'-indoline]-2',7(3H)-dione. **16**

A mixture of compound **12** (1.79 gm, 2.5 mmol) and 4-chlorobenzaldehyde (0.35 gm, 2.5 mmol) was refluxed in a mixture of glacial acetic acid/acetic anhydride (3:1) containing

anhydrous sodium acetate (0.18 gm, 2.5 mmol) for 3 h. The reaction mixture was cooled and poured gradually with stirring into cool water (100 mL). The formed solid was filtered off, dried, and recrystallized from dioxane to give **16**. Yield 64%, m.p. 206-207 ºC; IR(KBr, ν, cm^{-1}): 1739(CO, spiro indole), 3376(NH, spiro indole), 1672(CO, 4-thiazolidinone), 1064 & 1273(C-Cl); ^{1}H-NMR δ (ppm): 5.7(s, 1H, pyrimidine), 6.50-7.30(m, 19H, Ar-H & methylene H), 8.38(s, 1H, -NH broad, D_2O exchangeable), 2.44(t, 2H, THTP), 3.18(t, 2H, THTP), 3.66(s, 2H, THTP); ^{13}C-NMR δ (ppm): 82.4(spiro carbon), 112.7-154.6(aromatic & alkenes carbons), 163.2, 176.4(both C=O), 23.8, 45.2, 46.2(aliphatic carbon), 53.6(methylene carbon); MS, m/z (%): 839.03; Calculated (%) for $C_{40}H_{27}Cl_2N_5O_4S_4$ (839.03); C: 57.14, H: 3.24, N: 8.33, S: 15.25, found (%);C: 57.13, H: 3.25, N: 8.31, S: 15.27.

9-(4-chlorophenyl)-3-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl)-6-(2,3,4,5,6-penta hydroxyhexylidene)-6,9-dihydrospiro[dithiazolo[3,2-a:4',5'-d]pyrimidine-2,3'-indoline]-2',7(3H)dione. **17**

Compound **12** (1.79 gm, 2.5 mmol) in dioxane (25 mL) containing a few drops of acetic acid was stirring into a solution of glucose (0.83 gm, 2.5 mmol) in water (0.5 ml) at 60 ºC for 4 h. The product that separated out on cooling was filtered off, washed with water followed by ethanol, and then dried to give compound **17**. Yield 55%, m.p. 170-171 ºC; IR (KBr, ν, cm^{-1}): 3378-3405(OH), 1735(CO, spiro indole), 3419(NH, spiro indole), 1681(CO, 4-thiazolidinone); ^{1}H-NMR δ (ppm): 5.62(d, 1H, methylene H), 5.28(s, 1H, pyrimidine), 6.43-7.54(m, 14H, Ar-H), 8.42(s, 1H, -NH broad, D_2O exchangeable), 3.38-3.94(m, 6H, glucose), 4.66-4.98(m, 5H, OH, D_2O exchangeable), 2.46(t, 2H, THTP), 3.14(t, 2H, THTP), 3.62(s, 2H, THTP); ^{13}C-NMR δ (ppm): 82.5(spiro carbon), 115.6-156.8(aromatic & alkenes carbons), 165.2, 173.9(both C=O), 24.7, 45.1, 46.5(aliphatic carbon), 52.6(methylene carbon), 60.7-73.6(glucose carbon); Calculated (%) for $C_{39}H_{34}ClN_5O_9S_4$ (879.09); C: 53.20, H: 3.89, N: 7.95, S: 14.57, found (%);C: 53.21, H: 3.87, N: 7.94, S: 14.56.

RESULTS AND DISCUSSION

The post products of 3'-(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl) phenyl) spiro[indoline-3,2'-thiazolidine]-2,4'-dione **5** was synthesized from 4-(6,7-dihydrothieno[3,2-c] pyridin-5(4H)-ylsulfonyl)aniline, in good yield (cf. the Experimental section; Scheme 1, 2, 3, 4).

The assigned structure was proved based on elemental and spectral analysis. The infrared (IR) spectrum of the isolated product **5** showed absorption bands at 1742 cm^{-1} (spiro indole CO) [19] and 1695 cm^{-1}(thiazolidinone CO) [19]. The ^{1}H NMR spectrum revealed signals at δ 2.58 ppm, δ 3.47 ppm and δ 4.26 ppm attributed to pi-pyridine protons, signal at δ 3.62 ppm attributed to thiazole ring protons, also broad peak at 8.23 ppm correspond to isatine and multiplet at δ 6.88-7.28 ppm corresponding to aromatic protons. Furthermore, the mass spectra gave a molecular ion peak at m/z 497.05. Also, compound **5** was confirmed chemically via condensation with D-glucose and p-chlorobenzaldehyde to afford **6** and **7**, respectively. The structures of the latter compounds were elucidated from their correct data (cf. the Experimental section). For example, the IR spectrum of compound **7** showed an absorption band at 1697 cm^{-1} (thiazolidinone CO) due to conjugation, ^{1}H NMR spectrum showed absence of thiazolomethylene protons, and its mass spectrum showed the M^+ peak at m/z 619.05, all of which support its molecular formula. Compound **7** was used as starting material for further synthesis of other heterocyclic compounds. It reacted with thiourea, hydrazine hydrate derivatives, malononitrile, and ethyl cyanoacetate to afford compounds **8-11**, respectively (Scheme 2).

The structures of these compounds were confirmed from their correct data (cf. the Experimental section). For example, the IR spectrum of compound **8** showed the absence of the band characteristic for (thiazolidinone CO) and the presence of absorption bands at 3142, 3120 cm^{-1} (NH), and 1218 cm^{-1}(CS). Also, its ^1H NMR spectrum revealed signals at δ 4.60 ppm characteristic of the pyrimidine ring and at d 8.48, 9.24 and 11.20 ppm for 3NH protons that are D_2O exchangeable. Mass spectra showed M^+ peak at m/z 677.05, which supports its molecular formula (cf. the Experimental section; Scheme 2).

On the other hand, compound **8** was allowed to react with halo compounds, namely dichloroacetone and chloroacetic acid, to afford compounds **12** and **13**, respectively. Also, compound **8** was reacted with acrylonitrile via Michael addition to afford **14**, and its reaction with hydrazine hydrate afforded hydrazine pyrimidine derivative **15** (Scheme 3).

Finally, bis-thiazolopyrimidine derivative **12** was condensed with p-chlorobenzaldehyde and D-glucose to afford **16** and **17**, respectively. The structures of all compounds were confirmed by their correct data (cf. the Experimental section; Scheme 4).

Antimicrobial Activity

Some of the synthesized compounds **5, 7, 8, 9b, 10**, **11**, **12**, **15**, and **16** were tested in concentrations of 0.1 g/ml using dimethylformamide (DMF) as a solvent. The microorganisms used were as follows: Gram-negative bacteria, *E. coli* and *P. aeruginosa*; Gram-positive bacteria, *B. subtilis*, *S. aureus*, and *S. lutea*; and yeast, *C. albicans*.

Medium:

The cap-assay method containing (g/l) peptone (6.0), yeast extract (3.0), meat extract (1.5), glucose (1.0), and agar (20.0) were used. The medium was sterilized and divided while hot (50-60 ºC) into 15-ml portions among sterile Petri dishes 9 cm in diameter. One ml of the spore suspension of each microorganism was spread all over the surface of the cold solid medium placed in the Petri dish.

Table- 1. Antimicrobial activities of the tested compounds

Tested compounds and standards	Inhibition zone (mm)					
	Gram-negative bacteria		Gram-positive bacteria			Yeast
	E. coli.	*P.aeruginosa*	*B. subtilis*	*S. aureus*	*S. lutea*	*C. albicans*
10, 11, 15 and 16Penicillin	16	15	22	17	19	-
Nystalin	-	-	-	-	-	18
5	09	11	13	07	12	10
7	11	08	12	10	10	13
8	13	10	16	12	15	17
9b	14	14	18	19	20	14
10	12	11	15	17	18	22
11	11	13	24	15	19	19
12	20	17	15	20	21	14
15	14	19	21	18	17	20
16	21	16	22	17	22	19

Notes. *Highly sensitive: inhibition zone 21–30 mm.; Fairly sensitive: inhibition zone 16–20 mm. Slightly sensitive: inhibition zone 10–15 mm.*

Method [20]:
Portions of 0.5 g of each tested compound were dissolved in 5ml of DMF. An amount of 0.1 ml of the test solution was placed on Whatman paper disc, 9 mm in diameter, and the solvent was left to evaporate. These saturated discs were placed carefully on the surface of the inoculated solid medium; each Petri dish contained at least three discs. The Petri dishes were incubated at 5 ºC for an hour to permit good diffusion, then transferred to an incubator at 85 ºC overnight, and then examined. The results were recorded by measuring the inhibition zone diameters.

CONCLUSIONS

The results of antimicrobial activity of several compounds showed interesting degrees of antibacterial activity. Penicillin was used as a reference to evaluate the potency of the tested compounds. Compounds **9b**, **11**, **12**, **15** and **16** showed greater antibacterial activities than the standard drug (*Penicillin*) against many microorganisms. Compounds **5** and **7** were slightly sensitive and compounds **8** and **10** were fairly sensitive against the tested microorganisms, whereas compounds **15** and **16** showed greater activity against almost all the microorganism which was comparable with standard drug (*Penicillin*). Also compounds **10**, **11**, **15** and **16** were showed interesting degrees of activity against yeast (*C. albicans*). *Nystalin* was used as a reference to evaluate the potency of the tested compounds. These results of biological activities encourage further work on such ring system (Table 1).

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