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Design, Synthesis and in Vitro Evaluation of Antimicrobial and Anticancer Activity of Some Novel *α,β*-Unsaturated Ketones and their Corresponding Fused Pyridines

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ABSTRACT

Objective: This study aimed synthesis of fused pyridine due to the importance of these heterocycles as antimicrobial and anticancer. **Method**: Some novel substitutedpyrido[3,2-c]pyran-6-one,pyrido[2,3-c]isoxazole,pyrazolo[4,3-c] pyridine, pyrido[4,3-c]pyrimidine, pyrido[3,2-c]pyrimidine[2,3-b]triazine-2-thione and pyrido[3,2-c]pyrano[2,4-d] pyrimidine-2-thione derivatives have been reported to possess various pharmacological activities like antimicrobial and antitumor. **Results**: A novel series of azoles and azines were designed and prepared via reaction of 3-(arylidene)-1-methy-4-piperidonewith some electrophilic and nucleophilic reagents. The structures of target compounds were confirmed by elemental analyses and spectral data. **Conclusion:** It could be concluded that the tested compounds **14a,e, 13a, 11b and 17d1** have highest antibacterial activity. Compounds **11b, 13a, 14c,e,g, 16e, 17d1** have antifungal activity than antibiotic standard (Nystatin) used. Compound **13a and 25a** have shown good anticancer agent.

Keywords: *Antibacterial; Antifungal; Anticancer; Pyrido[3,2-c] pyranone; Pyrazolo [3,4-c] pyridine; Pyrido[4,3-c] pyrimidine; Pyrido[3,2-c]pyrano[2,4-d] pyrimidine.*

INTRODUCTION

Designing of novel class of bioactive heterocycles and develop efficient methods for their synthesis with predefined functionalities is a challenging task in modern organic chemistry. Aza-heterocycles are essential scaffold for generating wide range of chemical libraries drug-like candidates for their application to obtain desired therapeutic pharmacological activity. Heterocyclic ring systems that containing the ring fused pyran, pyridine. pyrimidine and pyrazole are interesting classes of compounds both chemically and biologically.[1-4] For example, pyrazolopyridines exhibited various biological activities such as antimicrobial, anti-inflammatory and antitumor.[4-12]

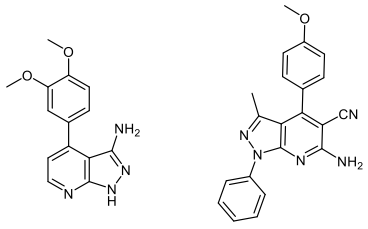


Figure 1. Pyrazolo[3,4-b]pyridine derivatives reported as anti-inflammatory.

Also, pyrano[2,3-B]pyridine and pyridopyrimidines which possess antimicrobial and antioxidant [13,20]. Encouraged with the above survey, the present study aimed to develop and synthesize novel compounds bearing pyranopyridine, pyridopyrimidine and pyrazolopyridine rings and test their biological activity as antimicrobial, antifungal and anticancer.

MATERIAL AND METHODS

Part 1-chemistry

All melting points were uncorrected and measured using Gallen Kamp melting apparatus . Infrared spectra were obtained on Nexus 470- 670 - 870. ^{13}C and ^{1}H-NMR run on JEOL-400 MHZ in DMSO-d_6.All chemicals used as starting materials and reagents in this study were reagent grade and were purchased from Sigma and Aldrich. The mass spectra were recorded on Ms-S988 operating at 70evand the elemental analyses were determined at the Micro analytical center, Cairo University, Egypt.

General method for preparation of 3-arylidene-1-methyl-4-piperidone (1a,b*)*

A mixture of 1-methyl-4-piperidone (0.40 mmol) and the appropriate aldehyde (4-chlorobenazldeyde) and thipophene-2-carbaldehyde (0.08 mmol),in alcoholic NaOH (50 ml, 10%) was stirred at room temperature for 8-hours. The mixture was neutralized with 10% HCl (3 ml). The separated solid was filtered, washed with water, dried and recrystallized from ethanol.

Compound 1a, yield 40%; m.p. 115-117°C. ^{1}H NMR: δ 2.50 (s, 3H, N–CH_3), 2.70-2.68 (2s 4H, H_2C–N-CH_2), 2.75-2.72 (m, 2H,–CH_2), 7.21 (s, 1H, HC=C), 7.32 (d, 2H, C_3–H, C_5–H,P-Cl phenyl ring, J = 8.25 Hz), 8.13 (d, 2H, C_2–H, C_6–H, P-Cl phenyl, AA'x'x system, J = 9.54 Hz). IR(cm^{-1}) 3119 (Ar–CH), 2927-2789 (aliph.–CH), 1718 (C=O); Anal. Calcd for $C_{13}H_{14}NOCl$: C, 66.24; H, 4.91; N, 5.04; Found: C, 66.20, H, 4.92; N, 5.00.

Compound 1b, yield 50%; m.p.>360°C. $^{1}HNMR$: δ 2.50 (s, 3H, N–CH_3), 2.73-2.70 (2s, 4H, H_2C–N-CH_2), 2.70-2.63 (m, 2H,–CH_2), 7.24 (s, 1H, HC=C), 7.21-7.45(m, 3H, H-Thiophen ring). IR (cm^{-1})3225(CH–Ar), 2950(aliph.–CH),1750(C=O);Anal. Calcd. for $C_{11}H_{13}NOS$: C, 63.76; H, 6.28; N, 5.04; Found: C,63.70; H, 6.00; N, 5.30.

Synthesis of 5-acetyl-4-hydroxy- 3-(4-chloro benzylidene or 2-theinylidene)-1-methyl pyridine (2a,b). A mixture of 3-(arylidene)-l-methyl-4-piperidone **la,b** (0.40 mol), 100 gm of anhydrous sodium acetate and 120 ml of acetic anhydride was stirred and heated under reflux for 12 hours. The cooled reaction mixture was poured onto 700 gm of crushed ice and extracted with butanol 100ml. The solid was filtered and purified by crystallization with ethanol.

Compound 2a, yield 85%; m.p. 280-282°C. ^{1}H NMR: δ2.25(s,3H,N–CH_3),2.72–2.50(2s,4H,H_2C-N-CH_2), 3.00 (s,3H,CO-CH_3),7.1 (s, lH, HC=C), 7.87 (d,2H,C_3-H,C_5-H,P-Cl-phenylring, J= 9.50 Hz),8.04 (d,2H,C_2-H,C_6-H, p-Cl phenyl, J=5.50Hz), 8.83 (s, lH, OH). IR(cm^{1}) 3444(OH), 3050 (ArCH), 2900(aliph.CH), 1708(C=O), 1600(C=C).; Anal. Calcd. for $C_{15}H_{16}NO_2Cl$: C, 64.86; H, 5.76; N, 5.04; Found: C, 64.70; H, 8.80; N, 5.00.

Compound2b, yield 70%; m.p. 100-102 °C. $^{1}HNMR$δ2.22(s, 3H,N-CH_3),2.70-2.50(2s,4H,H_2C-N-CH_2), 3.15(s,3H,CO-CH_3), 7.23 (s,lH, HC=C),6.90-6.50(m,3H,H-Thiophenring),8.82(s, lH, OH) IR(cm^{-1}) :3460(OH),3100(Ar-CH), 2923 (aliph.CH), 1680(C=O), 1630(C=C). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.65; H, 6.02; N, 5.62; Found: C, 62.60; H, 6.60; N, 5.80.

Synthesis of 2-(4-chlorobenzylidene)-8-hydroxy-4-methyl-2,3,4,5-tetrahydropyrido[3,2-*c*] pyran-6-one3a. Sodium methoxide (3.25g, 60 mmoles) was suspended in 60 ml of ethylformate at 0°C .The mixture was allowed to warm to room temp and a solution of the appropriate hydroxy piperidone **2a** (20 mmoles) in minimum amount of tetrahydrofuran was added drop wise. After stirring for 9 hours, water (100 ml) was added to thick suspension and then acetic acid 4.5 ml. The separated solid was filtered, and recrystallized from ethanol and dioxane; yield 75%; m.p.> 360°C. $^{1}HNMR$δ2.18(s,3H,N-CH_3),2.58–2.50(m,4H,H_2C-N-CH_2),2.72(dd,3-H_a,J=16.5and J=4.20 Hz),2.88 (dd,3'-H_b, J=16.5 and 3.00Hz),3.58 (t,2-H,J=3.9 Hz),3.90 (s,lH, OH), 6.97 (s, lH, HC=C), 7.97,7.55 (2d, 4H,C_3-H,C_5-H,C_2-H.C_6-H,AA'XX'systemP-C1 phenyl ring) IR(cm^{-1}) 3417 (OH), 3050 (Ar-CH), 2900-2875 (aliph.CH) 1680(C=O), 1600 (C=C); Anal. Calcd. for $C_{16}H_{16}NO_3Cl$: C, 62.84; H, 5.23; N, 4.58; found: C, 62.80; ; H, 5.30; N, 4.60.

Synthesis of 2-(4-chlorobenzylidene)-7-hydroxymethyl-4-methyl- 2,3,4,5-tetrahydropyrido [3,2-*c*]pyran-6-one 5a. A solution of **3a** (10 mmoles), sodium acetate (40 mg, 0.5 mmol) and aqueous solution of formaldehyde'(1ml, 12 mmol, 37%) in 40 ml of acetone was stirred for 6 hours at room temperature. Then concentrated hydrochloric acid (1ml) was added and the solution was stirred over night at room temperature , the resulting crystal were filter, washed with ethanol, dried and recrystalized from ethanol., yield 80%; m.p. 320-322 °C. $^{1}HNMR$δ2.26(s,3H,N-CH_3), 2.48-2.95(m,4H,H_2C-N-CH_2), 4.74(d,2H,CH_2, J= 10 Hz), 4.34 (t, lH, OH,J=6.11), 6.83 (s, lH,C=CH),8.00 (s,lH,C_2-H-pyran ring J= 3.00 Hz), 3-58 (t,2-H,J=3.9), 7.97-7.55(2d,4H,C_3-H,C_5-H, C_2-H,C_6-H,AA'XX'system

P-C1 phenyl ring),9.70 (br.s, lH, OH, exchange ablewithD_2O); IR(cm^{-1}) 3360(OH), 3095(Ar-CH),2900(aliph.CH), 1636(C=O),1585(C=C); Anal. Calcd. for $C_{17}H_{16}NO_3Cl$: C, 64.25; H, 5.03; N, 4.40; found: C, 64.29; H, 5.08; N, 4.45.

Synthesis of 3-(4-chlorobenzylidene)-4-hydroxy-5-dimethyl amine propenanone-2-l-methyl pyridine 6a. A mixture of **2a** (0.01 mol) and DMF DMA(0.01 mol) was fused at room temperature for 1 hour .The formed reddish orange paste was washed with ethanol and then filtered. The residual yellow solid was then crystallized from ethanol; yield 65%; m.p.>360°C. IR (cm^{-1}) 3370(OH), 3094 (Ar-CH), 3020 (aliph-CH), 1622 (C=O).Anal. Calcd for $C_{18}H_{21}N_2O_2Cl$: C, 64.96; H, 6.31; N, 8.42; found: C, 64.90; H, 6.22; N, 8.30.

Synthesis of3-(4-chlorobenzylidene)-4-hydroxy-7-(4-chloro benzylidene)-propen-l-one-l-methylpyridine 7a. The mixture of aldehyde (4-chlorobenzaldehyde) (0.02mol) and **2a** (0.01 mol) in alcoholic NaOH (50ml, 10%) was stirred at room temperature for 2 hours. The solid product was then, recrystallized from ethanol; yield 63%; m.p.> 360°C..^{1}HNMRδ2.50 (s,3H,N-CH_3),3.00-3.05(m,4H, H_2C-N-CH_2), 6.52,6.55,6.98 (3s,3H,HC=CH,C=CH), 7.95 (d,2H,C_3-H,C_5-H,P-Cl phenyl ring, J=5.37Hz, AA'XX'),7.36(d,2H,C_2-H,C_6-H,P-Cl,phenyl, J=9.00Hz), 10.52(s,lH,OH). IR:3429(OH),3100 (Ar-CH),2927 (aliph.CH), 1630 (C=O),1603(C=C). Anal. Calcd for $C_{22}H_{19}NO_2Cl_2$: C, 66.01; H, 4.75; N, 3.50; found: C, 66.11; H, 4.80; N, 3.80.

Synthesis of 7-(methylthio)-8-(4-chlorophenyl)-2-(4-chlorobenzylidene) 4-methyl-2,3,4,5-tetrahydro pyrido[3,2-c]pyran-6-one 8a. A mixture of **7a** (630 mg, 1mmol) and sulfuric acid (60 mg, 0,6, mmol) in Me_2SO (5 ml) was first heated at 100°C for 2 hour then cooled to room temperature. After adding Iodine (50mg, 0.2 mmol), the mixture was further heated, it was then poured into ice water and the precipitate was filtered, washed with water and dried to give a solid .The solid was recrystallized from mixed solvent (Ethanol, Dioxane, and Hexane); yield 80%; m.p. 290-292°C.^{1}HNMR: δ2.72 (s,3H,N-CH_3), 2.26(s,3H,N-CH_3),2.95-3.35 (m,4H,H_2C-N-CH_2), 6.91(s,1H,HC=C), 7.08,7.25–(2d,4H,H-P-Cl phenyl ring, J= 8.30, J=9.55);^{I3}CNMR:23.1(-S-CH_3),2100(N-CH_3),54.60,54.9 ($2CH_2$),(aromatic-CH) (125.30,126.11, 126.95,128.70,129.00, 130.17,131.55,132.28, 133.90, 135.36,136.47,137.00,137.85,138.80,139.38,140,141.81, 142.77),190(C=O);IR(cm^{-1}) 3078 (Ar-CH),2900-2875 (aliph.CH), 1679(C=O),1590(C=C); Anal. Calcd for $C_{23}H_{19}NO_2SCl_2$: C, 62.16; H, 4.27; N, 3.15; Found: C, 62.20 H, 4.22; N, 3.18.

Synthesis of 1-methyl-3-(4-chlorobenzylidene or 2-theinylidene)-2,3,4,5 tetrahydro pyridineoxitne 9a,b. To a mixture of the same number of gram of 3-(arylidene)-l-methyl-4-piperidone **la,b** and hydroxyl amine hydrochloride, five time (by volume) of absolute ethanol and pyridine were added the stirred reaction mixture was refluxed for 6-hours. After that the ethanol and pyridine were evaporated, the residue was washed with water and the oxime was obtained as solid, that was profiled by recrystallisation from ethanol.

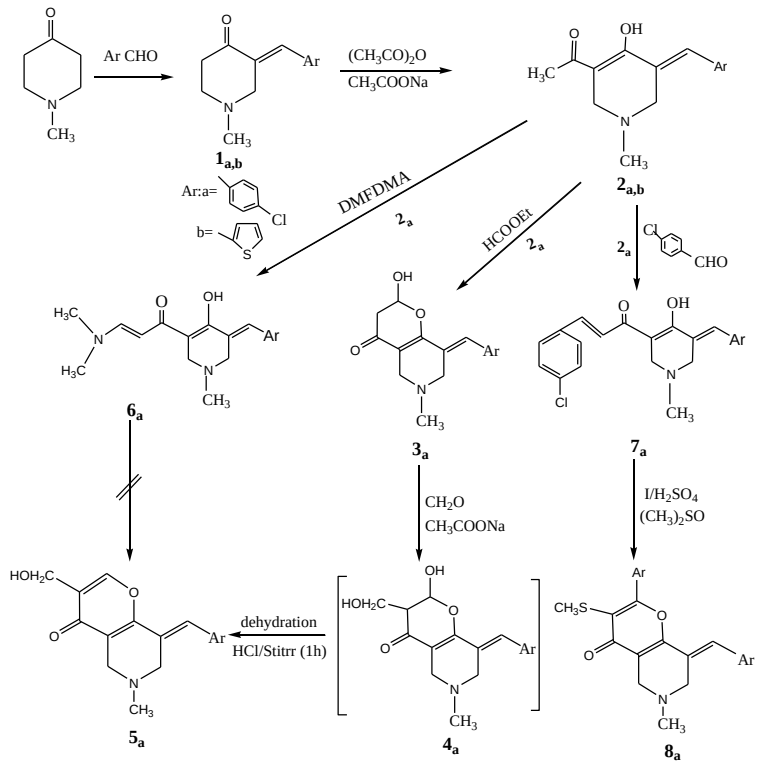
Compound 9a; yield 60%, m.p. 82-84°C. ^{1}HNMR82.21(s,3H,N-CH_3),2.48-2.40(m,4H,H_2C-NCH_2),3.78-3.55(m,2H,CH_2),7.12-7.09(s,1H,HC=C), 7.22-7.95(d,2H,C_3-H-H,P,C_5–H,p-Cl-phenylring, J=8.1l Hz), 8.12-8.00(d,2H) C_2-H)C_6-H,P-Cl phenyl, J=11.08Hz);Anal. Calcd for $C_{13}H_{15}N_2OCl$: C, 62.27; H, 5.98; N, 11.17; Found: C, 62.40 H, 5.60; N, 11.25. IR: 3400 (OH), 3050 (Ar-CH),2900(aliph.CH),1640(C=N).

Compound 9b, yield 70% , m.p.> 360°C. ^{1}H NMR δ 2.25 (s, 3H, N–CH_3), 2.50-2.44 (m, 4H, H_2C–N–CH_2), 4.02-3.95 (m, 2H, CH_2), 7.98 (s, 1H, HC=C),7.30-7.90(m,3H,H-Thiophen ring)14.38(S,1H,OH)IR(cm^{-1}) 3440(OH),3055(Ar-CH),2925 (aliph.CH), 1644(C=N) Anal. Calcd for $C_{11}H_{14}N_2OS$: C, 59.45; H, 6.30; N, 12.60; Found: C, 59.40 H, 6.27; N, 12.00.

Synthesis of 5-methyl-3-(2-thenylidene)-4,5,6,7-tetrahydropyrido [2,3-*c*] isooxazole 10b. To solution of **9b** in THF, sodium bicarbonate solution was added, the flask was protected from light and an aqueous solution of iodine and potassium iodide was added. The reaction mixture was stirred and refluxed for 8 hours. The solid product was obtained and recrystallized from ethanol, yield 80%; m.p.>360°C;IR(cm^{-1})3050(Ar-CH)2900 (aliph.CH), 1644(C=N),1595(C=C).Ms ,220(8.11%); Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 60.00; H, 5.45; N, 12.72; Found: C, 60.10; H, 5.35; N, 12.65.

Synthesis of 5-(arylidene)-l-methyl-5(1H)-pyrrol or morpholine-3-ylmethyl)-4-piperidone11a-c. The mixture of the appropriate 3-(arylidene)-l-methyl-4-piperidone **la,b** (20 mmol), and para formaldeyde (40 mmol) and secondary amine (pyrrol, morpholine).(20 mmol)in the presence of concentrated hydrochloric acid(0.3ml) was refluxed in ethanol (50ml)for 4hours. The solvent was evaporated and the residue was recrystallized by (THF,DMF)(1:1).

Compound 11a crystallized from mixed solvent (THF, DMF) (1:1); yield 95%; m.p.> 360°C. ^{1}HNMR δ 2.12 (s, 3H,N-CH_3),2. 64-2.36 (m, lH,H-3), 3.60-3.48 (m,4H,H_2C-N-CH_2),2.75-2.71(2Xdd,2H,CH_2(3α), J=6.00Hz),7.32(d,2H,C_3-H,C_5-H,H-P-C1-phenyl, J=9.1 Hz),7.68(d,2H,C_2-H,C_6-H,H-P-Cl-phenyl,J=11.13 Hz),



Scheme 1

7.81-8.11 (m,4H,Ar-H) IR- 3082 (Ar-CH),2880 (aliph.CH) 1660(C=O). Anal. Calcd. for $C_{18}H_{19}N_2OCl$: C, 68.85; H, 6.04; N, 8.20. Found: C, 68.65; H, 6.10; N, 8.80.

Compound 11b crystallized from (THF, DMF) (1:1), yield 95%, m.p.> 360°C. Anal. Calcd. For $C_{16}H_{18}N_2OS$: C, 67.13; H, 6.29; N, 7.79. Found: C, 67.15; H, 6.35; N, 7.85. ^{1}HNMRδ2.12 (s, 3H,N-CH_3),2.50-2.36 (m.lH,H-3),3.58-3.51 (m,4H,H_2C-N-CH_2),2.89,2.73(2Xdd,2H,CH_2(3α),J=6.50Hz),7.14-7.00(m,3H,Ar-H),7.38-7.33(m,4H,Ar-H).; IR (cm^{-1}) 3225 (Ar–CH), 2900 (alph.–CH), 1688 (C=O).

Compound 11c, crystallized from (THF, DMF) (1:1) yield 95%, m.p.> 360°C. ^{1}H NMR δ 2.12 (s, 3H,N-CH_3), 2.60-2.40 (m. lH,H-3), 3.50-3.38 (m,8H,H_2C-N-CH_2),2.73-2.70 (2Xdd,2H,CH_2(3a), J=7.00Hz), 7.32 (d,2H,C_3-H,C_5-H_3H-P-Cl-phenyl, J=8.13 Hz) 7.66 (d, 2H, C_2-H, C_6-H) H-P-Cl-phenyl J=14.18 Hz), 3.60-3.55 (m, 4H, H_2C-O–CH_2). Anal. Calcd. for $C_{18}H_{23}N_2O_2Cl$: C, 64.57; H, 6.87; N, 8.37; Found: C, 64.55; H, 6.85; N, 8.30. IR(cm^{-1}) 3090(Ar-CH),2900 (aliph-CH),1680(C=O).

Synthesis of 3-(4-chlorobenzylidene)-5-dimethyl amino methylene-1-methyl - 4-piperidone 12a. *N*,*N*-dimethylformamide dimethylacetal (0.13g, l, lmmol) was added to a solution of **la** (0.20 g, 0.94 mmol) in dry xylene (10 ml) and the resulting mixture was refluxed for 5hours. The solvent was evaporated to dryness and the residue was recrystallized from ethanol, yield70%;m.p.180-182°C. ^{1}HNMR: δ 2.2l-.25, 2.63 (2s,9H,N(CH_3),N(CH_3)$_2$),3.51-3.58 (m,4H,H_2C-N-CH_2),6.62(s, lH, HC=C),8.12 (s, lH, HC=C),7.32-7.30 (d,2H,C_2H,C_6-H,H-P-Cl-phenyl,J=8.81Hz), 7.72,7.66 (d,2H,C_3-H,C_5-H,-P-Clphenyl,J=14.11Hz); IR(cm^{-1}) 3100 (Ar-CH),2995-2883(aliph.CH),1680 C=O). Anal. Calcdfor$C_{16}H_{19}N_2OCl$: C, 66.09; H, 6.54; N, 9.63; Found: C, 66.15; H, 6.60; N, 9.70.

Synthesis of 2-phenyl-5-methyl-7-(4-chloro benzylidene) 4,5,6,7-tetrahydro pyrazolo [4,3-*c*] Pyridine 13a. An equimolar mixture of **12a** (0.01 mol) and phenyl hydrazine (0.01 mol) in 50 ml ethanol was refluxed for 8 hours. The solid product obtained after cooling was collected and recrystalized from ethanol, yield 85%, m.p 130-132°C. ^{1}H NMR δ2.23 (s,3H,N-CH_3),2.57-2.49 (m,2H,N-CH_2),3.43-3.18 (m,2H,CH_2-N),9.60(s,H-Pyrazolring), 6.68 (s,lH, HC=C),7.46-7.12 (m,9H,Ar-H)Ms ,335.5(2.1%),77(100%); IR(cm^{-1}) 3050(Ar-CH),2885(aliph. CH) 1644(C=N), 1595 (C=O); Anal. Calcd. for $C_{20}H_{18}N_3Cl$: C, 71.53; H, 5.36; N, 12.51; Found: C, 71.58; H, 6.40; N, 12.65.

General method for preparation of 1-methyl 3,5-bis-(arylidiene)-4-piperidone 14c,e-g. A mixture of l-methyl-4-piperidone (0.01 mol) and the appropriate aldehyde,(4-chlorobenzaldehyde,thiophen-2-carbaldeyde,2-hydroxy-benzaldehyde, 2choloro benzaldehyde, furaldehyde,4-hydroxybenzaIdehydeand-4-Nitro-phenoxybenzaldehyde) (0.02mol) in alcoholic NaOH (50ml, 10%) was stirred at room temperature for 2hours. The mixture was neutralized with10% HC1 (3ml). The separated solid was filtered, washed with water, dried and recrystallized from the ethanol.
compound **14c**: 50% yield, m.p. 190-192°C. ^{1}H NMR: δ52.25(s,3H,N-CH_3), 3.00-2.58 (m,4H,H_2C-N-CH_2), 6.51(s,lH,HC=C),7.50(d,2H,C_3-H,C_5-H,2-phenyl=8.35Hz)7.60(d,2H,C_2-H,C_6-H,2-OH-phenyl, J=9.80 Hz), 10.5(s,lH, OH), 7.51-8.01(m,4H,Ar-H)IR: 3400(OH), 3052(Ar-CH),2900-2885(aliph.CH), 1715 (C=O). Anal. Calcd. for $C_{20}H_{19}N_2O_3$: C, 74.76; H, 5.91; N, 4.36; Found: C, 74.30; H, 5.89, N, 4.34.

Compound 14e, **yield 90%; m.p. 122-124°C;** ^{1}H NMR δ 2.50 (s, 3H, N–CH_3), 3.60-3.48 (m, 4H, H_2C–N–CH_2), 7.25 (s, 1H, HC=C)), 6.62 (m, 6H furan ring); IR (cm^{-1}), 3090(Ar–CH), 2885 (aliph. CH)); 1595 (C=O) Anal. Calcd. for : $C_{16}H_{15}NO_3$: C, 71.37; H, 5.57; Nm 5.20; Found: C, 71.30, H, 5.60; N, 5.22.

Compound 14f, yield 80%, m.p. 90-92°C. ^{1}HNMRδ2.50(s,3H,N-CH_3),3.80-3.65(m,4H,H_2C-N-H_2),7.21(s,lH, HC=C),7.36 d,2H,C_3-H,C_5-H,P-OH-phenyl,J=8.60Hz),7.60(d,2H,C_2-H,C_6-H,H-2-P-OH-henyl,J=9.5Hz) ,11.0(s,lH, OH),7.81-8.1 l(m,4H,Ar-H); Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.76; H, 5.91;N,4.36;Found:C, 74.72; H, 5.90, 4.33 IR(cm^{-1}) 3080(Ar-CH),2925-2900(aliph.CH), 1718(C=O).

Compound 14g, yield 96%, m.p. 138-140°C. ^{1}H NMR δ2.50(sJ3H,N-CH_3),3.58-3.51 (m, 4H,H_2C-N- CH_2), 7.30(s,lH, HC=C),7.38-7.33(m,8H,Ar-H) Anal. Calcd. for $C_{32}H_{25}N_3O_3$: C, 68.20; H, 4.44; N, 7.46; Found: C, 68.25; H, 4.40; N, 7.42.IR(cm^{-1}) 3067(Ar-CH),2930-2847(aliph.CH), 1700 (C=O).

Synthesis of 7-arylidene -3-aryl (2-carbomoyl or 2-iso-thiocarbomoyl)3,3a,4,5,6,7-hexahydro-5-methyl-2H-pyrazolo [*4,3-c*] pyridine 15a,d,e,17d,e. The mixture of semicarbazide or thiosemicarbazide (30 mmol) and -the corresponding l-methyl-3,5-bis (4-chlorobenzylidene,2-chlorobenzylidene and furalidene)-4-piperidone **14a,d,e** (10 mol)was refluxed for 6-hours in ethanol (110ml) containing 9%conc.HCl .The reaction mixture was cooled down, the solid product was filtered and washed, with water dried and recrystallized from ethanol.

Compound 15a yield 60%; m.p. 220-222°C. ^{1}HNMRδ2.50(s,3H,N-CH_3),3.15-3.11(m,5H,H_2C-N-$CH_2$and H-3a),4.63 (s,2H,NH_2),6.40(d,lH,H-3, J=4.00 Hz),7.66,7.32 (2d, 4H.P-Cl-phenyl ,J=8.20 Hz), 8.04 (s,lH,HC=C),6.31(s,2H,3-Hpyrazole ring) Anal. Calcd for $C_{21}H_{20}N_4SCl_2$: C, 58.46; H, 4.64; N, 12.99; Found: C, 58.50; H, 4.70; N, 12.95. IR(cm^{-1})3422, 3268(NH_2) (Ar–CH), 2900 (aliph.CH), 1633 (C=N).

Compound 15d yield 65%; m.p.185-187°C. ^{1}H NMR δ2.50 (s, 3H,N-CH_3), 3.25-3.30 (m, 5H,H_2C-N- CH_2 andH-3a),4.85 (s,2H,NH_2)6.44(d,lH,H-3, J=3.30Hz),7.60,7.35 (2d,4H,2-Cl-phenyl J=8.50Hz), 8-50 (s,lH,HC=C). Anal. Calcd. For $C_{21}H_{20}N_4SCl_2$: C, 58.46, H, 4.64; N, 12.99; Found: C, 58.50; H, 4.70; N, 12.90. IR: 3448,3280 (NH_2),3120(Ar-CH),288(aliph.CH),1617(C=N).

Compound 15e, yield 60%, m.p.> 360°C.^{1}HNMRδ2.50(s,3H,N-CH_3),3.00-3.40 (m,5H, H_2C-N-CH_2 and H-3a),4.22 (s,2H,NH_2),6.50(d,lH,H-3,J=3.80 Hz), 7-66,7.32, 8.04 (s,lH,HC=C),6.62 (m,7H,6H-furan and (HC=C); Anal. Calcd for $C_{17}H_{18}N_4O_2S$: C, 9.64; H, 5.26; N, 16.37; Found: C, 59.60; H, 5.29; N, 16.35. IR(cm^{-1}) 3400,3320 (NH_2), 3090 (Ar-CH), 2950 (aliph. CH), 1667(C=N).

Compound 17d1, yield 70%; m.p. 250-252°C^{1}HNMR δ 2.42(s,1H,N-CH_3), 2.73-2.50 (m,4H, CH_2-N-CH_2), 3.48-3.41 (m. lH.3a- H),6.35(d,lH,3H, J=9.22Hz), 4.00(s,2H,NH_2), 7.94-7.73(m,8H,Ar-H).8.01 S,1H, HC=C).^{13}C-NMR:42.03(N-CH3),53.37(3a-H), 55.43(N-CH_2),55.81(N-CH_2),63.01(H-3),124.21 (HC=C),135.86 (C-7),152.70(C-7a), C-aromatic(129.60, 131.66,134.07, 135.86,137.30, 138.11,1 39.00,140.24), 181.10 (C=O); Anal. Calcd for $C_{21}H_{20}N_4OCl_2$: C, 60.72; H, 4.81; N, 13.49; Found: C, 60.70; H, 4.85; N, 13.47. IR(cm^{-1}) 3460(OH),3164(NH),3066(Ar-CH),2980/ (aliph.CH),1723(CO),1658(C=N).

Compound 17d2, yield 80%; m.p. 180-182°C. ^{1}H NMR: δ2.02(s,lH,N-CH_3),2.85-2.67(m, 4H,CH_2-N-CH_2),3.40 (d,lH,3a-H), 4.24(d,lH,3-H, J=l l.50 Hz), 5.11 (s,2H,NH_2),8 32-7.91 (m,8H,Ar-H and HC=C) ; Anal. Calcd for $C_{21}H_{20}N_4OCl_2$: C, 60.72; H, 4.81; N, 13.49; Found: C, 60.75; H, 4.75; N, 13.40.IR(cm^{-1}) 3665(OH),3160(NH),3050(Ar-CH).

Compound 17e, yield 50%; m.p.> 360°C. ^{1}HNMRδ2.02(s,3H,N-CH_3),2.85-2.67(m,4H,CH_2-N-CH_2), 3.40 (d,lH, 3_a-H), 4.24 (d,lH,3-H,J= 11.50 Hz), 5.11 (s,2H,NH_2),8.32-7.91 (m,8H,Ar-H and HC=C), IR(cm^{-1})3455(OH),3165(NH),3060(Ar-CH). Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.52; N, 17.17; Found: C, 62.55; H, 5.50; N, 17.15.

Synthesis of 7-arylidene -3-aryl -2-(3-4-nitro phenyl thiazole)-3,3a,4,5,6,7-hexahytdro-5-methyl-2H-pyrazolo[4,2-c] pyridine 16a,d,e. The mixture of **15a,e,d** (26 mmol) and the corresponding 4-nitro phenyl bromide (45.6 mmol) was refluxed in ethanol (25ml) for 6 hours. The solid, product was filtered and recrystallization from ethanol.

Compound 16a; yield 60%, m.p.> 360°C. ^{1}HNMRδ2.50(s, 3H,N-CH_3), 3.22-2.80(m, 5H,CH_2-N-CH_2 and 3a-H), 7.41-7.50(2d, 4H,C_2-H,C_6-H and C_3-H,C_3-H-P-CI phenyl -AA'XX' system, J=8.03H_2),6.01(s, lH,H-3),7.90,8.05(2d,4H,C_2-H,C_6-H,C_3-H,C_5-H-P-NO_2-Phenyl-AA'XX'system,J= 11.50Hz),8.50,8.45 (2s,4H;H-3-Thiazole ring HC=C). Anal. Calcd for $C_{29}H_{23}N_5O_2SCl_2$: C, 60.41; H, 3.99; N, 12.15; Found: C, 60.45; H, 3.97; N, 12.20.IR(cm^{-1}) 3050 (Ar-CH),2950 (aliph.CH), 1640(C=N).

Compound 16d; yield 55%; m.p. 250-252 °C. ^{1}HNMRδ2.50(s,3H,N-CH_3),3.00-2.80(m,5H,CH_2-N-$CH_2$and 3a-H), 7.31,7.40(2d,4H,C_2-H,C_6-H and C_3-H,C_5-H-P-C1 phenyl -AA'XX' system, J=8.33Hz), 6.11(s,lH,H-3)7.91,8.03(2d,4H,C_2-H, C_6–H,C_3-H,C_5-H-P-No_2- Phenyl - AA'XX' system, J=11.00 Hz), 8.41,8.38 (2s,4H,H-3-Thiazole ring HC=C). Mass:363 (50%),111.5(100%),75(100%),Anal. Calcd for $C_{29}H_{23}N_5O_2SCl_2$: C, 60.41; H, 3.99; N, 12.15; Found: C, 60.42; H, 3.98; N, 12.17. IR(cm^{-1}) 3050 (Ar-CH),2950 (aliph.CH),1640(C=N) .

Compound 16e, yield 60%; m.p> 360°C. ^{1}HNMRδ2.50(s,3H,N-CH_3),3.05-2.90 (m,5H,CH_2-N-$CH_2$and 3a-H), 8.55,8.25(2s,2H,H-3-Thiazole ring, HC=C), Anal. Calcd for $C_{25}H_{21}N_5O_4S$: C, 61.60; H, 4.31; N, 14.37; Found: C, 61.62; H, 4.35; N, 14.40. IR(cm^{-1}) 3190(Ar-CH),2880(aliph.CH),1630(C=N).

Synthesis of 7-arylidene -3-aryl(-2-carboximid amide)3,3a, 4,5,6,7-hexahydro-5-methyl-2-pyrazolo-2[4,3-*c*] pyridine 18a,c. The mixture of aminoguanidine hydrogen carbonate (1.36 g,10mmol)and l-methyl-3,5-bis (4-chlorobenzyliden and 2-hydroxy-benzylidene)-4-piperidone **14a,c** (10 mmol) in n-butanol (30ml) was refluxed under stirring for 3 hours . The Solid product was isolated by filtration, washed with n-butanol, dried and recrystallized from ethanol.

Compound 18a; yield 60%; m.p.> 360°C. ^{1}HMRδ2.25(s,lH,N-CH_3),2.30-2.40(m)4H,CH_2-N–CH_2), 2.50-2.49(m,lH,3a-H),6.10 (s,1H,3-H),4.60 (s,4H, NH_2), 5.70-7.00 (br.3H, NH_2,NH), 7.25(dt,1H, J=8.00 and 1.5Hz-5'-H),7.33(dd, lH, J=8.5 and1.3 Hz, 3'-H), 7.65,7.55 (m, lH, 4'-H),7.47-7.34 (m, 1H, 6'-H), Anal. Calcd for $C_{21}H_{21}N_5Cl_2$: C, 60.86; H, 5.07; N, 16.90; Found: C, 60.80; H, 5.10; N, 16.92.IR(cm^{-1})3155, 3400(NH,NH_2), 3200 (Ar-CH), 2850(aliph. CH), 1645 (C=N).

Compound 18c; yield 55%; m.p.> 360°C. ^{1}H NMR δ2.18(s, 1H, N-CH_3), 2.28-2.22 (m, 4H, CH_2–N–CH_2), 2.50-2.49(m,lH,3a- H),6.04(s,1H,3-H),4.42 (s,4H,NH_2), 5.70-7.00 (br.4H,OH,NH_2)NH),7.13(dt,lH,J=8.1 andl.3 Hz, 5'-H),7.33(dd,1H,J=8.1 and 1.2 Hz, 3'-H),7.65,7.55 (m,1H, 4'-H),7.47-7.34 (m,lH, 6'-H). Anal. Calcd for $C_{21}H_{23}N_5O_2$: C, 66.84; H, 6.10; N, 18.56; Found: C, 66.89; H, 6.15; N, 15.58.IR(cm^{-1})3153,3390 (OH,NH,NH_2), 3100 (Ar-CH), 2980(aliph.CH), 1642 (C=N).

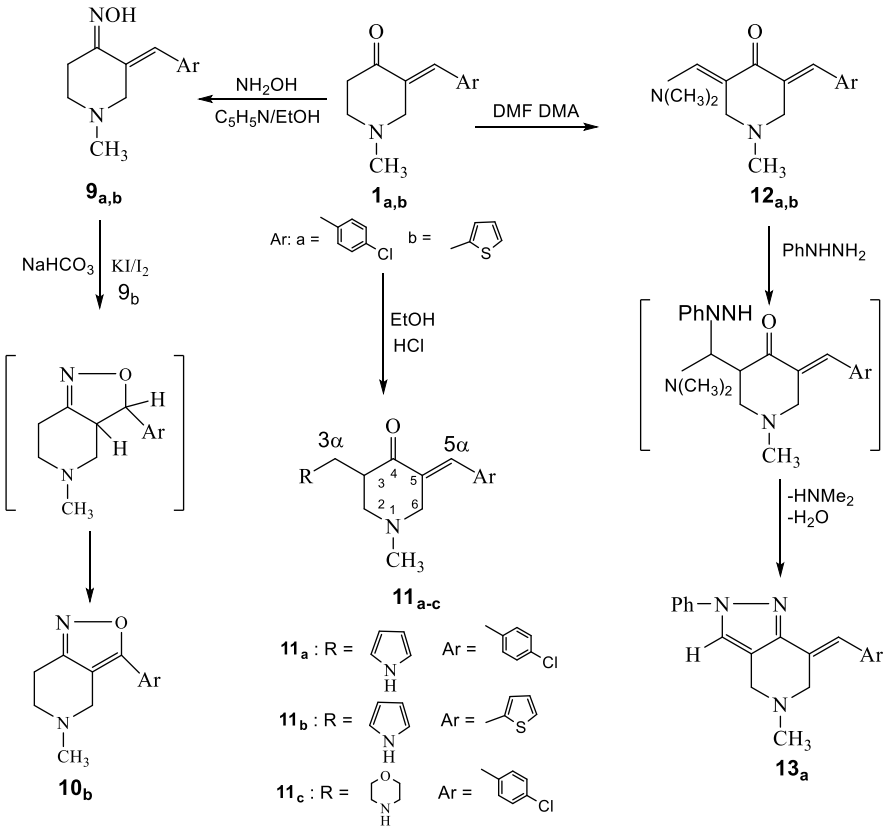
Synthesis of l,4-(4-chlorophenyl)-3-(cyano or carboxamide)6-(4-chlorobenzylidene)-8-methyl-4,5-dihydrospiropyrazolo7,8,9-trihydro-pyridine-5-one19a,f. An equimolar mixture of 1-methyl 3,5-bis (4-chloro benzylidene or 4-hydroxybenzylidene)-4-piperidone14a,f (0.01 mol)and dicyanomethanohydrazonylhalid or α-amide methano-hydrazonylhalid (0.01mol) was, refluxed 6hoursin chloroform (40 ml) and triethylamine (0.7ml).The solvent was evaporated and the residue left was collected and recrystallization from ethanol.

Compound 19a; yield 50%; m.p.>360°C. ^{1}H NMRδ 5.50 (s, 1H, PyrazoloC$_4$–H), 8.22-7.31 (m, 11H, Ar–H). Anal. Calcd for $C_{28}H_{21}N_4Cl_3$: C, 62.27; H, 3.92; N, 10.45; Found: C, 62.30; H, 3.98; N, 10.50,IR(cm^{-1}) 2219 (C≡N)3075 (Ar-CH), 2922 ((aliph.CH), 1680(C=N). 1640 ()C=N).

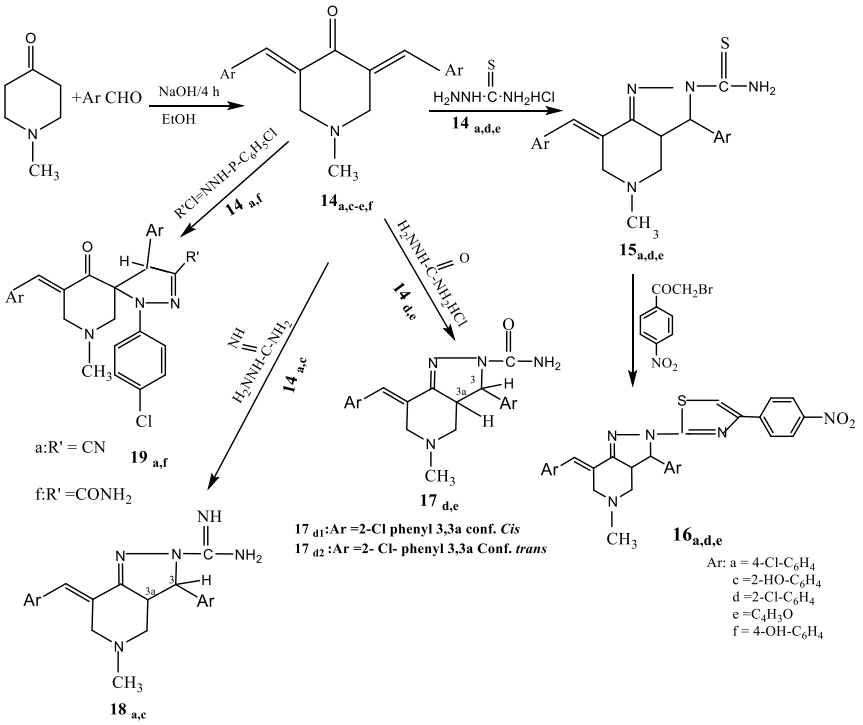
Compound 19f; yield 45%; m.p.220-222°C. ^{1}H NMR δ 5.52 (s, 1H, PyrazoloC$_4$–H), 6.52 (s, 2H, NH_2) 7.01 (m, 11H, Ar–H) .Anal. Calcd for $C_{28}H_{23}N_4O_4Cl$: C, 65.30; H, 4.47, N, 10.88; Found: C, 65.33; H, 4.49; N, 10.85;IR(cm^{-1})3400, 3180 (NH_2)3088 (Ar–CH), 2910(aliph.CH), 1680 (C=O).

Synthesis of 8-arylidene-2-amino or imido-4-aryl-4,4a, 4,5,6,7,8-hexahydro-6-methyl-2H-pyrido[4,3-*c*]pyrimidine 20a,e. The mixture of guanidine sulphate (0.01 mmol) and the corresponding 1-methyl 3,5-bis (4-chlorobenzylidene and furalidene)-4-piperidone 14a,e (0.01 mmol)was refluxed in ethanol (50ml) and 5 ml was added of NaOH 40% drop by drop from the starting of 3-hours,the mixture was refluxed for 6-hours, cooled down, the precipitate was filtered and crystallized from ethanol.

Compound20ayield40%m.p.>360°C^{1}HNMRδ2.26(s,3H,N-CH_3))2.84-3.95(2s,4H,H_2C-N-CH_2),6.21(d,lH,4-H-pyrimidine,J=8.00z),4.48-4.12(m,lH,Hpyridine), 5.20 (s,2H,NH_2), 7.31,7.40(2d,4H,C_2-H)C_6-H and C_3-H,C_5-H-P-C1 phenyl -AA'XX' system, J=8.34Hz,6.11 (s,lH,H-3)



Scheme 2



Scheme 3

7.91,8.03(2d,4H,C_2-H)C_6-H,C_3-H,C_5-H-P,J=11.30 Hz). Anal. Calcd for $C_{21}H_{20}N_4Cl_2$: C, 63.31; H, 5.01, N, 14.03; Found: C, 63.35; H, 5.03; N, 14.06.IR(cm^{-1}) 3400, 33380 (NH_2)3065 (Ar–CH), 2930(aliph.CH).

Compound 20e yield 40% m.p.100-102°C. ^{1}HNMRδ2.26(s,3H,N-CH_3),2.87-3.91(2s,4H,H_2C-N-CH_2),6.23(d,lH,pyrimidine,J=7.50 Hz),4.48-4.01 (m,lH,3-H-pyridine),5.15 (s,2H,NH_2), 7.81 - 6.62(m,7H,6H-furan and HC=C). Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 58.28; H, 5.42, N, 16.00; Found: C, 58.30; H, 5.45;N,16.05IR(cm^1)3400, 3338(NH_2) 3065 (ArCH),2930(aliph.CH).3445,3330(NH_2),3055(Ar-CH),2900(aliph.-CH).

Synthesisof4-(4-chlorophenyl)-5-furan-7-methyl-9-furalidene-5,6,7,8,9-pentahydropyrido[3,2-*c*]pyrimidine[2,3-*b*]triazine-2-thione21$_e$,4-furalidene-8'furan-6-methyl,4,4a,5,6,7,8-hexaHydropyrido[4,3-*c*]pyrimidine-2-(4-chlorobenzamide) 22e. To solution of ammoniumthiocynate (0.01 mol) in acetone equimolar quantity of benzoylchloride was added drop-wise with shaking after heating 1 hour, pyridopyrimidine**20e was added** and reflux for 2 hours. The solvent was distilled and the residue treated with ice-cold water. The solid that separated was filtered, dried and recrystalization from mixed solvent ether and ethanol.

Compound 21e; yield 40%; m.p.> 360°C. ^{1}HNMRδ2.22(s,3H,N-CH_3),2.72-2.85(m,4H, H_2C-N-CH_2),4.42-4.00 (m.lH.3-H-Pyridine ring), 6.33(d, 1H, 4-H-pyrimidine, J=7.80 Hz),7.88-6.60 (m,7H,6H-furan and HC=C). Anal. Calcd for $C_{25}H_{20}N_5O_2SCl$: C, 61.28; H, 4.08, N, 14.30; Found: C, 61.30; H, 4.10; N, 14.35.IR(cm^{-1})3055(Ar-CH),2990(aliph.CH), 644(C=N).

Compound 22e; yield 25%; m.p. 100-102°C. ^{1}HNMRδ2.50(s;3H,N-CH_3)2.88-3.91(2s,4H,H_2C-N-CH_2),6.80(d,lH,Hpyrimidine,J=7.87 Hz),4.40-4.22 (m,lH,3-H-pyridine ring), 7.87-7.17 (m,6H,H-furan),6.99(s,lH, HC=C) Anal. Calcd for $C_{24}H_{21}N_4O_3Cl$: C, 64.21; H, 4.68, N, 12.48; Found: C, 64.25; H, 4.64; N, 12.45. IR(Cm^{-1})3388(NH),3100(Ar-CH),2930 (aliph.CH), 1660(C=O), 1621(C=N).

Synthesis of 2-amino-3-cyano-4-(4-chlorophenyl)-6-methyl-8-(4-chlorobenzylidene) -5, 6, 7, 8~tetrahydro -(4H)-pyrido[3,2-*c*]pyran23a. The mixture of malononitrile (0.1 mmol)and the corresponding3,5-bis(4-chlorobenzylidehe)-4-piperidone **14a** (0.01 mmol) in ethanol (30 ml),in the presence of catalytic amount of piperidine, resulting solution was stirred at room temperature for 20 hours, precipitated product was filtered and recrystallized from ethanol. Yield 75%' m.p. 190-192°C.^{1}H NMR δ2.50 (s,3H,N-CH_3),2.74-3.51 (m, 4H, H_2C–N-CH_2), 6.68 (S,1H,HC=C), 4.01 (d, 1H,4-H-pyran, J=6.18 Hz),6.49 (s,2H,NH_2),7.97 -7.00 (m,7H, Ar-H); IR(cm^{-1})3400,3885(NH_2),3048(Ar-CH), 2900 (aliph-CH), 2349 (C=N), 1608 (C=C).; Anal Calcd. for $C_{23}H_{19}N_3OCl_2$: C, 65.09; H, 4.48; 9.90; Found : C, 65.12, H, 4.52; N, 9.93.

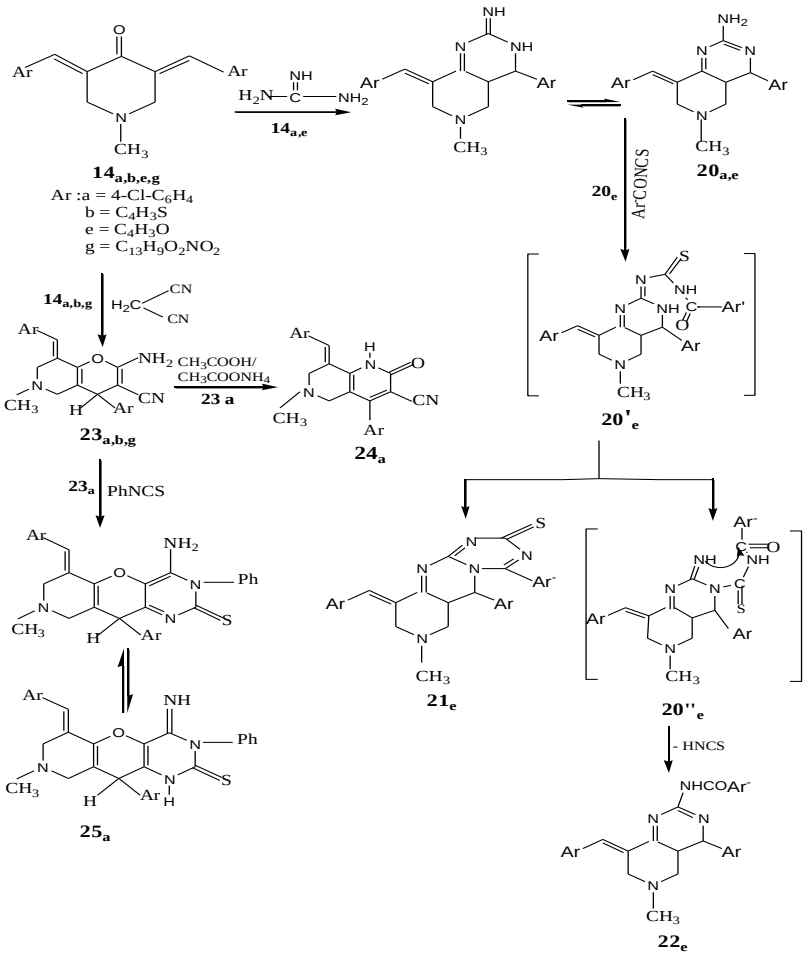
Synthesis of 2-amino3-cyano-4-aryl-6-methyl-8-arylidine-5,6, 7,8-tetrahydro-(4H) pyrido[3,2-*c*] pyran23b,g. The mixture of malononitrile(0.01 mmol) and the corresponding 1-methyl 3,5-bis(2-thenylidene and 4-nitrophenoxy-benzylidene)-4-piperidone (14b,g) (0.01 mmol) in ethanol (50ml) in the presence of catalytic amount of piperidine was heated under reflux for 6 hours. The precipitated was filtered and recrystallized from ethanol.

Compound 23b; yield 65%; m.p. 110-112°C. ^{1}HNMRδ2.50 (s, 3H, N-CH_3),2.84-3.55 (m,4H,H_2C-N-CH_2), 6.80 (S,1H,HC=C), 4.32 (d,lH,4-H-pyran, J=6.50 Hz),6.50 (s,2H,NH_2),7.97 -7.50 (m,7H,Ar-H); Anal Calcd for $C_{19}H_{17}N_3OS_2$: C, 62.12; H, 4.63; 11.44; Found: C, 62.15, H, 4.60; N, 11.48.IR(cm^{-1})3885-3400(NH_2),3048(Ar-CH),2900 (aliph-CH), ' 2349 (C=N), 1608(C=C).

Compound 23 g; yield 75%; m.p. 190-192°C. ^{1}HNMRδ2.22(s,3H,N-CH_3),2.74-3.51(m,4H,H_2C-NCH_2),6.68(S,1H,HC=C),4.01(d,lH,4-H-pyran,J=6.18 Hz),6.49 (s,2H,NH_2),7.97-7.00(m,7H,Ar-H), Anal. Calcd. for $C_{35}H_{27}N_5O_7$: C, 66.77; H, 4.29; 11.12; Found: C, 66.74, H, 4.32; N, 11.10. IR(cm^{-1})3452,3344(NH_2),3048(Ar-CH),2990(aliph.-CH),2190 (C=N), 1590 (C=C).

3-Cyano-4-(4-chlorophenyl)-6-methyl-8-(4-chlorobenylidene)-5,6,7,8, tetrahydro pyrido[3,2-*c*]pyridine 1(H) -2-one. 24a. A solution of compound **23a** (0.01 mol) in acetic acid (30 ml) and ammonium acetate (2g) was heated under refluxed for 6hours. The mixture allowed to cool at room temperature then poured onto ice-cooled water. The solid product was collected by filtration and recrystallized from ethanol. yield 65%; m.p 290-292°C.^{1}HNMR δ2.33(s,3H,N-CH_3),2.70-3.81(m,4H,H_2C-N-CH_2),7.48 - 7.22 (m,8H,Ar- H), 10.08(brs, 1H,NH), 6.84 (s,lH, HC=C); Anal. Calcd for $C_{23}H_{17}N_3OCl_2$: C, 65.40; H, 4.02; N, 9.95; Found: C, 65.45; H, 4.08; N, 9.92. IR (cm^{-1}) 3400(OH),3068(Ar-CH),2932(aliph.–CH), 2220 (C=N).

Synthesis of 10-amino or imido 1-phenyl-4(4-chloro phenyl -6-methyl-8(4-chlorobenzylidene)-4,5,6,7,8-pentahydropyrido[3,2-c]pyrano[2,4-*d*]pyrimidine-2-thione 25a. The mixture of phenylisothiocynate (0.01 mol) ,the corresponding **23a** (0.01mmol), dioxan (15ml)



Scheme 4

and pyridine (2ml) was heated under reflux for 2 hours. The reaction mixture was then cooled, poured onto crushed ice, the resulting solid was washed with water, dried and recrystallized from ethanol. yield 60%; m.p. 190-192°C.^{1}H NMR δ2.50 (s,3H,N-CH_3),3.67-2.72(m,4H,H_2C-N-CH_2),4.32(s,1H,4-H-pyran), 6.40 (s, 1H,HC=C),8.74 (s,1H,NH),7.42-7.08 (3s,8``H,Ar-H); IR(cm^{-1})3207(2NH),3100(Ar-CH),2933(aliph.-CH), 1199(C=S); Anal calcd for $C_{30}H_{24}N_4OSCl_2$: C, 64.40; H, 4.29; N, 10.01; Found C, 64.45; H, 4.25; N, 10.05.

RESULT AND DISCUSSION

Part 1-Chemistry

1-Methyl-4-piperidone and aromatic aldehyde (4-chlorobenzaldehyde or thiophen-2-carbaldehyde) were reacted at room temperature to yield the corresponding 3-(4-chlorobenzylidene or 2-thienylidene)-1-methyl-4-piperidone **1a,b.** These chalcones were employed as key intermediates for further synthesis of the other biological active compounds.

Compound **1a,b** was heated with acetic anhydride and sodium acetate togive 5-acetyl-4-hydroxy-3-(4-chloro-benzylidene or 2-thenylidene)-l-methyl pyridine(**2a,b)**. The IR spectrum displayed a strong hydrogen bonded carbonyl absorption 1708 cm^{-1} and a weak broad hydroxyl absorption 3444cm^{-1}. In the ^{1}H NMR spectrum one proton singlet in a low magnetic field δ 8.83ppm was observed for **2a** which could be ascribed to the hydroxylpyridine.

Claisen condensation of this hydroxy pyridine with ethyl formate, to give condensation product was isolated as the cyclic hemiacetal 2-(4-chlorobenzylidene)-8-hydroxy-4-methyl-2,3,4,5-tetrahydro pyrido [3,2-*c*] pyran-6-one (**3a**).Ring chain tautomerism has been described for 2-hydroxy pyran-4-one, shown to exist in solution in an equilibrium between dicarbonyl, keto-enol and the cyclic hemiacetal form. The IR spectrum of compound **3a** displayed the characteristic absorption band for the pyran ring carbonyl 1680 cm^{-1}. One proton singlet in a low magnetic field δ 3.90 ppm was observed in NMR for **3a,** which could be ascribed as hydroxy proton. Treatment

of compound **3a** with formaldehyde in the presence of a trace of basic catalysts at room temperature afforded2-(4-chlorobenzylidene)-7-(hydroxylmethyl)-8-hydroxy-4-methyl-2,3,4,5-tetra-hydropyrido[3,2-clpyran-6-one**4a**.This intermediate isprovedto be unstable and difficult to be isolated. Thus, the reaction mixture was acidified to give the corresponding 2-(4-chlorobenzylidene)-7-hydroxymethyl -4-methyl-2,3,4,5-tetrahydropyrido[3,2-*c*]pyran-6-one (**5a)** which was isolated in good yield. The structure of **5a** was established for the reaction product based on its elemental analysis and spectral data. Thus ^{1}H-NMR spectrum showed a singlet at δ8.00 ppm for pyran-2H,in addition to multiplets at δ 7.97-7.55,4.34 and 4.74 ppm, corresponding to aromatic, hydroxy and methylene protons. Enamino ketone **6a** can be prepared by treatment of compound **2a**with N,N-dimethyl formamide dimethyl acetal,itsacid cyclization does not give pyrano[3,2-*c*] pyridine derivatives **5a**

Table 1. Screening of the effect of some chemical compounds and standard antibiotics on *Bacillus cereus*

No	Name of compound	Inhibition zone diameter (mm)
1	11_a	-
2	11_b	8
3	13_a	15
4	14_a	-
5	14_c	13
6	14_e	14
7	14_g	19
8	15_a	-
9	15_d	10
10	15_e	11
11	16_d	9
12	16_e	13
13	17_{d1}	10
14	17_{d2}	-
15	18_c	10
16	20_c	10
24	DMF	R
25	Augmentin	10
26	Colifuron	-
27	Negram	10
28	Tetracycline	21
29	Gentamycin	16
30	Ceftazidime	18
31	Trimethoprimsulfamethoazole	14

Hydroxy chalcones 7awas obtained by reacting compound **2a** with4-chlorobenzaldehyde under base catalysed Aldol condensation. Compound **7a** was first heated at 100°C for 15 min. with dimethyl sulfoxide and small amount of sulfuric acid, then a catalytic amount of iodine was added the mixture was heated at 100°C for 2h. The major product obtained in 63% yield after purification was characterized as 7-(methylthio)-8-(4-chlorophenyl)-2-(4-chloro-benzylidene)-4-(methyl)-2,3$_3$4,5-tetrahydro pyrido[3,2-c]pyran-6-one (**8a)**. The structure of **7a** and **8a** were confirmed on the basis of its elemental analysis and spectral date. Reasonable mechanism [21] for these reactions is that shown in (**Figure 2**). The starting chalcones isomerises in the presence of concentrated sulfuric acid to the compound **7a** which undergoes iodination and reaction with dimethyl sulfoxide to give **7b** which converted to**7c**by loss of methyl iodide, further iodination and dehydro-halogenation leading to **8a**.

The synthesis of the oxime **9a,b** was carried out by the reaction of α,β-unsaturated cyclic ketones containing anexocyclic double bond 3-(4-chlorobenzylidene or 2-thenylidene)-1-methyl-4-piperidone **1a,b** with hydroxylaminehydrochloride in the presence of pyridine and absolute ethanol as solvent . The conversion of the oximes into the isoxazole derivatives was carried out by heating with iodine and potassium iodide, for eight hours, in a THF-water solution containing sodium bicarbonate, it was noticed that shorter reaction times led to substantially higher yields in the isoxazole synthesis **10b**. On the other hand, it was observed that the use of twice the amount of iodine and potassium iodide gave higher yields. On the basis of the results reported by Meisenheimer[21]it could be deduced that the oximes obtained from α,β-unsaturated ketones cyclized' to isoxazolines probably according to (**Scheme 2**), but that they cannot be transformed directly into the isoxazole derivatives without the presence of an oxidizing agent. The formation of isoxazole derivatives by cyclization of unsaturated oxime in the presence of iodine and sodium bicarbonate explained by Büchi and Vederas [21] as shown in (**Figure 3**) through any of the two intermediatesa and which lead to c and d by internal nucleophilic substitution unsaturated system in conjugation with aromatic substituent on theβ-carbon atom and so the groups on the aromatic ring should have some sort of influence in the cyclization reaction. On the contrary, in adipolar intermediate ion like b, the carbon atom in β of the oximate is positive enough to be attacked easily by an ionic oxygen of this attack involves the cyclic transition state, the substituents should not have an appreciable influence.

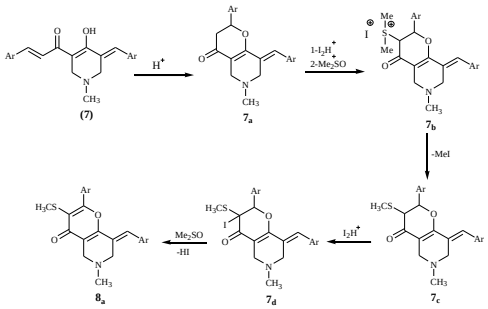


Figure 2. Possible mechanisms for the formation of compounds 7a and 8a.

The Unsaturated Mannich ketones **11a-c** have been prepared from the corresponding 3-(arylidene)-l-methyl piperidone **la,b,** secondary amines (pyrrol or morpholine), formaldehyde and ethanol as solvent in presence of HC1 as a catalyst. The high chemical shifts of their methylene hydrogen δ 2.70 ppm is due to isotopic neighboring effect of the near living carbonyl, influence one of the hydrogens.

Condensation of **1a** with dimethyl formamide dimethyl acetal (DMFDMA)gave 3- (4-chlorobenzylidene)-5-dimethylaminomethylene-1-methyl-4-piperidone**(12a)**, which when treated with phenyl hydrazineyielded2-phenyl-5-methyl-7-(4-chloro benzylidene)4,5,6,7-tetrahydro-pyrazolo [4,3-c] pyridine (**13a)** ,with loss of dimethyl amine and water molecule. However, the product **12a** was assigned based on the 'H-NMR which revealed the presence of a singlet corresponding to methyl at δ 2.63 ppm. The structure of **13a** was confirmed by instrumental and elemental analysis. Especially, the ^{1}H-NMR spectrum of **13a** showed a resonance of δ 9.60 ppm corresponding to H-3 of N-phenyl pyrzole.

The designed target compounds depicted in (Scheme 3)were obtained by reacting the starting material l-methyl-4-piperidone with variety of aromatic aldehydes under aldol condensation conditions to produce the α,β-unsaturated ketone analogues **14a,c-e,f.**

Compounds **14a,d,e** were subjected to cycloaddition condensation reaction using thiosemicarbazides under acidic conditions yielded only one diastereoisomer of 3-H, 3a-H*cis* **15a,d,e** which have been separated.

Table 2. Effect of a series of dose levels of the highly active compounds in the agar diffusion assay using *Bacillus cereus*.

Conc. of compound (μg/ml)	Square of mean diameter of inhibition zone (mm^2)			Log dose (μg/ml)
	14g	14e	13a	
100	36	12	16	2.0
200	42	16	20	2.3
400	49	20	25	2.7
800	56	25	36	3.0
1600	64	30	49	3.2
3200	72	36	56	3.5
46000	81	42	64	3.9
12800	90	49	72	4.1
Potency (μ/ml)	6.3	19.9	31.7	

The IR spectrum of isolated products showed in each case the absence of carbonyl bond and revealed the presence of two bonds in the regions of 3422-3268 cm^{-1} due to the NH_2 protons, two singlet signal at δ 6.31, 3.48 ppm, for pyrazole -3H and pyridine-3H, in addition to multiplets at δ7.66-7.32and 2.50 ppm, corresponding to aromatic and methylene protons In order to obtain potentially antibacterial substance, compounds **15a,d,e** were further utilized for another cyclocondensation reaction using 4-nitrophencylbromid in refluxing ethanol containing catalytic amount of piperidine to afford the 7-arylidene-3-aryl- 2-[3-(4-nitrophenylthiazole) 3,3a,4, 5,6,7-hexahydro-5-methyl-2H-pyrazolo[4,3-*c*] pyridine (**16a,d,e)**.

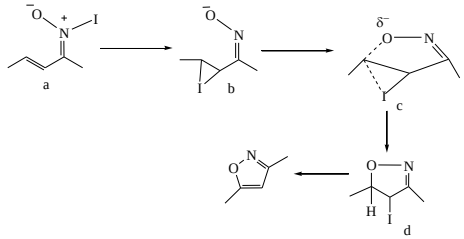


Figure 3. The formation of isoxazole derivatives

On the other hand, when the cyclization performed between α,β-unsaturated ketones **l4d,e** and semicarbazide afforded the mixture of 3-H,3a-H*cis* and *trans* diasteroisomer,7-arylidene-3-aryl-2-carbomoyl, 3,3a,4,5,6,7-hexahydro-5-methyl-2H-pyrazolo[4,3-*c*] pyridine (**17d,e)**. The structure and relative configuration of the compounds **17d,e** have been determined by ^{J}H-NMR and ^{13}C-NMRspectroscopic method. The vicinal H-3, H-3a coupling is 9.30 and 11.50 Hz for isomer , while the value are in accordance with expected ratio ^{3}Jcis>^{3}J *trans* [22]difference is far two small for affirm differentiation of *cis or trans* configuration in the case of single compounds without their counter parts moreover, because of broadened signals ,it was not possible to determine the value of this coupling constant for all compounds and in most cases the splitting was between the two values (about 10-11 Hz) measured for the 17d1 and **17d2** On the outlay, the ^{13}C-NMR field effect arising in the *cis* isomers is affirm base to identify the C-3, C- 3a configurations

In continuation for preparing highly functionalized 2-pyrazolines, treatment of **14a,c** with aminoguanidinehydrogencarbonate gave 7-arylidene-3-aryl-(2-carboximidamide)3,3a,4$_5$5,6,7,hexahydro-5-methyl-2H-pyrazolo[4,3-c]pyridine (**18a,c)**.

The mass spectrum of the product furnished a significant proof the amidine structure 18a.The prominent peaks at m/z=(401), (386) and (385) were produced by loss of neutral molecules of NH_3, HN=C=NH and the H-N=C-NH_2 radical from the molecular ion (m/z=401). In addition, the second most abundant peak at m/z $(CHN)^+$ was a clue that indicated a pyrazolinium species. All cycloadducts **18a-,c** gave satisfactory elemental and the spectra data the ^{1}H-N MR

of each compound showed a singlet at δ 2.50-2.49 ppm assignable to the proton at position $\mathbf{3_{a\text{-}H}}$.

Furthermore, refluxing equimolar amounts of **14a,f** with hydrozonylhalides and triethylamine for 6 h. in Chloroform gave after work up in each case only one spirocycloadducts. All cycloadducts **19a,f** gave satisfactory elemental analyses and spectral data the ^{1}H-NMR spectrum of each compound showed a singlet signal at δ5.50 ppm assignable to proton at position 4 satisfactory elemental analyses and spectral data the ^{1}H-NMR spectrum of each compound showed a singlet signal at δ5.50 ppm assignable to proton at position **4**.

Table 3. Screening of the effect of some chemical compounds and standard antibiotics on *Staphylococcus aureus*.

No.	Name of compound	Inhibition zone diameter (mm)
1	11_a	-
2	11_b	15
3	13_a	-
4	14_a	12
5	14_c	11
6	14_e	-
7	14_g	13
8	15_a	-
9	15_d	10
10	15_e	11
11	16_d	8
12	16_e	12
13	17_{d1}	15
14	17_{d2}	-
15	18_c	8
16	20_c	12
24	DMF	-
25	Augmentin	-
26	Colifuron	-
27	Negram	-
28	Tetracycline	R
29	Gentamycin	R
30	Ceftazidime	8
31	Ttimethoprimsulfamethoazole	7

Compounds **14a,e** on reaction with guanidine sulfate yielded 8-arylidene-2-amine or imido-4-aryl-4,4a,5,6,8-hexahydro-6-methyl-2H-pyrido[4,3-c]pyrimidine (**20a,e)**. Mechanistically, in presence of base, guandine sulphate is converted to free base which can act as a bidentate nucleophile and facilitate Michael type addition with α,β-unsaturated system or internal condensation with carbonyl group of **14** followed by cyclization will result in the unstable dihydropyrimidine derivatives **20a**,**e**. Structural determination of **20e**wasconfirmed on the basis of elemental analysis and spectral data. Its IR spectrum showed amino stretch at 3445,3330 cm'^{1} and ^{1}H-NMR spectrum showed in addition to the aromatic signals, singlet integration for two protons at δ 5.15ppm which was attributed to the 2-amino group protons and doublet atδ6.23ppm integrating for7H-pyrimidine ring the reaction of **20e** with aroylisothiocynates gave two compounds which were separated **21e, 22e**, were the intermediate $\mathbf{20'_e}$is not isolated , but it through dehydrocyclization provides a simple and more facile route for the synthesis of biologically active 1,3,5-triazine system**21e**.This is due to the behaviour of 2-amino pyrimidine molecule in amino-imino form which facilitates condensation and dehydration. Compound $\mathbf{22_e}$was also obtained in 20-25% yields. The formation of **22e** can be explained through elimination of thiocyanic acid from **20'e**.

The IR spectrum of **22e** showed the absorption bands corresponding to NH 3388 cm^{-1} and carbonyl 1660 cm^{-1}. The ^{1}H-NMR spectrum of **21e,22e** showed a resonance at 6.33 and 6.80ppm corresponding to H-4 of pyrimidine ring. The mass spectrum of **21e** furnished a significant proof of the structure **21e**. The prominent peaks atm/z (257),(11.5%) and (83) were produced by loss of natural molecules of NH_3 and H_2S.

Reacting **14a,b,g** with malononitrile in refluxing butanol produced the pyrido [3,2-*c*] pyran **23a,b,g**. Thus, the IR spectrum of **23a,b,g** showed as amino and nitrile at 3452,3444, and 2190 cm^{-1}, respectively, are compatible with assigned structure. ^{1}H-NMR spectrum showed in each case, abroad signal (D_2O exchangeable) at δ 6.49 ppm due to NH_2 protons in addition to a singlet signal at δ 4.03 ppm for pyran-4H. Rearrangement of 2-amino pyrans into pyridines on refluxing in a mixture of acetic acid and ammonium acetate, compound **23a** was converted into 3-cyano-4-aryl-6-methyl-8-arylidene-5,6,7,8-tetrahydro-lH-pyrido [3,2-c]pyridine-2-one **(24a)**. IR spectrum of **24a** showed on OH and CN absorption bonds at 3400 and 2220cm^{-1}, the ^{1}H-NMR spectrum of **24a** showed broad signal atδ10.08 ppm (NH) group. Reaction of **23a**with phenylisothiocynate for a long time furnished 10- amino or imido-1-phenyl-4-(4-cnlorophenyl-6-methyl)-8-(4-chloro-benzylidene)-4,5,6,7,8-pentahydropyrido[3,2-c] pyrano[2,4-*d*] pyrimidine-2-thione (**25a)**. The IR spectrum of **25**shows absorption at 3207 cm^{-1} (2NH),1199 (C=S), The ^{1}H-NMR spectrum of **25a** showed a resonance at 4.32 and 8.74 ppm corresponding to H-4 pyran and (NH)group.

Part 2-Biological results

Preliminary screening for the antimicrobial activity of the synthesized compounds using the agar diffusion technique against *Bacillus cereus*, *Staphylococcus aureus* and *Candida albicans* showed that a concentration of 200 μg/ml dissolved in dimethylformamide (DMF). It is the proper

concentration for evaluation compared with standard antimicrobial agents augmentin, amoxicillin-clavulanic acid, colifuran, gentamycin, negram, nystatin, tetracycline, trimethoprim- sulfamethoazole and ceftazidime.

Table 4. Effect of a series of dose levels of the highly active compounds in the agar diffusion assay using *Staphylococcus aureus*.

Conc. of Compound (µg/ml)	Square of mean diameter of inhibition zone (mm^2)		Log dose (µg/ml)
	11b	17d1	
100	16	16	2.0
200	20	20	2.3
400	25	25	2.7
800	30	30	3.0
1600	36	36	3.2
3200	42	42	3.5
46000	49	49	3.9
12800	56	56	4.1
Potency (µ/ml)	10	10	

The representative dose responses for the highly active compounds were plotted and the potencies were determined. The antimicrobial activity of the highly active compounds compared with standard antimicrobial agents showed that in case of *Bacillus cereus* (**Tables 1** and **2** and **Figure 4**) the compound **14g** had higher antibacterial activity amongst the tested compounds and is nearly equal to that of the standard antibiotic ceftazidime.

Staphylococcus aureus (**Tables 3, 4** and **Figure 4**) showed higher antibacterial activity against compounds **11b** and **17d1** these activities were more higher than that against the standard antibiotics, Todar[23] reported that many of the community associated Staphylococcal infections were now methicillin resistant. These organisms were uniformly resistant to penicillins and cephalosporins.

Candida albicans (**Tables 5, 6 and Figure 5**) had higher antifungal activity against compounds **11b,13a,14c,e,g, 16e,** and **17d1** in comparison with standard antifungal nystatin.

Cytotoxicity evaluation using viability assay

For cytotoxic assay, the cells were seeded in 96-well plate at a cell concentration of 1 x 10^4 cells per well in 100 µl of growth medium.Fresh medium containing different concentrations of the test sample was added after 24 h of seeding. Serial two-fold dilutions of tested chemical compound were added to confluent cell monolayers dispensed into well, flat-bottomed microtiter plates (falcon, NJ, USA) using a multichannel pipette.The microtiter plates were incubated at 37°C in a humidified incubator with 5% CO_2 for a period of 48 h.Three wells were used for each concentration of the sample. Control cells were incubated without test sample and with or without DMSO (the little percentage of DMSO present in the wells) was found not to affect the experiment.

After incubation of the cells for 24 hrs. at 37°C, various concentrations of sample (50,25,12.5,6.25,3.125,1.56 µg) were added, and the incubation was continued for 48 hrs. and viable cells yield was determined by calorimetric method. In brief, after the end the incubation period, media were aspirated and the crystal, violet solution (1%) was added to each well for a least 30 minutes.The stain was removed and the plates were rinsed using tap water until all excess stain is removed. Glacial acetic acid (30%) was then added to all wells and mixed thoroughly, and then the absorbance of the plates were measured after gently shaken on microplate using a test wavelength of 490 nm. All results were corrected for background absorbance detected in wells without added stain. Treated samples were compared with the cell control in the absence of the tested compounds. All experiments were carried out in triplicate. The cell cytotoxic effect of each tested compound was calculated.

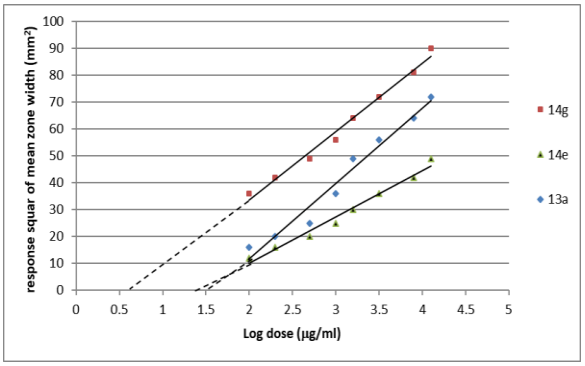


Figure 4. Response of a series of dose levels at the highly active compounds in the agar diffusion assay using *Bacillus cereus.*

Structural activity relationship

A. For *Bacillus cereus* Gram positive rods)

The compounds **14g,e** have highest antibacterial activity due to presence of α,β-unsaturated ketones group presence olefin group [24] and N-methyl piperid-4-one[24] in the structure of the compounds ,all this groups affect activity of the compounds. The compound **13a** have antibacterial activity due to presence of pyrazolo [3,2-c] pyridine system and olefin group[24] in the structure of the compound, all this affect activity of the compounds.

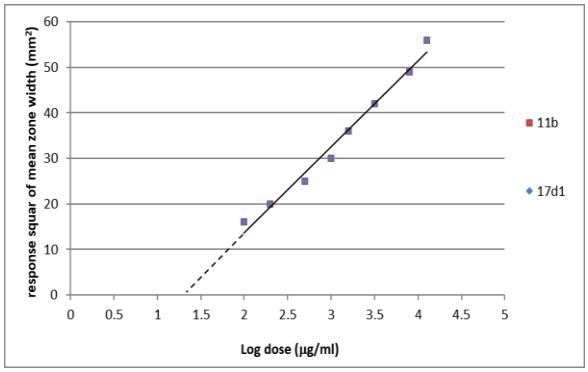


Figure 5. Response of a series of dose levels at the highly active compounds in the agar diffusion assay using *Staphylococcus aureus*

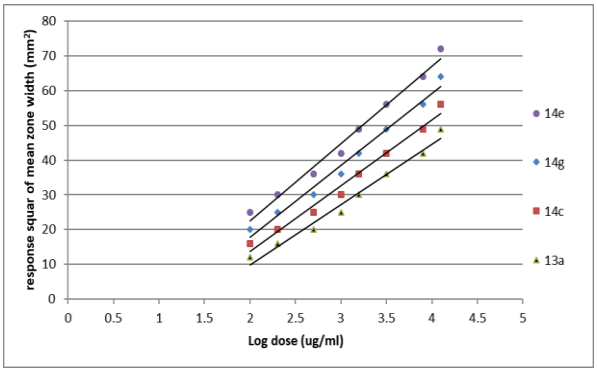


Figure 6. Response of a series of dose levels at the highly active compounds in the agar diffusion assay using *Candida albicans*.

B. For *Staphylococcus aureus* Gram positive *cocci*

Compounds **11b** Mannich ketone compound and **17d1** pyrazolo [3,2-*c*] pyridine derivative have equal higher antibacterial activity than antibiotic standard used due to the two compounds contain olefin group[24].

C. For *Candida albicans* (yeast like fungi)

Compounds **11b, 13a,14c,e,g 16e, 17d1** have antifungal activity than antibiotic standard used due to compounds **13a,16e,17d1** are derivatives of pyrazolo [3,2-c] pyridine and Compound **11_a** Mannich ketone compounds. These compounds system have biological activity. Compound **14c,e,g** contain N. methyl piperidone[24] (chalcones) with two olefin group.[24]

Cytotoxic activity

In this study ,seven of newly synthesized compound that show cytotoxic activity against HEPG2 human liver cell line and MCF-7 human breast cell line using Vinblastine as a standard drug control. Each cell line was incubated with six concentrations (1.56-50µg) for each compound and was used to create compound concentration versus survival fraction curves. The response parameter (IC_{50}) was calculated for each cell line (**Tables 7, 8**).

The IC_{50} value corresponds to the compound's concentration causing a net 50% loss of initial cells at the end of the incubation period (48 h).

The Cytotoxic activity was measured in vitro on HEPG2 human liver cell line, and MCF-7 human breast cell line using Vinblastine (reference drug control)assay applying the method of Mosmann[25].

The cells were propagated in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum, 1% L-glutamine, HEPES buffer and 50g/ml gentamycin. All cells were maintained at 37°C in a humidified atmosphere with 5% CO_2 and were subcultured two times a week.

Cell toxicity was monitored by determining the effect of the test sample on cell morphology and cell viability.

Table 5. Screening of the effect of some chemical compounds and standard antifungal on *Candida albicans*.

No.	Name of compound	Inhibition zone diameter (mm)
1	11_a	-
2	11_b	16
3	13_a	14
4	14_a	-
5	14_c	15
6	14_e	17
7	14_g	16
8	15_a	12
9	15_d	10
10	15_e	13
11	16_d	12
12	16_e	17
13	17_{d1}	14
14	17_{d2}	13
15	18_c	13
16	20_c	11
24	DMF	-
25	Nystatin	-

The activity of the tested compounds could be correlated to structure variation and modifications, investigating the variation in selectivity of the tested compounds over the two cell lines, it was revealed that nearly all of the compounds are nitrogen heterocyclic piperdines are an important group of compounds in the field of medicinal chemistry with interesting biological and pharmacological properties.

Table 6. Effect of a series of dose levels of the highly active compounds in the agar diffusion assay using *Candida albicans*.

Conc. of compound (µg/ml)	Square of mean diameter of inhibition zone (mm^2)							Log dose (µg/ml)
	11b	17d1	14g	14c	14e	16e	13a	
100	20	12	20	16	25	25	12	2.0
200	25	16	25	20	30	30	16	2.3
400	30	20	30	25	36	36	20	3.7
800	36	25	36	30	42	42	25	3.0
1600	42	30	42	36	49	49	30	3.2
3200	49	36	49	42	56	56	36	3.5
46000	56	42	56	49	64	64	42	3.9
12800	64	49	64	56	72	72	49	4.1
Potency (µ/ml)	7.9	25.1	7.9	19.9	5.0	5.0	25.1	

Table 7. Result in vitro Cytotoxic; activity of the test compounds on HEPG2 human liver cell line

Compound No.	Percentage of the surviving (viability) HEPG2 cells at each concentration in (µg)							IC_{50} in µg
	0	1.56	3.125	6.25	12.5	25	50	
5a	100.00	100.00	100.00	100.00	98.61	90.08	82.87	>30.00
11a	100.00	100.00	100.00	100.00	100.00	99.12	95.06	>50.00
11b	100.00	100.00	100.00	100.00	100.00	98.74	93.2	>50.00
13a	100.00	100.00	91.14	77.08	59.84	48.92	37.67	23.50
20e	100.00	100.00	100.00	100.00	100.00	91.36	82.72	>30.00
21e	100.00	100.00	100.00	100.00	100.00	98.05	94.92	>50.00
25a	100.00	100.00	100.00	97.6	89.22	61.38	32.94	36.20
(vinblastine)	100.00	72.13	55.00	45.13	24.25	16.13	14.38	4.60

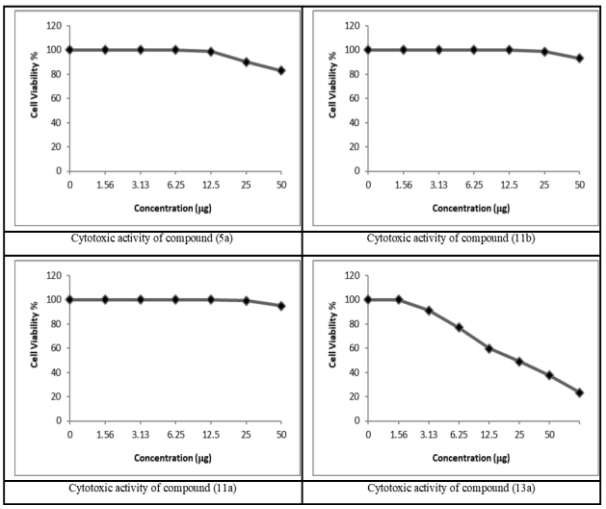


Figure 7. Cytotoxic activity of the test compounds (5_a,11_a, 11_b and 13_a) on HEPG2 human liver cell line.

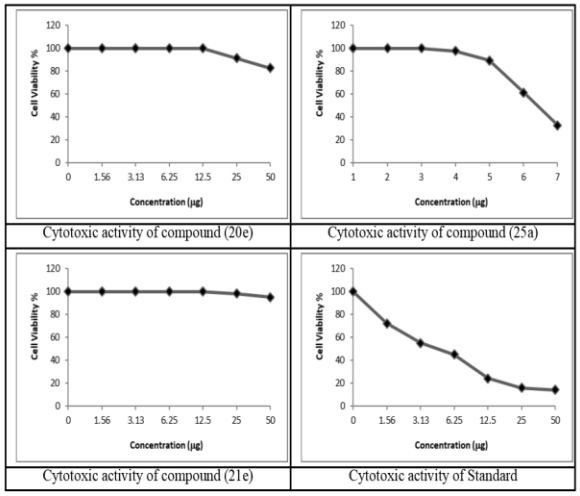


Figure 8. Cytotoxic activity of the test compounds (20_e,21_e, 25_a and standard) on MCF-7 human breast cell line.

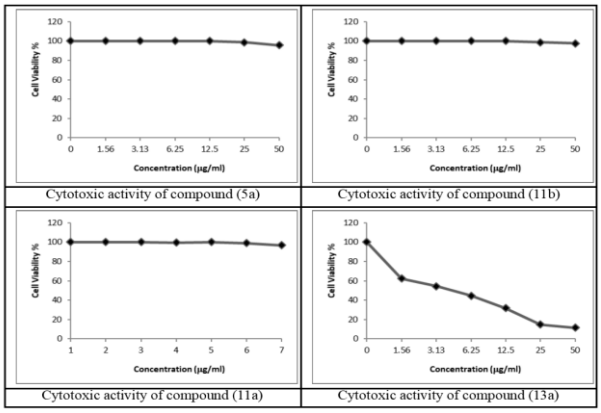


Figure 9. Cytotoxic activity of the test compounds (5_a,11_a,11_b and 13_a) on MCF-7 human breast cell line.

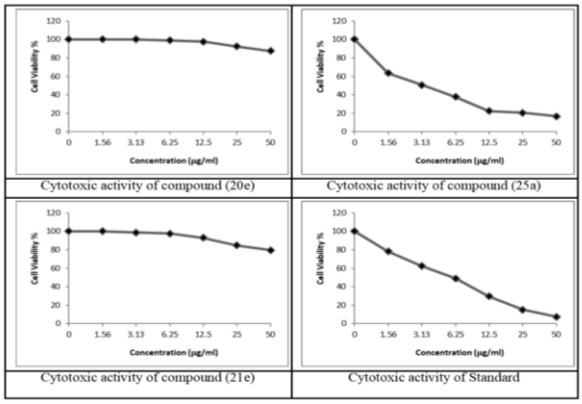


Figure 10. Cytotoxic activity of the test compounds (20_e,21_e, 25_a and standard) on HEPG2 human liver cell line.

Table 8. Result in vitro Cytotoxic; activity of the test compounds on MCF-7 human breast cell line

Compound No.	Percentage of the surviving (viability) MCF-7 cells at each concentration in (µg)							IC_{50} in µg
	0	1.56	3.125	6.25	12.5	25	50	
5_a	100.00	100.00	100.00	100.00	100.00	98.78	95.86	>50.00
11_a	100.00	100.00	100.00	99.68	100.00	98.94	96.76	>50.00
11_b	100.00	100.00	100.00	100.00	100.00	98.74	97.62	>50.00
13_a	100.00	62.32	54.44	54.56	31.67	14.78	11.56	4.70
20_e	100.00	100.00	100.00	98.98	97.64	92.56	87.66	>30.00
21_e	100.00	100.00	98.88	97.52	92.96	84.78	79.65	>30.00
25_a	100.00	63.33	50.56	37.78	22.35	20.56	16.67	3.65
(vinblastine)	100.00	78.24	62.37	48.95	29.6	15.16	7.42	11.60

In compound **13_a** pyrazolo [4,3-c]pyridine have shown good anticancer agent. Presence olefinic group in compound and aromatic ring substituted in pyrazolo ring may be increase the anticancer activity in compound **13_a** IC_{50} = 4.70 against MCF-7 human breast cell line higher activity than standard used IC_{50}=l1.60 and against HEPG2 human liver cell line compound **13_a** showed activity less than standard used IC_{50} =4.60 and IC_{50} =23.50 of compound **13_a**.

In compound **25_a** presence of pyrimidine-2-thion derivative have antitumor activity and Showed activity against MCF-7 human breast cell line IC_{50}=3.75 than standard, and showed activity against HEPG2 human liver cell line IC_{50} = 36.20 less than standard

CONCLUSION

It could be concluded that the tested compounds **14a,e** have highest antibacterial activity due to presence of α,β-unsaturated ketones group and the presence of olefinic group. The compound **13a** have antibacterial activity due to presence of pyrazolo[3,2-*c*] pyridine system and olefinic group. Compound **11b** and **17d1** pyrazolo[2,3-*c*] pyridine derivatives have equal higher antibacterial activity than antibiotic standard. Compounds **11b, 13a, 14c,e,g, 16e, 17d1** have antifungal activity than antibiotic standard used, . Compound **13a** pyrazolo[4,3-*c*] pyridine have shown good anticancer agent.

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Conflict of Interest

The authors declare that they do not have any conflict of interest.

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