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Application of Chalcone in Synthesis of New Heterocycles Containing 1,5-Benzodiazepine Derivatives

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AbstractA series of some new [1,5]-benzodiazepineshas been synthesized using condensation reaction of *o*-phenylenediamine and various substituted chalcones in presence of DMF as solvent and screened against some bacteria and fungi strain.

Keywords Chalcone, *O*-phenylenediamine, [1,5]-benzodiazepines, Antimicrobial activity

1. Introduction

"Chalcones; either natural or synthetic are well known to exhibit promising biological activities such as antibacterial, antitumor, anti-inflammatory analgesic, anti-malarial, and antituberculosis antipyretic[1]. Chalcones are used new for the synthesis of various classes of heterocyclic compounds such as thiazines, pyrazolines, isoxazolines and to benzodiazepines [2] etc. "Benzodiazepines have recently received considerable attention because of their promising biological activities such as anticonvulsant, antioxidant, anthelmintic and antibacterial activities [3,4]. Due their wide range of pharmacological, industrial in addition to synthetic applications, the synthesis of 1,5 - benzodiazepines have received considerable attention. Generally, new series of benzodiazepines was synthesized involves cyclocondensation *o*-phenylenediamine with α, β-unsaturated carbonyl compounds, using $Ga(OTf)_3$ [5], HPW/SiO_2 [6], sulfated zirconia [7] and use of microwave irradiation technique [8] have well established. However, most of these methods suffer from several disadvantages such as long reaction time, expensive reagent, long reaction conditions and high reflux temperature. We wish in our work to report our results on the synthesis and antimicrobial activities of some novel [1, 5]-benzodiazepine derivatives containing quinoline nucleus (Scheme 1).

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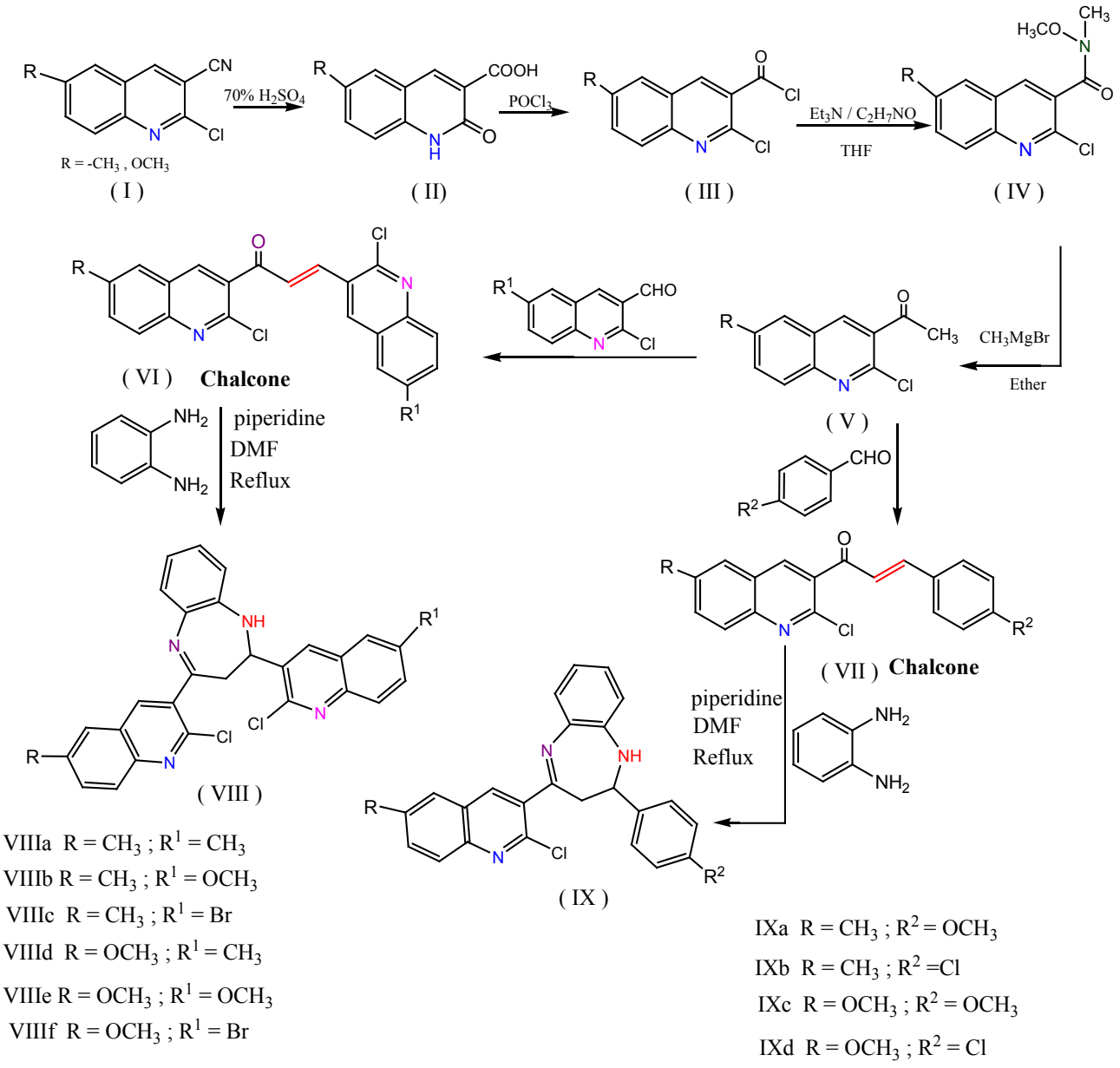
2. Experimental

2.1. General

All Melting points were carried on Gallenkamp melting point apparatus and are uncorrected. Microanalyses were carried out on Brucker-Vector-22-FT-IR spectrophotometer using the potassium bromide disc technique. 1HNMR spectra were performed either on a Jeol ECA (500 MHz) or Gemini 300BB (300MHz) spectrometer, using TMS as internal standard and DMSO-*d6* as solvent; the chemical shifts are reported in ppm (δ) and coupling constant (J) values are given in Hertz (Hz). The impact ionisation (IE) mass spectra were recorded on AZH- Ph- AR-XO_2 at 70 ev. Elemental analysis was performed on a CHN analyzer. All analyses were performed at the Microanalytical Center Unit of Cairo University, Cairo, Egypt. Acid hydrolysis of **I** with H_2SO_4 (70%) in ethanol gave 6-substituted 2-oxo-2, 3-dihydroquinoline-3-carboxylic acids (**II)** in good yields**)** which heated in boiling phosphoryl chloride to producesubstituted 2-chloroquinoline-3-carbonyl chloride **(III)**. Accordingly when compounds **III** were reacted with *N,O*-dimethylhydroxylamine in the presence of triethylamine and THF it give 2-chloro-N-methoxy-N-methylquinoline-3-carboxamide derivatives (**IV**) that dried and crystallized from ethanol. This on further reaction with methyl magnesium bromidein ammonium chloride and ether at room temperature gave 2-chloro-3-acetylquinoline derivatives (**V**). The started compound **I-V** were synthesized according to reported procedures [9-13]. The synthesis of the designed compounds was achieved following the routes depicted in Scheme 1.



Scheme 1

2.1.1. General Procedure for the Preparation of ChalconesVIa-f andVIIa-d

A mixture of 2-chloro-3-acetylquinoline derivatives (0.02 mol), aldehyde derivatives (0.02 mol) and sodium acetate (0.033 mol) in glacial acetic acid (5ml) was refluxed for 5h.The reaction mixture was cooled and poured into water. The resulting solid was filtered, washed with water, and recrystallized from aq. ethanol to furnish pure product of VI or VIIrespectively, on usingderivatives of 2-chloroquinoline-3-carbaldehyde or derivatives of bezaldehyde.

1,3-bis(2-chloro-6-methylquinolin-3-yl)prop-2-en-1-one (VIa).

Yield 78%, m.p. 193-194 ℃. (KBr, cm^{-1}):3062, 2883, 1632.^{1}HNMR ($CDCl_3$): δ 2.18 (s, 6H,2(CH_3)), 7.34 (d, 1H,$H_β$, J=12.6 Hz),7.48(s, 2H, H_5-2quinoline), 7.50-7.52 (d,2H, H_7,-2quinoline), 7.55-7.56(d, 2H, H_8-2quinoline), 7.83(d, 1H, $H_α$, J= 12.6 Hz), 8.58 (s, 2H,H_4, -2quinoline). Mass(IE): m/z 407.29 (22.9, M^+), 409 (7.5, M^{+2}), 205 (100). Anal. Calc. For $C_{23}H_{16}Cl_2N_2O$: C, 67.83; H, 3.96; N, 6.88. Found.C, 77.12; H, 4.30; N, 7.03

3-(2-chloro-6-methoxyquinolin-3-yl)-1-(2-chloro-6-methylquinolin-3-yl)prop-2-en-1-one (VIb).

Yield 81%, m.p. 186-187 ℃. (KBr, cm^{-1}): 3055, 2880,1635.^{1}HNMR ($CDCl_3$): δ 2.38 (s, 3H,CH_3), 3.64(s, 3H, OCH_3) 7.41 (d, 1H, $H_β$, J = 12.4 Hz),7.48(s, 2H, H_5-2quinoline), 7.50-7.52(d,2H, H_7,-2quinoline), 7.55-7.56 (d, 2H, H_8-2quinoline), 7.94(d, 1H, $H_α$, J= 12.4 Hz), 8.58 (s, 2H,H_4, -2quinoline).Anal.Calc. For $C_{23}H_{16}Cl_2N_2O_2$: C,

65.26; H, 3.81; N, 6.62.Found.C, 65.51; H, 3.47; N, 6.11

3-(2-chloro-6-bromoquinolin-3-yl)-1-(2-chloro-6-methyl quinolin-3-yl)prop-2-en-1-one (VIc).

Yield 74%, m.p. 184-185℃. (KBr, cm^{-1}): 3065, 2890, 1639. ^{1}HNMR ($CDCl_3$): δ 2.35 (s, 3H,CH_3), 7.41 (d, 1H, H_β, J= 15.8 Hz),7.44-7.83(m, 6H, 2quinoline), 7.94(d, 1H, H_α, J= 15.8 Hz), 8.28 (s, 1H,H_4, -quinoline), 8.51 (s, 1H,H_4, -quinoline).Mass(IE):m/z 469.96(34, M^+) Anal. Calc. For $C_{22}H_{13}$ $BrCl_2N_2O$: C, 55.96; H, 2.78; N, 5.93.Found.C, 55.49; H, 2.85; N, 5.97

3-(2-chloro-6-methy1quinolin-3-yl)-1-(2-chloro-6-metho xyquinolin-3-yl)prop-2-en-1-one (VId).

Yield 76%, m.p. 182-183℃. (KBr, cm^{-1}):3065, 2890,1639. ^{1}HNMR ($CDCl_3$): δ 2.33 (s, 3H,CH_3), 3.55(s, 3H, OCH_3) 7.38 (d, 1H, H_β, J= 15.5 Hz),7.40 -7.85(m, 6H, 2quinoline), 7.88(d, 1H, H_α, J= 15.5 Hz), 8.23 (s, 1H,H_4, -quinoline), 8.60 (s, 1H,H_4, -quinoline). Mass(IE): m/z 423.29(25, M^+)Anal. Calc. For $C_{23}H_{16}$ $Cl_2N_2O_2$: C, 65.26; H, 3.81; N, 6.62. Found.C, 65.04; H, 3.42; N, 6.62

1,3-bis(2-chloro-6-methoxyquinolin-3-yl)prop-2-en-1-on e (VIe).

Yield 76%, m.p. 173-174℃. (KBr, cm^{-1}): 3069, 2895, 1642. ^{1}HNMR ($CDCl_3$): δ 3.67(s, 6H, OCH_3) 7.45 (d, 1H, H_β, J= 14.6 Hz),7.49(s, 2H, H_5-2quinoline), 7.59-7.61 (d,2H, H_7,-2quinoline), 7.75-7.77(d, 2H, H_8-2quinoline), 7.90(d, 1H, H_α, J= 14.6 Hz), 8.61 (s, 2H,H_4, -2quinoline). Mass(IE): m/z 439.29(25, M^+)Anal. Calc. For $C_{23}H_{16}$ $Cl_2N_2O_3$: C, 62.88; H, 3.67; N, 6.30.Found.C, 64.90; H, 3.52; N, 6.29

3-(6-bromo-2-chloroquinolin-3-yl)-1-(2-chloro-6-methox yquinolin-3-yl)prop-2-en-1-one (VIf)

Yield 73 %, m.p. 198-199℃. IR (KBr, cm-1): 3094, 2891, 1655. (.^{1}H NMR ($CDCl_3$): δ 3.42 (s, 3H, O-CH_3), 7.23-7.25 (d, 1H, H_β, J=11.2 Hz),7.38(s,1H,H_5-quinoline-CH_3), 7.40-7.42 (d,1H, H_7,-quinoline-CH_3), 7.44-7.46(d,2H,H_8-2quinoline), 7.68 (s, 2H,H_5, -2quinoline), 7.70-7.72 (d,1H,H_7-quinoline-Br), 7.87(d, 1H, H_α, J = 11.2 Hz), 8.10(s,1H,H_4-quinoline-Br). Mass (IE): m/z 485.95 (25.1, M^+), 487 (8.3, M^{+2}).Anal.Calc. For $C_{22}H_{13}BrCl_2N_2O_2$: C, 54.13; H, 2.68; N, 5.74.Found.C, 53.85; H, 2.78; N, 6.13

1-(2-chloro-6-methylquinolin-3-yl)-3-(4-methoxyphenyl) prop-2-en-1-one (VIIa)

Yield 85%, m.p. 165-166 ℃. IR (KBr, cm^{-1}):3069, 2880,1635.^{1}HNMR ($CDCl_3$): δ 2.39 (s, 3H,- CH3), 3.12(s, 3H, OCH_3), 6.27-6.30(d,2H,H_3,H_5-phenyl), 7.19-7.22 (d, 1H, H_β, J= 14.5 Hz),7.27-7.30 (d, 2H,H_2,H_6-phenyl), 7.39(s,1H,H_5-quinoline), 7.47-7.50(d, 1H ,H_7-quinoline) 7.65-7.67(d,1H,H_8,-quinoline),7.80 (d, 1H, H_α, J= 14.5Hz), 8.44(s,1H,H_4,quinoline).Anal.Calc. For $C_{20}H_{16}$ $ClNO_2$: C, 71.11; H, 4.77; N, 4.15.Found.C, 70.88; H, 4.35; N, 4.02.

1-(2-chloro-6-methylquinolin-3-yl)-3-(4-chlorophenyl)pr op-2-en-1-one (VIIb)

Yield 80 %, m.p. 184-185℃. IR (KBr, cm^{-1}):3115,2980, 1635. ^{1}HNMR ($CDCl_3$): δ 2.39 (s, 3H,- CH3),7.12-7.15 (d, 2H,H_2,H_6-phenyl), 7.17-7.19 (d, 1H, H_β, J= 11.4 Hz), 7.32-7.34(d,2H,H_3,H_5-phenyl),7.45(s,1H,H_5-quinoline),7.55 -7.58(d,1H,H_7-quinoline), 7.67-7.68(d,1H,H_8,-quinoline),7. 89 (d, 1H, H_α, J= 11.4 Hz), 8.73(s,1H,H_4,quinoline). Mass(IE): m/z 341.04 (32.2, M^+), 343 (10.4, M^{+2}). Anal.Calc. For $C_{19}H_{13}$ Cl_2NO: C, 66.68; H, 3.83; N, 4.09.Found.C, 66.39; H, 3.49; N, 4.32.

1-(2-chloro-6-methoxyquinolin-3-yl)-3-(4-methoxypheny l)prop-2-en-1-one (VIIc)

Yield 92%, m.p. 176-168℃. IR (KBr, cm^{-1}):2950, 2819, 1640.^{1}HNMR ($CDCl_3$): δ 2.87 (s, 6H,2-OCH_3),6.92-6.94 (d, 2H,H_2,H_6-phenyl),7.13-7.14(d,2H,H_3,H_5,-phenyl), 7.18-7.20 (d, 1H, H_β, J=15.5 Hz), 7.04(s,1H,H_5,-quinoline),7.11-7.14 (d,1H,H_7-quinoline), 7.68-7.70(d,1H,H_8,-quinoline), 7.81 (d, 1H, H_α, J= 15.5 Hz), 8.65(s,1H,H_4,-quinoline). Mass: m/z 353.08 (15.3, M^+). Anal.Calc. For $C_{20}H_{16}$ $ClNO_3$: C, 67.90; H, 4.56; N, 3.96.Found.C, 67.57; H, 4.31; N, 4.19.

1-(2-chloro-6-methoxyquinolin-3-yl)-3-(4-chlorophenyl) prop-2-en-1-one (VIId)

Yield 76%, m.p. 180-181℃. Mass: m/z 357.03 (19.5, M^+).^{1}HNMR ($CDCl_3$): δ 3.17 (s, 3H, - OCH_3), 6.90-6.93(s, 2H,H_5,-quinoline),7.13-7.14(d,2H,H_3,H_5,-phenyl), 7.24 (d, 2H,H_2,H_6-phenyl), 7.38-7.41 (d, 1H, H_β, J= 14.5 Hz), 7.44-7.47(d,1H,H_7-quinoline), 7.61-7.63(d,1H,H_8,-quinoline), 7.92 (d, 1H, H_α, J= 14.5 Hz), 8.41(s,1H,H_4,-quinoline). Anal.Calc. For $C_{19}H_{13}$ Cl_2NO_2: C, 63.71; H, 3.66; N, 3.91.Found.C, 63.42; H, 3.21; N, 4.11.

2.1.1.1. General Procedure for the Preparation of New Derivatives of 2,3,-dihydro[1,5]-benzodiazepines (VIIIa-f) and (IXa-d)

A reaction mixture of new chalcones **VI a-f** (1 mmol) and *o*-phenylenediamine(1.5mmol) in DMF (15 ml) with few drops of piperidinewas heated to reflux for 4-6 h. The progress of the reaction was monitored by using TLC. After completion of reaction, the reaction mixture was distilled to remove the excess solvent and poured into crushed ice. The crude solid product obtained was filtered, washed with water and recrystalized from ethanol to get product **VIIIa-f** in good yields with high purity. Similarly other derivatives **IXa-d** were also synthesized by condensation of chalcone **VIIa-d**by the same previously procedure to get a compound **IXa-d** in good yield and high purity .

2,4-bis(2-chloro-6-methylquinolin-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (VIIIa)

Yield 75%, m.p. 130-131℃. .IR(KBr, cm^{-1}):3430, 3095, 2842, 1592.^{1}HNMR (DMSO,D_2O): δ 2.10 (s, 6H,-CH_3), 3.01-3.06 (dd, 1H, CH_2-H_A, J_{AX}= 4.40Hz, J_{AB} = 13.50 Hz), 3.05-3.11 (dd, 1H, CH_2-H_B, J_{BX}=6.84 Hz, J_{BA}=13.50Hz), 5.18-5.21 (t, 1H, CH-Hx, J_{XA}= 3.6Hz,J_{XB} = 6.32Hz), 5.52(s, 1H, NH, that exchangeable with D_2O), 6.40-6.63(t, 2H, H_4,H_6-phenyl), 6.83-7.03(d,2H,H_3,H_5-phenyl), 7.35 (s, 2H,H_5-quinoline), 7.59(s, 2H,H_7-quinoline), 8.01(s,1H,H_4-quinoline-CH_3), 8.20(s,1H,H_4-quinoline-OCH_3). Anal.Calc.

For $C_{29}H_{22}Cl_2N_4$: C, 70.02; H, 4.46; N, 11.26.Found,C, 69.80; H, 4.50; N, 11.59.

2-(2-chloro-6-methoxyquinolin-3-yl)-4-(2-chloro-6-methylquinolin-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (VIIIb)

Yield 82%, m.p. 125-126 ℃. IR (KBr, cm^{-1}): 3420, 3090, 2870, 1590. ^{1}HNMR (DMSO,D_2O): δ 2.29 (s, 3H,-CH_3), 3.00-3.05 (dd, 1H, CH_2-H_A, J_{AX} = 4.51Hz, J_{AB} = 13.70 Hz), 3.07-3.13 (dd, 1H, CH_2-H_B, J_{BX} = 6.90 Hz, J_{BA} = 13.70Hz), 3.54 (s,3H, -OCH_3), 5.22-5.24 (t, 1H, CH-Hx, J_{XA} = 3.80Hz, J_{XB} = 6.32Hz), 5.83(s, 1H, NH, that exchangeable with D_2O), 6.20-6.23(t, 2H, H_4,H_5-phenyl), 6.30-6.33(d,2H,H_3,H_6-phenyl), 7.35 (s,1H,H_5-quinoline-CH_3), 7.37(s,1H,H_5-quinoline-OCH_3), 7.39 (d,1H, H_7-quinoline-CH_3), 7.41(d,1H, H_7-quinoline-OCH_3), 7.44-7.46(d,1H,H_8, quinoline-CH_3), 7.46-7.48(d,1H,H_8, quinoline-OCH_3), 7.98 (s, H,H_4, -quinoline-CH_3), 8.18(s,1H,H_4-quinoline-OCH_3). Mass (IE): m/z 512.12 (12. 8,M^+). Anal.Calc. For $C_{29}H_{22}Cl_2N_4O$: C, 67.84; H, 4.32; N, 10.91.Found,C, 67.12; H, 4.54; N, 11.24 .

2-(6-bromo-2-chloroquinolin-3-yl)-4-(2-chloro-6-methylquinolin-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepine(VIIIc)

Yield 83%, m.p. 125-126℃. IR (KBr, cm^{-1}): 3405, 3105, 2890, 1601. ^{1}HNMR (DMSO,D_2O): δ 2.15 (s, 3H,-CH_3), 3.02-3.08 (dd, 1H, CH_2-H_A, J_{AX}= 6.78Hz, J_{AB} = 16.80 Hz), 3.10-3.17 (dd, 1H, CH_2-H_B, J_{BX}= 7.98 Hz, J_{BA} = 16.80Hz), 5.20-5.22 (t, 1H, CH-Hx, J_{XA}= 3.30Hz,J_{XB} = 6.64Hz), 5.75(s, 1H, NH, that exchangeable with D_2O), 6.40-6.65(t, 2H,H_4,H_6-phenyl), 7.00-7.02(m,2H,H_3,H_5-phenyl), 7.30-7.32 (s,1H,H_5, quinoline-CH_3),7.35-7.37(d,1H, H_7,-quinoline-CH_3), 7.40-7.42(d,2H,H_8-2quinoline), 7.77-7.79 (d,1H,H_7-quinoline-Br), 7.80(s,1H,H_5-quinoline –Br),8.02 (s,2H,H_4-quinoline-CH_3) 8.38 (s, H,H_4,-quinoline-Br).Mass (IE): m/z 560.02 (9.4,M^+), 562 (3.2, M^{+2}).Anal.Calc. For $C_{28}H_{19}BrCl_2N_4$: C, 59.81; H, 3.41; N, 9.96.Found, C, 60.02; H, 3.93; N, 10.12.

4-(2-chloro-6-methoxyquinolin-3-yl)-2-(2-chloro-6-methylquinolin-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (VIIId)

Yield 79 %, m.p. 137-138℃. IR (KBr, cm^{-1}): 3415, 3110, 2893, 1589.^{1}HNMR (DMSO,D_2O): δ 2.25 (s, 3H,-CH_3), 3.01-3.06 (dd, 1H, CH_2-H_A, J_{AX}= 4.51Hz, J_{AB} = 13.70 Hz), 3.08-3.14 (dd, 1H, CH_2-H_B, J_{BX}= 6.92 Hz, J_{BA} = 13.70Hz), 3.59 (s,3H, -OCH_3), 5.22-5.24 (t, 1H, CH-Hx, J_{XA}= 3.80Hz, J_{XB} = 6.32Hz), 5.54(s, 1H, NH, that exchangeable with D_2O), 6.19-6.22(t, 2H, H_4,H_5-phenyl), 6.88-6.91(d,2H,H_3,H_6-phenyl), 7.33(s,1H,H_5-quinoline-CH_3), 7.39(s,1H,H_5-quinoline-OCH_3), 7.43 (d,1H, H_7-quinoline-CH_3),7.47(d,1H, H_7-quinoline-OCH_3), 7.49-7.52(d,1H,H_8, quinoline-CH_3), 7.67-7.70(d,1H,H_8, quinoline-OCH_3), 8.38 (s, H,H_4, -quinoline-CH_3), 8.54(s,1H,H_4-quinoline-OCH_3).Anal.Calc. For $C_{29}H_{22}Cl_2N_4O$: C, 67.84; H, 4.32; N, 10.91.Found, C, 67.65; H, 4.73; N, 11.17.

2,4-bis(2-chloro-6-methoxyquinolin-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (VIIIe)

Yield 89%, m.p. 121-122℃. ^{1}HNMR (DMSO,D_2O) 3.44 (s, 6H,2 -OCH_3), 2.63-2.69 (dd, 1H, CH_2-H_A, J_{AX}= 4.81Hz, J_{AB} = 16.38 Hz), 2.87-2.90 (dd, 1H, CH_2-H_B, J_{BX}= 6.02 Hz, J_{BA} = 16.38Hz), 4.60(s, NH,that exchangeable with D_2O). 6.12-6.14(t, 2H,H_4,H_5-phenyl), 6.20-6.22(d,2H,H_3,H_6-phenyl), 7.31-7.33(s,2H,H_5-2quinoline),7.36-7.38(d,2H, H_7,-2quinoline), 7.46-7.48(d,2H,H_8-2quinoline-), 7.92 (s, 2H,H_4, -2quinoline). Anal.Calc. For $C_{29}H_{22}Cl_2N_4O_2$: C, 65.79; H, 4.19; N, 10.58.Found, C, 65.82; H, 4.52; N, 10.26.

2-(6-bromo-2-chloroquinolin-3-yl)-4-(2-chloro-6-methoxyquinolin-3-yl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (VIIIf)

Yield 70%, m.p. 142-143℃.^{1}HNMR (DMSO,D_2O): δ 3.01-3.07 (dd, 1H, CH_2-H_A, J_{AX}= 6.75Hz, J_{AB} = 16.10 Hz), 2.95-3.02 (dd, 1H, CH_2-H_B, J_{BX}= 7.84 Hz, J_{BA} = 16.10Hz), 3.15 (s, 3H,-OCH_3), 5.14-5.17 (t, 1H, CH-Hx, J_{XA}= 2.70Hz, J_{XB} = 6.01Hz), 5.32(s, 1H, NH, that exchangeable with D_2O), 6.32-6.35(t, 2H,H_4,H_6-phenyl), 6.91-6.93(m,2H,H_3,H_5-phenyl), 7.35-7.37(s,1H,H_5, quinoline-OCH_3),7.40-7.43 (d,1H,H_7,-quinoline-OCH_3), 7.75-7.78(d,2H,H_8-2quinoline), 7.87-7.90(d,1H,H_7-quinoline-Br), 8.00(s,1H,H_5-quinoline –Br),8.30(s,2H,H_4-quinoline-OCH_3) 8.63 (s, H,H_4,-quinoline-Br). Mass (IE): m/z 578.28 (17.5, M+), 580 (9.4, M+2)Anal. Calc. For $C_{28}H_{19}BrCl_2N_4O$: C, 58.15; H, 3.31; N, 9.69.Found, C, 57.72; H, 3.07; N, 9.52.

4-(2-chloro-6-methylquinolin-3-yl)-2-(4-methoxyphenyl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (IXa)

Yield 70%, m.p. 142-143℃.). IR (KBr, cm^{-1}): 3420, 3092, 2890, 1595.^{1}HNMR (DMSO,D_2O), δ 2.12 (s, 3H ,-CH_3), 3.01-3.06 (dd, 1H, CH_2-H_A, J_{AX}= 5.80Hz, J_{AB} = 13.5 Hz), 2.95-3.02 (dd, 1H, CH_2-H_B, J_{BX}= 7.77 Hz, J_{BA} = 13.50Hz), 3.15 (s, 3H,-OCH_3), 5.11-5.14 (t, 1H, CH-Hx, J_{XA} = 2.50Hz, J_{XB} = 7.50Hz), 5.10(s, 1H, NH, that exchangeable with D_2O), 6.21-6.23(t, 2H, H_4, H_5-phenyl),6.42-6,44(d, 2H, H_3, H_6-phenyl), 6.81-6.83(d, 2H, H_3, H_5-phenyl-OCH_3), 6.93-6.95(d,2H, H_2, H_6-phenyl-OCH_3), 7.28-7.52(s,1H, H_5, -quinoline), 7.58-7.60(d, 1H, H_7, -quinoline), 7.64-7.66(d, 1H, H_8,-quinoline), 7.90(s, 1H, H_4, -quinoline). Anal.Calc. For $C_{26}H_{22}ClN_3O$: C, 72.97; H, 5.18; N, 9.82.Found,C, 73.44; H, 5.39; N, 10.26.

4-(2-chloro-6-methylquinolin-3-yl)-2-(4-chlorophenyl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (IXb)

Yield 95%, m.p. 147-148℃. : IR (KBr, cm^{-1}): 3450, 2955,2880,1593^{1}HNMR (DMSO,D_2O), δ 2.33 (s, 3H,-CH_3),2.90-2.96 (dd, 1H, CH_2-H_A, J_{AX}= 5.40Hz, J_{AB} = 15.66 Hz), 2.95-3.02 (dd, 1H, CH_2-H_B, J_{BX}= 7.77 Hz, J_{BA} = 15.66Hz),5.22-5.25 (t, 1H, CH-Hx, J_{XA}= 2.52Hz,J_{XB} = 7.54Hz), 4.49(s, 1H, NH, that exchangeable with D_2O), 6.40-7.01(m, 4H, -benzo) 7.05-7.32(m, 4H, -phenyl), 7.48-7.52(s,1H, H_5, -quinoline), 7.58-7.60(d, 1H, H_7, -quinoline), 7.64-7.66(d, 1H, H_8,-quinoline).7.90(s, 1H,

H_4,-quinoline). Anal.Calc. For $C_{25}H_{19}Cl_2N_3$: C, 69.45; H, 4.43; N, 9.72.Found, C, 69.71; H, 4.61; N, 10.22.

4-(2-chloro-6-methoxyquinolin-3-yl)-2-(4-methoxyphenyl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (IXc)

Yield 80%, m.p. 139-140 ℃ .^{1}HNMR (DMSO,D_2O) 2.55-2.61 (dd, 1H, CH_2-H_A, J_{AX}= 5.44Hz, J_{AB} = 16.20 Hz), 3.07-3.13 (dd, 1H, CH_2-H_B, J_{BX}= 6.30 Hz, J_{BA} = 16.20Hz), 3.38 (s, 6H,2 -OCH_3), 4.59(s, NH,that exchangeable with D_2O), 6.44-7.20(m, 4H, -benzo) 7.22-7.52(m, 4H, -phenyl), 7.48-7.52(s,1H, H_5, -quinoline), 7.58-7.60(d, 1H, H_7, -quinoline), 7.64-7.66(d, 1H, H_8,-quinoline).7.90(s, 1H, H_4, -quinoline). Mass (IE): m/z 443.14 (25, M^+). Anal.Calc. For $C_{26}H_{22}ClN_3O_2$: C, 70.34; H, 5.00; N, 9.47.Found,C, 70.57; H, 4.59; N, 9.81 .

4-(2-chloro-6-methoxyquinolin-3-yl)-2-(4-chlorophenyl)-2,3-dihydro-1H-benzo[b][1,5]diazepine (IXd)

Yield 75 %, m.p. 133-134℃. IR (KBr, cm^{-1}): 3423,2995, 2877, 1596. ^{1}HNMR (DMSO, D_2O) 2.42-2.48 (dd, 1H, CH_2-H_A, J_{AX}= 5.85Hz, J_{AB} = 15.78 Hz), 3.07-3.13 (dd, 1H, CH_2-H_B, J_{BX}= 6.06 Hz, J_{BA} = 15.78Hz),3.27 (s, 3H,2 -OCH_3), 4.74(s, NH,that exchangeable with D_2O), 6.21-6.25(t, 2H, H_4, H_5-phenyl), 6.47-6.49(d, 2H, H_3, H_6 -phenyl), 7.26-7.28(d, 2H, H_2, H_6, -phenyl-Cl), 7.43-7.45(d, 2H, H_3, H_5, -phenyl-Cl), 7.52 (s, 1H, H_5, -quinoline), 7.65-7.67(d,1H, H_7, -quinoline),8.07-8.09(d,1H, H_8, -quinoline), 8.13(s, 1H, H_4, quinoline). Mass (IE): m/z 447.09 (23.5, M^+), 449 (8.1, M^{+2})Anal. Calc. For $C_{25}H_{19}Cl_2N_3O$: C, 66.97; H, 4.27; N, 9.37.Found,C, 67.19; H, 4.16; N, 9.88.

3. Result and Discussion

In the present work, involves the synthesis of new derivatives The key intermediate, 2-oxo-1,2-dihydroquinoline-3-carboxylic acid derivatives which prepared according to the reported procedure[9-13].The structures of compound (II) were confirmed by ^{1}HNMR,^{13}C-NMR,In the ^{1}H-NMR spectra, where two sharp proton signal observed at the δ 5.4 and 11.68 ppm, one belong OH at C-2 and one belong COOH respectively, and due to resonance isomerism the NH (secondry amine) it appear at higher chemical shift at 8.9 as abroad signal more than expected due to neighboring carbonyl group, In the ^{13}C-NMR spectra of these compounds one C=O peak at about 178 ppm and one around 166 ppm corresponded to the signals of the 3-carboxylic acid and carbonyl groups in the quinoline rings. On contrary the IR spectra of compound III showed the disappearance of OH stretching band and this explain the conversion of acid into acid chloride and the mass spectra of compound III confirm the conversion of carbonyl at C-2 into chloride moiety , so when the compound III react with *N,O*-dimethyl hydroxylamine it produce the compound IV which IR spectra confirm the presence of these compound because it showed clearly decreasing of stretching absorption band of C=O from 1812 $cm^{-1}$and appearance of sharp medium stretching absorption bands at range of 1636 cm^{-1}which belong to (C=O) for amide, when compound IV react with alkyl Grignard reagent it produce compound V, which react with quinoline-3-carbaldehyde derivatives or benzaldehyde derivatives it afford new Chalcones VI and VII respectively, the IR spectra of new Chalcones confirmed by the presence of two stretching bands at 1660-1590, this due to C=O and CH=CH, in addition the ^{1}HNMR of Chalcone have two doublet signal one at 7.40 ppm which belong CH_β, and one at 6.90 which belong CH_α. upon cyclocondensation of Chalcones with *o*-phenelendiamine it produce new 1,5-benzodiazepine derivatives VIII and IX respectively, where the elemental analysis and spectral data confirm the existence of this cyclocondensation reaction where the ^{1}HNMR of new 1,5-benzodiazepines contain two signal one at 2.50 ppm due one hydrogen of (C-2) in benzodiazepine ring and another one at 3.80 ppm due two hydrogen of (C-3) in benzodiazepine ring that prove the cyclocondensation well occur. in addition the disappearance of sharp stretching of carbonyl and appearance of starching at 1590 (C=N of diazepine) and all this fact will prove this cyclocondensation reaction and formation of 1,5-benzothiazepine ring with good yield 65-95%. It was observed clearly that carbonyl aldehyde carrying electron withdrawing substituents of the phenyl ring afforded low yields of [1,5]-benzodiazepines. The structures of some the compounds were established from the spectral data of the resulting compounds.

4. Antimicrobial Activity

The cup plate agar diffusion method [14] was employed for determining the antimicrobial activity of the newly synthesized compounds VIII, IX against two gram positive bacteria viz., Bacillus subtilis, Staphylococci aureus and two gram negative bacteria viz., Escherichia coli, Pseudomonas aeruginosa in addition to fungi(Candida albicans). The solutions of different compounds under test at a concentration of 500 and 600µg/mlin 5% *DMSO* were poured in the cup/well of bacteria seeded agar plates. These plates were incubated at 37℃ for 24 hours for E. coli, whereas plates of other three bacteria were incubated at 27℃ for 24 hr. The standard antibiotics used were ampicillin (all at 500 µg/ml). and standared antifungal used were nystatin at 500 µg/ml. The solution without compound i.e. only 5% *DMSO* was used as control which did not reveals any inhibition. The zone of inhibition produced by each compound was measured in mm. The results of antmicrobial studies are given in Table 1.

From screening results, it was observed that final compounds $VIII_a$, IX_a possessed significant antimicrobial activity but other compound showed moderate antimicrobial activity. The discussion and comparison of antibacterial activity were given with respect to ampicillin antibiotic and antifungal screening were compared with Nystatin. Microbiological testing of the newly synthesized compounds were performing in the Regional Center for Mycology and Biotechnology, Department of Microbiology, Faculty of Science, Al-Azher university, Cairo, Egypt.

Table 1. Antimicrobial activity of novel synthesized 1,5-Benzodiazepines (VIIIa-f) and (IXa-d)

COMP. NO.	Concent-ration (µg/ml)	Microorganism (inhibition zone(mm))				
		Basillus Subtilis	*Staphylococcusaureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*
$VIII_a$	500	15.0	16.0	17.0	15.0	12.0
	600	15.6	16.5	17.3	15.5	12.4
$VIII_b$	500	12.0	16.0	18.0	14.0	12.0
	600	12.3	16.5	18.3	14.5	12.2
$VIII_c$	500	12.0	14.0	12.0	10.4	9.0
	600	12.4	14.3	12.5	11.0	9.2
$VIII_d$	500	11.5	16.0	17.0	12.0	11.0
	600	12.3	17.0	17.4	13.5	11.5
$VIII_e$	500	14.0	16.0	16.0	14.0	13.0
	600	14.3	16.5	16.5	15.0	13.8
$VIII_f$	500	13.5	15.0	13.5	11.7	11.0
	600	14.4	15.3	13.2	12.5	12.6
IX_a	500	19.0	17.0	18.0	17.0	15.0
	600	19.5	17.5	18.5	17.5	15.5
IX_b	500	12.0	14.0	12.0	10.0	9.0
	600	13.0	14.0	12.0	11.0	9.0
IX_c	500	17.0	17.0	17.0	16.0	14.0
	600	18.0	17.5	17.5	16.5	14.3
IX_d	500	12.6	13.5	11.5	10.0	8.0
	600	13.0	14.0	12.0	10.5	8.5
Ampicillin	500	24.0	21.3	25.0	20.17	-
Nystatine	500	-	-	-	-	19.8

REFERENCES

[1] Kalirajan R, Shivkumar SU, Jubir S, Gowramma B, Surash B: Synthesis and Biological evaluation of some heterocyclic derivatives of Chalcones. Int. J. Chem. Tech. Res. 2009; 1: 27-34.

[2] Ahmed K, Shankarajah N, Prabhakar S, Ratna R Ch, Markandeya N, Laxma RK, Devaiah V. Solid-phase synthesis of new pyrrolobenzodiazepine–chalcone conjugates: DNA-binding affinity and anticancer activity. Bioorg. Med. Chem. Lett. 2008; 18(7): 2434-2439.

[3] Zizhao G, Chunlin Z, Lingjian Z, Yongqiang Z, Jianzhong Y, Guoqiang D, Shengzheng W, Yang L, Hai C, ChunquanSh, Zhenyuan M, Wannian Z: Structure–activity relationship and antitumor activity of thio-benzodiazepines as p53– MDM2 protein-protein interaction inhibitors. E. J. Med. Chem. 2012; 56: 10-16.

[4] Rajesh k, Joshi YC: synthesis, Spectral Study and Biological activity of benzodiazepines. Arkivok 2007; xiii: 142-149.

[5] Balakrishna M S, KaboudinB: A simple and new method for the synthesisof1, 5-benzodiazepine derivatives on a solid surface. Tetrahedron Lett. 2001, 42, 1127-1129.

[6] Yadav JS, Reddy BVS, Kumar SP, Nagaiah K: A novel and efficient reagent for the rapid synthesis of 1,5-benzodiazepines under solvent-free conditions. Synthesis 2005, 480-484.

[7] Reddy BM, Sreekanth PM, Lakshmanan P: Sulfated zirconia as an efficient catalyst fororganic synthesis and transformation reactions. J. Mol. Catal. A: Chem. 2005, 237, 93-100.

[8] Janardan SY, Srivastava YK: Microwave assisted rapid and efficient synthesis, characterization and pharmacological evaluation of some novel benzimidazole assembled 1,5-benzodiazepine and 1,5 benzothiazepine derivatives. Der. Pharm. Lett. 2011, 3(2): 284-291.

[9] Wright T L, U.S.Pat.4,540,786 (1985).

[10] Neelima B Bhat, Amiya P Bhaduri.J.Het.Chem.,23, 295, 1986, 925-930.

[11] Cyrous O, Kangani, David E .Kelly, Billy W Day, Tetrahedron letters, vol.47, 35, 6289-92 (2006).

[12] Monir A S, Mohamad M Ismail, Saber E S Barakat, Ashraf A A Abdul-rahman, Ashraf H Bayomi, Kamal M A El-gaml: synthesis and antimicrobial activity of some new 1H-pyrazolo [3,4-b] Qinoline derivatives, Bull. Pharm. Sci.-Assiut. Univ, vol.27, part2, 2004, 237-245.

[13] Kamal MEl-Gaml, One-Pot Synthesis and antimicrobial screening of new [1, 5] –Benzodiazepine Derivatives Catalyzed by TBAB, Al-azh .j.ph.Sci,vol.46,161-168, (2012).

[14] Barry AL. Procedure for testing antimicrobial agents in agar media. In: V.L. Corian (Ed.). Antibiotics in Laboratory Medicine. Williams and Wilkins, Baltimore, MD, 1, (1991).