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SYNTHESIS OF SOME NOVEL HETEROCYCLIC COMPOUNDS CONTAINING PHTHALAZINE OR 1- OXOPHTHALAZINE MOIETY WITH EXPECTED BIOLOGICAL ACTIVITY

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ABSTRACT

Synthesis of new series of phthalazine derivatives starting from phthalic anhydride **1** with benzene or chlorobenzene in the presence of $AlCl_3$ anhydrous afforded **2(a,b)**, further cyclisation with hydrazine hydrate afforded **3(a,b),** by chlorination with $POCl_3$ in DMF gave **4(a,b)**, phthalazine derivatives **5,6(a-c)** were formed by reaction **4(a,b)** with aromatic amines. On the reaction of **3(a,b)** with chlorosulphonic acid with excess of thionyl chloride at 0°C to afforded **7(a,b)** which reacted with hydrazine hydrate afforded **8(a,b)**, phthlazine sulphonylhydrazone derivatives **9,10(a-d)** and **11,12(a-c)** were formed by reaction **8(a,b)** with aromatic aldehydes or sugar aldehydes. On the reaction **3(a,b)** with phenylisocyanate or phenylisothiocyanate in benzene afforded **13,14(a,b)**, according to Mannich condition **15(a,b)** were formed by reaction **3(a,b)** with pipredine and formaldehyde solution and one drop HCl were refluxed in ethanol. The structures of the synthesized compounds were confirmed by IR, Mass spectra, ^{1}HNMR and ^{13}C NMR spectral data. The biological activities of synthesized compounds were studied.

KEYWORDS: Phthalic anhydride, phthalazine derivatives, phthlazine sulphonylhydrazone, biological activity.

INTRODUCTION

Phthalazines and 1-oxophthalazines derivatives unique well-known classes of nitrogen-containing heterocyclic compounds, possessing versatile chemical, industrial and biological properties. Among the important pharmacological activities exhibited therapeutic properties.[1-4] Phthalazines and 1-oxophthalazines have been reported to possess antimicrobial[5-7], antitumor[8-11], antihypertensive[12,13], antithrombotic[14], antidiabetic[15-17], anti-T-Cruzi[18], anti-inflammatory[19-25], antiallergic[26], anticonvulsant[27,28] and anticancer.[29,30] In view of the aforementioned facts, it seemed most interesting to synthesize Phthalazines and 1-oxophthalazines derivatives via synthesized 1-chloro-phthalazine derivatives **4(a,b)**[25,26] and phthalazine sulphonylchloride **7(a,b)**[32,33] as starting compounds reacted with different reagent affording phthalazines and 1-oxophthalazines derivatives. These are examples of nitrogen heterocyclic that possess exciting biological properties.[26-31]

MATERIALS AND METHODS

Determinations of melting points were performed in open glass capillaries using electrothermal **BUCHI (B-540)** hot storage melting-point apparatus and are uncorrected. Infra-red **(IR)** spectra were carried out at the Micro analytical Center, Cairo University and data were recorded on Shimadzu 435 Spectrometer, using KBr discs and values were represented in cm^{-1}. **(MS)** Mass spectra were run on Shimadzu QP-2010 spectrometer at the Micro analytical Center, Cairo University. **^{1}HNMR** spectra was recorded on Bruker (300MHz) FT-NMR spectrometer using DMSO and chemical shifts are given in δ (ppm) using tetramethylsilane (TMS) as an internal standard. The compounds was made by thin layer chromatography (TLC) on silica gel-precoated aluminum sheets and the spots were detected by the aid of iodine vapor and by exposure UV lamp at λ254 nm for few seconds. Solvents used such as MeOH, DMF, CH_2Cl_2 and diethylether were commercially available and dried before as reported in literature.

General procedure for the synthesis of compounds 3(a,b)

Aroylation of aromatic system by reaction with phthalic anhydride under Friedel Craft's conditions yields the o-aroyl benzoic acid.

The reaction of benzene or chlorobenzene with phthalic anhydride in the presence of anhydrous aluminum chloride was carried out to produced **2(a,b)**. To prepared phthalazin-1-ones via the condensation of the aroyl benzoic acid with hydrazine hydrate in boiling ethanol afforded the **3(a,b)** 4-phenylphthalazin-1(2H)-one **3a**m.p: 240-244°C in 68% yield, 4-(4-chlorophenyl) phthalazin-1(2H)-one **3b** m.p: 270-274°C in 73% yield.

General procedure for the synthesis of compounds 4(a,b)

A Solution of **3(a,b)** (0.01 mol) with phosphorus oxychloride (20 mL) was heated on water bath at 70°C for 2h. The reaction mixture was cooled and dilute with ice water and the resulting precipitate was collected by filtration and then crystallized from chloroform to give: **4(a,b)**.

1-chloro-4-phenylphthalazine 4a

Yield: 95%, brown crystals, m.p158-159°C; IR(KBr) cm^{-1} 759(C-Cl), 1627(C=N) and devoid any band for (C=O); ^{1}HNMR (300 MHz, DMSO-d6) ppm: 7.4-8.4(m, 9H, ArH) with devoid any band for (NH).

1-chloro-4-(4-chlorophenyl)phthalazine 4b

Yield: 92%, brown crystals, m.p183-185°C; IR(KBr) cm^{-1} 759(C-Cl), 1663(C=N) and devoid any band for (C=O); ^{1}HNMR (300 MHz, DMSO-d6) ppm: 7.6-8.2(m, 8H, ArH) with devoid any band for (NH).

General procedure for the synthesis of compounds 5,6(a-c)

A mixture of **4(a,b)** (0.1g, 0.3 mol) dissolved in chloroform and an excess of appropriate 4-substituted aniline 1.2 eq were heated refluxed at 60-70°C in presence of 10 eq Et3N. TLC monitoring was used to ensure the completion of reaction by using EtOAC/CH2Cl2 (1:5) as eluent. The resulting crude product was extracted by chloroform: water (5:10), the organic layer was evaporated under vacuum and the separated solid was washed with H2O, dried to afford the pure product.

N,4-diphenylphthalazin-1-amine 5a

Yield: 60%, brown solid. m.p (218-220°C); IR (KBr) cm^{-1}, 3433 (NH), 1584 (C = N); ^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.01 (t, 1H, J = 6.1Hz), 7.52 (dd, 2H, J = 6.8, J = 6.8Hz), 7.53-7.85 (m, 5H, ArH), 7.53-8.01 (m, 6H, ArH), 9.40 (s, NH); Mass spectrum showed molecular ion peak at m/z = 297(M^+).

4-phenyl-N-(p-tolyl)phthalazin-1-amine 5b

Yield: 72%, brown solid. m.p (172-174°C); IR (KBr) cm^{-1}, 3430 (NH), 1566 (C = N); ^{1}H NMR (300 MHz, DMSO-d6) ppm: 2.51 (s, 3H, Ar-CH3), 7.59 (d, 2H, J = 16.5 Hz, Aromatic), 8.39-8.35 (dd, 2H, J = 3Hz, J =3.3Hz,Aromatic), 7.94-7.53 (d, 2H, J = 12Hz, Aromatic), 8.28-7.96 (m, 7H, ArH), 12.84 (s, 1H, NH); Mass spectrum showed molecular ion peak at m/z = 311(M^+).

N-(4-chlorophenyl)-4-phenylphthalazin-1-amine 5c

Yield: 63%, brown solid m. p(189-192°C), IR (KBr) cm^{-1}, 3154,3029 (NH), 1664 (C = N), 662 (C – Cl); Mass spectrum showed molecular ion peak at m/z = 332(M^+).

4-(4-chlorophenyl)-N-phenylphthalazin-1-amine 6a

Yield: 64%, brown solid. m.p (234-238°C); IR (KBr) cm^{-1}, 3200 (NH), 1661 (C = N), 543 (C – Cl); ^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.60-8.34 (m, 13H, ArH), 12.86 (s, 1H, NH); Mass spectrum showed molecular ion peak at m/z = 332(M^+).

4-(4-chlorophenyl)-N-(p-tolyl)phthalazin-1-amine 6b

Yield: 71%, brown solid. m.p (206-208°C); IR (KBr) cm^{-1}, 3433 (NH), 1662 (C = N), 616 (C – Cl); ^{1}H NMR (300 MHz, DMSO-d6) ppm: 2.36 (s, 3H, Ar-CH3), 7.31-8.35 (m, 12H, ArH), 12.86 (s, 1H, NH).

N,4-bis(4-chlorophenyl)phthalazin-1-amine 6c

Yield: 66%, brown solid. m.p (244-247°C); IR (KBr) cm^{-1}, 3432 (NH), 1663 (C = N), 636 (C – Cl); ^{1}H NMR (300 MHz, DMSO-d6) ppm: 7.31 (s, 1H, Aromatic), 7.59 (d, 2H, J = 16.5, Aromatic), 7.96-8.28 (m, 5H, ArH), 8.35 (dd, 4H, J = 9Hz, J = 4.5Hz,Aromatic), 12.009 (s, 1H, NH).

General procedure for the synthesis of compounds 7(a,b)[32,33]

The compound **3(a,b)** (0.01 mol) was added portion wise to chlorosulphonic acid (5 mL) and excess amount of thionyl chloride at 0°C with stirring, after one hour the temperature was elevated gradually to 90°C and kept this temperature for 72 hours, the reaction mixture was poured into crushed ice the products were filtered off and crystallized from ethanol to give **7(a,b)**.

1-oxo-4-phenylphthalazine-2(1H)-sulfonyl chloride 7a

Yield: 82%, yellow solid. m.p(280-283°C); IR (KBr) cm^{-1}, 1753 (C = O), 1606 (C=N), 1284 (-SO2-Cl); ^{1}H NMR (300 MHz, DMSO) PPM: 7.65-8.14(m, 9H, ArH) with devoid any band for (NH); ^{13}C NMR (75.4 MHz, DMSO-d6), showed signal at (δ ppm), 162.59 (C=O), 135.51 (N=C), 136.51-122.85 for (aromatic carbons); Mass spectrum showed molecular ion peak at m/z = 321(M^+).

4-(4-chlorophenyl)-1-oxophthalazine-2(1H)-sulfonyl chloride 7b

Yield: 85%, yellow solid. m.p(>300°C); IR (KBr) cm^{-1}, 1755 (C = O), 1619 (C=N), 1283 (-SO2-Cl), 707 (C-Cl); ^{1}H NMR (300 MHz, DMSO) ppm: 8.42-7.86(m, 8H, ArH) with devoid any band for (NH).

General procedure for the synthesis of compounds 8(a,b)

A solution of 1-oxophthalazine sulfonylcloride **7(a,b)** (0.01 mol) in THF (50 mL), hydrazine hydrate (0.02

mol) was added at room temperature with stirring for about 30 min., heat to 40- 50°C. for further 30 min., then pour the reaction mixture into water and filtered off and then crystallized from ethanol.

1-oxo-4-phenylphthalazine-2(1H)-sulfonohydrazide 8a
Yield: (78%), white solid. mp(>300°C), IR(KBr) cm^{-1}, 3430,3320 (NH_2), 3210 (NH), 1763 (C=O), 1604 (C=N), 1079 (-SO_2-NH); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.5 (s, H, NH), 8.22-7.65 (m, 9H, ArH), 3.31(s, 2H, NH_2)with exchangeable in D_2O; Mass spectrum showed molecular ion peak at m/z = 316 (M^+).

4-(4-chlorophenyl)-1-oxophthalazine-2(1H)-sulfonohydrazide 8b
Yield: (74%) white solid. m.p (>300°C); IR (KBr) cm^{-1}, 3530 (NH_2), 3110 (NH), 1650 (C=O), 1607 (C=N), 1320,1080 (-SO_2-NH); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.5 (s, H, NH), 8.16-7.86 (m, 8H, ArH), 3.29(s, 2H, NH_2) with exchangeable in D_2O; Mass spectrum showed molecular ion peak at m/z = 350 (M^+).

General procedure for the synthesis of compounds 9,10(a-d) and 11,12(a-c)
A mixture of 1-oxophthalazine sulfonyl hydrazide **8(a,b)** (0.01 mol) and (0.01 mol) of aldehyde derivatives such as benzaldehyde, p-chlorobenzaldehyde, anisaldehyde, and m-bromobezaldehyde or sugar derivatives such as D-glucose, D-arabinose and D-xylose in ethanol (20 mL) with catalytic amount of glacial acetic acid were boiling under reflux for 2 hours; after concentration and cooling the precipitation filtered off and crystallized from ethanol.

(Z)-N'-benzylidene-1-oxo-4-phenylphthalazine-2(1H)-sulfonohydrazide 9a
Yield: (85%), white solid. mp(210-212°C), IR(KBr) cm^{-1}, 3435,3018 (NH), 1729 (C=O), 1659 (C=N),1301,1024(-SO_2-NH); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 12.84 (s, H, NH), 8.79 (s, 1H, N=CH), 8.35 (d, 2H, J=3.3Hz, ArH), 8.39 (d, 2H, J=3Hz, ArH), 8.29-7.96 (m, 6H, ArH), 7.93(d, 2H, J=6Hz, ArH); Mass spectrum showed molecular ion peak at m/z = 404 (M^+).

(Z)-N'-(4-chlorobenzylidene)-1-oxo-4-phenylphthalazine-2(1H)-sulfonohydrazide 9b
Yield: (83%), bale yellow solid. mp(198-200°C), IR(KBr) cm^{-1}, 3167,3017 (NH), 1728 (C=O), 1660 (C=N), 1348,1079(-SO_2-NH), 682 (C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 12.85 (s, H, NH), 8.75 (s, 1H, N=CH), 8.34-7.60 (m, 13H, ArH).

(Z)-N'-(4-methoxybenzylidene)-1-oxo-4-phenylphthalazine-2(1H)-sulfonohydrazide 9c
Yield: (80%), yellow solid. mp(224-227°C), IR(KBr) cm^{-1}, 3166,3126 (NH), 1723,1660 (C=O), 1601 (C=N),1322,1033(-SO_2-NH); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.50 (s, H, NH), 8.70 (s, 1H, N=CH), 8.35-7.31 (m, 13H, ArH), 3.31(s, 3H, OCH_3); Mass spectrum showed molecular ion peak at m/z = 434 (M^+).

(Z)-N'-(3-bromobenzylidene)-1-oxo-4-phenylphthalazine-2(1H)-sulfonohydrazide 9d
Yield: (87%), yellow solid. mp(213-216°C), IR(KBr) cm^{-1}, 3167,3018 (NH), 1728 (C=O), 1660 (C=N),1260,1079 (-SO_2-NH); Mass spectrum showed molecular ion peak at m/z = 483 (M^+).

(Z)-N'-benzylidene-4-(4-chlorophenyl)-1-oxophthalazine-2(1H)-sulfonohydrazide 10a
Yield: (83%), orang solid. mp(273-276°C), IR(KBr) cm^{-1}, 3165,3016 (NH), 1660 (C=O), 1600 (C=N),1301,1163(-SO_2-NH), 862(C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.5 (s, H, NH), 8.5 (s, 1H, N=CH), 8.34-7.85 (m, 13H, ArH).

(Z)-N'-(4-chlorobenzylidene)-4-(4-chlorophenyl)-1-oxophthalazine-2(1H)-sulfonohydrazide 10b
Yield: (78%), yellow solid. mp(239-241°C), IR(KBr) cm^{-1}, 3125,3017 (NH), 1661 (C=O), 1601 (C=N),1367,1302 (-SO_2-NH), 682(C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 12.86 (s, H, NH), 8.76 (s, 1H, N=CH), 8.34-7.58 (m, 12H, ArH).

(Z)-4-(4-chlorophenyl)-N'-(4-methoxybenzylidene)-1-oxophthalazine-2(1H)-sulfonohydrazide 10c
Yield: (85%), reddish yellow. mp(261-263°C), IR(KBr) cm^{-1}, 3123,3017 (NH), 1660 (C=O), 1550 (C=N),1376,1079 (-SO_2-NH), 787(C-Cl); Mass spectrum showed molecular ion peak at m/z = 469 (M^+).

(Z)-N'-(3-bromobenzylidene)-4-(4-chlorophenyl)-1-oxophthalazine-2(1H)-sulfonohydrazide 10d
Yield: (87%), yellow solid. mp(178-180°C), IR(KBr) cm^{-1}, 3165,3017 (NH), 1660 (C=O), 1660,1559 (C=N),1218,1020(-SO_2-NH), 562(C-Br); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.50 (s, H, NH), 8.75 (s, 1H, N=CH), 8.14-7.85 (m, 8H, ArH), 8.15(d, 2H, J=2.4Hz, ArH), 7.65(d, 2H, J=61.5Hz, ArH).

(E)-1-oxo-N'-(2,3,4,5,6-pentahydroxyhexylidene)-4-phenylphthalazine-2(1H)-sulfonohydrazide 11a
Yield: (87%), yellow solid. mp(222-224°C), IR(KBr) cm^{-1}, 3434,3017 (NH, OH), 1728,1660 (C=O), 1601,1555 (C=N),1329,1080(-SO_2-NH); Mass spectrum showed molecular ion peak at m/z=478(M^+).

(E)-1-oxo-4-phenyl-N'-(2,3,4,5-tetrahydroxypentylidene)phthalazine-2(1H)-sulfonohydrazide 11b
Yield: (85%), bale yellow solid. mp(233-235°C), IR(KBr) cm^{-1}, 3126,2807 (NH, OH), 1720,1660 (C=O), 1601,1556 (C=N),1329,1299(-SO_2-NH); Mass spectrum showed molecular ion peak at m/z = 448 (M^+).

(E)-1-oxo-4-phenyl-N'-(2,3,4,5-tetrahydroxypentylidene)phthalazine-2(1H)-sulfonohydrazide 11c

Yield: (82%), orang solid. mp(226-228°C), IR(KBr) cm^{-1}, 3342,3172 (NH, OH), 1661 (C=O), 1556 (C=N),1133,1051(-SO_2-NH); Mass spectrum showed molecular ion peak at m/z = 448 (M^+).

(E)-4-(4-chlorophenyl)-1-oxo-N'-(2,3,4,5,6-pentahydroxyhexylidene)phthalazine-2(1H)-sulfonohydrazide 12a

Yield: (88%), orang solid. mp(161-163°C), IR(KBr) cm^{-1}, 3412,2898 (NH, OH), 1659,1602 (C=O), 1556 (C=N),1376,1301(-SO_2-NH), 787(C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.50 (s, H, NH), 8.39 (s, 1H, N=CH), 3.63 (s, 1H, HO-2), 8.38-7.84 (m, 8H, ArH), 5.2(s, 1H, H-1), 4.22(d, 1H, J=7.5Hz,OH-1), 3.59(m, 2H, HO-3, HO-4), 3.22(m, 3H, H-2, H-3, H-4), 2.96(m, 2H, CH_2-OH).

(E)-4-(4-chlorophenyl)-1-oxo-N'-(2,3,4,5-tetrahydroxypentylidene)phthalazine-2(1H)-sulfonohydrazide 12b

Yield: (79%), orang solid. mp(170-172°C), IR(KBr) cm^{-1}, 3165,2898 (NH, OH), 1660 (C=O), 1556 (C=N),1329,1302(-SO_2-NH), 825(C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.50 (s, H, NH), 8.34-7.84 (m, 8H, ArH, 1H, CH=N), 4.80(t, 2H, J=12.5Hz, J=3.3Hz, H-1, H-2), 4.2(d, 2H, J=7.5Hz, OH-1, OH-2), 3.1(m, 6H, HO-3, H-2, H-3, HO-4, CH_2-OH).

(E)-4-(4-chlorophenyl)-1-oxo-N'-(2,3,4,5-tetrahydroxypentylidene)phthalazine-2(1H)-sulfonohydrazide 12c

Yield: (84%), yellow solid. mp(144-147°C), IR(KBr) cm^{-1}, 3341,3171 (NH, OH), 1660 (C=O), 1601 (C=N), 1258 (-SO_2-NH), 785(C-Cl); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.4 (s, H, NH), 8.34(d, 1H, J=2.1Hz, N=CH), 8.33-7.85 (m, 8H, ArH), 4.2(s, 1H, HO-1), 4.8(d, 1H, J=14.7Hz,H-1), 3.8(s, 1H, HO-2), 3.65-3.22(m, 6H, HO-3, H-2, H-3, HO-4, CH_2-OH).

General procedure for the synthesis of compounds 13,14(a,b)

A mixture of compound 3(a,b) (0.001 mol) and phenylisocyanate or phenylisothiocyanate (0.001 mol) in benzene (30 mL) was refluxed for 8 hours, the solvent was evaporated under vacuum, the solid obtained was filtered off and recrystallized from pet.ether to give 13,14(a,b).

1-oxo-N,4-diphenylphthalazine-2(1H)-carboxamide 13a

Yield: (61%), white solid. mp(>300°C), IR(KBr) cm^{-1}, 3220,3294 (NH), 1671 (C=O), 1546 (C=N),1599(-CO-NH); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 9.08 (s, H, NH), 8.34-7.25 (m, 14H, ArH).

1-oxo-N,4-diphenylphthalazine-2(1H)-carbothioamide 13b

Yield: (56%), white solid. mp(>300°C), IR(KBr) cm^{-1}, 3208,3108 (NH), 1660 (C=O), 1544 (C=N),1189 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6) ppm: 11.5 (s, H, NH), 8.34-7.25 (m, 14H, ArH).

4-(4-chlorophenyl)-1-oxo-N-phenylphthalazine-2(1H)-carboxamide 14a

Yield: (53%), white solid. mp(>300°C), IR(KBr) cm^{-1}, 3295,3216 (NH), 1670 (C=O), 1548 (C=N),1599 (-CO-NH), 757 (C-Cl); ^{13}C NMR (75.4 MHz, DMSO-ds), showed signal at (δ ppm), 161.97 (C=O),154.63 (C=N),141.00 (C-Cl), 136.09-119.25 for (aromatic carbons); Mass spectrum showed molecular ion peak at m/z = 375 (M^+).

4-(4-chlorophenyl)-1-oxo-N-phenylphthalazine-2(1H)-carbothioamide 14b

Yield: (50%), white solid. mp(>300°C), IR(KBr) cm^{-1}, 3016,2904 (NH), 1659 (C=O), 1554 (C=N),1295 (C=S), 786(C-Cl); Mass spectrum showed molecular ion peak at m/z = 391 (M^+).

Reaction with pipredine under Mannich condition

A mixture of compound **3(a,b)** (0.001 mol) and pipredine (0.001 mol) and formaldehyde solution 38% (2 mL) and one drop of HCl in ethanol (30 mL) was refluxed for 4 hours, the solvent was evaporated under vacuum, the solid obtained was filtered off and recrystallized from ethanol to give **15(a,b).**

4-phenyl-2-(piperidin-1-ylmethyl)phthalazin-1(2H)-one 15a

Yield: (82%), orang solid. mp(>300°C), IR(KBr) cm^{-1}, 2776 (CH), 1642 (C=O),1519 (C=N); Mass spectrum showed molecular ion peak at m/z = 319 (M^+).

4-(4-chlorophenyl)-2-(piperidin-1-ylmethyl)phthalazin-1(2H)-one 15b

Yield: (76%), reddish solid. mp(>300°C), IR(KBr) cm^{-1}, 2776 (CH), 1643 (C=O), 1455 (C=N), 1085 (C-Cl); ^{13}C NMR (75.4 MHz, DMSO-ds), showed signal at (δ ppm), 154.63 (C=O), 135.01 (C in C=N), 130.41-122.85 for (aromatic carbons),132.51(C in C-N), 61.08, 53.94, 26.03, 24.23 and 15.09 (5 Carbons of CH_2-).

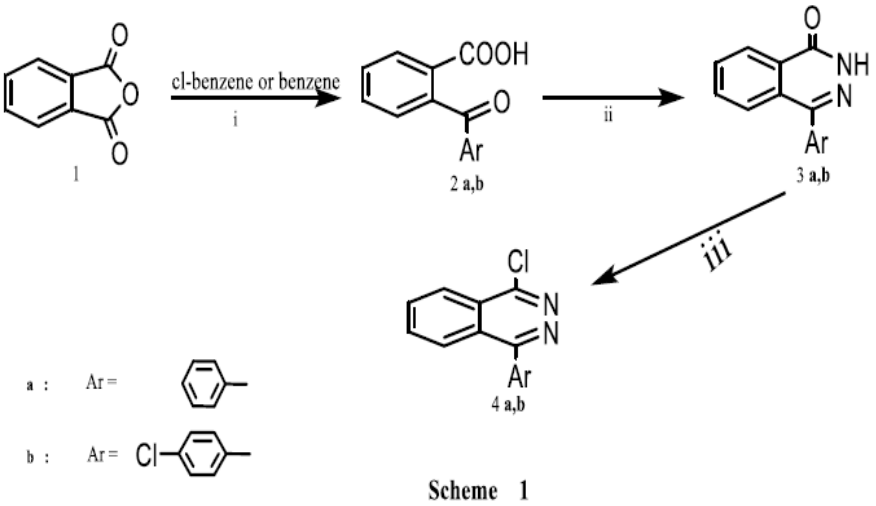
RESULTS AND DISCUSSION

The aim of the work is synthesis of some heterocyclic compound containing phthalazine or 1- oxophthalazine moiety with study biological activity.

Preparation of the key intermediate phthalazinone derivative 3(a,b)

The first step in the synthetic pathway Scheme 1 consists of aroylation of aromatic system by reaction with phthalic anhydride under Friedel-Crafts conditions yields the 2-aroyl benzoic acid derivatives 2(a,b). In a typical experiment, the reaction of phthalic anhydride 1 with benzene or chlorobenzene in the presence of anhydrous

aluminum chloride were carried out under reflux condition at 80°C for 6 hours to produce aroyl benzoic acid derivatives 2(a,b). Further cyclisation with hydrazine hydrate in boiling ethanol for 2 hours afforded the corresponding intermediate phthalazin-1(2H)-one 3(a,b) in 68%, 73% yield.



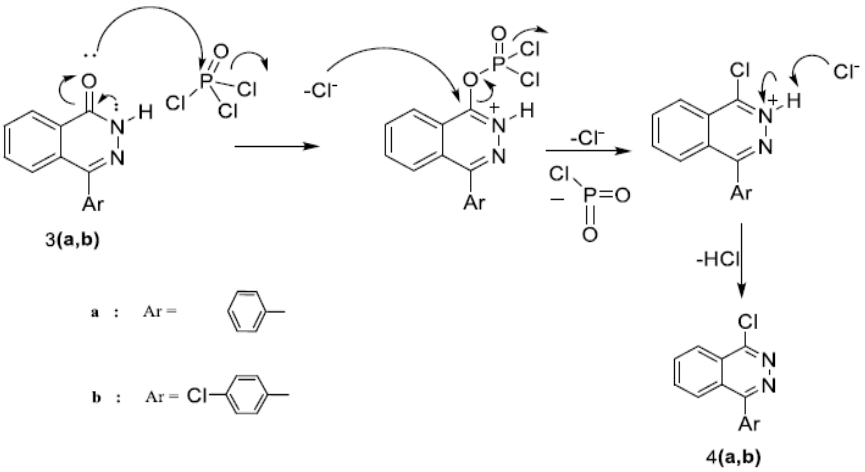
Scheme 1

i) $AlCl_3$(anhydrous) reflux for 6h at 80 °C
ii)$NH_2NH_2.2H_2O$,dry ETOH reflux for 2h at 70 °C
iii)$PoCl_3$,DMF,CH_3CN

Synthesis of chloro phthalazines derivatives 4(a,b)

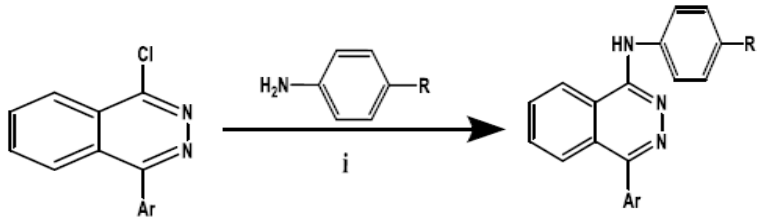
The key intermediate phthalazine derivatives **4(a,b)** as shown in **Scheme 1** was synthesized by chlorination of the key intermediate phthalazinone derivatives **3(a,b)** through dehydroxychlorinated by $POCl_3$ in a heating mixture of dimethylformamide(DMF) and acetonitrile. After base neutralization and work-up the chloro compounds were obtained as pure brown crystals in 95%, 92% yield. The structure of **4(a,b)** were confirmed by IR which showed a characteristic peaks at 1627, 1663 cm^{-1} (C=N) for the imine group with the disappearance of the carbonyl group, with appearance of a new peaks at 759, 756 cm^{-1} for (C-Cl). In the structures **4(a,b)** by ^1H NMR showed multiple signals (ppm) characteristic Ar-H protons, with devoid any bands for NH.

The reaction possibly proceeds according the following mechanism:



Synthesis of amino phthalazine derivatives 5,6(a-c)

Reactions of phthalazine derivatives **4(a,b)** with nitrogen containing nucleophiles such as aniline, m- methyl aniline and p-chloro aniline in dry chloroform. The reactions mixture were heated refluxed at 60-70°C in the presence of drops of triethyl amine, TLC monitoring was used to ensure the completion of reaction. The resulting crude product was extracted by chloroform: water (5:10), the organic layer was evaporated under vacuum, separated solid was washed with H_2O, dried to afford the pure products using **5,6(a-c)** in good yields as depicted in **Scheme 2**.



4 a,b 5,6 (a-c)

Scheme 2

a : Ar =

b ; Ar = Cl

R= a : H

b : CH_3

c : CL

i) EtN/$CHCl_3$/reflux at 60-70 °C

The characterizations of all synthesized compounds were accomplished by spectroscopic data.

The **IR** spectra showed absorption bands of (NH) groups at 3433, 3430, 3154 cm^{-1} and for (C=N) at 1584, 1566, 1664 cm^{-1} for **5a**, **5b**, **5c** respectively.

^{1}H NMR showed chemical shifts (ppm) of (Ar-CH_3) at expected values at 2.51(s, 3H, Ar-CH_3) for compound **5b**, and shows signals (ppm) for (NH) group at 9.40, 12.84 for **5a, 5b.**

Mass spectrum showed molecular ion peaks at m/z(M^+) 297, 311, 332 for compounds **5a, 5b**, **5c** Respectively.

The characterizations of all synthesized compounds were accomplished by spectroscopic data.

The **IR** spectra showed absorption bands of (NH) groups at 3200, 3433, 3432 cm^{-1} for compounds **6a**, **6b**, **6c** respectively and for (C=N) at 1661, 1662, 1663 cm^{-1} and for (C-Cl) at 543, 616, 636 cm^{-1} for compounds **6a**, **6b**, **6c** respectively.

^{1}H NMR shows signals at (ppm) for (NH) group at 12.86, 12.86, 12.009 for compounds **6a**, **6b**, **6c** respectively, compound **6b** shows signal (ppm) 2.36(s, 3H, Ar-CH_3)**.**

Mass spectra shows molecular ion peaks at m/z (M^+) 332 for compound **6a.**

Compound **5b** its fragmentation pattern is given in ***chart 1***.

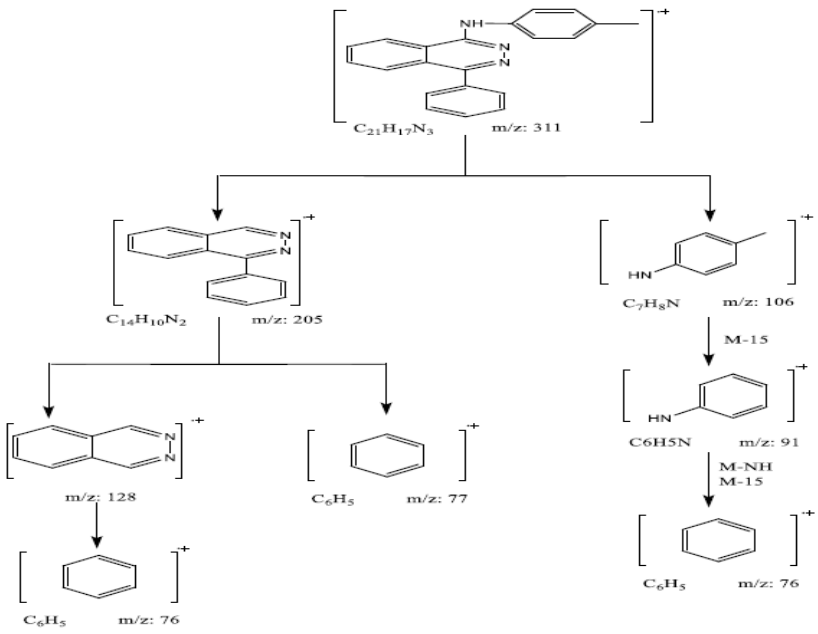
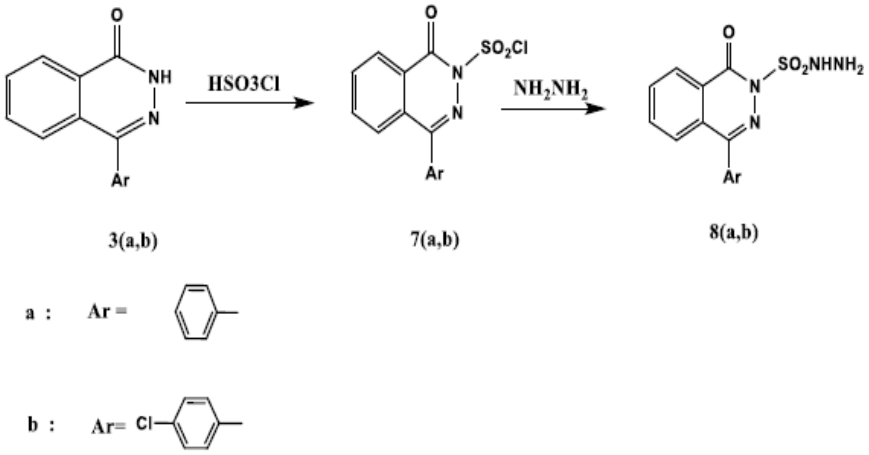


Chart 1.

Synthesis of 1-oxo-arylphthalazine sulphonylchloride 7(a,b)[32,33]

1-oxo-arylphthalazine derivatives **3(a,b)** were added portion wise to chlorosulphonic acid in the presence of excess amount of thionylchloride at 0°C with stirring, after one hour the temperature was elevated gradually to 90°C and kept it for 72 hours, the reaction mixture was poured into crushed ice, the products were filtered off and crystallization from ethanol to give **7(a,b)** in good yield. (*C.f.* **Scheme 3**).



Scheme 3

The characterizations of all synthesized compounds were accomplished by spectroscopic data.

The **IR** spectra showed absorption bands of (C=O) at 1753, 1755 cm^{-1} and (C=N) at 1606, 1619 cm^{-1} and (SO_2-Cl) at 1284, 1283 cm^{-1} for compounds **7a** and **7b** respectively, for compound **7b** appear absorption band of (C-Cl) at 707 cm^{-1}.

^{1}H NMR showed signals at (ppm) 7.65-8.14 (m, 9H, ArH) with devoid any band for (NH) for compounds **7a**, **7b**.

^{13}C NMR of compound **7a** showed signals at (ppm) 162.5 for carbon of (C=O), 135.51 (N=C), 136.51-122.85 for aromatic carbons.

Mass spectrum showed molecular ion peaks at m/z = 321(M^+) for compound **7a.**

Synthesis of 1-oxophthalazine sulphonylhydrazide 8(a,b)

In **Scheme 3** a solution of 1-oxophthalazine sulfonylcloride **7(a,b)** in tetrahydrofuran (THF), hydrazine hydrate was added at room temperature with stirring for about 30 min., heating further 30 min. at 40 - 50°C, then pour the reaction mixture into water and filtered off and then crystallized from ethanol to give **8(a,b)** in good yields.

The characterizations of synthesized compounds **8(a,b)** were inferred from spectroscopic data.

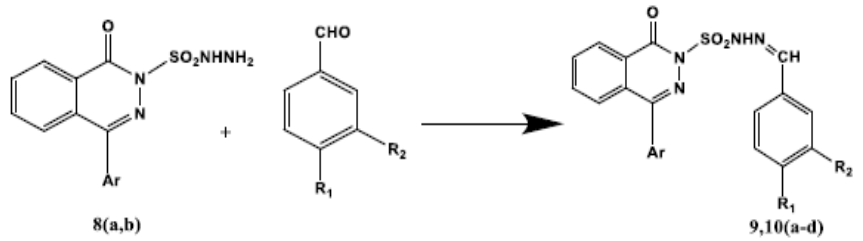
IR showed absorption bands of (NH_2) at 3320, 3530 cm^{-1} and (NH) at 3210, 3110 cm^{-1} and (C=O) at 1763, 1650 and (C=N) at 1604, 1607 cm^{-1} and (-SO_2-NH) at 1080, 1079 cm^{-1} for compounds **8a** and **8b** respectively.

^{1}H NMR spectra showed signals at (ppm) for (NH) at 11.50, 11.507 and (NH_2) at 3.31, 3.29 for compounds **8a**, **8b** with exchangeable in D_2O.

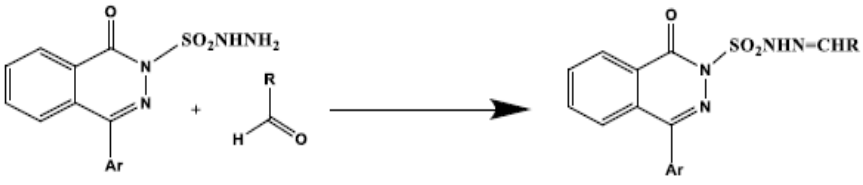
Mass spectrum showed molecular ion peaks of compounds **8a** and **8b** at m/z(M^+) = 316, 350.

Synthesis of 1-oxophthalazine sulphonylhydrazone derivatives 9, 10(a-d) and 11, 12(a-c)

A mixture of 1-oxophthalazine sulfonylhydrazide **8(a,b)** and aldehyde derivatives such as benzaldehyde, p-chlorobenzaldehyde, anisaldehyde, and m-bromobenzaldehyde or sugar derivatives such as D-glucose, D-arabinose and D-xylose in ethanol with catalytic amount of glacial acetic acid were boiling under reflux for 2 hours; after concentration and cooling the precipitation filtered off and crystallized from ethanol to give **9,10(a-d)** and **11,12(a-c)** in good yields. (*C.f.* **Scheme 4, 5**).



Scheme 4



Scheme 5

The characterizations of synthesized compounds **9(a-d)** were inferred from spectroscopic data.

The **IR** spectra showed absorption bands of (NH) at 3435-3018, 3167-3017, 3166-3126, and 3167-3018 cm^{-1} and (C=O) at 1729, 1728, 1723, and 1728 cm^{-1} and (C=N) at 1659, 1660, 1601 and 1660 cm^{-1} and (- SO2-NH) at 1024, 1079, 1033, 1079 cm^{-1} attributed to compounds **9a, 9b, 9c** and **9d** respectively.

^{1}H NMR spectra showed signals (ppm) for (NH) at 12.84, 12.85 and 11.50 and (N=CH) at 8.79, 8.75 and 8.70 for compounds **9a**, **9b** and **9c** respectively.

Mass spectrum showed molecular ion peaks at m/z = 404(M^+), 434(M^+) and 483(M^+) of compounds **9a**, **9c** and **9d** respectively.

For compound **9c** **^{1}H NMR** spectra showed signals (ppm) 3.31 (s, 3H, OCH_3).

The characterizations of all synthesized compounds **10(a-d)** were inferred from spectroscopic data.

The **IR** spectrum showed absorption bands of (NH) at 3165-3016, 3125-3017, 3123-3017, and 3165-3017 cm^{-1} and for (C=O) at 1660, 1661, 1660, and 1660 cm^{-1} and for (C=N) at 1600, 1601, 1550 and 1559 cm^{-1} and (-SO2-NH) at 1163, 1302, 1079 and 1020 cm^{-1} and (C-Cl) at 862, 682, 787 and 562 cm^{-1} attributed to compounds **10a, 10b, 10c** and **10d** respectively.

^{1}H NMR spectra showed signals (ppm) for (NH) at 11.50, 12.86 and 11.50 and (N=CH) at 8.5, 8.76 and 8.75 for compounds **10a**, **10c** and **10d** respectively.

For compound **10c** Mass spectrum showed molecular ion peaks at m/z = 469(M^+).

For compound **11a** its fragmentation pattern is given in ***chart 2.***

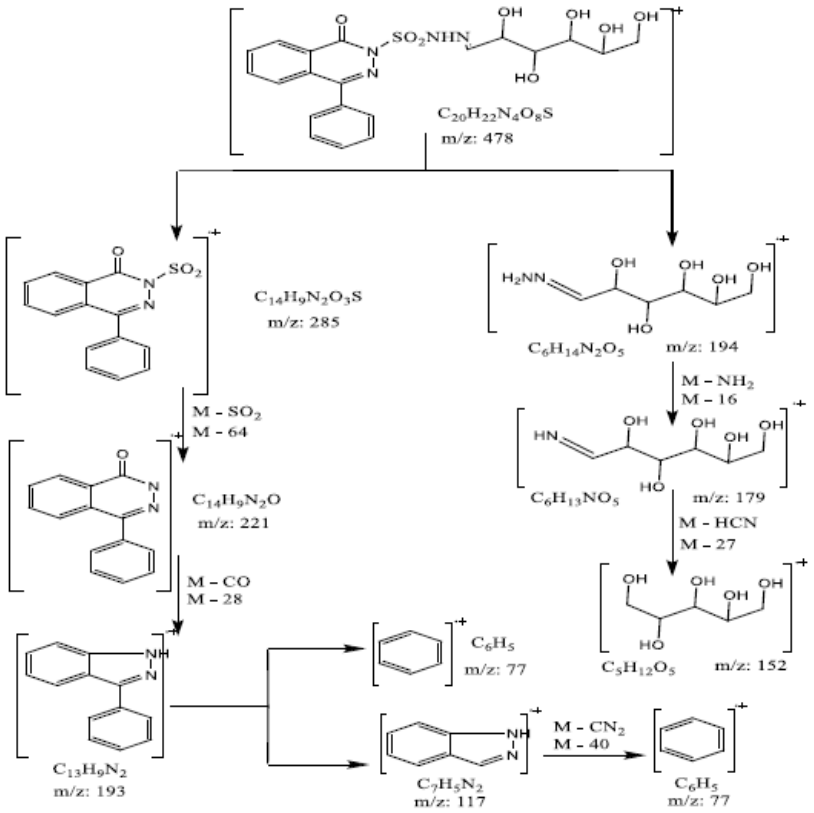


Chart 2

Synthesis of 1-oxophthalazine sulphonylhydrazone sugar derivatives 11, 12(a-c).
A mixture of 1-oxophthalazine sulfonylhydrazide **8(a,b)** in ethanol with aldose sugar derivatives such as D-glucose, D-arabinose and D-xylose with catalytic amount of glacial acetic acid under reflux for 2 hours to compounds **11,12(a-c)**. (*C.f.* **Scheme 5**).

The characterizations of all synthesized compounds were inferred from spectroscopic data.

IR spectrum showed absorption bands of (NH,OH) at 3434-3017, 3126-3807 and 3342-3172 cm^{-1} and for (C=O) at 1728, 1720 and 1661 cm^{-1} and for (C=N) at 1555, 1556 and 1556 cm^{-1} and (-SO2-NH) at 1080, 1299 and 1051 cm^{-1} attributable compounds **11a, 11b, 11c** respectively.

Mass spectrum showed molecular ion peaks at m/z = 478(M^+), 448(M^+) and 448(M^+) attributable compounds **11a, 11b** and **11c** respectively.

The characterizations of all synthesized compounds **12(a-c)** were accomplished by spectroscopic data.

The **IR** spectra showed at absorption bands of (NH,OH) at 2412-2898, 3165-2898 and 3341-3171 cm^{-1} and for (C=O) at 1659, 1660 and 1660 cm^{-1} and for (C=N) at 1556, 1556 and 1601 cm^{-1} and (-SO2-NH) at 1301, 1302 and 1258 cm^{-1} and for (C-Cl) at 787, 825 and 785 attributable for compounds **12a, 12b, 12c** respectively.

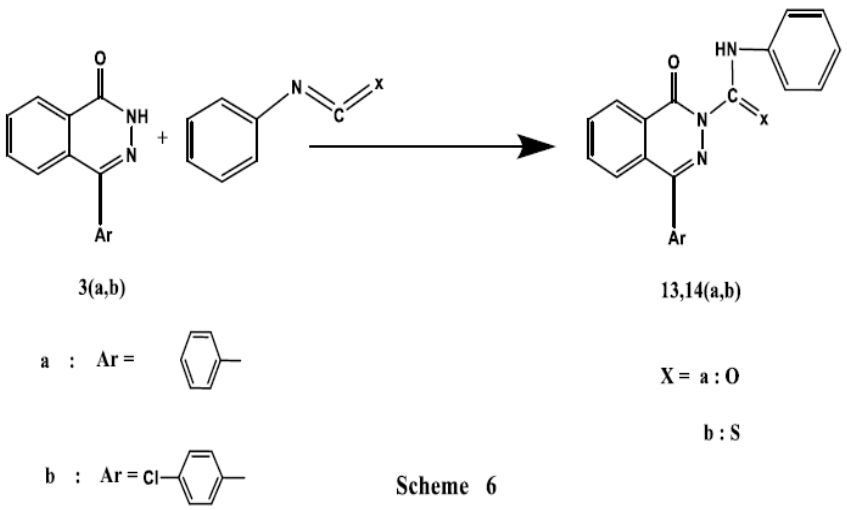
^{1}H NMR spectra showed signals (ppm) for (NH) at 11.50, 11.50 and 11.40 and (N=CH) at 8.39, 8.34 and 8.34 for compounds **12a**, **12b** and **12c** respectively.

For compound **12a** showed signals at (ppm) 3.63 (s, 1H, HO-2), 5.2(s, 1H, H-1), 4.22(d, 1H, HO-1), 3.59(m, 2H, HO-3, HO-4), 3.22(m, 3H, H-2, H-3, H-4), 2.96(m, 2H, CH2-OH).

12b give signals at (ppm) 4.80(t, 2H, H-1, H-2), 4.2(d, 2H, OH-1, OH-2), 3.1(m, 6H, HO-3, H-2, H-3, HO-4, CH2-OH).

12c give signals at (ppm) 4.2(s, 1H, HO-1), 4.8(d, 1H, H-1), 3.8(s, 1H, HO-2), 3.65-3.22(m, 6H, HO-3, H-2, H-3, HO-4, CH2-OH).

Synthesis of 1-oxophthalazine carboxamide and carbothioamide derivatives 13, 14(a,b).
A mixture of compound **3(a,b)** and phenylisocyanate or phenylisothiocyanate in benzene was refluxed for 8 hours, the solvent was evaporated under vacuum, the solid obtained was filtered off and crystallized from pet.ether to give **13,14(a,b)** in good yields. (*C.f.* **Scheme 6**).



Scheme 6

The characterizations of all synthesized compounds 13(a,b) attributable to spectroscopic data.

The **IR** spectra showed absorption bands of (NH) at 3294 and 3108 cm^{-1} and for (C=O) at 1671 and 1671 cm^{-1} and for (C=N) at 1546 and 1544 cm^{-1} attributed to compounds **13a** and **13b** respectively, for compound **13a** (-CO-NH) at 1599 cm^{-1} and for compound **13b** (C=S) at 1189 cm^{-1}.

^{1}H NMR showed signals (ppm) for (NH) at 9.08 and 11.50 for compounds **13a** and **13b** respectively. The characterizations of all synthesized compounds **14(a,b)** attributable to spectroscopic data.

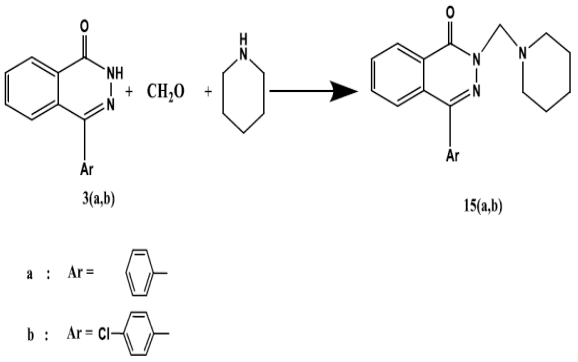
The **IR** spectra showed absorption bands of (NH) at 3295 and 3016 cm^{-1} and for (C=O) at 1670 and 1659 cm^{-1} and for (C=N) at 1548 and 1554 cm^{-1} and (C-Cl) at 757 and 786 cm^{-1} attributed to compounds **14a** and **14b** respectively, for compound **14a** (-CO-NH) at 1599 cm^{-1} and for compound **14b** (C=S) at 1295 cm^{-1}.

Mass spectrum showed molecular ion peaks at m/z = 375(M^{+}) and 391(M^{+}) attributable compounds **14a** and **14b** respectively.

For compound **14a** **^{13}C NMR** showed signal at (δ ppm), 161.97 (carbon of C=O), 154.63 (C=N), 141.00 (C- Cl), 136.09-119.25 for (aromatic carbons).

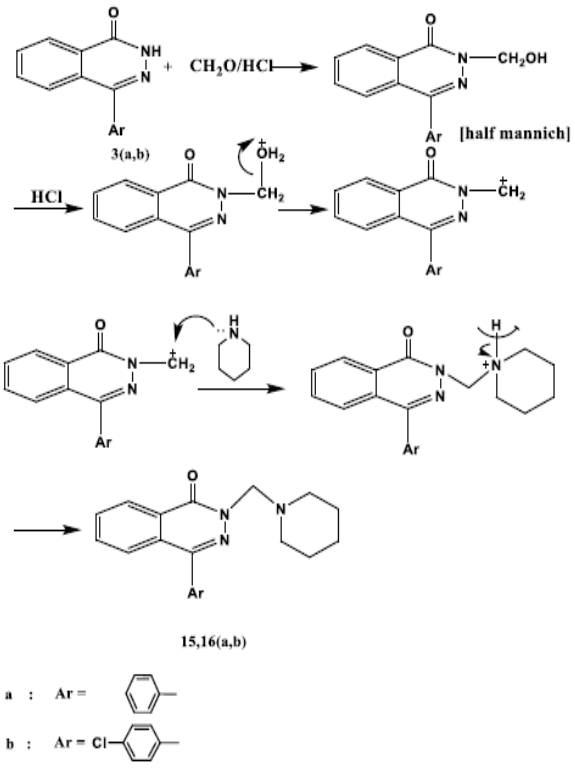
Reaction with pipredine under Mannich condition 15(a,b).

A mixture of compound **3(a,b)** and pipredine and formaldehyde solution 38% (2 mL) and one drop of HCl in ethanol was refluxed for 4 hours, the solvent was evaporated under vacuum, the solid obtained was filtered off and recrystallized from ethanol to give **15(a,b)**. (*C.f.* **Scheme 7**).



Scheme 7

The reactions possibly take place via the following mechanism:-



The characterizations of all synthesized compounds attributed by spectroscopic data.

The **IR** spectra showed absorption bands of (-CH-) at 2776 and 2776 cm^{-1} and for (C=O) at 1642 and 1643 cm^{-1} and for (C=N) at 1519 and 1455 cm^{-1} attributed to compounds **15a** and **15b** respectively.

For compound **15a** Mass spectrum showed molecular ion peak at m/z = 319(M^+).

For compound **15b** showed bands of (C-Cl) at 1085 cm^{-1} and **^{13}C NMR** showed signal at (δ ppm), 154.63 (carbon of C=O), 135.01 (C=N), 130.41-122.85 for (aromatic carbons), 132.51(C in C-N) and 61.08, 53.94, 26.03, 24.23 and 15.09 for 5 carbons (-CH_2-).

BIOLOGICAL ACTIVITY

Larvicidal effects of some synthesized compounds on *Culex Pipiens* larvae

Mosquitoes are important vector for several diseases on earth in Egypt, ***Culex Pipiens*** is the most common species and an important vector of several human pathogenic agents, such as *filarial worm*, *Wuchereia bancrofti* (more than 100 million people are infected worldwide with *W. bancrofti*[34]), Rift valley fever virus[35,36] and West Nile virus[37], mosquito control is becoming increasingly difficult in Egypt because of the emergence of resistance of ***C. Pipiens*** to many insecticides, Traditionally used synthetic insecticides are quick effective and most popular methods of pest control.

Insect Culture

The mosquito, ***C. Pipiens*** used in the present study was obtained from susceptible reared strain of research of Medical Entomology, Dokki, Egypt, The colony was maintained in laboratory of Zoology Department, Faculty of Science, Menoufia University at 27±2°C and 75±5% R.H.

Larvae were reared in de chlorinated water and fed daily on 5% yeast suspension, adult male fed on 10% sugar solution while females received blood meals periodically from pigeons for egg production.

Bio assay

The tested compounds were dissolved in Dimethyl Formamide (**DMF**) (0.1 mg/ml solvent +100ml water) (1 ppm), twenty five 2nd instar larval of ***C. Pipiens*** were put in aplastic cup (100ml) containing the test solution of each compound, Four replicates were run for each compound, control test were carried out in parallel with the required amount of solvent in water, mortality counts were made after 24, 48 hours and the end of larval period exposure, the larval considered dead when they were immobile and unable to reach the water surface

RESULTS

Data presented in table (1) shows that the tested compounds at (1ppm) induced larval mortality of *C. Pipiens* larval treated at 2nd larval instar, the larval mortality after 24 hours of exposure was 100, 25, 15, 10, 65, 15, 10, 5, 50 and 95% with the compounds 4a, 4b, 5b, 6b, 6c, 10b, 11a, 12b, 13b and 16a respectively, while the larval mortality after 48 hours from treatment was 100, 70, 20, 65, 15, 90, 15, 15, 20, 30, 20, 30, 100 and 100% with the compounds 4a, 4b, 5a, 5b, 6b, 6c, 7a, 8b, 10b, 10c, 11a, 12b, 13b and 16a respectively, while the total (cumulative) larval mortality at the end of larval period (after several days) was 100, 100, 50, 75, 20, 100, 25, 40, 35, 10, 35, 70, 60, 55, 60, 100 and 100% with the compounds 4a, 4b, 5a, 5b, 6b, 6c, 7a, 8a, 8b, 9a, 9d, 10b, 10c, 11a, 12b, 13b and 16a respectively (table 1 and fig 1), there is larval mortality in control group.

All the tested compounds induced larval mortality of ***C. Pipiens***, the present larval mortality increased with the increasing of period of treatment (exposure), the compounds **4a** and **16a** showed significant higher effect 24 hours, followed by the compounds **6c** and **13b**, the present data are in harmony with results obtained by other investigator using different compounds against ***C. Pipiens*** larval; it's concluded that the tested compounds proved to a promising controlling against ***C. Pipiens*** larval**.**

Table (1): Effect (1ppm) of some compounds on the larval mortality of *Culex Pipiens.*

Series	Reference	% larval mortality after 24 hours	% larval mortality after 48 hours	% total larval mortality
1	4a	100	100	100
2	4b	25	70	100
3	5a	-	20	50
4	5b	15	65	75
5	6b	10	15	20
6	6c	65	90	100
7	7a	-	15	25
8	8a	-	-	40
9	8b	-	15	35
10	9a	-	-	10
11	9d	-	-	35
12	10b	15	20	70
13	10c	-	30	60
14	11a	10	20	55
15	12b	5	30	60
16	13b	50	100	100
17	16a	95	100	100
18	Control (1)	0.0	0.0	0.0
19	Control (2)	0.0	0.0	0.0

Control (1): With water
Control (2): With solvent (DMF)

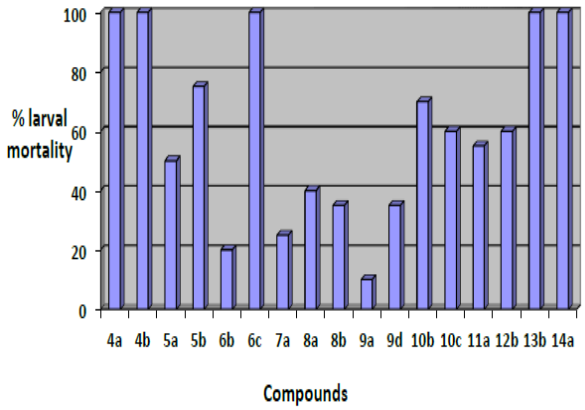


Fig (1): Effect of the tested compounds on the larval mortality of *Culex Pipiens.*

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