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Synthesis of Novel Phthalazines Containing Heterocyclic Moieties

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Abstract: ***The phthalazine (1) was allowed to react with 2-aminoethanol, allyl bromide, benzoyl chloride, 2-chloroethanol, phosphorous pentasulfide, ethyl cyanoacetate, phenyl isothiocyanate, piperazine and ethyl piperazine-1-carboxylate to give (2), (18), (17), (12), (9), (15), (19), (7) and (8). The compound (2) was allowed to react with phenyl isothiocyanate, acetic anhydride and piperonaldehyde giving (3), (5) and (6). (3) reacted with diethyl malonate to give the pyrimidine derivative (4). The thione (9) reacted with hydrazine hydrate followed by anisaldehyde to give (10) and (11). The phthalazinone derivative (12) reacted with phenol and catechol to give (13a,b). Acetylation of (13b) gave the diacetyl derivative (14). Finally (15) reacted with phenyl hydrazine gave the propenoic acid phenylhydrazide (16). The new compounds were synthesized with the objective of studying their antifungal and antimicrobial activity. Some of them gave positive results. The newly synthesized compounds were characterized on the basis of their spectral (^{1}H-NMR, Mass spectrum, IR and Elementary analysis).***

Keywords: Piperazine, phenylhydrazine, allyl bromide, diethylmalonate.

1. Introduction

Nitrogen-containing heterocycles posses diverse chemo-therapeutic activities [1, 2]. Among a large variety of nitrogen-containing heterocyclic compounds, phthalazin-1(2H)-ones, they were reported to be used as efficient antitumor [3] and therapeutic agents [4]. On the other hand, phthalazinones bearing a substituent at C-4 represent key intermediates in the synthesis of various compounds with highly interesting clinical applications of pharmacological properties, such as anti-heart disease, blood platelet aggregation inhibitors and cardiovascular antihypertensive agents [5-9]. In addition, a number of phthalazinone derivatives are well known to be active as anticonvulsant [10], cardiotonic [11], vasorelaxant [12], also used as anticancer agents and antitumor activity [13].

2. Results and Discussion

When the previously prepared phthalzinone **(1)** [14] was allowed to react with ethanolamine in oil bath at 150 °C, afforded 2-[2-(amino) ethyl]-4-tetryl-phthalazin-1-(2H)-one **(2)**. The reaction possibly takes place via nucleophilic attack on the more electrophilic center of alcoholic moiety. The structure was deduced from correct microanalytical data. The IR spectrum revealed strong absorption bands at ν 1658, 3154 and 3407 cm^{-1} attributable to C=O and NH. The structure was proved chemically via interaction with phenyl isothiocyanate furnished 2[2(phenylthiocabamoylamino) ethyl]-4-tetryl-phthalazin-1(2H)-one **(3)**. The ^{1}H NMR spectrum showed 1.42 (t, 2H, CH_2) 1.8 (s, 4H, β- methylene protons of tetryl moeity), 2.86 (t, 6H, α- methylene protons of tetryl moiety and N-CH_2), 7.2-8.5 (3 m, 12H, Ar-H), 10.49 (s, 2H, 2 NH, exchangeable with D_2O). The structure was inferred chemically via its interaction with diethylmalonate and yielded (**4).** Its structures were deduced from correct microanalytical data. The IR spectrum revealed strong absorption bands at ν 1156 and 1667 cm^{-1} attributable to C=S and C=O and laked any band for NH. The EIMS showed *m/z* at 522 corresponding to M^+ (molecular ion pea k). Also acetylation with acetic anhydride, afforded 2[2-(acetylamino) ethyl]-4-tetryl phthalazin-1(2H)-one **(5)**. ^{1}H NMR spectrum showed δ: 1.2 (t, 2H, CH_2) 1.7 (s, 4H, β- methylene protons of tetryl moeity), 2.05 (s, 3H, CH_3), 2.8 (t, 6H, α- methylene protons of tetryl moiety and N-CH_2), 7.2-7.9 (2m, 7H, Ar-H), 10.29 (s, 1H, NH, exchangeable with D_2O). The IR spectrum revealed strong absorption bands at ν 1666 and 3155 cm^{-1} attributable to C=O and NH. Also interaction with piperonal (3,4-methylene dioxo-benzaldehyde) yielded 2[2-(3,4-methylene dioxobenzylidene amino)-ethyl]-4-tetryl-phthalazin-2(1H)-one **(6)**. The IR spectrum revealed strong absorption bands at ν 1662 and 1675 cm^{-1} attributable to C=N and C=O. When the phthalazin-1(2H)-one **(1)** was submitted to react with piperidine and formaldehyde in the presence of few drops of HCl yielded 2-piperidinomethyl-4-tetryl-phthalazin-1(2H)-one **(7)**. The EIMS showed *m/z* at 373 corresponding to M^{+}(molecular ion peak). On the other hand when **(1)** was allowed to react with ethoxycarbonyl piperazine and formaldehyde in the presence of drops of HCl afforded **(8)**. The structure was deduced from correct microanalytical data. The IR spectrum revealed strong absorption bands at ν 1653, 1702, 2859 and 2927 cm^{-1} attributable to two carbonyl groups (the lower frequency of C=O of ester is due to the presence of lone pair of electron on the adjacent nitrogen) and CH and devoid any band for NH. The ^{1}H NMR spectrum also showed δ: 1.1 (t, 3H, $CH_2\underline{CH_3}$), 1.8 (s, 4H, β- methylene protons), 2.8 (s, 4H, α-methylene protons), 4.1 (q, 2H, $\underline{CH_2}$ CH_3), 4.3(m, 8H of piperizyl moeity), 5.5 (s, 1H, NCH_2N), 7.2-7.8 (m, 7H, Ar-H). Interaction of **(1)** with P_2S_5 in boiling xylene afforded 4-tetrylphthalazin-1(2H)-thione **(9)**. The structure of the thione was inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands at 1205, 1428,

2855, 2932 and 3147 cm^{-1} attributable to C=S, CH and NH. The EIMS showed *m/z* at 292, 293 and 294 corresponding to M^{+}, M^{+}+1 and M^{+}+2. Also the structure of **(9)** was inferred chemically via its interaction with hydrazine hydrate to yield 1-hydrazino-4-tetrylphthalazine **(10)**. The structure of **(10)** was inferred from correct microanalytical data. The IR spectrum showed bands at 3100-3300 attributed to NH. The EIMS showed *m/z* at 291 corresponding to M^{+}. Interaction of hydrazine derivative with 4-methoxybenzaldehyde in boiling ethanol yielded the hydrazone derivative **(11)**. ^{1}H NMR spectrum of **(11)** showed δ: 1.7 (s, 4H, β-methylene protons of tetryl moeity), 2.5 (s, 3H, CH_3) 2.7 (t, 4H, α-methylene protons of tetryl moiety), 7.2-7.9 (3m, 11H, Ar-H), 11.92 (s, 2H, NH, exchangeable with D_2O). The IR spectrum devoid any band of NH_2. The EIMS showed *m/z* at 409 corresponding to M^{+}.

When **(1)** was submitted to react with 2-chloroethanol, benzoyl chloride and allyl bromide in boiling dry acetone and anhydrous potassium carbonate for 24 hours afforded 2-(2-hydroxyethyl)-4-tetryl phthalazin-1(2H)-one **(12)**, 2-benzoyl-4-tetrylphthalazin-1(2H)one **(17)** and 2-allyl-4-tetryl-1(2H)phthalazinone **(18)** respectively. Their structures were deduced from correct microanalytical data. The IR spectrum of **(12)** revealed strong absorption bands at ν 1632, 2852, 2921, and 3436 cm^{-1} attributable to C=O, CH and OH. The EIMS showed *m/z* at 320 corresponding to M^{+}(molecular ion peak). ^{1}H NMR spectrum also showed δ: 1.7 (s, 4H, β- methylene protons of tetryl moeity), 2.7 (t, 6H, α- methylene protons of tetryl moiety and N-CH_2), 4.1 (t, CH_2OH), 7.2-7.9 (2m, 7H, Ar-H), 8.37 (s, 1H, OH, exchangeable with D_2O). The reaction takes place via SN_2 mechanism involving nucleophilic attack of lone pair of nitrogen atom of NH group of phthalazinone moiety on the alkyl chloride moiety of 2-chloroethanol. The IR spectrum of **(17)** revealed strong absorption bands at ν 1668, 2852 and, 2920 cm^{-1} attributable to C=O and CH. The reaction proceeds via tetrahedral mechanism in which the N-C bond was formed before C-Cl bond which started to break and consequently a lot of energy is accumulated in the reaction medium, which offset the activation energy of the reaction and a facile conversion occurred. The IR spectrum of **(18)** revealed strong absorption bands at ν 1660, 2853 and 2923 cm^{-1} attributable to C=O and CH and devoid of any band for NH. The EIMS showed *m/z* at 316 corresponding to M^{+}(molecular ion peak). The reaction takes place via SN_2 mechanism and the role of K_2CO_3 is pulling of bromide ion as KBr and abstract of H^{+} and converted to $KHCO_3$.
The structure of **(12)** was verified chemically via its reaction with compounds containing an active hydrogen namely phenol and catechol in boiling ethanol to give Mannich bases type **(13a,b)**. Their structures were inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands in the region at ν 1665-1670 and 3400-3430 cm^{-1} attributable to C=O and OH. ^{1}H NMR spectrum of **(13b)** showed δ: 1.7 (t, 2H, CH_2), 1.8 (s, 4H, β-methylene protons of tetryl moeity), 2.85 (t, 6H, α- methylene protons of tetryl moiety and N-CH_2), 6.64-7.9 (3m, 11H, Ar-H), 10.28 (s, 2H, OH, exchangeable with D_2O). Acetylation of **(13b)** yielded diacetoxyl derivative **(14)**. The IR spectrum revealed strong absorption bands at ν 1666 and 1761 cm^{-1} attributable to two C=O and devoid any band for OH. On the other hand when **(1)** was submitted to react with ethyl cyanoacetate in boiling ethanol yielded ethyl-3-amino-3-(1-oxo-4(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)propenoate **(15)**. The reaction takes place via nucleophilic addition on CN rather than tetrahedral nucleophilic substitution at acyl moiety(addition takes place easily than substitution which involving bond breakage, while addition required bond polarization) . The structure of **(15)** was inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands in the region at ν 1603, 1667, 1748, 2907, 2932, 3152 and 3296 cm^{-1} attributable to C=C, two C=O, CH and NH. Also the structure was supported chemically from its interaction with phenyl hydrazine in boiling ethanol and yielded 3-amino-3-(1-oxo-4(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin(1H) ropenoic acid phenylhydrazide **(16)**. The structure of **(16)** was inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands in the region at ν 1604, 1665, 2854, 2932, 3100 and 3208 cm^{-1} attributable to C=C, C=O, CH and NH.^{1}H NMR spectrum also showed δ: 1.7 (s, 4H, β-methylene protons of tetryl moeity), 2.7 (t, 4H, α- methylene protons of tetryl moiety), 7.19-8.6 (3m, 12H Ar-H), 10.8 (broad, 4H, NH_2, 2 NH, exchangeable with D_2O). . The EIMS showed *m/z* at 451 corresponding to M^{+}. Interaction of **(1)** with phenyl isothiocyanate in boiling benzene yielded 2-phenyl thiocarbonyl-4-tetryl-phthalazin-1(2H)-one **(19).** The structure of **(19)** was inferred from correct microanalytical data. The IR spectrum revealed strong absorption bands at ν 1156, 1665 and 3155 cm^{-1} attributable to C=S, C=O and NH. The EIMS showed *m/z* at 411, 412 and 413 corresponding to M^{+}, M^{+} +1 and M^{+}+2 (See **Scheme 1** on last page.**)**

2.1 Antimicrobial Activity

The antibacterial activity of the synthesized compounds was tested against *Bacillus subtilis, Staphylococcus aureus* (Gram-positive bacteria), *Escherichia coli*, *Pseudomonas sp.* (Gram-negative bacteria) using nutrient agar medium. The antifungal activity of the compounds was tested against *Candida albicans and Aspergillus niger* using Sabouraud dextrose agar medium.

2.2 Agar Diffusion Medium

All compounds were screened *in vitro* for their antimicrobial activity against, by agar diffusion method (Cruickshank *et al*.1975) [15]. A suspension of the organisms were added to sterile nutrient agar media at 45 °C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 10 mm in diameter were made using a cork borer). An amount of 0.1 ml of the synthesized compounds was poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 h at room temperature as a period of pre-incubation diffusion to minimize the effects of variation in time between the applications of the different solutions. The plates were then incubated at 37 °C for 24 h and observed for antimicrobial activity. The diameters of zone of inhibition were measured and compared with that of the standard. Ciprofloxacin (50 µg/ml) and Fusidic acid (50 µg/ml) were used as standard for antibacterial and antifungal activity respectively. The observed zone of inhibition is presented in Table 1.

Table 1: Antibacterial and antifungal activities of the newly synthesized compounds

Microorganism						Compds
Fungi		Gram –ve bacteria		Gram +ve bacteria		
Aspergillus	*Candida*	*Pseudomonas aeuroginosa*	*Escherichia coli*	*Staphylococcus aureus*	*Bacillus subtilis*	
+ve	+++ ve	++++ ve	++++ ve	+++ ve	++++ ve	**1**
-ve	-ve	-ve	-ve	-ve	-ve	**4**
-ve	+ ve	+ ve	+ ve	+ ve	+ ve	**6**
-ve	+ ve	+ ve	+ ve	+ ve	+ ve	**10**
-ve	++ ve	++ ve	++ ve	++ ve	++ ve	**12**
-ve	+ ve	+ ve	+ ve	+ ve	+ ve	**13b**
-ve	++ ve	++ ve	++ ve	++ ve	++ ve	**15**
+ve	+++ ve	++++ ve	++++ ve	+++ ve	++++ ve	**18**
+ve	+++ ve	++++ ve	++++ ve	+++ ve	++++ ve	**19**

Moderately active (+++) = (inhibition zone 16-29) nm
Slightly active (++) = (inhibition zone 13-15) nm
Weakly active (+) = (inhibition zone 11-12) nm
Inactive = (inhibition zone < 11) nm

3. Experimental

All melting points are uncorrected and were measured on an electrothermal melting point apparatus. Elemental analyses were performed using a Heraeus CHN Rapid analyzer at the Microanalytical unit, Cairo University. Thin-layer chromatography (TLC) was performed on Merk TLC aluminium sheets silica gel 60 $F_{254}$with detection by UV quenching at 254nm. IR spectra were measured on a Unicam SP-1200 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were measured in DMSO-d_6 on a Varian plus instrument (300 MHz). Mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument operating at 70 eV in EI mode

2-(2-Aminoethyl)-4-(5, 6, 7, 8-tetrahydronaphthalen-2-yl) phthalazin-1(2H) one (2)
A mixture of **(1)** (0.01 mol) 2.7 gm, (0.02 mol) 1.2 gm of 2 aminoethanol in 20 mL pyridine was heated under reflux for 3 hs. After cooling, the reaction mixture was poured on ice/HCl to separate a solid which was separated, filtered and crystallized from ethanol to give **(2)**, 90 % yield, m.p. 235 ℃. IR (KBr) ν 1658, 3154 and 3407 cm^{-1} attributable to C=O and NH. Anal cald for $C_{26}H_{30}N_4O_3$: C 75.21, H 6.63, N 13.16; found C 75.48, H 5.90, N 13.51

2[2(Phenylthiocabamoylamino) ethyl]-4-(5, 6, 7, 8-tetra-hydronaphthalen-2-yl) phthalazin-1(2H)-one (3).
A mixture of **(2)** (0.001 mol) 0.3 gm, and phenyl isothiocyanate (0.002 mol) 0.27 gm in 20 mL benzene was heated under reflux for 3 hs. After cooling a solid was separated and crystallized from benzene to give **(3)**, 60 % yield, m.p. 270 ℃. The ^{1}H NMR δ: 1.42 (t, 2H, CH_2) 1.8 (s, 4H, β- methylene protons of tetryl moeity), 2.86 (t, 6H, α-methylene protons of tetryl moiety and N-CH_2), 7.2-8.5 (3m, 12H, Ar-H), 10.49 (s, 2H, 2 NH, exchangeable with D_2O). IR (KBr) ν 1156, 1667 and 3443 cm^{-1} attributable to C=S, C=O and NH. Anal cald for $C_{20}H_{20}N_2O_2$: C 74.98, H 6.29, N 8.74; found C 75.48, H 5.90, N 8.21 Anal cald for $C_{27}H_{26}N_4OS$: C 71.34, H 5.76, N 12.32; found C 71.68, H 6.20, N 11.97

1-(2-(1-Oxo-4-(5, 6, 7, 8-tetrahydronaphthalen-2-yl) phthalazin-1(2H)-yl) ethyl)-3-phenyl-2-thioxodihydro-pyrimidine-4, 6(1H, 5H)-dione (4)
A mixture of **(3)** (0.003 mol) 1.3 gm and (0.003 mol) 0.48 gm diethylmalonate in 20 mL ethanol was heated under reflux for 3 hs. After cooling a solid was separated and crystallized from ethanol to give **(4)**, 50 % yield, m.p. 240 ℃. MS, *m*|z (%);$M^{\cdot+}$, $M^{\cdot+}$+1 and $M^{\cdot+}$+2, 522 (1), 523 (1.5), 524 (0.6). IR (KBr) ν 1156 and 1667 cm^{-1} attributable to C=S and C=O .Anal cald for $C_{30}H_{26}N_4O_3S$: C 68.95, H 5.01, N 10.72; found C 67.48, H 5.29, N 10.21.

2[2-(Acetylamino) ethyl]-4-(5,6,7,8-tetrahydronaphthalen -2-yl)phthalazin-1(2H)-one (5).
Acetic anhydride (0.002 mol) 0.19mL was added rapidly to a boiling solution of **(2)** (0.001 mol) 0.3 gm in 20 mL ethanol was heated under reflux for 2 hs, cooled and poured on cold water to give a solid which was separated and crystallized from benzene to give **(5)**, 65 % yield, m.p. 190 ℃.). ^{1}H NMR δ: 1.2 (t, 2H, CH_2) 1.7 (s, 4H, β- methylene protons of tetryl moeity), 2.05 (s, 3H, CH_3), 2.8 (t, 6H, α- methylene protons of tetryl moiety and N-CH_2), 7.2-7.9 (2m, 7H, Ar-H), 10/29 (s, 1H, NH, exchangeable with D_2O). IR (KBr) ν 1666 and 3155 cm^{-1} attributable to C=O and NH. Anal cald for $C_{22}H_{23}N_3O_2$: C 73.11, H 6.41, N 11.63; found C 73.48, H 5.90, N 11.21

2[2-(3, 4-Methylenedioxobenzylideneamino)-ethyl]-4-(5, 6, 7, 8-tetrahydronaphthalen-2-yl)-phthalazin-2(1H)-one (6).
A mixture of **(2)** (0.001 mol) 0.3 gm and piperonaldehyde (0.001 mol) 0.18 gm in 20 mL ethanol was heated under reflux for 3 hs. After cooling a solid was separated and crystallized from ethanol to give **(6)**, 40 % yield, m.p. 220 ℃. MS, *m*|z (%);$M^{\cdot+}$, 373 (13), 276 (73) and 248 (20), 230 (17), 161 (100). IR (KBr) ν 1662 and 1675 cm^{-1} attributable to C=N and C=O. Anal cald for $C_{28}H_{25}N_3O_3$: C 74.48, H 5.58, N 9.31; found C 74.58, H 5.90, N 9.97

2-(Piperidin-1-ylmethyl)-4-(5, 6, 7, 8-tetrahydronaphth-alen-2-yl) phthalazin-1(2H) one (7)
A mixture of **(1)** (0.01 mol) 2.7 gm, 1 mL formaldehyde, few drops HCl and few drops of piperidine in 20 mL methanol was heated under reflux for 4 hs. After cooling a solid was separated and crystallized from ethanol to give **(7)**, 60 % yield, m.p. 175 ℃. MS, *m*|z (%);$M^{\cdot+}$, 373 (13), 276 (73) and 248 (20), 230 (17), 161 (100). IR (KBr) ν 1654, 1583, 2929 cm^{-1} attributable to C=O, C=N and CH. Anal cald for $C_{20}H_{20}N_2O_2$: C 74.98, H 6.29, N 8.74; found C 75.48, H

5.90, N 8.21 Anal cald for $C_{24}H_{27}N_3O$: C 77.18, H 7.29, N 11.25; found C 76.68, H 6.90, N 11.97

Ethyl 4-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl) phthalazin-2(1H)-yl)methyl)piperazine-1-carboxylate (8)
A mixture of **(1)** (0.01 mol) 2.7 gm, 1 mL formaldehyde, few drops HCl and few drops of ethyl piperazinecarboxylate in 20 mL methanol was heated under reflux for 4 hs. After cooling a solid was separated and crystallized from ethanol to give **(8)**, 60 % yield, m.p. 170 ℃. ^{1}H NMR δ: 1.1 (t, 3H, $CH_2\underline{CH_3}$), 1.8 (s, 4H, β- methylene protons), 2.8 (s, 4H, α- methylene protons), 4.1 (q, 2H, $\underline{CH_2}$ CH_3), 4.3(m, 8H of piperizyl moeity), 5.5 (s, 1H, NCH_2N), 7.2-7.8 (m, 8H, Ar-H). MS, *m*|z (%); M^+, 446 (3), 401 (2) ,3732 (3), 290 (34), 171 (69). IR (KBr) ν 1653, 1702, 2859 and 2927 cm^{-1} attributable to two C=O, and CH. Anal cald for $C_{26}H_{30}N_4O_3$: C 74.98, H 6.29, N 8.74; found C 75.48, H 5.90, N 8.21 Anal cald for $C_{24}H_{27}N_3O$: C 69.93, H 6.77, N 12.55; found C 69.23, H 6.90, N 11.97

4-(5,6,7,8-Tetrahydronaphthalen-2-yl)phthalazin-1(2H)-thione (9)
A mixture of **(1)** (0.01 mol) 2.7 gm and 2 gm of phosphorous pentasulphide in 20 mL xylene was heated under reflux for 2 hs. After cooling a solid was separated and crystallized from methanol to give **(9)**, 40 % yield, m.p. 190 ℃. MS, *m*|z (%);M^+, M^++1 and M^++2, 292 (100), 293 (20) and 294 (6) corresponding to M^+, and M^++2, 259 (21). IR (KBr) ν 1205, 1428, 2855, 2932 and 3147 cm^{-1} attributable to C=S, CH and NH. Anal cald for $C_{18}H_{16}N_2S$: C 73.94, H 5.52, N 9.58; found C 73.48, H 5.90, N 8.71

1-Hydrazinyl-4--(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydrophthalazine (10)
A mixture of **(1)** 1gm and 1 mL of hydrazine hydrate was fused for 2 hs. After cooling a solid was obtained and crystallized from ethanol to give **(10)**, 30 % yield, m.p. 195 ℃. MS, *m*|z (%);M^+,291 (26), 273 (28), 246 (30). IR (KBr) ν 3100-3300 cm^{-1}, attributed to NH and NH_2. Anal cald for $C_{18}H_{20}N_4$: C 73.94, H 6.89, N 19.16; found C 73.48, H 5.90, N 18.41.

(E)-1-(2-(4-methoxybenzylidene)(hydrazinyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-1,2-dihydrophthalazine (11)
A mixture of **(10)** (0.01 mol) 0.7 gm, (0.01 mol) 1.3 gm anisaldehyde in 20 mL ethanol was refluxed for 3 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give **(11),** 30 % yield, m.p. 140 ℃. ^{1}H NMR δ: 1.7 (s, 4H, β- methylene protons of tetryl moeity), 2.5 (s, 3H, CH_3) 2.7 (t, 4H, α- methylene protons of tetryl moiety), 7.2-7.9 (3m, 11H, Ar-H), 11.92 (s, 2H, NH, exchangeable with D_2O). MS, *m*|z (%); M^+,409 (22), 273 (18), 135 (100). IR (KBr) ν 1601, 1508 cm^{-1}, attributed to C=N. Anal cald for $C_{26}H_{26}N_4O$: C 76.07, H 6.38, N 13.65; found C 75.68, H 5.90, N 14.41.

2-(2-Hydroxyethyl)-4-(5, 6, 7, 8-tetrahydronaphtalen-2-yl) phthalazin-1(2H)-one (12)
A mixture of **(1)** (0.01 mol) 2.7 gm , (0.01 mol) 0.8 gm chloroethanol and (0.04 mol) 6.7 gm potassium carbonate in 30 mL dry acetone was refluxed for 24 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give **(13),** 50 % yield, m.p. 110 ℃. ^{1}H NMR δ: 1.7 (s, 4H, β- methylene protons of tetryl moeity), 2.7 (t, 6H, α- methylene protons of tetryl moiety and N-CH_2), 4.1 (t, CH_2 OH), 7.2-7.9 (2m, 7H, Ar-H), 8.37(s, 1H, OH, exchangeable with D_2O). MS, *m*|z (%); M^+, 320 (23), 302 (2.2) 290 (35), 276 (100), 248 (40). IR (KBr) ν 1632, 2852, 2921, and 3436 cm^{-1} attributable to C=O, CH and OH.. Anal cald for $C_{20}H_{20}N_2O_2$: C 74.98, H 6.29, N 8.74; found C 75.48, H 5.90, N 8.21.

2-(1-Hydroxyphenyl-2-yl)-4-(5,6,7,8-tetrahydro-naphtalen-2-yl)phthalazin-1(2H)-one (13a)
A mixture of **(12)** (0.01 mol) 2.7 gm, (0.01 mol) 0.9 gm of phenol in 20 mL ethanol was refluxed for 3 hs. After cooling a ppt. was formed and crystallized from ethanol to give **(13a),** 80 % yield, m.p. 240 ℃. IR (KBr) ν 1665 and 3400 cm^{-1} attributable to C=O and OH. Anal cald for $C_{26}H_{22}N_2O_2$: C 79.18, H 5.58, N 7.10; found C 79.78, H 5.9, N 7.41

2-(3,4-Dihydroxyphenethyl)-4-(5,6,7,8-tetrahydro-naphtalen-2-yl)phthalazin-1(2H)-one (13b)
A mixture of **(12)** (0.01 mol) 2.7 gm, (0.01 mol) 1 gm of catechol in 20 mL ethanol was refluxed for 3 hs. After cooling a ppt. was formed and crystallized from ethanol to give **(13a),** 80 % yield, m.p. 210 ℃. ^{1}H NMR δ: 1.7 (t, 2H, CH_2), 1,8 (s, 4H, β- methylene protons of tetryl moeity), 2.85 (t, 6H, α- methylene protons of tetryl moiety and N-CH_2), 6.64-7.9 (3m, 11H, Ar-H), 10.28 (s, 2H, OH, exchangeable with D_2O). IR (KBr) ν 1670 and 3410, 3430 cm^{-1} attributable to C=O and OH. Anal cald for $C_{26}H_{24}N_2O_3$: C 75.71, H 5.86, N 6.79; found C 76.38, H 5.29, N 6.41.

4-(2-(1-Oxo-4-(5,6,7,8-tetrahydronaphtalen-2-yl) phthalazin-2(1H)-yl)ethyl)-1,2-phenylene diacetate (14)
A mixture of **(13b)** (0.01 mol) 4 gm and 10 mL acetic anhydride was refluxed for 1 h,then poured on water, A ppt. was formed, filtered and crystallized from ethanol to give **(14),** 30 % yield, m.p. 187 ℃. IR (KBr) ν 1666 and 1761 cm^{-1} attributable to two C=O. Anal cald for $C_{30}H_{28}N_2O_5$: C 72.56, H 5.68, N 5.68; found C 72.38, H 5.29, N 6.31

(E)-ethyl-3-amino-3-(1-oxo-4-(5,6,7,8-tetrahydro-naphtalen-2-yl)phthalazin-2(1H)-yl)acrylate (15)
A mixture of **(1)** (0.01 mol) 2.7 gm, (0.01 mol) 1 gm of ethyl cyanoacetate in 20 mL ethanol was refluxed for 3 hs. After cooling a ppt. was formed and crystallized from ethanol to give **(15),** 80 % yield, m.p. 240 ℃. IR (KBr) ν 1603, 1667, 1748, 2907, 2932, 3152 and 3296 cm^{-1} attributable to C=C, two C=O, CH and NH. Anal cald for $C_{23}H_{23}N_3O_3$: C 70.93, H 5.95, N 10.79; found C 70.38, H 5.31, N 11.31

(E)-3-amino-3-(1-oxo-4-(5, 6, 7, 8-tetrahydronaphtalen-2-yl) phthalazin-2(1H)-yl)-N'-phenylacrylohydrazide (16)
A mixture of **(15)** (0.001 mol) 0.38 gm and (0.001 mol) 0.1 gm of phenyl hydrazine in 20 mL ethanol was refluxed for 3 hs. After cooling a ppt. was formed and crystallized from ethanol to give **(16),** 40 % yield, m.p. 230 ℃. ^{1}H NMR δ: 1.7 (s, 4H, β- methylene protons of tetryl moeity), 2.7 (t, 4H, α- methylene protons of tetryl moiety), 7.19-8.6 (3m, 12H Ar-H), 10.8 (broad, 4H, NH_2, 2 NH, exchangeable with D_2O). MS, *m*|z (%) M. +, 451 (6), 343 (4), 317 (4). 276(100). IR (KBr) ν 1604, 1665, 2854, 2932, 3100 and 3208 cm^{-1} attributable to C=C, C=O, CH and NH. Anal cald for $C_{27}H_{25}N_5O_2$: C 71.82, H 5.58, N 15.51; found C 71.38, H 5.29, N 16.11

2-Benzoyl-4-(5, 6, 7, 8-tetrahydronaphthalen-2-yl) phthalazin-1(2H)-one (17)

A mixture of **(1)** (0.01 mol) 2.7 gm , (0.04 mol) 5 gm benzoyl chloride and (0.04 mol) 6.7 gm potassium carbonate in 30 mL dry acetone was refluxed for 24 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give **(17),** 60 % yield, m.p. 100 ℃. IR (KBr) ν 1668, 2852 and, 2920 cm^{-1} attributable to C=O and CH. Anal cald for $C_{25}H_{20}N_2O_2$: C 78.93, H 5.30, N 7.36; found C 78.75, H 5.35, N 7.61

2-Allyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one (18)

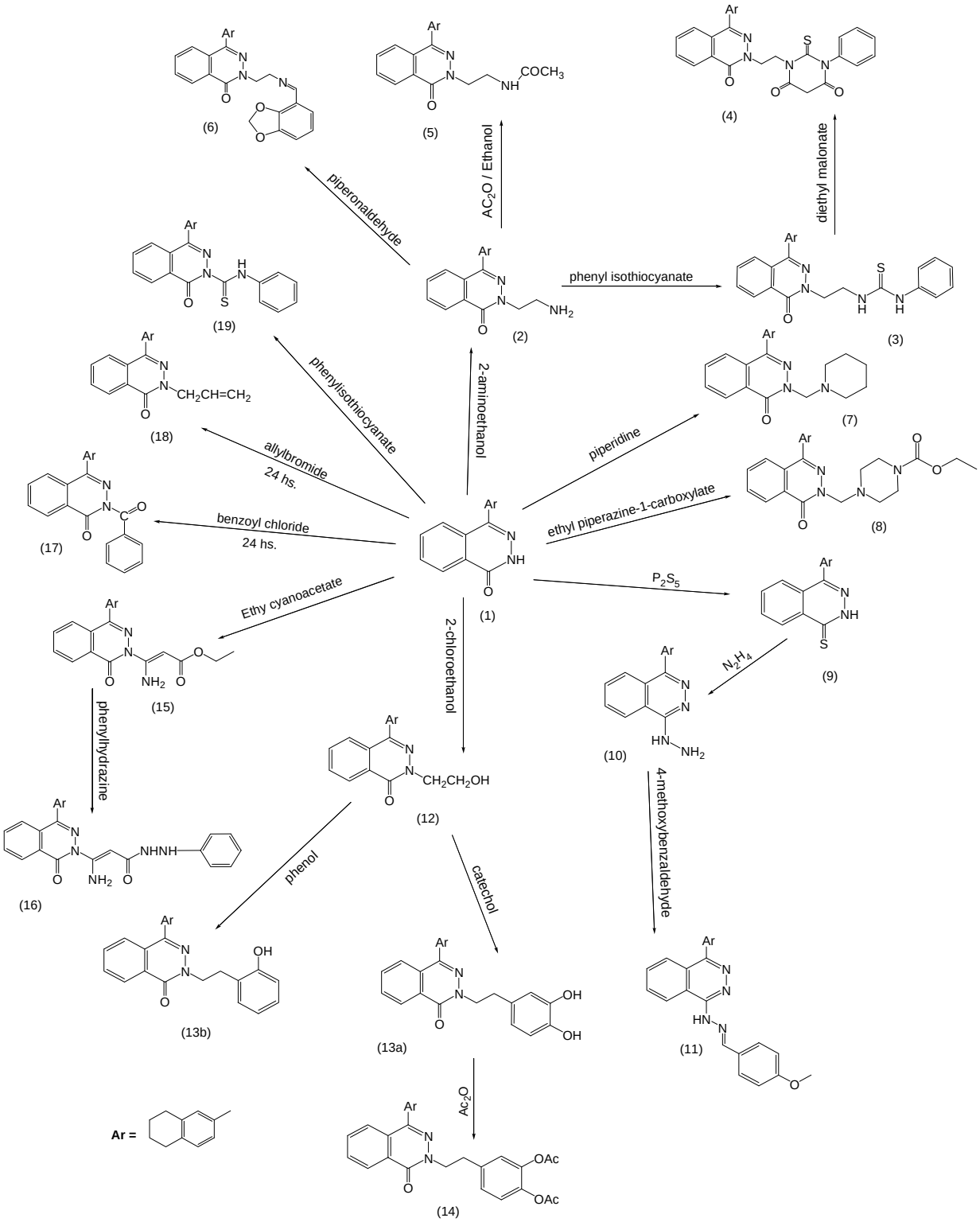
A mixture of **(1)** (0.01 mol) 2.7 gm , (0.01 mol) 1 gm allyl bromide and (0.04 mol) 6.7 gm potassium carbonate in 30 mL dry acetone was refluxed for 24 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give **(21),** 50 % yield, m.p. 110 ℃. MS, *m*|z (%); $M^{\cdot+}$, 316 (7.6), 290 (18), 276 (33). IR (KBr) ν 1660, 2853 and 2923 cm^{-1} attributable to C=O and CH. Anal cald for $C_{21}H_{20}N_2O$: C 79.72, H 6.37, N 8.85; found C 80.38, H 5.90, N 8.21

1-Oxo-N-phenyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl) phthalazin-2(1H)-carbothioamide (19).

A mixture of (**1**) (0.001 mol) 0.2 gm and (0.001mol) 0.13 gm of phenyl isothiocyanate in 20 mL methanol was refluxed for 5 hs. After evaporation of the solvent, a ppt. was formed and crystallized from ethanol to give **(19),** 30 % yield, m.p. 95 ℃. IR (KBr) ν : 1156, 1665 and 3155 cm^{-1} attributable to C=S, C=O and NH. MS, *m*|z (%); $M^{\cdot+}$, 411, (3), 412 (5) and 413 (2) corresponding to M^{+}, M^{+} +1 and M^{+}+2, 275 (100), 247 (30). Anal cald for $C_{25}H_{21}N_3OS$: C 72.97, H 5.14, N 10.21; found C 73.25, H 5.85, N 10.70

References

[1] F. Al-Assar, K. N. Zelenin, E. E. Lesiovskaya, I. P. Bezhan, B. A. Chakehir, Pharm. Chem. J. 36 (2002) 598-603.
[2] R. P. Jain, J. C. Vederas, Bioorg. Med. Chem. Lett. 14 (2004) 3655-3658.
[3] J. S. Kim, H. J. Lee, M. E. Suh, H. Y.Park Choo, S. K. Lee, H. J. Park, C. Kim, S. W. Park, C. O. Lee, Bioorg. Med. Chem. 14 (2004) 3683.
[4] A. E. Porter, A. E. Katriky, D. Bartond, W. D. Ollis, Comprehensive Organic Chemistry, Oxford (1979) 7-85.
[5] A. I. Sugimoto, Y. Eguchi, H. Tanaka, Y. Takashima, M. Ishikawa, Inst. Med. Chem. Chim. Ther. 19 (1984) 223-228.
[6] Y. Eguchi, M. Ishikawa, Chem. Pharm. Bull. 39 (1991) 1846-1848.
[7] E. Del-Olmo, B. Barboza, M. Ybarra, J. Ló pez-Perez, R. Carrón, M. Sevilla, C. boselli, A San-Feliciano, Bio. Med. Chem. Lett. 16 (2006) 2786-2787.
[8] E. N. Scott, G. Meinhardt, C. Jacques et al, Expert Opin Investig. Drugs 16 (2007) 830-835.
[9] G. Scheffler, J. Engel, B. Kutscher, W. S. Sheldrick, P. Bell, Archiv. Der. Pharmazie 321 (1988) 205-208.
[10] S. Grasso, G. De Sarro, A. De Sarro, N. Micale, M. Zappala, G. Puia, M. Baraldi, C. De Micheli, J. Med. Chem. 43 (2000) 2851-2859.
[11] Y. Nomoto, H. Obase, H. Takai, M. Teranishi, J. Nakamura, K. Kubo, Chem. Pharm. Bull. (Tokyo) 38 (1990) 2179-2182.
[12] N. Watanabe, Y. Kabasawa, Y. Takase, M. Matsukura, K. Miyazki, H. Ishihara, K. Kodama, H. Adachi, J. Med. Chem. 41 (1998) 3357-3372.
[13] M. Yamaguchi, K. Kamei, T. Koga, N. Ohi, J. Med. Chem. 36 (1993) 4052-4060.
[14] M. A. El-Hashash; D. B. Guirguis; M. A. Kadhim; J. of American Science, 9 (2013)(12)
[15] R. Cruickshank; J. P. Duguid; B. P. Marion; R. H. A. Swain; Medicinal Microbiology, twelfth ed., vol. II, Churchill Livingstone, London, (1975) pp. 196-202.



Scheme 1