Synthesis of Novel Series of Phthalazine Derivatives with Antibacterial and Antifungal Evaluation

Maher A El-Hashash1, Dalal B Guirguis*, Nayera AM Abd El-Wahed2 and Mohamed A Kadhim2

1Chemistry Department, Faculty of Science, Ain Shams University, Abassia 11566, Cairo, Egypt
2Department of Chemistry of Natural and Microbial Products, Division of Pharmaceutical Industries, National Research Center, El Behos street, Dokki, Egypt

Abstract

The oxirane derivative (2) was allowed to react with hydrazine hydrate, 4-amino benzoic acid and o-phenylene diamine to give β-hydrazine alcohol derivative (3) and β-amino derivatives (4) and (5). The hydrazide (8) reacted with glucose, phthalic anhydride and aromatic aldehydes to give the phthalazine derivatives (9), (15) and (16a-c). A new heterocyclic molecules were synthesized using ethyl acetocetate, acetyl acetone and benzoyl chloride with the hydrazide (8) to give the pyrazole derivatives (12), (14) and the oxadiazole derivative (18). 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 (1H-NMR, Mass spectrum, IR and Elementary analysis).

Keywords: Pyrazole; Epichlorohydrin; Glucose; Oxadiazole

Introduction

Phthalazin-1(2H)-ones are of considerable interest due to their anti diabetic [1], antiallergic [2], vasorelaxant [3], PDE4 inhibitors [4], VEGF (vascular endothelial group factor) receptor tyrosine kinases for the treatment of cancer [5,6], antiasthmatic agents with dual activities of thromboxane A2 (TXA2) synthetase inhibition and bronchodilation [7], herbicidal [8]. A number of established drug molecules like Hydralazine [9,10], Burdralazine [11,12], Azelastine [13,14], Ponalrest [15], and Zopolrest [16] are prepared from the corresponding phthalazines. Several phthalazine derivatives have been reported to possess antitumor [17-20], anti hypertensive [21,22], anticoagulant [23,24], antimicrobial [25], antitrypanosomal [26], and anti-inflammatory activities [27,28]. Most of the current nonsteroidal anti-inflammatory drugs (NSAIDs) show serious side effects including gastrointestinal disorders and kidney damage. These studies for developing safer NSAIDs lacking the gastrointestinal and renal side effects of current used ones have recently been of interest for many researches. Most of the classical NSAIDs exerts their side effects by inhibition of COX-1 enzyme since the COX-1 is the constitutive one that is responsible for regulation of physiological processes, and the COX-2 isomer is discovered to be the enzyme induced by an inflammatory stimuli, selective inhibition of COX-2 provides a rationale for developing anti-inflammatory and analgesic agents. Although the diaryl heterocyclic compounds are mainly studied as new class of NSAIDs without gastric side effects, many studies have also focused on a different type of compounds to develop safer NSAIDs [27]. Also in terms of this aspect, many studies have been focused on pyridazin-(3H)-ones, which are characterized to possess good analgesic and anti-inflammatory activities. Beside pyridazines, these studies have indicated that the heterocyclic ring substitutions at the six position, and the presence of acetamide side chain when linked to the lactam nitrogen of pyridazinone ring at the two position of the pyridazinone ring, improve the analgesic and anti-inflammatory activity along with nil or very low ulcerogenicity [29-34]. In view of the aforementioned facts, it seemed most interesting to synthesize some 4-(2-tetrayl)-2-substituted phthalazin-1(2H)-one derivatives with the aim to obtain more precise information about the course of reactions and biological activities.

Results and Discussion

Upon reacting (1) [35] with epichlorohydrin in the presence of anhydrous potassium carbonate in dry acetone on heating water bath afforded 2-(oxiran-2-yl methyl-4-tetrayl phthalazin-1(2H)-one) (2). The structure of (2) was inferred from correct microanalytical data as well as IR spectrum which revealed strong absorption bands at ν 1134, 1655, 2852, 2952 cm\(^{-1}\) attributable to O-C, C=O, and CH with devoid of any band for NH. 1H NMR spectrum also showed δ: 1.26 (t, 4H, β-methylene protons of tetryl moiety), 1.26 (t, 4H, α-methylene protons of tetryl moiety), 2.86 (2H, octet), 3.5 (1H, octet stereogenic protons), 3.91 (2H, oxirane proton), 5.67 (1H, oxirane proton). The reaction possibly takes place via the following mechanism (Figure 1).

The mechanism involves opening of the more reactive oxirane nucleus followed by ring closure via SN\(_2\) mechanism. The function of KCO\(_3\) is to augment the removal of leaving group (chloride ion).

Also the structure of (2) was verified chemically with nitrogen nucleophiles namely hydrazine hydrate, p-aminobenzoic acid and o-phenylene diamine. Thus when (2) reacted with hydrazine hydrate in boiling ethanol yielded the β-hydrazino alcohol 2-(4-hydrazinyl-2-hydroxybutyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one (3) in good yield with high regioselectivity with preferential attack at the nonbenzilic type terminal carbon (less hindered). The IR spectrum which revealed strong absorption bands at ν 1134, 1663, 2857, 2927 and broad peak centered at 3374 cm\(^{-1}\) attributable to O-C, C=O, CH, NH, and OH. 1H NMR spectrum also showed δ: 1.7 (s, any band for NH. 1H NMR spectrum also showed δ: 1.26 (t, 4H, β-methylene protons of tetryl moiety), 1.26 (t, 4H, α-methylene protons of tetryl moiety), 2.86 (2H, octet), 3.5 (1H, octet stereogenic protons), 4.5 (2H, diastereotopic protons), and 7.2-7.8 (m, 7H, Ar-H). The EIMS showed m/z at 332 corresponding to M\(^+\) (molecular ion peak). The reaction possibly takes place via the following mechanism (Figure 1).

*Corresponding author: Dalal B Guirguis, Chemistry Department, Faculty of Science, Ain Shams University, Abassia 11566, Cairo, Egypt, Tel: +20233335994; E-mail: dalal.guirguis@hotmail.co.uk

Received March 07, 2014; Accepted April 28, 2014; Published April 30, 2014


Copyright: © 2014 El-Hashash MA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
The previously prepared hydrazide (8) [35] namely 2-(1-oxo-4(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-yl)-acetohydrazide was allowed to react with glucose which on turn reacted with acetic anhydride afforded the corresponding sugar hydrazones E-2(1-oxo-4(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)-N'-2,3,4,5,6-pentahydroxyhexylidene)acetohydrazide and 5-2(1-oxo-4(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetamido)pentane-1,2,3,4-pentyl pentaacetate (9) and (10). The structure of (9) was inferred from correct microanalytical data as well as IR spectrum which revealed strong absorption bands at v 1625, 1643, 1687, 2917, 2938, 3313 and 3409 cm⁻¹ attributable to C=O, C=O, CH, NH, and OH. On the other hand the IR spectrum of compound (10) revealed strong absorption bands at v 1658, 1752, 2850, 2936, 3300 cm⁻¹ attributable to C=O, C=O, CH, NH and OH. The IR spectrum revealed strong microanalytical data (c.f. experimental).

Interaction of the hydrazide (8) with ethylacetoacetate in boiling ethanol for 3 hours afforded the ester derivative (E)-ethyl-3-(2-(1-oxo-4(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetamido)butanoate (11). The structure of (11) was inferred from correct microanalytical data as well as IR spectrum which revealed strong absorption bands at v 1660, 1742, 2854 and 2924 and 3211 cm⁻¹ due to two carbonyl group, CH and NH which agreed well with the proposed structure. On the other hand when the reaction was subjected for prolonged reflux (9 hours), 3-methyl-5-hydroxy pyrazole derivative 2-(2-(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)-4-(5,6,7,8-tetrahydrodnapthalen-2-yl)phthalazin-1(2H)-one (12) was obtained. The structure of the pyrazole (12) was deduced from correct microanalytical data, IR spectrum revealed strong absorption bands at v 1629, 1666 and 3200 cm⁻¹ attributed to two carbonyl groups and OH. The EIMS exhibits m/z at 414. Compound (12) present in enol form due to extended conjugation and intramolecular H-bond. Also the hydrazide (8) reacted with acetylactone in boiling ethanol for 3 hours to give the acetone derivative Z-2-(1-oxo-4(5,6,7,8-tetrahydrodnapthalen-2-yl)phthalazin-2(1H)-yl)-N'-(4-oxopentantylidene)acetohydrazide (13). The IR spectrum revealed strong absorption bands at v 1620, 1721, 2930 and 3210 cm⁻¹ attributed to two carbonyl group, CH and NH which agreed well with the proposed structure. The EIMS exhibit m/z 412 (M'-H,O). On the other hand when the reaction was carried out in boiling ethanol for 8 hours, the pyrazole derivative 2-(2-(3,5-dimethyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)-4-(5,6,7,8-tetrahydrodnapthalen-2-yl)phthalazin-1(2H)-one (14) was obtained. The IR spectrum revealed strong absorption bands at v 1654, 1680, 2925 cm⁻¹ attributed to two carbonyl groups and CH. The EIMS exhibits m/z 412 (M').

When the hydrazide (8) was allowed to react with phthalic anhydride in oil bath at 150°C, yielded the corresponding phthalimide derivative N-(1,3-dioxoisodolin-2-yl)-2-(1-oxo-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetamide (15). The structure of (15) was inferred from the IR spectrum which revealed strong absorption bands at v 1650, 1733, 1791 cm⁻¹ (mechanical coupling of imide, 2860, 2929, 2999 and 3180 cm⁻¹ attributable to C=O, CH, and NH. The EIMS showed m/z 474 (M''-4H), 333 (M''-phthalimide) as well as correct micro analytical data (c.f. experimental).

The hydrazide (8) reacted with some aromatic aldehydes namely benzaldehyde, anisaldehyde and piperonaldehyde afforded 2-(2-(2-arylmethyl diazainyl)-2-oxoethyl)-4(5,6,7,8-tetrahydrodnapthalen-2-yl)phthalazin-1(2H)-one namely N'-benzylidene-2-(4-(1,2,3,4-tetrahydrodnapthalen-2-yl)-1-oxophthalazin-2(1H)-yl)acetohydrazide, N'-4-methoxybenzylidene-2-(4-(1,2,3,4-tetrahydrodnapthalen-2-yl)-1-oxophthalazin-2(1H)-yl)acetohydrazide, (Z)-N'- (benzoyl)[(1,3)dioxol-4-methylene]-2-(1-oxo-4(5,6,7,8-tetrahydrodnapthalen-2-yl)phthalazin-2(1H)-yl)acetohydrazide (16a-c). The structure of (16a-c) was inferred from
The phthalazinone acetic acid hydrazide (8) used as versatile starting material for the synthesis of several heterocyclic derivatives through its reactions with a variety of activated reagents. Thus the hydrazide (8) reacted with benzoyl chloride to give N[(2-(1-oxo-4-(1,2,3,4-tetrahydro-2-yl)phthalazin-2(1H)-yl)]benzoyl acetohydrazide (18). The IR spectrum of (18) revealed strong absorption bands at ν 1615, 1687, 1715 cm⁻¹ attributed to three carbonyl groups (high values due to mutual inductions between the groups), 2925 and 3234 and cm⁻¹ attributable to CH and NH. The EIMS showed m/z 434 (M⁺-H₂O) in addition to elemental analysis as well as ¹H NMR (c.f. experimental). On the other hand when the hydrazide (8) reacted with benzoyl chloride in pyridine gave the cyclized oxadiazolophthalazine 2-(5-phenyl-2,3-dihydro-1,3,4-oxadiazol-2-yl)methyl)-4-(5,6,7,8-tetrahydro-2-yl)phthalazin-1(2H)-one (17). The IR spectrum of (17) exhibited band at ν 1660 cm⁻¹ attributed to C=O, and devoid any band for NH (scheme 1).

**Scheme 1: The synthesis of several heterocyclic derivatives.**

**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.

**Agar Diffusion Medium**

All compounds were screened in vitro for their antimicrobial activity against, by agar diffusion method [36]. 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 observe zone of inhibition is presented in Table 1.

**Experimental**

All melting points are uncorrected and were measured on an
2-(Oxiran-2yl methyl-4-tetryl phthalazin-1(2H)-one [2]

A mixture of (1) (0.01 mol) (2.7 g), epichlorohydrin (0.01 mol) (0.8 g) and potassium carbonate (0.04 mol) (6.7 g) in 30 mL dry acetone was refluxed for 24 hs. The resultant solid was filtered and crystallized from ethanol to give (2), 50% yields as colorless crystals mp 120-121°C. 1H NMR (DMSO-d6, 300 MHZ) δ: 1.7 (s, 4H, β- methylene protons of tetryl moeity), 7.2-7.8 (m, 7H, Ar-H). IR (KBr) γ: 1655(C=O), 1579 (C=N), 3459 (OH), 3360 (NH), 1670, 1629 (C=O), 15798 (C=N), 1158 (C-O) cm⁻¹ MS, m/z (%); M⁺, 441 (13), 290 (22), 276 (100). Anal cald for C₂₂H₂₆N₄O₂: C 70.43, H 6.35, N 14.40

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

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Microorganism</th>
<th>Gram +ve bacteria</th>
<th>Gram –ve bacteria</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacillus subtilis</td>
<td>Staphylococcus aureus</td>
<td>Escherichia coli</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>1</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
<tr>
<td>2</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
<tr>
<td>8b</td>
<td>+ ve</td>
<td>+ ve</td>
<td>+ ve</td>
<td>+ ve</td>
</tr>
<tr>
<td>7</td>
<td>++ ve</td>
<td>++ ve</td>
<td>++ ve</td>
<td>++ ve</td>
</tr>
<tr>
<td>8</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
<tr>
<td>9</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
<tr>
<td>12</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
<tr>
<td>13</td>
<td>+ ve</td>
<td>+ ve</td>
<td>+ ve</td>
<td>+ ve</td>
</tr>
<tr>
<td>15</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
<tr>
<td>16c</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
<tr>
<td>17</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
<tr>
<td>18</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
<td>+++ ve</td>
</tr>
</tbody>
</table>

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 Merck TLC aluminum sheets silica gel 60 F 254 with detection by UV quenching at 254 nm. IR spectra were measured on a Unicam SP-1200 spectrophotometer using KBr wafer technique. 1H NMR spectra were measured in DMSO-d6 on a Varian plus instrument operating at 70 eV in El mode. MS, m/z (%); M⁺, 441 (13), 290 (22), 276 (100). Anal cald for C₂₂H₂₆N₄O₂: C 70.43, H 6.35, N 14.40

2-(Hydrazinyl-2-oxo-2-hydrosylbutyl)-4-(5,6,7,8-tetrahydrophthalen-2-yl)phthalazin-1(2H)-one [3]

A mixture of (2) (0.01 mol) (3.3 g) and o-phenylenediamine (0.01 mol) (14 g) in 30 mL ethanol was refluxed for 3 hs. The resultant solid was filtered and crystallized from ethanol to give [4], 40% yields as colorless crystals mp 78°C. IR (KBr) γ: 3459 (OH), 3360 (NH), 1670, 1629 (C=O), 15798 (C=N), 1158 (C-O) cm⁻¹ MS, m/z (%); M⁺, 469 (1), 451 (2), 276 (5), 248 (2), 121 (100). Anal cald for C₂₉H₂₈N₄O₂: C 72.03, H 6.04, N 8.69; found C 71.75, H 6.25, N 8.31

2-(Hydrazinyl-2-hydroxybutyl)-4-(5,6,7,8-tetrahydrophthalen-2-yl)phthalazin-1(2H)-one [5]

A mixture of (2) (0.01 mol) (3.3 g) and hydrazine hydrate (0.01 mol, 1.2 g) was refluxed in 20 mL of absolute ethanol for 3 hs. The resultant solid was filtered and crystallized from ethanol to give [6], 40% yield as colorless crystals mp 78°C. IR (KBr) γ: 3459 (OH), 3360 (NH), 1670, 1629 (C=O), 15798 (C=N), 1158 (C-O) cm⁻¹ MS, m/z (%); M⁺, 469 (1), 451 (2), 276 (5), 248 (2), 121 (100). Anal cald for C₂₉H₂₈N₄O₂: C 72.03, H 6.04, N 8.69; found C 71.75, H 6.25, N 8.31

2-(Hydroxy-3-(2-hydrosylbenzylideneamino)phenylamino)propyl)-4-(5,6,7,8-tetrahydrophthalen-2-yl)phthalazin-1(2H)-one [6a]

A mixture of (5) (0.01mol, 4.5 g) and 1-naphthaldehyde (0.01 mol, 1.5 g), was refluxed in 20 mL of absolute ethanol for 3 hs. The solid obtained upon cooling was collected by filtration, dried, and crystallized from ethanol to give [6a], 60% yield, mp 195°C , IR ν: 1650, 1687, 3052 and 3400 cm⁻¹ attributable to C=N, C=O, CH, NH, and OH. Anal cald for C₃₈H₃₄N₄O₂: C 73.98, H 6.65, N 12.33; found C 73.43, H 6.25, N 11.72

2-(Hydroxy-3-(2-(naphtmetylenecarnimo)phenylamino) propyl)-4-(5,6,7,8-tetrahydrophthalen-2-yl)phthalazin-1(2H)-one [6b]

A mixture of (5) (0.01mol, 4.5 g) and 2-hydroxy benzaldehyde (salicylaldehyde) (0.01mol, 1.2g), was refluxed in 20 mL of absolute ethanol for 3 hs. The solid obtained upon cooling was collected by filtration, dried, and crystallized from the ethanol to give [6b], mp 235°C , yield 50% IR: ν 1650, 1687, 3052, cm⁻¹ attributable to C=N, C=O, CH, NH, and OH.
C=O, CH, NH, and OH. Anal cald for C\textsubscript{19}H\textsubscript{15}N\textsubscript{2}O\textsubscript{3}: C 74.98, H 5.92, N 10.29; found C 75.32, H 6.15, N 9.71

E-2(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)-N'-(2,3,4,5,6-pentahydropyrimidin-4(3H)-yl)acetohydrazide[9]

A mixture of (8) (0.001 mol) (0.3 g) and glucose (0.001 mol) (0.8 g) in 30 mL ethanol was refluxed for 3 hs and cooled at room temperature. The resultant solid was filtered and crystallized from ethanol to give (9), 70% yields as colorless crystals mp 200°C. IR (KBr) γ: 3409, 3313 (OH) (NH), 2917 (CH) 1687, 1643 (C=O), 1574 (C=N) cm\textsuperscript{-1}. Anal cald for C\textsubscript{29}H\textsubscript{28}N\textsubscript{4}O\textsubscript{3}: C 69.53, H 5.12, N 12.43. Found C 69.32, H 5.52, N 12.82

2-(2-(3,5-Dimethyl-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one [14]

A mixture of (8) (0.001 mol) (0.3 g) and acetyl acetone (0.001 mol) (0.1 g) in 20 mL n-butanol was refluxed for 10 hs. The resultant solid was filtered and crystallized from ethanol to give (14), 50% yields as colorless crystals mp 130-135°C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 300 MHz) δ: 1.644 (s, 3H, methyl), 1.663 (s, 3H, methyl), 1.72 (m, 4H, methylene), 1.76 (2H, 5.8 (s, 2H), 4.89 (s, 2H, CH\textsubscript{2}O), 7.27-7.92 (m, 7H, Ar-H). IR (KBr) γ: 1680, 1654 (C=O), 1583 (C=N) cm\textsuperscript{-1}. MS, m/z (%): M+ 474 (9), 333 (21), 313 (21), 289 (100), 276 (22), 247 (42), 105 (25). Anal cald for C\textsubscript{35}H\textsubscript{38}N\textsubscript{4}O\textsubscript{12}: C 72.43, H 6.33, N 13.52; found C 72.25, H 5.92, N 14.1.

N-(1,3-dioxoisooindolin-2-yl)-2-(1-oxo-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetamide [15]

A mixture of (8) (0.001 mol) (0.3 g) and phthalic anhydride (0.001 mol) (0.14 g) in 15 mL acetic acid was refluxed for 8 hs and cooled at room temperature. The resultant solid was filtered and crystallized from ethanol to give (15), 60% yield as colorless crystals mp 165°C. IR (KBr) γ: 3180 (NH), 1793, 1733, 1650 (C=O), 1579 (C=N) cm\textsuperscript{-1}. MS, m/z (%): M+ 474 (9), 333 (21), 313 (21), 289 (100), 276 (22), 247 (42), 105 (25). Anal cald for C\textsubscript{25}H\textsubscript{26}N\textsubscript{4}O\textsubscript{3}: C 70.27, H 4.46, N 11.71; found C 70.35, H 5.12, N 12.43.

N'-benzylidene-2-(1,2,3,4-tetrahydronaphthalen-2-yl)-1-oxophthalazin-2(1H)-yl)acetohydrazide [16a]

A mixture of (7) (0.001 mol) (0.3 g) and benzaldehyde (0.001mol) (0.1g) in 20 mL ethanol was refluxed for 3 hs and cooled at room temperature. The resultant solid was filtered and crystallized from ethanol to give (16a), 40% yield as colorless crystals mp 188-190°C. IR (KBr) γ: 3408 (NH), 1696, 1647 (C=O), 1574 (C=N) cm\textsuperscript{-1}. Anal cald for C\textsubscript{29}H\textsubscript{28}N\textsubscript{4}O\textsubscript{7}: C 61.17, H 5.92, N 10.97; found C 60.88, H 5.46, N 10.50.

2-(2-(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one [16b]

A mixture of (7) (0.001 mol) (0.3 g) and p-methoxybenzaldehyde (0.001mol) (0.14g) in 20 mL acetic acid was refluxed for 8 hs and cooled at room temperature. The resultant solid was filtered and crystallized from ethanol to give (16b), 60% yields as colorless crystals mp 140°C. IR (KBr) γ: 3195 (NH), 1663, 1603 (C=O), 1578 (C=N) cm\textsuperscript{-1}. Anal cald for C\textsubscript{34}H\textsubscript{25}N\textsubscript{4}O\textsubscript{5}: C 74.29, H 5.54, N 12.84; found C 74.57, H 5.32, N 12.61.

N'-4-methoxybenzylidene-2-(4-(1,2,3,4-tetrahydronaphthalen-2-yl)-1-oxophthalazin-2(1H)-yl)acetohydrazide [16b]

A mixture of (8) (0.001 mol) (0.3 g) and p-methoxybenzaldehyde (0.001mol) (0.13 g) in 20 mL benzyl alcohol was refluxed for 8 hs and cooled at room temperature. The resultant solid was filtered and crystallized from ethanol to give (16b), 30% yields as colorless crystals mp 260°C. IR (KBr) γ: 3408 (NH), 1696, 1647 (C=O), 1574 (C=N) cm\textsuperscript{-1}. Anal cald for C\textsubscript{34}H\textsubscript{25}N\textsubscript{4}O\textsubscript{5}: C 74.29, H 5.54, N 12.84; found C 74.57, H 5.32, N 12.61.

(Z)-N'-([benzo[d][1,3]dioxol-4-ylmethylene]-2-(1-oxo-tetrahydronaphthalen-2-yl)-1-oxophthalazin-2(1H)-yl)acetohydrazide [16c]

A mixture of (8) (0.001 mol) (0.3 g) and piperonaldehyde (0.001mol) (0.18 g) in 20 mL ethanol was refluxed for 3 hs and cooled at room temperature. The resultant solid was filtered and crystallized from ethanol to give (16c), 40% yields as colorless crystals mp 230°C. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 300 MHz) δ: 1.1 (t, 4H, β methylene of tetryl moeity), 1.644 (s, 3H, methyl), 1.663 (s, 3H, methyl), 1.72 (m, 4H, methylene), 1.76 (2H, 5.8 (s, 2H), 1.66 (s, 2H, NCH\textsubscript{2}O), 7.27-7.92 (m, 7H, Ar-H). IR (KBr) γ: 3480 (NH), 1669, 1647 (C=O), 1574 (C=N) cm\textsuperscript{-1}. Anal cald for C\textsubscript{35}H\textsubscript{38}N\textsubscript{4}O\textsubscript{12}: C 72.43, H 6.33, N 13.52; found C 72.25, H 5.92, N 14.1.

Z-2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)N'-(4-oxopentan-2-yldiene) acetohydrazide [13]

A mixture of (8) (0.001 mol) (0.3g) and acetyl acetone (0.001 mol) (0.1g) in 20 mL ethanol was refluxed for 3 hs. The resultant solid was filtered and crystallized from ethanol to give (13), 50% yields as colorless crystals mp 87-88°C. IR (KBr) γ: 3210 (NH), 1742, 1660 (C=O), 1582 (C=N) cm\textsuperscript{-1}. MS, m/z (%): M+ 430 (1), 415 (5), 316 (100), 289 (50), 262 (15). Anal cald for C\textsubscript{25}H\textsubscript{24}N\textsubscript{4}O\textsubscript{3}: C 69.75, H 5.09, N 13.01; found C 70.35, H 5.52, N 12.82.
A mixture of (8) (0.001 mol) (0.3 g) and benzoyl chloride (0.001 mol) (0.14 g) in 20 mL ethanol was refluxed for 3 hs and cooled at room temperature. The resultant solid was filtered and crystallized from ethanol to give [18]. 30% yield as colorless crystals mp 243°C. IR (KBr) γ: 1660 (C=O), 1582 (C=N), 1205 (C-O) cm⁻¹. MS, m/z (m, 13H, Ar-H), 10.3 (s, 2H, NH, exchangeable with water). IR (KBr) γ: 3234 (NH), 1715, 1687, 1651 (C=O), 1581 (C=N) cm⁻¹. Anal cald for C₂₇H₂₄N₄O₂: C 74.29, H 5.54, N 12.84; found C 74.75, H 5.62, N 13.22.

References
