

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

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## Abstract

The oxirane derivative (2) was allowed to react with hydrazine hydrate, 4-aminobenzoic acid and o-phenylene diamine to give  $\beta$ -hydrazine alcohol derivative (3) and  $\beta$ -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 acetoacetate, 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 antidiabetic [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 phthalazinones. Several phthalazine derivatives have been reported to possess antitumor [17-20], antihypertensive [21,22], anticovulsant [23,24], antimicrobial [25], antitypanosomal [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 isoform is the constitutive one that is responsible for regulation of physiological processes, and the COX-2 isoform is discovered to be the enzyme induced by a 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 pyridazinones, 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-teteryl)-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-teteryl 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  $\nu$  1134, 1655, 2852, 2952  $\text{cm}^{-1}$  attributable to O-C, C=O, and CH with devoid of any band for NH. <sup>1</sup>H NMR spectrum also showed  $\delta$ : 1.26 (t, 4H,  $\beta$ -methylene protons of teteryl moiety), 1.26 (t, 4H,  $\alpha$ -methylene protons of teteryl 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<sup>+</sup>(molecular ion peak). 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<sub>2</sub> mechanism. The function of KCO<sub>3</sub> 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  $\beta$ -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 nonbenzyl type terminal carbon (less hindered). The IR spectrum which revealed strong absorption bands at  $\nu$  1158, 1663, 2857, 2927 and broad peak centered at 3374  $\text{cm}^{-1}$  attributable to O-C, C=O, CH, NH, and OH. <sup>1</sup>H NMR spectrum also showed  $\delta$ : 1.7 (s,

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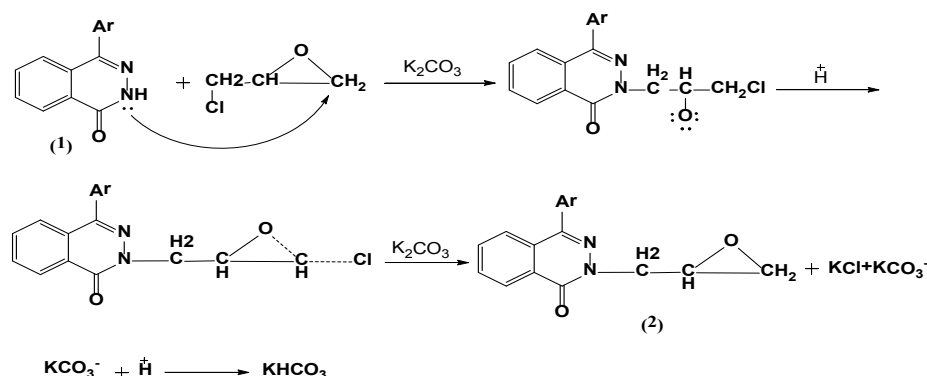


Figure 1: [4-(2-teteryl)-2-substituted phthalazin-1(2H)-one] derivatives.

4H,  $\beta$ -methylene protons of tetrylmoeity), 2.8 (s, 4H,  $\alpha$ -methylene protons of tetryl moeity), 3.7 (m, 1H, stereogenic protons), 4.5 (m, 4H, diastereotopic protons), 7.2-7.8 (m, 7H, Ar-H), 8.5-(2, 2H, NH<sub>2</sub>), and 10.4 (s, 1H, NH). Also upon interaction of oxirane derivative (2) the  $\beta$ -amino alcohol derivative 4-(3-hydroxy-4(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)butyl amino)benzoic acid (4). The reaction exhibited regioselective hetero ring opening at carbon atom. Since the  $\beta$ -amino alcohol are versatile compounds with pharmaceutical and biological importance, this prompted us to extend the reaction of oxirane derivative (2) with *o*-phenylene diamine with the aim of obtaining the  $\beta$ -amino alcohol 2-(4-(2-aminophenylamino)-2-hydroxybutyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one (5). The reaction takes place via hetero ring opening of oxirane nucleus regioselectivity at the primary carbon atom leading to the desired product (5). EIMS showed  $m/z$  at 441 corresponding to  $M^+$  (molecular ion peak) at 332 corresponding to  $M^+$  (molecular ion peak). Also the <sup>1</sup>H NMR and IR spectra were in good agreement with the desired structure (c.f. experimental). The structure of (5) was inferred chemically via its interaction with aromatic aldehydes namely naphthaldehyde and salicylaldehyde (6a,b) showing strong absorption bands at  $\nu$  1650, 1687, 3052,  $\text{cm}^{-1}$  attributable to C=N, C=O, CH, NH, and OH.

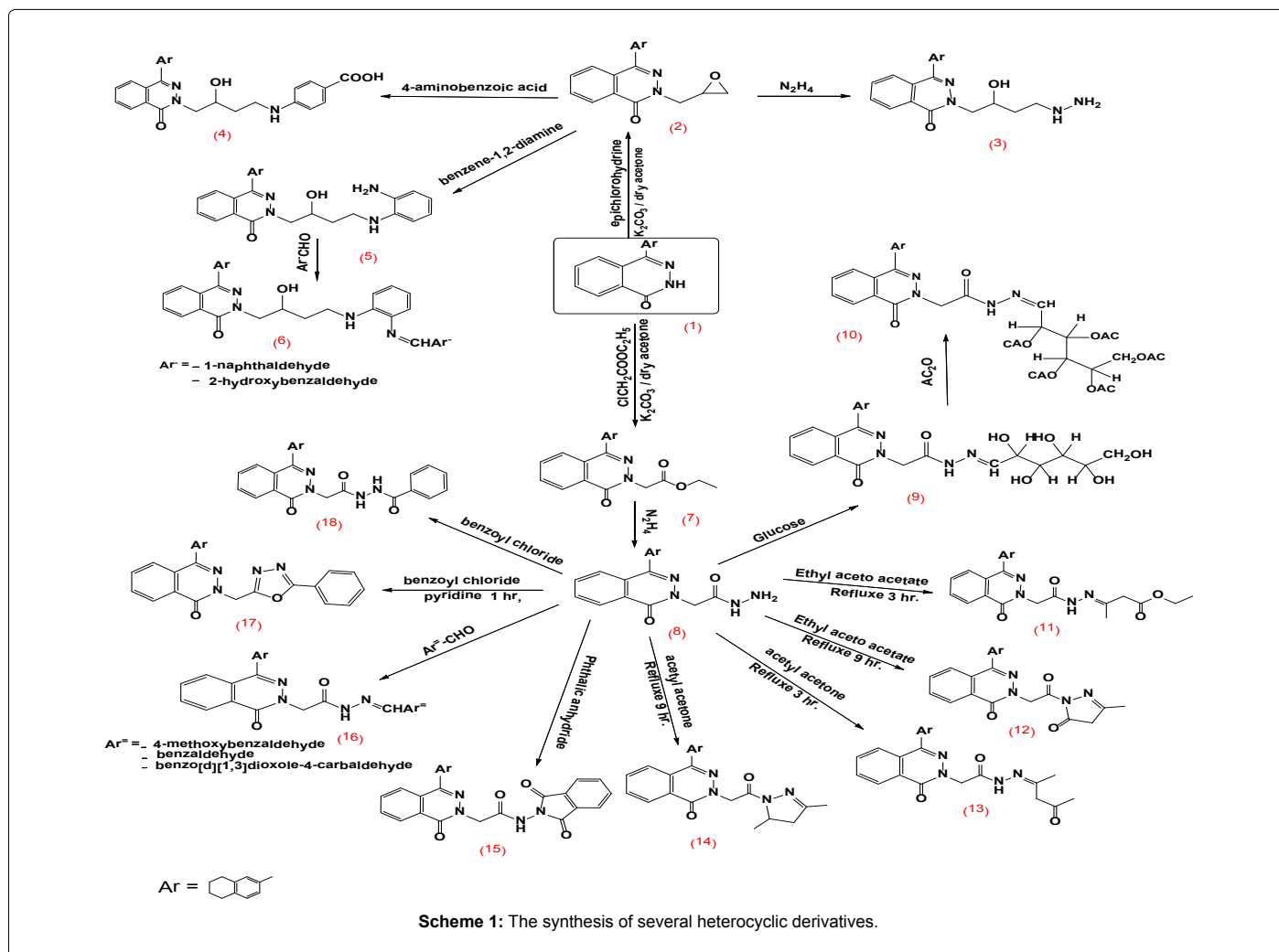
The previously prepared hydrazide (8) [35] namely 2-(1-oxo-4(5,6,7,8-tetrahydronaphthalen-2-yl)-phthalazin-2(1H)-yl) acetohydrazide was allowed to react with glucose which on turn reacted with acetic anhydride afforded the corresponding sugar hydrazones E-2(1-oxo-4(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)-N<sup>2</sup>-(2,3,4,5,6-pentahydroxyhexylidene)acetohydrazide and 5-2(2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetyl)hydrazono)pentane-1,1,2,3,4-pentyl pentaacetate (9) and (10). The structure of (9) was inferred from correct microanalytical data as well as IR spectrum which revealed strong absorptipn bands at  $\nu$  1625, 1643, 1687, 2917, 2938, 3313 and 3409  $\text{cm}^{-1}$  attributable to C=N, C=O, CH, NH, and OH. On the other hand the IR spectrum of compound (10) revealed strong absorptipn bands at  $\nu$  1658, 1752, 2860, 2936, 3300  $\text{cm}^{-1}$  attributed to C=N, C=O, CH, NH and devoid any band for OH. Also the <sup>1</sup>H NMR was in good agreement with the desired structure (c.f. experimental).

Interaction of the hydrazide (8) with ethylacetoacetate in boiling ethanol for 3 hours afforded the ester derivative (E)-ethyl-3-(2-(2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetyl)hydrazono)butanoate (11). The structure of (11) was inferred from correct microanalytical data as well as IR spectrum which revealed

strong absorption bands at  $\nu$  1660, 1742, 2854 and 2924 and 3211  $\text{cm}^{-1}$  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-tetrahydronaphthalen-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  $\nu$  1629, 1666 and 3200  $\text{cm}^{-1}$  attributed to two carbonyl group 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 acetylacetone in boiling ethanol for 3 hours to give the acetone derivative Z-2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)-N<sup>2</sup>-(4-oxopentane-2-ylidene)acetohydrazide (13). The IR spectrum revealed strong absorption bands at  $\nu$  1660, 1721, 2930 and 3210  $\text{cm}^{-1}$  attributed to two carbonyl groups, CH and NH which agreed well with the proposed structure. The EIMS exhibit  $m/z$  412 ( $M^+$ -H<sub>2</sub>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-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one (14) was obtained. The IR spectrum revealed strong absorption bands at  $\nu$  1654, 1680, 2925  $\text{cm}^{-1}$  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-dioxoisindolin-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  $\nu$  1650, 1733, 1791  $\text{cm}^{-1}$  (mechanical coupling of imide moeity), 2860, 2929, 2999 and 3180  $\text{cm}^{-1}$  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-(aryl)methyl diaziny)l)-2-oxoethyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one namely N<sup>2</sup>-benzylidene-2-(4-(1,2,3,4-tetrahydronaphthalen-2-yl)-1-oxophthalazin-2(1H)-yl)acetohydrazide, N<sup>2</sup>-4-methoxybenzylidene-2-(4-(1,2,3,4-tetrahydronaphthalen-2-yl)-1-oxophthalazin-2(1H)-yl)acetohydrazide, (Z)-N<sup>2</sup>-(benzo[d][1,3]dioxol-4-ylmethylene)2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetohydrazide (16a-c). The structure of (16a-c) was inferred from



correct microanalytical and IR spectrum which revealed strong absorption bands in the region  $\nu$  1660-1647, 1669-1664, and 3196-3190  $\text{cm}^{-1}$  attributed C=O and NH.

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<sup>2</sup>-(1-oxo-4-(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)benzoyl aceto hydrazide (18). The IR spectrum of (18) revealed strong absorption bands (high values due to mutual inductions between the groups), 2925 and 3234 and  $\text{cm}^{-1}$  attributable to CH and NH. The EIMS showed  $m/z$  434 ( $\text{M}^+ - \text{H}_2\text{O}$ ) in addition to elemental analysis as well as  $^1\text{H}$  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-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one (17). The IR spectrum of (17) exhibited band at  $\nu$  1660  $\text{cm}^{-1}$  attributed to C=O, and devoid any band for NH (scheme 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.

### 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  $\mu\text{g}/\text{ml}$ ) and Fusidic acid (50  $\mu\text{g}/\text{ml}$ ) 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

Compounds	Microorganism					
	Gram +ve bacteria		Gram -ve bacteria		Fungi	
	<i>Bacillus subtilis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Candida albicans</i>	<i>Aspergillus niger</i>
1	++++ ve	+++ ve	++++ ve	++++ ve	+++ ve	+ve
2	++++ ve	+++ ve	++++ ve	++++ ve	+++ ve	+ve
6b	+ ve	+ ve	+ ve	+ ve	+ ve	-ve
7	++ ve	++ ve	++ ve	++ ve	++ ve	-ve
8	++++ ve	+++ ve	++++ ve	++++ ve	+++ ve	+ve
9	++++ ve	+++ ve	++++ ve	++++ ve	+++ ve	+ve
12	++++ ve	+++ ve	++++ ve	++++ ve	+++ ve	+ve
13	+ ve	+ve	+ve	+ve	+ve	-ve
15	++++ ve	+++ ve	++++ ve	++++ ve	+++ ve	+ve
16c	++++ ve	+++ ve	++++ ve	++++ ve	+++ ve	+ve
17	++++ ve	+++ ve	++++ ve	++++ ve	+++ ve	+ve
18	+++ ve	++ ve	+++ ve	+++ ve	++ ve	-ve

Highly active (++++) = (inhibition zone > 20 mm)  
 Moderately active (+++) = (inhibition zone 16- 20 mm)  
 Slightly active (++) = (inhibition zone 13 - 15 mm)  
 Weakly active (+) = (inhibition zone 11 - 12 mm)  
 Inactive = (inhibition zone < 11 mm)

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

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<sub>254</sub> with detection by UV quenching at 254 nm. IR spectra were measured on a Unicam SP-1200 spectrophotometer using KBr wafer technique. <sup>1</sup>H NMR spectra were measured in DMSO-d<sub>6</sub> 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-(Oxiran-2-yl methyl-4-teteryl 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. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ: 1.26 (t, 4H, β- methylene protons of teteryl moiety), 1.26 (t, 4H, α- methylene protons of teteryl moiety), 2.86 (2H, octet), 3.5 (1H, octet stereogenic protons), 4.5 (2H, diastereotopic protons), 7.2-7.8 (m, 7H, Ar-H). IR (KBr) γ: 1655(C=O), 1579 (C=N), 1134 (C-O) cm<sup>-1</sup>; MS, m/z (%); M<sup>+</sup>, 332 (14), 290 (22), 276 (100). Anal cald for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>: C 75.87, H 6.07, N 8.43; found C 76.23, H 6.15, N 9.72

## 2-(4-Hydrazinyl-2-hydroxybutyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one [3]

A mixture of (2) (0.01 mol) (3.3 g) and 3 mL hydrazine hydrate in 30 mL ethanol was refluxed for 3 hs. The resultant solid was filtered and crystallized from ethanol to give (3), 30% yield as colorless crystals mp 85°C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ: 1.7 (s, 4H, β- methylene protons of teteryl moiety), 2.8 (s, 4H, α- methylene protons of teteryl moiety), 3.7 (m, 1H, octet stereogenic protons), 4.5 (m, 4H, diastereotopic protons), 7.2-7.8 (2m, 8H, Ar-H), 8.5 (s, 2H, NH<sub>2</sub>, exchangeable with water), 10.4 (s, 1H, NH, exchangeable with water). IR (KBr) γ: 3376 (OH), 2927, 2857 (NH), 1669, 1647 (C=O), 1574 (C=N) cm<sup>-1</sup>. Anal cald for C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>O<sub>2</sub>: C 69.82, H 6.92, N 14.80; found C 70.43, H 6.35, N 14.40

## 4-(3-Hydroxy-4(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)butyl amino)benzoic acid [4]

A mixture of (2) (0.001 mol) (0.3 g) and p-aminobenzoic acid

(0.001 mol) (0.14 g) in 30 mL ethanol was refluxed for 3 hs. The resultant solid was filtered and crystallized from ethanol to give [4], 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<sup>-1</sup> MS, m/z (%); M<sup>+</sup>, 469 (1), 451 (2), 276 (5), 248 (2), 121 (100). Anal cald for C<sub>29</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>: C 72.03, H 6.04, N 8.69; found C 71.75, H 6.35, N 8.31

## 2-(4-(2-Aminophenylamino)-2-hydroxybutyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one [5]

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 [5], 40% yields as colorless crystals mp 78°C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ: 1.2 (s, 4H), 2.48-2.8 (m, 8H, 4-methylene), 3.27 (s, 2H, NH<sub>2</sub> exchangeable with water), 4.31 (s, methine proton), 6.3-7.26 (m, 11H, Ar-H), 7.45 (s, 1H, NH), 7.9 (s, 1H, OH, exchangeable with water). IR (KBr) γ: 3384, 3362 (NH<sub>2</sub>), 3287 (OH), 3280 (NH), 1633 (C=O), 1589 (C=N) cm<sup>-1</sup> MS, m/z (%); M<sup>+</sup>, 441 (13), 290 (16), 104 (21). Anal cald for C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>2</sub>: C 73.98, H 6.65, N 12.33; found C 73.43, H 6.25, N 11.72

## 2-(2-Hydroxy-3-(2-(naphthylamino)phenylamino)propyl)-4-(5,6,7,8-tetrahydronaphthalen-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<sup>-1</sup> attributable to C=N, C=O, CH, NH, and OH. Anal cald for C<sub>38</sub>H<sub>34</sub>N<sub>4</sub>O<sub>2</sub>: C 78.87, H 5.92, N 9.68; found C 79.28, H 5.36, N 10.1

## 2-(2-Hydroxy-3-hydroxybenzylideneamino)phenylamino)propyl)-4-(5,6,7,8-tetrahydronaphthalen-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<sup>-1</sup> attributable to C=N,

C=O, CH, NH, and OH. Anal calcd for  $C_{34}H_{32}N_4O_3$ : 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-pentahydroxyhexylidene)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)  $\gamma$ : 3409, 3313 (OH) (NH), 2917 (CH) 1687, 1643 (C=O), 1574 (C=N)  $cm^{-1}$ . Anal calcd for  $C_{26}H_{30}N_4O_7$ : C 61.17, H 5.92, N 10.97; found C 60.88, H 5.46, N 10.50

### **5-2(2-(1-Oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetyl)hydrazono)pentane-1,1,2,3,4-pentyl pentaacetate [10]**

A mixture of (9) (0.001 mol) (0.4 g) and 10 mL acetic anhydride was refluxed for 1 h, poured on water. The resultant solid was filtered and crystallized from benzene to give [10], 40% yield as colorless crystals mp 160-161°C.  $^1H$  NMR (DMSO- $d_6$ , 300  $MHz$ )  $\delta$ : 1.72 (m, 4H, methylene), 2.2 (s, 1H,  $CH_3CO$ ), 4.13-4.16 (m, methine and methylene  $CH_2O$ ), 4.89 (s, 2H,  $NCH_2CO$ ), 5.36 (s, 1H, azamethine), 7.27-7.92 (m, 7H, Ar-H), 8.36 (s, 1H, NH, exchangeable with water). IR (KBr)  $\gamma$ : 3300, 2936, (NH), 2860 (CH), 1752, 1658 (C=O), 1582 (C=N)  $cm^{-1}$ . Anal calcd for  $C_{35}H_{38}N_4O_{12}$ : C 59.48, H 5.42, N 7.93; found C 58.9, H 5.82, N 7.45.

### **(E)-ethyl-3-(2-(2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetyl)hydrazono)butanoate [11]**

A mixture of (8) (0.001 mol) (0.34 g) and ethyl acetoacetate (0.001 mol) (0.13 g) in 20 mL ethanol was refluxed for 3 hs. The resultant solid was filtered and crystallized from ethanol to give (11), 40% yield as colorless crystals mp 160-162 °C. IR (KBr)  $\gamma$ : 3211 (NH), 1742, 1660, (C=O), 1581 (C=N)  $cm^{-1}$ . Anal calcd for  $C_{26}H_{28}N_4O_4$ : C 67.81, H 6.13, N 12.17; found C 67.35, H 5.9, N 11.

### **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 [12]**

A mixture of (8) (0.01 mol) (3.4 g) and ethyl acetoacetate (0.01 mol) (1.3 g) in 30 mL ethanol was refluxed for 9 hs. The resultant solid was filtered and crystallized from ethanol to give (12), 50% yields as colorless crystals mp 185-187°C. IR (KBr)  $\gamma$ : 1666, 1626 (C=O), 1583 (C=N)  $cm^{-1}$ . MS,  $m/z$  (%);  $M^+$ , 414 (46), 399 (46), 371 (20), 289 (15), 125 (44), 97 (100). Anal calcd for  $C_{24}H_{22}N_4O_3$ : C 69.55, H 5.35, N 13.52; found C 68.35, H 5.52, N 12.82

### **Z-2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)-N'-(4-oxopentan-2-ylidene)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% yield as colorless crystals mp 87-88°C. IR (KBr)  $\gamma$ : 3210 (NH), 1742, 1660 (C=O), 1582 (C=N)  $cm^{-1}$ . MS,  $m/z$  (%);  $M^+$ , 430 (1), 415 (5), 316 (100), 289 (50), 262 (15). Anal calcd for  $C_{25}H_{26}N_4O_3$ : C 69.75, H 5.09, N 13.01; found C 70.35, 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) (0.3g) 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.  $^1H$  NMR (DMSO- $d_6$ , 300  $MHz$ )  $\delta$ : 1.644 (s, 3H, methyl), 1.663 (s, 3H, methyl), 1.72 (m, 4H, methylene), 2.5 (t, 4H), 5.8 (s, 2H), 4.89 (s, 2H,  $NCH_2CO$ ), 7.27-7.92 (m, 7H, Ar-H). IR (KBr)  $\gamma$ : 1680, 1654 (C=O), 1583 (C=N)  $cm^{-1}$ . MS,  $m/z$  (%);  $M^+$ , 412 (5), 316 (100), 290 (45), 261 (30), 247 (27). Anal calcd for  $C_{25}H_{26}N_4O_2$ : C 72.43, H 6.33, N 13.52; found C 72.25, H 5.92, N 14.1.

### **N-(1,3-dioxoisindolin-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)  $\gamma$ : 3180 (NH), 1793, 1733, 1650 (C=O), 1579 (C=N)  $cm^{-1}$  MS,  $m/z$  (%);  $M^+$ , 474 (9), 333 (21), 313 (21), 289 (100), 276 (22), 247 (42), 105 (25). Anal calcd for  $C_{28}H_{22}N_4O_4$ : C 70.27, H 4.46, N 11.71; found C 70.35, H 5.12, N 12.43.

### **N'-benzylidene-2-(4-(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 (0.001 mol) (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)  $\gamma$ : 3480 (NH), 1669, 1647 (C=O), 1574 (C=N)  $cm^{-1}$ . Anal calcd for  $C_{27}H_{24}N_4O_2$ : 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 (0.001 mol) (0.13 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 [16b], 60% yields as colorless crystals mp 140°C. IR (KBr)  $\gamma$ : 3195 (NH), 1663, 1603 (C=O), 1578 (C=N),  $cm^{-1}$ . Anal calcd for  $C_{28}H_{26}N_4O_3$ : C 72.09, H 5.62, N 12.01; found C 72.57, H 5.32, N 12.81

### **(Z)-N'-(benzo[d][1,3]dioxol-4-ylmethylene)2-(1-oxo-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)acetohydrazide [16c]**

A mixture of (8) (0.001 mol) (0.3 g) and piperonaldehyde (0.001 mol) (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 220°C.  $^1H$  NMR (DMSO- $d_6$ , 300  $MHz$ )  $\delta$ : 1.1 (t, 4H,  $\beta$  methylene of tetryl moiety), 2.5 (m, 4H,  $\alpha$ -methylene of tetryl moiety), 5.2 (s, 2H,  $N-CH_2$ ), 6.02 (s, 1H,  $N=CH-Ar$ ) 6.92-8.75 (m, 11H, Ar-H), 9.8 (s, 2H, NH, exchangeable with water). IR (KBr)  $\gamma$ : 3076 (NH), 1628, 1600 (C=O), 1500 (C=N), 1257 (C-O)  $cm^{-1}$ . Anal calcd for  $C_{28}H_{24}N_4O_4$ : C 69.99, H 5.03, N 11.66; C 69.53, H 5.50, N 11.33

### 2-(5-Phenyl-2,3-dihydro-1,3,4-oxadiazol-2-yl)methyl)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2H)-one [17]

A mixture of (8) (0.001 mol) (0.3 g) and benzoyl chloride (0.001 mol) (0.14 g) in 20 mL pyridine was refluxed for 1 h, then poured on ice and hydrochloric acid. The resultant solid was filtered and crystallized from ethanol to give [17], 30% yield as colorless crystals mp 243°C. IR (KBr)  $\gamma$ : 1660 (C=O), 1582 (C=N), 1205 (C-O)  $\text{cm}^{-1}$ . Anal calcd for  $\text{C}_{27}\text{H}_{24}\text{N}_4\text{O}_2$ : C 74.29, H 5.54, N 12.84; found C 74.75, H 5.62, N 13.22.

### $\text{N}^2$ -(1-oxo-4-(1,2,3,4-tetrahydronaphthalen-2-yl)phthalazin-2(1H)-yl)benzoyl acetohydrazide [18]

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], 60% yields as colorless crystals mp 140°C.  $^1\text{H}$  NMR (DMSO- $d_6$ , 300  $\text{MHz}$ )  $\delta$ : 1.1 (t, 4H,  $\beta$  methylene of tetryl moiety), 2.5 (m, 4H,  $\alpha$  -methylene of tetryl moiety), 5.2 (s, 2H, N- $\text{CH}_2$ ), 7.13-8.25 (m, 13H, Ar-H), 10.3 (s, 2H, NH, exchangeable with water). IR (KBr)  $\gamma$ : 3234 (NH), 1715, 1687, 1651 (C=O), 1581 (C=N)  $\text{cm}^{-1}$  MS,  $m/z$  (%);  $\text{M}^{+}-\text{H}_2\text{O}$  434 (7), 276 (40). Anal calcd for  $\text{C}_{27}\text{H}_{23}\text{N}_4\text{O}_3$ : C 71.67, H 5.35, N 12.38; found C 72.35, H 5.02, N 12.92.

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