Convenient Synthesis of Some Novel 4-Benzyl-1(2*H*)-Phthalazinone Derivatives of expected anticancer activity

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Abstract

Series of new synthesized biologically active phthalazinone derivatives were obtained. Starting from the amino acid methyl esters of 4-benzyl-1(2*H*)-phthalazinone **2a,b** which were synthesized from the aceto hydrazide of 4-benzyl-1(2*H*)-phthalazinone **1** *via* azide coupling method. The hydrazides **3a,b** were prepared from hydrazinolysis of corresponding esters **2a,b**. *N*-substituted-2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-methyl-acetamide **4a-f** and the dipeptides methyl {2-[2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-acetylamino]-acetylamino}-alkanoates **6a-c** were obtained by the reaction of corresponding hydrazide **3a** with amines and amino acid esters respectively *via* azide coupling method.

Similarly; *N*- substituted -*3*-[2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-acetyl amino] propionamide **5a-f** and the dipeptides methyl{3-[2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-acetylamino]-propionylamino} alkanoates **7a-c** were obtained by the reaction of corresponding hydrazide **3b** with amines and amino acid esters respectively *via* azide coupling method

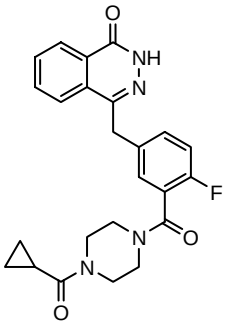
Keywords: Chemoselective, phthalazinone, azide, amines, amino acids, dipeptide

Introduction

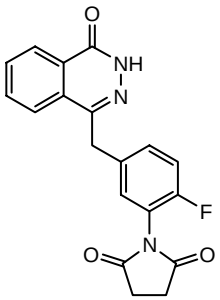
Cancer is one of the most difficult diseases to treat and it is a major disease responsible for deaths worldwide, it can be considered as one of the foremost health problems[1]. Therefore, anticancer drugs research is never ending to obtain lower toxicity and more selectivity products towards tumor cells. It is an urgent need to give much attention to update and modify drug leads from the point of view of medicinal chemistry and drug design to fulfill more potent and effective therapies. Recently, Our research group focused their efforts on searching for new anticancer drugs[2,3].

phthalazinone derivatives have found application in clinical medicine due to their pronounced antihypertensive properties[4] , cardiotonic[5,6] , anticonvulsant[7,8], antidiabetic[9,10] ,antithrombotic[11] , antimicrobial[12,13] antipyretic , analgesic, antitumor[14-17] and cytotoxic[18].

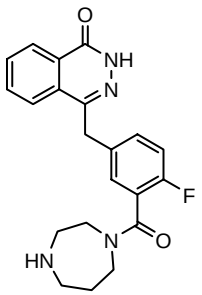
A series of 4-substituted-2H-phthalazin-1-ones have been investigated as potent orally bioavailable PARP (poly (adenosine diphosphate-ribose) polymerases) inhibitor[19-26] Olaparib **I**, MRU-868 **II** and KU0058958 **III** are the most interesting PARP inhibitors based on the 4-substituted-2H-phthalazin- 1-one scaffold and compound **IV** inhibits aurora-A kinase based upon a 4-(pyrazole-3-ylamino)phenyl-2H-phthalazin-1-one scaffold and has in vitro cytotoxic activity against HCT116 colon cell line[27] , these commercial phthalazinone derivatives are shown in figure 1 .



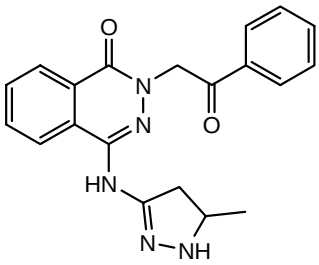
Olaparib **I**



MRU-868 **II**



KU0058958 **III**



4-(5-Methyl-4,5-dihydro-1*H*-pyrazol-3-ylamino)-2-(2-oxo-2-phenyl-ethyl)-2*H*-phthalazin-1-one

IV

Figure 1: Some phthalazinone anticancer drugs

We will present new compound designs from N-substituted phthalazin-1-one derivatives based on the 4- benzylphthalazin-1-one scaffold in an attempt to obtain a potent anticancer agent.

Discussion

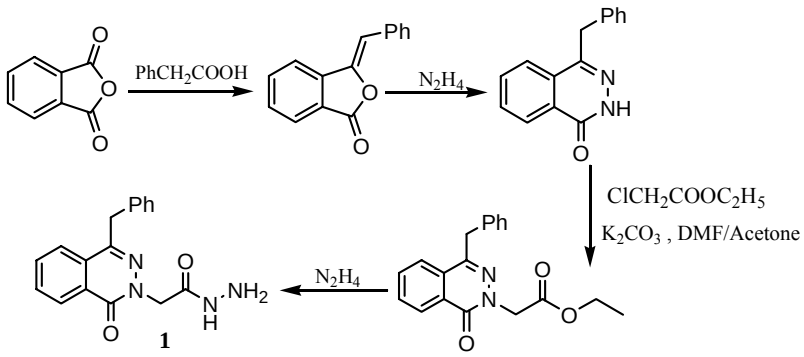
Our research group reported early that[28-31], how we can control on chemoselective alkylation in both amides and thioamides. As extension of these studies, we achieve N-alkylation of 4-Benzyl-2H-phthalazin-1-one to the corresponding methyl-4-Benzyl-1-oxo-1H-phthalazin-2-yl-acetate to the corresponding (4-Benzyl-1-oxo-1H-phthalazin-2-yl)-acetic acid hydrazide (**1)** which used as a precursor for the preparation of our targeted newly phthalazinone molecules.

The alkylation reaction proceeds selectively on N atom not at O atom or even in competition reaction at both atoms. We can explain that depending on their behavior towards electrophiles according to reaction control points as basisty and neucleophilicity of both N and O atoms. The product was methyl-4-Benzyl-1-oxo-1H-phthalazin-2-yl-acetate prove that the N atom in present system is stronger neucleophile more than Oxygen i.e this reaction is new evidence for basis of chemoselective reactivity of heterocyclic amides towards electrophiles scheme1.

The chemoselectivity alkylation proved that occur on the N- atom not the O-isomer so this reaction is N- regioselective and this can be dedicated by the structure characterization using ^{1}H and ^{13}C - NMR spectroscopy.

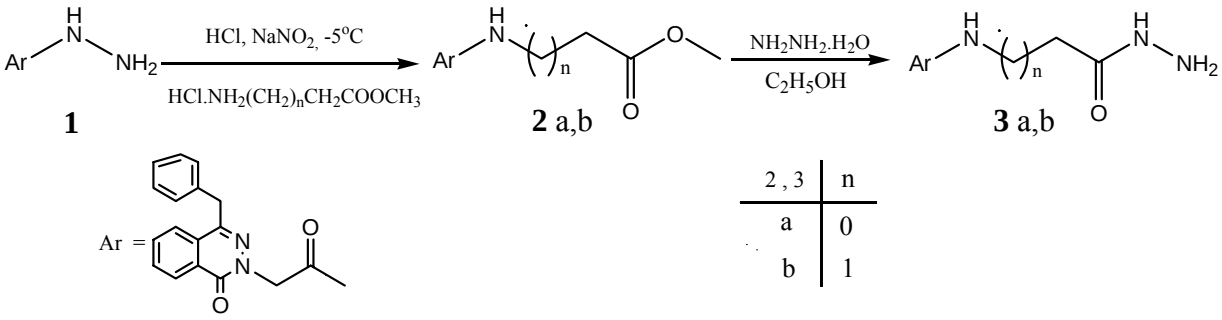
General procedure for 4-Benzyl-1-oxo-1H-phthalazin-2-yl)-acetic acid hydrazide (**1)**

The phthalazine aceto hydrazide **1** was prepared by four steps procedure as outlined in scheme 1 starting from the fusion of phthalic anhydride with phenyl acetic acid in the presence of fused sodium acetate in sand bath from 230 to 240°C yielding 3-benzal phthalide[32], which reacted with hydrazine hydrate in boiling ethanol to give the benzyl phthalazinone derivative [33]. The benzyl phthalizinone derivative was refluxed with ethyl chloro acetate in the presence of anhydrous K_2CO_3 in boiling DMF/ acetone (1:1) led to the oxophthalazinyl acetate compound that was converted to the desired acetohydrazide **1** by reaction with hydrazine hydrate in boiling ethanol[34].



Scheme (1): Synthesis of hydrazide **1**

According to the azide coupling method[35], the aceto hydrazide derivative **1** was stirred with sodium nitrite and hydrochloric acid mixture at -5°C forming azide molecule that in ethyl acetate solution react with amino acid ester hydrochloride in the presence of tri ethyl amine afforded the N-substituted amino acid methyl esters of 4-benzyl-1(2*H*)-phthalazinone **2a,b** (Gly and β-Ala) in good yield in scheme 2.



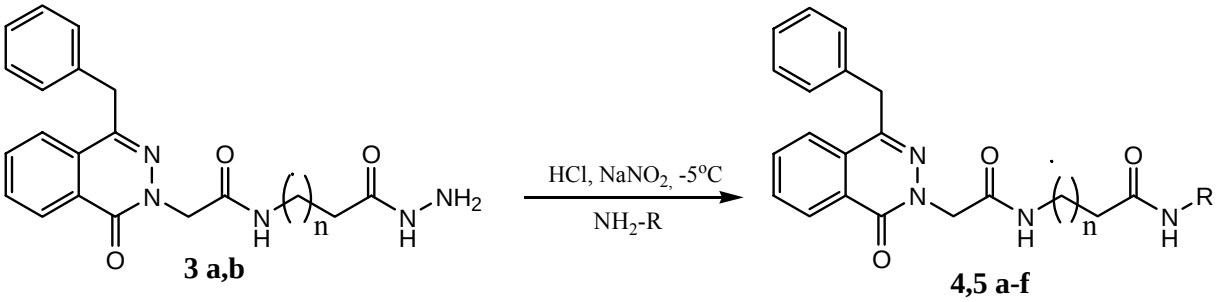
Scheme 2: Preparation of amino acid ester compounds **2a,b** and their corresponding hydrazides **3a,b**

The glycine methyl ester of 4-benzyl-1(2*H*)-phthalazinone **2a** has the ^{1}H- NMR spectrum of characteristic signals at 3.64 , 4.2 , 4 and 4.9 ppm for O-CH_3, N-CH_2 , CH_2.CO and CH2-Ph groups respectively and the ^{13}C- NMR spectrum has signals at 159.78, 167.72 169.99 for 3C=O groups 54.8 , 52.27 , 41.29 and 38.91 ppm, O-CH_3, N-CH_2 , CH_2.CO and CH_2-Ph groups respectively .

N-substituted amino acid methyl esters of 4-benzyl-1(2*H*)-phthalazinone **2a,b** were considered key intermediates for our chemical structure modification of phthalazinone nucleus. The esters **2a,b** underwent hydrazinolysis *via* reflux with hydrazine hydrate in ethanol forming corresponding hydrazides **3a,b.**

Under azide coupling condition, the 2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-N-hydrazinocarbonylmethyl-acetamide **3a** was treated with a mixture of sodium nitrite and HCl solution to give its corresponding azide solution which further treatment with different amines like n-benzyl, n-propyl, n-butyl, cyclohexyl, tetra decyl and allyl amines gave corresponding *N*- substituted -2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)- methyl-acetamide**s 4a-f**.

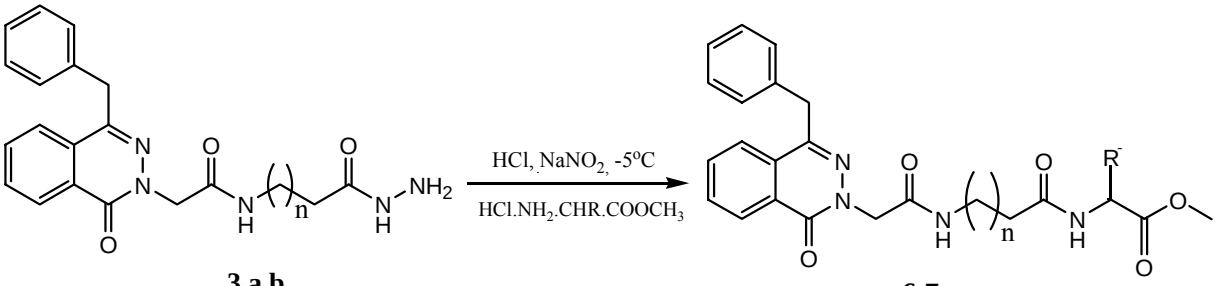
Similarly, starting from the 2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-N-(2-hydrazinocarbonyl-ethyl)-acetamide **3b** under same azide coupling condition, *N*-substituted -*3*-[2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-acetyl amino]propionamide **5a-f** were obtained as shown in scheme 3.



4	n	R	5	n	R
a	0		a	1	
b	0	CH_3-CH_2-CH_2	b	1	CH_3-CH_2-CH_2
c	0	CH_3-CH_2-CH_2-CH_2	c	1	CH_3-CH_2-CH_2-CH_2
d	0		d	1	
e	0	CH_3- $(CH_2)_{14}$	e	1	CH_3- $(CH_2)_{14}$
f	0		f	1	

Scheme 3: Synthesis of *N*-substituted-2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-amides **4,5a-f**

The azide form of 1-oxo-1H-phthalazin-2-yl)-N-hydrazino carbonyl methyl-acetamide **3a** was coupled with different amino acid methyl esters of glycine, β-alanine and valine affording (dipeptides) methyl-2-[2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-acetylamino]-acetylamino-alkanoates in reasonable yield **6a-c**. Under the same condition, methyl-3-[2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-acetylamino]-propionylamino-alkanoates **7a-c** were synthesized from corresponding hydrazide 2-(4-Benzyl-1-oxo-1H-phthalazin-2-yl)-N-(2-hydrazinocarbonyl-ethyl)-acetamide **3b** as shown in scheme 4**.**



3 a,b **6,7 a-c**

6	n	R	7	n	R
a	**0**	**H**	**a**	**1**	**H**
b	**0**	**H-CH_2**	**b**	**1**	**H-CH_2**
c	**0**	**CH_3-CH-CH_3**	**c**	**1**	**CH_3-CH-CH_3**

Scheme 4: Synthesis of dipeptide derivatives **6,7**a-c.

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