Organic Chemistry
Current Research
ISSN: 2161-0401

El-Azm et al., Organic Chem Curr Res 2015, 4:1
DOI: 10.4172/2161-0401.1000132

Review Article Open Access

Recent Developments in Chemistry of Phthalazines

Fatma SM Abu El-Azm*, Mahmoud R Mahmoud, and Mohamed H Hekal

Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt

Abstract

This review highlights the methods used for the synthesis of phthalazine derivatives and fused phthalazinones. Their reactivity and synthetic importance were investigated. Phthalazine derivatives can be used as building blocks for heterocycles as well as fused heterocyclic compounds.

Keywords: Phthalazine derivatives; Pyrazolophthalazines; Indazolophthalazines; [1,2,4] Triazolophthalazines

Introduction

Among a large variety of nitrogen-containing heterocyclic compounds, heterocyclic containing hydrazine has received considerable attention because of their pharmacological properties and clinical applications [1-6]. Phthalazine derivatives were reported to possess anticonvulsant [7-10], cardiotonic [11], antitumor [12-16], antihypertensive [17-19], antithrombotic [20], a ntidiabetic [21,22], antimicrobial [23,24], antitry-panosomal [25], anti-inflammatory [26-32], cytotoxic [14], vasorelexant [19] and vascular endothelial growth factor receptor 11(VEGFR-2) inhibitory [33]. Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives [34-41]. These properties are more fully detailed in the supplementary material. The review comply published data on the synthesis of new phthalazine derivatives until 2013.

Synthesis of Phthalazine derivatives

From hydrazine and hydrazine derivatives

Hydrazine and hydrazine derivatives are the most common reagents used for the synthesis of phthalazinone derivatives via their reactions with phthalic anhydride, phthalides, phthalimides etc.

Hydrazines with anhydrides: Several methods were reported for the preparation of phthalazinones derivatives. These methods mainly involve the reaction of phthalic anhydrides with hydrazine hydrate in the presence of acetic acid [42-44].

Phthalazinones **5,7-9** were synthesized from commercially available phthalic anhydride in **2-3** steps as depicted in (Scheme 1 and 2) [45-51].

Additionally, reaction of phthalic anhydride and aromatic hydrocarbons in the presence of anhydrous aluminum chloride under Friedel-Craft's conditions afforded 2-aroylbenzoic acids **10** which treated with hydrazine hydrate and hydrazine derivatives to give the phthalazine (2*H*)-1-one **11,12** [52-57] (Scheme 3).

In 2006, Salvi et al. [58] reported that 2-[1-(4-oxo-3,4-dihydrophthalazin-1-yl)alkyl]-1H-isoindole-1,3-(2H)-diones **15** were obtained from fusion of phthalyl derivatives of amino acid **13** with phthalic anhydride in the presence of anhydrous sodium acetate followed by cyclization with hydrazine hydrate in n-butanol (Scheme 4).

Fifteen novel 1,4-disubstituted phthalazinylpiperazine derivatives were designed and synthesized using a convenient seven-step procedure starting from phthalic anhydride depicted in (Scheme 5). The cytotoxicities against A549, HT-29 and MDA-MB-231 cancer cell lines were tested [59]. An expeditious one-pot method has been developed for the synthesis of aryl, heteryl thiadiazinyl-phthalazin-1,4-diones via a multicomponent approach. Reaction of phenacyl bromides **22** with thiocarbohydrazide **23** and phthalic anhydride afforded corresponding aryl thiadiazinyl-phthalazine-1,4-diones **24** similarly, reaction of 3-(2-bromoacetyl) coumarins **25** with thiocarbohydrazide and phthalic anhydride afforded required heterylthiadiazinyl-phthalazine-1,4-diones **26** under the same reaction conditions in excellent yields [60] (Scheme 6).

Hydrazines with 2-acyl benzoic acids: Kirill et al. [31] reported the cyclization of 2-nitro-5-chloro phenylhydrazine**27** with acyl benzoic acids **28** yielded 2-(2-nitro-5-chlorobenzene)-4-substituted phthalazin-1-ones **29** (Scheme 7)**.**

Lukacs and Simig [61] adopted a novel method for the synthesis of phthalazine derivatives **32** via the reaction of benzophenones**30** with chromium (VI) oxide in a mixture of acetic anhydride and sulphuric acid followed by cyclization of the products with hydrazine hydrate in refluxing ethanol (Scheme 8).

Hydrazine with 1,2-diester: The dimethylphthalate derivative **33** reacted with hydrazine to yield the desired phthalhydrazide**34** which undergo chlorination with phosphorus oxychloride to give **35**. Subsequent treatment with sodium methoxide afforded the methoxychloride **36** [62] (Scheme 9).

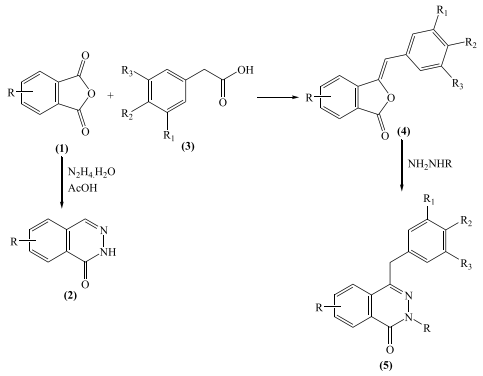
Hydrazines with Phthalides: Chloroformylation of 3-methoxy benzoic acid **37** and subsequently radical bromination of **38** produced **39** in good yield. Treatment with triphenyl phosphine gave **40** and wittig olefination with 3,5-dichloro-4-pyridine carboxaldehyde **41** afforded the phthalide **42**. Hydrazine cyclization of **42** resulted phthalazine derivative **43** [42] (Scheme 10).

Cockcroft et al. [12] synthesized the phthalazinone derivative **47** according the following (Scheme 11).

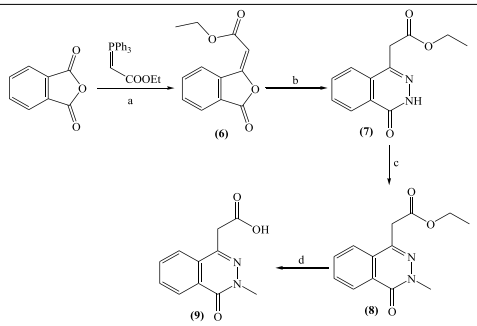
***Corresponding author:** Fatma SM, Abu El-Azm, Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt, Post code 11566, Tel: 0201220383276 ; E-mail: ftmsaber@yahoo.com

Received September 16, 2014; **Accepted** December 25, 2014; **Published** January 01, 2015

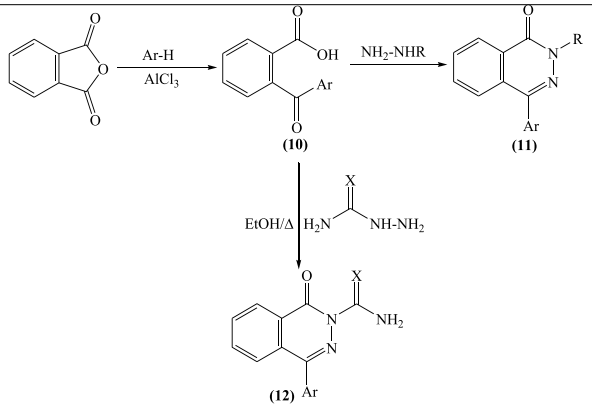
Citation: El-Azm FSMA, Mahmoud MR, Hekal MH (2015) Recent Developments in Chemistry of Phthalazines. Organic Chem Curr Res 1:132. doi:10.4172/2161-0401.1000132



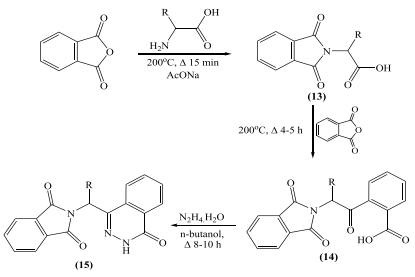
Scheme 1: Synthesis of phthalazinone derivatives **2** and **5**



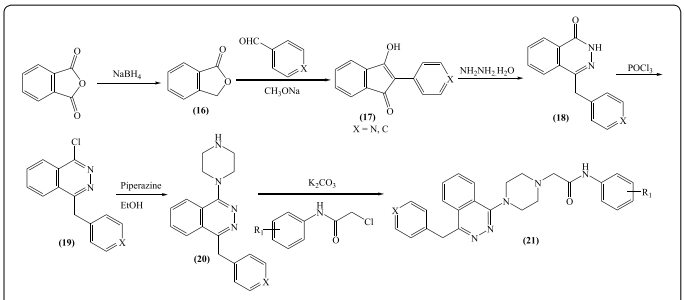
Scheme 2: Synthesis of phthalazinone derivatives **7-9**. Reagents and conditions: (a) $CHCl_3$, reflux, 5 h, 51%; (b) hydrazinehydrate, EtOH, addition at rt and then reflux, 90˚C, 2 h, 71%; (c) MeI, KOBu^t, DMF, 30 min, 80%; (d) LiOH, THF:MeOH:water (1:1:1), rt, 8–10 h, 81%.



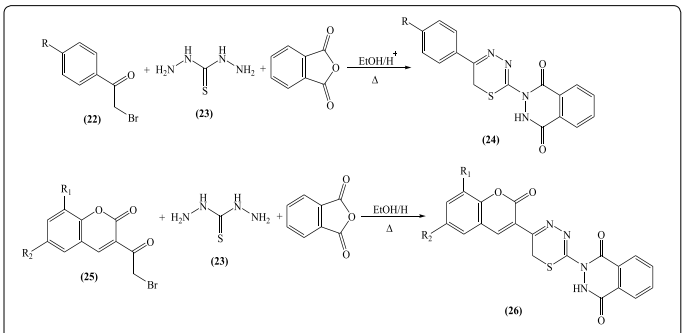
Scheme 3: Synthesis of phthalazin(2*H*)-1-one **11, 12**



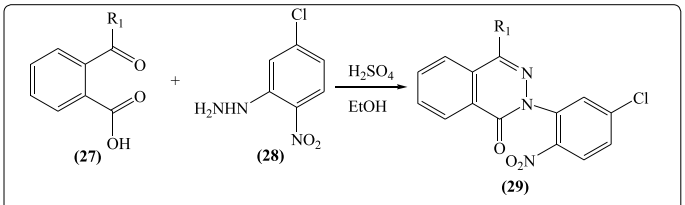
Scheme 4: Synthesis of 2-[1-(4-oxo-3,4-dihydrophthalazin-1-yl)alkyl]-1*H*-isoindole-1,3-(2*H*)-diones



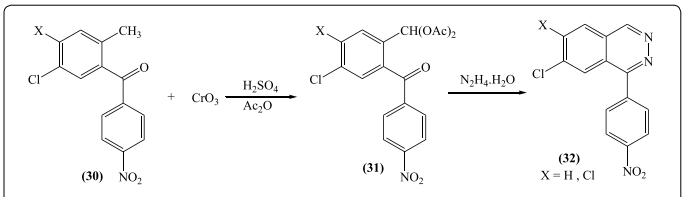
Scheme 5: Synthesis of 1,4-disubstituted phthalazinylpiperazine derivatives **21**



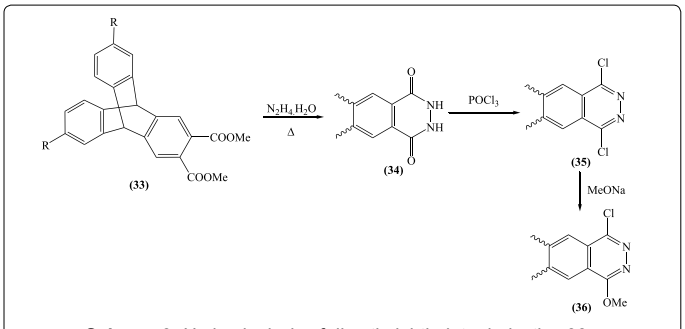
Scheme 6: One-pot Synthesis of thiadiazinyl-phthalazine-1,4-diones **24** and **26**



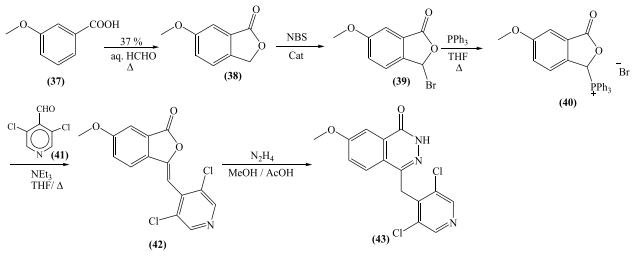
Scheme 7: Synthesis of 4-substituted phthalazin-1-ones **29.**



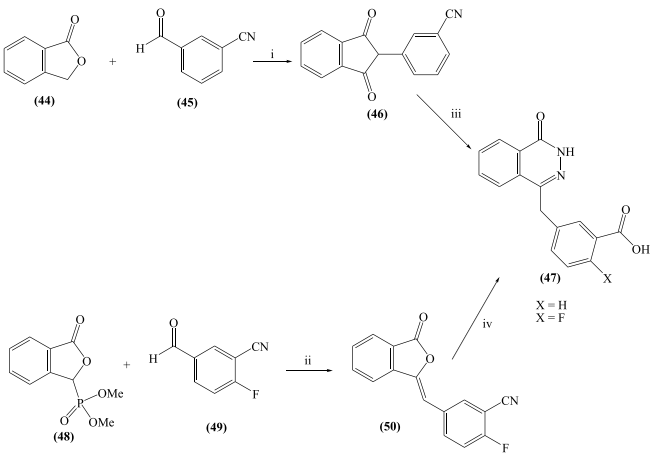
Scheme 8: Synthesis of phthalazine derivatives **32**



Scheme 9: Hydrazinolysis of dimethylphthalate derivative **33**



Scheme 10: Synthesis of phthalazine derivative **43**



Scheme 11: Synthesis of phthalazinone derivative **47**. Reagents and conditions (i) NaOMe/ MeOH/ reflux; (ii) NEt_3 / THF / reflux; (iii) $N_2H_4.H_2O$ / reflux; (iv) a) aq. NaOH / THF; b) $N_2H_4.H_2O$ / reflux

Hydrazines with phthalimide: Novel three-step method to prepare 4-substituted chlorophthalazines from phthalimide was reported [63] (Scheme 12).

Hydrazines with phthaloyl chloride: Recently [64] it was reported that the reaction of phthaloyl chloride **56** with *N*-methyl acetophenone hydrazones **57** leads to the formation of 2-ethenyl-3-methyl-2,3-dihydrophthalazine-1,4-diones **58** (Scheme 13).

Hydrazines with 2-iodobenzyl bromide and diiodide: The systematic investigation of the cycloaminocarbonylation of bifunctional 2-iodobenzyl bromide and 1,2-diiodobenzene substrates towards tetrahydrophthalazin-one (tetrahydrophthalazindione) derivatives was described [65].

2-Iodobenzyl bromide **59** was reacted with hydrazine derivatives, such as methylhydrazine, phenylhydrazine, hydrazine, 1,2-dimethylhydrazine and 1,1-dimethyl hydrazine under atmospheric carbon monoxide pressure in DMF in the presence of palladium(0) catalysts generated *in situ* from palladium(II) acetate catalytic precursor and yielded the phthalazinones **60-64** (Scheme 14).

1,2-Diiodobenzene **65** was reacted with hydrazines and gave the phthalazin-1,4-dione **66** together with side products (Scheme 15).

Recently, practical synthesis of 2-substituted 1,2-dihydro phthalazines **69** that based on the reaction between 2-(bromomethyl) benzaldehyhdes and arylhydrazines under basic conditions and with $FeCl_3$ as the catalyst [66] (Scheme 16).

From 3,2-benzoxazine-4-one

The reaction of 3,2-benzoxazin-4-ones with different nitrogen containing reagents, was successfully used in the preparation of different phthalazinone derivatives. For example, reaction of 1-aryl-3,2-benzoxazin-4-ones **70** with hydrazine in refluxing ethanol yielded bis-phthalazinone **71**.

Fusion of benzoxazin-4-one with ammonium acetate at 115°C gave 4-aryl-1(2*H*)-phthalazinone **72**. The 4-aryl-2-(4-methylphenyl) phthalazinones **73** were obtained by reacting the benzoxazine-4-ones and p-toludine in refluxing ethanol [67]. In addition, Kassab [68] prepared 4-phenyl-1(2*H*) phthalazinone **72** by ammonolysis of 1-aryl-3,2-benzoxazine-4-one with formamide (Scheme 17).

From 3,1-benzoxazine-4-ones

Kassab et al. [69] used 3,1-benzoxazine-4-ones for the preparation of phthalazinone derivatives. Thus, the reaction of 3,1-benzoxazine-4-one derivative **74** with thioglycolic acid in refluxing n-butanol yielded the 1-oxo-phthalazinyl thioglycolic acid derivative **75**. In a similar manner [69] reaction of **74** with 2-amino pyridine in refluxing n-butanol gave 2-[2-(*N*-4-pyridyl-carboxamide) phenyl]-4-(4-bromophenyl) phthalazin-1-one **76** (Scheme 18).

Fromcis-diol

Inverse Diels-Alder reaction of tetrazine **77** with benzene cis-diol [70] **78** as a dienophile in $CHCl_3$ has been examined to give the addition product **81**.

The adduct **81** was submitted to phenyl iodo-bis(trifluoroacetate) oxidation and yielded the fully aromatic compound 5-hydroxy phthalazine **82** was formed as the sole product in 62% yield. Furthermore, treatment of the adduct **81** with $MnO_2$and O_2 afforded phthalazine derivatives **83** and **84** (Scheme 19).

Synthesisof Fused Phthalazine Derivatives

PyrazoloPhthalazines

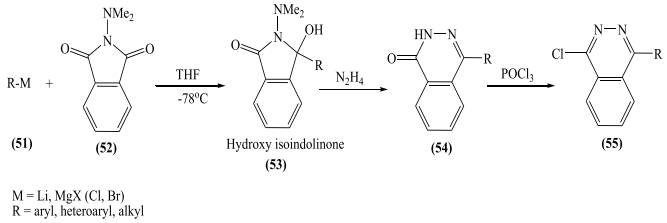
Synthesis of highly functionalized 1H-pyrazolo[1,2-b]phthalazine-1,2-dicarboxylates **87** via a one-pot isocyanide-based multi-component reactions (IMCRs) of various cyclic anhydrides, hydrazine hydrate, isocyanides **85** and dialkyl acetylene dicarboxylates **86** in EtOH/ acetone (1:1) at room temperature was reported [71,72] (Scheme 20).

One-pot four-component condensation reaction of phthalimide, hydrazine hydrate, aromatic aldehydes and malononitrile or ethyl cyanoacetate catalysed by Lewis acid $NiCl_2.6H_2O$ was reported [73] to give 1H-pyrazolo[1,2-b] phthalazin-5,10-dione derivative **88** (Scheme 21).

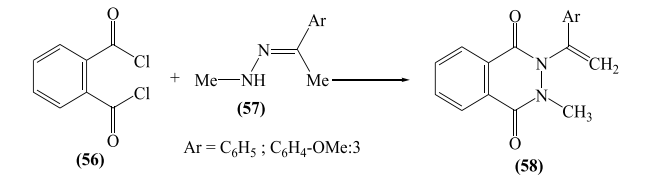
Treating pyrazolidindione **89** with 1,2-bis (bromomethyl) benzene **90** afforded the tricyclic 1*H*-pyrazolo[1,2-b] phthalazindione **91** [74] (Scheme 22).

Pyrazolo[1,2-b]phthalazindione derivatives [75] were reported as anti-inflammatory, analgesic, antihypoxic and antipyretic agents [4].

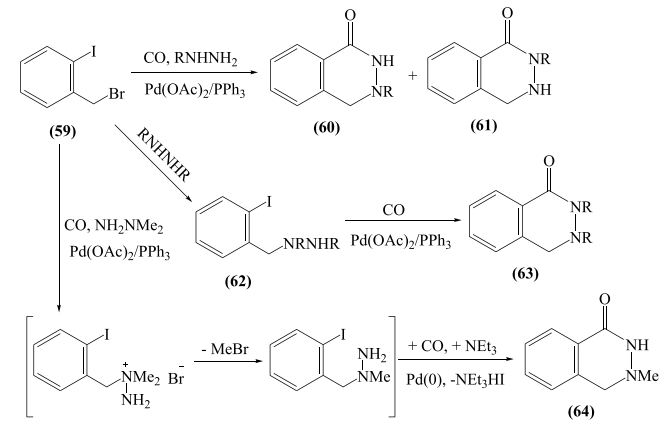
There are only several literatures about the multi component synthesis for 1*H*-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives, which were synthesized by a one pot three component reaction of phthalhydrazide, aromatic aldehydes and malononitrile or ethyl cyanoacetate catalyzed by PTSA [76], Et_3N [77] or [Bmim]OH [78].



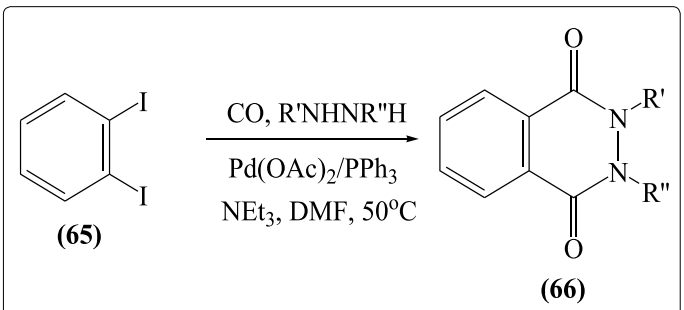
Scheme 12: Synthesis of 4-substituted chlorophthalazines



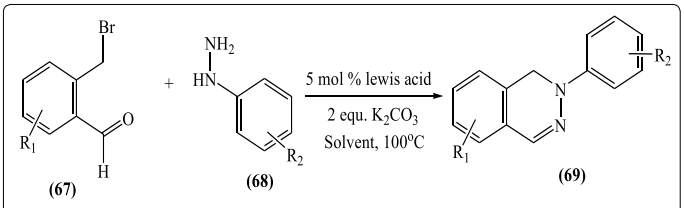
Scheme 13: Synthesis of 2-ethenyl-3-methyl-2,3-dihydrophthalazine-1,4-diones **58**



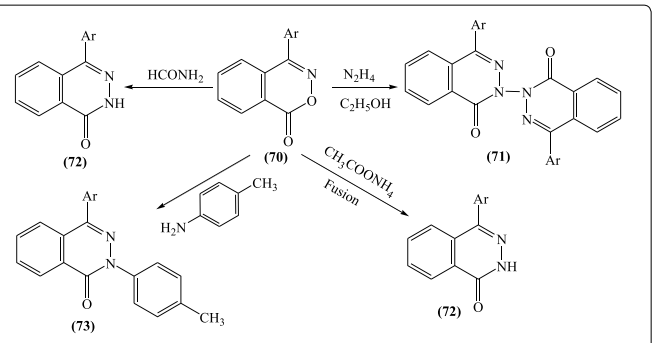
Scheme 14: Synthesis of phthalazinones **60-64.**



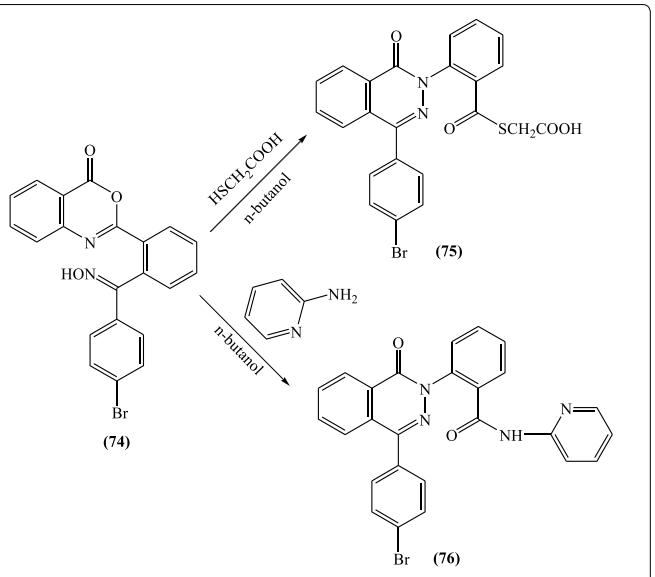
Scheme 15: Synthesis of phthalazin-1,4-dione **66.**



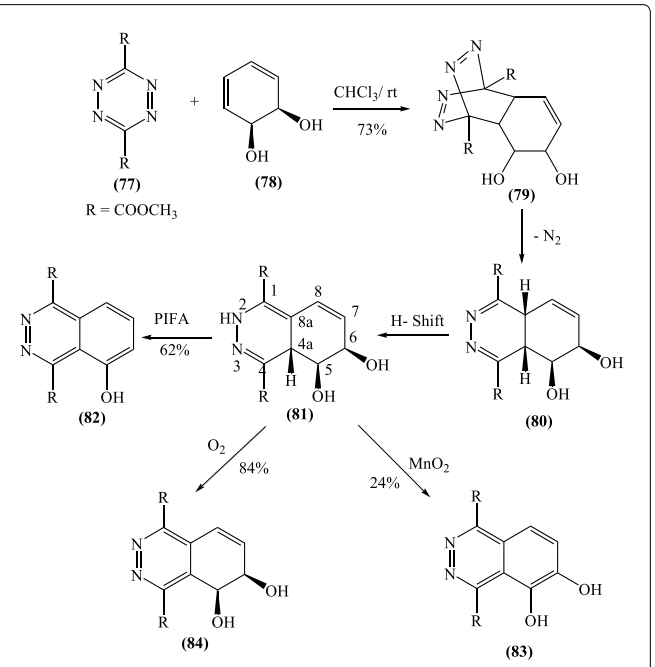
Scheme 16: Synthesis of 2-substituted 1,2-dihydro phthalazines **69**



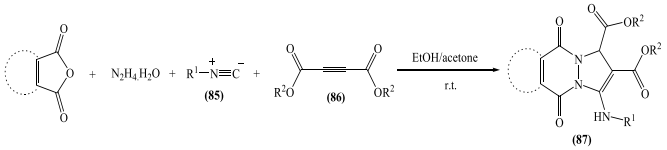
Scheme 17: Reaction of 1-aryl-3,2-benzoxazin-4-ones **82** with different nitrogen nucleophiles



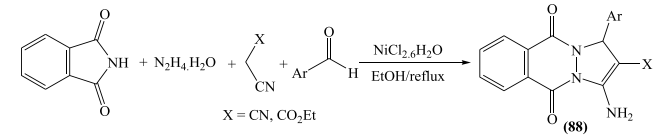
Scheme 18: Synthesis of phthalazin-1-one **75, 76.**



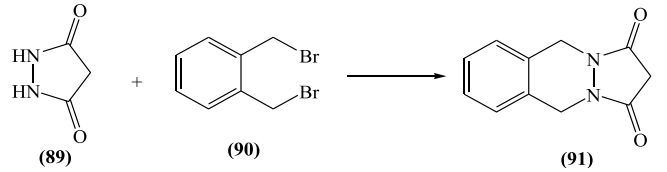
Scheme 19: Synthesis of phthalazine derivatives **83**, **84**



Scheme 20: Synthesis of 1H-pyrazolo[1,2-b]phthalazine-1,2-dicarboxylates **87**



Scheme 21: Synthesis of 1H-pyrazolo[1,2-b]phthalazin-5,10-dione derivative **88**.



Scheme 22: Synthesis of 1*H*-pyrazolo[1,2-b]phthalazindione **91**

Ghahremanzadeh et al. [76] synthesized 1*H*-pyrazolo [1,2-b] phthalazin-5,10-dione derivatives **92** via the simple condensation reaction of malononitrile or ethylcyanoacetate, phthalhydrazide and aldehydes in the presence of a catalytic amount of p-toluene sulphonic acid (PTSA) in ionic liquid 1-butyl-3-methyl imidazolium bromide as solvent at 100°C (Scheme 23).

Recently, the synthesis of 2*H*-indazolo [2,1-b] phthalazintriones has been reported by Bazgir and co-workers using (PTSA) as catalyst [79].

A simple efficient and green practical approach to 1*H*-pyrazolo [1,2-b] phthalazine-5,10-diones **95** from phthalhydrazide, aldehydes and malononitrile/ethyl cyanoacetate has been developed that uses inexpensive and readily available $InCl_3$ as a catalyst in solvent free [80].

A schematic mechanism for the catalytic activity of $InCl_3$ in the synthesis of titled compounds **95** should be postulated as shown in (Scheme 24).

The synthesis of 1H-pyrazolo[1,2-b] phthalazine-5,10-dione derivatives **97** via condensation reaction of 2-chloro-3-formyl quinolines **96**, malononitrile/ethyl cyanoacetate and 2,3-dihydro-1,4-phthalazinedione using a catalytic amount of piperidine in refluxing ethanol has been described. All the synthesized compounds were screened for their antibacterial activity against a panel of pathogenic strain of bacteria and fungi [81] (Scheme 25).

A direct and efficient approach for the preparation of pyrazolo phthalazinyl spirooxindoles **99** has been developed through one-pot three-component reaction of easily available isatin, malononitrile or cyanoacetic ester, and phthalhydrazide catalyzed by nickel chloride in polyethylene glycol 600. Desired products were obtained in high to excellent yields using a simple workup procedure [82,83] (Scheme 26).

Sonocatalysis synthesis of a novel class of spiroacenaphthylene-1,1'-pyrazolo[1,2-b]phthalazines **101** via a facile, atom-economical and one pot three-component condensation reaction was investigated [84] (Scheme 27).

The1-{[(1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1*H*-pyrazolo[1,2-b] phthalazine-5,10-dione derivatives **104** were synthesized by a simple and efficient method, i.e., by the four-component, one-pot condensation reaction of phthalohydrazide, a (propargyloxy) benzaldehyde **102**, an active methylene compound (malononitrile or ethyl cyanoacetate), and an azide**103** in the presence of $Cu(OAc)_2$/sodium L-ascorbate as catalyst [85] (Scheme 28).

IndazoloPhthalazines

Shaterian et al. [86] reported an efficient method for the preparation of 2*H*-indazolo[2,1-b]phthalazine-triones derivatives **106** using silica sulfuric acid as recyclable solid acid catalyst under solvent-free conditions (Scheme 29).

A new green protocol has been developed for the synthesis of 2*H*-indazolo[1,2-b]phthalazine-triones **107** via one-pot, three-component condensation reaction of aromatic aldehydes with 1,3-dicarbonyl compounds and phthalhydrazide using reusable dodecylphosphonic acid (DPA) as heterogenous solid acid catalyst under solvent-free conditions. This protocol provides a novel and improved method for obtaining 2*H*-indazolo[1,2-b] phthalazine-triones in terms of good yields with little catalyst loading [87] (Scheme 30).

1H-Imidazo Phthalazindiones

Kim et al. [14] reported a series of 1-substituted 2-methyl 1*H*-imidazo[4,5-g] phthalazine-4,9-dione derivatives **112** as depicted in (Scheme 31).

Yavari et al. [88] reported the synthesis of imidazophthalazines**116** via nucleophilic substitution of chlorine atom with secondary alicyclic amines in the side benzene ring of phthalazine (Scheme 32).

[1,2,4] TriazoloPhthalazines

Lebsack et al. [75] synthesized [1,2,4] triazolo [3,4-a]phthalazine derivative **118** as follows: (Scheme 33).

A general method is reported for the solid-phase synthesis of [1,2,4] triazolo [3,4-a] phthalazine **122** and tetrazolo [5,1-a] phthalazine derivatives **123** based on the cyclization of resin-bound chlorophthalazines with various hydrazides or sodium azide. The resin-bound chlorophthalazines produced by nucleophilic aromatic substitution reaction of dichloro-phthalazine with the secondary amines resins served as the key intermediate for subsequent triazolophthalazine resins and tetrazolophthalazine resins [40,89] (Scheme 34).

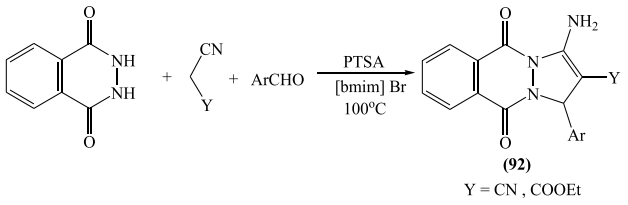
4-(3,4-Dimethylphenyl)-1(2H)-phthalazinone **124** was used as key starting material for synthesis of fused [1,2,4]triazolophthalazines depending on the principles of lactam-lactim dynamic equilibrium phenomena [90,91] (Scheme 35).

Reactions of Phthalazines

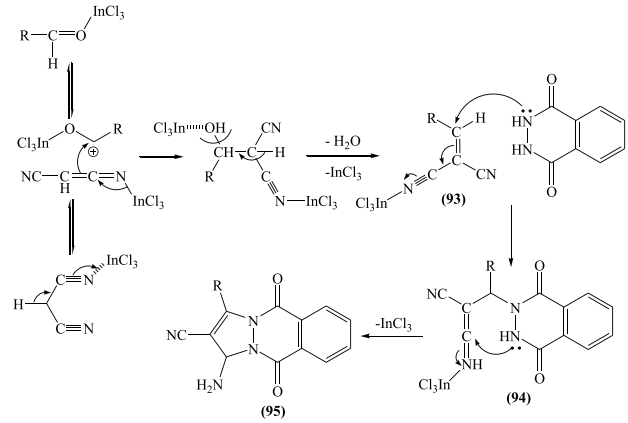
Reaction with acetylinic compounds:

Ghahremanzadeh et al. [92] reported the reaction of phthalhydrazide and acetylene dicarboxylates in the presence of *N*-heterocycles to afford **130**, **131** and **132** as follows: (Scheme 36).

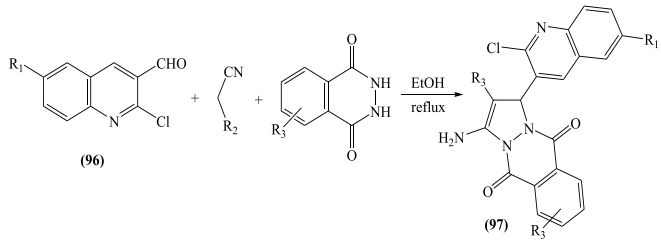
Iwamoto et al. [93] reported that in the reaction of 1-substituted phthalazines with ynamines, there are three patterns of ring



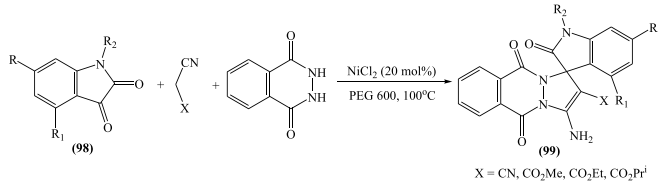
Scheme 23: Synthesis of 1*H*-pyrazolo [1,2-b] phthalazin-5,10-dione derivatives **92**



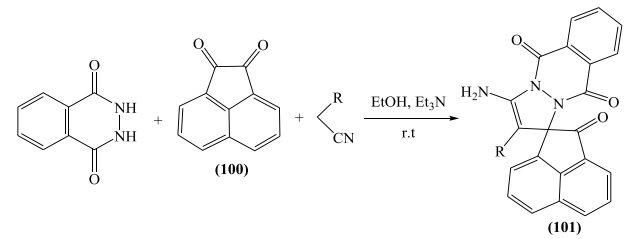
Scheme 24: A plausible mechanism for the synthesis of 1*H*-pyrazolo[1,2-b] phthalazine-5,10-diones **95**



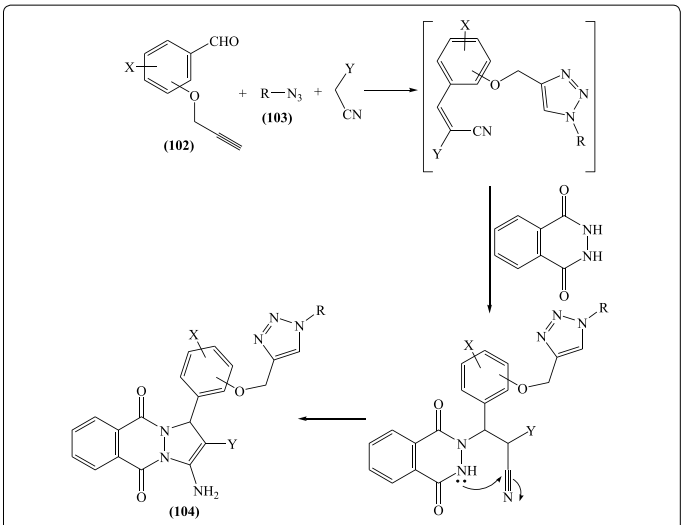
Scheme 25: Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives **97.**



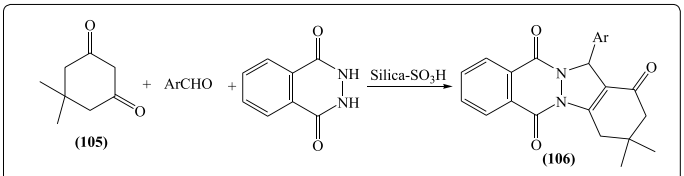
Scheme 26: Synthesis of pyrazolophthalazinyl spirooxindoles **99**



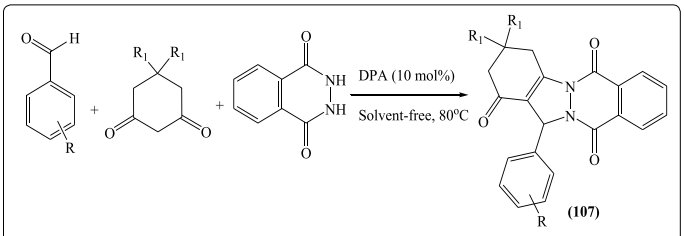
Scheme 27: Synthesis of spiroacenaphthylene-1,1′-pyrazolo[1,2-b]phthalazines **101**



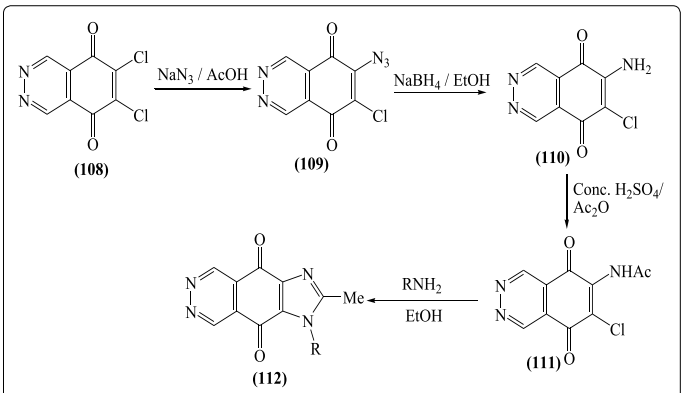
Scheme 28: Synthesis of 1-{[(1*H*-1,2,3-triazol-4-yl)methoxy]phenyl}-1*H*-pyrazolo[1,2-b] phthalazine-5,10-dione derivatives **104**



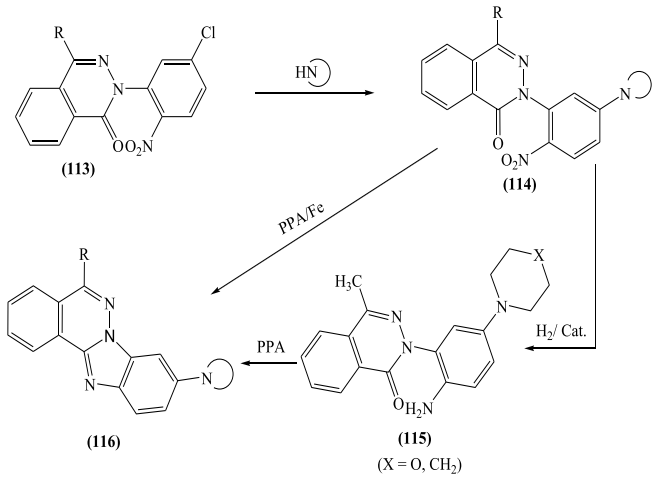
Scheme 29: Synthesis of 2*H*-indazolo[2,1-b]phthalazine-triones derivatives **106**.



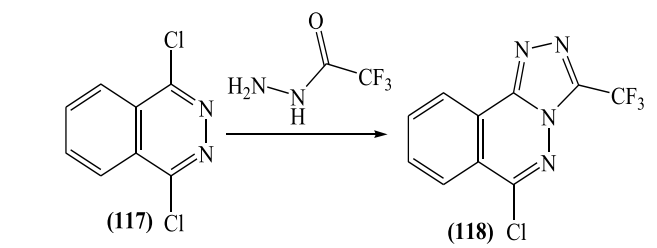
Scheme 30: Synthesis of 2*H*-indazolo[1,2-b] phthalazine-triones **107**



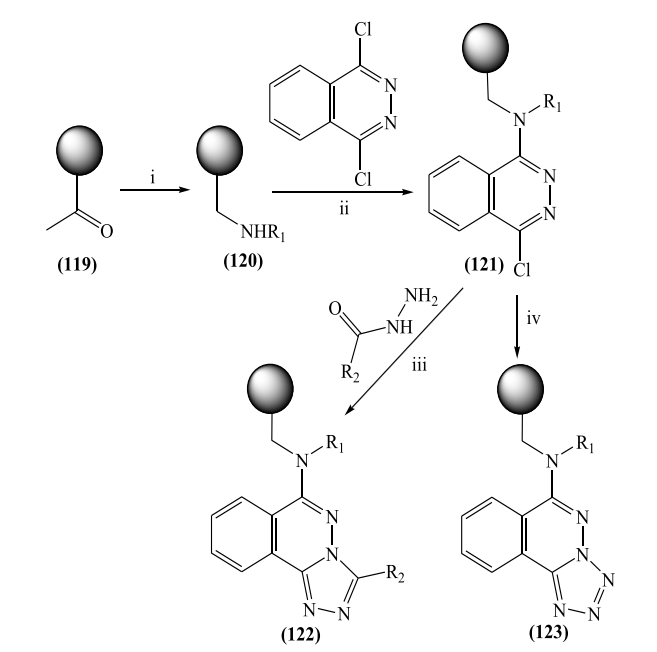
Scheme 31: Synthesis of 1*H*-imidazo[4,5-g] phthalazine-4,9-dione derivatives **112**.



Scheme 32: Synthesis of imidazo phthalazines **116.**

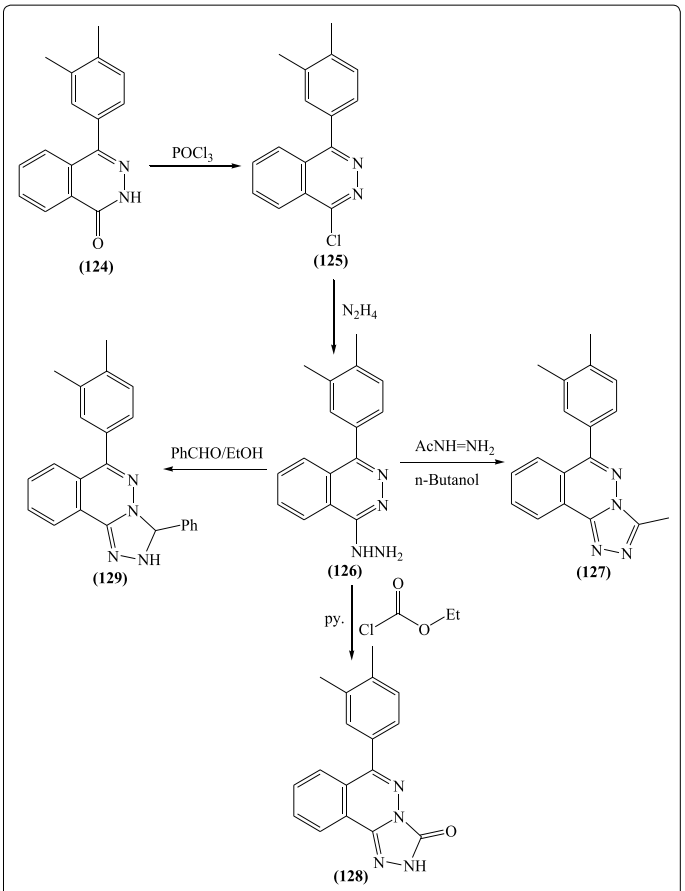


Scheme 33: Synthesis of [1,2,4] triazolo [3,4-a]phthalazine derivative **118.**

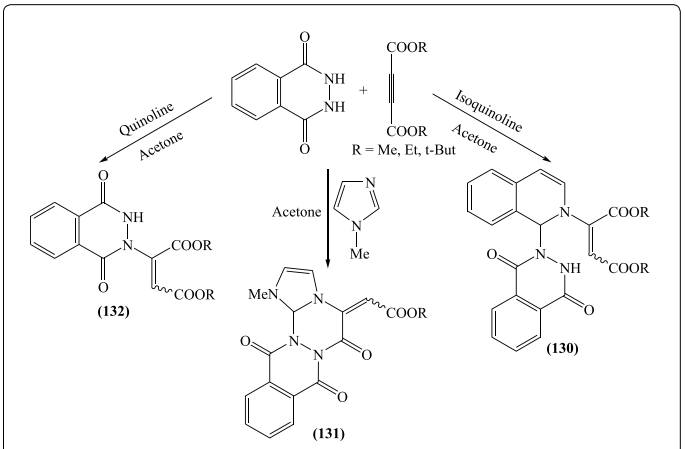


Reagents and conditions: (i) R_1NH_2, $NaBH(OAc)_3$, AcOH, DMF, rt, 24 h; (ii) TEA, DMSO, 80°C, 12 h; (iii) TEA, xylene, 110° C, 24 h;(iv) NaN_3, NMP, 120° C, 24 h.

Scheme 34: Synthesis of [1,2,4] triazolo [3,4-a]phthalazine **122** and tetrazolo [5,1-a] phthalazine derivatives **123**



Scheme 35: Synthesis of fused [1,2,4]triazolo phthalazines **127-129**



Scheme 36: Reaction of phthalhydrazide with acetylene dicarboxylates.

transformation giving naphthalene derivatives **133** through addition-cyclization denitrogenation **(type A),** giving benzodiazocine derivatives **134** through addition-cyclization-ring expansion **(type B)** and giving pent substituted pyridine derivatives **135** through N-N bond cleavage of the pyridazine ring **(type C)** (Scheme 37).

A highly effected silver-catalysed formal inverse electron-demand Diel's Alder (IEDDA) reaction of phthalazine **136** and siloxy alkynes **137** has been reported [94,95]. The reactions provided ready access

to a wide range of siloxynaphthalenes **139** and anthracenes which are formed in good to high yields, under mild reaction conditions using low catalyst loadings (Scheme 38).

A series of novel 3-(indolyl) prop-1-ynyl substituted phthalazines **142** were prepared via a concise pathway by palladium catalyzed cross coupling of appropriate halogens **140** and N-propargylindoles **141** [15,96] (Scheme 39).

Reaction with Amines: (Nucleophilic substitution reactions)

The activity of halogen attached to either or both carbons of the azine ring was analogous to similar activity in 2-or 4-halogeno-quinolines. In general the reaction of 1-halogeno or 1,4-dihalogeno phthalazines with ammonium derivatives (primary or secondary amines) [97] afforded **144**.

Snaz et al. [98] showed the synthesis of mono and bi (alkyl amino) benzo [g] phthalazine derivatives **145** and **146** as follow: (Scheme 40).

It has been achieved [99] by the reaction of 1,4-dichlorobenzo[g] phthalazine with the corresponding poly amines a new series of mono and binuclear 1-alkylamino-4-chlorobenzo[g]phthalazine derivatives **147-149** containing flexible polyaminic chains. (Scheme 41)

Piatnitski et al. [100] reported that, commercially available 1,4-dichlorophthalazine **150** was first reacted with an amine to give the mono substituted adduct **151** [101]. The remaining chloride was then coupled with boronic acid or boronic acid ester under Suzuki reaction conditions with microwave irradiation to give the desired final compound **152** (Scheme 42).

Reaction with chalcones

Cyclocondensation of 1-aryl-3-ferrocenyl-2-propen-1-ones **153** with hetaryl hydrazine resulted in *N*-hetaryl-3-aryl-5-ferrocenyl pyrazolines**155** [102] (Scheme 43).

Alkylation

Treatment of phthalazine or its alkyl derivatives with alkyl halides yields *N*-alkyl phthalazinium halides **156** and when treated with Ag_2O and KOH afforded the N-alkyl derivatives **157** and **158**, respectively [103] (Scheme 44).

A novel series of phthalazine derivatives bearing isoindol-1,3-dione moiety were synthesized by treating 2-(4-(4-oxo-3,4-dihydrophthalazin-1-yl)phenyl)isoindoline-1,3-dione **159** with various chemical alkylating reagents [104,105] (Scheme 45).

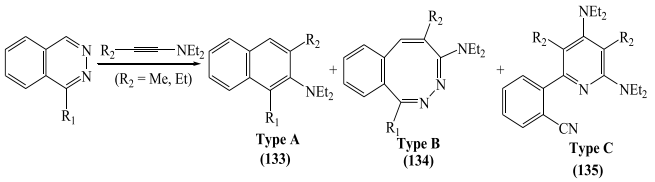
4-(3,4-Dimethylphenyl)-1(2H)-phthalazinone **124** was used as key starting material for synthesis a new series of 1,4-disubstituted phthalazines, and 2,4-disubstituted phthalazinones depending on the principles of lactam-lactim dynamic equilibrium phenomena [90,91] (Scheme 46).

Acylation

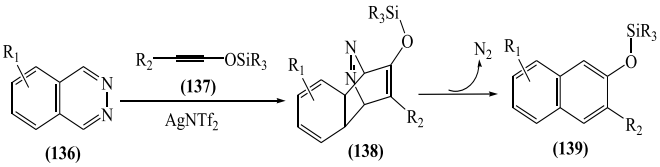
Acylation of 2-benzyl-2,3-dihydrophthalazine-1,4-dione **167** with 2-(bromomethyl)-benzoyl chloride **168** yielded **169** [106] (Scheme 47).

Reaction with galactopyranose and ribofuranose

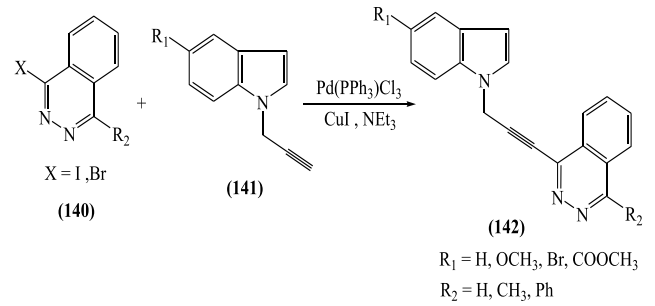
Coupling of trimethylsilyl derivative of (2*H*) phthalazine-1-one **170** with 1,2,3,4,6-penta-O-acetyl-α-D-galactopyranose **171** in the presence of stannic chloride gave the respective glycosides, 2-(per-O-acetyl-D-glycosyloxy) phthalazines **172**. Under the same conditions 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose **173** gave 1-(2,3,5-tri-O-acetyl-α-D-ribofuranosyloxy) phthalazine **174** [16] (Scheme 48).



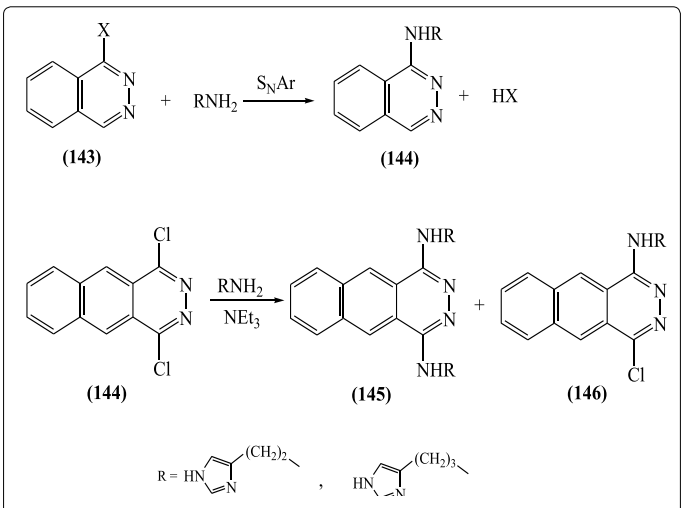
Scheme 37: Reaction of phthalazines with ynamines.



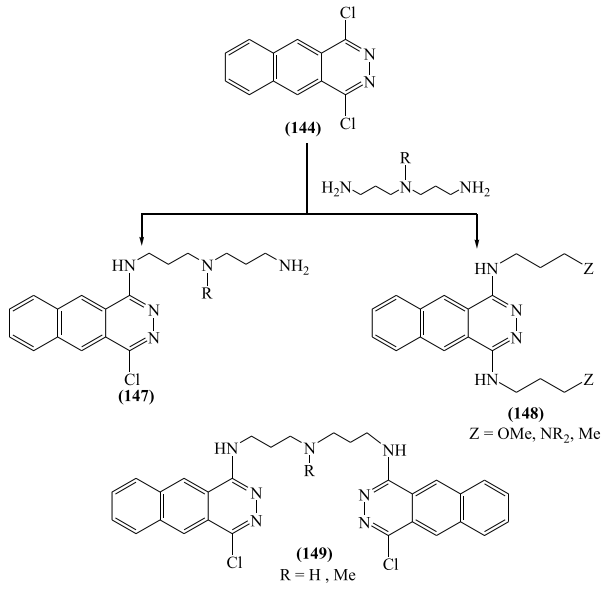
Scheme 38: Reaction of phthalazine **136** with siloxy alkynes **137.**



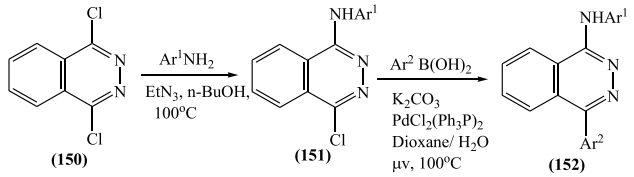
Scheme 39: Synthesis of 3-(indolyl) prop-1-ynyl substituted phthalazines **142**.



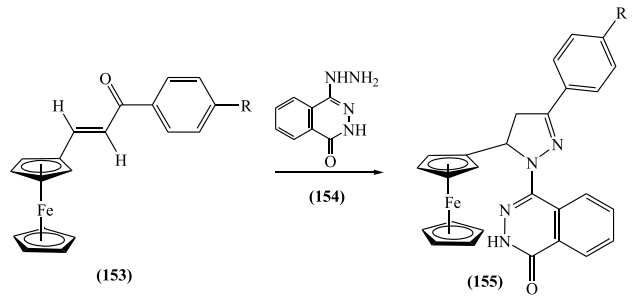
Scheme 40: Synthesis of benzo[g] phthalazine derivatives **145** and **146.**



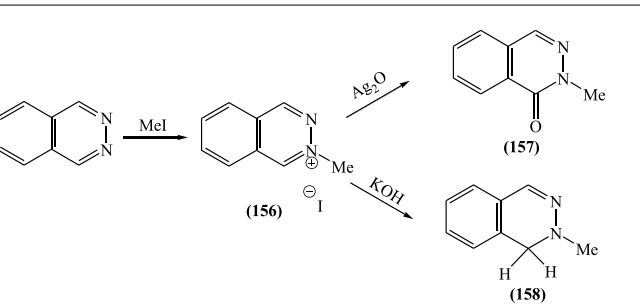
Scheme 41: Synthesis of 1-alkylamino-4-chlorobenzo[g]phthalazine derivatives **147-149.**



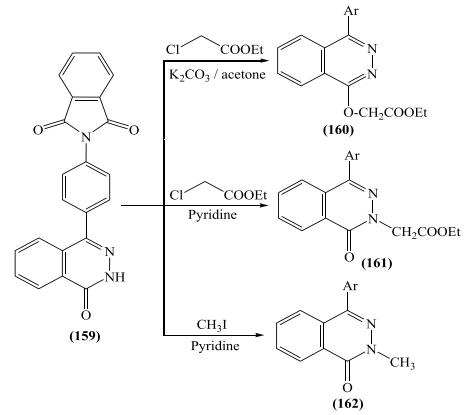
Scheme 42: Reaction of 1,4-dichlorophthalazine **150** with amine



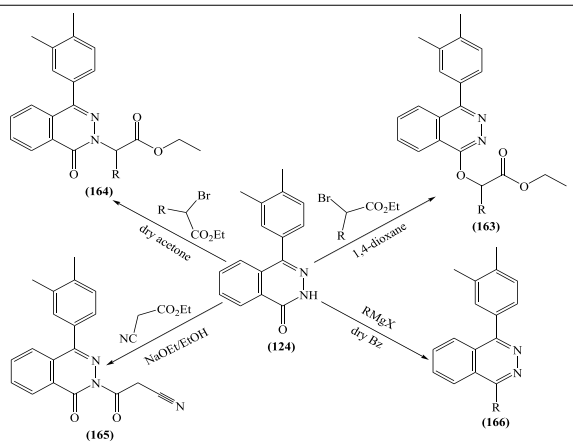
Scheme 43: Synthesis of *N*-hetaryl-3-aryl-5-ferrocenyl pyrazolines **155**.



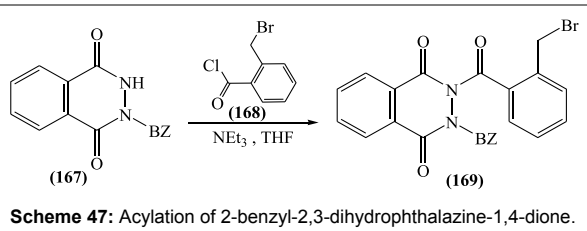
Scheme 44: Reaction of phthalazine with alkyl halides



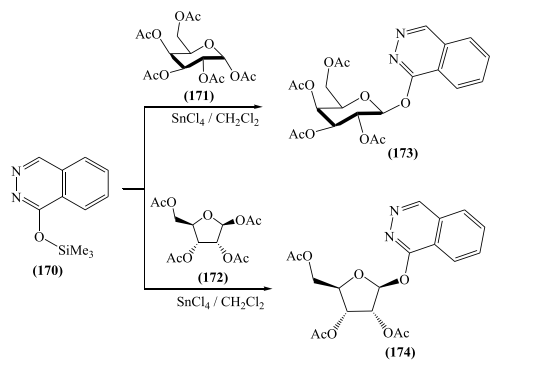
Scheme 45: Synthesis of novel phthalazine derivatives bearing isoindol-1,3-dione moiety



Scheme 46: Synthesis of a new series of 1,4-disubstituted phthalazines, and 2,4-disubstituted phthalazinones.



Scheme 47: Acylation of 2-benzyl-2,3-dihydrophthalazine-1,4-dione.



Scheme 48: Coupling of trimethylsilyl derivative of (2*H*) phthalazine-1-one **170** with galactopyranose and ribofuranose.

References

1. Lichtenthaler FW (2002) Unsaturated O- and N-heterocycles from carbohydrate feedstocks. Acc Chem Res 35: 728-737.
2. Litvinov VP (2003) Multicomponent cascade heterocyclisation as a promising route to targeted synthesis of polyfunctional pyridines. Russ Chem Rev 72: 69-85.
3. Xu Y, Guo QX (2004) Syntheses of Heterocyclic Compounds under Microwave Irradiation. Heterocycles 63: 903-974.
4. Al-Assar F, Zelenin KN, Lesiovskaya EE, Benzhan IP, Chakchir BA (2002) Synthesis and Pharmacological Activity of 1-Hydroxy-, 1-Amino-, and 1-Hydrazino-Substituted 2, 3-Dihydro-1H-pyrazolo[1, 2-a]pyridazine-5, 8-diones and 2, 3-Dihydro-1H-pyrazolo[1, 2-b]phthalazine-5, 10-diones. Pharm Chem J 36: 598-603.
5. Jain RP, Vederas JC (2004) Structural variations in keto-glutamines for improved inhibition against hepatitis A virus 3C proteinase. Bioorg Med ChemLett 14: 3655-3658.
6. Carling RW, Moore KW, Street LJ, Wild D, Isted C, et al. (2004) 3-phenyl-6-(2-pyridyl)methyloxy-1, 2, 4-triazolo[3, 4-a]phthalazines and analogues: high-affinity gamma-aminobutyric acid-A benzodiazepine receptor ligands with alpha 2, alpha 3, and alpha 5-subtype binding selectivity over alpha 1. J Med Chem 47: 1807-1822.
7. Grasso S, De Sarro G, De Sarro A, Micale N, Zappalà M, et al. (2000) Synthesis and anticonvulsant activity of novel and potent 6, 7-methylenedioxyphthalazin-1(2H)-ones. J Med Chem 43: 2851-2859.
8. Kornet MJ, Shackleford G (1999) Microwave synthesis and anticonvulsant activity of 2-benzyl-1(2H)-phthalazinones. J HeterocyclChem 36: 1095-1096.
9. Nassar OM (1997) Indian J HeterocyclChem7: 105-108.
10. Sivakumar R, Kishore Gnanasam S, Ramachandran S, Leonard JT (2002) Pharmacological evaluation of some new 1-substituted-4-hydroxy-phthalazines. Eur J Med Chem 37: 793-801.
11. Nomoto Y, Obase H, Takai H, Teranishi M, Nakamura J, et al. (1990) Studies on Cardiotonic Agents. II: Synthesis of Novel Phthalazine and 1, 2, 3-Benzotriazine Derivatives. Chem Pharm Bull 38: 2179-2183.
12. Cockcroft XL, Dillon KJ, Dixon L, Drzewiecki J, Kerrigan F, et al. (2006) Phthalazinones 2: Optimisation and synthesis of novel potent inhibitors of poly(ADP-ribose)polymerase. Bioorg Med ChemLett 16: 1040-1044.
13. Loh VM Jr, Cockcroft XL, Dillon KJ, Dixon L, Drzewiecki J, et al. (2005) Phthalazinones. Part 1: The design and synthesis of a novel series of potent inhibitors of poly(ADP-ribose)polymerase. Bioorg Med ChemLett 15: 2235-2238.
14. Sung Kim J, Lee HJ, Suh ME, Choo HY, Lee SK, et al. (2004) Synthesis and cytotoxicity of 1-substituted 2-methyl-1H-imidazo[4, 5-g]phthalazine-4, 9-dione derivatives. Bioorg Med Chem 12: 3683-3686.
15. Haider N, Kabicher T, Käferböck J, Plenk A (2007) Synthesis and in-vitro antitumor activity of 1-[3-(indol-1-yl)prop-1-yn-1-yl]phthalazines and related compounds. 12: 1900-1909.
16. Haikal AZ, El Ashry el SH, Banoub J (2003) Synthesis and structural characterization of 1-(D-glycosyloxy)phthalazines. Carbohydr Res 338: 2291-2299.
17. Demirayak S, Karaburun AC, Beis R (2004) Somepyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities. Eur J Med Chem 39: 1089-1095.
18. Hoffman BB (2006) Therapy of hypertension. In: 11th edition, Brunton LL(Ed). Goodman and Gilman's: The pharmacological basis of therapeutics, McGraw-Hill Medical publishing Division, New York 860-862.
19. Watanabe N, Kabasawa Y, Takase Y, Matsukura M, Miyazaki K, et al. (1998) 4-Benzylamino-1-chloro-6-substituted Phthalazines: Synthesis and Inhibitory Activity toward Phosphodiesterase 5. J Med Chem 41: 3367-3372.
20. Johnsen M, Rehse K, Pertz H, Stasch JP, Bischoff E (2003) New antithrombotic 1-phthalazinamines with serotonin antagonistic properties. Arch Pharm (Weinheim) 336: 591-597.
21. Madhavan GR, Chakrabarti R, Kumar SK, Misra P, Mamidi RN, et al. (2001) Novel phthalazinone and benzoxazinone containing thiazolidinediones as antidiabetic and hypolipidemic agents. Eur J Med Chem 36: 627-637.
22. Lenz EM, Wilson ID, Wright B, Partridge EA, Rodgers CT, et al. (2002) A comparison of quantitative NMR and radiolabelling studies of the metabolism and excretion of Statil (3-(4-bromo-2-fluorobenzyl)-4-oxo-3H-phthalazin-1-ylacetic acid) in the rat. J Pharm Biomed Anal 28: 31-43.
23. Cardia MC, Distinto S, Maccioni E, Delogu A (2009) Synthesis and biological activity evaluation of differently substituted 1, 4-dioxo-3, 4-dihydrophthalazine-2(1H)-carboxamides and -carbothioamides. J HeterocyclChem 40: 1011-1015.
24. Shetgiri NP, Nayak BK (2005) Synthesis and antimicrobial activities of oxadiazoles, phthalazines and indolinones. Ind JChem 44B: 1267-1272.
25. del Olmo E, Armas MG, López-Pérez JL, Ruiz G, Vargas F, et al. (2001) Anti-Trypanosoma activity of some natural stilbenoids and synthetic related heterocyclic compounds. Bioorg Med ChemLett 11: 2755-2757.
26. Dogruer DS, Kupeli E, Yesilada E, Sahin MF (2004) Synthesis of new 2-[1(2H)-phthalazinon-2-yl]acetamide and 3-[1(2H)-phthalazinon-2-yl]propanamide derivatives as antinociceptive and anti-inflammatory agents. Arch Pharm (Weinheim) 337: 303-310.
27. Napoletano M, Norcini G, Pellacini F, Marchini F, Morazzoni G, et al. (2000) The synthesis and biological evaluation of a novel series of phthalazine PDE4 inhibitors I. Bioorg Med ChemLett 10: 2235-2238.
28. Chakraborti AK, Gopalakrishnan B, Sobhia ME, Malde A (2003) Comparative molecular field analysis (CoMFA) of phthalazine derivatives as phosphodiesterase IV inhibitors. Bioorg Med ChemLett 13: 2473-2479.
29. Van der Mey M, Hatzelmann A, Vanklink GB, Van der laan, IJ, Sterk GJ, et al. (2001) Novel Selective PDE4 Inhibitors. 1. Synthesis, Structure−Activity Relationships, and Molecular Modeling of 4-(3, 4-Dimethoxyphenyl)-2H-phthalazin-1-ones and Analogues. J Med Chem 44: 2511-2522.
30. Van der Mey M, Boss H, Couwenerg D, Hatzelmann A, Timmerman H (2002) Novel selective phosphodiesterase (PDE4) inhibitors. 4. Resolution, absolute configuration, and PDE4 inhibitory activity of cis-tetra- and cis-hexahydrophthalazinones. J MedChem 45: 2526-2533.
31. Kirill MS, Kuznetsov VA, Galishev VA (2004) Synthesis of benzo[4, 5]imidazo[2, 1-a]phthalazines. Tetrahedron Lett 45: 1407-1408.
32. Herberich B, Cao GQ, Chakrabarti PP, Falsey JR, Pettus L, et al. (2008) Discovery of highly selective and potent p38 inhibitors based on a phthalazine scaffold. J Med Chem 51: 6271-6279.
33. DunctonMA, Piatnitski EL, Katoch-Rouse R, Smith LM 2nd, Kiselyov AS, et al. (2006) Arylphthalazines. Part 2: 1-(Isoquinolin-5-yl)-4-arylamino phthalazines as potent inhibitors of VEGF receptors I and II. Bioorg Med ChemLett 16: 1579-1581.
34. Sheradsky T, Moshenberg R (1986) Bridgehead hydrazines. 3. Unusual photorearrangement of 1, 4-diphenylpyridazino[1, 2-b]phthalazine-6, 11-dione. J OrgChem 51: 3123-3125.
35. Heine HW, Baclawski LM, Bonser SM, Wachob GD (1976) Diaziridines. 5. Reaction of some 1-aroyl- and 1, 2-diacyldiaziridines. J OrgChem 41: 3229-3232.
36. Ramtohul YK, James MN, Vederas JC (2002) Synthesis and evaluation of keto-glutamine analogues as inhibitors of hepatitis A virus 3C proteinase. J Org Chem 67: 3169-3178.
37. Liu LP, Lu JM, Shi M (2007) PhI(OAc)2 -mediated novel 1, 3-dipolar cycloaddition of methylenecyclopropanes (MCPs), vinylidenecyclopropanes (VCPs), and methylenecyclobutane (MCB) with phthalhydrazide. Org Lett 9: 1303-1306.
38. Csxmpai A, Kormendy K, Ruff F (1991) Chain length dependent reactivity of 2-(ω-hydroxyalkyl)-4-(ω-hydroxyalkylamino)phthalazin-1(2h)-ones in azeotropichydrobromic acid. Tetrahedron 47: 4457-4464.
39. Amarasekara AS, Chandrasekara S (2002) Reaction of 1, 4-phthalazinedione with furfural: formation of the [5, 6]benza-3a, 7a-diazaindane system via an unusual skeletal rearrangement. Org Lett 4: 773-775.
40. Hwang JY, Choi HS, Gong YD (2005) Solid-phase synthesis of [1, 2, 4] triazolo[3, 4-a]phthalazine and tetrazolo[5, 1-a]phthalazine derivatives. Tetrahedron Lett46: 3107-3110.
41. Gökce H, Bahceli S (2010) Analysis of molecular structure and vibrational spectra of 1(2H)-phthalazinone. J Molecular Structure 967: 42-46.

42. Napoletano M, Norcini G, Pellacini F, Marchini F, Morazzoni G, et al. (2001) Phthalazine PDE4 inhibitors. Part 2: The synthesis and biological evaluation of 6-methoxy-1, 4-disubstituted derivatives. Bioorg MedChemLett 11: 33-37.

43. Bruno C, Elivo B (1969) Farmac Ed Sci 24: 833.

44. Napoletano M, Norcini G, Pellacini F, Marchini F, Moraazzoni G, et al. (2002) Phthalazine PDE4 inhibitors. Part 3: The synthesis and in vitro evaluation of derivatives with a hydrogen bond acceptor. Bioorg Med ChemLett 12: 5-8.

45. Bedoya LM, del Olmo E, Sancho R, Barboza B, Beltrán M, et al. (2006) Anti-HIV activity of stilbene-related heterocyclic compounds. Bioorg Med ChemLett 16: 4075-4079.

46. Ikuo M, Fujinori S (1973) JapanKokai, 73, 44, 281.

47. Taketo H (1995) Eur Pat ApplEp 652: 213.

48. Viña D, Olmo ED, Pérez JLL, Feliciano AS (2009) Pyrazolo[3, 4, 5-de] phthalazine. Syntheses of a practically unknown heterocyclic system. Tetrahedron 65: 1574-1580.

49. del Olmo, Barboza B, Ybarra MI, López-Pérez JL, Carrón R, et al. (2006) Vasorelaxant activity of phthalazinones and related compounds. Bioorg Med ChemLett 16: 2786-2790.

50. Havaldar FH, Dabholkar BV, Mule GB (2013) Microwave-Promoted Synthesis of Some Novel 4-(4-Methyl-phenyl)-Substituted Phthalazin-1-one Derivatives. Synth Commun 43: 1127-1137.

51. Agrawal M, Kharkar P, Moghe S, Mahajan T, Deka V, et al. (2013) Discovery of thiazolyl-phthalazinoneacetamides as potent glucose uptake activators via high-throughput screening. Bioorg Med ChemLett 23: 5740-5743.

52. Xiao S, Wang J, Jin K, Jian X, Peng Q (2003) Synthesis and characterization of a fluorinated phthalazinone monomer 4-(2-fluoro-4-hydroxyphenyl)-phthalazin-1(2H)-one and its polymers from polycondensation reactions. Polymer 44: 7369-7376.

53. AbdAlla MS, Hegab MI, Abo Taleb NA, Hasabelnaby SM, Goudah A (2010) Synthesis and anti-inflammatory evaluation of some condensed [4-(3, 4-dimethylphenyl)-1(2H)-oxo-phthalazin-2-yl]acetic acid hydrazide. Eur J Med Chem 45: 1267-1277.

54. Abubshait SA, Kassab RR, Al-Shehri AH, Abubshait HA (2011) Synthesis and reactions of some novel 4-biphenyl-4-(2H)-phthalazin-1-one derivatives with an expected antimicrobial activity. J Saudi ChemSoc 15: 59-65.

55. Smith CD, Tchabanenko K, Adlington RM, Baldwin JE (2006) Synthesis of linked heterocycles via use of bis-acetylenic compounds. Tetrahedron Lett 47: 3209-3212.

56. Knöpfel TF, Zarotti P, Ichikawa T, Carreira EM (2005) Catalytic, enantioselective, conjugate alkyne addition. J Am ChemSoc 127: 9682-9683.

57. Deshpande SR, Ghongade AM, Pai VK (2010) Synthesis and biological evaluation of 2-(N-substituted)-3H-phthalazin-1, 4-diones and 1-(N-substituted) 2, 4, 5-trihydropyridazin-3, 6-diones as potent vasodilators. Indian. J Pharm Educ Res 44: 1-7.

58. Salvi VK, Bhambi D, Jat JL, Talesara GL (2006) Synthesis and antimicrobial activity of some 2-[1-(4-oxo-3, 4-dihydrophthalazine-1-yl)alkyl]-1H-isoindole-1, 3(2H)-dione and their imidoxy derivatives ARKIVOC 14: 133-140.

59. Liu Y, Zhang S, Li Y, Wang J, Song Y, et al. (2012) Synthesis and cytotoxic evaluation of some new phthalazinylpiperazine derivatives. Arch Pharm (Weinheim) 345: 287-293.

60. Chunduru VSR, Rao VR (2013) Synthesis of Aryl and Heteryl 1, 3, 4-Thiadiazinyl-phthalazine-1, 4-dione Derivatives via a Multicomponent Approach. Synth Comunn 43: 923-929.

61. Lukacs G, Simig G (2009) Synthesis of new 1, 2-dihydrophthalazines. J HeterocyclChem39: 989-996.

62. BouffardJ, Eaton RF, Müller P, Swager TM (2007) Iptycene-derived pyridazines and phthalazines. J Org Chem 72: 10166-10180.

63. Nguyen HN, Cee VJ, Deak HL, Du B, Faber KP, et al. (2012) Synthesis of 4-substituted chlorophthalazines, dihydrobenzoazepinediones, 2-pyrazolylbenzoic acid, and 2-pyrazolylbenzohydrazide via 3-substituted 3-hydroxyisoindolin-1-ones. J Org Chem 77: 3887-3906.

64. Ryu CK, Park RE, Ma MY, Nho JH (2007) Synthesis and antifungal activity of 6-arylamino-phthalazine-5, 8-diones and 6, 7-bis(arylthio)-phthalazine-5, 8-diones. Bioorg Med ChemLett 17: 2577-2580.

65. Marosvolgyi-HaskoD, Petz A, Takacs A, Kollar L (2011) Synthesis of tetrahydrophthalazine and phthalamide (phthalimide) derivatives via palladium-catalysedcarbonylation of iodoarenes. Tetrahedron 67: 9122-9128.

66. Aljaar N, Conrad J, Beifuss U (2013) Synthesis of 2-aryl-1, 2-dihydrophthalazines via reaction of 2-(bromomethyl)benzaldehydes with arylhydrazines. J Org Chem 78: 1045-1053.

67. Soliman AY, El-Komy MAS (1999) Egyptian "Synthesis and Reactions of 1-(substituted) -4H-3, 2- Benzoxazin -4- ones". J Chem 42: 301-308.

68. Kassab EA (2003) Egypt J Chem 46B, 357.

69. Kassab EA, El-Hashash, SolimanMA, AliFMARS (2001) Egypt J Chem 44B 169.

70. Ozer G, Saracoglu N, Menzek A, Balci M (2005) Synthesis of the possible carcinogenic dihydrodiol and diol epoxide of phthalazine. Tetrahedron 61: 1545-1550.

71. Sun XI, Zheng JC, Tang Y (2010) Iron carbenoid-mediated ylide reactions. Pure ApplChem 82: 625-634.

72. Keshipour S, Shojaei S, Shaabani A (2012) A novel one-pot isocyanide-based four-component reaction: synthesis of highly functionalized 1H-pyrazolo[1, 2-b]phthalazine-1, 2-dicarboxylates and 1H-pyrazolo[1, 2-a]pyridazine-1, 2-dicarboxylates. Tetrahedron 68: 6141-6145.

73. Song SH, Zhong J, He YH, Guan Z (2012) One-pot four-component synthesis of 1H-pyrazolo[1, 2-b]phthalazine-5, 10-dione derivatives. Tetrahedron 53: 7075-7077.

74. D'Alo G, Conti G, Cadel S, Dalla VR, (1978) Farmaco Ed Sci 33: 106.

75. Lebsack AD, Gunzner J, Wang B, Pracitto R, Schaffhauser H, et al. (2004) Identification and synthesis of [1, 2, 4]triazolo[3, 4-a]phthalazine derivatives as high-affinity ligands to the alpha 2 delta-1 subunit of voltage gated calcium channel. Bioorg Med ChemLett 14: 2463-2467.

76. Ghahremanzadeh R, Shakibaei GI, Bazgir A (2008) An Efficient One-Pot Synthesis of 1H-Pyrazolo[1, 2-b]phthalazine-5, 10-dione Derivatives. Synlett 8: 1129-1132.

77. Nabid MR, Rezaei SJ, Ghahremanzadeh R, Bazgir A (2010) Ultrasound-assisted one-pot, three-component synthesis of 1H-pyrazolo[1, 2-b] phthalazine-5, 10-diones. UltrasonSonochem 17: 159-161.

78. Raghuvanshi DS, Singh KN (2011) A highly efficient green synthesis of 1H-pyrazolo[1, 2-b]phthalazine-5, 10-dione derivatives and their photophysical studies. Tetrahedron Lett 52: 5702-5705.

79. Sayyafi M, Seyyedhamzeh M, Khavasi HR, Bazgir(2008) One-pot, three-component route to 2H-indazolo[2, 1-b]phthalazine-triones. A Tetrahedron64: 2375-2378.

80. Reddy MV, Jeong YT (2013) InCl3-catalyzed green synthesis of 1H-pyrazolo[1, 2-b]phthalazine-5, 10-diones under solvent-free conditions. Tetrahedron Lett 54: 3546-3549.

81. Shah NM, Patel MP, Patel RG (2012) An Efficient and Facile Synthesis of 1H-Pyrazolo[1, 2-b]phthalazine-5, 10-dione Derivatives of Biological Interest. J HeterocyclChem 49: 1310-1316.

82. Zhang XN, Li YX, Zhang ZH (2011) Nickel chloride-catalyzed one-pot three-component synthesis of pyrazolophthalazinylspirooxindoles. Tetrahedron 67: 7426-7430.

83. Chen H, Shi DQ (2013) Efficient One-Pot Synthesis of Spiro[indoline-3, 1′-pyrazolo[1, 2-b] phthalazine] Derivatives via Three-Component Reaction. J HeterocyclChem 50: 56-60.

84. Rezaei SJT, Bide Y, Nabid MR (2012) An efficient ultrasound-promoted one pot synthesis of spiroacenaphthylenepyrazolotriazole and pyrazolophthalazine derivatives. Tetrahedron Lett 53: 5123-5126.

85. Torkian L, Dabiri M, Salehi P, Bararjanian M (2011) An Efficient One-Pot, Four-Component Synthesis of {[(1H-1, 2, 3-Triazol-4-yl)methoxy]phenyl}-1H-pyrazolo[1, 2-b]phthalazine-5, 10-dione Derivatives. HelvChimicaActa 94: 1416-1425.

86. Shaterian HR, Ghashang M, Feyzi M (2008) Silica sulfuric acid as an efficient catalyst for the preparation of 2H-indazolo[2, 1-b]phthalazine-triones. Applied Catalysis A: General 345, 128-133.

87. Kidwai K, Jahan A, Chauhan R, Mishra NK (2012) Dodecylphosphonic acid (DPA): a highly efficient catalyst for the synthesis of 2H-indazolo[2, 1-b] phthalazine-triones under solvent-free conditions. Tetrahedron Lett 53: 1728-1731.

88. Yavari I, Djahaniani H, Nasiri F (2004)A simple synthesis of highly functionalized 1-azabutadienes and ketenimines. Collect Czech ChemCommun69, 1499-1505.

89. Mavel S, Thery I, Gueiffier A (2002) Synthesis of imidazo[2, 1-a]phthalazines, potential inhibitors of p38 MAP kinase. Prediction of binding affinities of protein ligands. Arch Pharm (Weinheim) 335: 7-14.

90. El-Hashash MA, El-Badry YA (2012) Behavior of 4-(3, 4-dimethyl-phenyl)-1(2H)-phthalazinone towards carbon electrophiles and carbon nucleophiles. J Chem Pharm Res 4: 2354-2361.

91. Abd El-Ghaffar NF, Mohamed MA, Ghanem HM, Zaki HM (2011) Synthesis and Biochemical Evaluation of Some Substituted Phthalazines. J Am Sci 7: 771-781.

92. Ghahremanzadeh R, Ahadi S, Sayyafi M, Bazgir A (2008)Reaction of phthalhydrazide and acetylenedicarboxylates in the presence of N-heterocycles: an efficient synthesis of phthalazine derivatives. Tetrahedron Lett 49: 4479-4482.

93. Iwamoto K, Suzuki S, Oishi E, Tanji K, Miyashita A, Higashino T (1995) Chem Pharm Bull 43: 679-682.

94. Oishi E, Taido N, Iwamoto K, Miyashita A, Higashino T (1990)Chem Pharm Bull 38: 3268.

95. Türkmen YE, Montavon TJ, Kozmin SA, Rawal VH (2012) Silver-catalyzed formal inverse electron-demand Diels-Alder reaction of 1, 2-diazines and siloxy alkynes. J Am ChemSoc 134: 9062-9065.

96. Haider N, Käferböck J (2004) Intramolecular [4+2] cycloaddition reactions of indolylalkylpyridazines: synthesis of annulated carbazoles. Tetrahedron 60: 6495-6507.

97. Orru RVA, De Greef M (2003) Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds. Synthesis 4: 1471-1499.

98. Sanz AM, Gómez-Contreras F, Navarro P, Sánchez-Moreno M, Boutaleb-Charki S, et al. (2008) Efficient inhibition of iron superoxide dismutase and of Trypanosomacruzi growth by benzo[g]phthalazine derivatives functionalized with one or two imidazole rings. J Med Chem 51: 1962-1966.

99. Rodríguez-Ciria M, Sanz AM, Yunta MJ, Gomez-Contreras F, Navarro P, et al. (2003) Synthesis and cytotoxic activity of N, N-bis-(3-[N-(4-chlorobenzo[g]-phthalazin-1-yl)]aminopropyl)-N-methylamine: a new potential DNA bisintercalator. Bioorg Med Chem 11: 2143-2148.

100. Piatnitski EL, Matthew AJD, Alexander SK, Reeti KR, Dan S, et al. (2005) Bioorg MedChemLett 15: 2496-2698.

101. Guery S, Parrot I, Rival Y, Wermuth CG (2001) Synthesis of 4-Aryl-1-(4-methylpiperazin-1-yl)phthalazines by Suzuki-type Cross-coupling Reaction. Synthesis 4: 699-701.

102. Warrener RN, Butler DN, Liu L, Margetic D, Russell RA (2001) Incorporation of a molecular hinge into molecular tweezers by using tandem cycloadditions onto 5, 6-dimethylenenorbornene. Chemistry 7: 3406-3414.

103. Wasfy AF, Aly AA, Behalo MS, Mohamed NS (2013) An efficient synthesis of some new 1, 4-disubstituted phthalazine derivatives and their anticancer activity. Der PharmaChemica 5: 82-96.

104. Wasfy AF, Aly AA, Behalo MS, Mohamed NS (2013) Chemical and Process Eng Res 10: 20-32.

105. Pal M, Batchu VR, Parasuraman K, Yeleswarapu KR (2003) Aluminum chloride-induced heteroarylation of arenes and heteroarenes. 2. A new synthesis of 4-substituted phthalazin-1(2H)-ones. J Org Chem 68: 6806-6809.

106. Tukhvatullin OR, Sakhautdinov IM, Galin FZ (2008) UDK (Russia) 13: 254-255.