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An Overview of Different Synthetic Routes for the Synthesis of Phthalazine Derivatives

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

This review paper describes the different synthetic routes used for the synthesis of substituted phthalazine derivatives. Phthalazines have been used as building blocks for the synthesis of a new molecule with heterocyclic structure. These new molecules are highly useful in medicinal chemistry for the researchers leading to the further development of new molecules which have potency and effectiveness to produce a desired pharmacological response.

Keywords: Phthalazine; phthalazinone; thiazolo; phthalic anhydride.

1. INTRODUCTION

Phthalazines are a unique well-known class of nitrogen-containing heterocyclic compounds. The discovery of the first naturally occurring pyridazine derivative was a milestone in the recognition of the potential of 1, 2-diazine core nucleous as a valuable unit in medicinal

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chemistry [1]. Hydralazine also has been used pharmacologically as anti-hypertensive and vasodilating agent [2]. More recently, some 3,6-substituted phthalazines have been reported as a pharmacologically active scaffold for anticonvulsants activity.

Phthalazines are important building blocks in the construction of a new molecular system for biologically active molecules [3,4,5]. The development of new and efficient methodologies for the potentially bioactive 4-hydrazinophthalazine-1-one derivative is important.

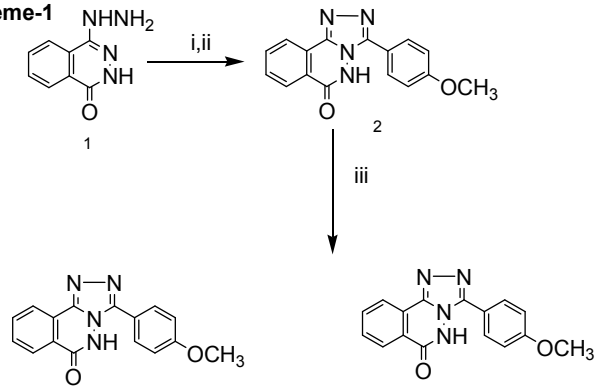
Mostly, 4-hydrazinophthalazine-1-one is used as starting material for the synthesis of various derivatives. Triazolo phthalazine is also considered as pharmacologically highly active molecule having different pharmacological activities like anti inflammatory [6,7], PDE4 inhibitors [8,9], cardiotonic [10], antitumor [11,12,13], vasorelaxant [14], antibacterial [15], antimicrobial [15], antioxidant [16], antidiabetic [17] and anticonvulsant [3,5,18]. Various established drug molecules like budralazine [16] and Azelastine [8,19] are prepared from the corresponding phthalazine-1- one.

The current review paper suggests new ways for researchers to develop more effective and safer drugs hence may be imperative and challenging in medicinal chemistry [20].

2. SYNTHESIS OF PHTHALAZINE DERIVATIVES BY VARIOUS SYNTHETIC ROUTE

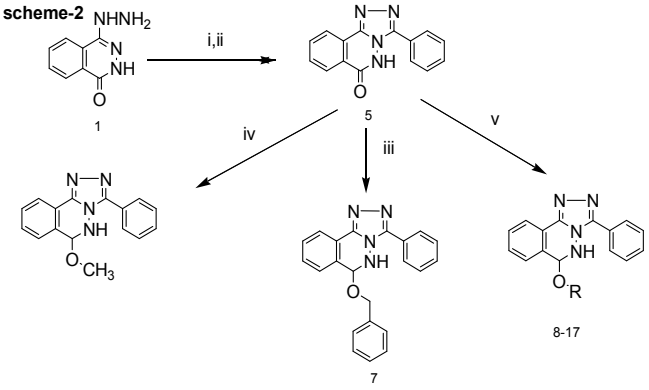
Robert W. Carling *et al*. reported the synthesis of 3-phenyl–6-(2 pyridyl) methyloxy -1, 2, 4- triazolo (3, 4 - a) Phthalazines derivatives.

scheme-1



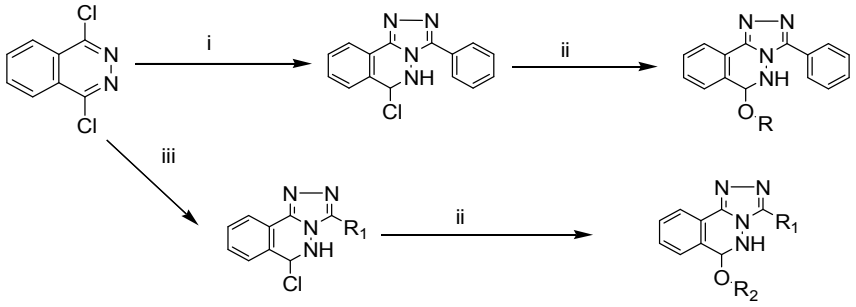
Reagents: (i)4methoxy benzoyl chloride,Et_3N,1,4dioxane,room temp;(ii) DMF,reflux(iii)NaH,DMF,Ph_2Br 100 temp.

scheme-2



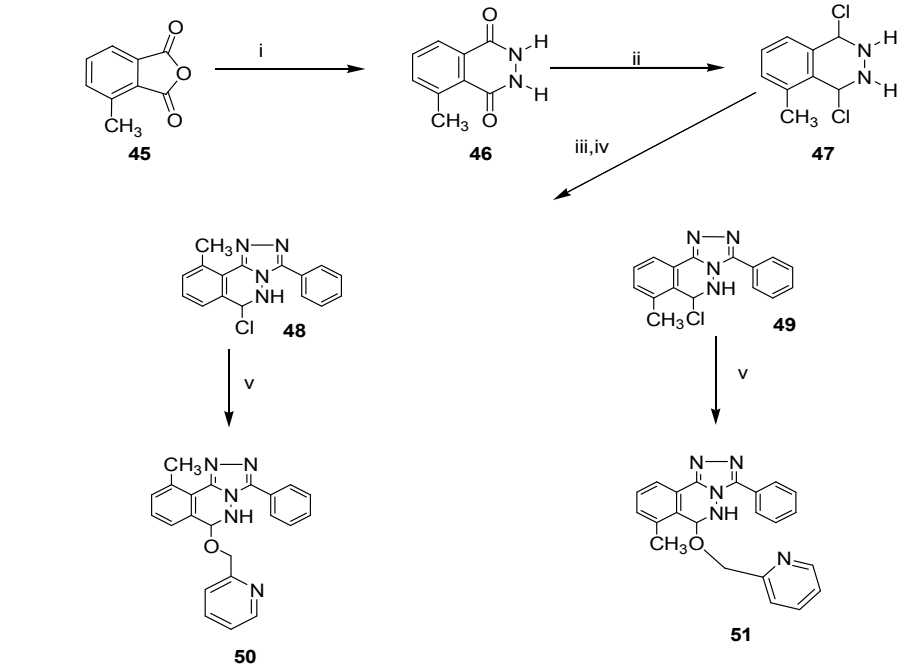
Reagents: (i)benzoyl chloride,Et_3N,1,4 dioxan,room temp;(ii) DMF, reflux (iii) NaH,DMF,$PhCH_2Br$,100 temp (iv) NaH,DMF,CH_3I (V)NaH,DMF,RCH_2Br or RCH_2Cl.

scheme-3



Reagents: (i) $PhCONHNH_2$, Et_3N, Diaxone, reflux; (ii)ROH, NaH, DMF; (iii)$R_1CONHNH_2$,Et_3N, Xylene, Reflux; (iv)R_1COCl, Et_3N, Diaxone, reflux.

scheme-4



Reagents: (i) $NH_2NH_2.H_2O$, AcOH,NaOAC,reflux; (ii) $POCl_3$,reflux,(iii) $PhCONHNH_2$, Et_3N,xylene,reflux(iv) chromatography;(v) ROH, NaH, DMF.

Lei Zhang introduced a new series of derivatives that contains 6 – alkoxy – (1,2,4,) triazolo (3, 4 -a) phthalazines nucleus. 1, 4 dichlorophthalazine proceeded for reaction with formic hydrazide and appropriate alcohol in the presence of xylene. (Shown in Table-1) to produce a number of phthalazine derivatives.

Scheme-5

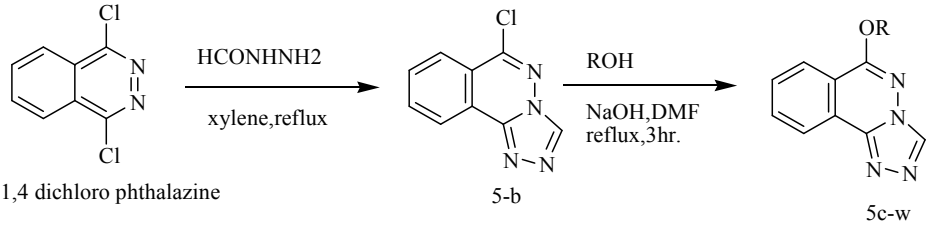


Table 1. Different R substituent's showed below (5c-5w)

5c -C_6H_5	5j-$C_{10}H_7$	5q-C_3H_7
5d -C_6H_4(O-CH_3)	5k-C_6H_4(o-OCH_3)	5r-n-C_4H_9
5e- C_6H_4(m-CH_3)	5l-C_6H_4(p-OCH_3)	5s-n-C_6H_{13}
5f-C_6H_4(p-CH_3)	5m - C_6H_4(p-NO_2)	5t-nC_7H_{15}
5g-C_6H_4(p-F)	5n- C_6H_4(p-NH_2)	5u-nC_8H_{17}
5h-C_6H_4(p-Cl)	5o-CH_3	5v-n$C_{10}H_{21}$
5i-$CH_2C_6H_3$(2,4-Cl_2)	5p-C_2H_5	5w-nC_5H_{11}

A new series of 6 – alkoxy (1, 2, 4) triazolo (3, 4 - a) phthalazine – 3 (2H) one was prescribed by Ching in 2011 using appropriate amount of 1-chloro- 4 – alkoxy phthalazine as starting material and reacting it with methyl hydrazine carboxylate. 1 chloro – 4 – alkoxy phthalazines (6d-u) were synthesized from phthalic anhydride. (6d-u) further treated with hydrazine hydrate in the presence of ethanol to yield 6-substituted 1, 2, 4 triazolo [3,4-a] phthalazin-3(2H)-one derivatives.

2,3 dihydrophthalazine 1,4 dione further reacted with phosphorous oxychloride to give 1,4 di chlorophthalazine which then reacted with appropriate alkanol and substituted phenol in dimethyl formamide to give different derivatives. These derivatives were used as a reactant to react in the presence of dimethyl sulfoxide with methyl hydrazine carboxylate. In this way, the researcher was able to produce a series of 6-alkoxy (1,2,4) triazolo (3,4-a) phthalazine- 3(2H)-one derivatives. (Cheng –Xi et al., 2011).

For the synthesis of 2 – (4 – (4 phenoxyphenyl) phthalazine – 1 – yl) – malononitrile, an equimolar amount of chlorophthalazine (0.01 mol) was made to react with ethylene in ethanol containing sodium ethoxide. This reaction mixture was refluxed for 6 hours at 70°C temperature. After the completion of the reaction the reaction mixture was poured into ice. The solid was collected and washed with a suitable solvent to give respective derivatives.

A mixture of (2-(4-(4-phenoxyphenyl) phthalazin-1-yl) malononitrile (0.1 mol), ethyl 2-cyano-2-(4-(4-phenoxyphenyl)phthalain-1yl) acetate (0.01 mol) and hydrazine hydrate (0.01 mol) in methanol (20 ml) were taken in round bottom flask and refluxed for 6 hour, then allowed to cool and product was collected by filtration and finally recrystalized using appropriate solvent.

Scheme-6

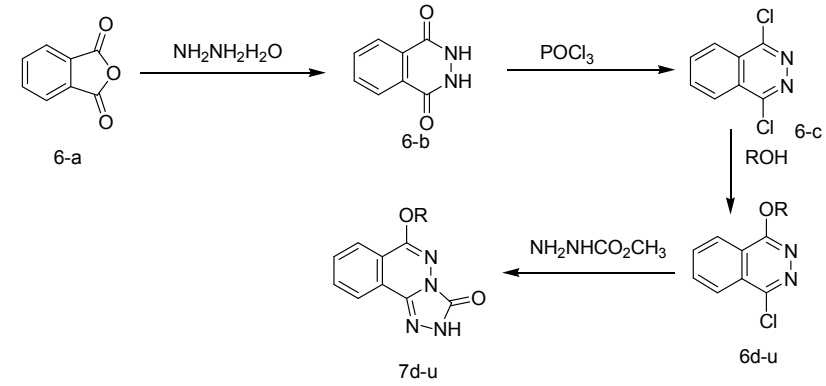
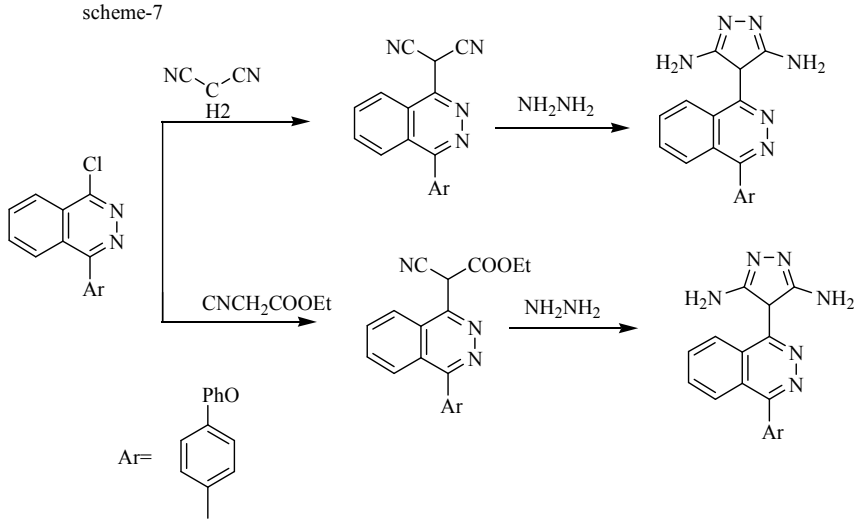


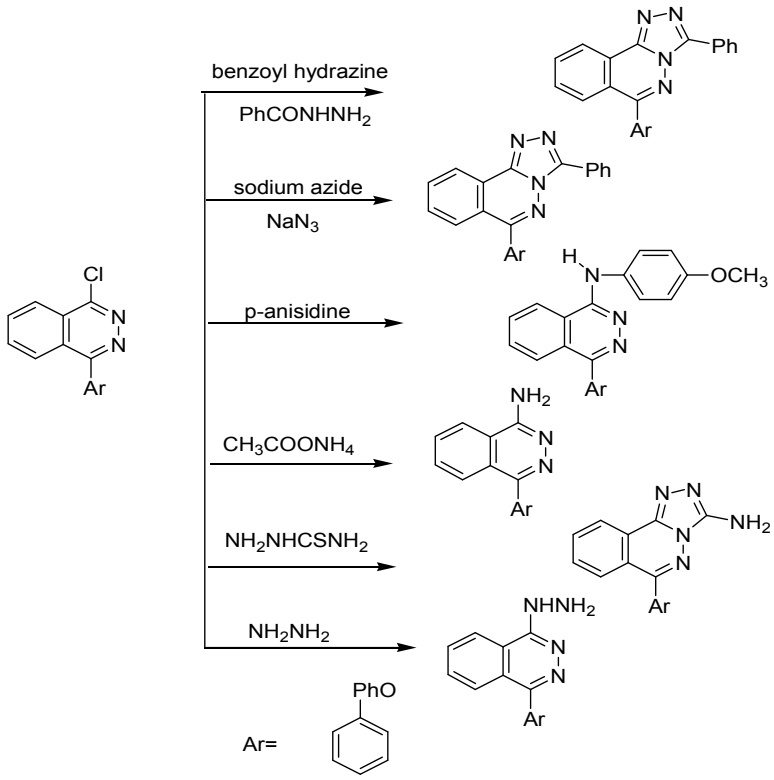
Table 2. Different R substituent's shown below (7d-7u)

7d = n-C_4H_9	7j= -C_6H_5	7p =-C_6H_4 (4-Br)
7e= n-C_5H_{11}	7k= -C_6H_4 (4-F)	7q= -C_6H_4 (2-CH_3)
7f = n-C_6H_{13}	7l= -C_6H_4(2-Cl)	7r= -C_6H_4 (3-CH_3)
7g = n-C_7H_{15}	7m= -C_6H_4(3-Cl)	7s= -C_6H_4 (4-CH_3)
7h = n-C_8H_{17}	7n = -C_6H_4(4-Cl)	7t= -C_6H_4 (2-OCH_3)
7i= n-$C_{10}H_{21}$	7o= -C_6H_3(2,4-Cl_2)	7u= -C_6H_4 (4-OCH_3)

scheme-7



Scheme-8



Synthesis of 4- (4 – (4- phenoxyphenyl) phthalazine – 1- yl) 4H – pyrazole – 3, 5 di – amine

In this scheme (8), chlorophthalazine was reacted with benzoyl hydrazine using n-butanol as a solvent. Under the refluxed condition, it gave 6 – (4 – phenoxy phenyl) – 3 phenyl – (1, 2, 4) triazolo (3, 4-a) phthalazine.This is further treated with sodium azide. In this scheme, chlorophthalazine was treated with Para anisidine to give phthalazine derivatives.

When chlorophthalazine was reacted with ammonium acetate it gave amino phthalazine. On the other hand, chlorophthalazine upon

reaction with thiosemicarbozone produce amino triazolo phthalazine derivatives.

When chlorophthalazine reacted with hydrazine hydrate in the presence of ethanol it gave 1 – hydrazinyl – 4 – (4 – phenoxyphenyl) phthalazine derivatives [21].

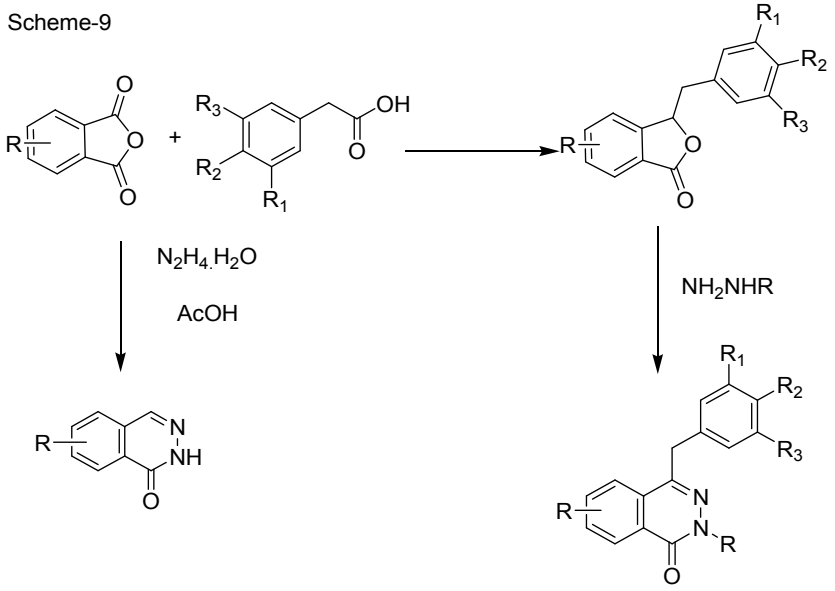
Phthalic anhydride was used as starting material for the synthesis of phthalazinones derivatives as depicted in the following scheme.

For the synthesis of phthalazinone derivatives, reactant phthalic anhydrides were reacted with hydrazine hydrates in the presence of acetic acid.

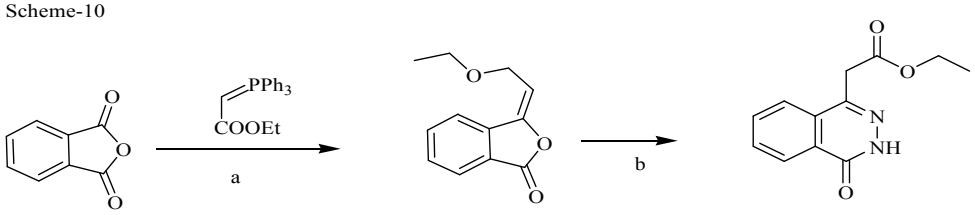
In this scheme (11), phthalic anhydride was used as starting material for the synthesis of phthalazine (2H) -1-one derivatives. Initially, aromatic hydrocarbons reacted with anhydrous aluminium chloride it gives an intermediate product. This intermediate product reacted with hydrazine hydrates and substituted hydrazine. Upon completion of reaction, phthalazine (2H) -1-one derivatives were produced as shown in scheme 11.

In 2004, K.M. Shubin prescribed the synthesis of benzimidazo phthalazines using aryl hydrazines substituted in the benzene ring to introduce the N–N group. Cyclization of such hydrazines with o-acylbenzoic acids in the scheme leads to the generation of the phthalazine ring. This makes it easier to change substituents in position 4 of the phthalazinone. Thus, the employment of different o-acyl substituted benzoic acids gave a set of C-5 substituted benzimidazophthalazines. In this work o-acetylbenzoic, o-benzoylbenzoic, and 2-(4-toluoyl) enzoic acids were used. The reactions will continue in boiling an ethanolic solution of concentrated sulfuric acid. Cyclization of 2-nitro-5-chlorophenyl hydrazine with acyl benzoic acids produced 2-(2-nitro-5-chlorobenzene)-4-substituted phthalazin-1-ones derivatives. A chlorine atom in the p-position relative to the nitro group of the benzene ring was sufficiently activated for nucleophilic aromatic substitution and was easily exchanged by aliphatic amines. Applying this reaction, phthalazinones (4a–f) were prepared. Nitro compounds (3a–c) and (4a–f) were reduced to the corresponding anilines (5a–i) by hydrogenation with hydrogen at room temperature and at normal pressure. This process was carried out in a THF solution because of the solubility of the reagents and products. When a Pd catalyst or fresh Raney nickel was used, only selective nitro group reduction occurred. Other fragments of the molecule remain unchanged. Anilines were obtained which were pured by TLC, by crystallization from the reaction mixture (after filtration of the catalyst) and by dilution with petrol ether (40–70°C) in a 1:8 ratio. Heating the amino phthalazinones (5a–i) in polyphosphoricacid (PPA) to 100–120°C for a short time yielded benzimidazophthalazines (6a–i) by intramolecular cyclodehydration [22].

Scheme-9

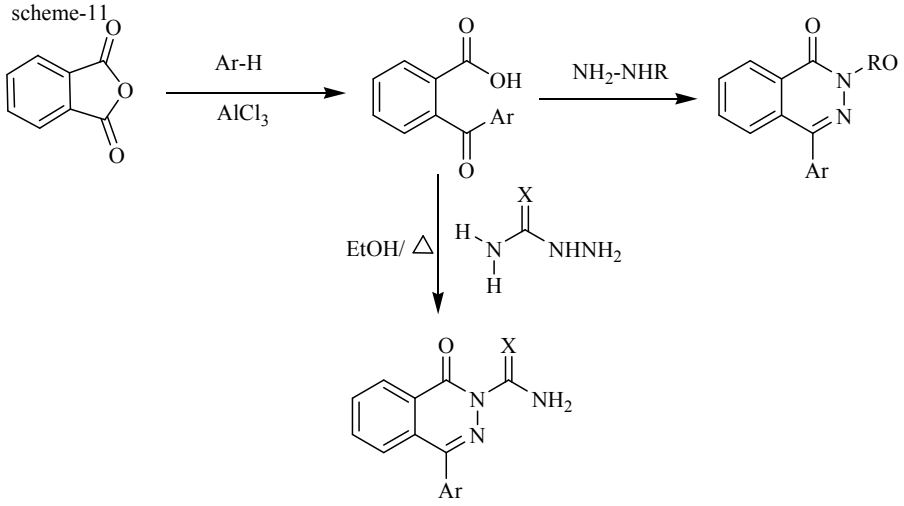


Scheme-10



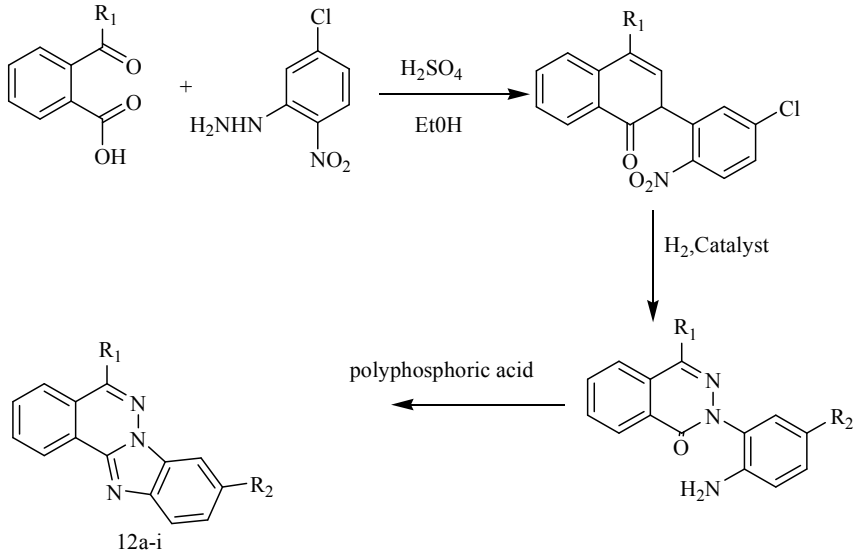
reagents: (a)$CHCl_3$,reflux,5hr,(b)hydrazinehydrate,EtOH,addition at room temp,reflux,2hr

scheme-11



Synthesis of phthalain(2H)-1-one

Scheme-12



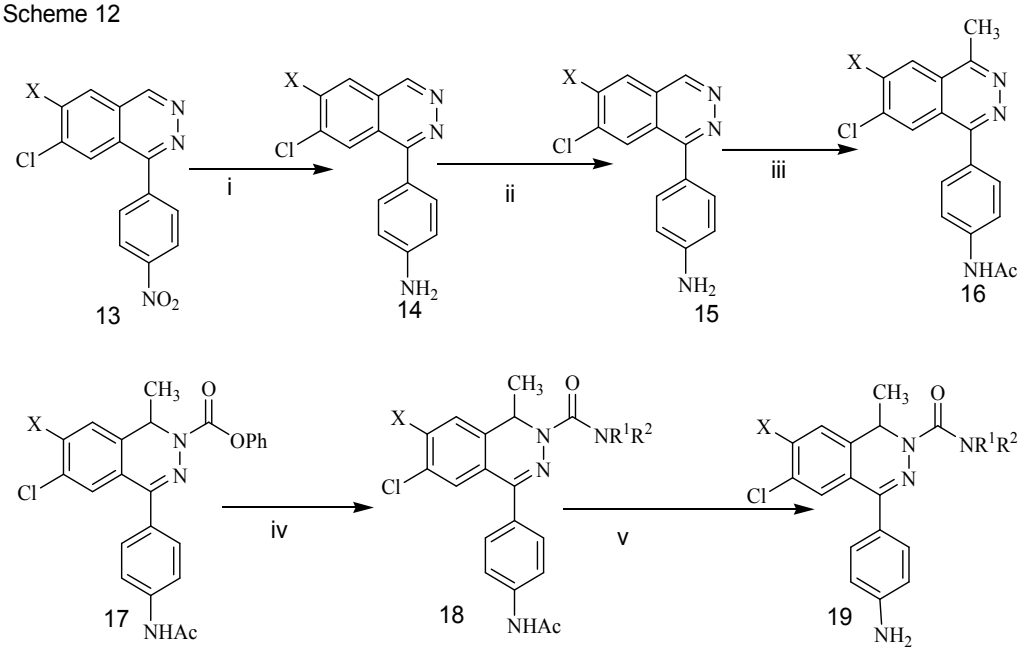
12a-i

Gyula Lukacs and Gyula Simig synthesized new 1,2-dihydrophthalazines derivatives in 2009 using different synthetic pathways. 6,7-dichloro-1-(4-nitrophenyl) phthalazine or 7-chloro-1-(4-nitrophenyl) phthalazines were the key intermediates for the synthesis of different derivatives as shown in scheme 12.

In this synthesis, 3-methoxy benzoic acid was used as a starting material which undergone chloroformylation followed by radical bromination of next intermediate favourable for improvement of the yield of next derivatives. The reaction of phthaloyl chloride with N-methyl acetophenone hydrazones lead to the formation of phthalazine derivative.

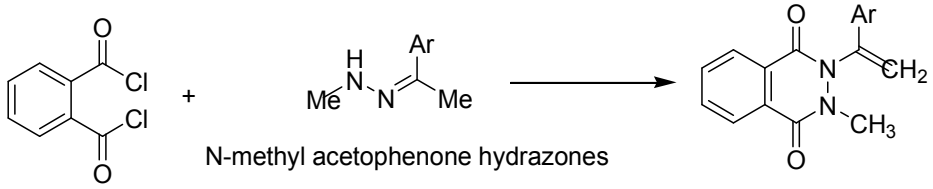
3,2-benzoxazin-4-ones reacted with various type of nitrogen-containing reactants, successfully produced a different type of phthalazinone derivatives. When 1-aryl- 3,2-benzoxazin-4-ones reacted with hydrazine and ethanol in refluxing condition yielded bis-phthalazinone. Fusion of benzoxazin-4-one with ammonium acetate at 115°C gave 4-aryl-1(2*H*)-phthalazinone. The 4-aryl-2-(4-methylphenyl) phthalazinones were obtained by reacting the benzoxazine-4-ones and p-toludine in refluxing ethanol. (Scheme 14).

Scheme 12



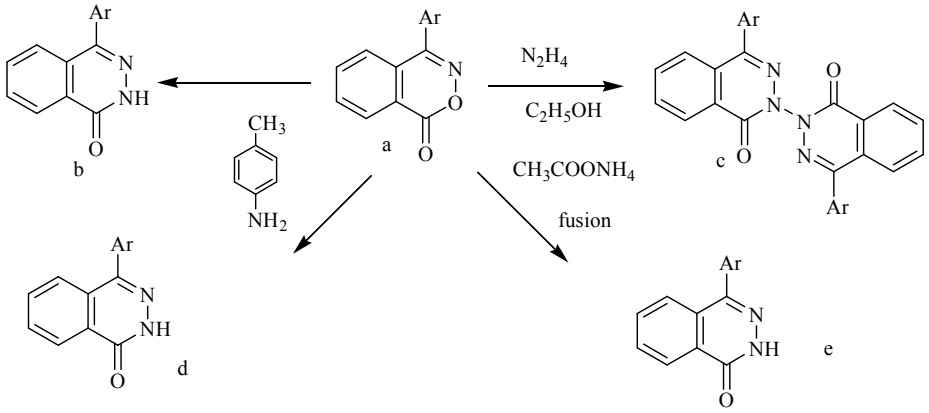
reagents-: i) Iron, Hydrochloric acid, ethanol ii) AC_2O, Methanol iii) tetrahydro furan iv) PhOCOCl, TEA, THF v) nNR^1R^2, DMF vi) NaOH, water, methanol.

Scheme-13



phthaloyl chloride

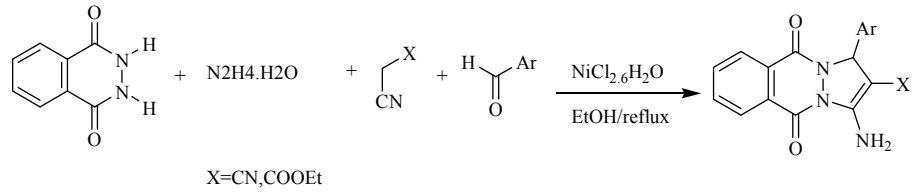
scheme-14



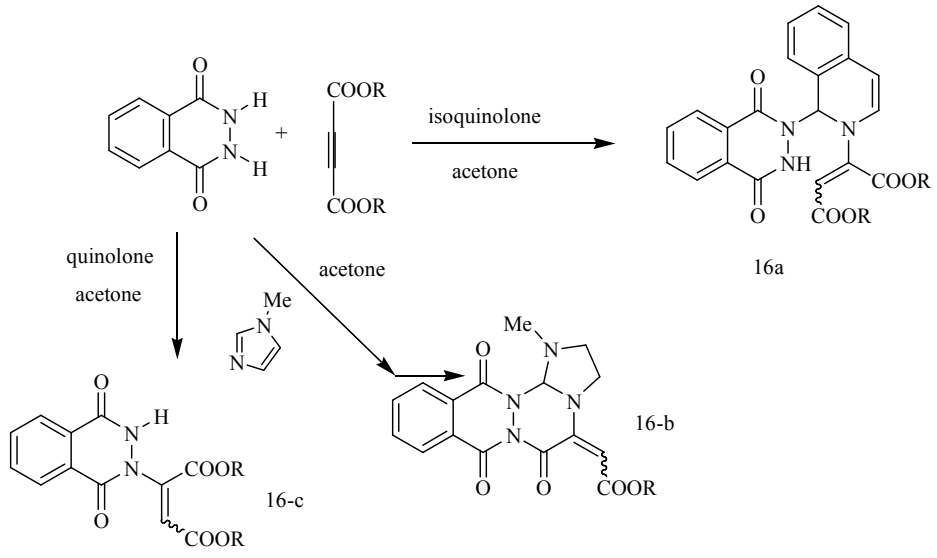
a- benzoxazin-1-one, b,e-4-aryl-1(2-H)phthalazinone, c-bis-phthalazinone,d-4-aryl-2-(4methylphenyl)phthalazinones

R. Ghahremanazadeh et al. worked on synthesis of various phthalazine-5, 10-dione derivatives and was able to suggest an efficient one-pot condensation reaction between phthalhydrazide, aromatic aldehydes, and malononitrileor ethyl cyanoacetate with excellent yields.

scheme-15



scheme-16

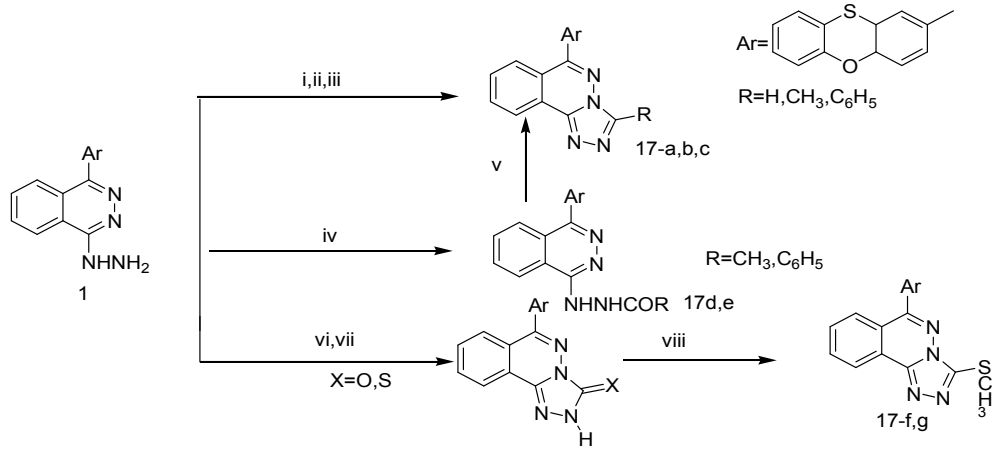


A. A. Aly et al. [23] described the synthesis of triazolo (3, 4 -a) phthalazine with reactants 1-chloro – 4 – phenoxathin – 2 yl – phthalazine and hydrazine hydrate which gave the 1 – hydrazine – 4 –phenoxathiin - 2 – yl – phthalazine in the presence of ethanol. This compound gave 6 – phenoxathiin – 2 –yl – (1, 2, 4) triazolo (3, 4 - a) phthalazine (2a) and 3 methyl – 6 –phenoxathiin – 2yl – (1, 2, 4) triazolo (3, 4 - a) – phthalazine when synthesized with aliphatic acids (formic and acetic acid).

In this scheme (18), 1-(4- phenylphthalazin-yl)-hydrazine was used as starting material which gives a reaction in the presence of benzyl isothiocyanate in boiling ethanol produced number of derivatives like 18-a,18-b.

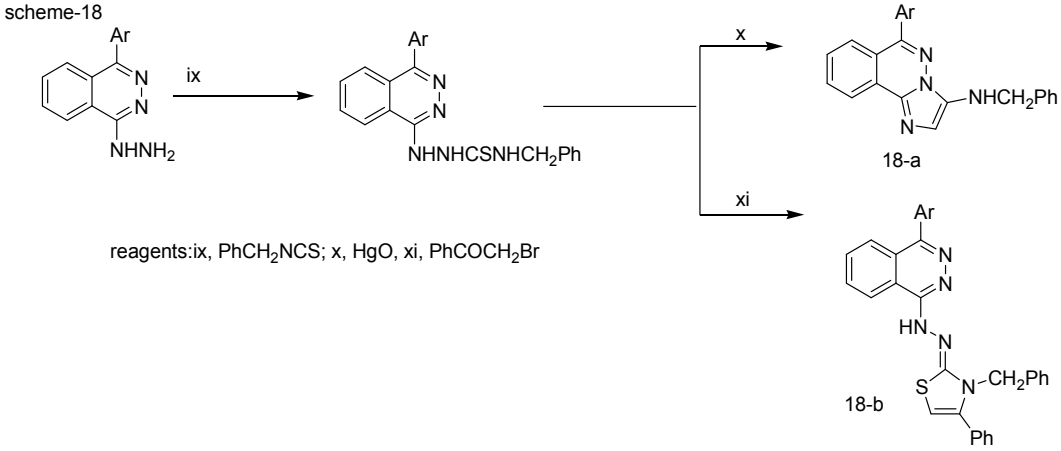
X.-Y. Sun et al. [11], synthesized some novel 6 alkoxys (phenoxy) – (1, 2, 4) triazolo (3, 4 - a) phthalazine – 3 – amino derivatives. The starting material phthalic anhydride and hydraine hydrate reacted in presence of ethanol to yield 2,3-dihydrophthalazine-1,4-dione. Refluxing it further in the presence of phosphorus oxychloride ($POCl_3$) yielded 1, 4-dichlorophthalazine. 1,4-dichlorophthalazine reacted further with $NHNH_2.H_2O$ in tetrahydrofuran yielded 1-hydrazine-4-chrorophthalazin. Then, 1-hydrazine -4-chrorophthalazine and cyanogene bromide was cyclised in the presence of sodium carbonate to yield 6-chloro-[1,2,4]triazolo[3,4-a]phthalazine-3-amine. At the end of the reaction, 6-chloro-[1,2,4]triazolo[3,4-a]phthalazine - 3-amine reacted with appropriate alkanol and substituted phenol to produce the target compounds, 6-alkoxy(phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives (20a-20u).

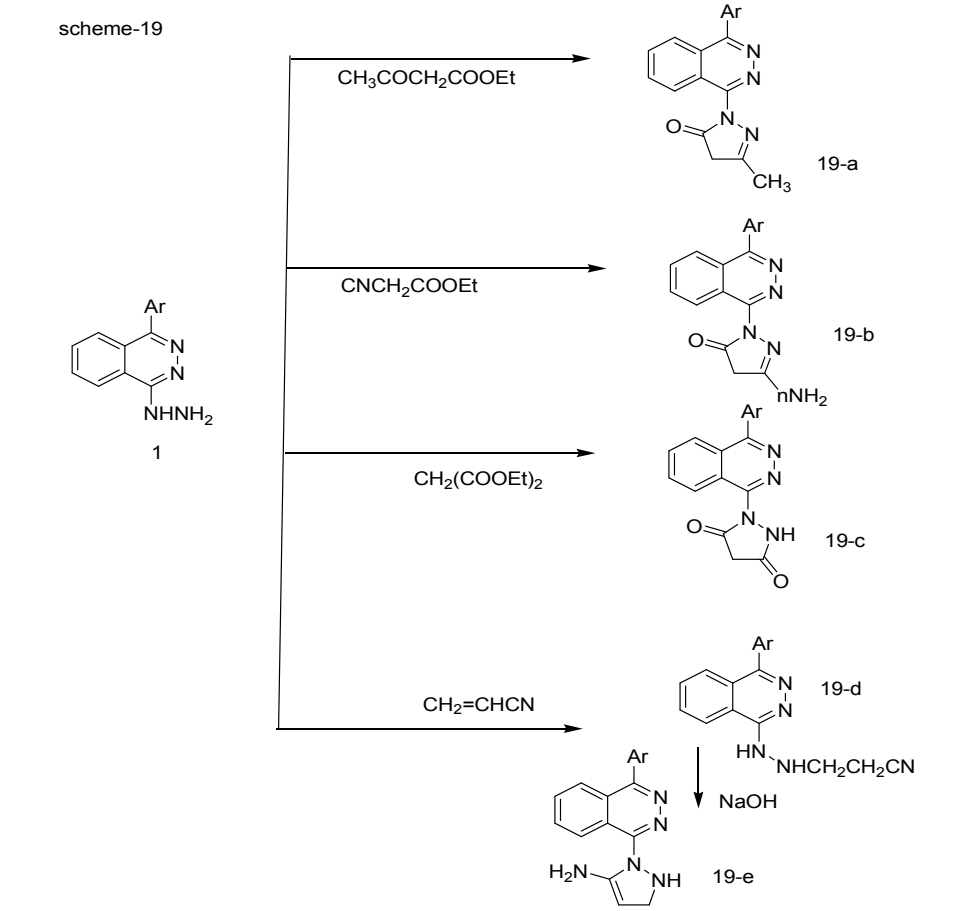
scheme-17

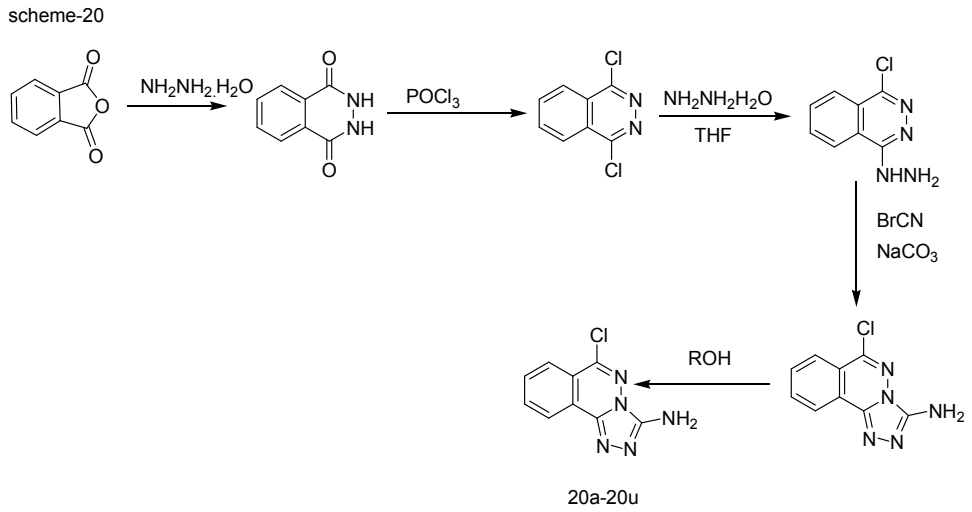


Reagents-: i) RCOOH ii) RC (COOEt)$_3$ iii) PhCOOH iv) RCOCl v) phosphorous oxy chloride vi) NH_2CONH_2 vii) CS_2 viii) CH_3I

scheme-18







Waleed et al. 2014, synthesized different phthalazines in the prescribed scheme. For these derivatives, pthalalic anhydride was used as starting material which produces 4 hydroxy – 2 – phenylphthalazine – 1 – (2H) one which was further converted into potassium salts when reacted with potassium hydroxide in the presence of isopropyl alcohol. On continuous stirring it gives a clear solution of potassium 4 – oxo – 3 – phenyl -3, 4- dihydrophthalazine -1 – olate.

The compound (21-b) when treated with 10 mmol chloroacetic acid and 25 ml of ethanol. Refluxed

for 10 hours with stirring, produced a final product which was subjected to TLC ANALYSIS to establish its purity.

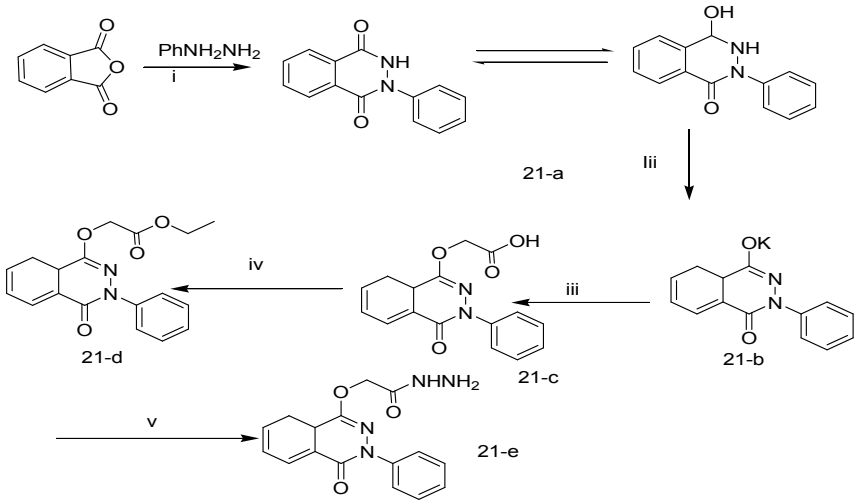
10 mmol compound (21-c) was treated with a mixture of ethanol (50 ml) and conc. sulphuric acid (1 ml). The reaction mixture was refluxed for 24 hours, cooled at room temp and 5% of sodium bicarbonate solution was added to this until effervescences ceased. The resultant solid was collected and washed with cold water.

The compound (21-d), (10 mmol) was put in the mixture of hydrazine hydrate (5ml) in ethanol (25 ml) and the reaction mixture was refluxed for 8 hours. The solid precipitated was collected after filtration, washed with ethanol and dried for the collection of the final product (21-e).

T. Haack et al. in [8], synthesized some derivatives that had PDE IV inhibitors properties. The following scheme was followed.

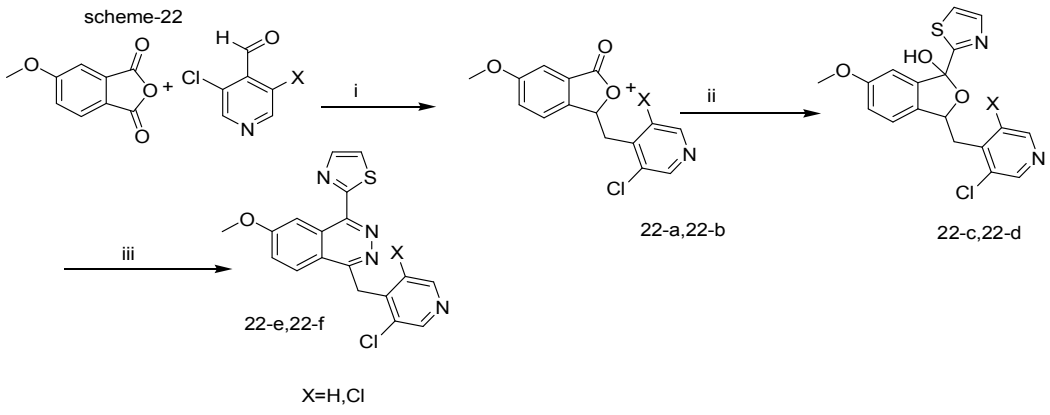
Street et al. 2004, synthesized 3 – heterocyclyl – 7, 8, 9, 10 tetrahydro – (7, 10 ethanol) – 1, 2, 4 – triazolo (3, 4 - a) phthalazine ring. 20 gm of 1, 4 di chlorophthalazine was reacted with 37.3 ml of a boiling solution of hydrazine monohydrate in ethanol (500 ml) and then this reaction mixture was heated at reflux for 30 minutes. The mixture was collected and the collected product after filtration was washed with ether.

scheme-21



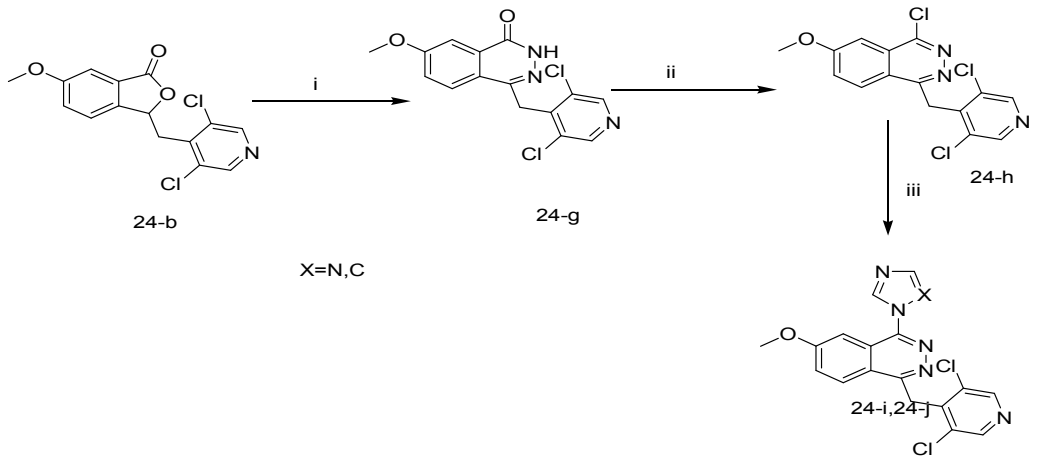
Reagents-: i)$PhNHNH_2$, CH_3COOH, HCl, reflux, 10 hour ii) KOH, isopropyl, stirring, 1 hour iii) $ClCH_2COOH$, ethanol iv) ethanol, sulphuric acid, reflux, 24-hour v) $NHNH_2.H_2O$, ethanol, reflux, 8 hours

scheme-22



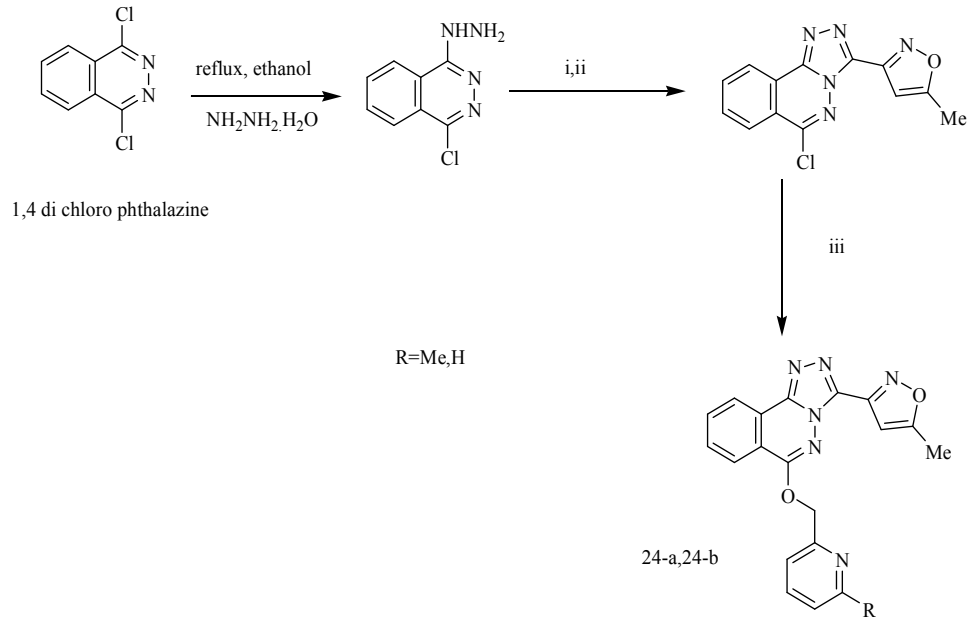
Reagents-: i) acetic anhydride, toluene, reflux,10 hour ii) 2- bromo thiaole, LDA,2hr iii) hydrazine hydrate, methanol, AcOH, reflux, 6hour(X=H, Cl)

Scheme 23



Reagents-: i) hydrazine hydrate, methanol, AcOH, reflux 2 hours ii) phosphorus oxychloride, reflux, 4hour iii) imidazole or triazolo, NaOH, dimethylformamide, 100°C temperature, X=N, C

Scheme-24



Reagents: i) 5-methylisoxazole-3-carboxylic acid, bis (2-oxo-3-oxazolidinyl) phosphoric chloride, triethylamine, dichloromethane ii) xylene, NEt_3 ,16hour iii) pyridine-2- methanol, NaH, Dimethyl formamide

3. CONCLUSION

In this review article, an attempt has been made to summarize the recent development in the synthesis of different Phthalazines derivatives, thus suggesting ways to the researchers to look out a different path in the synthesis of Phthalazines. Such type of work would be very useful for new researchers. The new researcher is able to find out a different path for the synthesis of a Phthalazines. After incorporation of fused components and different functional

groups, it produces pharmacologically active compounds with lesser side effect maintaining their potent action. An exhaustive study of the literature survey incorporated in this review article has been able to explore the possibility of synthesis of more appropriate and useful pthalazine derivatives. Different synthetic routes have been explaining leading to the possible development of the phthalazine derivatives. In this way, the article may offer an opportunity for new horizons in futuristic research.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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