Review Paper

ADVANCED DEVELOPMENTS OF DIFFERNET SYNTHETIC ROUTES OF PHTHALAZINE DERIVATIVES IN MEDICINAL CHEMISTRY

Abstract –

In this review paper the different methods are highlighted that are used for the synthesis of phthalazine derivatives. They are used as building blocks for the heterocyclic compounds. These building blocks are very useful in medicinal chemistry for the research work in the development of new molecule. Those molecules that have most potent and effective in pharmacological responses. In such a way it provides a new pathway for the researches.

Keywords: Phthalazine, Phthalainone, Thiaolo, phthalic anhydride.

Introduction –

Phthalazine is a nitrogen containing compounds and due to their heterocyclic structure it plays an important role in the development of different types of heterocyclic derivatives (Mohamed Sayed et al., 2017).

The chemistry of Phthalazine derivatives increased the interest due to their chemotherapeutic application. These types of ring system are widely used in organic chemistry as intermediate for the synthesis of numerous compounds (Xu et al., 2004).

On the other hand phthalazine derivatives were studies as bioactive compounds. They posses remarkable biological activity such as anticonvulsant (Quan et al., 2009; Zhang et al., 2009), cardio tonic (Nomato et al., 1990), antihypertensive (Hoffman et al., 2006), antitumor (Sung et al., 2004; Haider et al., 2007), antidiabetic (Madhavan et al., 2001), anti-inflammatory (Dogruer et al., 2004; Sun et al., 2010), antimicrobial (Shetgiri et al., 2005), antioxidant (Bayoumi et al., 2014), PDE IV Inhibitors (Haack et al., 2005), vasorelaxant (Vatanave et al., 1998), antithrombotic (Johnson et al., 2003) etc.

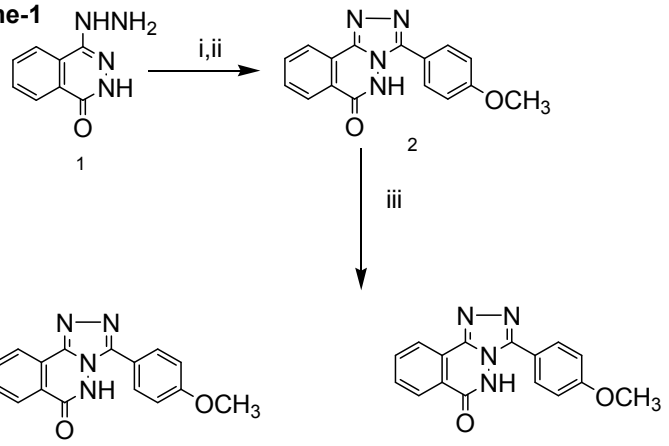
Therefore a variety of methods has been reported for the synthesis of phthalazine derivatives. In this review paper it is tried to compile the different synthetic routes for the synthesis of phthalazine containing derivatives.

Synthesis of Phthalazine derivatives –

In 2004 Robert W. Carling et al., reported that 3- phenyl – 6 - (2 pyridyl) methyloxy -1, 2, 4- triazolo (3,4 - a) phthalazines and analogues have g affinity γ – aminobutyric acid.

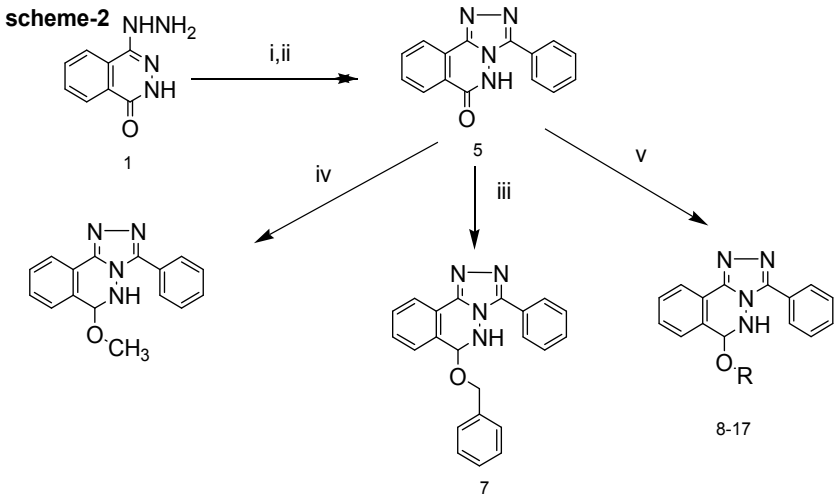
A benzodiazepine receptor ligands with α_2, α_3 and α_5 subtype binding selectivity over α_1 are synthesized from different synthetic routes-:

scheme-1



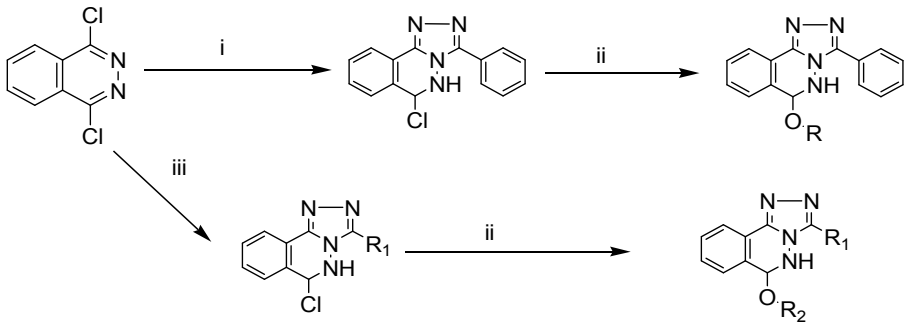
Reagents: (i)4methoxy benzoyl chloride,Et_3N,1,4dioxane,room temp;(ii) DMF,reflux(iii)NaH,DMF,Ph_2Br 100 temp.

scheme-2



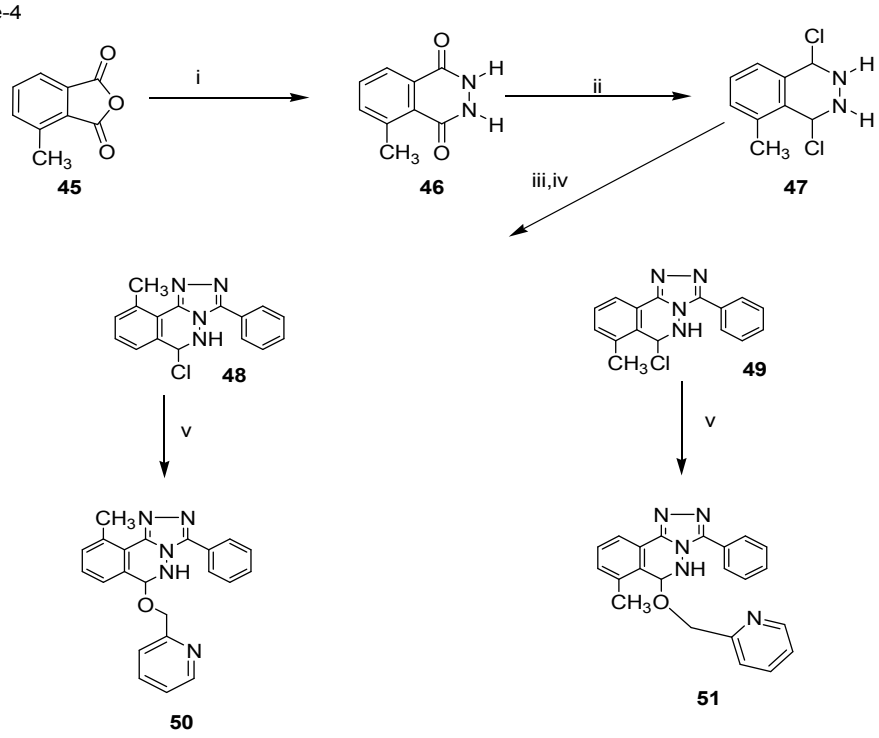
Reagents: (i)benzoyl chloride,Et_3N,1,4 dioxan,room temp;(ii) DMF, reflux (iii) NaH,DMF,$PhCH_2Br$,100 temp (iv) NaH,DMF,CH_3I (V)NaH,DMF,RCH_2Br or RCH_2Cl.

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.

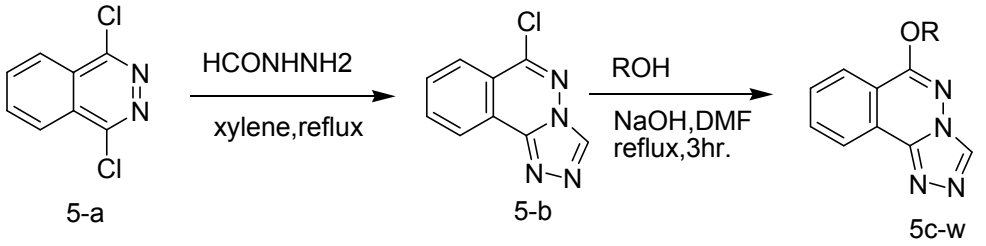
scheme-4



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.

In 2009 Lei Zhang et al., synthesized a new series of 6 – alkoxy – (1, 2, 4,) triazolo (3, 4 -a) phthalazines by using a solution of starting material (compound a) that is 1, 4 dichlorophthalazine reacted with formic hydrazide in the presence of xylene which is further reacted with appropriate alcohol and substituted phenol to produce various phthalazine derivatives.

Scheme-5

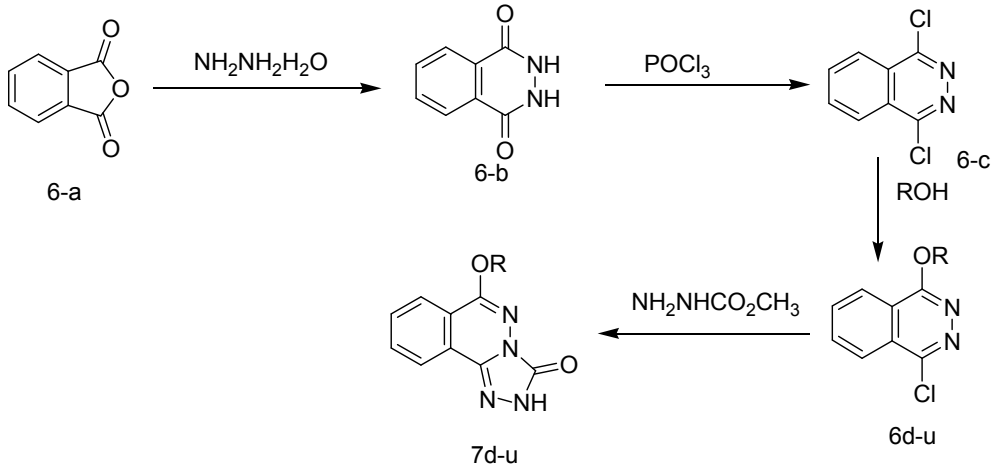


5c - C_6H_5	**5j** - $C_{10}H_7$	**5q** - C_3H_7
5d - $C_6H_4(O\text{-}CH_3)$	**5k** - $C_6H_4(o\text{-}OCH_3)$	**5r** - $n\text{-}C_4H_9$
5e - $C_6H_4(m\text{-}CH_3)$	**5l** - $C_6H_4(p\text{-}OCH_3)$	**5s** - $n\text{-}C_6H_{13}$
5f - $C_6H_4(p\text{-}CH_3)$	**5m** - $C_6H_4(p\text{-}NO_2)$	**5t**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

Synthesis route of compounds **5c-5w**

In 2011 Chingxiet et al., synthesized a new series of 6 – alkoxy (1, 2, 4) triazolo (3, 4 - a) phthalazine – 3 (2H) one derivative by using as starting material appropriate 1- chloro- 4 – alkoxy phthalazine with methyl hydrazine carboxylate. 1 chloro – 4 – alkoxy phthalazine synthesized from phthalic anhydride reated with hydrazine hydrate in ethanol to yield 2, 3 dihydrophthalazine 1, 4 dione.

Scheme-6



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)

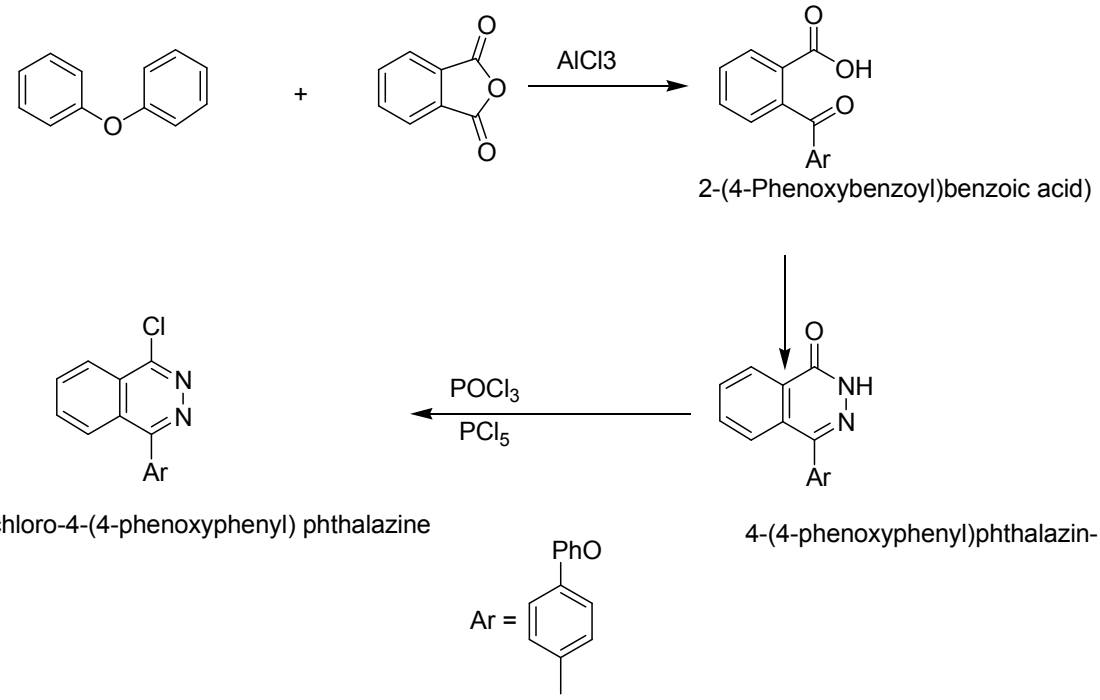
Synthesis route of compounds **7d-7u**

2,3 dihydrophthalazine 1,4 dione further reacted with phosphorous oxy chloride to give 1,4 di chlorophthalazine which is further reacted with appropriate alkanol and substituted phenol in di methyl formamide that give different derivatives (4a – 4r). These compounds reacted with methyl hydrazine carboxylate in the presence of dimethyl sulfoxide that give final series of 6-alkoxy (1,2,4) triazolo (3,4-a) phthalazine- 3(2H)-one (Cheng –Xi et al., 2011).

In 2007 Mohamed Sayed et al., synthesized a new series of phthalazine derivatives by using chloro - 4 – (4 - phenoxyphenyl) phthalazine as a starting material, In this synthesis process an eqimolar amount of chlorophthalazine (0.01mmol) and active methylene compound (0.01mmol) was heated under reflux for 6 hours and then the reaction mixture was poured into ice/ H_20. The obtained solid product was collected and finally wash with appropriate solvent to give

derivatives.

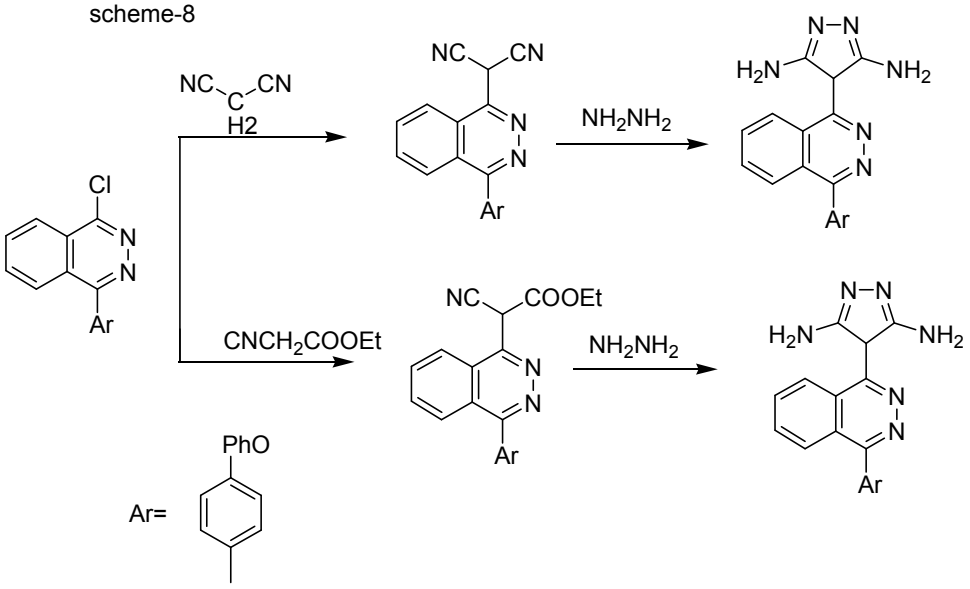
Scheme-7



For the synthesis of 2 – (4 – (4 phenoxyphenyl) phthalazine – 1 – yl) – malononitrile, they have using an eqimolor amount of chloro phthalazine (0.01 mol) and ethy----- in ethanol containing sodium ethoxide was heated under reflux for 6 hours and then reaction mixture was poured into ice/H_2O. The solid was collected and wash with proper solvent to give respective derivation.

A mixture of compound (2-(4-(4-phenoxyphenyl) phthalazin-1-yl)malononitrile and ethyl 2-cyano-2-(4-(4-phenoxyphenyl)phthalain-1yl)acetate (0.01mol) and hydrazine hydrate (0.01 mol) in methanol (20 ml) was heated under reflux for 6 hours then allowed to cool and then the precipitated solid was collected by filtration and recrystalized by using proper solvent.(8a,8b)

scheme-8



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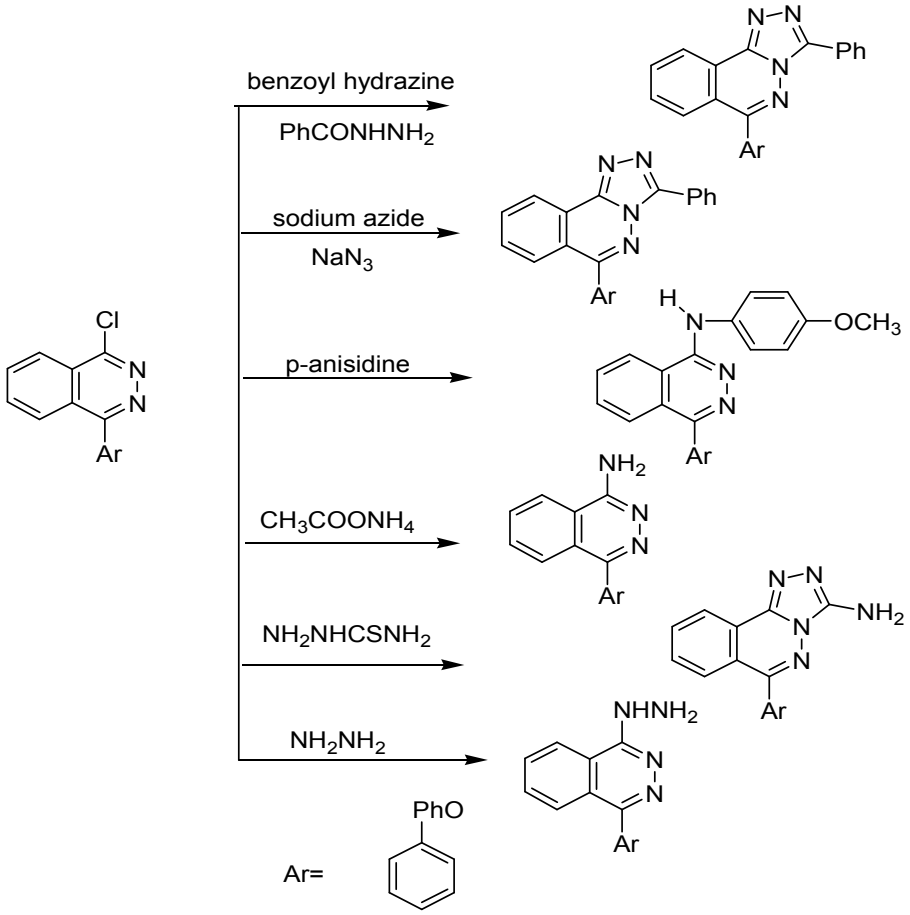
Scheme-9



87

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

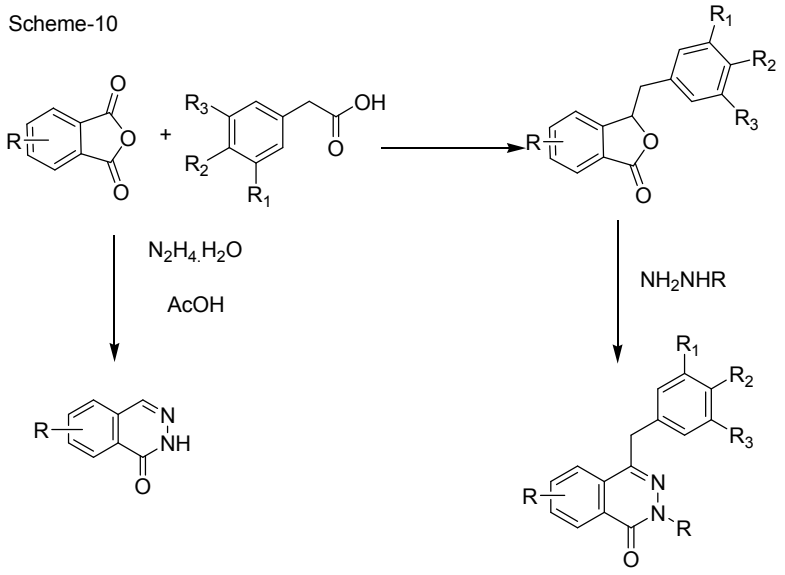
Mohamed Sayed et al., in 2017 developed a new series of heterocyclic derivatives that exhibited also other pharmacological activity like antitumor and antioxidant activities.

In this scheme (9) chlorophthalazine react with benzoylhydrazine under reflux in the presence of n-butanol give 6 – (4 – phenoxy phenyl) – 3 phenyl – (1, 2, 4) triazolo (3, 4-a) phthalazine (9a). This is further treated with sodium azide give (9b). In this scheme chlorophthalazine treated with P – anisidine give phthalazine derivatives (9c). Further chlorophthalazine fusion with ammonium acetate gives amino phthalazine (9d). When chlorophthalazine react with thiosemicarbozone and give amino triazolophthalazine derivatives (9e). In this reaction chlorophthalazine reacted with hydrazine hydrate in ethanol to give 1 – hydrazinyl – 4 – (4 – phenoxyphenyl) phthalazine(9f).

In 2015 El Azm et al., given a review in that he has describe different synthetic route for the synthesis of substituted phthalazine derivatives.

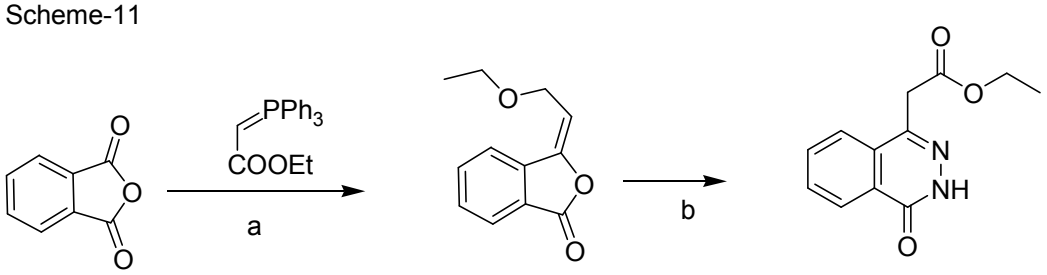
Phthalazinones were synthesized by using phthalic anhydride as a starting material in the following schemes.

Scheme-10



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

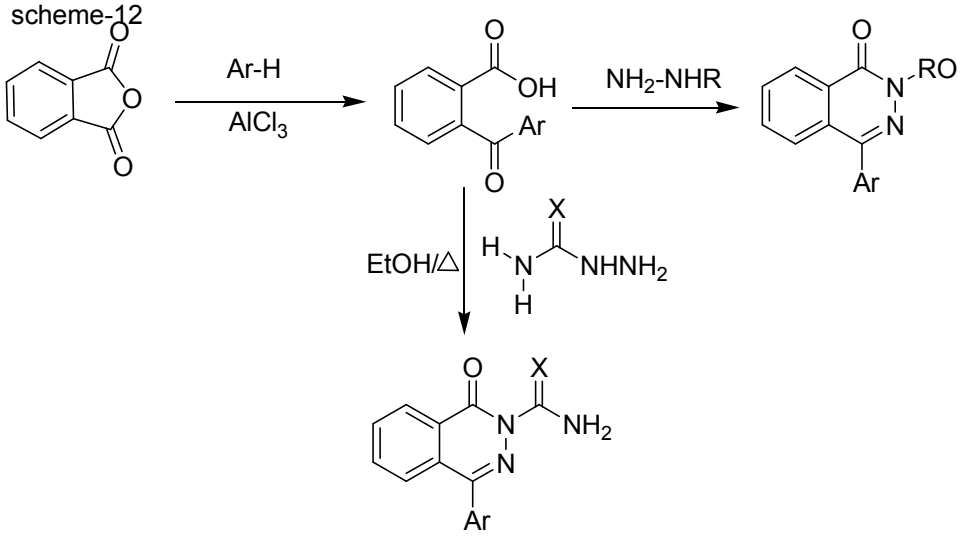
Scheme-11



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

In this scheme(12) phthalic anhydride and aromatic hydrocarbons in the presence of anhydrous aluminium chloride give intermediate which is further treated with hydrazine hydrates and alkyl substituted hydrazine give the phthalazine (2H) -1 – one derivatives.

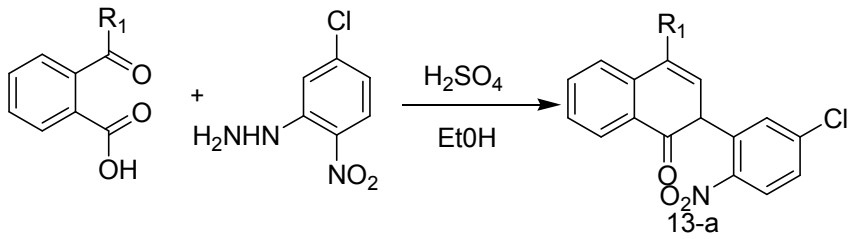
scheme-12



Synthesis of phthalain(2H)-1-one

Kirill et al in 2004 given the cyclization of 2 – nitro – 5 – chloro phenyl hydrazine when reacted with acylbenzoic acids. This reaction derived 2 – (2 – nitro – 5 – chlorobenzene) – 4 – substituted phthalazine – 1 – ones derivatives (13a).

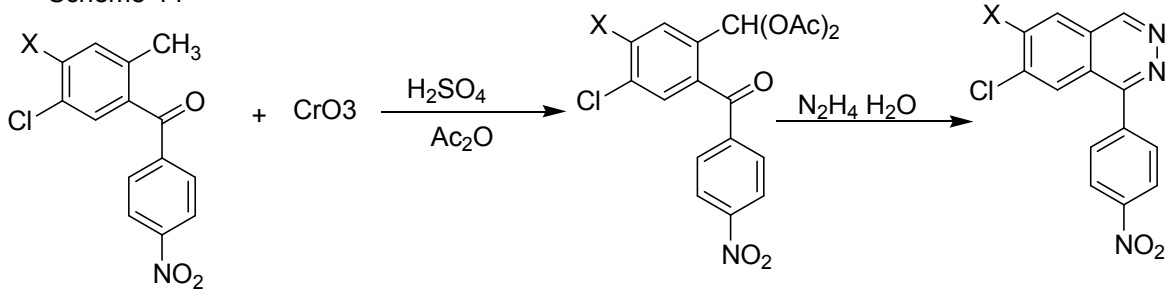
Scheme-13



13-a

Luikacs and Siming G. et al in 2009 describe a different pathway for the synthesis of phthalazine derivatives by using benzophenone with chromium oxide in the mixture of actic acid anhydride and sulphuric acid give intermediate which is futher react with hydraine hydrate in refluxing ethanol give derivative (14 a)

Scheme-14

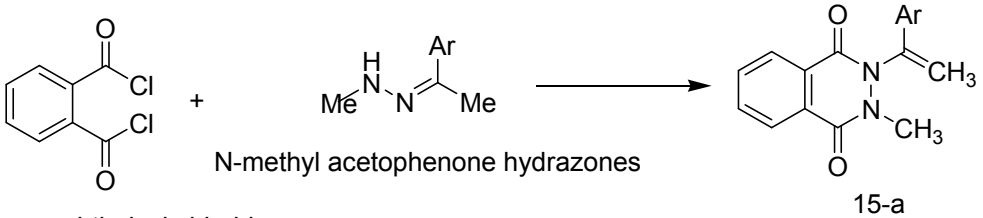


14-a

X=H,Cl

In this synthesis 3 – methoxy benzoic acid was used as a starting material undergoes chloroformylation and then redicalbromination of next intermediate which is favour for next derivatives to improve their yield.

Scheme-15



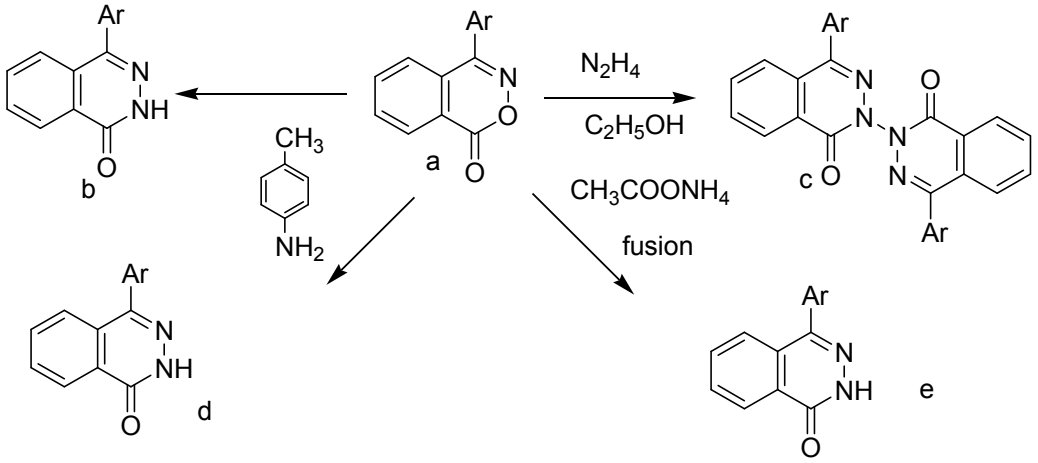
N-methyl acetophenone hydrazones

phthaloyl chloride

15-a

Reaction of phthaloyl chloride with N-methyl acetophenone hydrazones leads to the formation of phthalazine derivative(15-a).

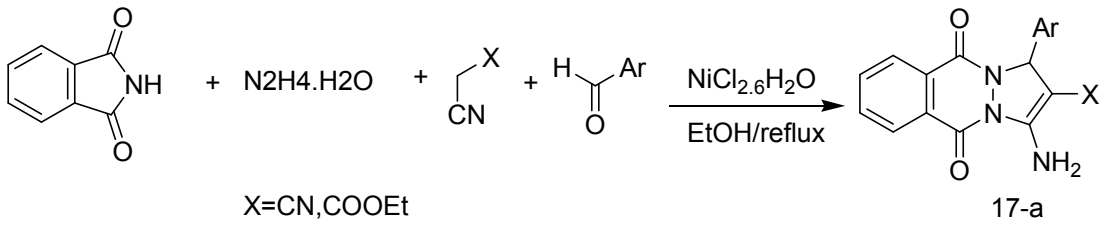
Scheme-16



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

In the condensation reaction of phthalimids with hydrazine hydrate,aromatic aldehydeand malononitrile or ethyl cyano acetate catalysed by NiCl2.6H2O give derivative of phthalazine dione(17-a) SCHEME-17

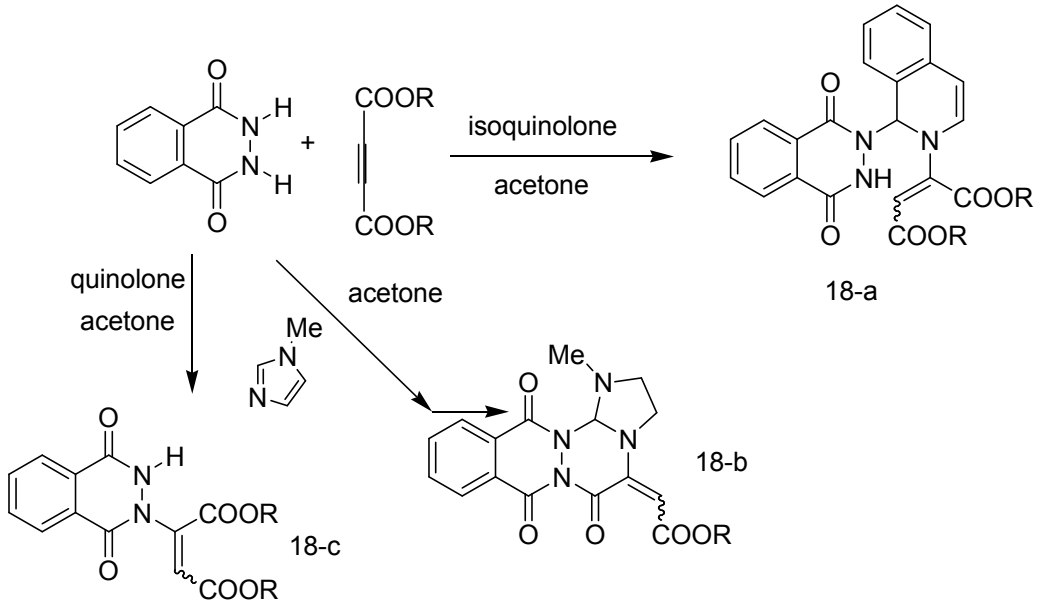
scheme-17



synthesis of 1H-Pyrazolo[1,2-b]phthalazin-5,10-dione derivative

Ghahremanadeh et al 2008 synthesized phthalazines.in this reaction phthalhydrazide and acetylene dicarboxylates in the presence of N-heterocycles give the derivatives -18a,18-band 18-c.(scheme-18)

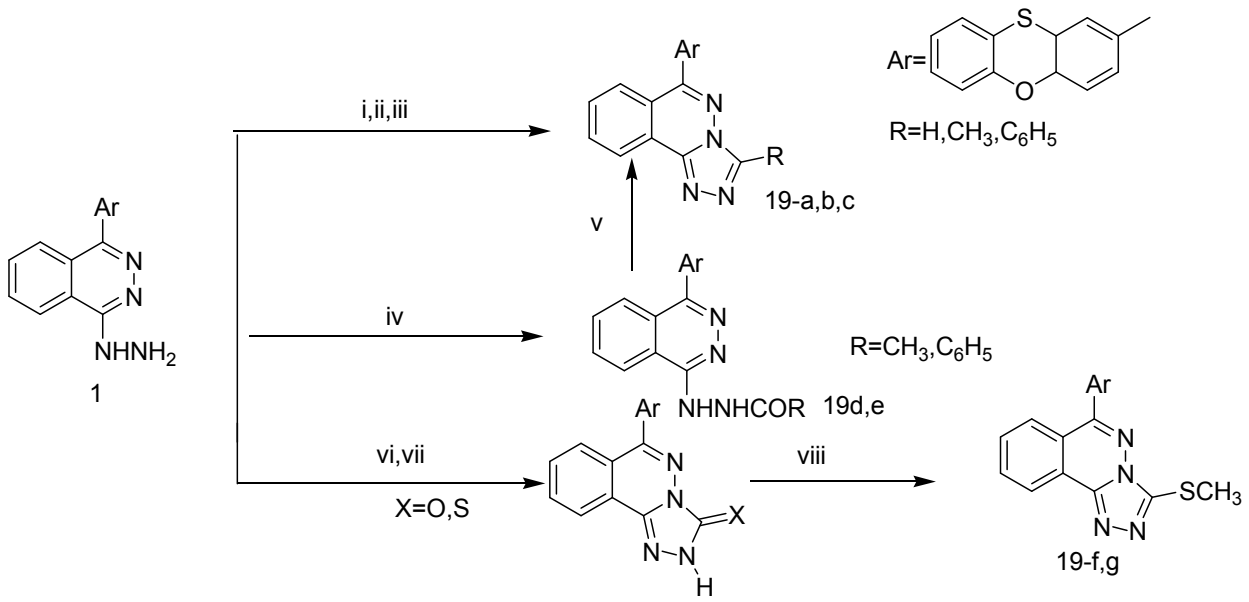
scheme-18 reaction of phthalhydrazide with acetylene dicarboxylates.



A. A. Aly et al in 2005 focus on the synthesis of s – triazolo (3, 4 -a) phthalazine by using as a reactant. 1- chloro – 4 – phenoxathin – 2 yl – phthalazine and hydrazine hydrate in ethanol give the 1 – hydrazine – 4 –phenoxathiin - 2 – yl – phthalazine(1).(used as a starting material for the reaction)

Synthesis of (1) with aliphatic acids (formic and acetic acid) give 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.

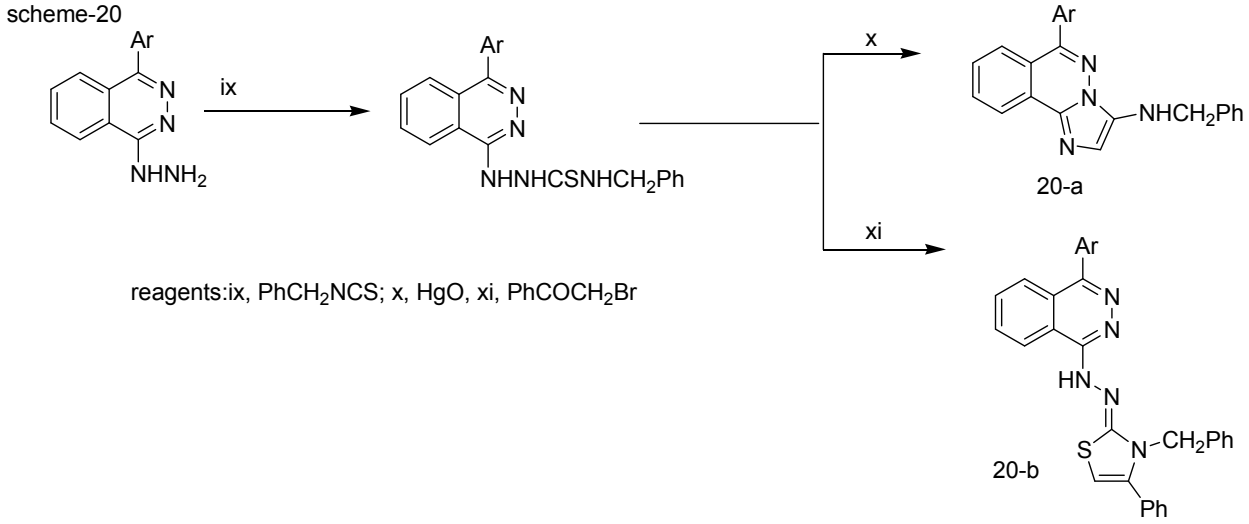
scheme-19



147

148 reagents:i-RCOOH ii-$RC(COOEt)_3$ iii-PhCOOH iv-RCOCl v-$POCl_3$ vi-NH_2CONH_2 viiCS_2viiiCH_3I

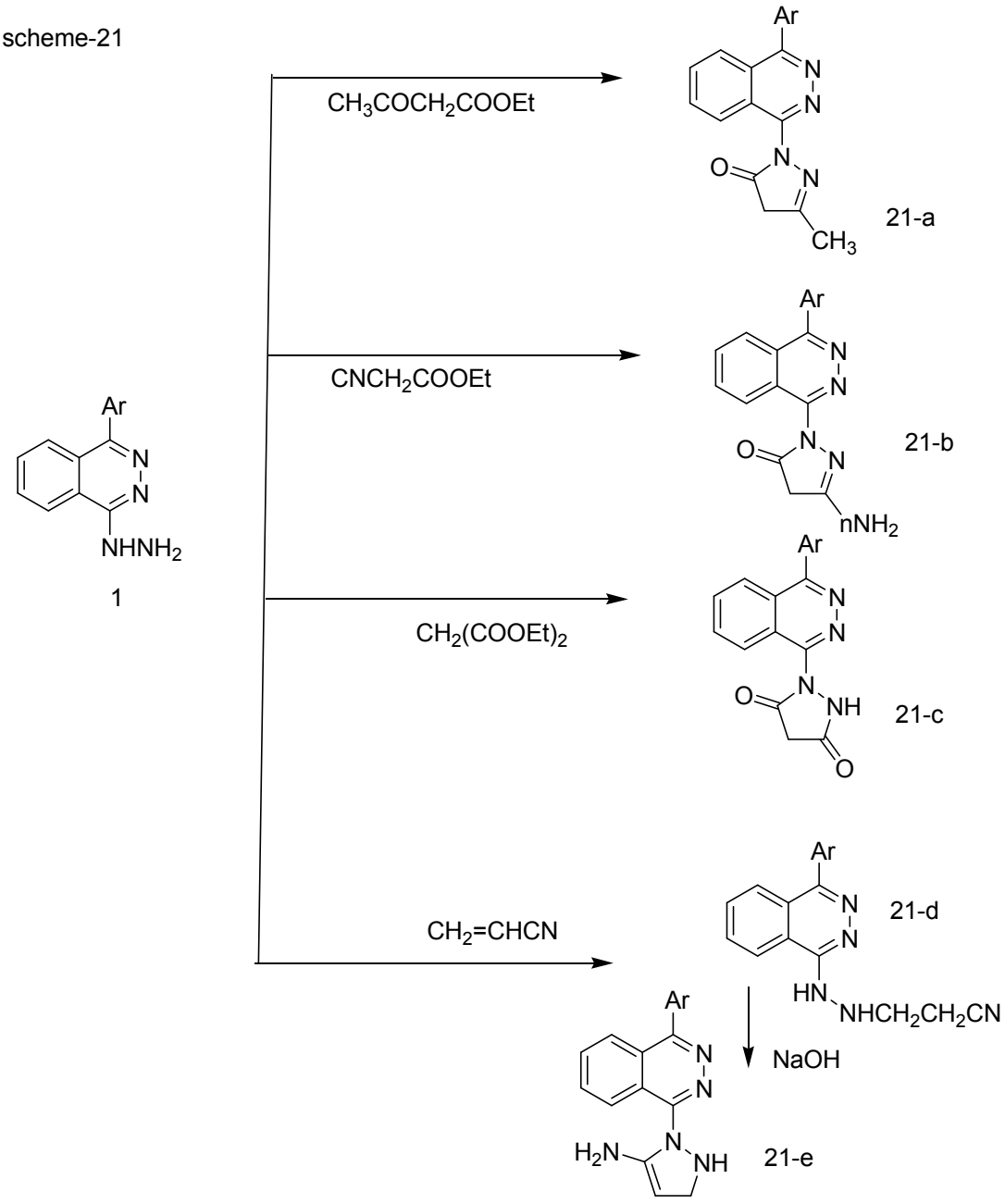
scheme-20



149

150 In this scheme(20) 1 taken as a starting material that react with benzyl isothiocyanate in boiling
151 ethanol give derivatives 20-a,20-b.

scheme-21

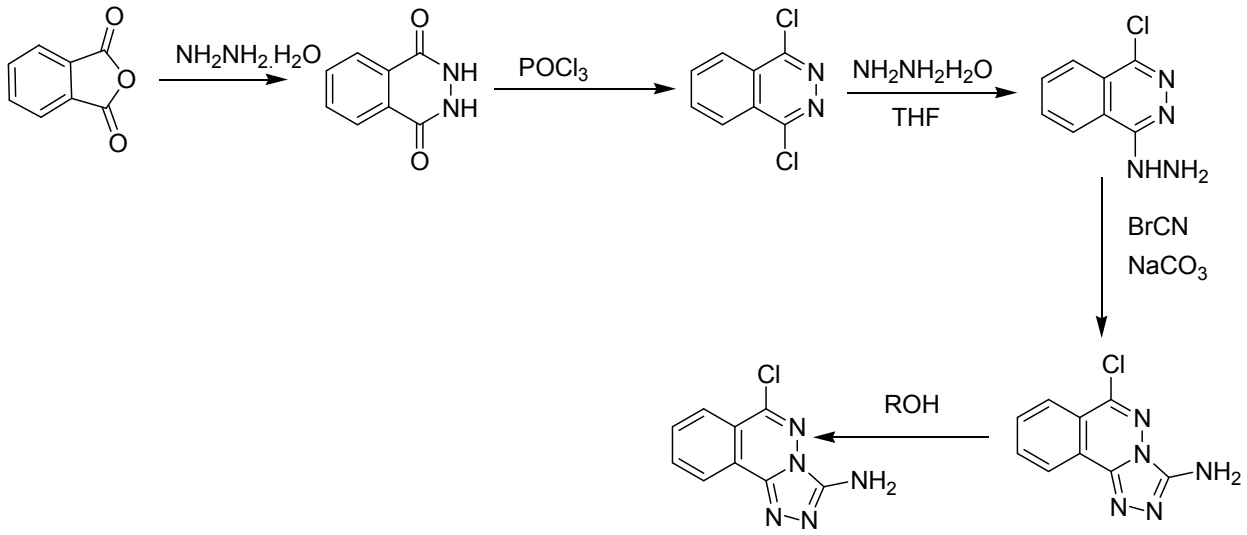


152

153 In 2010 X. Y Sin et al synthesized some novel 6 alkoxy (phenoxy) – (1, 2, 4) triazolo (3, 4 - a)
154 phthalazine – 3 – amino derivatives. Phthalic anhydride taken as starting material which reacted
155 with hydrazine hydrate in ethanol to yield 2,3-dihydrophthalazine-1,4-dione (22-b), which
156 reacted further with the refluxing with phosphorus oxychloride (POCl3) that give 1,4
157 dichlorophthalazine (22-c).Compound (22-c) further reacted f with hydrazine hydrate in tetra
158 hydro furan(THF) to produce compound (1-hydrazine-4-chrorophthalazin).Then, 6-chlorom-
159 [1,2,4]triazolo[3,4-a]phthalazine-3-amine 5 was prepared by cyclising compound 4 with

cyanogene bromide in the presence of sodium carbonate . Finally, compound (22-e) reacted with appropriate alkanol or substituted phenol to produce the 6-alkoxy(phenoxy)-[1,2,4]triazolo[3,4-a] phthalazine-3-amine derivatives (22a-22u).scheme-22

scheme-22

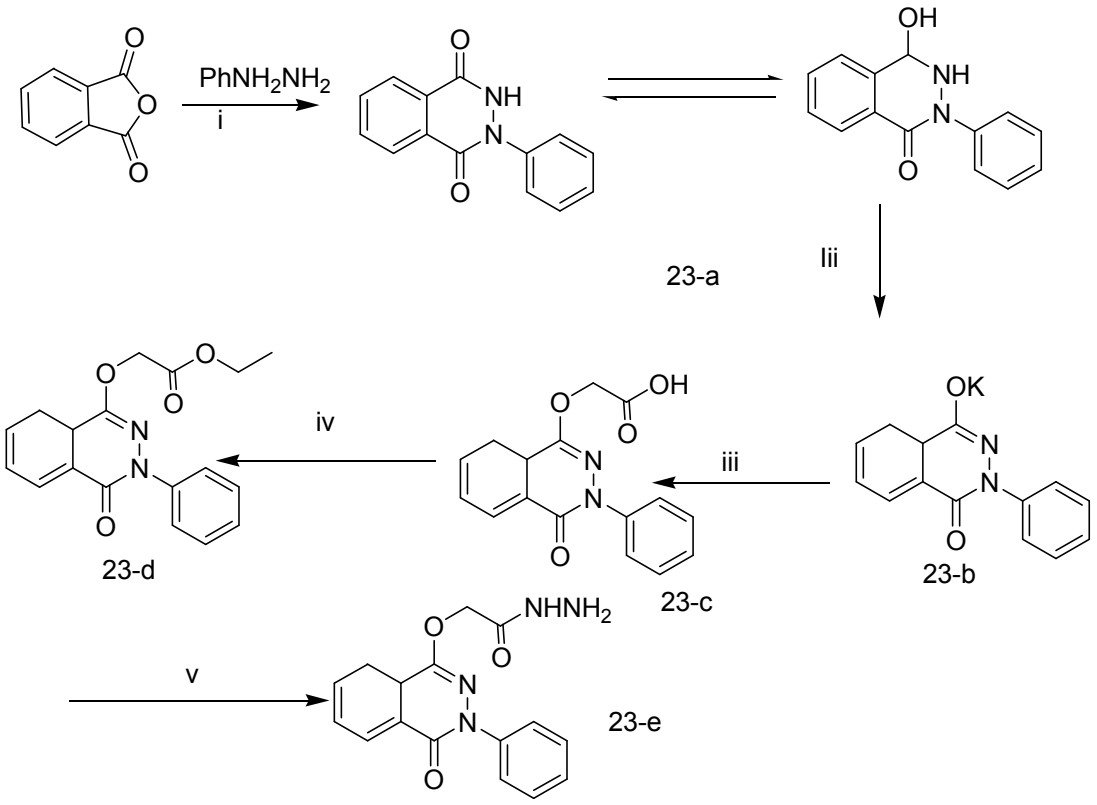


27a-27u

In 2014 Waleed et al., synthesized new phthalazine derivative in the given scheme.

Phthalic anhydride used as a starting material for such type of derivative which produces 4 hydroxy – 2 – phenylphthalazine - 1 – (2H) one (1) was converted into potassium salts (2) in the presence of KOH in isopropyl alcohol and vigorously stirred than a clear solution is obtained that is potassium 4 – oxo – 3 – phenyl -3, 4 – dihydrophthalazin – 1 - olate.

scheme-23



171

172 reagents; (i)$PhNHNH_2$,H_2O,CH_3COOH,HCl, reflux,10hr. (ii) KOH, isopropyl,stirring,1hr;(iii)$ClCH_2COOH$,ethanol
173 (iv)ethanol,H_2SO_4,reflux, 24hr(v$NH_2NH_2.H_2O$,ethanol,reflux,8hr)

174

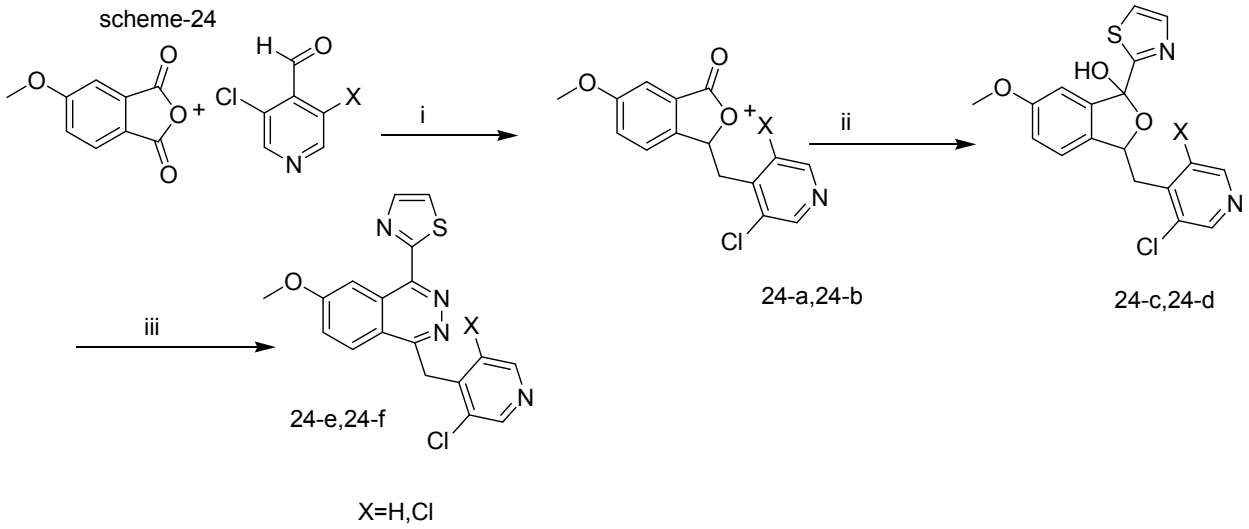
175 A compound (23-b) reacted with chloroacetic acid (10 m mol) and add absolute ethanol (25 ml)
176 with continuous stirring 10 hours with reflux assembly. After the completion of process resulted
177 compound was collected. A compound (23-c) (10 m mol) absolute ethanol (50 ml) and conc.
178 H_2SO_4 (1ml) was refluxed for 24 hours then allow to cool at room temp. and then in ice water.
179 5% of sodium bicarbonate cold solution was prepared and added until effervescence ceased.
180 Obtained solid was collected after filtration it is added in sodium bi carbonate solution and
181 stirred for removing remains unreacted acid at the end of procedure. Product was collected and
182 washed with cold water.

183

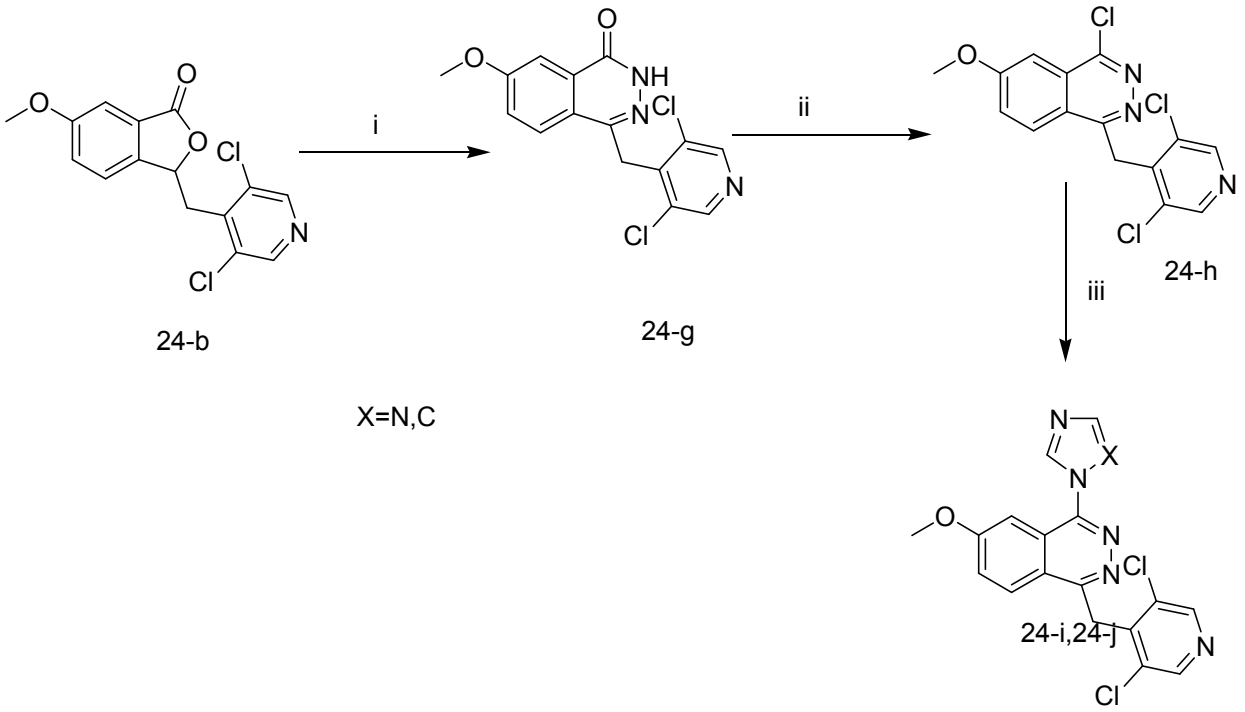
Compound (23-d) (10 m mol) and hydrazine hydrate (5ml) in ethanol (25 ml) was refluxed for 8 hours than precipitated was collected after filtration washed with ethanol and dried for collection of product (23-e).

T. Haack et al., in 2005 given the study of some 6 – methoxy – 1, 4 disubstituted derivatives that have PDE IV inhibitors properties. In the following scheme they are synthesized.

scheme-24



reagents;(i) acetic anhydride,toluene,reflux,10hr (ii) 2-bromothiaole,LDA,2 hr (iii) hydrazine hydrate,MeOH,AcOH,reflux, 6hr (X=H,X=Cl)



193

194 reagents; (i)hydrazine hydrate,MeOH,AcOH,reflux, 2hr (ii) POCl3,reflux,4hr(iii) imidazole or triazole,NaH,DMF,100 temp,20 hr. X=N OR C

195

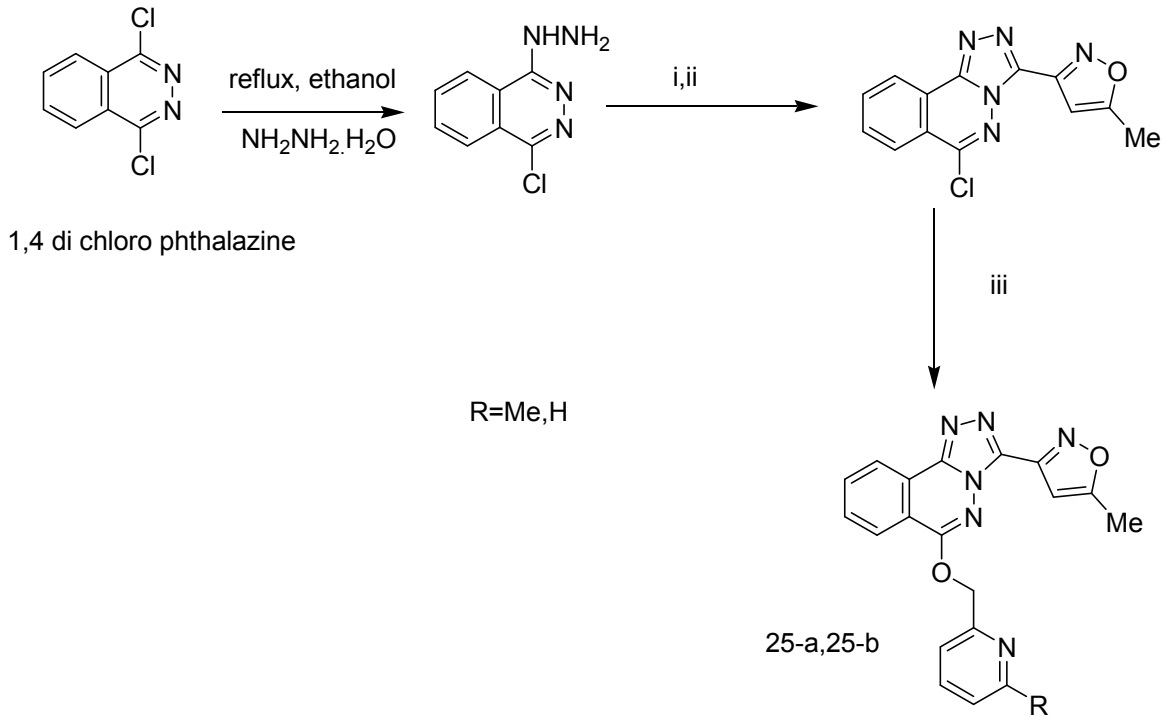
196 Street et al., 2004 synthesized 3 – heterocyclyl – 7, 8, 9, 10 tetrahydro – (7, 10 ethano) – 1, 2, 4 –
197 triazolo (3, 4 - a) phthalazine ring was found as showing excellent binding selectivity & oral
198 bioavailability for GABA receptor inverse agonist 3 – (5 – methyl isoxazol – 1 -3 - yl) 6 – (2
199 - pyridyl) methyloxy – 1, 2, 4 triazolo (3, 4 - a) phthalazine (43) provide new therapeutic
200 alzheimer's disease with greater therapeutic window & fewer side effect than to currently
201 available drugs in market. 1, 4 di chloro phthalazine (20gm, 0.100 mol) was reacted with boiling
202 solution of hydrazine monohydrate (37.3ml, 0.765 mol) in ethanol (500ml) and the mixture of
203 this heated at reflux for 30 min, cool the mixture and collected the product by filtration and wash
204 with ether.

205

206

207

scheme-25



Reagents: i) 5-methylisoxazole-3-carboxylic acid,bis(2-oxo-3-oxazolidinyl)phosphonic chloride,triethylamine,DCM ii)xylene,NEt3.HCl,reflux,16hr. iii)pyridine-2-methanol,NaH,DMF

Conclusion –

Phthalaine is a heterocyclic compound which is obtained from different reactants like Phthalazine phthalate, Hydraine hydrate etc. When phthalaine is incorporated with different functional rings and fused components gives pharmacologically active compound that have less side effect with potent action. With the help of found litrature the newer activites of different phthalaine derivatives are more beneficiary than the older compound. In this review paper it has been tried to provide best possible synthetic routes for the development of different derivative of phthalazine moiety that will provide a plateofrm to the reserchers.

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