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Advanced Developments of Differnet Syntheticroutes of Phthalazine Derivatives in Medicinal Chemistry

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ABSTRACT

Phthalazine is a nitrogen containing compound due to their heterocyclic structure it play an important role in the development of different type of heterocyclic derivatives. In this review paper there are different type of methods are highlighted that are used for the synthesis of different type of phthalazine derivatives. Synthesized new pharmacophore 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 molecule that have most potent and effective in pharmacological responce. In such a way it provides a new pathway for the researches.

Keywords: Phthalazine, Phthalainone, Thiazolo, Phthalic anhydride.

INTRODUCTION

Phthalazine is a nitrogen containing compounds and due to their heterocyclic structure it play an important role in the development of different types of heterocyclic derivatives [1]. 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.

On the other hand phthalazine derivatives were studies as bioactive compounds. They possess remarkable biological activity such as anticonvulsant [2,3] cardio tonic [4], antihypertensive, antitumor [5,6] antidiabetic [7], anti-inflammatory [8,9], antimicrobial [10], antioxidant [11], PDE IV Inhibitors [12]. vasorelaxant [13], antithrombotic [14], 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 Substitued 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 α2,α3 and α5 subtype binding selectivity over α1 are synthesized from different synthetic routes.

4-Hydrazinophthalazin-1-one (1a, 3g, 0.17 mol) was suspended in dioxan (45 mL) with triethylamine (2.6 mL, 1.1 mol equiv), and 4-methoxybenzoyl chloride (3.2 g, 1.1 mol equiv) in dioxan (10 mL) was added dropwise over 10 min at room temperature. The reaction mixture was stirred at room temperature for 30 min, and then the dioxan was removed by rotary evaporation. The residue was dissolved in DMF (50 mL), and the mixture was then heated under reflux for 4 h, after some time water was added drop wise until the solution became cloudy. After this the mixture was allowed to cool, a solid was collected by filtration, washed with water, and vacuum-dried the compound (1b). This solid (1b, 2.8 g, 0.0098 mol) was dissolved in DMF (80 mL), and sodium hydride (0.432 g of a 60% dispersion in oil, 1.1 mol equiv) was added in portions. When the addition was complete, the reaction mixture was heated at

100 °C for 15 min and benzyl bromide (1.29 mL, 1.1 mol equiv) was added in one portion. After 1 h, the reaction mixture was allowed to cool and the solvent was removed by rotary evaporation. The residue was heated with water (100 mL), and a solid was collected by filtration. This solid was recrystallized from methanol, and pure compound (1c, 1d) both are collected by filtration in 1:49 ratio (Figure 1).

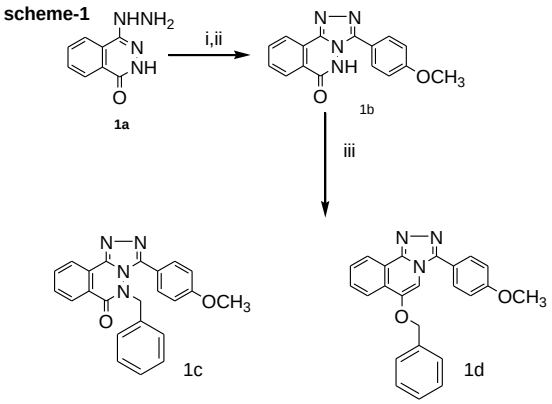

Figure 1: Reagents : (i) 4-Methoxy Benzoyl Chloride, Et3N, 1,4-dioxane, Room Temp, (ii) DMF, Reflux (iii) NaH, DMF, Ph2Br , 100°C

4-Hydrazinophthalazin-1-one (2a, 4.5 g, 0.0256 mol) was suspended in dioxan (50 mL) with triethylamine (3.92 mL, 1.1 mol equiv), and benzoyl chloride (3.27 mL, 1.1 mol equiv) in dioxan (20 mL) was added dropwise over 10 min at room temperature. The reaction mixture was stirred at room temperature for 15 min and then heated at reflux temperature for 2 h. The dioxan was then removed by rotary evaporation, and the residue was dissolved in DMF (50 mL). The mixture was then heated under reflux for 4 h, after which time water was added dropwise until the solution became cloudy. After the solution was allowed to cool, a solid was collected by filtration, washed with water, and vacuum-dried This solid (2b, 0.262 g, 0.001 mol) was dissolved in DMF (30 mL), and sodium hydride (0.044 g of a 60% dispersion in oil, 1.1 mol equiv) was added in portions. When the addition was complete, the reaction mixture was heated at 80 °C for 15 min and allowed to cool to room temperature and then methyl iodide (0.069 mL, 1.1 mol equiv) was added in one portion. After 4 h, the solvent was removed by rotary evaporation. The residue was heated with water (50 mL), and a solid was collected by filtration. This solid was recrystallized from methanol, and pure compound (2c) was collected by filtration:

Compound (2b) (0.262 g, 0.001 mol) was dissolved in DMF (30 mL), and sodium hydride (0.044 g of a 60% dispersion in oil, 1.1 mol equiv) was added in portions. When the addition was complete, the reaction mixture was heated at 80 °C for 15 min and then benzyl bromide (0.131 mL, 1.1 mol equiv) was added in one portion. After 1 h the solvent was removed by rotary evaporation, the residue was heated with water (50 mL), and a solid was collected by filtration. This solid was recrystallized from methanol, and pure compound (2d) was collected by filtration (Figure 2).

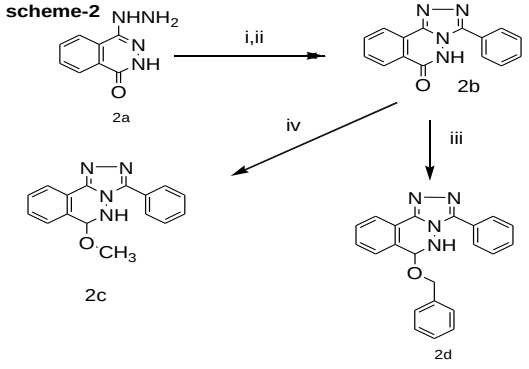

Figure 2: Reagents: (i) Benzoyl chloride,Et3N, 1,4 dioxan, Room Temp, (ii) DMF, Reflux (iii) NaH, DMF, PhCH2Br, 100°C. (iv) NaH,DMF,CH3I.

Solution of benzyl alcohal(0.22 ml) was dissolved in DMF (10 mL) was added at room temperature was added sodium hydride (0.044 g of a 60% dispersion in oil, 1.1 mol equiv) and the reaction mixture was stirred at room temperature for 15 min. After some time (3b 0.5 gm) was added and the reaction mixture was heated at 700C for 3 hr .water was added until the solution become cloudy, a solid was collected by filtration. This solid was recrystallized from methanol, and pure compound (3c) was collected by filtration.
Compound (3d) was prepared by reacting 1,4-dichloro phthalazine(3a) with benzohydrazine (C6H5CONHNH2) in the presence of triethylamine, xylene, reflux for 3 hr (Figure 3).
The compound(3e) was prepared using the method above for the formation of (2c) using acetyl chloride in place of benzoyl chloride and 2-picolyl chloride instead of methyl iodide (Figure 2).

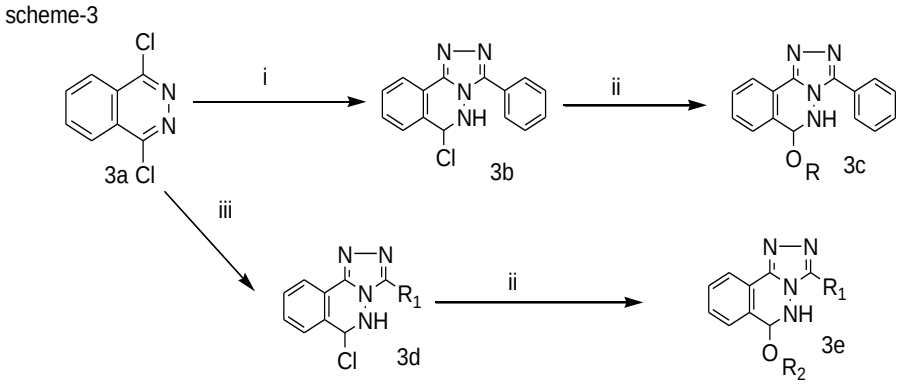

Figure 3: Reagents: (i) PhCONHNH2, Et3N, Diaxone, Reflux (ii) ROH, NaH, DMF, (iii)R1CONHNH2, Et3N, Xylene, Reflux (iv)R1COCl, Et3N, Diaxone, Reflux

To a solution of 3-methylphthalic anhydride (4a, 15 g, 0.093 mol) in aqueous acetic acid (300 mL of 40%) was added hydrazine hydrate (5.4 mL, 0.11 mol) and sodium acetate (15.1 g, 0.11 mol), and the reaction mixture was heated at reflux for 18 h. When the mixture was cooled, the resultant solid was collected by filtration and dried. This material was redissolved in aqueous acetic acid (500 mL of 40%) with hydrazine hydrate (3.6 mL, 0.072 mol) and sodium acetate (10 g, 0.072mol), and the reaction mixture was heated under reflux for a further 72 h. When the mixture was cooled, the solid was collected by filtration to yield 5-methylphthalazinedione (4b).

A solution of 5-methylphthalazinedione (4b, 5.5 g) in phosphorus oxychloride (200 mL) was refluxed for 18 h, cooled, and evaporated to dryness. The resulting material was dissolved in DCM (150 mL) and cold water (200 mL). Solid sodium hydrogen carbonate was added carefully until pH 11 was attained, the aqueous layer was extracted with DCM (2 x100 mL), and then the combined organic layers were washed with brine. The organic layer was dried over MgSO4, then filtered, and collected 1,4-dichloro-5-methylphthalazine (4c).
To a solution of 1,4-dichloro-5-methylphthalazine (4c, 5.5 g, 0.026 mol) in xylene (100 mL) was added triethylamine (4.36 mL, 1.2 mol equiv) and benzoic hydrazide (3.85 g, 1.1 mol equiv). This mixture was heated at reflux for 24 h under nitrogen. After cooling, the reaction mixture was concentrated under vacuum and the solid obtained was partitioned between dichloromethane (2 x100 mL) and water (1 x 50 mL). The organic layer was dried over MgSO4, filtered, and concentrated in vacuo to leave a solid that was collected to yield 6-chloro-3-phenyl-7-methyl-1,2,4 triazolo[3,4-a]- phthalazine (4d and 4e).
To a solution of 2-hydroxy methyl pyridine (0.197 mL, 0.002 mol) in DMF (30 mL) at room temperature was added sodium hydride (0.082 g of a 60% dispersion in oil, 0.002 mol), and the reaction mixture was stirred at room temperature for 15 min. After this time 4d or 4e (0.5 g, 0.0017 mol) was added one by one seperately and the reaction mixture was stirred at room temperature for 18 h, after which time TLC showed 80% conversion. More sodium hydride (0.016 g of a 60% dispersion in oil, 0.0004 mol) was added, and the reaction mixture was stirred for a further 3 h. The reaction mixture was concentrated under vacuum, and the solid obtained was partitioned between dichloromethane (2x100 mL) and water (1 x 50 mL). The organic layer was dried (MgSO4), filtered, and concentrated in vacuo to leave a solid. Recrystallization from a mixture of ethyl acetate and dichloromethane gave pure (4f or 4g) simultaneously (Figure 4).

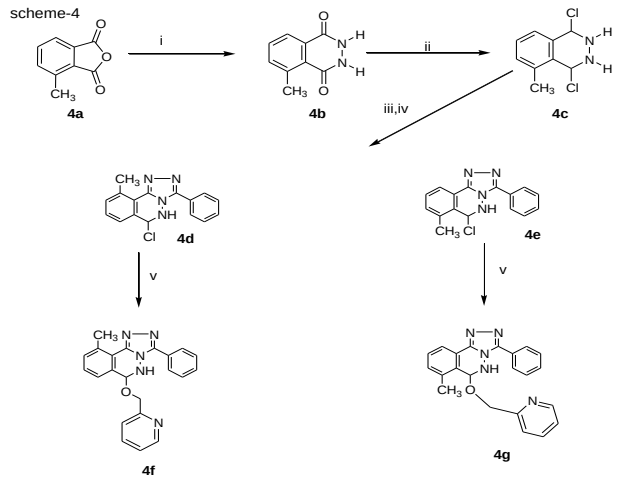

Figure 4: Reagents: (i) NH2NH2.H2O, AcOH,NaOAC, Reflux, (ii) POCl3, Reflux,(iii) PhCONHNH2, Et3N, Xylene, Reflux (iv) Chromatography,(v) ROH, NaH, DMF, 2-hydroxy pyridine.

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 5a) 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(5c-w) which are listed in Table 1 (Figure 5) [15].

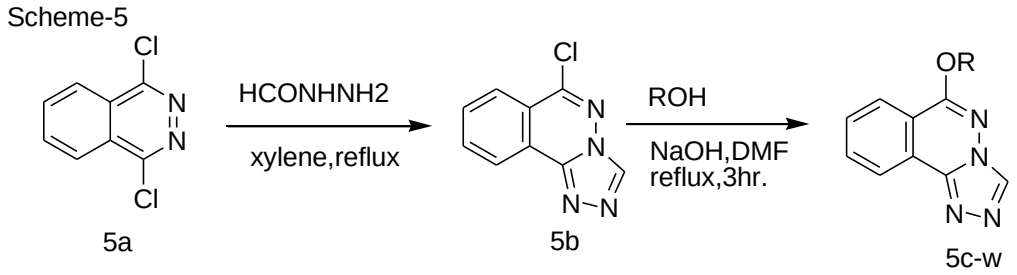

Figure 5: Formic hydrazide in the presence of xylene which is further reacted with appropriate alcohol and substituted phenol to produce various phthalazine derivatives

Table 1: Synthesized phthalazine derivatives

5c -C6H5	5j-C10H7	5q-C3H7
5d -C6H4(O-CH3)	5k-C6H4(o-OCH3)	5r-n-C4H9
5e- C6H4(m-CH3)	5l-C6H4(p-OCH3)	5s-n-C6H13
5f-C6H4(p-CH3)	5m - C6H4(p-NO2)	5t-nC7H15
5g-C6H4(p-F)	5n- C6H4(p-NH2)	5u-nC8H17
5h-C6H4(p-Cl)	5o-CH3	5v-nC10H21
5i-CH2C6H3(2,4-Cl2)	5p-C2H5	5w-nC5H11

In 2011 Chingxi et al., synthesized a new series of 6 – alkoxy (1, 2, 4) triazolo (3, 4-a) phthalazine – 3 (2H) one derivative [16]. The series of reaction will be started from phthalic anhydride by using as starting material for the synthesis of appropriate 1- chloro-4-alkoxy phthalazine derivatives which is used as key substrate for this reaction. 1- chloro-4-alkoxy phthalazine reacted with methyl hydrazine carboxylate give different derivatives (6a-6r). These compounds further 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 derivatives (7a–7r), which are listed in Table 2 (Figure 6).

Scheme-6

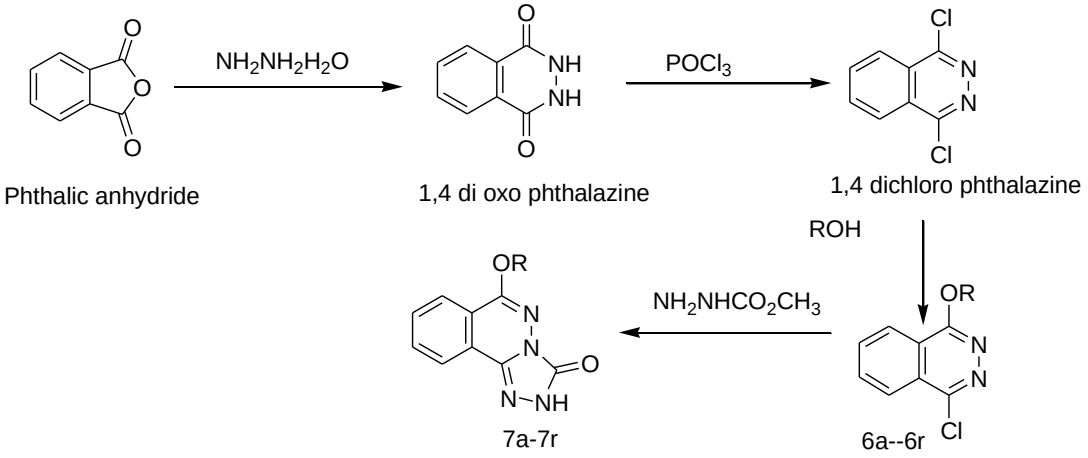

Figure 6: Formation of 6-alkoxy (1,2,4) triazolo (3,4-a) phthalazine- 3(2H)-one derivatives

Table 2: Series of 6-alkoxy (1,2,4) triazolo (3,4-a) phthalazine- 3(2H)-one derivatives

6a,7a =n-C4H9	6g,7g=-C6H5	6m,7m =-C6H4 (4-Br)
6b,7b=n-C5H11	6h,7h=-C6H4 (4-F)	6n,7n=-C6H4 (2-CH3)
6c,7c=n-C6H13	6i,7i-C6H4(2-Cl)	6o,7o=-C6H4 (3-CH3)
6d,7d =n-C7H15	6j,7j=-C6H4(3-Cl)	6p,7p=-C6H4 (4-CH3)
6e,7e =n-C8H17	6k,7k =-C6H4(4-Cl)	6q,7q=-C6H4 (2-OCH3)
6f,7f=n-C10H21	6l,7l=-C6H3(2,4-Cl2)	6r,7r=-C6H4 (4-OCH3)

In 2007 Mohamed Sayed et al., synthesized a new series of phthalazine derivatives by using1-chloro-4-(4-phenoxyphenyl) phthalazine(7c) as a starting material, In the Figure 7 describe the synthesis of starting material(7c) [1].

Scheme-7

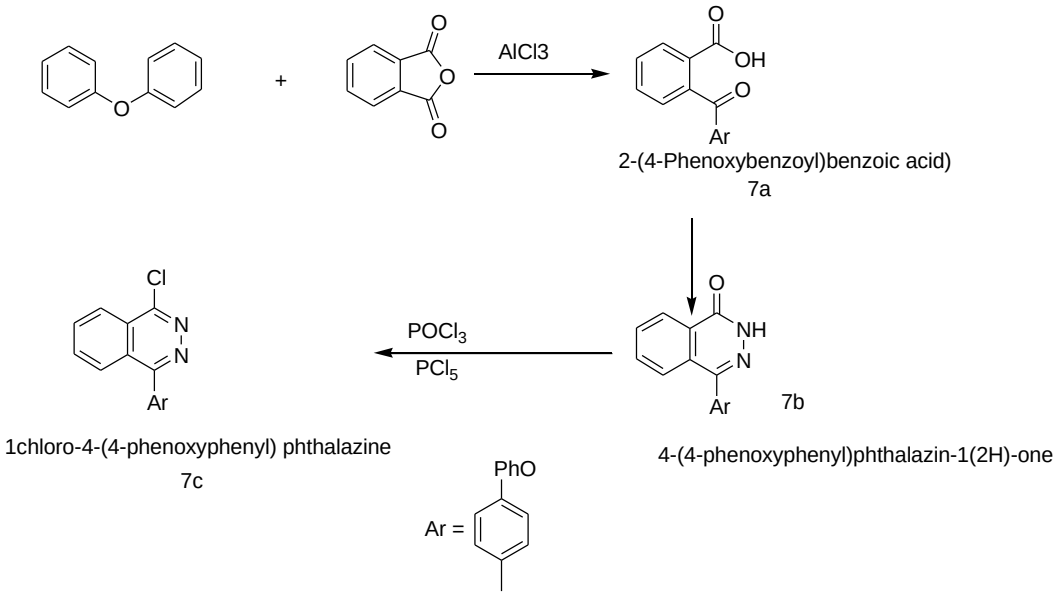

Figure 7: The synthesis of starting material(7c)

Synthesis of compound (2-(4-(4-phenoxyphenyl) phthalazin-1-yl)malononitrile(8a) and ethyl 2-cyano-2-(4-(4-phenoxyphenyl)phthalain-1yl)acetate(8b) by using 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/ H20. The obtained solid product was collected and finally wash with appropriate solvent to give derivatives (8a, 8b) from the Figure 8.

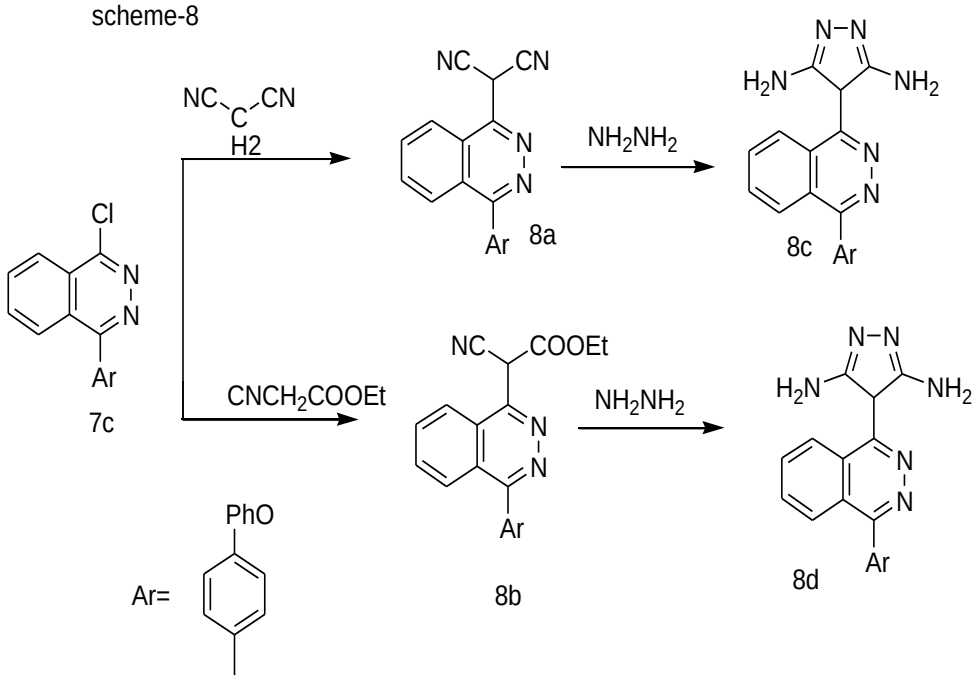

Figure 8: Obtaining derivatives using appropriate solvents

Mohamed Sayed et al., in 2017 also developed a new series of heterocyclic derivatives that exhibited also other pharmacological activity like antitumor and antioxidant activities that are showed by compounds(9a-9f). Chlorophthalazine(7c) reacted with benzoylhydrazine under refluxed in the presence of n-butanol (30ml) for 24 hr, given 6-(4-phenoxy phenyl)-3-phenyl-(1, 2, 4) triazolo (3,4-a) phthalazine derivative (9a). Compound (7c) further treated with sodium azide in eqimolar amount than reflux for 6 hr under reflux, cooled the mixture at the end of reaction pour into ice given derivative (9b) [1]. Further chlorophthalazine treated with p-anisidine in n-butanol(30ml) under reflux for 6 hr then reaction mixture was concentrated by evaporation, and solid was collected, that was phthalazine derivative (9c). Further chlorophthalazine fusion with ammonium acetate in equimolar amount and gives amino substitutedphthalazine derivatives (9d). When chlorophthalazine reacted with thiosemicarbozone in equimolar amount it give amino triazolophthalazine derivatives (9e). In this reaction chlorophthalazine reacted with hydrazine hydrate in ethanol to give 1-hydrazinyl-4-(4- phenoxyphenyl) phthalazine (9f) (Figure 9).

Scheme-9

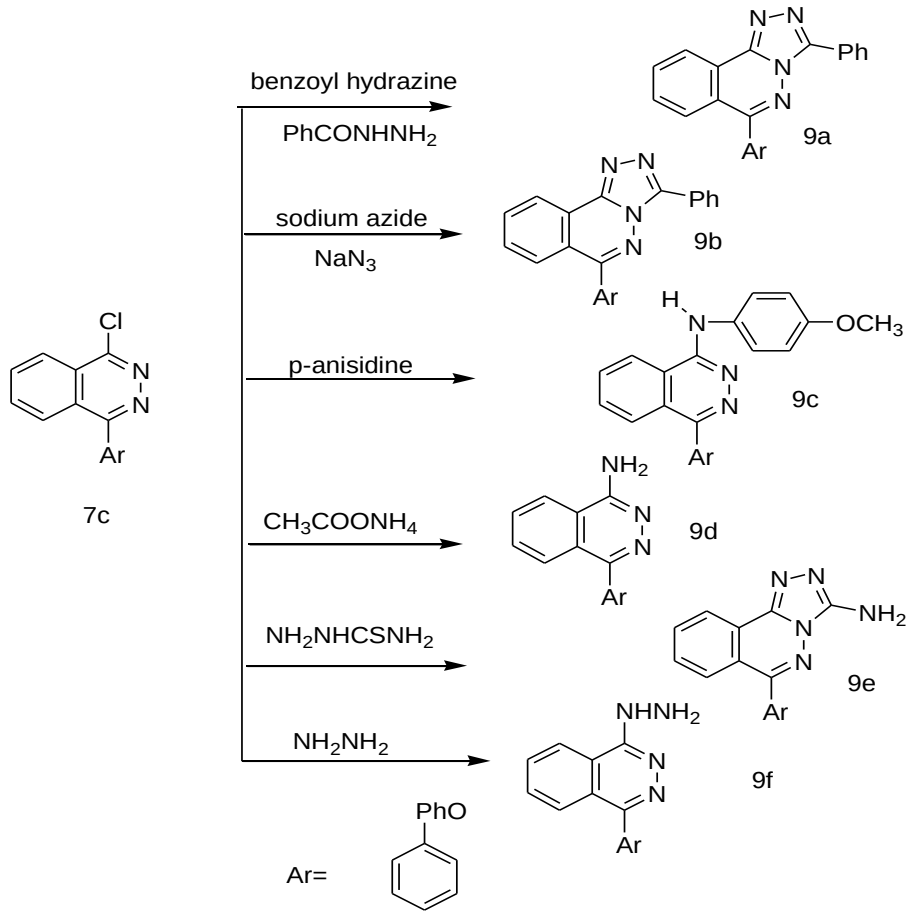

Figure 9: Obtaining 1-hydrazinyl-4-(4- phenoxyphenyl) phthalazine

In 2015 El Azmet al., repoted a review that different synthetic route for the synthesis of substituted phthalazine derivatives. Phthalazinones derivatives were synthesized by using phthalic anhydride as a starting material in the following (Figures 10 and 11) [17].

For the synthesis of phthalazinone derivatives (10a,10b and 10c) R-substituted phthalic anhydrides which reacted with hydrazine hydrates in the presence of AcOH give the derivative(10a) [18].

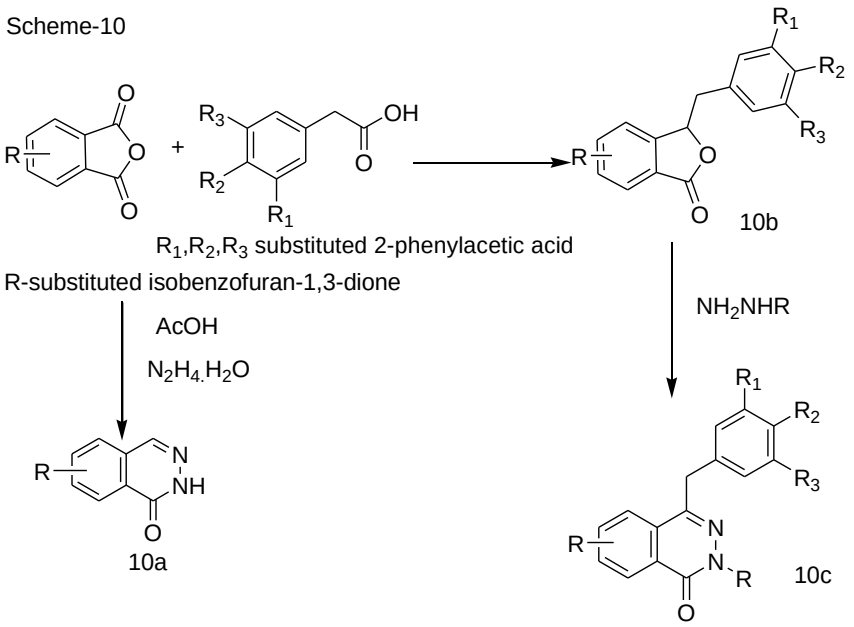

Figure 10: Synthesis of Phthalazinones derivatives

Phthalazinones (11a,11b and 11c) were synthesied from phthalic anhydride in 2-3 steps that are showed in Figure 11 [19].

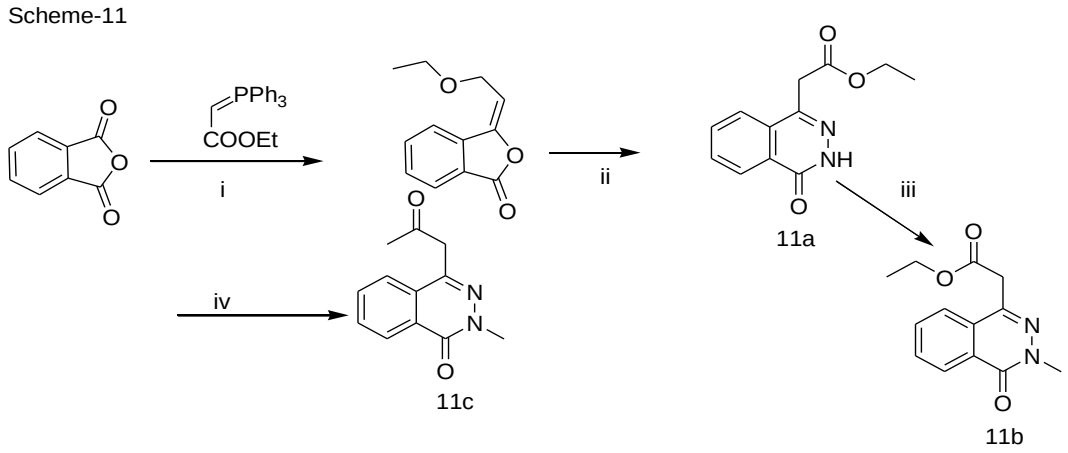

Figure 11: Synthesis of Phthalazinones

Reagents: (i) CHCl3, Reflux, 5hr,(ii)Hydrazine hydrate,EtOH, Addition At Room Temp, Reflux, 2hr.(iii) Mel, KOBu, DMF, 30min (iv) LiOH, THF:Water:MeOH(1:1:1), Room Temp, 8-10hr.

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 (12a,12b) (Figure 12).

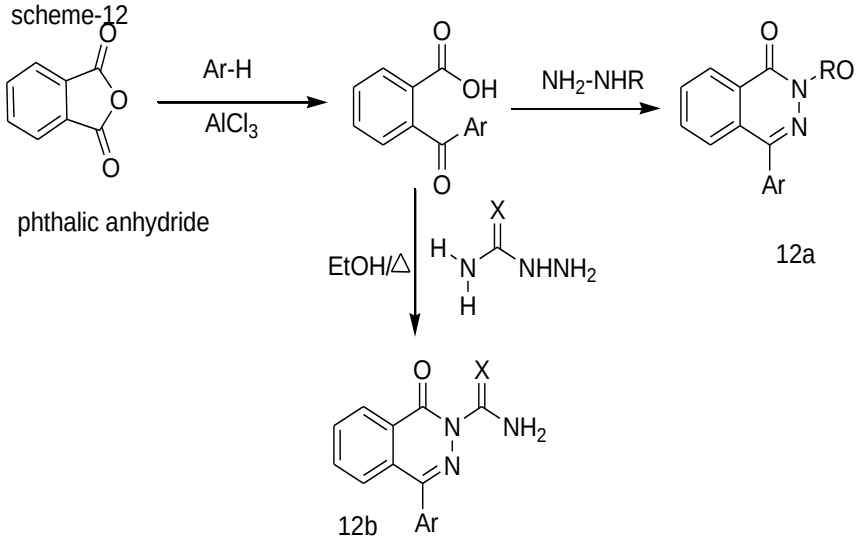

Figure 12: Synthesis of (2H) -1 – one derivatives

Kirill et al in 2004 reported the cyclization of 2-nitro-5-chloro phenyl hydrazine(13b) when reacted with acylbenzoic acids (13a). This reaction give the product 2-(2-nitro-5-chlorobenzene)-4-substituted phthalazine- 1 -ones derivatives (13c) (Figure 13).

Scheme-13

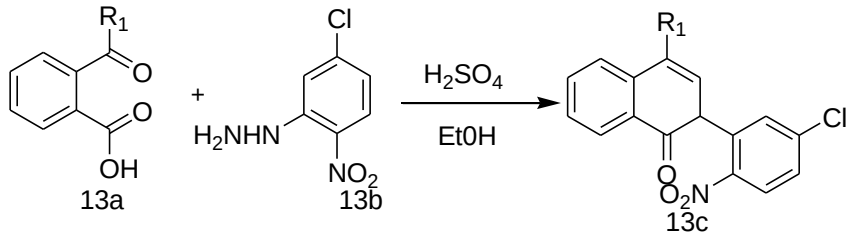

Figure 13: Synthesis of 2-(2-nitro-5-chlorobenzene)-4-substituted phthalazine- 1 -ones derivatives

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

Scheme-14

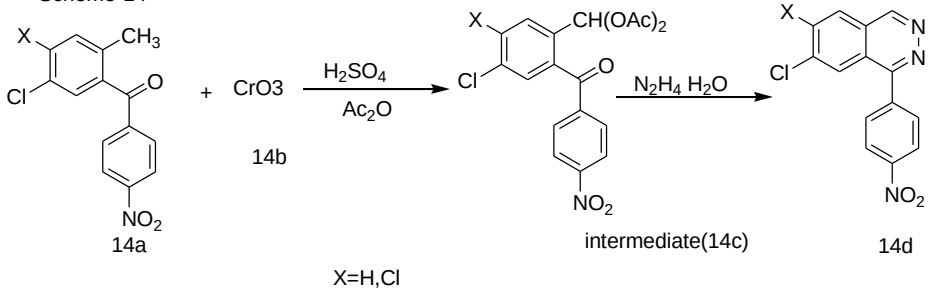

Figure 14: The synthesis of phthalazine derivatives

In the reaction of 3,2-benzoxazin-4-ones with different nitrogen containing reagents, was successfully used in the preparation of different phthalazinone derivatives(15a,15b,15c,15d). The reaction of 1-aryl- 3,2-benzoxazin-4-ones (15)with hydrazine in refluxing ethanol yielded bis-phthalazinone(15a). Fusion of benzoxazin-4-one with ammonium acetate at 115°C gave 4-aryl-1(2H)-phthalazinone15b.The 4-aryl-2-(4-methylphenyl) phthalazinones (15c) was obtained by reacting the benzoxazine-4-ones and p-toludine in refluxing ethanol. Kassab et al.,2003

prepared 4-phenyl-1(2H) phthalazinone (15d) by ammonolysis of 1-aryl- 3,2-benzoxazine-4-one with formamide (Figure 15).

Scheme-15

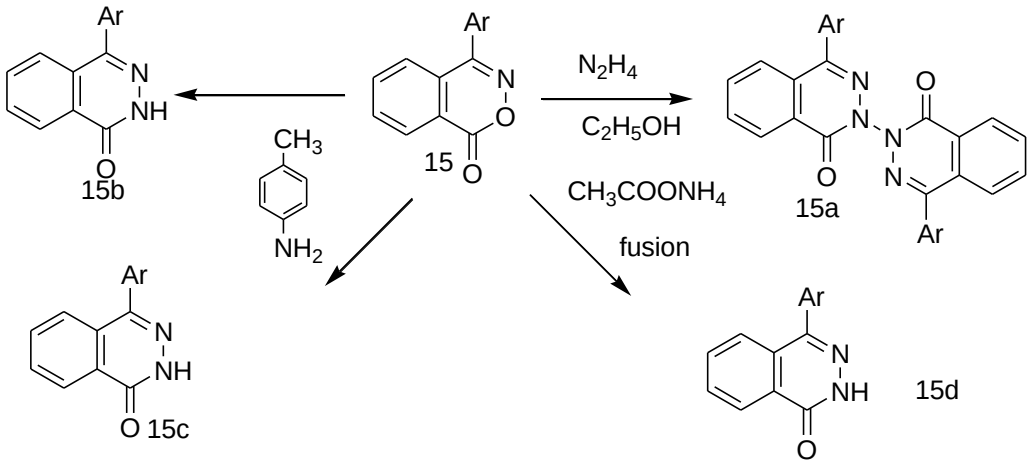

Figure 15: Preparation of 4-phenyl-1(2H) phthalazinone

15)benzoxazin-4-one, 15b,15d) 4-aryl-1(2-H)phthalazinone, 15a) bis-phthalazinone, 15c) 4-aryl-2-(4methylphenyl)phthalazinones

In the condensation reaction of phthalimids with hydrazine hydrate, aromatic aldehyde and malononitrile or ethyl cyanoacetate catalysed by NiCl2.6H2O give derivative of phthalazinedione [1H-Pyrazolo[1,2-b]phthalazin-5,10-dione derivative(16a)] (Figure 16)

scheme-16

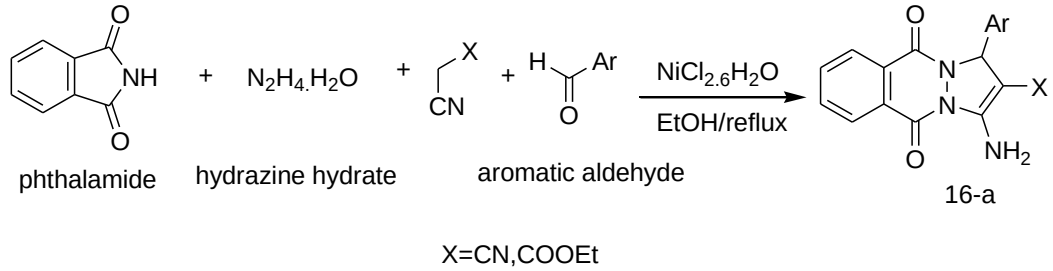

Figure 16: Preparation of derivatives of derivative of phthalazinedione

Ghahremanadeh et al., 2008 synthesized phthalazines, in this reaction phthalhydrazide and acetylene dicarboxylates in the presence of N-heterocycles give the various derivatives such as 17a,17b and 17c (Figure 17)

scheme-17 reaction of phthalhydrazide with acetylene dicarboxylates.

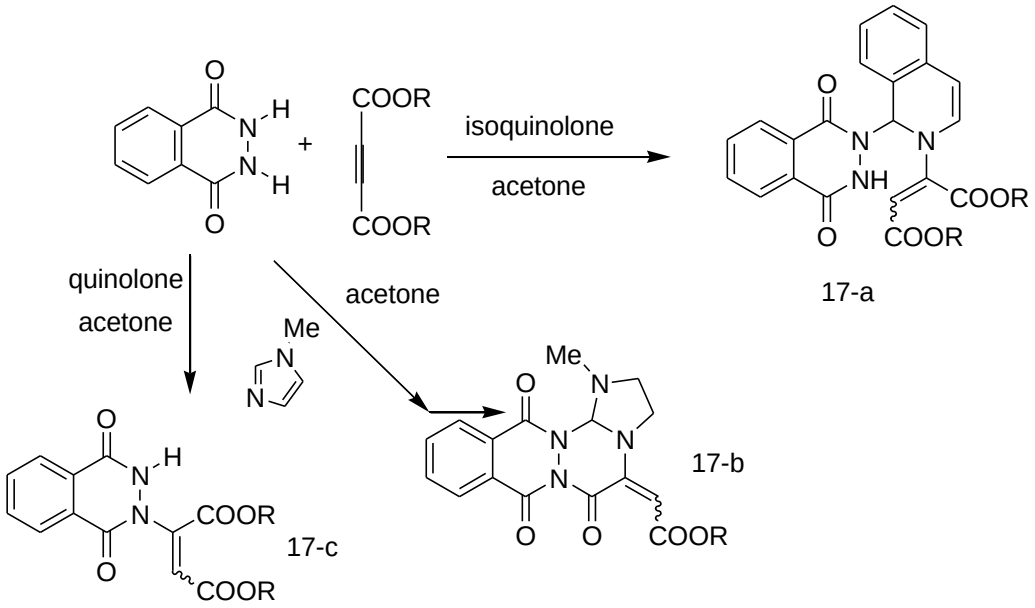

Figure 17: Reaction of phthalhydrazide with acetylene dicarboxylates

AA 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) which is used as a starting material for the further reaction [20,21], Synthesis of (1) with aliphatic acids (formic and acetic acid) give 6-phenoxathiin-2-yl-(1,2,4)triazolo(3,4-a)phthalazine (18a) and 3 methyl-6–phenoxathiin-2yl-(1,2,4)triazolo(3,4-a)–phthalazine (18b). Hyrazinophthalaine 1 in dry pyridine the acid chloride (acetyl chloride,benzoyl chloride) was added dropwise, then reaction mixture was heated for 2 hr on steam bath with continous stirring at room temperature for 45 min. then this reaction mixture was poured into ice, solid product (18d,18e) was collected by after recrystalization. Mixture of (18e) and phosphorous in toluene was heated under reflux for 6 hr. Reaction mixture w as treated with ice and 10% NaOH solution, solid product was collected after crystallizationwith sutaible solvents(18c). A mixture of (1) and urea was heated at 180-1900C for 6 hr. The reaction mixture was cooled and added to a solution of sodium hydroxide(5% solution) , then the product was treated with dil HCl solid product was collected after recrystalition with ethanol (18f). A suspension compound 1 in ethanol, carbon disulfide and pottasium hydroxide was added and the reaction mixture was refluxed for 4 hr then the product was treated with dil HCl solid product was collected after recrystalition with ethanol(18g). A solution of thiol (10 mmol) in sodium hydroxide (20ml 1.5N) and methyl iodide (30mmol) was stirred at room temperature for 1hr. The reaction mixture was extracted with chloform, dried over Na_2SO_4 after this product was recrystalized with dioxane that give (18h,18i) (Figure 18).

scheme-18

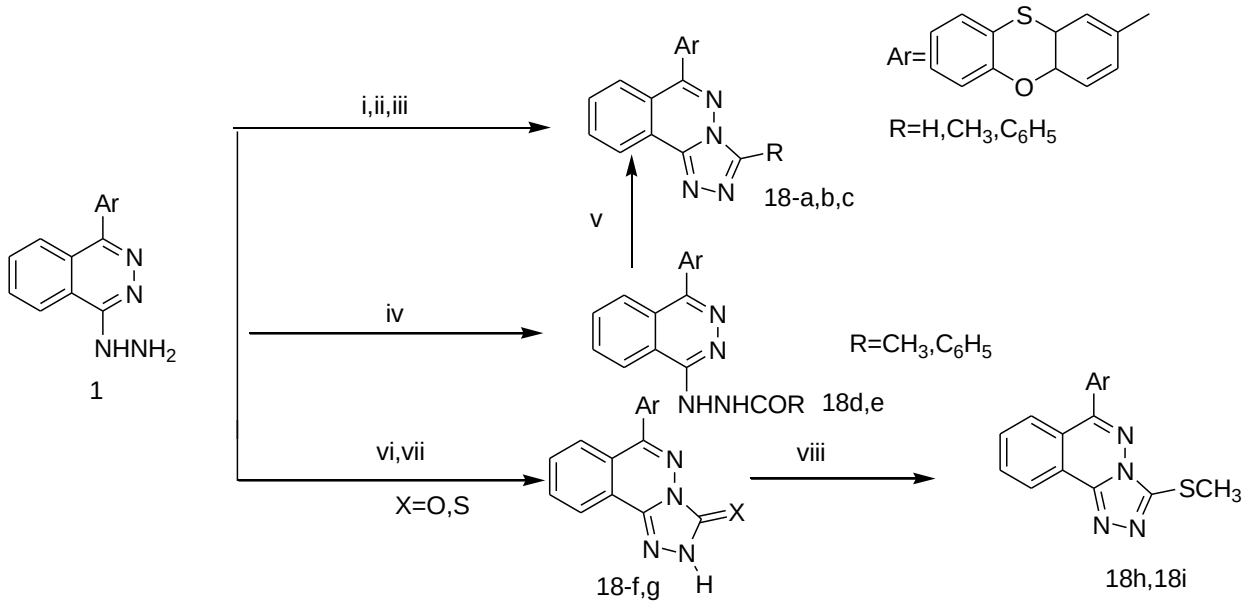

Figure 18: Reagents: i)RCOOH ii)RC(COOEt)3 iii)PhCOOH iv)RCOCl v)POCl3 vi) NH2CONH2 vii) CS2viii) CH3

In this reaction (1) taken as a starting material that react with benzyl isothiocyanate in boiling ethanol give derivatives (19a,19b) (Figure 18)

scheme-19

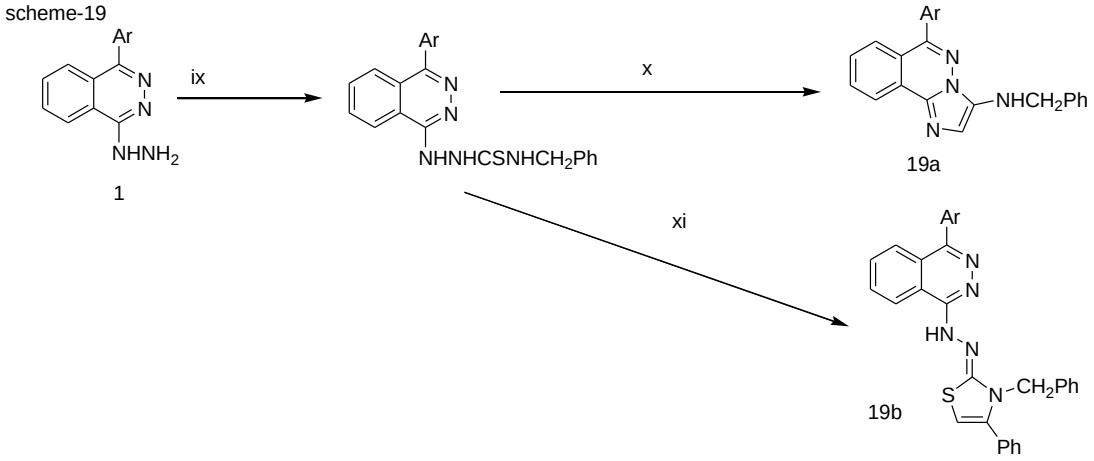

Figure 19: Reagents: ix) PhCH2NCS, x) HgO, xi)PhCOCH2Br

Street et al., 2004 synthesized 3-heterocyclyl-7,8,9,10 tetrahydro-(7, 10 ethano)-1,2,4- triazolo(3, 4 - a) phthalazine was found as showing excellent binding selectivity & oral bioavailability for GABA receptor inverse agonist. 3-(5-methyl isoxazol-1-3-yl) 6-(2 - pyridyl)methyloxy-1,2,4 triazolo(3,4-a)phthalazine provide new therapeutic alzheimer's disease with greater therapeutic window & fewer side effect than currently available drugs in market [22] .

1, 4 di chloro phthalazine (20gm, 0.100 mol) was reacted with boiling solution of hydrazine monohydrate (37.3ml, 0.765 mol) in ethanol (500ml) and the mixture of this heated at reflux for 30 min, cool the mixture and collected the product by filtration and wash with ether give the derivatives (20a, 20b) from the (Figure 19) [23-27].

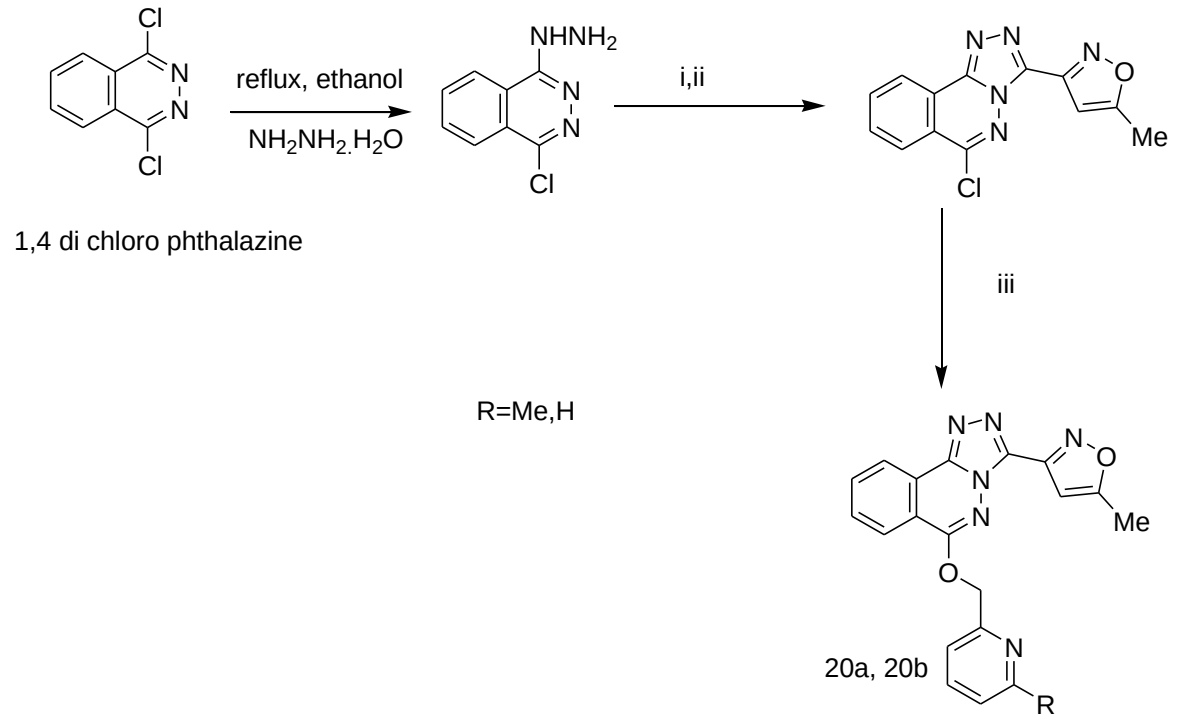

Figure 20: Reagents: i) 5-methylisoxazole-3-carboxylic acid, bis(2-oxo-3-oxazolidinyl)phosphonic chloride, triethylamine, DCM ii) xylene, NEt3.HCl, Reflux, 16hr. iii) Pyridine-2-methanol, NaH, DMF

In 2010 XY Sin et al., synthesized some novel 6 alkoxy(phenoxy)-(1, 2, 4)triazolo(3,4-a)phthalazine-3-amino derivatives. Phthalic anhydride taken as starting material which reacted with hydrazine hydrate inethanol to yield 2,3-dihydrophthalazine-1,4-dione (21b), which reacted further with the refluxing with phosphorus oxychloride(POCl3) that give 1,4 dichlorophthalazine (21c).Compound (21c) further reacted f with hydrazine hydrate in tetra hydro furan (THF) to produce compound (1-hydrazine-4-chrorophthalazin).Then 6-chlorom-[1,2,4] triazolo[3,4-a]phthalazine-3-amine was prepared by cyclising compound with cyanogene bromide in the presence of sodium carbonate . Finally, compound (21e) reacted with appropriate alkanol or substituted phenol to produce the 6-alkoxy(phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives (21a-21u), which are listed in Table 3 (Figure 20) [27-40].

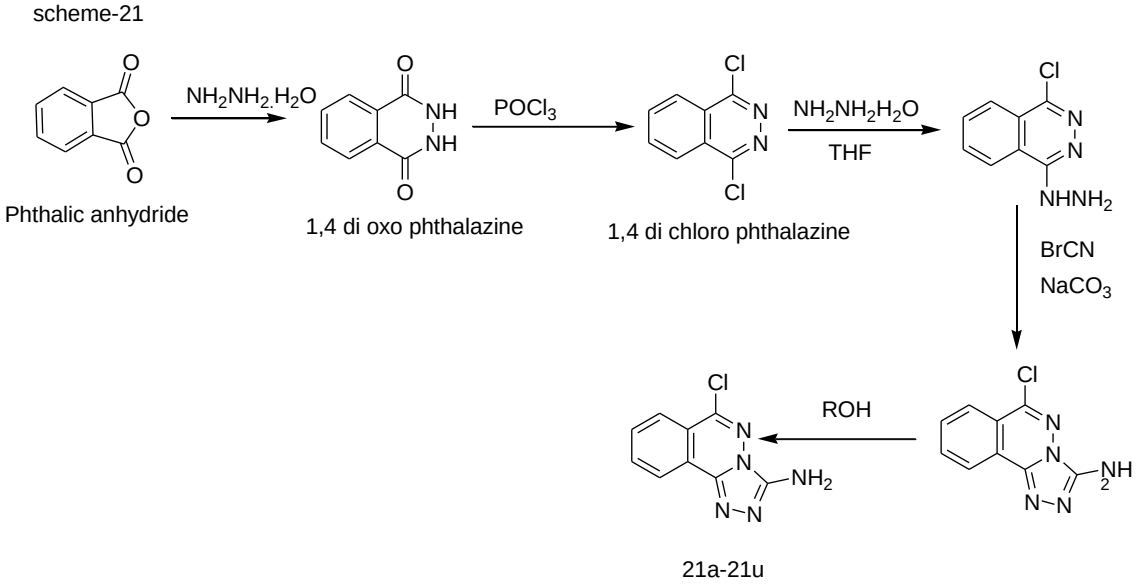

Figure 21: Synthesis of 6-alkoxy(phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives

Table 3: 6-alkoxy(phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives

21a -C6H5	21h-C10H7	21o-C3H7
21b -C6H4(O-CH3)	21i-C6H4(o-OCH3)	21p-n-C4H9
21c- C6H4(m-CH3)	21j-C6H4(p-OCH3)	21q-n-C6H13
21d-C6H4(p-CH3)	21k - C6H4(p-NO2)	21r-nC7H15
21e-C6H4(p-F)	21l- C6H4(p-NH2)	21s-nC8H17
21f-C6H4(p-Cl)	21m-CH3	21t-nC10H21
21g-CH2C6H3(2,4-Cl2)	21n-C2H5	21u-nC5H11

In 2014 Waleed et al., synthesized new phthalazine derivatives in the given reactions. Phthalic anhydride used as a starting material for such type of derivative which produces 4 hydroxy-2-phenylphthalazine-1-(2H) one (22a) was converted into potassium salts (22b) 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 (22c). A compound (22b) reacted with chloroacetic acid (10 m mol) and add absolute ethanol (25 ml) with continuous stirring 10 hours with reflux assembly. After the completion of process resulted compound was collected. A compound (22c) (10 m mol) absolute ethanol (50 ml) and conc. H2SO4 (1ml) was refluxed for 24 hours then allow to cool at room temp. and then in ice water. 5% of sodium bicarbonate cold solution was prepared and added until effervescence ceased. Obtained solid was collected after filtration it is added in sodium bi carbonate solution and stirred for removing remains unreacted acid at the end of procedure. Product was collected and washed with cold water [41-48].

Compound (22d) (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 (22e) (Figure 22).

scheme-22

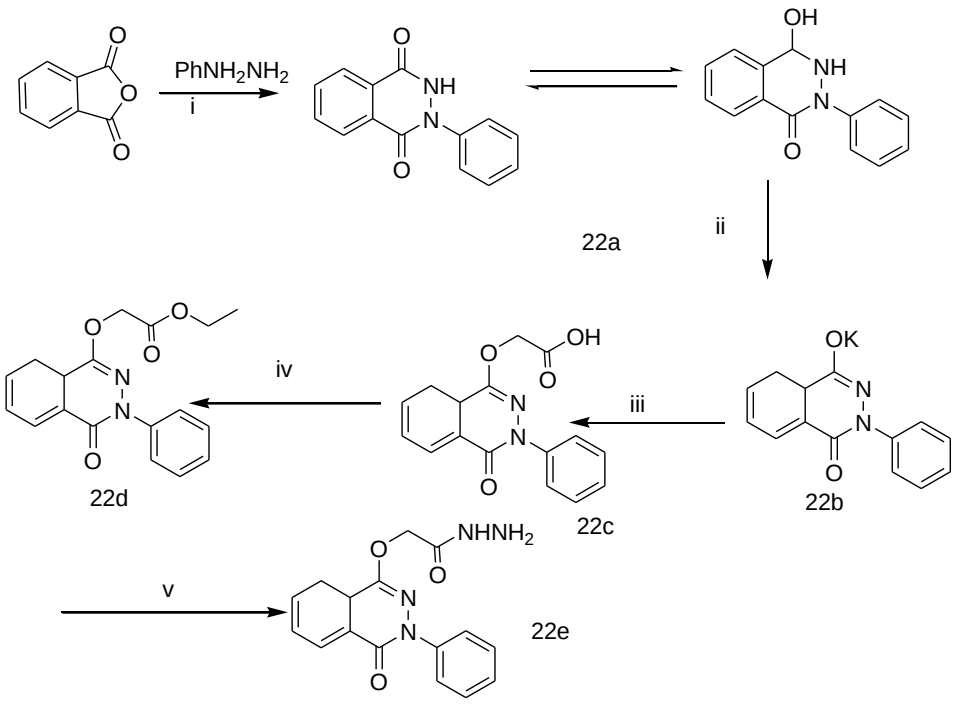

Figure 22: Reagents,(i)PhNHNH2,H2O,CH3COOH, HCl, Reflux,10hr. (ii) KOH, Isopropyl, Stirring, 1hr (iii)ClCH2COOH,ethanol, (iv)ethanol,H2SO4,Reflux, 24hr(v) NH2NH2.H2O, Ethanol, Reflux,8hr

CONCLUSION

Phthalazine is a heterocyclic compound which is obtained from different reactants like Phthalazine phthalate, Hydraine hydrate etc. When phthalazine 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 phthalazine 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 derivatives of phthalazine moiety that will provide a new platform for the researchers [48-54].

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