Review Paper

AN OVERVIEW OF DIFFERENT SYNTHETIC ROUTES FOR THE SYNTHESIS OF PHTHALAZINE DERIVATIVES

Smita Singh[1], Nitin Kumar,*[2]KiyawaSalihuAbdullahi[3]

[1]Researech Scholar, IFTM University, Muradabad, Uttar Pradesh, India
[2]SMAS, K. R. Mangalam University, sohna Road, Gurugram
[3]Department of Chemistry, Kabale University, PO Box 317, Uganda

***Address for correspondence-**

Prof. Nitin Kumar

Professor& Head
Department of Pharmaceutical Chemistry,
School of Medical & Allied sciences,
K R Mangalam University
Sohna Road, Gurugram, 122103
Mob.-9717893319
E.mail.-nitinvermakr@gmail.com

AN OVERVIEW OF DIFFERENT PHTHALAZINE DERIVATIVES SYNTHESIS BY SYNTHETIC ROUTES.

SmitaSngh[1], Nitin Kumar*[2], KiyawaSalihuAbdullahi[3]

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 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 effectivess to produce desire pharmacological response.

Keywords: Phthalazine, Phthalazinone, Thiazolo, Phthalic anhydride.

1. INTRODUCTION

Phthalazines are an unique well known class of nitrogen- containing heterocyclic compounds.The discovery of first naturally occuring pyridazine derivative was a milestone in the recognition of the potential of 1, 2-diazine core nucleous as a valuable unit in medicinal chemistry [1]. Hydralazine also has been used pharmacologically as anti-hypertensive and vasodialating agent [2]. More recently, some 3,6-substituted phthalazines have been reported as pharmacologically active scaffold for anticonvulsants activity.

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

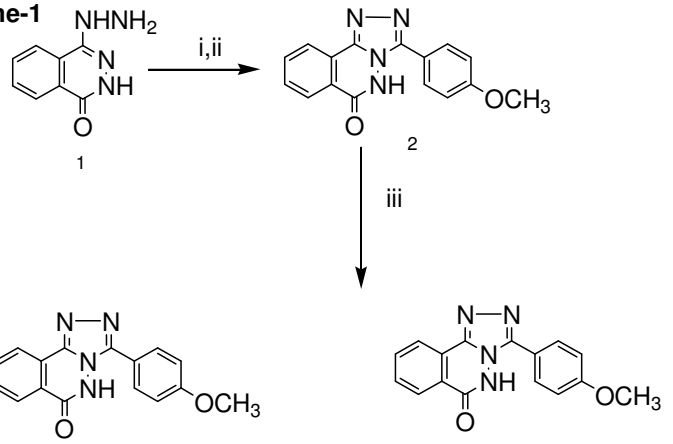
Mostly, 4-hydrazinophthalazine-1-one is used as starting material for the synthesis of various derivatives.Triazolo phthalazine is also considered as pharmacologically highly active molecule having different pharmacological activities like anti inflammtory [16,56], PDE4 inhibitors[14,57], cardiotonic [47], antitumor [40,48,49], vasorelaxant [6], antibacterial [55], antimicrobial [55], antioxidant [13], antidiabetic [17] and anticonvulsant [3,5,7]. Various established drug molecules like budralazine [13] and Azelastine [14,15] are prepared from the corresponding phthalazine-1- one.

The current review paper suggests new ways to researchers to develope more effective and safer drugs hence may be imperative and challenging in medicinal chemistry.[21]

SYNTHESIS OF PHTHALAZINE DERIVATIVES BY VARIOUS SYNTHETIC ROUTE

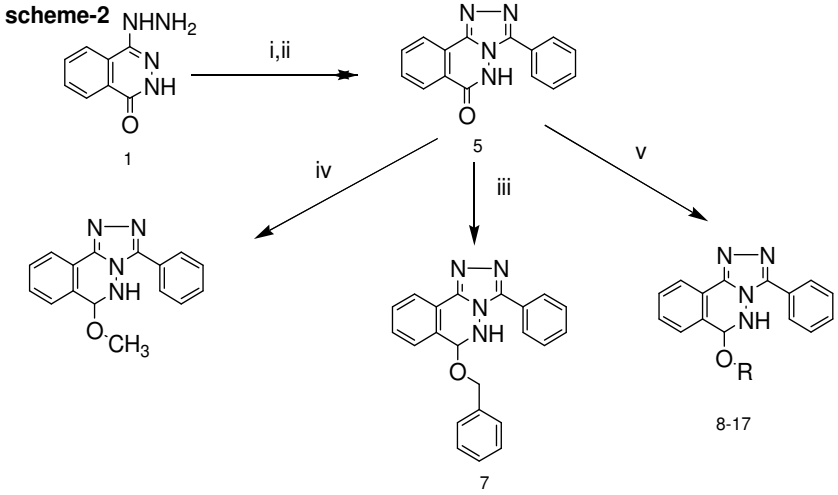
Robert W. Carling *et al*., reported the synthesis of 3- phenyl – 6- (2 pyridyl) methyloxy -1,2, 4-triazolo (3,4 - a) phthalazine derivatives.

scheme-1



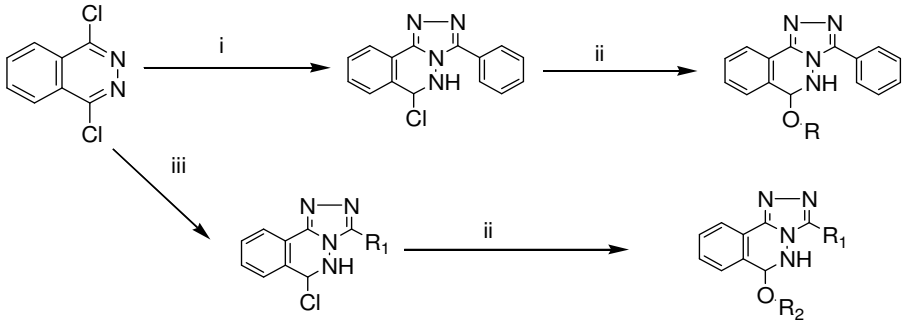
Reagents: (i)4methoxy benzoyl chloride,Et_3N,1,4dioxane,room temp;(ii) DMF,reflux(iii)NaH,DMF,Ph_2Br 100 temp.

scheme-2



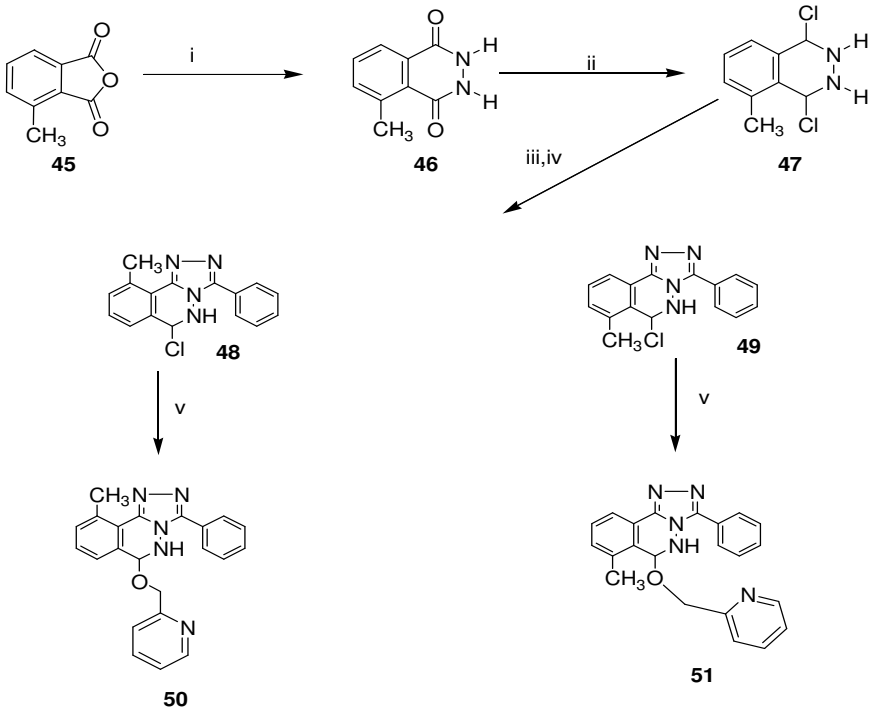
Reagents: (i)benzoyl chloride,Et_3N,1,4 dioxan,room temp;(ii) DMF, reflux (iii) NaH,DMF,$PhCH_2Br$,100 temp (iv) NaH,DMF,CH_3I (V)NaH,DMF,RCH_2Br or RCH_2Cl.

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.

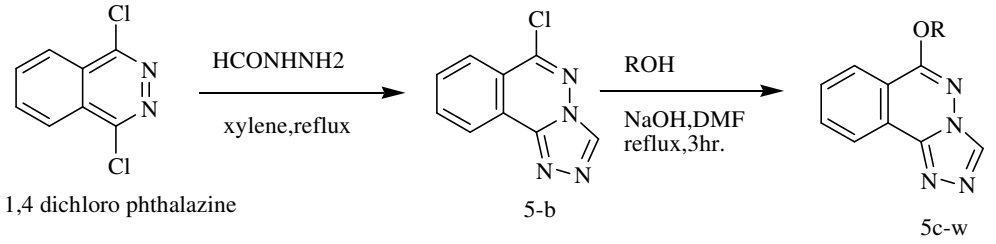
scheme-4



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 nucleous. 1, 4 dichlorophthalazine procceded for reaction with formic hydrazide and appropriate alcohol in the presence of xylene.(shown in table-1) to produce number of phthalazine derivatives.

Scheme-5



1,4 dichloro phthalazine

5-b

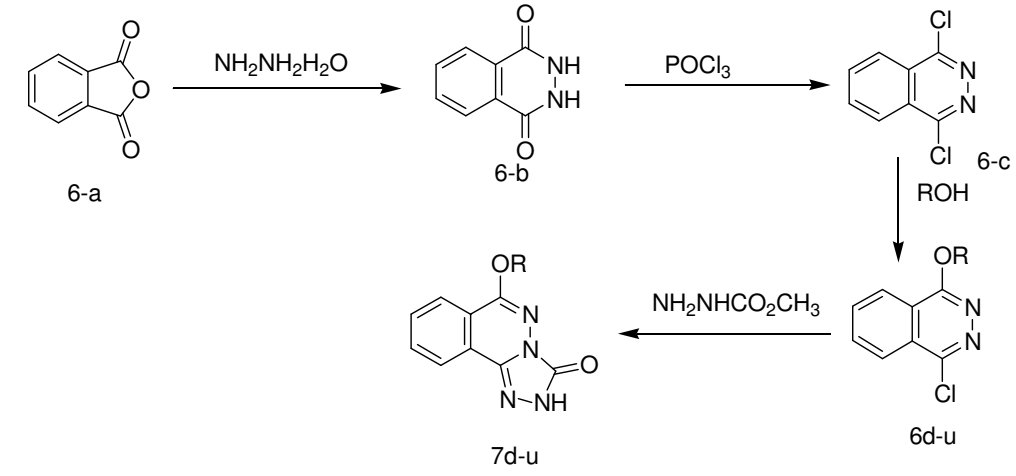
5c-w

Table 1.Different R substituents 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 reated with hydrazine hydrate in the presence of ethanol to yield 6-substituted 1, 2, 4 triazolo [3,4-a] phthalazin-3(2H)-one derivatives.

Scheme-6



6-a

6-b

6d-u

7d-u

Table 2.Different R substituents shown below(7d-7u)

7d = n-C_4H_9	7j= -C_6H_5	7p =-C_6H_4 (4-Br)

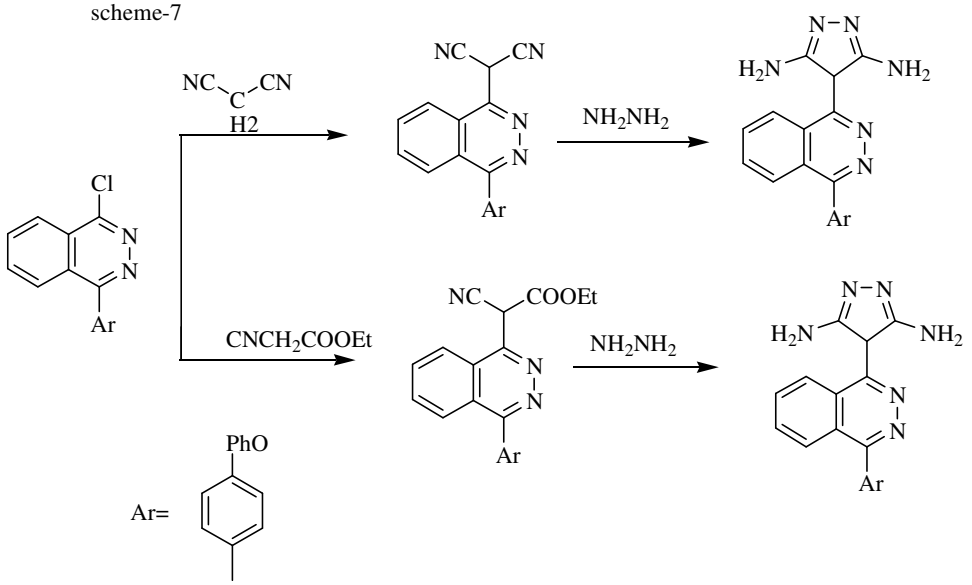
7e= n-C_5H_{11}	7k= -C_6H_4 (4-F)	7q= -C_6H_4 (2-CH_3)
7f = n-C_6H_{13}	7l= -C_6H_4(2-Cl)	7r= -C_6H_4 (3-CH_3)
7g = n-C_7H_{15}	7m= -C_6H_4(3-Cl)	7s= -C_6H_4 (4-CH_3)
7h = n-C_8H_{17}	7n = -C_6H_4(4-Cl)	7t= -C_6H_4 (2-OCH_3)
7i= n-$C_{10}H_{21}$	7o= -C_6H_3(2,4-Cl_2)	7u= -C_6H_4 (4-OCH_3)

2,3 dihydrophthalazine 1,4 dione further reacted with phosphorous oxychloride to give 1,4 di chlorophthalazine which is than reacted with appropriate alkanol and substituted phenol in di methyl formamide to give different derivatives. These derivatives were used as reactant to react in the presence of dimethyl sulfoxide with methyl hydrazine carboxylate. In this way, the researcher were 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)

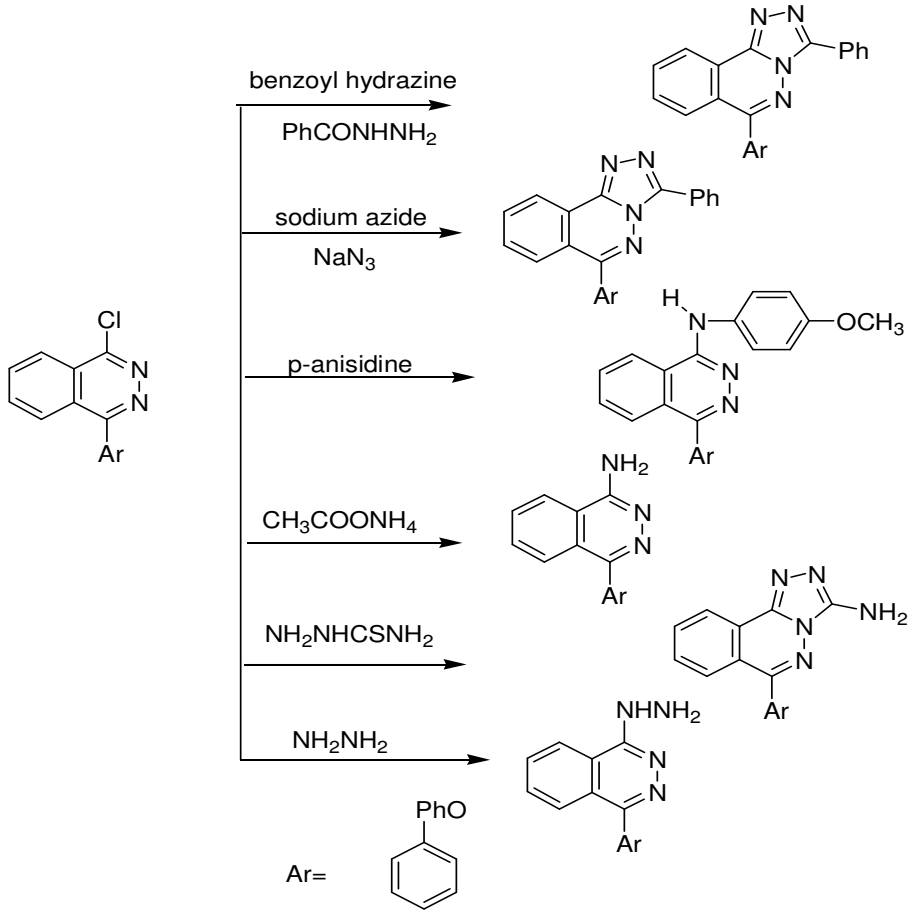
For the synthesis of 2 – (4 – (4 phenoxyphenyl) phthalazine – 1 – yl) – malononitrile, an eqimolor amount of chlorophthalazine (0.01 mol) was made to react with ethylene in ethanol containing sodium ethoxide. This reaction mixture was refluxed for 6 hours at 70 ^oC temperature. After the completion of reaction the reaction mixture was poured into ice. The solid was collected and washed with 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 (0.01mol) 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-7



Scheme-8



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

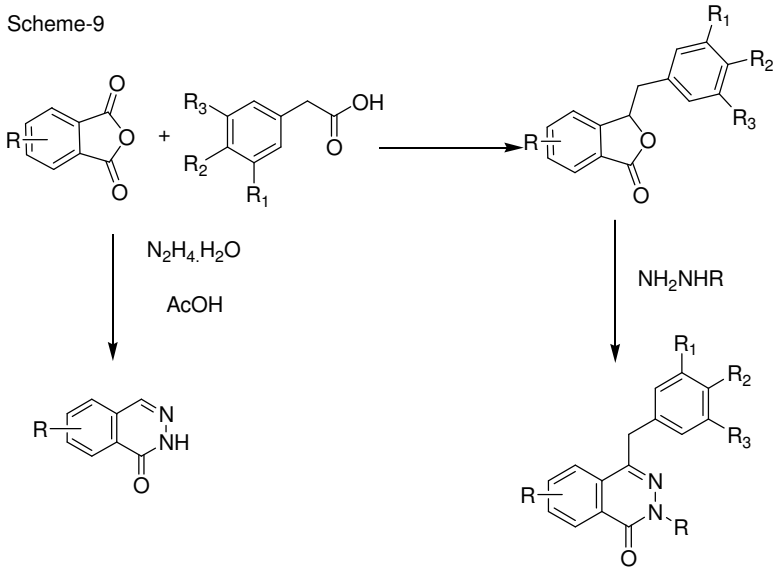
In this scheme(8), chlorophthalazine was reacted with benzoyl hydrazine using n-butanol as solvent. Under refluxed condition, it gave 6 – (4 – phenoxy phenyl) – 3 phenyl – (1, 2, 4) triazolo (3, 4-a) phthalazine.This is further treated with sodium azide. In this scheme, chlorophthalazine was treated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

When chlorophthalazine was react 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.(El Azm et al., 2015)

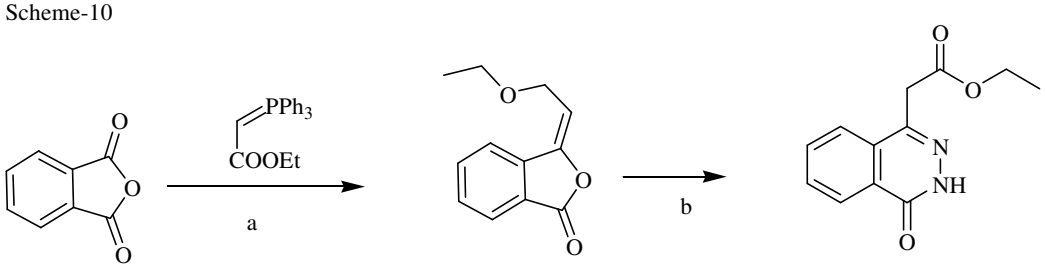
Phthalic anhydride was used as starting material for the synthesis of phthalazinones derivatives as depicted in following scheme.

Scheme-9



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

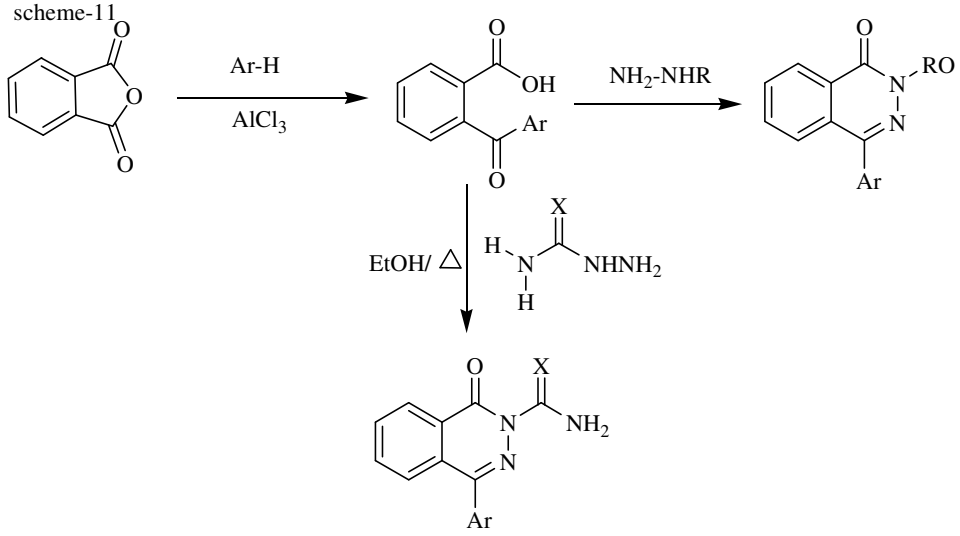
Scheme-10



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

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 give an intermediate product. This intermediate product reacted with hydrazine hydrates and substituted hydrazine. Upon complition of reaction, phthalazine (2H) -1-one derivatives were produced as shown in scheme 11.

scheme-11

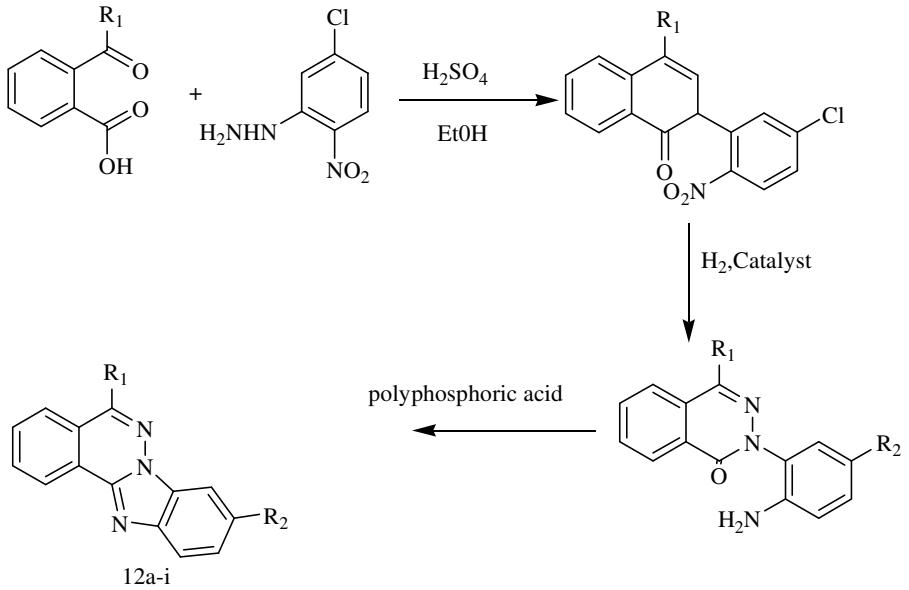


Synthesis of phthalain(2H)-1-one

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 continued in boiling ethanolic solution of concentrated sulfuric acid. Cyclization of 2-nitro-5-chlorophenyl hydrazine with acylbenzoic 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 cyclo dehydration.[K. M. Shubin et al.; 2004]

Scheme-12

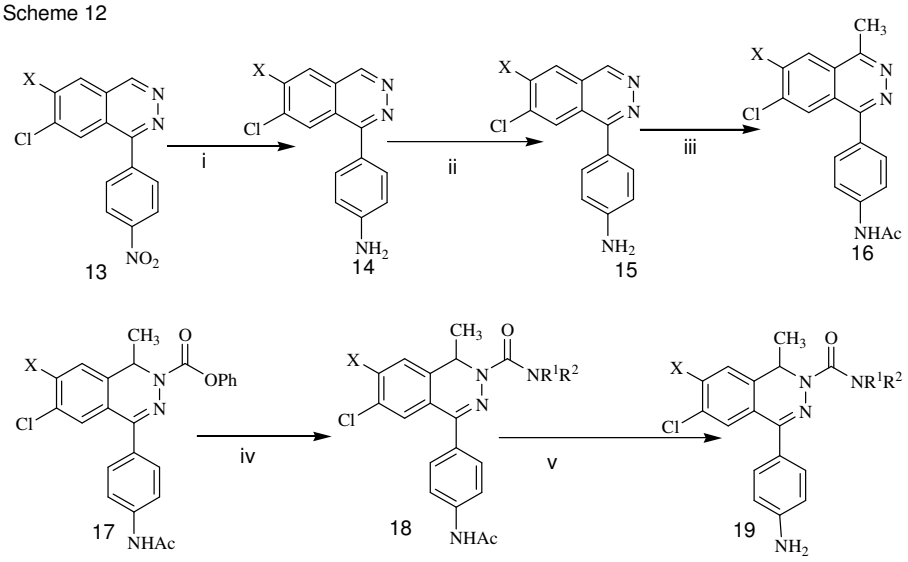


12a-i

GyulaLukacs and GyulaSimig 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 dervatives as shown in scheme 12.

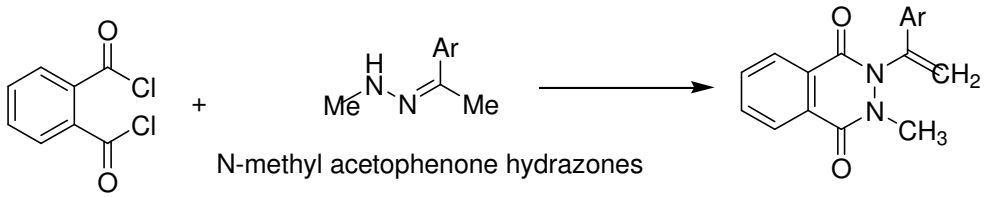
Scheme 12



reagents-: i)Iron, Hydrochloric acid,ethanol ii) Ac_2O, Methanol iii)tetrahydrofuran iv)PhOCOCl,TEA,THF v) nNR^1R^2, DMF vi) NaOH, water, methanol.

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

Scheme-13

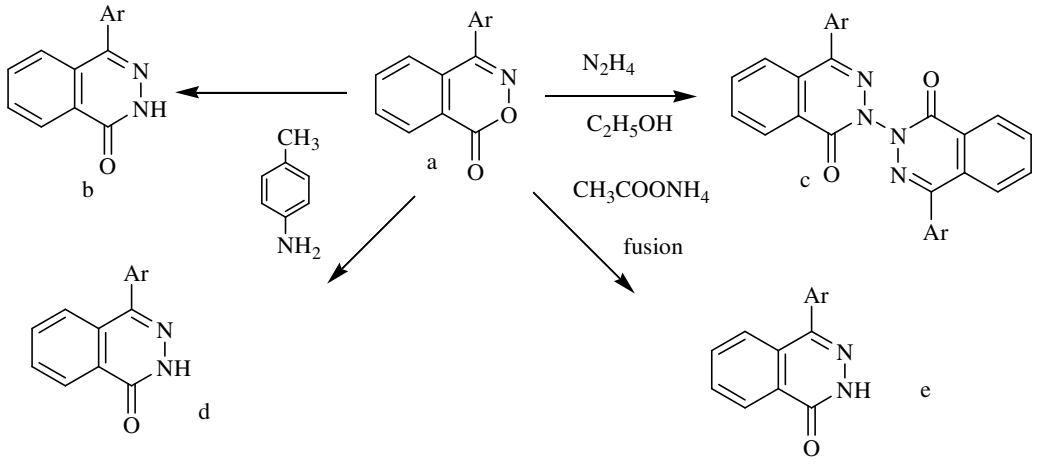


phthaloyl chloride

3,2-benzoxazin-4-ones reacted with various type of nitrogen containing reactants, successfully produced 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)

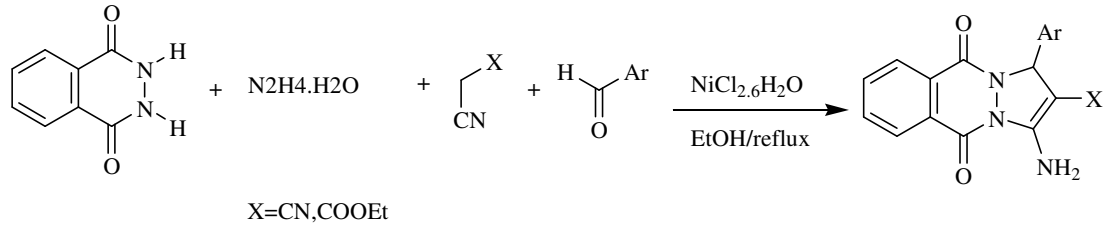
scheme-14



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

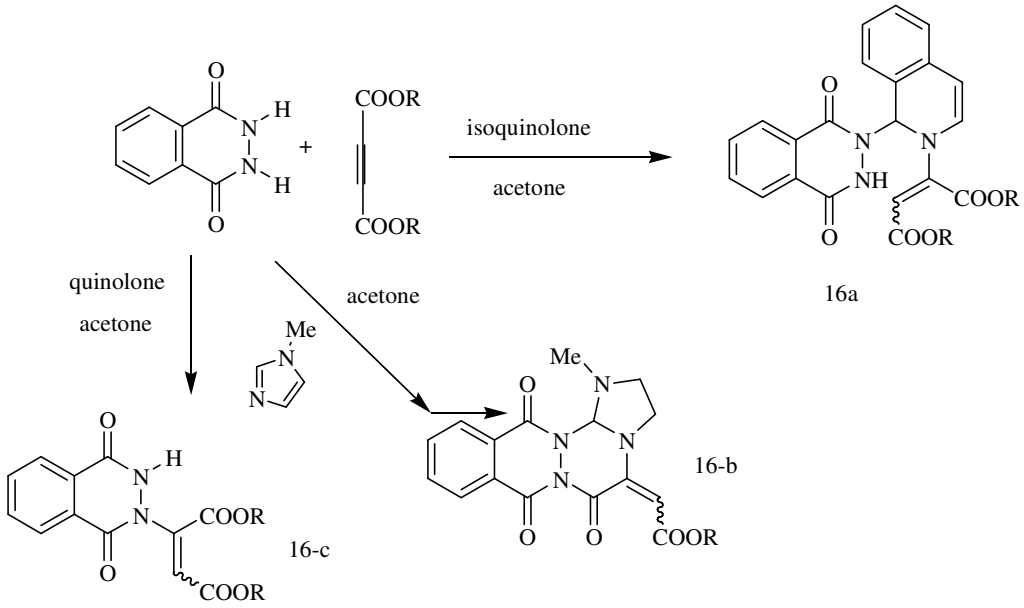
R.Ghahremanazadeh *et al* worked on synthesis of various phthalazine-5,10-dione derivatives, and were able to suggest an efficient one-pot condensation reaction between phthalhydrazide, aromatic aldehydes, and malononitrileor ethyl cyanoacetate with excellent yields.

scheme-15



X=CN,COOEt

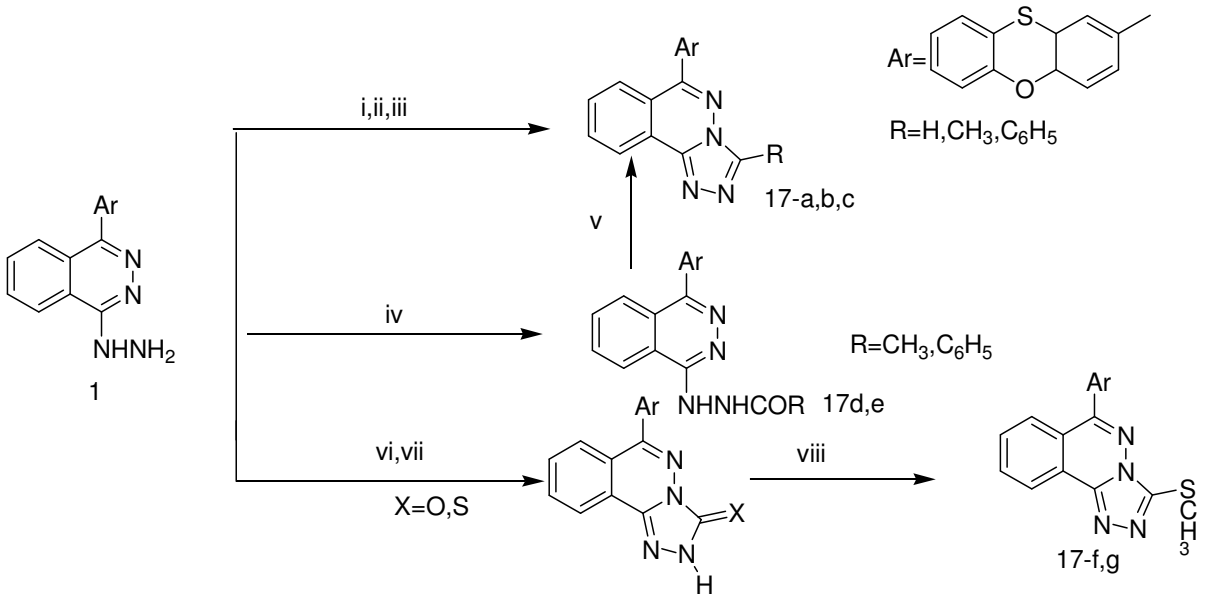
scheme-16



A. A. Aly *et al*., 2005 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).

.

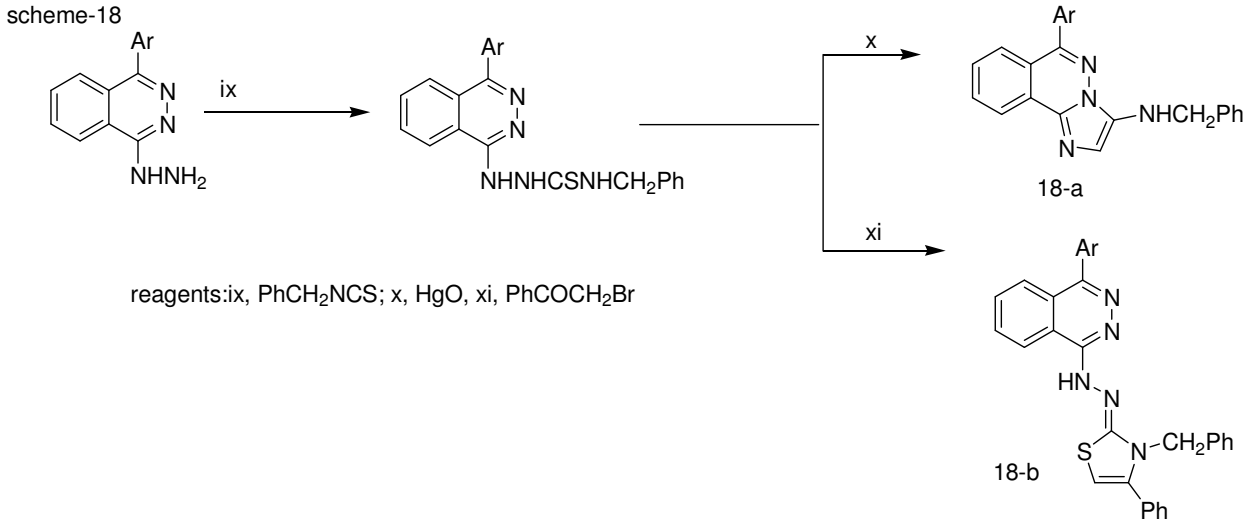
scheme-17



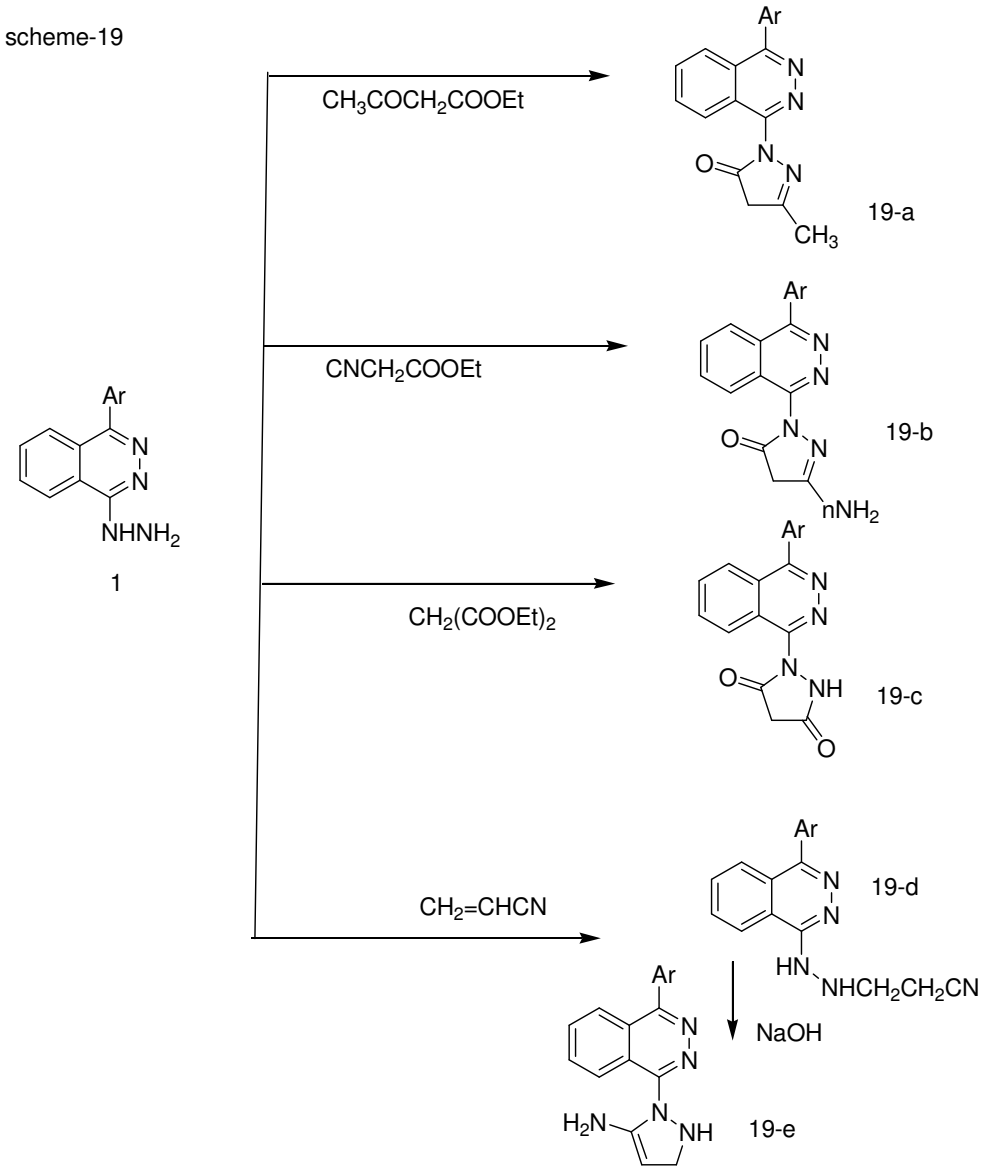
reagents-:i)RCOOH ii)$RC(COOEt)_3$ iii)PhCOOH iv)RCOCl v)phosphorousoxychloride vi) NH_2CONH_2vii) CS_2 viii) CH_3I

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

scheme-18



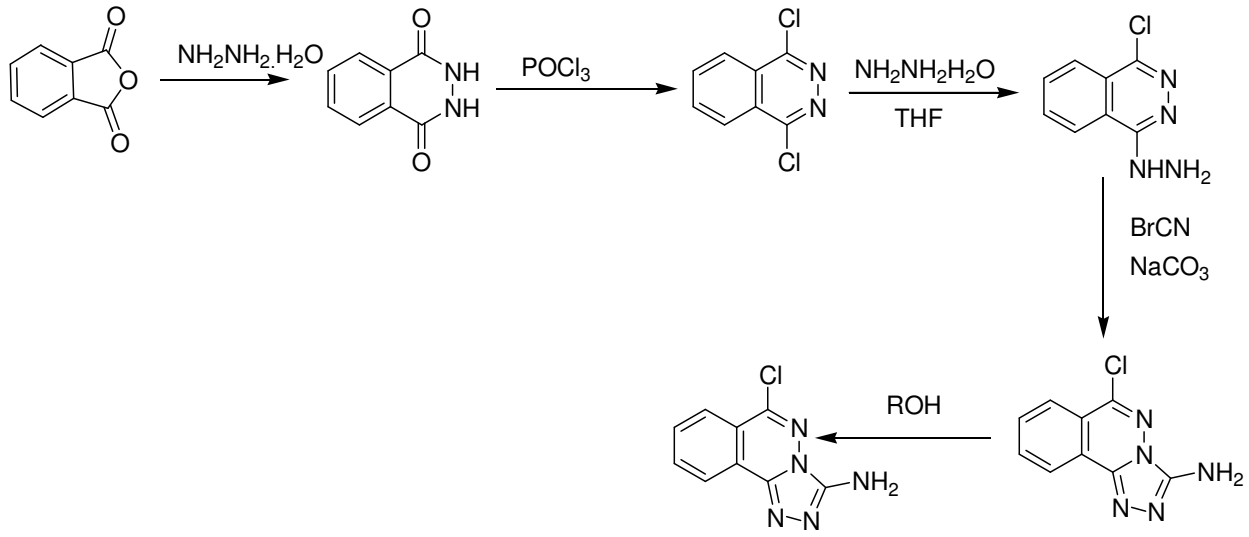
reagents:ix, $PhCH_2NCS$; x, HgO, xi, $PhCOCH_2Br$



X.-Y. Sun *et al*., 2010, synthesized some novel 6 alkoxy (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).

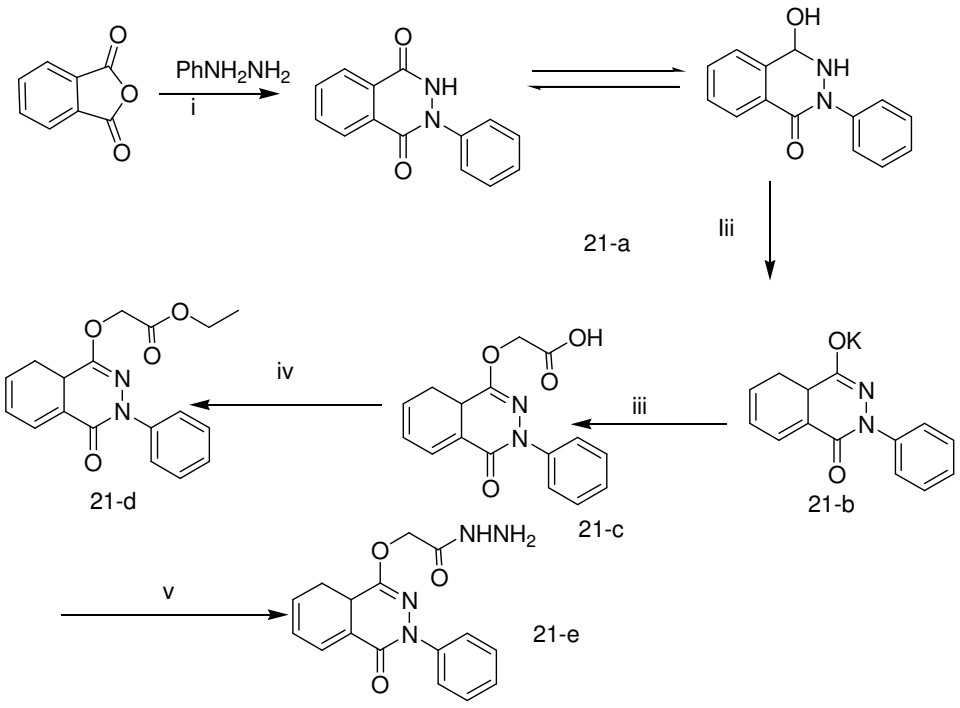
scheme-20



20a-20u

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 aclohol. On continious stirring it gives a clear solution of potassium 4 – oxo – 3 – phenyl -3, 4- dihydrophthalazine -1 –olate.

scheme-21



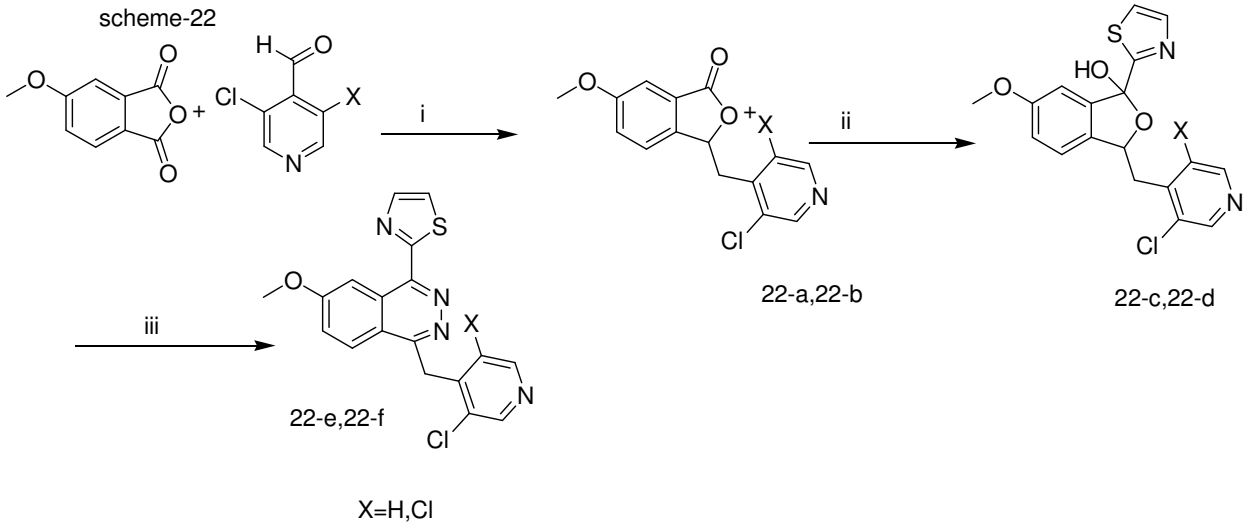
reagents-:i)$PhNHNH_2$, CH_3COOH, HCl, reflux, 10 hour ii) KOH, isopropoyl, stirring, 1 hour iii) $ClCH_2COOH$, ethanol iv) ethanol, sulphuric acid, reflux, 24 hour v) $NHNH_2.H_2O$, ethanol, reflux, 8 hour .

the compound (21-b) when treated with 10 m mol chloroacetic acid and 25 ml of ethanol. refluxed for 10 hours with stirring, produced final product which was subjected to TLC ANLTSIS to establise its purity.

10 m mol compound (21-c) was treated with a mixture of ethanol (50 ml) and conc. sulphuric acid (1ml). 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.

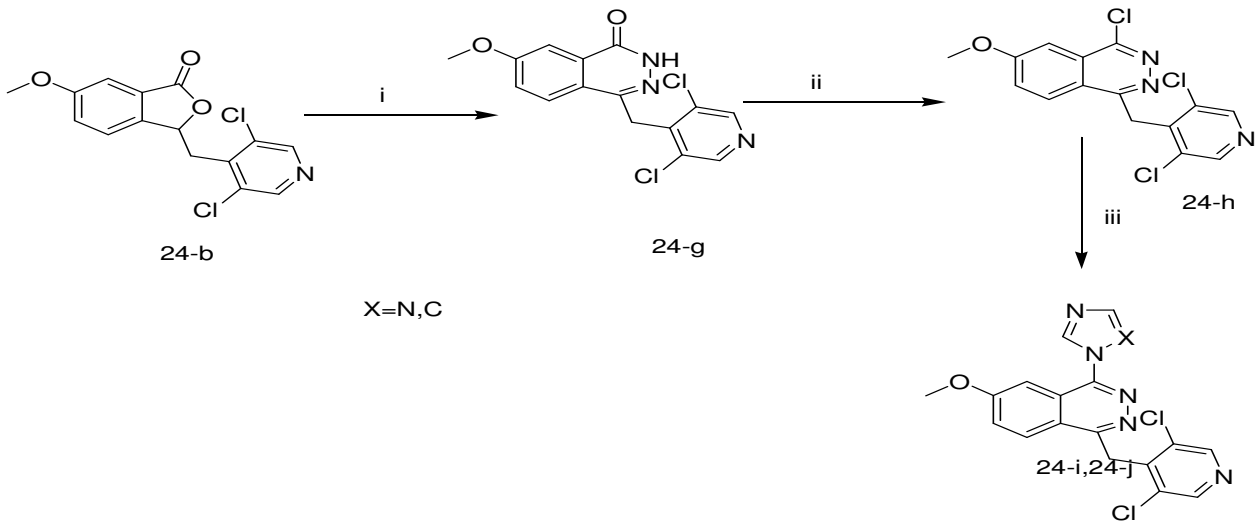
The compound (21-d), (10 m mol) was put in the mixture of hydrazine hydrate (5ml) in ethanol (25 ml) and the reaction mixture was refluxed for 8 hours. The solid precipitated was collected after filtration, washed with ethanol and dried for collection of final product (21-e).

T. Haack *et al*., in 2005, synthesized some derivatives that had PDE IV inhibitors properties. The following scheme was followed.



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

scheme 23

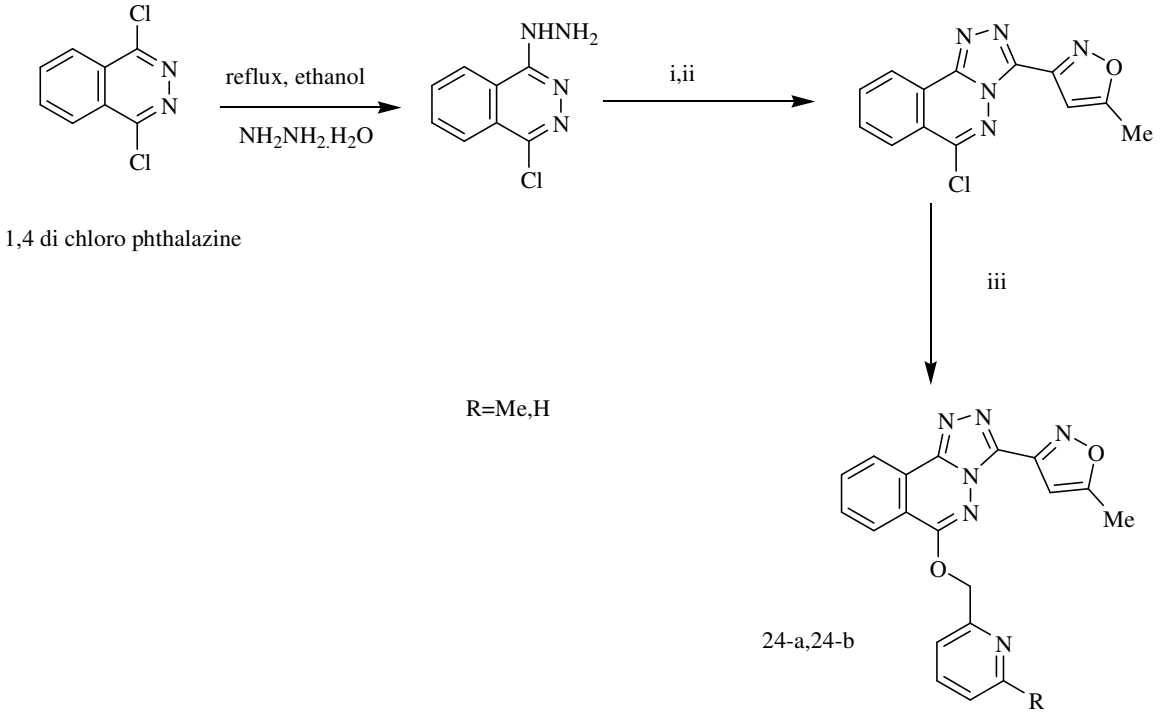


reagents-: i) hydrazine hydrate, methanol, AcOH,reflux 2 hours ii) phosphorus oxy chloride, reflux, 4hour iii) imidazole or triazole, NaH,dimethylformamide, 100°C temperature, X=N,C

Street *et al*., 2004, synthesized 3 – heterocyclyl – 7, 8, 9, 10 tetrahydro – (7, 10 ethano) – 1, 2, 4 – triazolo (3, 4 - a) phthalazine ring. 20 gm of 1, 4 di chlorophthalazine was reacted with 37.3ml of boiling solution of hydrazine monohydrate in ethanol (500ml) and then this reaction mixture

was heated at reflux for 30 minute. The mixture was collected and the collected product after filteration was wash with ether.

scheme-24



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

Conclusion –

In this review article, attemped has been made to summerize the recent development in the synthesis of different phthalazine derivatives, thus suggesting ways to the researchers to look out different path in the synthesis of phthalazines. such type of work would be very useful for the new researchers. new researcher are able to find out different path for the synthesis of a phthalazine. 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 litrature survey in corporated in this review article has been able to explore the possibility of synthesis of more approriate and useful pthalazine derivatives. Different synthetic routes have been

explain leading to the possible development of the pthalazine derivatives. In this way, the article may offer opportunity for new horizones in futurestic research.

REFERENCES

1. Nahed, F., Ghaffar, A. E., Mona, A., Ghanem, H. M., Zaki, H. M., 2011.Journal of American Science.7, 771-781.
2. Aziz, M.A., Youssef, A., Essam, I., 2012.Turk. J. Chem. 36, 347–366.
3. Quan, Z. S., Sun, X. Y., Guan, L. P., 2009. Chem. Biol. Drug Des. 73, 313-319.
4. Gschwind, H. P., Jalava, T., 2006. Drug Metabolism and Disposition. 34, 1817.
5. Zhang, S., Zhao, Y., Liu, Y., Chen, D., Lan, W., Zhao, Q., Dong, C., Xia, L,. Gong, P., 2010. Eur. J. Med. Chem. 45, 3504.
6. Lebsack, A. D., Gunzner, J., Wang, B., Pracitto, R., Schaffhauser, H., Santini, A., Aiyar, J., Bezverkov, R., Munoz, B., Liuc, W. Venkatraman, S., 2004. Bioorg. & Med. Chem. Lett. 14, 2463.
7. Jhang, L., Guan, L.P., Sun, X. Y., 2009. ChemBiol Drug Des. 73, 313-319.
8. Shan, Q. Z., Xi, W.C., Nan,L.F.,2011. Asian journal of chemisrty. 23,127-131.
9. Sayed,M., Rafaat, R., 2017. Der Pharma Chemica. 9, 30 – 38.
10. El Azm, F. S. A., Mahmoud, M.R., Hekal,M.H.,2015. Organic Chemisrty Current Resaerch. 4,1-12.
11. Aly,A. A.,GadEl-Karim, I. A., 2005. Phosphorus,Sulfurand Silicon.180,1997-2011.
12. Carling, R. W., Moore, K. W., Street, L. J., Wild, D., Isted, C., Leeson, P. D., Thomas, S., O'Connor, D., McKernan, R. M., Quirk, K., Cook, S. M., Atack, J. R.,Wafford, K. A., Thompson, S. A., Dawson, G. R., Ferris, P., Castro, J. L., 2004.J. Med. Chem.47, 1807.
13. Bayoumi,W.A., Barghash,A.M., Gineinah,M.M., Massoud,M.A., 2014.Der.pharmachemica. 6, 89-102.
14. Haack,T., Fattori,R.,Pellacini,F.,Fronza,G.,Ganazzoli,F., 2005.13,4425-4433.
15. De, P., Yoya, G. K., Constant, P., Bedos-Belval, F., Duran, H., Saffon, N., Daffe, M., Baltas, M., 2011. J. Med. Chem.54, 1449.
16. Sun, X., Hua, C., Deng, X., Wei, C., Sun, Z., Quan, Z., 2010.Eur. J. Med. Chem. 45, 4807.
17. Lukacs, G., Simig, G. Synthesis of New 1,2-Dihydrophthalazines. 2002.Heterocyclic Chem. 39, 989.
18. Johansson, P.O., Jansson, K., Vrang, L. Hamelink, E., Hallberg, A., Rosenquist, A., Samuelsson, B. 2006.Bioorg. Med. Chem. 14, 5136.

19. Ortqvist, P., Peterson, S. D., kerblom, E. A., Gossas, T., Sabnis, Y. A., Fransson, R., Lindeberg, G. Danielson, U. H., Karlen, A., ,A. 2007.Bioorg. Med. Chem.15, 1448.

20. Jacobson, I. C., Reddy,P. G., Wasserman, Z. R., Hardman,F. D., Covington, M. B., Arner, E. C., Copeland, R. A., Decicco, C. P., Magolda,R. L., 1998.Bioorg. Med. Chem. Lett. 6, 837.

21. Sani, M., Belotti, D., Giavazzi, R., Panzeri, W., Volonterio, A., Zanda,M., 2004. Tetrahedron Lett. 45, 1611.

22. Fray, M. J., Dickinson,R. P., Huggins, J. P., Occleston,N. L., 2003.J.Med. Chem. 46, 3514.

23. Chevallier, C., Richardson, A.D., Edler, M.C., Hamel, E. Harper, M.K., Ireland, C. M., 2003. Org. Lett. 5, 3737.

24. Matsunaga, S., Fusetani, N., Konosu, S., 1985. Tetrahedron Lett. 26, 855.

25. Ryu, G., Matsunaga, S.,N, Fusetani., 1994. Tetrahedron Lett. 35, 8251.

26. Nakanishi, K., 1967.Pure Appl.Chem. 14, 89.

27. Nakanishi, K., Habaguchi, K., Nakadaira, Y., Woods, M. C., Maruyama, M., Major, R. T., Alauddin, M. A., Patel, R., Weinges,K., Bahr, W., 1971.J. Am. Chem. Soc., 93, 3544.

28. Hu, L., Chen, Z., Cheng, X., Xie, Y., 1999.Pure Appl. Chem. 71, 1153.

29. Vogensen, S. B., Strmgaard, K., Shindou, H., Jaracz, S., Suehiro, M., Ishii, S., Shimizu, T., Nakanishi, K., 2003. J. Med. Chem. 46, 601.

30. Mujumdar, R. B., Rama, A.V., Rao, S., Rathi, S., Venkataraman, K., 1975. Tetrahedron Lett. 16, 867.

31. Kotake, C., Yamasaki, T., Moriyama, T., Shinoda, M., Komiyama, N., Furumai, T., Konishi, M., Oki,T., 1992. J. Antibiot. 45, 1442.

32. Chan, W.S. Hui, W.H., 1973. J. Chem. Soc. Perkin Trans. 1, 490.

33. Li, X., Djerassi, C., 1983.Tetrahedron Lett. 24, 665.

34. Giner , J.L., Djerassi, C., 1991. Phytochemistry. 30, 811.

35. Pettit, G. R., Gao, F., Sengupta, D., Coll, J. C. Herald, C. L., Doubek, D. L., Schmidt, J. M., Van Camp, J. R., Rudloe, J. J., Nieman, R. A., 1991. Tetrahedron. 47, 3601.

36. Hwang J. Y., Choi H. and Gong Y., 2005. Tetrahedron Lett. 46, 3107.

37. Carling, R. W., Moore, K. W., Street, L. J., Wild, D., Isted, C., Leeson, P. D., Thomas, S., O'Connor, D., McKernan, R. M., Quirk, K., Cook, S. M., Atack, Wafford, J. R., Thompson, K. A., S. A., Dawson, G. R., Ferris, P., Castro, J. L., 2004. J. Med. Chem. 47, 1807.

38. Street, L. J., Sternfeld, F., Jelley, R. A., Reeve, A. J., Carling, R. W., Moore, K. W., McKernan, R. M., Sohal, B., Cook, S., Pike, A., Dawson, G. R., Bromidge, F. A.,

Wafford, K. A., Seabrook, G. R., Thompson, S. A., Marshall,G., Pillai,G. V., Castro, J., Atack ,J. R., MacLeod, A. M., 2004. J. Med. Chem. 47, 3642.

39. Tarzia, G., Occelli, E., Toja, E., Barone, D., Corsico, N., Gallico, L., Luzzani, F., 1988. J. Med. Chem. 31, 1115.

40. Sun, X. Y., Quan,Z.S., Sun, Z,G., Deng,X.Q., 2010. Eur. J. Med. Chem. 45: 4807-12.

41. Kumar,N., Singh, S.,2014.World journal of pharmacy and pharmacutical sciences.3,729-736.

42. Xu Y, Guo QX (2004) Syntheses of Heterocyclic Compounds under Microwave Irradiation. Heterocycles 63: 903-974.

43. Al-Assar, F., Zelenin, K.N., Lesiovskaya, E.E, Benzhan, I.P., Chakchir, B.A.,2002.. Pharm Chem J. 36, 598-603.

44. Shubin K M., Kuznetsov, V A., Galishev V. A. Synthesis of benzo[4,5]imidazo[2,1-a]phthalazines. 2004.Tetrahedron Letters. 45, 1407–1408.

45. Kornet, M.J., Shackleford, G., 1999. J HeterocyclChem. 36, 1095-1096.

46. Sivakumar, R., Kishore, Gnanasam., S, Ramachandran, S., Leonard, J.T.,2002. Eur J Med Chem. 37, 793-801.

47. . Nomoto, Y., Obase, H., Takai, H., Teranishi, M,, Nakamura, J., 1990. Chem Pharm Bull 38, 2179-2183.

48. Sung, Kim. J., Lee, H.J, Suh, M.E, Choo, H.Y, Lee, S.K., 2004. Bioorg Med Chem. 12 3683-3686.

49. Haider, N., Kabicher, T., Käferböck, J., Plenk, A., 2007.12,1900-1909.

50. . Demirayak, S., Karaburun, A.C., Beis, R.,2004. Eur J Med Chem. 39, 1089-1095.

51. Watanabe, N., Kabasawa, Y., Takase, Y., Matsukura, M., Miyazaki, K.,1998. J Med Chem. 41, 3367-3372.

52. Madhavan, G.R., Chakrabarti, R., Kumar, S.K., Misra, P., Mamidi, R.N., 2001. Eur J Med Chem. 36, 627-637.

53. Johnsen, M., Rehse, K., Pertz, H., Stasch, J.P., Bischoff, E.,2003. Arch Pharm (Weinheim). 336, 591-597.

54. Cardia, M.C, Distinto, S., Maccioni, E., Delogu, A.,2009. J HeterocyclChem. 40, 1011-1015.

55. Shetgiri, N.P., Nayak, B.K., 2005. IndJchem. 44B, 1267-1272.

56. Dogruer, D.S., Kupeli, E., Yesilada, E., Sahin, M.F 2004. Arch Pharm (Weinheim). 337, 303-310.

57. Napoletano, M., Norcini, G., Pellacini, F., Marchini, F., Morazzoni, G.,2000. Bioorg Med ChemLett. 10, 2235-2238.

58. Bedoya, L.M., delOlmo, E., Sancho, R., Barboza, B., Beltrán, M., 2006. Bioorg Med ChemLett.16, 4075-4079.

59. Soliman, A.Y., El-Komy, M.A.S., 1999. J Chem. 42, 301-308.

60. Abu El-Azm, F. S., Mahmoud, R.M., Mohamed, H. H. 2015. Organic Chem Curr Res.4,1-12.

61. Singh,S.,kumar,N. 2018. J. Chem. Pharm. Res. 10(8), 175-190.

62. http://shodhganga.inflibnet.ac.in/bitstream/10603/43152/12/12.%20chapter%20iii.pdf