

A Concise Review on Phthalazine Derivatives and its Biological Activities

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Abstract

Phthalazine has good attention in the field of research study due to its wide spectrum of biological activity and therapeutic applications. Phthalazine is a good lead compound for the synthesis of novel drugs. There is a growing interest in the synthesis of several phthalazines derivatives as better drug candidates for the treatment of various diseases. Phthalazine contains a strong pharmacophoric moiety and ring structure it attracts the researchers to this nucleus for the synthesis of novel drugs. Through this review, introduce a new way for a researcher by introducing this nucleus and develop a novel class of drugs who have a better therapeutic profile. In this review, mainly discuss the different pharmacological activity of phthalazine which has already discussed by the researcher. These reports have resulted in a great number of contributions in diverse areas of interest. This study may produce a new way for the researchers to design and develop the phthalazine derivatives with good pharmacological activities.

Keywords: Anticancer drug, anticonvulsant activity, antimicrobial agent, phthalazine and tuberculosis.

INTRODUCTION

Phthalazine is a nitrogen-containing heterocyclic compound. Several research studies are focused on the phthalazine nucleus due to their wide applicability. Phthalazine derivatives are promising drug candidate for the treatment of various diseases. And these heterocycles are more found in medicinal compounds. The pharmacological activities exhibited by phthalazines are anti-inflammatory, antihypertensive, cytotoxic, antitumor, anticancer, anticonvulsant, antibacterial, antitubercular and antifungal activity. There is a number of phthalazine based drugs are available. Hydralazine, budralazine, vatalanib, olaparib, azelastine are the commercially available phthalazine based drugs.

Many researchers consider the phthalazine is a good therapeutic target for studying different pharmacological activities. Phthalazine forms a different derivative with interesting biological properties due to the presence of better pharmacophoric moiety. The phthalazine has a versatile pharmacophore with more medicinal significance. The medicinal chemist has more attention towards the phthalazine nucleus. It is an attractive building block for the synthesis of many drugs.

Phthalazine derivatives act as an intermediate for the synthesis of many compounds and also it is a starting material for the design of novel drugs. It is a versatile lead for the development of new drugs. Among a large variety of nitrogen-containing heterocyclic compounds, heterocyclic containing hydrazine has considerable attention because of their pharmacological properties and clinical applications.

Phthalazines have recently been reported to potentially inhibit serotonin reuptake and are considered antidepressant agents. Phthalazines are also one of the important biological active pharmacophore components in medicinal chemistry. A number of established drug molecules like Hydralazine, Budralazine, Azelastine, Ponalrestat, and Zopolrestat are prepared from the corresponding phthalazinones. The diverse biological

activities of phthalazine (figure 1) and phthalazin-1(2H)-one (figure 2), encouraged us for the designing of new molecules [1].

PHARMACOLOGICAL ACTIVITIES OF PHTHALAZINE DERIVATIVES

Antibacterial activity

A new series of phthalazine-based 1,2,3-triazole derivatives were synthesized and evaluated their antibacterial activities against three bacterial strains *Micrococcus luteus*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* by a well-diffusion method using tetracycline as a standard anti-bacterial agent. Most of the phthalazine derivatives showed good antibacterial activity than the reference compound. Among them 2,3-bis[(1-aryl)-1H-1,2,3-triazole-4-yl)methyl]-2,3-dihydro phthalazine-1,4-diones derivatives (1a) (figure 3) showed the highest antibacterial activity against *Pseudomonas aeruginosa*. And 1b (figure 4) showed the highest antibacterial activity against *E. coli* and *Pseudomonas aeruginosa* [2].

The 6-(chloropyridin-3-yl)methyl substituted phthalazine 1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles were investigated for their antimicrobial activity. The derivatives substituted with 5-nitro-thiazole to triazolothiadiazole (1c) (figure 5) and methylthiophenyl to triazolo thiadiazines (1d) (figure 6) showed better activity compared to other derivatives. The 3-substituted methyl 3-methoxy-2-(4-oxo-3,4-dihydro phthalazine-1-yl) acrylates phthalazine methoxyacrylate compounds substituted at C3 position with different functional groups starting from commercially available phthalic anhydride. Investigated their antimicrobial activity of compounds revealed that, compounds substituted methyl 2-{3[(6-chloropyridin-3-yl)methyl]-4-oxo-3,4-dihydrophthalazin-1-yl}-3-methoxyacrylate (1c), methyl 2-[3-(4,6-dimethoxy pyrimidin-2-yl)-4-oxo-3,4-dihydrophthalazin-1-yl]-3-methoxy acrylate (1d) showed better activity compared to other derivatives [3].

Anti-inflammatory activity

A novel Phthalazinedione derivatives were synthesized by condensation of dibenzobarallene with thiosemicarbazides and evaluated their anti-inflammatory and analgesic activities by collagen II-adjuvant induced paw edema test in rats. The phthalazine derivatives 1,4-Dioxo-3,4,4e,5,10,10a-hexahydro-1H5,10-benzo-benzo[g]-phthalazin-2-yl-Npyridin-2-ylthioamide shows better results in a reduction of rheumatoid index compared to other compounds. The analgesic effect of the synthesized compounds was determined by pain tolerance. The results showed that compound 2a (figure 7) showed better results than piroxicam and the pain scoring of compounds 2a and 2b (figure 8) were more effective than piroxicam [4].

A novel series of 6-phenoxy-[1,2,4]triazolo[3,4-a]phthalazine-3-carboxamide derivatives were synthesized as potent anti-inflammatory agents, which acted on tumor necrosis factor (TNF- α) as inhibitors of NF- κ B activation. The compounds 3a (6-(3-tolyloxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-carboxamide) (figure 9) showed more prominent anti-inflammatory activity than other compounds, with similar activities as the reference drug dihydrotanshinone. The compound 3a showed the lowest cellular toxicity among the tested compounds. In vivo evaluation of the anti-inflammatory activity showed that compound 3a exhibited excellent anti-inflammatory activity [5].

Antitubercular activity

A novel 2-[3-(4-bromo-2-fluorobenzyl)-4oxo-3,4-dihydro-1-phthalazinyl]acetic acid amides were synthesized from phthalic anhydride. Then studied their invitro and in vivo evaluation against log- and starved phase of mycobacterial species and Mycobacterium tuberculosis isocitrate lyase enzyme inhibition studies. Among the synthesized compounds 2-(2-(4-bromo-2-fluorobenzyl)-1,2-dihydro-1-oxophthalazin-4-yl)-N-(2,6-dimethylphenyl)acetamide(4a) (figure 10) inhibited all eight mycobacterial species with MIC's ranging from 0.08 to 5.05 IM and was non-toxic to Vero cells till 126.43 IM. Four compounds were tested against a starved culture of Mycobacterium tuberculosis and they inhibited with MIC's ranging from 3.78 to 23.2 IM. Some compounds showed 40–66% inhibition against Mycobacterium tuberculosis isocitrate lyase enzyme at 10 IM. The docking studies also confirmed the binding potential of the compounds at the isocitrate lyase active site. In the in vivo animal model, 4a reduced the mycobacterial load in lung and spleen tissues with 1.38 and 2.9log₁₀ protections, respectively, at 25 mg/kg body weight dose [6].

Anticancer activity

A novel series of phthalazine derivatives containing isoindol-1,3-dione moiety were synthesized by reaction with ethyl{4-[4(1,3-dioxo-1,3-dihydroisoindole-2-yl)-phenyl]phthalazin-1-yloxy}acetate and {4-[4-(1,3-Dioxo-1,3dihydroisoindol-2-yl)phenyl]phthalazin-1-yloxy} acetic acid hydrazide. The antitumor activity of synthesized compounds was screened against MCF-7 cells using MTT assay. The Compounds 5a (figure 11) and 5d (figure 12)

showed strong cytotoxic effect against MCF-7 with IC₅₀ values 50, 70 μ g/ml. Compounds 5b (figure 13) and 5c (figure 14) showed moderate cytotoxic effect against MCF-7, as concluded from their IC₅₀ values 150, 180, 100 μ g/ml respectively [7].

A new different series of isatin-phthalazine hybrids 6a–h were designed and synthesized using molecular hybridization approach. The invitro anti-proliferative activity of the newly synthesized hybrids was evaluated against breast cancer. The compound 6a (figure 15) displayed the highest potency with IC₅₀ values of 12.00 \pm 0.13IM. The apoptosis induction potential of the compound 6a was estimated. The compound 10g proved to induce apoptosis, which was assured by the reduced expression of the anti-apoptotic protein Bcl-2 in addition to the enhanced expression of the pro-apoptotic protein Bax as well as the upregulated active caspase-9 and caspase-3 levels together with a harmonized increase in the Bax/Bcl-2 ratio [8].

A series of 1- substituted 2-methyl-1H-imidazo [4,5-g]phthalazine-4,9 dione derivatives were evaluated for their in vitro cytotoxicity against several human tumor cell. Most of the tested derivatives showed potential cytotoxicity activity higher than reference compounds. Derivatives 1,2-Dimethyl-1H-imidazo[4,5-g]phthalazine-4, 9-di-one (6b) (figure 16), 2-Methyl-1-isopropyl-1H-imidazo [4,5-g]phthalazine-4, 9-dione(6c) (figure 17), 1-n-Butyl-2methyl-1H-imidazo [4,5-g]phthalazine-4, 9-di-one (6d) (figure 18) and 2-Methyl 1phenyl-1H-imidazo [4,5-g]phthalazine-4,9-di-one (6e) (figure 19) was found higher active than other derivatives [9,1].

A series of novel 1-anilino-4-(aryl sulfanyl methyl)phthalazine and evaluated their anticancer activity by using the microculture tetrazolium method. They found some derivatives showed higher activity than cisplatin against two different cancer cell lines. Those analogues are 1-(4-fluoro-3trifluoromethylanilino)-4-(3,4-difluorophenyl-thiomethyl)phthalazine (6f) (figure 20) and 1-(3-chloro-4-fluoroanilino)-4-(3,4difluoro-phenyl-thiomethyl) phthalazine (6g) (figure 21) [10,1].

Anticonvulsant activity

A series of 2,3-dihydro phthalazine-1,4-dione derivatives with triazole and other heterocyclic substituents were synthesized. Their anticonvulsant activities were evaluated using the maximal electroshock test. The neurotoxicity was evaluated using the rotarod neurotoxicity test. The results showed that5-(3-trifluoromethyl)benzyl)-[1,2,4]triazolo[3,4-a]phthalazin-6(5H)-one (7a) (figure 22) had the most potent anticonvulsant activity with an ED₅₀ value of 6.8mg/kg and protective index (PI =TD₅₀ / ED₅₀) VALUE OF 11.5. Its anticonvulsant activity was found to be stronger than that of the lead compound and the standard drug carbamazepine [11].

A series of 6- alkoxy-(1,2,4)triazolo(3,4-a)phthalazine were synthesized and their anticonvulsant activity and neurotoxicity were evaluated by using maximal electroshock (MES) test and Rotarod test. The significant anticonvulsant activity was shown by the number of derivatives, but derivative 6-(4-chlorobenzoyloxy)-

[1,2,4]triazolo[3,4-a]phthalazine (7b) (figure 23) and 6heptyloxy-[1,2,4]triazolo (3,4-a) phthalazine (7c) (figure 24) was shown most active derivatives among all the derivatives [12].

A series of 1-substituted-4-hydroxyphthalazines and then these compounds were assayed against seizures induced by MES and pentylenetetrazole (scPTZ) model and the neurologic deficit was evaluated by the rotarod test. The decrease in the elevated motor activity by interoceptive chemical stimuli (amphetamine antagonistic activity) was studied at the dose level of 25 and 50 mg/kg and cardiac activity were also studied. All the compounds exhibited significant anticonvulsant activity, but compounds (7d (figure 25), 7e (figure26), 7f (figure 27) and 7g (figure 28)) were most active from the synthesized series against MES-induced seizures [13,1].

Carbonic anhydrase inhibitory activity

A new series of phthalazine substituted urea and thiourea derivatives were synthesized, and their inhibitory effects on the activity of purified human carbonic anhydrases (hCAs I and II) were evaluated. 2H-indazolo[2,1-b]phthalazine-trione derivative was prepared with 4-nitrobenzaldehyde, dimedone, and phthalhydrazide in the presence of TFA in DMF, and the nitro group was reduced to amine derivative with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$. The compound was reacted with isocyanates and isothiocyanates to get the final products (8a) (figure 29). The results showed that all the synthesized compounds inhibited the CA isoenzymes activity. 8a ($\text{IC}_{50} = 6.40 \mu\text{M}$ for hCAI and $6.13 \mu\text{M}$ for hCAII) has the most inhibitory effect. The synthesized compounds are very bulky to be able to bind near the zinc ion, and they much more probably bind as the coumarin derivatives [14].

β -adrenergic blocking activity

Novel 4-(4-bromophenyl) phthalazine and phthalazinone derivatives connected through a 2-propanol spacer to N-substituted piperazine residue were synthesized. All the new compounds were screened for their effect on β -adrenergic blocking activity on the norepinephrine-induced precontracted aortic ring module. Most test compounds displayed appreciable β -adrenolytic activity compared to propranolol as a reference standard. The results have shown that compounds 9a (figure 30), 9b (figure 31), 9c(figure 32) and 9d(figure33) displayed appreciable inhibition of norepinephrine-induced aortic ring contraction [15].

Figure 1: Phthalazine

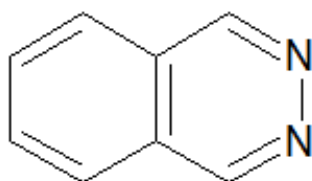


Figure 2: Phthalazinone

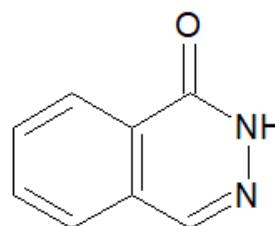


Figure 3: Compound 1a

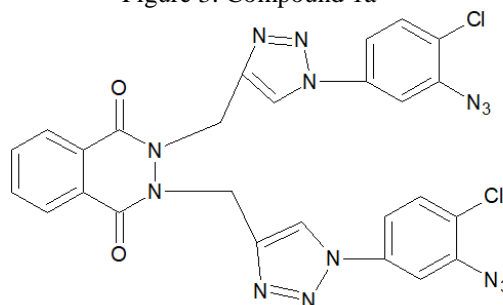


Figure 4: Compound 1b

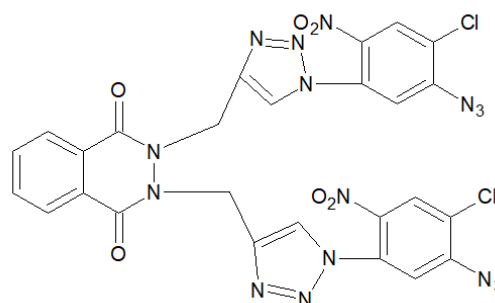


Figure 5: Compound 1c

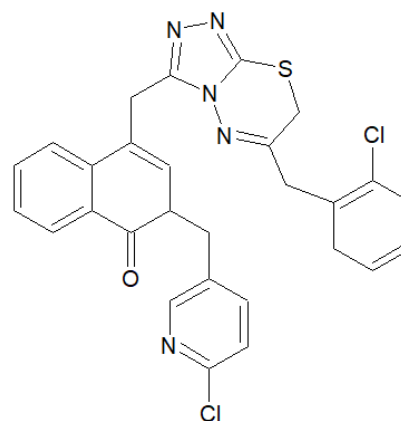


Figure 6: Compound 1d

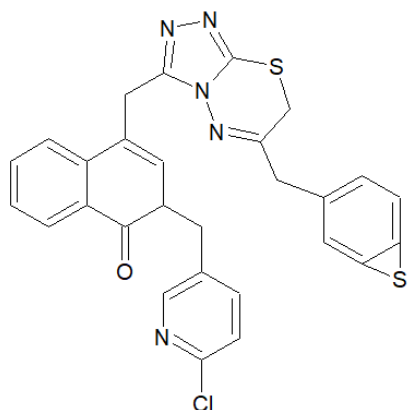


Figure 10: Compound 4a

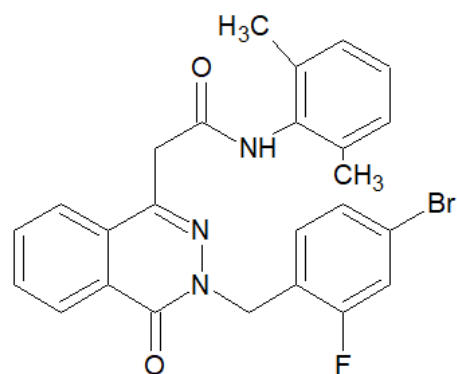


Figure 7: Compound 2a

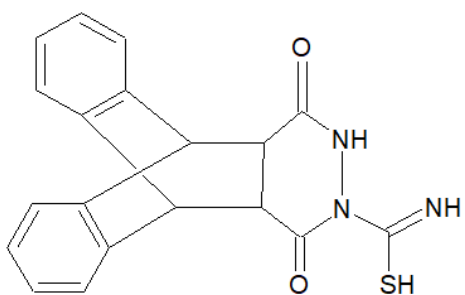


Figure 11: Compound 5a

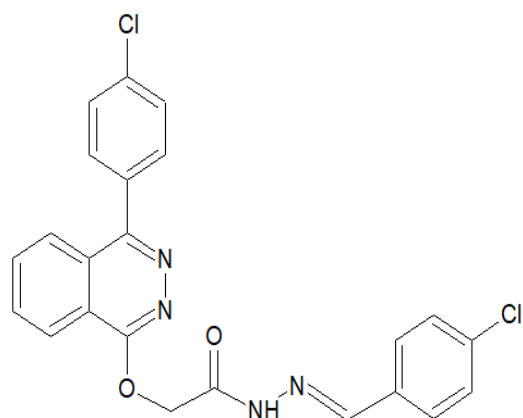


Figure 8: Compound 2b

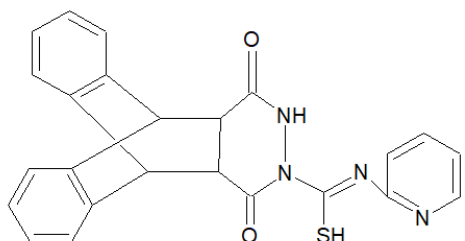


Figure 12: Compound 5d

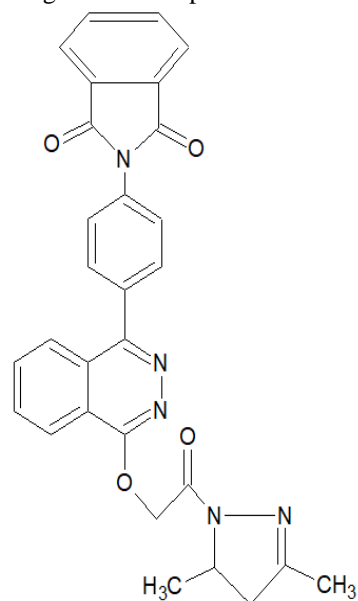


Figure 9: Compound 3a

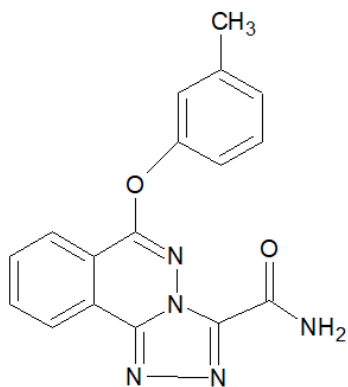


Figure 13: Compound 5b

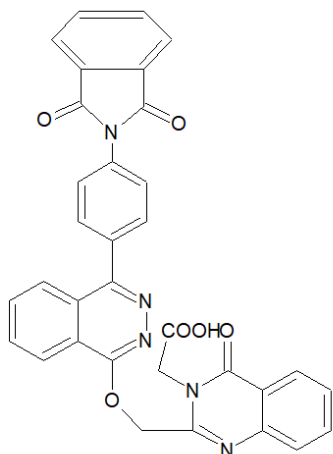


Figure 14: Compound c

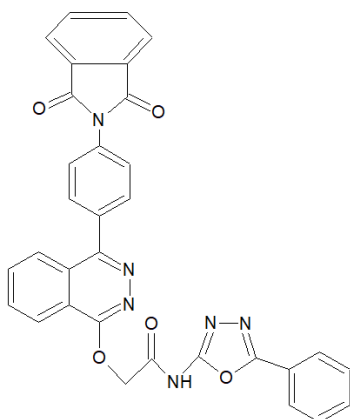


Figure 15: Compound 6a

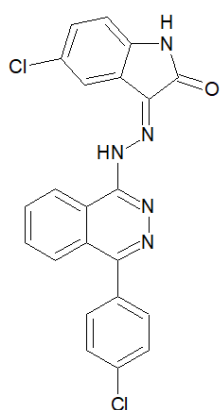


Figure 16: Compound 6b

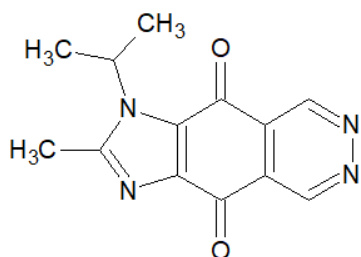


Figure 17: Compound 6c

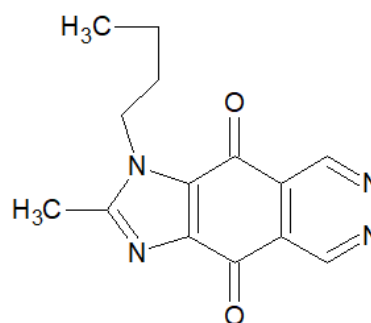


Figure 18: Compound 6d

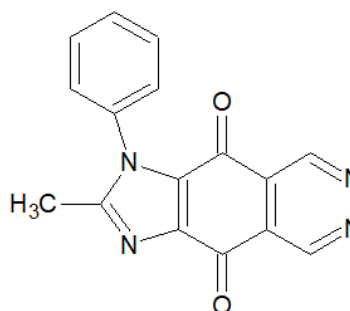


Figure 19: Compound 6e

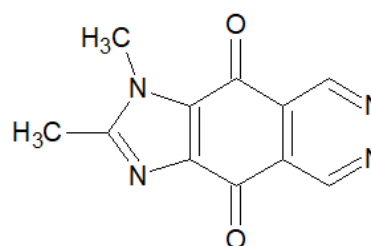


Figure 20: Compound 6f

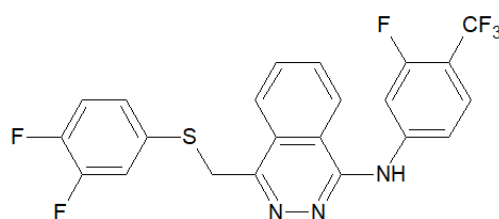


Figure 21: Compound 6g

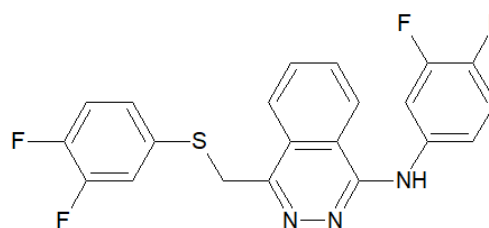


Figure 22: Compound 7a

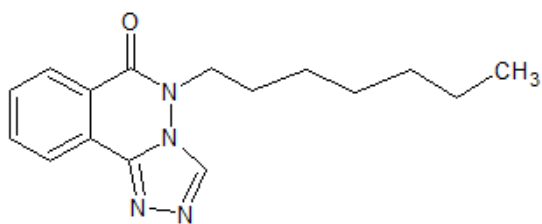


Figure 23: Compound 7b

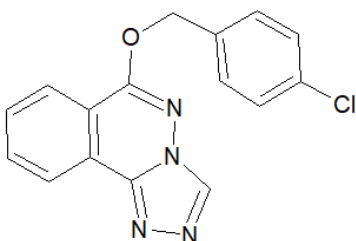


Figure 24: Compound 7c

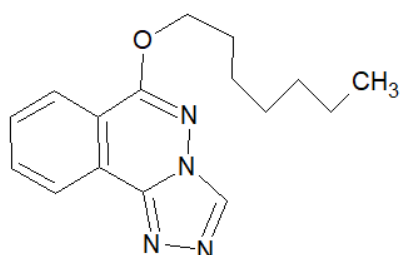


Figure 25: Compound 7d

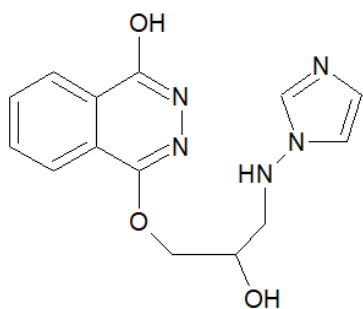


Figure 26: Compound 7e

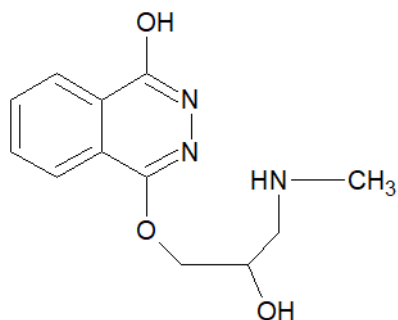


Figure 27: Compound 7f

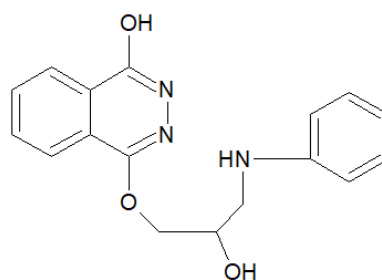


Figure 28: Compound 7g

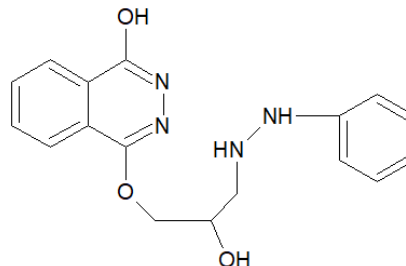


Figure 29: Compound 8a

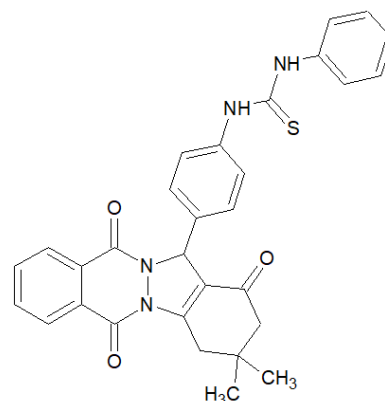


Figure 30: Compound 9a

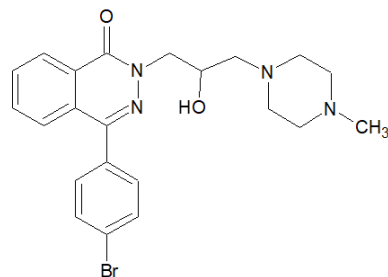
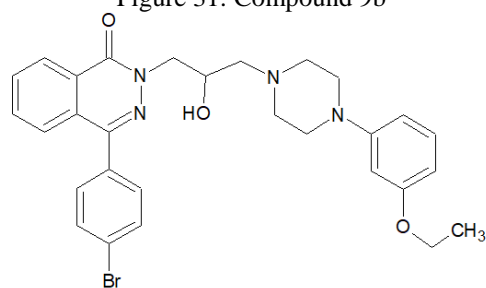
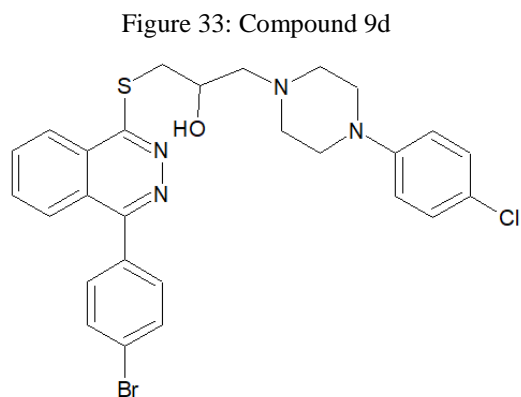
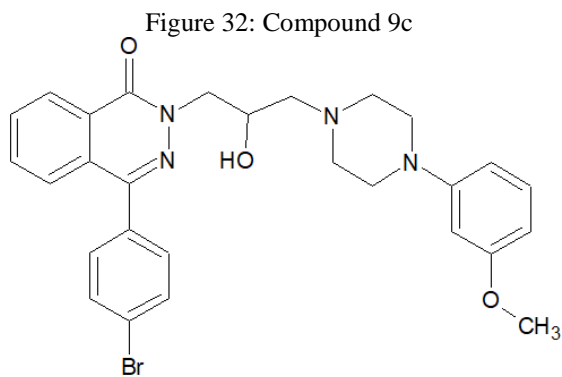


Figure 31: Compound 9b





CONCLUSION

According to the research works, phthalazines have been reported to possess, anticonvulsant, cardiotoxic, antimicrobial, antitumor, antihypertensive, analgesics, anti-inflammatory, antitubercular, vasorelaxant and other anticipated activities. It can be concluded that phthalazines have great potential for the synthesis of novel drugs. Because of the strong pharmacophoric group and ring position present in the phthalazine nucleus. The substitution of various functional groups in the phthalazine rings leads to various novel phthalazine derivatives with diverse biological activities. It is a promising lead molecule for the design and development of new drugs with potent biological activities.

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