ROLE OF PHARMACOLOGICAL ACTIVE PHTHALAZINE SCAFFOLDS IN MEDICINAL CHEMISTRY: A MINI-REVIEW

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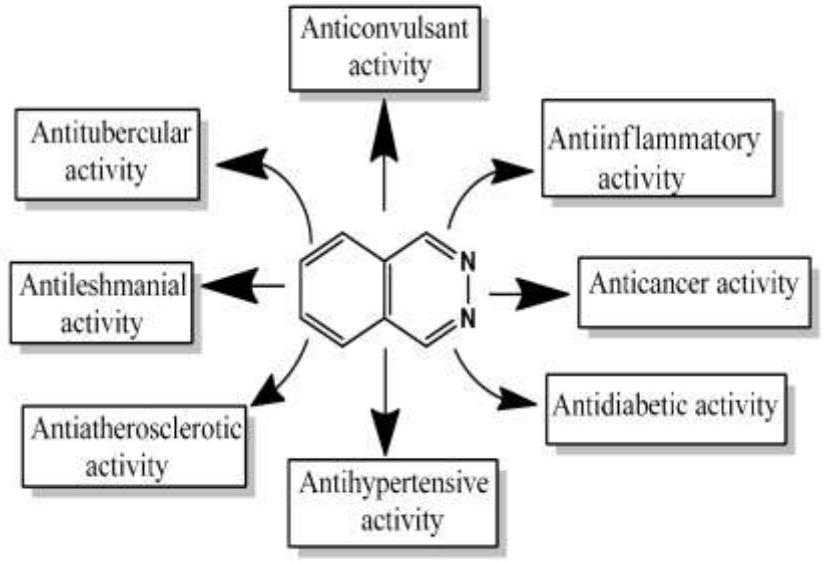
Graphical Abstract



Pharmacological activities of various phthalazine derivatives

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1. Introduction

The application of nitrogen-containing heterocyclic molecules in many fields, such as pharmaceuticals, has gotten a lot of interest. Phthalazine and its oxygenated derivatives, phthalazinone, are nitrogen-containing heterocyclic compounds (Figure 1) (Almahli et al., 2018). Phthalazine is an important essential ingredient since it defines the structural profile for a variety of physiologically active chemicals (Boraei et al., 2019; Cheng et al., 2022). Due to their broad application for the treatment of a variety of disorders, phenazine derivatives are attractive therapeutic candidates (Rizk et al., 2021). Several types of studies have been conducted on the pharmacology of phthalazine derivatives, with several contributions in a variety of fields (Glišić et al., 2016).

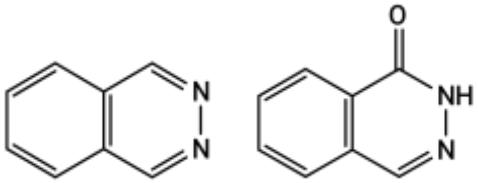
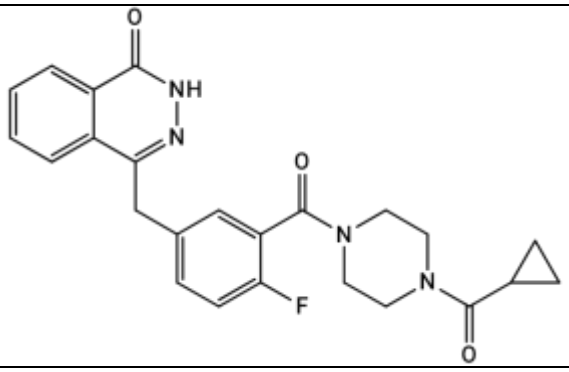
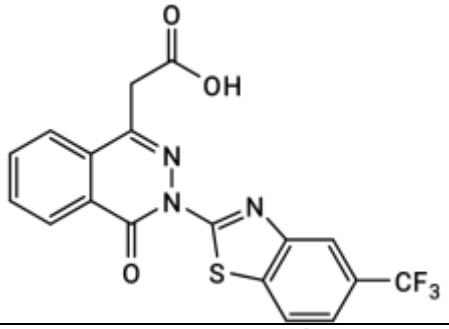
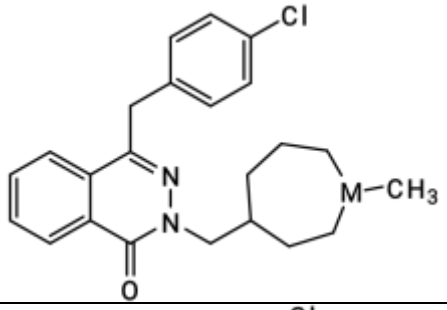
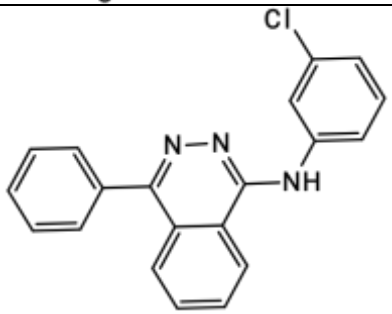
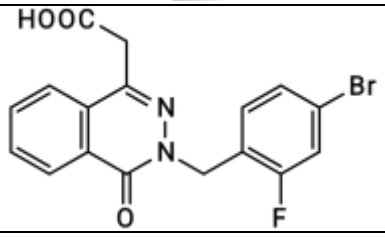
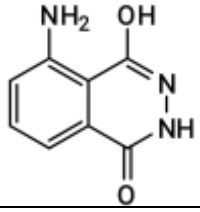
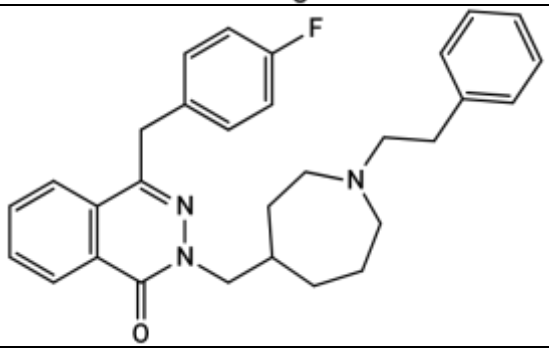


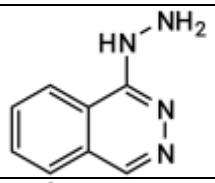
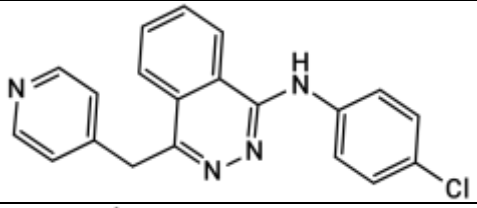
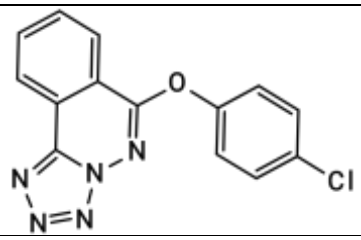
Figure 1. Phthalazine and Phthalazinone.

The chemistry of phthalazine is well-known, and it is frequently employed as intermediates in the preparation of numerous compounds in organic chemistry (Marzouk et al., 2016; Mood et al., 2017). Phthalazine derivatives have been posses various types of pharmacological activities such as anti-inflammatory, antibacterial, antiviral, antihypertensive, antifungal, anticancer, anticonvulsant, and other pharmacological properties (Munín et al., 2019; Malik et al., 2021). There are a variety of phthalazine-based medications on the market, including hydralazine, budralazine, vatalanib, olaparib, and azelastine (Malinowski et al., 2021; Izuogu et al., 2020). The phthalazine nucleus is the focus of the medicinal chemist's attention. It's an appealing building block for numerous drug syntheses (Sherif et al., 2008; Terán et al., 2019). Phthalazine derivatives are used as a starting material for the development of new medications and as an intermediary in the synthesis of various chemicals (Vila et al., 2015; Jalili-Baleh et al., 2017). It's a flexible lead for novel medication development (Wang et al., 2018; Yang et al., 2016). Because of their pharmacological activity and therapeutic potential, heterocyclic-containing hydrazine has gotten a lot of interest among the many nitrogen-containing heterocyclic compounds (Lu et al., 2018; Ibrahim et al., 2014). Phthalazines have been shown to block serotonin reuptake and are thus used as antidepressants (Eldehna et al., 2017; Han et al., 2019). In medicinal chemistry, phenazines are one of the most significant biologically active pharmacophore (Berber et al., 2015; Asif 2015). Azelastine, Ponalrestat, Hydralazine, Budralazine, and Zopolrestat are examples of well-known drug compounds made from phthalazinones (Table 1). The phthalazine's wide range of biological actions inspired us to create new compounds (Aswathy 2019; Nahed et al., 2011).

Table 1. Commercially used Phthalazine derivatives

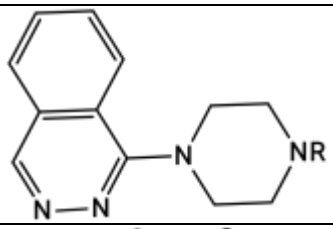
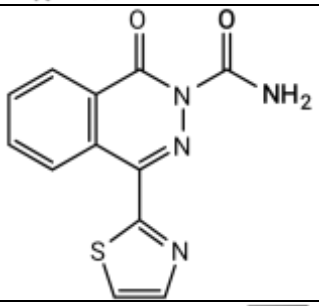
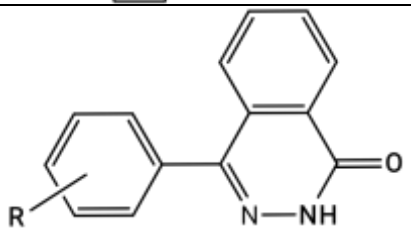
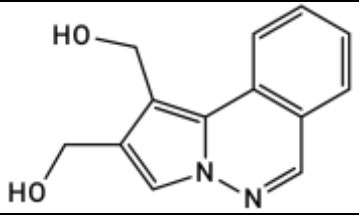
Compound Name	Structure	Biological activity
Olaparib		Anticancer agent

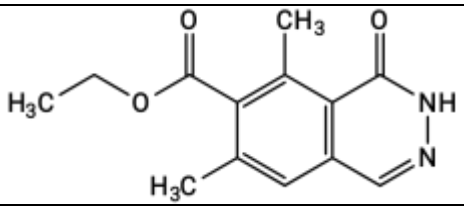
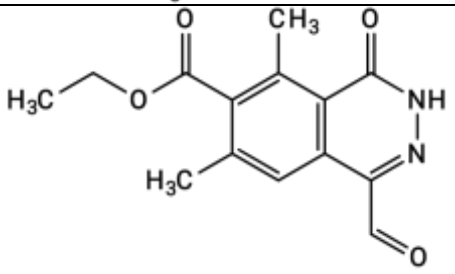
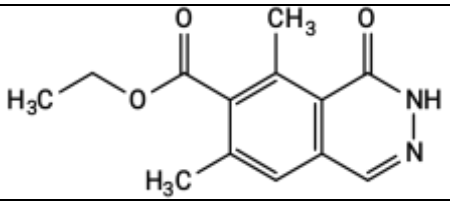
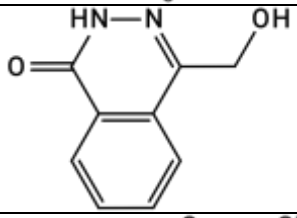
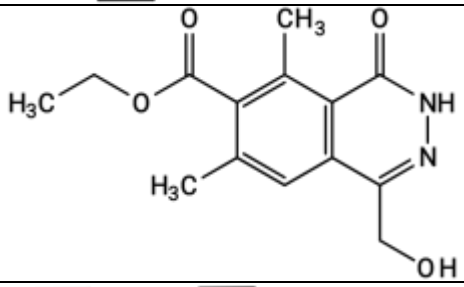
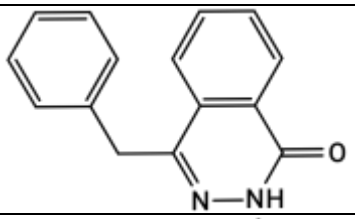
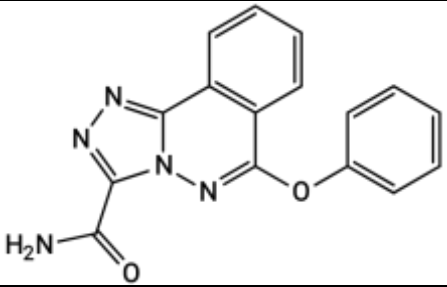
Zopolrestat		Antidiabetic agent
Azaleatine		Antihistaminic agent
MY5445		Phosphodiesterase Inhibitor
Ponalrestat		Antidiabetic agent
Luminol		Chemiluminescence
Flezelastine		Antihistaminic agent

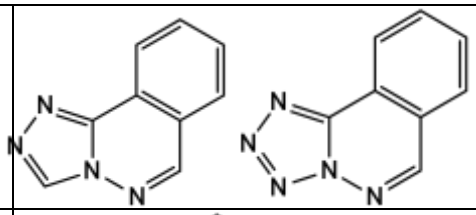
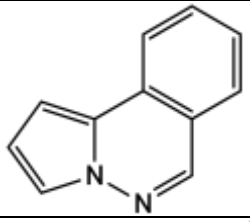
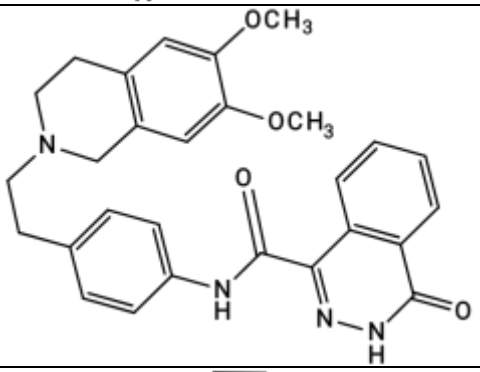
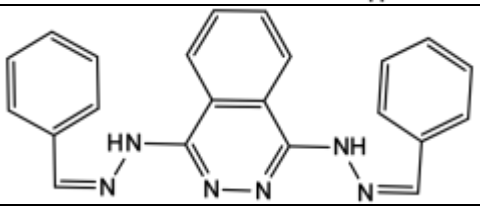
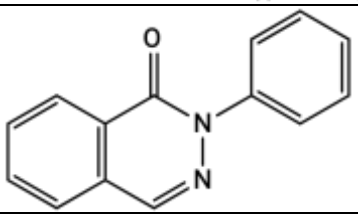
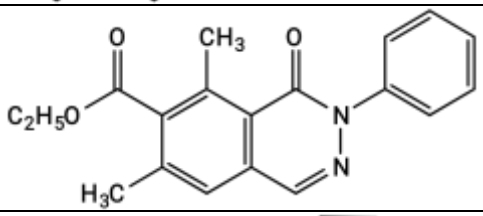
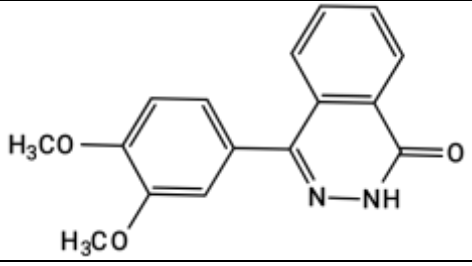
Hydralazine		Vasodialator
Vatalanib (PTK-787)		Anticancer agent
OUAN-0808		Anticancer agent

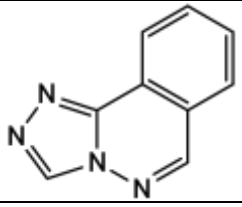
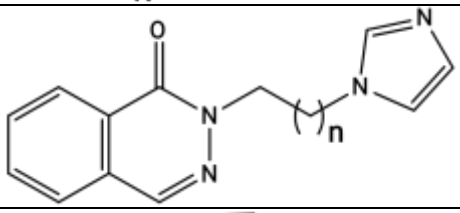
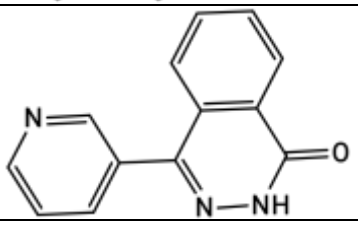
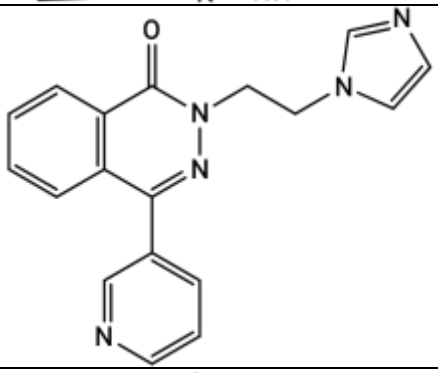
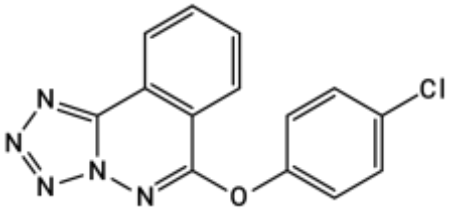
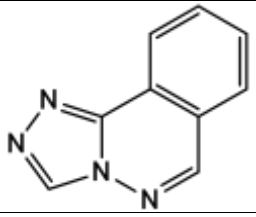
In the literature, phthalazines have been shown to have anticonvulsant, cardiotonic, antitrypanosomal, antibacterial, anticancer, antihypertensive, antithrombotic, antidiabetic, anti-inflammatory, and vasorelaxant effects (Table 2) (Hameed et al., 2016; Azab et al., 2016). Phthalazines are also thought to be antidepressants since recent research has shown that they prevent serotonin reuptake.

Table 2. Some phthalazine derivatives and their biological activity.

S.No.	Compound	Structure	Activity
1.	1-Piperazinyl-phthalazine derivatives		VEGFR-2 inhibitors and anticancer agents
2.	Thiazolyl-phthalazinone acetamide derivatives		Glucose uptake activators
3.	4-Aryl-2(1H)-phthalazinone Derivatives		Cyclooxygenase-2 inhibitors
4.	1,2-Bis(hydroxymethyl) pyrrolo[2,1-a] phthalazine Hybrids		Anticancer agents

5.	7-ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone		Antiatherosclerotic agents
6.	7-ethoxycarbonyl-4-formyl-6,8-dimethyl-1(2H)-phthalazinone derivative derivatives		antiatherosclerotic agents
7.	4-aryl derivatives of 7-ethoxycarbonyl-6,8-dimethyl-1(2H)-phthalazinone		platelet aggregation inhibitor
8.	4-hydroxymethyl-1(2H)-phthalazinone derivatives		antiatherosclerotic agents
9.	7-ethoxycarbonyl-4-hydroxymethyl-6,8-dimethyl-1(2H)-phthalazinone (EG 626)		Spinal trigeminal, phosphodiesterase inhibitor, thromboxane A2 inhibitor, antiatherosclerotic and anti-aggregating agents
10.	4-benzyl-1-(2H)-phthalazinone derivative		androgen receptor antagonists
11.	6-phenoxy-[1,2,4]triazolo[3,4-a]phthalazine-3-carboxamide derivatives		anti-inflammatory activity

12.	[1,2,4]triazolo[3,4-a]phthalazine and tetrazolo[5,1-a]phthalazine derivative		positive inotropic agents
13.	pyrrolo[2,1-a]phthalazine derivative		Anticancer agents
14.	N-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamide derivatives		P-glycoprotein inhibitors
15.	1,4-bis(substituted benzalhydrazino)phthalazine derivatives		Antileishmanial agent
16.	2-phenyl-1(2H)-phthalazinone derivative		platelet aggregation inhibitor
17.	7-(Ethoxycarbonyl)-6,8-dimethyl-2-phenyl-1(2H)-phthalazinone derivative		platelet aggregation inhibitor
18.	4-(3,4-dimethoxyphenyl)-2H-phthalazin-1-one derivatives		PDE-4 inhibitors

19.	1,2,4-triazolo[3,4-a]phthalazine derivative		anticancer
20.	2-[2-(1-Imidazolyl)alkyl]-1(2H)-phthalazinone derivatives		thromboxane A2 synthetase inhibitor
21.	4-(3-Pyridyl)-1(2H)-phthalazinone derivatives		thromboxane A2 synthetase inhibitor
22.	2-[2-(1-Imidazolyl)ethyl]-4-(3-pyridyl)-1(2H)-phthalazinone derivatives		thromboxane A2 synthetase inhibitor
23.	6-(4-chlorophenoxy)-tetrazolo[5,1-a] phthalazine		Anticoagulant agent
24.	1,2,4-triazolo [3,4-a] phthalazine derivatives		Antimicrobial agent

BIOLOGICAL ACTIVITIES OF PHTHALAZINE DERIVATIVES

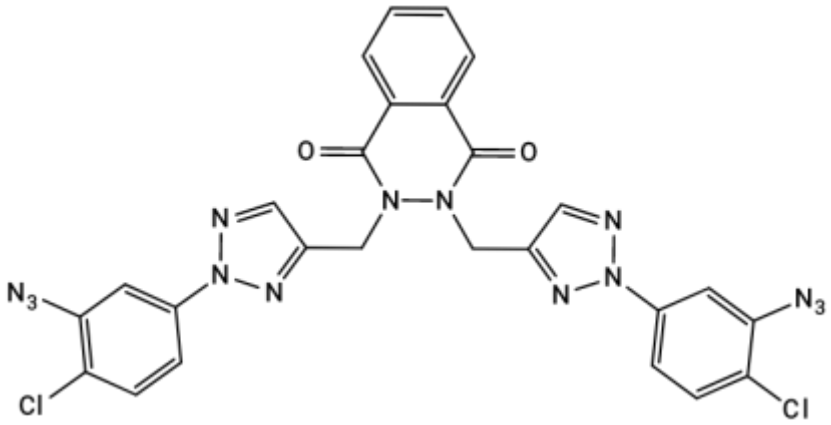
Because the phthalazine nucleus is involved in so many biological processes, we decided to develop a novel lead chemical with a wide range of pharmacological characteristics. Derivatives of phenazine have been the subject of extensive bioactive chemical research. They exhibit considerable biological activity, as previously described (Madhavan et al., 2001; Sangshetti et al., 2019). Phthalazines are said to have properties such as anticonvulsant, cardiotonic, antimicrobial, anticancer, antihypertensive, antithrombotic, anti-inflammatory, antidiabetic, antitrypanosomal, and vasorelaxant, according to the literature. Because they have recently been demonstrated to impede serotonin reuptake, phenalazines are also believed to be antidepressants (Aziz et al., 2012).

Antibacterial activity

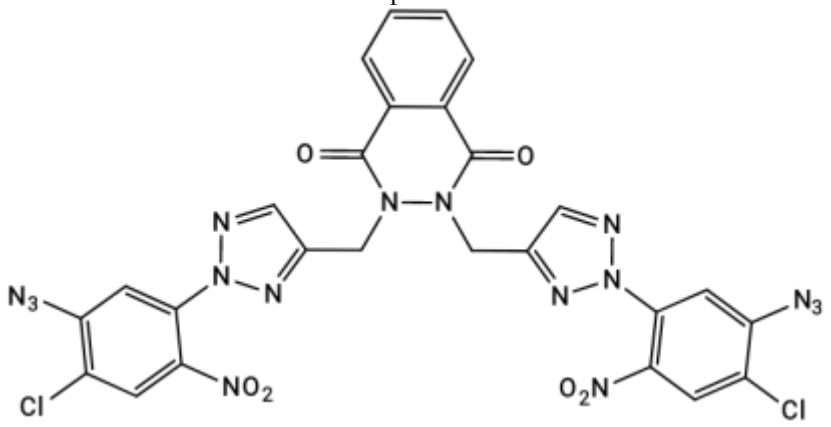
Figure 2 shows the antibacterial activity of several phthalazine derivatives against a variety of harmful

microorganisms. Using a well-diffusion approach and tetracycline as a reference medication, a variety of phthalazine-based 1,2,3-triazole analogs were investigated for antibacterial activity against three bacterial strains: Bacillus subtilis, Pseudomonas aeruginosa and Micrococcus luteus. The majority of phthalazine derivatives out performed conventional medication in terms of antibacterial activity. Among them, 2,3-bis[(1-(aryl)-1H-1,2,3-triazole-4-yl)methyl)-2,3-dihydrophthalazine-1,4-dione (**1a**) was exhibited the highest activity against P. aeruginosa and compound (**1b**) was exhibited the highest activity against E. coli and P. aeruginosa (Mohammad et al., 2018).

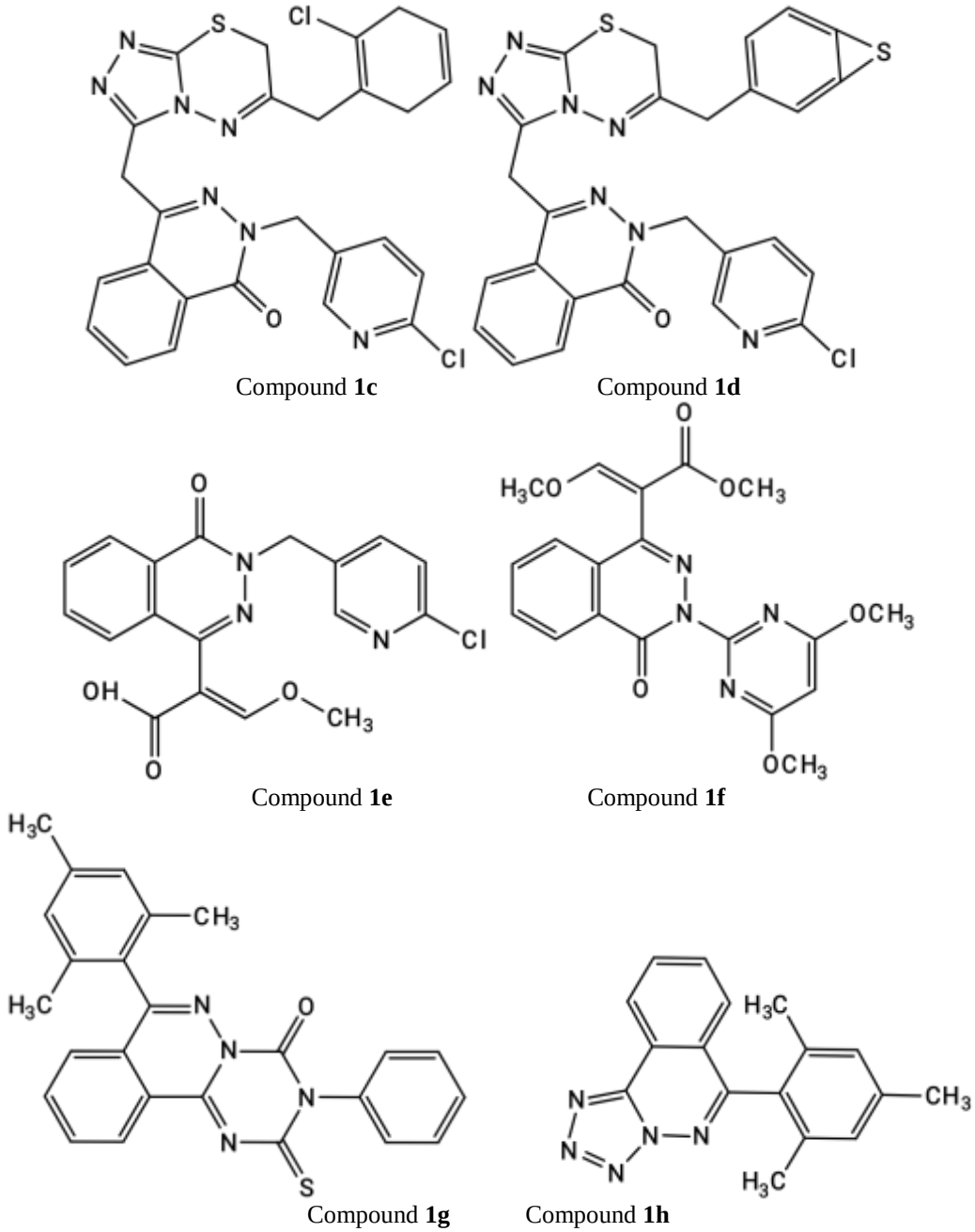
The antibacterial activity of the 6-(chloropyridin-3-yl)methyl-phthalazine-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles was investigated. Compounds substituents with 5-nitro-thiazole to triazolothiadiazole (**1c**) and methylthiophenyl to triazolothiadiazines (**1d**) showed greater activity (Sridhara et al., 2011). The 3-substituted methyl 3-methoxy-2-(4-oxo-3,4-dihydro-phthalazine-1-yl)acrylates are phthalazine methoxyacrylates with various functional groups substituted at the C3 position. Compounds substituted methyl 2-{3[(6-chloropyridin-3-yl)methyl]-4-oxo-3,4-dihydro-phthalazin-1-yl}-3-methoxyacrylate (**1e**), methyl2-[3-(4,6dimethoxy pyrimidin -2-yl)-4-oxo-3,4-dihydrophthalazin-1-yl]-3-methoxyacrylate (**1f**) were exhibited better antimicrobial activity compared to other derivatives (Sridhara et al., 2010). Some annelated phthalazines and acyclo C nucleosides from 1-chloro-4-(2,4,6-trimethylphenyl) phthalazine precursor were exhibited antimicrobial activity and found that 1,2,4-triazolo[3,4-a]phthalazines, 1,3,5-triazino[4,3-a]phthalazine **(1g),** and tetrazolo[5,1-a]phthalazine **(1h)** were exhibited most active compounds (Maher et al., 2012).



Compound **1a**



Compound **1b**



Compound **1c** Compound **1d**

Compound **1e** Compound **1f**

Compound **1g** Compound **1h**

Figure 2. Antimicrobial activities of some phthalazine derivatives.

Anti-inflammatory activity

Several phthalazine derivatives were exhibited anti-inflammatory activities are reported in Figure 3. Phthalazinedione derivatives were synthesized from dibenzobarallene and thiosemicarbazides were exhibited anti-inflammatory and analgesic activity. The phthalazine analogs 1,4-Dioxo-3,4,4e,5,10,10a-hexahydro-1H-5,10-benzeno-benzo[g]-phthalazin-2-yl-N-pyridin-2-ylthioamide was exhibited better results in a reduction of the rheumatoid index compared to other compounds. The pain scoring of compounds (**2a**) and (**2b**) were found more effective than piroxicam (Yousery et al., 2018).

A series of 6-phenoxy-[1,2,4]triazolo[3,4-a]phthalazine-3-carboxamides were exhibited as potent anti-inflammatory agents, which acted on tumor necrosis factor (TNF-α) as inhibitors of NF-κB activation. The compounds 6-(3-tolyloxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-carboxamide (**2c**) was exhibited more anti-inflammatory activity than other compounds, with similar activities as reference drug dihydrotanshinone. Compound **2c** was showed the lowest cellular toxicity among the tested compounds. In vivo test of the anti-inflammatory activity was showed that compound **2c** was showed excellent activity (Da-Chuan et al.,

2016). Various 4-(3,4-dimethyl-phenyl)phthalazine-1(2H)-ones were exhibited anti-inflammatory activity. Compound 4-(3,4-dimethylphenyl)-2-[(4,5-dihydro-5-thiooxo-1,3,4-oxadiazol-2-yl)]phthalazine-1(2H)-one (**2d**), 1-{2-[4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1H)-yl]acetyl}4-benzylthiosemicarbazide (**2e**), N'-(ethoxymethylene)-2(4-(3,4-dimethyl phenyl)-1-oxophthalazine-2(1H)-yl)acetohydraide (**2f**) and 5-methyl-3-oxo-2[1'(2H)-oxo-4'-(3,4-dimethylphenyl)phthalazine-2'-ylmethylcarbonyl]-3,4-dihydropyrazol (**2g**) were showed most active compounds as compared to reference drug indomethacin (Mosaad et al., 2010).

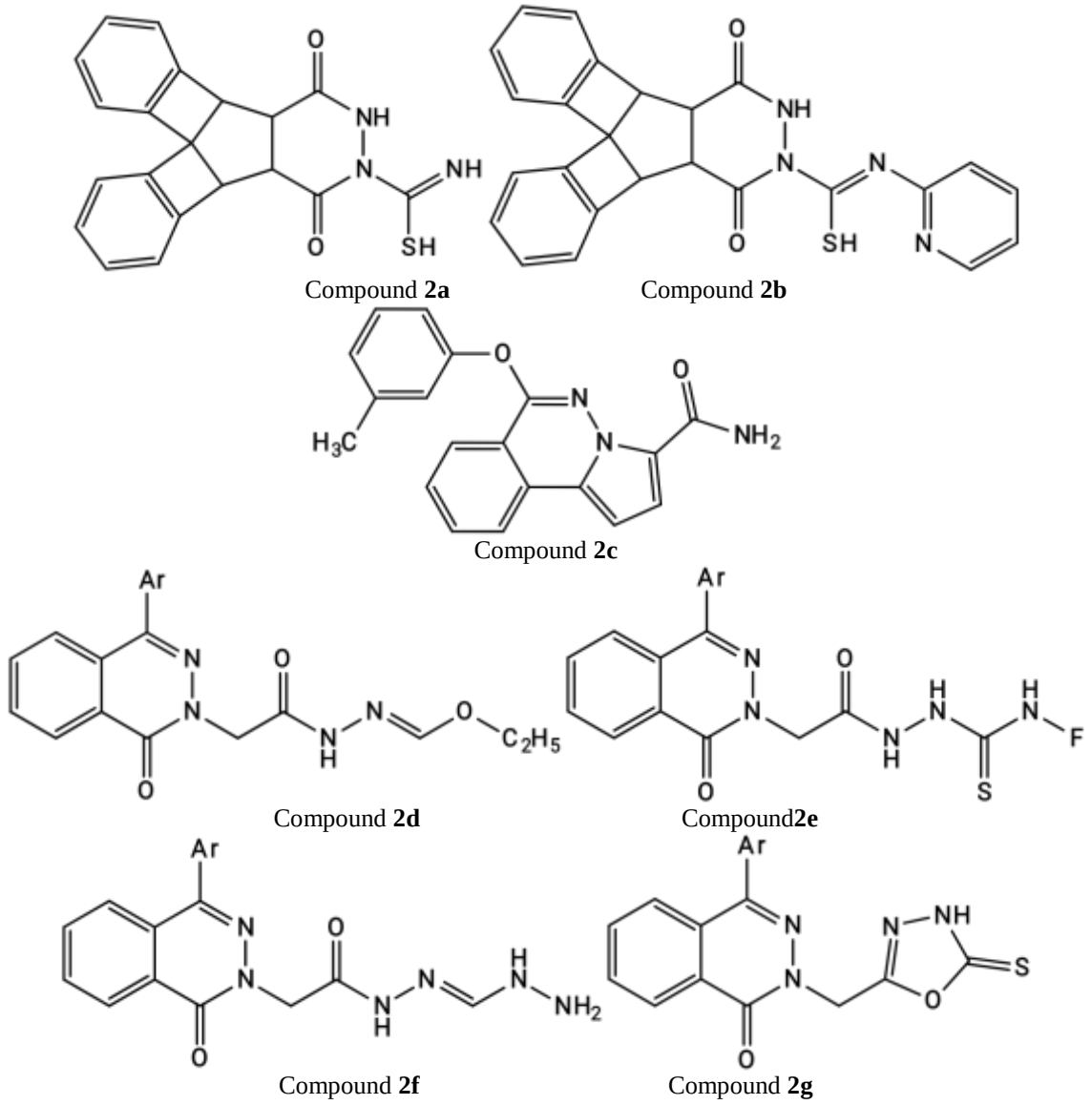


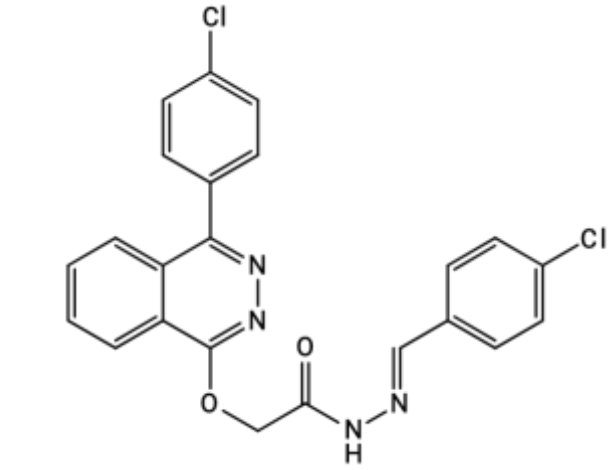
Figure 3. Anti-inflammatory activities of some phthalazine derivatives.

Anticancer activity

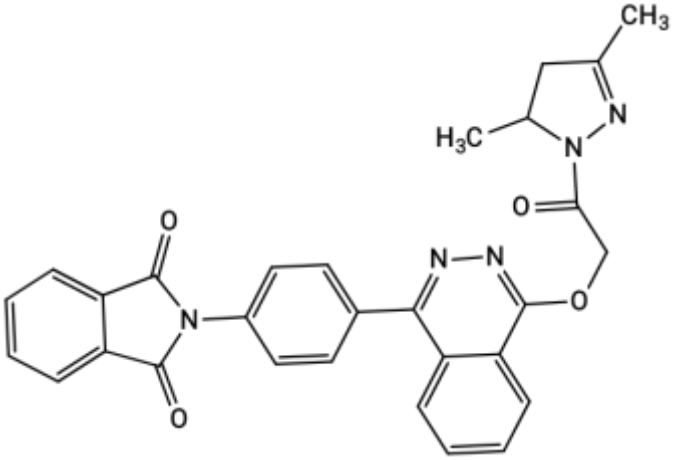
Several phthalazine derivatives were exhibited anticancer activity (Figure 4). A series of phthalazine analogs containing isoindol-1,3-dione moiety were synthesized from ethyl{4-[4(1,3-dioxo-1,3-dihydroisoindole-2-yl)-phenyl]phthalazin-1-yloxy}acetate and {4-[4-(1,3-Dioxo-1,3dihydroisoindol-2-yl)phenyl]phthalazin-1-yloxy}acetic acid hydrazide. The anticancer activity of compounds was tested against MCF-7 cells using MTT assay. Compounds **3a** and **3b** were showed a strong cytotoxic effect against MCF-7 with IC_{50} values 50, and 70 µg/ml. Compounds **3c** and **3d** were showed moderate cytotoxic effects against MCF-7, as concluded from their IC_{50} values 150, 180, and 100 µg/ml respectively (Ashraf et al., 2013). A series of isatin-phthalazine hybrids were synthesized. The in-vitro anti-proliferative activity of these hybrids was tested against breast cancer. Compound **4a** was exhibited the highest potency

with IC_{50} values of 12.00±0.13l M. The apoptosis induction potential of compound **4a** was estimated (Wagdy et al., 2019). A series of 1-substituted 2-methyl-1H-imidazo [4,5-g] phthalazine-4,9-diones were exhibited in-vitro cytotoxicity against several human tumor cell. Most of the compounds were showed potential cytotoxicity activity higher than reference drugs. Compounds 1,2-Dimethyl-1H-imidazo[4,5-g]phthalazine-4,9-di-one (**4b**), 2-Methyl-1-isopropyl-1H-imidazo[4,5-g] phthalazine-4,9-dione (**4c**), 1-n-Butyl-2methyl-1H-imidazo[4,5-g]phthalazine-4,9-di-one (**4d**) and 2-Methyl 1phenyl-1H-imidazo [4,5-g]phthalazine-4,9-di-one (**4e**) were exhibited higher active than other compounds (Kim et al., 2004).

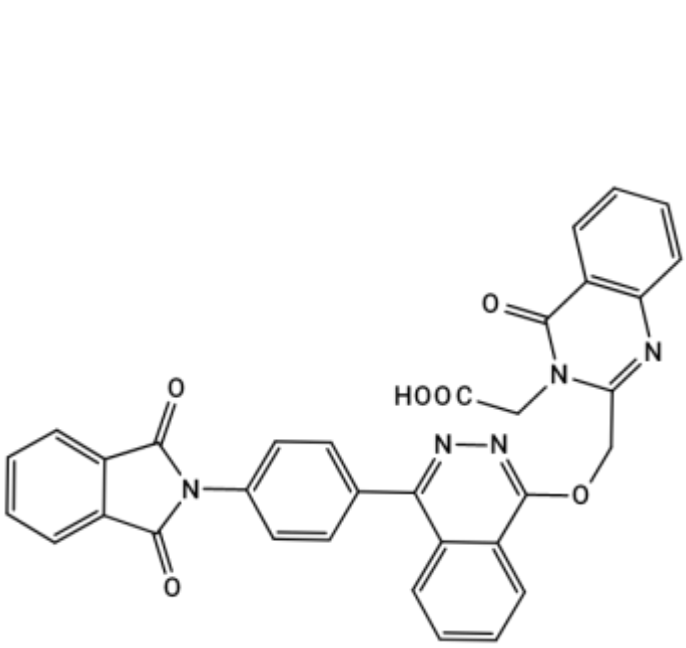
A series of 1-anilino-4-(aryl sulfanyl methyl) phthalazine were exhibited anticancer activity. Some compounds, 1-(4-fluoro-3trifluoromethylanilino)-4-(3,4-difluorophenyl-thiomethyl)phthalazine (**4f**) and 1-(3-chloro-4-fluoroanilino)-4-(3,4difluoro-phenyl-thiomethyl) phthalazine (**4g**) were showed higher activity than cisplatin against two different cancer cell lines. Some 1,4-disubstituted phthalazine were exhibited in-vitro cytotoxicity in human liver cancer cell lines. Compounds containing 3,4-difluoro-phenylthimethyl group at position 4 of phthalazine ring showed more potent inhibitory activity than cisplatin. Substituents with phenyl thiomethyl moiety would increase cytotoxicity (Gong et al., 2008).



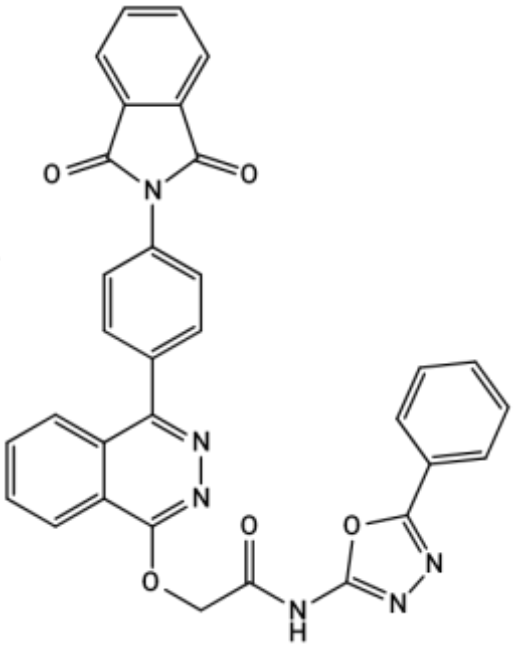
Compound **3a**



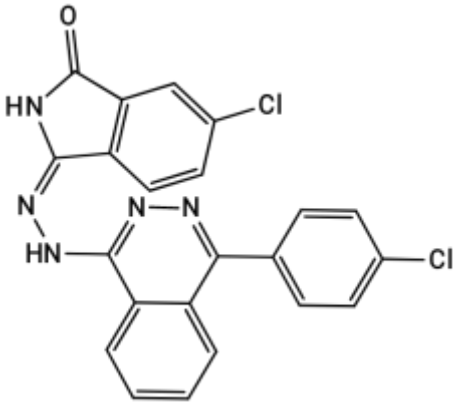
Compound **3b**



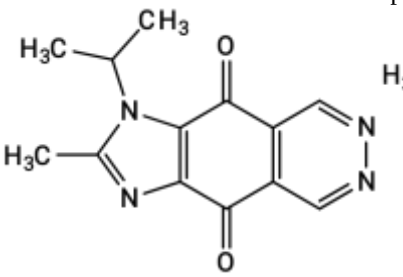
Compound **3c**



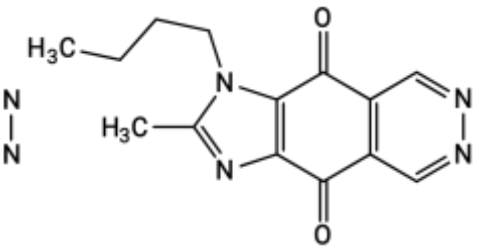
Compound **3d**



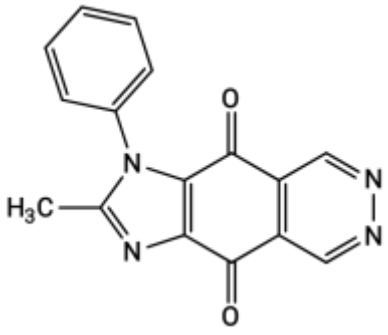
Compound **4a**



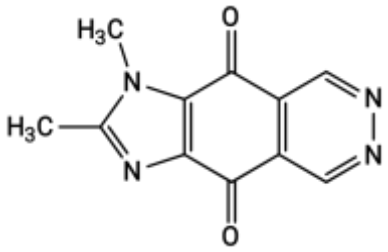
Compound **4b**



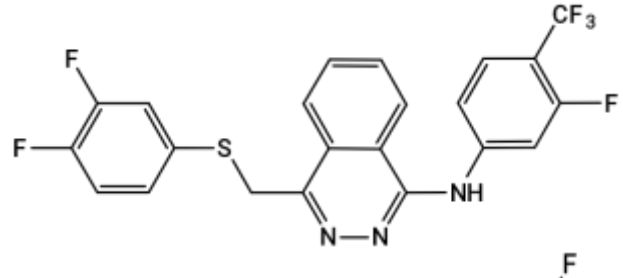
Compound **4c**



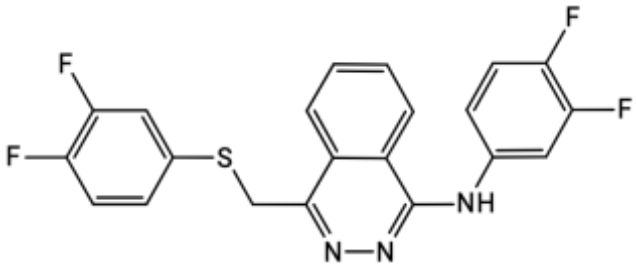
Compound **4d**



Compound **4e**



Compound **4f**



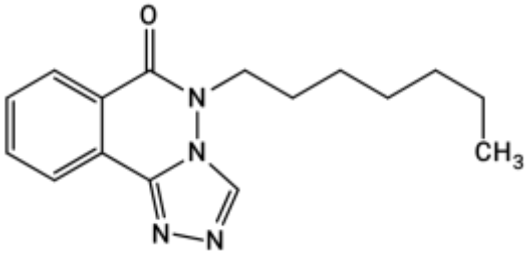
Compound **4g**

Figure 4. Anticancer activities of some phthalazine derivatives.

Anticonvulsant activity

Some phthalazine derivatives were exhibited anticonvulsant activities against various models of experimentally induced seizures are reported in Figure 5. The 2,3-dihydro phthalazine-1,4-dione derivatives with triazole and other heterocyclic substituents were tested for anticonvulsant activity by using the maximal electroshock (MES) method. The neurotoxicity was tested by using the rotarod neurotoxicity test. Compound 5-(3-trifluoromethyl)benzyl)-[1,2,4]triazolo[3,4-a]phthalazin-6(5H)-one (**5a**) was found the most potent anticonvulsant activity with an ED_{50} value of 6.8mg/kg and protective index ($PI=TD_{50}/ ED_{50}$) value of 11.5. Its anticonvulsant activity was found to be stronger than the standard drug carbamazepine (Xiang et al., 2017). A series of 6-alkoxy-(1,2,4)triazolo(3,4-a)phthalazine were tested for their anticonvulsant activity and neurotoxicity by using MES and Rotarod test respectively. The significant anticonvulsant activity was found in some derivatives, but compound 6-(4-chlorobenzyloxy)-[1,2,4]triazolo[3,4-a]phthalazine (**5b**) and 6heptyloxy-[1,2,4]triazolo(3,4-a)phthalazine (**5c**) were found the most active compounds among all the derivatives (Lei et al., 2009).

A series of 1-substituted-4-hydroxy phthalazines were tested against MES and pentylenetetrazole (scPTZ) induced seizures models and the neurologic deficit was tested by the rotarod test. The reduction 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 were exhibited significant anticonvulsant activities, but compounds (**5d, 5e, 5f**, and **5g**) were found most active from these series of compounds against MES-induced seizures (Sivakumar et al., 2002).



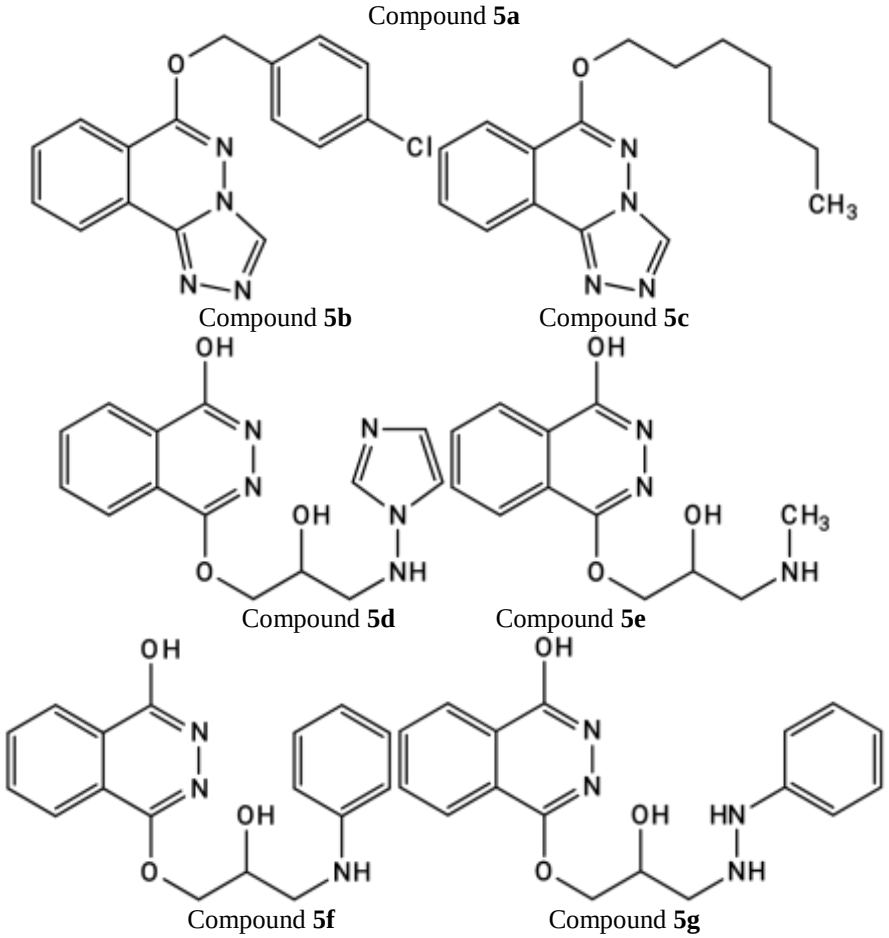
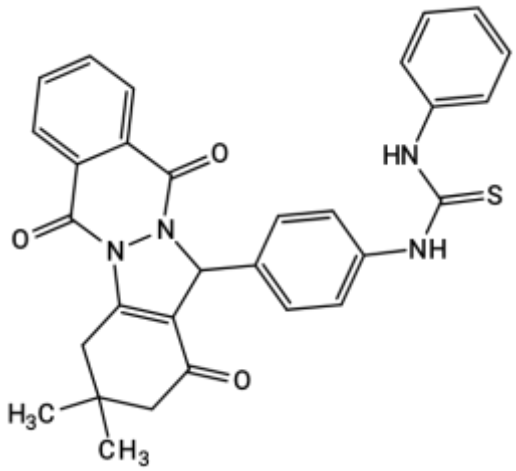


Figure 5. Anticonvulsant activities of some phthalazine derivatives.

Carbonic anhydrase inhibitory activity

Some phthalazine derivatives were exhibited carbonic anhydrase inhibitory or diuretic activities (Figure 6). A series of phthalazine substituted urea and thiourea derivatives were exhibited inhibitory effects on the human carbonic anhydrases (hCAs I and II). 2H-indazolo[2,1-b]phthalazine-triones (**6a**) were inhibited the CA isoenzymes activity. Compound **6a** (IC_{50} =6.40 $\mu\mu$M for hCAI and 6.13 $\mu\mu$M for hCAII) has the most inhibitory effect (Nurcan et al., 2013).

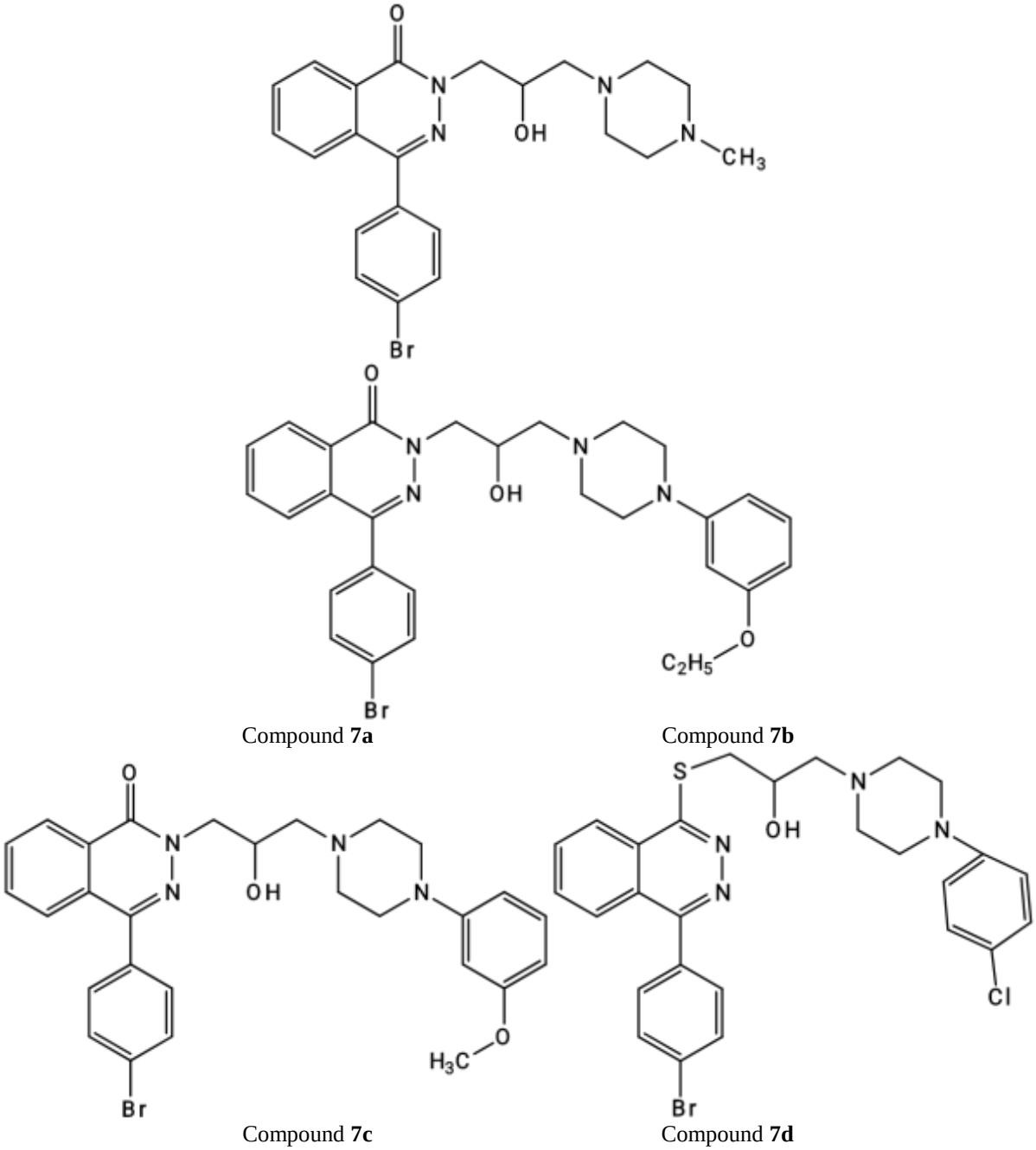


Compound **6a**

Figure 6. Carbonic anhydrase inhibitory activity of phthalazine derivative.

β- adrenergic blocking activity

Some phthalazine derivatives were exhibited β-adrenergic blocking or antihypertensive activities (Figure 7). The 4-(4-bromophenyl) phthalazine and phthalazinones connected through a 2-propanol spacer to N-substituted piperazine residue were exhibited β-adrenergic blocking activity. Most of the tested compounds were exhibited appreciable β-adrenolytic activity compared to propranolol. Compounds (**7a, 7b, 7c**, and **7d**) were exhibited appreciable inhibition of norepinephrine-induced aortic ring contraction (Khaled et al., 2012).



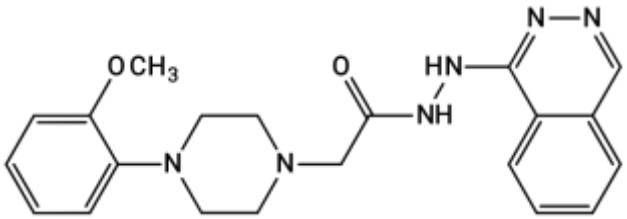
Compound **7a** Compound **7b**

Compound **7c** Compound **7d**

Figure 7. β-adrenergic blocking activity of phthalazine derivatives.

Vasorexalant activity

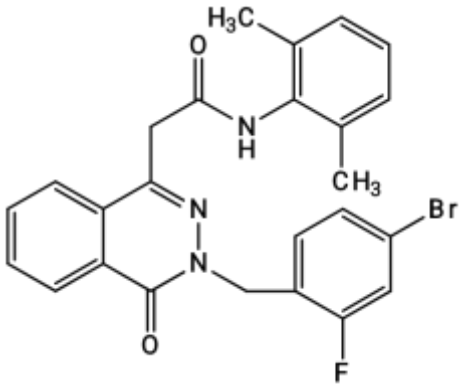
Some phthalazine derivatives were exhibited vasorelaxant or vasodilator activities (Figure 8) against nor-adrenaline-induced spam on thoracic rat aorta rings and compared with reference drug prazosin. Several derivatives were showed higher vasorelaxant activity than refrence drugs, but compound 3-{4-(2-methoxyphenyl)piperain-1-yl)-N-phthalazin-1-yl}propane hydrazide (**8a**) have an IC_{50}=0.10 nM (Awadallah et al., 2012).



Compound **8a**

Antitubercular activity

Some phthalazine derivatives were exhibited antitubercular activity against Mycobacterium species (Figure 9). A 2-[3-(4-bromo-2-fluorobenzyl)-4oxo-3,4-dihydro-1-phthalazinyl]acetic acid amides were exhibited in-vitro and in vivo antitubercular activity against Mycobacterium tuberculosis. Among the compounds 2-(2-(4-bromo-2-fluorobenzyl)-1,2-dihydro-1-oxophthalazin-4-yl)-N-(2,6-dimethyl phenyl) acetamide (**9a**) was inhibited mycobacterial species with MIC's ranging from 0.08 to 5.05 lM and was non-toxic to Vero cells till 126.43 lM. Four compounds were tested against a starved culture of M. tuberculosis and they were inhibited with MIC's ranging from 3.78 to 23.2 lM. Some compounds were showed 40–66% inhibition against M. tuberculosis isocitrate lyase enzyme at 10 lM. Compound **9a** reduced the mycobacterial load in lung and spleen tissues with 1.38 and 2.9 log10 protections, respectively, at 25 mg⁄kg body weight dose (Dharmarajan et al., 2010).



Compound **9a**

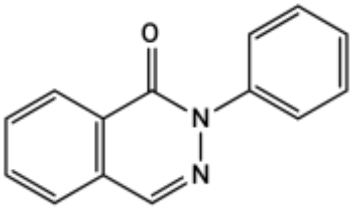
Figure 9. The antitubercular activity of phthalazine derivative.

Miscellaneous biological activities

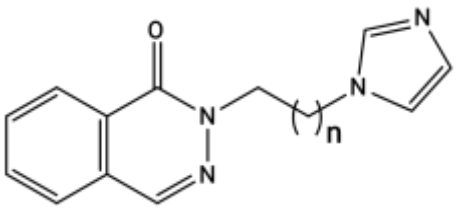
Large numbers of phthalazine derivatives were exhibited the diverse type of pharmacological activities are reported in Figure 10. Phthalazine derivatives have exhibited various types of biological activities such as the 2-phenyl-1(2H)-phthalazinones (**10a**) were exhibited antiplatlets action (Sugimoto et al., 1985). The 2-[2-(1-Imidazolyl)alkyl]-1(2H)-phthalazinone derivatives (**10b**), 4-(3-Pyridyl)-1(2H)-phthalazinones (**10c**), and 2-[2-(1-Imidazolyl)ethyl]-4-(3-pyridyl)-1(2H)-phthalazinones (**10d**) were exhibited antiasthmatic activity with dual thromboxane A2 synthetase inhibition and bronchodilator actions (Yamaguchi et al., 1993; Yamaguchi et al., 1994; Van der Mey et al., 2001). The 4-(3,4-dimethoxyphenyl)-2H-phthalazin-1-one analogues (**10e**) were exhibited selective phosphodiestrase-4 (PDE-4) inhibitor activity (Agrawal et al., 2013). The thiazolyl-phthalazinone acetamides (**10f**) were exhibited potent glucose uptake activators (Xue et al., 2014). Several 1,2,4-triazolo[3,4-a]phthalazines (**10g**) were exhibited anticancer activities (Yu et al., 2014). Some 6-(4-chlorophenoxy)-tetrazolo[5,1-a]phthalazine derivative (**10h**) were exhibited anticoagulation in mice and act as inhibition of thrombosis in rats (Zhang et al., 2014).

Several 1,2,4-triazolo [3,4-a]phthalazines (**10i**) were exhibited antimicrobial activities against pathogenic microbes (Ma et al., 2014). Various [1,2,4]triazolo[3,4-a]phthalazine (**10i**) and tetrazolo[5,1-a]phthalazine (**10j**) bearing substituted piperazine moieties were exhibited positive inotropic effects (Inoue et al., 2015). Some 4-benzyl-1-(2H)-phthalazinones (**10k**) were exhibited androgen receptor antagonists (Hasabelnaby et al., 2015). Various 4-Aryl-2(1H)-phthalazinones (**10l**) were exhibited Cyclooxygenase-2 (COX-2) inhibitor activity and given promising anti-inflammatory activity (Abou-Seri et al., 2016). The 1-Piperazinylphthalazines (**10m**) were exhibited potential VEGFR-2 inhibitor and anticancer activities (Liu et al., 2016). The 6-phenoxy-[1,2,4]triazolo[3,4-a]phthalazine-3-carboxamides

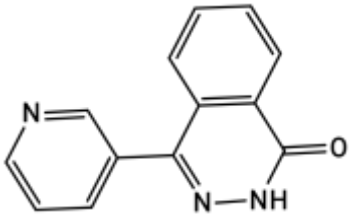
(**10n**) were exhibited anti-inflammatory activity (Chang et al., 2019). Some 1,2-Bis(hydroxy-methyl)pyrrolo[2,1-a]phthalazine Hybrids (**10o**) were exhibited potent anticancer activity that inhibits angiogenesis and induces DNA inter strand cross-links (Popovici et al., 2019). Various pyrrolo[2,1-a]phthalazines (**10p**) were exhibited anticancer activities (Qiu et al., 2019). Various N-(4-(2-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)phenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxamides (**10q**) were exhibited P-glycoprotein inhibitor activity for overturning multidrug resistance (Romero et al., 2019). Some 1,4-bis(substituted benzalhydrazino)phthalazines (**10r**) were exhibited antileishmanial activity (Gong et al., 2006).



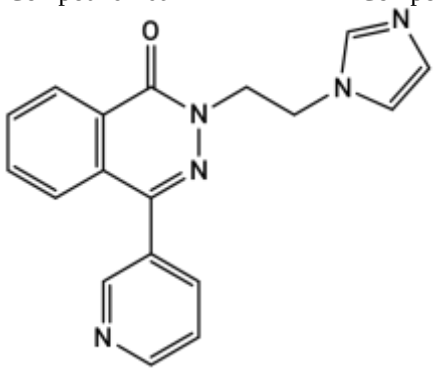
Compound **10a**



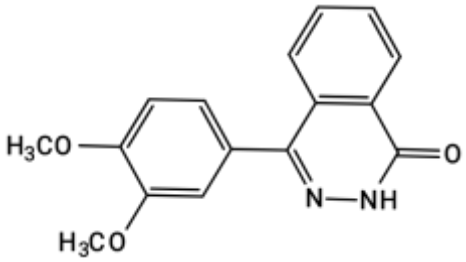
Compound **10b**



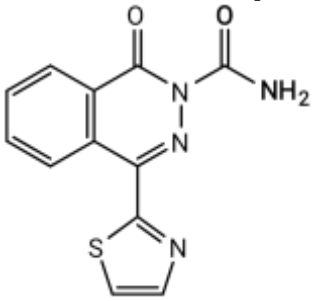
Compound **10c**



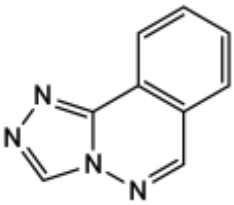
Compound **10d**



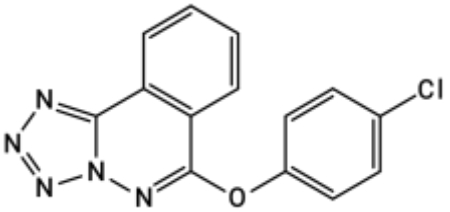
Compound **10e**



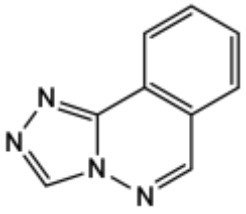
Compound **10f**



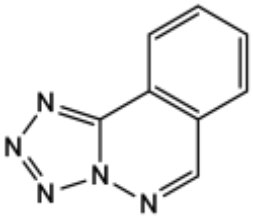
Compound **10g**



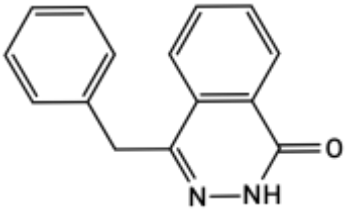
Compound **10h**



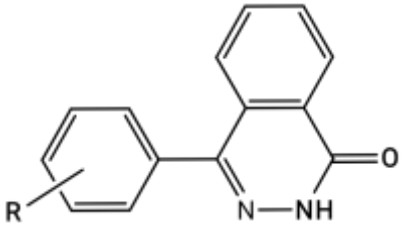
Compound **10i**



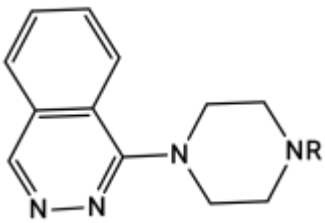
Compound **10j**



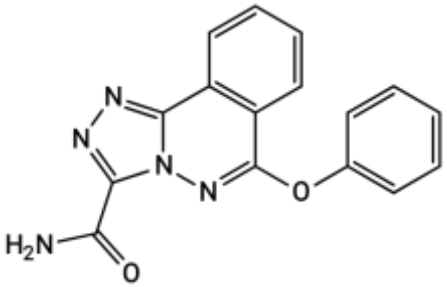
Compound **10k**



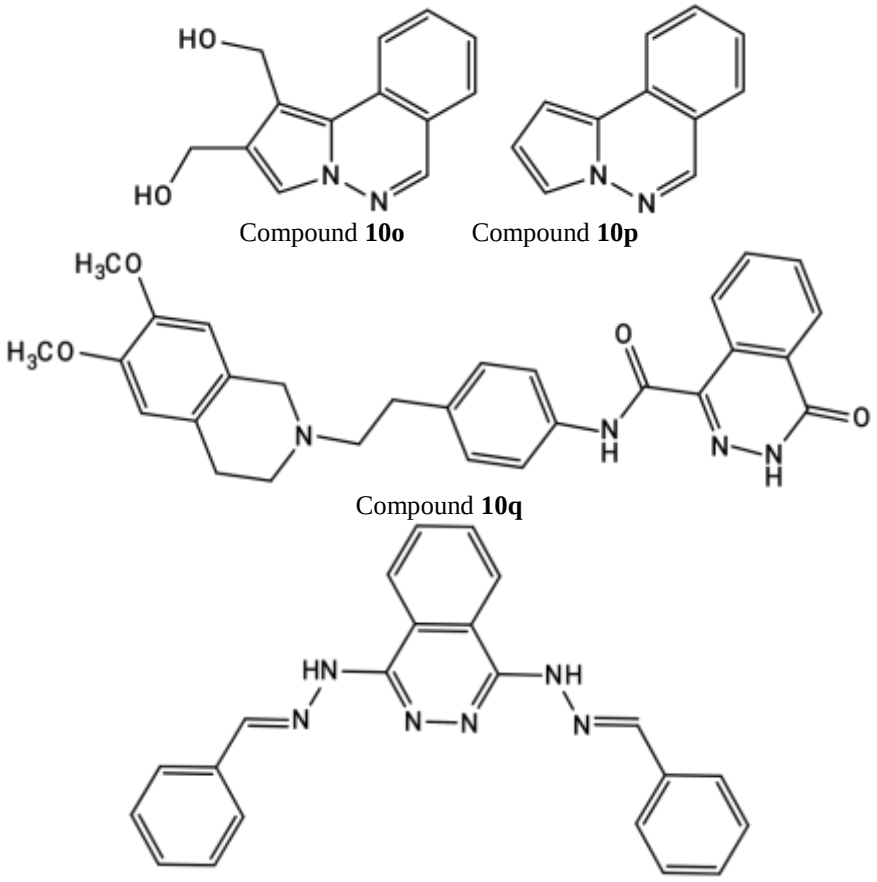
Compound **10l**



Compound **10m**



Compound **10n**



Compound **10o** Compound **10p**

Compound **10q**

Compound **10r**

Figure 10. Miscellaneous biological activities of various phthalazine derivatives.

2. Discussion

Many scientists believe that phthalazine is an excellent therapeutic target for researching a variety of pharmacological effects (Quan et al., 2009; Singh et al., 2014). Phthalazine produces a novel derivative with intriguing biological and chemical properties because it contains a more potent pharmacophoric moiety (Abo-Elmagd et al., 2018; Lu et al., 2017; El-Helby et al., 2019). The phthalazine pharmacophore offers greater therapeutic potential and is more adaptable (Turkes et al., 2019; Zaheer et al., 2016). Phthalazines are also one of the most significant biological active pharmacophore components in medicinal chemistry as antiallergic (Olmo et al., 2015), antidiabetic (Singh et al., 2019), vasorelaxant (Nahed et al., 2011), phosphodiestrase (PDE) inhibitors (Aziz et al., 2012; Haack et al., 2005), vascular endothelial growth factor (VEGF) receptor inhibitor (Sung et al., 2004; Lebsack et al., 2004; Bayoumi et al., 2014), tyrosine kinase inhibitors, antiasthmatic and herbicidal like activities (Jhang et al., 2009; De et al., 2010; El Azm et al., 2015). Many well-known pharmaceutical substances, including Hydralazine, Budralazine, Azelastine, Ponalrestat, and Zopolrestat, are made from phthalazinones (Chung et al., 2021; Khalifa et al., 2022). The wide range of biological activities of phthalazinone pharmacophores prompted us to develop novel molecular systems with biologically active compounds (Amirmahani et al., 2020; Antoci et al., 2020). This review article attempts to outline the current development of several Phthalazines derivatives, therefore pointing researchers in the direction of Phthalazines (Procopiou et al., 2017; Mood et al., 2017). This sort of study would be extremely beneficial to novice researchers. The fresh researcher has discovered a variety of phthalazines (Johnson et al., 2013; Derita et al., 2013). Phthalazines are crucial components in the development of a novel molecular system for physiologically active compounds (Cho et al., 2006; Elmeligie et al., 2019). The equivalent phthalazinone is used to make a variety of well-known medicinal compounds (Popovici et al., 2019; Eldehna et al., 2017). It creates pharmacologically active molecules with fewer adverse effects while keeping their potency after incorporating fused components and diverse functional groups (Li et al., 2006; Abd El-Wahab et al., 2011; Sławiński et al., 2014). A thorough review of the literature included in this review article allowed researchers to investigate the possibility of synthesising more

appropriate and useful pthalazine derivatives. Various synthesis methods have been described that might lead to the production of phthalazine derivatives.

3. Conclusion

A new molecule with a heterocyclic structure was created using the substituted phthalazine derivatives presented in this review article as the building blocks. In order to create novel compounds with the necessary potency and effectiveness to elicit the intended pharmacological response, these new molecules are incredibly helpful to medicinal chemistry researchers. Phenazines have been described as having anticonvulsant, analgesic, cardiotonic, antibacterial, anticancer, anti-inflammatory, anti-tubercular, antihypertensive, vasorelaxant, and other anticipated activities. It can be inferred that phthalazines have great promise for the synthesis of novel medications due to the high pharmacophoric group and ring position found in the phthalazine nucleus. As various functional groups are added to the phthalazine rings, novel phthalazine derivatives with various biological activities are produced. It is an exciting lead molecule for the development of novel pharmaceuticals with strong biological effects. Phthalazine derivatives have been created using a range of substituents, and a range of models have been used to evaluate their pharmacological effects. The review claims that phthalazine is a significant biologically active pharmacophore in medicinal chemistry and a new class of beneficial and safe medications for researchers.

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