Phthalimide as a versatile pharmacophore scaffold: unlocking its diverse biological activities

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Abstract

Phthalimide, a pharmacophore exhibiting diverse biological activities, holds a prominent position in medicinal chemistry. In recent decades, numerous derivatives of phthalimide have been synthesized and extensively studied for their therapeutic potential across a wide range of health conditions. This comprehensive review highlights the latest developments in medicinal chemistry, specifically focusing on phthalimide-based compounds that have emerged within the last decade. These compounds showcase promising biological activities, including anti-inflammatory, anti-Alzheimer, antiepileptic, anti-schizophrenia, antiplatelet, anticancer, antibacterial, antifungal, antimycobacterial, antiparasitic, anthelmintic, antiviral, and anti-diabetic properties. The physicochemical profiles of the phthalimide derivatives were carefully analyzed using the online platform pkCSM, revealing the remarkable versatility of this scaffold. Therefore, this review emphasizes the potential of phthalimide as a valuable scaffold for the development of novel therapeutic agents, providing avenues for the exploration and design of new compounds.

KEYWORDS:
Phthalimide, thalidomide, drug design, medicinal chemistry, new drugs, bioactive compounds

1. INTRODUCTION

Phthalimide is a pharmacophore scaffold that features an isoindoline-1,3-dione core with an imide ring (Kushwaha & Kaushik, 2016). Its biological properties are influenced by several chemical characteristics, including hydrophobicity, which enables its movement across biological membranes in vivo (Bansode et al., 2009; Almeida et al., 2020). It also has a hydrogen bonding subunit, an electron donor group, and an aromatic hydrophobic site (Kushwaha & Kaushik, 2016; Siddiqui et al., 2017). Among the drug-containing phthalimide scaffold, the immunomodulatory drugs (IMIDs) thalidomide, pomalidomide and lenalidomide (Figure 1) are the most representatives agents. Thalidomide, a drug with a notorious past due to its teratogenic effects, comprises phthalimide and a glutarimide ring containing the chiral center. The drug was firstly administered as a racemic mixture of its (−)-*S*- and (+)-*R*-enantiomers, although years later the teratogenic effects was associated with the (−)-*S*-enantiomer. Subsequent research to attempt the chiral resolution revealed that the two enantiomers of thalidomide can interconvert under physiological conditions, making it challenging to administer the enantiopure form (Franks et al., 2004; Almeida et al., 2020; Vargesson, 2015).

Nowadays, thalidomide has been used to treat Erythema Nodosum Leprosum (ENL) and multiple myeloma (Hastings et al., 1970; Singhal et al., 1999; Richardson et al., 2002). Based on thalidomide structure, two other phthalimide derivatives, pomalidomide and lenalidomide (Figure 1) were approved by the FDA for multiple myeloma (Fouquet et al., 2014; Richardson et al., 2006). Thalidomide's immunomodulatory, anti-inflammatory, and antiangiogenic properties are associated with modulation of cytokine production, such as TNFα, interferon, interleukins 10 (IL-10) and 12, cyclooxygenase 2 (COX-2), and nuclear factor κβ (Franks et al., 2004).

In recent years, medicinal chemistry has seen an increase in the discovery of new phthalimide-based derivatives (Júnior et al., 2019). *N*-substituted analogues have shown promising biological activities, such as anti-inflammatory (Barbosa et al., 2022; Alanazi et al., 2015; Lima et al., 2002; Lamie et al., 2015), antioxidant (Bisht & Bisht, 2021), antitumor (Noguchi et al., 2005; Pessoa et al., 2007), anticonvulsant (Ragavendran et al., 2007; Vamecq et al., 2000), antimicrobial (Khidre et al., 2011; Akgun et al., 2012), anti-HIV (Penta et al., 2013), and others (Antunes et al., 1998; Shinji, et al., 2005; Hassanzadeh et al., 2007; Hassanzadeh et al., 2014). Recent progress has been observed in the medicinal chemistry of phthalimide and thalidomide derivatives (Bosquesi et al., 2011; Dos Santos et al., 2011, 2012), with growing interest in their multiple therapeutic applications, such as proteolysis targeting chimaeras (PROTACs) and molecular glues. PROTACS are heterobifunctional small molecules that can target specific proteins of interest and mark them to be degraded by the ubiquitin-proteasome system (Khan et al., 2020; Krajcovicova et al., 2019; Chou, 2017; Schirmeister et al., 2016; Winter et al., 2015). For this approach, the glutarimide moiety is the pharmacophoric group

responsible for recognition by the E3 ubiquitin ligase cereblon [38]. This review will focus exclusively on phthalimides of purely synthetic origin published in the last decade. It is worth mentioning that PROTACs and molecular glues are outside the scope of this review, and interested readers can find reviews on this topic elsewhere (Dong et al., 2021; Qi et al., 2021; Zeng et al., 2021; Zhou et al., 2020).

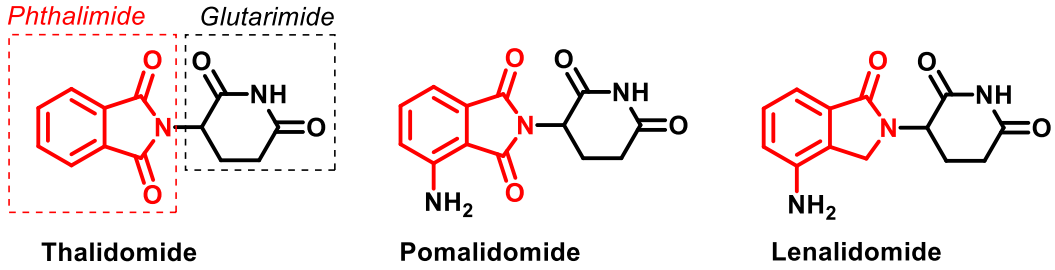

FIGURE 1. Phthalimide-containing drugs approved by the FDA.

2. PHTHALIMIDES AS ANTI-INFLAMMATORY AGENTS

In the field of drug discovery, phthalimide derivatives have gained significant attention due to their anti-inflammatory properties (Pophale et al., 2010; Sharma et al., 2010). Recently, Szkatua et al. (2021) synthesized and characterized nine novel piperazine derivatives (**1**–**9**) and evaluated their anti-inflammatory effects against two cyclooxygenase enzymes, COX-1, and COX-2, at a concentration of 100 µM (Szkatuła et al., 2021). The compounds were also tested for cytotoxicity in Primary Normal Human Dermal Fibroblasts (NHDF) cells from human skin, and their impact on the levels of reactive oxygen species (ROS), reactive nitrogen species (RNS), and reduction of DNA damage. All compounds demonstrated scavenging activity against ROS. Among the tested compounds, **2**, **4**, and **5** showed the most potent inhibition of COX-1 with IC_{50} values of 71.0, 66.2, and 76.7 µM, respectively, while the remaining compounds had IC_{50} values between 94.4 and 238.3 µM (Figure 2) (Szkatuła et al., 2021). On the other hand, compounds **2**–**9** exhibited inhibitory effects on COX-2 with IC_{50} values ranging from 43.8–72.8 µM, while compound **1** had an IC_{50} value of 107.2 µM (Figure 2). In terms of cytotoxicity, compounds **4** and **7**–**9** exhibited half maximal cytotoxicity (CC_{50}) values ranging from 90.2 to 96.7 µM, whereas compounds **1**–**3** and **5**–**6** showed nontoxic effects. Molecular docking studies showed that compound **7** had the highest inhibition constant (Ki) against COX-1 (Ki = 4.3 µM) and COX-2 (Ki = 0.54 µM). Additionally, all compounds complied with Lipinski's rule with logP values between 2.1–4.61 (Szkatuła et al., 2021).

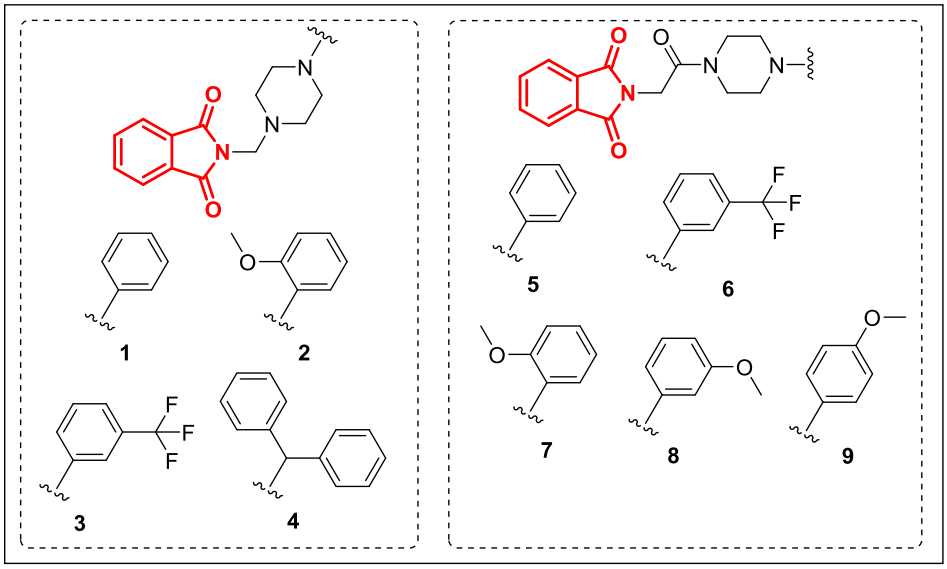

FIGURE 2. Phthalimide derivatives with anti-inflammatory effects.

Abdel-Aziz et al. (2020) conducted a study to evaluate the anti-inflammatory activities of 14 new phthalimide derivatives (Figure 3) (Abdel-Aziz et al., 2020). Compounds **20**–**23** showed activity against COX-1 with IC_{50} values ranging from 10.9 to 24.8 µM, while analogues **10**–**19** had IC_{50} values greater than 50 µM (celecoxib IC_{50} > 50 µM). Compounds **10**–**11**, **14**–**16**, and **19** were found to be the most potent against COX-2, with IC_{50} values ranging from 0.15 to 0.2 µM. The derivatives **12**–**13** and **17**–**18** showed IC_{50} values between 0.8–4.0 µM, while the compounds **20**–**23** exhibited IC_{50} values between 22.3–36.3 µM (celecoxib IC_{50} = 0.129 µM) (Abdel-Aziz et al., 2020). The anti-inflammatory effects of these compounds were evaluated in a rat model of carrageenan-induced paw edema. Compounds **10**–**11**, **14**–**16**, and **19** demonstrated inhibition values of 77–82.9% for paw edema, while compounds **12**–**13**, **17**–**18**, and **20**–**23** exhibited values ranging from 33.1 to 64.4%. Furthermore, compounds **11**, **14**–**16**, and **19** (at 80 mg/kg) were tested in a murine model of carrageenan-induced paw edema, with inhibition values ranging from 86.1% to 91.9% (celecoxib inhibition = 93.5%). Additionally, the ulcerogenic effects of these compounds in mice were assessed, with compound **19** showing the least amount of ulcerogenic effects and causing an average of 2 ulcers. On the other hand, compounds **11** and **14**–**16** caused 4–6 ulcers. In comparison, celecoxib and diclofenac caused 5 and 10 ulcers, respectively (Abdel-Aziz et al., 2020).

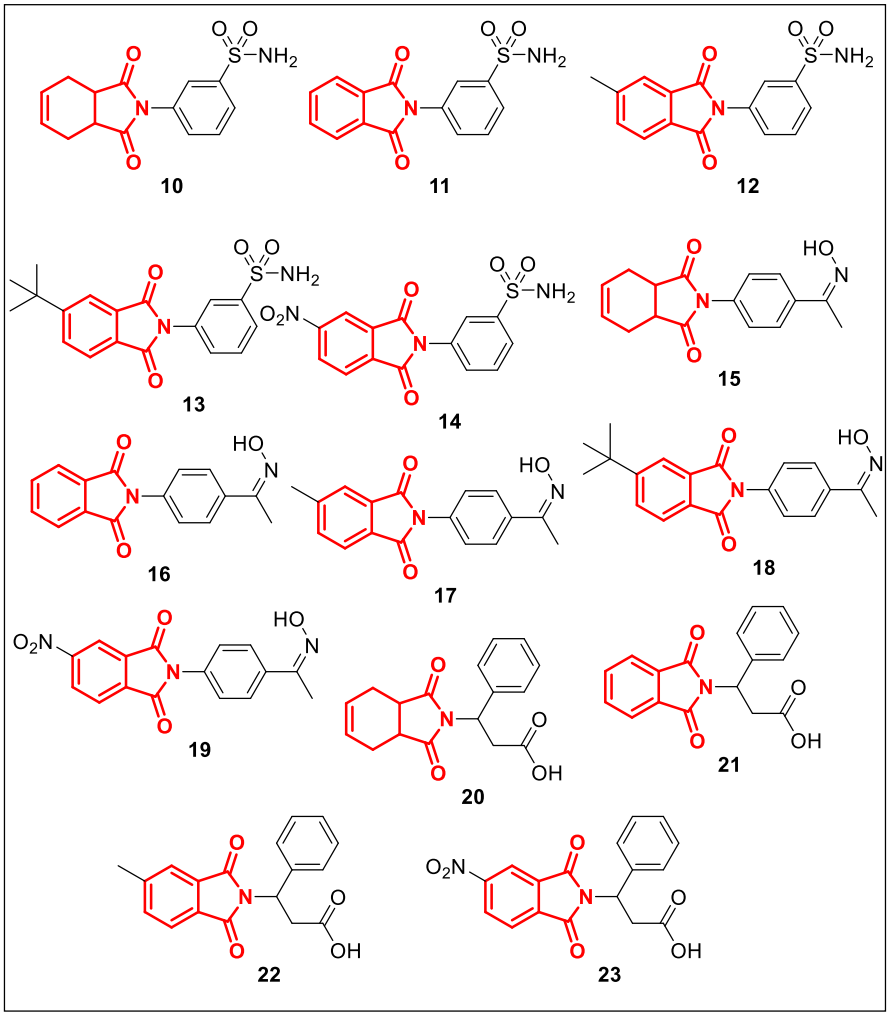

FIGURE 3. Phthalimide derivatives with anti-inflammatory activity.

Machado et al. (2020) conducted a study on a murine model of ulcerative colitis evaluating the effectiveness of new derivatives of prednisolone (**24**–**26**) and budesonide (**27**–**29**) bearing the phthalimide moiety (Figure 4) (Machado et al., 2020). Histopathological analysis showed that compounds **28**-**29** exhibited the highest efficacy in reducing ulceration in the animal, reducing 83.3% and 75.0% of ulceration, respectively, whereas compounds **24** and **26**-**27** caused a reduction of 20.0-33.3%. Compound **25** was unable to inhibit ulcer damage, while prednisolone inhibited 16.7% and budesonide inhibited 100% of ulceration (Machado et al., 2020). In a separate study, El-Aarag et al. (2021) investigated the potential therapeutic effects of a new phthalimide-based derivative (Figure 5) in an animal model of liver damage (El-Aarag et al., 2021). The mice were induced with hepatic damage using carbon tetrachloride (100 µM, 0.4 mL/kg) twice a week for six weeks. Compound **30** was administered (30 mg/kg, intraperitoneal) five times a week for two weeks. The results revealed that compound **30** reduced levels of malondialdehyde to less than 80 nmol/g tissue, nitric oxide (NO) to less than 60 µmol/L, vascular endothelial growth factor (VEGF) to less than 15%, TNF-α to less than 15%, and NF-κB to less than 15% when compared to the untreated group and the thalidomide-

treated group. Additionally, treatment with compound **30** resulted in higher levels of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase (El-Aarag et al., 2021).

Su et al. (2017) discovered a phthalimide-based derivative, PD1 (**31**) (Figure 5), with promising anti-inflammatory activity. Compound **31** did not display any cytotoxic effects on human embryonic kidney cells (HEK293T), rat liver cells (Ac2F), and murine macrophages (RAW264.7). In macrophages (RAW264.7), **31** (50 μM) exhibited reduced expression of COX-2/GAPDH, interleukin-1β, inducible nitric oxide synthase, TNF-α/GAPDH, interleukin-6, NO, and NF-κB p-p65/β-actin compared to the untreated lipopolysaccharide (LPS)-induced control group (Su et al., 2017). Moreover, **31** demonstrated an increase in interleukin-10 mRNA expression compared to the untreated LPS-induced group. In vivo carrageenan-induced experiments revealed that rats treated with **31** exhibited reduced paw thickness (≤ 7.0 mm) than untreated rats (> 8.0 mm). Histopathological analysis of rats treated with **31** demonstrated lower dermal thicknesses (800 μm) than untreated rats (1100 μm) (Su et al., 2017).

Liu et al. (2019) synthesized a series of fangchinoline and tetrandrine-based analogues and evaluated their anti-inflammatory effects against IL-1β released upon induction with lipopolysaccharide/nigericin (Liu et al.; 2019). Compound **32** (Figure 5) was the most potent, exhibiting an IC_{50} value of 3.7 μM against IL-1β stimulation in THP-1 cells (Liu et al., 2019). Additionally, compound **32** demonstrated a high interaction with the nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome, identified as one of the responsible to produce IL-1β (Franch et al.; 2009; Chen et al., 2017), during computational analysis (Liu et al., 2019). Wani et al. (2017) investigated the anti-inflammatory activity of compound **33** (Figure 5), through multi-spectroscopic and molecular docking analyses (Wani et al., 2017). The results indicated that compound **33** spontaneously binds to bovine serum albumin (BSA) with negative ΔG0 (-298 K), ΔH0 (-303 K), and ΔS0 (-308 K) values and can bind to subdomain IIIA of BSA (Wani et al., 2017). Recently, Verma et al. (2022) reported five new ethoxy phthalimides containing a pyrazole scaffold (**34**–**38**) using computer-assisted drug design against IL-17A and IL-18 in gout (Figure 5) (Verma et al., 2022). Molecular docking studies using gout IL-17A (PDB 4HR9) demonstrated that these compounds have binding interaction values of -13.5 to -3.32 kcal/mol, while studies using gout IL-18 (PDB 3WO2) demonstrated interaction values of -10.4 to -3.18 kcal/mol (Verma et al., 2022).

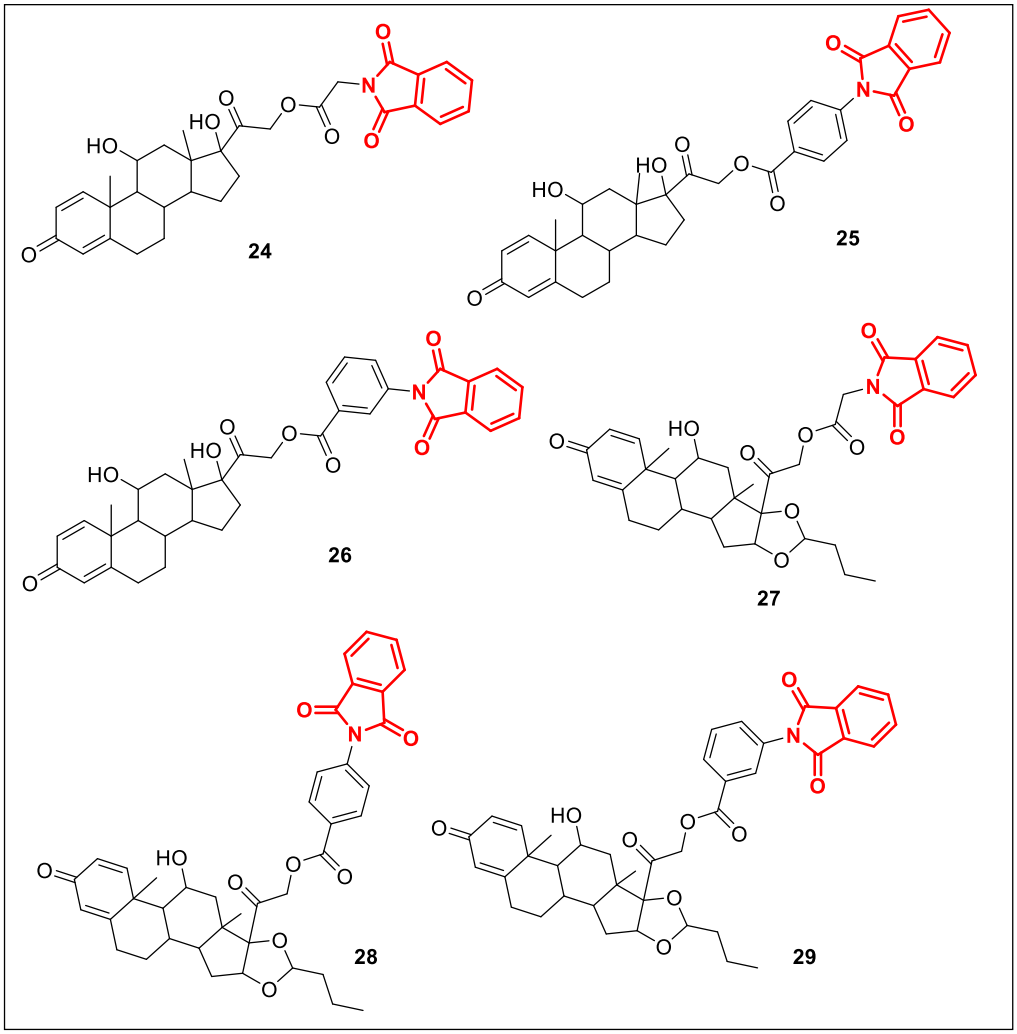

FIGURE 4. Prednisolone and budesonide derivatives with anti-ulcerative effects.

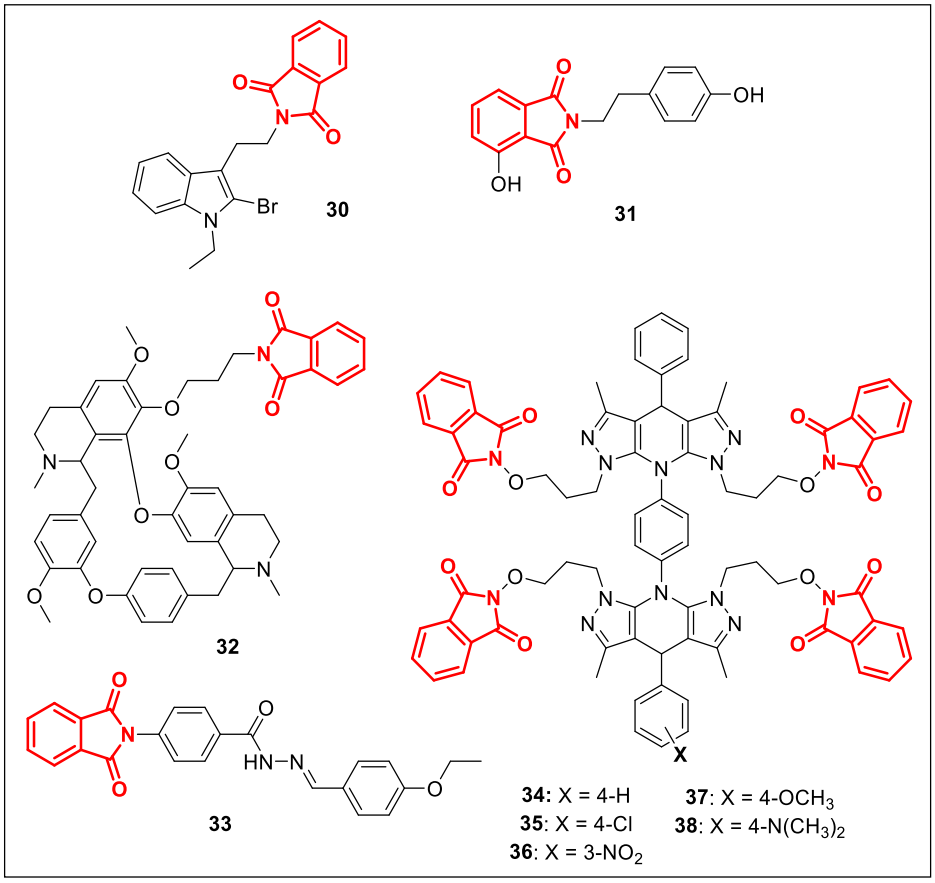

FIGURE 5. Phthalimide-based derivatives with anti-inflammatory effects.

Tang and colleagues (2018) conducted a study in which they synthesized and assessed a range of thalidomide analogues (Figure 6). The IL-6 and TNF-α inhibitory activity of all compounds (**39**-**57**) was evaluated, and the results indicated that compounds **39**-**47** and **55**-**57** demonstrated inhibition values between 1.35%-44.83% for IL-6. The most potent compounds were **53** and **54,** which showed inhibition values of 69.44% and 62.12%, respectively (Tang et al., 2018). For TNF-α inhibition, derivatives **39**-**47** and **54**-**57** exhibited inhibition values ranging from 5.11 to 39.77%, whereas compound **53** demonstrated the highest inhibition value of 75.01% (Tang et al., 2018). In addition, all compounds exhibited excellent cell viability in HaCaT cells, ranging from 90.7 to 100%. In human keratinocyte cell lines, compound **53** (at 10 μM) was found to be the most promising compound, exhibiting a reduction in IL-1β, IL-6, and IL-24. Furthermore, compound **53** was observed to have inhibitory effects on JNK1/2 and ERK1/2, which are known to regulate pro-inflammatory pathways via the mitogen-stimulated protein kinase (MAPK) pathways in psoriasis disease (Tang et al., 2018).

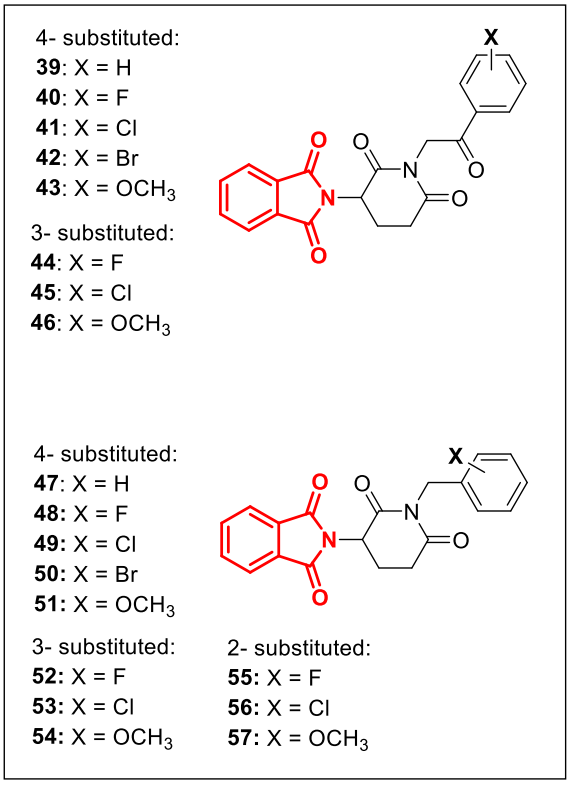

FIGURE 6. Thalidomide analogues with IL-6 and TNF-α inhibitory activities.

3. PHTALIMIDE DERIVATIVES DISCOVERED FOR NEUROLOGICAL DISORDERS

3.1. Anti-Alzheimer activity

Alzheimer's disease (AD) is a neurodegenerative disorder associated with a decline in acetylcholine (ACh) levels (Kumar et al., 2019). The main strategy for AD treatment involves the use of acetylcholinesterase inhibitors (Kumar et al., 2019). Hassanzadeh et al. (2021) reported the synthesis and evaluation of a series of isoindoline-1,3-dione-containing phthalimide derivatives (Figure 7) as AChE inhibitors (Hassanzadeh et al., 2021). The most potent analogues, including **58**, **60**, **62**–**63**, and **65**, exhibited AChE inhibition with IC_{50} values of 2.1–2.9 µM, while compounds **59**, **61**, **64**, and **66** showed IC_{50} values ranging from 4.8–7.4 µM (Hassanzadeh et al., 2021). In another study, Panek et al. (2017) synthesized and evaluated a series of phthalimide derivatives containing piperazine, hexahydropyrimidine, 3-aminopyrrotidine, and 3-aminopiperidine moieties (Figure 7) as AChE inhibitors (Panek et al., 2017). Compounds **67**–**76** exhibited IC_{50} values of 10–41.8% against electric eel-derived AChE (EeAChE), while compound **77** demonstrated an IC_{50} value of 6.47 µM. All compounds exhibited inhibition values of 10–28.3% against butyrylcholinesterase from equine serum. Moreover, compounds **67**–**76** were evaluated for their inhibitory effects against human recombinant BACE1 (hBACE1) and exhibited inhibition values between 28.0% and 48.3%. Compound **77** exhibited an inhibition value of 26.3% (Panek et al., 2017). A molecular docking analysis revealed that compound **77** targets the catalytic and peripheral positions of the AChE

enzyme. In a subsequent study, the same group reported the synthesis and evaluation of a series of phthalimide analogues containing 2-(benzylamino-2-hydroxyalkyl)isoindoline-1,3-diones (Figure 8) as potential anti-AD agents (Panek et a., 2018). The most potent compounds, including **89** and **91**–**92**, exhibited IC_{50} values of 3.32, 2.13, and 1.95 µM, respectively, against EeAChE, whereas compound **90** exhibited an IC_{50} value of 11.07 µM. Analogues **78**–**88** exhibited IC_{50} values of 10 to 32.7% against EeAChE. Furthermore, all compounds showed inhibition values ranging from 7.8–36.0% and 10–45.0% against EqBuChE and hBACE1. Additionally, compounds **78**–**92** were evaluated for their Aβ-aggregation activities (at 10 µM), with values ranging from 10–24.9% (Panek et a., 2018).

In a study conducted by Sang et al. (2017), 28 new phthalimide derivatives with alkylamine conjugates were described, with five compounds (Figure 8) showing promising activity against EeAChE with IC_{50} values ranging from 0.13 to 0.9 µM (Sang et al., 2017). Compound **94** demonstrated the highest activity against EqBuChE, with an IC_{50} value of 2.5 µM, while compounds **93** and **95**–**97** exhibited values of 7.3–31.0 µM. All compounds were also evaluated for their activity against RatAChE and RatBuChE, with IC_{50} values ranging from 0.04–0.6 µM and 2.2–18.9 µM, respectively. Additionally, compounds **93**–**97** exhibited IC_{50} values in the range of 0.28–4.5 µM and 3.8–15.3 µM against HuAChE and HuBuChE, respectively. Although they were not active against monoamine oxidase A, they demonstrated IC_{50} values in the range of 2.6–11.7 µM against monoamine oxidase B. Furthermore, compound **94** exhibited good cell viability at 1 µM and 10 µM and 80% viability at 100 µM, and it also showed good BBB permeability in the PAMPA assay (Sang et al., 2017). In another study by Mohammadi-Farni et al. (2017), ten 2-(2-(4-benzoylpiperazin-1-yl)ethyl)isoindoline-1,3-dione phthalimide conjugates were synthesized (Figure 8) (Mohammadi-Farani et al., 2017). Compounds **102** and **106** were the most effective against AChE, with IC_{50} values of 0.0071 and 0.0203 µM, respectively. Compounds **101** and **105** exhibited IC_{50} values of 3.6 and 1.3 µM, respectively, while derivatives **98**–**100**, **103**–**104**, and **107** exhibited IC_{50} values of 50.6 to >1000.0 µM. Molecular docking studies demonstrated a high binding interaction between the most promising compound **102** and the active site of AChE (Mohammadi-Farani et al., 2017). Andrade-Jorge et al. (2018) developed a new 2-(2-(3,4-methoxyphenyl) ethyl)isoindoline-1,3-dione-containing phthalimide (**108**) (Figure 8). This compound was evaluated against AChE, with a Ki of 0.33–0.93 µM. The minimum lethal dose (LD_{50}) for compound **108** was greater than 1600 mg/kg (Andrade-Jorge et al., 2018).

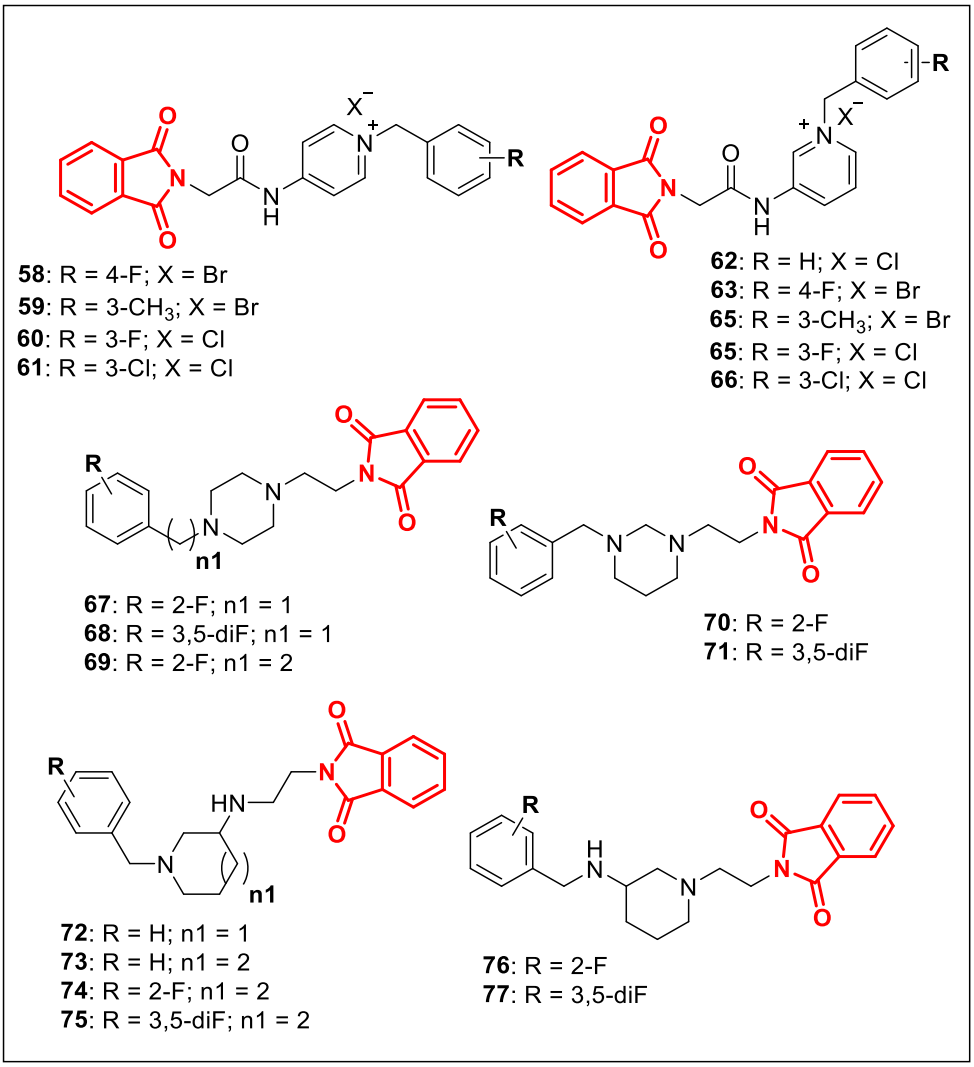

FIGURE 7. Isoindoline-1,3-dione-containing phthalimide derivatives with anti-AD activity.

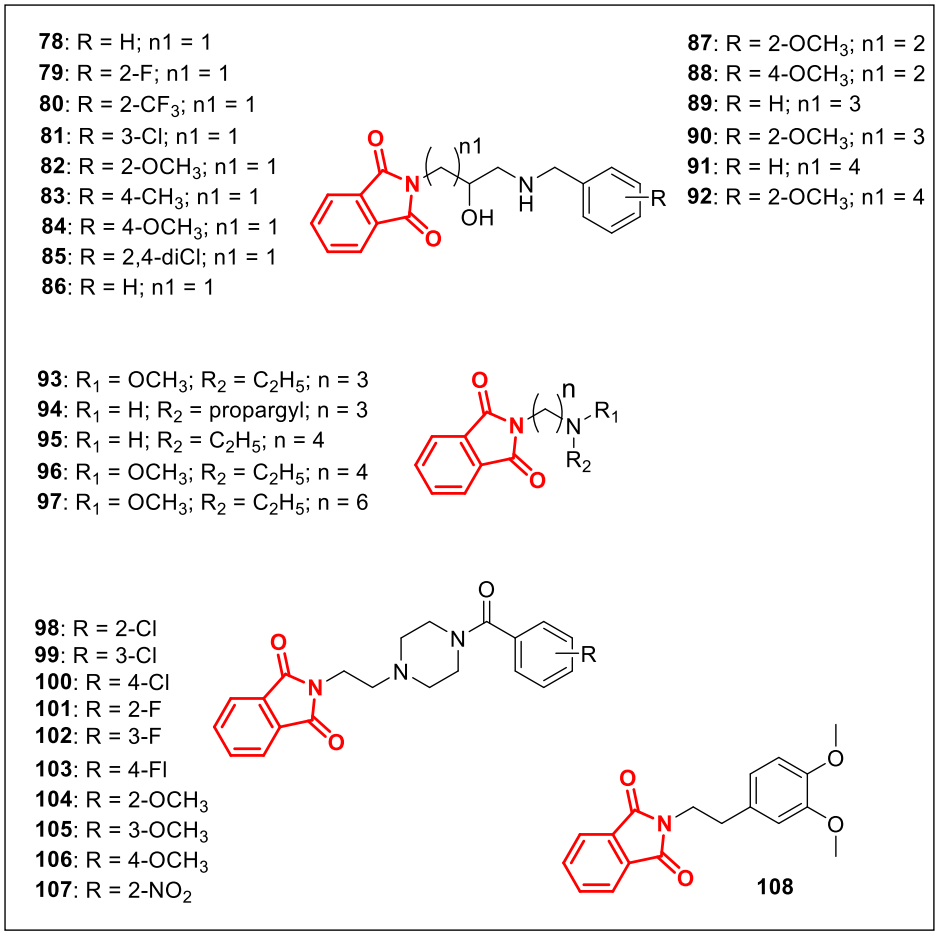

FIGURE 8. Phthalimide derivatives discovered for AD treatment.

3.2. Antiepileptic activity

Epilepsy is a neurological condition that is characterized by seizures (Simonato et al., 2018). In general, a seizure happens with a disparity involving neuronal inhibition and excitation in the brain tissue triggering an increasing of the Na^+ channel and glutamate concentration while reducing gamma-aminobutyric acid (GABA) and K^+ channel effects (Fountain, 2000; Lee, 2020). Thalidomide has been found to have anticonvulsant properties similar to valproic acid (Palencia et al., 2007). Recently, Amanlou et al. (2021) discovered three novel phthalimide derivatives (**109**-**111**) with potent anticonvulsant effects (Amanlou et al., 2021). These compounds were evaluated using two different models of seizures induced by pentylenetetrazole (PTZ) and lithium-pilocarpine. Compounds **109** and **111** had latency times of 692.6 s and 654.8 s, respectively, for PTZ-induced seizures. Compound **110** exhibited a latency time of 780.8 s, which is comparable to the values of diazepam and thalidomide. In the case of lithium-pilocarpine-induced epileptics, compound **109** (1 mg/kg) showed the most potent latency time of 22 min, with a mortality rate of 25%. Compounds **110** and **111** (at 100 mg/kg) exhibited values of 56 and 42 min, respectively, with mortality rates of 25% and 50%. Molecular docking and physicochemical properties analysis of compounds **109**-**111** revealed LogP

values between 2.52-4.43 and binding energies at the gamma-aminobutyric acid A (GABAA) site of -9.95 to -9.6 kcal/mol (Amanlou et al., 2021). In another study, Asadollahi et al. (2021) reported the anticonvulsant activity of five new analogues (**110**, **112-116**) bearing aniline amino acid groups. All compounds were tested in a murine model using lithium-pilocarpine-induced epileptic phases. Compound **110** exhibited the most promising latency time of fewer than 800 s, while compounds **112-114** had less than 200 s, and compounds **115-116** had less than 500 s. The physicochemical profiles and computational analysis of the compounds revealed LogP values between 3.67-4.79 and binding energies at the GABAA site of -9.95 to -8.97 kcal/mol (Asadollahi et al., 2019).

Iman et al. (2017) developed and assessed the efficacy of six novel *N*-isoindoline-1,3-dione-containing phthalimide derivatives (**117-122**) (Figure 9) for their anti-epileptic properties using a PTZ-induced seizure model. Compound **118** exhibited the most promising results, with a chronic seizure threshold value of 62.46 min, while compounds **117** and **119-122** demonstrated values between 36.1-45.61 min (at 40 mg/kg). The tonic seizure threshold of all the phthalimide-based analogues ranged between 48.64 and 92.76 min. The study also evaluated the molecular docking of all analogues, indicating binding energies at the GABAA site ranging from 1.26-4.16 and -7.18 to -4.81 kcal/mol (Iman et al., 2017). In 2018, the same authors developed and tested 16 4-fluoro-phthalimide derivatives, with compound **123** (Figure 9) demonstrating excellent efficacy (at 40 mg/kg) against PTZ-induced seizure with a value of 100% in animals without convulsive crises. Compound **123** also showed a value of 20% against maximal electroshock (MES)-induced seizure in animals without epileptic crises (Iman et al., 2018). Davood et al. (2017) identified a promising anti-epileptic phthalimide-based compound (**124**) (Figure 9) that exhibited higher clonic seizure threshold values (71.42 to 81.28 min) compared to the phenytoin group in the PTZ-induced assay at three different concentrations (20, 40, and 80 mg/kg). In comparison to the MES test, compound **124** demonstrated a 100% capacity for tonic seizures (at 80 mg/kg), thus avoiding mortality in all tested animals (Davood et al., 2017). In a recent study, Oliveira et al. (2022) synthesized and characterized nine novel compounds containing a hiazolidine-2,4-dione moiety and anticonvulsant properties. The most potent derivative (**125**) (Figure 9) reduced pro-inflammatory cytokine levels of IL-17 and IFN-gamma and demonstrated promising latency times with values of <80 s at three different concentrations (100, 300, and 600 mg/kg) in a PTZ-induced seizure model. In vivo assay revealed that **125** is nontoxic, and molecular studies suggested a possible interaction with the GABAA receptors (GABAAR) (de Oliveira et al., 2022).

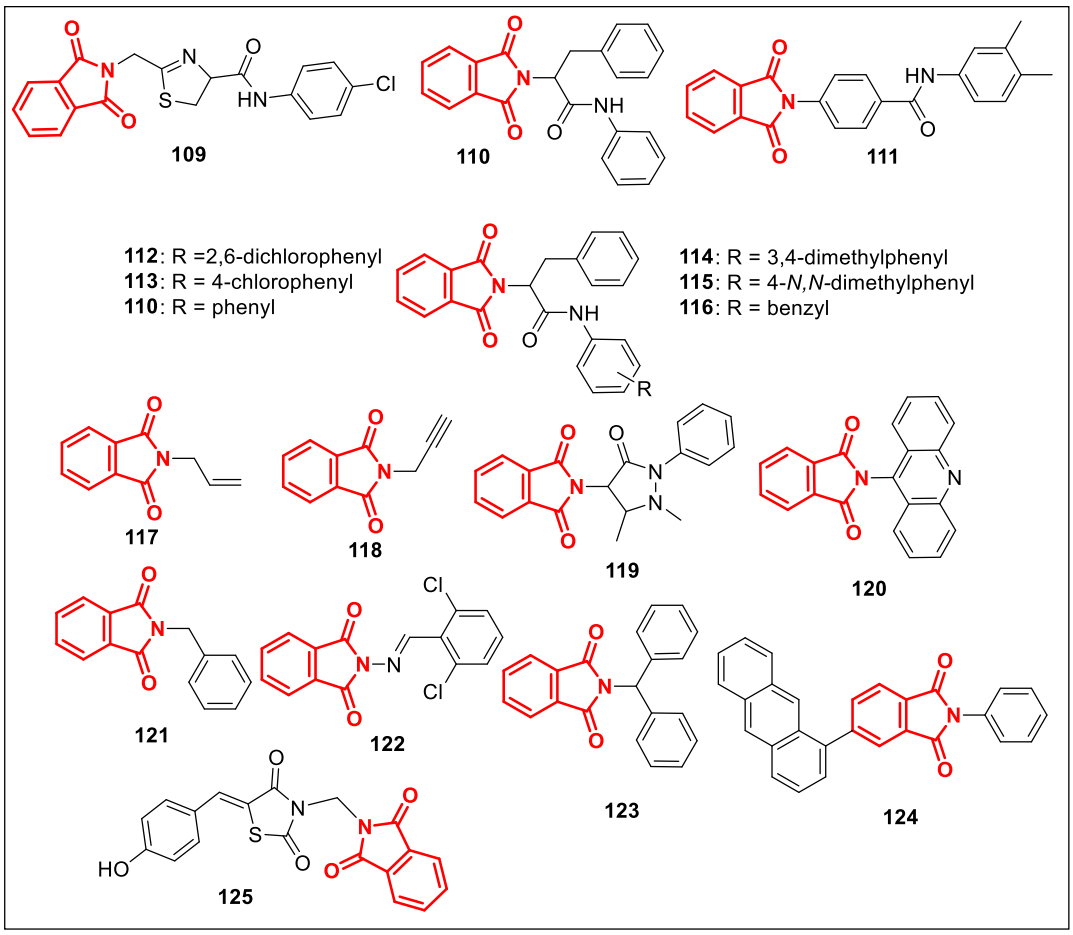

FIGURE 9. Phthalimide conjugates with anti-epileptic and anticonvulsant activities.

Human carbonic anhydrases (hCAs) are a family of zinc-containing metalloenzymes that have been identified as potential therapeutic targets in various diseases, including epilepsy (Ciccone et al., 2021; Mishra et al., 2020; Thiry et al., 2007) In a recent study, Sethi et al. (2021) synthesized and evaluated a series of sulfonamide-based analogues containing phthalimide moieties (**126**–**136**) (Figure 10) for their inhibitory activity against four different hCA enzymes (hCAI, hCAII, hCAIX, and hCAXII). The results showed that compounds **126**–**132** and **134**–**136** exhibited potent Ki values in the range of 0.159–0.463 µM against hCAI, while phthalimides **127**–**132** and **134**–**136** showed strong inhibition against hCAII with Ki values ranging from 0.0024 to 0.044 µM. Compounds **129**–**130** were found to be the most effective against hCAIX, with excellent Ki values between 0.0097 and 0.559 µM, whereas derivatives **126**–**128** showed Ki values ranging from 0.933 to 4.898 µM. Moreover, the phthalimide conjugates displayed promising K_i values against hCAXII, ranging from 0.014 to 0.316 µM (Sethi et al., 2021). In another study, El-Azab et al. (2016) reported three new phthalimide-based derivatives (**137**–**139**) (Figure 10) with potent inhibitory effects against various hCA isoenzymes, with Ki values ranging from 0.0336 to 0.0466 µM (hCAI), 0.0089 to 0.0138 µM (hCAII), 0.0727 to 0.4956 µM

(hCAIV), 0.00031 to 0.00046 µM (hCAVII), and 0.0041 to 0.0444 µM (hCAXII) (El-Azab et al., 2016).

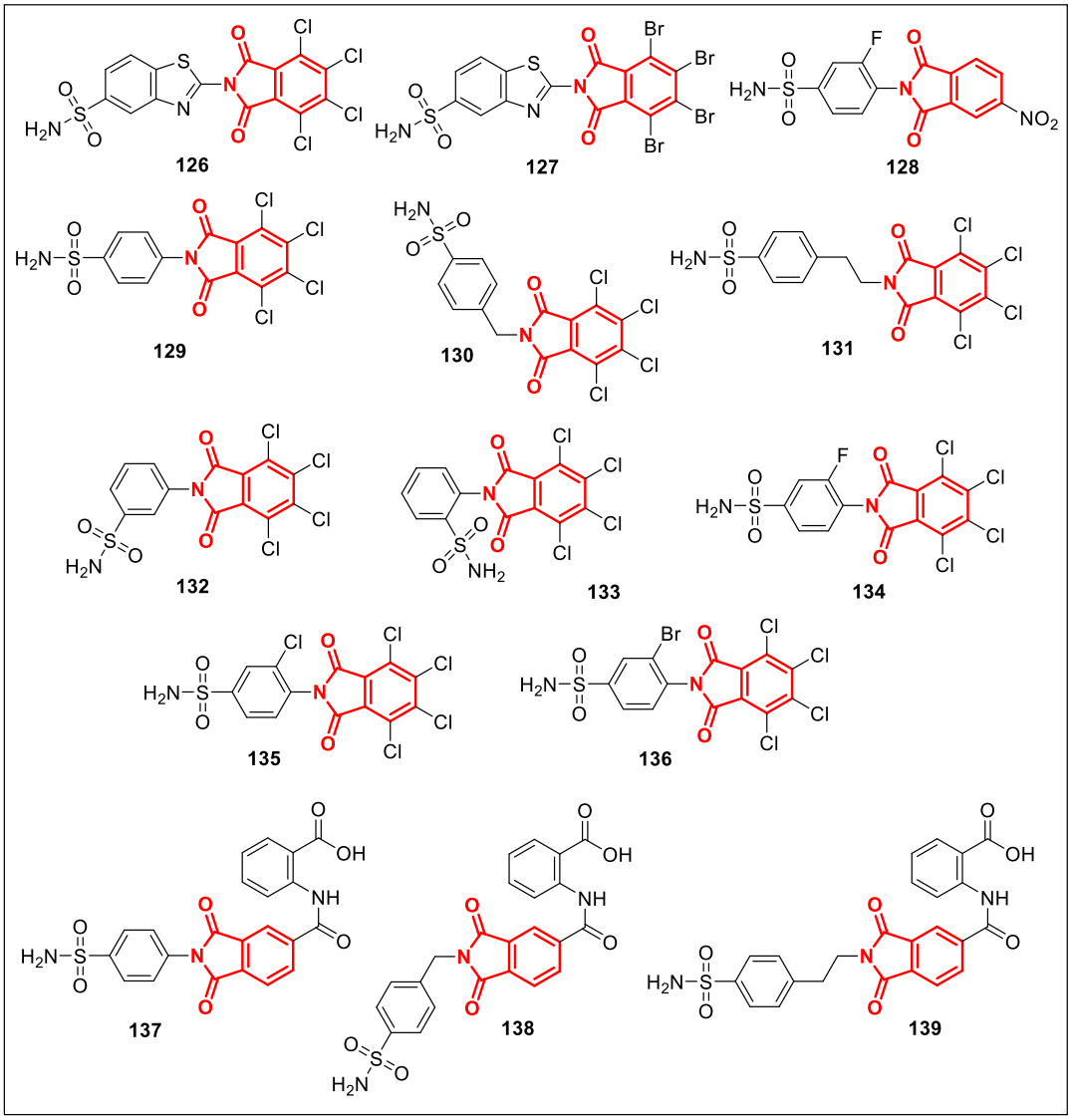

FIGURE 10. Phthalimide-sulfonamide conjugates with activity against hCA enzymes.

3.4. Phthalimides developed for treatment of schizophrenia

Given the significant role of glutamate transmission mediated by serotonin receptors, the inhibition of serotonin-based pathways emerges as a promising approach in the development of chemical entities for schizophrenia treatment. These inhibitors hold potential due to their ability to target G protein-based receptors, which are well-established molecular targets for schizophrenia intervention (Meltzer et al., 2003). Phosphodiesterase 10A (PDE10A) is a promising target for the treatment of cognitive deficits related to schizophrenia and negative symptoms in patients with schizophrenia due to its modulation of both D2-dependent and D1-dependent signaling and high expression in spiny

neurons of the striatal medium (MSNs) (Siuciak & Strick, 2011; Jan & Jacob, 2006). Czopek et al. (2020) identified five phthalimides (**140**–**144**) (Figure 11) with good activity against PDE10A and serotonin receptors (5-HTR1A and 5-HTR7). Compound **142** was the most potent, exhibiting an IC_{50} value of 0.8 µM and a 92% inhibition (at 10 µM) against PDE10A, while compounds **140**–**141** and **143**–**144** showed IC_{50} and inhibition values in the range of 1.0–6.7 µM and 70–86%, respectively. In addition, phthalimides **141**–**144** presented binding affinity values in the range of 16–28% and 3–15% for 5-HT1A and 5-HT7, except for compound **140**, which exhibited values of 44% and 0%, respectively. Compound **142** (at 60 mg/kg) demonstrated antipsychotic effects in an AMPH-d-amphetamine-induced murine model, with <1000 numbers of movements detected by the behavioral machine model after 10 min of monitoring. Molecular docking studies revealed an interaction binding between **142** and the active part of the PDE10A enzyme (Czopek et al., 2020). Another promising compound is the aryl piperazine-phthalimide conjugate (**145**) (Figure 11) evaluated by Cao et al. (2018) against dopamine receptors (D3R and D2R). This compound exhibited promising Ki values of 0.019 and 2.16 µM against D3R and D2R, respectively, with a D2R/D3R ratio of 112 (Cao et al., 2018).

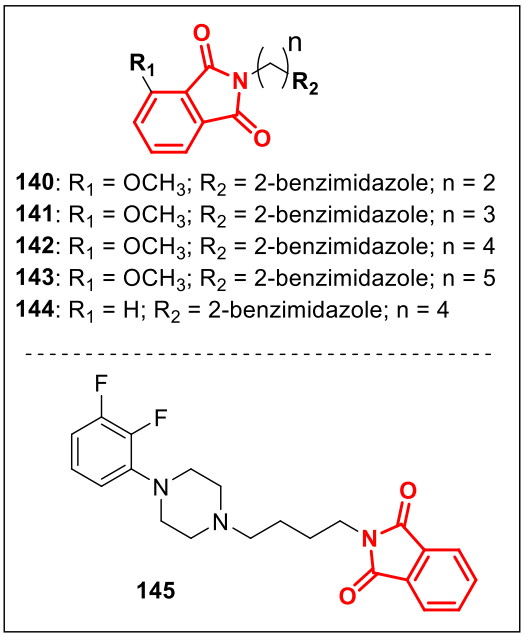

FIGURE 11. Phthalimide conjugates developed for the treatment of schizophrenia.

4. PHTHALIMIDES AS FETAL HEMOGLOBIN INDUCERS

Sickle cell disease (SCD) is a genetic disorder caused by a single-point mutation of β-globin, which produces sickle Hb (HbS) when valine is substituted for glutamic acid in the β-chain of hemoglobin (Pavan & dos Santos, 2021; Kato et al., 2018; dos Santos & Chin, 2011). The polymerization of HbS under deoxygenated conditions causes red blood cells to take on a sickle shape, resulting in cellular

aggregates, vaso-occlusion, and inflammation (Osunkwo1 et al., 2021). One promising approach for treating SCD is to induce fetal haemoglobin (HbF), which does not polymerize, thus preventing haemoglobin polymerization (Ware et al., 2017; Sankaran, 2011). Chelucci et al. (2019) developed new phthalimide derivatives (**146-156**) that were evaluated for their antiplatelet effects and TNF-α inhibition. In platelet-based plasma experiments, compound **150** was the most potent for inhibiting adenine diphosphate (ADP), while compounds **149-150** and **153** were the most promising for inhibiting collagen. The most potent analogues, **151** and **154**, exhibited values of 998.8 and 678.5 seconds, respectively, in an in vivo bleeding time assay. In terms of TNF-α inhibition, compounds **148** and **156** demonstrated the highest inhibition values (Chelucci et al., 2019). Lanaro et al. (2017) reported on a phthalimide-based analogue containing the hydroxyurea moiety (**146**) and its effects on HbF production and pro-inflammatory profiles in sickle cell animal models. Compound **146** increased HbF protein levels by 53% compared to the vehicle and exhibited anti-inflammatory properties by reducing the production of inflammatory cytokines in monocyte cultures from SCA mice. Compared to hydroxyurea and dexamethasone, compound **146** exhibited lower values for pro-inflammatory levels, indicating its potential as a promising SCD treatment (Lanaro et al., 2017).

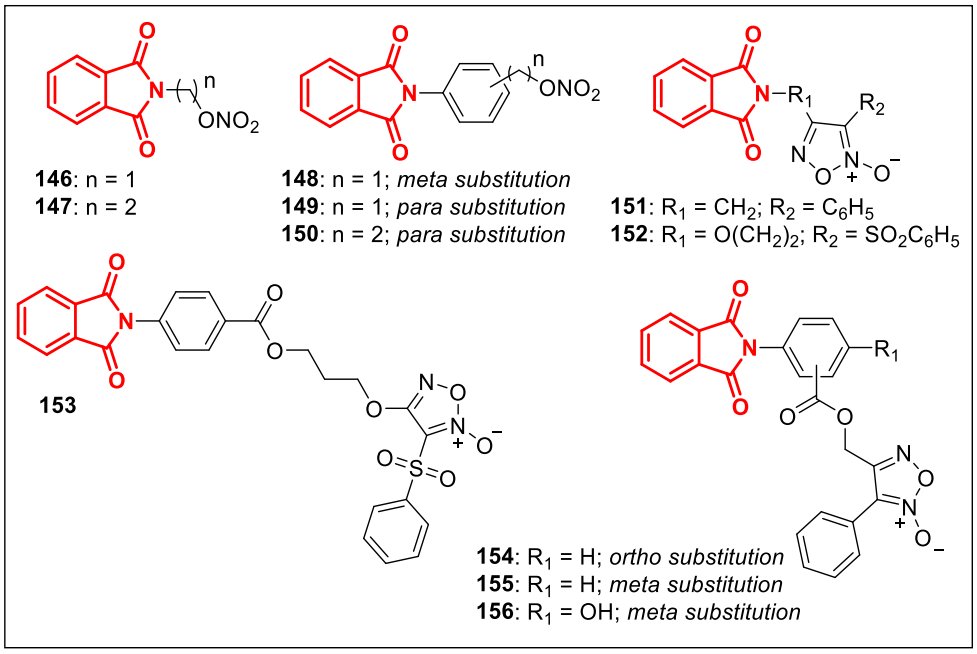

FIGURE 12. Phthalimide derivatives with antiplatelet effects and TNF-α inhibition for SCD treatment.

In 2018, Melo et al. reported seven new phthalimide-furoxan conjugates (**157**–**163**) (Figure 13), and all the compounds were assessed for their antiplatelet properties. The research evaluated the prevalence of ADP and NO in platelet-based plasma using in vitro techniques. Among the derivatives,

compounds **159**–**160** were found to be the most effective in inhibiting ADP, with values of 84.0% and 76.1%, respectively, while analogues **157**–**158** and **162**–**163** had values ranging from 1.2% to 26.5% (Melo et al., 2018). Compounds **157**–**160** were observed to promote nitrite formation via their *N*-oxide moiety. The release of NO was measured by the Griess reaction, and the results, expressed as % of nitrite (NO_2^-; mol/mol), ranged from 16.4% to 30.1%. In the TNF-α inhibitory assay, only compounds **159**–**160** (at 25 µM) were effective, with values of 73.6 and 76.5%, respectively. At 100 µM, compounds **159**–**160** displayed high levels of γ-globin in K562 cell lines after 96 h. Moreover, in an in vitro assay, compound **160** was found to be non-cytotoxic, non-mutagenic, and non-genotoxic (Melo et al., 2018). Later in 2021, the same group reported new analogues (**164**–**169**) (Figure 13) for the treatment of SCD (Mela et al., 2018). Nitrite quantification (Griess reaction) assays demonstrated that compounds **166**–**167** exhibited NO-releasing profiles, with values of 28.1 and 30.3%, respectively, whereas derivatives **164**–**165** and **168**–**169** had values ranging from 0.3% to 6.3%. Treatment of CD34+ cells with compound **168** (at 2.5 µM), hydroxyurea (at 10 µM), and pomalidomide (at 1 µM) for 14 days showed significant induction of HbF by **168** compared to DMSO induction (control). Compound **168** (at 2.5 µM) displayed TNF-α inhibitory effects and reduced TNF-α levels compared to pomalidomide (Mela et al., 2021).

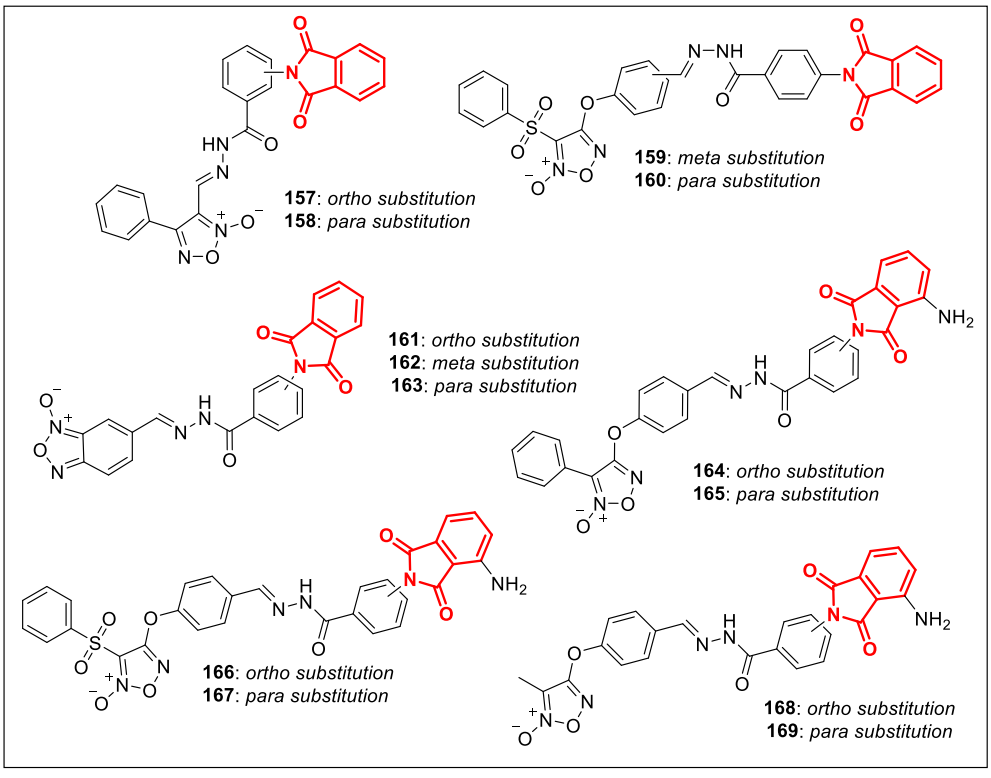

FIGURE 13. Phthalimide-furoxan conjugates discovered for SCD treatment.

5. PHTALIMIDE DERIVATIVES AS ANTICANCER AGENTS

Phthalimide-based derivatives such as thalidomide and pomalidomide are currently used as second-generation (IMIDs) for the treatment of multiple myeloma. In efforts to discover more potent analogues, several studies have investigated the molecular structure of these drugs (Kim et al., 2021; Tehrani et al., 2019; Da Costa et al., 2015; Ali et al., 2012; Schallreuter et al., 2008). For instance, Abdellattif et al. (2021) developed novel oxazinethione-phthalimide derivatives (**170-174**) (Figure 14) with antiproliferative properties against MCF-7, HeLa, and Ovcar-3 cancer cell lines, with IC_{50} values ranging from 12.31 to 21.7 µg/mL for MCF-7 cells and 0.09-15.86 µg/mL for HeLa and Ovcar-3 cells. Moreover, the analogues exhibited low CC_{50} values (89.34-206.5 µg/mL) in normal rhesus monkey kidney epithelial cell lines (Abdellattif et al., 2021). Similarly, Hassanzadeh et al. (2021) synthesized and characterized four new derivatives (**178-181**) (Figure 14) that were evaluated for their inhibition of MCF-7 and HeLa cells, with IC_{50} values ranging from 67.0 to 92.0 µM in MCF-7 cells and 29.0 to 77.0 µM in HeLa cells (Hassanzadeh et al., 2021).

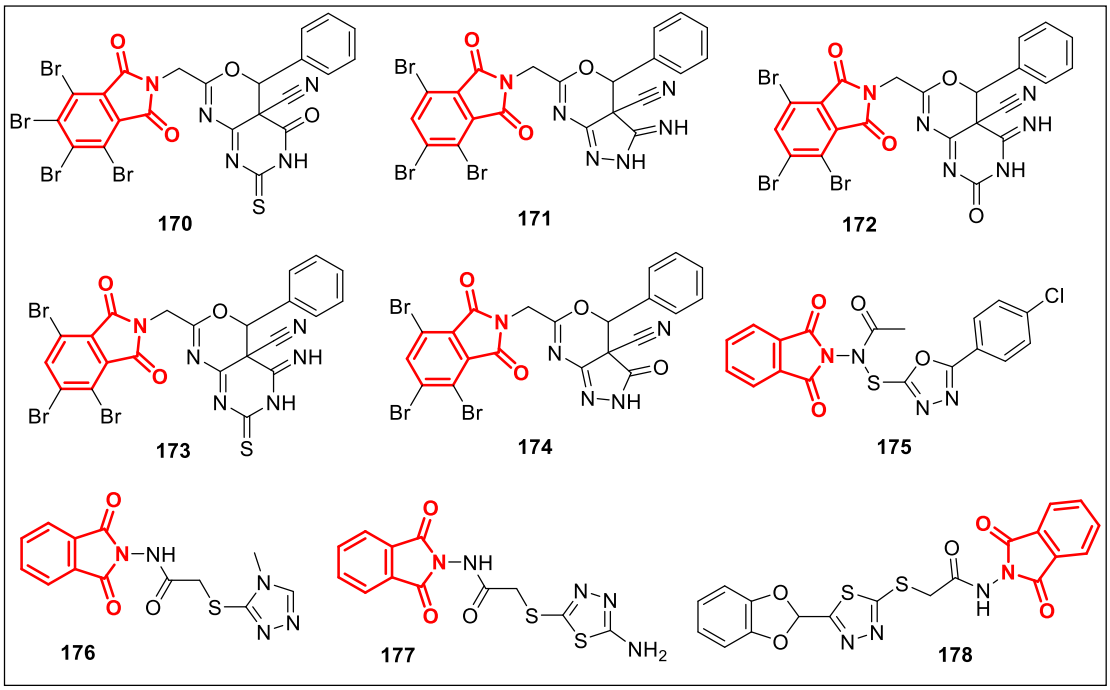

FIGURE 14. Phthalimide derivatives developed as anticancer agents.

Tavallaei et al. (2021) reported 11 novel conjugates containing the 1,3-thiazole and phthalimide moieties and their evaluation against human breast tumor cells (MDA-MB-468 and MCF-7) (Figure 15). Compounds **180-189** showed promising IC_{50} values ranging from 0.6-2.6 µM in MDA-MB-468 cells, while **179** exhibited an IC_{50} value of 4.0 µM. In MCF-7 cells, compounds **181-182** and **184-189** demonstrated potent IC_{50} values of 0.2-1.7 µM, except for **182-183**, which had an IC_{50} value of 4.7 µM (Tavallaei et al., 2021). Philoppes et al. (2019) investigated the antiproliferative effects of 12

novel benzoxazole/benzothiazole derivatives (**190**-**201**) (**Figure 15**) on human breast tumor (MCF-7) and human liver tumor (HepG2) cell lines. The results showed that these compounds had potent IC_{50} values in the range of 0.013-0.468 µM and 0.011-0.724 µM in MCF-7 and HepG2 cells, respectively. Moreover, the cytotoxic activities of these analogues were assessed with CC_{50} values ranging from 28.8-122.3 µM against non-cancerous fibroblast cell lines (WI-38 3T3) (Philoppes et al., 2019). Tumosiene et al. (2020) discovered a new 3-[(4-methoxyphenyl)amino]propanehydrazide-phthalimide conjugate (**202**) (Figure 16) with anticancer activity, which was tested on proliferative cells of MDA-MB-231 and human glioblastoma (U-87). The results showed cell viability values of ≥80% and >70% for MDA-MB-231 and U-87, respectively. Additionally, the compound showed antioxidant effects with a percentage of scavenging activity of 79.62% as evaluated by the DPPH assay (Tumosiene et al., 2020). Donarska et al. (2021) reported novel phthalimide-thiazole conjugates (**203**-**216**) (Figure 17) with antiproliferative activities against MCF-7 cells, human leukemia (MV4–11 cells), and lung carcinoma (A549 cells). Compound **214** was found to be the most potent against MCF-7 cells with an IC_{50} value of 9.06 µM, while **203**-**213** exhibited IC_{50} values in the range of 13.14-62.48 µM. However, **215**-**216** did not show any activity in the MCF-7 and A549 tumor cell lines. In A549 cells, **203**-**205**, **207**-**208**, and **213**-**214** exhibited promising IC_{50} values in the range of 6.69-14.17 µM, while **206** and **209**-**212** had IC_{50} values in the range of 23.38-53.3 µM. Moreover, **203**-**204** and **206**-**211** showed IC_{50} values in the range of 5.56-16.1 µM in MV4-11 cells, and **205** and **212**-**213** exhibited IC_{50} values in the range of 39.69–115.42 µM (Donarska et al., 2021) (Figure 17).

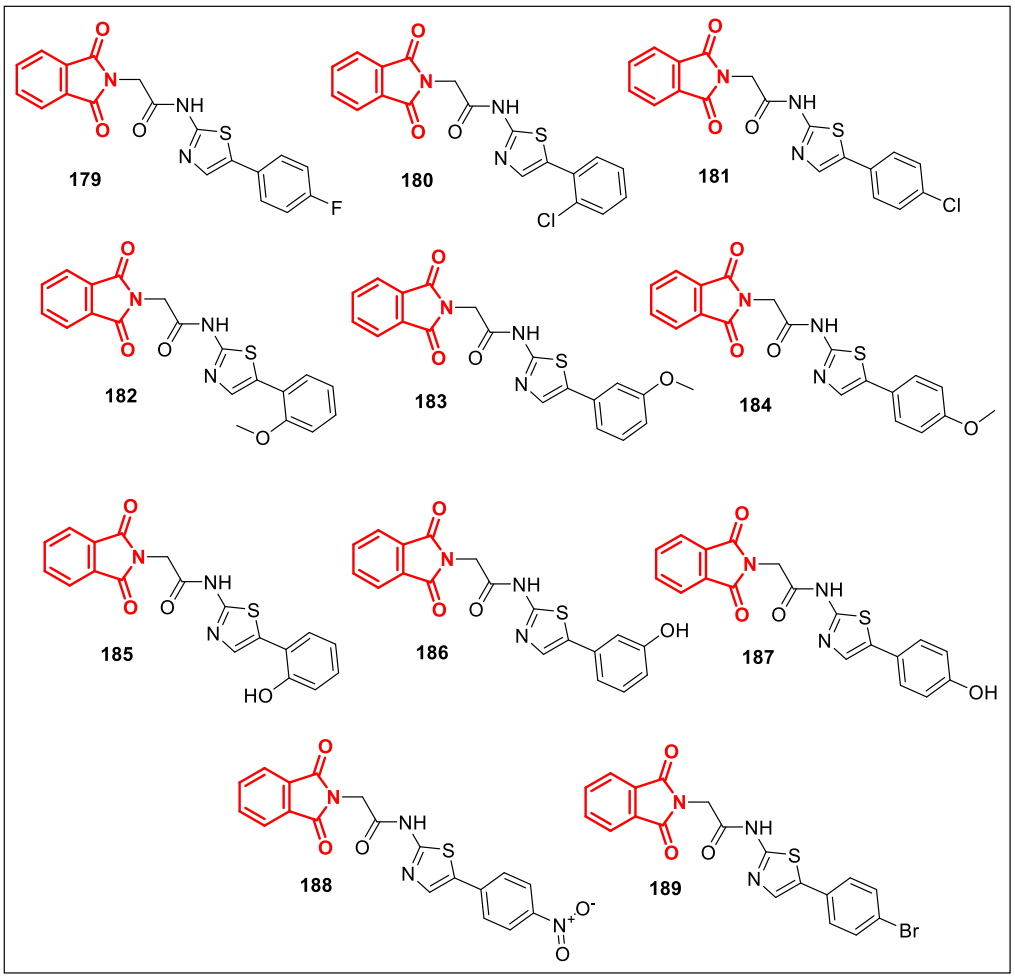

FIGURE 15. Phthalimide-1,3-thiazole conjugates with antiproliferative activities.

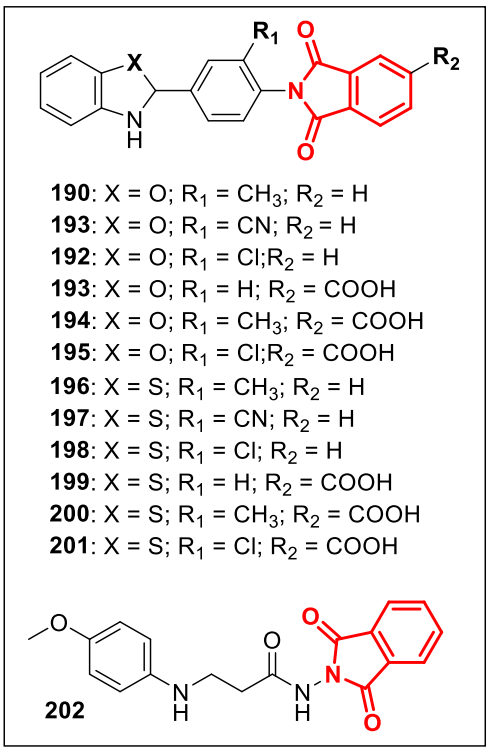

FIGURE 16. Phthalimide derivatives developed as anticancer agents.

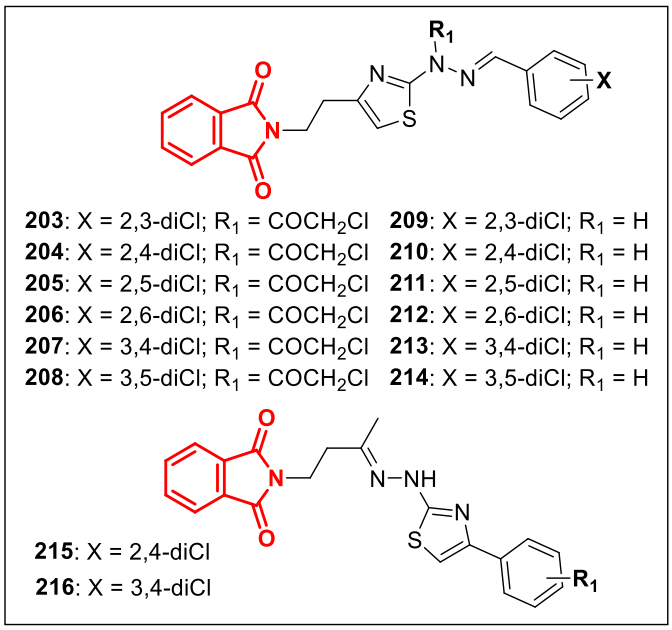

FIGURE 17. Phthalimide-thiazole conjugates as anticancer agents.

In 2019, Cieslak et al. reported new phthalimide derivatives (**217-227**) (Figure 18) showing antitumor activity against HeLa and human leukemia cell lines (K562 and HL-60 cells). Compound **222** demonstrated the most potent activity against HeLa cells with an IC_{50} value of 1.0 µM, while **217-221** and **223-227** exhibited IC_{50} values ranging from 20.0 to >200.0 µM. In K562 cells, three compounds were the most active with IC_{50} values of 2.0 (**219**), 1.0 (**221**), and 1.0 (**222**), respectively. The compounds **217-218**, **220**, and **223-224** presented IC_{50} values in the range of 4.5-12.0 µM, and the compounds **225-227** had IC_{50} values ranging from 25.0 to >200.0 µM. In HL-60 cells, two derivatives exhibited good IC_{50} values of 2.0 (**221**) and 5.0 µM (**222**), while four compounds (**217-220**) had IC_{50} values of >100.0 µM. These derivatives were also evaluated for their cytotoxic activities against human umbilical vein endothelial cell line (HUVEC cells). CC_{50} for these compounds were greater than 100 µM (Cieslak et al., 2019). Later, the same authors reported on 26 new derivatives that were evaluated against HeLa and K562 cancer cell lines. Four compounds (**228-231**) showed promising IC_{50} values in the range of 2.0-3.2 µM and 2.0-5.8 µM against HeLa and K562 tumor cell lines, respectively (Figure 19). Cytotoxic profiles were also assessed using HUVEC cells, and compounds **230-231** exhibited CC_{50} values of 0.4 µM, while derivatives **228** and **229** exhibited CC_{50} values of 30.0 and 3.3 µM, respectively (Cieslak et al., 2021).

In a study conducted by El-Aarag et al. (2017), two new phthalimides (**232-233**) were tested for their antiproliferative effects on A549 tumor cell lines (Figure 19) [102]. Results showed that at 25 µM, these compounds had inhibitory values of 21.1% (**232**) and 34.7% (**233**) in A549 cells. In addition, both compounds reduced cancer mass by 30.11% (**232**) and 53.52% (**233**) in an in vivo murine model.

In an in vitro assay testing the compounds' inhibition of vascular endothelial growth factor165 (VEGF165) and matrix metalloproteinase-2 (MMP-2), compound **233** exhibited greater inhibition of VEGF165 (53.2%) and MMP-2 (52%) compared to compound **232**, which had inhibition values of 42.0% (VEGF165) and 45.0% (MMP-2) (El-Aarag et al., 2017). Belluti et al. (2018) described three new curcumin derivatives (**234**-**236**) that demonstrated promising anticancer effects against PC3 and DU145 cell lines (Figure 19). Compound **234** showed a growth inhibition (GI_{50}) of 7.9 µM and 8.6 µM against PC3 and DU145 cells, respectively. Compounds **235**-**236** exhibited GI_{50} values of 12.4 (**235**) and 16.7 (**236**) in PC3 cells, and GI_{50} values of 12.5 (**235**) and 13.2 µM (**236**) in DU145 cells (Belluti et al., 2019).

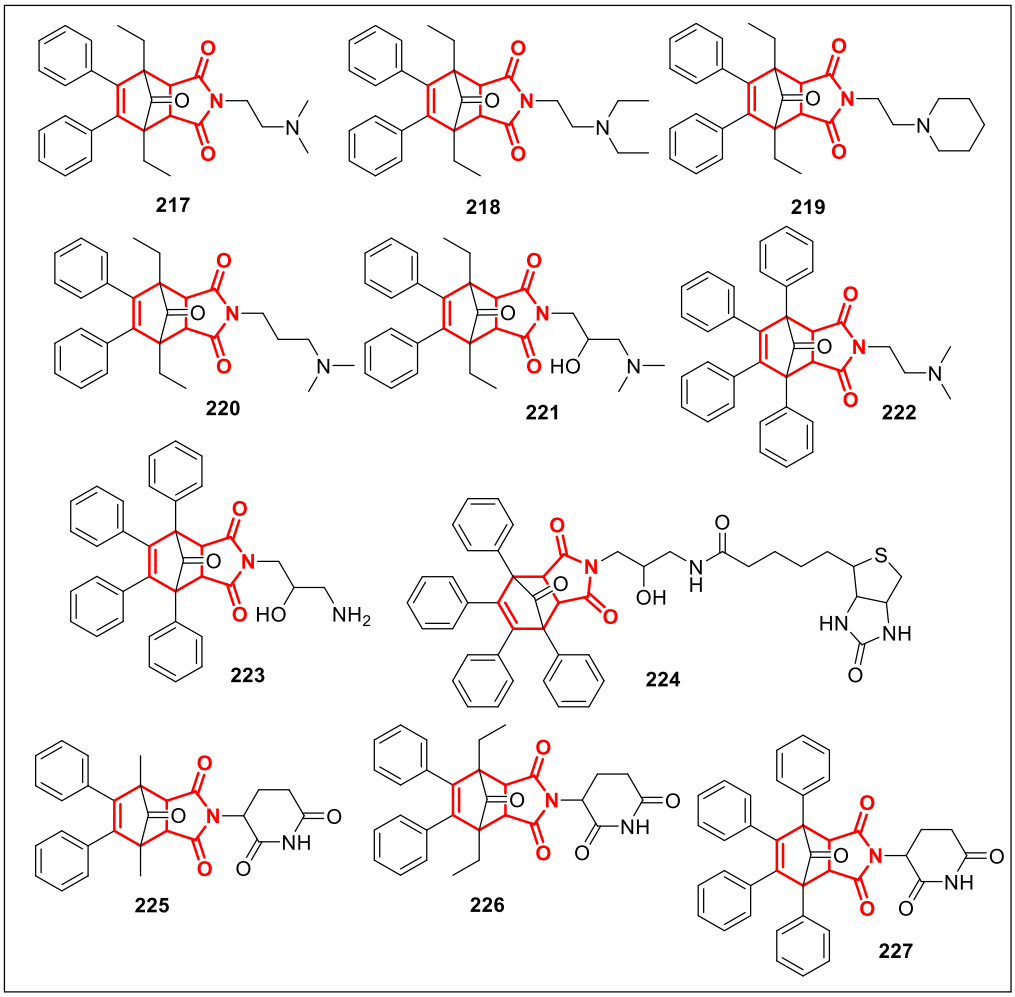

FIGURE 18. Phthalimide-based dicarboximide derivatives with proliferative activity.

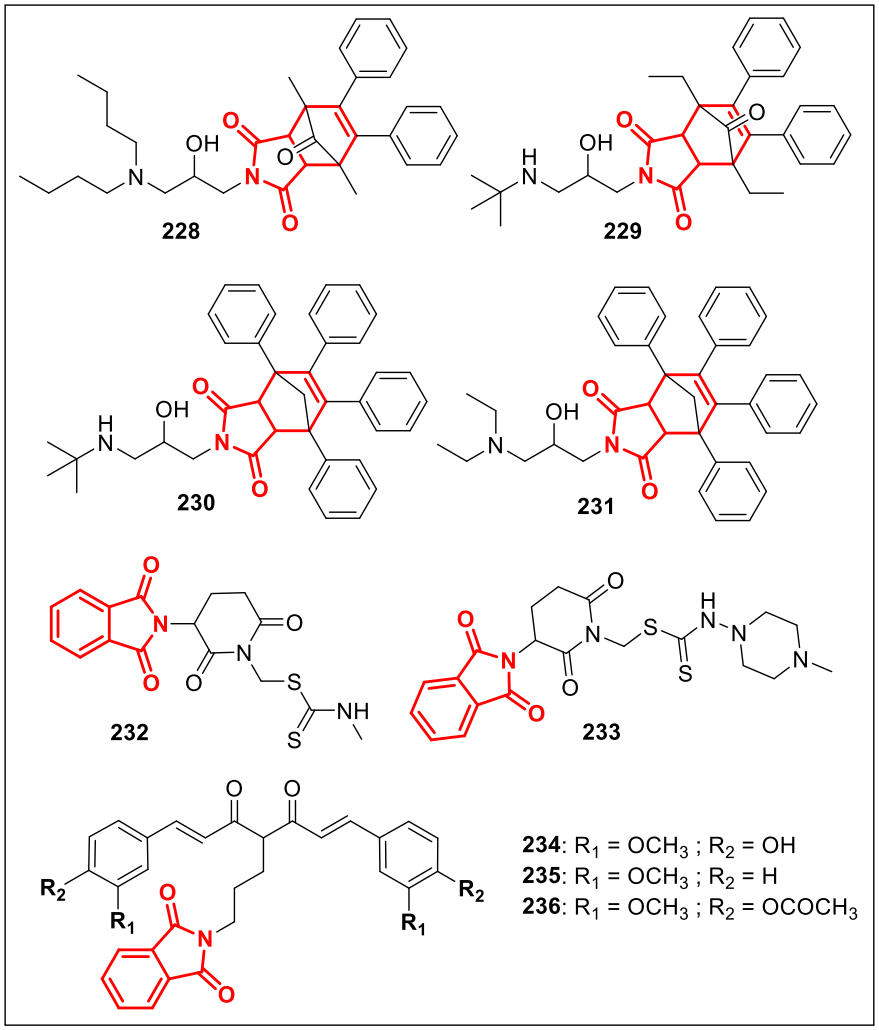

FIGURE 19. Phthalimide derivatives discovered as antitumor agents.

In 2020, Peach et al. discovered novel phthalimide derivatives (**237**–**245**) that showed antiangiogenic effects in an in vivo murine model (Figure 20). These compounds demonstrated strong antiangiogenic activities in an in vivo aortic ring assay, with growth inhibitory values ranging from 100.57 to 182.51% (Peach et al., 2020). Similarly, Steinebach et al. (2018) reported 30 new compounds and found six novel polyfluorinated phthalimide derivatives (**246**–**251**) that exhibited antiangiogenic effects using in vivo models (Figure 20). Compound **247** showed the most potent outgrowth value of 81%, while compounds **246** and **248**–**251** exhibited values in the range of 10–59% (Steinebach et al., 2018).

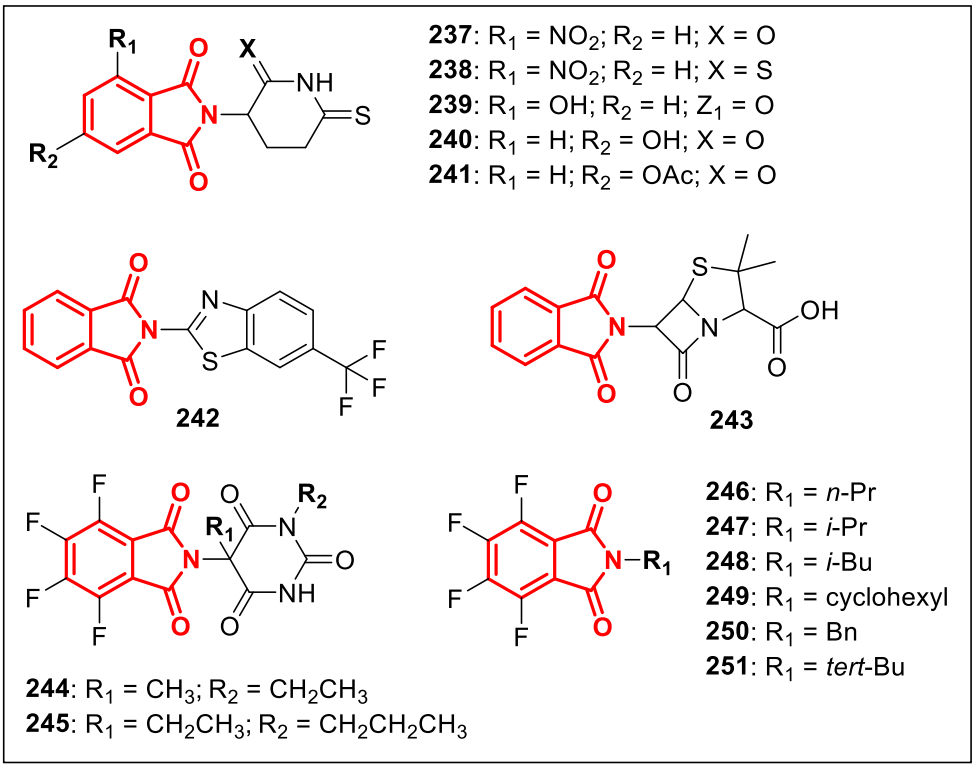

FIGURE 20. Phthalimide derivatives with antiangiogenic effects.

6. PHTALIMIDES AS ANTIBACTERIAL AND ANTIFUNGAL AGENTS

Compounds containing phthalimide moiety have been extensively investigated for their antimicrobial activity. *N*-substituted phthalimides have demonstrated strong antibacterial activity, with minimal inhibitory concentrations (MICs) comparable to clinically used antibiotics (Orzesko et al., 2007a; 2007b). Recently, Durairaju et al. (2021) developed new phthalimide-chalcone conjugates (**252**–**254**) (Figure 21) with antibacterial and antifungal effects against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger*. At 100 µg/mL, the compounds displayed significant zone of inhibition values: 10.0 (**252**), 16.0 (**253**), and 18.0 mm (**254**) against *E. coli*; 10.0 (**252**), 18.0 (**253**), and 23.0 mm (**254**) against *S. aureus*; 12.0 (**252**), 12.0 (**253**), and 22.0 mm (**254**) against *C. albicans*; and 18.0 (**252**), 20.0 (**253**), and 24.0 mm (**254**) against *A. niger* (Durairaju et al., 2021).

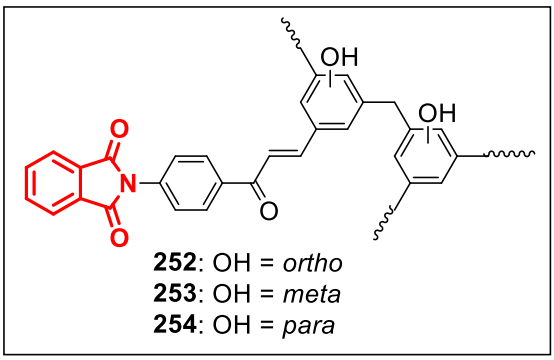

FIGURE 21. Phthalimide-chalcone conjugates with antibacterial and antifungal activity.

In 2016, Rateb and colleagues evaluated new phthalimide conjugates (**255**-**263**) for their antimicrobial activity against Gram-positive and Gram-negative bacteria, fungi, and *Mycobacterium tuberculosis* (Figure 22) (Rateb et al., 2016). The compounds **255**-**256** and **258**-**263** demonstrated MIC values in the range of 1.95-31.25 µg/mL against Gram-positive bacteria, while the most active derivative **257** exhibited a MIC value of 0.49 µg/mL against *Streptococcus pneumoniae*. Similarly, compounds **255**-**256** and **259**-**263** showed MICs in the range of 0.95-3.9 µg/mL against *Bacillus subtilis*, and the most potent analogues **257**-**258**, exhibited MIC values of 0.49 µg/mL against *B. subtilis*. Against *Staphylococcus aureus*, compounds **255**-**256** and **258**-**263** exhibited MIC values in the range of 1.95-31.25 µg/mL, and the most promising derivative **257** demonstrated a MIC value of 0.49 µg/mL. For Gram-negative bacteria, the compounds **255**-**256** and **259**-**263** exhibited MIC values in the range of 0.98-3.9 µg/mL, while the most active derivative **257** showed a MIC value of 0.49 µg/mL against *Escherichia coli*. Similarly, the most potent analogues **257** and **258** demonstrated MIC values of 0.49 µg/mL against *Salmonella typhimurium*, while compounds **255** and **258**-**263** exhibited MIC values in the range of 0.98-31.25 µg/mL. Regarding antifungal activity, compounds **255**-**256** and **259**-**263** exhibited MIC values in the range of 1.95-31.25 µg/mL against *Aspergillus fumigatus*, and compounds **257**-**258** showed MIC values of 0.98 µg/mL. Similarly, compounds **255**-**256** and **258**-**263** demonstrated MIC values in the range of 0.98-31.25 µg/mL against *Syncephalastrum racemosum*, while compounds **257** and **258** exhibited MIC values of 0.49 µg/mL. Finally, compounds **255**-**256** and **258**-**263** showed MIC values in the range of 0.98-15.63 µg/mL against *Geotricum candidum*, and **257** demonstrated a MIC value of 0.49 µg/mL (Rateb et al., 2016).

Othman and colleagues (2019) reported on novel phthalimide derivatives (**264**-**368**) that demonstrated antibacterial activity against both Gram-positive (*S. pneumoniae* and *B. subtilis*) and Gram-negative (*P. aeruginosa* and *E. coli*) bacteria, as well as antifungal activity against *A. fumigatus*. The most potent derivative, **264**, exhibited an MIC of 1.98 µg/mL against *S. pneumoniae* and 0.98 µg/mL against *B. subtilis*, while compounds **265**-**368** showed MICs in the range of 3.9-7.81 µg/mL and 1.95-7.81 µg/mL against Gram-positive bacteria, respectively. Against Gram-negative bacteria, derivatives **265**-**368** displayed MICs ranging from 15.63-62.51 µg/mL, but the most promising compound **264** demonstrated an MIC of 0.98 µg/mL against *P. aeruginosa*. Compounds **266**-**268** were particularly potent against *E. coli*, with MICs ranging from 1.95-3.9 µg/mL, while compounds **264** and **265** exhibited the most potent activity, with an MIC of 0.49 µg/mL. Regarding antifungal activity, compounds **264**-**268** showed MICs ranging from 1.95-15.63 µg/mL against *A. fumigatus* but did not exhibit activity against *C. albicans* (Othman et al., 2019).

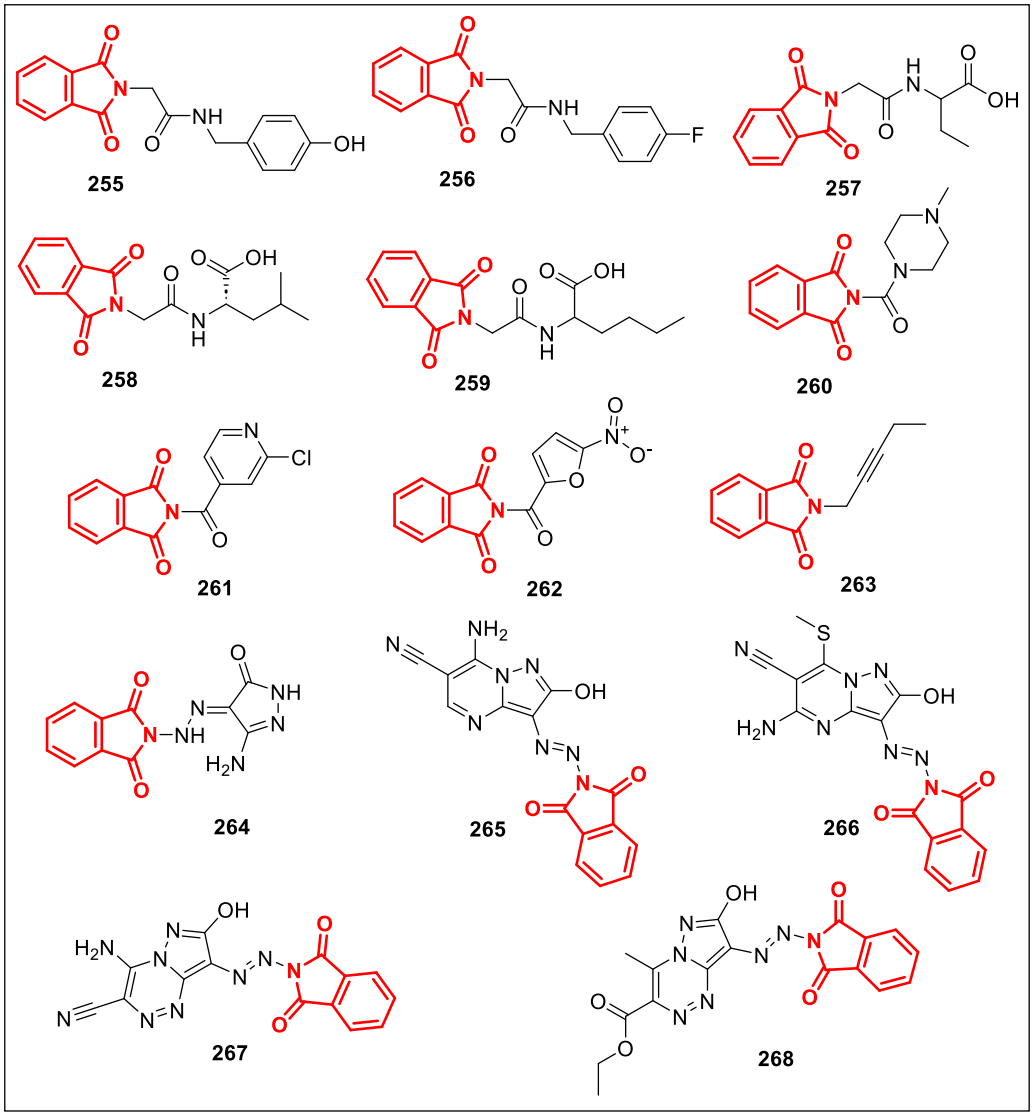

FIGURE 22. Phthalimide derivatives identified as antimicrobial agents.

In 2020, Koshelev et al. discovered a new phthalimide (**269**) that exhibited antibacterial properties against several bacterial strains (Figure 23). The compound showed growth inhibition values of 16.81% against *S. aureus*, 7.56% against *E. coli*, 20.34% against *Klebsiella pneumonia*, 10.92% against *Acinetobacter baumannii*, and 12.56% against *P. aeruginosa* (Koshelev et al., 2020). In the same year, Amiranashvili et al. (2020) reported a 5-α-androstane derivative (**270**) with antibacterial and antifungal effects (Figure 23). The analogue displayed antibacterial activity with MIC values of 0.2 mg/mL against *S. aureus*, 0.037 mg/mL against methicillin-resistant *S. aureus* (MRSA), 0.2 mg/mL against *Listeria monocytogenes*, 0.1 mg/mL against *P. aeruginosa*, 0.2 mg/mL against *P. aeruginosa* resistant, 0.05 mg/mL against *E. coli*, 0.15 mg/mL against *E. coli* resistant, and 0.2 mg/mL against *S. typhimurium*. Furthermore, the compound demonstrated antifungal effects with MIC values of 0.037 mg/mL against *A. fumigatus*, 0.015 mg/mL against *Aspergillus versicolor*, 0.037 mg/mL against *A. niger*, 0.015 mg/mL against *Penicillium funiculosum*, 0.037 mg/mL against *Penicillium*

ochrochloron, and 0.3 mg/mL against *Penicillium verrucosum* var. cyclopium (Amiranashvili et al., 2020). In 2019, Arif et al. reported a new phthalimide derivative (**271**) with antimicrobial activities against *E. coli* and *Streptococcus mutants* (Figure 23). The compound exhibited minimum bactericidal concentration (MBC) values of 100 µg/mL against *E. coli* and 150 µg/mL against *S. mutants* (Arif et al., 2019). Hewage et al. (2019) described seven new fluoroquinolone-phthalimide conjugates (**272**–**278**) in the same year. Compounds **273** and **275**–**278** exhibited IC_{50} values in the range of 121.0–258.0 µM against *P. aeruginosa* (Figure 23) (Hewage et al., 2019). Phatak et al. (2019) reported the phthalimide derivatives (**279**–**390**) (Figure 23) for their anti-Mtb activity. Compounds **282** and **290** showed MIC values of 12.5 µg/mL, while compounds **279**–**281** and **283**–**289** exhibited a MIC value of 25.0 µg/mL (Phatak et al., 2019).

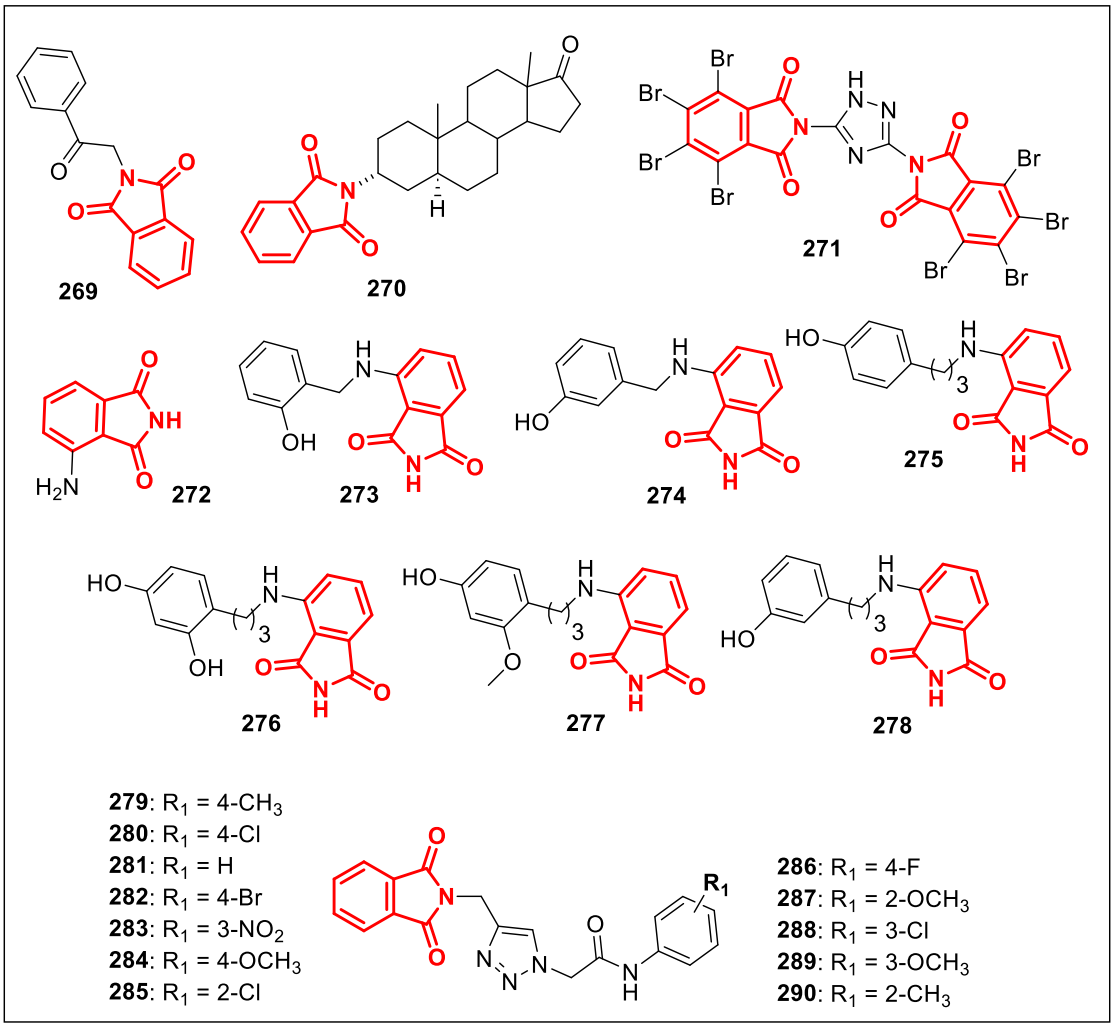

FIGURE 23. Phthalimide derivatives with various antimicrobial activities.

7. PHTALIMIDES AS ANTIPARASITIC AGENTS

7.1. Anti-*Plasmodium* spp activity

In a recent study, phthalimide derivatives were found to show promising antimalarial activity, especially those containing chiral phthalimides functionalized with cyclic amines. A symmetric structure of phthalimides containing isoleucine was found to be essential for their antimalarial activity (Singh et al., 2015). In a study conducted by Rani et al. (2020), phthalimide derivatives (**291**-**310**) were evaluated for their antimalarial activity against *Plasmodium falciparum*. Compound **308** had an IC_{50} value of 0.006 µM and a selective index (SI) of 4216, while compounds (**291**-**307, 309**-**310**) showed IC_{50} values in the range of 0.01–0.37 µM (Rani et al., 2020). In another study, Kumar et al. (2017) synthesized more than 30 phthalimides and found that compounds (**311–313**) were the most active against malaria. These compounds had IC_{50} values ranging from 0.7 to 0.9 µM and were effective in reducing parasitemia levels in an in vivo model infected with *Plasmodium berguei* (Kumar et al., 2017). Okada-Junior et al. (2018) developed 12 novel phthalimide conjugates, of which two analogues (**314** and **315**), showed IC_{50} values of 4.2 and 6.8 µM against *P. falciparum* 3D7 strain, respectively (Okada-Junior et al., 2018).

7.2. Anti-Kinetoplastid activity

Phthalimide derivatives are promising antiparasitic agents, with potent anti-kinetoplastid activity (Kasséhin et al., 2015). Phthalimides were evaluated against *Trypanosoma cruzi* and six promising compounds (**316–321**) (Figure 25) were identified with IC_{50} values in the range of 4.0–12.2 µM against trypomastigote forms of *T. cruzi* (Y strain). In addition, compounds **317–321** presented IC_{50} values in the range of 103.4–269.2 µM against the epimastigote forms, while compound **316** exhibited an IC_{50} value of 14.2 µM (Gomes et al., 2016). In 2020, the same group reported three new phthalimide derivatives (**322–324**) (Figure 25) with IC_{50} in the range of 3.6–4.9 µM against *T. cruzi* (Y strain) (Gomes et al., 2020).

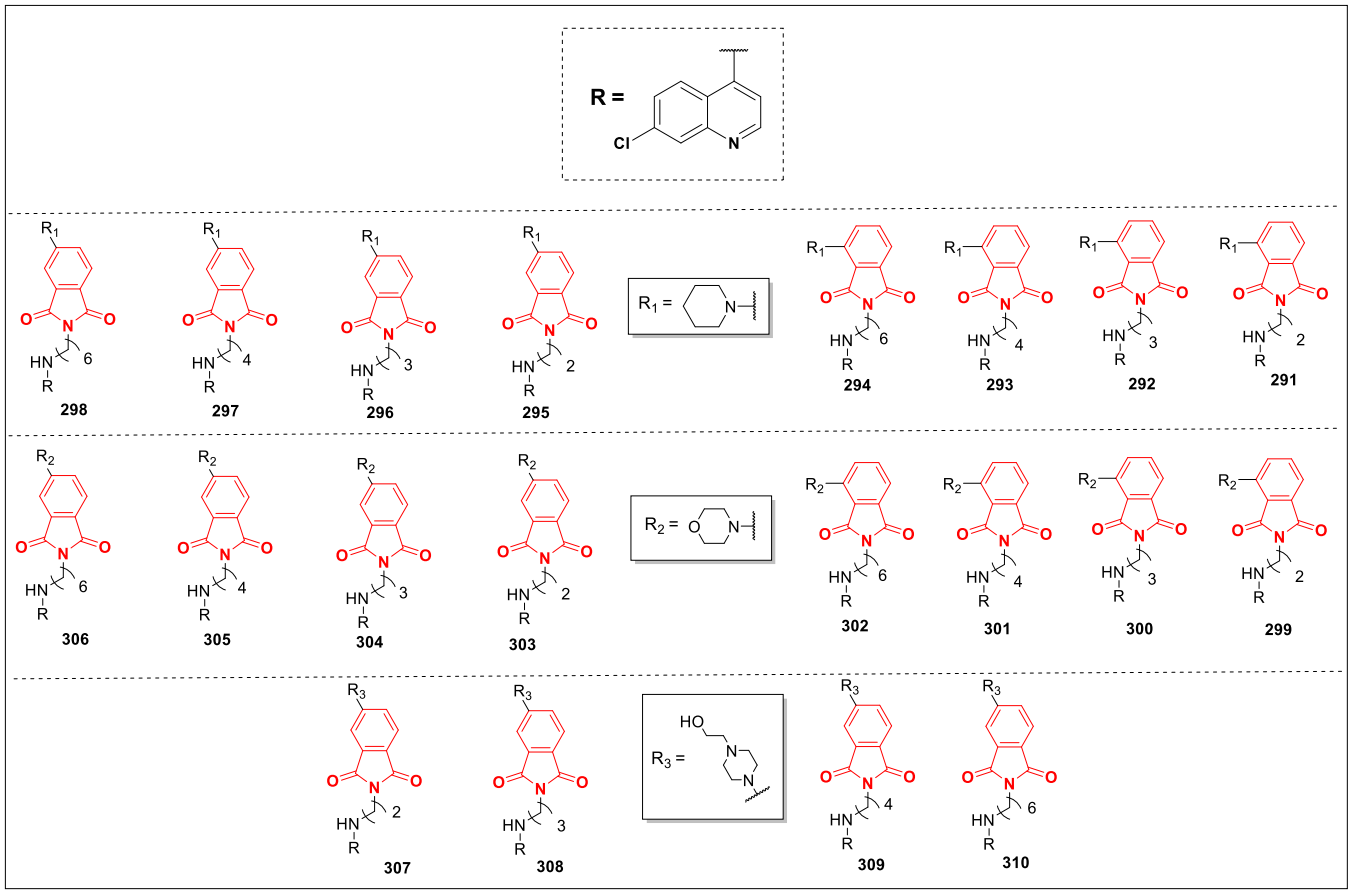

FIGURE 24. Phthalimide derivatives identified as anti-*P. falciparum*.

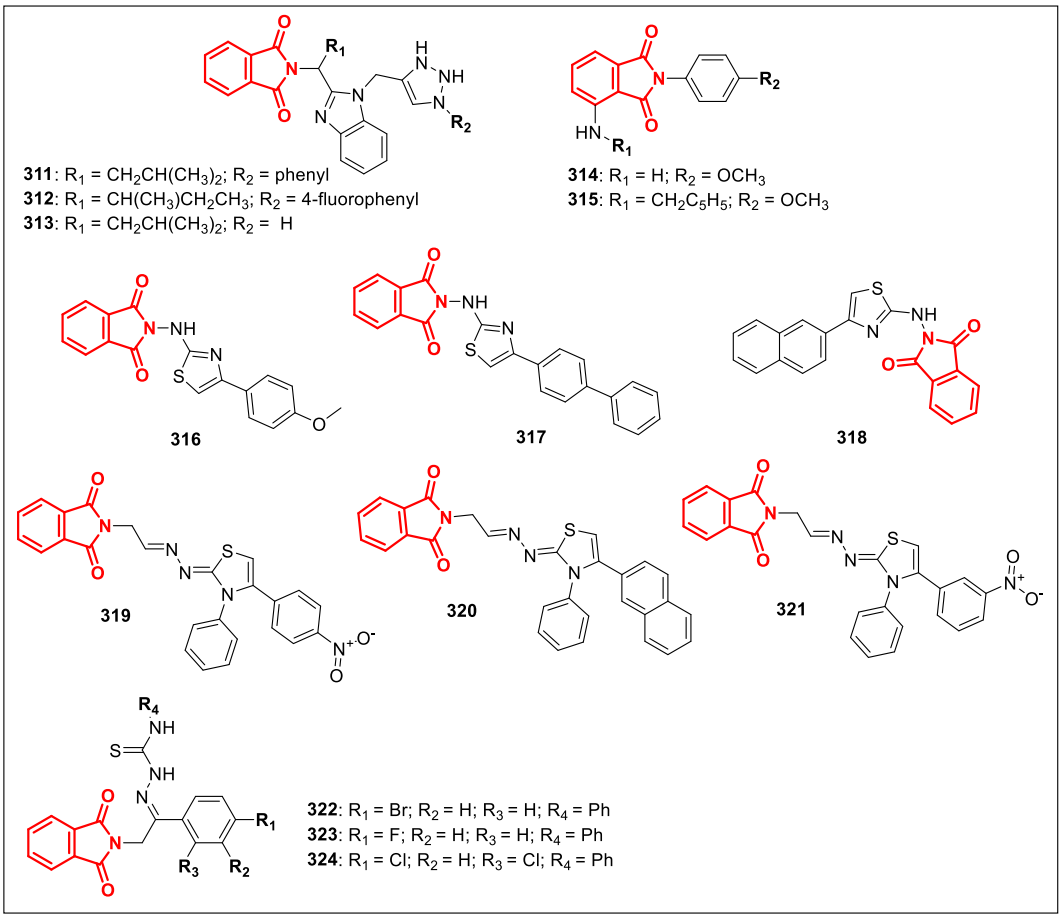

FIGURE 25. Phthalimide derivatives as anti-*T. cruzi* agents.

In a study conducted by Presser et al. (2018), the phthalimide derivatives (**325**-**326**) were identified as anti-*Trypanosoma brucei rhodesiense* (STIB900 strain) and anti-*P. falciparum* (NF54 strain) agents. The analogues showed promising IC_{50} values of 1.58 µM (**325**) and 5.71 µM (**326**) against *T. brucei*, and 3.24 µM (**325**) and 3.78 µM (**326**) against *P. falciparum* (Presser et al., 2018). Aliança et al. (2017) investigated thiazole derivatives for their anti-*Leishmania infantum* activity and identified compound **327** (Figure 26) with an IC_{50} value of 9.8 µM against the promastigote form and 15.5 µM against the amastigote form (Aliança et al., 2017).

7.3. Anti-Toxoplasma activity

The incorporation of metal complexes has been shown to enhance the biological activity of numerous compounds (Peter & Aderibigbe, 2019). For instance, it was demonstrated that the addition of a ferrocenyl moiety resulted in an inhibitory effect against two strains of *Toxoplasma gondii* (Baramee et a., 2006). Carradori et al. (2017) described three new ferrocene derivatives (**328**-**330**) with biological activity against *Toxoplasma gondii* (Figure 26). The compounds exhibited promising IC_{50} values of 88.0 µM (**328**), 78.0 µM (**329**), and 82.0 µM (**330**). Furthermore, compound **330** was evaluated for its ability to prevent the parasite-induced host cell intake of tachyzoites and it showed

a significant reduction in invasion with values <1 tachyzoites per vacuole, whereas sulfadiazine showed a value >1.0 tachyzoites per vacuole (Carradori et al., 2017).

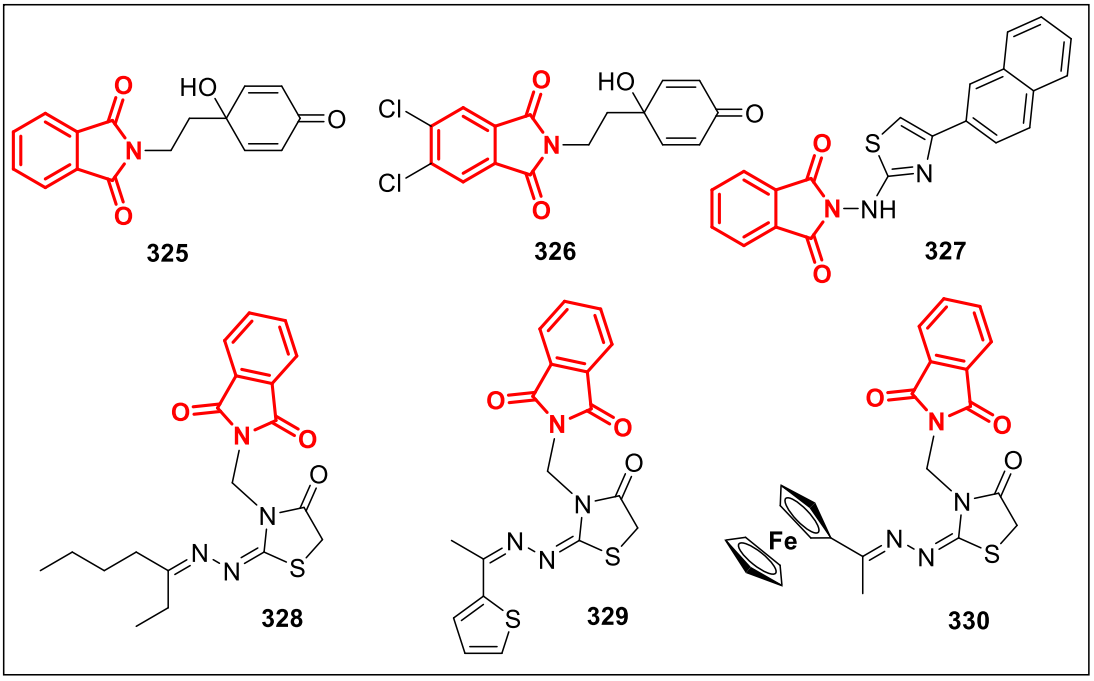

FIGURE 26. Phthalimide derivatives with activity against *T. brucei*, *P. falciparum*, and *Toxoplasma gongii*.

8. PHTALIMIDES AS ANTHELMINTIC AGENTS

In a recent study, a phthalimide-thiazol conjugate was found to exhibit potent schistosomicidal activity, causing significant ultrastructural alterations in both male and female worms and leading to the destruction of the tegument (Santiago et al., 2014). Singh et al. (2020) reported 47 triazole derivatives with anthelmintic activity. Compounds (**331**–**342**) showed potent activity at 72 h, with 100% inhibition against some forms of *Schistosoma mansoni* (Figure 27). Compounds **331**, **335**, and **341** showed promising inhibitory effect at 24 h, with inhibition values of 100% against adult forms of *S. mansoni*. Compounds **332**–**334**, **336**–**340**, and **342** reported inhibition values in the range of 25%–75% (Singh et al., 2020). In another study, Oliveira et al. (2018) evaluated the anti-*S. mansoni* effects of phthalimides **343**–**346** (Figure 27) over a longer period of 192 h. Compounds (**344**–**346**) showed 100% inhibition against adult forms of *S. mansoni*, while compound **343** exhibited inhibition of 54%. Moreover, the four compounds were evaluated for their cytotoxicity effects in spleen cells of Balb/c mice, with CC_{50} values in the range of 138.09–302.97 µM (de Oliveira, 2018).

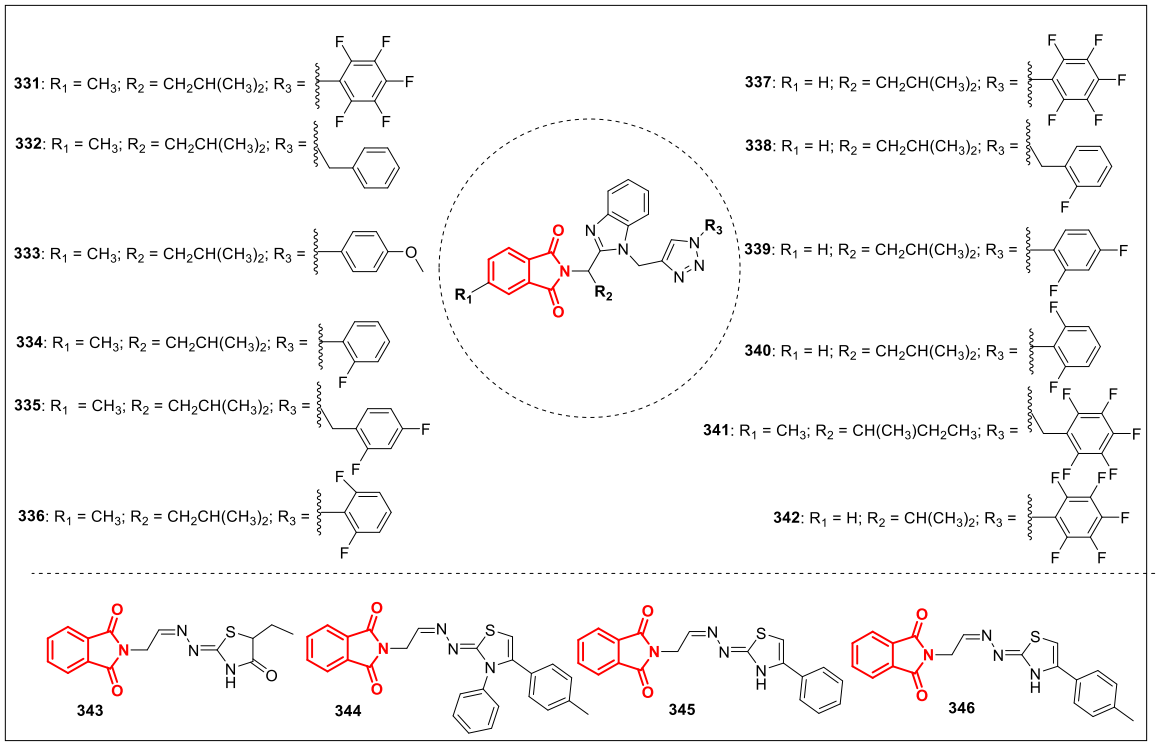

FIGURE 27. Phthalimide derivatives as anthelmintic agents.

9. PHTALIMIDES AS ANTIVIRAL AGENTS

Numerous drug targets for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at different stages of the virus life cycle have been identified (Sanders et al., 2020). The most extensively explored target is the chymotrypsin-like protease (3CLpr° or Mpr°), which is the main protease of the virus (Jin et al., 2020). Another significant protease in the virus life cycle is the papain-like protein (PLpro), which has also been explored as a drug target (Ma & Wang, 2022). Inhibitors of two transmembrane serine proteases (TMPRSS2) and the angiotensin 2 converting enzyme (ACE-2) receptor proteins can prevent virus entry into cells (Ragia, & Manolopoulos, 2020). Phthalimide derivatives have been identified through in silico studies against various targets of SARS-CoV-2, including the Mpr°, PLpro, and ACE-2 proteins. Gupta et al. (2021) conducted docking studies with phthalimide **347** (Figure 28) against Mpr°. One of the phthalimide moieties of the molecule displayed H-bond interactions with amino acid residues Gln189, Thr26, and Ser46 through the C=O group, while the other phthalimide moiety showed alkyl interactions with residues Cys44, Cys145, His41, Leu27, and Met49 through the methyl group. Compound **347** was assessed for anti-SARS-CoV-2 activity using an in vitro spread assay and exhibited an IC_{50} value of 14.71 µM (Gupta et al., 2021). Phthalimides with anti-HIV activity have also been identified. Tricyclic phthalimide analogues demonstrated potent HIV integrase inhibition, with IC_{50} values in the nanomolar range (Verschueren et al., 2005). Wadhwa et al. (2019) reported phthalimides and their HIV-1 integrase (IN) inhibitory activity. Compounds **348** and **349** (Figure 28) exhibited IC_{50} values of 4.01 and 3.90 µM, respectively

(Wadhwa et al., 2019). Dantas et al. (2021) identified triazole derivatives with anti-Zika virus (ZIKV) activity. Compound **350** showed promising results against ZIKV compared to the non-treated control. Compound **350** displayed 91.1% viral inhibition, with an IC_{50} value of 146.0 µM (Figure 28). Molecular dynamics studies suggested significant binding affinity for the NS5 RdRp protein of ZIKV (Dantas et al., 2021).

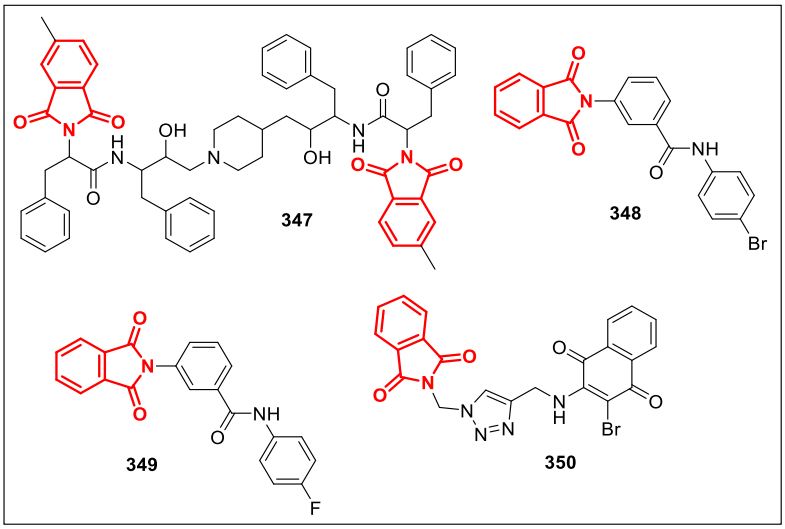

FIGURE 28. Phthalimide derivatives as antiviral agents.

10. PHTALIMIDES AS ANTIDIABETIC AGENTS

Diabetes mellitus is a chronic condition affecting an increasing number of people in both developed and developing countries (Reimann et al., 2009). Type 2 diabetes mellitus (DM2) is characterized by a group of metabolic disorders, such as insulin resistance and glucose homeostasis variations, resulting in hyperglycemia (Tahrani et al., 2011). In a recent study by Mourad et al. (2021), dihydropyrimidine-phthalimide conjugates (**351**–**360**, Figure 29) were identified as promising dipeptidyl peptidase-4 (DPP-4) inhibitors, a common target in MD2 therapy. In an in vitro assay, compounds **357** and **359** exhibited the most potent effect against human recombinant DPP-4, with IC_{50} values of 0.51 and 0.66 nM, respectively. Compounds (**351**–**356** and **358**, **360**) showed IC_{50} values in the range of 1.42–14.71 nM (Figure 29). Moreover, these compounds were evaluated against dipeptidyl peptidase-8 (DPP-8) and dipeptidyl peptidase-9 (DPP-9) with IC_{50} values > 100 µM. The cytotoxicity profile of these compounds was determined using normal liver LO2 cells at concentrations of 10, 30, and 50 µM, where they showed 72.57–101.2% cell viability. In an in vivo DPP-4-based model, compounds **357** and **359** showed greater activity than the control group. Furthermore, compounds **355**, **357**, and **359** demonstrated promising glycemic control activity in an in vivo model (Mourad et al., 2021).

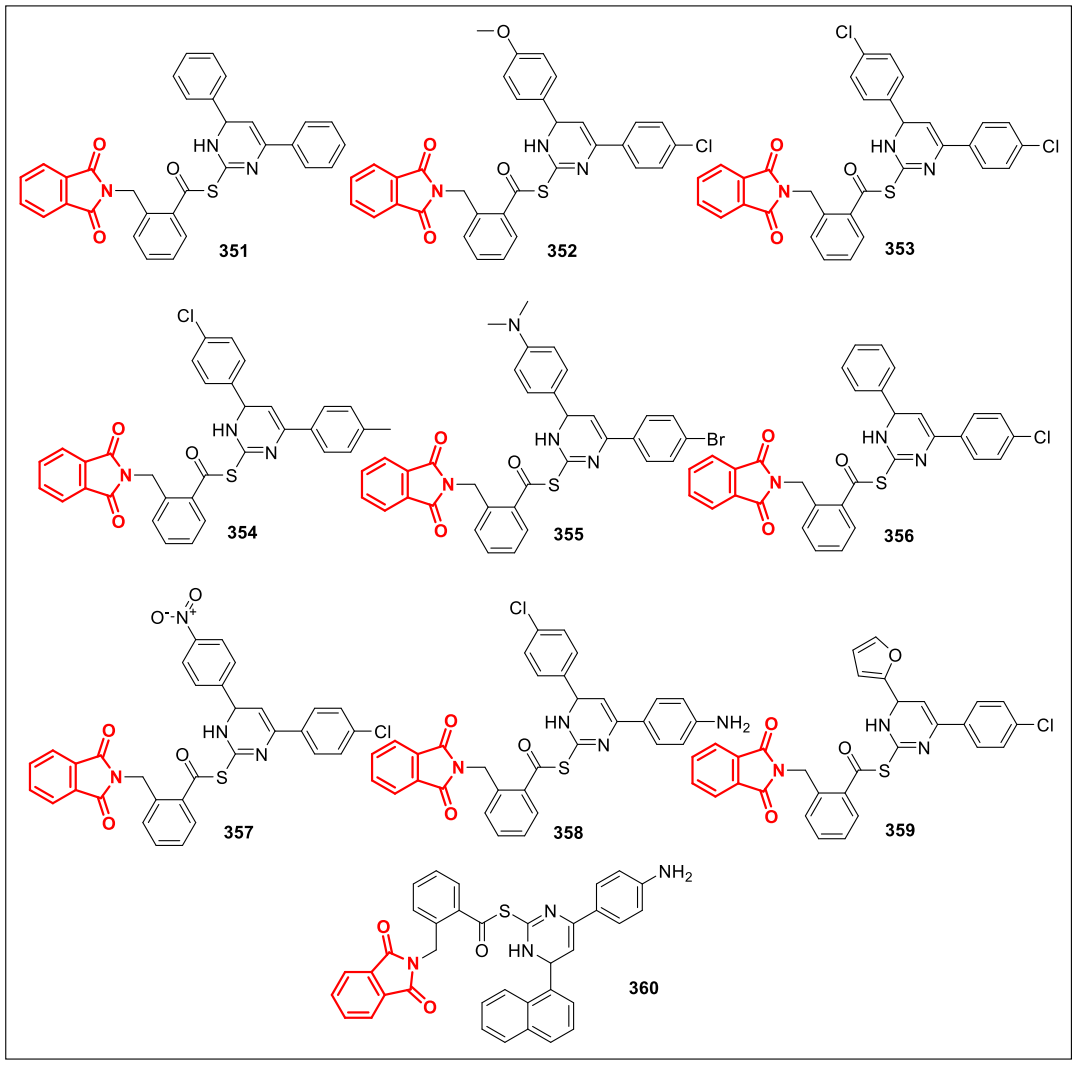

FIGURE 29. Phthalimide derivatives developed for the treatment of diabetes mellitus.

El-Zahabi et al. (2019) reported sulfonylurea derivatives with antihyperglycemic properties and exhibiting activities in an STZ-induced hyperglycemic animal model. Compounds (**361–366**) (Figure 30) reduced blood glucose profiles by 21.22–24.43%, and their relative potency (RP) compared to the standard drug glibenclamide was in the range of 0.73–0.83 (El-Zahabi et al., 2019). Wang et al. (2017) reported phthalimide-rhodanine conjugates (**367–370**) with promising effects against the α-glucosidase enzyme, presenting IC_{50} values in the range of 5.44–7.91 μM (Figure 30) (Wang et al., 2017).

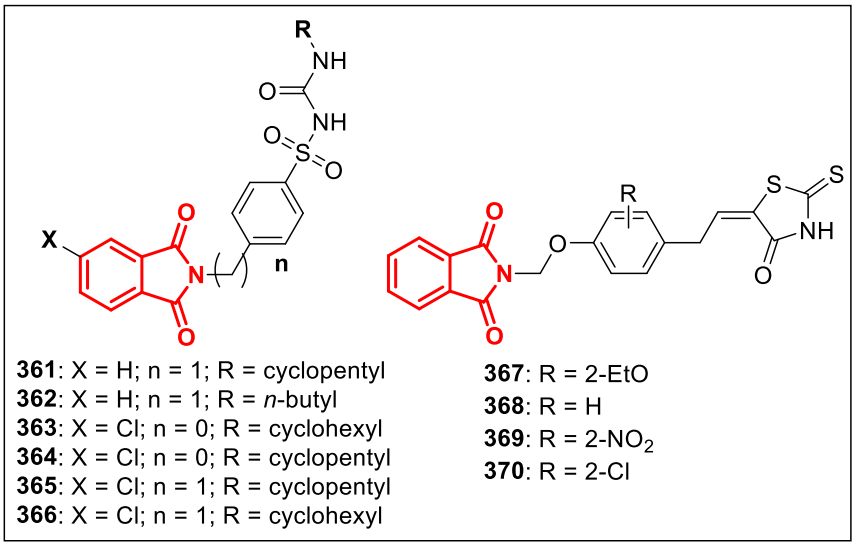

FIGURE 30. Phthalimide with antihyperglycemic effects and anti-α-glucosidase activity.

11. CONCLUSION

This review provides an overview of the recent advances in the medicinal chemistry of phthalimide-based compounds, revealing the use of such scaffold for multifaceted therapeutic applications, including anti-inflammatory, anticancer, antibacterial, antifungal, antimycobacterial, and antiviral properties. Among the well-established effects, the use of phthalimide to design anti-inflammatory and analgesic compounds is the most found in the literature. Part of this effect is due to the ability of several derivatives to decrease the levels of pro-inflammatory cytokines, such as tumor necrosis factor alpha.

Under pharmacodynamic perspective, phthalimide is a privileged scaffold with ability to interact by hydrogen bonding through the carbonyl of imide and form hydrophobic interactions due to the aromatic subunit. It also commonly increases the lipophilicity of molecules, despite of this ability to hydrolyse in vivo in biological medium. Concerns about the teratogenic effect remains due to the stigma of carrying a thalidomide subunit, however, several studies associated the teratogenic effects with the glutarimide subunit, which is able to interact with cereblon (CRBN). Despite of this knowledge, assays to evaluate mutagenic and teratogenic effects should be to carry out in order to show the absence of toxicity of phthalimide analogues, mainly for those that make progress to pre-clinical studies.

This review article emphasizes the versatility of phthalimide as a scaffold for drug discovery due to its broad activity across various biological pathways, acceptable toxicity levels, and straightforward chemistry. The analysis of physicochemical parameters of the most active compounds described here demonstrates that a significant majority of the compounds meet Lipinski's rule criteria, indicating their potential as drug candidates. This information provides valuable insights for medicinal chemists

to refine, modify and explore phthalimide-based compounds as a privileged scaffold, enhancing their pharmacokinetic and pharmacodynamic properties.

ABBREVIATIONS

FDA: US Food and Drug Administration; ENL: erythema nodosum leprosum; COX-1: cyclooxygenase-1; COX-2: cyclooxygenase 2; CRBN: E3 ubiquitin ligase cereblon; PROTAC: proteolysis-targeting chimera; RA: rheumatoid arthritis; ROS: reactive oxygen species; RNS: reactive nitrogen species; CCl_4: carbon tetrachloride; MDA: malondialdehyde; NO: nitric oxide; VEGF: vascular endothelial growth factor; TNF-α: tumor necrosis factor-alfa; NF-κB: nuclear factor kappa B; SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase; LPS: lipopolysaccharide; MAPKs: mitogen-stimulated protein kinases; CNS: central nervous system; AD: Alzheimer's disease; ACh: acetylcholine; AChEi: acetylcholinesterase inhibitors; AChEi: acetylcholinesterase; *Ee*AChE: acetylcholinesterase *electric eel*; EqBuChE: butyrylcholinesterase from equine serum; RatBuChE: butyrylcholinesterase from rat serum; HuBuChE: butyrylcholinesterase from human serum; IL-10: interleukins 10; IL-6: interleukins 6; BBB: blood-brain barrier; PTZ: pentylenetetrazole; GABAA: gamma-aminobutyric acid A; GABAAR: gamma-aminobutyric acid A receptors; MES: maximal electroshock; hCA: Human carbonic anhydrases; SCD: Sickle cell disease; HbF: fetal hemoglobin; IMiDs: immunomodulatory drugs; IC_{50}: half maximal inhibitory concentration; CC_{50}: half maximal cytotoxicity concentration; MIC: minimal inhibitory concentration; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; PLpro: papain-like protein; TMPRSS2: 2 transmembrane serine protease; $3CL^{pro}$ or M^{pro}: chymotrypsin-like protease; ACE-2: angiotensin 2 converting enzyme.

AUTHOR'S CONTRIBUTION

C.B.S. and G.F.S.F.; designed the article review, analysed the data, and papers, and performed the studies, as well as wrote the manuscript, with input from J.R.L.; J.L.S. All authors reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data was created or analyzed in this study.

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