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REVIEW ARTICLE

Cyclic Imides Derivatives: A Potential Scaffold for the Synthesis of Anticonvulsant Agents

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SUMMARY

Cyclic non-aromatic nitrogen heterocycles such as phthalimides, maleimides, and succinimides are an intriguing class of compounds with an immense range of biological activities such as anti-convulsant, anti-inflammatory, anti-microbial, analgesic, and hypolipidemic activities as well as numerous pharmaceutical uses. Phthalimide, maleimide, and succinimide have an imide functional group and can be considered nitrogen analogs of anhydrides. The imide ring and general structure -CO-N(R)- CO- found in cyclic imides, including phthalimides, maleimides, succinimides, and their derivatives, imparts hydrophobicity and neutral properties onto the respective derivatives. The unsubstituted cyclic imide is a crucial feature that has been shown to retain considerable biological activity. In this article, we intend to investigate several phthalimides, maleimides, and succinimide derivatives, their vast biological activities, chemistry, structural activity relationship (SAR), and anticonvulsant activity.

Key Words: *Heterocyclic compounds, Imide ring, Phthalimides, Maleimides, Succinimides, Structural activity relationship, Anticonvulsant activity.*

Halkalı İmid Türevleri: Antikonvülsan Ajanların Sentezi için Potansiyel Bir İskelet

ÖZ

Ftalimidler, maleimidler ve süksinimidler gibi aromatik olmayan azotlu heterohalkalar, anti-konvülsan, anti-inflamatuar, anti-mikrobiyal, analjezik ve hipolipidemik aktivite gibi çok çeşitli biyolojik aktivitelerin yanı sıra çok sayıda farmasötik kullanıma sahip ilgi çekici bir bileşik sınıfıdır. Ftalimid, maleimid ve süksinimid, bir imid fonksiyonel grubuna sahiptir ve anhidritlerin nitrojen analogları olarak kabul edilebilir. Ftalimidler, maleimidler, süksinimidler ve bunların türevleri dahil olmak üzere halkalı imidlerde bulunan imid halkası ve genel yapısı -CO-N(R)-CO-, ilgili türevlere hidrofobiklik ve nötr özellikler kazandırır. Sübstitüe edilmemiş halkalı imid, önemli ölçüde biyolojik aktiviteyi koruduğu gösterilen çok önemli bir karakteristiktir. Bu makalede çeşitli ftalimidler, maleimidler ve süksinimid türevlerini, bunların geniş biyolojik aktivitelerini, kimyasını, yapı aktivite ilişkisini (SAR) ve antikonvülsan aktiviteyi araştırmayı amaçlıyoruz.

Anahtar Kelimeler: *Heterosiklik bileşikler, İmid halkası, Ftalimidler, Maleimidler, Süksinimidler, Yapı aktivite ilişkisi, Antikonvülsan aktivite.*

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INTRODUCTION

Organic chemists are particularly interested in the chemistry of heterocyclic molecules due to their strong coordination, high electron-donating abilities, and numerous applications(Sabir, Alhazza, & Ibrahim, 2016). Synthetic cyclic imides, including phthalimides, maleimides, succinimides, and their derivatives have a common structural similarity that has the potential for pharmaceutical and biological activity. Due to the presence of general structure -CO-N(R)-CO- and an imide ring, their derivatives become hydrophobic and neutral, quickly permeating through a biological membrane (Hargreaves et al., 1970). The amide (Figure 1) is the imide form with two carbonyl groups attached to the nitrogen atom. Any chemical that includes the divalent radical "-C(=O)-NH-C(=O)-" is referred to as an imide (Figure 2). These compounds are synthesized from ammonia or primary amine, replacing two hydrogen atoms with a bivalent acid group or two monovalent acid groups, leading to the emergence of two carboxylic acid groups or one dicarboxylic acid(Al-Azzawi et al., 2011). Despite the wide range of biological effects associated with cyclic imides, much of their biological and toxicological action mechanism at the molecular and cellular levels are currently unknown and need to be elucidated.

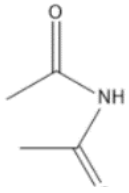


Figure 1. Amide

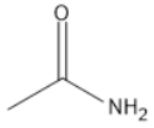


Figure 2. Imide

Phthalimide

Chemistry of Phthalimide

Phthalimide (1,3 isoindoline-dione) (Figure 3) is a white-colored, solid aromatic imide with an amine functional group and two carbonyl groups. It is critical to start synthon for organic synthesis to produce a wide range of physiologically active compounds. Its alkali metal salt is commonly employed in the Gabriel amine synthesis (Figure 4) (Gabriel, 1887). Most imides are cyclic compounds generated from dicarboxylic acids, and their names are derived from the parent acid. Such as phthalimide, which is derived from phthalic acid, and succinimide, which is derived from succinic acid, are two examples. Since imides have the formula NH and are strongly polar, they are soluble in polar fluids. The N-H core of ammonia-derived imides is acidic and can engage in hydrogen bonding(Kushwaha et al., 2016). Phthalimides are an intriguing type of bicyclic non-aromatic nitrogen heterocycles. Several alkaloids and pharmacophores have been synthesized using phthalimides as starting materials and intermediates.

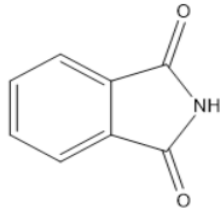


Figure 3. Phthalimide (1,3-isoindolinedione)

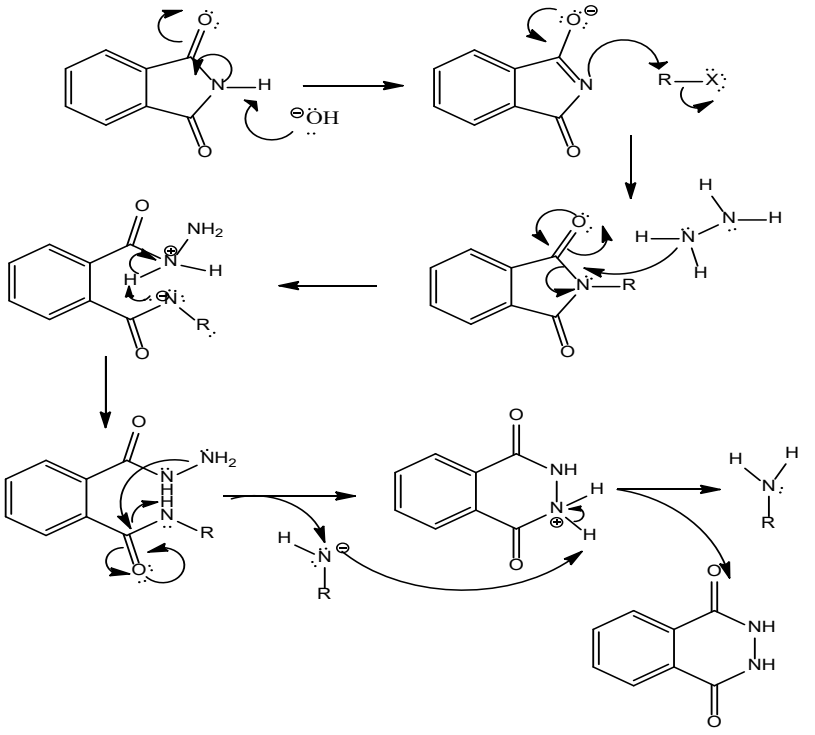


Figure 4. Gabriel amine synthesis

Phthalimide consists of two carbonyl groups surrounding a nitrogen atom. Because of the placement of the carbonyl group around the nitrogen atom, the molecules involved are mildly acidic. This effect is caused by neutral phthalimide molecules and their conjugate base (the anion generated by proton elimination) being resonance stabilized (Figure 5). As a result, for phthalimide, we may write multiple resonance forms that result in charge delocalization(Ginsburg, 1967).

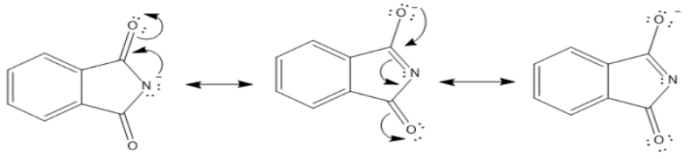
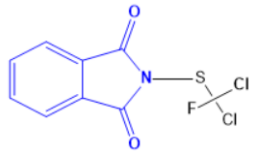
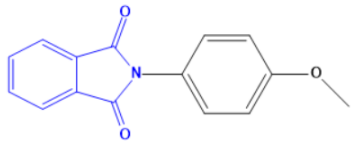
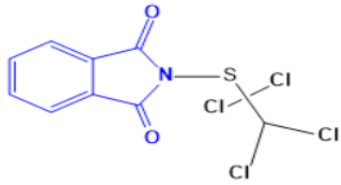
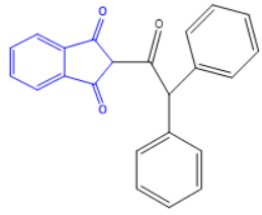
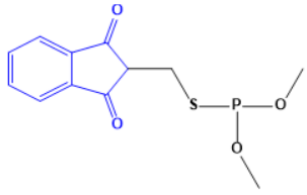
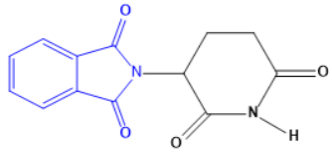
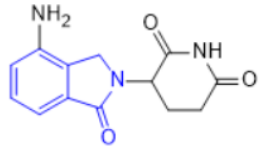
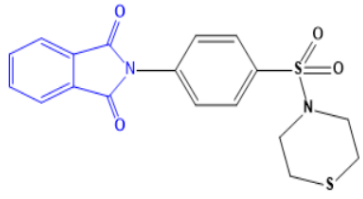


Figure 5. Resonance stabilization of Phthalimide

Due to their crucial biological effects, Phthalimide and N-substituted Phthalimides are an essential family of chemicals. Their action is distinguished by the following structural features: an electron-donor group, a hydrophobic aryl ring, a hydrogen bonding domain, and an additional distal hydrophobic location (Bhat & Al-Omar, 2011). Below is a list of some marketed phthalimido-containing drugs (Table 1.).

Table 1. Some biological active marketed Phthalimide derivatives

S.No.	Name	Structure	Use	Reference
1.	Fluorofolpet		Fungicide	(Paulus, 2004)
2.	Anisindione		Anticoagulant	(Plesinac et al., 2006)
3.	Captafol		Fungicide	(Schreurs, 1969)
4.	Diphacinone		Anticoagulant	(Rattner et al., 2012)
5.	Phosmet		Pesticide	(Shaw et al., 2002)
6.	Thalidomide		Immunomodulatory and antineoplastic	(Gao et al., 2016)
7.	Lenalidomide		Immunomodulatory and antineoplastic	(Segler and Tsimberidou, 2012)
8.	LASSBio-468		Anti-inflammatory and useful lead to treating rheumatoid arthritis	(De Castro Barbosa et al., 2012)

Anticonvulsant Activity of Phthalimide Derivatives

Tabatabaei Rafiei *et al.,* in 2020, synthesized and evaluated a novel series of phthalimide-4,5-dihydrothiazole-amide derivatives for their anti-convulsant properties against seizures in mice generated by pentylenetetrazole (PTZ). Considering all of the chemical substances synthesized the 4-chloro derivative (Figure 6) was most potent with zero mortality during the PTZ examination. Docking of molecules was also executed to analyze the modes of interaction between $GABA_A$ receptors and synthesized compounds. Docking results showed that the 4-chloro derivative had the lowest binding energy and highest effective anti-convulsant properties. All the synthesized compounds were compared to thalidomide, used as a standard anti-epileptic agent (Tabatabaei Rafiei et al., 2020).

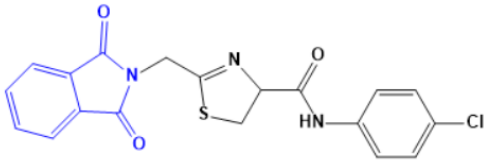


Figure 6

Asadollahi *et al.,* in 2019, synthesized a sequence of N-aryl-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamides derivatives under microwave radiation to create 2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoic acid, that participated in the amination reaction with different anilines. The pentylenetetrazole at 70mg/kg induced seizure threshold technique was used to assess the anticonvulsant efficacy of the synthesized compounds in male mice (n=5) and compare it to thalidomide (70mg/kg) and aqueous DMSO (10% v/v), which served as positive and negative controls, respectively. The findings showed that the latency times for compound 7 (Figure 7) and thalidomide were substantially longer than those seen with aqueous DMSO ($P< 0.005$). Molecular docking studies were also performed to examine the interactions with the $GABA_A$ receptor compound 6 has the lowest binding energy and the highest interactions with the receptor's active site(Asadollahi et al., 2019).

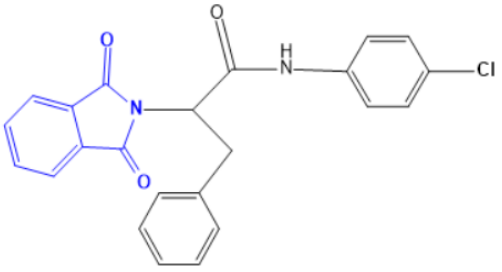


Figure 7

Ahuja *et al., 2*014 synthesized and investigated the anti-convulsant properties of novel N-(2-(benzylamino)-1-substituted-2-oxoethyl)-4-(1,3-dioxoisoindolin-2-yl)butanamide derivatives were created by combining the GABA-phthalimide moiety with an essential amino acid substituted on it. The intraperitoneal (i.p) maximal electroshock test and subcutaneous pentylenetetrazole (scPTZ) test investigated the anticonvulsant activity in Swiss male albino mice and adult Wistar rats. Neurotoxicity was also determined by the minimal motor impairment using the rota-rod test. The quantitative investigation in mice showed that the protective index (PI), essential for developing drugs with anticonvulsant efficacy, increased by 1.7, 2.3, and 4 times over phenytoin. On administration of the active compounds, the levels of gamma-aminobutyric acid in the various brain areas likewise elevated, with compound 8 (Figure 8) and it was the most effective derivative since it produced a substantial increase in the anticonvulsant activity (Ahuja et al., 2014).

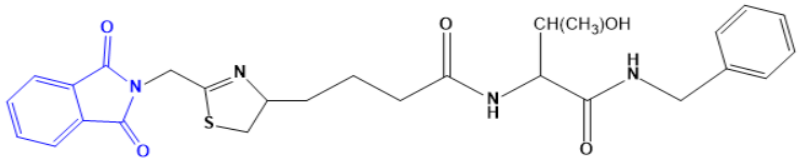


Figure 8

Fourteen analogs of 2-substituted phthalimide pharmacophore were synthesized by Davood *et al.,* in 2016 and also demonstrated their anticonvulsant activity using maximal electroshock seizure (MES) and pentylenetetrazole-induced seizures (PTZ) models. *In vivo* screening shows that all the synthesized compounds could show protection against PTZ and MES models. The maximum impact of these drugs was felt 30 minutes after administration. The two most potent analogs were compounds 9 and 10 (Figure 9 and Figure 10), while the substances with 100% protection in MES were compounds 9, 10, 11, 12, 13, and 14 (Figure 11- Figure 14). Molecular docking results demonstrated that the ligands mainly formed hydrogen bonds with the NAV 1.2 residues II-S6 and had additional hydrophobic interactions with other domains in the inner pore of the channel. The most effective analog for treating tonic and clonic seizures is compound 8, which has a robust lipophilic property and is more effective than phenytoin as a standard treatment and can be considered for further investigation (Davood et al., 2017).

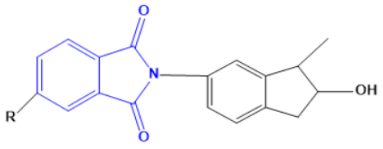


Figure 9

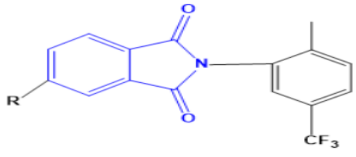


Figure 10

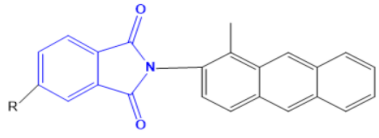


Figure 11

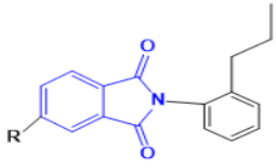


Figure 12

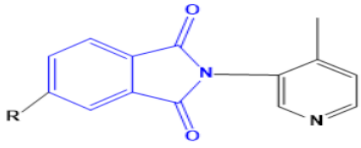


Figure 13

R=H

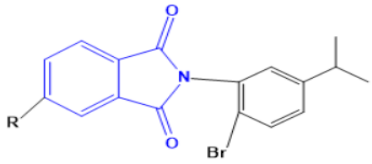


Figure 14

Mashooq *et al.,* synthesized novel sequences of 1,3,4-oxadiazole derivatives of phthalimides, and their anticonvulsants and neurotoxicity were also performed. The SAR studies show that the methoxy group is present in ring B, which makes the molecules more lipophilic. The production of the alkoxy group at the distal aryl ring boosted the lipophilic nature. During metabolism, alkoxy groups were thought to have been dealkylated and replaced with hydrogen in these molecules. Paramethoxy substituent compound 15 (Figure 15) in the MES test showed that it was possible to make the distal hydrophobic core more lipophilic than the phenyl ring. The distal hydrophobic center modifies the bioavailability of drugs. The current findings suggest that several phthalimide derivatives display a spectrum of efficacy in anticonvulsant screens, with compound 15 exhibiting anti-MES activity equivalent to phenytoin (Bhat & Al-Omar, 2011).

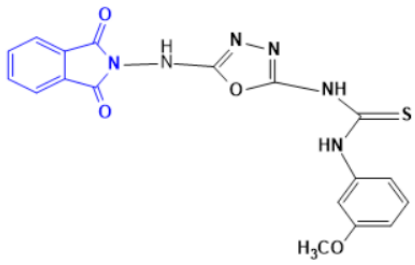


Figure 15

Two series of pharmacophoric hybrids of phthalimide-GABA-anilids/hydrazones i.e. 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2yl)-N-(substituted phenyl) butanamides (Figure 16) and N-aryl/alkylidene-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butanoyl (Figure 17) hydrazides were designed, synthesized, and evaluated by Jegadeesan et al., 2006 their anticonvulsant and neurotoxic studies were also performed. *In vivo,* screening was performed using sc strychnine (scSTY) and intraperitoneal picrotoxin (ipPIC)- induced seizure threshold tests. The synthesized compounds were inactive against the MES test. The majority of the compound were active in scSTY and ipPIC animal models however, only a few compounds demonstrated protection in the scPTZ model (Ragavendran et al., 2007).

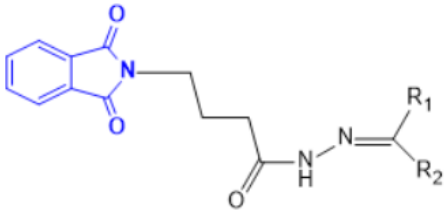


Figure 16

R_1	R_2
H	C_6H_5
H	3-NO_2-C_6H_4
H	4-NO_2-C_6H_4
H	2-OH-C_6H_4
H	4-OH, 3-OCH_3-C_6H_3
CH_3	C_6H_5
CH_3	4-NO_2-C_6H_4
CH_3	2-OH-C_6H_4
CH_3	4-OH-C_6H_4
CH_3	3-NH_2-C_6H_4
CH_3	4-CH_3-C_6H_4
C_2H_5	CH_3
C_6H_5	C_6H_5

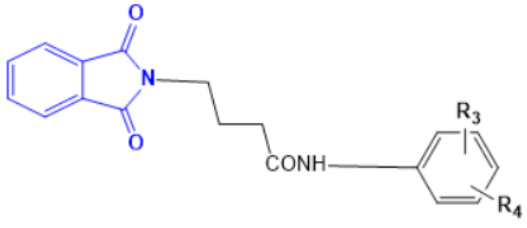


Figure 17

R_1	R_2
H	4-Cl
H	2-CF_3
H	3-F
2-CH_3	6-CH_3
2-CH_3	5-CH_3
4-Br	3-CH_3
2-CH_3	4-CH_3
H	4-CH_3
H	2-Br
3-Cl	2-CH_3

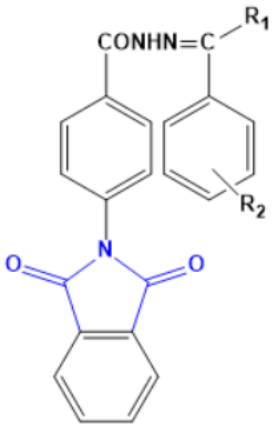


Figure 18

R1	R2
H	4-OH
H	$3,4(OCH_3)_2$
H	$3\text{-}NO_2$
CH_3	2-OH
CH_3	4-OH
CH_3	$4\text{-}CH_3$
CH_3	4-Cl
CH_3	$4\text{-}NO_2$
CH_3	$4\text{-}OCH_3$
CH_3	$2,4\text{-}(Cl)_2$
CH_3	2-OH
CH_3	$2\text{-}NO_2$

Bhat *et al.* 2011 synthesized a series of Schiff bases of Phthalimide and evaluated them for their anticonvulsant and neurotoxicity activity. *In vivo,* screening was performed using the MES. The anticonvulsant evaluation was performed using the MES test at three doses (30, 100, 300 mg/kg). Compound 18 (Figure 18) was the most promising anticonvulsant drug with little neurotoxicity and nitro substitution at the ortho position of the distal aryl ring. All the reported compounds were less neurotoxic than phenytoin (Bhat and Al-Omar, 2011).

Structure-Activity Relationship (SAR) of Phthalimide Derivatives As An Anticonvulsant

The review paper presents a summary of the work on the structure-activity relationship of phthalimide derivatives as anticonvulsants. The imide group at N2 position acts as a hydrogen bond donor which is essential for anticonvulsant activity. Furthermore, the substitution of a methoxy group at a distant phenyl ring shows a highly potent derivative. The SAR is shown in (Figure 19).

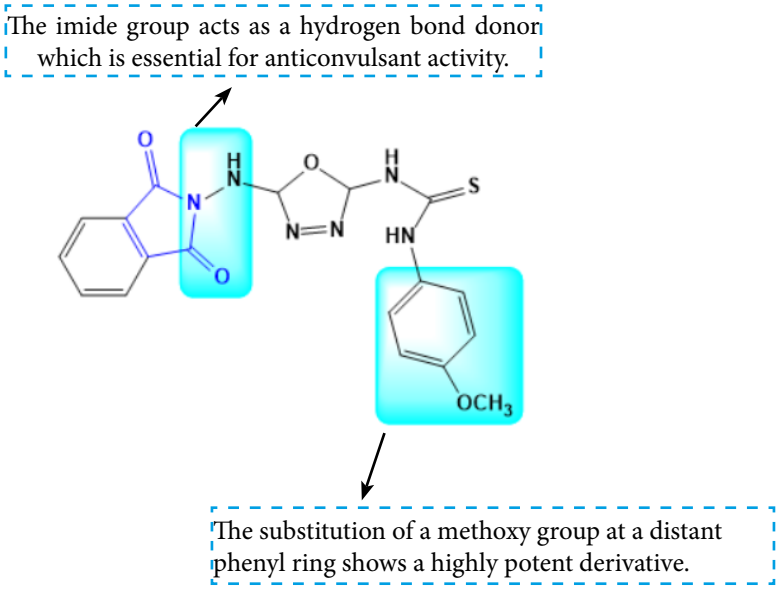


Figure 19. SAR of Phthalimide bearing derivative.

Succinimides

Chemistry of Succinimides

Succinimide (pyrrolidine-2,5-dione) (Figure 20) is a pyrrolidine dicarboximide with oxo groups substituting positions 2 and 5. It is a dicarboximide and a pyrrolidinone. Its chemical formula is $(CH_2)_2(CO)_2HN$.

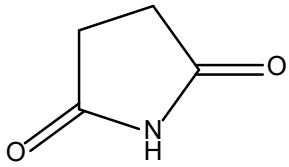
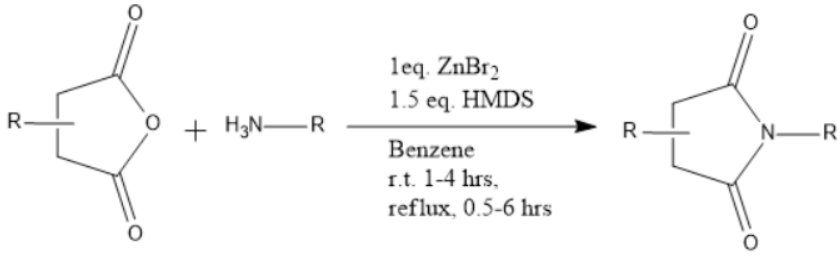


Figure 20. Succinimide (pyrrolidine-2,5-dione)

There have been several vital practical ways for synthesizing succinimides, which are listed below.

The easy technique is described in Scheme 1, for the direct synthesis of substituted succinimides 23, in which succinic anhydride 21 was reacted with amine 22 utilizing a Lewis acid catalyst, in the presence of Hexamethyldisilazane



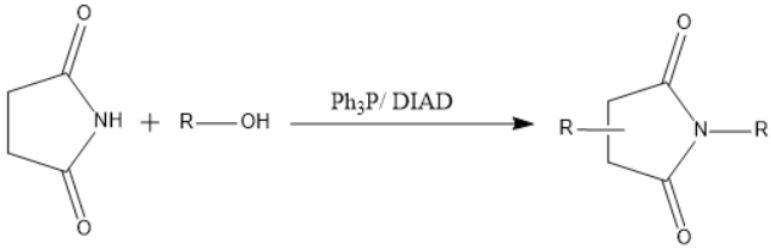
21 **22** **Scheme 1** **23**

The newly established method for producing succinimide derivative 24 from succinic anhydride 25 by solvent-free synthesis. $TaCl_5$ and Lewis acid catalyze the reaction Scheme 2 (Chandrasekhar et al., 1997).

24 **25**

Scheme 2

The synthesis of N-substituted succinimide 28 was accomplished by a modified Mitsunobu reaction that involved the interaction of succinimide 26 with alcohol 27 in the presence of triphenylphosphine and the reagent diisopropyl azodicarboxylate (DIAD) Scheme 3 (Kosinska et al., 2021).



26 **27** **28**

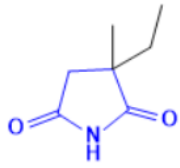
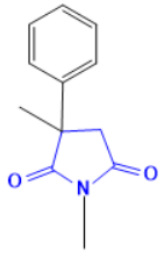
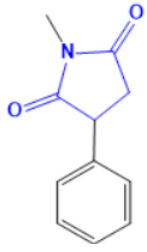
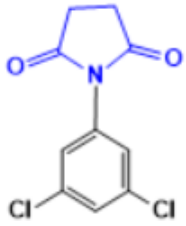
Scheme 3

Reacting succinic anhydrides 27 and amine 28 using microwave-assisted reactions, substituted succinimides 29 were prepared. The reaction was carried out in DMF, acetic anhydride, or water as a solvent. Compared to the conventional approach, the yield obtained by the microwave-assisted reaction was outstanding (Mandal's Sip et al., 2014).

29 **30** **31**

R= benzyl; R= (CH2)6; **R**=4-methyl phenyl; **R**= 4,4'-methanediphenyl; **R**= 1-naphthyl **Scheme 4**

Table 2. Some biological active marketed Succinimide derivatives

S.No.	Name	Structure	Use	Reference
1.	Ethosuximide		Anticonvulsant (treat petit mal seizures)	(Battino et al., 1982)
2.	Methsuximide		Anticonvulsant (treat petit mal seizures)	(Teschendorf and Kretzschmar, 1985)
3.	Phensuximide		Anticonvulsant (treat petit mal seizures)	(Teschendorf and Kretzschmar, 1985)
4.	N-(3,5-Dichlorophenyl) succinimide (NDPS)		Antifungal	(Li et al., 2015)

Anticonvulsant Activity of Succinimide Derivatives

A series of 27 novel 1-(4-phenylpiperazine-1-yl)- or 1-(morpholin-4-yl)-2,5-dioxopyrrolidin-1-yl)propanamides and (2,5-dioxopyrolidin-1-yl) butanamides as potential anticonvulsants were synthesized by Kamiński *et al.,* in 2015. Antiepileptic drugs (AEDs) such as lacosamide, levetiracetam, and ethosuximide were utilized to join the fragments of the novel hybrid molecule. In the MES test, the subcutaneous pentylenetetrazole (scPTZ) test, and the six-hertz (6Hz) model of pharmacoresistant limbic seizures, compound **32, 33, 34** and **35** (Figure 32-35) showed a wide range of action. Compound 30 provides the best protection (ED MES=88.4 mg/kg, ED50 scPTZ= 59.9mg/kg, and ED50 6Hz= 21.0 mg/kg). Even at higher doses (TD50>1500 mg/kg), this molecule produced excellent protective indices (PI MES> 16.97, PI PTZ> 25.04, PI 6 Hz> 71.43), this compound did not affect the animal's ability to coordinate their movements during the chimney test. Although ethosuximide, lacosamide, and valproic acid are therapeutically significant AEDs, compound 32 showed a noticeably superior safety profile than those drugs (Kamiński et al., 2015).

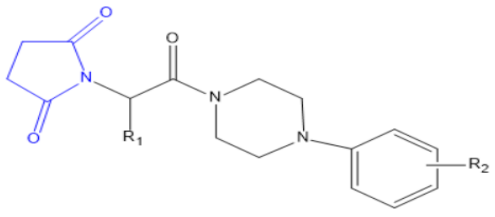


Figure 32-35

Compound	R1	R2
32	CH_3	4-Cl
33	CH_3	2-CF_3
34	CH_3	3- CF_3
35	C_2H_5	3- CF_3

In 2016, Kamiński *et al* synthesized a series of 21 novel N-phenyl-2-(2,5-dioxopyrrolidin-1-yl) propanamides, 2-(3-methyl-2,5-dioxopyrrolidin-1-yl)propanamides, and 2-(2,5-dioxopyrrolidin-1- yl) butanamides as potential hybrid anticonvulsant agents. The "classical" MES and scPTZ tests were used for the initial anticonvulsant screening in mice (i.p), as well as in the 6 Hz model of pharmacoresistant limbic seizures. The rotarod test was used to detect acute neurological toxicity. All preclinical seizure models demonstrated a broad spectrum of efficacy for compounds 36, 37, 38, and 39 (Figure 36-39). In the 6 Hz test, the butanamide derivatives 38 and 39 was the most effective. The best level of protection and a significant safety profile were shown in the rotarod test for derivative 36 by quantitative pharmacological tests in mice administered intraperitoneally. This substance was identified as the most promising with positive protective indexes (PI MES = 3.5, PI scPTZ = 4.4, PI 6 Hz = 7.6). The *in vitro* binding experiments demonstrated that the influence on the voltage-sensitive sodium channel and the diltiazem site of the L-type calcium channel in neurons was the most likely mechanism of action for compound 36 (Kamiński et al., 2016a).

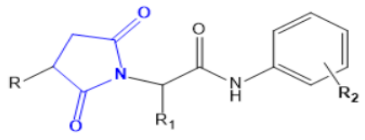


Figure 36-39

Compound	R	R1	R2
36	H	CH_3	H
37	H	CH_3	3-Cl
38	H	C_2H_5	H
39	CH_3	CH_3	H

A series of 34 novel 3-methyl- and 3,3-dimethyl-(2,5- dioxopyrrolidin-1-yl)propanamides or butanamides hybrid anticonvulsant agents were synthesized. The "classical" MES and scPTZ test and the 6 Hz model of pharmacoresistant limbic seizure were used in the initial anticonvulsant screening in mice (i.p). The chimney test was used to assess acute neurological toxicity. Compounds **40**, **41**, **42**, and **43** (Figure 40-43) demonstrated a broad spectrum of efficacy in all preclinical seizure models. The quantitative pharmacological tests in mice (i.p) indicated the best protection and a satisfactory safety profile in the chimney test for compound 41. Compared to traditional AEDs, this chemical emerged as the most promising molecule with favorable protective indexes. In addition, six anticonvulsants demonstrated decisive antinociceptive action in mice's formalin model of tonic pain. The *in vitro* binding tests for compound 41 shows that the impact on neuronal voltage-sensitive sodium and L-type calcium channels was the most probable molecular mechanism of anticonvulsant and antinociceptive activity(Kamiński et al., 2016b).

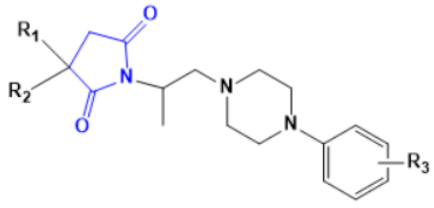


Figure 40-42

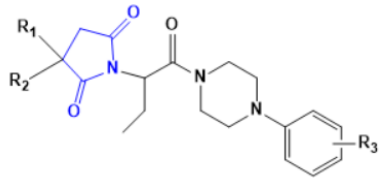


Figure 43

Compound	R_1	R_2	R_3
40	CH_3	H	H
41	CH_3	H	3-CF_3

R_1= CH_3, **R_2**= H, **R_3**= 3-CF_3

The series of N-Mannich bases of 3-phenyl-, 3-(2-chloro-phenyl)-, 3-(3-chlorophenyl)- and 3-(4-chlorophenyl)-pyrrolidine-2,5-diones were synthesized and investigated for their anticonvulsant properties by Kaminski *et al.,* in 2013. The primary synthetic techniques involve the synthesis of 3-substituted pyrrolidine-2,5-diones followed by an amino alkylation reaction (Mannich-type) with formaldehyde and corresponding secondary amines, yielding the final compounds. The findings demonstrated that most compounds protected MES. Several substances were also active in seizures induced by pentylenetetrazole (scPTZ) and psychomotor (6Hz). The most active 1-(morpholinomethyl)-3-phenyl-pyrrolidine-2,5-dione (Figure 44) was effective in the MES, scPTZ, 6-Hz, and pilocarpine-induced status prevention (PISP) tests, indicating its potential utility in tonic-clonic, absence, and refractory epilepsy, as well as *status epilepticus*. This compound, as the most promising in the series, inhibited CYP3A4 activity very little *in vitro* and is unlikely to interact with other CYP3A4 metabolized medicines *in vivo*(Kamiński et al., 2013).

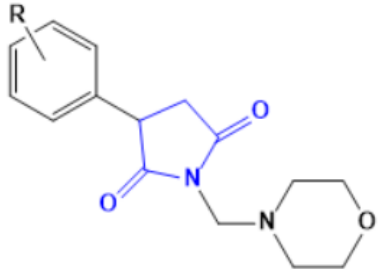


Figure 44

The library of 28 novel 1,3-substituted pyrrolidine-2,5-dione as potential anticonvulsant agents was synthesized and evaluated by Rybka *et al* in 2017. Anticonvulsant action was assessed in mice using three acute seizure models MES, subcutaneous pentylenetetrazole (scPTZ), and psychomotor seizure tests (6-Hz). The rotarod test was used to evaluate neurotoxicity. N-[morpholin-1-yl-methyl]-3-benhydryl-pyrrolidine-2,5-dione (Figure 45) was determined to be the most promising chemical, since it was active in the MES (ED50= 41.0 mg/kg), scPTZ (ED50= 101.6 kg/mg), and 6Hz (ED50= 45.42 mg/kg) assays. This compound outperformed antiepileptic medications like ethosuximide, lacosamide, and valproic acid regarding a favorable protection index (PI). Furthermore, *in vitro* tests revealed that for compound 45 the most likely mechanism of action is the inhibition of neuronal volage-sensitive sodium and L-type calcium channels (Rybka et al., 2017).

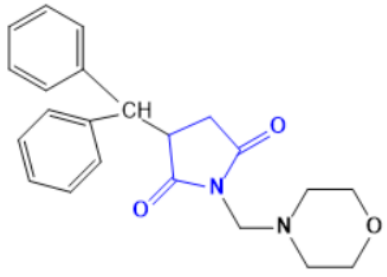


Figure 45

A series of sixteen novel 1-[(4-arylpiperazin-1-yl)-propyl]-3-methyl-3-phenyl- and 3-ethyl-3-methylpyrrolidine-2,5-dione derivatives as possible anticonvulsant drugs were synthesized by Obniska *et al.,* in 2012. MES, subcutaneous pentylenetetrazole (scPTZ), and psychomotor seizure tests (6-Hz) tests were used for the evaluation of anticonvulsant properties. The rotarod screening was also performed to investigate acute neurological toxicity. The 1-{3-[4-(3-chlorophenyl)-piperazin-1-yl]-propyl}-3-methyl-3-phenyl-pyrrolidine-2,5-dione (Figure 46) was the most active compound from whole series with the ED50 value of 28.2mg/kg, TD50 value of 268.5mg/kg, and protective index (PI) of 9.52 after *po* administration in rats (Obniska et al., 2012).

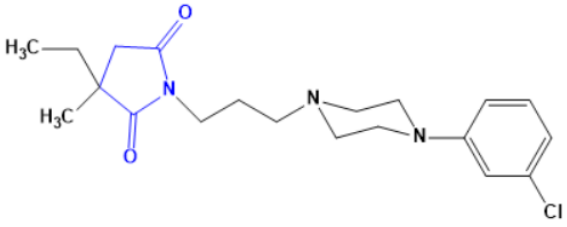


Figure 46

A series of N-[(4-arylpiperazin-1-yl)-methyl] derivatives of 3-arylpyrrolidine-2,5-dione and 2-aza-spiro[4,4]nonane-1,3-dione were synthesized by Obniska *et al.,* in 2003 and also anticonvulsant activity was assessed in the maximum electroshock seizure (MES) and pentylenetetrazole- induced seizures (scPTZ) tests. The N-[{4-(3-chlorophenyl)-piperazin-1-yl}-methyl]-3-(2-chlorophenyl)-pyrrolidine-2,5-dione (Figure 47) (ED50= 14.18 mg/kg) and N-[{4-(2-methoxyphenyl)-piperazin-1-yl}-methyl]-3-(3-bromophenyl)-pyrrolidine-2,5-dione (Figure 48) (ED50= 33.64 mg/kg) was the most potent compound amongst the whole series (Obniska and Zagorska, 2003).

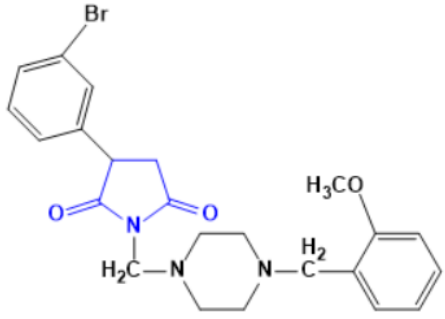


Figure 47

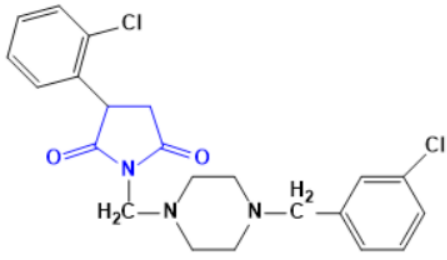


Figure 48

Obniska *et al.,* 1999 synthesized new N-pyridyl derivatives of 3-phenyl and 3,3-diphenyl succinimides and described their physicochemical properties. The synthesized compounds were evaluated for anticonvulsant activity. The N-pyridyl derivatives of 3-phenylsuccinimides (Figure 49-54) were ineffective in protecting against MES and scMET-induced seizures. The Molecular electrostatic potential (MEP) was also performed, and it was found that the active compounds differ significantly from the inactive ones (Obniska et al., 1999).

Structure-Activity Relationship (SAR) of Succinimide Derivatives As An Anticonvulsant

The review paper presents a summary of the work on the structure-activity relationship of succinimide derivatives as anticonvulsants. The substitution of the pyridyl ring at the imide group at the N2 position is a characteristic property of anticonvulsants. The pyridyl ring can be further substituted with the methyl group which aids in the establishment of the hydrogen bond with the receptor. Also, the substitution of the aromatic ring at the C5 position of succinimide moiety gives an active compound (Figure 49-54). The SAR of succinimide moiety is shown in (Figure 55) (Obniska, Zejc, & Karolak-Wojciechowska, 1999).

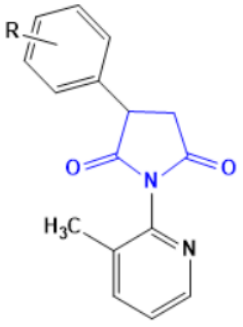


Figure 49-54

Compound	R
49	4-F
50	3-F
51	2-Cl
52	3-Br
53	2-OCH_3
54	3-OCH_3

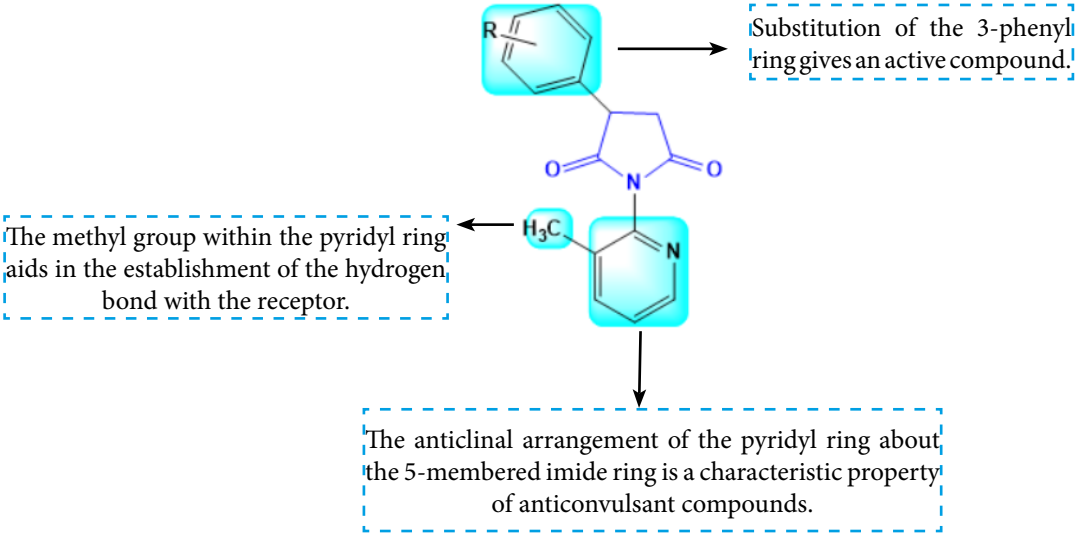


Figure 55. SAR of Succinimide bearing derivative(Obniska et al., 1999)

Maleimide

Chemistry of Maleimide

Maleimide (Pyrrole-2,5-dione) (Figure 56) is an example of cyclic dicarboximide in which the two carbonyl groups on nitrogen combine to generate a 1H-pyrrole-2,5-dione structure. Maleimide is an effective moiety, wherein the NH group is replaced by an alkyl or aryl group, such as a methyl or phenyl, as suitable. Meanwhile, a maleimide moiety with a 1.2-disubstituted ethylene structure can have its vinylene group polymerized using radical or anionic initiators to produce a material with high thermostability or heat resistance, which can then be copolymerized with vinyl (Jarzyński et al., 2023).

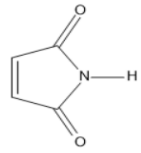
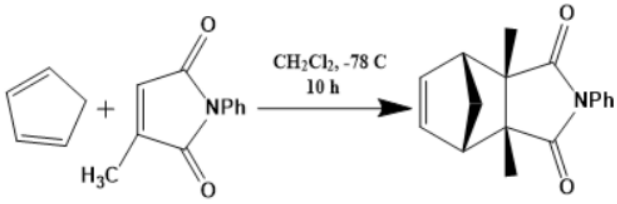


Figure 56. Pyrrole-2,5-dione

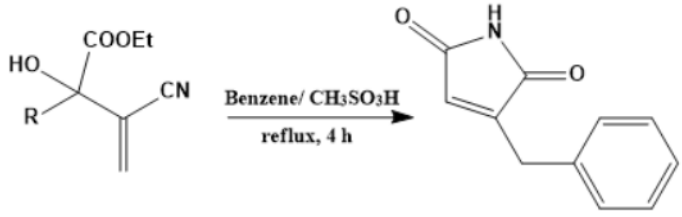
In terms of chemical reactivity, maleimide derivatives are particularly appealing compounds. They catalyze several reactions, such as the Diels-Alder reaction with dienes(Mukherjee and Corey, 2010) and the nucleophilic Michael-type addition of thiols or amines to the vinylene molecules (Abel and McCormick, 2016).



(Cyclopentadiene) (N-Phenylmaleimide) (Exo/endo diels product)

Figure 57

Friedel-Crafts reaction of Baylis-Hillman adducts maleimide: Synthesis of 4-substituted 3-benzyl-1H-2,5-dione derivatives (Basavaiah et al., 2011).



(3-ethoxycarbonyl-3 -hydroxy-3aryl(alkyl)-2-Methylenepropanenitrile)

(4-substituted 3-benzyl-1H-2,5-dione derivative)

R= aryl/alkyl

Figure 58

A unique modification of the Mitsunobu reaction allows for a high-yield synthesis of N-alkyl maleimides (Walker, 1995).

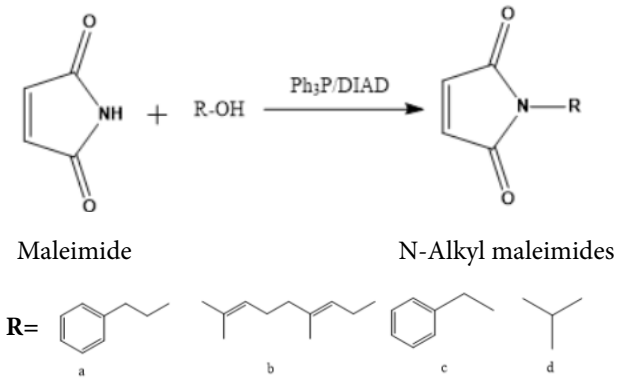


Figure 59

Anticonvulsant Activity of Maleimide Derivatives

Abram M *et al.* 2021 generated a series of water-soluble hydrochlorides of pyrrolidine-2,5-dione derivatives developed as possible anticonvulsants with added antinociceptive characteristics. Preclinical results in mice demonstrated that these drugs provided strong protection and broad-spectrum efficacy in many animal models of seizures, including the MES, 6 Hz (32/44 mA), and, scPTZ tests. Compound 60 demonstrated the most favorable anticonvulsant effects [ED50 MES= 49.6 mg/kg, ED50 Hz (32 mg/kg), ED50 scPTZ= 67.4 mg/kg] and safety profile(Abram et al., 2021).

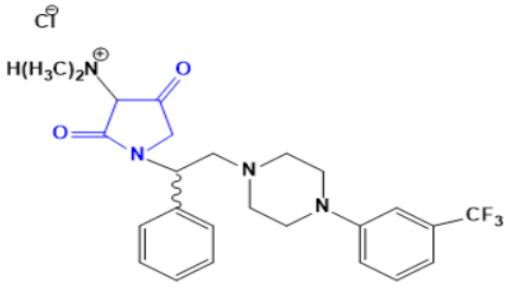
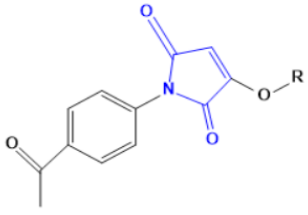


Figure 60

A novel series of Michael adducts as a 1-(4-acetyl-phenyl)-3-aryloxypyrrolidine-2,5-dione derivatives utilizing cellulose sulfuric acid catalyst to obtain lead compounds for future development as anti-convulsants were evaluated by Jigarkumar *et al.*, in 2013. Among the fourteen Michael adducts of 1-(4-acetylphenyl)-pyrrole2,5-dione, 1-(4-acetyl-phenyl)-3-(4-Bromophenyloxy)-pyrrolidine-2,5-di-one (Figure 61a) and 1-(4-acetylphenyl)-3-(salicylde-hydroxy)-pyrrolidine-2,5-dione (Figure 61b) *in vitro* brain GABA-transaminase activity was higher with IC_{50} values of (100.5, 5.2mM) and IC50 (160.4, 6.2 mM) respectively. The investigation utilized fluoro-metric analytical assessment data compared to vigab-atrin, a reference standard (Patel et al., 2013a).



Compound	R
61a	p-Br-C_6H_4
61b	o-CHO-C_6H_4

Figure 61

A series of 4-dialkyl amino-2-butynyl-maleimide and hydantoin derivatives were designed for dual-acting anticonvulsant and antimuscarinic activity by Roberto *et al.,* in 1997, and compound 62 (Figure 62) derivatives were found to be the most potent (Hudkins et al., 1997).

Structure-Activity Relationship (SAR) of Maleimide Derivatives As An Anticonvulsant

The review paper presents a summary of the work on the structure-activity relationship of maleimide derivatives as anticonvulsants. Substituting the bromine atom which is an electron-donating group to a phenyl ring at position gives Michael adduct with maleic amide moiety results in considerable GABA-T activity. Substituting CHO (aldehyde group) at the ortho position of the same phenyl ring gives potent derivatives (Figure 61). The SAR of maleimide moiety is shown in (Figure 63)(Patel, Dholakiya, & Mishra, 2013).

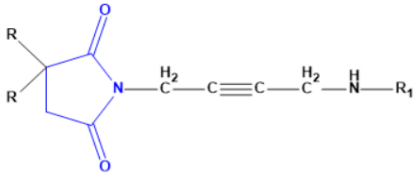


Figure 62

Compound	R	R1
62a	Ph	C_2H_5
62b	2-dinitrosubrane	C_2H_5

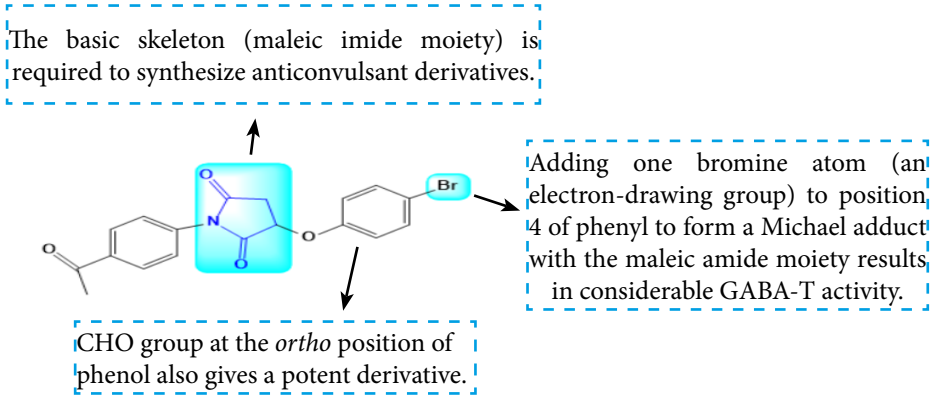
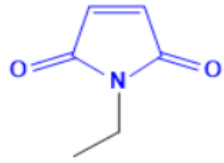
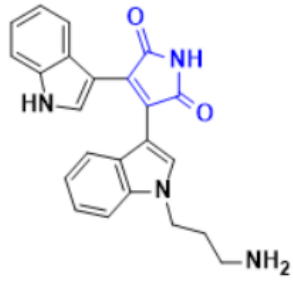
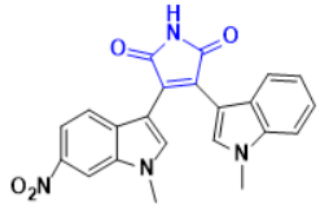
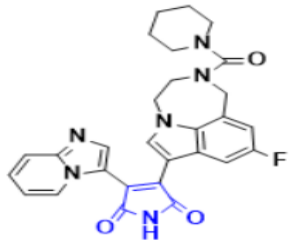


Figure 63. SAR of Maleimide bearing derivatives (Patel et al., 2013b)

Table 3. Some biologically active experimental maleimide derivatives

S.No.	Name	Structure	Use	Reference
1	N-ethylmaleimide		Anti-coronaviral agent	(Wenge and Bönisch, 2008)
2	Bisindolylmaleimide III		Protein kinase C inhibitor	(Brehmer et al., 2004)
3	MKC-1		Antineoplastic activity	(Faris et al., 2012)
4	LY2090314		Antineoplastic activity	(Magnus et al., 2010)

CONCLUSION

Based on prior studies, we concluded that the cyclic imide derivatives had significant biological activity. Cyclic imide derivatives are considered an important class of medications used as anticancer, antibacterial, anti-inflammatory, analgesic, and antituberculosis agents. Diverse phthalimide, maleimide, and succinimide derivatives could be further engineered and developed to produce unique and more effective therapeutically active compounds by including new pharmacophores at various places. The structure-activity relationship of different cyclic imide derivatives reveals that substituting a methoxy group at a distant phenyl ring shows a highly potent derivative in the case of Phthalimide derivatives e.g. **Figure 19**. Furthermore, for succinimide derivative's structure-activity relationship divulges that the anticlinal arrangement of the pyridyl ring about the 5-membered imide ring is a characteristic property of anticonvulsant compounds. Also, the methyl group within the pyridyl ring helps in the formation of the H bond with the receptor e.g., **Figure 55**. Also, the SAR study of maleimide reveals that the introduction of one Bromine atom (Electron withdrawing group)

in position 4 of phenyl to form Michael adduct with maleic amide moiety offers high GABA-T action; additionally, the presence of the basic skeleton (maleic imide moiety) is crucial for the development of the anticonvulsant derivatives e.g. **Figure 63**. From the overall study, we may thus conclude that the numerous synthetic cyclic imide compounds help treat epilepsy.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Conception & design were given by S Singh, Acquisition of the data was done by A J Rana, drafting of the article was seen by M Rana, Collection and assembly of data was done by S Singh, A V Pargaein, Administrative, technical, or logistic support was provided by M Rana and H Joshi, Plagiarism was checked by H K Awasthi.

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