Antimicrobial & Anticonvulsant Activity Show Some Newer Phthlimido Derivatives

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Abstract: The aim of the study was to design, synthesize and investigate the antimicrobial & fungal activity of some α-N-Phthlimido derivatives of amino acids by Srinivasan et al; 2010. The chemical structures of the titled compound were confirmed by IR, 13CNMR and elemental analysis. All the compounds are screened for antimicrobial activity against gram positive, gram negative bacteria (Escherichia coli, Klebsiella, Staphlococcus epidermitis, Bacillus cereus, Micrococcus leteus, Staphylococcus aureus) and fungal strains (Candida albicans, Aspergillus niger). Synthetic heterocyclic compounds have been found to possess important biological properties including anticonvulsant effects in man and animals. This study was aimed at highlighting the anticonvulsant properties of two phthlimido derivatives (N-cyclopentylphthalimide and N-benzylphthalimide). N-Cyclopentlyphthalimide and N-benzylphthalimide were synthesized by Iniaghe et al; 2010 and screened for anticonvulsant properties using adult Swiss mice. Convulsion was induced using maximum electroshock therapy.

Keywords: 13CNMR, Staphylococcus aureus, electroshock therapy, α-N-Phthlimido derivative

1. Introduction

The anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. An effective anticonvulsant would prevent the spread of the seizure within the brain and offer protection against possible excitotoxic effects that may result in brain damage. Some studies have reported that anticonvulsants themselves are linked to lowered intelligent quotient (IQ) in children. Seizures are basically divided into two major groups: partial and generalized. Partial (focal, local) seizures are those which originate from a localized origin, usually in a portion of one hemisphere in the brain. Partial seizure may be further subdivided into simple partial, complex partial and partial seizure evolving into secondarily generalized seizures. Generalized seizure may be subdivided into absence (nonconvulsive), myoclonic, clonic, tonic, tonic-clonic and atomic seizures.

2. The Antiseizure Drugs Used in Treatment of Various Seizures

The major molecular targets of marketed anticonvulsant drugs are voltage-gated sodium channels and components of the Gamma Amino Butyric Acid (GABA) system, including GABA<sub>A</sub> receptors, the GABA transporter – 1 (GAT-1), and GABA transaminase. Additional targets include voltage-gated calcium channels, synaptic vesicle glycoprotein 2 A (SV2A), and voltage dependent calcium channel subunit alpha 2 delta (α2δ). And the types of seizure are shown in table 1.

<table>
<thead>
<tr>
<th>Types of Seizures</th>
<th>Seizures</th>
<th>Characters</th>
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<tbody>
<tr>
<td>(1) Partial seizures (focal, local)</td>
<td>A. Simple partial seizures</td>
<td>Without impairment of consciousness, including convulsions to a single limb or muscle group.</td>
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<td>B. Complex partial seizures</td>
<td>Attacks of confused behavior, with impairment of consciousness, with a variety of clinical manifestations.</td>
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<td>C. Partial seizures secondarily generalized</td>
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Drugs
- Aldehydes: Paraldehyde
- Aromatic allylic alcohols: Stiripentol
- Barbiturates: Phenobarbital, Methylphenobarbital, Metharbital, Barbexamone
- Benzodiazepines: Clobazam, Clonazepam, Clorazepate, Diazepam, Midazolam, Lorazepam, Nitrazepam, Temazepam, Nimetazepam
- Bromides: Potassium bromide
- Carbamates: Felbamate
- Carboxamides: Carbamazepine, Oxcarbazepine, Eslicarbazepine acetate
- Fatty acids: Valproic Acid, Sodium Valproate, Divalproex Sodium, Vigabatrin, Pregabide, Tiagabine
- Fructose derivatives: Topiramate
- GABA analogs: Gabapentin, Pregabalin
- Hydantoins: Ethotoin, Phenytin, Fusphenytoin, Mephenytin
- Oxazolidinediones: Paramethadione, Trimethadione, Ethadione
- Propionates: Beclamide
- Pyrimidinediones: Primidone
- Pyrrolidines: Brivaracetam, Levetiracetam, Seletracetam
- Succinimides: Ethosuximide, Phensuximide
- Sulfonamides: Acetazolamide, Sulthiame, Methazolamide, Zonisamide
- Triazines: Lamotrigine
- Ureas: Pheneturide, Phenacemide
- Valproylamides (amide derivatives of valproate): Valpromide, Valnoctamide.

Table 1: Types of seizures
Antimicrobial

An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes (microbicidal) or prevent the growth of microbes (microbiostatic). Disinfectants are antimicrobial substances used on non-living objects or outside the body.

Classification by mechanism of action:
1) Drugs that inhibit bacterial wall synthesis or activate enzymes that disrupt the cell wall.
2) Drugs that increase cell membrane permeability (causing leakage of intracellular material)
3) Drugs that cause lethal inhibition of bacterial protein synthesis.
4) Drugs that cause nonlethal inhibition of protein synthesis (bacteriostatics).
5) Drugs that inhibit bacterial synthesis of nucleic acids
6) Inhibitors of viral enzymes.

3.3 Phthalimide

Phthalimide is an imide, which is a chemical compound with two carbonyl groups bound to a secondary amine or ammonia. It is a white solid at room temperature.

IUPAC name: Isoindole-1,3-dione.

Structure:

![Phthalimide Structure](image)

Properties:
Molecular Formula: C₈H₈NO₂
Molar mass: 147.13 g mol⁻¹
Appearance: White solid
Melting point: 238 °C, 511 K, 460 °F
Boiling point: 336 °C, 609 K, 637 °F (sublimes)
Solubility in water: <0.1 g/100 ml (19.5 °C)
Acidity (pKₐ): 8.3
Basicity (pKₐ): 5.7
4. Biological Activity of Pthalimide Derivatives along with Sar Study

1) Anticonvulsant Activity
Synthetic heterocyclic compounds have been found to possess important biological properties including anticonvulsant effects in man and animals. This study was aimed at highlighting the anticonvulsant properties of two phthalimide derivatives (N cyclopentylphthalimide and N benzylphthalimide). N-Cyclopentylphthalimide and N-benzylphthalimide were synthesized by Iniaghe et al; 2010 and screened for anticonvulsant properties using adult Swiss mice. Convulsion was induced using maximum electroshock therapy. The compounds were found to be seizure protective and protection was observed even after forty eight hours.

2) Anti-Inflammatory Activity
This paper describes the synthesis and anti-inflammatory activity of new N-phenyl-phthalimide sulfonamides (3a–e) and the isosters N-phenyl-phthalimide amides (4a–e), designed by Lidia et al; 2002, as hybrids of thalidomide and aryl sulfonamide phosphodiesterase inhibitor. In these series, compound 3e (LASSBio 468), having a sulfonyl-thiomorpholine moiety, showed potent inhibitory activity on LPS-induced neutrophil recruitment with ED50=2.5mg kg⁻¹, which was correlated with its inhibitory effect on TNF-α level.

3) Analgesic Activity
Phthalimide derivatives syntheses were carried out by Suvarna et al; 2012 eco-friendly microwave irradiation methods where, montmorillonite-KSF was used as the reusable clay catalyst. These compounds were characterized by TLC, melting point determination, and by IR and 1H NMR spectroscopy. The acute oral toxicity studies of the compounds were carried out using OECD guidelines. The compounds were than screened for analgesic activity using Aspirin as the standard and activity was correlated with FISA (Hydrophilic component of the total accessible surface area). The molecular modeling software, Maestro, from Schrodinger, USA, was used for QSAR studies.

4) Antifungal Activity
4-(1,3-dioxoisooindolin-2-yl) benzohydrazide (1) undergoes facile condensation with aromatic aldehydes to afford the corresponding N'-arylidene-4-(1,3-dioxoisooindolin-2-yl) benzohydrazide (2a–e) in good yields. Cyclcondensation of compounds (2a–e) with chloro acetyl chloride yields N-(3-chloro-2-oxo-4- arylazetidin-1-yl)-4-(1,3-dioxoisooindolin-2-yl)benzamid (3a–e). The structures of these compounds were established on the basis of analytical and spectral data. The newly synthesized compounds by Gunvantsinh et al; 2011 were evaluated for their antibacterial and antifungal activities.
5) Anticancer Activity

To improve the therapeutic efficacy of 20(s)-camptothecin (CPT) polymeric drugs containing CPT have been designed. A new CPT-conjugate, 3,6-endo-methylene-1,2,3,6 tetrahydrophthalimidoacetamidoglycine camptothecin ester (ETPA-gly-CPT), was synthesized by Neung et al. linking its hydroxyl group to the phthalimido monomer through a glycine–glycine spacer.

The monomer and its polymers were characterized by IR, 1H and 13CNMR. The ETPA-gly-CPT content in poly(ETPA-gly-CPT-co-AA) obtained by elemental analysis was 40 wt.%. The number-average molecular weights of the polymers determined by gel permeation chromatography were as follows: Mn ¼ 15,000 for poly(ETPA-gly-CPT), Mn ¼ 18,700 for poly(ETPA-gly-CPT-co-AA). The IC50 values of ETPA-gly-CPT and its polymers against cancer cells were much larger than that of CPT.

5. Conclusion

Aryl semicarbazones and thiosemicarbazones have emerged as naturally novel anticonvulsant. Aryl semicarbazides are reported to display excellent anticonvulsant activity in mice and rats compared to that of phenytoin. But these show various toxic effect are gum hypertrophy, Hirsutism, and rats compared to that of phenytoin. But these show various toxic effect are gum hypertrophy, Hirsutism, etc.

Epilepsy being one of the world oldest recognised disorder, it is surrounded fier, discrimination, social p& frighlening manifestation. In the recent year much efforts have been devoted for the development of novel therapeutics.

Drugs like Zonisamide, lamotrigene etc have proven to be effective in reducing seizure, while their therapeutics efficacy is overcome by some undesirable side effect such as headache, nausea, drowsiness.

Such for newer condition that can treat this disorder better & have no or minimal toxicity is the major area of concern. Phthalimide derivative have proven excellent anticonvulsant & antimicrobial agents. In this present study our main objective is to synthesize newer phthalimide derivative with no minimal side effect.

References

[2] Lemke, T.L; Williams D.A.R, Roche, V F; Zito, S W. Foye’s Principle of Medicinal Chemistry, 6th ed; Lippincot Willium & Wilkins; New Delhi, 2008; P-523
[4] Desai T; Singh; Synthesis & Biological activity of novel phthalimide containing Aztidimone; Scholar research Library Der pharmacia Chimica, 3(6);124-129(2011).
[8] Gaikwad V; Kishor; Jadhave B; Satish; Rathod D; Santilal; Indian journal of chemistry vol.49B, P 131-136(2010).

[20] N. Siddique; M. A. Bhat; M. A.-Al-Omar, synthesis & anticonvulsant and neurotoxicity of some novel 1,3,4-oxadiazole derivative of phthalimide, Scholar research library, Der pharma chemical (2010).