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A REVIEW ON PHARMACOLOGICAL PROFILE OF PHENYTOIN AND THEIR DERIVATIVES

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ABSTRACT

Purpose: Phenytoin is an aromatic heterocyclic compound, Antiepileptic Properties which is used as Anti-convulsant agent but also used in the CNS disorder drugs. Phenytoin was first made in the year 1908 by the German chemist Heinrich Blitz and found useful for seizure in 1963. But as a drug Phenytoin is an oral and injectable anti-seizure medication was focused in 1908s, as 10-substituted derivatives. Along with this phenytoin also has anti-seizure, toni-clonic seizures, and focal seizures effect. Most prominent use of these derivatives is as tranquilizer because it has defused an anti-epileptic effect. It is also reported to have anti-cancer, antitubercular, anti-inflammatory, anticonvulsant, Anti-arrhythmic, Skeletal muscle relaxant effects. The biological evaluation for the CNS agent activity has been performed. From the biological investigation, it is found that out of all the synthesized two compounds show potent CNS agent activity. **Conclusion**: The literature proves that Phenytoin show effects like cytotoxic activity, antiarrhythmic activity, anticonvulsant, CNS agent etc. From result and discussion we come to know that the substitutions on aromatic amine have great significance on yield value. The percentage yield is increased by substitution at para and Meta position of the ring whereas it decreases in case of ortho substitution due to steric effect. The steps included condensation followed by N Acylation, Vilsmeier-Haack reaction or Thermal cycloaddition. This article provides various methods to prepare more derivatives of Phenytoin to explore more activities of phenytoin.

KEYWORDS: Phenytoin, Heterocyclic compound, CNS Agent.

INTRODUCTION

Phenytoin Derivatives are Antiepileptic Drug which is available in the market, different type of drugs are available in the market. For Antiepileptic belongings to brand mephabarbitol drugs are available in the market. Which is used for all types of tonic clonic Seizure or absence seizure in one and the other human being and animal. Phenytoin has molecular formula $C_{15}H_{12}N_2O_2$.

The intravenous form is used for status epileptics that does not improve with benzodiazepines. This is the application of certain pericardium to normal heartbeat patterns or thyroid disorders and chronic obstructive pulmonary disease (COPD). It can be Drug Administration Deeper tissues or by or orally ingestion is the oldest and commonest mode of drug administration. The Deeper tissues form commonly go about active within 30 min. and is effectual for 24 hrs. Lifeblood quantity could be. Uniformity to determined the regular dosage.

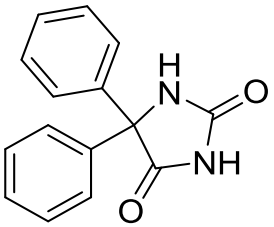

Fig. 1: Sodium 5, 5-diphenyl-2, 4-imidazolidinedione.

Common side effects include nausea, stomach pain, and loss of appetite, poor coordination, increased hair growth, and enlargement of the gums. The serious side effects include sleepiness, self-harm, liver problems, bone marrow suppression, low blood pressure, and toxic epidermal necrolysis. As evidence, the use results in the abnormalities in the babies. It appears to be safe to use when breastfeeding. Alcohol may interfere with the medication's effects.

Tonic-clonic seizures: Mainly used in the prophylactic management of tonic-clonic seizures with complex symptomatology (psychomotor seizures). For anticonvulsant effects, a period of 5-10 days may be required.

Focal seizures: The main function is protection against the development of focal seizures with complex symptomatology (psychomotor and temporal lobe seizures). The effect can be seen in controlling partial seizures with autonomic symptoms also.

Absence seizures: Due to risk for increasing frequency of seizures, it is not used in treatment of pure absence seizures. However, the combination can be used with other anticonvulsants during combined absence and tonic-clonic seizures. Seizures during surgery: A 2018 meta-analysis found that, in the first week after neurosurgery for brain tumors early antiepileptic treatment with either phenytoin or phenobarbital reduced the risk of seizure.

Status epilepticus: Considered after failed treatment using a benzodiazepine due to slow onset of action.

Phenytoin CNS agent are Central nervous system agents are the most widely used group of pharmacologic agents that affect the central nervous system (CNS). These agents are used to treat a wide range of neurologic and psychiatric disorders like anxiety, psychosis, depression, mania, convulsion, Parkinson, Alzheimer's disease etc. Almost all the drugs having CNS effects act on specific receptors which modulate synaptic transmission. A very few agents such as general anesthetics and alcohol may have non-specific actions on membranes (although these exceptions are not fully accepted), but even these non–receptor-mediated actions result in demonstrable alterations in synaptic transmission.

Literature Review of Phenytoin

A researcher who is primarily interested in the synthesis of some particular medicinal agents, however, will often find that he must consult either the original literature review or some specialised articles was performed from the chemical abstracts of National & International journals. Thus, through our survey we found the following references:-

Saunthwal R *et al.*, (2019) carried out the synthesis of 5, 5-disubstituted hydantoins by tandem a-amination and α-arylation of silyl ketene acetals. The product subdues ring closure to a hydantoin, which may itself be unprotected and featured. Aryl migration is successful with rings of various electronic character and with esters bearing functionalised and unfunctionalised chains, and the products have features in common with several bioactive compounds.

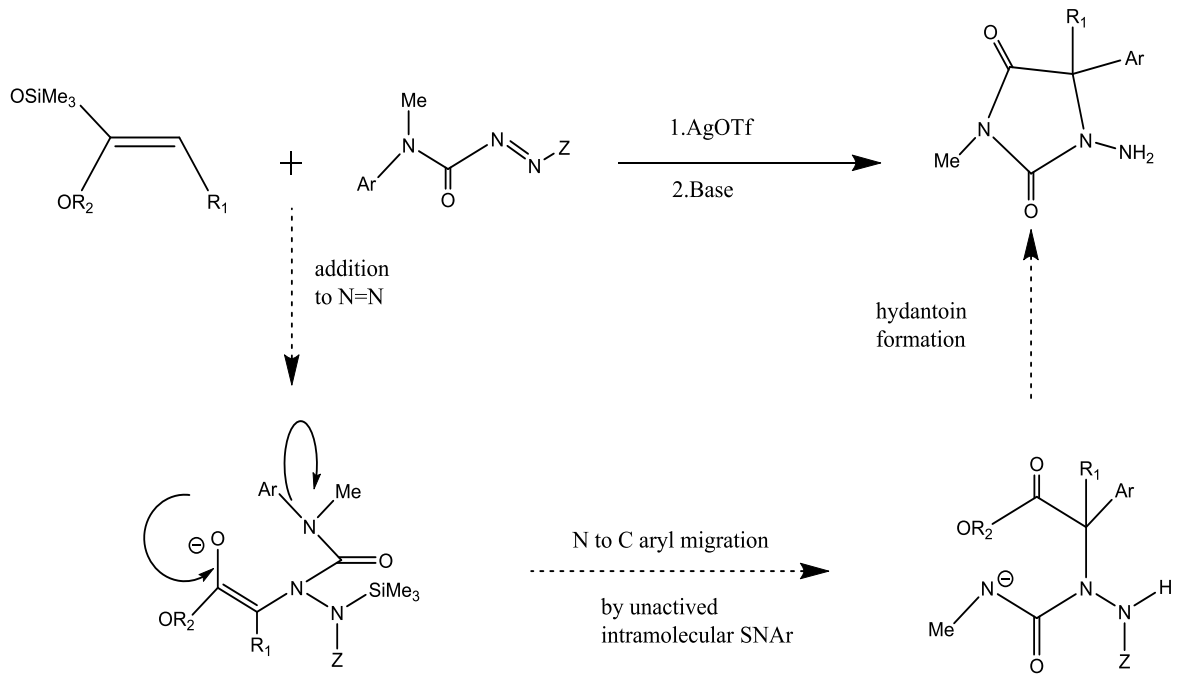

Fig. 2.

Clayden J *et al.*,(2018) carried out the enantioselectively functionalised phenytoin derivatives by auxiliary-directed N to C aryl migration in lithiated α-amino nitriles. That may be hydrolysed to give chiral 5, 5-diarylhydantoins relate to Phenytoin. The resulting N'-lithiated ureas come by spontaneous cyclisation to iminohydantoins.

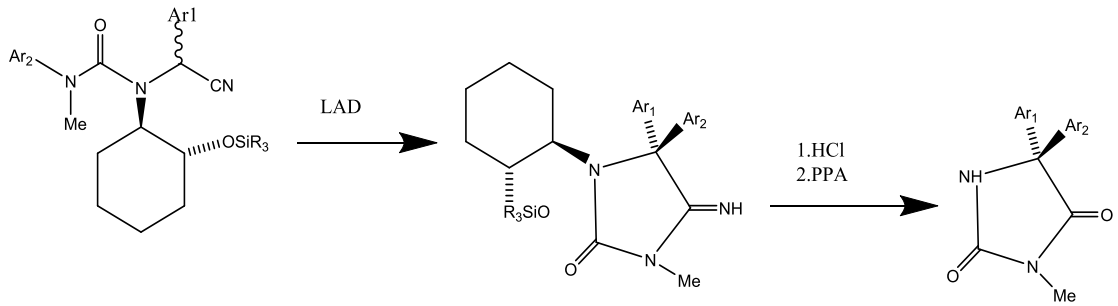

Fig. 3.

Verma. S *et al.*, (2017) carried out the synthesis of one pot synthesis of 1, 5-benzodiazepines and its chloroacetylated derivatives. The synthesized compounds and its physicochemical parameters were evaluated in order to determine the potency of the compounds for good CNS activity. Glacial acetic acid was used to make this reaction solvent free and very efficient with highyield.[15-19]

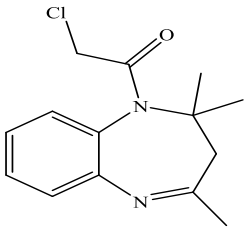

Fig. 4.

Verma. S *et al.*,(2017) Carried out the synthesis of A series of new N-(2-benzoyl-4-chlorophenyl)-2-(4-(substituted phenyl) piperazin-1-yl) acetamides. The compounds were screened for the anxiolytic and skeletal muscle relaxant activity in which computational studies with molecular docking revealed that the target compounds correctly dock into the binding pocket of the GABAA receptor.

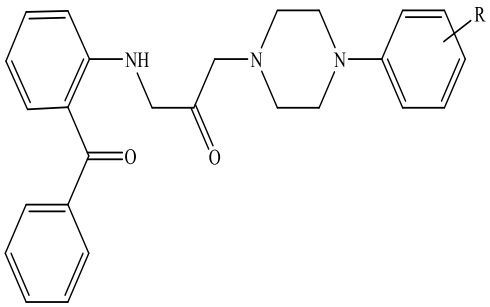

Fig. 5.

Śladowska K *et al.*,(2017) carried out the modification in chemical structure of phenytoin. A possible cytotoxic activity of three bromoalkyl phenytoin analogs and this modification in structure give possible antileukemic action. (Śladowska, K., Opydo-Chanek, M., Król, T., Trybus, W., Trybus, E., Kopacz-Bednarska, Anna. Handzlik, J., Kieć-Kononowicz, K., & Mazur, Lidia. Cell cycle and fine structure of blood cancer when you develop leukemia, your bone marrow begins to make abnormal white blood cells (WBCs). In vitro impact of Bromoalkyl phenytoin Derivatives on regulative Death.

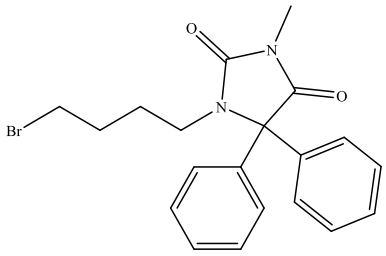

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Fig. 6.

Singh *et al.*,(2015) carried out the synthesis of 2-amino-5-chlorobenzophenone derivatives. The all drugs were synthesized in such a way that they have the physicochemical parameters the blood brain barrier (BBB) through online software found to be CNS active. The log P value of all the were determined experimentally and calculated through very much similar to values of log P online softwares and was calculated by chemsilico method. required for good CNS activity. The compounds were screened for the skeletal muscle relaxant activity and from the investigation.

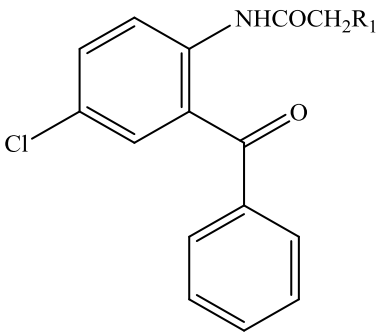

Fig. 7.

Saeedia *et al.*,(2014) carried out the synthesis some novel sulfonamide and amide derivatives containing coumarin moieties. The compounds were screened for their antimicrobial and antioxidant activities. Their antimicrobial activity was assigned using the conventional agar dilution method and the antioxidant activity was assessed using two methods, 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method and ferric reducing antioxidant power (FRAP) assay.

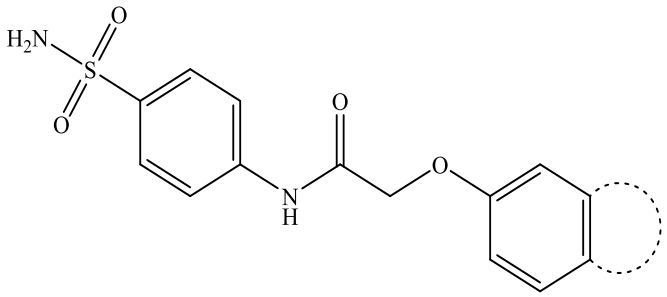

Fig. 8.

Pusuluri *et al.*,(2014) carried out synthesis of pyrrolo[1,4] benzodiazepines derivatives by both conventional and microwave assisted intramolecular cyclocondensation and evaluated for anticonvulsant, sedative and anxiolytic activity by drug-induced convulsion model, a pentobarbital induced hypnotic model and elevated plus-maize in mice.

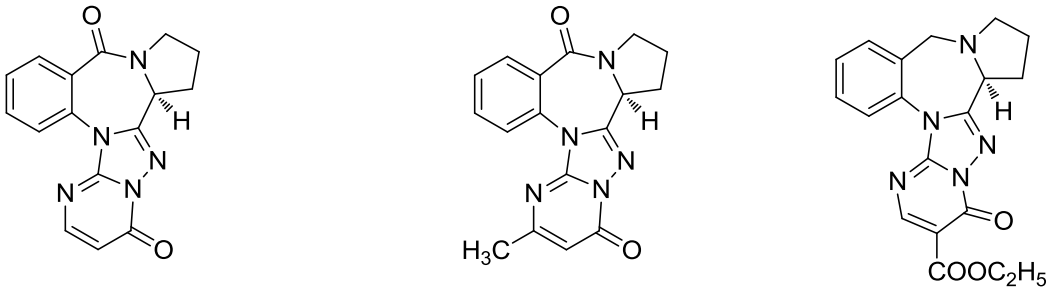

Fig. 9.

Botros S *et al.,* (2013) carried out the synthesis of new phenytoin derivatives. In this, Hybrids between phenytoin and thiosemicarbazide, 1, 3, 4-oxadiazole, 1, 3, 4-thiadiazole or 1, 2, 4-triazole were synthesized and tested for anticonvulsant activity. Initially anticonvulsant subcutaneous pentylenetetrazole (scPTZ) screen in mice and screening was performed used standard maximal electroshock (MES). (Botros S, Khalil NA, Naguib, BH, El-Dash Y (2013). Synthesis and anticonvulsant activity of new phenytoin derivatives. European Journal of Medicinal Chemistry, 60: 57–63).

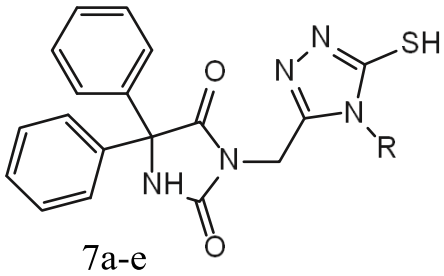

Fig. 10.

Sharma *et al.,*(2013) carried out an efficient method for synthesis of some novel 7-(1*H*-benzimidazol-2-ylazo)-1, 3-dimethyl-6,8-disubstituted-1*H* pyrimido [4,5-*b*]-[1,4] diazepine-2,4-diones in water to obtain the compounds in high yield by simple and inexpensive manner. The compounds were screened for antianxiety activity in mice.

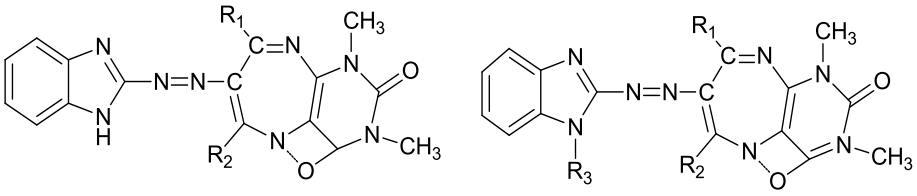

Fig. 11.

Ramadhan UH *et al.*, (2012) carried out the synthesis of new Phenytoin Derivative. In this, the Carrageenan induced inflammation model was used to determine the anti-inflammatory activity. The Inflammations were induced by sub-plantar injection of homogenous suspension of (1%) carrageenan in water. The Phenytoin derivative (with histidine) has significant.

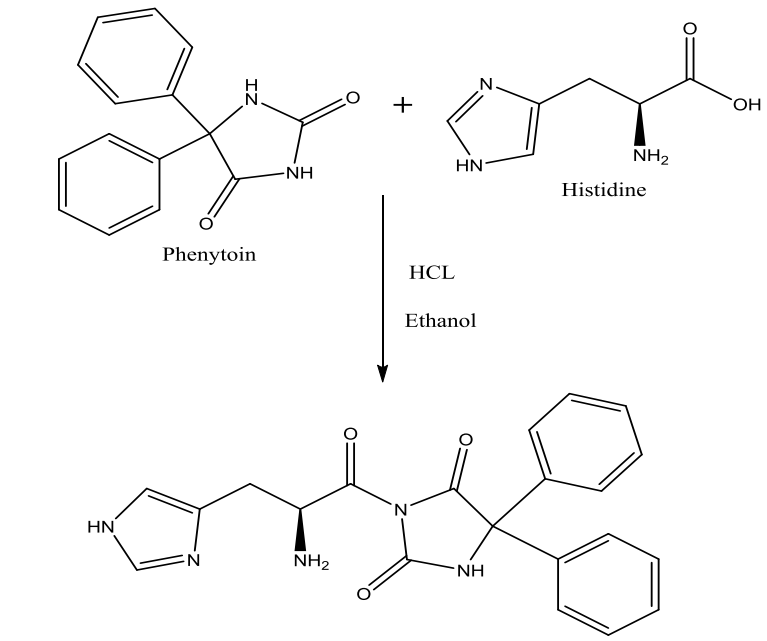

Fig. 12.

Gbaguidi FA *et al.*,(2011) carried out the synthesis of phenytoin and related compounds using microwave activation. In which first step involves the treatment of a benzil derivative by thiourea in dimethylsulfoxide (DMSO) in aqueous KOH under microwave activation. The corresponding hydantoin using perhydrol in dimethylformamide (DMF) in acetic acid, the resulting 2-thiohydantoin was then oxidized. High yield is proceeded in both the cases. African Journal of Pure and Applied Chemistry, 5(7), 168-175).

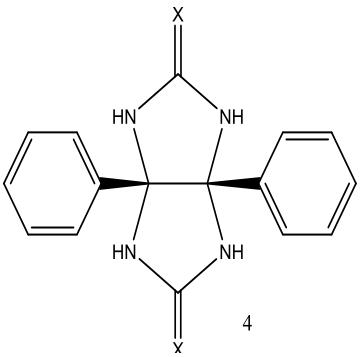

Fig. 13.

Deodhar M *et al.*,(2009) carried out the synthesis of phenytoin derivatives by 2,5-Dioxo-4,4-diphenylimidazolidine-1-carboxylic acid was reacted with methyl ester of different amino acids and substituted benzhydrols in pyridine to yield a series and in the presence of N,N dicyclohexyl carbodiimide (DCC) of the title compounds, These newly synthesized derivatives of phenytoin were evaluated of anticonvulsant activity.

Safari J *et al.*,(2009) carried out the preparation of phenytoin derivatives under solvent-free Conditions using microwave irradiation.

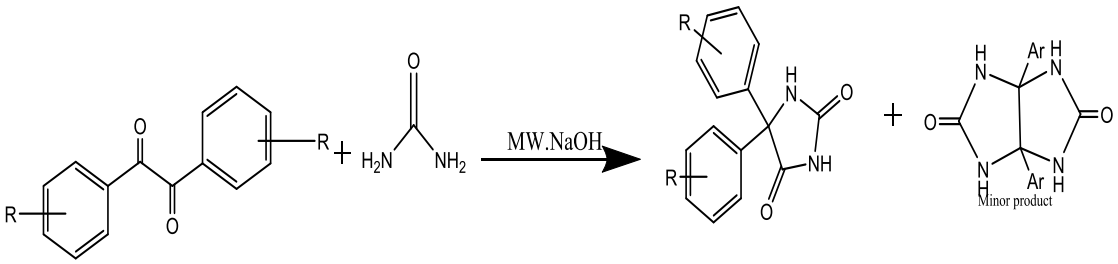

Fig. 14.

CONCLUSION

From the above discussion, it can be concluded that the various methods had been reported for the preparation of Phenytoin derivatives. The literature proves that Phenytoin show effects like cytotoxic activity, antiarrhythmic activity, anticonvulsant, CNS agent etc. From result and discussion we come to know that the substitutions on aromatic amine have great significance on yield value. The percentage yield is increased by substitution at para and Meta position of the ring whereas it decreases in case of ortho substitution due to steric effect. The steps included condensation followed by N Acylation, Vilsmeier-Haack reaction or Thermal cycloaddition. This article provides various methods to prepare more derivatives of Phenytoin to explore more activities of phenytoin.

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