International Journal of Research in Engineering and Science (IJRES)
ISSN (Online): 2320-9364, ISSN (Print): 2320-9356
www.ijres.org Volume 12 Issue 1 ǁ January 2024 ǁ PP. 206-210

Study on the Synthesis, Characterization and Antimicrobial Activities of 5-Substituted Hydantoins.

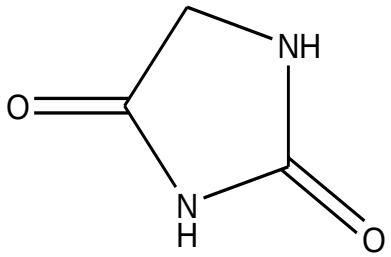
GAJANAN B. INGLE and DR. SANJAY V. KOLHE
Department of Chemistry, Shri Shivaji Arts, Commerce and Science College, Akot, Dist.Akola-444101, (Maharashtra), India.
**Corresponding author E-mail: gajananpatilingle19@gmail.com*

Abstract
Hydantoin, imidazolidine-2,4-dione, demonstrated by its use in a number of clinically authorized medications, including phenytoin, nitrofurantoin, and nilutamide etc. is a highly valued and preferred heterocyclic scaffold in the field of medicinal chemistry. Numerous pharmacological and biological characteristics, such as antibacterial, anticonvulsant, antidiabetic, anticancer, and anti-inflammatory effects, are displayed by the hydantoin scaffold. The main objective of this thorough review is to investigate the potential of hydantoin derivatives as antimicrobial agents and clarify their various mechanisms of action.
Keywords: *Hydantoin, Drugs, Antimicrobial properties, Pharmacophores, Heterocycles, Bioactive molecules, etc.*

Date of Submission: 07-01-2024 Date of acceptance: 20-01-2024

I. Introduction

Hydantoin is a heterocyclic compound with five members, also referred to as imidazolidine-2,4-dione. The class of chemicals that use the hydantoin substructure as a scaffold is generally referred to as "hydantoins" [1]. Heterocyclic-based scaffolds are well known to be extremely useful for finding bioactive molecules.



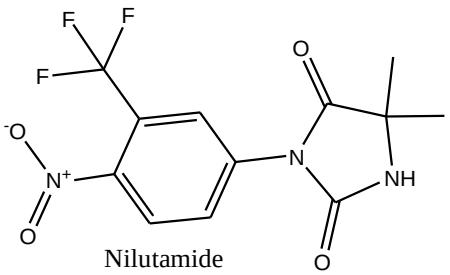
Hydantoin

imidazolidine-2,4-dione

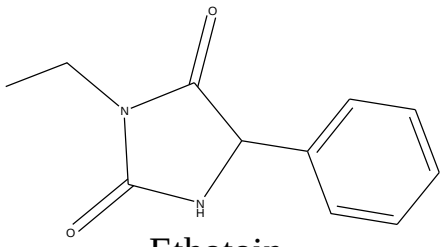
These scaffolds have one carbon atom in the ring structure plus at least one heteroatom, such as nitrogen, sulfur, or oxygen. They may successfully generate intermolecular hydrogen bonds with biological targets thanks to their structural arrangement, which allows them to behave as hydrogen bond donors or acceptors [2]. Consequently, because these compounds have important pharmacophoric moieties or structural features and may find use in business and medicine, they have been thoroughly studied [2].

Hydantoin has four hydrogen donors and acceptors despite its small size [3]. The androgen receptor antagonists nilutamide, andenzalutamide, the muscle relaxants nitrofurantoin and dantrium, and the anticonvulsants phenytoin, mephenytoin,ethotoin, and fosphenytoin are a few examples of clinically approved medications containing the hydantoin moiety [1]. Many pharmacological and biological properties, such as anticancer [4-6], anti-inflammatory [7,8], antidiabetic [9], antibacterial [10,11], adrenoceptor modifying [12–14], anticonvulsant [15,16], antiplatelet [17], and anti-HIV activity [18,19], are exhibited by compounds based on hydantoin. Additionally, there are two widely used synthetic techniques for the manufacture of hydantoin. The first technique uses the Bucherer Bergs reaction, a single-step reaction involving potassium cyanide and ammonium carbonate that makes use of the matching cyclic ketones.

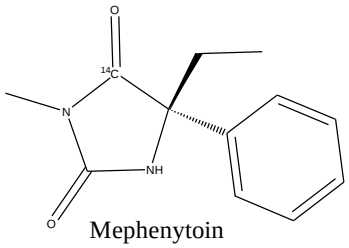
In summary, we described the importance and recent applications of hydantoin, 2-thiohydantoin, and selenohydantoin scaffolds in medicinal chemistry owing to their wide range of pharmacological properties. The data presented herein showed that many drug discovery projects took advantage of the chemical diversifiability and readiness for the synthesis of hydantoin. The hydantoin moiety functioned in two ways, specifically to frame structural components as medicinal scaffolds and pharmacophores as…



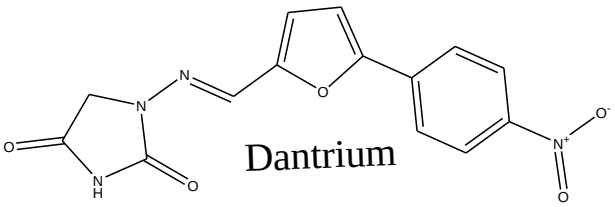
Nilutamide



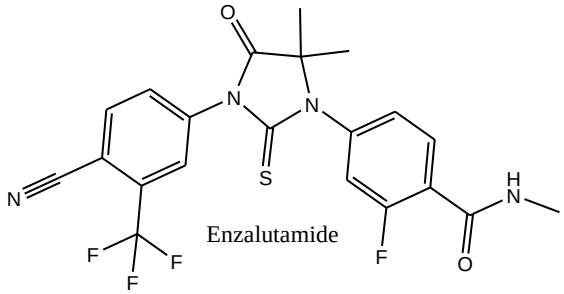
Ethotoin



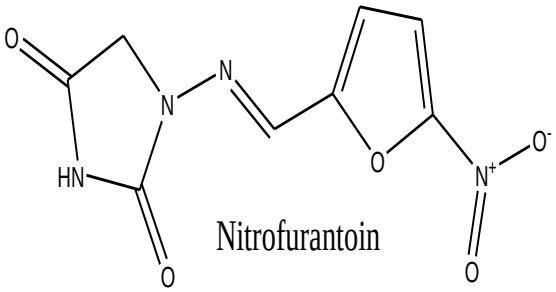
Mephenytoin



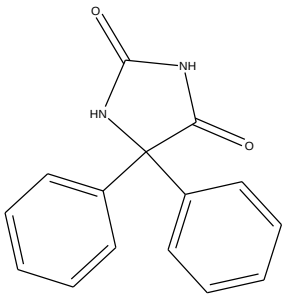
Dantrium



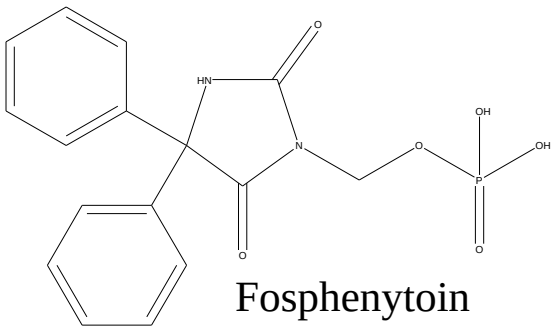
Enzalutamide



Nitrofurantoin



Phenytoin



Fosphenytoin

Figures: Some Clinically approved drugs containing the hydantoin moiety

Infectious diseases are stay chief deaths cause especially in rising countries, for instance new infectiousdiseases ascend and a developing number of multi-drug resistant strains of microbial pathogens occur [1]

Multidrug resistance indicates acritical function in the letdown of remedy of cancer and infectious illnesses [2]. Microorganisms have developedvarious approaches to face up to the antibiotics poisonous effects and different capsules [3],[4]. Discovery ofchemotherapeutic marketers played a very necessary position in controlling and preventing such diseases. Chemotherapeutic dealers are remoted both from dwelling organisms recognized as antibiotics, or they arechemical compounds organized throughchemist [5],[6]. Hydantoin derivatives have a diversity of biochemical andpharmacological traits and are used to deal with quite a few human ailments and extensive vary of otherpharmacological characteristics.

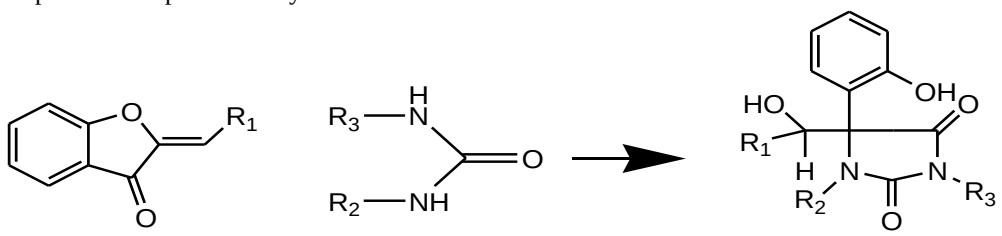
Fujisaki et al. 2013, reportedthe study investigates molecular modifications of new oxazolidinones against Gram-positive and Gram-negative strains. It investigates 4-aminomethyloxazolidin-2-ones, 4-

acylaminomethyloxazolidin-2-one derivatives, twin-drug type molecules, and synthesizes of additional 4-dialkylaminomethyloxazolidin-2-ones.

II. Material and method

All chemicals and reagents used in this research were commercially sourced and of analytical grade. The purity of resultant compoundwas check by using TLC. The IR spectra were recorded in KBr by using FT-(IR Perkin Elmer-Spectrum RX-FTIR). Mass spectra were recordedon mass spectrometer while 1 HNMR wererecorded on FT NMR Spectrometer (BrukerAvance Neo 500 MHz).

General Procedure for synthesis ofhydantoinderivatives: - Equimolar Aurone and N-substituted urea were taking in round bottom flaskalong with KOH and Ethanol as a solvent. Areaction mixture was reflux for few hours. After thisperiod, the mixture was poured in to ice cold waterand filter it by using Buchner funnel and suction pump. The final productrecrystallized with Ethanol.



Synthesis of5-(2-hydroxy-2-(4-methoxyphenyl)ethyl)-5-(2-hydroxyphenyl)-3-methylimidazolidine-2,4-dione (3a):2-(4-methoxybenzylidene)benzofuran- 3(2H)-one reflux withN-methyl ureain presence of KOH and appropriateethanol solvent up to few hours. After completion ofreaction, cooled the mixture and poured in to ice coldwater. The solid product obtained which was filterand washed with dilute HCl and water. The productwas crystallized by using ethanol.

Mol. Formula: $C_{19}H_{20}O_5N_2$: YellowishCrystalline solid. **m. p.** 248^oC **yield** 75%, **Elemental analysis** (%): C, 64.04; H, 5.66; N, 7.86; O,22.45; **IR** (KBr cm-1) 3627.5 (OH), 3020 (=CH), 1625(C=N), 1442 (Ar C=C), **ESI-MS[M+H]** + Calculated for$C_{19}H_{20}O_5N_2$: m/z 356.14, 357.14, 358.14; **1 H-NMR**(500 MHz, DMSO) 2.29-2.41 (s, 3H), 2.35 (s, 1H), 3.33 (m, J=8.4,1.1 Hz, 11H), 3.74-4.58(m, 6H).

Synthesisof5-(2-hydroxy-2-(4-methoxyphenyl) ethyl)-5-(2-hydroxyphenyl)-3-phenylimidazolidine-2,4-dione(3b):2-(4-methoxybenzylidene) benzofuran- 3(2H)-one reflux with N-phenyl ureain presence of KOH and appropriate ethanolsolvent up to few hours. After completion of reaction,cooled the mixture and poured in to ice cold water.The solid product obtained which was filter andwashed with dilute HCl and water. The product wascrystallized by using ethanol.

Mol. Formula $C_{24}H_{22}N_2O_5$: faintyellowish Crystalline solid, **m.p.** 258^oC, **yield**78%,**Elemental analysis** (%): C,68.89; H,5.30; N, 6.69;O, 19.12; **IR** (KBr cm -1) 3645.5 (OH), 3032 (=CH), 1631 (C=N), 1455 (Ar C=C),**ESI-MS[M+H]**+ Calculated for$C_{24}H_{22}O_5N_2$: m/z 418.15, 419.16, 420.16,**1 H-NMR** (500 MHz, DMSO) 6.0 (s, 1H), 7.08(m, J=8.0,7.0 Hz, 1H), 7.64(m, J=8.3,1.6,0.5 Hz,8H), 7.68 (m, J=8.0,1.4 Hz, 1H).

Antibacterial Assay: The Antibacterial activity was checked by following Zone Inhibition Method (Kirby-Bauer method). The MHA plates were inoculated by spreading with 100 µl of Bacterial culture, *E. coli* (adjusted to 0.5 McFarland Unit - Approx cell density (1.5 X 10^8 CFU/mL) and followed by placing the discs containing 10 µl of different concentration (0 to 100 mg/ml). 10 % of the sample was taken and serially diluted to achieve the required amount to be loaded on the disc. One disc in each plate was loaded with solvent alone which served as vehicle control and Ciprofloxacin disc (10µg) were taken as positive control. The plates of *E. coli* were incubated at 37 °C for 24 hrs. A clear zones created around the disc were measured and recorded.

Antifungal Assay: The Antifungal activity was checked by following Zone Inhibition Method (Kirby-Bauer method). The PDA plates were inoculated by spreading with 100 µl of fungal culture, A. niger (adjusted to 0.5 McFarland Unit - Approx cell density (1.5 X 108 CFU/mL) and followed by placing the discs containing 10 µl of different concentration (0 to 100 mg/ml). One disc in each plate was loaded with solvent alone which served as vehicle control and Amphotericin B (50µg) were taken as positive control. The plates of A. niger were incubated (Basil Scientific Corp. India- Incubator) at 37 °C for 48 hrs. The clear zones created around the disc were measured and recorded.

III. Results and Discussion

Based on the study, in the experimental work when test organism E. coli,A.niger,M. tuberculosis ,S. aureus was exposed with different amounts of disks on agar plate, sample 3a , 3b were found active against E. coli A.niger,M.tuberculosis,S.aureus and shown antibacterial activity against the organisms. Sample **3a** shown zone of inhibition (17mm) around the disk at highest dose of 1000 µg with respect to positive control 23.67 mm diameter zone at 10 µg dose while Sample **3b** shown highest zone of inhibition (6 mm) around the disk at highest dose of 1000 µg with respect to positive control 22.33 mm diameter zone at 10 µg dose.

IV. Conclusion

A novel set of imidazolidine-2, 4-dione compounds **3a** and **3b** have synthesized and characterized successfully. The screening of antimicrobial activity shows that both compounds possess antimicrobial activities. In addition, the objective of the study was succeeded with the promising molecules, which are proving to be a potential treatment of bacterial infection candidates.

Aim of the Study

Synthesis and analyzing for new hydantoin derivative (compound) as a precise antimicrobial action which maybe suitable to be used as chemotherapeutic means.

Acknowledgement

We are thankful to Principal Dr. S.H. Pande and Department of chemistry Shri Shivaji Art's, Commerce and Science College Akot for providing lab equipment's. Also thankful to Shri D. M. Jakate for his cooperation. We are also thankful to CIL and SAIF, Panjab University, Chandigarh for providing spectral data, Aakaar Biotech, Lucknow for providing antimicrobial screening data.

Declaration of Competing Interest

The authors declare no conflict of interest.

References

[1]. S.H. Cho, S.H. Kim, D. Shin, Recent applications of hydantoinand thiohydantoin in medicinal chemistry, Eur. J. Med. Chem. 164 (2019) 517 -545.https://doi.org/10.1016/j.ejmech.2018.12.066B

[2]. M.A.Tantawy, M.S. Nafie, G.A. Elmegeed, I.A.I. Ali,Auspicious role of the steroidal heterocyclic derivatives as a platform foranti-cancer drugs, Bioorg. Chem. 73 (2017) 128–146.https://doi.org/10.1016/j.bioorg.2017.06.006

[3]. C. Avendaño, J.C. Menendez, Hydantoin and Its Derivatives, in: Kirk-Othmer Encycl. Chem. Technol., John Wiley & Sons, Inc.,Hoboken, NJ, USA, 2000.https://doi.org/10.1002/0471238961.0825040101220514.a01

[4]. C. V. Kavitha, M. Nambiar, C.S. Ananda Kumar, B. Choudhary, K. Muniyappa, K.S. Rangappa, S.C. Raghavan, Novel derivatives ofspirohydantoin induce growth inhibition followed by apoptosis inleukemia cells, Biochem. Pharmacol. 77 (2009) 348–363.https://doi.org/10.1016/j.bcp.2008.10.018.

[5]. C. Carmi, A. Cavazzoni, V. Zuliani, A. Lodola, F. Bordi, P.V.Plazzi, R.R. Alfieri, P.G. Petronini, M. Mor, 5-Benzylidene-hydantoins asnew EGFR inhibitors with antiproliferative activity, Bioorganic Med.Chem. Lett. 16 (2006) 4021–4025.https://doi.org/10.1016/j.bmcl.2006.05.010.

[6]. Basappa, C.S. Ananda Kumar, S. NanjundaSwamy, K.Sugahara, K.S. Rangappa, Anti-tumor and anti-angiogenic activity ofnovelhydantoin derivatives: Inhibition of VEGF secretion in livermetastatic osteosarcoma cells, Bioorganic Med. Chem. 17 (2009) 4928–4934. https://doi.org/10.1016/j.bmc.2009.06.004 .

[7]. S.M. Sondhi, J. Singh, A. Kumar, H. Jamal, P.P. Gupta,Synthesis of amidine and amide derivatives and their evaluation for anti-inflammatory and analgesic activities, Eur. J. Med. Chem. 44 (2009) 1010–1015. https://doi.org/10.1016/j.ejmech.2008.06.029 .

[8]. A.S.H. Da Silva Guerra, D.J. Do Nascimento Malta, L.P. MoraisLaranjeira, M.B. Souza Maia, N. CavalcantiColaço, M. Do CarmoAlvesDe Lima, S.L. Galdino, I. Da Rocha Pitta, T.Gonçalves-Silva, Anti-inflammatory and antinociceptive activities of indole-imidazolidinederivatives, Int. Immunopharmacol. 11 (2011) 1816–1822.https://doi.org/10.1016/j.intimp.2011.07.010.

[9]. D. Sergent, Q. Wang, N.A. Sasaki, J. Ouazzani, Synthesis ofhydantoin analogues of (2S,3R,4S)-4-hydroxyisoleucine withinsulinotropic properties, Bioorganic Med. Chem. Lett. 18 (2008) 4332–4335. https://doi.org/10.1016/j.bmcl.2008.06.081.

[10]. J. Handzlik, E. Szymańska, J. Chevalier, E. Otrbska, K. Kieć-Kononowicz, J.M. Pags, S. Alibert, Amine-alkyl derivatives of hydantoin:New tool to combat resistant bacteria, Eur. J. Med. Chem. 46 (2011) 5807–5816. https://doi.org/10.1016/j.ejmech.2011.09.032.

[11]. F. Fujisaki, K. Shoji, M. Shimodouzono, N. Kashige, F. Miake, K.Sumoto, Antibacterial Activity of 5-Dialkylaminomethylhydantoins andRelated Compounds, Chem. Pharm. Bull. 58 (2010) 1123–1126.https://doi.org/10.1248/cpb.58.1123

[12]. P.A. Procopiou, V.J. Barrett, N.J. Bevan, P.R. Butchers, R.Conroy, A. Emmons, A.J. Ford, S. Jeulin, B.E. Looker, G.E. Lunniss, V.S.Morrison, P.J. Mutch, R. Perciaccante, M. Ruston, C.E. Smith, G. Somers,The discovery of long-acting saligenin β 2 adrenergic receptor agonistsincorporatinghydantoin or uracil rings, Bioorganic Med. Chem. 19 (2011)4192–4201. https://doi.org/10.1016/j.bmc.2011.05.064.

[13]. J.J. Handzlik, E. Szymańska, K. Ndza, M. Kubacka, A. Siwek, S.Mogilski, J.J. Handzlik, B. Filipek, K. Kieć-Kononowicz, Pharmacophoremodels based studies on the affinity and selectivity toward 5-HT1A withreference to α1-adrenergic receptors among arylpiperazine derivatives ofphenytoin, Bioorganic Med. Chem. 19 (2011) 1349–1360.https://doi.org/10.1016/j.bmc.2010.11.051.

[14]. J. Handzlik, D. Maciag, M. Kubacka, S. Mogilski, B. Filipek, K.Stadnicka, K. Kieć-Kononowicz, Synthesis, α1-adrenoceptor antagonistactivity, and SAR study of novel arylpiperazine derivatives of phenytoin,Bioorganic Med. Chem. 16 (2008) 5982–5998.https://doi.org/10.1016/j.bmc.2008.04.058.

[15]. Q. Zhu, Y. Pan, Z. Xu, R. Li, G. Qiu, W. Xu, X. Ke, L. Wu, X. Hu,Synthesis and potential anticonvulsant activity of new N-3-substituted5,5-cyclopropanespirohydantoins, Eur. J. Med. Chem. 44 (2009) 296–302.https://doi.org/10.1016/j.ejmech.2008.02.024.
[16]. H. Byrtus, J. Obniska, A. Czopek, K. Kamiński, Synthesis andanticonvulsant activity of new N-Mannich bases derived from 5cyclopropyl-5-phenyl-hydantoins, Arch. Pharm. (Weinheim). 344 (2011)231–241. https://doi.org/10.1002/ardp.201000241.
[17]. H.U. Stilz, W. Guba, B. Jablonka, M. Just, O. Klingler, W. König,V. Wehner, G. Zoller, Discovery of an orally active non-peptide fibrinogenreceptor antagonist based on the hydantoin scaffold, J. Med. Chem. 44(2001) 1158–1176. https://doi.org/10.1021/jm001068s.
[18]. D. Kim, L. Wang, C.G. Caldwell, P. Chen, P.E. Finke, B. Oates, M. MacCoss, S.G. Mills, L. Malkowitz, S.L. Gould, J.A. DeMartino, M.S.Springer, D. Hazuda, M. Miller, J. Kessler, R. Danzeisen, G. Carver, A.Carella, K. Holmes, J. Lineberger, W.A. Schleif, E.A. Emini, Discovery ofhuman CCR5 antagonists containing hydantoins for the treatment of HIV-1 infection, Bioorg. Med. Chem. Lett. 11 (2001) 3099–3102.https://doi.org/10.1016/S0960-894X(01)00654-0.
[19]. D. Kim, L. Wang, C.G. Caldwell, P. Chen, P.E. Finke, B. Oates,M. MacCoss, S.G. Mills, L. Malkowitz, S.L. Gould, J.A. DeMartino, M.S.Springer, D. Hazuda, M. Miller, J. Kessler, R. Danzeisen, G. Carver, A.Carella, K. Holmes, J. Lineberger, W.A. Schleif, E.A. Emini, Design,synthesis, and SAR of heterocycle-containing antagonists of the humanCCR5 receptor for the treatment of HIV-1 infection, Bioorg. Med. Chem.Lett. 11 (2001) 3103–3106. https://doi.org/10.1016/S0960-894X(01)00655-2.
[20]. K.WianiHidayat, T.Yee,Y. David, S.T..C. Black, and R.W. Read, Biological evaluation of certain substitutedhydantoins and benzalhydantoins against microbes.IOP Conf. Ser.: Mater. Sci.Eng.107-012058.2016.
[21]. D.Zhang, J. Xia,Y. Xu ,M. Gong , Y. Zhou, L. Xie, et al. . Biological features of biofilm forming ability ofAcinetobacterbaumannii strains derived from 121 elderly patients with hospital-acquired pneumonia. Clin. Exp.Med. 16: 73–80.2016.
[22]. C.Ding, and J.He, . Effect of antibiotics in the environment on microbial populations. ApplMicrobiolBiotechnol; 87(3): 925-941.2010.
[23]. L.Gatti ,G.L,Beretta G, Cossa F. Zunino, and P. Perego : ABC transporters as potential targets formodulation of drug resistance. Mini Rev Med Chem. 9(9): 1102-1112. 2009.
[24]. I. Su, M.S.Xia, P.Teng, A. Nimmagadda, C. Zhang, T. Odom, A. Cao,Y. Hu, and J. Cai, . Membrane-ActiveHydantoin Derivatives as Antibiotic Agents.J. Med. Chem, 60 (20); 8456–8465.2017.
[25]. Z.H. Chohan, In-vitro antibacterial, antifungal and cytotoxic properties of metal-based furanylderivedsulfonamides J.Appl.Organomet. Chem., 20; 112-116, 2006.