The Pharmaceutical and Chemical Journal, 2020, 7(3):100-107

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Exploring the Therapeutic Potential of Hydrazide-Hydrazone Derivatives: A Comprehensive Review

Shalini Agarwal, Anju Goyal

Faculty of Pharmacy, B N University, Udaipur, Rajasthan 313001

Abstract The exploration of novel compounds with antibacterial, anticancer, and anticonvulsant activities is a significant area of research due to the rising challenges posed by drug-resistant bacterial strains, cancer, and neurological disorders. The continual rise of drug-resistant bacterial strains, the complex challenges associated with cancer, and the persistent enigma of neurological disorders have fueled an ongoing quest for innovative therapeutic agents. Among the myriad compounds under investigation, hydrazide-hydrazone derivatives have emerged as promising candidates with diverse biological activities. This comprehensive review delves into recent advancements in the synthesis and multifaceted biological roles of hydrazide-hydrazone derivatives, particularly focusing on their antibacterial, anticancer, and anticonvulsant properties. The hydrazide-hydrazone moiety is known for its ability to form coordination complexes with metal ions, which can influence the biological activity of the compounds. Additionally, the hydrazone group may act as a bioisostere for the carbonyl group in various drug molecules. Researchers have synthesized and studied a variety of hydrazide-hydrazone derivatives to explore their structure-activity relationships and optimize their pharmacological properties. The versatility of these derivatives allows for the development of compounds with specific activities against different biological targets. It's important to note that the therapeutic potential of hydrazide-hydrazone derivatives is a broad and evolving field, and ongoing research may uncover new applications or refine our understanding of their mechanisms of action.

Keywords Hydrazide-Hydrazone, bioisostere, Therapeutic Potential

1. Introduction

In recent years, the field of medicinal chemistry has witnessed a surge in research focused on novel compounds with promising therapeutic potential. Among these, hydrazide-hydrazone derivatives have emerged as a class of compounds exhibiting diverse pharmacological activities, making them intriguing candidates for drug development. This comprehensive review aims to delve into the molecular intricacies and therapeutic capabilities of hydrazide-hydrazone derivatives, shedding light on their structural diversity, synthetic strategies, and multifaceted pharmacological applications.

Hydrazide-hydrazone derivatives, characterized by the presence of a hydrazide moiety (-$CONHNH_2$) and a hydrazone linkage (-NHN=), manifest an extensive structural diversity that underlies their varied biological activities. The synthesis of these compounds involves versatile methodologies, allowing for the modification of substituents to tailor their physicochemical properties. The integration of diverse functional groups into the hydrazide-hydrazone scaffold imparts unique characteristics, influencing their interactions with biological targets. Hydrazide-hydrazone derivatives exhibit diverse chemical properties owing to their unique molecular structures.

The presence of hydrazide groups imparts nucleophilic characteristics, facilitating interactions with various electrophilic species. Concurrently, the hydrazone moiety introduces potential for tautomerism, influencing the compound's reactivity and stability. Understanding these properties is crucial for elucidating their behavior in different chemical environments.

Understanding the synthetic routes is pivotal for designing derivatives with optimized pharmacological profiles. Researchers have employed classical methods such as condensation reactions, as well as modern techniques like microwave-assisted synthesis and click chemistry, to access a spectrum of hydrazide-hydrazone derivatives. This section of the review will provide an in-depth analysis of the synthetic strategies employed, emphasizing the impact of structural modifications on the pharmacological outcomes.

The therapeutic potential of hydrazide-hydrazone derivatives spans a wide range of biological activities, positioning them as versatile candidates for drug development. Notably, these compounds have exhibited antimicrobial, anticancer, anti-inflammatory, antiviral, and antioxidant activities, among others. The molecular mechanisms underlying these diverse effects are intricately linked to the structural attributes of hydrazide-hydrazone derivatives and their interactions with specific cellular targets. Exploration of these aspects in the review will elucidate the molecular pathways involved, providing a comprehensive view of the therapeutic landscape for these derivatives [1-10].

2. Synthesis Methods: Synthesis of various hydrazide derivatives

Several synthetic routes have been developed for the preparation of hydrazide-hydrazone derivatives, each method tailored to yield specific structural motifs. One common approach involves the condensation of hydrazides with carbonyl compounds, such as aldehydes or ketones, leading to the formation of hydrazone linkages. Alternatively, reactions involving acyl chlorides and hydrazine derivatives have been employed, highlighting the versatility in synthetic pathways.

Narang, Rakesh, et al reported compounds **4-21** in 2012 with different derivatives shown in figure 1. The newly synthesized compounds of nicotinic acid and benzylidene hydrazide derivatives were also tested for in vitro studies for antimicrobial activity in opposition to M. tuberculosis, antiviral and antimicrobial (*S. aureus, B. subtilis, E. coli, C. albicans* and *A. niger*). The studies showed that in presence of electron-withdrawing halogen groups at para position gave significant antimicrobial activity [11].

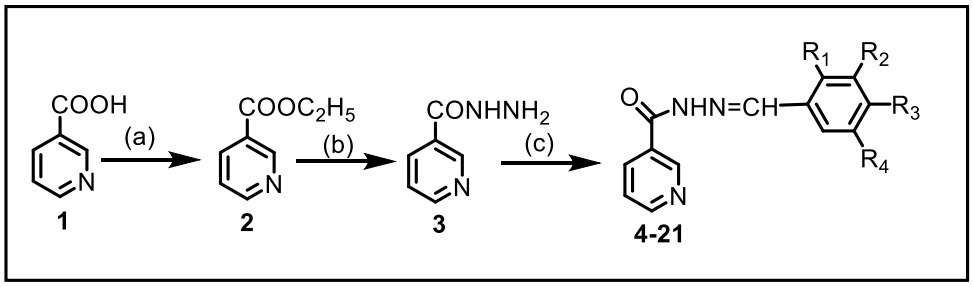

Figure 1: Synthesis of compound 4-21(a) EtOH/Δ (b) NH_2NH_2/H_2O (c) Ar-CHO

The studies done also suggested that these derivatives were not effective against other viral replication. The compounds having dimethoxy and nitro substituents showed significant activity against tested strains for antimicrobial activity

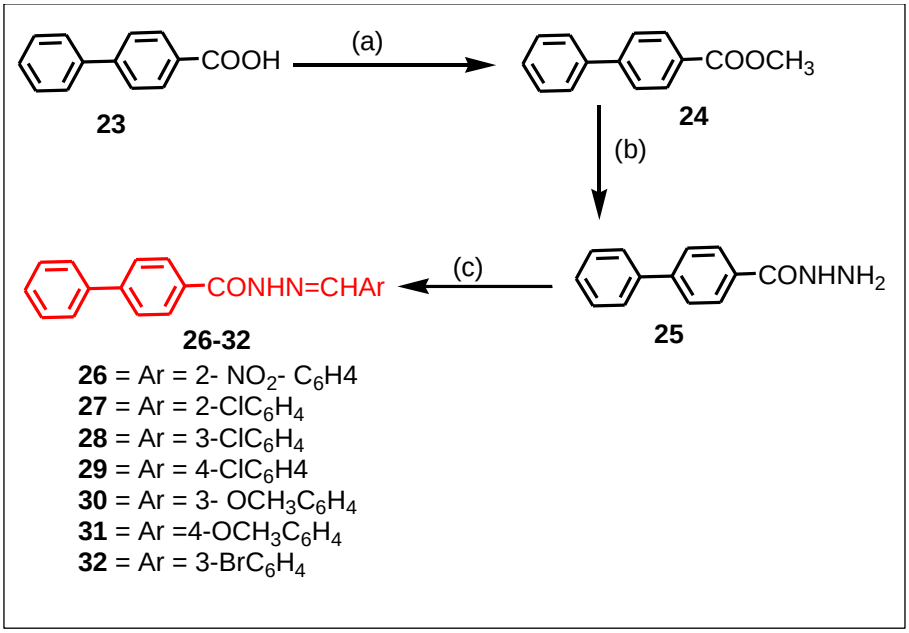

Figure 2: Synthesis of compound 26-32 (a)H_2SO_4/ROH (b) $CH_3OH/N_2H.H_2O$ (c) Ar-CHO

These compounds were also screened for in *vitro* antimicrobial activity *E. coli*, *P. aeruginosa*, *S. aureus*, *B. subtilis.* The results obtained from antimicrobial studies showed that in presence of halogen moiety in aromatic ring gave significant antibacterial activity however the presence of nitro group gave better results for antifungal studies in substituted hydrazides.

N.G. Kandile et.al reported in 2009 reported a general method for the synthesis of novel hydrazones compound 33-47. The 1-[4-(2-methoxybenzyl)-6-aryl pyridazin-3(2*H*)-ylidene] hydrazines or their tautomeric structures were reacted with different dialdehydes, aldehydes, a-dicarbonyl compounds and ketones. Simple carbohydrates were also afforded to dihydrazones and hydrazones. The characterisation technique like ^{1}H-NMR, ^{13}C NMR and mass spectroscopy was used to confirm the compounds. The antimicrobial studies were also done to screen their effifiancy against microorganisms like Staphylococcus aureus and Streptococcus faecalis, Escherichia coli and Pseudomonas aeruginosa. The highest biological activity was shown by (1-[4-(2-methoxybenzyl)-6-methylphenyl pyridazin-3(2H)-ylidene]-2-(2-carboxydiphenyl methyl) hydrazine [12].

Structural diversity among hydrazide-hydrazone derivatives arises from modifications in both hydrazide and hydrazone components. Variations in alkyl or aryl substituents, as well as electron-donating or -withdrawing groups, contribute to the compounds' overall physicochemical properties. Isomeric forms resulting from tautomerism further enhance structural complexity. Understanding the implications of these variations is pivotal for tailoring compounds to specific therapeutic applications.The chemical diversity inherent in hydrazide-hydrazone derivatives underlies their multifaceted applications in medicinal chemistry. Structural modifications can fine-tune pharmacokinetic and pharmacodynamic properties, influencing factors such as bioavailability, solubility, and target specificity. Moreover, the interaction of these derivatives with biological macromolecules, including proteins and nucleic acids, forms the basis for their therapeutic efficacy.

3. Pharmacological activities of drug containing hydrazide and hydrazone moiety

In the realm of antimicrobial activity, hydrazide-hydrazone derivatives have demonstrated efficacy against bacterial, fungal, and parasitic infections. Insights into their mode of action, including inhibition of key enzymes and disruption of microbial cell membranes, contribute to the understanding of their antimicrobial potential. Moreover, their anticancer properties have been investigated, revealing modulation of apoptosis pathways, cell cycle arrest, and interference with angiogenesis as key mechanisms driving their antineoplastic effects. The anti-inflammatory and

antioxidant activities of hydrazide-hydrazone derivatives are particularly relevant in the context of various inflammatory disorders and oxidative stress-related conditions.

Antibacterial Activity: Researchers have investigated the antibacterial potential of hydrazide-hydrazone derivatives by synthesizing compounds with varying substituents. Łukasz Popiołek et al. (2020) synthesized hydrazide-hydrazones of 5-nitrofuran-2-carboxylic acid, revealing higher activity against Gram-negative bacteria with short alkyl chains [13]. Van Hien Pham et al. (2019) synthesized hydrazide-hydrazones with 1-adamantane carbonyl moiety, demonstrating potent antibacterial activity against Gram-positive bacteria [14].

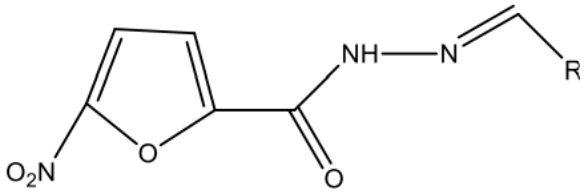

Figure 3: 5-nitrofuran-2-carboxylic acid hydrazide-hydrazones derivatives

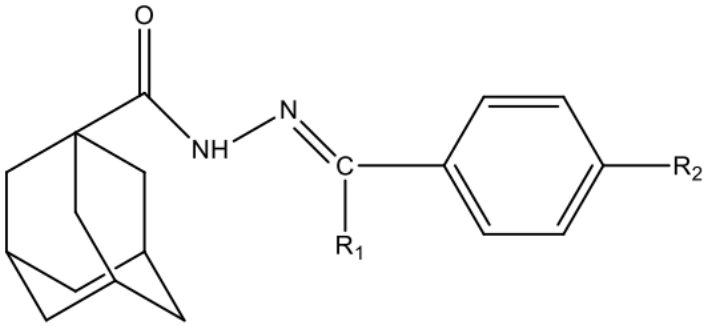

Figure 4: Hydrazide-hydrazones with 1-adamantane carbonyl

Samir Y Abbas et al. (2018) explored quinoxaline N-propionic and O-propionic hydrazide derivatives, revealing compound 13's fourfold potency against *A. fumigatus* [15]. Łukasz Popiołek et al. (2017) synthesized hydrazide hydrazones of 2,3-disubstituted propionic acid, with the 2,3-dibromo propionic acid showing good activity against both Gram-positive and Gram-negative bacteria [16].

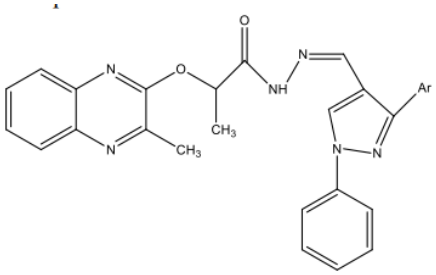

Figure 5: Propanoic acid derivative

G. Thirunarayanan et al. (2017) synthesized (E)-N'-1(substituted benzylidene) benzohydrazides, demonstrating significant antimicrobial activity against Gram-positive and Gram-negative bacteria [17]. Dommati et al. (2016) obtained novel benzohydrazide derivatives, showing high activity against both Gram-negative and Gram-positive bacteria [18].

Anticancer Activity: Hydrazide-hydrazone derivatives have also exhibited promising anticancer activities. Rafat M. Mohareb et al. (2019) synthesized hydrazide-hydrazone derivatives bearing 5H-chromen-5-one, which were evaluated for anticancer activity against various human cell lines [19].

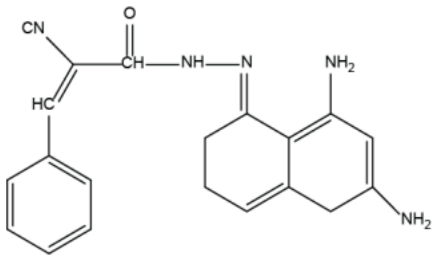

Figure 6: hydrazide–hydrazone derivatives bearing 5H-chromen-5-one

Additionally, Pefloxacin hydrazone derivatives synthesized in 2016 displayed excellent cytotoxicity against human prostate cancer cells, outperforming doxorubicin. Novel analogues of benzosuberones tethered with hydrazone-hydrazides exhibited anti-proliferative activity against different human cancer cell lines [20].

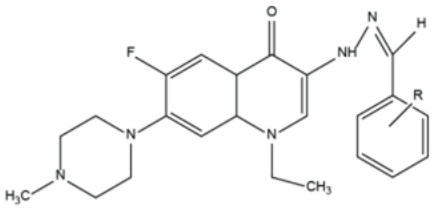

Figure 7: Pefloxacin derivative

Anticonvulsant Activity: Nadeem Siddiqui and Ruhi Ali (2015) synthesized a series of derivatives of N- (substituted-2-oxo-4-phenylazetidin-1-yl)-2-((6-substitutedbenzo[d]thiazol-2-yl)amino)acetamide, showing promising anticonvulsant activity in mouse models. The compounds demonstrated protective indices higher than standard drugs phenytoin and carbamazepine [21].

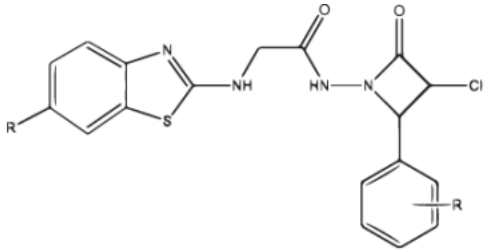

Figure 8: New Benzo[d]thiazol-2-yl-aminoaccetamides derivatives

4. Toxicology of Hydrazide-hydrazone derivatives:

Understanding the toxicological profile of hydrazide-hydrazone derivatives is imperative for assessing their safety and viability as potential therapeutic agents. This section delves into the intricacies of their toxicological considerations, addressing issues ranging from acute toxicity to potential long-term effects. Comprehensive evaluation of the current understanding of their toxicological properties is crucial for advancing these compounds through preclinical and clinical development [22].

The assessment of acute toxicity is a fundamental step in determining the safety of hydrazide-hydrazone derivatives. Studies involving various animal models aim to establish the dose at which adverse effects manifest rapidly. Factors such as route of administration, duration, and observed symptoms contribute to the characterization of acute toxicity. Initial findings suggest that, in general, hydrazide-hydrazone derivatives exhibit low acute toxicity, with lethal doses significantly higher than therapeutic doses.Moving beyond acute toxicity, understanding the effects of prolonged exposure becomes paramount. Subchronic and chronic toxicity studies provide insights into potential adverse reactions over an extended period. These investigations involve repeated administration of hydrazide-hydrazone

derivatives, mimicking prolonged therapeutic use. Evaluating organ-specific toxicity, histopathological changes, and systemic effects aids in delineating the compound's safety margin and potential long-term consequences [23].

Assessment of genotoxicity and mutagenicity is crucial for predicting the potential of hydrazide-hydrazone derivatives to induce genetic alterations. In vitro and in vivo assays, including Ames tests and chromosomal aberration assays, contribute to elucidating their impact on DNA integrity. Initial findings suggest a generally favorable genotoxicity profile, though specific structural modifications may influence outcomes. Rigorous testing is essential to ensure the safety of these compounds, especially considering their potential use as therapeutic agents. Understanding the impact of hydrazide-hydrazone derivatives on reproduction and development is critical for assessing their safety in vulnerable populations. Studies examining fertility, embryonic development, and teratogenicity provide insights into potential risks during pregnancy and fetal development. Preliminary results indicate a low likelihood of reproductive and developmental toxicity, but further investigations, especially in species closer to humans, are essential for comprehensive risk assessment [24-26].

Immunotoxicity: The interaction of hydrazide-hydrazone derivatives with the immune system requires meticulous evaluation. Immunotoxicity studies assess the compound's impact on immune cell function, cytokine production, and overall immune response. While initial data suggest a generally benign influence on the immune system, variations in immune parameters may occur based on structural modifications. Understanding these nuances is crucial for predicting potential immunological side effects during therapeutic use.

Clinical observations and reports from early-phase trials contribute valuable data to the understanding of adverse effects associated with hydrazide-hydrazone derivatives. Commonly reported side effects include mild gastrointestinal disturbances, headache, and, in rare cases, hypersensitivity reactions. These observations underscore the importance of continuous monitoring and surveillance during clinical trials to identify and manage potential safety concerns.Despite the promising therapeutic potential of hydrazide-hydrazone derivatives, several challenges hinder their seamless transition from bench to bedside. The review will critically evaluate these challenges, including issues related to toxicity, selectivity, and off-target effects. Additionally, potential strategies to overcome these challenges, such as structure-activity relationship (SAR) studies and molecular modeling, will be explored [25-27].

In summary, this comprehensive review aims to provide a thorough understanding of the structural, synthetic, and pharmacological aspects of hydrazide-hydrazone derivatives. By elucidating their diverse therapeutic applications and addressing existing challenges, this review seeks to contribute to the ongoing discourse in medicinal chemistry, inspiring further research and the development of novel therapeutic agents with enhanced efficacy and safety profiles.

5. Conclusion:

The diverse biological activities exhibited by hydrazide-hydrazone derivatives underscore their potential as therapeutic agents. Further research and exploration of structure-activity relationships will contribute to the development of new drugs with enhanced efficacy and reduced side effects. The concluding section will provide a forward-looking perspective on the future directions of research in this field. Emphasis will be placed on emerging trends, technological advancements, and innovative methodologies that hold the key to unlocking the full therapeutic potential of hydrazide-hydrazone derivatives. These findings pave the way for future investigations into the design and synthesis of novel hydrazide-hydrazone derivatives with improved pharmacological profiles.

References

[1]. Rollas S, Küçükgüzel SG. Biological Activities of Hydrazone Derivatives. Molecules. 2007;12(8):1910. https://doi.org/10.3390/12081910

[2]. Zhu J, Chen Y, Su F, Wang P. Synthesis of Novel Thiazolyl Hydrazine Derivatives and Their Antifungal Activity. J Chem. 2021;2021:6563871. https://doi.org/10.1155/2021/6563871

[3]. Özdemir A, Turan-Zitouni G, Kaplancikli ZA, Tunali Y. Synthesis and Biological Activities of New Hydrazide Derivatives. J Enzyme Inhib Med Chem. 2009;24(3):825-831. https://doi.org/10.1080/14756360802399712

[4]. Nassiri Koopaei M, Assarzadeh MJ, Almasirad A, et al. Synthesis and Analgesic Activity of Novel Hydrazide and Hydrazine Derivatives. Iran J Pharm Res. 2013;12(4):721-727.

[5]. Mane D, Pavase L. Synthesis and Antibacterial Activity of Novel Hydrazides Containing Thienopyrimidine. J Chem Pharm Res. 2015;7:670-675.

[6]. Shekarchi M, Navidpour L, Rajabi Khorami A, et al. Synthesis of N-Arylidene-2-(2-Phenoxyphenyl) Acetohydrazides as Anti-Inflammatory Agents. Iran J Pharm Res. 2011;10(2):369-377.

[7]. Liu T, Sun C, Xing X, et al. Synthesis and Evaluation of 2-[2-(Phenylthiomethyl)-1H-Benzo[d] Imidazol-1-Yl)Acetohydrazide Derivatives as Antitumor Agents. Bioorg Med Chem Lett. 2012;22(9):3122-3125. https://doi.org/10.1016/j.bmcl.2012.03.061

[8]. Verma G, Marella A, Shaquiquzzaman M, et al. A Review Exploring Biological Activities of Hydrazones. J Pharm Bioallied Sci. 2014;6(2):69-80. https://doi.org/10.4103/0975-7406.129170

[9]. Dandawate P, Khan E, Padhye S, et al. Synthesis, Characterization, Molecular Docking and Cytotoxic Activity of Novel Plumbagin Hydrazones against Breast Cancer Cells. Bioorg Med Chem Lett. 2012;22:3104-3108. https://doi.org/10.1016/j.bmcl.2012.03.060

[10]. Cui Z, Su H, Jiang J, Yang X, Nishida Y. Design, Synthesis and Bioactivity of N-Glycosyl-N'-(5-Substituted Phenyl-2-Furoyl) Hydrazide Derivatives. Int J Mol Sci. 2014. https://doi.org/10.3390/ijms15046741

[11]. Narang R, Narasimhan B, Sharma S, Sriram D, Yogeeswari P, De Clercq E, et al. Synthesis, Antimycobacterial, Antiviral, Antimicrobial Activities, and QSAR Studies of Nicotinic Acid Benzylidene Hydrazide Derivatives. Med Chem Res. 2012;21(8):1557–1576. https://doi.org/10.1007/s00044-011-9664-7.

[12]. Kandile NG, Mohamed MI, Zaky H, Mohamed HM. Novel pyridazine derivatives: Synthesis and antimicrobial activity evaluation. Eur J Med Chem [Internet]. 2009;44(5):1989–96. Available from: http://dx.doi.org/10.1016/j.ejmech.2008.09.047

[13]. Popiołek Ł, Rysz B, Biernasiuk A, Wujec M. Synthesis of promising antimicrobial agents: hydrazide-hydrazones of 5-nitrofuran-2-carboxylic acid. Chem Biol Drug Des. 2020;95(2):260–9.

[14]. Pham VH, Phuong T, Phan D, Phan DC, Vu BD. Synthesis and Bioactivity of Hydrazide Hydrazones with the 1-Adamantyl-Carbonyl Moiety. 2019;1–11.

[15]. Abbas SY, Shehry Mohamed F. El, Farrag AM, Eissa SI, Fouad SA, Ammar YA. Design, synthesis and biological evaluation of quinoxaline Npropionic and O-propionic hydrazide derivatives as antibacterial and antifungal agents. 2018; Medicinal Chemistry Research.2235-44

[16]. Popiołek Ł, Biernasiuk A. New Hydrazides and Hydrazide-Hydrazones of 2,3-Dihalogen Substituted Propionic Acids: Synthesis and in vitro Antimicrobial Activity Evaluation. Chem Biodivers. 2017;14(8).

[17]. Thirunarayanan G, Manikandan V, Balaji S, Senbagam R, Vijayakumar R, Rajarajan M, Vanangamudi G, et al. Synthesis and antimicrobial activities of some (E)-N'-1-(substituted benzylidene)benzohydrazides. Int J Adv Chem. 2017;5(1):17-24

[18]. Dommati, L., Satyanarayana, B., Hela, P. G., Ram, B., & Srinivas, G. (2016). Synthesis and Antibacterial Activity of (E)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]- substituted benzohydrazide Derivatives. Asian Journal of Chemistry, 28(7), 1584–1588. doi:10.14233/ajchem.2016.19776

[19]. Mohareb RM, EL-Sharkawy KA, Al Farouk FO. Synthesis, cytotoxicity against cancer and normal cell lines of novel hydrazide–hydrazone derivatives bearing 5H-chromen-5-one. Med Chem Res [Internet]. 2019;28(11):1885–900. 2.

[20]. Allaka TR, Polkam N, Rayam P, Sridhara J, Garikapati NS, Kotapalli SS, Ummanni R, Anireddy JS. Design, synthesis and biological activity evaluation of novel pefloxacin derivatives as potential antibacterial agents. Medicinal Chemistry Research. 2016 May;25:977-93.

[21]. Ali R, Siddiqui N. New Benzo [d] thiazol-2-yl-aminoacetamides as Potential Anticonvulsants: Synthesis, Activity and Prediction of Molecular Properties. Archiv der Pharmazie. 2015 Apr;348(4):254-65.

[22]. Abidov M. Pharmacological aspects of hydrazides and hydrazide derivatives. Health Promotion & Physical Activity. 2017 Jun 30;2(3):9-24.

[23]. Angelova V, Karabeliov V, Andreeva-Gateva PA, Tchekalarova J. Recent developments of hydrazide/hydrazone derivatives and their analogs as anticonvulsant agents in animal models. Drug Development Research. 2016 Nov;77(7):379-92.

[24]. Rollas S, GünizKüçükgüzel Ş. Biological activities of hydrazone derivatives. Molecules. 2007 Aug 17;12(8):1910-39.

[25]. Popiołek Ł, Gawrońska-Grzywacz M, Dziduch A, Biernasiuk A, Piątkowska-Chmiel I, Herbet M. Design, Synthesis, and In Vitro and In Vivo Bioactivity Studies of Hydrazide–Hydrazones of 2, 4-Dihydroxybenzoic Acid. International Journal of Molecular Sciences. 2023 Dec 14;24(24):17481.

[26]. Valcheva V, Simeonova R, Mileva M, Philipov S, Petrova R, Dimitrov S, Georgieva A, Tsvetanova E, Teneva Y, Angelova VT. In Vivo Toxicity, Redox-Modulating Capacity and Intestinal Permeability of Novel Aroylhydrazone Derivatives as Anti-Tuberculosis Agents. Pharmaceutics. 2022 Dec 26;15(1):79.

[27]. Abidov M. Pharmacological aspects of hydrazides and hydrazide derivatives. Health Promotion & Physical Activity. 2017 Jun 30;2(3):9-24.