

Piperazine acid

Table of Contents

summary

Properties

- Chemical Structure and Composition

- Synthesis and Yield

- Biological Activity

 - Mechanism of Action

 - Therapeutic Applications

 - Toxicity and Side Effects

- Formulation and Application

- Stability and Interaction

Synthesis

- Combinatorial Chemistry Approaches

 - Photolithography and Spatially-Addressable Synthesis

- Other Synthetic Strategies

Applications

- Therapeutic Uses

- Formulation and Administration

- Combinatorial Libraries

Pharmacokinetics

- Drug-Drug Interactions

- Absorption and Metabolism

Regulatory Status

Related Compounds

- Combinatorial Libraries of Piperazine Derivatives

- Pharmacological Activity

- Synthesis and Modifications

- Therapeutic Applications

Check <https://storm.genie.stanford.edu/article/1208920> for more details

The generated report can make mistakes.
Please consider checking important information.
The generated content does not represent the developer's viewpoint.

summary

Piperazine Acid is a class of chemical compounds that includes piperazine and its derivatives, known for their diverse biological activities and therapeutic applications. Characterized by their structural flexibility, piperazine acids have been studied for their roles in pharmacology, particularly in the treatment of various neurological and psychological disorders, infections caused by nematodes, and pain management.-
[\[1\]\[2\]](#) Their ability to interact with neurotransmitter systems, including GABA and dopamine receptors, underpins their significance in modern medicine, highlighting their potential for addressing complex health issues such as depression, anxiety, and parasitic infections.[\[3\]\[4\]](#)

Notably, piperazine acid derivatives are synthesized through various methods that allow for the modification of their chemical structures, resulting in a vast library of compounds with unique pharmacological properties.[\[5\]](#) These compounds can exhibit effects ranging from anti-inflammatory and anti-microbial to anthelmintic, making them versatile agents in both therapeutic and experimental contexts.[\[6\]](#) The innovative use of combinatorial chemistry and photolithographic techniques has further enhanced the synthesis and exploration of these derivatives, enabling the identification of novel therapeutic agents that may improve patient outcomes.[\[7\]](#)

Despite their therapeutic benefits, piperazine acids are not without controversy. Regulatory challenges arise due to their potential for misuse as recreational substances, leading to increased scrutiny and control in several countries.[\[8\]](#) Concerns surrounding side effects, particularly neurological impacts, necessitate caution in their clinical application, particularly for patients with pre-existing conditions such as epilepsy.[\[9\]](#) As research continues to evolve, understanding the balance between their therapeutic potential and regulatory implications remains crucial in the development of piperazine acid derivatives for clinical use.[\[10\]](#)

Properties

Chemical Structure and Composition

Piperazine acid derivatives exhibit a range of chemical structures, with one common representation being that of a compound with the formula $C_{27}H_{34}ClN_3O_2$. For example, compound 12, synthesized from 1-(2-hydroxyphenyl)piperazine and cesium carbonate, demonstrated a molecular weight of 469 g/mol as indicated by its LRMS data (m/z) = 469 (MH^+)[\[1\]](#). The ability to modify the substituents on the piperazine ring allows for a diverse library of compounds, each with unique properties.

Synthesis and Yield

The synthesis of piperazine acid compounds often involves reactions with various reagents such as potassium carbonate, di tert-butyl dicarbonate, and different piperazine derivatives. For instance, compound 8 was prepared with a yield of 46% from starting materials including 1-(2-fluorophenyl)piperazine and cesium carbonate[1]. Similarly, compound 7 was synthesized with a yield of 42%, emphasizing the efficiency of the employed synthetic methods[1].

Biological Activity

Piperazine acid and its derivatives exhibit a variety of biological activities, primarily through their interactions with neurotransmitter systems and cell receptors. These compounds have been shown to alter dopamine function, impacting various neurological pathways and providing therapeutic benefits against a range of ailments.[1]

Mechanism of Action

The mechanism of action for piperazine compounds largely revolves around their role as GABA (gamma-aminobutyric acid) agonists, particularly in the treatment of parasitic infections. Piperazine induces muscular paralysis in worms by increasing the permeability of their cell membranes to chloride ions, which leads to hyperpolarization of the nerve endings. This process effectively immobilizes the parasites, allowing them to be expelled from the host's body through natural physiological processes such as peristalsis.[2][3] Furthermore, piperazine derivatives may also influence other neurotransmitter systems, including serotonergic and dopaminergic pathways, potentially contributing to their pharmacological efficacy and therapeutic applications.[4]

Therapeutic Applications

Piperazine derivatives are primarily used in the treatment of various diseases, including infections caused by nematodes, as well as having potential applications in psychiatry and pain management.[5][2] The compounds demonstrate activity that can include anti-inflammatory, anti-microbial, and anthelmintic effects, showcasing their versatility in addressing different health conditions.[5]

Toxicity and Side Effects

While piperazine acid and its derivatives are generally well-tolerated, they can produce side effects such as nausea, vomiting, and dizziness. In rare cases, more severe reactions, including allergic responses and neurological effects, may occur. Patients with a history of seizure disorders, such as epilepsy, are advised to use these compounds with caution due to their action on the GABAergic system, which could lead to increased neurotransmitter levels and potential seizures.[2]

Formulation and Application

The versatility of piperazine acid derivatives extends to their formulation in various pharmaceutical preparations, including ointments, creams, and gels. These formulations may contain excipients such as fats, oils, and waxes, which aid in the delivery of the active compound[1]. Moreover, the potential for utilizing encoded combinatorial libraries allows for the exploration of a vast array of piperazine acid derivatives, facilitating the discovery of new therapeutic agents[1].

Stability and Interaction

Light-directed chemical synthesis techniques have been employed to improve the stability and interactions of piperazine acid compounds with other molecules. This method allows for precise control over the synthesis process, enabling the generation of diverse compound libraries based on the photolithographic patterns used during the synthesis[1]. The positioning of each compound is meticulously recorded, which is critical for assessing its interactions with various biological targets[1].

Synthesis

The synthesis of piperazines has advanced significantly through various methodologies that emphasize operational simplicity and efficiency. A notable recent method allows for the synthesis of alkyl-, alcohol-, amine-, and ester-extended tosylpiperazines under mild conditions, yielding good results. This approach is particularly relevant for pharmaceutical and natural product synthesis due to its straightforward process and the availability of reactants[6].

Combinatorial Chemistry Approaches

Combinatorial chemistry techniques have also been leveraged to enhance piperazine synthesis. A compound library is often utilized, incorporating an encoded tagging system to identify active compounds. This system allows for the parallel synthesis and screening of numerous compounds simultaneously[1]. Techniques such as mass spectrometry (MS) are increasingly used to characterize the compounds derived from these libraries, enabling the determination of their chemical constitution[1].

Photolithography and Spatially-Addressable Synthesis

Recent innovations in spatially-addressable synthesis have employed photolithography techniques. This method allows for the controlled addition of chemical reagents to specific locations on a solid support, effectively miniaturizing the synthesis process[1]. The use of photolabile protecting groups facilitates this approach by enabling selective activation of reagents when exposed to light, thereby allowing the synthesis of a diverse array of piperazine derivatives in a compact format[1].

Other Synthetic Strategies

In addition to combinatorial methods, other synthetic routes for piperazines have emerged. For instance, a (pyridyl)phosphine-ligated ruthenium(II) complex has been

shown to catalyze a diol-diamine coupling, resulting in the formation of piperazines and diazepanes. This method is notable for its ability to tolerate various amines and alcohols, which are significant in medicinal chemistry[6]. Furthermore, a palladium-catalyzed method has provided an efficient synthetic route to biologically relevant arylpiperazines under aerobic conditions[6].

These developments in piperazine synthesis not only highlight the versatility of modern synthetic techniques but also the potential for these compounds in medicinal applications.

Applications

Piperazine acid and its derivatives exhibit a wide range of therapeutic applications, particularly in the treatment of various ailments and conditions affecting mammals. The compounds derived from piperazine are often used in pharmacological contexts for their efficacy against multiple disorders.

Therapeutic Uses

Piperazine compounds have shown potential in treating numerous psychological and physiological conditions, including but not limited to:

Mental Health Disorders: These compounds are relevant in managing conditions such as addiction, anxiety, depression, obsessive-compulsive disorder, and schizophrenia[1]. Their interaction with neurotransmitter systems, particularly dopamine and serotonin, positions them as promising agents for addressing these ailments[1-][7].

Neurological Conditions: Piperazine derivatives are explored for their role in treating neurological disorders like Alzheimer's disease, Parkinson's disease, and restless leg syndrome, contributing to improvements in cognition and motor function[1].

Pain Management: The analgesic properties of piperazine compounds make them suitable for addressing various types of pain, including inflammatory and neuropathic pain[1][7].

Endocrine and Metabolic Disorders: Applications extend to conditions like obesity and hypertension, where piperazine derivatives may help regulate metabolic processes[1].

Gastrointestinal Disorders: The use of these compounds is also noted in treating conditions like irritable bowel syndrome and emesis (vomiting)[1].

Formulation and Administration

Piperazine compounds can be administered through various routes, including oral, nasal, rectal, and parenteral methods, ensuring flexibility in therapeutic settings[1]. They are often formulated into pharmaceutical compositions suitable for systemic administration, allowing the compounds to enter the patient's system effectively and exert their therapeutic effects[1][7].

Moreover, the piperazine derivatives are integral to combinatorial chemistry approaches, enabling the synthesis of libraries for drug discovery aimed at identifying compounds with desirable biological activities[\[1\]](#).

Combinatorial Libraries

The creation of combinatorial libraries of piperazine compounds facilitates the screening for specific biological activities related to pharmaceutical applications[\[1\]](#). This approach allows for the exploration of diverse chemical entities, broadening the scope of potential therapeutic uses and enhancing the understanding of the compounds' effects on mammalian receptors and transporters[\[7\]](#).

Pharmacokinetics

Piperazine compounds exhibit a complex pharmacokinetic profile that can vary significantly based on formulation and co-administration with other drugs. Recent studies have highlighted the pharmacokinetics of piperazine dithioctate (PDT) and its interactions with other medications, such as glimepiride (GMP). The pharmacokinetic characteristics of PDT have been shown to be comparable to other formulations, indicating a consistent absorption profile across different delivery methods[\[8\]](#).

Drug-Drug Interactions

A key focus of pharmacokinetic research has been the potential for drug-drug interactions between GMP and PDT. In one study, a validated LC-MS/MS bioanalytical method was developed to assess these interactions in rats[\[9\]](#). It was observed that the oral co-administration of PDT significantly reduced the plasma exposure of GMP by approximately 80% when GMP was administered as a suspension. This suggests that PDT may alter the absorption dynamics of GMP, potentially leading to decreased therapeutic efficacy[\[10\]](#). However, when PDT was co-administered with a GMP solution, there was no significant change in the pharmacokinetics of GMP, indicating that the formulation of the drug can impact the nature of the interaction[\[10\]](#).

Absorption and Metabolism

The absorption of piperazine is generally unaffected by food, which is an important consideration for its therapeutic use[\[11\]](#). The pharmacokinetics of piperazine compounds can also be influenced by their metabolic pathways. For example, in the context of piperazine derivatives, N-demethylation, reduction, and oxidation are key phase I metabolic processes observed in human and rat models[\[12\]\[13\]](#). Notably, a significant portion of the drug is excreted unmodified, which underscores the importance of understanding the factors affecting its metabolism and excretion[\[14\]](#).

Regulatory Status

Piperazine and its derivatives are subject to various regulatory controls across different jurisdictions due to their pharmacological effects and potential for misuse.

In the European Union, following a risk assessment by Europol and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2007, the Council Decision of 2008 was enacted to introduce controls on benzylpiperazine (BZP) and similar substances, which includes certain piperazine compounds[\[15\]](#). This regulatory framework aims to mitigate the risks associated with these drugs, particularly concerning their use as recreational substances.

In Canada, while piperazine analogues such as mephedrone have been reported in media as being seized by police, there remains ambiguity regarding their legal status. The assistant director of the Centre for Addictions Research of British Columbia noted a lack of "clear illegality" surrounding these substances under the Controlled Drugs and Substances Act[\[12\]](#). This has raised concerns about enforcement and the potential health risks associated with their consumption.

The Synthetic Drug Abuse Prevention Act of 2012 in the United States permanently classified various synthetic drugs, including some piperazine derivatives, as controlled substances, reflecting a broader trend towards stricter regulation of synthetic drugs[\[16\]](#). This legislation aims to combat the rising use of synthetic drugs that mimic the effects of illegal narcotics.

Additionally, specific health ministries in countries like Romania have established lists of psychoactive substances, including piperazine compounds, to be banned based on their dangerous health implications[\[12\]](#). As regulations continue to evolve, the classification and control of piperazine and its derivatives remain a significant public health concern, necessitating ongoing review and adjustment of legal frameworks to address their risks effectively.

Related Compounds

Combinatorial Libraries of Piperazine Derivatives

Piperazine derivatives are often utilized in the development of combinatorial libraries aimed at discovering new therapeutic agents. The synthesis of these libraries can be achieved through various methods, allowing for the screening of numerous compounds with potential biological activity. The combinatorial approach is particularly beneficial as it enables the generation of large libraries, often ranging from 16 to over 1,000,000 diversomers, which can be screened for specific pharmacological properties[\[1\]\[17\]](#). These libraries may be created using solid supports or in solution, and they allow for the simultaneous evaluation of related compounds in drug discovery processes[\[1\]](#).

Pharmacological Activity

Piperazine derivatives exhibit a diverse range of pharmacological activities, making them promising candidates for the development of new medications. Notably, these compounds have been studied for their potential in treating neurological disorders such as anxiety and depression[\[18\]\[19\]](#). The structural flexibility of piperazine allows for modifications that enhance their efficacy and specificity in targeting different

therapeutic areas[20][21]. For instance, certain piperazine derivatives have shown effectiveness in the treatment of central nervous system (CNS) disorders, as they can easily cross the blood-brain barrier, facilitating their therapeutic actions[22][21].

Synthesis and Modifications

The preparation of piperazine derivatives often involves various synthetic strategies, including acylation reactions with piperazine and its derivatives. Such modifications can lead to the formation of novel compounds with improved pharmacokinetic properties, as well as enhanced lipophilicity, which is critical for cell permeability[16][20]. Additionally, the development of these derivatives can include the introduction of functional groups, such as halogens, which serve to further optimize their biological activity and therapeutic potential[16][20].

Therapeutic Applications

Piperazine derivatives are not only being investigated for their use in treating anxiety and depression, but they are also being explored for their potential in addressing neurodegenerative disorders and issues related to cocaine abuse[23]. These applications underline the versatility of piperazine as a scaffold in medicinal chemistry, leading to the development of innovative therapeutic compositions that could significantly impact patient care[24][23].

References

- [1]: [Piperidine-piperazine ligand for neurotransmitter receptors](#)
- [2]: [What is Piperazine Citrate used for? - Patsnap Synapse](#)
- [3]: [What is Piperazine used for? - Patsnap Synapse](#)
- [4]: [Structural and Molecular Insight into Piperazine and Piperidine ...](#)
- [5]: [Biological Activities of Piperazine Derivatives](#)
- [6]: [Piperazine synthesis - Organic Chemistry Portal](#)
- [7]: [The Recent Development of Piperazine and Piperidine Derivatives ...](#)
- [8]: [Pharmacokinetic evaluation of a newly developed piperazine ...](#)
- [9]: [Preclinical pharmacokinetics of a promising antineoplastic prototype ...](#)
- [10]: [Effect of Piperazine Dithioctate on the Oral Pharmacokinetics of ...](#)
- [11]: [Piperazine: Uses, Interactions, Mechanism of Action - DrugBank](#)
- [12]: [Mephedrone - Wikipedia](#)
- [13]: [Disposition and Metabolism of the 1-Aryl-Piperazines Formed](#)
- [14]: [Piperazine - an overview | ScienceDirect Topics](#)
- [15]: [Benzylpiperazine \(BZP\) and other piperazines drug profile - EUDA](#)
- [16]: [Second-generation piperazine derivatives as promising radiation ...](#)
- [17]: [Method for the preparation of piperazine and its derivatives](#)
- [18]: [Piperazine Derivatives Overview - Ontosight.ai](#)

- [19]: ["Synthesis and characterization of unsaturated diacyl and alkyl-acyl ...](#)
- [20]: [The medicinal chemistry of piperazines: A review](#)
- [21]: [Discovery of a novel piperazine derivative, cmp2: a selective TRPC6 ...](#)
- [22]: [\[PDF\] a potentially tool for the treatment of neurological disorders](#)
- [23]: [Diagnostic and therapeutic alkyl piperidine/piperazine compounds ...](#)
- [24]: [Therapeutic Role of Heterocyclic Compounds in Neurodegenerative ...](#)