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SYNTHESIS OF QUINOLINE HETEROCYCLIC COMPOUNDS ANILINE USING MICROWAVE-ASSISTED METHODS

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Abstract

The synthesis of bioactive heterocyclic compounds has received considerable interest in the realm of medicinal chemistry owing to their wide range of biological activity and prospective uses in therapy. Microwave-assisted methodologies have developed as very effective instruments in the field of organic synthesis, facilitating expeditious and proficient alterations. The objective of this study is to investigate the use of microwave-assisted methodologies for the synthesis of bioactive heterocyclic compounds, with particular emphasis on the utilization of starting materials generated from natural sources. The usage of natural beginning materials has several benefits, including sustainability, accessibility, and the prospect of uncovering new molecules possessing distinctive biological features. The present study aims to elucidate the fundamental concepts behind microwave-assisted synthesis, while emphasizing current progress in this field. Furthermore, this review will exemplify the synthesis of bioactive heterocyclic compounds derived from natural starting materials. Moreover, this paper will examine the biological properties and possible practical uses of these substances, with a particular focus on the importance of microwave-assisted synthesis in the field of pharmaceutical research and advancement.

Keywords: Bioactive heterocyclic compounds; microwave-assisted methodology; natural compounds; biological properties

1. Introduction

In recent years, there has been a shift in research focus towards the development of ecologically friendly responses. The multicomponent reaction approach is a method used to integrate the economic elements of novel reactions with their corresponding environmental considerations. The aforementioned procedure involves a series of two or more synthetic stages, whereby the separation of any intermediate is omitted. Consequently, this approach effectively minimizes reaction time, energy consumption, and raw material use (Ganpatrao, 2023).

In recent decades, there has been a significant increase in the attention and focus on environmentally friendly chemical processes, both within academic circles and in the industrial sector. Volatile, poisonous, and dangerous organic solvents are being consistently substituted via the use of solvent-free procedures, as well as the utilization of ionic liquids, water, and phase-transfer catalysts. The use of polyethylene glycol (PEG) as a reaction solvent offers significant advantages due to its neutral nature, which facilitates the preservation of various functional groups that are vulnerable to either acidic or basic conditions (Mathew et al., 2020).

Heterocyclic chemistry has significant importance within the field of organic chemistry, constituting about one-third of contemporary scholarly publications. Indeed, it is worth noting that around two-thirds of organic molecules may be classified as heterocyclic compounds. A carboxylic compound is a cyclic organic molecule in which all carbon atoms are arranged in a ring configuration. A compound is classified as heterocyclic if it has a ring structure in which at least one element, other from carbon, is present. Nitrogen, oxygen, and sulfur are commonly recognized as the most prevalent heteroatoms in heterocyclic rings; however, it is worth noting that heterocyclic rings incorporating alternative heteroatoms have also gained significant recognition in academic literature. A significant quantity of heterocyclic compounds has been identified, and this quantity is seeing a fast growth (Alamgir and Alamgir, 2018; Bansal, 2020; Taterao, 2023).

The field of heterocyclic chemistry has its roots in the realms of organic synthesis, natural products chemistry, and medicinal chemistry. Many heterocyclic chemists identify themselves as organic chemists, and a significant number also believe themselves to be natural products chemists and medicinal chemists. The interconnection across disciplines emerges due to the fact that heterocyclic molecules serve as essential foundational components inside biological systems. Heterocyclic chemistry has been extensively used in several sectors, including biology, dyes, optical sensitizers, coordination compounds, polymeric materials, and numerous other areas. Considering the fact that a majority of biologically active compounds exhibit heterocyclic properties, it is crucial to acknowledge their significance in the field of combinatorial chemistry. This value lies in the ability to find potential starting points and enhance the structures of these compounds (Rao et al., 2018). Based on the aforementioned information, the purpose of this study is to investigate the use of microwave-assisted methodologies for the synthesis of bioactive heterocyclic compounds, with a concentration on the use of starting materials derived from natural sources.

2. Literature Review

2.1. Microwave-assisted Synthesis of Complex Heterocyclic Molecules

During the nineteenth century, chemical processes were conducted using a Bunsen burner. The exothermic nature of the flame facilitated the execution of a chemical process by providing a source of heat energy. Subsequently, oil baths and hot plates were introduced as alternatives, thus eliminating the need for open flames and thereby mitigating the potential hazards associated with fire incidents (Adhikari et al., 2022). During the late 1980s, scientific literature began to document instances of chemical synthesis being conducted using domestic microwave ovens. Despite significantly reducing response time, the monitoring of reaction parameters posed challenges (Shalaby et al., 2023).

Over time, specialized reactors were developed for the purpose of conducting chemical reactions, equipped with the capability to monitor the temperature and pressure of the reaction (Zarecki et al., 2020). Microwave-assisted synthesis quickly gained prominence due to its ability to achieve complete conversion of reagents used in chemical methodologies, resulting in a significant reduction in reaction time. Additionally, the molecules are generated with excellent efficiency. The functioning of this process is based on the alignment of dipoles in reagents under the influence of an external field, which is stimulated by microwaves, following a well-established chemical approach for the synthesis of specific molecules.

Microwave radiation encompasses a range of electromagnetic radiation frequencies spanning from 30 gigahertz (GHz) to 300 megahertz (MHz). The utilization of microwave-assisted organic reactions in conjunction with organic reactions conducted in water or under neat circumstances was first shown in the year 1990 by Verma (1999), and afterwards further explored by subsequent researchers. Literature extensively showcases several instances whereby microwave irradiation has been effectively used in organic synthesis inside environmentally friendly reaction media, as shown by Sharma et al. (2018), as well as under solvent-free settings, as demonstrated by Shaikh (2018). The use of microwave irradiation in benign reaction media offers significant benefits, including time efficiency and enhanced yields in the fields of classical medicinal chemistry and the synthesis of heterocyclic systems.

2.2. Synthesis of Bioactive Heterocyclic Compounds from Natural Starting Materials

Alkaloids are a category of naturally occurring chemicals that are renowned for their extensive range of biological activities, including anticancer, antibacterial, and analgesic effects. The use of microwave-assisted synthesis has shown its efficacy as a proficient approach in the synthesis of diverse alkaloids derived from natural source materials. Indole alkaloids represent a significant category of alkaloids that manifest a diverse array of biological properties, including but not limited to anticancer, anti-inflammatory, and antibacterial actions. The use of microwave-assisted methodologies has shown to be effective in the production of indole alkaloids, offering a quick and effective means of obtaining these very valuable chemical compounds. For example,

microwave irradiation has been utilized for the synthesis of reserpine, an important indole alkaloid with antihypertensive and antipsychotic properties, starting from natural sources such as *Rauvolfia serpentina* (Bellavita et al., 2022).

Quinoline alkaloids represent a distinct category of biologically active molecules that may be found in a diverse range of natural sources, such as plants, fungus, and marine animals. The alkaloids have a wide range of pharmacological effects, including antimalarial, anticancer, and antiviral characteristics. The use of microwave-assisted synthesis has been exploited as an effective method to acquire quinoline alkaloids derived from natural sources. An example of a successful synthesis is camptothecin, a highly effective quinoline alkaloid with anticancer properties. This compound has been synthesized utilizing microwave irradiation, which offers a faster and more sustainable method of production (Mahato et al., 2018).

Terpenoids, also referred to as isoprenoids, include a broad and varied category of naturally occurring chemicals that possess noteworthy biological properties, such as anticancer, anti-inflammatory, and antiviral actions. The use of microwave-assisted synthesis has been implemented to achieve a high level of efficiency in the synthesis of terpenoids derived from natural sources. Furan-based terpenoids represent a distinct category of terpenoids, characterized by their possession of a furan ring structure. These compounds have been shown to display a diverse range of biological activities, including but not limited to anticancer and antibacterial properties. The use of microwave-assisted methodologies has been employed in the synthesis of terpenoids based on furan, facilitating expedited and specific conversions. An example can be found in the literature where the microwave irradiation technique was used to synthesize artemisinin, a prominent furan-based terpenoid with antimalarial properties, obtained from Artemisia annua. This method proved to be very effective in facilitating the production of this important molecule (Kasmi et al., 2018).

Pyran-based terpenoids represent a distinct subclass of terpenoids, characterized by a wide range of biological actions such as anticancer, antifungal, and anti-inflammatory properties. The use of microwave-assisted synthesis has been implemented in the efficient synthesis of pyran-based terpenoids derived from natural sources. An example of a successful synthesis of paclitaxel, a well-recognized pyran-based terpenoid with anticancer properties, has been accomplished by the use of microwave irradiation. This method presents a faster and more environmentally sustainable approach to synthetic production (Eckl, 2022).

Flavonoids, a category of naturally occurring chemicals, exhibit a broad range of biological actions in many plant species. These activities include antioxidative, anticancer, and anti-inflammatory properties. The use of microwave-assisted synthesis has been implemented to achieve a high level of efficiency in the synthesis of flavonoids derived from natural sources. Flavones, which belong to the subclass of flavonoids, demonstrate a range of pharmacological activity, including but not limited to anticancer, anti-inflammatory, and antiviral characteristics. The use of microwave-assisted methodologies has been implemented in the synthesis of flavones,

enabling a quick and effective means of obtaining these chemical compounds. One example of this is the successful synthesis of apigenin, a well-recognized flavone compound renowned for its anticancer and anti-inflammatory properties. This synthesis method utilizes microwave irradiation and utilizes naturally occurring sources such as chamomile (Orsat and Routray, 2017).

Isoflavones represent a distinct category of flavonoids that have diverse biological properties, including estrogenic, anticancer, and anti-inflammatory actions. The use of microwave-assisted synthesis has been implemented as an effective method for the proficient synthesis of isoflavones derived from natural sources. An example may be found in the field of organic chemistry, where researchers have successfully used microwave irradiation to synthesize genistein, an isoflavone compound that is well recognized for its potential as an anticancer agent and neuroprotective agent. This innovative method offers a fast and environmentally friendly approach to the synthesis of genistein (Kshatriya et al., 2015).

In general, the use of microwave-assisted synthesis has become a prominent and effective method for the production of bioactive heterocyclic compounds derived from natural sources, while also promoting sustainability. Microwave irradiation has been shown to facilitate expeditious and discerning transformations, so presenting notable benefits including diminished reaction durations, heightened product yields, and augmented ecological viability. The flexibility and promise of microwave-assisted approaches in the synthesis of varied bioactive compounds are shown by the presented instances of alkaloids, terpenoids, flavonoids, and other natural starting materials. These technological breakthroughs play a crucial role in the domain of medicinal chemistry and drug discovery, enabling the development of new therapeutic agents that have the potential to be used in a wide range of illnesses and conditions (Seth et al., 2017).

2.3. Biological Activities and Potential Applications

2.3.1. Anticancer Activity

Numerous bioactive heterocyclic compounds obtained from natural sources have shown substantial efficacy in inhibiting cancer growth. These chemicals have the capability to impede the proliferation of cancer cells, trigger apoptosis (a process of planned cell death), and hinder the spread of cancer cells. Anticancer medications may be developed by targeting many molecular pathways implicated in the formation and progression of cancer, making them very promising options.

Indole alkaloids, namely vinblastine and vincristine, which are produced from *Catharanthus roseus* (commonly known as *Madagascar periwinkle*), have shown significant anticancer efficacy via the disruption of microtubule assembly inside malignant cells. In a similar vein, paclitaxel, a terpenoid produced from *Taxus brevifolia* (Pacific yew) and characterized by its pyran structure, is a commonly used chemotherapeutic agent that effectively impedes cellular proliferation by promoting the stabilization of microtubules (Newman and Cragg, 2012; Yue et al., 2017).

2.3.2. Antimicrobial Activity

Bioactive heterocyclic compounds obtained from natural sources have been shown to possess notable antibacterial action against many microorganisms, including bacteria, fungus, viruses, and parasites. These chemicals possess the ability to impede the growth and multiplication of microbial infections, so rendering them viable contenders for the creation of antimicrobial agents. For example, the antibacterial action of flavonoids, namely quercetin and apigenin, produced from diverse plant sources, has been shown against a broad spectrum of microbes. Microbial cell membranes may be disrupted, microbial enzymes can be inhibited, and microbial DNA replication can be interfered with (Górniak et al., 2019; Takó et al., 2020).

2.3.4. Anti-inflammatory Activity

Moreover, it is noteworthy that bioactive heterocyclic compounds produced from natural sources have substantial anti-inflammatory action. These substances have the ability to control pathways associated with inflammation, decrease the synthesis of pro-inflammatory mediators, and hinder the activation of enzymes involved in inflammation. Consequently, they hold promise as possible candidates for the advancement of anti-inflammatory pharmaceuticals (Karunakaran and Sadanandan, 2019).

One such instance is curcumin, a polyphenolic substance obtained from *Curcuma longa* (turmeric), which has shown significant anti-inflammatory efficacy via the inhibition of inflammatory enzymes and the reduction of pro-inflammatory cytokine production. Likewise, several indole alkaloids and terpenoids have shown anti-inflammatory properties (Hussain et al., 2017).

2.3.5. Antioxidant Activity

It is well observed that bioactive heterocyclic compounds obtained from natural sources possess significant antioxidant properties. Antioxidants play a crucial role in safeguarding cellular integrity against the detrimental effects of oxidative stress. This is achieved via their ability to counteract the harmful impact of free radicals and reactive oxygen species, which have the potential to induce cellular harm and contribute to the development of many pathological conditions (Ozcan and Ogun, 2015).

For example, it has been shown that flavonoids, like quercetin and catechins, which are obtained from botanical sources, have potent antioxidant properties. These compounds possess the ability to scavenge free radicals, suppress lipid peroxidation, and augment the functionality of natural antioxidant enzymes. Moreover, several terpenoids and alkaloids have also shown antioxidative properties (David et al., 2016).

2.3.6. Additional Bioactivities

Apart from the aforementioned activities, bioactive heterocyclic compounds originating from natural sources exhibit a diverse array of additional bioactivities. The neuroprotective effect of some bioactive compounds has been observed, indicating their potential as therapeutic agents for the treatment of neurodegenerative disorders including Alzheimer's and Parkinson's disease. These compounds have shown the capability to safeguard neurons against damage and degeneration (Newman and Cragg, 2012).

The antidiabetic action of some bioactive substances has shown the capacity to modulate blood glucose levels and enhance insulin sensitivity, therefore presenting encouraging prospects for the management of diabetes. Specific bioactive compounds have been shown to possess cardioprotective properties via mechanisms such as cholesterol reduction, inhibition of platelet aggregation, and enhancement of blood vessel function. These activities have potential for the prevention and treatment of cardiovascular illnesses (Balachandran, 2022).

Certain bioactive chemicals have shown antiviral capabilities by impeding the reproduction and propagation of viruses, including those accountable for ailments such as influenza, HIV, and hepatitis. The antiparasitic activity of certain bioactive chemicals produced from plants has been shown, indicating their potential as therapeutic agents for illnesses caused by parasitic organisms, including malaria and leishmaniasis. The antifungal characteristics of bioactive compounds originating from natural sources have been observed, leading to the inhibition of fungal pathogen development and dissemination (Beshbishy et al., 2020).

3. Methodology

3.1. Materials

The products were procured from either Acros or Sigma Aldrich, based on their respective availability, and were used without undergoing further purification processes. The solvents used in this study were procured from Carlo Erba. The reactions were monitored using thin-layer chromatography (TLC) on an aluminium sheet coated with Kieselgel 60F254 MERCK. Detection of the compounds was achieved using either UV light or an acidic solution of potassium permanganate. Silica gel with a particle size range of 40-60 μm was used for the execution of column chromatography. The experimental procedure included the use of an automated Grace system for flash column chromatography, using silica gel cartridges. The examination of the reactants and products included both qualitative and quantitative methods. This was conducted using a Shimadzu HPLC system, using a reversed phase technique with a C18 column and a PDA detector. Products were detected by a process of comparing them with genuine samples. Experiments with microwaves were carried out using a specialized commercial microwave reactor specifically built for use in synthetic chemistry.

The Monowave300, developed by Anton Paar in Austria, is a mono-mode cavity equipped with a microwave power delivery system that spans a power range of 0 to 850 W. The temperatures of the reactions were primarily measured using a non-contact infrared pyrometer, which was

calibrated in control experiments using a fiber-optic contact thermometer. The response time may be divided into two scenarios: one with a duration of 15 minutes, characterized by a heating ramp of 36 °C min−1 followed by a 10-minute period at 200 °C; and another with a duration of 40 minutes, characterized by a heating ramp of 6 °C min−1 followed by a 10-minute period at 200 °C. The experimental setup included the use of hermetically sealed containers, together with the inclusion of a magnetic stir bar positioned inside each container. The temperature and power profiles were monitored in both instances using the software supplied by the manufacturer.

The NMR spectra of the products were obtained using a Bruker apparatus with proton running at a frequency of 400.17 MHz, carbon operating at 100.63 MHz, and fluor operating at 376.49 MHz. The solvents used for the NMR measurements were CDCl3 (D, 99.5%) and DMSO-d6 (D, 99.8%). The Agilent 5975 Series MSD apparatus was used to conduct GC/MS (EI) analysis. A HP5-MS column with dimensions of 30 m × 250 μ × 0.25 μ was utilized for the study. The melting points are measured using a Stuart SMP 10 apparatus and remain unadjusted.

3.2. Synthesis of Quinoline Derivatives

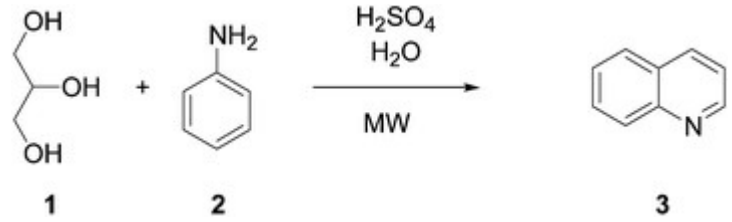
A sealed jar with a volume of 30 mL was filled with aniline derivative (10 mmol), glycerol (1, 30 mmol, 3.0 equivalents), H2SO4 (30 mmol, 3 equivalents), and water (10 mL). The combination underwent irradiation at a sufficiently high-power level to achieve the anticipated temperature, using a heating rate of 36 °C per minute, followed by a temperature of 200 °C for a duration of 10 minutes. Following the process of cooling to room temperature, the pH of the solution was modified to a range of 8-9 by the introduction of NaOH. Subsequently, the resulting mixture underwent extraction using ethyl acetate, with a total volume of 20 mL repeated three times. The organic layers were mixed and afterwards subjected to drying using $MgSO_4$. The resulting mixture was then filtered and subjected to evaporation under decreased pressure. The crude residue underwent purification using column chromatography using a mixture of cyclohexane and ethyl acetate as the eluent on a silica gel stationary phase, resulting in the isolation of the desired quinoline compound.

4. Results and Discussion

In the first series of tests, the exclusion of highly hazardous reagents such as arsenic oxide and nitrobenzene was implemented, and water was included as an environmentally friendly solvent. This alteration in solvent composition resulted in modifications to both temperature and activation processes, deviating from the typical Skraup reaction. In this study, we conducted a model reaction involving the interaction of glycerol (1) with aniline (2) in the presence of sulfuric acid (1 equiv.). The reaction was performed under microwave irradiation at a temperature of 200 °C in pure water. The experimental details are shown in Figure 1.

The combination underwent irradiation at a sufficiently enough power level to attain the anticipated temperature, using a heating ramp of 36 °C min−1, followed by a temperature of 200 °C for a duration of 10 minutes (resulting in a total time of 15 minutes). The target compound

quinoline (3) was synthesized with a yield of 8% and a low conversion of aniline (14%) under the experimental conditions. Compound 3 was obtained with a yield of 44% and complete the conversion of aniline 2 when the catalyst loading was increased to 300 mol% H_2SO_4. Under environmentally friendly and solvent-free circumstances, the synthesis of heterocycle 3 was carried out in the presence of varying quantities of H_2SO_4 (100 mol% and 300 mol%). However, it should be noted that the extraction process was more challenging when the reaction was conducted without water as a solvent.



1 2 3

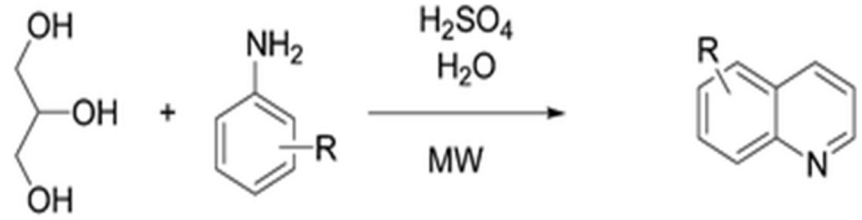
Furthermore, the use of a continuous flow approach in the scale-up process may not be suitable unless water is included as a solvent. The microwave activation technique underwent modification to include a heating ramp with a rate of 6 °C per minute, followed by a temperature of 200 °C for a duration of 10 minutes. The extended reaction period of 40 minutes resulted in comparable yields to those achieved using the first heating ramp technique, which had a total duration of 15 minutes. The only exception was seen in the Skraup reaction conducted in the absence of solvent, where the presence of 300 mol% of H_2SO_4 was used. In this particular instance, the use of water as a solvent resulted in a greater yield (43% compared to 21%). It is worth mentioning that the yield of heterocycle 3 did not exceed 5% when the aforementioned circumstances were used with conventional thermal activation.

In order to identify a catalyst with improved efficiency, the subsequent phase included investigating several acids, including $FeCl_3$, H_2SO_4–$FeCl_3$, $FeCl_3$–AcOH, $Fe_2(SO_4)_3$, H_2SO_4–$Fe_2(SO_4)_3$, and altering their concentration (ranging from 1.0 equiv. to 5 equiv.) under the experimental parameters outlined before. Although the various acids or acid mixtures facilitated the synthesis of quinoline (3), none of these acids exhibited the same level of effectiveness as H_2SO_4 (3 equivalents). The reduction of temperature from 200 °C to 100 °C resulted in a decrease in the yield of the desired compound 3. The efficiency of acrolein creation as an intermediate from glycerol (1) was found to be inadequate and hindered the successful synthesis of the desired heterocycle 3 with a high yield when the reaction temperature was below 200 °C. The temperature of 200 °C was selected based on the yield achieved.

After obtaining the optimum reaction conditions, we conducted a screening of several aniline derivatives with varying electronic and steric demands in the Skraup synthesis. The experimental procedure included the use of glycerol (1, 30 mmol, 3 equivalents), an aniline derivative (10 mmol, 1 equivalent), and H_2SO_4 (300 mol%) in a 10 mL aqueous solution. The reactions were conducted at a temperature of 200 °C for a duration of 15 minutes, as shown in Figure 2. The aniline derivatives containing electron donating groups in the para position mostly yielded the Skraup

adducts 4-11, with yields ranging from 18% to 66%. A satisfactory yield of 6-hydroxyquinoline (4) was obtained from the starting material 4-hydroxyaniline, with a yield of 66%.

The outcome of this study demonstrated a superior performance compared to the results achieved via the implementation of our earlier protocol, with a success rate of 66% as opposed to 27% (Saggadi et al., 2014). It is worth mentioning that the use of nitrobenzene in the synthesis of 6-hydroxyquinoline (4) resulted in a higher yield (77%) of the desired hydroxyl derivative (Taylor et al., 2016). This was achieved by a modified Skraup reaction and Bamberger rearrangement. The number provided by the user is 18. The thiomethyl group exhibited a moderate yield of 28%, but the thiol functionality resulted in a poor yield of just quinoline 3.



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5. Conclusion

Finally, bioactive heterocyclic compounds produced from natural sources have a diverse spectrum of biological properties and have shown tremendous promise for a variety of uses. These chemicals have shown promise anticancer action by targeting several molecular pathways involved in the genesis and progression of cancer. They also have significant antibacterial action against bacteria, fungi, viruses, and parasites, making them excellent candidates for antimicrobial agent development.

In summary, the present research investigation showcases the efficacious synthesis of bioactive heterocyclic compounds by the utilization of microwave-assisted synthesis techniques, using natural starting materials. The approach has many benefits, including enhanced reaction efficiency and decreased reaction durations, making it a useful asset in the realm of pharmaceutical research. Potential avenues for future study might include the examination of supplementary natural source materials, refinement of reaction parameters, and deeper analysis of the biological properties shown by the produced molecules.

However, further study is needed to completely understand the mechanisms of action, maximize their effectiveness, and assure human safety. Additionally, efforts should be made to investigate sustainable and environmentally friendly ways of manufacturing in order to fulfill the rising demand for these substances.

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