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Heterocyclic Substituted Flavones: Bridging Natural Products and Medicinal Chemistry

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Abstract

Heterocyclic substituted flavones represent a unique and promising class of flavonoid derivatives, gaining significant attention in recent years due to their diverse and enhanced biological activities. These compounds are characterized by the incorporation of heterocyclic moieties such as quinoline, pyridine, thiazole, imidazole, oxazole, and pyrazole into the flavone structure, which significantly alters and often enhances their bioactive properties. This structural modification has made heterocyclic flavones particularly appealing as candidates for therapeutic applications. The inclusion of heterocyclic groups in flavones not only diversifies their chemical structure but also imparts a wide range of biological activities. Among these, their antioxidant, anti-inflammatory, antimicrobial, and neuroprotective properties stand out, with particular emphasis on their potential as anticancer agents. Moreover, the mechanisms underlying the biological activities of heterocyclic flavones are explored, offering insights into how these compounds interact at the molecular level to exert their effects. This understanding is crucial for the rational design of new derivatives with improved efficacy and selectivity. The growing interest in heterocyclic flavones is fueled by their potential to address various unmet medical needs, particularly in the development of new drugs and therapeutic agents. This review highlights the importance of continued research in this field, particularly focusing on innovative modifications that could unveil new biological activities. By expanding our knowledge of flavonoid chemistry and the therapeutic applications of heterocyclic flavones, there is a significant opportunity to develop novel treatments that could benefit patients across a range of conditions.

Keywords: Flavone derivatives, heterocyclic substituted flavones, anticancer potential, therapeutic applications, structure-activity relationships

INTRODUCTION

Heterocyclic Compounds

Chemicals classified as heterocyclic, have one or more rings made up of carbon atoms plus at least one atom of an element other than carbon, such as sulfur, nitrogen, oxygen, or other non-carbon elements. The heteroatoms that make up these non-carbon atoms are responsible for the various characteristics and roles that heterocyclic compounds accomplish. Heterocycles are widely prevalent in nature and are found in many biologically important molecules, pharmaceuticals, and other organic substances [1].

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Here are some key points about heterocyclic compounds [2–4]:

1. *Diversity:* Heterocyclic compounds exhibit a wide range of structures, sizes, and chemical properties. The presence of heteroatoms can impart unique reactivity and functionality to these compounds.

1. *Biological significance*: Many biologically active compounds, including vitamins, nucleic acids (DNA and RNA), and most pharmaceutical drugs, contain heterocyclic structures. For example, heterocyclic compounds include purine and pyrimidine bases found in DNA.
2. Heterocycles can be classified according to the size of the ring and the number of heteroatoms. Common examples include:
   - *Azoles:* Five-membered ring structures containing nitrogen, such as pyrrole and imidazole.
   - *Oxazoles and thiazoles:* Five-membered ring structures containing oxygen and sulfur, respectively.
   - *Pyridines and pyrimidines:* Six-membered ring structures containing nitrogen.
   - *Furan and thiophene:* Five-membered ring structures containing oxygen and sulfur, respectively.
   - *Quinoline and isoquinoline:* Compounds with a fused benzene ring to a pyridine ring.
3. *Synthesis:* Heterocyclic compounds can be synthesized via a variety of methods, including cyclization reactions, ring closing reactions, and other organic synthesis methods. Some heterocycles are naturally occurring, while others are synthesized for medicinal or industrial purposes [5].
4. *Medicinal chemistry:* Many drugs and pharmaceuticals are based on heterocyclic structures. The presence of heteroatoms can influence the pharmacokinetics and pharmacodynamics of a compound, affecting its bioavailability and interaction with biological targets.
5. *Electron density:* The heteroatoms in heterocyclic compounds often have lone pairs of electrons, making these compounds more polar and potentially more reactive than their purely carbon-based counterparts.

Because heterocyclic compounds often exhibit significant biological activity, they are important in the discovery and development of new drugs. Scientists are still searching for and creating new heterocyclic compounds for applications in materials science, health and agriculture, and other fields [6, 7].

Flavones

Flavones, also known as flavonoids, are a class of highly polyphenolic compounds in the plant kingdom. These compounds are responsible for the colors in fruits, vegetables and flowers. In addition, their antioxidant properties are well established. Because flavonoids, including flavonoids, can reduce oxidative stress by neutralizing free radicals, the potential health benefits of flavonoids have been investigated (Figure 1) [8, 9].

Some of the major properties of flavones are as follows:

1. *Chemical structure*: Characteristics of flavones are a heterocyclic ring (C ring), containing an oxygen atom, and two phenyl rings (A and B rings) on a 15-carbon skeleton. The C ring is often connected at position 2 and 3 of the C6-C3-C6 carbon skeleton [10].
2. *Common sources*: Flavones are found in a variety of plant-based foods, such as citrus fruits (e.g., oranges, lemons), parsley, celery, chamomile tea, and some grains. They are often present in the form of glycosides, where the flavone molecule is bound to sugar molecules [11].
3. *Antioxidant properties:* Due to their antioxidant properties, flavones help neutralize reactive oxygen species (ROS) and protect cells from oxidative damage. The hydroxyl groups on the phenyl rings are responsible for this antioxidant capability [12].
4. Several flavones have shown antioxidant properties by modulating antioxidant pathways and reducing the production of inflammatory mediators [13].
5. Biological applications of flavones have been studied, including antimicrobial, carcinogenic and neuroprotective properties. Their ability to interfere with cellular signaling pathways is largely responsible for these reactions [14].

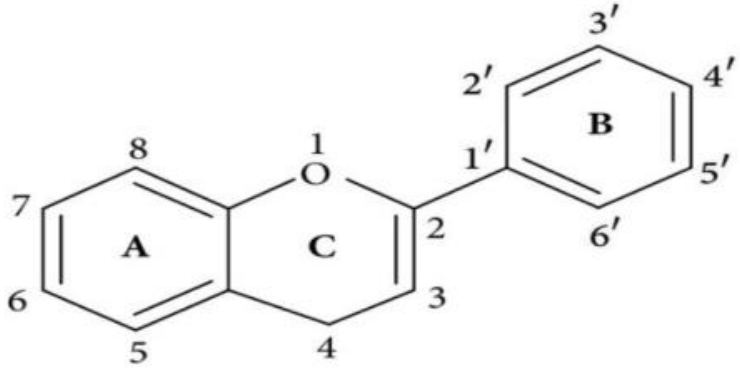

Figure 1. Basic structure of flavones.

6. *Health benefits:* While research is ongoing, flavones are being investigated for potential health benefits, such as cardiovascular protection, cancer prevention, and neuroprotection. However, it is important to note that the bioavailability of flavones and their potential health effects can vary based on the specific compounds and their sources [15].
7. *Dietary intake:* Consuming a diet rich in fruits, vegetables, and other plant-based foods provides a natural source of flavones. The health effects of flavones are often associated with their presence in a balanced and varied diet [16].

It is worth noting that individual flavones may have distinct properties, and research continues to explore their specific mechanisms of action and potential therapeutic applications. Ongoing studies aim to understand how flavones and other flavonoids contribute to human health and disease prevention.

Heterocyclic Substituted Flavones

Heterocyclic substituted flavones refer to a class of compounds that are derivatives of flavones, with additional heterocyclic moieties incorporated into their structure. One flavonoid is flavones, a widespread naturally occurring group of chemicals found in the plant kingdom [17]. Flavones are known for their diverse biological activities, including antioxidant, anti-inflammatory, and potentially anticancer properties.

When heterocyclic substitutions are introduced into flavones, it can alter their chemical and pharmacological properties, potentially enhancing their biological effects. The structure of heterocyclic substituted flavones may vary based on the specific heterocyclic moieties added. Some common heterocyclic groups that can be substituted onto flavones include pyridine, pyrimidine, imidazole, thiazole, and others. These substitutions can affect the solubility, stability, and interaction with biological targets.

Potential areas of interest and research regarding heterocyclic substituted flavones include [18–21]:

1. *Medicinal properties:* Investigating the potential pharmacological activities of these compounds, such as their antioxidant, anti-inflammatory, and anticancer effects.
2. *Structure-activity relationships (SAR):* Understanding how different heterocyclic substitutions impact the biological activity of flavones, helping in the design of more potent and selective compounds.
3. *Cancer research:* When exploring the potential of these compounds as anticancer agents, including their ability to inhibit cancer cell growth, induce apoptosis, and disrupt signaling pathways that contribute to cancer metastasis.
4. *Synthesis and chemical modification:* Developing efficient methods for synthesizing heterocyclic substituted flavones and exploring diverse chemical modifications to optimize their properties.

5. *Bioavailability and pharmacokinetics:* Studying how the introduction of heterocyclic moieties influences the absorption, distribution, metabolism, and excretion of flavones in the human body.

Various Biological Activities of Flavone Derivatives

Flavone derivatives, which are modified forms of the natural compound flavone, have been studied for various biological activities. The chemical composition of these extracts allows for a wide range of applications [22]. Some of the notable biological activities associated with flavone derivatives include:

1. *Antioxidant activity:* Many flavones and their derivatives have antioxidant properties that help remove reactive oxygen species (ROS) and protect cells from oxidative damage. It is the presence of hydroxyl groups in the phenyl rings that gives them their antioxidant properties [23].
2. *Effect on inflammation:* Flavone derivatives have shown anti-inflammatory effects by modulating inflammatory pathways and inhibiting inflammatory mediators. These substances could be investigated for ailments linked to persistent inflammation [24].
3. *Anti-cancer properties:* Some flavone derivatives have been studied for their potential anti-cancer properties. They induce cancer cell growth, induce apoptosis, or programmed cell death, and interfere with the signaling pathways that drive tumor growth. Structural changes aim to develop their anti-cancer cell abilities greater than [25].
4. *Antibacterial activity:* Studies have shown that flavone derivatives have antibacterial, antifungal properties. The potential of these compounds can be explored as antimicrobial agents or in combination with existing antibiotics [26].
5. *Antiviral properties:* Some flavone derivatives exhibit antiviral activity against certain viruses. Research has explored their potential in inhibiting viral replication or entry into host cells [27].
6. *Neuroprotective effects:* Flavone derivatives have been studied for their neuroprotective properties, which may be attributed to their antioxidant and anti-inflammatory activities. These compounds could have potential applications in neurodegenerative disorders [28].
7. *Antidiabetic effects:* Research suggests that certain flavone derivatives may have antidiabetic effects by modulating glucose metabolism, improving insulin sensitivity, and protecting pancreatic beta cells [29].
8. *Cardioprotective effects:* Flavone derivatives may have cardio-protective effects by influencing factors such as blood pressure, lipid metabolism, and reducing oxidative stress in the cardiovascular system [30].
9. *Anti-Allergic activity:* Some flavone derivatives have demonstrated anti-allergic effects by inhibiting allergic responses and the release of histamine [31].
10. *Antiangiogenic properties:* The compounds from flavones can inhibit atherosclerosis, which is necessary for the birth of new blood vessels and essential for tumor growth. This antiangiogenic effect is relevant in the context of cancer therapy [32].

It is important to note that the specific biological activities of flavone derivatives can vary based on their chemical structures, substitutions, and concentrations. Furthermore, new derivatives and their potential applications in various industries including agriculture and medicine are still being explored through continuous research.

Anticancer Potentials of Flavones

Flavones, a subgroup of flavonoids found in various plants, have been studied for their potential anticancer properties. Leishmaniasis and tropical medicine: explain the complications of neglected tropical disease [33]. Here are some of the ways in which flavones may contribute to anticancer effects:

1. *Antioxidant activity:* Flavones have antioxidant properties, meaning they can neutralize free radicals and reduce oxidative stress. Overexposure to oxidative stress has been associated with cancer initiation and metastasis. Flavones can help protect cells from DNA damage and prevent the development of cancer by damaging free radicals [34].

2. *Anti-inflammatory effect:* High cancer risk is associated with chronic inflammation. Flavones have been shown to reduce inflammation by modulating inflammatory pathways. Flavones can help prevent cancer by reducing inflammation [35].
3. *Programmed cell death induction:* Some flavones have been shown to induce systemic death of cancer cells. A malfunction in the natural process of apoptosis, which destroys abnormal or damaged cells, can lead to cancer. Flavones may activate signaling pathways leading to programmed cell death in cancer cells [36].
4. *Cell cycle arrest:* Flavones may interfere with the cell cycle, leading to the arrest of cancer cells at specific stages. This can prevent uncontrolled cell growth and division, a major hallmark of cancer [37].
5. *Angiogenesis*: It is the process of creating new blood vessels, is critical for cancer growth and spread. The lymph nodes are disturbed. Some flavones have shown evidence of antiangiogenic properties, which means they can block new blood vessels and therefore reduce the amount of blood flowing to the tumor [38].
6. *Interference with signaling pathways:* Flavones may interfere with specific signaling pathways involved in the growth and survival of cancer cells. For example, they may target the PI3K/Akt/mTOR pathway or the NF-κB pathway, which play crucial roles in cancer development [39].
7. *Modulation of enzymes and proteins:* Flavones may modulate the activity of enzymes and proteins involved in cancer progression. For instance, they may inhibit enzymes such as matrix metalloproteinases (MMPs) that play a role in tumor invasion and metastasis [40].
8. *Hormonal regulation:* Some flavones may exert hormonal effects that can be relevant in hormone-dependent cancers. For example, they may interact with estrogen receptors and influence hormonal signaling pathways [41].

It is important to note that the specific anticancer mechanisms can vary among different flavones and may depend on factors such as their chemical structure, concentration, and the type of cancer being studied. While promising, the use of flavones as anticancer agents is still an area of active research, and further studies, including clinical trials, are needed to establish their efficacy and safety for cancer prevention and treatment.

Heterocyclic Flavone Derivatives with Their Chemical Information and Activities

Heterocyclic flavone derivatives are flavones that have been chemically modified to include heterocyclic groups. These derivatives often exhibit enhanced or novel biological activities compared to their parent flavones [42]. Here are several notable types of heterocyclic flavone derivatives, including their chemical information and reported biological activities.

1. *Derivatives of quinoline flavones:* Quinoline is an aromatic heterocyclic organic molecule with one nitrogen atom in its ring structure. A quinoline-flavone derivative is produced when that flavone combines with the backbone. Derivatives of quinoline flavones have shown anticancer activity by inducing apoptosis and inhibiting cancer cell growth. Many signaling pathways required for cancer cell survival and proliferation can be disrupted. These compounds have broad antimicrobial activity against bacteria and fungi [43].
2. *Pyridine-flavone derivatives:* Each of the six members of the ring of the original heterocyclic organic complex pyridine contains a nitrogen atom. Pyridine rings can be attached to various positions on the flavone structure. Pyridine-flavone derivatives have been found to possess significant anticancer activity, often through mechanisms involving cell cycle arrest and apoptosis induction. These derivatives can reduce inflammation by inhibiting pro-inflammatory cytokines and enzymes [44].
3. *Thiazole-flavone derivatives:* A molecule with a nitrogen sulfur atom in the center of a five-membered ring is called a thiazole. Thiazole rings can be incorporated into the flavone scaffold. Thiazole-flavone derivatives show promising anticancer properties, particularly against breast and

prostate cancers, through mechanisms like apoptosis induction and inhibition of angiogenesis. They also exhibit strong antioxidant activities, helping to protect cells from oxidative damage [45].

4. *Imidazole-flavone derivatives:* Imidazole is a ring with five members and two nitrogen atoms. When fused or attached to a flavone molecule, it forms imidazole-flavone derivatives. These compounds can arrest the cell cycle and inhibit the growth of cancer cells. Their ability to inhibit important signaling pathways in cancer cells has been investigated. Imidazole-flavone derivatives exhibit significant antifungal activities, making them potential candidates for antifungal drug development [46].
5. *Oxazole-flavone derivatives:* Oxygen atoms and nitrogen atoms form a five-membered ring called an azole. The flavone structure allows the azozole groups to be attached to multiple sites. Oxazole-flavone derivatives have demonstrated potential anticancer effects, particularly in inhibiting the proliferation of certain cancer cell lines. Oxygen atoms and nitrogen atoms form a five-membered ring called an azole. The flavone structure allows the azozole groups to be attached to multiple sites [47].
6. *Pyrazole-flavone derivatives:* Pyrazole is a five-membered ring, separated by two nitrogen atoms. Pyrazole groups can be added to the flavone system. The ability of pyrazole-flavone derivatives to inhibit cancer cell proliferation and induce apoptosis is under investigation. It has shown efficacy against various types of cancer cells. In addition, by inhibiting inflammatory mediators, these compounds help reduce inflammation [48].

CONCLUSION

A diverse class of compounds known as heterocyclic flavone derivatives hold great promise for pharmaceutical applications. The incorporation of heterocyclic groups into the flavone structure can enhance or modify their biological activities, making them promising solution for the development of new therapeutic agents. Their properties include antioxidant, inflammatory, anticancer, antibacterial and antifungal properties. Each type of heterocyclic flavone derivative offers unique properties that can be further explored for specific therapeutic applications.

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