Some Important Coumarin Derivatives and Their Pharmacological Activities

Chattopadhyay SK

Assistant Professor, Department of Chemistry, Santipur College, Santipur-741404, Nadia, West Bengal, India

Corresponding author: Assistant Professor, Department of Chemistry, Santipur College, Santipur-741404, Nadia, West Bengal, India; Email: s.k.chattopadhyay@gmail.com

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ABSTRACT
Coumarins occupy an important position in the area of natural products and synthetic organic chemistry due to their various applications. Owing to the wide spectrum of biological activities like anti-inflammatory, anti-cancer, anti HIV etc, coumarin and its derivatives have attracted organic chemists to research on it. Besides isolation from natural sources, several new pharmacologically potential coumarins have been synthesized in laboratories. This review article provides recent informations and pharmacological activities of some important coumarins either fused or linked with heterocycle scaffolds.

Key Words: Coumarin, Anticancer, Anti-inflammatory, Anti HIV.
1. INTRODUCTION

The world of chemistry has been playing the pivotal role for the service of mankind. The discovery and development of numerous organic compounds have added a new direction in the advancement of civilization. Among such all, coumarin and its derivatives (Borges, F. et al., 2005; O’Kennedy, R. et. al., 1997 and Marrero, J. G. et al., 2015) whether naturally occurring or chemically synthesized have attracted significant scientific interests, emerged from their broad spectrum of pharmacological activities.

In recent years, compounds having more than one heterocyclic ring have been found to exhibit interesting biological activities. Especially, numerous coumarins containing heterocyclic moiety either in fused state or as substituent are of great interests as this incorporation of another heterocycles into coumarin show promising or even unprecedented pharmacological properties (Venugopala, K. N. et al., 2013 and Kale, M. et al., 2014). A number of reviews covering biological aspects of natural and functionalized coumarins have been reported and none of them have focused specifically on coumarins containing heterocyclic moiety. In view of this, an overview of some important coumarins containing heterocycles, either as substituent or in a fused component and their pharmacological activities as reported in recent literatures has been described in this short review.

2. CLASSIFICATIONS

Coumarin, being one of the members of benzopyrone family constitutes large variety of compounds. Depending upon the chemical structure, coumarin containing heterocycles are broadly classified into two main categories - coumarin linked with heterocyclic moiety and coumarin fused with other heterocyclic ring which is further subdivided into three main classes: furanocoumarins (Figure 2), pyranocoumarins (Figure 3) and pyrrolocoumarins (Figure 2) (Rio, J. A. D. et al., 2014).

![Figure 1: Classifications of Coumarins containing heterocycles.](image)

Again, based on the position of fused ring pyrano and furano coumarins are further subdivided into two major categories - linear type and angular type. Besides these, complex heterocycles like tetracyclic coumarin compounds (Figure 4) have also been reported in literature. Coumarins linked with heterocyclic moiety (Figure 5) are of different kinds depending upon the nature of heterocycle linked with the coumarin moiety.

3. NATURAL OCCURANCES

Natural coumarin was first isolated in 1822 from tonka bean, coumarou. Since then, near about 1350 coumarins have been identified from different plants, bacteria and fungi [1]. Besides these, a large number of heterocycles linked with coumarins have been designed and synthesized in laboratories because of pharmaceutical interests (Medina, F. G. et al. 2015 and Kale, M. et al. 2014). A list of some important coumarins either fused or linked with heterocycles and their natural sources from which they are isolated are summarised below:
### TABLE 1

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Name of coumarins</th>
<th>Sources from where isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Psoralen</td>
<td>seeds of <em>Psoralea corylifolia</em>, Common fig.</td>
</tr>
<tr>
<td>02</td>
<td>Imperatorin</td>
<td><em>Angelica dahurica</em></td>
</tr>
<tr>
<td>03</td>
<td>Anthogenol</td>
<td>Green fruit of <em>Aegle</em></td>
</tr>
<tr>
<td>04</td>
<td>Bergapten, (+)-S-Marmesin, (-)-S-Marmesin, Xanthyletin</td>
<td>Whole plants of <em>Fatoua Pilosa</em></td>
</tr>
<tr>
<td>07</td>
<td>Methoxalen</td>
<td>Seeds of the <em>Ammi majus</em></td>
</tr>
<tr>
<td>08</td>
<td>Angelicin</td>
<td><em>Bituminaria bituminosa</em></td>
</tr>
<tr>
<td>09</td>
<td>Ayapin</td>
<td><em>Eupatorium ayapana</em> (Asteraceae), <em>Helianthus annuns</em>, <em>Aetemisa apiacea</em></td>
</tr>
<tr>
<td>10</td>
<td>Felamidin</td>
<td><em>Ferula compestis</em></td>
</tr>
<tr>
<td>11</td>
<td>Grandivittin, Agasylin, Aegelinol benzoate</td>
<td>Roots of <em>Ferula compestis</em> (Apiaceae)</td>
</tr>
<tr>
<td>12</td>
<td>Mamea A/AB cyclo E</td>
<td>Stem Bark of <em>Calophyllum dispar</em> (Clusiaceae)</td>
</tr>
<tr>
<td>13</td>
<td>Khellactone</td>
<td><em>Phlojodicarpus sibircus</em></td>
</tr>
<tr>
<td>14</td>
<td>Visnadine</td>
<td>Fruit of <em>Ammi visnaga</em></td>
</tr>
<tr>
<td>15</td>
<td>Calanolide A, B, C, F and pseudocordatolide C</td>
<td><em>Calophyllum Lanigerum</em> (Clusiaceae)</td>
</tr>
<tr>
<td>16</td>
<td>Inophyllum A, B, C, D, E, and P</td>
<td>Giant African Snail <em>Achatina fulice</em></td>
</tr>
<tr>
<td>17</td>
<td>Ningalin B, Lamellarin D</td>
<td>Marine Alkaloid</td>
</tr>
<tr>
<td>18</td>
<td>Psoralidin</td>
<td><em>Psoralea corylifolia</em></td>
</tr>
<tr>
<td>19</td>
<td>Decursin</td>
<td><em>Angelica gigas</em> root</td>
</tr>
</tbody>
</table>

### 4. PHARMACOLOGICAL ACTIVITIES

Natural and synthetic coumarins containing heterocyclic moiety have been found to exhibit a wide range of pharmacological activities such as anti-inflammatory, antibacterial, antiviral, antifungal, anticancer and many other pharmacological activities.

#### (a) Anti-inflammatory activities:

Imperatorin (1), a furano coumarin, shows anti-inflammatory activity by blocking the protein expression of inducible nitric oxide synthase and cyclooxygenase 2 in hypolysaccharide-stimulated RAW264.7 (Huang, G-J. et al., 2012). Again, heterocycles linked with coumarin moiety have also been found to possess appreciable inflammatory activities. Two important compounds in this regard, coumarins when linked with benzofuran moiety by ether linkage (37) (Ghate, M. et al., 2005) and coumarins when linked with styryl carbonyl unit (38) (Melagraki, G. et al., 2009) have been used as inhibitors of lipooxygenase (LOX) and cyclooxygenase (COX) in arachidonic pathway.

#### (b) Antibacterial activities:

Several furano- and pyranocoumarins like imperatorin (1), anthogenol (3), felamidin (9), grandivittin (15), agasylin (16) and aegelinol benzoate (17) show excellent results of antibacterial activities against Gram (+ve) and Gram (-ve) bacterial strains, e.g., *Shigella dysenteriae*, *Enterococcus*, *Staphylococcus aureus*, *Salmonella typhi*, *Enterobacter cloacae* and *Enterobacter aerogenes* (Souzaa, S. M. D. et al., 2005). Coumarins linked with heteroaromatic moiety have also been screened for their antibacterial activities. Compound 39 is found to possess this property targeting selectivity towards metronidazole-resistant strains of *Helicobacter pylori* (Smania Jr. A. Z. et al., 2009). This pharmacological activity against *Staphylococcus typhi*, *Staphylococcus pyogenus* and *Vibrio cholera* by broth dilution has been found positive for coumarin linked benzodiazepine (40) (Kale, M. et al., 2014).

#### (c) Antifungal activities:

The antifungal activities against plant pathogen have been examined and imperatorin (1) and psoralen (2) are found most effective (Smania Jr. A. Z. et al., 2008). Again, coumarin linked with thiazole unit (41) (Gummu, A. et al., 2010) and 4-aminomethylcoumarin crown ether derivatives (42) (Bagley, M. C. et al., 2011) have attracted much attention for their antifungal activities. The coumarin-thiazole compound has been assessed against fungal strain of *Candida albicans*. 

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Figure 2: Examples of linear and angular furano- and pyrrolocoumarins
(d) Anti-HIV activities:
Numerous natural products have been evaluated as anti-HIV agents (Yadav, I. K. et al. 2009). Among them, some compounds containing coumarin moiety have been found to be significant in inhibiting different stages in the HIV replication cycle (Kostova, I. et. al., 2006 and Kumar, K. A. et al., 2015). The appreciable HIV inhibitory activities are observed by the inophyllums (24, 25, 27, 28, 29, 30, 34 and 35) and calanolides (23, 26, 31, 32 and 33) (Bartus, H. R. et al., 1993 and Madden, T. L. et al., 1998). Again, imperatorin (1) also inhibits either vesicular stomatitis virus-pseudotyped or gp160-enveloped recombinant HIV-1 infection in several T cell lines and in HeLa cells (Munoz, E. et al., 2004). Khellactone coumarins, like suksdorfin (20), an angular pyranocoumarin, plays important role as an anti-HIV agents (Lee K-H. et al., 2003). Another compound, 3',4'-di-o-(-)-camphanoyl-(+)-cis-khellactone (DCK) (43), a modified suksdorfin, demonstrate extremely potent inhibitory activity against HIV-1 replication in H9 lymphocytic cells (Lee K-H. et al., 2003). Coumarin derivatives ningalin B (12) and lamellarin D (13) were derived from the marine alkaloids, which exhibit HIV-1 integrase inhibition, immunomodulatory activity and cytotoxicity (Kumar, K. A. et al., 2015).
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23 Calanolide C (R₁ = n-pr, R² = OH, R³ = H)
24 Inophyllum A (R₁ = Ph, R² = OH, R³ = H)
25 Inophyllum D (R₁ = Ph, R² = H, R³ = OH)
26 (+)-Ccalanolide A (R₁ = n-pr, R² = OH, R³ = H)
27 Inophyllum B (R₁ = Ph, R² = OH, R³ = H)
28 Inophyllum P (R₁ = Ph, R² = H, R³ = OH)
29 Inophyllum C (R₁ = R⁴ = H, R² = R³ = CH₃)
30 Inophyllum E (R₁ = R³ = H, R² = R⁴ = OH)
31 (-)-Calanolide B
32 Pseudocordatolide C
33 Calanolide F
34 Inophyllum G1
35 Inophyllum G2
36 Mammes A/AB dioxalanocyclo F

Figure 3: Examples of tetracyclic coumarins
Figure 5: Examples of Coumarin linked with other heterocycles
(e) Anticancer activities:
A marginal cytotoxic activity against the A549 lung cancer cell line (Bruno M. et al., 2009) is being exhibited by grandivittin (15), agasylin (16) and aegelinos benzoxide (17). Imperatorin (1) has also been found to possess the anticancer property (Liu, F. et al., 2011). Furanocoumarin psoralidin (11) in combination of TRAIL (tumor necrosis factor related apoptosis inducing ligand) enhances the potential of TRAIL for inducing apoptosis in sensitized TRAIL-resistant LNCAp (prostate cancer cells) (Krol. W. et al., 2011). Pyranocoumarin, decursin (22) possess inhibitory property against proliferation in bladder cancer 235J cells and also in colon cancer HCT-1116 cells (Moon. S. et al., 2010). In recent years exhaustive studies have been carried out for the synthesis of coumarin compounds having potentiality to act as anticancer agents (Klenkar, J. et al., 2015), for example, coumarin-linked 3,4- dihydroxypropiolazole (44) have shown activity as tumor necrosis inhibitor. A new hybrid molecule coumarin-monostrol (45) has showed the most potent selective activity against breast cancer cell lines MCF-7 and MDA-MB-231 (Sashidhara, K. V. et al., 2013). The same activity against breast cancer cell has also been exhibited by coumarin-benzothiazole derivatives (46) (Mubeen. M. et al., 2012).

(e) Other pharmacological activities:
Naturally isolated coumarins like bergapten (4), (+)-S-marmesin (5), (-)-S-marmesin (6) and xanthyletin (14) have exhibited their potentiality to act as anti tuberculosis agent (Venugopala, K. N. et al., 2013). Visnadine (21), angular pyrano coumarin, exhibiting peripheral and coronary vasodilator activities, is used for the treatment of angina pectoris (Durate, J. et al., 1997). Newly developed hydrazinyl thiazolyl coumarin derivatives (47) have shown significant radical scavenging activity that is comparable or better than the known antioxidants, quercetin, BHT and Trolox (Bagley. M. et al., 2012). Heterobicycle-coumarin conjugated compounds with the –SCH2- linker such as imidazopyridine-coumarin (48), purine-coumarin (49) and benzoazole-coumarin (50) have been found as inhibitor of HCV replication at an EC50 of 6.8, 2.0 and 12 μM respectively (Hwu. J. R. et al., 2009). Methoxalen (7) and coumain-imiazole derivative (51) have been proven to be the most promising compounds as cytochrome P450 enzyme inhibitors (Descatoire, V. et al., 1987 and Zhou, C. H. et al., 2014).

5. CONCLUSION
Coumarin and its derivatives whether they come from wide variety natural sources or being synthesized in laboratory on regular basis have been of great interest due to their significant pharmacological activities. In this mini review, effort has been given on the search of coumarins that are either fused with or linked with other heterocyclic moiety with respect to their wide array of pharmacological activities. For the last decades, a great involvement on the design, synthesis and screening of biological activities of coumarins linked with other heterocycles are going on and promising new drug discovery in future.

REFERENCES