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Design and synthesis of 4-quinolinone 2-carboxamides as calpain inhibitors

Dong Hyuk Nam,[a,b] Kwang Seob Lee,[c] Sang Hoon Kim,[a,b] Sung Min Kim,[a,b,c] Seo Yun Jung,[a] Sung Hyun Chung,[a,b] Hyoung Ja Kim,[c] Nam Doo Kim,[d] Changbae Jin[c] and Yong Sup Lee[a,b,*]

[a]*Department of Pharmaceutical Sciences, Kyung Hee East-West Pharmaceutical Research Institute, College of Pharmacy, Kyung Hee University, Seoul 130-701, Republic of Korea*
[b]*Department of Life and Nanopharmaceutical Science, Kyung Hee University, Seoul 130-701, Republic of Korea*
[c]*Life Sciences Research Division, Korea Institute of Science and Technology, Seoul 130-650, Republic of Korea*
[d]*R&D Center, Equispharm Inc., Gyeonggi Bio-center, Suwon, Gyeonggi-do 443-766, Republic of Korea*

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Dedicated to Professor Hokoon Park on the occasion of his 60th birthday.

Abstract—Calpains are involved in a variety of calcium-regulated cellular processes, such as signal transduction, cell proliferation, differentiation, and apoptosis. Excessive calpain activation contributes to serious cellular damage and has been reported in many pathological conditions. 4-Quinolinone 2-carboxamide derivatives were prepared and evaluated for μ-calpain inhibitory activities. Of the compounds synthesized, **3a** and **3k**, which possess a primary amide and 4-methoxyphenethyl amide at P_1' region, were found to most potently inhibit μ-calpain with IC_{50} values of 0.71 ± 0.07 and 0.73 ± 0.23 μM, respectively. On the other hand, the incorporation of pyridine-containing amides decreased inhibitory activity.
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Calpains are calcium-dependent, intracellular proteolytic enzymes and are found in many cells. Calpains are referred to as cysteine proteases because they utilize a cysteine residue in the catalytic process.[1] Two major forms of calpains have been identified: calpain I (or μ-calpain) and calpain II (or m-calpain), which require micromolar and millimolar concentrations of calcium ions for activation, respectively.[2] Calpains are involved in a variety of calcium-regulated cellular processes, such as signal transduction, cell proliferation, differentiation, and apoptosis. However, excessive calpain activation contributes to serious cellular damage or even cell death. The involvement of μ-calpain in neurological disorders such as stroke[3] and Alzheimer's disease[4] has attracted much interest in calpain inhibitors as potential therapeutic agents. Most of the known calpain inhibitors bind to the catalytic site in a competitive manner and are derived from small peptides (e.g., **1**, MDL 28,170), which are structurally related to the cleavage site of calpain substrates.[5,6] However, **1** suffers from the disadvantages of nonselectivity, instability during storage, and excessive metabolism due to its peptide character and the high reactivity of its aldehyde moiety.[7] In connection with our work to find a less peptidic scaffold for μ-calpain inhibitors, we recently reported that a chromone carboxamide **2** is a conformationally restricted cyclic analog of **1**.[8] The chromone skeleton of **2** was designed based on the expectation that the formation of additional hydrogen bonds might be possible via an interaction between carbonyl oxygen of the pyran ring and calpain residues. However, this increased binding affinity might be compromised by the loss of probable hydrogen bonding in the active site by the replacement of the hydrogen bond donor –NH in **1** by the hydrogen bond acceptor oxygen at position-1 of the chromone ring. Therefore, we designed a 4-quinolinone ring as a new scaffold for μ-calpain inhibitors. In this case, it was expected that the NH group in the 4-quinolinone ring would interact with the residue in the catalytic site as a hydrogen bond donor, and that this would lead to increased binding affinity, and thus, increased μ-calpain

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* Corresponding author. Tel.: +82 2 961 0370; fax: +82 2 966 3885; e-mail: kyslee@khu.ac.kr

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inhibitory activity. Herein we present the synthesis of 4-quinolinone 2-carboxamide derivatives **3** and their biological evaluation for μ-calpain inhibition (Fig. 1). Ketoamide was used as a warhead in the new inhibitors since several ketoamide-derived inhibitors have shown improved in vitro and in vivo metabolic stability.[9] To investigate the influence of substituents located in the warhead position of inhibitors, we introduced variations in the amide region (R).

Compound **7** was synthesized as previously reported with slight modification (Scheme 1).[10] Briefly, diethyl oxalpropionate (**4**) was condensed with aniline in acetic acid to give anilino-maleate **5**. Compound **5** was heated at 250 °C in mineral oil to form the cyclized product, quinolinone **6**. The ethyl ester group in **6** was hydrolyzed with KOH to yield 4-quinolinone 2-carboxylic acid **7**. Compound **7** was then coupled to various 3-amino-2-hydroxybutanoic acid amides (**8a–l**),[11] the P_1 building blocks, using EDC/HOBt to afford hydroxy-amides **9a–l**, which were subsequently transformed into the 4-quinolinone 2-carboxamide derivatives **3a–l** by oxidation under Dess–Martin periodinane conditions (Scheme 2).[12] The yields of coupling and oxidation reactions are summarized in Table 1.[13]

The μ-calpain inhibitory activities of the prepared 4-quinolinone 2-carboxamide derivatives **3a–l** were then evaluated using human calpain I, which was isolated from erythrocytes. Suc-Leu-Tyr-AMC was used as the fluorogenic substrate.[14,15] Results are summarized in Table 1. MDL 28,170 (**1**) and the chromone derivative **2** were also tested for comparisons. Primary amide **3a** most potently inhibited μ-calpain (IC_{50} = 0.71 μM), and it was observed that the potencies decreased as the bulkiness of substituents increased. When *N*-alkylaryl substituents were incorporated in the warhead region (R), a clear structure–activity relationship, but different pattern to the *N*-alkyl substituted derivatives (**3a–c**) was found. It is believed that the aryl group participates in a specific interaction with adjacent hydrophobic pocket in the catalytic site since more bulky *N*-alkylaryl substituted derivatives showed potent inhibitory activities. Compounds containing a 4-methoxy substituent at the benzene ring (**3f**, **3k**) were more potent than unsubstituted *N*-alkylaryl derivatives (**3e**, **3j**). Incorporation of a pyridine (**3i**, **3l**) decreased inhibitory activity, indicating that lipophilic residues are preferred in this region. However, compounds **3a** and **3k**, the most potent μ-calpain inhibitors of the series, were 10- and 20-fold less potent than MDL 28,170 (**1**) and the parent chromone derivative **2**, respectively. By visual inspection, it might be supposed that the decreased inhibitory activities of 4-quinolinone derivatives are partly due to the presence of tautomeric structures, 4-hydroxyquinolines, which would result in the loss of expected H-bonding interactions at position-1 of **1** and position-4 of the chromone derivative **2**. However, it is well known that 4-pyridones and their benzo analogs exist predominantly in the keto form rather than the 4-hydroxypyridine form.[16] The predominant presence of 4-quinolinone structures was also

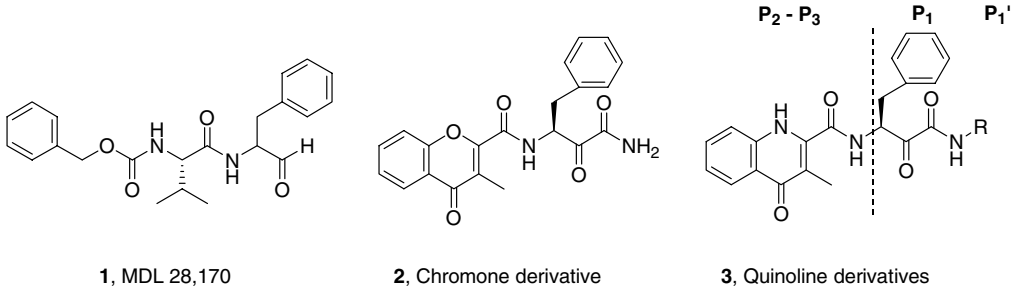
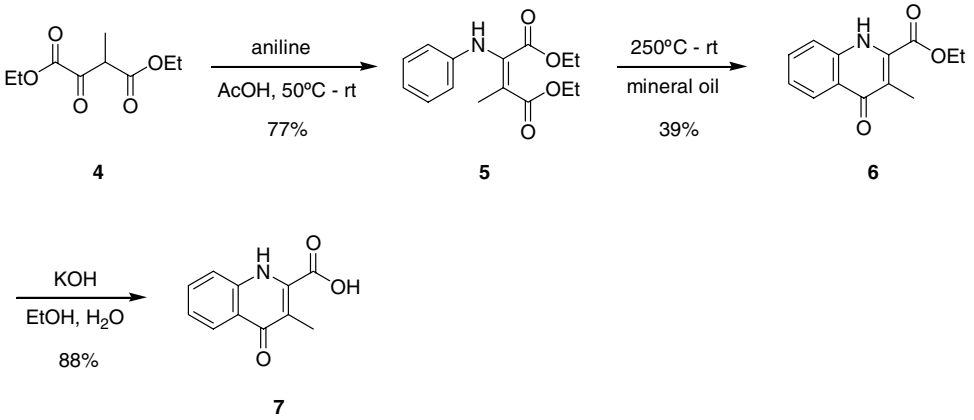


Figure 1. Design of 4-quinolinone derivatives as new μ-calpain inhibitors.



Scheme 1.

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