2-Methylacrylamide as a bioisoster of thiourea group for 1,3-dibenzylthioureido TRPV1 receptor antagonists

Seol Rin Park a, Juhyun Kim a, Sun Young Lee a, Young-Ho Park b, Hee-Doo Kim a,⇑

a College of Pharmacy, Sookmyung Women's University, Seoul 04310, South Korea
b AmorePacific R & D Center, Yongin-Si, Gyeonggi-do 17014, South Korea

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In order to replace thiourea group with the more drug-like moiety for 1,3-dibenzylthioureas having TRPV1 antagonist activity, we introduced a set of functional groups between the two aromatic rings based on bioisosteric replacement. The synthesized bioisosteres of 1,3-dibenzylthioureas were tested for their antagonist activities on TRPV1 by 45Ca2+-influx assay using neonatal rat cultured spinal sensory neurons. Among the tested 14 kinds of bioisosters, 2-methylacrylamide group was the best candidate to replace thiourea group. Compound 7c, 2-methylacrylamide analog of ATC-120, showed as potent as ATC-120 in its antagonist activity. In addition, 2-methylacrylamide analog 7e having vinyl moiety showed the most potent activity with 0.022 μM of IC50 value, indicating that thiourea group of 1,3-dibenzylthioureas could be replaced to 2-methylacrylamide without loss of their potencies.

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The transient receptor potential vanilloid-1 (TRPV1) is a ligand-gated nonselective cation channel with high Ca2+ permeability,1 emerging as an attractive target for the treatment of chronic and inflammatory pain.2 Capsaicin, resiniferatoxin,3 and SDZ-2494824 represent the most well-known agonists to date. However, due to their undesirable side effects such as pungency and/or hypothermia responses,5 recent efforts have been focused on the discovery of novel antagonists.6 We and co-workers discovered the potent antagonists (MK-056,7a SC-0030,7b,7c and ATC-120d) by changing inflammatory pain.2 Capsaicin, resiniferatoxin,3 and SDZ-2494824

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At first, we made urea analog 7a as a thiourea bioisoster of ATC-120, as shown in Scheme 2. (S)-4-Methanesulfonamido-α-methylbenzalmine 5a was treated with 4-tert-butylbenzylisocyanate 6a under basic condition followed by deprotection to give the urea analog 7a in 17% yield. Next, we focused on the design and synthesis of amide analogs due to their drug-like properties. Amides, acrylamides, thioamides, and thioacrylamides were designed and prepared via the route outlined in Scheme 3. (S)-4-Methanesulfonamido-α-methylbenzalmines (5a–c) were treated with (E)-3-[4-(tert-butyl)phenyl] acrylic acid (6b) or (E)-3-[4-(tert-butyl)phenyl]-2-methylacrylic acid (6c) with an aid of coupling agent DEPC under basic condition.
in DMF to produce the corresponding (methyl)acrylamides 7b–e in 55–94% yields. Double bond reduction of (methyl)acrylamides 7b–c by hydrogenolysis gave the (methyl)amides 7f–g in good yields.

Treatment of 7b or 7f with Lawesson’s reagent gave the corresponding thio(acryl)amide 7h or 7i respectively.

We also designed the glycolamides 7j–l and its analogs 7m as a bioisoster of thiourea ATC-120. Synthesis of 7j–m are outlined in Scheme 4. (S)-4-Methanesulfonamido-α-methylbenzylamines (5a–b) were treated with 2-[4-(tert-butyl)phenoxy]acetic acid (6d) with an aid of coupling agent DEPC under basic condition in DMF to produce the corresponding glycolamides 7j–k. Treatment of 7j with Lawesson’s reagent gave the corresponding thioglycolamide 7l in 88% yield. By reacting with cyanamide and HgCl2, thio-glycolamide 7l could be converted to the corresponding N-cyanoacetimidamide 7m in 98% yield.

Finally, we designed propiolamide as a bioisoster of thiourea of ATC-120. (S)-4-Methanesulfonamido-α-methylbenzylamine (5a) was treated with 2-[4-(tert-butyl)phenyl] propiolic acid (6e) with an aid of coupling agent DEPC under basic condition in DMF to produce the corresponding propiolamide 7n, as shown in Scheme 5.

The prepared bioisosters for ATC-120 were tested for their antagonist activities on TRPV1 by 45Ca2+-influx assay using neonatal rat cultured spinal sensory neurons. As is anticipated, urea analog 7a showed 13-fold decrease in antagonist activity compared to thiourea analog ATC-120. Amide analogs 7f, methyl-branched amide 7g, and thioamide 7h were less potent than thiourea analog ATC-120, but more active than urea analog 7a. When an oxygen atom is introduced to β-position in place of

![Fig. 1. Structure of capsaicin and 1,3-dibenzythioureas.](image_url)

![Scheme 1. Synthesis of chiral amine 5c: (a) ICl, CH2Cl2, 47%; (b) Bu3SnCH = CH2, LCl, Pd(PPh3)4, DMF, reflux, 72%; (c) (CH3SO2)2O, pyridine, CH2Cl2, 47%; (d) CF3CO2H, CH2Cl2, 100%.)](image_url)

![Scheme 2. Synthesis of urea 7a: (a) TEA, CH2Cl2, then CF3CO2H, 17%.)](image_url)

![Scheme 3. Synthesis of amides and thioamides: (a) DEPC, TEA, DMF, 55–94%; (b) H2, Pd/C, quant.; (c) Lawesson’s reagent, toluene, reflux, 87%; (d) Lawesson’s reagent, toluene, reflux, 87%.)](image_url)

![Scheme 4. Synthesis of glycolamides and its analogs: (a) DEPC, TEA, DMF, 77–88%; (b) Lawesson’s reagent, toluene, reflux, 88%; (c) HgCl2, H2NCN, TEA, DMF, 98%.](image_url)
phenyl ring, providing propiolamide. Next, we introduced a triple bond between amide and 4-butyramide into the amide. The introduction of glycolamide instead of acrylamide analogs focusing on the replacement of thiourea functionality to improve drug-likeness. Among the tested 14 kinds of bioisosteres, 2-methylacrylamide group was the best candidate to replace thiourea group. Compound 7c, 2-methylacrylamide analog of ATC-120, showed as potent as ATC-120 in its antagonist activity. In addition, 2-methylacrylamide analog 7e showed the most potent activity with an IC50 value of 0.022 μM of IC50 value, indicating that the less druggable thiourea group of 1,3-dibenzylthioureas could be replaced by the more drug-like 2-methylacrylamide group without loss of their potencies. This bioisosteric replacement might enable us to jump into the new chemical space of TRPV1 related antagonists.

Acknowledgements

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References


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<tr>
<th>Compound</th>
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<td>−NHCH=−</td>
<td>Agonist (EC50)</td>
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<tr>
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Note: EC50 (the concentration of derivatives necessary to produce 50% of the maximal response) and IC50 values (the concentration of derivatives necessary to reduce to 0.5 μM capsaicin by 50%) were estimated with at least 3 replicates at each concentration. Each compound was tested in two independent experiments. Antagonist data were fitted with a sigmoid function.

Table 1

45Ca2+-influx activity of the bioisosters of 1,3-dibenzylthioureido TRPV1 receptor antagonist.
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