

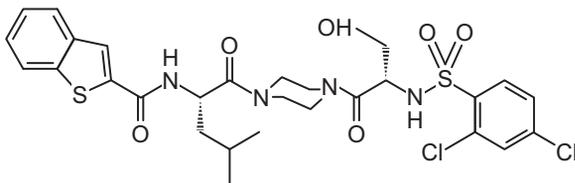
REPLY TO THORNELOE ET AL.

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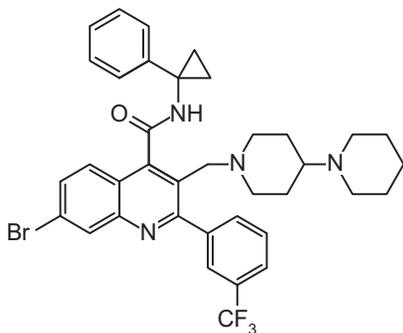
TO THE EDITOR: At the outset, we are, of course, happy to correct the molecular representation, and referencing, of the GSK drugs mentioned in **FIGURE 7**, as follows:

GSK1016790A



GSK2193874: 401; GSK1016790A: 402; GSK205: 318

GSK2193874



Thornloe and colleagues complain that we have failed to recognize the efficacy of GSK1016790A as an agonist of TRPV4 and, in particular, that an entry in **FIGURE 7** (p. 933) describes it as “non-selective.” Their concerns would have been allayed had they continued reading for several pages

where (on p. 936) the following appears: “Endothelial Ca^{2+} is increased by the application of GSK1016790A, a selective TRPV4 agonist which also induces marked dilation of small mesenteric arteries from normal mice, but not those from mice lacking TRPV4.”

We cannot accept the statement by Thornloe and colleagues that we did not recognize the doubtful selectivity of 4 α -PDD because immediately after the sentence quoted by Thornloe and colleagues (from p. 931), we state that 4 α -PDD “is widely employed experimentally, although its exclusivity for TRPV4 as its target receptor has been put in issue by the claim that it can activate cultured mouse DRG neurons independently of TRPV4,” citing Alexander et al. (Alexander R, Derby A, Aubdool AA, Power AR, Grover S, Gentry c Grant AD. 4Alpha-phorbol 12,13-didecanoate activates cultured mouse dorsal root ganglia neurons independently of TRPV4. *Br J Pharmacol* 168: 761–772, 2013). Furthermore, in *paragraph 4* of their letter, Thornloe and colleagues quote us as stating (at p. 935), “A selective antagonist of TRPV4 has yet to be definitively identified” without continuing to quote the conclusion of that same sentence, which states, “but HC-067047 is believed to be selective for TRPV4.”

Thornloe and colleagues further complain that we have not included their GSK2193874 product as a selective antagonist because they “would argue that GSK2193874 is quite a selective TRPV4 antagonist, perhaps the most selective reported in the literature to date.” This is premised on a rather elastic concept of “selectivity.” By any standard, “argument” by authors (no matter how learned) that their compound is “quite a selective TRPV4 antagonist” does not constitute proof that it is indeed a selective antagonist. We must also reject the claim by Thornloe and colleagues that we ought to have mentioned all screened GSK compounds that have been reported as having an antagonist effect at TRPV4. We do not consider this to be the function of independent reviewers.

We also have to decline Thornloe and colleagues’ criticism as “unfair” the opinion that we have expressed concerning the risks of collateral injury presented by even a selective TRPV4 antagonist when therapeutically administered. As we said on p. 935: “However, as with TRPV1, the difficulty in developing an antagonist of TRPV4 for therapeutic purposes resides in identifying a potent, selective, and bioavailable small molecule that can target the TRPV4 channels of interest while preserving the function of TRPV4 channels necessary for non-pathological physiology.”

This is a reply to a Letter to the Editor (Thornloe KS, Cheng M, Holt D, Willette RN. Properties of the activator GSK1016790A and antagonist GSK2193874. *Physiol Rev* 97: 1231–1232, 2017).

These reasons were further elaborated on at p. 959–960 in a further detailed discussion at the conclusion of the review, which would appear to have entirely escaped the attention of Thornloe and colleagues.

Finally, as regards the complaints made by Thornloe and colleagues in the ultimate and penultimate paragraphs of their letter, we believe that the contributions that have been made by them were fairly and adequately addressed in the review, and we do not believe that the purpose of a review ought to be either to promote particular products or to provide a detailed record of the work of every scientist on the subject. Therefore, while we very much regret that

Thornloe and colleagues feel that they have not received sufficient attention and recognition in the review, we do not accept that there are any grounds for altering the views that we have expressed except, of course, to correct the molecular representation of, and references relating to, their GSK products mentioned in **FIGURE 7**.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).