Published in final edited form as:

Trends Endocrinol Metab. 2020 November ; 31(11): 801–802. doi:10.1016/j.tem.2020.08.005.

Letter Biased Opioid Receptor Ligands: Gain without Pain

Tyler C. Beck^{1,2,*}, Thomas A. Dix¹, Russell A. Norris^{2,*}

¹Department of Drug Discovery & Biomedical Sciences, Medical University of South Carolina, Charleston, SC, 29425, USA

²Department of Regenerative Medicine and Cell Biology, Medical University of South Carolina, Charleston, SC, 29425, USA

In response to the Spotlight article entitled ‘Biased Opioid Receptor Ligands: Gain without Pain’, the featured small molecule triazole 1.1 (Figure 1A) lacks significant blood–brain barrier (BBB) penetration [1].

One hundred million American adults experience chronic pain [2]. Current pain medications of use are largely μ -opioid agonists (MOAs), which promote central nervous system (CNS)-mediated adverse effects such as abuse liability, respiratory depression, and sedation. κ Opioid agonists (KOAs) have been explored as nonaddictive alternatives to MOAs, demonstrating efficacy in models of acute and chronic pain [3]. However, CNS-penetrating KOAs are also associated with negative adverse effects, including dysphoria, sedation, hallucinations, and psychosis.

Activated κ opioid receptors (KORs) signal through two independent G-protein-coupled receptor (GPCR) and β -arrestin pathways [1,4]. These signaling pathways are linked to distinct outcomes: activation of the GPCR pathway attenuates pain and itch signals, whereas β -arrestin activation in the CNS promotes untoward adverse effects. These findings denote a promising avenue for the development of pathway-biased KOAs. The KOA triazole 1.1 has received significant attention due to its selectivity for the favorable GPCR pathway [4–7]. Furthermore, triazole 1.1 demonstrates potent antinociceptive and antipruritic activity, without the induction of adverse effects [5].

While several articles have been published highlighting the pathway-biased nature of triazole 1.1, none of these papers describe triazole 1.1 as being peripherally selective [1,4–7]. In rats, a threefold dose escalation of triazole 1.1 ($IC_{50} = 31.0$ nM) was required to achieve equimolar striatal drug concentrations relative to the well-established CNS-penetrating KOA U50,488H ($IC_{50} = 31.7$ nM) [4,8]. Despite empirical evidence of peripheral selectivity, triazole 1.1 and U50,488H demonstrated indistinguishable efficacy in multiple models of acute pain when administered to rats at identical drug concentrations [4]. Using the ‘Brain Or IntestinaL Estimated’ permeation method (BOILED-Egg), a highly accurate predictive model that works by computing the lipophilicity and polarity of small molecules to estimate biological barrier penetration, we found that triazole 1.1 has a limited capacity to cross the BBB [9] (Figure 1B). These data suggest that the analgesic activity of

*Correspondence: beckt@musc.edu (T.C. Beck) and norrisra@musc.edu (R.A. Norris).

9. Smith JS et al. (2018) Biased signaling: from simple switches to allosteric microprocessors. *Nat. Rev. Drug Discov* 17, 243–260 [PubMed: 29302067]
10. Brooks J and Tracey I (2005) From nociception to pain perception: imaging the spinal and supraspinal pathways. *J. Anat* 207, 19–33 [PubMed: 16011543]

Figure 1. Triazole 1.1 Is Peripherally Selective.

(A) Chemical structure of triazole 1.1. (B) BOILED-Egg plot demonstrating the poor predicted oral bioavailability and BBB permeation of triazole 1.1. The y axis represents lipophilicity (WLOGP) and the x axis represents total polar surface area (TPSA). Abbreviations: BBB, blood–brain barrier; BOILED-Egg, Brain Or IntestinaL EstimatedD permeation method; HIA, high intestinal absorption; PGP, p-Glycoprotein substrate.