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COMMENTARY

Two receptors, one molecule: Reprogramming bile acid signaling for cardioprotection

KEY WORDS

Cardioprotective;
TGR5;
FXR;
Bifunctional (multi-target) drug design

Myocardial ischemia/reperfusion injury remains a major unresolved problem in cardiovascular therapy. Restoring blood flow remains the cornerstone of therapy for ischemic myocardium, yet reperfusion itself can initiate a cascade of damaging events, including excessive reactive oxygen species generation, mitochondrial disruption, calcium overload, inflammatory activation, and cardiomyocyte death[1]. This biological complexity has made cardioprotection difficult to achieve clinically. Many agents that performed well in preclinical models have failed to translate into effective therapies, in part because they were designed to modulate only one component of a highly interconnected injury network[2]. In this context, the identification of the sulfonyl benzoic acid derivative **E6** as a bifunctional TGR5 agonist and FXR antagonist represents an important and timely advance in rational multi-target drug design[3].

The central appeal of this work lies in its strategic use of bile acid receptor biology. TGR5 activation has been linked to anti-inflammatory, metabolic, and cardioprotective actions[4,5], whereas FXR signaling has been associated with cardiomyocyte apoptosis and the progression of myocardial ischemia/reperfusion injury[6]. Instead of approaching these receptors as isolated therapeutic targets, the authors recognized their potential functional interplay and proposed a more integrated strategy: activate the protective TGR5 pathway while simultaneously blocking the potentially deleterious FXR pathway. This dual mechanism offers a conceptually elegant way to address the multifactorial nature of reperfusion injury.

From a medicinal chemistry standpoint, the study is particularly compelling because the bifunctional profile of **E6** was not an unexpected finding. The authors began with structure-based virtual screening against TGR5 and identified **T26** as an initial weak bifunctional hit. They then pursued optimization through a clear and rational structural hypothesis: maintain the molecular features required for TGR5 agonism while extending the compound toward the FXR functional pocket to disrupt coactivator recruitment. This design logic reflects a broader principle in modern medicinal chemistry, in which ligands for GPCRs and nuclear receptors can be refined by carefully tuning receptor-specific pharmacophores[7]. Through systematic structure−activity relationship exploration, the investigators converted **T26** into **E6**, a non-steroidal bifunctional modulator with enhanced FXR antagonism, preserved TGR5 agonistic activity, and improved physicochemical characteristics.

Equally important is the study's mechanistic breadth. Transcriptomic and experimental validation data indicate that **E6** influences multiple biological processes relevant to reperfusion injury, including inflammation, apoptosis, metabolic regulation, and cardiomyocyte survival. The involvement of inflammatory mediators, including IL-10-related signaling, is particularly consistent with earlier evidence that endogenous anti-inflammatory pathways can shape the extent of myocardial ischemia/reperfusion injury[8]. Rather than acting through a single linear pathway, **E6** appears to reshape a broader injury−response network. This is precisely the kind of pharmacological behavior that may be required for complex acute cardiovascular syndromes, where oxidative stress, inflammation, mitochondrial injury, and cell death are deeply intertwined[1,2].

Taken together, this study offers more than the discovery of a promising cardioprotective lead compound. It provides a persuasive example of how structure-guided design, SAR (Structure−Activity Relationship)-based optimization, and disease-mechanism-driven pharmacology can converge to produce a single molecule capable of coordinating two biologically

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connected receptor systems. **E6** therefore has value not only as a candidate for further therapeutic development but also as a chemical probe for dissecting bile acid receptor crosstalk in myocardial ischemia/reperfusion injury. More broadly, this work reinforces an increasingly important message in cardiovascular drug discovery: in diseases driven by networks of injury rather than single molecular defects, intelligently designed polypharmacology may offer a more realistic path to meaningful cardioprotection.

References

1. Heusch G. Myocardial ischaemia−reperfusion injury and cardioprotection in perspective. *Nat Rev Cardiol* 2020;**17**:773−89.
2. Davidson SM, Ferdinandy P, Andreadou I, Bøtker HE, Heusch G, Ibáñez B, et al. Multitarget strategies to reduce myocardial ischemia/reperfusion injury: JACC review topic of the week. *J Am Coll Cardiol* 2019;**73**:89−99.
3. Zhao XY, Chang TQ, Wu X, Huo TY, Peng J, Liu YM, et al. Discovery of sulfonyl benzoic acid derivatives with joint TGR5-agonist and FXR-antagonist activity for myocardial ischemia/reperfusion injury protection. *Acta Pharm Sin B* 2026;**16**:3802−72.
4. Wang J, Zhang J, Lin X, Wang Y, Wu X, Yang F, et al. DCA−TGR5 signaling activation alleviates inflammatory response and improves cardiac function in myocardial infarction. *J Mol Cell Cardiol* 2021;**151**:3−14.
5. Wang H, Wang J, Cui H, Fan C, Xue Y, Liu H, et al. Inhibition of fatty acid uptake by TGR5 prevents diabetic cardiomyopathy. *Nat Metab* 2024;**6**:1161−77.
6. Pu J, Yuan A, Shan P, Gao E, Wang X, Wang Y, et al. Cardiomyocyte-expressed farnesoid-X-receptor is a novel apoptosis mediator and contributes to myocardial ischaemia/reperfusion injury. *Eur Heart J* 2013;**34**:1834−45.
7. Pellicciari R, Gioiello A, Macchiarulo A, Thomas C, Rosatelli E, Natalini B, et al. Discovery of 6alpha-ethyl-23(*S*)-methylcholic acid (S-EMCA, INT-777) as a potent and selective agonist for the TGR5 receptor, a novel target for diabesity. *J Med Chem* 2009;**52**:7958−61.
8. Yang Z, Zingarelli B, Szabó C. Crucial role of endogenous interleukin-10 production in myocardial ischemia/reperfusion injury. *Circulation* 2000;**101**:1019−26.

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