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Design and synthesis of the first NO- and haem-independent sGC activator BAY 58–2667 for the treatment of acute decompensated heart failure

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Soluble guanylate cyclase (sGC) is a signal-transduction enzyme activated by nitric oxide (NO) and plays a key role in a variety of physiological processes such as vasodilatation, antiaggregation, antiproliferation and neuronal signaling as well as in a variety of disorders of these functions. Current therapies that involve the use of organic nitrates and other NO donors have limitations, including non-specific interactions of NO with various biomolecules and lack of response and the development of tolerance [1,2]. Compounds that activate sGC in an NO-independent manner might therefore provide considerable therapeutic advantages.

High throughput screening led to the identification of a series of dicarboxlic acids as potent sGC activators. Lead structure **1** showed promising *in vitro* potency (sGC over-

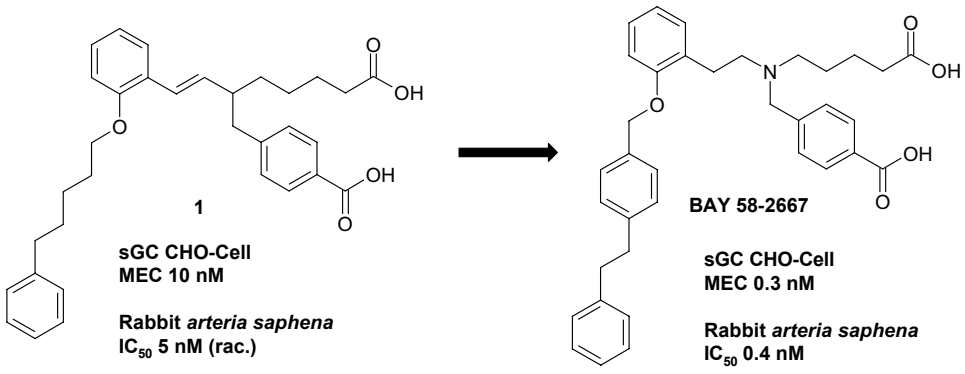

Figure 1
Discovery of sGC activators via ultra-high throughput screening using sGC-overexpressing CHO cell lines.

expressing CHO-cells and relaxation of precontracted rabbit arteria saphena rings) and haemodynamic effects in anaesthetized rats (Fig. 1). Extensive chemical derivatization resulted in conclusive structure activity relationships, which will be presented. Eventually, optimization led to the discovery of BAY 58–2667, a highly potent sGC activator which is currently in clinical trials in patients for the treatment of acute decompensated chronic heart failure.

References

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