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Discovery of riociguat (BAY 63-2521): a potent, oral stimulator of soluble guanylate cyclase for the treatment of pulmonary hypertension

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Soluble guanylate cyclase (sGC) is a key signal-transduction enzyme activated by nitric oxide (NO). Impairments of the NO-sGC signaling pathway have been implicated in the pathogenesis of cardiovascular and other diseases. Direct stimulation of sGC represents a promising therapeutic strategy particularly for the treatment of pulmonary hypertension (PH), a disabling disease associated with a poor prognosis. Previous sGC stimulators such as the pyrazolopyridines BAY 41-2272 and BAY41-8543 demonstrated beneficial effects in experimental models of PH, but were associated with unfavorable drug metabolism and pharmacokinetic (DMPK) properties. Herein we disclose an extended SAR exploration of this compound class to address these issues. Our efforts led to the identification of the potent sGC stimulator riociguat, which exhibits an improved DMPK profile and exerts strong effects on pulmonary hemodynamics and exercise capacity in patients with PH. Riociguat (BAY 63-2521) is currently being investigated in phase III clinical trials for the oral treatment of PH.