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THE DESIGN OF (-)-(*S*)-2-NITROOXYETHYL 1,4-DIHYDRO-2,6-DIMETHYL-3-NITRO-4-(2-TRIFLUOROMETHYLPHENYL)PYRIDINE-5-CARBOXYLATE: A CARDIOSELECTIVE POSITIVE INOTROPIC DERIVATIVE OF BAY K 8644

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Abstract: The title compound, (-)-(*S*)-**9**, is a novel cardioselective calcium channel modulator that exhibits a calcium channel agonist effect on heart, a weak calcium channel antagonist effect on smooth muscle, and releases nitric oxide in vitro. (-)-(*S*)-**9** is a useful lead-compound for the design of positive inotropic agents to treat congestive heart failure, and to study the structure-function relationship of calcium channel modulation.

The design of tissue selective calcium channel (CC) modulators that are useful for the treatment of congestive heart failure (CHF) dictates that their undesirable smooth muscle vasoconstrictor effect be eliminated and/or separated from the desired cardiac positive inotropic stimulant property.[1] For example, racemic Bay K 8644 acts as a calcium channel agonist on both smooth and cardiac muscle since the agonist (-)-(*S*)-enantiomer is about ten times more potent as an activator than its (+)-(*R*)-antipode is as an antagonist.[2] The discovery that nitric oxide (•NO) is an endogenous activator of guanylate cyclase, the enzyme responsible for vascular muscular relaxation, and that organic nitrovasdilators act in vivo by by-passing the NO-generating system in the endothelium to deliver •NO directly to muscle cells in the artery prompted us,[3,4] and others,[5,6] to design Hantzsch-type 1,4-dihydropyridine calcium channel antagonists that have the potential to simultaneously release •NO. We now report the synthesis and calcium channel modulation activities of the cardioselective positive inotrope [(-)-(*S*)-**9**] in which the 3-methoxycarbonyl substituent of Bay K8644 (**10**) is replaced by a 3-(2-nitrooxyethoxycarbonyl) substituent.

Synthesis

The modified Hantzsch reaction of the chiral 3-aminocrotonate ester (**5**), prepared in 4 steps from D-threonine (**1**), with 2-CF_3-C_6H_4-CHO and $MeCOCH_2NO_2$ afforded a mixture of the two diastereomers **6** and **7** that were separated by silica gel column chromatography. The base-induced (DBU) β-elimination reaction of **6** gave the acid (+)-(*S*)-**8**, which on reaction with $BrCH_2CH_2ONO_2$ afforded (-)-(*S*)-**9** (≥96% ee). Similar reactions of diastereomer **7** gave the (+)-(*R*)-enantiomer of **9** (≥96% ee). The absolute configuration of (+)-(*S*)-**8** was confirmed by conversion to (-)-(*S*)-**10**.[7]

Calcium Channel (CC) Modulation Activities and Nitric Oxide (•NO) Release Data

In vitro CC smooth muscle antagonist, and CC cardiac agonist, assays were performed as described previously.[8] (-)-(*S*)-**9** (ED_{50} = 9.2 x 10^{-7} M), like (-)-(*S*)-Bay K 8644 (**10**), is a cardiac CC agonist; but unlike (-)-

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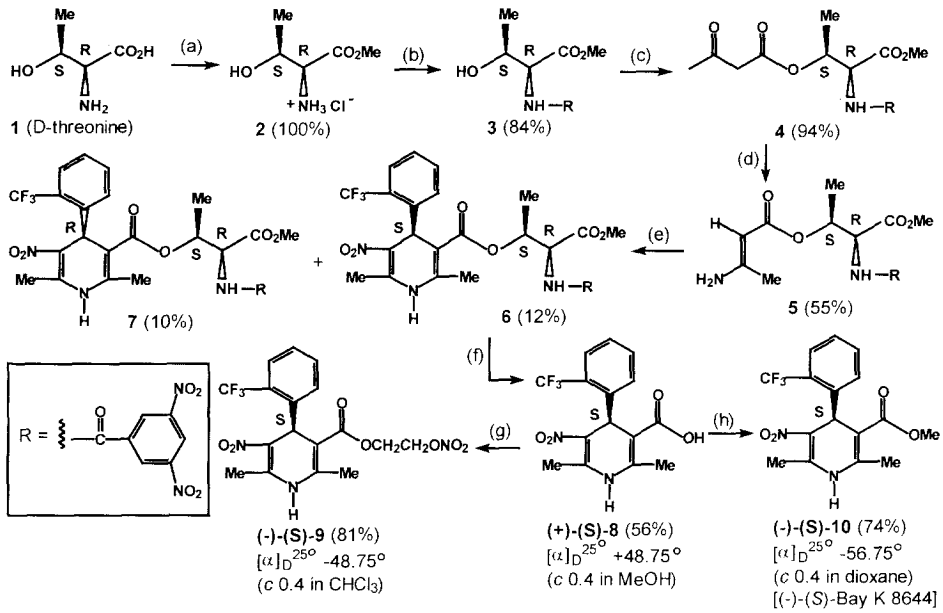
(*S*)-BAY K 8644 is a smooth muscle CC antagonist (IC_{50} = 1.6 x 10^{-5} M). The (+)-(*R*)-enantiomer of **9** exhibited CC antagonist effects on both heart (IC_{50} = 1.6 x 10^{-5} M) and smooth muscle (IC_{50} = 7.9 x 10^{-8} M). In vitro •NO release, determined by quantitation of nitrite using the Griess reaction,[9] for racemic-**9** and the reference drug glycerol trinitrate was 1.09±0.02% and 0.18±0.00%/ONO_2 in the absence, and 2.70±0.02% and 5.30±0.00%/ONO_2 in the presence, of N-acetylcysteamine, respectively (n = 3).



Reagents: (a) $SOCl_2$, MeOH, 25 °C, 48 h; (b) K_2CO_3, 3,5-dinitrobenzoyl chloride, EtOAc/H_2O, 25 °C, 17 h; (c) 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, xylene, 150 °C, 30 min; (d) 4-Me-C_6H_4-SO_3H, NH_3, toluene, 130 °C, 4 h; (e) 2-CF_3-C_6H_4-CHO, $MeCOCH_2NO_2$, EtOH, reflux, 80 °C, 17 h; (f) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 25 °C, 4 h; (g) $BrCH_2CH_2ONO_2$, DMF, K_2CO_3, 25 °C, 24 h; (h) CH_2N_2, MeOH, 25 °C, 15 min.

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References and Notes

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