Discovery of 1-(2,4-dichlorophenyl)4-ethyl-5-(5-(2-(4-(trifluoromethyl) phenyl) ethynyl)thiophen-2-yl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide as A Potential Peripheral Cannabinoid-1 Receptor Inverse Agonist

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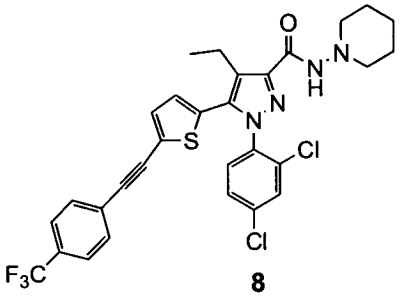
A novel class of aryl alkynylthiophene compounds has been designed to target peripheral CB1R to eliminate/minimize CNS side effects as observed with **1**, a typical brain CB1R-acting agent. The titled compound, 1-(2,4-dichlorophenyl)-4-ethyl-5-(5-(2-(4-(trifluoromethyl)phenyl)ethynyl)thiophen-2-yl)-*N*-(piperidin-1-yl)-1*H*-pyrazole-3-carboxamide (**8**), is tentatively recognized as a peripheral inverse agonist based on its negative central effects in CB1R agonist-induced hypothermia and analgesia models, and low brain exposure (B/P = 1/33) measured at a time point of 2 hours following oral administration. The chronic study of **8** in DIO mice is currently underway. A full account of the *in vivo* studies, with particular emphasis on addressing issues of central drug accumulation and peripheral metabolic benefits, as well as further SAR studies on the series will be reported elsewhere in due course.



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