New Product Highlights

L-Nafadotride, GR 218231 and GR 103691: D_3 dopamine receptor antagonists

Two families of vertebrate dopamine receptors are currently recognized; the D_1-like family, composed of D_1 and D_5 receptor types and the D_2-like family, composed of D_2, D_3 and D_4 receptor types. Because the receptors from the D_2-like family occur at low concentrations in various tissues, they have generally been difficult to study *in situ*. Furthermore, until recently their study has been hampered by the lack of pharmacological tools selective for the various receptor types. Identification of D_3-selective ligands has been of special interest since this receptor is implicated in schizophrenia, depression, Parkinson's disease and drug abuse [1]. The discovery of selective D_3 dopamine receptor agonists, such as **PD 128,907** (Prod. No. **P-216**) and **R(+)-7-OH-DPAT** (Prod. No. **H-168**), helped to verify that this receptor is localized predominantly in the limbic regions of the brain [2]. However, the D_3 dopamine receptor partial agonists **(–)-DS121** (Prod. No. **D-206**) [3] and **BP 897** (Prod. No. **B 9308**) [4], and D_3 dopamine receptor antagonists, such as **U 99194A** (Prod. No. **U-116**) [5], (±)-S11566 [6], (+)-AJ 76, (+)-UH 232 [7] and SB-277011 [8], display only low selectivity for D_3 vs. D_2 dopamine receptors. [9,10].

Sigma-RBI is pleased to introduce three new selective D_3 dopamine receptor antagonists, **GR 103691** (Prod. No. **G 0544**), **GR 218231** (Prod. No. **G 9168**), and **L-Nafadotride** (Prod. No. **N 3535**). GR 103691 is an improved ligand for the characterization and differentiation of activity at D_3 vs. D_2 dopamine receptors *in vitro*, displaying K_i values of 0.4 nM and 4.9 nM, respectively, versus [^{3}H]-(+)-PD 128,907 binding at human recombinant D_2 and D_3 dopamine receptors [11]. GR 218231 exhibits approximately 400-fold selectivity for D_3 vs. D_2 dopamine receptors [12] and displays a 100-fold higher affinity at D_3 vs. D_2 dopamine receptors [13]. L-Nafadotride displays ten-fold selectivity for D_3 vs. D_2 dopamine receptors with a K_i value of 0.3 nM versus [^{125}I]-iodosulpride binding at human recombinant D_3 dopamine receptors [14]. In *in vivo* studies, nafadotride induces catalepsy [11] and inhibits the increase in locomotion observed in rats exposed to repetitive administration of amphetamine [15].

Together these tools should prove useful for the exploration of the pathophysiological significance of D_3 dopamine receptors.

GR 103691 and GR 218231 are sold for research purposes under agreement from GlaxoSmithKline.

References

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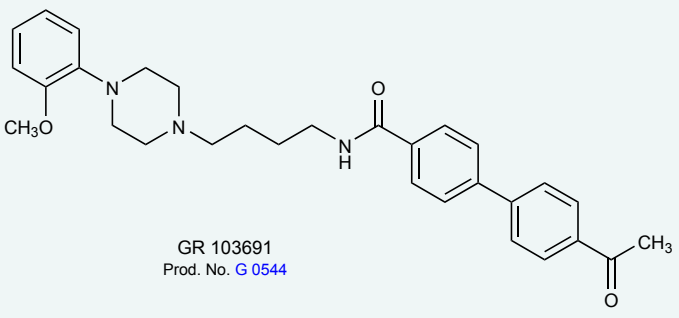
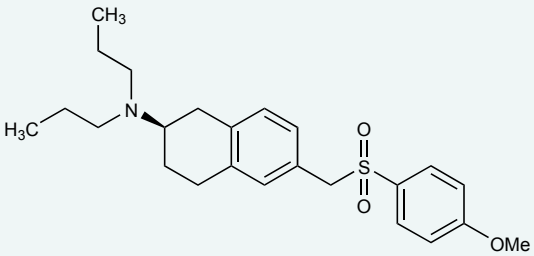


GR 103691
Prod. No. G 0544



GR 218231
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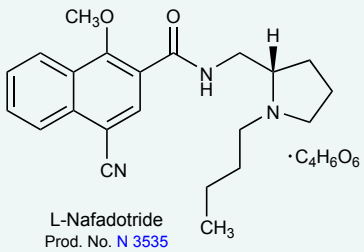

L-Nafadotride
Prod. No. N 3535