N-Oxide analogs of WAY-100635: new high affinity 5-HT_{1A} receptor antagonists
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WAY-100635 [N-(2-(1-(4-(2-methoxyphenyl)piperazinyl)ethyl))-N-(2-pyridinyl)cyclohexanec arboxamide] 1 and its O-desmethyl derivative DWAY 2 are well-known high affinity 5-HT"1"A receptor antagonists, which when labeled with carbon-11...

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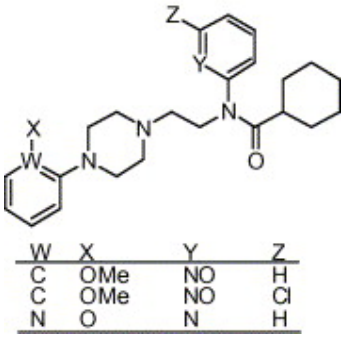
Abstract

WAY-100635 [*N*-(2-(1-(4-(2-methoxyphenyl)piperazinyl)ethyl))-*N*-(2-pyridinyl)cyclohexanecarboxamide] **1** and its *O-desmethyl* derivative DWAY **2** are well-known high affinity 5-HT_{1A} receptor antagonists, which when labeled with carbon-11 (β^+; $t_{1/2}$ = 20.4 min) in the carbonyl group are effective radioligands for imaging brain 5-HT_{1A} receptors with positron emission tomography (PET). In a search for new 5-HT_{1A} antagonists with different pharmacokinetic and metabolic properties, the pyridinyl *N*-oxide moiety was incorporated into analogs of **1** and **2**. NOWAY **3**, in which the pyridinyl ring of **1** was oxidized to the pyridinyl *N*-oxide, was prepared via nucleophilic substitution of 2-[4-(2-methoxyphenyl)piperazin-1-yl]ethylamine on 2-chloropyridine-*N*-oxide followed by acylation with cyclohexanecarbonyl chloride. 6Cl-NOWAY **4**, a more lipophilic (*pyridinyl*-6)-chloro derivative of **3**, was prepared by treating 1-(2-methoxyphenyl)-4-(2-(2-(6-bromo)aminopyridinyl-*N*-oxide)ethyl)piperazine with cyclohexanecarbonyl chloride for acylation and concomitant chloro for bromo substitution. NEWWAY **5**, in which the 2-hydroxy-phenyl group of **2** is replaced with a 2-pyridinyl *N*-oxide group with the intention of mimicking the topology of **2,** was prepared in five steps from 2-(chloroacetylamino)pyridine. *N*-Oxides **3**–**5** were found to be high affinity antagonists at 5-HT_{1A} receptors, with **3** having the highest affinity and a K_i value (0.22 nM) comparable to that of **1** (0.17 nM). By

calculation the lipophilicity of **3** (Log *P* = 1.87) is lower than that of **1** by 1.25 Log *P* units while TLC and reverse phase HPLC indicate that **3** has slightly lower lipophilicity than **1**. On the basis of these encouraging findings, the *N*-oxide **3** was selected for labeling with carbon-11 in its carbonyl group and for evaluation as a radioligand with PET. After intravenous injection of [*carbonyl*-^{11}C]**3** into cynomolgus monkey there was very low uptake of radioactivity into brain and no PET image of brain 5-HT_{1A} receptors was obtained. Either **3** inadequately penetrates the blood–brain barrier or it is excluded from brain by an active efflux mechanism. Rapid deacylation of **3** was not apparent in vivo; in cynomolgus monkey plasma radioactive metabolites of [*carbonyl*-^{11}C]**3** appeared less rapidly than from the radioligands [*carbonyl*-^{11}C]**1** and [*carbonyl*-^{11}C]**2**, which are known to be primarily metabolized by deacylation. Ligand **3** may have value as a new pharmacological tool, but not as a radioligand for brain imaging.

Graphical abstract



W	X	Y	Z
C	OMe	NO	H
C	OMe	NO	Cl
N	O	N	H

Keywords: WAY-100635; 5-HT_{1A} Receptor antagonist; High affinity; Pyridinyl *N*-oxide; PET; Aromatic nucleophilic substitution

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