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Original article

Novel fluoroalkyl derivatives of selective kappa opioid receptor antagonist JDTic: Design, synthesis, pharmacology and molecular modeling studies

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ABSTRACT

Novel *N*- and *O*-fluoroalkyl derivatives of the highly potent KOR antagonist JDTic were designed and synthesized. Their opioid receptor properties were compared in both *in vitro* binding assays and modeling approach. All compounds displayed nanomolar affinities for KOR. The fluoropropyl derivatives were more active than their fluoroethyl analogues. *N*-Fluoroalkylation was preferable to O-alkylation to keep a selective KOR binding. Compared to JDTic, the *N*-fluoropropyl derivative **2** bound to KOR with an only 4-fold lower affinity and a higher selectivity relative to MOR and DOR [$Ki_{(\kappa)}$ = 1.6 nM; $Ki_{(\mu)}/Ki_{(\kappa)}$ = 12; $Ki_{(\delta)}/Ki_{(\kappa)}$ = 159 for **2** *versus* $Ki_{(\kappa)}$ = 0.42 nM; $Ki_{(\mu)}/Ki_{(\kappa)}$ = 9; $Ki_{(\delta)}/Ki_{(\kappa)}$ = 85 for JDTic]. Modeling studies based on the crystal structure of the JDTic/KOR complex revealed that fluorine atom in ligand **2** was involved in specific KOR binding. Ligand **2** was concluded to merit further development for KOR exploration.

1. Introduction

The kappa opioid receptor (KOR, OPRK or κ) belongs to the subfamily of G-protein–coupled receptors (GPCRs) and is closely associated to the action of dynorphin (DYN) peptides as specific endogenous ligands [1]. KOR shares extensive homology with mu (MOR, OPRM or μ) and delta (DOR, OPRD or *δ*) opioid receptor subtypes, but remains unique by its pharmacology and physiological effects [2]. The three opioid receptors, KOR, MOR and DOR, regulate major functions including pain, emotional tone, appetite and reward circuitry. It is well established that KOR agonists produce an aversive effect, whereas agonists at the MOR and DOR sites are rewarding and reinforcing [3–6]. KOR is widely expressed in human throughout the central and peripheral nervous system, and is the most abundant OR in brain [7–11]. High levels of KOR mRNA have been detected in cerebral regions such as the ventral tegmental area, nucleus accumbens, prefrontal cortex, hippocampus, striatum, amygdala and hypothalamus, thought to be critical in mood modulation, motivation, stress reactivity, perception, learning memory, and behavior response to drugs. Growing evidence indicates that changes in DYN/KOR system contribute to symptom clusters that are shared by various psychiatric and addictive disorders (i.e., decreased motivation and negative affect), and that KOR disruption produces anti-stress effects [12–16]. Consequently, KOR is strongly believed to be a molecular key-target to investigate the mechanisms involved in the psychopathologies and to elaborate new therapeutic strategies. This finding has recently stimulated interest in the development of KOR antagonists as pharmacotherapies to treat depression, anxiety, schizophrenia, alcoholism, drugs seeking and relapse [17–22]. Specific KOR antagonists also represent valuable candidates as *in vivo* imaging agents to map KORs in brain and to examine their functions both in healthy and pathological conditions. Indeed, the successful development of selective radiotracers for KOR imaging by positron emission tomography (PET) would allow new investigations of

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neuropsychiatric and addictive disorders, and help the development of novel therapeutic agents by correlating dose, *in vivo* pharmacokinetic parameters, and receptor occupancy of novel KOR-targeting drugs.

Very few pure selective KOR antagonists are reported so far (Chart 1). Classically, the reference agents were nor-BNI (norbinaltorphimine) and GNTI (5′-guanidinonaltrindole) [23,24]. Both compounds are derived from naltrexone and depend on the *N*-cyclopropylmethyl group for their antagonist properties. First discovered nor-BNI was commonly used as the standard tool in opioid pharmacology [23], and subsequently generated GNTI was found to be slightly more potent than norBNI [norBNI: $Ki_{(\kappa)}$ = 0.24 nM, $Ki_{(\mu)}/Ki_{(\kappa)}$ = 204, $Ki_{(\delta)}/Ki_{(\kappa)}$ = 170; GNTI: $Ki_{(\kappa)}$ = 0.18 nM, $Ki_{(\mu)}/Ki_{(\kappa)}$ = 125; $Ki_{(\delta)}/Ki_{(\kappa)}$ = 257] [24,25]. *In vivo*, both morphinan-derivatives were showed to display a very slow brain uptake and release, and to antagonize the actions of KOR agonists for a long time (up to several weeks) [26–29]. Recently, a new class of aminobenzyloxyarylamides has been identified as KOR antagonists with, however, a lower potency in terms of *in vitro* affinity and selectivity compared to norBNI [30]. Among them, LY2456302 [$Ki_{(\kappa)}$ = 0.8 nM, $Ki_{(\mu)}/Ki_{(\kappa)}$ = 30, $Ki_{(\delta)}/Ki_{(\kappa)}$ = 194 *versus* $Ki_{(\kappa)}$ = 0.15 nM, $Ki_{(\mu)}/Ki_{(\kappa)}$ = 216, $Ki_{(\delta)}/Ki_{(\kappa)}$ = 43 for norBNI in the same set of evaluation experiment] was found to exhibit short-acting pharmacokinetic properties *in vivo*, and to reduce ethanol self-administration in alcohol-preferring rats [31]. LY2456302 also demonstrated activity in mouse model predictive of antidepressant-like efficacy [31], and has been advanced to phase II clinical trials for the augmentation of the antidepressant therapy in treatment-resistant depression [32]. The analogue LY2795050 was lastly labelled with carbon-11 (β^+ emitter, $t_{1/2}$ = 20.4 min) and demonstrated favorable pharmacokinetic properties and binding profile in primate by PET imaging [33,34]. To date, JDTic [35–37] that belongs to the trans-(3*R*,4*R*)-3,4-dimethyl-4-(3-hydroxylphenyl)piperidine class of compounds, represents the best established pure selective KOR antagonist in *in vitro* experiments [$Ki_{(\kappa)}$ = 0.03 nM, $Ki_{(\mu)}/Ki_{(\kappa)}$ = 338, $Ki_{(\delta)}/Ki_{(\kappa)}$ = 4935 to be compared to the above cited values for norBNI and LY2456302] [31]. A recent study has reported that there was no non-opioid target from a broad panel of 43 receptors and transporters for which JDTic showed a significant affinity [38]. *In vivo*, JDTic also demonstrated highly specific KOR antagonist properties; JDTic was reported to block the KOR agonist U50488-induced antinociception in mouse, while not antagonizing mu-subtype opioid receptor (MOR) agonist-induced analgesia [37,39]. Despite having a poor brain penetration, JDTic was found to produce in mouse, rat and rhesus monkeys, long-lasting antagonistic effects [28,29], and to display a robust effectiveness in various rodent models of depression, anxiety, alcohol seeking, nicotine withdrawal and stress-induced cocaine relapse [39–42]. JDTic has been evaluated in phase I clinical trials as drug in the treatment of cocaine addiction [43]. However adverse ventricular tachycardia effects were noticed, that were unpredictable based on the absence of cardiotoxicity in the non-human primate [44].

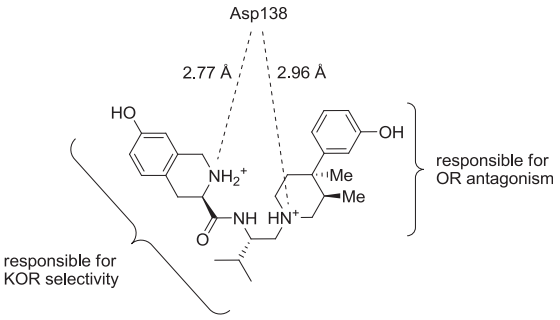

Chart 2. JDTic.

Due to its remarkable pharmacological properties, JDTic remains an important lead ligand for KOR exploration. Structural features of the receptor binding pocket were recently provided by KOR/JDTic complex co-crystallisation revealing a tight fit of JDTic in the bottom of the binding cleft forming ionic polar and extensive hydrophobic interactions with the receptor [45]. The protonated amines in both piperidine and tetrahydroisoquinoline moieties in JDTic formed salt bridges with a highly conserved aspartic acid (Asp138) side chain, probably fixing the ligand in a stabilized V-shaped conformation (Chart 2). From numerous structure–activity relationship studies conducted on JDTic, it has been well established that the (3*R*,4*R*)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine moiety provided pure opioid antagonist properties while KOR selectivity was a consequence of the N-substituent [35,36,46–51]. Only a few structural modifications on JDTic structure were allowed to retain binding properties. Introduction of a methyl group at the nitrogen atom and the hydroxyl group of the tetrahydroisoquinoline ring to give RTI-5989-97 and RTI-5989-212 respectively (Chart 1), led to minimal alteration of *in vitro* intrinsic antagonism activity [JDTic: $Ke_{(\kappa)}$ = 0.02 nM, $Ke_{(\mu)}/Ke_{(\kappa)}$ = 1255, $Ke_{(\delta)}/Ke_{(\kappa)}$ = 3830; RTI-5989-97: $Ke_{(\kappa)}$ = 0.16 nM, $Ke_{(\mu)}/Ke_{(\kappa)}$ = 1313, $Ke_{(\delta)}/Ke_{(\kappa)}$ = 3070; RTI-5989-212: $Ke_{(\kappa)}$ = 0.06 nM, $Ke_{(\mu)}/Ke_{(\kappa)}$ = 857, $Ke_{(\delta)}/Ke_{(\kappa)}$ = 1970] [36,47]. Surprisingly, the *N*-methyl derivative RTI-5989-97 was found to be a long-acting antagonist *in vivo* like JDTic, whereas the *O*-methyl analogue RTI-5989-212 displayed short duration of action [29]. In previous works, we developed the radiolabelling with carbon-11 of RTI-5989-97 (named as [^{11}C]Me-JDTic) [52]. *Ex vivo* evaluation in mouse revealed a very high specific binding of [^{11}C]MeJDTic for

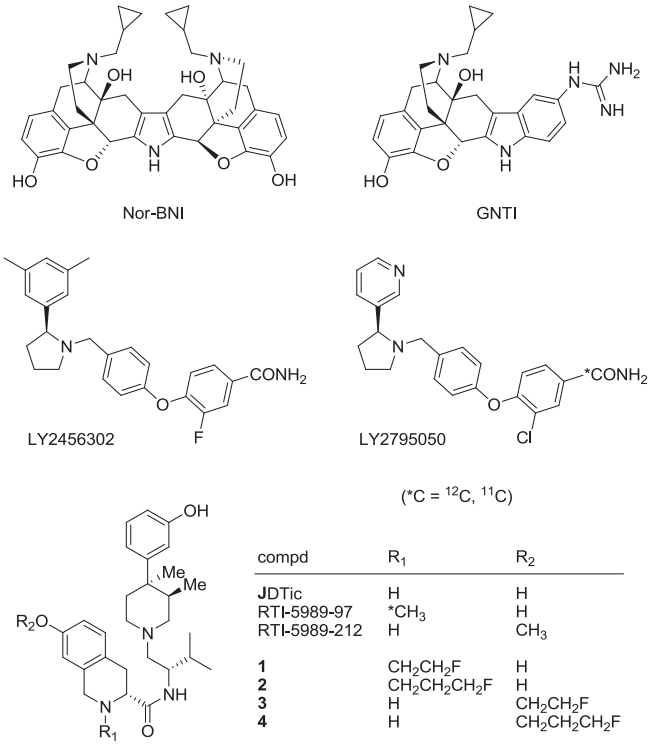

Chart 1. Structures of known potent KOR antagonists and of target compounds **1**–**4**.