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Bioorganic & Medicinal Chemistry Letters 16 (2006) 2955–2959
Bioorganic & Medicinal Chemistry Letters

Synthesis and biological investigations of dopaminergic partial agonists preferentially recognizing the D4 receptor subtype

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Received 16 January 2006; revised 24 February 2006; accepted 25 February 2006
Available online 24 March 2006

Abstract—Aminomethyl-substituted biaryls bearing a pyrazole or triazole moiety were synthesized and investigated for dopamine and serotonin receptor binding. The *N*-arylpyrazoles **3b**,**f**,**g** and **4** revealed K_i values in the subnanomolar range (0.28–0.70 nM) for the dopamine D4 receptor subtype. Employing both mitogenesis and GTPγS assays, ligand efficacy was evaluated indicating partial agonist properties. Interestingly, the tetrahydropyrimidine **4** (FAUC 2020) displayed significant intrinsic selectivity for $D2_{long}$ over $D2_{short}$.
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The dopamine D4 receptor subtype received much attention as a pharmacological target for the treatment of schizophrenia, Parkinson's disease, depression, and attention deficit hyperactivity disorder (ADHD).[1] As a consequence, ongoing efforts have been made to find selective ligands revealing high affinity for the D4 receptor. Thus, an *N*-arylpiperazine framework proved to be a privileged structural unit,[2] which can be labeled as an integral part of a majority of potent D4 receptor ligands. The second nitrogen atom of the piperazine moiety is preferably attached to a benzylic CH_2 position of a fused heteroaryl or a biaryl substructure (Chart 1). Starting from the highly selective D4 ligand L-745,870 displaying weak partial agonist properties,[3,4] structural variations proved to be highly beneficial when ligand efficacy could be tuned. Thus, FAUC 213 turned out to be a complete antagonist exhibiting atypical antipsychotic properties in behavioral and neurochemical models of schizophrenia.[5,6] Very recently, the D4 agonist ABT-724 was discovered as a drug candidate for the treatment of erectile dysfunction (ED).[7]

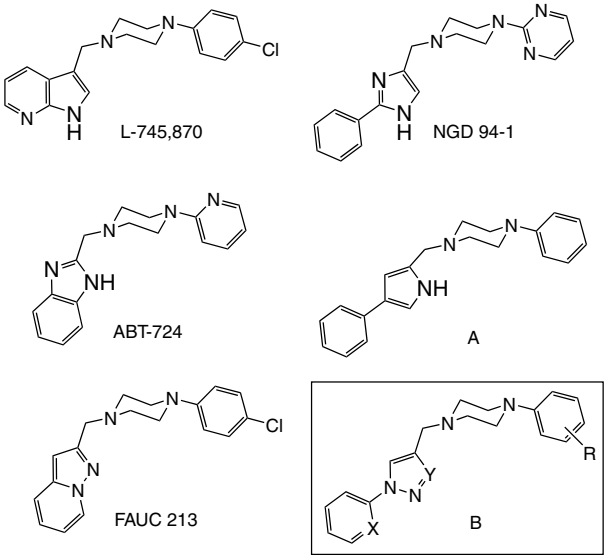

Chart 1. Structures of D4 selective lead and target compounds.

The phenylimidazole NGD 94-1 is a prominent member of the biaryl type class of D4 selective ligands being reported to act as a full antagonist.[8] Following studies indicated partial agonist effects.[9] Recently, we reported on the synthesis and receptor binding of dehydroimidazole and pyrrole analogs of type A,[10,11] demonstrating that the phenyl nucleus can be displaced by a 1,1-dicyanovinyl substituent.[12] Having in mind that a negative molecular electrostatic potential (MEP) exerted by the lone pair of an endocyclic sp^2 nitrogen proved to be beneficial for preferential D4 binding of the fused

Keywords: Dopamine; D4; Partial agonist; Regioselective synthesis; Subtype selectivity.
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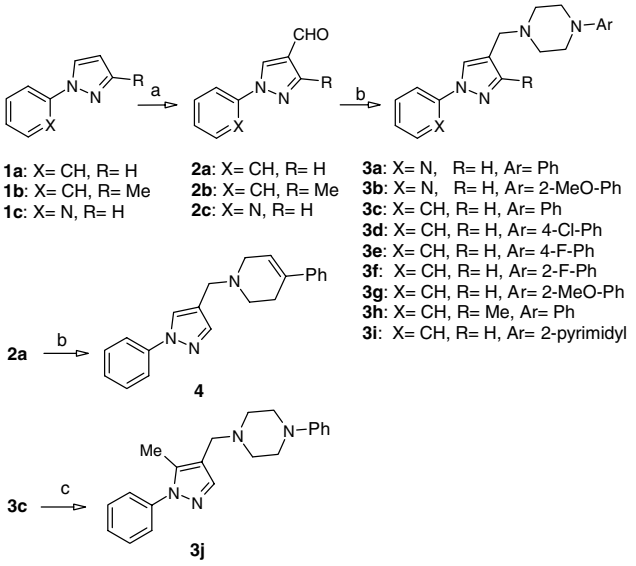
doi:10.1016/j.bmcl.2006.02.075

heteroarene derivatives,[13] we envisioned to prepare heterocyclic biaryl analogs of type B revealing a pyrazole or triazole nucleus in combination with a benzene or pyridine ring.[14] Further structural manipulations were envisaged including the exchange of the positions of the five- and the six-membered heteroarene units and the introduction of a tetrahydropyridine moiety replacing the piperazine ring.[15]

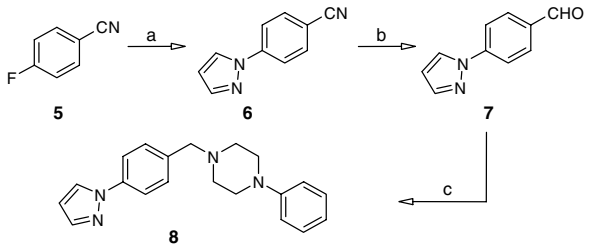
Starting from *N*-phenylpyrazoles **1a**,**b**[16] and the pyridine analog **1c**,[17] we employed a Vilsmeier formylation reaction to obtain the respective pyrazole carbaldehydes **2a**–**c**, which could be transformed into the piperazinylmethylpyrazoles **3a**–**i** by reductive amination in 78–88% yield (Scheme 1). Regiodirected lithiation of the azole moiety of **3c** followed by alkylation with MeI gave access to the 5-methyl derivative **3j**. Treatment of **2a** with 4-phenyl-1,2,5,6-tetrahydropyridine in the presence of $Na(OAc)_3BH$ resulted in formation of the aminomethylpyrazole **4**.

To prove our hypothesis that the relative orientation of the negative MEP is crucial for preferential D4 binding, we synthesized the regioisomer of the phenylpyrazole **3c** featuring an exchange of the rings within the biaryl moiety. Thus, 4-fluorobenzonitrile (**5**) was reacted with pyrazole to give the *N*-arylazole **6**.[18] DIBAL-H reduction furnished the respective carbaldehyde **7**, which was converted into the desired phenylpiperazine **8** by reductive amination (Scheme 2).

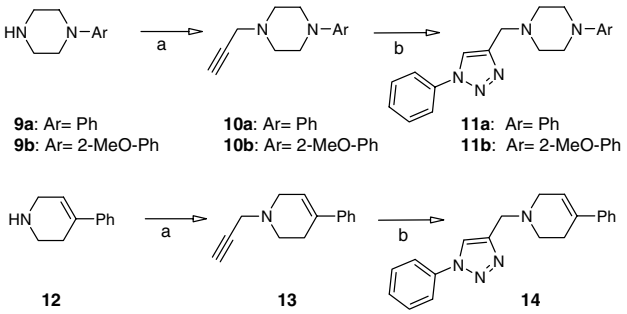
As an extension, we synthesized triazole analogs of the above-mentioned pyrazoles **3c**,**g** and **4**. Thus, alkylation of the secondary amines **9a**,**b** and **12** with propargyl bromide gave the 3-aminopropynes **10a**,**b** and **13**, respectively. Employing a slightly modified 'click chemistry' protocol,[19] we transformed the respective intermediates into the triazoles **11a**,**b** and **14** employing 1,3-dipolar



Scheme 1. Reagents and conditions: (a) Ref. 18; (b) arylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, rt, 16 h (78–88%); (c) 1—*n*-BuLi, THF, −78 to −30 °C, 2 h; 2—MeI, −78 to 0 °C, 1.5 h (62%).



Scheme 2. Reagents and conditions: (a) pyrazole, K_2CO_3, DMSO, 120 °C, 16 h (84%); (b) DIBAL-H, toluene, −60 °C (55%); (c) phenylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, rt, 16 h (80%).



Scheme 3. Reagents and conditions: (a) Ref. 20; (b) phenylazide, $CuCl_2$, Na-ascorbate, *i*-PrOH, rt, 24 h (62–68%).

cycloaddition with phenyl azide in the presence of Cu(II) and Na-ascorbate (Scheme 3).

The final products **3a**–**j**, **4**, **8**, **11a**,**b**, and **14**[20] and the phenylpyrrole A as a reference compound were evaluated in vitro for their abilities to displace [^{3}H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$,[21] D3,[22] and D4.4[23] being stably expressed in CHO cells.[24] The D1 affinities were determined by employing porcine striatal membrane preparations and the D1 selective antagonist [^{3}H]SCH 23390.

Receptor binding studies clearly indicated that the target compounds reveal only poor affinity to the D1 subtype. Depending on the substitution pattern of the aryl piperazine group, K_i values ranged from 11 to 6000 nM, 8 to 14,000 nM, and 33 to 4900 nM for $D2_{long}$, $D2_{short}$, and D3, respectively (Table 1). Interestingly, incorporation of a halogen atom in *para*-position (**3d**,**e**) strongly decreases D2 and D3 binding whereas *ortho*-substituents bearing a negative electrostatic potential caused an increase of affinity (**3b**,**f**,**g** and **11b**). In contrast, the 2-pyrimidyl-substituted NGD 94-1 analog **3i** displayed poor receptor binding for all GPCRs investigated. With the exception of the pyrimidine **3i** and the reversed regioisomer **8**, all target compounds displayed extraordinarily high D4 affinity with K_i values in the subnanomolar and single digit nanomolar range. Thus, the arylpyrazole and aryltriazole scaffold causes a substantial increase of affinity when compared to the phenylpyrrole substructure of the reference D4 ligand of type A. SAR observations indicate that the introduction of a further sp^2 nitrogen into the six- or five-membered arenes resulting in formation of the pyridylpyrazoles

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