

Correction to “(3S)-3-(2,3-difluorophenyl)-3-methoxypyrrolidine (IRL752) – a Novel Cortical-Preferring Catecholamine Transmission – and Cognition-Promoting Agent”

The above article [Hjorth S, Waters S, Waters N, Tedroff J, Svensson P, Fagerberg A, Edling M, Svanberg B, Ljung E, Gunnergren J, McLean SL, Grayson B, Idris NF, Neill JC, and Sonesson C (2020) *J Pharmacol Exp Ther*, **374**: 404-419; DOI: <https://doi.org/10.1124/jpet.120.000037>] was published with several errors introduced by the compositor:

The “h” in the title of Table 1 should be “human.” The last line of the first column should be “Noradrenaline transporter, NAT (h).” The corrected Table 1 is provided below.

In Table 2, in both the fifth and the last column, “n.c.^α” in the second line should be “n.c.^α.” The corrected Table 2 is provided below.

In Table 5, “DOPA” should be “DOPAC” in lines 6 and 8 of the first column. “PO” should be “p.o.” in the fifth line of the third, fourth, and fifth columns and was removed from the second sentence of the table’s footnote. The corrected Table 5 is provided below.

The PDF and HTML versions of the article have been corrected.

The compositor apologizes for any inconvenience caused by these errors.

TABLE 1

IRL752 IC₅₀/K_i values for selected human target proteins

For assay details, see <https://www.eurofindiscovery.com/cms/cms-content/services/in-vitro-assays/>.

Assay	Radioligand(Type)	IC ₅₀ (μM)	K _i (μM)
5-HT7 (h)	[³ H]-LSD (agonist)	2.7	0.98
σ1 (h)	[³ H]-(+)-pentazocine (agonist)	2.4	1.2
Serotonin transporter, SERT (h)	[³ H]-imipramine (inhibitor)	5.4	2.5
α2C (h)	[³ H]-RX 821002 (antagonist)	12	3.8
α2A (h)	[³ H]-RX 821002 (antagonist)	15	6.5
5-HT2C (h)	[¹²⁵ I]-(+)-DOI (agonist)	7.3	6.6
5-HT2A (h)	[¹²⁵ I]-(-)-DOI (agonist)	11	8.1
Noradrenaline transporter, NAT (h)	[³ H]-nisoxetine (inhibitor)	11	8.1

h, human; LSD, lysergic acid diethylamide; DOI, 2,5-Dimethoxy-4-iodoamphetamine.

TABLE 2

Antagonist effects in cellular functional assay (human receptors)

For assay details, see <https://www.eurofindiscovery.com/cms/cms-content/services/in-vitro-assays/>.

Assay	Source	Measured Component	Stimulus	IC ₅₀	K _b
α2A	CHO cells	Bioimpedance	Adrenaline(100 nM)	35 μM	10 μM
α2C	CHO cells	Fluorescence(HTRF)	Adrenaline(1 μM)	n.c. ^α	n.c. ^α
5-HT7	CHO cells	cAMP	Serotonin(300 nM)	~1000 μM	
5-HT2A	HEK-293 cells	IP1	Serotonin(100 nM)	150 μM	21 μM
5-HT2C	HEK-293 cells	IP1	Serotonin(10 nM)	3700 μM	830 μM

^αn.c.; IC₅₀ not calculable. CHO, chinese hamster ovary; HEK, human embryonic kidney; HTRF, homogenous time-resolved fluorescence; IP, inositol phosphate.

TABLE 5

Summary overview of microdialysis, behavioral, and gene expression effects of IRL752 and selected procognitive comparators

Sources for comparator data cited: Atomoxetine: Bymaster et al., 2002; Swanson et al., 2006; Tzavara et al., 2006; Cain et al., 2011; IRL AB, unpublished data. Methylphenidate: Gerasimov et al., 2000; Bymaster et al., 2002; Marsteller et al., 2002; Berridge et al., 2006; Tzavara et al., 2006; Banerjee et al., 2009; Seu and Jentsch, 2009; Rowley et al., 2014; IRL AB, unpublished data. Clozapine: Hertel et al., 1997; Westerink et al., 2001; Ichikawa et al., 2002; Shirazi-Souhalli et al., 2002; Devoto et al., 2003; Shilliam and Dawson, 2009; Abdul-Monim et al., 2006; Grayson et al., 2007; Robbins et al., 2008; IRL AB, unpublished data. Cariprazine: Neill et al., 2016; Kehr et al., 2018; Huang et al., 2019; Waters et al., 2020; IRL AB, unpublished data. Vortioxetine: Mørk et al., 2013, 2018; du Jardin et al., 2014; Wallace et al., 2014; IRL AB, unpublished data. Atipamezole: Kauppila et al., 1991; Haapalmaa et al., 1998; Tellez et al., 1999; Devoto et al., 2003; Lapiz and Morriak, 2006; Bondi et al., 2010; Mervaala et al., 1993; IRL AB, unpublished data. Idazoxan: Devaegans and Sara, 1990; Coull et al., 1996; Hertel et al., 1997; Tellez et al., 1999; Swanson et al., 2006; Uys et al., 2017b; IRL AB, unpublished data. Fluparoxan: Tellez et al., 1999; Millan et al., 2000; Borthwick, 2017; IRL AB, unpublished data. Disclaimer: Permutations of experimental conditions and differences in set-ups between laboratories preclude direct head-to-head comparisons of efficacies and responses among agents. This applies broadly but may be particularly apparent with regard to cognitive behavioral testing.

Compound	Atomoxetine	Methylphenidate	Clozapine	Cariprazine	Vortioxetine	Atipamezole	Idazoxan	Fluparoxan	IRL752
Key targets	NAT	DAT/NAT	5-HT ₂ , α ₂ , H1	D3, D2, 5-HT _{1A}	SERT, 5-HT ₃	α ₂	Variable	Variable	5-HT ₇ , α ₂ , SERT, σ ₁
Procognitive	Yes (ADHD)	Yes (ADHD)	Yes (Schiz)	Yes (Schiz)	Yes (Depr)	Variable	Variable	Variable	TBD 10.6 mg/kg = 50 μmol/kg, s.c.
Dose range	0.3-3 mg/kg = 1.2-12 μmol/kg, i.p.	0.5-30 mg/kg = 2.15-129 μmol/kg, i.p. or p.o.	0.1-100 mg/kg = 0.3-300 μmol/kg, s.c., i.p. or p.o.	0.2-3 mg/kg = 0.23-7 μmol/kg, p.o. or s.c.	2.5-10 mg/kg = 8.4-34 μmol/kg, s.c.	0.5-4.5 mg/kg = 2.4-21.2 μmol/kg, i.p. or s.c.	0.25-20 mg/kg = 1.23-98 μmol/kg, i.p. or s.c.	0.63-10 mg/kg = 3.2-51.3 μmol/kg, s.c. or i.p.	
NA PFC	Increase (~300)	Increase (~290)	Increase (~350-390)	No effect	Increase (~270)	Increase (~250)	Increase (~250)	Increase (~240)	Increase (~380)
DA PFC	Increase (~325)	Increase (~350)	Increase (~360-400)	No effect	Increase (~275)	Increase (~260)	Increase (~210)	Increase (~150)	Increase (~285)
DOPAC PFC	Increase (~150)	No effect	Increase (~250)	N/A	Increase (~150)	Increase (~180)	Increase (~135)	Increase (~180%)	No effect
5-HT PFC	No effect	No effect	Increase (~25)	No effect	Increase (~410)	Increase (~160)	No effect	No effect	Increase (~220)
DA Stri	No effect	Increase (~210-250)	Increase (~150-170)	N/A	No effect	No effect	No effect	No effect	No effect
DOPAC Stri	No effect	N/A	Increase (~190)	N/A	No effect	No effect	No effect	No effect	No effect
5-HT Stri	Increase (~150)	Increase (~320)	Increase (~65)	N/A	Increase (~360)	No effect	Increase (~50)	Increase (~70)	Increase (~170)
ACH PFC	Increase (~300)	Increase (~250-300)	Increase (~500-625)	No effect	Increase (~250)	Increase (~250)	Increase (~275)	Increase (~300)	Increase (~250)
LMA, normal	No effect	Increase (Arc)	Increase (c-fos)	Increase (Arc, c-fos)	No effect	No effect	No effect	Increase (Arc, c-fos)	Increase (Arc, c-fos)
IEGs FEX	No effect	Increase (Arc)	No effect	No effect	No effect	Increase (Arc)	Increase (Arc, c-fos)	Increase (Arc, c-fos)	Increase (Arc, c-fos)
IEGs Stri	No effect	Increase (Arc)	Increase (c-fos)	Increase (Arc, c-fos)	Increase (Arc)	Increase (Arc, c-fos)	Increase (Arc, c-fos)	Increase (Arc, c-fos)	Increase (Arc, c-fos)
NOR	Yes	No	Yes	Yes	Yes	N/A	N/A	N/A	Yes
RL or ASST	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes

Figures in brackets refer to approximate peak level (% of corresponding baseline), DAT, dopamine transporter; ADHD, Attention Deficit Hyperactive Disorder; ASST, Attentional Set-Shifting Test; Depr, Depressive disorder; LMA, locomotor activity; N/A, data not available; No effect, not significantly different from corresponding control treatment; Schiz, Schizophrenia; Stri, striatum; Fex, frontal cortex; TBD, To be determined.