Conformationally restricted 3-phenyltropanes: Highly selective dopamine transporter ligands for PET

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Introduction: Dopamine reuptake mediated by the dopamine transporter (DAT) plays a key role in the regulation of dopaminergic signal transduction. Dopaminergic malfunctions have been observed in psychosis or attention deficit/hyperactivity syndrome ADHS. In the case of Parkinson´s desease (PD), a major neurodegenerative disorder, a diminished dopamine DA biotransformation is buffered by a significant up-regulation of available DAT binding sites. Using molecular imaging, these alterations are detectable in an early state of PD, facilitating early diagnosis and hopefully therapeutic approaches before movement constriction and neurological issues usually occur. In addition DAT radioligands can be utilised to monitor therapeutic effects of PD-pharmaceuticals and in general to understand DA-reuptake related pathologies and mechanisms.
Therefore quantitative non-invasive imaging of DAT-availability using PET remains of significant clinical relevance. N-4-[^{18}F]fluorobut-2-en-1-ylated tropane derivatives like LBT-999 (R"=Me) or FBCFT (R"=F) show both good affinity and high selectivity to the DAT. We deduced a structure-affinity-relation (SAR) study to determine the contribution of 4-fluorinated, conformationally restricted C_4 chains R' at the tropane nitrogen to affinity, pharmacokinetic properties and selectivity.

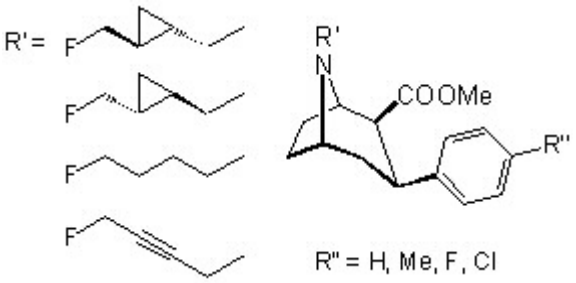

Figure 1:
lead-structure and intended variations of R' and R''

Method: (-)-Anhydroecgonin methyl ester was prepared from commercially available cocaine hydrochloride, addition of an appropriate Grignard reagent and subsequent N-demethylation afforded compounds nortropanes, which were alkylated with appropriate ω-fluoro-halides, prepared in 4-7 steps, to yield the reference compounds. Labelling precursors were synthesised via sulfonylation of ω-hydroxy analogues. ^{18}F was introduced via the common ^{18}F-cryptate procedure. All compounds were evaluated in hEK cell lines stable transfected with hDAT, hSERT and hNET for [^{3}H]dopamine, [^{3}H]5-HT and [^{3}H]norepinephrine monoamine reuptake inhibition and inhibition characteristics.

Results: 16 novel 3β-phenylnortropanes were prepared from cocaine hydrochloride. Affinities and ratios of DAT to SET and NERT affinity are summarised in Table one for selected derivatives 1c,d,e,f and compared with LBT999 and βCFT.

Table 1: Results from binding assays

entry	$K_{i,hDAT}$ / nM	$K_{i,hSERT}$ / nM	$K_{i,hNET}$ / nM	SERT / DAT	NET / DAT
LBT999	25.9	698.8	151.1	27	5.8
βCFT	23.2	2933	54.7	126	2.4
1c	32.8	3962	136.4	120	4.2
1d	3.3	239.8	31.0	74	9.5
1e	9.4	1456	79.4	155	8.5
1f	9.1	1196	134.9	120	14.5

1d-e show low nanomolar affinity and high selectivity. Compared to LBT999 and CFT (WIN35,428), other established selective DAT-ligands, the novel candidates 1d-f provide improved affinity and selectivity.

Conclusions: A set of novel tropane derivatives containing a conformational restricted C_4 chain has been prepared for *in vitro* and *in vivo* SAR studies. Preliminary evaluations in rodent are presently ongoing with [^{18}F]1c-e for comparative studies of dopaminergic signal pathways involving [^{18}F]FP.

References:

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