Review

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Fluorine in psychedelic phenethylamines

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The so-called psychedelic phenethylamines represent a class of drugs with a large range of psychoactive properties in humans, ranging from naturally occurring mescaline to amphetamine analogues and homologues. The interest in many of these compounds, occasionally referred to as designer-drugs, is widely dispersed across popular culture and political and scientific communities. In recent decades, fluorine has become a powerful and important tool in medicinal chemistry. In addition, fluorine-containing compounds and medicines can be found in numerous commercially successful pharmaceuticals that have gained a market share of some 5–15%. One might anticipate this trend to increase in the future. As far as fluorinated phenethylamines are concerned, much less is known about their chemistry and pharmacology. This paper provides an overview regarding the biological properties of over 60 fluorinated phenethylamines and discusses both historical and recent chemistry-related developments. It was shown that the introduction of fluorine into the phenethylamine nucleus can impact greatly on psychoactivity of these compounds, ranging from marked loss to enhancement and prolongation of effects. For example, in contrast to the psychoactive escaline (70), it was observed that its fluoroescaline (76) counterpart was almost devoid of psychoactive effects. Difluoroescaline (77), on the other hand, retained, and trifluoroescaline (78) showed increased human potency of escaline (70). Difluoromescaline (72) and trifluoromescaline (73) increasingly surpassed human potency and duration of mescaline (22) effects. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction

It was in the late 1950s when the British psychiatrist Humphrey Osmond coined a new term when attempting to describe the effects of mind altering compounds such as *d*-lysergic acid diethylamide (LSD) or mescaline: 'psychedelic'.[1,2] A semantic drift occurred in the following years and anything of abstract decoration or multiple bright colours began to be described as psychedelic. On the other hand, this particular term is increasingly used in the scientific literature as a descriptor for a class of compounds whose primary action involves a dramatic change in mood, perception, and cognition. As psychedelic compounds can cause visual distortions and synesthesia, they are generally referred to as hallucinogens. This can be somewhat misleading since true hallucinations, i.e. the inability to recognize them as such, appear to occur extremely rarely.[3] Dissociatives such as ketamine or the tropane derivative scopolamine can induce *true* hallucinations and they have their own modes of action. As such, psychedelics are typically recognized as their own class.

There are a vast number of psychedelics that can affect the state of mind in various ways which offers the potential to employ some of them as powerful tools in the research field of perception and the nature of consciousness. With the use of these receptor probes, it is hoped to understand the underlying neuropharmacological mechanisms involved in mental functioning and disease. The highest congregations of such compounds are found particularly in phenethylamines,[3–5] followed by tryptamines.[6] Despite the fact that many of these derivatives have been explored recreationally to some extent, the safety profile remains to be investigated in detail. In addition, further research is required to elucidate the extent to which some of these derivatives might be explored within a potential therapeutic context.[3–5] A reflection of increased interest in a range of potential clinical applications includes the use of LSD and psilocybin for the treatment of anxiety in patients suffering from terminal cancer.[7–10]

Among other structural developments in the field of phenethylamines,[5] recent developments of modern fluorine chemistry or fluorinated reagents on phenethylamines has led to the availability of several new derivatives. This paper reviews the literature in respect to the established fluorinated analogs as well as the latest knowledge about some forty fluorinated, potentially psychoactive phenethylamines developed and investigated in recent years.

Why fluorine?

Fluorine-containing compounds and medicines can be found in numerous commercially successful pharmaceuticals, such as the blood cholesterol lowering agent atorvastatine (Lipitor®, Sortis®) or fluticasone propionate used to treat asthma (Flovent®, Flixotide®) or allergic rhinitis (Flonase®, Flixonase®), as well as the well-known antidepressant fluoxetine (Prozac®). Over the past five decades, fluorinated derivatives appeared to represent some 5–15% of marketed drugs[11] with a tendency to rise. A commonly used example of diagnostic value is fluorodeoxyglucose (^{18}F-FDG), which, among others, allows the monitoring of metabolic processes by positron emission tomography (PET) through the positron emitting radioactive isotope ^{18}F.[12] The influence of fluorine in medicinal chemistry, particular in the alteration of metabolism or binding affinity for a biological target has been described extensively.[11,13] Its dramatic influence on acidity and basicity has also been shown on numerous amines and

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carboxylic acids[11] which means that acids become more acidic and bases become less basic. Fluorine (3.98) shows the highest electronegativity according to the Pauling scale, and based on new data, its Van der Waals radius is considered to be slightly larger (20%) than hydrogen (1.47 vs. 1.20 Å). Fluorine is more isosteric to oxygen (1.52 Å)[13] and is the smallest substituent that can replace hydrogen.

The phenethylamine pharmacophore

Today, several hundred psychoactive phenethylamines are known and a large range of data are reported in the popular literature.[3–5] From these data, extensive structure-activity relationships (SAR) have been described and most commonly three distinct simple phenethylamine classes are recognized, namely the *stimulants*, the *entactogens*, and the *psychedelics* (Figure 1A). The term 'simple' addresses non-tethered, non-rigidified phenethylamines without heteroatoms present at the side chain and each member of the three structural classes show distinct psychopharmacological effects that correlate with specific neuronal mechanisms. Within the group of simple phenethylamines, stimulants generally bear an α-methylphenethylamine (= amphetamine) structure with no substituents at the aromatic part (e.g. amphetamine, **1**, and methamphetamine, **2**). They may enhance wakefulness, alertness, and locomotion as well as temporarily improve psychological or physical activity. They are generally considered to be of high abuse potential. Some amphetamines, however, have proven to be medically beneficial, for example, for the treatment of attention-deficit hyperactivity disorder (ADHD).[14] Entactogens (to touch within, derived from the roots *en* (Greek: within), *tactus* (Latin: touched) and *gen* (Greek: produce)[15]) such as MDMA (Ecstasy, **3**) generally bear the 3,4-methylenedioxyamphetamine structure (compounds **3–7**;). They show the ability to produce significant sociable and emotional effects. The third class, the psychedelic-type phenethylamines (mind-manifesting, derived from the Greek words ψυχή (*psyche*, mind) and δηλεῖν (*delein*, to manifest)[1,2]) is represented by the largest part of psychoactive phenethylamines. Perception, mood, and cognition can be changed profoundly and visual distortions and synesthesia can occur. Within the psychedelic phenethylamines, there are three relevant subclasses, with the following general order of increasing serotonin 5-HT_{2A} receptor affinities as well as human potencies: 3,4,5-trisubstituted < 2,4,6-trisubstituted < 2,4,5-trisubstituted phenethylamines (structures **8–10** reviewed in references[3,5,16,17]). The α-methylated phenethylamines (amphetamines or 3C derivatives) are generally more potent in both humans and *in vivo* animal studies than the corresponding phenethylamines (2C derivatives) and show a longer duration of effect. Although the affinities at the serotonin 5-HT_{2A} receptor, the primary target thought to be responsible for the psychedelic effects,[18–22] do not significantly change by the introduction of a racemic α-methyl group into substituted phenethylamines,[18,23–25] the metabolic stability,[18,26] hydrophobicity,[27] and intrinsic activity[25,28] increase, which as a consequence leads to higher *in vivo* potencies. For α-methylated psychedelic phenethylamines an $R > S$ enantioselectivity has generally been observed for *in vivo* potency,[3,29] receptor affinities,[25,30–32] and receptor activation.[25,32] Stimulants and entactogens show $S > R$ enantioselectivity, but they act through monoamine transporters and not receptors. Although all psychedelic phenethylamines show 5-HT_{2A} and 5-HT_{2C} receptor affinities and the agonistic activation of the former seems to be of great significance in the mechanism of action,[33,34] it has been shown only recently that these derivatives are not as selective as originally thought and other receptor systems may be significantly involved in their overall psychological effects.[35] In substructures **8–10**, the overall pharmacological profile is greatly influenced by the nature of the 4-subsituent and small, lipophilic substituents lead to agonists whereas large, lipophilic substituents lead to antagonists.[24] Polar substituents abolish receptor affinities[32,36] and greatly decrease *in vivo* potencies.[3]

Which fluorinated phenethylamines are known so far?

Although there are numerous fluorinated phenethylamines described in the literature, this review focuses only on simple psychoactive phenethylamines or structurally closely related candidates. A look at the phenethylamine pharmacophores (Figure 1A) reveals numerous positions where a hydrogen atom could potentially be replaced by fluorine. Several investigations have been carried out so far with some starting in the 1960s when Pinder and Burger evaluated the presence of three fluorine atoms at the terminal methyl group of amphetamine.[37] When compared to amphetamine (**1**), 2-amino-3-phenyl-1,1,1-trifluoropropane (**11**) was found to be inactive when testing anorectic, antiemetic, central nervous system, monoamine oxidase inhibitory and pressor activities. Later, this was explained by electronic effects[38]; the trifluoromethyl group dramatically lowers the basicity of the amine (amphetamine $pK_a = 9.93$, **11** $pK_a = 4.97$). As a consequence, under physiological conditions **11** cannot be protonated anymore and its body distribution may be significantly altered. A similar structural investigation was done with the psychedelic 3,4,5-trimethoxyamphetamine (TMA, **12**) whereby the trifluoromethyl analog **13** showed only one-tenth of the activity of TMA (**12**) in the head-twitch test in mice which is associated with 5-HT_{2A} receptor activation of psychedelic phenethylamines.[38]

The (+)-enantiomer of 2-amino-3-fluoro-1-phenylpropane (**14**) bears only one fluorine at the terminal methyl group. In mice, it increased locomotor activity similar to (+)-amphetamine during the first hour, followed by a sedative effect, while with amphetamine mice still remained stimulated.[39] The β- and β,β-fluorinated derivatives **15–16** have also been shown to significantly impact on the overall effects of amphetamine.[40–42] The pK_a values decreased with increasing degree of fluorination from 9.5 (amphetamine) to 8.4 and 7.0, respectively. The results of an i.p. administration (rats) correlated with the pK_a values; **15** showed similar distribution to amphetamine while **16** was mainly detected in fatty tissue. In mice, **16** was shown to display a much shorter half-live in brain than for amphetamine and likewise, higher doses were required for **16** to maintain elevated locomotor stimulation.[42]

The *N*-trifluoroethyl analogue **17** of amphetamine has also been described.[43] Apparently, this derivatization of amphetamine (**1**) leads to almost complete loss of the stimulating properties. The same *N*-substituent has been introduced into the well known derivative 3,4-methylenedioxyamphetamine (MDA, **3**), an entactogenic, stimulating and psychedelic compound.[3] Only investigated in humans so far, 3,4-methylenedioxy-*N*-trifluoroethylamphetamine (MDTFEA, **18**) seems to be inactive up to 500 mg[3] while its fluorine-free analog MDEA (**5**) is a well known entactogen and active in the range of 100–200 mg with a duration of 3–5 h.[3] While steric effects might play a role it has been shown that an *N*-trifluoroethyl derivative loses its amine properties and that this group was used successfully as a bioisostere to replace an amide group.[11] Amide analogs of psychoactive phenethylamines are generally considered

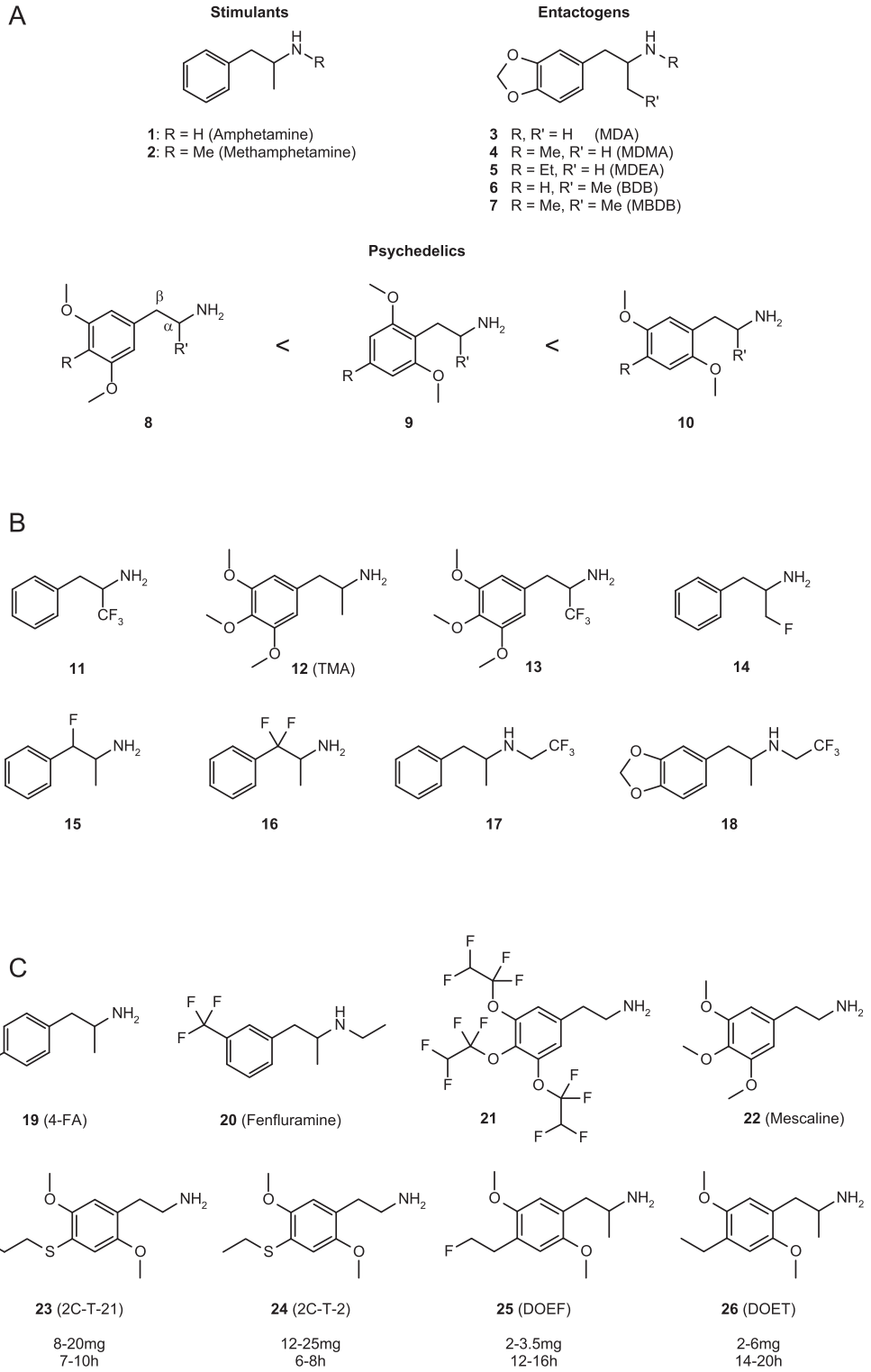

Figure 1. (A) The three main phenethylamine-type core structures stimulants (**1**, **2**), entactogens (**3–7**) and psychedelics (**8–10**). Structures **8–10**: General trend for serotonin 5-HT_{2A} receptor affinities as well as human potencies (which do not necessarily correlate). (B) Some side chain (**11**, **13–16**) or *N*-alkyl (**17**, **18**) fluorinated phenethylamine analogs investigated by several scientists. C: Some aryl (**19**) or aryl substituent (**20**, **21**, **23** and **25**) fluorinated phenethylamines.

to be inactive in humans.[44,45] Similar electronic effects might apply to derivatives **11** and **13**.

The effects of a simple introduction of a 4-fluorine at the aryl moiety of amphetamine has been investigated by several scientists.[46–48] This compound, 4-fluoroamphetamine (4-FA or PFA, **19**) has been compared *in vitro* and *in vivo* to amphetamine (**1**) and its other three related 4-halo amphetamines revealing that it resembles more amphetamine (**1**) than other 5-HT releasing-type amphetamines (e.g. MBDB, **7**).[47] It appeared on the black market and is believed to be an active stimulant with

euphoric and possibly some entactogenic effects in the range of 100–200 mg for 6–8 h.[49]

The presently obsolete appetite suppressant fenfluramine (Pondimin, Adifax, **20**)[50] showed that the presence of the 3-trifluoromethyl group separated the stimulating and anorexic effects of amphetamine (the *N*-ethyl group in **20** helped as well but to a lesser extent).[51,52]

With the derivative **21**, Alpermann and Werner presented a polyfluorinated homolog of mescaline (**22**) in 1979.[53] In mice, the authors could not detect any sympathomimetic effects known from mescaline (**22**) and they mentioned the absence of the typical mescaline-like hallucinogenic effects.

The psychedelic fluoro derivative 2,5-dimethoxy-4-(2-fluoroethylthio)phenethylamine (2C-T-21, **23**) has been prepared and was initially investigated by Shulgin and Shulgin.[3] Psychoactive effects have been reported to last 7-10 h at dosage levels of 8–12 mg[3] and 10–20 mg,[54] respectively. It is structurally related to numerous other 2C-T derivatives and most closely related to the fluorine-free derivative 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2, **24**. 12–25 mg, 6–8 h), which is only slightly less potent although it was reported to vary in its psychological effects.[3]

Another potent fluorinated psychedelic is 2,5-dimethoxy-4-(2-fluoroethyl)amphetamine (DOEF, **25**).[3,55] In comparison to its fluorine-free counterpart DOET (**26**. 2–6 mg, 14–20 h) it showed about twice the potency (2–3.5 mg) and a shorter duration of action (12–16 h) in humans.[3] At the agonistic [^{125}I]DOI-labelled serotonin r5-HT$_{2A}$ receptor (frontal cortex) DOEF (**25**, $K_i = 9.1$nM) proved to be a high affinity ligand (D.E. Nichols, personal communication in 2009), while the counterpart DOET (**26**) showed high affinity at the antagonistic [^{3}H]ketanserin-labelled serotonin r5-HT$_{2A}$ receptor (frontal cortex, $K_i = 100$nM).[18,56]

The derivative 2,5-dimethoxy-4-fluoroamphetamine (DOF, **27**) is a fluorinated analog of the well known potent serotonin 5-HT$_{2A/C}$ agonists DOB (**29**, R = Br) and DOI (**30**, R = I), as well as the less known DOC (**28**, R = Cl, Figure 2, A).[36] With the ^{77}Br and ^{125}I radioactive isotopes, respectively, both DOB (**29**) and DOI (**30**) are used extensively as standard agonist radio ligands in competitive 5-HT$_{2A/C}$ receptor binding experiments.[23,57] Their high affinities at the h5-HT$_{2A}$ binding site (both $K_i < 1$nM, [^{125}I]DOI-labelled[36]) is reflected in their human potency; both are active in the range of 1–3 mg and have a 16–30 h duration of action.[3] DOB (**29**) and DOI (**30**) are among the most potent simple phenethylamines known, and the chloro-analog DOC (**28**, 2–5 mg, 12–24 h) is only slightly less potent.[3] In contrast to this, the fluorinated derivative (DOF, **27**) showed a significant lower affinity at the serotonin h5-HT$_{2A}$ binding site ($K_i = 41.7$nM[36]) and in rat drug discrimination (DD) studies it proved to be some six times less effective in DOM (**31**) stimulus generalization experiments when compared to DOB (**29**) and DOI (**30**).[58] A direct relationship has been shown between the ED$_{50}$ values obtained from animal DD studies and human potencies[58] and according to that, DOF (**27**) was predicted to show a human activity of about four to six times less than the heavier halide derivatives DOB (**29**) and DOI (**30**).[3,58] According to limited trials, DOF (**27**) showed no psychedelic activity but some stimulating effects were noted at 3x6 mg (spaced by 1 h, each).

The α-desmethylated analog 2C-F (**32**) was evaluated in humans up to 250 mg where it proved to be essentially inactive.[3] In comparison the well-known bromo-analog 2C-B (**33**) is a fairly potent psychedelic phenethylamine (12–25 mg, 4–8 h).[3]

In addition to the low serotonin 5-HT$_{2A}$ receptor affinities of DOF (**27**), and most probably also 2C-F (**32**), the molar refraction of the important 4-substituent in these ligands may be too low to activate the receptor sufficiently.[20] Furthermore, DOF (**27**) rather resembles the 4-unsubstituted 2,5-dimethoxyamphetamine than DOC, DOB or DOI (**28–30**).

The 4-trifluoromethyl derivative 2C-TFM (**34**) was identified as a potent 5-HT$_{2A/C}$ receptor agonist by Nichols *et al.* in 1994.[28] Together with its α-methyl congener DOTFM (**35**) it is among the most potent simple phenethylamines at these binding sites, showing comparable or slightly higher binding affinities than DOB (**29**) and DOI (**30**).[28] Compared to DOB (**29**) and DOI (**30**), both compounds **34** and **35** turned out to be of equal, or slightly increased potency in DD studies (rats, training drug: LSD).[28] Within the context of a DD study, this was the first time for a 2C derivative to be found equally potent to the potent 3C derivatives DOB (**29**) and DOI (**30**). In humans, initial experiments seem to be consistent with high potencies (**34**: 3–5 mg; **35**: 0.3 mg or more. A.T. Shulgin, personal communication in 2003).[4]

Toxicological considerations

There are dozens of marketed and safe fluorinated pharmaceuticals. Fluorine as a chemical substituent may help enormously in drug design, for example, helping improve target selectivity and/or binding properties, metabolic stability issues, body distribution, and excretion.[11,13] However, fluorine in elemental form or as hydrogen fluoride is extremely corrosive and highly toxic. Also certain fluorine compounds are considered to be among the most poisonous derivatives such as soman and sarin, both highly effective chemical warfare agents. Nature even produces a very toxic organofluoro compound, namely fluoroacetate (**36**).[59] It shows its extreme toxic effects towards mammals wherein it cannot be distinguished from acetate; fluoroacetate underlies the same metabolic pathways (enzymatic transformations as follows: together with coenzyme A, fluoroacetate forms fluoroacetyl-CoA, which in the tricarboxylic acids cycle (TCA cycle) substitutes for acetyl-CoA. The resulting fluorocitrate interferes with the citric acid cycle ending in disruption (enzymatic blockage)[59]). As a consequence it causes an accumulation of citrate in blood ending in energy deprivation of cells. Considering this, organofluoro derivatives, see for example Figures 1, 3–6, containing a monofluoroethyl moiety (or generally an even-numbered monofluoroalkyl residue FC2, FC4, FC6 etc.) could possibly be metabolized to fluoroacetate.[60,61] But in general fluorine that is covalently bound to a carbon cannot be abstracted metabolically and will also leave the body at the same carbon. The only exceptions are acyl fluorides or analogous compounds. Finally, the influence of fluorine atoms on pharmacodynamics and pharmacokinetics may be rich, unpredictable and should be investigated carefully as with any other newly designed molecule.

Recent developments in fluorinated phenethylamines

Fluorine in 2,4,5-trisubstituted phenethylamines

The 2,4,5-trisubstituted phenethylamines can be considered as the most important class since the initial investigations of compounds with such a substitution.[5] Very briefly, within this class the most potent 5-HT$_{2A}$ receptor agonists bear a 2,5-dimethoxy substitution pattern paired with a small, lipophilic substituent in

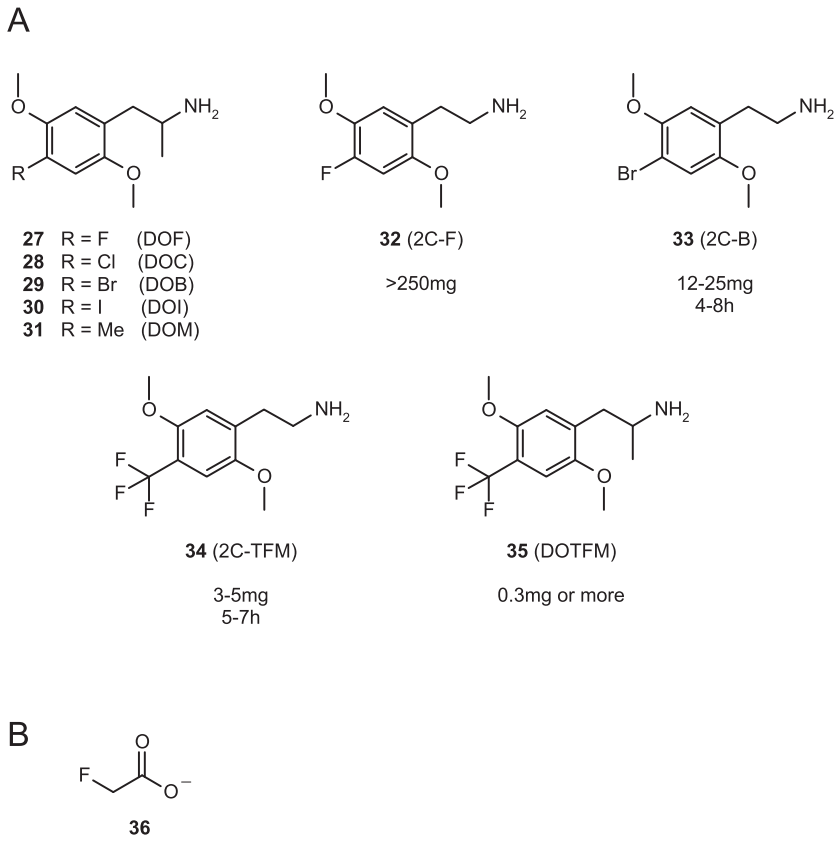

Figure 2. (A) Aryl halogenated phenethylamines (**27–33**) and two 4-trifluoromethyl derivatives (**34–35**). (B) Fluoroacetate (**36**), a highly toxic natural product found in several plants.

the 4-position (Me, Et, Cl, Br, I, F_3C, EtS etc.) as indicated in structure **10** in Figure 1A. Simultaneously, these types of compounds have proven to be among the most potent psychedelics in humans.[3] Larger lipophilic 4-substituents (e.g. Bu, *t*-Bu) lead to potent antagonists which seem to be devoid of psychedelic effects.[3,5] Generally, an α-methylated phenethylamine (amphetamine) shows higher *in vivo* potency than the corresponding phenethylamine although affinities at the 5-HT_{2A} receptor do not necessarily change, and α-ethylation as well as *N*-alkylation lead to a dramatic if not complete loss of biological activity.[3] An exception, however, appears to be found in *N*-benzylated derivatives.[62–66] Thus, focus was set towards the 4-substituent position over the past decades and numerous analogs have been scientifically tested. Despite that, within the 2,4,5-series there were only a few fluorinated derivatives described and investigated so far such as compounds **23**, **25**, **27**, **32**, **34–35**.

To get more insight into the influence of fluorine atoms on such compounds the existing series of 2,5-dimethoxy-4-thioalkyl-substituted phenethylamines (2C-T derivatives)[3] was expanded and characterized further.[67] In comparison with 2C-T-2 (**24**: 12–25 mg, 6–8 h), progressive terminal fluorination of the 4-EtS group either increased (2C-T-21, **23**: 8–12 mg, 7–10 h, shown by Shulgin[3]) or maintained (2C-T-21.5, **37**: 12–30 mg, 8–14 h) human potency according to the 'double conscious' technique (Figure 3, A).[68] The trifluoroethyl derivative 2C-T-22 (**38**) was not investigated sufficiently to draw any conclusions. At the [^{3}H]LSD labelled cloned h5-HT_{2A} receptor, 2C-T-21.5 (**37**; $K_i = 146$ nM) and 2C-T-22 (**38**; $K_i = 69$nM) showed fairly high affinities but no further comparison can be made as the affinities of **24** and **23** are currently unknown. Unless mentioned otherwise, binding affinities of all compounds mentioned herein were measured by standard procedures.[69]

The 4-PrS derivative 2C-T-7 (**39**: 10–30 mg, 8–15 h)[3] has also been investigated in humans and compared with its monofluorinated analog 2C-T-28 (**40**: 8–20 mg or more, 8–10 h).[67] It binds at the [^{3}H]LSD labelled h5-HT_{2A} receptor with a $K_i = 75$nM.

Further homologs, 2C-T-19 (**41**; $K_i = 14$nM) and 2C-T-30 (**42**; $K_i = 47$nM) were tested in radioligand binding assays using [^{3}H] LSD labelled cloned h5-HT_{2A} receptors, indicating a high affinity of **41** at this binding site. In this case fluorine seemed to decrease affinity slightly by a factor of around three. Virtually nothing is known about their human activities. 2C-T-30 (**42**) was tested up to 6 + 3 mg which revealed no detectable effects.

Within the group of the 2,4,5-trisubstituted phenethylamines, a few *4-alkoxy* analogs have been described before (Figure 3, B).[3] Both 2C-O (**43**; >300 mg) and 2C-O-4 (**44**; >60 mg) proved to be inactive in humans, at least at the levels tested.[3] Whether they underlie a strong metabolism[70] or show low affinities towards the serotonin 5-HT_{2A} receptor[36] remains to be established. In humans, the α-methylated 3C analogs TMA-2 (**45**; 20–40 mg, 8–12 h) and MEM (**46**; 20–50 mg, 10–14 h) are fairly active compounds,[3] probably resulting from increased metabolic resistance, higher lipophilicity and pronounced receptor activation.

The 4-alkoxy derivatives seem to have lower hydrophobic properties and showed distinctly decreased affinities at the [^{125}I]DOI labelled cloned h5-HT_{2A} receptor (TMA-2, **45**: $K_i = 58$nM and MEM, **46**: $K_i = 73$nM) in comparison to the potent agonist DOI (**30**: $K_i = 0.7$nM).[36] Some fluorinated analogs (**47–52**) of 2C-O (**43**) and TMA-2 (**45**) were prepared. Whether their

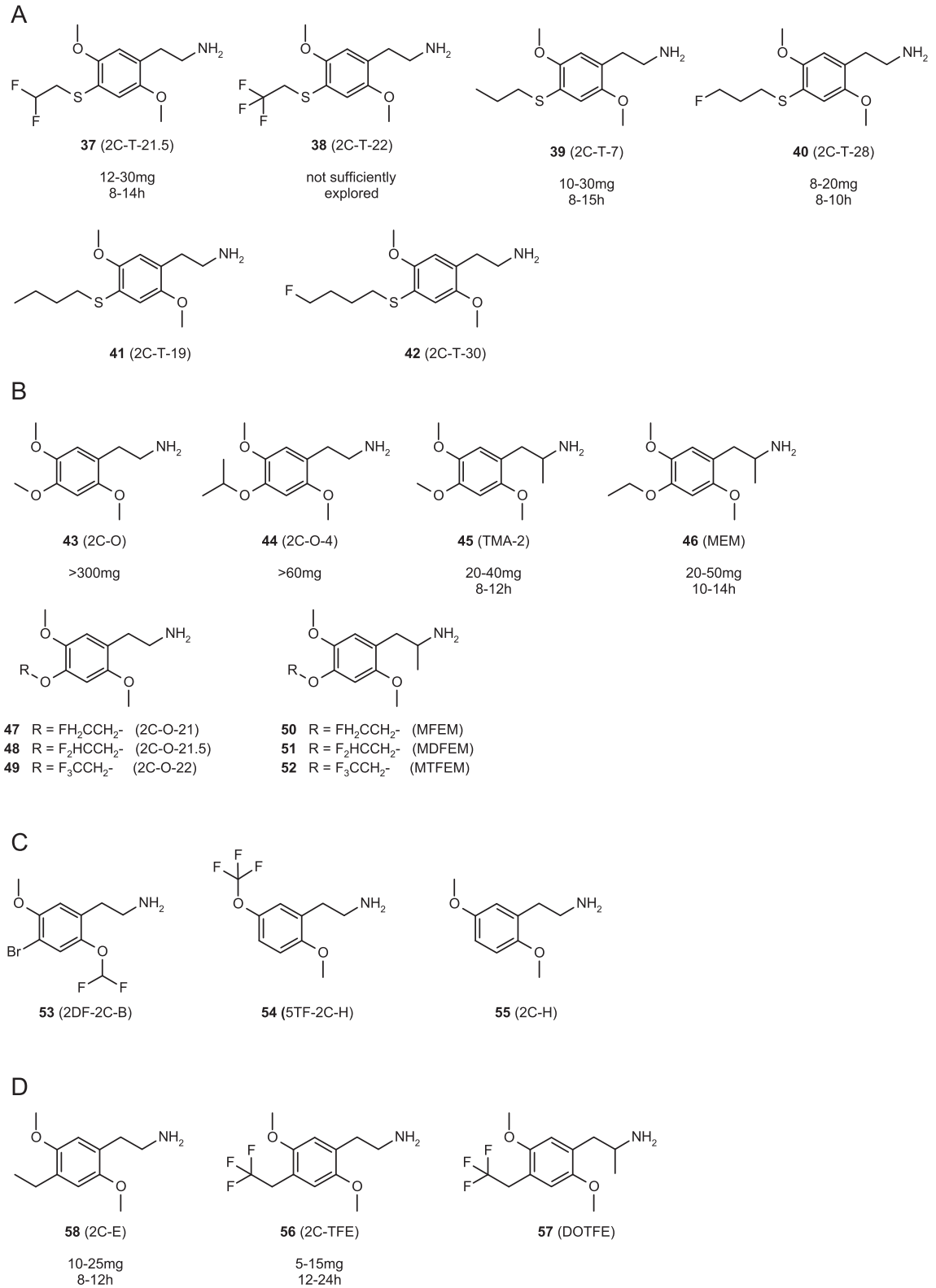

Figure 3. Some novel fluoro analogues of the 2,4,5-trisubstituted phenethylamines. (A) 2C-T derivatives and fluoro analogues. (B) Representative analogues of the 2C-O series and fluorinated derivatives. (C) Fluorinated analogs of 2C-B (**33**) and 2C-H (**55**). (D) 4-Alkyl-fluorinated derivatives of 2C-E (**58**).

potentially changed metabolism and increased 5-HT_{2A} receptor affinities lead to *in vivo* activity is presently almost unknown. A single experiment with 42 + 15 mg of **49** revealed this level to be a potential threshold dose.

The effect of methoxy fluorination in 2,5-dimethoxy derivatives on 5-HT_2 receptor affinities has been tested (Figure 3, C). A determination of the h5-HT_{2A} and r5-HT_{2C} receptor affinities for the 2-difluoromethoxy derivative 2DF-2C-B (**53**) and the 4-

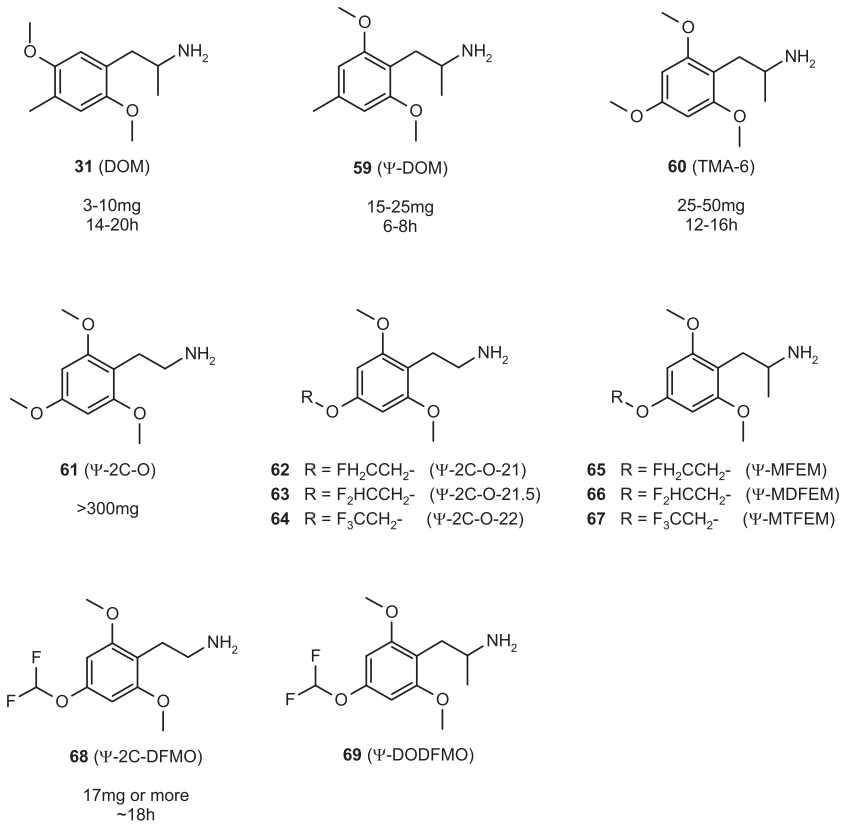

Figure 4. DOM (**31**), some representatives of 2,4,6-trisubstituted phenethylamines (**59–61**) and fluorinated derivatives (**62–69**) of the 2,4,6-series.

unsubstituted 5-trifluoromethoxy derivative 5TF-2C-H (**54**) revealed a certain 2C over 2A subtype selectivity (Table 1). Antagonistic labelling experiments showed a ratio of 2C:2A = 29 for 2DF-2 C-B (**53**) and 5TF-2C-H (**54**) presented a six-fold 2C subtype selectivity.

The higher affinities of the trifluoromethoxy derivative 5TF-2 C-H (**54**) in comparison to its non-fluorinated analog 2C-H (**55**) may be explained by the increased lipophilicity present in the 5-position.[71,72] Interestingly, with the presence of two F-atoms in the 2-position of 2DF-2C-B (**53**), 5-HT_{2A} affinity markedly decreases (K_i = 1100nM) and 5-HT_{2C} affinity slightly increases (K_i = 38nM) in comparison to its non-fluorinated analog 2C-B (**33**: K_i = 16nM and 190nM, respectively[24]). It would be interesting to evaluate the effects of methoxy fluorination on receptor affinities and selectivity in more detail, since the issues surrounding serotonin 2C/2A subtype selectivity remain challenging, especially when developing agonists.[20,24,73]

Table 1. Affinities (K_i) at the h5-HT_{2A} and r5-HT_{2C} receptors of some fluoro analogs of 2C-H (**55**) and 2C-B (**33**). Values in nM.[69,105]

Nr.	Name	h5-HT_{2A} K_i [^{3}H]Ketanserin (nM)	r5-HT_{2C} K_i [^{3}H]Mesulergine (nM)
55	2C-H	3000[a]	5520[a]
54	5TF-2C-H	1873	316
33	2C-B	16[a; b]	190[a; b]
53	2DF-2C-B	1100	38

[a]Both transfected r5-HT_{2A} or r5-HT_{2C} receptors.[24] [b] Affinities of K_i = 34 and 36nM at r5-HT_{2A} and r5-HT_{2C} receptors from rat brain homogenate (frontal cortex), respectively.[18]

The importance of the 2,5-dimethoxy groups upon agonistic properties as well as the H-acceptor abilities of the involved MeO groups for agonistic binding modes of these molecules has been shown extensively[19,20,24,72,74–77] and are most probably changed by fluorination. If a strong electron withdrawing group is attached in the neighborhood of a phenolic ether, the oxygen loses its basicity and so loses its capability to accept hydrogens with its lone pair electrons. Through this one might expect the compound to gain additional lipophilicity. In other words, Ar-O-CH_3 is an H acceptor and therefore, to a certain degree, extends hydrophilicity, whereas the lone pair electrons at Ar-O-CF_3 cannot accept a hydrogen, rendering this substituent to be much more lipophilic. Fluorine itself could act as an H-acceptor or undergo so-called multipolar interactions but these effects are generally considered to be less pronounced.[11,13]

Expansion from MeO to EtO or modification to MeS of either of the 2,5-MeO groups has been investigated in humans which revealed a drop in human potency with greater impact of the 2-position.[3] Replacements by Br or Me of one of the MeO groups dramatically alters human potencies.[3,78,79] Receptor binding studies showed that replacement of a methoxy group by either F[72] or Et[77] diminished serotonin 5-HT_{2A} receptor affinities. These experiments provided further support for the idea that, for high human potency and 5-HT_{2A} receptor affinities, structural modification of the 2-position seems less well tolerated in comparison to changes at the 5-position. Nothing is known about human activity of these compounds (**53, 54**).

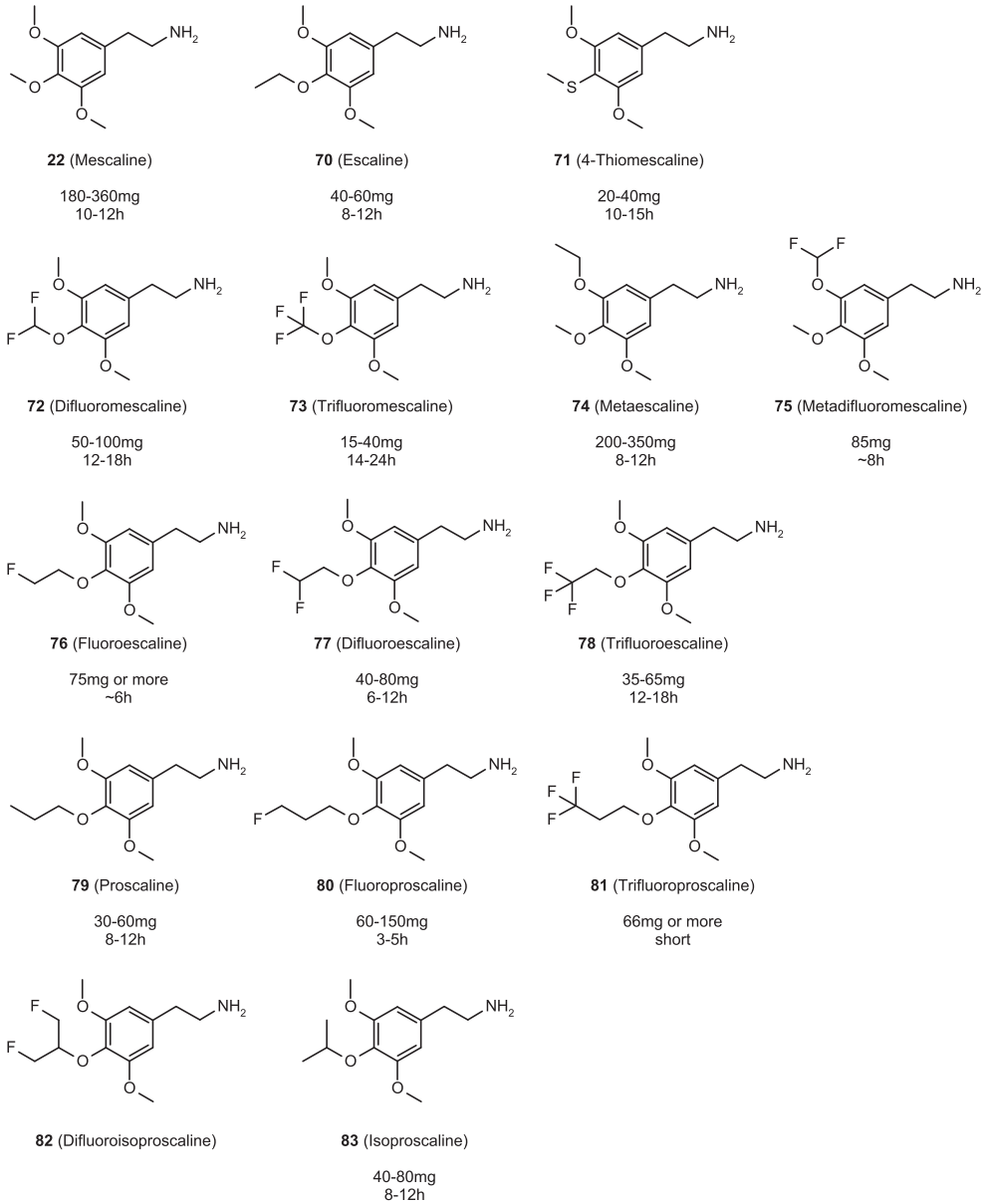

Figure 5. Mescaline (**22**) and several other 3,4,5-trisubstituted derivatives. Influence of homologization or fluoro derivatization on human dose and duration of action.

Within the *4-alkylated* 2,5-dimethoxyphenethylamines two novel fluorinated derivatives have been prepared and investigated (Figure 3, D). These compounds, 2C-TFE (**56**) and DOTFE (**57**) can be considered to be homologs of the potent serotonin 5-$HT_{2A/C}$ receptor agonists 2C-TFM (**34**) and DOTFM (**35**)[28] and analogs of the non-fluorinated potent psychedelics 2C-E (**58**) and DOET (**26**), respectively,[3] as well as of the mono-fluorinated DOEF (**25**).[3] At the [^{3}H]ketanserin-labelled cloned h5-HT_{2A} receptor 2C-TFE (**56**: $K_i = 116$nM) showed slightly decreased affinity in comparison to 2C-TFM (**34**: $K_i = 74.5$nM, rat brain homogenate from frontal cortex[28]). In humans, 2C-TFE (**56**) proved to be a potent (5–15 mg) and long-lasting (12–24 h) psychedelic. The homolog DOTFE (**57**) turned out to be without effects in a single 0.56 mg trial. One might expect this to be a potent 5-HT_{2A} receptor agonist with a potential for high human potency but further studies are needed.

Fluorine in 2,4,6-trisubstituted phenethylamines

The fact that 2,4,6-trisubstituted phenethylamines are much less investigated might result from the more complex nature of organic synthesis. A few derivatives, for example, **59** and **60**, however, have been evaluated (Figure 4) and it was suggested that every psychoactive 4-substituted 2,5-dimethoxyphenethylamine could lead to an active 4-substituted 2,6-dimethoxyphenethylamine positional isomer.[3] These 2,4,6-substituted compounds are the so-called pseudo derivatives (the Greek *Psi*, Ψ is used as a prefix), in which the 5-MeO group of a known 2,4,5-derivative has been shifted to the 6-position.[3] The preservation of human activity, paired with an occasional decrease of potency, has been shown with a few examples so far and examples include DOM (**31**) → Ψ-DOM (**59**) and TMA-2 (**45**) → TMA-6 (**60**).[3] An *in vitro* and *in vivo* decrease in potency for Ψ-DOM (**59**)

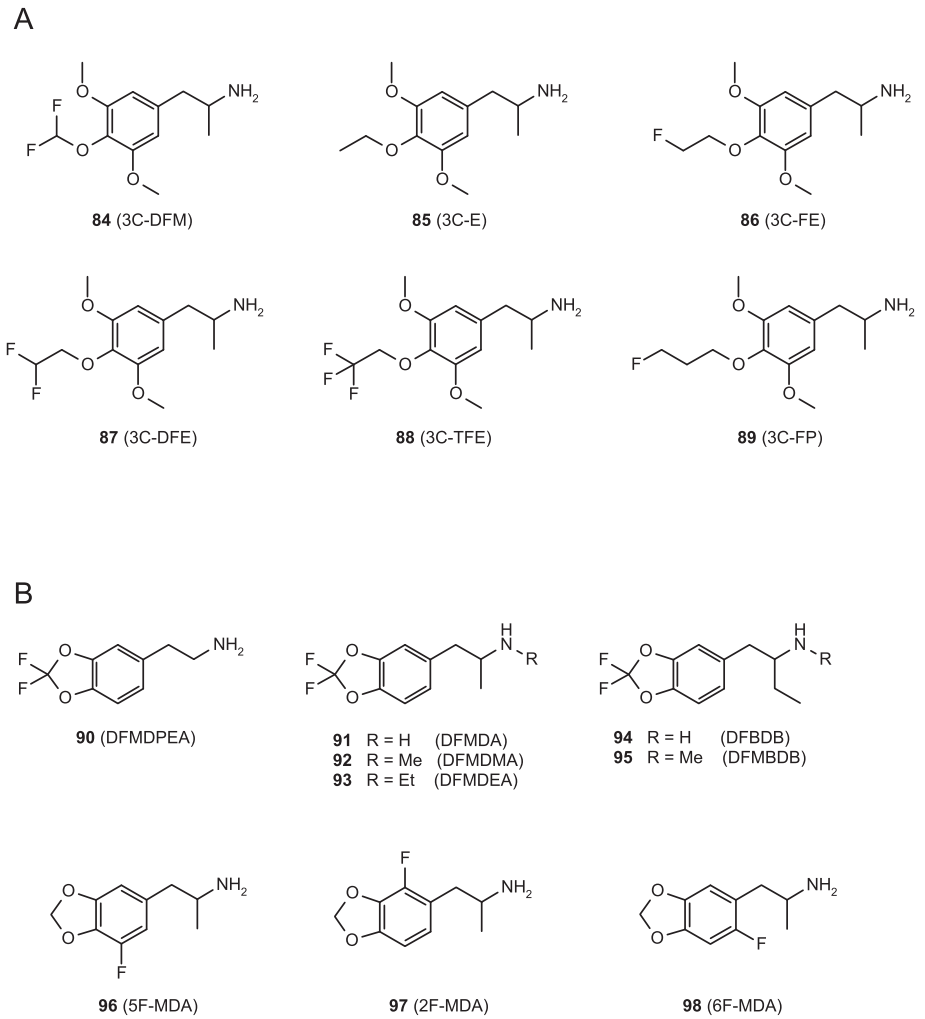

Figure 6. (A) 3,4,5-trisubstituted α-methylated phenethylamines. (B) Fluorinated 3,4-methylenedioxyphenethylamines.

over DOM (**31**) has been shown for 5-HT_{2A} receptor affinities[22,72,80] and in DD studies,[75,80,81] respectively. In humans, Ψ-DOM (**59**: 12–25 mg, 6–8 h) was distinctly less potent than DOM (**59**: 3–10 mg, 14–20 h).[3] The two derivatives TMA-2 (**45**: ED_{50} = 3.59 mg/kg) and TMA-6 (**60**: ED_{50} = 3.69 mg/kg) both substituted nearly with similar potency in rats trained to discriminate between DOM (**31**: ED_{50} = 0.44 mg/kg) and saline.[82] Similar to the 2,4,5-derivatives the Ψ-derivatives seem to behave as 5-HT_{2A} receptor agonists[22,80] and may exert their psychoactive effects by similar neuropharmacological mechanisms.

Similar to 2C-O (**43**: >300 mg[3]), Ψ-2C-O (2,4,6-TMPEA, **61**: >300 mg) did not show any human activity (P. Rausch, personal communication in 2009) and interestingly, the 3,4,5-trimethoxy isomer mescaline (**22**: 180–360 mg) does.[3] A couple of fluorinated Ψ-2C and Ψ-3C derivatives have been prepared (compounds **62–69**, Figure 4).

The introduction of two fluorine atoms into the 4-MeO group of Ψ-2C-O (**61**) seems to change biological activity distinctly and leads to a fairly active and long acting compound (Ψ-2C-DFMO, **68**. A single experiment with 17 mg was stated to be only moderately intense although a relatively long duration around 18 h was observed. Its α-methyl analog Ψ-DODFMO (**69**) has been shown to be moderately active in a single experiment with 2x5 mg, which had a long duration of action (around 20 h) as well.

Fluorine in 3,4,5-trisubstituted phenethylamines

The class of 3,4,5-trisubstituted phenethylamines has been investigated rather intensely and its prototype structure is represented by mescaline (3,4,5-trimethoxyphenethylamine, **22**, Figure 5). It was Arthur Heffter who isolated it from the Mexican Peyote cactus first in 1896.[83] The first synthesis of mescaline was published by Ernst Späth in 1919.[84] Up until the present day, the chemical structure of mescaline has served as a lead compound for probably hundreds of homologs, analogs and related derivatives.[3–5] Mescaline (**22**) itself is not a very potent psychedelic in terms of human dosage (180–360 mg) but its effects (10–12 h duration) can be very intense and accompanied by visual distortions and synesthesia.[3] It is believed that like other phenethylamine-type psychedelics, mescaline acts primarily as a serotonin 5-HT_{2A} receptor agonist.[85] Its low human potency could be explained, at least partially, with its relatively low affinity at this receptor subtype. At the [^{125}I]DOI labelled 5-HT_{2A} receptor it showed an affinity of K_i = 551nM,[85] and in comparison, the potent

psychedelic DOB (**29**) had an affinity of $K_i = 0.6$nM.[36] With a slightly higher affinity, mescaline also acts as a 5-HT_{2C} receptor agonist ($K_i = 302$nM, [^{125}I]DOI labelled)[85] and it has been shown that, among other phenethylamines, it may interact with other receptor systems as well.[35]

With the simple transformation of the 4-MeO in mescaline (**22**) to a 4-EtO group, i.e. escaline (**70**), a five times more potent analogue is obtained (Figure 5).[3] An even more dramatic increase of human potency has been observed with a 4-*O* to 4-*S* substitution. 4-Thiomescaline (4-TM, **71**) is one order of magnitude more potent than mescaline.[3] It seems that the 5-HT_{2A} receptor affinities do not increase sufficiently by these structural modifications to explain the increased human potency; the enhanced lipophilicity and receptor activation could also play an important role.[85]

Among numerous modifications of the 4-position,[3,86] 4-fluoroalkoxy derivatives have been prepared and investigated (Figure 5).[86] The smallest investigated fluoro analogs of mescaline (**22**: 180–360 mg, 10–12 h), namely difluoromescaline (**72**: 50–100 mg, 12–18 h) and trifluoromescaline (**73**: 15–40 mg, 14–24 h) proved to show psychedelic properties, with **73** being one of the most potent mescaline derivatives so far discovered. At least for **72** ($K_i = 5949$nM) the affinity at the antagonistic [^{3}H]ketanserin-labelled serotonin h5-HT_{2A} receptor was determined, which was not significantly different from mescaline (**22**. $K_i = 5500$nM[85]). As observed with escaline (**70**),[85] affinity alone cannot explain increased *in vivo* activity. The long lasting effects of **72** and **73** could also result from enhanced metabolic stabilities as a consequence of fluorination.

It has been shown that enlargement of the 3-MeO group in mescaline (**22**) up to 3-EtO retains human potency (metaescaline, **74**: 200–350 mg, 8–12 h), although the nature of psychological effects were changed significantly.[3] Larger substituents seem to abolish human activity[3] and therefore a small fluorinated analog was investigated. In comparison to mescaline (**22**), metadifluoromescaline (MDFM, **75**: $K_i = 2988$nM) has shown a slight increased affinity at the [^{3}H]ketanserin-labelled serotonin h5-HT_{2A} receptor. With **75** (85 mg, ~8 h), an anecdotal report states some rather unpleasant effects.

Three fluoro analogs (**76–78**) of escaline (**70**) have been investigated.[86] At the [^{3}H]ketanserin-labelled serotonin h5-HT_{2A} receptor both fluoroescaline (**76**: $K_i = 7628$nM) and difluoroescaline (**77**: $K_i > 10000$nM) showed low affinities. Interestingly, with monofluorination the human potency of **76** (75 mg, ~6 h) decreased distinctly, while the difluoro analog **77** (40–80 mg, 6–12 h) regained similar potency to the non-fluorinated derivative escaline (**70**: 40–60 mg, 8–12 h). The trifluoroethyl derivative **78** (35–65 mg, 12–18 h) proved to be a psychedelic compound of similar or slightly increased human potency with a prolonged duration of action.

A fluorinated analog of proscaline (**79**)[3] was also investigated.[86] At the cloned [^{3}H]ketanserin-labelled serotonin h5-HT_{2A} receptor fluoroproscaline (**80**: $K_i = 8792$nM) showed only low affinity and in humans, fluoroproscaline (**80**: 60–150 mg, 3–5 h) was distinctly less potent and of shorter duration than proscaline (**79**: 30–60 mg, 8–12 h). Similarly, limited trials suggest that trifluoroproscaline (**81**: 66 mg or more) might be less potent as well.

The preparation of difluoroisoproscaline (**82**), a fluoro analog of the psychedelic derivative isoproscaline (**83**),[3] has been achieved.[5]

A series of 4-fluoroalkoxy analogs of 3,4,5-trimethoxyamphetamine (TMA, **12**: 100–200 mg, 6–8 h[3]) has also been investigated (Figure 6, A).[86] The influence of fluorine introduction could not yet fully be determined, as at present too little biological data of either the non-fluorinated derivatives (**85**[3] and compounds described in Trachsel[86]) or the fluoro analogs **84** and **86–89** is available. For some fluorinated 3,4,5-substituted compounds some volunteers reported skin itching during experiments. Whether this might point towards the involvement of other targets, such as the histamine receptors, remains to be seen.

Some effects upon α-methyl introduction into the 3,4,5-series could also be observed. Among the very limited data so far, a slight increase of affinities for the α-methyl derivatives over their counterparts could be suggested at the 5-HT_{2A} receptor (Table 2; s. pairs **72**/**84**; **76**/**86**; **77**/**87**; **80**/**89**). This would be in contrast to the well investigated 4-substituted 2,5-dimethoxy derivatives where similar affinities were found for the phenethylamines and their racemic α-methyl congeners. For the compounds described in Table 2 an increase of affinities did not appear to be evident as far as 5-HT_{2C} receptor data were concerned. It might be worthwhile to carry on with agonist receptor labelling rather than with antagonistic labelling experiments.

Interestingly, the few data available from human comparison[3,5] indicate that α-methylated 4-alkoxysubstituted 3,5-dimethoxyphenethylamines have only slightly increased potency and similar duration of action when compared to their α-methyl-free congeners (data not shown although an exception is mescaline (**22**) and TMA (**12**)[3]). This stands in marked contrast to most of the 2,4,5-trisubstituted derivatives, where introduction of an α-methyl group increases human potency by a factor of up to ten in addition to prolonged duration of action.[3,5] The influence of an α-methyl group on lipophilicity, metabolic stability and 5-HT_{2A} receptor activation should certainly be considered for an explanation of these observations. Another issue must be taken into account at this point. It was found that different methoxy substitution patterns at the aromatic moiety also seriously influence the extent of amine oxidation.[70] For mescaline (**22**) and TMA (**12**) there were also observed differences in the extent of CYP2D6 interaction.[87]

At least for one α-methylated derivative of the 3,4,5-series, namely TMA (**12**), higher intrinsic activities have been shown for the h5-HT_{2A} receptor, i.e. activation of phospholipase A_2 (PLA_2) and phospholipase C (PLC) stimulation, than for its

Table 2. Affinities of several 4-(fluoroalkoxy) 3,5-dimethoxyphenethylamines and their α-methyl analogs at h5-HT_{2A} and r5-HT_{2C} receptors. K_i values in nM.[69,105]

Nr.	Name	h5-HT_{2A} K_i [^{3}H]Ketanserin (nM)	r5-HT_{2C} K_i [^{3}H]Mesulergide (nM)
70	E	2100 [a]	nd [b]
85	3C-E	2582	1° assay <50%
72	DFM	5949	5820
84	3C-DFM	2335	1594
76	FE	7628	1210
86	3C-FE	5987	>10000
77	DFE	>10000	5682
87	3C-DFE	2695	>10000
88	3C-TFE	1825	1659
80	FP	8792	>10000
89	3C-FP	4581	3872

[a]values taken from ref.[85]
[b]not determined.

α-methyl-free congener, mescaline (**22**).[34] This follows the trend also observed with derivatives of the 2,4,5-series.[25,34,88]

At this moment, the reasons for the different behaviors observed between the 2,4,5- and 3,4,5-series are currently unknown and more work has to be done in this field. Recent research also suggests that receptor dimerization between the 5-HT_{2A} receptor and the mGlu2/3 receptor could play a role in the effects observed in humans, in addition to simple agonist receptor stimulation.[89]

Fluorine in 3,4-methylenedioxyphenethylamines

The 3,4-methylenedioxyphenethylamines, particularly 3,4-methylenedioxymethamphetamine (MDMA, *Ecstasy*, **4**) gained tremendous attention in scientific research and became very popular in so-called techno parties as a recreational drug. As an entactogen MDMA (**4**) differs from stimulants and psychedelics not only mechanistically but also in its psychological effects. Very briefly, MDMA has the ability to cause feelings of closeness, a desire to socialize and an enhanced feeling of empathy as well as an increase in euphoria and energy which appealed to people attending dance parties.[3,54] Its unique pharmacological properties also made it attractive for psychotherapy, and currently there are clinical trials which investigate MDMA (**4**) assisted psychotherapy in patients with posttraumatic stress disorders (PTSD) and anxiety associated with terminal cancer.[90]

The underlying neuropharmacological mechanisms of MDMA (**4**) have been studied comprehensively[5,91,92] and its neurotoxic potential have been debated controversially over the years.[5,92–96] In contrast to the psychedelic phenethylamines, MDMA acts via monoamine transporters and not as a 5-HT receptor agonist. Briefly, MDMA (**4**) is known to release serotonin (5-HT) and, to a lesser extent dopamine (DA) as well as norepinephrine (NE).[93,97] All three monoamines may contribute to the psychological effects.[98–100] It also increases 5-HT levels by inhibiting the serotonin transporter (SERT).[93,101] It is believed that MDMA-mediated elevations of oxytocin hormone levels may at least partially contribute to the subjective pro-social effects.[102,103]

The first fluorinated 3,4-methylenedioxyphenethylamines described in the scientific literature were compounds **90–95**, all bearing a 3,4-(difluoromethylenedioxy) moiety (Figure 6, B).[96] It was hoped that this introduction of fluorine could lower the formation of potentially neurotoxic metabolites of MDMA[96] by either blocking formation of neurotoxic α-methyldopamines via increased methylene bridge stability or formation of glutathione adducts via changing the electron density of the aromatic nucleus. Only few pharmacological characterizations have been carried out so far. Initial *in vitro* investigations showed DFMDA (**91**: $K_i = 1200$nM) to have a SERT affinity between that of MDA (**3**: $K_i = 700$nM) and MDMA (**4**: $K_i = 1600$nM) using a functional assay.[104] DFMDA (**91**) did not appear to show any activity in humans up to 250 mg, whereas MDA (**3**) showed its full activity at a dose of 80–160 mg.[3] The difluoro analog DFMDMA (**92**) was inactive at levels up to 120 mg (MDMA, **4**: 80–150 mg[3]).

Derivatives **96–98** have been investigated for their interaction with monoamine transporters using radioligand competition assays.[105] [^{3}H]WIN-35428, [^{3}H]nisoxetine and [^{3}H]citalopram were employed as radioligands at the DAT, NET und SERT, respectively, with K_i values above 10000nM for all compounds and transporters. An exception was 2 F-MDA (**97**) with a $K_i = 8064$nM at SERT. Similarly, MDMA (**4**) was reported to show values above 10000nM[69] whereas MDA (**3**) has not yet been described so far in these competitive assays. Correspondingly, it would be interesting to investigate monoamine transporter interactions for **96–98** using functional assays to determine their monoamine releasing properties as well. How strong fluorine and its position on the aromatic moiety can influence the binding properties on adrenergic and dopaminergic receptors has been shown extensively on fluoro analogs of DA and NE.[106–108]

Discussion and future directions

Within the *2,4,5-series*, some 14 novel fluorinated derivatives have been described (**37**, **38**, **40**, **42**, **47–54**, **56**, **57**). Perhaps the most recent findings were obtained with compounds 2DF-2C-B (**53**) and 5TF-2C-H (**54**). Fluorination of either the 2-MeO or 5-MeO group produced an impact on binding properties, making them more selective for the serotonin 5-HT_{2C} than 5-HT_{2A} receptor (Table 1). Further derivatives should be investigated with the application of progressive fluorination in order to assert the extent of subtype selectivity.

Up to now only very little biological data can be found for the derivatives of the *2,4,6-series*. Compounds **62–69** may further help understanding the structure-activity relationships of this class. At least two novel derivatives have been assayed. A modification of the human inactive Ψ-2C-O (**61**, >300 mg) to the 4-difluoromethoxy analog Ψ-2C-DFMO (**68**, 17 mg) could greatly change the pharmacological properties in humans leading to a fairly potent derivative. The derivative Ψ-DODFMO (**69**) showed some effects at a dose of 2x5 mg. Although too little data are available so far, this suggests that similarly to the 3,4,5-series, from the presence of an α-methyl group in the 2,4,6-series only a modest difference in human dose may result.

A total number of 14 fluorinated mescaline analogs/homologs have been described (**72**, **73**, **75–78**, **80–82**, **84**, **86–89**; *3,4,5-series*). The simplest analogs, difluoromescaline (**72**: 50–100 mg, 12–18 h) as well as trifluoromescaline (**73**: 15–40 mg, 14–24 h) have proven to be more potent and showed distinctly longer duration of action in humans when compared to mescaline (**22**: 180–360 mg, 10–12 h). With compounds **76–78** it has been shown that fluorination of the 4-ethoxy group of escaline (**70**) can change the (psycho)pharmacological properties profoundly. While monofluorination causes loss of psychoactivity (compound **76**), difluorination retains human potency (compound **77**) and the trifluoroethoxy derivative **78** proved to be a long-lasting psychedelic with similar or slightly increased potency.

In addition to fluorination some differences have been observed in regards to α-methylation of the 3,4,5-series when compared to derivatives of the 2,4,5-series. In other words, introduction of the α-methyl group can dramatically increase human potency as well as duration of action but only a moderate impact was observed for derivatives of the 3,4,5-series. There is some indication that 5-HT_{2A} receptor affinities might be increased by introduction of the α-methyl group into some derivatives of the 3,4,5-series, at least on an antagonist binding assay (Table 2). This would clearly contrast with the 2,4,5-series, wherein no apparent effects on affinities could be observed following introduction of the α-methyl group.

Fluorine introduction was also performed with the *3,4-methylenedioxyphenethylamines* and a total of nine derivatives (**90–98**) were described. Monoamine transporter binding properties described so far did not elucidate the extent to which these

compounds show similar neuropharmacological mechanisms of action in comparison to MDMA (**4**). Further work would also be required to shed more light on the impact of fluorination on the formation of potential neurotoxins.[93,95,96] What has been found so far is that human activity of DFMDA (**91**, >250 mg) or DFMDMA (**92**, >120 mg) appears to be absent which reveals that the significant properties responsible for the unique action of MDMA (**4**) have been changed by fluorine introduction into the 3,4-methylenedioxy bridge.

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