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ORIGINAL PAPER

Correlating the Metabolic Stability of Psychedelic 5-HT_{2A} Agonists with Anecdotal Reports of Human Oral Bioavailability

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Abstract 2,5-Dimethoxyphenethylamines and their *N*-benzylated derivatives are potent 5-HT_{2A} agonists with psychedelic effects in humans. The *N*-benzylated derivatives are among the most selective 5-HT_{2A} agonists currently available and their usage as biochemical and brain imaging tools is increasing, yet very little is known about the relationships between the structure of the ligands and their pharmacokinetic profile. In order to evaluate the potential of these compounds for in vivo applications we have determined the microsomal stability of 11 phenethylamines and 27 *N*-benzylated derivatives thereof using human liver microsomes. We found that the *N*-benzylated phenethylamines have much higher intrinsic clearance than the parent phenethylamines. We hypothesize that their low hepatic stability renders them orally inactive due to first pass metabolism, which is supported by anecdotal data from recreational use of these compounds.

Keywords Phenethylamines · *N*-benzylphenethylamines · Microsomal stability · 5-HT_{2A} agonists · Psychedelics

Special Issue: In honor of Krogsgaard-Larsen.

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Introduction

Psychedelic drugs have had a profound effect on human society, art and culture. In both ancient and modern times psychedelics have been used as sacraments in religious ceremonies, as agents of healing and transcendence, as creativity tools or nootropics, and as recreational drugs [1–3]. It is now generally accepted that the effects of psychedelic drugs (like mescaline, psilocybin and LSD) are primarily (if not solely) mediated via agonism of the serotonin 2A receptor (5-HT_{2A}) [4]. 5-HT_{2A} agonists induce mental states that are indistinguishable from mystical and spiritual experiences which can lead to long-term improvements in attitude and behavior [5–7]. Psychedelics have been utilized in experimental psychiatry to alleviate fear and anxiety in terminally ill cancer patients, treat alcohol dependency, and help sufferers of obsessive compulsive disorder [8–10]. In light of the resurgence of psychedelics in experimental medicine, there is a growing need for selective 5-HT_{2A} agonists that can be used to elucidate the underlying mechanisms of the psychedelic states. Such tool compounds may pave the way for new treatment paradigms in a number of CNS-related diseases.

Despite the possible legal repercussions and safety concerns, recreational users are continuing to investigate and disseminate their experiences with different psychedelic drugs, and anecdotal reports have accumulated on the internet over the last decades. These reports contain a vast amount of anecdotal information about the effects of these compounds in humans: effective doses, delivery routes (oral, parenteral, buccal etc.), duration of effects which give clues to the in vivo potency and pharmacodynamic behavior of the compounds. Researchers have data mined internet forums in an effort to structure this information, and have also been able to differentiate between different

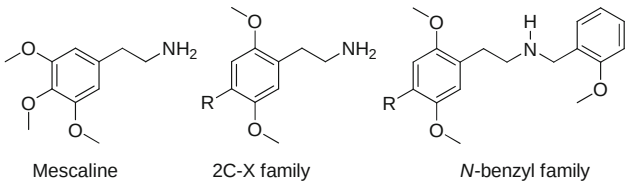


Fig. 1 Chemical structure of the classic psychedelic drug mescaline and two related compound classes with increasing potency and 5-HT_{2A}-selectivity

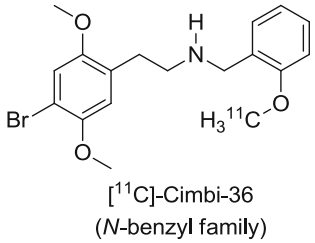


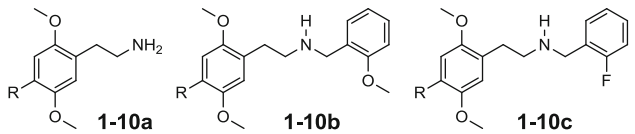
Fig. 2 Structure of [^{11}C]-CIMBI-36 a potent 5-HT_{2A} agonist in development as a PET-tracer. The unlabelled compound is also known as 25B-NBOMe and is available on the clandestine market

drugs based on the occurrence of different keywords in the reports [11].

Several compound classes have been developed as 5-HT_{2A} agonists [12]. One of those has evolved from Mescaline, a natural product isolated from the cactus *Lophophora Williamsii* (or peyote/hikuri) in 1897 [13], see Fig. 1. Moving the methoxy groups around the aromatic ring resulted in a drastic increase in potency with a 2,5-configuration being optimal for 5-HT_{2A} agonism, where the R-group in the 4-position should be a small substituent—preferably of lipophilic nature [14]. Compounds from this class are often referred to as "2C-X" where X denominates the R-substituent. Although these compounds are potent agonists of the 5-HT_{2A} receptor they lack selectivity towards the 5-HT_{2C} receptor which is also present in the CNS. Later it was found that introduction of a 2-methoxy-*N*-benzyl substituent (the *N*-benzyls, see Fig. 1) increased the potency of the compounds further and for the first time notable selectivity for 5-HT_{2A} over 5-HT_{2C} was observed. Members of the *N*-benzylphenethylamine family (the *N*-benzyls) have provided some of the most potent and selective 5-HT_{2A} agonists reported to date [15, 16].

As part of our efforts to develop agonist PET-ligands for the visualization of the 5-HT_{2A} receptor we have investigated several members of this class of 5-HT_{2A} agonists [17, 18]. [^{11}C]-Cimbi-36, see Fig. 2 (which is the *N*-(2-methoxybenzyl) substituted derivative of 2C-B, also known as 25B-NBOMe), emerged as the best candidate and is currently being evaluated in humans as a PET-ligand.

Table 1 Hepatic stability of psychedelic 2C-X's (**1a–10a**) and *N*-benzyls (**1b–10b** and **1c–10c**) given as intrinsic clearance (CL_{int} in L/kg/h)



R	CL_{int} (L/kg/h)		
I	**1a**: 0.20	**1b**: 4.1	**1c**: 99
CH_3	**2a**: 0.27	**2b**: 4.4	**2c**: 6.3
SEt	**3a**: 0.48	**3b**: 19	**3c**: 42
Br	**4a**: 0.51	**4b**: 3.3	**4c**: 5.4
CN	**5a**: 0.58	**5b**: 5.0	**5c**: 7.6
SPr	**6a**: 0.61	**6b**: 13	**6c**: 36
CF_3	**7a**: 0.62	**7b**: 8.8	**7c**: 8.4
Sme	**8a**: 0.65	**8b**: 12	**8c**: 29
Cl	**9a**: 0.74	**9b**: 2.9	**9c**: 5.8
H	**10a**: 8.9	**10b**: 14	**10c**: 16

The compounds are listed according to the metabolic rate of the 2C-X series

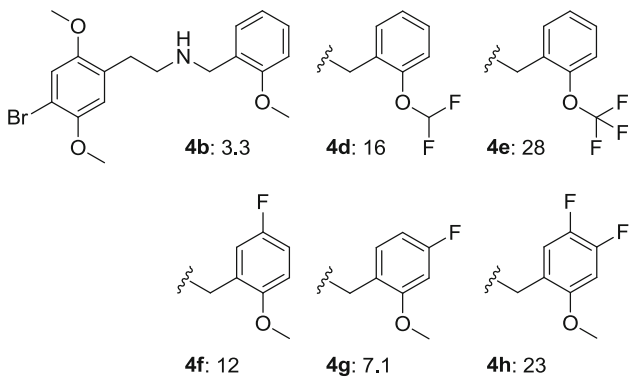


Fig. 3 Fluorine scan on scaffold **4b**. Intrinsic clearance (CL_{int} in L/kg/h)

Encouraged by their success as PET-ligands in humans we became interested in developing a selective 5-HT_{2A} agonist for in vivo use from this compound class. Several members of the *N*-benzyl family of psychedelics have lately become available for purchase from online vendors, [19] and overdose case studies (both fatal and non-fatal) have also been published raising concern about the use of these compounds in pharmacological doses [20]. Since very little is known about the pharmacokinetics of the *N*-benzyls we decided to investigate and compare the metabolic profile of the 2C-X and *N*-benzyl series and

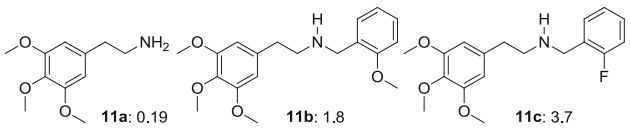


Fig. 4 Mescaline (**11a**) and its *N*-benzylated derivatives **11b** and **11c**. Intrinsic clearance (CL_{int} in L/kg/h)

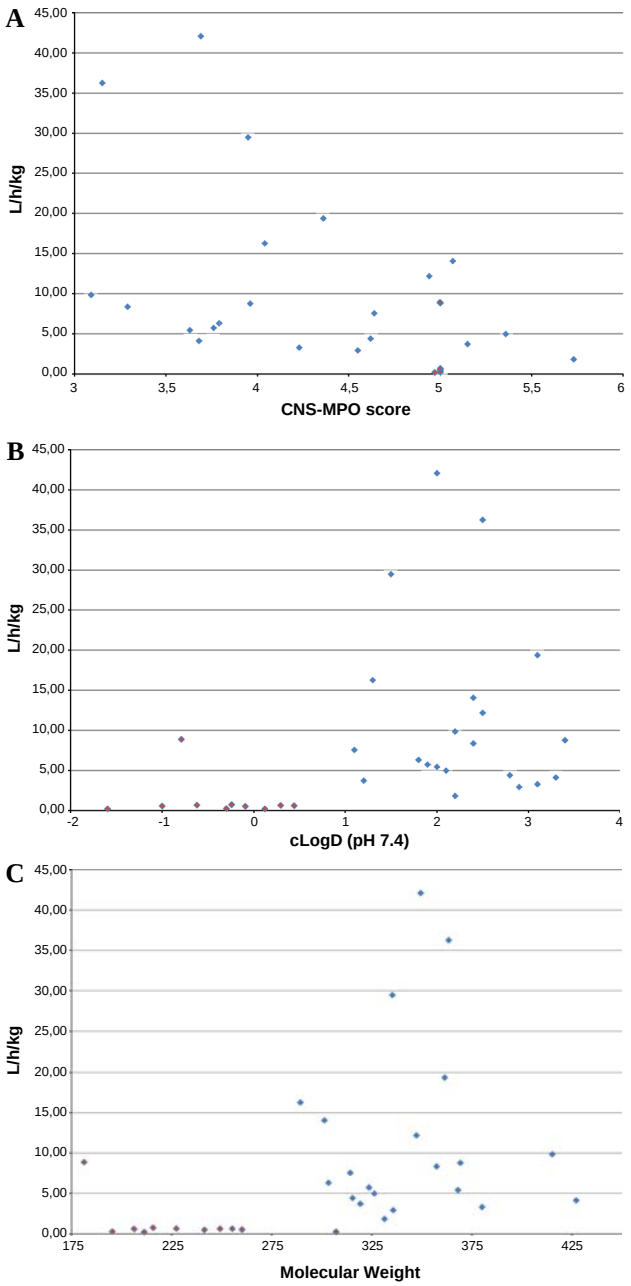


Fig. 5 Correlation of effect of physicochemical properties on intrinsic clearance. **a** CNS-MPO score, **b** MW, **c** cLogD. 2C-Xs are *red* and *N*-benzyls are *blue* (Color figure online)

correlate this with anecdotal reports of their use in humans with the aim of evaluating the potential of this compound class as 5-HT_{2A}-selective agonists for clinical applications.

Results and Discussion

We took note of anecdotal evidence stating that the *N*-benzyls would only have an effect if taken by parenteral routes or via buccal, sublingual or nasal absorption [21]. This was surprising since the primary phenethylamines (the 2C-X's) from which the *N*-benzyls are derived are known to be orally active. The reported potency of the *N*-benzyls when taken by other routes than oral, is 50–100 times greater (by weight) than their parent 2C-Xs [22, 23], which correlates well with the relative in vitro potency of the compounds.

We hypothesized that the reason for the *N*-benzyls seemingly low oral bioavailability could be a consequence of low metabolic stability. To test our hypothesis we assessed the metabolic rate of a set of ten 2C-Xs and their corresponding *N*-(2-methoxybenzyl derivatives via incubations with human liver microsomes. The metabolism of 2C-B has been studied in detail in the literature, [24–26] as this compound has been very popular amongst recreational users, whereas reports on the metabolic fate of other 2C-Xs (2C-D [27], 2C-E [28], 2C-I [29], 2C-T-2 [30], 2C-T-7 [31]) and the *N*-benzyls are more scarce.

In Table 1 the intrinsic clearance (CL_{int}) in L/kg/h is listed. This is a measure of the volume of blood from which the compounds is cleansed. The CL_{int} of a compound in this assay indicates the rate by which it would be metabolized by the liver in vivo, and whether or not first-pass metabolism will be a factor that affects oral bioavailability [32, 33]. The human liver blood flow is 1.3 L/kg/h so a CL_{int} higher than this is an indication of extensive first pass metabolism.

All 2C-X's with a substituent in the 4-position ($R \neq H$) are quite stable towards microsomal degradation (average $CL_{int} = 0.5$ L/kg/h), which is in good agreement with the fact that they are all (except **10a**) known to be orally active in humans, see Table 1. The unsubstituted **10a** (known as 2C-H, where $R = H$) has a very high intrinsic clearance ($CL_{int} = 8.9$ L/kg/h) suggesting a very high first pass metabolism. Again, this is mirrored in the anecdotal reports where **10a** is inactive when taken orally.

The addition of an *N*-(2-methoxybenzyl) moiety to the 2C-X core has a dramatic effect on the metabolic stability of the compounds, giving an average $CL_{int} = 9$ L/kg/h, see Table 1. This is much higher than the human liver blood flow of 1.3 L/h/kg, which indicates that none of the *N*-(2-methoxybenzyl) compounds (**1b**–**10b**) should be orally active due to first-pass metabolism in the liver [34].

We assumed that the loss of oral activity upon going from 2C-X to *N*-benzyl was due to CYP-mediated hydroxylation of the 2-methoxybenzyl ring, a metabolic pathway that should be highly influenced by the electron density of the substrate [35]. Thus, we wanted to explore this by changing the electronic nature of the benzyl ring by

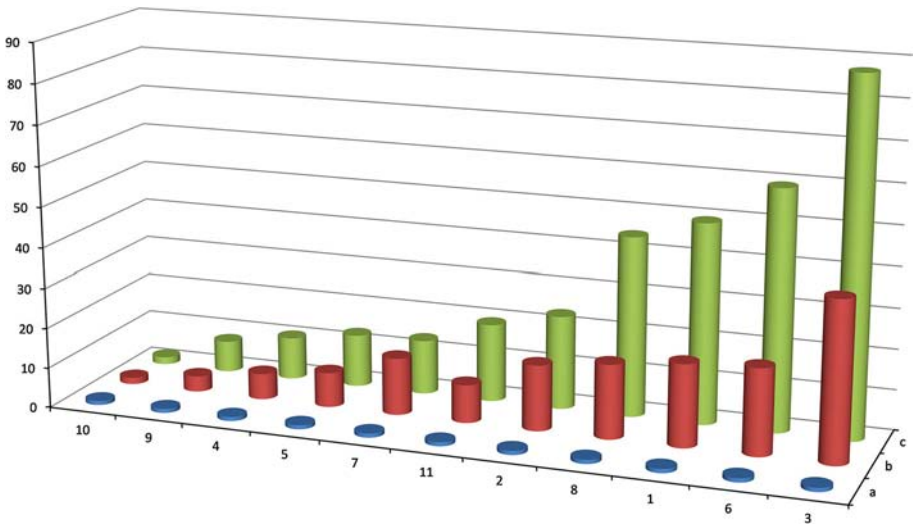


Fig. 6 Intrinsic Clearence (CL_{int}) of *N*-benzyls relative to parent 2C-X. The intrinsic clearance of the parent 2C-X is normalized to one (*blue*), and they are sorted from lowest relative effect on clearance upon going from 2C-X to *N*-(2-fluorobenzyl) (**10a–c**) to highest effect of *N*-benzyl substitution (**3a–c**) (Color figure online)

substituting the electron donating 2-methoxy substituent with an electron withdrawing 2-fluoro substituent. Thus, the same ten 2C-X compounds with an *N*-(2-fluorobenzyl) group (compounds **1c–10c**) were investigated, see Table 1. To our surprise this led to even higher clearance values, with an average $CL_{int} = 17$ L/kg/h. With the exception of **7b/7c** the switch from the OMe to F lead to an increased CL_{int}.

A small fluorine scan on compound **4b** was performed resulting in the fluorinated analogs **4d–4h**, see Fig. 3. **4d** and **4e** should be less prone to *O*-demethylation which is a common metabolic pathway for anisoles and **4f–4h** should have blocked ring hydroxylation as previously described, but none of these modifications to the structure of **4b** led to an increase in metabolic stability.

These observations clearly suggest that the *N*-benzyl ring may not be the only metabolic soft spot (if at all), and that the linker or the phenethylamine core could be the main site of metabolism. If that hypothesis is true, benzylation of the 2C-Xs increases intrinsic clearance via other mechanisms, possibly by giving the compounds unfavorable physicochemical properties.

Mescaline (**11a** in Fig. 4) is known to be metabolized very slowly in humans, with more than 87 % of the ingested dose being excreted unchanged with the urine within 24 h [36]. We decided to investigate the effect of *N*-benzylation of mescaline to see if the high metabolic stability of mescaline could be maintained in a *N*-benzyl derivative, but we found that **11b** and **11c** were also metabolized rapidly, see Fig. 4. The relative CL_{int} of **11a**:**11b**:**11c**, is 1:9.6:20 which is on par with the average CL_{int} of the other 2C-Xs.

To estimate which physical properties of the compounds that might explain the relative clearance of all the investigated compounds, we utilized a CNS multiparameter optimization algorithm (CNS-MPO) published in 2010 by scientists at Pfizer [37]. The CNS-MPO incorporates a number of different parameters to score compounds from 1 to 6. A score of 4 or above indicates that a compound will have a high probability of low toxicity, high metabolic stability and good brain penetration. All the 2C-Xs have a CNS-MPO score close to 5, whereas the *N*-benzyls achieve a score between 3 and 5.5. When plotting the intrinsic clearance against the CNS-MPO score (See Fig. 5a) there appears to be a trend that the higher the MPO-score the higher the metabolic stability, which is also to be expected. We looked at all the individual parameters that are built into the CNS-MPO score, but we could not find any significant correlations that could give clues to the reason for the high metabolic rate of these compounds. In Fig. 5b, c the CL_{int} is plotted against MW and cLogD, and as can been seen there are no clear correlations between any of these physicochemical parameters and metabolic stability (Fig. 5).

The higher molecular weight and lipophilicity of the *N*-benzyls compared to the 2C-Xs could be a factor in their higher intrinsic clearance, but no such correlation between size/lipophilicity and CL_{int} is apparent within the 2C-X or *N*-benzyl family. The *N*-(2-fluorobenzyl) moiety generally results in less metabolically stable *N*-benzyls than the *N*-(2-methoxybenzyl) moiety, as the average CL_{int} for the two series is 9 and 17 L/kg/h respectively. This is visualized in Fig. 6, wherein the CL_{int} from Table 1 is shown with the values normalized to the CL_{int} for the parent 2C-X.

For the 2,5-dimethoxylated 2C-Xs there appears to be a soft spot in the 4 position (with compound **10a** having a clearance of 8.87 L/kg/h) that can be blocked by a wide range of substituents to yield metabolically stable and thereby orally active compounds. 4-thioethyl-2,5-dimethoxy (**3b** and **3c**) is the most labile motif (followed by the

other 4-thioalkylated *N*-benzyls—**6b** and **6c**), and exhibits the largest relative fold change in clearance from 2C-X to corresponding *N*-benzyl.

Conclusion

The *N*-benzyls are the most recent class of 5-HT_{2A} agonists and are being used with increasing frequency as tools in neurochemical research and as recreational drugs. This work represents the first comparative pharmacokinetic profiling and SAR of this chemotype, and reveals an obstacle in developing *N*-benzyls into compounds with clinical applications: high intrinsic clearance. We are currently trying to establish the identity of metabolites in order to circumvent this issue. In conclusion, the metabolic liability of the *N*-benzyls remains a big challenge that has to be addressed before a selective 5-HT_{2A} agonist for clinical applications can be developed from this compound class.

Furthermore, the seemingly unpredictable metabolic profile of the *N*-benzyls serves as further warning to recreational users. Fatalities linked to the use of these very potent substances may partly be explained by the differences in the metabolism from individual to individual.

Methods

All of the tested ligands were prepared as previously described from the known phenethylamines (2C-Xs) and the corresponding commercially available aldehydes [16].

Microsomal Stability Determination

Microsomal intrinsic clearance was determined by assessing the depletion of test compound over time. The test compounds were incubated at 1 μM with human liver microsomes (0.5 mg/mL; Xenotech) for 60 min, using NADPH (2 mM) as cofactor. Immediately prior to incubation, the microsomes and NADPH stock solutions were prepared. The microsomes were thawed at room temperature and diluted with potassium phosphate buffer (100 mM, pH 7.4) to a concentration of 0.6 mg/mL. A 6.25 mM NADPH stock solution was prepared by dissolving NADPH (Sigma Aldrich) in potassium phosphate buffer (100 mM, pH 7.4). Using a liquid handling robot (Hamilton Robotics) the compounds were individually mixed with microsomes and allowed to pre-incubate for 10 min. The reaction was started by addition of NADPH to the reaction mixtures. The reaction was stopped at 0, 5, 15, 30, 45 and 60 min, by adding 25 μL aliquots from the reaction mixtures to 150 μL ice cold acetonitrile. The samples were centrifuged at 1,960*g* (3,300 RPM, 4 °C; Haereus) followed by transfer of 100 μL of the supernatants to an equal amount of water, before being analyzed using liquid chromatography (Acquity UPLC, Waters) coupled to a tandem mass spectrometer (API4000, AB Sciex). The intrinsic clearances were calculated from the slope (k) of the linear regressions of percentages of compound remaining in incubation against incubation time. $CL_{int} = (0.693/T½) \times$ (mL incubation/mg microsomal protein) where $T½ = 0.693/k$.

Conflict of interest The authors declare no conflict of interest associated with the present study.

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