A Novel Synthetic Route Towards Acyloxymethyl Prodrugs of Psilocin and Related Tryptamines

Judith Stirn, Christian D. Klein*

Medicinal Chemistry, Institute of Pharmacy and Molecular Biotechnology IPMB, Heidelberg University, Im Neuenheimer Feld 364, D-69120 Heidelberg, Germany

*Email: c.klein@uni-heidelberg.de

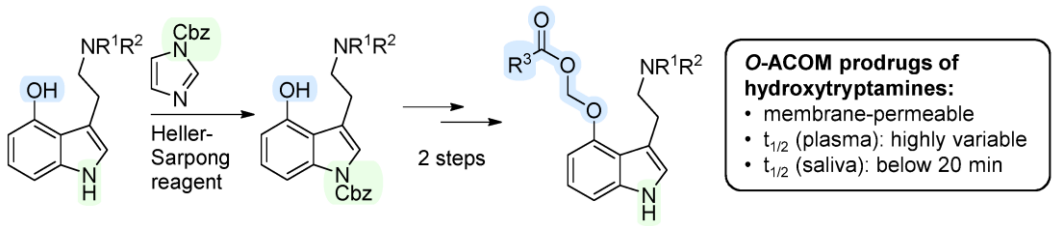
ORCIDs:

Judith Stirn orcid.org/0009-0007-9105-3894

Christian D. Klein orcid.org/0000-0003-3522-9182

Acyloxymethyl (ACOM) ethers of hydroxytryptamines such as psilocin are potential prodrugs for the psychedelic treatment of mental disorders. Previous synthetic approaches suffer from insufficient selectivity and very low yields. We report a novel synthetic route towards ACOM derivatives of tryptamines, including the chemoselective installation of a carbamate protecting group at the indole nitrogen by means of a Heller-Sarpong reagent and final deprotection under extremely mild conditions. This enables delicate transformations such as the *O*-acyloxymethylation of hydroxytryptamines or the N^2-acyloxymethylation of sumatriptan. Several *O*-ACOM ethers of hydroxytryptamines have thus been obtained and their membrane permeability and stability in various media including human saliva and plasma were studied. The pharmacokinetic profile of the ACOM ethers is governed by the steric bulk of the acyl moiety. Short half-lives in human saliva will likely preclude the sublingual or buccal application of ACOM ethers of hydroxytryptamines, while other routes of administration may be pursued.

Graphical Abstract



Keywords

Psilocin, sumatriptan, acyloxymethylation, prodrugs, Heller-Sarpong reagent, in-vitro pharmacokinetic profiling

Main Text

Tryptamines such as sumatriptan and psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine) are of considerable interest in medicinal chemistry. Psilocin is currently under evaluation in multiple clinical trials for the treatment of depressive disorders (e.g. NCT04670081, NCT05624268) in the form of its highly polar phosphate ester prodrug psilocybin.[1] Administration routes of these tryptamines beyond the classical peroral or intravenous mode can be used in several areas of application to implement an optimized therapy, such as nasal sprays of triptans for the acute treatment of migraine.[2, 3]

However, the suitability of tryptamine drugs for this application route is variable, and highly polar tryptamines such as psilocybin are incompatible with intranasal or sublingual administration. Therefore, tryptamine prodrugs with an improved passive membrane permeation profile are of great interest for therapeutic applications. The lipophilic promoiety of such prodrugs may be further tailored to the target pharmacokinetic profile and to increase shelf life, thus providing additional benefits compared to the parent drug.[4, 5]

Recently, acyloxymethyl (ACOM) derivatives of tryptamines have been pursued for this purpose. These include N^1-ACOM derivatives of sumatriptan[6] and psilocin[7, 8] as well as *O*-ACOM derivatives of psilocin[7-10] and psilocybin[8]. N^1-ACOM derivatives of tryptamines are synthetically easier to access but form rather stable N^1-hydroxymethyl intermediates, which may significantly retard the release of the parent drug.[6, 11] Besides pH and temperature of the medium, the pK_a of the parent NH group plays a pivotal role for the rate of *N*-hydroxymethyl self-immolation.[12] According to the structure-reactivity relationship established by Bundgaard and Johansen, *N*-hydroxymethyl intermediates self-immolate with a half-life of less than one hour under physiological conditions (pH 7.4, 37°C), provided that the pK_a of the parent NH group is below 13. The NH group of indole has a pK_a of around 17 (in water).[13] Thus, a half-life of several days may be predicted for N^1-hydroxymethyl derivatives of tryptamines under physiological conditions. Consequently, we decided to focus on N^1-unsubstitued ACOM derivatives which we expected to display a more favorable pharmacokinetic profile. In the present work, we successfully addressed the challenging synthesis of N^1-unsubstitued ACOM derivatives of tryptamines using 4-hydroxytryptamines including psilocin as model drugs. With respect to the significant first pass effect of psilocybin after peroral administration,[14] lipophilic psilocin prodrugs such as *O*-ACOM ethers may constitute a promising new avenue for clinical development in psychiatric medicine.

ACOM ether prodrugs of psilocin **1** and its congeners are difficult to access synthetically due to (1) the presence of three (pro)nucleophilic sites in psilocin (indole nitrogen, aliphatic amino group, phenolic hydroxy group); (2) the presence of two electrophilic sites in the commonly used halogenomethyl carboxylate reagents (ester moiety, chloromethyl moiety)[15, 16]; and (3) the lability of the acetal linker.[17] As a consequence, the yield of such transformations is

generally low. For example, the *O*-pivaloyloxymethyl derivative of psilocin **2** has been obtained with a 2–3 % yield by reaction with a halogenomethyl pivalate (Figure 1).[7, 8] For the structurally closely related sumatriptane, the acyloxymethylation of the sulfonamide sidechain failed entirely, likely due to a lack of chemoselectivity.[6]

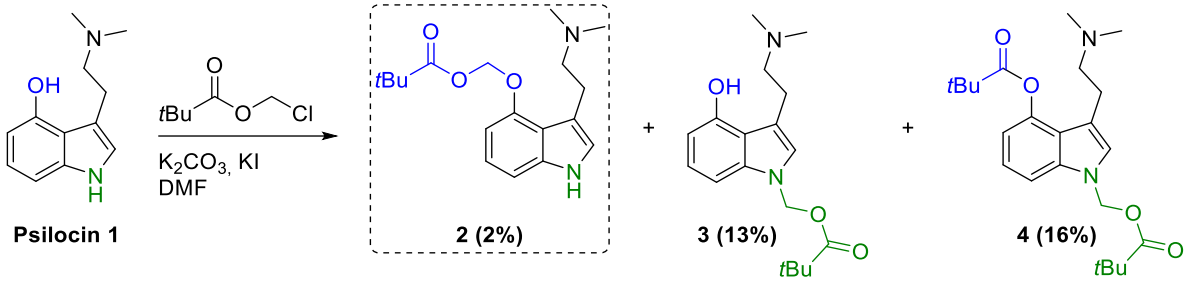


Figure 1: *Product spectrum obtained by direct acyloxymethylation of psilocin along with isolated yields. The targeted product is framed with a dashed line.*[8]

Considering the detrimental reactivity of the indole nitrogen towards halogenomethyl carboxylates (Figure 1), we set out to improve the synthetic accessibility of *O*-ACOM derivatives of psilocin. Due to legal restrictions, we carried out the entire synthetic optimization using the closely related tryptamine **5** (4-HO-MET).

With respect to a comparative evaluation of various prodrugs, the modular assembly of the ACOM promoiety would be very attractive. Such a strategy has already proven advantageous for the synthesis of a library comprising ACOM ether fluorescein derivatives, which sparked our interest in the *O*-chloromethyl ether **7** as versatile synthetic intermediate (Figure 2A).[18] Despite various attempted syntheses, compound **7** remained elusive, presumably due to chemical instability and/or a lack of chemoselectivity. In addition, the reaction of **5** with iodomethyl pivalate failed (not shown), which is in line with the minuscule yield reported for the closely related pivaloyloxymethyl ether of psilocin **2**.[7, 8]

Aiming to reduce the number of (pro)nucleophilic sites and thus potential side reactions, we devised a concise protecting group strategy for the *O*-acyloxymethylation of psilocin and related indole alkaloids. Initially, we opted for *N*-protection of the glyoxylamide **9** which is a synthetic precursor of **5** (Figure 2B). However, subsequent reduction with $LiAlH_4$ failed to afford the targeted tryptamine **11** in an isolable amount, likely because the protecting group precludes the involvement of the indole nitrogen in the reduction of the β-hydroxy intermediate, which is considered the rate-limiting step.[19]

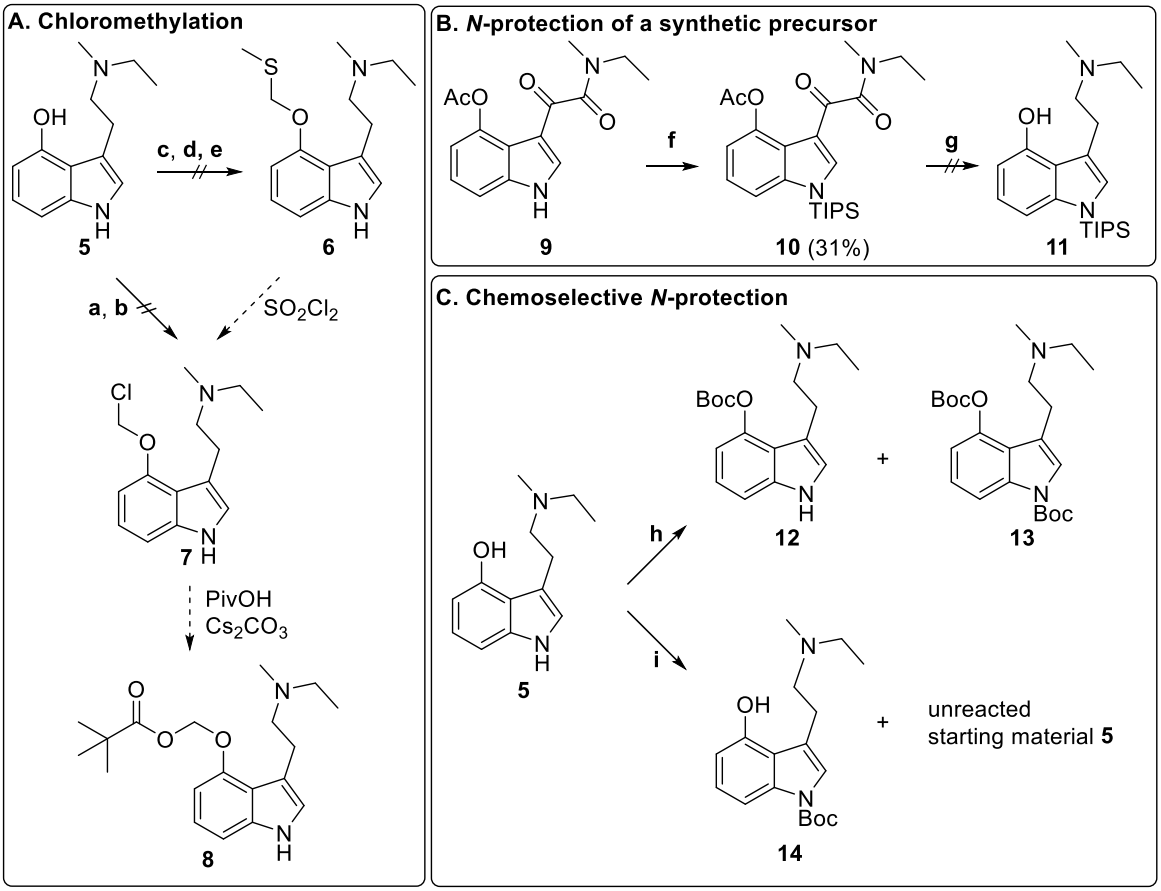


Figure 2: *Discarded approaches to an improved acyloxymethylation procedure. Reaction conditions:* ***a.*** *Ar, THF, 60–65°C 1) 2.00 eq NaOH, 1 h; 2) 30.0–90.0 eq CH_2BrCl, 2–3 h;* ***b.*** *DME 1) 1.05 eq NaH, 0°C, 15 min; 2) 5.00 eq ICH_2Cl, 0°C – rt, 20 h; 3) 80°C, 3.5 h;* ***c.*** *1.10 eq Ag_2O, 1.10 eq $MeSCH_2Cl$, Ar, MeCN, rt, 17 h;* ***d.*** *DMF 1) 1.20 eq NaH, 0°C, 30 min; 2) 1.20 eq $MeSCH_2Cl$, 0°C – rt, 12 h;* ***e.*** *1.10 eq AgOTf, 1.10 eq $MeSCH_2Cl$, Ar, MeCN, rt, 2 h;* ***f.*** *THF 1) 1.10 eq LiHMDS, 0°C, 15 min; 2) 1.20 eq TIPSCl, 0°C – rt, 2 h;* ***g.*** *3.20 eq $LiAlH_4$, 2-Me-THF, 80°C, 4–40 h;* ***h.*** *0.20 eq DMAP, 1.02 eq Boc_2O, DCM/NEt_3 (11:1), rt, 3 h;* ***i.*** *1.10 eq 1-Boc-imidazole, 0.50 eq DBU, MeCN, rt, 24 h.*

Consequently, we focused on the chemoselective *N*-protection of psilocin. The reaction with di-*tert*-butyldicarbonate[20] led to preferential *O*-substitution (Figure 2C, h). Under thermodynamic control, however, the indole nitrogen is chemoselectively acylated by Heller-Sarpong reagents (1*H*-imidazole-1-carboxylates). As demonstrated by Heller *et al.*, the acyl transfer reaction is reversible in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and imidazole, resulting in the formation of the thermodynamically most stable, N^1-substituted product.[21] Upon reaction of **5** with 1-Boc-imidazole (Figure 2C, i), we observed the slow formation of **14** (c.f. SI, Figures 6 and 7), which we confirmed by its isolation from the not yet equilibrated reaction mixture after a reaction time of 24 h. While equilibration using 1-Boc-imidazole was slow, likely due to steric hindrance, 1-Cbz-imidazole proved to be a suitable reagent to achieve prompt *N*-protection of 4-hydroxyindoles **1** and **5** under mild conditions (Figure 3).

The obtained carbamates **15** and **16** were allowed to react with selected iodomethyl carboxylates. These are easily accessible from commercially available chloromethyl carboxylates by a Finkelstein reaction[22, 23] and were obtained in excellent yield as analytically pure colorless oils after aqueous workup of the reaction mixture. Several methods were tested for purifying the crude product obtained by reacting iodomethyl carboxylates with carbamates **15** and **16**. Column chromatography using silica (EtOAc/MeOH gradient, 1% TEA) and Florisil (Cyclohexane/EtOAc gradient and EtOAc/ACN gradient) as stationary phases failed to afford the pure product. However, RP chromatography on a C-18 column using an ACN/H_2O (+0.1% TFA) gradient was found to yield the targeted products as trifluoroacetates. The salt form was not converted into the free base as protonation of the amino group was considered advantageous for the subsequent Pd-catalyzed hydrogenolysis of the carbamate moiety. Indeed, no reaction occurred when the crude product obtained in the acyloxymethylation step was directly subjected to hydrogenolysis in ethyl acetate supplemented with 0.1% acetic acid. To the contrary, the HPLC-pure tryptammonium trifluoroacetates **17**-**20** did not poison the catalyst and were quantitatively deprotected within a few hours. This suggests that quantitative protonation of the tertiary amino group by a strong acid is pivotal for an efficient Pd-catalyzed deprotection of *N*-Cbz tryptamines. In order to rule out palladium contamination of the final product, the deprotected TFA salts were subjected to HPLC purification. Basic aqueous workup of the eluted product fractions yielded the free bases of the ACOM ether prodrugs **2**, **8**, **21** and **22** as viscous oils. Notably, the sequence of *N*-Cbz protection, acyloxymethylation, and hydrogenolysis (Figure 3) afforded **2** with a more than 6-fold higher yield than the direct acyloxymethylation of psilocin (Figure **1**), which demonstrates the utility of our synthetic methodology.

The free bases of the ACOM ether prodrugs **2**, **8**, **21** and **22** were finally precipitated from acetone as pharmaceutically acceptable tryptammonium fumarates (2:1 stoichiometry). The corresponding fumarates **23**–**26** were obtained as colorless, free-flowing solids which are more suitable for handling and storage than the viscous free bases. In addition, the mesylate and hydrochloride salt forms were targeted. The mesylate **27** initially formed an oil which slowly solidified upon standing, whereas the hydrochloride remained elusive due to decomposition of **8** upon addition of HCl in diethyl ether.

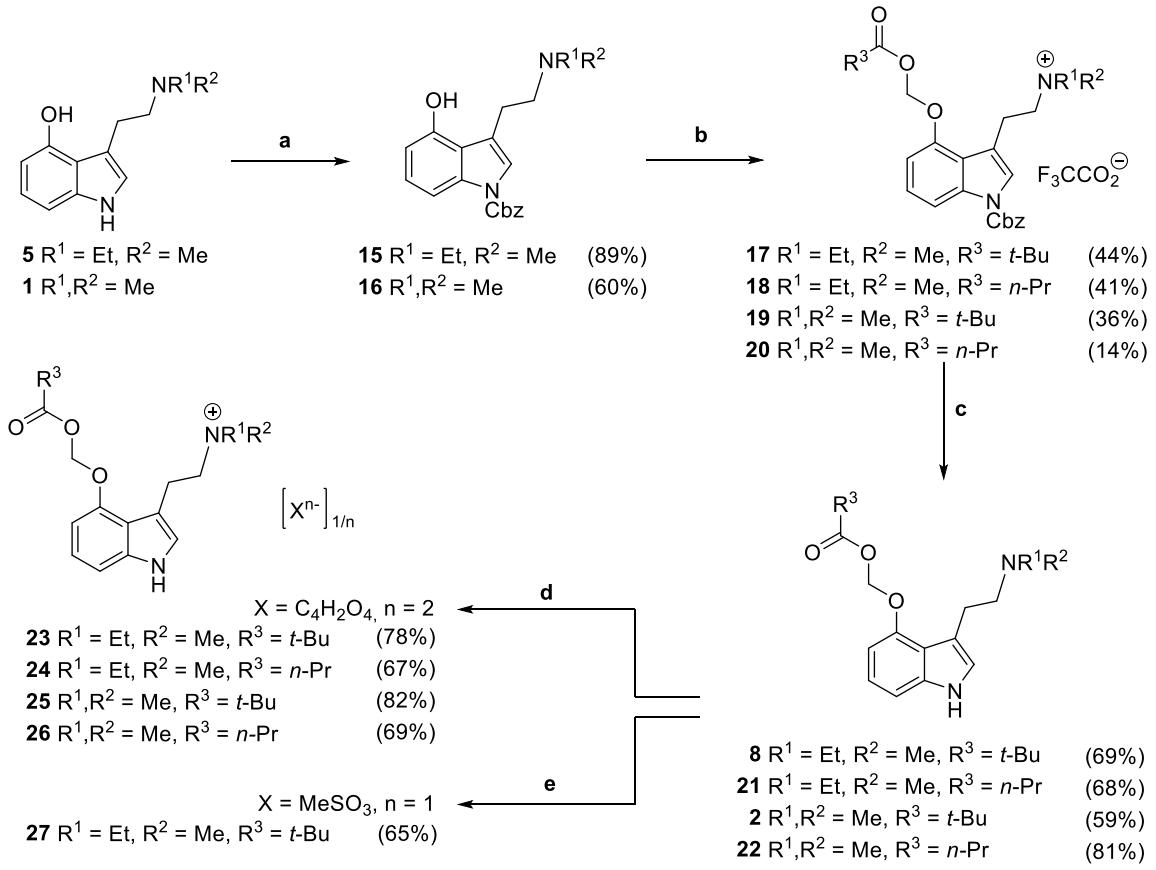


Figure 3: *Overview of the synthetic route. Reaction conditions:* ***a.*** *1.10 eq 1-Cbz-imidazole, 0.50 eq DBU, MeCN, rt, 18–26 h;* ***b.*** *DMF/THF, -50°C to rt 1) 1.50 eq NaH, 5–30 min; 2) 1.00–1.50 eq iodomethyl carboxylate, 2–5 h;* ***c.*** *1 atm H_2, 12–15 mol% Pd/C, EtOAc, rt, 4.5–16 h;* ***d.*** *0.50 eq fumaric acid, acetone, 5°C, 1.5–6 h;* ***e.*** *1) 1.00 eq $MeSO_3H$, acetone, 5°C, 2 h; 2) cyclohexane.*

In order to test the versatility of our synthetic approach, we additionally targeted the unprecedented N^2-acyloxymethyl derivatives of sumatriptan. To our delight, compound **30** was obtained without any optimization of the reaction conditions (Figure 4), which demonstrates that our concept is not limited to hydroxytryptamines.

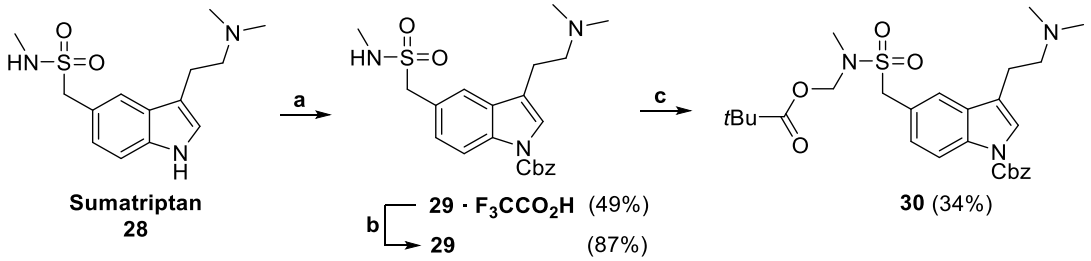
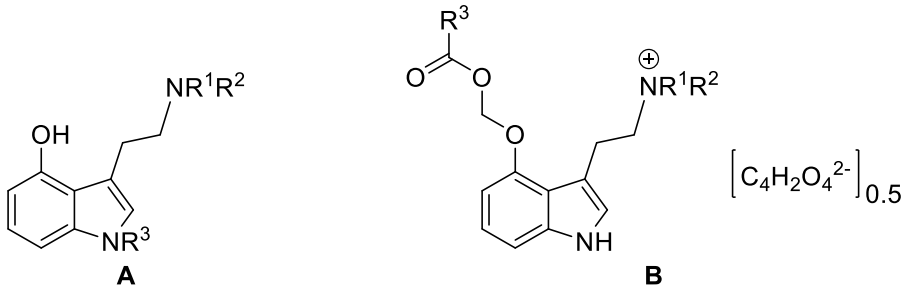


Figure 4: *N^2-acyloxymethylation of sumatriptan via our synthetic strategy.* ***a.*** *1.06 eq 1-Cbz-imidazole, 0.71 eq DBU, MeCN, rt, 40 h;* ***b.*** *$NaHCO_3$ (aq) / DCM extraction.* ***c.*** *DMF/THF, -50°C to rt 1) 2.12 eq NaH, 5 min; 2) 1.55 eq iodomethyl carboxylate, 3 h.*

The ACOM hydroxytryptamines **23**–**26** as well as the *N*-carbamates **15** and **16** prepared in our synthetic study were characterized *in vitro* to evaluate their suitability as prodrugs.

Table 1: *In-vitro* pharmacokinetic and biophysical characterization.



A **B**

Cpd.	Structure			Passive Membrane Permeability		Half-life $t_{1/2}$ [min]			
						in PBS buffer at 80°C[d]	in human saliva at 37°C[a]	in human 10% plasma at 37°C	in human 100% plasma at 37°C
	R^1	R^2	R^3	P_e [10^{-6} cm/s]	R [%]				
	A								
15	Et	Me	Cbz	n.d.	n.d.	136 ± 4	n.d.	n.d.	> 5700[c,d]
16	Me	Me	Cbz	n.d.	n.d.	184 ± 5	n.d.	n.d.	> 5700[c,d]
	B								
23	Et	Me	*t*Bu	9.7 ± 0.6	2	534 ± 12	< 20	n.d.	> 240[d]
24	Et	Me	*n*Pr	8.0 ± 0.3	6	73.3 ± 1.2	< 10	4.2 ± 0.1[c]	n.d.
25	Me	Me	*t*Bu	9.1 ± 0.5	4	458 ± 23	< 20	n.d.	> 240[c,d]
26	Me	Me	*n*Pr	8.1 ± 0.8[b]	7[b]	58.6 ± 3.5	< 10	3.5 ± 0.8[c]	0.48 ± 0.10
	References								
ASA	Acetylsalicylic acid			n.d.	n.d.	27.9 ± 0.3	> 60	n.d.	146 ± 19[e]
31	4-HO-MET·F			11 ± 1	29	n.d.	n.d.	n.d.	n.d.

[a] Mean of three measurements performed with fresh samples of three individuals. [b] Mean of six replicates. [c] No clear distinction between zero and first order kinetics possible. [d] No replicates. [e] $[ASA]_0$ = 560 µM; $t_{1/2}$ (lit.) =(130 ± 48) min.[24]

As expected, all tested prodrugs have a high propensity for passive passage across an artificial membrane at pH 7.4 (≥ $8 \cdot 10^{-6}$ cm/s). Interestingly, however, the parent compound **31** (tryptammonium fumarate salt form of **5** in 2:1 stoichiometry) had the highest membrane

permeability. The loss of the intramolecular hydrogen bond[25] between the phenolic hydroxy group and the tertiary amino group upon *O*-substitution appears to decrease the membrane permeability of the prodrugs in comparison to the parent drug. This effect is apparently not compensated by the ACOM promoiety, which in itself is not completely apolar due to the acetal and ester oxygens. The intramolecular hydrogen bond may reduce the polarity of 4-hydroxytryptamines by introducing a conformational restraint and thereby favoring conformations with a smaller polar surface area and a lower dipole moment, and by decreasing hydrogen bonding to the aqueous solvent.

In addition, the intramolecular hydrogen bond in 4-hydroxytryptamines lowers the pKa of the amine and therefore shifts the protonation equilibrium towards the neutral species. The higher proportion of the uncharged species in 4-hydroxytryptamines compared to their *O*-substituted congeners further increases the difference in passive membrane permeability.[26] It should be noted that the mass retention (R%) of **31** is remarkably high and the passive permeability reported here may therefore be inaccurate. However, the opposing effects of lipophilic *O*-derivatization and the loss of the intramolecular hydrogen bond should be taken into account in the design of novel 4-hydroxytryptamine prodrugs.

As a preliminary assessment of the drug release kinetics in the systemic blood circulation, we determined the half-lives of **15**, **16**, and **23**–**26** in pooled human plasma. Neither the *N*-carbamates **15** and **16** nor the sterically hindered pivaloyloxymethyl ethers **23** and **25** showed significant drug release in undiluted human plasma during the observation period. In contrast, half-lives below 5 minutes were observed for the ACOM ethers **24** and **26** in 10% human plasma. This illustrates that the drug release kinetics in human plasma are highly dependent upon the chosen acyl residue, which allows for tailoring the prodrug's pharmacokinetic profile to the therapeutic requirements. In order to assess the contribution of non-specific hydrolysis to the observed kinetics, we incubated the prodrugs at the same concentration in the buffer used to dilute the plasma samples. Even at 80°C, **24** and **26** were significantly more stable in buffer than in plasma, which supports the assumption of enzymatic prodrug cleavage.

Finally, we studied the stability of the compounds in human saliva. Considering the large interindividual variability of the salivary esterase activity,[27, 28] we determined the half-life of every compound in samples of resting saliva from three subjects and grouped the mean half-lives into four categories (< 10 min, 10–20 min, 20–60 min, > 60 min). In line with the literature, the stability of a given compound in human saliva varied considerably between subjects, which is illustrated in Figure 5. Despite the significant interindividual variability it is evident that the assayed acyloxymethyl ethers are extremely labile in human saliva, irrespective of their steric hindrance (Table 1). Taking into account that the half-lives were determined in resting saliva

(without prior paraffin chewing to stimulate the salivary glands) and the stability *in vivo* may thus be even lower than observed *in vitro*,[29] we consider compounds **23**–**26** and related ACOM ethers of 4-hydroxytryptamines to be unsuitable for sublingual or buccal dosage forms. It may further be anticipated that enzymatic cleavage is also detrimental to this prodrug class in the later stages of the digestive tract, and that peroral formulations of ACOM ethers will require protection from various digestive fluids.

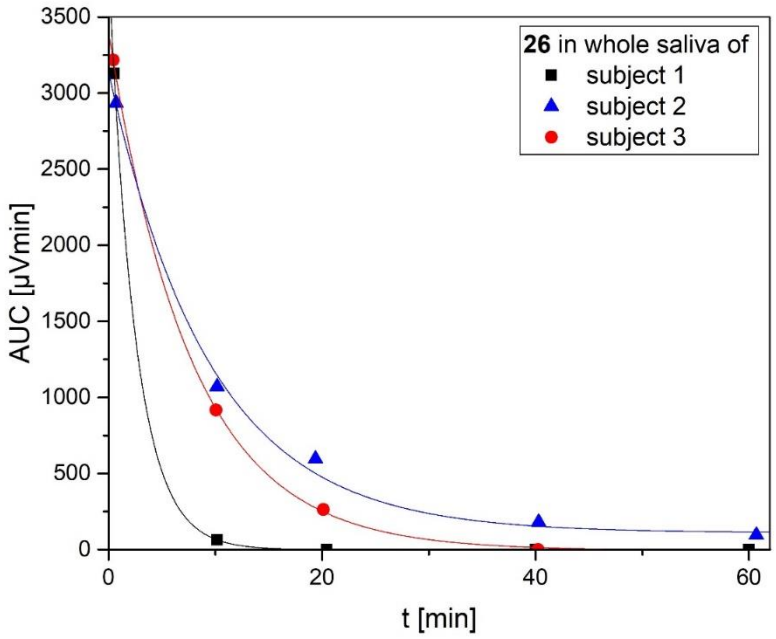


Figure 5: *Interindividual variability of the stability of prodrug **26** in human resting saliva at 37 °C depicted by plotting the analyte integral (AUC) against the sampling time. The initial prodrug concentration was 50 µM.*

In conclusion, we have developed a novel route for the acyloxymethylation of psilocin and related indole alkaloids addressing the chemoselectivity issues arising from the presence of multiple (pro)nucleophilic groups in the drug molecule. As exemplified by the N^2-acyloxymethylation of sumatriptane (sulfonamide pK_a ~ 17.5 in DMSO[30]), our strategy may be extended towards compounds where the indole NH is the only functional group with a pK_a of 19–23 (in DMSO).[21]

In addition, we and others[8, 10] have demonstrated that ACOM ethers of 4-hydroxytryptamines act as prodrugs *in vitro* and *in vivo*. The pharmacokinetic profile of these prodrugs primarily depends on the nature of the promoiety's acyl residue and to a lesser extent on the substituents of the aliphatic amino group, which qualifies 4-hydroxy-*N*-ethyl-*N*-methyltryptamine **5** as a viable model for the more strictly regulated psilocin **1**. We envision that our synthetic approach will aid further exploration of the structure-activity relationships of this prodrug class, which

should enable tailoring the pharmacokinetic profile to the requirements of a psychedelic treatment session. While the assayed ACOM ether prodrugs are likely unsuitable for sublingual administration due to their short half-lives in human saliva, other routes of administration such as peroral, intravenous, or transdermal are conceivable.

Supporting information

Experimental procedures and characterization of target compounds including ^{1}H NMR, ^{13}C NMR and ^{19}F spectra as well as detailed assay protocols are provided.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Acknowledgements

We thank Heiko Rudy for measuring ESI high resolution spectra and Tobias Timmermann for technical support and the acquisition of NMR spectra. We further appreciate the generous contribution of assay materials and the technical assistance in measuring half-lives by Dominik Mytzka and Leah Glanzmann. Dr. Stefan Hinkes and Dr. James Ayres supported this work by discussions on chemical strategies. Furthermore, Raphael Berger and Faye Howlin provided valuable suggestions during the preparation of the manuscript.

Conflict of interest

Heidelberg University has filed a patent application (EP24154403.0) covering the 4-hydroxytryptamine derivatives presented herein. The authors are named as inventors on this patent application.

Literature

1. Wang, S. M.; Kim, S.; Choi, W. S.; Lim, H. K.; Woo, Y. S.; Pae, C. U.; Bahk, W. M., Current Understanding on Psilocybin for Major Depressive Disorder: A Review Focusing on Clinical Trials. *Clin. Psychopharmacol. Neurosci.* **2024,** *22* (2), 222-231.
2. Dahlöf, C., Sumatriptan nasal spray in the acute treatment of migraine: a review of clinical studies. *Cephalalgia* **1999,** *19* (9), 769-778.
3. Tepper, S. J.; Chen, S.; Reidenbach, F.; Rapoport, A. M., Intranasal Zolmitriptan for the Treatment of Acute Migraine. *Headache* **2013,** *53* (S2), 62-71.
4. Rautio, J.; Meanwell, N. A.; Di, L.; Hageman, M. J., The expanding role of prodrugs in contemporary drug design and development. *Nat. Rev. Drug Discovery* **2018,** *17* (8), 559-587.
5. Fralish, Z.; Chen, A.; Khan, S.; Zhou, P.; Reker, D., The landscape of small-molecule prodrugs. *Nat. Rev. Drug Discovery* **2024,** *23* (5), 365-380.
6. Rodrigues, T.; Moreira, R.; Guedes, R. C.; Iley, J.; Lopes, F., Unanticipated Acyloxymethylation of Sumatriptan Indole Nitrogen Atom and its Implications in Prodrug Design. *Arch. Pharm.* **2008,** *341* (6), 344-350.
7. O'Meara, J.; Kaur, H.; Ali, A. M. Acetal, ketal, and hemiaminal analogs of psilocin, processes for the preparation thereof, and methods of use. WO 2024/081962 A2, 2024.
8. Clark, S.; Duncton, M. A. J. Prodrugs and derivatives of psilocin and uses thereof. WO 2023023347 A1, 2023.
9. Matinkhoo, K.; Press, D. J.; Cai, Y.; Jensen, G. E.; Lee, J. B.-J.; Hagel, J. M.; Facchini, P. J. C4-substituted tryptamine derivatives and methods of using. WO 2023173227 A1, 2023.
10. Raithatha, S. A.; Hagel, J. M.; Matinkhoo, K.; Yu, L.; Press, D.; Cook, S. G.; Sharma, G.; Dhananjaya, D.; Jensen, G.; Lee, J. B.; Cai, C.; Gallant, J.; Bains, J.; Tucker, J. E.; Facchini, P. J., Novel Psilocin Prodrugs with Altered Pharmacological Properties as Candidate Therapies for Treatment-Resistant Anxiety Disorders. *J. Med. Chem.* **2023**.
11. Zhu, Z.; Chen, H.-G.; Goel, O. P.; Chan, O. H.; Stilgenbauer, L. A.; Stewart, B. H., Phosphate prodrugs of PD154075. *Bioorg. Med. Chem. Lett.* **2000,** *10* (10), 1121-1124.
12. Bundgaard, H.; Johansen, M., Hydrolysis of N-(α-hydroxybenzyl)benzamide and other N-(α-hydroxyalkyl) amide derivatives: implications for the design of N-acyloxyalkyl-type prodrugs. *Int. J. Pharm.* **1984,** *22* (1), 45-56.
13. Sundberg, R. J.; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. S., Chapter 9. In *Indoles*, Elsevier Science: 1996.
14. Hasler, F.; Bourquin, D.; Brenneisen, R.; Bär, T.; Vollenweider, F. X., Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. *Pharm. Acta Helv.* **1997,** *72* (3), 175-184.
15. Sloan, K. B.; Koch, S. A. M., Reaction of (acyloxy)alkyl .alpha.-halides with phenols: effect of nucleofugicity and nucleophilicity on product distribution. *J. Org. Chem.* **1983,** *48* (21), 3777-3783.
16. Thomas, J. D.; Sloan, K. B., Reaction of alkylcarbonyloxymethyl halides with phenols: reevaluating the influence of steric hindrance. *Tetrahedron Lett.* **2006,** *47* (49), 8785-8787.
17. Robinson, R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooper, K.; Cronin, B. J.; Destito, R.; Donahue, K. M.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kuperman, A. V.; Liston, T. E.; Malloy, D.; Martin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F., Discovery of the Hemifumarate and (α-l-Alanyloxy)methyl Ether as Prodrugs of an Antirheumatic Oxindole: Prodrugs for the Enolic OH Group. *J. Med. Chem.* **1996,** *39* (1), 10-18.
18. Bassett, B.; Waibel, B.; White, A.; Hansen, H.; Stephens, D.; Koelper, A.; Larsen, E. M.; Kim, C.; Glanzer, A.; Lavis, L. D.; Hoops, G. C.; Johnson, R. J., Measuring the Global Substrate Specificity of Mycobacterial Serine Hydrolases Using a Library of Fluorogenic Ester Substrates. *ACS Infect. Dis.* **2018,** *4* (6), 904-911.
19. Sherwood, A. M.; Meisenheimer, P.; Tarpley, G.; Kargbo, R. B., An Improved, Practical, and Scalable Five-Step Synthesis of Psilocybin. *Synthesis* **2020,** *52* (05), 688-694.

20. Yamada, F.; Tamura, M.; Hasegawa, A.; Somei, M., Synthetic Studies of Psilocin Analogs Having Either a Formyl Group or Bromine Atom at the 5- or 7-Position. *Chem. Pharm. Bull.* **2002,** *50* (1), 92-99.
21. Heller, S. T.; Schultz, E. E.; Sarpong, R., Chemoselective N-Acylation of Indoles and Oxazolidinones with Carbonylazoles. *Angew. Chem., Int. Ed.* **2012,** *51* (33), 8304-8308.
22. Bandgar, B. P.; Sarangdhar, R. J.; Viswakarma, S.; Ahamed, F. A., Synthesis and Biological Evaluation of Orally Active Prodrugs of Indomethacin. *J. Med. Chem.* **2011,** *54* (5), 1191-1201.
23. Jones, D. J.; O'Leary, E. M.; O'Sullivan, T. P., An improved synthesis of adefovir and related analogues. *Beilstein J. Org. Chem.* **2019,** *15*, 801-810.
24. Harthon, L.; Hedström, M., Hydrolysis of Salicylsalicylic Acid in Human Blood and Plasma: A Comparison with Acetylsalicylic Acid. *Acta Pharmacol. Toxicol.* **1971,** *29* (4), 155-163.
25. Lenz, C.; Dörner, S.; Trottmann, F.; Hertweck, C.; Sherwood, A.; Hoffmeister, D., Assessment of Bioactivity-Modulating Pseudo-Ring Formation in Psilocin and Related Tryptamines. *ChemBioChem* **2022,** *23* (13), e202200183.
26. Migliaccio, G. P.; Shieh, T.-L. N.; Byrn, S. R.; Hathaway, B. A.; Nichols, D. E., Comparison of solution conformational preferences for the hallucinogens bufotenin and psilocin using 360-MHz proton NMR spectroscopy. *J. Med. Chem.* **1981,** *24* (2), 206-209.
27. Finer, Y.; Santerre, J. P., Salivary Esterase Activity and Its Association with the Biodegradation of Dental Composites. *J. Dent. Res.* **2004,** *83* (1), 22-26.
28. María, P.-J.; Carolina, M.-G.; María Ángeles, P.-B., Understanding human salivary esterase activity and its variation under wine consumption conditions. *RSC Adv.* **2020,** *10* (41), 24352-24361.
29. Hansen, L. B.; Christrup, L. L.; Bundgaard, H., Saliva-catalyzed hydrolysis of a ketobemidone ester prodrug: Factors influencing human salivary esterase activity. *Int. J. Pharm.* **1992,** *88* (1), 221-227.
30. Bordwell, F. G., Equilibrium acidities in dimethyl sulfoxide solution. *Acc. Chem. Res.* **1988,** *21* (12), 456-463.