RSC Medicinal Chemistry

ROYAL SOCIETY OF CHEMISTRY

RESEARCH ARTICLE

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Cite this: *RSC Med. Chem.*, 2025, **16**, 367

Continuous flow synthesis of *N*,*N*-dimethyltryptamine (DMT) analogues with therapeutic potential†

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Received 18th July 2024,
Accepted 6th October 2024

DOI: 10.1039/d4md00562g

rsc.li/medchem

Herein, we describe the continuous flow synthesis and in-line extraction of *N*,*N*-dimethyltryptamine (DMT) and several of its analogues using a Fischer indole reaction, along with a larger gram scale synthesis (4.75 g) of the model compound. These products could then be quickly transformed into their respective fumarate salts, making them easier to handle and stable for long time storage using a straightforward batch procedure. Additionally, the commercially available drug rizatriptan benzoate could be synthesised with high purity using this setup. The presented method employs relatively green solvents both for the synthesis and purification of the target products.

Introduction

Major depressive disorder (MDD) is a debilitating neuropsychiatric disorder that comes at a high cost for patients and society, resulting in a significant health care cost, productivity decrease and unemployment burden. MDD has been associated with high prevalence estimates and high rates of morbidity and mortality.[1] The World Health Organization (WHO) estimates the number of people living with depression to be 322 million.[2] This number has been further increased by the COVID-19 pandemic by a reported 27.6% compared to pre-pandemic levels,[3] making it an absolute priority to find effective and affordable treatments for patients dealing with this disorder.

Currently, the majority of prescribed antidepressants act by inhibiting the synaptic uptake of serotonin (SRIs), norepinephrine (NRIs) or both (SNRIs). However, these treatments are known to only reduce symptoms in about two thirds of patients, with half of these eventually exhibiting full remission and the remaining one third of patients not responding to these drugs at all, which is known as treatment-resistant depression (TRD).[4] An often overlooked fact is that even if the drugs have the desired effect, it generally has a slow onset and requires weeks to achieve a full treatment response. The detrimental effect of this delay is not to be underestimated. If a patient is forced to wait every time for symptom relief to occur, changing therapies or switching to another antidepressant can cause a significant delay in their treatment. This leaves the patient vulnerable to well-being issues, including the possibility of suicide.[4] Certain classes of antidepressants such as benzodiazepines are well documented to cause side effects and withdrawal symptoms. Therefore, there is a widely recognized urgency to finding alternatives to the commonly used, yet suboptimal, first-line antidepressants.[5]

After decades of tightened pharmaceutical regulations in the 1960s and 70s on hallucinogens[6] such as psilocybin, DMT, LSD, ketamine and MDMA, these compounds have gained renewed interest as potential candidates for the treatment of psychiatric disorders in recent years.[7] A standout example of this is the recent regulatory approval for intranasal administration of esketamine in conjunction with a conventional antidepressant for adults suffering from treatment resistant depression (TRD).[8] Additionally, increasing research is indicating a favorable effect of these psychoactive substances not only in the treatment of depression, but also post-traumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), cluster headaches, end of life pain and anxiety-related disorders.[7] Contrary to the earlier described conventional methods, it has been observed that a single exposure to one of these hallucinogenic agents can elicit an instantaneous and lasting improvement in symptoms for the patient. Some results last even long after the drug has been metabolized and excreted from the body.[7a,9] The biological effects produced by these psychedelics are mediated by the serotonergic 5-$HT_{1A/2A}$ receptors, which are present in the central and peripheral nervous system.[4,7a]

A common structural motif which is easily recognized in the structures of LSD (**2**), psilocybin (**3**), *N*,*N*-

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† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4md00562g

dimethyltryptamine (DMT) (**4**) and even commercial drugs such as sumatriptan (**5**) and rizatriptan (**14**) is that of tryptamine (**1**) (Fig. 1). Indeed, several naturally occurring tryptamines such as (nor)baeocystine, 5-MeO-DMT, 5-Br-DMT and others have been found to be effective agonists of the 5-HT receptors and can be found in low concentrations in mushrooms, toads and marine sponges, respectively.[10] Evaluating these different derivatives and their potency, time of metabolization, duration of therapeutic effect and diverse receptor subtype selectivity can help to identify a prime target for clinical development.[10c] In particular *N*,*N*-dimethyltryptamine (DMT) and its derivative 5-MeO DMT have received favorable attention recently in biological studies and, as a result, these compounds are currently being evaluated in a number of clinical trials.[11] To allow for these aforementioned trials to occur, suitable synthesis methods to deliver these compounds in high purity are in demand. A recent example in the literature has described the preparation of 5-MeO DMT in high purity, using a Fischer indole synthesis route.[10c]

Results and discussion

In order to further optimize the synthesis and throughput of this class of compounds in a scalable and safe manner, we were curious to investigate whether their synthesis is possible using continuous flow chemistry. This technology is praised for enabling an automated execution of one- or multi-step processes with high control over reaction parameters (*e.g.* temperature, pressure and residence time). The superior heat and mass transfer helps to reduce reaction time and increase yield and selectivity. Moreover, the consistency of the flowing reaction mixture can be monitored continuously, ensuring a constant and high quality of the eluting product. Finally, due to the small volume of reagents which are present in the reactor at any given time, safe handling of hazardous chemicals is possible.[12] Considering the acid catalyzed nature of the Fischer indole reaction, this is especially interesting. In the literature a number of reports describing a Fischer indole reaction in flow can be found, using a range of different catalysts such as acetic acid,[13] amberlite resins,[14] ionic liquids[15] or under microwave irradiation.[16] However to the best of our knowledge, no flow synthesis of hallucinogenic tryptamines has been published.

Finally, in order to prevent oxidation towards the respective *N*-oxides, a known degradation product of these compounds,[17] the fumarate salts of these products can be made to ensure stability for longer time storage under air. Fumarate is among the most common counterions used in basic chemical entities for the past 20 years and often used for tryptamine derivatives.[18]

Initially, we sought to optimize a Fischer indole reaction between two readily available starting products, phenylhydrazine hydrochloride and 4-(dimethylamino) butyraldehyde diethyl acetal, in an attempt to form *N*,*N*-dimethyltryptamine (**4**).‡ Inspired by a similar batch procedure used to synthesize high purity 5-MeO DMT,[10c] the initial conditions were chosen as follows: 40 °C and 1 eq. of sulfuric acid (entry 1, Table 1). However, when analyzing the ^{1}H NMR spectra obtained from this mixture, a peak commonly associated with an imine proton was observed. Together with the mass obtained from LC-MS analysis (M + H: 206 *m*/*z*), this data seemed to suggest that our reaction stalled at the intermediate hydrazone (**7**). In order to push the reactions towards cyclization, the temperature was increased significantly towards 120 °C. Consequently, this meant that we added a back-pressure regulator at the end of our flow setup to ensure proper mixing of the reaction stream without the formation of gas bubbles. We also added acetonitrile to the mixture as a co-solvent, considering prior literature[10c] had found that this could help to push the conversion. To our delight, the desired indole product was now formed and was present in the reaction mixture, albeit still only in 38% (entry 2, Table 1). Next, we opted to work with a fixed 5 %m concentration of sulfuric acid, instead of 1 equivalent, which pushed the reaction further toward 62% DMT (entry 3, Table 1). Further tuning of the temperature and residence time eventually allowed us to achieve a full conversion at 140 °C for 10 minutes (entry 6, Table 1). Using these same conditions but omitting the use of a co-solvent still allowed for a full conversion using only water as a green and sustainable solvent (entry 7) (Table 1).

When a full conversion was successfully achieved, we aimed to integrate the purification into the continuous setup. In batch, the work-up consisted of a basification with a 25% NaOH solution followed by extraction with ethyl acetate. After evaporation of the solvent, the pure freebase was obtained in excellent yield (97–99%). In order to make this process fully continuous, we made use of a continuous liquid–liquid

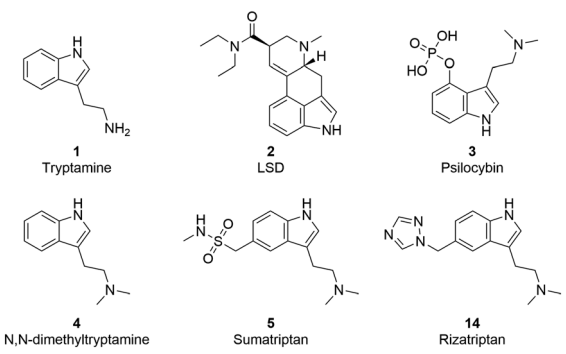
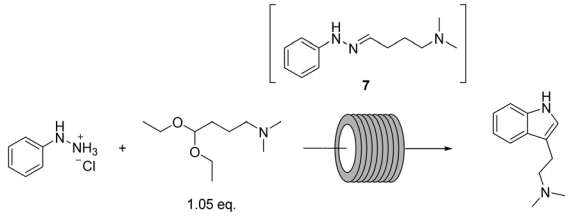


Fig. 1 Notable psychedelic compounds containing a tryptamine motif.

‡ Some of the products synthesized during this research are under strict regulation by government entities (*N*,*N*-dimethyltryptamine, 5-MeO-*N*,*N*-dimethyltryptamine), due to their psychotropic nature and consequent possibility for abuse. In order to perform this work, a license was obtained from the local authorities (No. 440032, FAGG, Belgium). We advise anyone who would replicate the experiments described herein, to first research their local legislature and to acquire the necessary permits. Some of the chemicals presented in this work are potent hallucinogens and should be handled with care.

Table 1 Optimization of the Fischer indole reaction in flow



Entry	Temp (°C)	H_2SO_4	Resid. Time[d] (min)	Solvent	4[b] : 7 (%)
1[a]	40	1 eq. (<1%)	10	Water	0 : 100
2[a]	120	1 eq. (<1%)	5	CH_3CN/water[a]	38 : 62
3	120	5%	5	CH_3CN/water	62 : 38
4	120	5%	10	CH_3CN/water	90 : 10
5	140	5%	5	CH_3CN/water	94 : 6
6	140	5%	10	CH_3CN/water	100 : 0
7	140	5%	10	Water	100[c] : 0

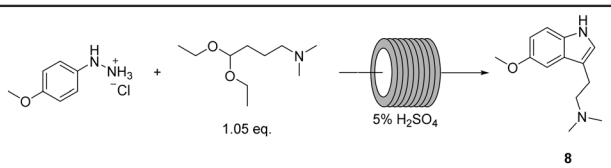
[a] 1/1 ratio of acetonitrile and water. [b] Evaluated through ^{1}H-NMR. [c] Freebase obtained in near quantitative yield after extraction (97–99%). [d] Internal volume of the reactor: 10 mL.

extraction device (Zaiput Flow Technologies). The reaction stream (1 ml min^{-1}) is first merged with the basic solution (25% NaOH, 1 ml min^{-1}) as well as ethyl acetate (2 ml min^{-1}) and mixed using static mixers which are placed within tubing of 2.6 mm internal diameter. Afterwards the combined streams are sent to a Zaiput device that is capable of separating these streams again, providing the organic fraction with the desired product in near quantitative yields (97–99%).

Next, we were curious to examine whether this process could be expanded to other therapeutically relevant tryptamines. As mentioned in the introduction 5-MeO-DMT has recently received significant attention in clinical trials[11] and is believed to be more potent and rapid acting than DMT itself, increasing interest in effective and scalable production methods for this compound.[10c] When the optimal conditions for DMT were applied to this derivative however, only 73% product was observed on ^{1}H-NMR (entry 1, Table 2). The starting product, 4-methoxyphenylhydrazine hydrochloride, seemed to be more poorly soluble in water. This prompted us to apply the co-solvent acetonitrile again, which helped to boost the conversion up to 90% (entry 3, Table 2). However, when reviewing the NMR data, we realized that the mixture did not contain the starting product or intermediate hydrazone this time, but rather unwanted side products. Based on literature precedent, a likely cause for these unwanted products was the formation of dimers and oligomers at these high temperatures.[10c] Therefore, we were eager to see if more mild reaction conditions could steer the reaction toward the desired indole scaffold. When the temperature was significantly lowered to 60 °C (entry 4) the mixture consisted of intermediate hydrazone and our target product (68%). Finally, the perfect balance was found when applying 100 °C, which delivered 5-MeO-DMT in full conversion (entry 5, Table 2). The continuous work-up described above was applied and the pure freebase product (**8**) could be obtained in excellent yield (98%).

The next derivative we were interested in synthesizing was 5-Br-DMT, a natural alkaloid found in marine sponges.[10b] The first trial run using the conditions (100 °C, 10 min.), which proved successful for the previous 5-MeO derivative, was not able to fully transform the starting product in this

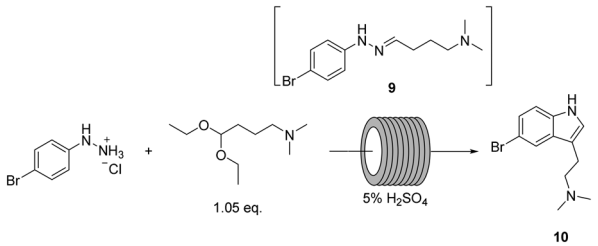
Table 2 Optimization of the flow synthesis of 5-MeO-DMT



Entry	Temp (°C)	Resid. Time[c] (min)	Solvent	**8** (%)
1	140	10	Water	73
2	140	10	CH_3CN/water	90
3	140	15	CH_3CN/water	92
4	60	10	CH_3CN/water	68[a]
5	100	10	CH_3CN/water	100[b]

[a] With 32% hydrazone (intermediate) present. [b] Continuous work-up yielded pure product (98%). [c] Internal volume of the reactor: 10 ml.

Table 3 Optimization of the flow synthesis of 5-Br-DMT



Entry	Temp (°C)	Resid. Time[b] (min)	Solvent	**10** : **9** (%)
1	100	10	CH_3CN/water	14 : 86
2	140	10	CH_3CN/water	81 : 19
3	140	15	CH_3CN/water	82 : 18
4	150	10	CH_3CN/water	96 : 4
5	160	10	CH_3CN/water	100 : 0[a]

[a] Continuous work-up yielded pure product (94%). [b] Internal volume of the reactor: 10 ml.

case and a large fraction of the intermediate hydrazone (**9**) could be observed on ^{1}H-NMR and LC-MS (entry 1, Table 3). Optimization of the reaction temperature and residence time eventually led to a complete conversion towards the desired product, applying 160 °C for 10 minutes (entry 5, Table 3). To achieve this temperature without formation of gas bubbles, a digital BPR was used which was set to a pressure of 12 bar. The final product (**10**) was obtained after continuous work-up, as the freebase, in excellent yield (94%).

Two more derivatives (**11** and **12**) were made from commercially available starting products using similar conditions (Fig. 2). The presence of fluorine atoms in therapeutic molecules has long been considered important in terms of (metabolic) stability and bioavailability.[19] These compounds (5-F and 5-Me-DMT) were successfully made with the presented flow setup, with full conversion and in good yields without the need for extensive optimization.

With an efficient synthesis method for these tryptamines now in hand, we diverted our attention to guaranteeing the longer term stability of these compounds. As briefly mentioned in the introduction, an often encountered degradation product of these compounds is the biologically inactive *N*-oxide, which forms under air, especially under heating as well as enzymatically in the body.[17] A possible solution for this is to transform the freebases to their respective organic salts. A commonly used formulation method for these compounds in recent clinical studies is the fumarate salt.[11,18] These 2 : 1 DMT : fumarate salts are easy to handle, stable solids, compared to the often sticky brown solidifying oils associated with the freebases. Dissolving the freebase products in a small amount of acetone, adding 0.5 equivalents of fumaric acid and subsequently stirring for one hour proved to be a quick and easy method to obtain these salts for all of the abovementioned derivatives. The desired products precipitate out of the acetone mixture and are easily filtered and washed to yield the high purity end products (Fig. 3).

In an attempt to reduce the amount of steps in the production process, we tried directly adding the fumaric acid to the ethyl acetate solution obtained from the continuous extraction. However, this proved to be unsuccessful and no product would precipitate from the mixture. This was most

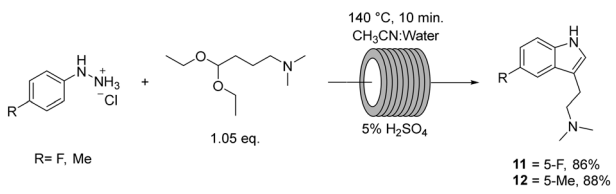


Fig. 2 Synthesis of 5-F and 5-Me-DMT derivatives in flow.

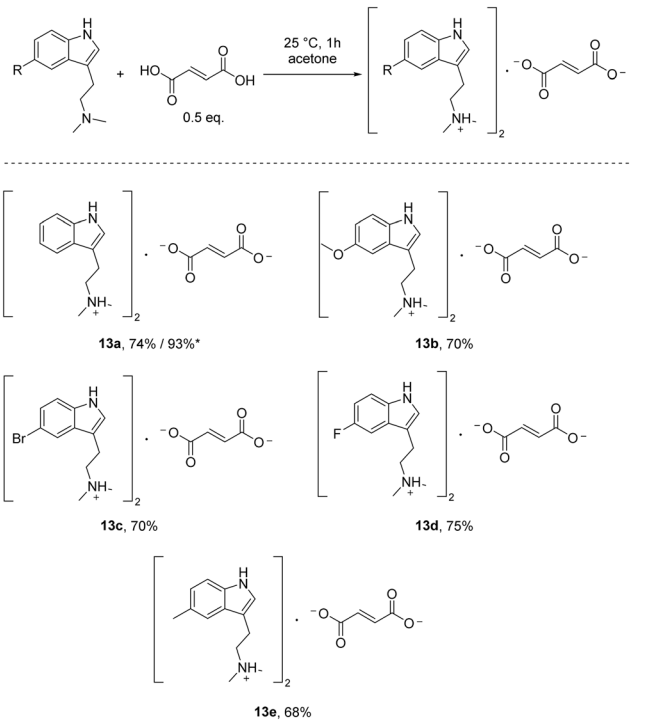


Fig. 3 Synthesis of several tryptamine fumarate salts. *Yield obtained from gram scale experiment (4.75 g).

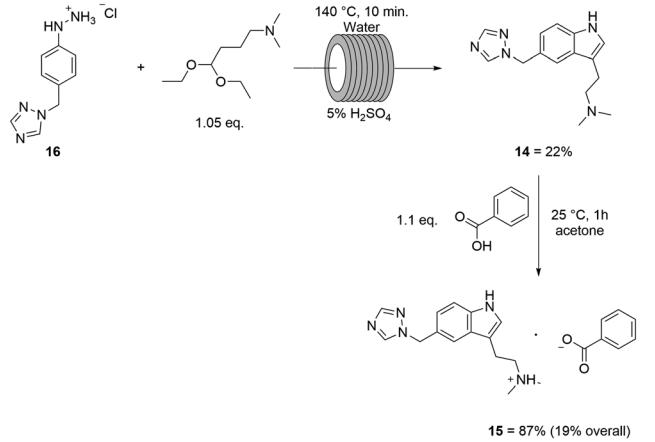


Fig. 4 Synthesis of rizatriptan benzoate/Maxalt®.

likely due to the worse solubility of fumaric acid in ethyl acetate, making the effective formation of the salts impossible.

Finally, having achieved an effective setup to obtain these therapeutically interesting tryptamines in a continuous manner, we wanted to see if it could be run for a prolonged period of time, producing a larger amount of product to demonstrate the scalability of this synthesis. In order to achieve this, the setup was run continuously for 5 hours, producing 4.75 grams of pure 2 : 1 DMT : fumarate product after subsequent salt formation in batch (93%). This larger scale production provided us with a more favourable yield of the salt compared to previous smaller scale experiments (74%). This showed us that the prior yield was mostly likely affected by our product's solubility in acetone, which caused significant losses on a smaller scale (Fig. 3).

Satisfied with our current setup we wanted to explore the possibility of using it to produce the commercially available drug rizatriptan, which is a prescription drug used against migraine headaches. In 2021, it was the 159th most prescribed drug in the United States with 3.5 million prescriptions.[20] In order to produce this compound using our setup, the commercially available 1-[(4-hydrazinophenyl) methyl]-1*H*-1,2,4-triazole hydrochloride **16** was purchased from BLD Pharmatech GmbH and used as a substrate. It should be noted that this chemical can also be made from the respective, more widely available amine through diazotisation with $NaNO_2$ followed by a reduction with sodium sulphite or stannous chloride.[21] After running the setup at 140 °C for 10 min with pure water as a solvent (Fig. 4), the resulting mixture contained predominantly the desired product (**14**, 69%), however this time requiring additional chromatographic workup to remove side products. After using an isocratic, polar mixture of 25% methanol in acetone, the desired freebase was obtained in high purity (>95%). The freebase product unfortunately incurs significant yield loss when employing silica chromatography and the rizatriptan freebase (**14**) was eventually obtained in 22% yield using these conditions. Possible further optimisation for this particular derivative might be achieved using milder temperatures with longer residence times as the patent literature for batch setups seems to point towards lower reaction temperatures.[21] However at this time we were satisfied in demonstrating the broader applicability and usefulness of our setup. In the case of rizatriptan, the freebase was converted to its benzoate salt (**15**, 87%) in a quasi-identical protocol as described earlier, given that this is the formulation available on the market (Maxalt®, MK462).

Conclusions

In the present work, we describe an easily accessible continuous flow setup to synthesize biologically active and therapeutically relevant freebase tryptamines. Purification could be achieved in a telescoped manner to deliver the target products as a freebase in nearly quantitative yields or further derivatize them towards their respective stable fumarate salts in a fast batch procedure. To demonstrate scalability, 4.75 grams (93%) of DMT fumarate was produced in a single run. The developed protocol makes use of environmentally benign solvents and could successfully be used to produce the commercial drug rizatriptan (Maxalt®).

Data availability

The data underlying this study are available in the published article and its ESI.† Raw NMR/IR data files can be provided upon request from the corresponding author.

Author contributions

Andreas Simoens: data curation, formal analysis, investigation, methodology, visualization, writing – original draft, writing – review & editing, conceptualization. Andreas Dejaegere: writing –review & editing, investigation, methodology. Marthe Vandevelde: writing – review & editing, investigation, methodology. Christian Stevens: conceptualization, project administration, supervision, validation, resources, funding acquisition, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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