molbank

MDPI

Communication

Synthesis of 2-(5-(2-Aminopropyl)-2-hydroxyphenyl)acetic Acid, a Metabolite of the Drug 5-APB

André L. Silva †, Inês Fino †, Luísa M. Ferreira * and Paula S. Branco *

Department of Chemistry, NOVA School of Science & Technolgy, Universidade NOVA Lisboa, LAQV REQUIMTE, 2829-516 Caparica, Portugal; aal.silva@campus.fct.unl.pt (A.L.S.); i.fino@campus.fct.unl.pt (I.F.)
* Correspondence: lpf@fct.unl.pt (L.M.F.); paula.branco@fct.unl.pt (P.S.B.)
† These authors contributed equally to this work.

Abstract: 5-(2-Aminopropyl)benzofuran (5-APB), also known as "Benzo Fury," is a novel psychoactive substance (NPS) belonging to a new class of synthetic phenethylamines. It acts by disrupting serotonergic circuits as a serotonin–norepinephrine–dopamine reuptake inhibitor and is classified as an entactogen, similar to MDMA and MDA. Despite its popularity among users, recent toxicity events have been associated with the consumption of 5-APB and other benzofurans, highlighting the need for a better understanding of their pharmacodynamics and toxicity. One way to achieve this is by developing the synthesis of 5-APB metabolites as biomarkers of exposure. In this study, we present a six-step synthesis for one of the 5-APB metabolites, 2-(5-(2-aminopropyl)-2-hydroxyphenyl)acetic acid (**1**), involving methylation, formylation, Aldol-type condensation, reduction, and hydrolysis reactions. The compound was obtained in an overall yield of 11%.

Keywords: reduction; Rieche formylation; hydrolysis; drug metabolite; aminopropylbenzofuran; Benzo Fury's

Citation: Silva, A.L.; Fino, I.; Ferreira, L.M.; Branco, P.S. Synthesis of 2-(5-(2-Aminopropyl)-2-hydroxyphenyl)acetic Acid, a Metabolite of the Drug 5-APB. *Molbank* **2023**, *2023*, M1629. https://doi.org/10.3390/M1629

Academic Editor: Ian R. Baxendale

Received: 29 March 2023
Revised: 18 April 2023
Accepted: 20 April 2023
Published: 23 April 2023

1. Introduction

The continuous emergence of new drugs of abuse presents a complex challenge and a serious public health problem. These substances are often marketed as "not for human consumption", but their psychoactive effects are designed to mimic those of illicit drugs. Law enforcement is constantly engaged in the hunt for drug dealers, and when a particular compound is regulated, new substitutes emerge in order to evade criminalization [1]. Benzofurans, commonly referred to as "Benzo Fury's", are a type of synthetic phenethylamine and fall under the category of novel psychoactive substances (NPSs), a rapidly growing group of designer drugs. 5-(2-Aminopropyl) benzofuran (5-APB) and 6-(2-aminopropyl) benzofuran (6-APB) were initially synthesized for research purposes [2] and made their appearance on the drug scene in 2010. These benzofurans have a similar chemical structure to MDMA (ecstasy) and MDA (Figure 1), two well-known illicit drugs [3,4]. Due to their popularity among users, reports of serious intoxication, including some fatalities, have emerged (there have been several fatal cases of the simultaneous consumption of 5-APB and 6-APB) [5–10]. Similar to MDMA and MDA, 5-APB and 6-APB are known for their entactogenic effects, which is a primary reason for their popularity among users. These substances work by blocking the monoamine transporters that are responsible for the reuptake of serotonin, norepinephrine, and dopamine, thereby inducing the release of these monoamines and disrupting the functioning of serotonergic circuits [11]. To date, there is a lack of comprehensive toxicological and clinical data regarding the effects of 5-APB and its metabolites on individuals. This lack of information is compounded by the difficulty of developing reliable detection methods. However, a recent breakthrough has been made in this area with the development of a highly sensitive method for the simultaneous detection and quantification of both 5-APB and 6-APB in human blood samples [10]. In vitro studies in primary rat hepatocytes of the two benzofurans, 6-APB and 5-APB, showed that 5-APB

displayed higher hepatotoxicity in these cellular models than its 6-isomer [12]. Some animal studies have revealed several metabolites in rat urine samples, which allowed the metabolism of 5- and 6-APB to be compared [13]. Generally, the phase I metabolism of these drugs involved (i) ring hydroxylation; (ii) ring cleavage; (iii) aldehyde reduction; (iv) aldehyde oxidation. Phase II metabolism included glucuronidation (Figure 2) [3].

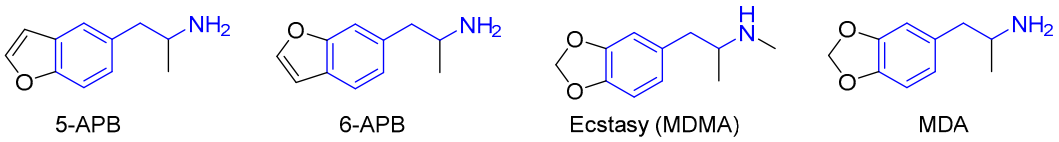


Figure 1. Structures of the psychoactive benzofurans 5-APB and 6-APB and their structural similarity to MDMA and MDA.

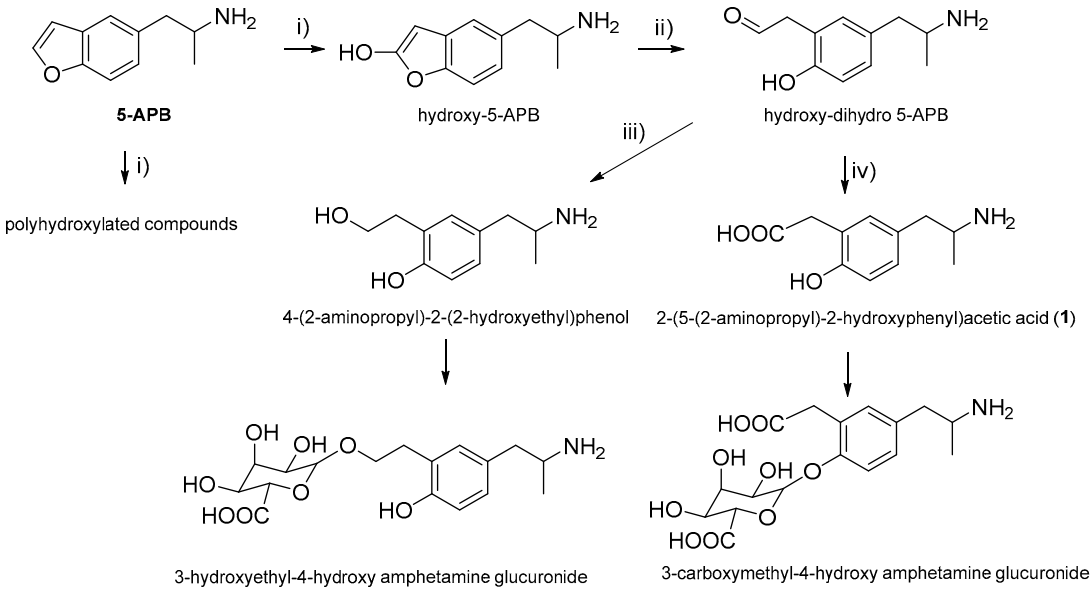
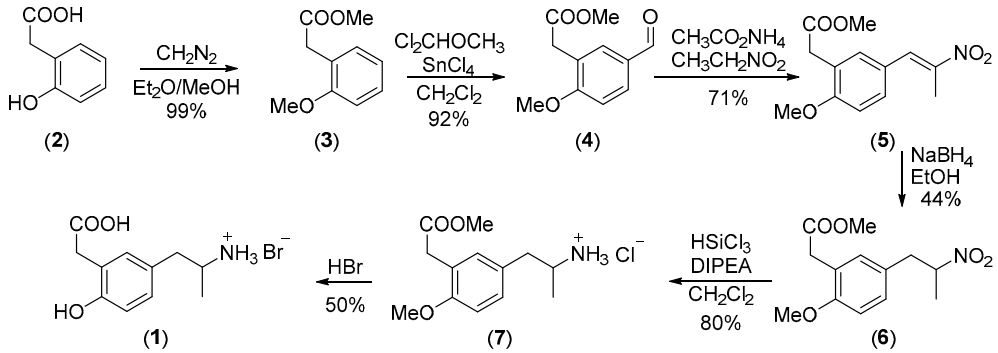


Figure 2. Metabolic pathways of 5-APB in rats. Phase I metabolism involves (i) ring hydroxylation; (ii) ring cleavage; (iii) aldehyde reduction; (iv) aldehyde oxidation. Phase II metabolism includes glucuronidation. Adapted from [14].

The most abundant metabolite found after the exposure of human hepatocytes to 5-APB was 2-(5-(2-aminopropyl)-2-hydroxyphenyl)acetic acid (**1**). Other identified metabolites were hydroxy-5-APB and hydroxy-dihydro 5-APB [10,14–16]. Although metabolism is often referred to as a detoxification process, bioactivation is also a frequent metabolic process of xenobiotics that results in the formation of reactive metabolites. Indeed, the synthesis of metabolites by bioactivation through their reaction with binucleophiles was essential to understanding the increased toxicity of conjugated forms, which can be more toxic than the parent compound in the case of MDMA [17]. It is imperative to develop synthetic methodologies to obtain metabolites not only to have standards on hand for analytical purposes but also to evaluate their bioactivity. Here, we present the synthesis of the 5-APB metabolite 2-(5-(2-aminopropyl)-2-hydroxyphenyl)acetic acid (**1**).

2. Results and Discussion

We aimed at the synthesis of 2-(5-(2-aminopropyl)-2-hydroxyphenyl)acetic acid (**1**), a 5-APB metabolite, starting from 2-hydroxyphenylacetic acid (**2**). The proposed synthetic methodology involves a methylation reaction, Rieche formylation, Aldol-type condensation, and reduction (Scheme 1).



Scheme 1. Synthetic methodology adopted for the synthesis of 2-(5-(2-aminopropyl)-2-hydroxyphenyl)acetic acid (**1**).

We started the synthesis with the methylation of the hydroxyl group and carboxylic acid of 2-hydroxyphenylacetic acid (**2**) with diazomethane, which was accomplished in a 99% yield. Diazomethane (CH_2N_2) is a versatile and useful reagent in organic synthesis, enabling the easy introduction of methyl or methylene groups into organic structures. However, its generation and utilization pose hazards, and it should be handled with caution due to its carcinogenicity and toxicity. Despite these risks, CH_2N_2 continues to be an important reagent, and new methods and techniques for its safe and convenient preparation and handling are constantly being developed [18]. This method proved to be advantageous due to the high yield obtained when compared to methylation with iodomethane and potassium carbonate. With this last condition, the consumption of **2** was completed overnight, but the reaction was not clean, and some collateral products were produced, with **3** being the major compound to be formed, although in a lower yield (53%). Next, we carry out the formylation of the aromatic group of **3**. Rieche formylation with dichloromethyl methyl ether (Cl_2CHOCH_3) in the presence of a Lewis acid catalyst ($SnCl_4$) was applied to **3** under an inert atmosphere at 0 °C [19]. It can be classified as a very efficient reaction with a short reaction time (2 h), with compound **4** being obtained in a very high yield of 92%. Next, we conducted Knoevenagel condensation to convert the aromatic aldehyde into the α,β-unsaturated nitro compound **5** following our previous procedure [20]. Condensation with nitroethane and ammonium acetate was applied to **4** at reflux in an inert atmosphere, and compound **5** was obtained in a 71% yield. Subsequently, it was necessary to reduce the α,β-unsaturated nitro group to attain the phenylethylamine scaffold; for this, catalytic hydrogenation using palladium on activated charcoal (Pd/C) as the catalyst was tested. The reduction was performed in methanol in the presence of TFA. Several compounds were identified in this reaction corresponding to the nitro compound (with the reduction of the double bond), the oxime intermediate, and the corresponding ketone from the hydrolysis of the oxime. We turned our attention to another procedure, where the reduction of the double bond, achieved with $NaBH_4$ [21], allowed **6** to be obtained, followed by the reduction of the nitro group with trichlorosilane and DIPEA to attain **7** [22]. For the final step, it was necessary to proceed with the simultaneous hydrolysis and demethylation reaction, which involved treating compound **7** with a solution of hydrobromic acid. The compound 2-(5-(2-aminopropyl)-2-hydroxyphenyl)acetic acid (**1**) was attained in a 50% yield.

3. Materials and Methods

All used reagents were commercially acquired and used without further purification. Thin-layer chromatography was performed on Merck Kieselgel GF 254 0.2 mm plates supported on aluminum, which were visualized under UV light (254 nm) and stained with ninhydrin or Dragendorff solutions. Column chromatography was performed with stationary phase LiChroprep RP-18 (Merck) with granulometry of 40–63 μm in reverse-phase chromatography. Infrared spectra were recorded using a Perkin Elmer Spectrum two

spectrometer in ATR mode. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker ARX 400 spectrometer and measured at 400 and 101 MHz, respectively (Supplementary Material). NMR signals are described with the chemical shift (δ, in ppm), multiplicity, with the respective coupling constant (*J*) given in Hertz (Hz), the number of protons, and attribution. Multiplicity is described as singlet (s), doublet (d), triplet (t), and multiplet (m). The ESI spectra were recorded in an LC Agilent 1200 Series with Binary pump/MS Agilent 6130B Single Quadrupole with an ESI source. High-resolution mass spectra (HRMS) were obtained at the University of Salamanca (Spain), Elemental Analysis, Chromatography and Mass Spectrometry Service (NUCLEUS), using a High-Performance Liquid Chromatography (HPLC) Agilent 1100 coupled to a QSTARXL Hybrid qTOF (AB Sciex, Framingham, MA, USA) mass spectrometer.

*3.1. Methyl 2-(2-Methoxyphenyl)acetate (**3**)*

To a solution of 2-hydroxyphenyl acetic acid (**2**) (0.513 g; 3.37 mmol) in ethyl ether (20 mL) and methanol (2 mL) was added 7 mL of diazomethane ethyl ether solution [23], and the solution was stirred and kept in an inert atmosphere for 140 h. The reaction was followed by TLC (CH_2Cl_2), and more diazomethane was added until the consumption of the starting material. In total, 12 mL of diazomethane ethyl ether solution was used. The reaction was concentrated under reduced pressure, and methyl 2-(2-methoxyphenyl) acetate (**3**) was obtained as a pale-yellow oil in a 99% yield (0.60 g). Spectroscopic data are in accordance with the literature [24].

*3.2. Methyl 2-(5-Formyl-2-methoxyphenyl)acetate (**4**)*

To a 0.3 M solution of methyl 2-(2-methoxyphenyl)acetate (**3**) (0.6 g; 3.33 mmol) in anhydrous dichloromethane (9 mL) under a nitrogen atmosphere at 0 °C was added dichloromethyl methyl ether (0.6 mL; 6.67 mmol; 2 eq.) and Tin(IV) chloride (0.57 mL; 4.77 mmol; 1.43 eq.). The progress of the reaction was monitored by TLC (CH_2Cl_2). After 2 h, the reaction mixture was carefully dropped into a beaker with water and ice and extracted with CH_2Cl_2. The organic phase was extracted with brine (20 mL), dried using anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Methyl 2-(5-formyl-2-methoxyphenyl)acetate (**4**) was obtained as a yellow oil in a 92% yield (0.64 g). Spectroscopic data are in accordance with the literature [25].

*3.3. Methyl (E)-2-(2-Methoxy-5-(2-nitroprop-1-en-1-yl)phenyl)acetate (**5**)*

To a 50 mL round-bottom flask equipped with a stir bar was added methyl 2-(5-formyl-2-methoxyphenyl)acetate (**4**) (0.64 g; 3.08 mmol), nitroethane (8.13 mL; 116.80 mmol; 38 eq.), and ammonium acetate (0.4948 g; 6.42 mmol; 2.1 eq.). The solution was refluxed under a nitrogen atmosphere. The progress of the reaction was followed by TLC (CH_2Cl_2). After 2 h, the reaction mixture was concentrated under reduced pressure to evaporate the nitroethane. The residue was dissolved in ethyl acetate and added to a decanting ampoule with water and extracted with more ethyl acetate (3 × 20 mL). The organic phase was washed with brine and dried using anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Methyl (*E*)-2-(2-methoxy-5-(2-nitroprop-1-en-1-yl)phenyl)acetate (**5**) was obtained as a yellow amorphous solid in a 71% yield (0.58 g). IR(ATR) ν_{max} (cm^{-1}): 2923 (C-H sp^3), 1505 (C=C aromatic), 1261 (C-N), 1066 (C-O ether); ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: δ 8.05 (s, 1H, ArCH), 7.40 (dd, *J* = 8.5, 2.4 Hz, 1H, *p*-CH_2ArH), 7.32 (d, *J* = 2.4 Hz, 1H, *o*-CH_2ArH), 6.95 (d, *J* = 8.6 Hz, 1H, *m*-CH_2ArH), 3.88 (s, 3H, OCH_3), 3.71 (s, 3H, $COOCH_3$), 3.66 (s, 2H, CH_2), 2.47 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.56, 158.87, 145.72, 133.34, 132.97, 131.18, 124.44, 123.68, 110.65, 55.60, 51.92, 35.32, 13.98. MS(ESI) *m*/*z* calculated for $C_{13}H_{15}NO_5Na$ $[MNa]^+$: 288.08; Found: 288.1.

*3.4. Methyl 2-(2-Methoxy-5-(2-nitropropyl)phenyl)acetate (**6**)*

To a 25 mL round-bottom flask equipped with a stir bar was added methyl (*E*)-2-(2-methoxy-5-(2-nitroprop-1-en-1-yl)phenyl)acetate (**5**) (0.130 g; 0.51 mmol) and ethanol

(11 mL), and the solution was cooled to −20 °C. After 10 min, $NaBH_4$ (47 mg; 1.3 mmol; 2.5 eq) was slowly added and the solution stirred for 1 h. Then, acetic acid (1 mL) was added, and the solution was allowed to rise to room temperature, followed by the addition of 10 mL of water and 20 mL of ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 15 mL). The organic phases together were washed with a saturated solution of NaCl and dried with Na_2SO_4, followed by evaporation to dryness. Methyl 2-(2-methoxy-5-(2-nitropropyl)phenyl)acetate (**6**) was obtained as a pale-yellow oil (50 mg) in a 44% yield. IR(ATR) ν_{max} (cm^{-1}): 2952(C-H), 1546(N-O, nitro), 1388(N-O, nitro). ^{1}H-NMR (400 MHz, $CDCl_3$) δ ppm: 7.04 (d, 1H, *J* = 8.3 Hz, ArH), 6.98(s, 1H, ArH), 6,80 (d, 1H, *J* = 8.3 Hz, ArH), 4,73 (m, 1H, $CHNO_2$), 3.79 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2CO_2Me), 3.24 (dd, 1H, *J* = 13.7, 7 Hz, CHH'CH), 2.94 (dd, 1H, *J* = 17.0, 7 Hz, CHH'CH), 1.53 (d, 3H, *J* = 5.5 Hz, $CHCH_3$).

*3.5. Methyl 2-(5-(2-Aminopropyl)-2-methoxyphenyl)acetate Hydrochloride (**7**)*

To a solution of methyl 2-(2-methoxy-5-(2-nitropropyl)phenyl)acetate (**6**) (12 mg; 0.046 mmol) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere, DIPEA (40.43 µL; 0.232 mmol, 5 eq.) was added. To this mixture, cooled to 0°C, trichlorosilane (14.08 µL; 0.139 mmol, 3 eq.) was slowly added. The mixture was allowed to return to room temperature and stirred for 5 h. The progress of the reaction was followed by TLC (CH_2Cl_2). The workup involved the addition of 3 mL of a saturated solution of $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The organic phases were washed with a saturated solution of NaCl and dried with Na_2SO_4, followed by evaporation to dryness. A pale-yellow oil of methyl 2-(5-(2-aminopropyl)-2-methoxyphenyl)acetate (**7**) (8.8 mg) was obtained in an 80% yield. ^{1}H-NMR (400 MHz, D_2O) δ ppm: 7.26 (dd, 1H, *J* = 2.3 and 8.4 Hz, ArH), 7.15(d, 1H, *J* = 2.3 Hz, ArH), 7,06 (d, 1H, *J* = 8.4 Hz, ArH), 3.83 (s, 3H, OCH_3), 3.75–3.68 (m, 9H, OCH_3, CH_2CO_2Me, DIPEA.HCl), 3.56–3.50 (m, 1H, $CHNH_2$), 2.91–2.79 (m, 2H, CH_2CH), 1.28 (d, *J* = 6.7 Hz, 3H, $CHCH_3$); ^{13}C-NMR (100 MHz, D_2O): 175.67, 156.58, 132.13, 130.07, 128.44, 123.19, 111.92, 55.85, 52.61, 49.19, 39.11, 35.61, 17.45; HRMS(ESI) *m*/*z* calculated for $C_{13}H_{20}NO_3$ $[MH]^+$: 238.14377; Found: 238.14377.

*3.6. 2-(5-(2-Aminopropyl)-2-hydroxyphenyl)acetic Acid Hydrobromide (**1**)*

A solution of methyl 2-(5-(2-aminopropyl)-2-methoxyphenyl)acetate (**7**) (8.8 mg; 0.037 mmol) in HBr 48% (1 mL; 18.42 mmol; 500 eq.) was refluxed for 2 h under a nitrogen atmosphere. The solution was concentrated at reduced pressure, and the residue was purified by chromabond RP-18 using the following gradient: water (5 mL), 10% MeOH (5 mL), 20% MeOH (5 mL), 50% MeOH (5 mL), 100% MeOH (10 mL). Each fraction was checked for the presence of the compound by TLC (CH_2Cl_2:MeOH, 90:10) and separated and evaporated to dryness. A pale-yellow oil of 2-(5-(2-aminopropyl)-2-hydroxyphenyl)acetic acid hydrobromide (**1**) (5.4 mg) was obtained in the water fractions in a 50% yield. ^{1}H-NMR (400 MHz, D_2O) δ ppm: 7.10–7.08 (m, 2H, ArH), 6,90 (d, *J* = 8.0 Hz, 1H, ArH), 3.61–3.56 (m, 3H, CH_2CO_2H, $CHNH_2$), 2.93 (dd, *J* = 6.1 and 14.1 Hz, 1H, CHH'CH), 2.78 (dd, *J* = 8.1 and 14.1 Hz, 1H, CHH'CH), 1.32 (d, *J* = 6.6 Hz, 3H, $CHCH_3$); ^{13}C-NMR (100 MHz, D_2O): 176.00, 153.36, 132.11, 129.20, 127.92, 124.26, 116.17, 49.27, 39.20, 17.60; HRMS(ESI) *m*/*z* calculated for $C_{11}H_{16}NO_3$ $[MH]^+$: 210.11247; Found: 210.11247.

4. Conclusions

To address the recurring problem of the potential toxicity associated with newly introduced drugs in the market, it is crucial to develop reliable methodologies for synthesizing metabolites. Doing so not only aids in accurately identifying consumers but also empowers the scientific community to assess the bioactivity of the compounds with greater precision. Our team successfully synthesized 2-(5-(2-aminopropyl)-2-hydroxyphenyl)acetic acid (**1**), which is the most abundant metabolite generated in human hepatocytes after exposure to 5-APB. The compound was obtained in an overall yield of 11% in a six-step synthesis in-

volving diverse reaction steps, such as methylation, reduction, Knoevenagel condensation, and hydrolysis.

Supplementary Materials: ^{1}H, ^{13}C NMR and Mass Spectra of compounds **1**, **3**–**7** are available at supplementary material (PDF).

Author Contributions: Conceptualization, P.S.B. and L.M.F.; methodology, P.S.B. and L.M.F.; laboratory work, A.L.S. and I.F.; writing—original draft preparation, P.S.B. and L.M.F.; writing—review and editing, P.S.B. and L.M.F.; funding acquisition, P.S.B. and L.M.F. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Associate Laboratory for Green Chemistry—LAQV, which is financed by national funds from FCT/MCTES (UIDB/50006/2020 and UIDP/50006/2020).

Data Availability Statement: Any data can be obtained from authors by request.

Acknowledgments: FCT/MCTES is acknowledged for the National NMR Facility (RECI/BBB-BQB/0230/2012. We acknowledge the Laboratório de Análises REQUIMTE for the technical support for the mass spectrometry analyses.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Zawilska, J.B.; Andrzejczak, D. Next Generation of Novel Psychoactive Substances on the Horizon—A Complex Problem to Face. *Drug Alcohol Depend.* **2015**, *157*, 1–17. [CrossRef]
2. Monte, A.P.; Maronalewicka, D.; Cozzi, N.V.; Nichols, D.E. Synthesis and Pharmacological Examination of Benzofuran, Indan, and Tetralin Analogs of 3,4-(Methylenedioxy)Amphetamine. *J. Med. Chem.* **1993**, *36*, 3700–3706. [CrossRef]
3. Bravo, R.R.; Carmo, H.; Carvalho, F.; Bastos, M.D.; da Silva, D.D. Benzo Fury: A New Trend in the Drug Misuse Scene. *J. Appl. Toxicol.* **2019**, *39*, 1083–1095. [CrossRef]
4. Roque Bravo, R.; Silva, J.P.; Carmo, H.; Carvalho, F.; Dias da Silva, D. The Toll of Benzofurans in the Context of Drug Abuse. In *Handbook of Substance Misuse and Addictions*; Patel, V.B., Preedy, V.R., Eds.; Springer: Cham, Switzerland, 2022.
5. Turcant, A.; Deguigne, M.; Ferec, S.; Bruneau, C.; Leborgne, I.; Lelievre, B.; Gegu, C.; Jegou, F.; Abbara, C.; Le Roux, G.; et al. A 6-Year Review of New Psychoactive Substances at the Centre Antipoison Grand-Ouest D'angers: Clinical and Biological Data. *Toxicol. Anal. Clin.* **2017**, *29*, 18–33. [CrossRef]
6. Barcelo, B.; Gomila, I.; Rotolo, M.C.; Marchei, E.; Kyriakou, C.; Pichini, S.; Roset, C.; Elorza, M.A.; Busaro, F.P. Intoxication Caused by New Psychostimulants: Analytical Methods to Disclose Acute and Chronic Use of Benzofurans and Ethylphenidate. *Int. J. Legal Med.* **2017**, *131*, 1543–1553. [CrossRef]
7. Deville, M.; Dubois, N.; Cieckiewicz, E.; De Tullio, P.; Lemaire, E.; Charlier, C. Death Following Consumption of Mdai and 5-Eapb. *Forensic Sci. Int.* **2019**, *299*, 89–94. [CrossRef]
8. McIntyre, I.M.; Gary, R.D.; Trochta, A.; Stolberg, S.; Stabley, R. Acute 5-(2-Aminopropyl)Benzofuran (5-Apb) Intoxication and Fatality: A Case Report with Postmortem Concentrations. *J. Anal. Toxicol.* **2015**, *39*, 156–159. [CrossRef]
9. Krpo, M.; Luytkis, H.C.; Haneborg, A.M.; Hoiseth, G. A Fatal Blood Concentration of 5-APB. *Forensic Sci. Int.* **2018**, *291*, E1–E3. [CrossRef]
10. Hofmann, V.; Sundermann, T.R.; Landmann, A.; Rechtsteiner, S.; Schmitt, G.; Bartel, M. Simultaneous Determination of 5-and 6-APB in Blood, Other Body Fluids, Hair and Various Tissues by HPLC-MS/MS. *J. Anal. Toxicol.* **2022**, *46*, 264–269. [CrossRef]
11. Rickli, A.; Kopf, S.; Hoener, M.C.; Liechti, M.E. Pharmacological Profile of Novel Psychoactive Benzofurans. *Br. J. Pharmacol.* **2015**, *172*, 3412–3425. [CrossRef]
12. Bravo, R.R.; Carmo, H.; Silva, J.P.; Valente, M.J.; Carvalho, F.; Bastos, M.D.; da Silva, D.D. Emerging Club Drugs: 5-(2-Aminopropyl)Benzofuran (5-APB) Is More Toxic Than Its Isomer 6-(2-Aminopropyl)Benzofuran (6-APB) in Hepatocyte Cellular Models. *Arch. Toxicol.* **2020**, *94*, 609–629. [CrossRef]
13. Brandt, S.D.; Walters, H.M.; Partilla, J.S.; Blough, B.E.; Kavanagh, P.V.; Baumann, M.H. The Psychoactive Aminoalkylbenzofuran Derivatives, 5-APB and 6-APB, Mimic the Effects of 3,4-Methylenedioxyamphetamine (Mda) on Monoamine Transmission in Male Rats. *Psychopharmacology* **2020**, *237*, 3703–3714. [CrossRef]
14. Welter, J.; Kavanagh, P.; Meyer, M.R.; Maurer, H.H. Benzofuran Analogues of Amphetamine and Methamphetamine: Studies on the Metabolism and Toxicological Analysis of 5-APB and 5-MAPB in Urine and Plasma Using GC-MS and Lc-(Hr)-Msn Techniques. *Anal. Bioanal. Chem.* **2015**, *407*, 1371–1388. [CrossRef]
15. Welter-Luedeke, J.; Maurer, H.H. New Psychoactive Substances: Chemistry, Pharmacology, Metabolism, and Detectability of Amphetamine Derivatives with Modified Ring Systems. *Ther. Drug Monit.* **2016**, *38*, 4–11. [CrossRef] [PubMed]
16. Labutin, A.V.; Temerdashev, A.Z. Identification of (2-Aminopropyl)Benzofuran and Its Metabolites in Human Urine. *J. Anal. Chem.* **2017**, *72*, 770–776. [CrossRef]

17. Capela, J.P.; Macedo, C.; Capela, J.P.; Branco, P.S.; Ferreira, L.M.; Lobo, A.M.; Fernanades, E.; Remião, F.; Bastos, M.L.; Dirnagl, U.; et al. Neurotoxicity Mechanisms of Ecstasy Metabolites. *Toxicol. Lett.* **2007**, *172*, S39–S40. [CrossRef]
18. Dallinger, D.; Pinho, V.D.; Gutmann, B.; Kappe, C.O. Laboratory-Scale Membrane Reactor for the Generation of Anhydrous Diazomethane. *J. Org. Chem.* **2016**, *81*, 5814–5823. [CrossRef]
19. Rieche, A.; Gross, H.; Hoft, E. Uber Alpha-Halogenather. 4. Synthesen Aromatischer Aldehyde Mit Dichlormethylalkylathern. *Chem. Ber.* **1960**, *93*, 88–94. [CrossRef]
20. Macedo, C.; Branco, P.S.; Ferreira, L.M.; Lobo, A.M.; Capela, J.P.; Fernandes, E.; Bastos, M.D.; Carvalho, F. Synthesis and Cyclic Voltammetry Studies of 3,4-Methylenedioxymethamphetamine (MDMA) Human Metabolites. *J. Health Sci.* **2007**, *53*, 31–42. [CrossRef]
21. Rossi, S.; Benaglia, M.; Porta, R.; Cotarca, L.; Maragni, P.; Verzini, M. A Stereoselective Catalytic Nitroaldol Reaction as the Key Step in a Strategy for the Synthesis of the Renin Inhibitor Aliskiren. *Eur. J. Org. Chem.* **2015**, *2015*, 2531–2537. [CrossRef]
22. Orlandi, M.; Tosi, F.; Bonsignore, M.; Benaglia, M. Metal-Free Reduction of Aromatic and Aliphatic Nitro Compounds to Amines: A $HSiCl_3$-Mediated Reaction of Wide General Applicability. *Org. Lett.* **2015**, *17*, 3941–3943. [CrossRef] [PubMed]
23. Vogel, A.I.; Tatchell, A.R.; Furnis, B.S.; Hannaford, A.J.; Smith, P.W.G. *Vogel's Textbook of Practical Organic Chemistry*; Pearson Education Limited: Essex, UK, 1989; p. 432.
24. Li, Y.H.; Wang, Z.C.; Wu, X.F. Palladium-Catalyzed Carbonylative Direct Transformation of Benzyl Amines under Additive-Free Conditions. *ACS Catal.* **2018**, *8*, 738–741. [CrossRef]
25. Detterbeck, R.; Hesse, M. An Improved and Versatile Method for the Rapid Synthesis of Aryidihydrobenzofuran Systems by a Boron Tribromide-Mediated Cyclization Reaction. *Helv. Chim. Acta* **2003**, *86*, 343–360. [CrossRef]