

Toward an Optical and Electrochemical Method for Marijuana Detection: A Simple Electrochemical Oxidation of Δ^9 -THC

Evan R. Darzi and Neil K. Garg*

Department of Chemistry and Biochemistry, University of California
Los Angeles, California 90095-1569, United States

Supporting Information Placeholder

ABSTRACT: Marijuana has long remained one of the most commonly used illicit drugs in the United States and other countries. Recently, it has been estimated that 55 million Americans use this psychoactive drug, with growing usage being attributed to the legalization of marijuana in several states. A concerning implication of increased marijuana use is the alarming number of individuals who report driving under the influence of the drug. It is estimated that nearly 12 million people in the US alone have driven a vehicle while being under the influence of marijuana. To counterbalance the growing use of marijuana and potential associated dangers, it is imperative to develop detection technologies for marijuana usage. An electrochemical-based detection technology, akin to the alcohol breathalyzer, would provide an attractive solution to this growing societal problem. The first step toward this goal is to develop a fundamental reaction that converts Δ^9 -tetrahydrocannabinol (Δ^9 -THC), the primary psychoactive substance in marijuana, to a derivative with diagnostic spectroscopic changes. We report the development of a mild electrochemical method for the oxidation of Δ^9 -THC to its corresponding *p*-quinone isomer. The photophysical and electrochemical properties of the resultant quinone show a dramatic shift in comparison to Δ^9 -THC. This exceedingly simple protocol provides a foundational step toward the development of an electrochemical-based marijuana breathalyzer.

INTRODUCTION

Marijuana has been used as a recreational drug for many millennia, with some reports of marijuana usage dating back to 3000 B.C. Its historic usage has been attributed to heightened sensations of euphoria, in addition to increased relaxation, amongst other effects (1). In modern times, marijuana has become one of the most commonly used drugs in the United States and many other countries. According to the 2018 Substance Abuse and Mental Health Service Administration (SAMHSA) national survey on drug use and health (2), approximately 45% of the general American population over the age of 12 years old (~124 million individuals) reported using marijuana in their lifetime. Of those surveyed, roughly 10% (>28 million individuals) reported using marijuana in the month prior to completing the survey.

Marijuana and other cannabinoid products have been considered illicit substances in many countries, including the United States. However, over the past decade, there have been notable efforts to legalize these drugs for recreational purposes, which have led to the legalization of marijuana use in eleven states in the United States, as well as the District of Columbia (Figure 1a). Recreational marijuana use is also legal or undergoing decriminalization in more than thirty countries, including Canada, Spain, Chile, the Netherlands, and Australia.

With the relaxation of laws and enforcement concerning marijuana, there has been a growing interest in safety, especially when it comes to driving motorized vehicles, akin to long-standing concerns about driving under the influence of alcohol. As of 2018, within the general population above sixteen years old, 4.6% (nearly 12 million individuals) reported driving under the influence of marijuana during the prior year. This is particularly striking given the well-known negative impact marijuana has on spatial and temporal judgment (3,4,5,6).

It is known that more than one hundred different cannabinoids are present in marijuana (7), however, the primary psychoactive component responsible for driving impairment is Δ^9 -tetrahydrocannabinol (Δ^9 -THC, **1**). Δ^9 -THC (**1**) can constitute between 5–30 wt% of a marijuana source (8) and is the ideal compound to identify when assessing potential marijuana usage. Current roadside tests for Δ^9 -THC (**1**) impairment are time-consuming and require special training, such as blood/saliva tests, or are based on behavioral signs and the officer's discretion. New chemical-based technologies can offer practical solutions for the growing problem of marijuana detection. Not surprisingly, many new inventions have been put forth in recent years, with the aim of developing technologies reminiscent of alcohol breathalyzers, which are used widely due to their simplicity and reliability. The current state-of-the-art Δ^9 -THC breathalyzers (9) require specialized mass spectrometry (Figure 1b) (10, 11), covalent modification for optical sensing (Figure 1c) (12, 13), and chemiresistors based on carbon nanotube (CNT) adsorption (Figure 1d) (14). Each method focuses on a single detection mode (mass spectrometry, photochemical, or electrochemical) to determine Δ^9 -THC (**1**) levels. Moreover, each suffers from limitations including highly specialized equipment in the case of mass detection, toxic reagents used for covalent modification, and batch-to-batch variability in CNT sensing. An electrochemical-based detection technology would provide an ideal alternative.

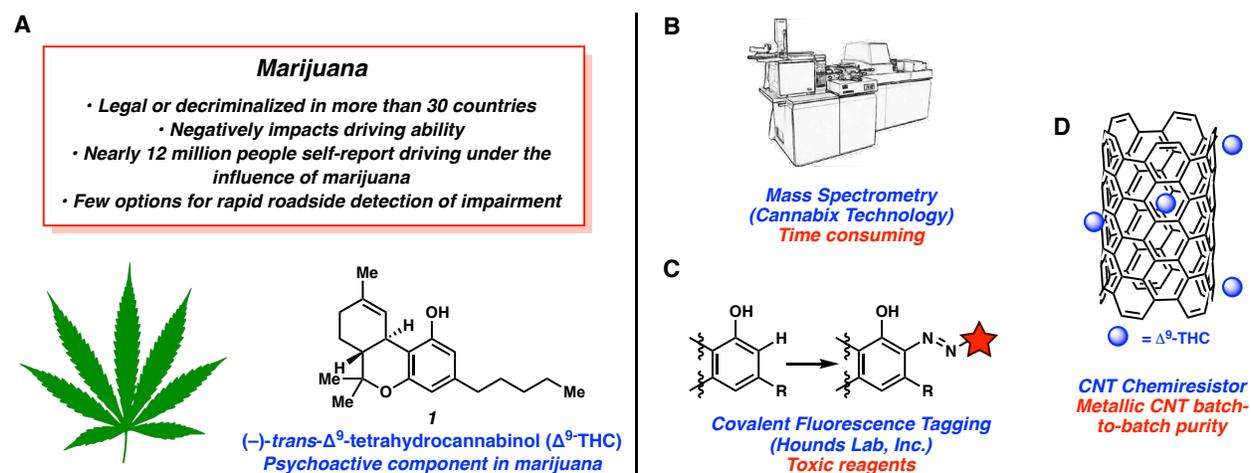


Figure 1. Overview of marijuana usage, Δ^9 -Tetrahydrocannabinol (1**), and state-of-the-art chemical-based detection methods. (A) Marijuana usage and statistics and chemical structure of Δ^9 -Tetrahydrocannabinol (**1**). (B) THC detection based on mass spectrometry. (C) THC detection based on covalent labeling. (D) THC detection based on chemiresistance.**

We report the development of a mild electrochemical method for the oxidation of Δ^9 -THC to its corresponding *p*-quinone isomer. This transformation is accompanied by diagnostic changes with regard to photophysical and electrochemical properties. Thus, the simple oxidation protocol described herein provides a foundational step toward the development of an electrochemical-based marijuana breathalyzer.

RESULTS AND DISCUSSION

We first sought to uncover a simple transformation of Δ^9 -THC (**1**) that would provide a derivative with diagnostic spectroscopic changes. As shown in Figure 2A, we hypothesized that a simple oxidation would transform Δ^9 -THC (**1**) into the corresponding *p*-quinone, Δ^9 -THCQ (**2**). Before performing experiments, we performed time-dependent density functional theory (TDDFT) calculations to predict the absorbance spectra for **1** and **2**. These calculations predicted a shift in absorbance from the UV range, in the case of **1**, into the visible range for **2**. Additionally, the oxidation of **1** to **2** would result in a lowering of the LUMO to a range that could be measured electrochemically. These findings encouraged us to pursue the key electrochemical transformation of Δ^9 -THC (**1**) to Δ^9 -THCQ (**2**) experimentally with the expectation that the oxidation event would be accompanied by a measurable change in electrochemical and photochemical properties. We hypothesized that these changes, as well as a diagnostic change in mass, could be used independently or in combination with current state-of-the-art detection methods described above.

Before pursuing an electrochemical conversion, we examined a more traditional chemical approach to access quinone **2**, as the conversion of THC (**1**) to **2** had not been reported (Figure 2B). Although many conditions are available for the oxidation of phenols to *p*-quinones, we were drawn to the hypervalent iodine reagent bis(trifluoroacetoxy)iodobenzene (PIFA), which has been used as a phenol oxidant for many decades (15). Mechoulam and coworkers have also used PIFA to make cannabinoids in the context of medicinal chemistry, although using the alkene isomer Δ^8 -THC instead of Δ^9 -THC (**1**) (16,17,18). We were delighted to find that treatment of Δ^9 -THC (**1**) with PIFA in aqueous media and under ambient conditions gave Δ^9 -THCQ (**2**) in moderate yield. Consistent with our computational predictions, the oxidized Δ^9 -THCQ (**2**) showed strong absorbance peaks in the UV region at 204 nm and 266 nm, as well as a diagnostic peak in the visible spectrum at 402 nm. DFT calculations demonstrate that **2** displays a net lowering of the LUMO energy, a narrowing of the HOMO–LUMO transition energy, and ultimately a red-shift into the visible spectrum for Δ^9 -THCQ (**2**) relative to Δ^9 -THC (**1**) (see the Supporting Information for details).

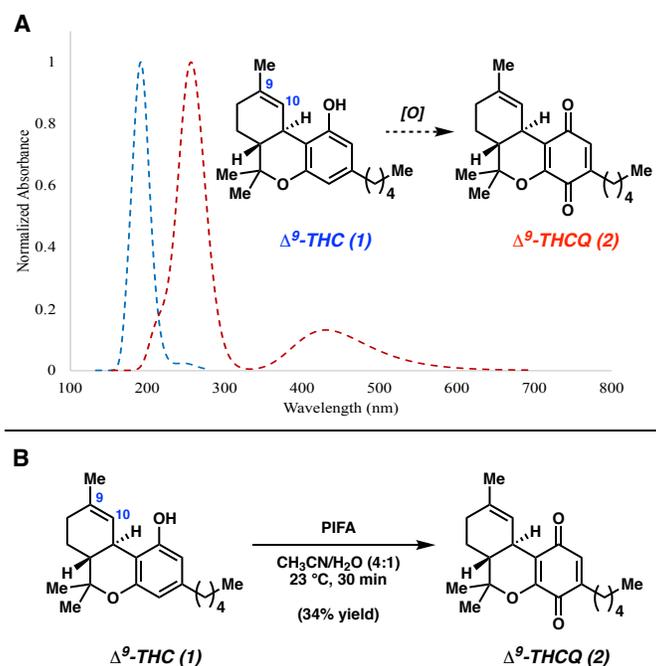


Figure 2. Oxidation of Δ^9 -THC (1) to Δ^9 -THCQ (2). (A) Strategic oxidation of Δ^9 -THC (1) to Δ^9 -THCQ (2) and predicted photophysical spectra using TDDFT / B3LYP/6-31g(d). (B) Chemical-based oxidation of Δ^9 -THC (1) to Δ^9 -THCQ (2) using PIFA (bis(trifluoroacetoxy)iodobenzene).

With the ultimate aim of performing the oxidation of Δ^9 -THC (1) electrochemically, which we deemed as being ideal for the long-term goal of making a reagentless detection device, we sought to understand the redox properties of both Δ^9 -THC (1) and Δ^9 -THCQ (2). Thus, Δ^9 -THC (1) and Δ^9 -THCQ (2) were assessed using cyclic voltammetry. First, the oxidation potential for 1 was measured, which showed an irreversible oxidation event at a peak potential of 1.02 V in line with reported values for 1 (Figure 3A) (19,20). The measured oxidation potentials for 2 showed an irreversible oxidation event at 1.71 V, along with a broad peak at 1.92 V. The HOMO of 2 is thought to be lower lying compared to the HOMO of 1, thus rendering the removal of an electron from 1 (i.e., oxidation) more favorable (see the Supporting information). Next, the reduction potentials for 1 and 2 were compared (Figure 3B). For 1, a negative scan from 0.0 V to -2.5 V showed no measurable reduction events, indicative of an inaccessible LUMO energy. Reduction of 2 showed two reversible reduction events at $E_{1/2}^{(1)} = -1.02$ V and $E_{1/2}^{(2)} = -1.17$ V. The reduction events for 2 are thought to arise from a single-electron reduction to the semiquinone and a second single electron reduction to arrive at the hydroquinone. These values are in line with previously reported reduction potentials for both benzoquinones (21) and synthetic cannabinoid analogues (22). The stark differences observed in redox (and photophysical properties) between Δ^9 -THC (1) and Δ^9 -THCQ (2) bode well for the use of electrochemical technologies for THC detection.

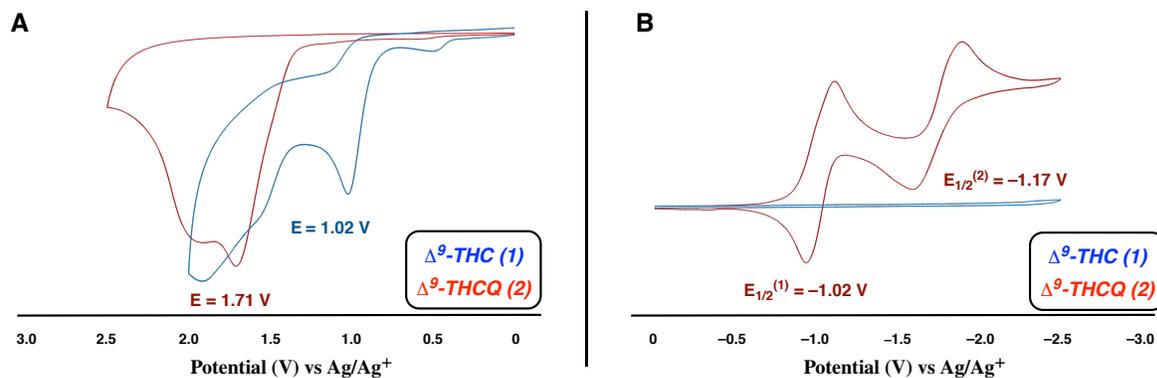


Figure 3. Cyclic Voltammograms of Δ^9 -THC (1) and Δ^9 -THCQ (2). (A) Oxidation potentials of Δ^9 -THC (1) and Δ^9 -THCQ (2). (B) Reduction potentials of Δ^9 -THC (1) and Δ^9 -THCQ (2). Δ^9 -THC (1) (blue trace) and Δ^9 -THCQ (2) (red trace) in dry MeCN with NBu₄BF₄ (0.1 M) as the support electrolyte at a scan rate of 100 mV/s. Each spectrum was collected using a glassy carbon working electrode, platinum counter electrode, and a Ag/Ag⁺ reference. See the Supporting Information for spectra vs Fc/Fc⁺.

Our final objective for the present study was to identify suitable conditions to achieve the electrochemical conversion of Δ^9 -THC (1) to Δ^9 -THCQ (2). This approach would offer an exceedingly simple oxidation protocol, akin to the fundamental technology used in widely used alcohol breathalyzers. Although the electrochemical oxidation of phenols to quinones bears precedent (23,24), the electrochemical oxidation of Δ^9 -THC (1) was unknown. In order to rapidly evaluate conditions in a reproducible manner, we elected to carry out all electrochemical studies using an ElectraSyn plate (25). The use of standardized equipment was essential to evaluate a variety of reaction parameters, including electrode combinations, electrolyte, current, concentration, solvent to water ratio, and the effect of additives. Detailed results are shown in the Supporting Information, while select examples using tetrabutylammonium tetrafluoroborate as electrolyte are shown in Figure 4. An initial survey of electrodes gave no conversion when graphite was used as both the anode and cathode (entry 1). However, changing the cathode and anode to platinum (entry 2) led to full consumption of phenol 1 and a 30% isolated yield of *p*-quinone 2. Encouraged by these results and guided by previous electrochemical oxidation reports the cathode was changed to glassy carbon (entry 3). This gave a comparable isolated yield of 2 (27% yield). Next, we tested the use of a graphite electrode in place of glassy carbon or platinum as an inexpensive alternative (entry 4). We were delighted to observe a substantial boost in isolated yield to 68%. Interestingly, we exclusively observe the formation of Δ^9 -THCQ (2) under the present electrochemical conditions, in contrast to the chemical oxidation used in Figure 2B, where several side-products were observed. Thus, the conversion of Δ^9 -THC (1) to Δ^9 -THCQ (2) can be achieved using inexpensive electrodes and simple electrochemical oxidation conditions.

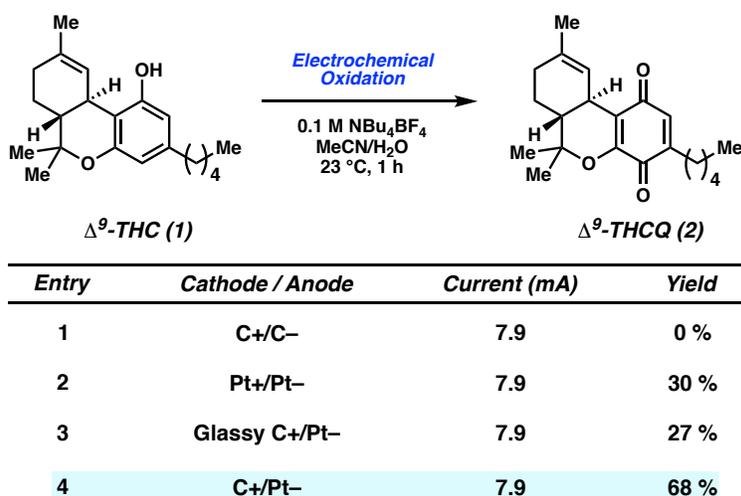


Figure 4. Electrochemical conversion of Δ^9 -THC (1) to Δ^9 -THCQ (2). Δ^9 -THC (1) was oxidized to give Δ^9 -THCQ (2) in 68% yield (entry 4). General conditions unless otherwise stated: Δ^9 -THC (1) (1.00 equiv, 22.3 μ M), 6.60 mM (0.100 M NBu₄BF₄ in MeCN), MeCN:H₂O (8:1), 23 °C, 1 h. Isolated yields of 2 are shown.

CONCLUSION

The recent legalization and decriminalization of marijuana has led to increased safety concerns for society. As noted earlier, nearly 12 million people in the US alone have reported driving a vehicle while being under the influence of marijuana, thus prompting the scientific community to invent roadside detection technologies for marijuana detection. An ideal solution to this problem would utilize electrochemical-based detection methods, akin to the widely used alcohol breathalyzer. Our studies have shown that Δ^9 -THC (1) undergoes facile oxidation to its *p*-quinone counterpart, Δ^9 -THCQ (2). In turn, Δ^9 -THCQ (2) displays dramatic differences in photophysical and redox properties, which is crucial for detection technologies. Moreover, we have found both chemical and electrochemical transformations can be employed for the oxidation, with the latter performing more efficiently and providing an exceptionally simple means to manipulate Δ^9 -THC (1). The present study is expected to prompt many future efforts, such as assessments of the substrate specificity of the oxidation reaction, studies regarding detection limits, and ultimately, device development to enable the practical analysis of breath. Nonetheless, the ability to oxidize Δ^9 -THC (1) to a product displaying different photophysical and redox properties, using simple electrochemistry, lays a foundation for a marijuana breathalyzer that could be used independently or in combination with existing technologies to address a growing societal problem.

ACKNOWLEDGEMENTS

The authors are grateful to the University of California, Los Angeles and the NIH-NIGMS (F32-GM122245 to E.R.D.). These studies were also supported by shared instrumentation grants from the NSF (CHE-1048804) and the National Center for Research Resources (S10RR025631).

REFERENCES

-
- ¹ M. Booth, *Cannabis: a history* (Thomas Dunne Books: New York, 2015), pp. 1–448.
- ² Substance Abuse and mental health services administration. (2019). *Results from the 2018 Survey on Drug Use and Health: Detailed tables*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data/>
- ³ R. L. Hartman, M. A. Huestis, Cannabis effect on driving skills. *Clin. Chem.* **59**, 478–492 (2013).
- ⁴ R. L. Hartman, T. L. Brown, G. Milavetz, A. Spurgin, R. S. Pierce, D. A. Gorelick, G. Gaffney, M. A. Huestis, Cannabis effects on driving lateral control with and without alcohol. *Drug Alcohol Depen.* **154**, 25–37 (2015).
- ⁵ M. G. Lenné, P. M. Dietze, T. J. Triggs, S. Walmsley, B. Murphy, J. R. Redman, The effect of cannabis and alcohol on stimulated arterial driving: Influences of driving experience and task demand. *Accid. Anal. Prev.* **42**, 859–866 (2010).
- ⁶ R. Compton, (2017, July). Marijuana-Impaired Driving - A Report to Congress. (DOT HS 812 440). Washington, DC: National Highway Traffic Safety Administration.
- ⁷ L. O. Hanuš, S. M. Meyer, E. Muñoz O. Taglialatela-Scafati, G. Appendino, Phytocannabinoids: a unified critical inventory. *Nat. Prod. Rep.* **33**, 1357–1448 (2016).
- ⁸ C. H. Ashton, Adverse effects of cannabis and cannabinoids, *Br. J. Anaesth.* **83**, 637–649 (1999).
- ⁹ It has been demonstrated that Δ^9 -THC (**1**) levels in the breath reliably correlate with time of marijuana consumption for four hours and with blood concentration levels. As such, breath-based methods offer an attractive means for roadside detection technologies. a) K. L. Lynch, Y. R. Luo, S. Hooshfar, C. Yun, Correlation of breath and blood Δ^9 -tetrahydrocannabinol concentrations and release kinetics following controlled administration of smoked cannabis. *Clin. Chem.* **65**, 1171–1179 (2019). b) S. K. Himes, K. B. Scheidweiler, O. Beck, D. A. Gorelick, N. A. Desrosiers, M. A. Huestis, Cannabinoids in exhaled breath following controlled administration of smoked cannabis. *Clin. Chem.* **59**, 1780–1789 (2013). c) A. Manolis, L. J. McBurnew, B. A. Bobbie, The detection of Δ^9 -tetrahydrocannabinol in the breath of human subjects. *Clin. Biochem.* **16**, 229–233 (1983).
- ¹⁰ R. Attariwala, K. Malhi, R. Yost, J. Boock, M. T. Costanzo, Device and method for the detection of cannabis and other controlled substances using FAIMS. International Patent No. WO 2017/147687 A2.
- ¹¹ M. T. Costanzo, J. J. Boock, R. H. J. Kemperman, M. S. Wei, C. R. Beekman, R. A. Yost, Portable FAIMS: Applications and future perspectives. *Int. J. Mass Spectrom.* **422**, 188–196 (2017).
- ¹² K. L. Lynch, Y. R. Luo, S. Hooshfar, C. Yun, Correlation of breath and blood Δ^9 -tetrahydrocannabinol concentrations and release kinetics following controlled administration of smoked cannabis. *Clin. Chem.* **65**, 1171–1179 (2019).
- ¹³ M. S. Lynn, H. R. Tang, K. L. Bechtel, P. A. Holst, Compositions and methods for detection of target constituent in exhaled breath. US Patent No. US 9,921,234 B1.
- ¹⁴ S. I. Hwang, G. F. Nicholas, M. A. Rothfuss, K. N. Bocan, L. Bian, D. L. White, S. C. Burkert, R. W. Euler, B. J. Spher, M. L. Vinay, E. Sejdic, A. Star, Tetrahydrocannabinol detection using

-
- semiconductor-enriched single-walled carbon nanotube chemiresistors. *ACS Sens.* **4**, 2084–2093 (2019).
- ¹⁵ Y. Tamura, T. Yakura, H. Tohma, K. Ki-kuchi, Y. Kita, Hypervalent iodine oxidation of *p*-alkoxy- and related phenols: A facile and efficient synthesis of *p*-quinones. *Synthesis*, 126–127 (1989).
- ¹⁶ N. M. Kogan, R. Rabinowitz, P. Levi, D. Gibson, P. Sandor, M. Schlesinger, R. Mechoulam, Synthesis and antitumor activity of quinoid derivatives of cannabinoids. *J. Med. Chem.* **47**, 3800–3806 (2004).
- ¹⁷ R. Mechoulam, N. M. Kogan, R. Rabinowitz, M. Schlesinger, Compositions including quinoid derivatives of cannabinoids for therapeutic use. US Patent No. US 8,497,299 B2.
- ¹⁸ R. Mechoulam, N. M. Kogan, R. Rabinowitz, M. Schlesinger, Therapeutic use of quinoid derivatives of cannabinoids. International Patent No. WO 2005,067917 A1.
- ¹⁹ M. A. Balbinom, M. M. Teles de Menezes, I. C. Eleotério, A. A. Saczk, L. L. Okumura, H. M. Tristão, M. F. de Oliveira, Voltammetric determination of Δ^9 -THC in glassy carbon electrode: An important contribution to forensic electroanalysis. *Forensic Sci. Int.* **221**, 29–32 (2012).
- ²⁰ M. A. Balbino, E. N. Oiue, M. F. M. Ribeiro, J. W. C. Júnior, I. C. Eleotéro, A. J. Ipólito, M. F. de Oliveira, Use of screen-printed electrodes for quantification of cocaine and Δ^9 -THC: adaptations to portable systems for forensic purposes. *J. Solid State Electrochem.* **20**, 2435–2443 (2016).
- ²¹ F. A. Khan, S. Choudhury, Synthesis and electrochemical properties of substituted *para*-benzoquinone derivatives. *Tetrahedron Lett.* **51**, 2541–2544 (2010).
- ²² P. Morales, D. Vara, M. Gómez-Cañas, M. C. Zúñiga, C. Olea-Azar, P. Goya, J. Fernández-Ruiz, I. Díaz-Lavida, N. Jagerovic, Synthetic cannabinoid quinones: Preparation, in vitro antiproliferative effects and in vivo prostate antitumor activity. *Eur. J. Med. Chem.* **70**, 111–119 (2013).
- ²³ T. A. Enache, A. M. Oliveira-Brett, Phenol and *para*-substituted phenols electrochemical oxidation pathways. *J. Electroanal. Chem.* **655**, 9–16 (2011).
- ²⁴ S. Quideau, L. Pouységu, D. Deffieux, A. Ozanne, J. Gagnepain, I. Fabre, M. Oxoby, Iodane mediates and electrochemical oxidative transformation of 2-methoxy- and 2-methylphenols. *Arkivoc* **6**, 106–119 (2003).
- ²⁵ For product description of the Electrasyn 2.0, see: <https://www.ika.com/en/Products-Lab-Eq/Electrochemistry-Kit-csp-516/>