



Can synthetic cannabinoids be reliably screened with electrochemistry? An assessment of the ability to screen for synthetic cannabinoids STS-135 and BB-22 within a single sample matrix



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ABSTRACT

Synthetic cannabinoids (SC) are one of the most prevalent classes of novel psychoactive substances (NPS) which have emerged onto the drug market in recent years. The incompatibility of traditional colorimetric screening methodologies with these new compounds has left a significant gap in the forensic tool kit available to tackle the importation and distribution of these substances. Electrochemical techniques have proven success for screening of such substances, but no consideration to date has been given to the impact upon the electrochemical behaviour when multiple SC are present within a single matrix. To this avail we investigate the impact of combining two SC, STS-135 and BB-22 into a single matrix to simulate a street sample composition. Interrogation of the combine two SC revealed a significant change to their electrochemical behaviour. Combination of the two indole species was revealed to undergo electrochemically induced indole polymerisation, forming a secondary species in the form of an indole dimer. Thus, removing an electrochemical centre from the formerly electroactive pyrrole group. This previously unseen mechanism revealed the inability of electrochemical screening techniques to accurately determine the number of species or indeed concentrations present given the change in structure and consequently the electrochemical behaviour observed. As such, further assessment of the feasibility of electrochemical techniques for the screening of SC is required with consideration now given to electrochemically induced competing side reactions which may occur between species within the matrix.

1. Introduction

Synthetic cannabinoids (SC) are a wide ranging class of novel psychoactive substances (NPS) group together based upon their affinity toward the CB1 and CB2 cannabinoid receptors. [1,3] Although typically species are classified due to their similar structural properties, surprisingly SC possess little chemical or structural resemblance to the active component Δ [9]-THC within the *Cannabis sativa plant*. [1] Instead they are named and classified due to their similar effects upon the cannabinoid receptors. [2–5] SC, are among a number of NPS, initially developed from failed pharmaceutical drug campaigns, with expired patents providing clandestine chemists with a wealth of information to draw upon, including synthetic routes, effects and by-products. [6–7] The emergence and popularity of NPS, attributed to their initial wide availability and legality, coincided with an increase in the number of associated hospitalization and subsequent deaths as a result of the unknown toxicity of these compounds. [4,8–10] Having

been synthesized within a lab environment with no clinical trials the pharmacology and potency of these compounds is unknown, yet users are often ignorant to this fact or falsely assume their safety given their colloquial terminology of “legal highs”. [11–12] SC are one of the major substances with a false perception of safety. Although likely linked to their terminology as ‘synthetic’ cannabinoids, many users associate them with the *Cannabis sativa plant* and often assume their effects and toxicity will be similar to that of Δ [9]-THC. Unfortunately, this is not the case, SC behave not as partial agonist to the CB1 and CB2 receptors as Δ [9]-THC does, but as full agonist. [2,3,13] This increases their potency, toxicity and psychoactive effects upon the user, often rendering them into a ‘zombie’-like state. [13–14]

SC first appearance on the drug market dates back to 2008 [15], and they quickly became popular amongst users. The next decade seen a growth in the availability and sear number and variety. Frequently impregnated upon herbal material, SC were sold often under the guise as decorative potpourri or room incense to evade detection and sei-

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zure. [16–17] The disclaimer of not for human consumption also meant suppliers circumvented the strict legislation in place for the distribution of food products. [7,18–19] The increase in use and subsequent deaths seen a worldwide increase in legislative control placed upon these substances. In spite of this, their popularity remains. Clandestine chemists would frequently alter the chemical structure of these products, bypassing legislation and maintaining their “legal” status. [20–23]

It has therefore become critical that SC can be readily identified. Of course, the gold standard remains the hyphenated chromatographic mass spectrometry systems. Indeed these are the primary technique recommended by the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG). [24] Recent advancements in these chromatographic techniques have addressed the initial limitations facing chromatographic techniques for employment as screening strategies with the ability to identify NPS not previously classified within the chromatographic library are available alongside the ability to discriminate and identify co-eluting species. [25–27] One significant hurdle remains, their huge cost and laboratory restricted specialised equipment, with access to gas cylinders necessary for mass spectrometry techniques. Their complexity also renders them unsuited for use in field or at border patrols, where non-specialised personnel are required to screen for illicit substances. With the traditional colorimetric techniques utilised at these locations often incompatible with SC there remains an urgent requirement for appropriate screening techniques. [28–29]

One such technique which has been frequently proposed for these screening purposes is electrochemistry. Electrochemistry meets a number of the criteria required for employment within this field, not only are instrumentation now portable and electrodes now disposable, they are significantly lower cost than spectroscopic alternative such as Raman [18,30–31], and are operationally simple. This is confirmed through the number of works which have employed electrochemistry for the detection of a range of NPS. [11,32–37] Interestingly despite a wide acceptance of electrochemical techniques as a viable alternative for NPS screening, little attention into their use for SC screening has been undertaken. Indeed only one prior work to date on their electrochemical detection is available. [33] This limited investigation of electrochemical techniques for their analysis is surprising given their structural functionalities indicating they are highly suited for such methods. Although we have previously discussed the utilisation of electrochemistry for SC detection [36], here we take this a step further and investigate the impact of multiple SC species present within a single matrix. Prior works have failed to assess or address any potential limitations facing the utilisation of electrochemical techniques within this area. As such, here we interrogate indole-based SC, STS-135 and BB-22, within a traditional electrochemical set up upon glassy carbon (GC) working electrodes. We investigate the electrochemical behaviour of these species individually, followed by electrochemical interrogation of these species when contained with a single matrix. By performing this analysis, we hope to assess the feasibility of electrochemical techniques for the screening of SC, by investigating samples containing multiple SC, to simulate those which would be encountered during seizures.

2. Materials and methods

2.1. Reagents and materials

Lithium perchlorate (LiClO_4) and HPLC grade acetonitrile (ACN) were purchased from Sigma Aldrich and VWR chemicals respectively. N-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-indole-3-carboxamide (STS-135) also referred to as 5F-APICA and 1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid, 8-quinolinyl ester (BB-22) were both pur-

chased from LGC Ltd. All chemicals were used as received and all solutions prepared in ACN.

2.2. Instrumentation

Electrochemical measurements were performed using the PalmSens EmStat Blue potentiostat and controlled by the PSTrace software. Lithium perchlorate was used as the supporting electrolyte within a conventional three-electrode cell with a 3 mm diameter glassy carbon (GC) working electrode, a silver wire reference electrode and a platinum counter electrode. Working electrodes were prepared via polishing with a alumina slurry ($1.0 \mu\text{m} - 0.3 \mu\text{m}$) felt pad and rinsed with deionised water and ACN prior to each measurement.

3. Results

3.1. Electrochemical behaviour of STS-135 and BB-22

The electrochemical behaviour of both STS-135 and BB-22 was interrogated upon GC working electrodes utilising differential pulse voltammetry (DPV). Our prior works have previously established the electrochemical behaviour and analytical performance of these species upon different electrode materials, determining GC to offer the optimum signal intensity and as such, did not warrant re-assessment within this contribution. [36] In spite of their structural functionality indicating their suitability toward electrochemical detection, to date the investigation of synthetic cannabinoids (SC) via these techniques is limited. [33,36] These studies showed the use of electrochemistry for the detection of STS-135 and 5F-ADB-PINACA, resulting in detection limits of 0.3 nM and 0.5 pM respectively. However, these were obtained utilizing pure synthetic cannabinoids (SC) which could hamper their detection ability in a real street sample which might contain multiple SCs. Both STS-135 and BB-22 were observed to produce multiple oxidation peaks upon bare GC working electrodes, refer to Fig. 1. STS-135 and BB-22 both belong to the structural indole class, which gifts them their electroactivity, with indole containing species having long been documented to undergo electrochemical oxidation upon a range of different electrode surfaces. [33,38–45][51][52] The oxidation process of SC containing the lone indole functionality, as present

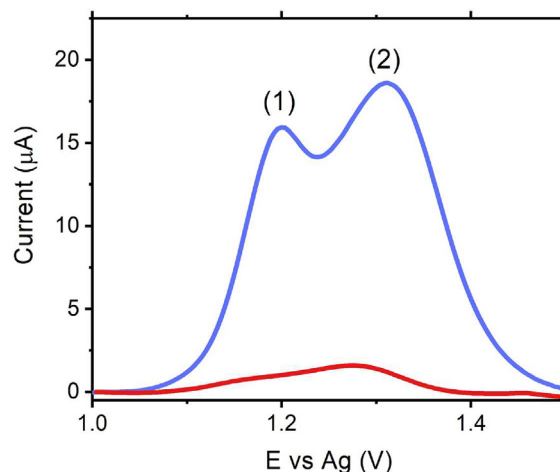


Fig. 1. DPV of 1 mM STS-135 (blue) and 0.0625 mM (red) in LiClO_4 as supporting electrolyte upon GC working electrodes across a potential range of $1 \leq E \leq 1.5$ V vs Ag at a scan rate of 100 mV s^{-1} . (1) indicates the oxidation peak resulting from C7 position (highlighted in Scheme 1 (A)) and (2) indicates the oxidation from the C2 position (highlighted in Scheme 1 (B)). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

within STS-135, has been previously report by Dronova *et al.* [33] However to date there has been no estimation of the responsible electro-oxidation mechanism accounting for the dual peak response of these indole containing SC, in fact no acknowledgement of this dual peak system had been given by Dronova *et al.* [33] Here we proposed a dual electro-oxidation mechanism of the single indole functionality seen within STS-135 within Scheme 1. The multiple peaks observed indicate two separate electro-oxidation reactions occur, similar to those seen for indole substituted compounds. [42] The first anodic peak at a potential of approximately 1.2 V (vs Ag) is believed to result from the electron abstraction from the C7 position of the benzene moiety within the indole group. [42] Scheme 1 highlights the C7 position, the corresponding electro-oxidation and subsequent resonance structures observed following electron abstraction. As this electro-oxidation process breaks the aromaticity of the benzene ring system it can be considered as energetically unfavourable. Hence, resulting in the lower intensity compared to the more positive anodic peak, in addition to the disappearance of this peak at lower STS-135 concentrations (refer to Fig. 1). The second anodic peak observed at ~ 1.33 V (vs Ag) is the result of electro-oxidation occurring at the C2 position of the pyrrole group within the indole functionality (see Scheme 1). In contrast to the C7 position, electron abstraction here maintains the benzene rings aromaticity and hence the radical cation formed is more stabilised, its formation is more favoured and thus a higher current intensity is observed.

In contrast to the sole indole functionality within STS-135, BB-22 belongs to a subgroup of indole SC, known to contain an additional functionality in the form of the naphthalene or quinoline moieties. [33] These addition functional groups produce a prominent second anodic wave at higher potential values. The structure of BB-22 reveals it to contain the quinoline moiety, which is responsible for the second anodic peak observed within its voltammograms, see Fig. 2, at a potential of ~ 1.47 V vs Ag. The predicted mechanism for the electron abstraction and subsequent radical formation for BB-22 is detailed within Scheme 2. The earlier anodic peak at ~ 1.33 V vs Ag, occurs via electron abstraction form the C2 position of the pyrrole group, identical to that observed within STS-135. The secondary peak how-

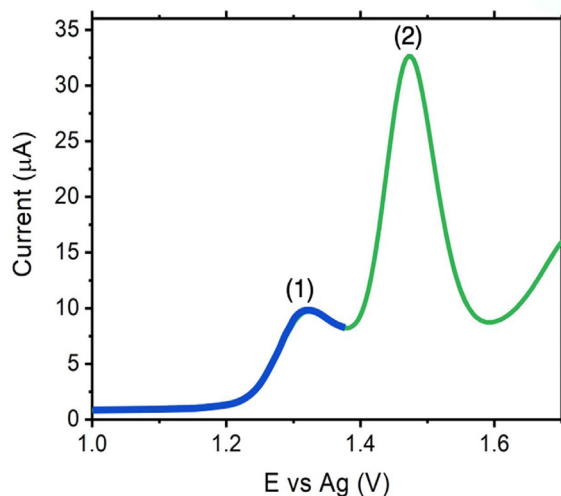
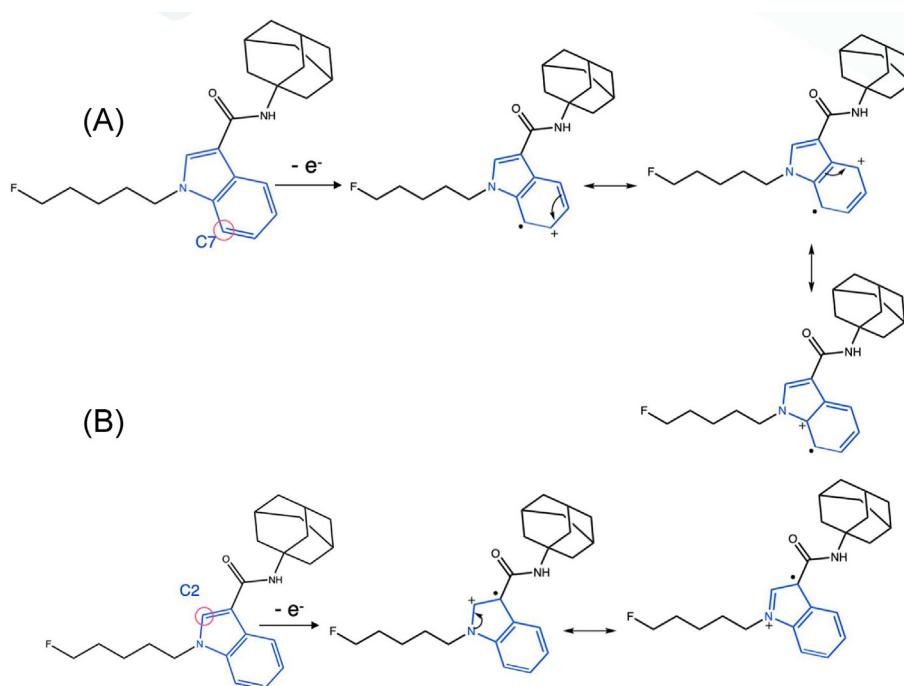
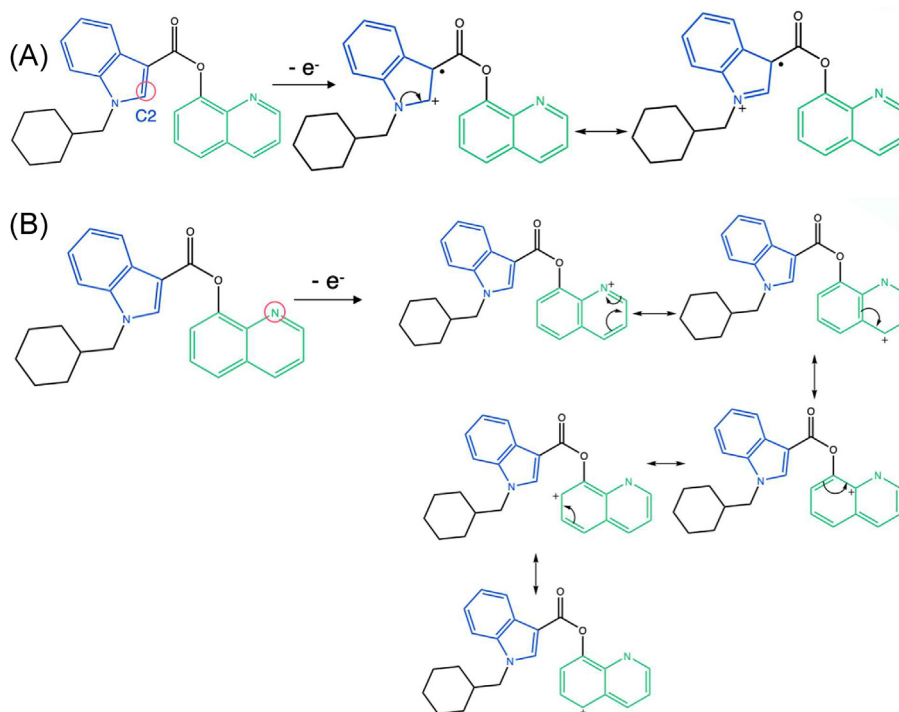


Fig. 2. DPV of 1 mM BB-22 in LiClO_4 as supporting electrolyte upon GC working electrodes across a potential range of $1 \leq E \leq 1.7$ V vs Ag at a scan rate of 100 mV s^{-1} . Blue portion accounts for electron abstraction from the pyrrole group and green section accounts for abstraction from the quinoline group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ever arises from electron abstraction form the nitrogen of the heterocyclic ring of the quinoline moiety. [33,46–47] Similar to the trend observed for STS-135, the stability of the quinoline radical formed results in the higher current intensity observed for the later anodic peak. The higher potential observed for the quinoline oxidation process is in agreement with the observations of Dronova *et al.* [33], whose investigation of a range of different SC including those with naphthalene or quinoline moieties demonstrated a secondary anodic peak at potentials greater than that attributed to the indole group. [33,46–47]



Scheme 1. Proposed electro-oxidation mechanism of STS-135 at (A) C7 benzene moiety and (B) C2 pyrrole moiety within the indole group of the SC, corresponding to Fig. 1 peaks.



Scheme 2. Proposed mechanism for the electro-oxidation of BB-22 at (A) C2 position of the pyrrole group and (B) at the nitrogen within the heterocyclic ring of the quinoline group.

3.2. Assessment of electrochemistry for screening of simulated street samples

The primary drive for the employment of electrochemical techniques for the detection of SC is as rapid screening techniques. The large number of SC structures and their frequent appearance on the drug market with slight structural modifications, sees electrochemistry fail to offer the specificity to accurately determine the present compound or indeed their quantification. These characteristics will remain in the unchallenged realm of mass spectrometry techniques. However, the lack of alternative screening methodologies remains a significant challenge in the detection and subsequent prevention of these illicit substances, with no traditional colorimetric techniques compatible with the majority SC. [48–49] Electrochemistry does stand to address this gap, with its proven suitability for the detection of SC. [33] However what has failed to be addressed to date is the impact of multiple species commonly contained within these sample types. Indeed, Dronova *et al.* [33], did discuss the ability to detect both an indazole and indole based SC but were unable to determine the number of SC present if species were formed from the same functional groups. As SC are primarily found in an impure form, typically with a multitude of different SC present, it becomes pertinent to assess the impact of multiple SC housed within a single matrix. To assess this a mixture of STS-135 and BB-22 was prepared. However, the trend observed differs from that expected. Intuitively it would be correct to assume that addition of the two SC both containing the indole functionality would result in an increase in the peak current associated with this oxidation process, at ~ 1.33 V vs Ag, with the overall indole concentration increasing. However, this was not the trend observed. In fact, a decrease in the peak associated with the pyrrole electro-oxidation process was seen, refer to Fig. 3.

3.3. Elucidation of reaction mechanism between STS-135 and BB-22

To gain a greater understanding of the mechanism behind this unexpected trend a variety of mixed samples with differing concentra-

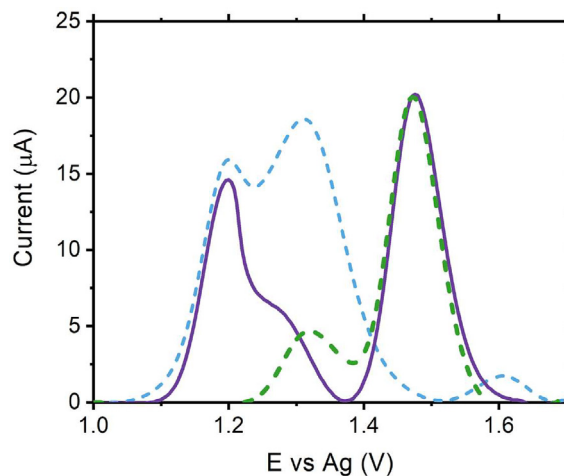


Fig. 3. DPV of 1 mM STS-135 (blue dash), 1 mM BB-22 (green dash) and 1 mM STS-135 and BB-22 mixed (solid purple) in LiClO_4 as supporting electrolyte upon GC working electrodes across a potential range of $1 \leq E \leq 1.7$ V vs Ag at a scan rate of 100 mV s^{-1} . Highlighting the unexpected decrease in current intensity at ~ 1.33 V vs Ag. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tions of STS-135 and BB-22 were prepared. Interrogation of the resultant DPVs reveals that as the STS-135 concentration is increased, while that of BB-22 is maintained, the current resultant from the pyrrole electro-oxidation decreases in direct proportion to the increasing STS-135 concentration. Consulting Fig. 4, it can be seen that peak 1 (P1) increases as the STS-135 concentration increases as expected, with the higher STS-135 concentration resulting in the increase in the oxidation at the C7 position of the benzene moiety. Peak 3 (P3) remains constant as this is the result of the quinoline oxidation within

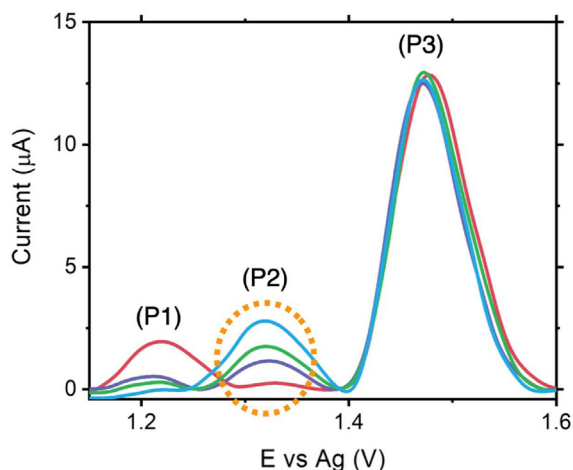


Fig. 4. DPV of 0.5 mM BB-22 with varying STS-135 concentrations from 62.5 μM (pink) to 10 μM (blue) in LiClO_4 as supporting electrolyte upon GC working electrodes across a potential range of $1.1 \leq E \leq 1.6$ V vs Ag at a scan rate of 100 mV s^{-1} . (P1) is the peak attributed to C7 oxidation of the benzene moiety in STS-135, (P2) is attributed to oxidation of the C2 position of the pyrrole group within the indole functionality in both compounds and (P3) is the oxidation of the quinoline group in BB-22. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the BB-22 structure. However peak 2 (P2) highlighted within Fig. 4, shows a decrease in current intensity with an increase in STS-135 concentration. This decrease suggests an alternative reaction is occurring between these two SC, which is reducing the amount of available pyrrole to undergo oxidation, indicating a consumption of the species or the removal of access of the C2 position for electron abstraction.

This theory of consumption of the C2 pyrrole position, was further confirmed through the interrogation of a constant concentration of STS-135 and varying BB-22 concentrations (Fig. 5), revealing the same trends observed as within Fig. 4. With the consistent current of the

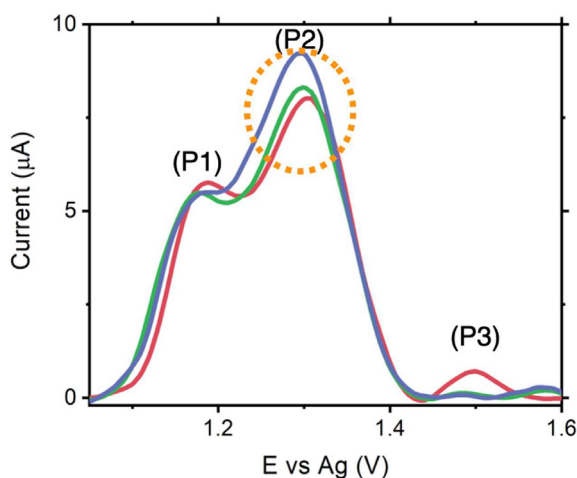


Fig. 5. DPV of 0.5 mM STS-135 with varying BB-22 concentrations from 62.5 μM (pink) to 25 μM (purple) in LiClO_4 as supporting electrolyte upon GC working electrodes across a potential range of $1.1 \leq E \leq 1.6$ V vs Ag at a scan rate of 100 mV s^{-1} . (P1) is the peak attributed to C7 oxidation of the benzene moiety in STS-135, (P2) is attributed to oxidation of the C2 position of the pyrrole group within the indole functionality in both compounds and (P3) is the oxidation of the quinoline group in BB-22. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

STS-135 seen in peak 1 and the increase in current from the BB-22 concentration seen in peak 3. Peak 2 again indicates the consumption of the pyrrole species, preventing its oxidation and hence the current reduction observed.

The consumption of the pyrrole group, suggests that conversion to a non-oxidisable form is proceeding, indicating possible substitution at the C2 position. One such mechanism which could achieve such a result would be indole polymerisation or dimerisation. Such mechanisms have been previously achieved via electrochemically induced polymerisation of indole and its derivatives. [38–41] Indole polymerisation typically sees the formation of bonds between the 2, 3 positions but has also been noted between the 1,3, 2,2 or 3,3 positions. [39–40] Within the compounds investigated the 1 and 3 positions are already substituted, resulting in polymerisation between the two C2 positions (2,2 polymerisation) of the pyrrole groups. As such, we propose that the two SC undergo electrochemically induced indole polymerisation, forming a dimer product of the structure shown in Fig. 6 (A). In an attempt to confirm the suspected polymerisation reaction, subsequent scans of STS-135 were performed to see if its polymerisation and subsequent deposition of the film upon the electrode surface could be induced. Fig. 6 shows the current decrease as subsequent scans proceed. Indole polymerisation has two distinct identify properties. At pH values less than 5 a conductive polymer is form, resulting in an increase in current with subsequent scans. [39] However when electro-polymerisation is performed at pH values greater than 5 a non-conductive indole polymer is observed. [39] This creates an insulating layer upon the electro surface which results in diminished current intensity with subsequent scans. [39] As our matrix is not under acidic conditions, polymerisation is suspected to lead to

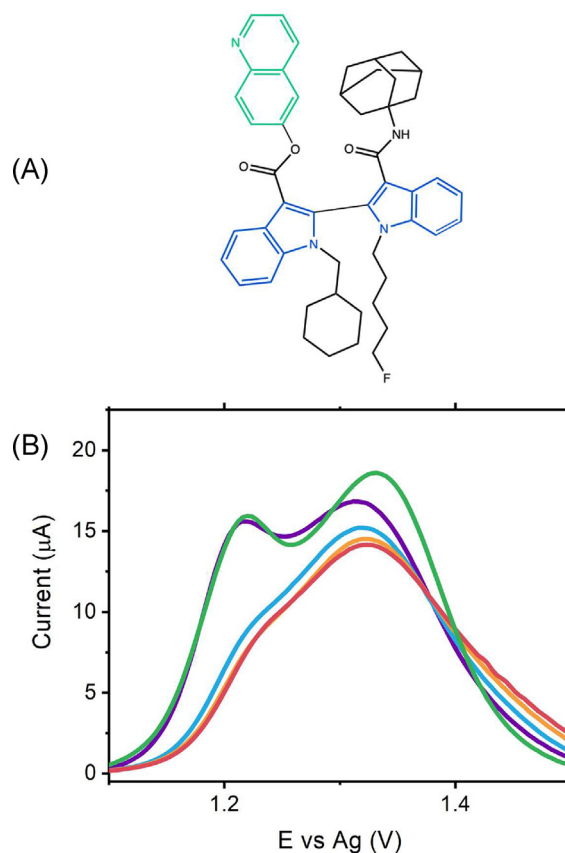


Fig. 6. (A) Proposed structure of indole dimer formed between BB-22 and STS-135 during electro-polymerisation. (B) Subsequent DPV scans of 1 mM STS-135 in LiClO_4 as supporting electrolyte upon GC working electrodes across a potential range of $1.1 \leq E \leq 1.5$ V vs Ag at a scan rate of 100 mV s^{-1} .

the formation of a non-conductive polymer producing an the insulating layer upon the electrode surface. This can be confirmed with the diminished current intensity recorded, Fig. 6 (B). The formation of the film was subsequently visually confirmed with inspection of the electrode surface. We therefore propose that the findings observed in Fig. 6 in combination with the relationships observed in Figs. 3 and 4, indicate the formation of a secondary species, most likely an indole dimer between the two SC.

To fully understand this proposed mechanism and observed behaviour, extensive chemical simulations would be beneficial and although outside the scope of this contribution are recommended in future works. This would likely require extensive analysis utilizing liquid or gas chromatography alongside mass spectrometry to confirm the formation of these dimers. Although here we present this reaction occurring between two specific indole SC, it is unknown if the same reaction will occur with other SC, for example those with the indole functionality and also those with indazole functionality or indeed with other cannabinoids. Considering the combination of mixtures analysed by Dronova *et al.* [33] and their ability to distinguish between indole and indazole species, with no reported determinant to current intensity this reaction may not occur for all indole SC. With such a diverse range of SC and their corresponding structures however it cannot be said with certainty that all indole SC would undergo this polymerisation and all indazole will not. Hence, an in-depth and wide-reaching study would be needed, encompassing a range of different SC structures. Such a study would indeed be a significant task, although hugely beneficial for the assessment of electrochemistry as a screening method going forward. Although, prior works have investigated the impact of common adulterants upon the electrochemical signals of illicit species, here we do not report this. This is explained by the composition of SC street samples. Street samples of SC have not been known to contain the more common adulterants such as paracetamol or caffeine, as their grey-area in terms of legality has like not encourage suppliers to adulterate their samples. Indeed, it is far more common that street sample analysis have instead revealed samples to comprise of a much of SC themselves, hence why this contribution is prudent to the field [50][51].

4. Conclusion

The lack of appropriate screening strategies for the rapid identification of SC and NPS in general has long been apparent to the forensic community. Traditional colorimetric tests are often not compatible with SC and to date no alternative has been developed and reliably implemented. Electrochemistry meets a number of criteria required for employment as screening strategies for these substances. They offer low cost, portable and rapid detection methods. Prior works have suggested the potential opportunity for the employment of electrochemical techniques such as CV or DPV for the detection of SC. These provided an initial concept proof for such employment but had failed to fully investigate the impact of the multiple species contained within these sample types. It is widely known that street samples, especially those of SC are not pure and unlikely to contain a single illicit species. Indeed, SC are specifically known to contain a multitude of different cannabinoid species within a single sample, but yet do not containing other common adulterants observed within traditional illicit street samples, such as paracetamol or caffeine. As such the prior works which have investigated the impact of these common adulterants have failed to acknowledge the composition likely to be encounter of these samples within the currently proposed methodologies. Knowing the likelihood of street samples to contain multiple SC it seemed prudent to investigate the impact upon the observed electrochemical behaviour. Here we observed an unexpected relationship between the multiple SC and the resultant voltammograms. Initially one may expect that the addition of two SC, both of which contain indole groups,

would have resulted in an increase in total current intensity of the peaks resultant from the indole electro-oxidation process. However, instead we observed a competing side reaction occurring between the two SC species instigated by the electrochemical interrogation of the samples. This side reaction is suspected to arise from electrochemical indole polymerisation, resulting in the consumption of the electroactive pyrrole C2 position preventing oxidation at this now substituted site. This was apparent from the decrease in current intensity associate with this process upon increasing concentrations of the SC present. Although further confirmatory analysis (such as HPLC-MS or GC-MS) would be prudent to establish the extent of this relationship across a range of different SC structures, we believe this demonstrates a previously unconsidered mechanism which will need to be fully understood prior to the wide scale employment of electrochemistry for the screening of SC and the herbal materials utilised for their distribution. However, it is important to note this finding does not mean that electrochemical techniques should be eradicated for potential future NPS screening methodologies, but that these processes should be taken into account and consideration given to the inability of such methods to determine the concentration or number of species present given these competing side reactions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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LD undertook the initial conceptualisation of this research and oversaw the supervision of the research team. AA and KB conducted the formal analysis and research investigation. All authors contributed to the interpretation of data, preparation, writing of the original draft and review and editing of the presented research.

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