Journal of Forensic Sciences – accepted/uncorrected Dec 2019

Prodrugs of new psychoactive substances (NPS): a new challenge

Simon Elliott[1,2*], Tanith Holdbrook[2], Simon Brandt[3]

[1] Elliott Forensic Consulting, Birmingham, UK
[2] King's College London, Department of Analytical, Environmental and Forensic Sciences, London, UK
[3] Liverpool John Moore's University, Department of Chemistry, Liverpool, UK

*** Correspondence:**
Simon Elliott
simontox@yahoo.co.uk

ABSTRACT

The concept of a substance acting as a prodrug for an intended drug is not new and has been known and utilised with particular benefits within medicine for efficacy and patient safety. Prodrugs of psychoactive substances are also not particularly new but this has also extended to considerations of prodrugs of new psychoactive substances (NPS). The continuing evolution of NPS has been a constant forensic challenge. In some countries this constant evolution has led to the introduction of various alternative methods of drug control. Whether for this reason or in the pursuit of user experimentation, prodrugs of NPS have been discussed, developed and exploited, posing some distinct forensic challenges. This is especially the case within toxicological analysis of biological fluids and for some substances, also forensic chemical analysis, through inherent instability of the prodrug or metabolism in the body. Particular examples of NPS prodrugs include 1-propanoyl-LSD, 1-butanoyl-LSD, 1-acetyl-LSD and 2C-B-AN. This is in addition to associated substances and medicines that may be used for an intended pharmacological effect. Various prodrugs for stimulant and hallucinogenic substances in particular have appeared in the literature and have been discussed within drug user forums and made available for purchase online. Presently, drug monitoring data from national and international systems indicate that prodrugs are not widely available or problematic. Nevertheless, it is important that there is sufficient awareness of the prodrug concept and potential impact and associated forensic implications, not just for chemical analysis but also for toxicological considerations when a substance has been used.

Keywords: new psychoactive substances (NPS), prodrugs, 2CB-aminonitrile (2C-B-AN), 1-propanoyl-lysergic acid diethylamide (1P-LSD), psilacetin

Introduction

The continuing evolution of what are now referred to as new psychoactive substances (NPS) has been a constant forensic challenge for many years. Typically mimicking the effects of classical controlled drugs such as amphetamine, cocaine, cannabis, heroin and LSD, NPS have often utilised various well-established templates (e.g. phenethylamine, piperazine, aminoindan, cathinone, etc.) with modifications to either bypass domestic or international drug legislation or to impart different effects or potencies – often resulting in increased harm to users (1). If subsequently banned through such drug control legislations, further chemistries and structural alterations are sought which is beginning to highlight the question related to chemical diversity in the NPS domain.

In some countries this constant evolution and game of "cat and mouse" has led to the introduction of various more generic methods of control of psychoactive substances including those that consider biological effect rather than chemical structures, predominantly in relation to prohibiting sale with a view to reducing the availability of a psychoactive substance. This has particularly been the case in the UK, whereby the Psychoactive Substances Act (PSA) came into force in May 2016 which created a blanket ban on the production, distribution, sale and supply of psychoactive substances in the UK intended for human consumption, with some exemptions (2). It was and continues to be operational in addition to the Misuse of Drugs Act 1971, which is the UK's primary legislation for drug control. Within the PSA, the definition of a psychoactive substance was and is "any substance which is capable of producing a psychoactive effect in a person who consumes it, and is not an exempted substance." It goes on to state "that a substance produces a psychoactive effect in a person if, 'by stimulating or depressing the person's central nervous system, it affects the person's mental functioning or emotional state.' In order to establish a substance's psychoactivity utilised for prosecution under the PSA, the UK government believe that *in vitro* testing procedures such as the implementation of receptor binding studies and functional assays at CB_1, $GABA_A$, $5HT_{2A}$, NMDA, μ-opioid receptors and monoamine transporters are sufficient to make such an assessment (3). The outcomes and the Act itself have garnered various opinions but in a UK Government review of the impact of the PSA, whilst it was stated that open sale of NPS had largely been eliminated there was mention of concerns regarding the supply of NPS by street dealers, movement of sale onto the darkweb, the continued development of new substances, the potential displacement from NPS to other harmful substances and continued use by homeless and prison populations (4).

In a similar timeframe of the last 5 years around the notified intent and the introduction of the PSA, there have been some discussions on Internet drug forums around the concept of prodrugs as a new direction for NPS (5). This has been coupled with the emergence on the NPS market of modifications of classical drugs (e.g. phencyclidine - PCP and lysergic acid diethylamide - LSD, etc.) as well as some other distinct substances that when ingested convert to a classical drug or NPS. Although the substance available for sale may not necessarily be controlled,

the resultant substance would be but its presence in the body does not allow prosecution in contravention of any particular Act (at least within UK legislation). It is possible that the concurrent development of these new drugs was in consideration of this, including recognition of potential *in vitro* testing methodologies used to determine psychoactive status – as conversion of a prodrug to a drug is an *in vivo* process that may not be reflected in such *in vitro* testing.

The concept of prodrugs has long been utilised in medicine with pharmaceutical products and formulations produced in an attempt to control efficacy, reduce toxicity and enhance patient compliance by also taking advantage of associated pharmacokinetics (6). The prodrug can effectively act as a precursor to the intended drug with examples including codeine and diamorphine (convert to morphine), primidone (converts to phenobarbital), acetylsalicylate (converts to salicylate), isavuconazonium (converts to isavuconazole) and aripiprazole lauroxil (converts to aripiprazole) (6). There can also be designed pharmacodynamic activity following metabolic transformation as found, for example, in tramadol, clopidogrel, carisoprodol and clorazepate which all produce intended active metabolites.

This article provides an introduction to known and potential prodrugs of NPS and related compounds cited in the literature as well as highlighting products available for sale via the Internet and presents data that reflect their potential as a prodrug.

Prodrugs of psychoactive substances

1.1 Prodrugs of stimulant substances

Psychostimulant drugs are a key pharmacological class of compounds abused for their central nervous system stimulant properties, with synthetic cathinones dominating the stimulant NPS scene (7,8). Some stimulant drugs are often amphetamine related in structure and action and indeed various prodrugs of amphetamine itself exist, invariably used (currently or previously) in a clinical setting but also mentioned in drug forums and online websites for purchase. Specifically, whilst there are various drugs that metabolise to amphetamine (or methamphetamine) as part of their normal metabolic process (e.g. selegiline, amphetaminil and famprofazone) (9,10), the following review sections focus on those in which there has been recent discussion, evidence of use within a prodrug setting, or advances in understanding regarding mechanisms of action.

1.1.1 Amphetamines

Lisdexamfetamine (*N*-(1-phenylpropan-2-yl)lysinamide) (Figure 1A) can be prescribed in the treatment of attention deficit hyperactivity disorder (ADHD) in children and binge eating disorder in adults and consists of dextroamphetamine (*d*-amphetamine) derivatised with the amino acid L-lysine (11,12). Whilst lisdexamphetamine itself is pharmacologically inactive, *in vivo* peptidase enzymes associated with red blood cells hydrolyse the amide bond, thereby allowing pharmacological effects being exerted through *d*-amphetamine (13). The delayed absorption and metabolic profile for formation of the active drug reduces

lisdexamfetamine's abuse liability and increases its safety profile (11,12). However, use of lisdexamfetamine has been mentioned in some Internet user forums as well as lysine-MDMA (5,14,15).

Clobenzorex ((*S*)-*N*-[(2-chlorophenyl)methyl]-1-phenylpropan-2-amine) (Figure 1A) is currently used for appetite suppression in some countries, having been used in the 1970s, but was noted to be identified on the illicit drug market in the 1990s (16). When ingested, it is metabolised to *d*-amphetamine through enzymatic cleavage of the chlorobenzyl moiety but metabolism also results in the production of 4-hydroxyclobenzorex which can be used as a marker for clobenzorex use in biological fluid (e.g. urine testing) (17).

Benzphetamine ((*S*)-N-benzyl-*N*-methyl-1-phenylpropan-2-amine) (Figure 1A) is another anorectic drug used for appetite suppression in some countries having been studied in the 1960s for obesity (18). As for clobenzorex, there is *in vivo* cytochrome P450 enzymatic cleavage of the benzyl moiety, producing (*S*)-methamphetamine with additional metabolism to (*S*)-amphetamine (19,20). This has resulted in some discussion in Internet user forums with online pharmacy availability as well as mention of potential chemical conversion to methamphetamine (21,22).

Fenethylline (1,3-dimethyl-7-{2-[(1-phenylpropan-2-yl)amino]ethyl}-3,7-dihydro-1*H*-purine-2,6-dione) (Figure 1A) is a covalently alkyl chain bonded combination of amphetamine and theophylline. It was originally developed in the 1960s and was used for ADHD symptomology and to an extent, narcolepsy and depression amongst some other therapeutic indications (23). Metabolic studies have shown that *in vivo* fenethylline metabolises to form various metabolites, including amphetamine and theophylline with subsequent amphetamine-like activity (24,25). In recent years, concern has surrounded the abuse of fenethylline (clandestinely synthesised and marketed using its prior trade name "captagon") especially in West Asian and Arab countries (26). It has also been discussed in Internet user forums within a prodrug context (27,28).

In 2017, Collins et al. reported the detection of the *para*-toluenesulphonyl derivative of methamphetamine in Australia (Figure 1A) in powder form entering the country through postal consignments (29). The authors surmised that the intention was to chemically mask methamphetamine to evade drug detection devices, with it being possible to subsequently recover methamphetamine by removal of the *p*-tosyl group through chemical means. However, the authors found that implementation of standard reaction conditions resulted in relatively low yields. On the other hand, the extent to which *p*-tosyl methamphetamine hydrolyses to methamphetamine in the presence of stomach acids and enzymes if orally consumed is unknown. However, it was speculated that high toxicity of *p*-tosyl methamphetamine might make this an unattractive route of administration for the recreational drug user.

Similarly, in 2015, Collins et al. had previously referred to the use of *tert*-butoxycarbonyl (t-BOC) as another protecting group used to mask methamphetamine and MDMA as detected in seized drug material (29,30). A further detection of t-BOC-MDMA impregnated on silica was reported in Germany in 2016. The derivatised drug was detected in a mixture with silica gel and extensively

characterised using standard analytical methods (31). As part of a prodrug assessment, Collins et al. also confirmed that the conditions reminiscent of those found in the stomach were sufficient to convert t-BOC-MDMA (Figure 1A) into MDMA but the toxicity of t-BOC-MDMA itself is not known (30). In 2017, the analysis of a liquid sample seized at the border of New Zealand was reported to reveal the detection of t-BOC methamphetamine (32).

1.1.2 Cathinones

Cathinones have featured as a popular class of NPS for over 10 years with numerous structural variations. It has long been known that the medicine amfepramone (diethylpropion, also known as *N*,*N*-diethylcathinone) metabolises to form *N*-ethylcathinone in the body (33). However, there are very few cathinone prodrugs mentioned in the literature and in drug forums (34). *N*-Ethylcathinone has been detected as a drug in its own right, but has also been found with a forum-mentioned prodrug, α-phthalimidopropiophenone (35) (Figure 1A). In 2007, capsules containing α-phthalimidopropiophenone and 2-fluoromethamphetamine or α-phthalimidopropiophenone with caffeine, 4-methylmethcathinone (mephedrone) and *N*-ethylcathinone were reported in Australia (35). A chemical conversion into cathinone is expected to be straightforward. Based on the reported metabolism of a somewhat similar compound (α-pyrrolidinopropiophenone, PPP) it was postulated that α-phthalimidopropiophenone, which is not pharmacologically active itself, might metabolise *in vivo* to cathinone and the compound continues to be available to purchase on “research chemical” websites.

It should also be noted that during their studies with t-BOC-MDMA, Collins et al. also produced t-BOC-mephedrone for analytical purposes but there have been no reports of t-BOC cathinones (30).

2-Methyl-1-[4-(methylsulfanyl)phenyl]-2-(morpholin-4-yl)propan-1-one (MMMP, also known as MTMP, Caccure 907 and Irgacure 907) is a fragmenting (Type 1) photoinitiator, used in industry for the fixing of thin films, plastics and inks. However, in the last few years, MMMP has been found in drug seizures in Europe, Australia and North America as well as in a fatality in addition to furanylfentanyl (36-38). In the fatality reported in Australia, MMMP was identified in off-white crystals and crystalline powder found at the scene (36). Chemically, MMMP is a synthetic cathinone derivative which may account for the decision of drug manufacturers to distribute it even though it seems unlikely to have cathinone-like effects. During investigation of the fatality, Nash et al. reported the detection of MMMP metabolites in the post-mortem urine, which were all hydroxylated products (β-hydroxy-MMMP, β-hydroxy-MMMP-sulfoxide and β-hydroxy-MMMP-sulfone) with no cleavage of the morpholine group which would have formed a methylthio-substituted alpha-methyl-cathinone. However, as the pharmacological activity of MMMP and the metabolites is not known it is not possible to determine whether the MMMP is indeed acting as a prodrug for pharmacologically active hydroxylated metabolites or not but it is seemingly not a prodrug for a cathinone absent of the morpholine chemical moiety.

1.2 Prodrugs of hallucinogenic substances

Hallucinogenic substances have always maintained their popularity within specific sections of recreational drug markets due to their ability to significantly induce altered states of consciousness that include changes in mood, emotions, thoughts, and sensory perception. However, significant research efforts related to exploring the clinical use of LSD has also re-emerged (39) that might also extend to some of its 1-acyl-substituted derivatives (below). Chemically, serotonergic hallucinogens include indolalkylamines (tryptamines) and phenylalkylamines with classical substances such as lysergic acid diethylamide (LSD), psilocybin ("magic mushrooms"), *N*,*N*-dimethyltryptamine (DMT) and mescaline in addition to other compounds. Other so-called non-classical representatives might include salvinorin A (from *Salvia divinorum*) and phencyclidine, PCP "Angel Dust"). In terms of NPS, over the last 25 years or so, the tryptamine and phenethylamine chemical frameworks have been used to produce hundreds of different substances that showed hallucinogenic properties (40,41). In more recent times, additional chemical variations have been developed, for example, found in various *N*-[(2-methoxyphenyl)methyl] derivatives of hallucinogenic phenethylamines (e.g. 2C-B, 2C-I etc.) called 'NBOMes' (42). Other examples include methoxy- or methylenedioxy- analogues of arylcyclohexylamines such as PCP (e.g. 3-MeO-PCP) and associated morpholine analogues (e.g. 3-MeO-PCMo and 3,4-MD-PCMo) or *N*-alkyl analogues (43-45). These substances have pharmacological activity in their own right and do not act as prodrugs (e.g. 3-MeO-PCP does not metabolise to form PCP), however, other derivatives and analogues of hallucinogenic substances (below) have been developed, discussed and made available for online purchase that could be considered to be prodrugs. On the other hand, 3-methoxy-based PCP analogues might be considered as prodrugs of their 3-hydroxy metabolites. 3-Hydroxy-PCP, for example, has been available as an NPS in its own right (45).

1.2.1 Tryptamines and lysergamides

Recently, a number of LSD derivatives and analogues have been investigated, namely 1-acetyl-LSD (1A-LSD, ALD-52), 1-propanoyl-LSD (1P-LSD), 1-butanoyl-LSD (1B-LSD), N^6-ethyl-nor-LSD (ETH-LAD), 1-propanoyl- N^6-ethyl-nor-LSD (1P-ETH-LAD), N^6-allyl-nor-LSD (AL-LAD), *N*-ethyl-*N*-cyclopropyl lysergamide (ECPLA), (2′S,4′S)-lysergic acid 2,4-dimethylazetidide (LSZ), and lysergic acid morpholide (LSM-775) (46-52) (Figure 1B). A biotransformation has been observed in lysergamides acylated at the indole nitrogen that in turn produce the corresponding "core" drug of LSD or ETH-LAD (52). Therefore, 1P-LSD, 1B-LSD and ALD-52 are all prodrugs of LSD and 1P-ETH-LAD is a prodrug of ETH-LAD. All of these drugs have been discussed in Internet drug forums and are currently available for purchase online (53-56). Although ALD-52 was known to be psychoactive in humans for a long time (57), the formation of LSD both *in vitro* and *in vivo* (rats) has only been confirmed recently (51,57). Recent investigations have also shown that the affinity of ALD-52, 1P-LSD and 1B-LSD to most monoamine receptors dropped by one to two

orders of magnitude compared to LSD and that they showed a weak efficacy or even acted as antagonists in Ca^{2+}- mobilisation assays. The fact that these substances however were able to induce the head-twitch response in mice and that LSD was detected in rat plasma samples was also consistent with the idea that 1-acyl-substituted LSD derivatives might serve as prodrugs (57).

The naturally occurring phosphorylated *N*,*N*-dimethyltryptamine, psilocybin is present in a large variety of psychoactive mushrooms, with psilocybin acting as a prodrug for psilocin (4-hydroxy-*N,N*-dimethyltryptamine) that is produced when such mushrooms are consumed (58). In a review about psilocybin Geiger et al. (58) also discussed the modified psilocin precursor, *O*-acetylpsilocin (4-acetoxy-*N*,*N*-dimethyltryptamine also known as psilacetin) which is available for purchase online having been mentioned in drug forums and to a limited extent in the literature (59,60). Chemically, an acetoxy group replaces the phosphoryloxy group found on psilocybin and is believed to be metabolised to produce psilocin during first-pass metabolism (58). The authors report that this modification obfuscates written laws in the United States when the product is designated “not for human consumption,” allowing pseudo-legal import and possession for research purposes only; however, if it were to be used *in vivo*, the user would be in violation of the Federal Analogue Act (58).

1.2.2 Hallucinogenic phenethylamines

2,5-Dimethoxy-4-bromophenethylamine (2C-B) is a psychedelic phenethylamine derivative that has been around for over 20 years (61,62). It is internationally controlled as a Schedule II listed substance in the Convention on Psychotropic Substances 1971. Within the last few years and particularly at the time of the UK Psychoactive Substances Act 2016, an aminonitrile analogue of 2C-B, namely {[2-(4-bromo-2,5-dimethoxyphenyl)ethyl]amino}(phenyl)acetonitrile (2C-B-AN) (Figure 1B) has been noted as being available and discussed within Internet drug forums as a prodrug of 2C-B (63-65). An early report from 2009 involving the ingestion of 50 mg suggested stimulant effects together with certain visual effects (not specified) and a duration between 5–8 hours (66). There are no published data or literature concerning 2C-B-AN to determine if this is the case. There are also no analytical data available to assist in the detection of the substance. Consequently, the authors of this review undertook a stability study of 2C-B-AN.

2C-B-AN was placed into a 2 mL Eppendorf vial followed by 500 µL of methanol:water solution (50:50 v/v). This was vortexed and 200 µL transferred into a HPLC vial. The solution was analysed by HPLC-DAD and UHPLC-QTOF-MS at time 0, 24, 48, 72, 96 and 408 min. Also, from the 2C-B-AN working solution, 100 µL was spiked into 0.5 mL of equine blood and extracted immediately utilising liquid-liquid extraction with sodium carbonate buffer (pH 12) and chlorobutane with back extraction into dilute sulphuric acid. All procedures were based on previously published methods (67).

Time profile analysis of the 2C-B-AN methanolic solution (through monitoring the chromatographic peak height of 2C-B-AN and 2C-B) exhibited a decrease of 2C-B-AN of 46% after 24 minutes and a decrease of 90% after 96 minutes with

corresponding production of 2C-B (Figure 2). Analysis of the equine blood spiked with 2C-B-AN (time 0) detected no 2C-B-AN and only 2C-B. These results indicated that 2C-B-AN rapidly degrades to 2C-B in solution and in biological fluid and confirmed that 2C-B-AN is indeed a prodrug for 2C-B, as whilst an *in vitro* experiment, this would be expected to similarly occur *in vivo*. Figures 3 and 4 provide UV and accurate mass-spectrometry (including MS/MS) data for other researchers and analytical toxicologists.

1.3 Prodrugs of other NPS

Other common pharmacological types of NPS include the synthetic opioids and synthetic cannabinoid receptor agonists (SCRAs, also known as synthetic cannabinoids) (7,68-70). Whilst chemical precursors for the synthesis of numerous fentanyl analogues (fentanils) have been seized and detected, there are no published data or accessible drug forum reports pertaining to specific fentanyl-based prodrugs. This is also the case for SCRAs and likewise, there are no published data or accessible drug forum reports pertaining to specific synthetic cannabinoid prodrugs.

Discussion

Whether to evade any particular drug legislation or in the pursuit of experimentation, regardless of the disparate reasons for the existence, development and exploitation of NPS prodrugs, they do pose some forensic challenges. This is especially the case within clinical, post-mortem, medico-legal and forensic toxicology in situations where only biological fluid is available for analysis and is the matrix in question. Specifically, those drugs that metabolise in such a way the originally ingested drug is not present for detection and confirmation of use (e.g. 1P-LSD etc.), but there may be some unique metabolites that allow such an interpretation to be made (e.g. 4-hydroxyclobenzorex) (17). However, as found and outlined by Wagmann et al. for many of the lysergamides, such metabolites may be present at only very low concentrations (undetectable) and even if detected may share a metabolic pathway for another drug, thus preventing absolute confirmation of the original drug consumed (51). This can be further compounded by inherent instability of the substance (one of the reasons in which it would serve as a prodrug in the first place) and for those drugs that have the potential to be rapidly and completely converted to the intended drug (e.g. 2C-B-AN) then this means it is not possible to determine the parent compound. This might also present challenges in situations where drug stability has to be evaluated as well (e.g. see 1P-LSD or 1P-ETH-LAD (44,48,52) and 2C-B-AN). Such challenges are not as problematic for the analytical chemist and drug analyst tasked with analysing a physical product (e.g. drug seizure or scene evidence) as direct analytical techniques such as infra-red or Raman spectroscopy as well as nuclear magnetic resonance spectroscopy allow capturing of chemical and physical information often without instigating an unstable environment. However, if some preparation was needed (e.g. dissolving the product into solution for ultra-violet spectrophotometry) then some of the same instability issues may persist (e.g.

2C-B-AN). As such it is important for toxicologists and analytical chemists to be aware of the existence of these known and potential prodrugs, not least within the changing and evolving context of NPS in particular. It should also be noted that prodrugs are different from known and regularly encountered precursor substances that may be used in the synthesis of a substance, although as with t-BOC-MDMA, the original substance may be chemically manipulated to produce the intended drug (i.e. MDMA) (30).

Conclusion

The concept of a prodrug is not new and has been known and utilised for many decades, with particular benefits within medicine for efficacy and patient safety. Prodrugs of psychoactive substances are also not particularly new including purposeful misuse of legitimate medicines for the intention of obtaining a certain pharmacological effect from the resultant substance(s) formed invariably *in vivo*. Based on the literature and information shared on the Internet, this has also extended to considerations of prodrugs of NPS (often internationally or domestically controlled). However, data from national and international early warning systems and law enforcement indicate that NPS prodrugs are not currently widely available or problematic, especially compared to the corresponding “classical” or associated drugs they are intend to be substituted for. Nevertheless, with ever changing drug markets, this may not always be the case and it is important that there is sufficient awareness of the concept and potential impact (legislative or otherwise) and associated forensic implications, not just for chemical analysis but also for toxicological considerations when a substance has been used.

References

1. Evans-Brown M, Sedefov R. New psychoactive substances: driving greater complexity into the drug problem. Addiction 2017;112(1):36–8.
2. UK Government. Psychoactive Substances Act 2016. http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted/data.htm (accessed November 29, 2019)
3. UK Government. Psychoactive Substances Act Forensic Strategy May 2016. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/524891/psychoactive-substances-act-forensic-strategy.docx (accessed November 29, 2019)
4. UK Government. Review of the UK Psychoactive Substances Act November 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/

attachment_data/file/756896/Review_of_the_Psychoactive_Substances_Act__2016___web_.pdf (accessed November 29, 2019)
5. Bluelight. A new direction for research chemicals - 2014. https://www.bluelight.org/xf/threads/a-new-direction-for-research-chemicals.724774/ (accessed November 29, 2019)
6. Rautio J, Kärkkäinen J, Sloan KB. Prodrugs - Recent approvals and a glimpse of the pipeline. Eur J Pharm Sci 2017;109:146–161.
7. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). European Drug Report 2019. http://www.emcdda.europa.eu/edr2019_en (accessed November 29, 2019)
8. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2019. https://wdr.unodc.org/wdr2019/prelaunch/WDR19_Booklet_4_STIMULANTS.pdf (accessed November 29, 2019)
9. Cody JD. Metabolic precursors to amphetamine and methamphetamine. Forensic Sci Rev 1993;5(2):109–27.
10. Musshoff F. Illegal or legitimate use? Precursor compounds to amphetamine and methamphetamine. Drug Metab Rev 2000;32(1):15–44.
11. Coghill DR, Caballero B, Sorooshian S, Civil R. A systematic review of the safety of lisdexamfetamine dimesylate. CNS Drugs 2014;28(6):497–511.
12. Jasinski DR, Krishnan S. Abuse liability and safety of oral lisdexamfetamine dimesylate in individuals with a history of stimulant abuse. J Psychopharmacol 2009;23(4):419-427.
13. Ermer JC, Pennick M, Frick G. Lisdexamfetamine dimesylate: prodrug delivery, amphetamine exposure and duration of efficacy. Clin Drug Investig 2016;36(5):341–356.
14. Bluelight. Vyvanse – 2010. https://drugs-forum.com/threads/vyvanse-recreational-dose.116110/ (accessed November 29, 2019)
15. Bluelight. Lisdexamfetamine – 2016. https://www.bluelight.org/xf/threads/vyvanse-lisdexamfetamine.805268/ (accessed November 29, 2019)
16. Young R, Darmani NA, Elder EL, Dumas D, Glennon RA. Clobenzorex: evidence for amphetamine-like behavioral actions. Pharmacol Biochem Behav 1997;56(2):311–16.
17. Cody JT, Valtier S. Amphetamine, clobenzorex, and 4-hydroxyclobenzorex levels following multidose administration of clobenzorex. J Anal Toxicol 2001;25(3):158–165.
18. Simkin B, Wallace L. A controlled clinical trial of benzphetamine (didrex) in the management of obesity. Curr Ther Res Clin Exp 1960;2:33–8.
19. Bach MV, Coutts RT, Baker GB. Metabolism of N,N-dialkylated amphetamines, including deprenyl, by CYP2D6 expressed in a human cell line. Xenobiotica 2000;30(3):297–306.

20. Cody JT, Valtier S. Detection of amphetamine and methamphetamine following administration of benzphetamine. J Anal Toxicol 1998;22(4):299–309.
21. Bluelight. Benzphetamine – 2007. https://drugs-forum.com/threads/is-benzphetamine-oral-didrex-any-good.29307/ (accessed November 29, 2019)
22. Bluelight. Benzphetamine – 2010. https://www.bluelight.org/xf/threads/benzphetamine.528761/ (accessed November 29, 2019)
23. Kristen G, Schaefer A, von Schlichtegroll A. Fenetylline: therapeutic use, misuse and/or abuse. Drug Alcohol Depend 1986;17(2-3):259–271.
24. Nickel B, Niebch G, Peter G, von Schlichtegroll A, Tibes U. Fenetylline: new results on pharmacology, metabolism and kinetics. Drug Alcohol Depend 1986;17(2-3):235–257.
25. Yoshimura H, Yoshimitsu T, Yamada H, Koga N, Oguri K. Metabolic fate of fenetylline in rat and man. Xenobiotica 1988;18(8):929–940.
26. Katselou M, Papoutsis I, Nikolaou P, Qammaz S, Spiliopoulou C, Athanaselis S. Fenethylline (Captagon) Abuse - Local problems from an old drug become universal. Basic Clin Pharmacol Toxicol 2016;119(2):133–140.
27. Bluelight. Captagon - 2013. https://drugs-forum.com/threads/captagon-amphetamine-compound.221698/ (accessed November 29, 2019)
28. Bluelight. Captagon – 2014. https://www.bluelight.org/xf/threads/real-captagon-pills.712348/ (accessed November 29, 2019)
29. Collins M, Bhattarai A, Salouros H. Another chemically masked drug: p-tosyl methylamphetamine. Drug Test Anal 2018;10(5):898–905.
30. Collins M, Donnelly C, Cameron S, Tahtouh M, Salouros H. Identification and characterization of N-tert-butoxycarbonyl-MDMA: a new MDMA precursor. Drug Test Anal 2017;9(3):399–404.
31. Westphal F, Girreser U, Holz K, Erkens M. Strukturaufklärung und analytische Daten eines ungewöhnlichen MDMA-Derivates [Structure elucidation and analytical data of an unusual MDMA derivative]. Toxichem Krimtech 2016;83(2): 92–102.
32. Johnson CS, Bogun B. Chemical camouflage: illicit drug concealment using di-tert-butyldicarbonate. Aust J Forensic Sci 2019; 51(Sup1): S217–S219.
33. Mihailova D, Rosen A, Testa B, Beckett AH. A pharmacokinetic investigation of the distribution and elimination of diethylpropion and its metabolites in man. J Pharm Pharmacol 1974;26(9):711–721.
34. Bluelight. 4-Methyl cathinone? – 2011. https://www.bluelight.org/xf/threads/4-methyl-cathinone.553445/ (accessed November 29, 2019)
35. Camilleri A, Johnston MR, Brennan M, Davis S, Caldicott DG. Chemical analysis of four capsules containing the controlled substance analogues 4-methylmethcathinone, 2-fluoromethamphetamine, alpha-phthalimidopropiophenone and N-ethylcathinone. Forensic Sci Int 2010;197(1-3):59–66.

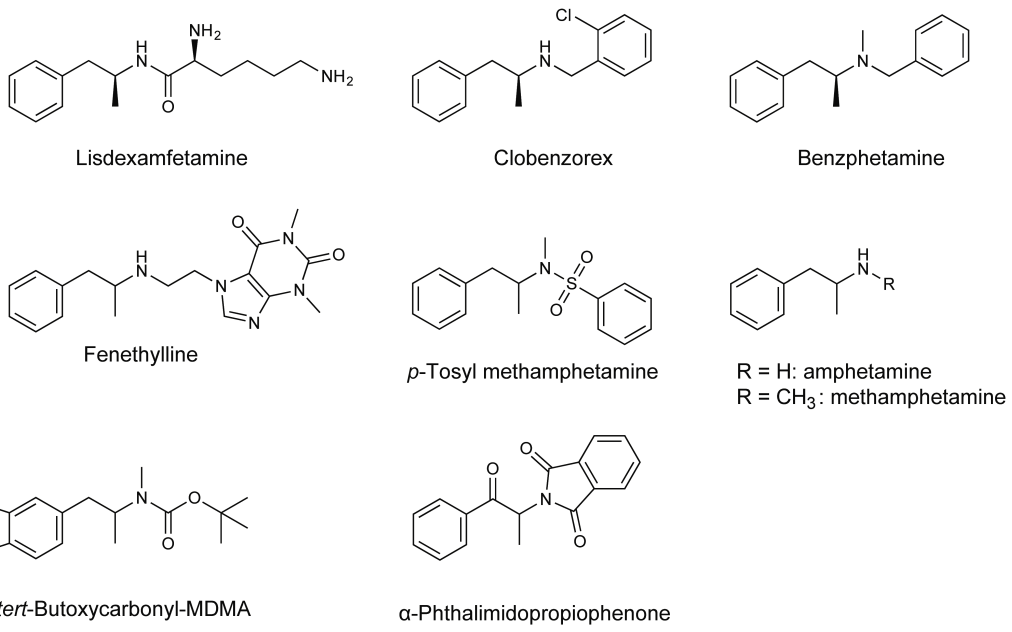
36. Nash C, Butzbach D, Stockham P, Scott T, Abroe G, Painter, B. et al. A fatality involving furanylfentanyl and MMMP, with presumptive identification of three MMMP metabolites in urine. J Anal Toxicol 2018;43(4):291–8.
37. United Nations Office on Drugs and Crime (UNODC). Early Warning Advisory NPS Portal. https://www.unodc.org/LSS/Home/NPS (accessed November 29, 2019)
38. Guillou C, Reniero F, Lobo Vicente J, Holland M, Kolar K, Chassaigne H et al. Collaboration of the Joint Research Centre and European customs laboratories for the identification of new psychoactive substances. Curr. Pharm. Biotechnol 2018;9(2):91–8.
39. Liechti ME. Modern clinical research on LSD. Neuropsychopharmacology. 2017;42(11):2114–2127.
40. Shulgin A, Shulgin A. PiHKAL: A chemical love story. California, USA: Transform Press, 1991.
41. Shulgin A, Shulgin A. TiHKAL: The continuation. California, USA: Transform Press, 1997.
42. Halberstadt AL. Pharmacology and toxicology of N-benzylphenethylamine ("NBOMe") hallucinogens. Curr Top Behav Neurosci 2017;32:283–311.
43. Colestock T, Wallach J, Mansi M, Filemban N, Morris H, Elliott SP et al. Syntheses, analytical and pharmacological characterizations of the 'legal high' 4-[1-(3-methoxyphenyl)cyclohexyl]morpholine (3-MeO-PCMo) and analogues. Drug Test Anal 2018;10(2):272–283.
44. Wallach J, Colestock T, Cicali B, Elliott SP, Kavanagh PV, Adejare A et al. Syntheses and analytical characterizations of N-alkyl-arylcyclohexylamines. Drug Test Anal 2016;8(8):801–815.
45. Wallach J, Brandt SD. Phencyclidine-based new psychoactive substances. Handb. Exp. Pharmacol 2018;251:261–303.
46. Brandt SD, Kavanagh PV, Westphal F, Stratford A, Elliott SP, Hoang K et al. Return of the lysergamides. Part I: Analytical and behavioural characterization of 1-propionyl-d-lysergic acid diethylamide (1P-LSD). Drug Test Anal 2016;8(9): 891–902.
47. Brandt SD, Kavanagh PV, Westphal F, Elliott SP, Wallach J, Colestock T et al. Return of the lysergamides. Part II: Analytical and behavioural characterization of N^6-allyl-6-norlysergic acid diethylamide (AL-LAD) and (2'S,4'S)-lysergic acid 2,4-dimethylazetidide (LSZ). Drug Test Anal 2017;9(1):38–50.
48. Brandt SD, Kavanagh PV, Westphal F, Elliott SP, Wallach J, Stratford A et al. Return of the lysergamides. Part III: Analytical characterization of N^6-ethyl-6-norlysergic acid diethylamide (ETH-LAD) and 1-propionyl ETH-LAD (1P-ETH-LAD). Drug Test Anal 2017;9(10):1641–9.
49. Brandt SD, Kavanagh PV, Twamley B, Westphal F, Elliott SP, Wallach J et al. Return of the lysergamides. Part IV: Analytical and pharmacological characterization of lysergic acid morpholide (LSM-775). Drug Test Anal 2018;10(2):310–322.

50. Halberstadt AL, Klein LM, Chatha M, Valenzuela LB, Stratford A, Wallach J et al. Pharmacological characterization of the LSD analog N-ethyl-N-cyclopropyl lysergamide (ECPLA). Psychopharmacology (Berl) 2019;236(2):799–808.
51. Wagmann L, Richter LHJ, Kehl T, Wack F, Bergstrand MP, Brandt SD et al. In vitro metabolic fate of nine LSD-based new psychoactive substances and their analytical detectability in different urinary screening procedures. Anal Bioanal Chem 2019;411(19):4751–4763.
52. Grumann C, Henkel K, Stratford A, et al. Validation of an LC-MS/MS method for the quantitative analysis of 1P-LSD and its tentative metabolite LSD in fortified urine and serum samples including stability tests for 1P-LSD under different storage conditions. J Pharm Biomed Anal. 2019;174:270–276.
53. Bluelight. ALD-52 – 2008. https://www.bluelight.org/xf/threads/ald-52-refined-cleaner-lsd.390717/ (accessed November 29, 2019)
54. Bluelight. The Big Dandy 1P-LSD – 2015. https://www.bluelight.org/xf/threads/the-big-dandy-1p-lsd-thread-volume-1.745848/ (accessed November 29, 2019)
55. The Hip Forums. 1P-LSD – 2015. https://www.hipforums.com/forum/threads/1p-lsd.465609/ (accessed November 29, 2019)
56. Reddit. 1B-LSD? – 2018. https://www.reddit.com/r/researchchemicals/comments/9iipsp/1b_lsd/ (accessed November 29, 2019)
57. Halberstadt AL, Chatha M, Klein AK, et al. Pharmacological and biotransformation studies of 1-acyl-substituted derivatives of d-lysergic acid diethylamide (LSD). Neuropharmacology. 2019:107856.
58. Geiger HA, Wurst MG, Daniels RN. DARK Classics in Chemical Neuroscience: Psilocybin. ACS Chem Neurosci 2018;9(10):2438–2447.
59. Drugs Forum. 4-Aco-DMT Experiences – 2006. https://drugs-forum.com/threads/4-aco-dmt-4-acetoxy-n-n-dimethyltryptamine-psilacetin-experiences.40643/ (accessed November 29, 2019)
60. Erowid. 4-Acetoxy-DMT – 2007. https://erowid.org/chemicals/4_acetoxy_dmt/4_acetoxy_dmt.shtml (accessed November 29, 2019)
61. Giroud C, Augsburger M, Rivier L, Mangin P, Sadeghipour F, Varesio E. 2C-B: a new psychoactive phenylethylamine recently discovered in Ecstasy tablets sold on the Swiss black market. J Anal Toxicol 1998;22(5):345–355.
62. Papaseit E, Farré M, Pérez-Mañá C, Torrens M, Ventura M, Pujadas M et al. Acute pharmacological effects of 2C-B in humans: an observational study. Front Pharmacol 2018;9:206.
63. Bluelight. 2C-B-AN – 2016. https://www.bluelight.org/xf/threads/the-small-handy-2c-b-an-2c-b-aminonitrile-thread-2c-b-prodrug.781753/ (accessed November 29, 2019)

64. Reddit. 2C-B-AN – 2016. https://www.reddit.com/r/researchchemicals/comments/420jhp/2cban/ (accessed November 29, 2019)
65. UK Chemical Research. 2C-B-AN – 2016. https://www.ukchemicalresearch.org/Thread-2C-B-AN-aminil (accessed November 29, 2019)
66. Trachsel D, Lehmann D, Enzensperger C. Phenethylamine: Von der Struktur zur Funktion [Phenethylamines: from structure to function]. Nachtschatten Science. Solothurn, Switzerland. 2012.
67. Soh Y, Elliott S. An investigation of the stability of emerging new psychoactive substances, Drug Test Anal 2013;6:696–704.
68. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2019. https://wdr.unodc.org/wdr2019/prelaunch/WDR19_Booklet_5_CANNABIS_HALLUCINOGENS.pdf (accessed November 29, 2019)
69. Moody MT, Diaz S, Shah P, Papsun D, Logan BK. Analysis of fentanyl analogs and novel synthetic opioids in blood, serum/plasma, and urine in forensic casework. Drug Test Anal 2018;10(9):1358–1367.
70. Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend 2014;144:12–41.

Figures

A



B

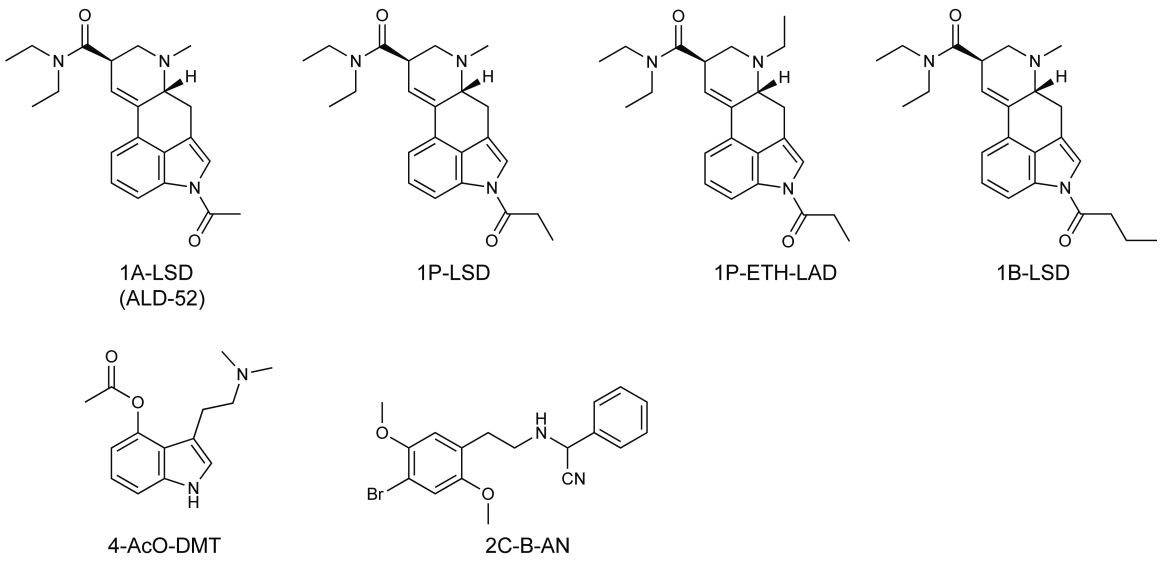


FIG. 1A-*Chemical structures of selected stimulant substance prodrugs.* FIG. 1B-*Chemical structures of selected hallucinogenic substance prodrugs*

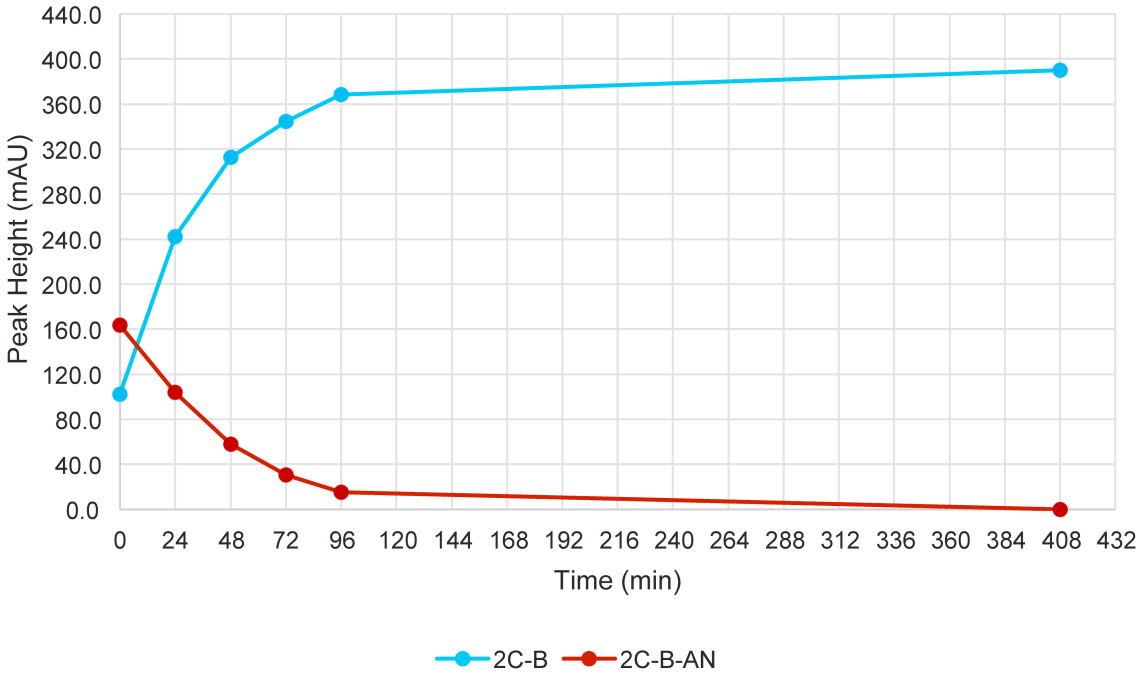


FIG. *2-Degradation profile of 2C-B-AN to 2C-B in methanol:water (50:50 v/v) monitored by HPLC-DAD*

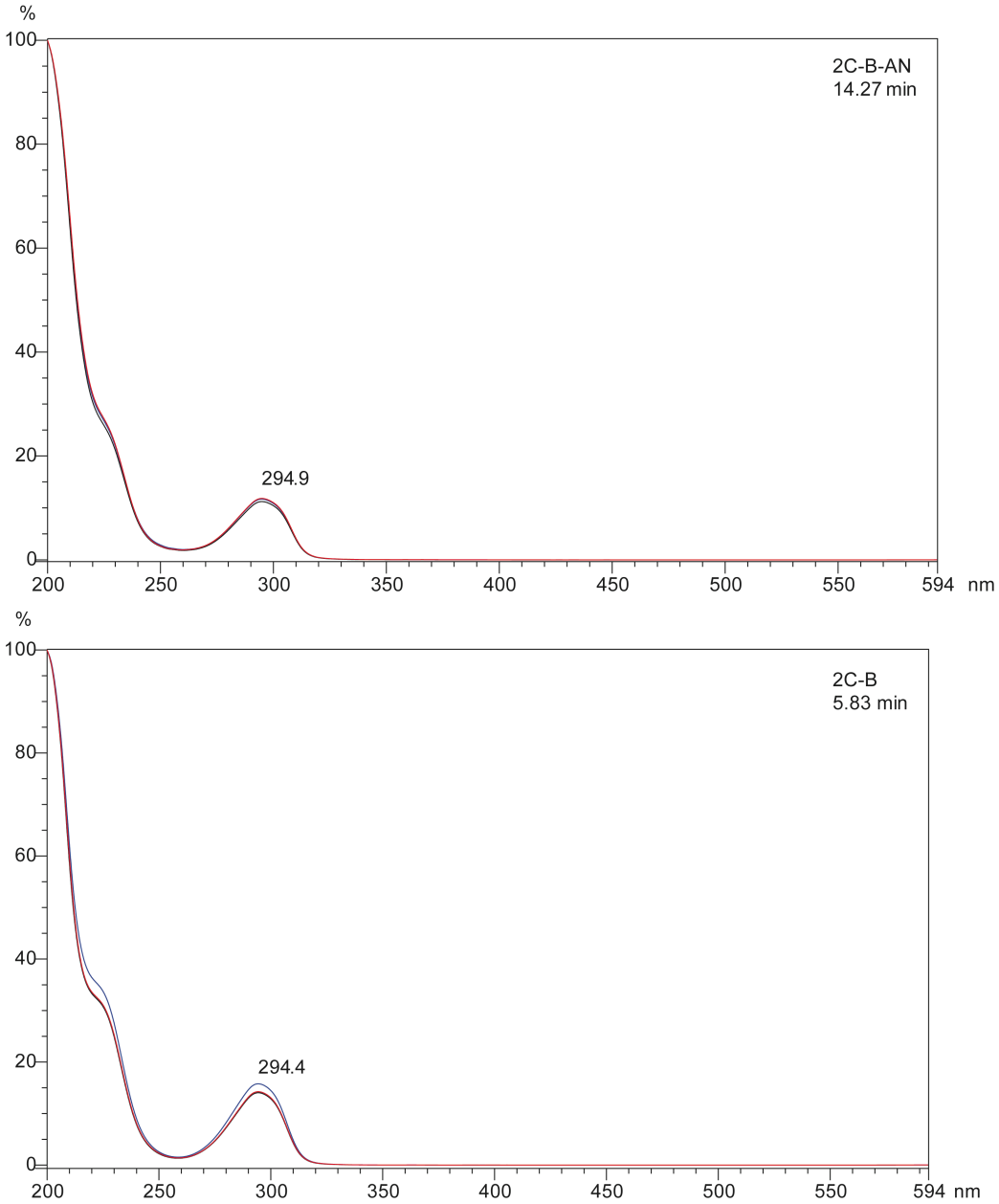


FIG. 3-*UV spectrum of 2C-B-AN and 2C-B*

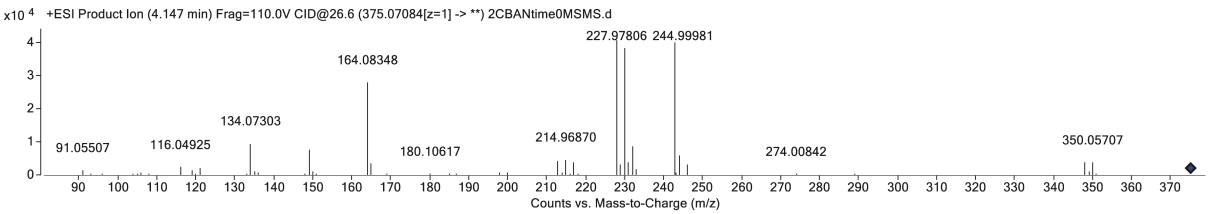


FIG. 4-*Accurate mass-spectrometry analysis of 2C-B-AN (m/z 375.07027)*