JOURNAL OF CHEMICAL EDUCATION

Article

pubs.acs.org/jchemeduc

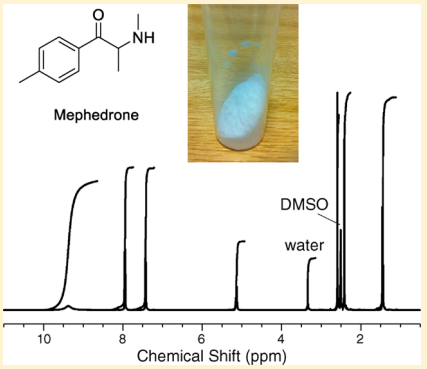
The Khat and Meow Meow Tale: Teaching the Relevance of Chemistry through Novel Recreational Drugs

Suzanne Fergus,* Kathryn Kellett, and Ute Gerhard

School of Life and Medical Sciences, Department of Pharmacy, University of Hertfordshire, College Lane, Hatfield AL10 9AB, United Kingdom

Supporting Information

ABSTRACT: Using current research and real-life scenarios to motivate students to understand chemistry principles is a key strategy in learning and teaching. An illustration of psychoactive drugs referred to as "legal highs" used in the U.K. and Europe is presented to highlight key chemistry principles and relate the importance of chemistry research in healthcare. Specific topics include stereochemistry, ^{1}H NMR characterization, organic synthesis, and functional groups, which can be used in chemistry curricula for high school students and also in higher education programs. A contextualized example focused on mephedrone is used during an interpretative spectroscopy exercise in a second-year bioscience program. Student evaluations on the use of this case study approach were very positive. This topic on psychoactive drugs integrates chemistry in social and legal issues relating to patient safety. It highlights public awareness of "legal highs" and the generalized perception that "natural products" are safe and nontoxic.



KEYWORDS: *General Public, Curriculum, Drugs/Pharmaceuticals*

INTRODUCTION

Contextualization of chemistry is a strategy using real life scenarios as a starting point in order to study and reinforce a scientific concept.[1] Such context-based approaches not only focus on the scientific activity of inquiry but also establish the scenario in a wider social context. Contextualization helps to answer the "*Why*?" in students' minds: *why* is this relevant, *why* should one learn this information? It is known that such approaches help motivate students and there have been continuous efforts to emphasize the usefulness and impact of using contextualization with learning and teaching of chemistry.[2−4] It is also important that students observe the link between current scientific research and their own personal learning. The following example, involving psychoactive substances referred to as "legal highs", has emerged as a social issue in the U.K. and Europe in recent years.[5] Officially, these chemicals are now referred to as Novel Psychoactive Substances (NPS) and are either still legal or have recently been made illegal. It has been reported that the identity of these substances is often different than that which is reported on the label.[6] This has led to the urgency for scientific information as healthcare professionals are dealing with patients admitted to Emergency Departments resulting from the consumption of these drugs. It is important that healthcare professionals, who engage with these drug issues, have a good working knowledge of new substances of abuse. This is where chemistry is essential in providing critical information to understand this phenomenon. The following article describes the development of mephedrone, a synthetically modified compound related to the psychoactive natural product cathinone, and this example supports such an approach used to discuss other drugs from natural sources.[7,8] The background information illustrates many concepts, such as stereochemistry, ^{1}H NMR characterization, organic synthesis, and functional groups, that teachers can use to emphasize learning outcomes in their own specific lesson plans. It has direct relevance for applied chemistry programs in higher education that involve patient safety but can also be used in high school chemistry curricula. A classroom activity was designed to provide students with evidence based on two Internet-purchased products. This simulates the current challenge of identifying novel psychoactive substances available for purchase. Students are asked to examine and interpret this evidence in order to propose the identity of the unknown products. This approach has been used previously in laboratory experiments; however, due to the legal restrictions related to the handling of controlled substances utilized in this activity, it is not feasible that students work directly with the compounds.[9,10] Student evaluations are discussed and highlight both the benefits and possible limitations using such an approach.

IN THE BEGINNING, THERE WAS KHAT

Khat (*Catha edulis*) is a shrub predominantly cultivated in Kenya, Yemen, and Ethiopia, where it is the second largest export after coffee. Its leaves are chewed daily by over 20 million people on the Arabian Peninsula and in East Africa.[11] The chewing of khat leaves produces a stimulatory and euphoric sensation that one could compare to a mild

dx.doi.org/10.1021/ed2004966 | J. Chem. Educ. XXXX, XXX, XXX−XXX

amphetamine high. Estimates suggest that approximately 7 tons of khat arrive at Heathrow airport in the U.K. weekly.[12] Cathinone is one of a number of alkaloids that can be isolated from the natural product (Figure 1) with its content varying

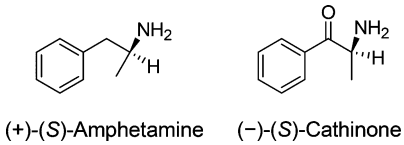


Figure 1. Chemical structures of (−)-(*S*)-cathinone and (+)-(*S*)-amphetamine.

from 0.9 to 3.3%, depending on the khat plant's origin.[13] Analysis using liquid chromatography−mass spectrometry (LC−MS) confirmed the presence of 62 alkaloids in crude methanolic extracts of fresh khat.[11]

The chemical structure of cathinone is very similar to amphetamine (1-phenylpropan-2-amine, Figure 1); it is a β-keto analogue of amphetamine due to the carbonyl functional group present in its chemical structure. The major active constituent of khat is (−)-(*S*)-cathinone, which has the same absolute configuration as (+)-(*S*)-amphetamine.[14]

Cathinone acts as a central nervous system stimulant and has a direct sympathomimetic mode of action, therefore facilitating effects at both the central dopaminergic and peripheral noradrenergic presynaptic sites.[11,13] Cathinone stimulates the release of, and then inhibits the reuptake of, monoamine neurotransmitters. This induced "fight-or-flight" response explains the effects of cathinone in the human body. The presence of the β-keto group reduces the ability of cathinone to cross the blood-brain barrier in comparison to amphetamine, and hence, cathinone has a similar effect to amphetamine, but with a lower potency.[15]

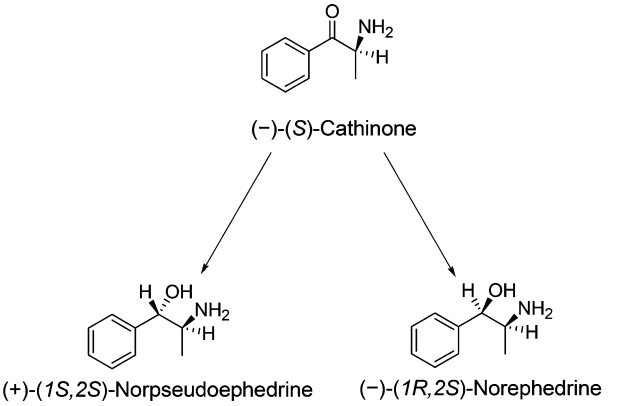
Cathine (norpseudoephedrine) is another alkaloid present in khat that is a milder psychostimulant compared to cathinone.[11] The World Anti-Doping Agency lists cathine as a prohibited substance and their regulations, used in Olympic Games, state its concentration limit in urine is 5 μg per milliliter.[16] If an amount greater than this is detected using analytical techniques, then an athlete is in breach of regulations and disqualified.[17]

Normally, fresh khat leaves contain a higher proportion of cathinone and, upon drying or storage, cathinone breaks down into cathine, explaining the demand for fresh leaves among khat chewers. After harvesting, the fresh khat leaves are wrapped with banana leaves to help retain their moisture and slow down the degradation process.[11]

The metabolism of cathinone (Scheme 1) by reduction to norephedrine and norpseudoephedrine is rapid and occurs mainly through the liver. Only about 2% of cathinone is excreted in urine.[18]

Khat consumption has adverse effects on health with raised blood pressure, heart rate, and an increase in myocardial infarction, liver failure, depression, psychoses, and dependence.[18] Cathinone is a controlled substance in the U.S. (Schedule 1 under U.S. Controlled Substance Act) and U.K. (Class C, Schedule 1). Deaths associated with khat consumption do occur.[19] So a natural product, cathinone, is known to have psychoactive properties and to be an illegal substance; what if the structure was altered slightly to produce synthetic derivatives that would circumvent the legal restrictions? Would these synthetic derivatives maintain a similar activity to the lead compound? This has led to the development of mephedrone.

Scheme 1. Products Formed from (−)-(*S*)-Cathinone during Storage or Metabolism



AND THEN THERE WAS MEOW MEOW

The addition of methyl groups at the amino group and at the 4 position on the benzene ring of cathinone results in the synthetic derivative mephedrone (4-methylmethcathinone, Figure 2), which does indeed display similar effects as cathinone.

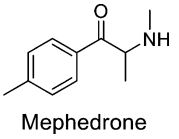
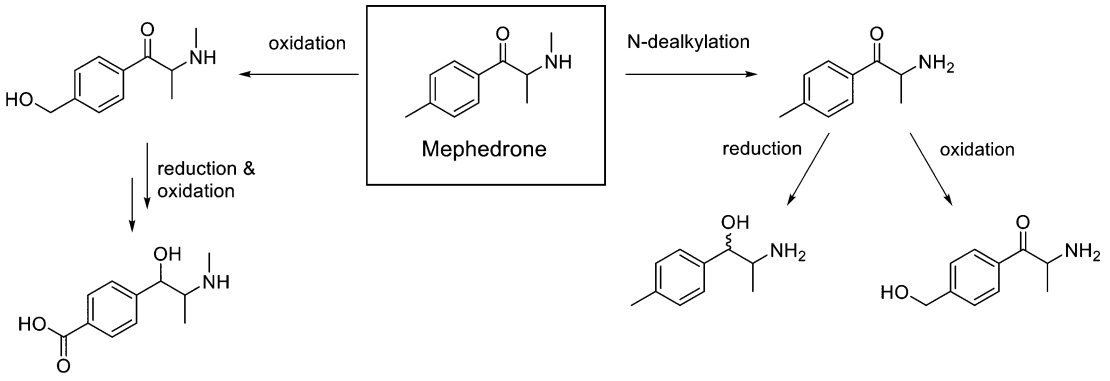


Figure 2. Chemical structure of mephedrone (4-methylmethcathinone).

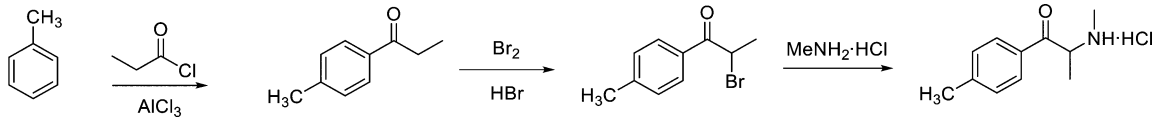
Mephedrone has grown in popularity in the U.K. and Europe as a recreational drug. It has other popular code names, including "Meow Meow", "Meph", "Bubbles", "Spice E", "Charge", "M-CAT", and "Rush", and is sold through Internet vendors and high street "head shops."[20] The pattern of recreational drug use has changed in the past decade, particularly in the club scene. There has been a fall in the reported use of MDMA (3,4-methylenedioxymethamphetamine or "ecstasy") from 79.3% in 1999 to 48.4% in 2009.[21] There has been an increase in other recreational drugs with dedicated Web sites, such as *Erowid*, providing a wide range of information relating to a number of these designer drugs, their effects, and also the legal implications.[22] The effects of mephedrone are regarded by users as both stimulant (like speed) and hallucinogenic (like ecstasy). The main physical effects of mephedrone include nose-bleeds, dilated pupils, blurred vision, dry mouth, hot flushes, fast and erratic heartbeats, and muscular tension in the jaw and limbs. Mental effects include euphoria, boundless energy, talkativeness, and time distortions. The after-effects involve fatigue, dizziness, and low mood.[23,24] Of 15 patients presented to Emergency Department following mephedrone consumption, 20% required treatment with benzodiazepines, predominantly for management of agitation.[20] Self-reported dosages range from 5 mg to 200 mg. The drug is often taken with alcohol or other drugs, including cocaine, cannabis, and ketamine.[24]

dx.doi.org/10.1021/ed2004966 | *J. Chem. Educ.* XXXX, XXX, XXX−XXX

Scheme 2. Metabolism of Mephedrone



Scheme 3. Synthesis of Mephedrone Hydrochloride



Mephedrone is a white powder sold on Internet sites as a research chemical or plant food not for human consumption. Typically prices range from £10 or $15 for 1 g of mephedrone.[24] Mephedrone and the cathinone derivatives possess an asymmetric carbon. The tetrahedral structure of this carbon and the different arrangement of its four atom substituents give rise to a pair of enantiomers. Mephedrone is available as a racemate, which contains equal proportions of both the *R*- and *S*- enantiomers. In the asymmetric environment of the human body, the two enantiomers may impart different interactions with receptors in the central nervous system and this could result in one enantiomer being more potent than the other. (−)-(*S*)-Cathinone is the major active constituent in fresh khat and is more potent than (−)-(*R*)-cathinone.[11] This is not confirmed yet for mephedrone.

A CLOSER LOOK AT MEPHEDRONE

Metabolism of mephedrone has been studied in rat and human urine using gas chromatography−mass spectrometry (GC−MS) techniques.[25] It was reported that six phase I metabolites of mephedrone were detected. The proposed outline (Scheme 2) of steps in the phase I metabolism of mephedrone includes *N*-demethylation to the primary amine and reduction of the keto moiety to the corresponding alcohol or oxidation of the 4-methyl group to the corresponding alcohol and carboxylic acid via the aldehyde.

Mephedrone can be synthesized from relatively simple starting materials.[26] Friedel−Crafts acylation of toluene using proprionyl chloride, followed by bromination of the resulting 4-methylpropiophenone, and finally reaction with methylamine yields mephedrone hydrochloride salt as a racemic product (Scheme 3).

Mephedrone is spectroscopically well characterized[27] and a proton NMR spectrum of mephedrone was used in the classroom activity available in the Supporting Information section.

OTHER DRUGS FROM THE CATHINONE SCAFFOLD

The cathinone scaffold (Figure 3) can be altered via substitution of the aromatic ring (R^1), N-alkylation (R^2, R^3, or inclusion of the nitrogen atom in a ring structure) and variation of the α-carbon substituent (R^4).

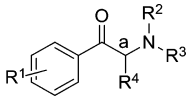


Figure 3. Cathinone scaffold.

Some cathinone derivatives encountered in the U.K. and Europe in recent years are shown in Table 1. More contemporary legislation in the U.K. has classified these derivatives as illegal since July 2010.[28]

As mephedrone is available for purchase via Internet sources, the products are normally advertised as being of "high purity." It is common that legal-high products contain other substances, such as lactose, mannitol, and saccharin. These chemicals are cutting agents used to dilute the drug product, as they cost less than the drug itself. Pharmaceutical drugs can also be present, for example, caffeine (stimulant), lidocaine (local anesthetic and antiarrhythmic), and procaine (local anesthetic). The pharmaceutical effect of these compounds can lead a user to think the product is having its desired effect. Therefore, what is obtained may not always correspond to what's on the label. "Legal-high" products purchased via Internet sites over a period of six months have been analyzed to determine their compositions.[29] Five products were found to contain a number of different cathinone derivatives different than what was advertised. Others contained benzocaine (a local anesthetic), lidocaine (a local anesthetic), and caffeine (stimulant).

Mephedrone was banned in the U.K. on 16 April 2010 after reports of associated deaths related to the consumption of this drug.[28] It is synthesized in nonprofessional laboratories and, prior to its ban, many people considered mephedrone not harmful because of its legal status. Since the ban on mephedrone, there has been a continuous emergence of newer, so-called "legal highs" (for example, NRG1, NRG2, MDAI),[30] and chemistry research is key to identify the chemical components, the purity of these drugs, and an understanding of their biological activity in the human body.

dx.doi.org/10.1021/ed2004966 | J. Chem. Educ. XXXX, XXX, XXX−XXX

Table 1. Some Cathinone Derivatives Encountered in the U.K. and Europe

Name	Common Name	R^1	R^2	R^3	R^4
3-Fluoromethcathinone	Flephedrone	4-F	Me	H	Me
4-Methylethcathinone	4-MEC	4-Me	Et	H	Me
Bk-MBDB	Butylone	3,4-methylenedioxy	Me	H	Et
MDPV	Methylenedioxypyrovalerone	3,4-methylenedioxy	pyrrolidinyl		*n*-Pr

CLASSROOM ACTIVITY

Using mephedrone as the central focus, a classroom activity was designed for use with second-year Bioscience students. The activity was used as a formative assessment during an Interpretative Spectroscopy exercise. Students covered spectroscopic techniques and their relevance to structure determination of organic compounds during lectures, followed by a series of two laboratory exercises (4 h duration each), prior to a summative assessment worth 15% of the module marks. The classroom activity was introduced as laboratory exercise number two, where students would have experienced in the first session some practice applying the theory of organic structure determination.

The activity was presented as a scenario where two legal-high products labeled M-CAT were purchased from an online Web site, each arriving as packets of 1 g of white powder. Evidence from the analyses of both products was provided, including the chemical structure of mephedrone, followed by a series of questions that students answered. The initial questions focused on the characterization of Product 1 (mephedrone), its relative molecular mass, identification of functional groups, and ^{1}H NMR characterization. Students were asked specifically to label each proton for mephedrone and the process for ^{1}H NMR characterization was structured because it had been observed in other activities that some students attempted to do this process too hastily and consequently made errors. A table was provided to complete the ^{1}H NMR characterization, as this format was also used in the previous laboratory activity. Product 1 and Product 2 were not identical, and the subsequent analysis of Product 2 aimed to challenge students' higher-level thinking to evaluate their interpretations and to compare Product 1 and Product 2. Common adulterants used in legal-high products include the stimulant caffeine and local anesthetics lidocaine and procaine. These were provided to help with the identification of Product 2 and offered further opportunities to interpret ^{1}H NMR spectra. The activity concluded with questions on the stereochemistry of mephedrone and its synthesis.

Anonymous student evaluations were obtained directly after the activity and were used to help understand what aspects of the activity students found beneficial and/or challenging. Twenty-five student responses were collected with a gender distribution of 13 males and 12 females. Twenty-one students (88%) agreed/strongly agreed that they found the activity interesting, one student neither agreed nor disagreed, and two students disagreed. In terms of using this case study approach to help students engage better with Interpretative Spectroscopy, there was a large response of agreement from 22 students (88%) with one student reporting it was the same as a normal spectral activity.

Students were asked "*Which aspect of the Activity did you find the most beneficial to your chemistry learning?*" and also "*Which aspect of the Activity did you find the most challenging?*" as open questions in order to obtain insights from the student perspective. From students' comments, the following themes emerged as benefits: integration of peaks in spectra, collaborative group work, chemical structure of mephedrone, and real world application. The activity provided an opportunity to obtain clarity on specifics relating to the interpretation of ^{1}H NMR spectroscopy, that is, integrals, coupling constants, and the additional hydrogen present in the spectrum of the mephedrone hydrochloride salt. Another benefit reported was working collaboratively in a group where students were "*able to converse on the topic of each question and gain a better understanding to get a feel for how spectra in real life are interpreted*". During the activity, students were encouraged to work in small groups to discuss the exercise. Staff and Ph.D. students were available to answer queries. The chemical structure of mephedrone was provided, and asking students to draw the structure showing all the hydrogens present was noted as a benefit—"*drawing out the hydrogens on the structure which helps when working out the ^{1}H NMR*". It was not expected that this aspect would be a specific benefit, but perhaps having used this strategy, it may be adopted in future exercises by students. Presenting the data in a different format to the previous activity using a real world application was also appreciated. In relation to aspects of the activity students found challenging, the following themes were identified: evaluation of chemical structures, coupling constants, stereochemistry, and the analysis of Product 2. The aspect of "*identifying two key features for the chemical structures of caffeine, lidocaine, and procaine*" was deemed challenging. This was expected, as it required both the interpretation of the data followed by its application to more than one chemical structure. This aligned to the higher order thinking skills of applying understanding, analysis, and evaluation according to Bloom's Taxonomy.[31] There was a contextualized question regarding the availability of mephedrone as a hydrochloride salt, and one student commented that "*answering questions which didn't apply to the interpretation e.g. why is mephedrone supplied as a hydrochloride salt?*" [sic] was the most challenging aspect of the activity. The feature of the additional hydrogen in the spectrum was evaluated as both a benefit and a challenge. It certainly encouraged students to think more and to discuss this feature during the activity.

A limitation of the activity identified from student evaluations and suspected by staff from the onset was the time constraint. There was significant content covered, particularly for a beginner to interpretative spectroscopy, as commented by one student "*they are useful but maybe on a smaller scale*". It may be more helpful to break this activity into smaller parts depending on the level of student and their familiarity with the techniques and topics included. Finally, students were asked, in general, about their opinions on using such activities in their studies. The comments were very positive regarding how the activity supported the students' learning: "*Highly useful in actually applying the knowledge based on a proposed scenario*", "*I would say it helped me think more about the topic and feel more confident*", and "*It is very helpful and makes sense to all the theoretical aspect*".

dx.doi.org/10.1021/ed2004966 | J. Chem. Educ. XXXX, XXX, XXX–XXX

CONCLUSION

The story of khat and meow meow highlighted very current social issues relating to recreational drugs, patient safety, and the legal challenge facing regulators. Chemistry was pivotal in understanding this phenomenon, and key principles that students learned were utilized for this purpose. This contextualized story can be used to highlight an awareness of "legal highs" and recreational drugs, the generalized perception that "natural products" are safe and nontoxic, and illustrate how analytical chemistry techniques are used to understand the identity and purity of such products.

ASSOCIATED CONTENT

Supporting Information

The mephedrone classroom activity. This material is available via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: s.fergus@herts.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The author would like to thank Andrew Hutt for useful discussions relating to the stereochemistry and metabolism of mephedrone and also to Master of Pharmacy undergraduate students Emildah Mudeke and Arzoo Shams for their input on a related "legal highs" project.

REFERENCES

(1) Pilot, A.; Bulte, A. Why do you "need to know"? Context-based education. *Int. J. Sci. Educ.* **2006**, *28*, 953−956.

(2) Bennett, J.; Luben, F.; Hogarth, S. Bringing Science to Life: A Synthesis of the Research Evidence on the Effects of Context-Based and STS Approaches to Science Teaching. *Sci. Educ.* **2007**, *91*, 347−370.

(3) Frerichs, V. A. ConfChem Conference on Case-Based Studies in Chemical Education: Use of Case Study for the Introductory Chemistry Laboratory Environment. *J. Chem. Educ.* **2013**, *90*, 268−270.

(4) Chowdry, M. A. Incorporating a Soap Industry Case Study to Motivate and Engage Students in the Chemistry of Daily Life. *J. Chem. Educ.* **2013**, *90*, 866−872.

(5) Schmidt, M. M.; Sharma, A.; Schifano, F.; Feinmann, C. "Legal highs" on the net—Evaluation of U.K.-based Websites, products and product. *Forensic Sci. Int.* **2011**, *206*, 92−97.

(6) Assi, S.; Fergus, S.; Stair, J. Identification of novel psychoactive substances (NPS) using hyphenated mass spectrometric techniques. *Spectroscopy Special Issue*. http://www.spectroscopyonline.com/spectroscopy/Mass+Spectrometry/Identification-of-Novel-Psychoactive-Substances-Us/ArticleStandard/Article/detail/765786 (accessed June 2014).

(7) Agosta, W. C. Medicines and Drugs from Plants. *J. Chem. Educ.* **1997**, *74*, 857−860.

(8) Rusterholz, D. B. Capsaicin, from Hot to Not; Can New Pain-Relieving Drugs Be Derived from This Substance Known to Cause Pain? *J. Chem. Educ.* **2006**, *83*, 1809−1815.

(9) Hasan, S.; Broomfield-Lee, D.; Oliver-Hoyo, M. T.; Cintron-Maldonado, J. A. Using Laboratory Chemicals to Imitate Illicit Drugs in a Forensic Chemistry Activity. *J. Chem. Educ.* **2008**, *85*, 813−816.

(10) Childs-Disney, J. L.; Kauffmann, A. D.; Poplawski, S. G.; Lysiak, D. R.; Stewart, R. J.; Arcadi, J. K.; Dinan, F. J. A Metabolic Murder Mystery: A Case-Based Experiment for the Undergraduate Biochemistry Laboratory. *J. Chem. Educ.* **2010**, *87*, 1110−1112.

(11) Feyissa, A. M.; Kelly, J. P. A review of the neuropharmacological properties of khat. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2008**, *32*, 1147−1166.

(12) Apps, A.; Matloob, S.; Dahdal, M. T.; Dubrey, S. W. Khat: an emerging threat to the heart in the U.K. *Postgrad. Med. J.* **2011**, *87*, 387−388.

(13) Patel, N. B. Mechanism of Action of Cathinone: The Active Ingredient of Khat (Catha Edulis). *East Afr. Med. J.* **2000**, *77*, 329−332.

(14) Dal Cason, T. A.; Young, R.; Glennon, R. A. Cathinone: An investigation of Several N-Alkyl and Methylenedioxy Substituted Analogs. *Pharmacol., Biochem. Behav.* **1997**, *58*, 1109−1116.

(15) *Advisory Council on the Misuse of Drugs on Consideration of the Cathinones*; Advisory Council on the Misuse of Drugs/ACMD: London, U.K., 2010, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119173/acmd-cathinodes-report-2010.pdf.

(16) *The 2011 Prohibited List International Standard*; World Anti Doping Agency: Montreal, Canada, 2011. https://wada-main-prod.s3.amazonaws.com/resources/files/WADA_Prohibited_List_2011_EN.pdf (accessed July 2011).

(17) Werner, T. C.; Hatton, C. K. Performance-Enhancing Drugs in Sports: How Chemists Catch Users. *J. Chem. Educ.* **2011**, *88*, 34−40.

(18) Cox, G.; Rampes, H. Adverse effects of khat: a review. *Adv. Psychiatr. Treat.* **2003**, *9*, 456−463.

(19) Corkery, J. M.; Schifano, F.; Oyefeso, A.; Ghodse, A. H.; Tonia, T.; Naidoo, V.; Button, J. "Bundle of fun" or "bunch of problems"? Case series of khat-related deaths in the U.K. *Drugs: Education, Prevention and Policy* **2014**, *18*, 408−425.

(20) Schifano, F.; Albanese, A.; Fergus, S.; Stair, J. L.; Deluca, P.; Corazza, O.; Davey, Z.; Corkery, J.; Siemann, H.; Scherbaum, N.; Farre, M.; Torrens, M.; Demetrovics, Z. A.; Hamid Ghodse, A. H. Psychonaut Web Mapping & ReDNet Research Groups. Mephedrone (4-methylmethcathinone; "meow meow"): chemical, pharmacological and clinical issues. *Psychopharmacology* **2011**, *214*, 593−602.

(21) Wood, D. M.; Greene, S. L.; Dargan, P. I. Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. *Emerg. Med. J.* **2011**, *28*, 280−282.

(22) Erowid. http://www.erowid.org/ (accessed July 2011).

(23) Brunt, T. M.; Poortman, A.; Niesink, R. J. M.; van den Brink, W. Instability of the ecstasy market and a new kid on the block: mephedrone. *J. Psychopharmacol. (London, U. K.)* **2011**, *25*, 1543−1547.

(24) Deluca, P.; Schifano, F.; Davey, Z.; Corazza, O.; Di Furia, L. Psychonaut Web Mapping Research Group. Mephedrone Report. Institute of Psychiatry, King's College London: London, U.K., 2009. http://www.psychonautproject.eu (accessed July 2011).

(25) Meyer, M. R.; Wilhelm, J.; Peters, F. T.; Maurer, H. H. Beta-keto amphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone, and methylone in urine using gas chromatography−mass spectrometry. *Anal. Bioanal. Chem.* **2010**, *397*, 1225−1233.

(26) Shiozawa, A.; Narita, K.; Izumi, G.; Kurashige, S.; Sakitama, K.; Ishikawa, M. Synthesis and activity of 2-methyl-3-aminopropiophenones as centrally acting muscle relaxants. *Eur. J. Med. Chem.* **1995**, *30*, 85−94.

(27) Gibbons, S.; Zloh, M. An analysis of the "legal high" mephedrone. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4135−4139.

(28) Home Office. http://www.homeoffice.gov.uk/about-us/corporate-publications-strategy/home-office-circulars/circulars-2010/010-2010/ (accessed July 2011).

(29) Davies, S.; Wood, D. M.; Smith, G.; Button, J.; Ramsey, J.; Archer, R.; Holt, D. W.; Dargan, P. I. Purchasing "legal highs" on the Internet—is there consistency in what you get? *Q. J. Med.* **2010**, *103*, 489−493.

(30) Gibbons, S. "Legal Highs" – novel and emerging psychoactive drugs: a chemical overview for the toxicologist. *Clin. Toxicol.* **2012**, *50*, 15–24.
(31) *A taxonomy for learning, teaching and assessing: A revision of Bloom's Taxonomy of educational objectives: Complete edition*; Anderson, L. W., Krathwohl, D. R., Eds.; Longman: New York, 2001.