



ORIGINAL ARTICLE

The next addiction-causing drug class 4-quinazolinone derivatives: analyses of methaqualone analogs including recently discovered 2-methoxyqualone by different modes of mass spectrometry

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Abstract

Purpose The information on analytical methods for 4-quinazolinone recreational drugs, such as methaqualone, etaqualone and 2-methoxyqualone, is almost scant. In this study, product ion spectra of gas chromatography–tandem mass spectrometry (GC–MS/MS) with different collision energies were presented for these drugs. Because 2-methoxyqualone is a new recreational drug discovered in dubious tablets very recently, much more detailed data obtained by different types of mass spectrometry instruments, and quantification data of 2-methoxyqualone in the tablet together with its validation were demonstrated.

Methods The methods for analyses were GC–MS/MS, high-resolution ultra-high-performance liquid chromatography–quadrupole time-of-flight mass spectrometry and liquid chromatography–tandem mass spectrometry.

Results The GC–MS/MS product ion spectra of the three compounds with different collision energies have not been reported before. They were very useful to tentatively identify unknown compounds. If a reference standard is available, the final identification and quantification can be achieved by measurements of product ion spectra and in selected reaction monitoring mode very easily by GC–MS/MS. The final identification and quantification for the new 2-methoxyqualone were performed in this way. The content of the compound was $69.8 \pm 0.5\%$ (w/w) in the tablet. Acetaminophen and caffeine coexisted in the tablet with approximate concentrations at 10 and 5%, respectively.

Conclusions In this article, we have presented product ion spectra of methaqualone, etaqualone and 2-methoxyqualone at different collision energies by GC–MS/MS for the first time. In addition, this is the first paper to describe the details of quantification of 2-methoxyqualone in the authentic seized product.

Keywords 2-Methoxyqualone · Methaqualone · Etaqualone · 4-Quinazolinone derivatives · New recreational drugs · GC–MS/MS

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Introduction

The sedative-hypnotic activity of methaqualone (structure see Fig. 1a), a 4-quinazolinone derivative, was first noted in 1955 in Europe. In 1962, methaqualone was patented in the U.S.A. by Wallace and Tiernan [1]. It was peaked in early 1970s for clinical treatment of insomnia, anxiety, and muscle stiffening. The drug rapidly gained unprecedented popularity among the younger age group and Vietnam war veterans especially due to notable symptoms of euphoria and aphrodisiac qualities. The pharmaceutical properties of methaqualone are very similar to those of benzodiazepines and barbiturates commonly acting as GABA_A receptor modulators [2], but characteristic properties of methaqualone different from those of benzodiazepines and barbiturates were noted. The differences of their actions can be explained by the unique and complicated structure of the GABA_A receptor; it comprises a plethora of receptors assembled from as many as 19 subunits. Methaqualone, benzodiazepines and barbiturates seem to exert their modulatory actions via different subunits included in the GABA_A receptor complex.

The recreational use of methaqualone had spread over the U.S.A., Europe, South America, Australia and Japan [3]. The users felt it as a safe drug at the beginning, but usually tolerance to the drug developed very soon. In 1980s, the number of fatal cases involving methaqualone ingestion becomes obvious; 246 methaqualone-related deaths were identified from January 1971 through December 1981 in the U.S.A. [4, 5]. Methaqualone is controlled in the U.S.A. (Schedule I), United Kingdom (Class B), Germany (Anlage II), Switzerland (Verzeichnis A), Austria (illegal), Canada (Schedule III), Australia (Schedule 9), and Japan (designated drug).

As the second 4-quinazolinone recreational drug etaqualone (structure see Fig. 1b) should be mentioned [6, 7]. It is a close analog of methaqualone. The dose and effects were reported to be similar to those of methaqualone, but shorter acting and slightly weaker. The drug was developed in 1960s and marketed mainly in France and some European countries. This drug is not scheduled in any country at this time.

As the third analog, the Inner Mongolia Hohhot Public Security Bureau very recently seized a package containing dubious tablets, and brought it to our laboratory to ask the analysis of unknown ingredient(s) in the tablets. We undertook the analysis and found a new psychoactive compound. To prevent further spread of the drug circulation, we have prepared and submitted a brief preliminary report on the new compound 3-(2-methoxyphenyl)-2-methylquinazolin-4(3*H*)-one (2-methoxyqualone) (structure see Fig. 1c), an analog of methaqualone, to this journal [8].

In this article, basic single-stage gas chromatography – mass spectrometry (GC–MS) spectra of

methaqualone, etaqualone and 2-methoxyqualone (Fig. 1), and product ion spectra of both methaqualone and etaqualone (Fig. 2), which were all acquired using a gas chromatography–tandem mass spectrometry (GC–MS/MS) instrument, are first presented. Second, much more details of analytical procedure and quantitative results for the newly emerging 2-methoxyqualone using ultra-high-performance liquid chromatography–quadrupole time-of-flight mass spectrometry (UHPLC–QTOF-MS), GC–MS/MS and liquid chromatography–tandem mass spectrometry (LC–MS/MS) were presented to enable easy identification and quantification of the circulating 2-methoxyqualone without difficulty.

Materials and methods

Reagents and chemicals

Methaqualone and etaqualone were purchase from Cayman chemical, Ann Arbor, MI, U.S.A.; 3-(2-methoxyphenyl)-2-methylquinazolin-4(3*H*)-one (2-methoxyqualone) (purity ≥ 97%) from BLD Pharmatech Ltd., Shanghai, China; methaqualone-*d*₇ (internal standard: IS) from LGC standards, Teddington, UK. Other common chemicals used were of the highest purity commercially available.

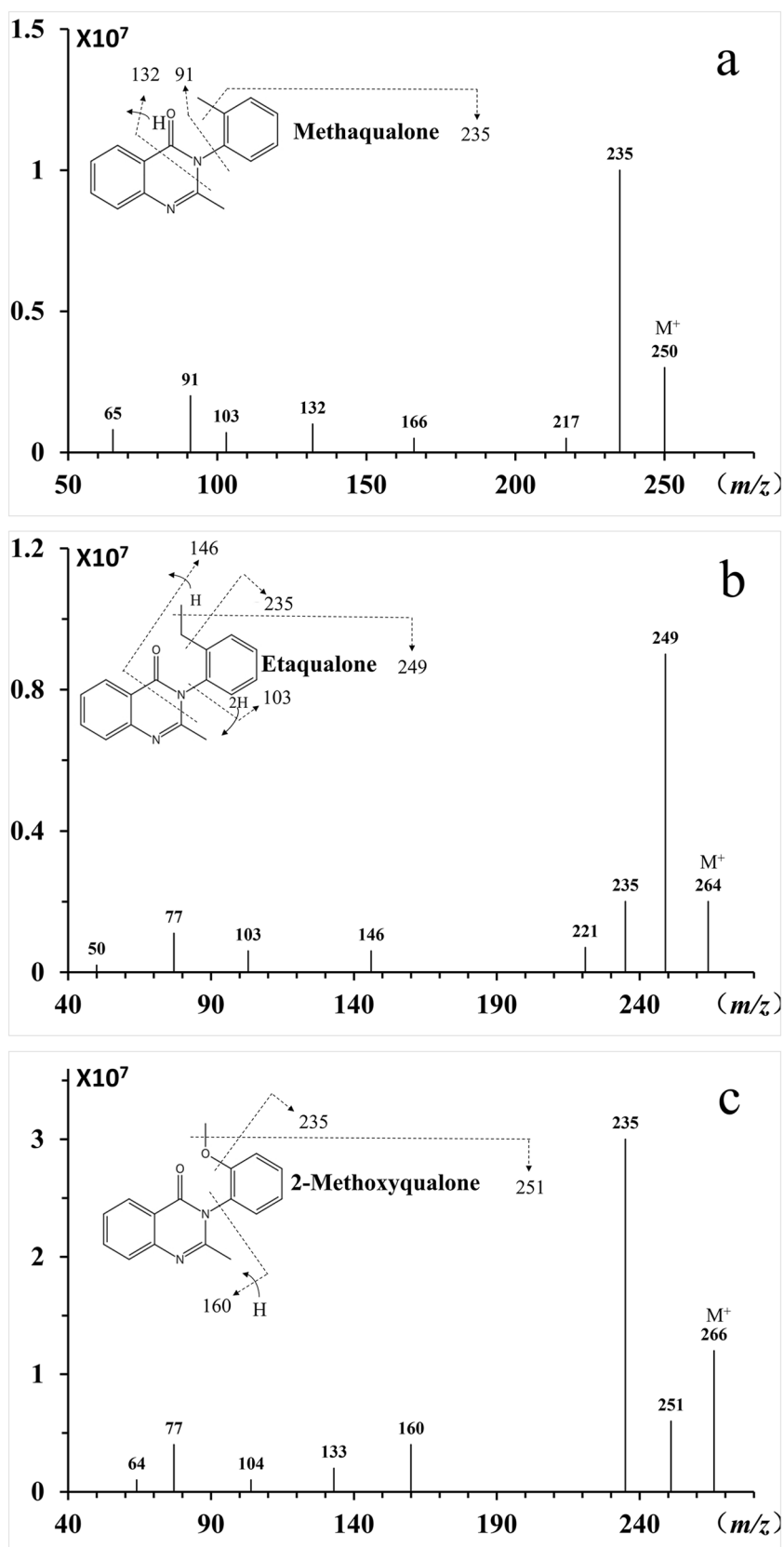
Preparation of standard solutions

The stock solutions of methaqualone, etaqualone and 2-methoxyqualone were appropriately diluted to 1000, 100, 10, 1.0 µg/mL with methanol; these working standard solutions were freshly prepared when required. The solutions were stored at -20 °C until used.

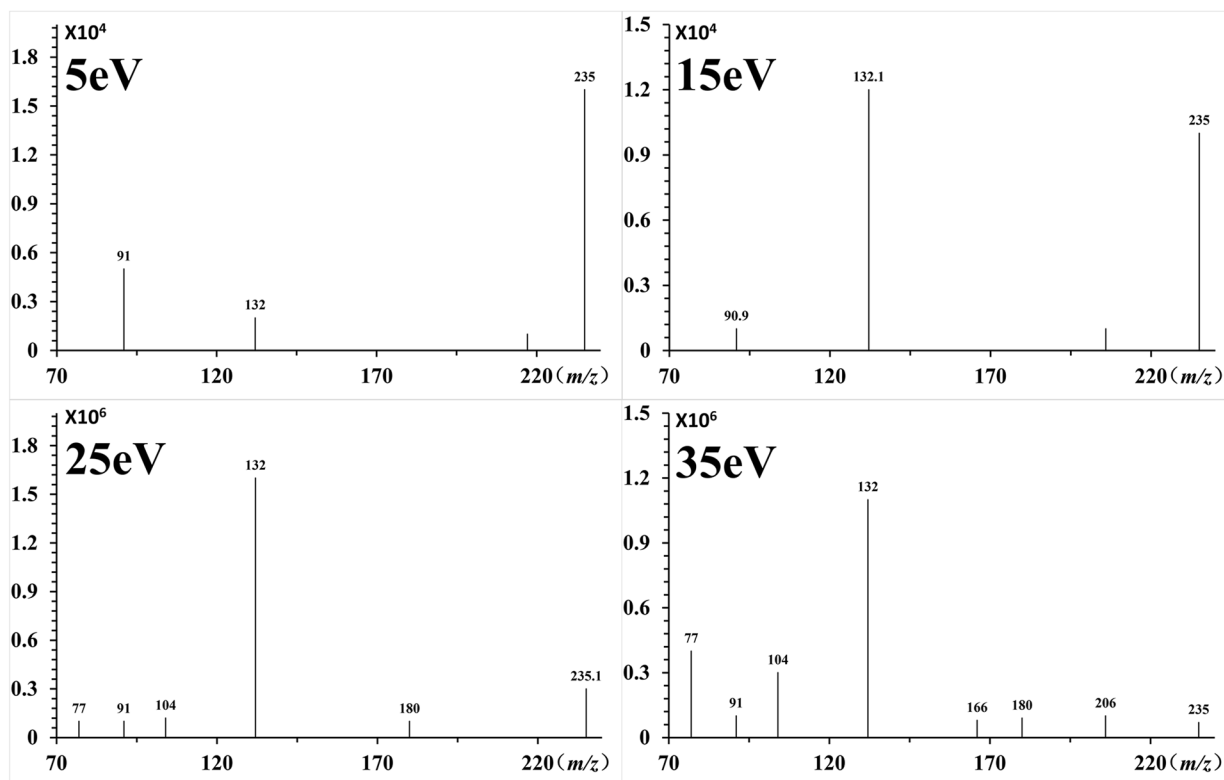
Pretreatments of the tablet in question for analysis by the standard addition method

The grayish tablet (Fig. 3) in the package was crushed and milled with a - 20 °C cryogenic grinder (JXFST-PRP-CL; Shanghai JinXin Industrial Development Co., Ltd., Shanghai, China). A 10 mg-weight of the tablet powder was placed in 15-mL centrifuge tube containing 10 mL methanol, and ultra-sonicated for 10 min. The suspension solution was diluted 10,000-fold with methanol; care was taken to maintain the homogeneity of the diluted suspension by shaking with a vortex mixer. Ten milliliters of the diluted suspension was placed in another 15-mL centrifuge tube. Seven 1.0-mL aliquots of the diluted suspension solution were separated independently to each small centrifuge tube. To the seven aliquots, 0, 10, 20, 40, 80, 100, and 200 ng of 2-methoxyqualone (all in 10 µL) were spiked respectively, and 100 ng of methaqualone-*d*₇ (IS)

Fig. 1 Single-stage gas chromatography – mass spectrometry spectra of **a** methaqualone, **b** etaqualone and **c** 2-methoxyqualone measured using the gas chromatography – tandem mass spectrometry (GC – MS/MS) instrument



a Methaqualone (precursor m/z 235)



b Etaqualone (precursor m/z 249)

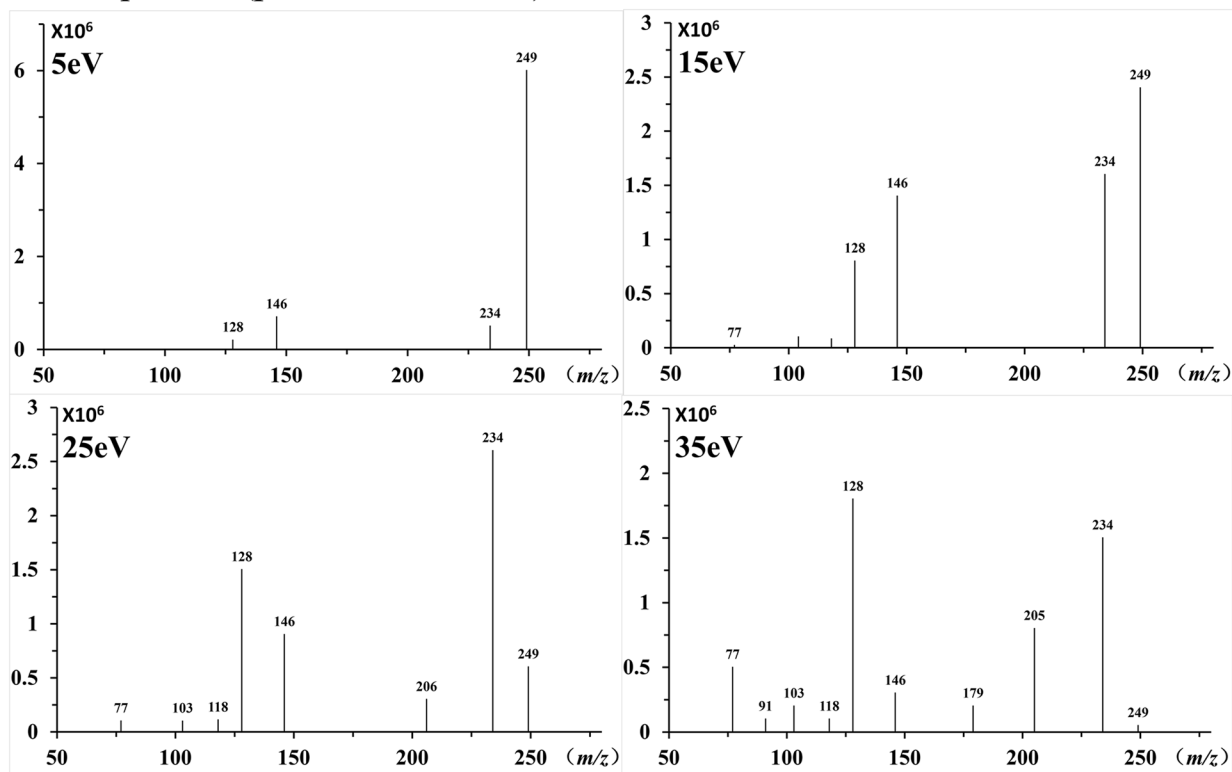


Fig. 2 Product ion mass spectra of **a** methaqualone, and **b** etaqualone measured by GC–MS/MS. For product ion spectra of 2-methoxyqualone, see below Fig. 7



Fig. 3 Photograph of an unknown tablet seized by the police

in 10 μ L was added to all aliquots to construct each standard addition calibration curve. The final suspension solutions were centrifuged at 3000 rpm for 5 min. Thus, each 1.0- μ L aliquot was subjected to injection into analytical instruments without further purification/steps.

Instrumental conditions

UHPLC – QTOF-MS

To identify an unknown compound, it is essential to detect its elemental composition delineating the probable chemical structures. An LC-40 ultra-high-performance liquid chromatography (UHPLC) combined with an LCMS-9030 high-resolution QTOF spectrometer (Shimadzu, Kyoto, Japan) was used.

Chromatographic separation was achieved with Shim-pack GIST C₁₈ column (100 $\times$ 2.1 mm, i.d., particle size 2 μ m; Shimadzu). Column conditions were: column temperature, 40 $^{\circ}$ C; mobile phases, water (A) and acetonitrile (B); injection volume, 1.0 μ L; flow rate, 0.4 mL/min; elution program, 5% B (0–1 min), 5–95% B (1–10 min), 95% B (10–12 min), 95–5% (12–12.1 min), 5% B (12.1–15 min). High-resolution MS conditions were: ionization mode, positive electrospray ionization-collision induced dissociation; ionization spray voltage, 4.5 kV; heating block temperature, 400 $^{\circ}$ C; atomization gas (N₂) flow rate, 3 L/min; drying gas (N₂) flow rate, 10 L/min; heating gas (air) flow rate, 10 L/min; mass scan range of the primary MS, m/z 100–1000; collision energy and mass scan range of the secondary MS, 30 $\pm$ 15 V and m/z 50 – 1000, respectively.

GC – MS/MS

Analyses were performed on a 7890B-7000D GC–MS/MS instrument (Agilent Technologies, Santa Clara, CA, U.S.A.). GC conditions were: column, HP-5MS capillary column (30 $\times$ 0.25 mm, i.d., film thickness 0.25 μ m; Agilent Technologies); carrier gas, high-purity helium; flow rate, 2.25 mL/min; oven temperature program, hold of the initial temperature at 100 $^{\circ}$ C for 1.5 min, ramp up to 280 $^{\circ}$ C at a rate of 25 $^{\circ}$ C/min and the final hold for 15 min to the total running time of 23.7 min; solvent delay time, 7.5 min; forward inlet temperature, 250 $^{\circ}$ C; split ratio, 5:1; injection volume 1.0 μ L. MS conditions were: ion source temperature, 230 $^{\circ}$ C; quadrupole temperature, 150 $^{\circ}$ C; single-stage GC – MS mode, positive electron ionization (EI) voltage at 70 eV; the product ion spectra, the ion showing the highest peak intensity observed in the primary mass spectrum that was used as the precursor ion for the spectra with collision energies at 5, 15, 25 and 35 eV.

LC – MS/MS

LC–MS/MS was conducted on a 1290 Infinity II LC system connected with a 6470 Triple Quad LC/MS tandem MS instrument (Agilent Technologies). For LC separation, an InfinityLab Poroshell 120 EC-C₁₈ column (50 $\times$ 2.1 mm, i.d., particle size 1.8 μ m; Agilent Technologies) was used. The LC conditions were: injection volume, 1.0 μ L; injection mode, splitless; flow rate, 0.3 mL/min; elution mode, isocratic with 50% distilled water (A)/50% acetonitrile (B); the temperature of the column and autosampler, 40 $^{\circ}$ C. The tandem MS conditions were: interface, positive electrospray ionization mode; ion source temperature, 300 $^{\circ}$ C; ion source voltage, 500 V; quantification, selected reaction monitoring mode; collision energies, 20, 25, 30 and 35 eV. Data acquisition, peak integration and other calculations were performed with a computer workstation (Masshunter, LC/MS Data Acquisition version 10.1 build 10.1.67, Qualitative Analysis Navigator B. 08.00; Agilent Technologies).

Standard addition method

For quantitative analysis, the most widely used method is the matrix-matched calibration technique. In this method, a blank matrix in the absence of a target compound is absolutely necessary [9]. However, in the present case, a newly emerging drug mixed in a dubious tablet should be quantified; because no corresponding tablets in the absence of the drug were available, we had to use the standard addition method that does not require the blank matrix [10, 11].

Results

Single-stage GC–MS spectra and product ion spectra

In Fig. 1, single-stage GC–MS spectra for methaqualone, etaqualone and 2-methoxyqualone with probable fragmentation modes are shown. Fragmentation along the amide group in the 4-quinazolinone core was observed for methaqualone and etaqualone (see Fig. 1a, b), but such phenomenon could not be observed for 2-methoxyqualone, probably because of the interaction of oxygen molecule attached to the phenyl ring in position 2'.

In Fig. 2, product ion spectra of methaqualone and etaqualone are shown according to collision energies at 5, 15, 25 and 35 eV. In comparison of the product ion spectra with different precursor ions with the single-stage mass spectra at 70 eV, some product ion peaks appeared at the same m/z for methaqualone and etaqualone, respectively, although peak height profiles were different.

Identification and quantification of 2-methoxyqualone that has emerged very recently

Case history

In late 2021, the Inner Mongolia Hohhot Public Security Bureau seized dubious drug package called “Huyouyou”, containing a number of tablets (Fig. 3). By screening of the ingredients of the tablets using a single-stage GC–MS in the police laboratory, the typical recreational drugs, such as methaqualone and etaqualone, circulated as “Huyouyou” could not be detected from the tablets, but some unknown peaks were detected. Thus, the Public Security Bureau brought the package contents (tablets) to our laboratory for drug testing of the ingredients.

Tentative identification of the unknown compound

As the first experiment, we measured the total ion current (TIC) chromatogram of the tablet extract by the high-resolution UHPLC–QTOF–MS (Fig. 4). The retention time of the main component was 6.595 min; the mass spectrum of the peak at 267.1128 is shown in Fig. 5. Based on this primary high-resolution MS information, the peak at the retention time was predicted that the molecular formula was $C_{16}H_{14}N_2O_2$, which has one more oxygen atom and one less carbon atom than etaqualone (Fig. 1b), using the Shimadzu Formula Predictor software. The possible fragmentation pattern of the main peak in the sample was deduced using the software ChemDraw in combination with the secondary high-resolution MS; it confirmed the molecular formula and supported the possible structure of the compound (Fig. 6).

Even if the elemental composition of the unknown compound is clarified, the final identification cannot be attained, because multiple compounds with the same elemental composition gives some positional isomers or stereoisomers. To finally identify a compound, the reference standard should be synthesized or should be found in the menu of reagent manufacturers/vendors. Very luckily, during the search for such a kind of compounds, we could find that the reference standard of 3-(2-methoxyphenyl)-2-methylquinazolin-4(3*H*)-one (CAS No. 4260-28-0) is commercially available, and could purchase it to test whether the reference standard is absolutely identical to the unknown compound.

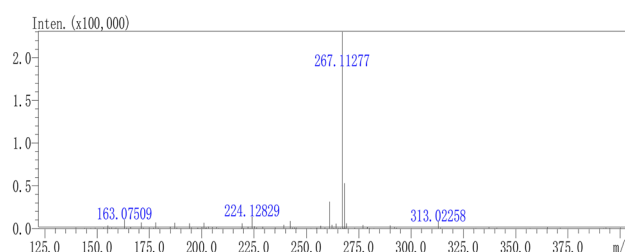
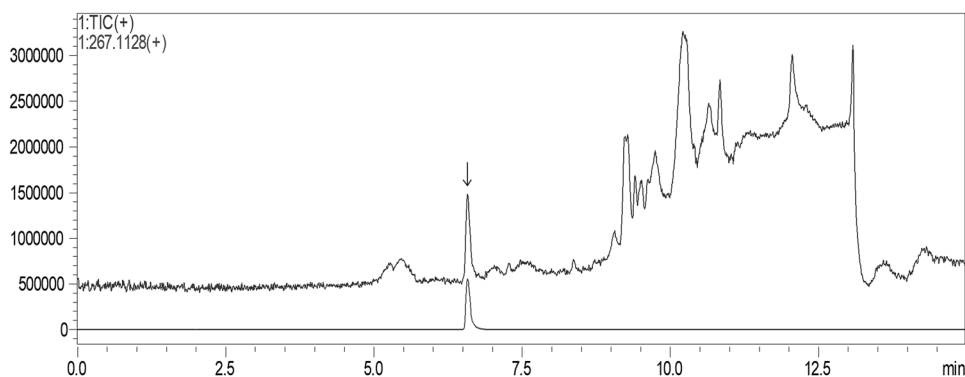


Fig. 5 High-resolution mass spectrum for the peak found in the TIC chromatogram obtained by HR UHPLC–QTOF–MS

Fig. 4 Total ion current (TIC) chromatogram for the extract of the unknown tablet measured by high-resolution ultra-high-performance liquid chromatography–quadrupole time-of-flight mass spectrometry (HR UHPLC–QTOF–MS). The arrow shows the location of the peak of target compound



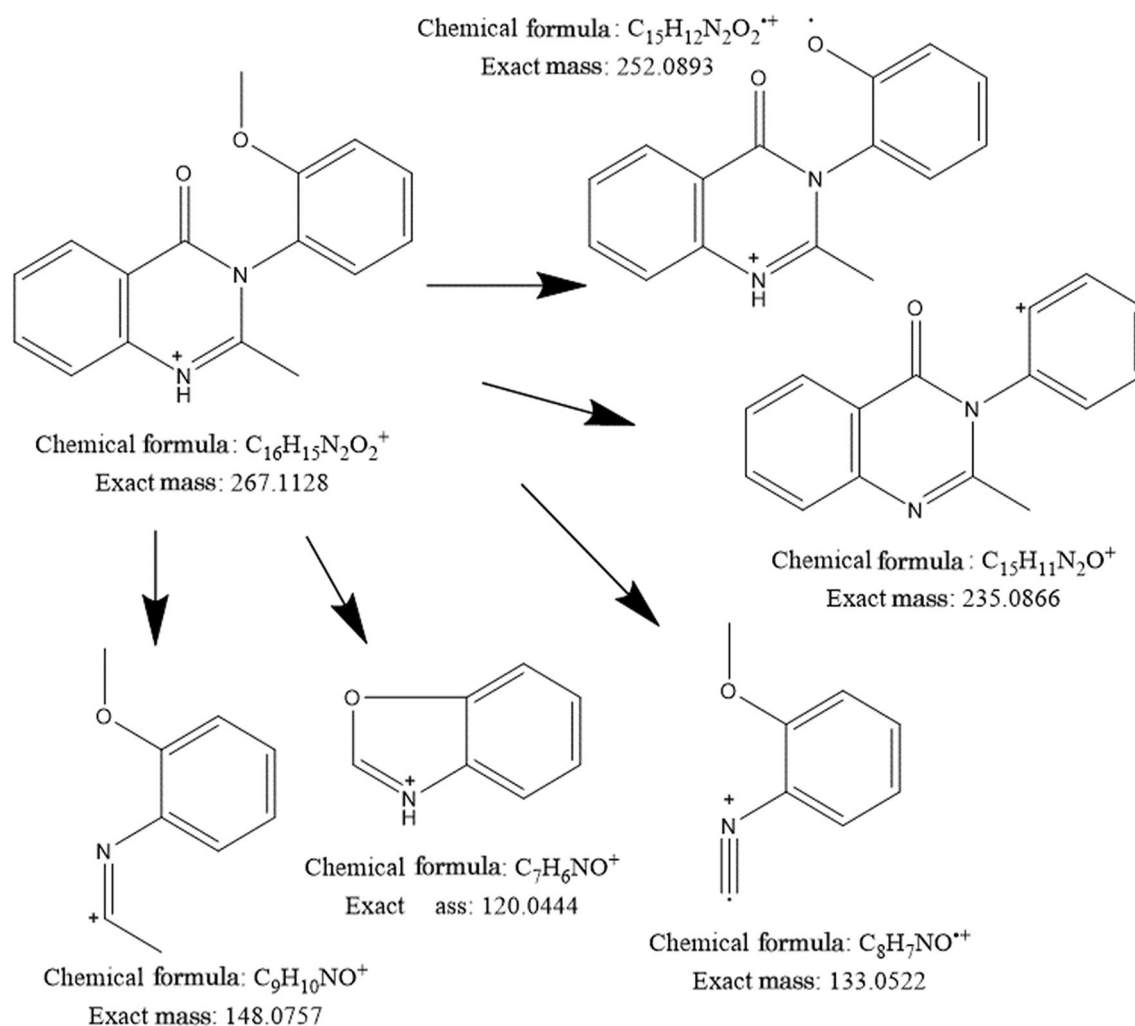


Fig. 6 Estimation of the structures of molecular and product ions of the target compound measured by HR UHPLC–QTOF–MS

Final identification of the unknown compound

Both above purchased reference standard and the extracted sample were subjected to the measurements of product ion mass spectra by both GC–MS/MS and LC–MS/MS with different collision energies (Figs. 7, 8). For GC–MS/MS and LC–MS/MS, the precursor positive ions at m/z 235 and 267 were used, respectively. For all spectra, the peak profiles of the extracted sample were identical with those of the reference standard with every collision energy, showing that the sample in question was 2-methoxyqualone.

Quantification of 2-methoxyqualone in the tablet

We found that more than a half of the tablet consisted of 2-methoxyqualone. Thus, we had to dilute the tablet powder suspension solution in methanol by more than 100,000-fold. Therefore, the final extract before injection to the GC–MS/MS instrument was very clean and transparent. Each 1.0- μ L

aliquot of the supernatant solution was injected into the GC–MS/MS instrument under the conditions as shown in Table 1.

The obtained standard addition calibration curve was linear and its regression equation for 2-methoxyqualone in the tablet was: $y=1.610x+1.1256$ with correlation coefficient (r) of 0.9997 (an example of the typical standard addition regression equations). The contents of 2-methoxyqualone were calculated to be $70.5 \pm 2.4\%$ (w/w) for intraday measurements ($n=5$) and $69.8 \pm 0.5\%$ (w/w) for interday measurements ($n=5$: once a day for five days) in the tablet powder. There was no statistical difference between the intraday and interday values (Table 2).

Validation of 2-methoxyqualone quantification

Upon looking at the quantifier peak shape of the preexisting 2-methoxyqualone without further addition (peak height and the range of the background fluctuation), the limit of

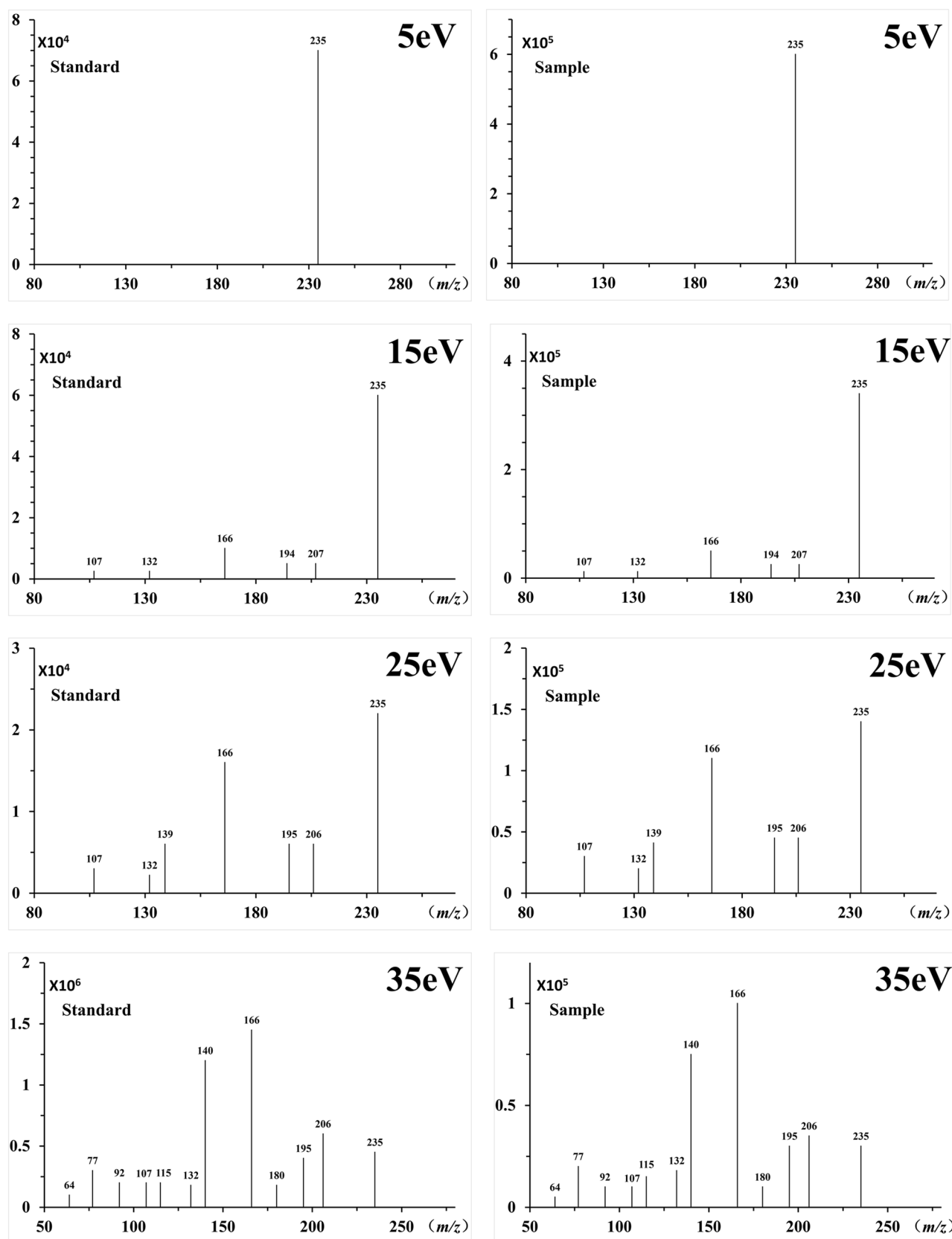


Fig. 7 Product ion spectra of 2-methoxyqualone measured with different collision energies using an intense primary peak at m/z 235 as the precursor ion obtained by GC–MS/MS

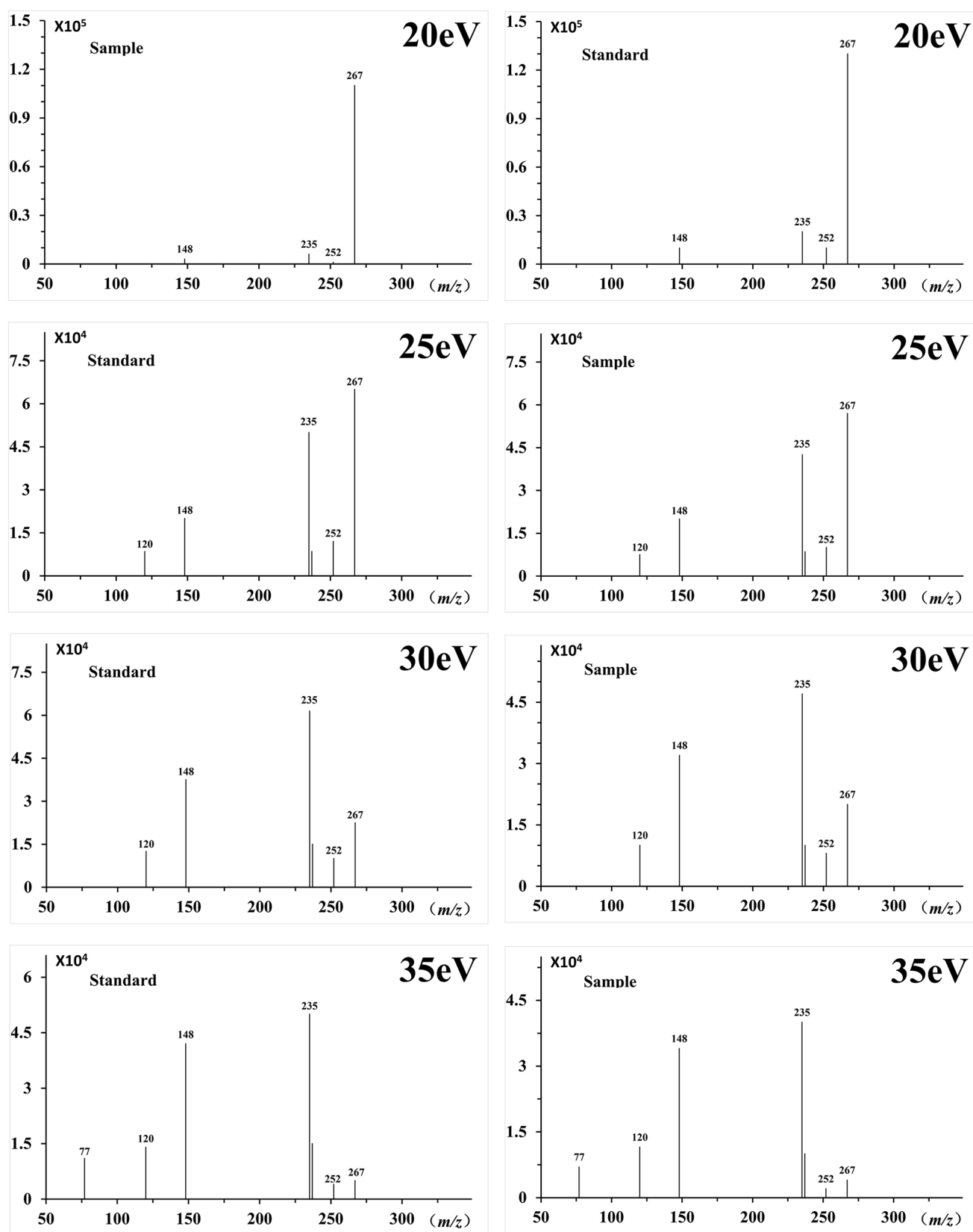


Fig. 8 Product ion spectra of 2-methoxyqualone measured with different collision energies using the protonated molecular ion at m/z 267 as the precursor ion obtained by liquid chromatography–tandem mass spectrometry

Table 1 Instrumental parameters of gas chromatography–tandem mass spectrometry for quantification of 2-methoxyqualone

Compound	RT (min)	Quantifier		Qualifier	
		Ion transition (<i>m/z</i>)	Collision energy (eV)	Ion transition (<i>m/z</i>)	Collision energy (eV)
2-Methoxyqualone	9.11	235/166	35	166/140	35
Methaqualone- <i>d</i> ₇ (IS)	8.63	241/137	25	256/241	10

RT retention time, *IS* internal standard

Table 2 Intraday and interday repeatabilities, recoveries and matrix effects for the quantification of 2-methoxyqualone in the tablet powder

Compound	Intraday (<i>n</i> = 5)		Interday (<i>n</i> = 5)		Recovery (% mean ± SD)	Matrix effect (% mean ± SD)
	Content (% in TP)	Repeatability (% RSD)	Content (% in TP)	Repeatability (% RSD)		
2-Methoxyqualone in the unknown tablet	70.5 ± 2.4	3.40	69.8 ± 0.5	0.72	91 ± 2.4	93 ± 1.2

SD standard deviation, *TP* tablet powder, *RSD* relative standard deviation

detection and the limit of quantification were roughly estimated to be 5 and 10 ng/mL, respectively, at the extraordinarily diluted step just before injection into GC–MS/MS instrument. In place of accuracies and precisions for the conventional matrix-matched calibration method, we presented the repeatability of the standard addition method [10, 11] for presentation of data validation, which were satisfactory. As shown in Table 2, the recovery rate and matrix effect were both more than 90%, which were also very satisfactory.

Coexisting compounds

We found two additional compounds in the TIC chromatogram of the extensively diluted extract by the single-stage GC–MS mode of the GC–MS/MS. They were tentatively identified with the aid of database connected to the GC–MS/MS system. The compounds were acetaminophen and caffeine appearing at 6.62 and 7.26 min, respectively. Although the two compounds were quantified in the same way as that for 2-methoxyqualone, the validation experiments were not performed. Thus, the concentrations were regarded as tentative quantification results; the contents of acetaminophen and caffeine were 0.11 and 0.04 mg/mg tablet powder, respectively.

Discussion

In this article, we have presented single-stage GC–MS spectra and detailed product ion spectra with different collision energies acquired by GC–MS/MS for methaqualone, etaqualone and 2-methoxyqualone. The 2-methoxyqualone has been discovered from a dubious package containing tablets

seized by the police in China very recently [8]. The chemical structures of the three compounds are quite similar (see Fig. 1). Although the methaqualone is the most typical drug highlighted in the world [3–5], it is being still a popular recreational drug in South Africa in tablets containing diphenhydramine, and is also being used recreationally in other parts of Africa and in India [12].

Not much data of analytical methods have been reported for the 4-quinazolinone drug class this time; only single-stage GC–MS [13, 14] and Fourier-transform infrared spectrometry (FTIR) [14] for methaqualone, and single-stage GC–MS, nuclear magnetic resonance spectroscopy, FTIR [15] and selected reaction monitoring by GC–MS/MS [6] for etaqualone. There are neither identification nor quantification by LC–MS/MS for both methaqualone and etaqualone. Methylmethaqualone, which differs from methaqualone by 2',4'-dimethylation on the phenyl ring, was synthesized illegally in Germany in 1990s, and sold on the black market in Germany; it is controlled only in Germany as an Anlage I drug. It is more potent than its parent drug methaqualone [16]; anecdotal reports from human users confirmed that it had a pro-convulsive effect, which has potential to make this compound particularly hazardous if taken in excessive doses [17]. Very recently 2021–2022, more two drugs of this class were identified in human specimens. One compound was mebroqualone identified and quantified with validation in two postmortem cases by GC–MS; case 1 was an accidental death involving a house fire, and the deceased was found to have a blood mebroqualone concentration at 10,228 ng/mL, and case 2 was a suicide death by train, and the deceased was found to have a blood concentration at 115 ng/mL. Mebroqualone is a methaqualone analog, where the methyl group attached to the 2'-position of the phenyl

ring of methaqualone is replaced by a bromine atom [12]. Another drug appearing recently is SL-164, where it is dichlorinated in the 4'-position of the phenyl ring and in the 5-position of the 4-quinazolinone nucleus. Romanek et al. [18] identified SL-164 in serum and urine collected from a living 22-year-old male by LC–QTOF-MS. Lund et al. [19] also identified SL-164 in pills and urine collected from a living 21-year-old male by LC–QTOF-MS. Both teams did not quantify SL-164, but only identified it as a new methaqualone analog compound. However, the SL-164 is not a newly developed drug, but had been developed as a sedative, hypnotic and anticonvulsant drug in the late 1960s by Sumitomo Pharmaceutical Co., Ltd. In Osaka, Japan; it was never marketed for clinical use [20].

Now we have six 4-quinazolinone recreational drugs circulating in the world including methaqualone. Most probably all drugs of this class of exert their neural action via certain types of GABA_A receptor complex. Although benzodiazepines and barbiturates also take actions via the GABA_A receptors, the 4-quinazolinone class drugs probably neither interact with benzodiazepines nor barbiturates because different subunits of GABA_A receptor complex are responsible for the 4-quinazolinone class drugs [2].

For investigating the symptoms of the 4-quinazolinone derivatives, most studied ones are for methaqualone [21], which is a central nervous system depressant effective for sedation at dosage ranges of 75 mg four times daily, and for sleep at dosages ranges of 150–400 mg. The onset of sedative-hypnotic action occurs within 10–30 min after oral ingestion, and lasts for 6–8 h. Adverse physiological reactions to methaqualone include headache, hangover, dryness of the mouth, nosebleed, dizziness, numbness, diarrhea and anorexia. The symptoms characterizing acute methaqualone toxicity differ from those with barbiturates and many other non-barbiturate sedative-hypnotics. The high doses of the latter drugs can cause respiratory and cardiovascular depression, decreased muscle tone, and coma. With methaqualone overdoses, respiratory and cardiovascular depression are generally less marked. Instead, the increase in muscle tone is pronounced, ranging in severity from hypertonia and muscle spasm to tonic-clonic convulsions. Such an increase in muscle tone, which is usually dose-dependent may persist for 4–5 days while the patient remains in deep coma. With very high doses of methaqualone such as 8 g, death has been reported. Methaqualone is particularly attractive to drug users because it can produce euphoric effects. As being nicknamed the “love drug”, methaqualone has developed a widespread reputation among drug users as an aphrodisiac effects or tingling sensations. Methaqualone is potentiated by other central nervous system depressants, such as barbiturates and alcohol. The addiction potential of methaqualone is enhanced not only by the above euphoric effects, but also easy building up of tolerance to methaqualone by repeating

its administration even with relatively low doses within a couple of days. It takes about 3–7 days for the tolerance to be reduced to a half, and 1–2 weeks to be back at the baseline in the absence of further consumption [22]. Methaqualone is largely used by oral ingestion, but is occasionally by smoking [1].

Conclusions

In this study, we have presented product ion spectra of methaqualone, etqualone and 2-methoxyqualone by GC–MS/MS. Because 2-methoxyqualone is a new recreational discovered very recently, much more detailed data for analysis of 2-methoxyqualone by different types of mass spectrometry instruments were also presented. To date, six compounds of 4-quinazolinone derivatives have been published in the scientific literature, but their information is quite insufficient for their toxicities, pharmacokinetics including metabolism, pharmacodynamics, detailed symptomatology and molecular mechanisms of their action except for methaqualone. Because legal controls are imposed only on methaqualone (in eight countries) and on methylmethaqualone (only in Germany), the rest four compounds are out of control for recreational uses this time. We should be on the alert for recreational uses of the uncontrolled drugs of this class and for expanding chemical syntheses of new drugs of the 4-quinazolinone derivative class, because most of benzodiazepines and barbiturates are controlled in many countries.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. The drug analyses were requested by the judicial authorities of the Inner Mongolia Hohhot City in China.

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