# CHEMICAL PROFILING OF ERIMIN-5 PILLS USING GC-MS FOR ACTIVE INGREDIENT DETECTION AND TLC FOR DYE DETECTION

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# CHEMICAL PROFILING OF ERIMIN-5 PILLS USING GC-MS FOR ACTIVE INGREDIENT DETECTION AND TLC FOR DYE DETECTION

By

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**PROFIL KIMIA BAGI PIL ERIMIN-5 MENGGUNAKAN GC-MS UNTUK PENGESANAN BAHAN AKTIF DAN TLC UNTUK PENGESANAN PEWARNA**

## ABSTRAK

Penyalahgunaan dadah menimbulkan kebimbangan yang tidak berkesudahan bagi pihak berkuasa penguatkuasaan undang-undang di seluruh dunia. Di Malaysia, tablet Erimin-5 masih disalahgunakan secara meluas seperti yang boleh dilihat berdasarkan kes yang kerap dilaporkan dalam berita. Dadah ini diketahui untuk mengandungi nimetazepam atau juga boleh digantikan dengan benzodiazepine lain. Benzodiazepine ialah bahan psikoaktif yang terdiri daripada gelang benzena dan cincin diazepin yang digabungkan bersama yang memberikan kesan sedatif dan menenangkan. Banyak benzodiazepin yang disenaraikan dalam Jadual IV Konvensyen Antarabangsa mengenai Bahan Psikotropik 1971 telah diklasifikasikan sebagai bahan terkawal dengan potensi rendah hingga sederhana untuk penyalahgunaan dan ketagihan di kebanyakan negara. Benzodiazepine yang digunakan dalam campuran tablet Erimin-5 tidak diketahui kerana ahli kimia di makmal haram dadah boleh menggantikan bahan aktif dengan pelbagai bahan lain berdasarkan bahan yang tidak dikawal oleh Akta Dadah Berbahaya. Dalam kajian ini, 50 sampel telah diperiksa menggunakan kromatografi gas-spektrometri jisim (GC-MS) bagi kajian kualitatif untuk mengenal pasti kehadiran bahan aktif dalam sampel Erimin-5. 50 sampel didapati menggunakan bahan aktif yang berbeza di mana bahan aktif yang paling biasa ialah etizolam, diikuti oleh flualprazolam, nimetazepam, clozapine, 7-aminonimetazepam dan alprazolam. Selanjutnya, untuk pencirian pewarna, 15 sampel dengan sampel pukal yang

mencukupi telah dipilih untuk pemprofilan pewarna yang diperiksa menggunakan kromatografi lapisan nipis (TLC). Profil pewarna menunjukkan bahawa kebanyakan sampel adalah berwarna kuning, yang kelihatan hampir serupa dengan tablet asal. Bergantung kepada pembuat di makmal haram dadah, pelbagai kombinasi pewarna yang berbeza boleh digunakan dalam menghasilkan warna tablet. Pewarna yang dikenal pasti dalam tablet yang diperiksa ialah tartrazine, kuning matahari terbenam dan ponceau 4R. Kesimpulannya, pemprofilan forensik telah berjaya dijalankan, sekurang-kurangnya untuk perbandingan sampel-ke-sampel. Trend benzodiazepin yang paling popular yang kini digunakan sebagai sebatian aktif juga berjaya dikenalpasti, dan sudah pasti, kajian sedemikan perlu dilakukan dari masa ke masa untuk memperoleh maklumat bagi kepintaran forensik dan juga untuk pembuat dasar.

**CHEMICAL PROFILING OF ERIMIN-5 PILLS USING GC-MS FOR ACTIVE INGREDIENT DETECTION AND TLC FOR DYE DETECTION**

## ABSTRACT

The abuse of the drug is a never-ending concern for law enforcement authorities all around the world. In Malaysia, Erimin-5 tablets are still being widely abused as can be seen based on the cases reported frequently in the news. These drugs are known to contain nimetazepam or other substituted benzodiazepines. A benzodiazepine is a psychoactive substance that is made up of a benzene ring and a diazepine ring fused together that gives sedative and tranquillizing effects. Many benzodiazepines listed in Schedule IV of the International Convention on Psychotropic Substances 1971 have been classified as controlled substances with a low to moderate potential for misuse and addiction in most countries. It is unknown what types of benzodiazepines are currently used in the formulation of Erimin-5 tablets simply because the clandestine drug chemist can substitute the active ingredients based on their availability as well as use the ingredients which are not controlled by the Dangerous Drug Act. In this study, 50 samples were examined using GC-MS for qualitative study for the presence of active ingredients in Erimin-5 samples. The 50 samples were found to have used different active ingredients where the most common one is etizolam, followed by flualprazolam, nimetazepam, clozapine, 7-aminonimetazepam and alprazolam. For further dye characterisation, 15 samples with sufficient bulk samples were selected for dye profiling using TLC. The dye profiles indicate that most of the samples were of yellow colour, which appeared to be almost similar to the original tablet. Depending on the chemist in the clandestine drug laboratory, different combinations of dyes can

be used in producing the tablets. The dyes identified in the examined tablets were tartrazine, sunset yellow and ponceau 4R. In conclusion, forensic profiling was successfully carried out, at least for sample-to-sample comparison. The trend of the most popular benzodiazepines currently used as active compounds is also successfully identified, and certainly, such profiling work shall be conducted from time to time to provide forensic intelligence as well as information for decision-makers.

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of Study

The abuse of drugs is a never-ending concern for law enforcement authorities all around the world. Based on the World Drug Report (2019), an estimation of 271 million people or equivalent to about 5.5 percent of the world population in 2017, were involved in some kind of drug usage. When compared to the statistics tabled in 2009, there was a 30 percent jump in the number of people who have used drugs. Globally, cannabis or marijuana is the most commonly and extensively used drug in the world, probably due to its availability and its long history of use, with an estimated 188 million people using it in the year 2017 (UNODC, 2019). Based on the most recent World Drug Report (2022), the total number of cannabis still remains on the top with a total of 209 million.

There was also a growth of indoor growth of cannabis cultivation. Other main categories of drugs of abuse, such as cocaine, amphetamine-type stimulants and new psychoactive substances (NPS) remain dynamic. Among them, NPS is the most complex category of drugs because it consists of a large group of substances. One of the subgroups in the NPS categories is benzodiazepines (UNODC, 2022). Based on a cross-sectional analysis conducted in the years of 2015 and 2016 National Survey on Drug Use and Health, out of 30.6 million adults who are involved in the use of benzodiazepines, 5.3 million are categorized under the misuse of drugs (Maust et al., 2019) indicating the degree of problems.

A benzodiazepine is a psychoactive substance that is made up of a benzene ring and a diazepine ring fused together that gives sedative and tranquillizing effects. Pharmacologically, the neurotransmitter gamma-aminobutyric acid (GABA) is enhanced by benzodiazepines (Mahadik et al., 2012), which then results in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, muscle relaxant and amnesic action (Lim et al., 2017; Mahadik et al., 2012). More than 30 substances of novel benzodiazepines were reported, including etizolam, phenazepam, pyrazolam, flualprazolam and didazepam (UNODC, 2022). Benzodiazepines are a very important chemical in medical use for anxiety, insomnia, agitation, seizures, muscular spasms, and alcohol withdrawal, as well as a premedication for medical or dental operations.

In a broader sense, benzodiazepines can differ from one another based on three categories. i.e. based on its onset of action, effect, and duration of action (Ogbru, 2021). First of all, for the category that is based on the onset of action, benzodiazepines can be further divided into three subcategories which are fast such as diazepam and clorazepate, intermediate such as lorazepam, alprazolam, and clonazepam, and slow such as oxazepam.

If benzodiazepines are categorised based on the effect, they can be subgrouped into hypnotics such as alprazolam, flurazepam and nitrazepam, antianxiety such as chlordiazepoxide and oxazepam and anticonvulsant such as clobazam. It is worth noticing that benzodiazepines that are used for anaesthetics effect are usually midazolam, lorazepam and diazepam.

If the categorisation is based on the duration of action, benzodiazepines can be categorized into three different categories as well. The short-acting ones, such as clorazepate, midazolam, triazolam and oxazepam have durations of action that will be around 3 to 8 hours (Lim et al., 2017; Ogbru, 2021). Alprazolam, lorazepam, estazolam

and temazepam are intermediate-acting agents which could last for 10 to 20 hours while the very long-acting ones such as chlordiazepoxide, clonazepam, diazepam, flurazepam and quazepam can last for 1 to 3 days.

Pharmacologically, in general benzodiazepine formulation the chemicals in work by binding to receptor sites near the GABAA receptor in the membranes of the neurons that control the fear response by boosting the natural calming effect and causing antianxiety, sedative-hypnotic and anticonvulsant effects (Kuhar et al., 2012). Gamma-aminobutyric acid (GABA) can bind to particular locations known as GABA receptors. The number of sites that can be occupied by GABA increases significantly when benzodiazepines are present because they increase the attraction between GABA molecules and GABAA receptors. Thus, there is an increase in desensitised neurons as well. In this approach, benzodiazepines enhance the calming effect of GABA on nerve activity, which reduces the terror response (Kuhar et al., 2012).

Nimetazepam, which was once marked under the brand name Erimin is a benzodiazepine that has a rapid onset of action and it is long-acting (Lim et al., 2017). It was marketed by Sumitomo in 5 mg tablets and widely prescribed before 2005. The effects felt by the consumer are hypnotic effects along with an anti-depressant, anxiolytic, sedative and skeletal muscle relaxant effect (Abdul Rahim, 2013). Erimin-5 tablet appeared in the illicit drugs markets in Malaysia, Singapore and Hong Kong in the mid-1980s, which then became one of the most abused sedative drugs, contributed by its wide availability and low cost (Chong et al., 2004).

Clandestine laboratory-produced Erimin tablets are known as Erimin-5. It was believed that the number 5 in the name represents the amount in milligrams of active ingredient it is an original formulation by Sumitomo (Lim et al., 2017). It was also reported that most Erimin-5 users were also users of heroin especially during the lower

availability of heroines (Chong et al., 2004). Methamphetamine users were reported to take Erimin-5 to facilitate sleep upon methamphetamines consumption (Chong et al., 2004).

It is important to note that two benzodiazepines, nimetazepam and flunitrazepam, have been included in Malaysia's first schedule of the Dangerous Drugs Act (1952) (Abdul Rahim, 2013; Abdullah et al., 2012). Nimetazepam, on the other hand, was once more typically found in illicit Erimin-5 pill samples compared to flunitrazepam but the trend of using other benzodiazepines which are not controlled in the Dangerous Drugs Act (1952).

## 1.2 Problem Statement

Erimin 5 pills and their seizures in Malaysia often become the headlines in the local newspaper. The discovery of a few clandestine manufacturing operations scale labs for this medication was frequently reported. Conventionally, nimetazepam is a common active ingredient in Erimin-5 pills and previous reports show that most of the Erimin-5 pills seized in Malaysia and Singapore contain nimetazepam as the sole active ingredient. However, due to the interchangeability of several substances that can be substituted for other benzodiazepines such as phenazepam and diazepam are also encountered as active ingredients. It is unknown on the profile of the Erimin-5 tablets in the market especially when it contains compounds not listed under the Dangerous Drugs Act (1952). This leads to an information gap as there are some studies lacking regarding other benzodiazepines which are currently used as active ingredients in Erimin-5 pills available in the drug market.

## 1.3 Scope of Study

This study examines 50 samples using GC-MS for qualitative study for the presence of active ingredients in Erimin-5 samples. No quantitation work by HPLC is done. For further dye characterisation, 15 samples with sufficient bulk samples were selected for dye profiling.

## 1.4 Objectives of Study

The aim of this study is to investigate the active ingredients found in Erimin-5 samples as were as to explore the common dyes used in tabletting. To achieve the aim, a few objectives were set as follows.

1) To screen and categorise the profile of active compounds in the Erimin-5 tablets.

2) To explore the composition of the dyes used in Erimin-5 tablets.

## 1.5 Significant of Study

This study will help the chemist who are dealing with cases regarding Erimin-5 to have a general idea related to the drug. The identification of the dye using the TLC can help the Malaysian police and customs to establish a link between the seized samples to a more specific distributor. Moreover, the substituted active compounds found from the case samples could be proposed to be regulated. The identified active compounds using GC-MS can be used as a database to compare the trend in the most popular benzodiazepines that are currently used as active compounds.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Introduction

The literature study on benzodiazepines is summarised in this chapter, with a focus on Erimin-5. There is also a general overview of the chemical nomenclatures and structures. With reference to a few selected cases in Malaysia, the causes of abuse as well as the severity and patterns of drug problems are briefly explored. A description of the analytical methods for drug analyses, particularly for benzodiazepines and Erimin-5 wherever relevant, is provided at the end of the chapter.

## 2.2 What is Erimin-5?

Erimin-5 is the street name for the drug called nimetazepam, even though it may or may not contain the active ingredient. In fact, Erimin is the brand name for nimetazepam introduced to the market by Sumitomo Pharmaceutical, Japan in 1977 (Abdul Rahim, 2013; Lim et al., 2017). The drug was reported to have been first synthesised in 1962 by a team from Hoffman La Roche (Solace Asia, 2021). The purpose of its production was originally for the treatment of short-term insomnia. Improper use of drugs can make them become addictive and bear harmful consequences. Its manufacturing in Japan ceased in early November 2015 due to unexplained reasons (Solace Asia, 2021). In the illicit market, the tablet was substituted with other benzodiazepines such as Etizolam and Flunitrazepam although it is packed and labelled as Erimin-5.

Nimetazepam, the active component in the original Erimin-5, has a chemical structure that classifies it as a benzodiazepine. In a strip of ten tablets, it is present in amounts of 5 mg per tablet, commonly in red packaging and the Sumitomo logo (Plate 2.1). Nimetazepam's chemical structure is shown in Figure 2.2, and its IUPAC name is 1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1, 4-benzodiazepin-2-one (UNODC, 1971).

The chemical formula for nimetazepam is $C_{16}H_{13}N_3O_3$ and weighs 295.3 g/mol. Pure nimetazepam is found to (98%) solidify very neatly at room temperature. Under the suitable condition, it has storage stability of over two years when kept at -20°C (Cayman Chemical, 2022). Many toxicological effects of this compound have not been adequately investigated. Based on the Cayman Chemical safety data sheet the oral $LD_{50}$ (on a mouse) was stated to be 970 mg/kg. Nimetazepam exhibits very good sedative, anxiolytic, and anticonvulsant characteristics with a moderately long duration of action. Upon investigation, it can be changed into its metabolite, nitrazepam, and has a reported elimination half-life of 14 to 30 hours (McMahon, 2010). Nimetazepam is susceptible to tolerance, dependency, and misuse like other benzodiazepines (McMahon, 2010), and this explains why it has become one of the most widely abused benzodiazepines that we observed in society today.

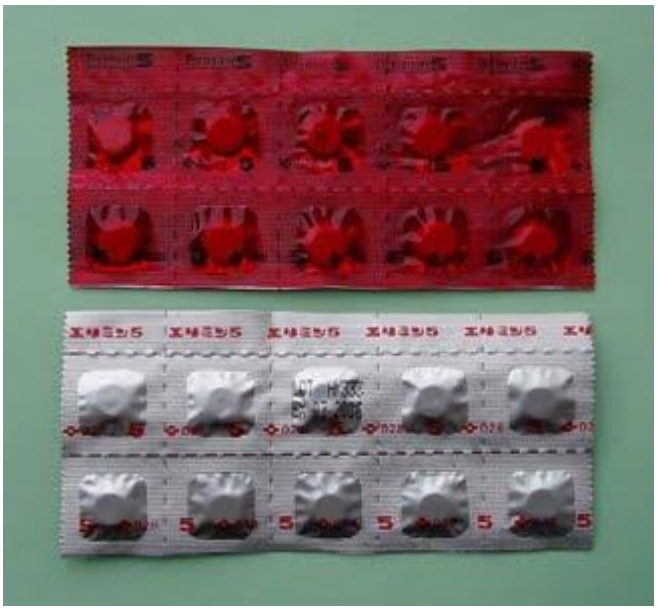

Plate 2.1: Example of Erimin-5 packaging

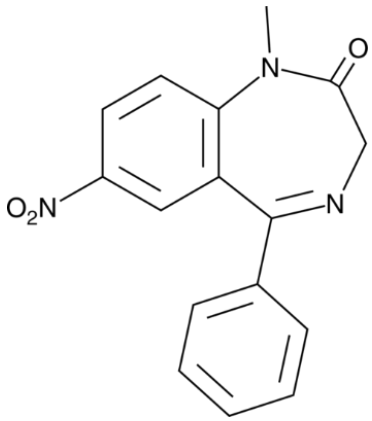


Figure 2.2: Chemical structure of nimetazepam

**2.3 Some Selected Benzodiazepines**

The most often prescribed class of medications is currently the benzodiazepine or methaminodiazepoxide family, due to the 1960 launch of chlordiazepoxide. The other brand name is Librium in capsule form. According to Figure 2.3, chlordiazepoxide is known by the IUPAC name 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide and the molecular weight is 299.75 amu. This compound has a unique structure with an oxygen atom on the nitrogen atom that is closer to the aromatic side ring. It is mainly used to treat insomnia, anxiety, the

suppression of convulsions, and panic attacks but was reported to be addictive if improperly used. To induce anaesthesia, lessen anxiety, and ensure that the patient has no unpleasant memories, chlordiazepoxide is also frequently employed in dentistry and surgery in some places (Kuhar et al., 2012).

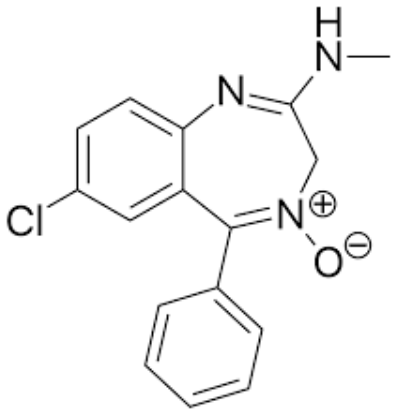


Figure 2.3: Chemical structure of chlordiazepoxide

Figure 2.4 shows the general structure of nimetazepam and its related compound. In this structure, a benzene ring is fused with the seven-membered ring containing two nitrogens. Based on this general structure, the related compounds to nimetazepam can be differentiated from one another based on the different substituents that are placed in positions X, Y, and/or Z (Mizuno et al., 2009). It is important to note that different substituents result in diverse features being exhibited by the chemical molecule, particularly when it comes to the property of the drugs on the active site of binding, as seen in many drugs. Rohypnol or flunitrazepam was reported to be many times more powerful than Valium or diazepam at the same dose. The difference at the Y and Z position, i.e. (Cl, H) in diazepam and ($NO_2$, F) in flunitrazepam has made a huge difference in the drug's effectiveness (Kuhar et al., 2012; Schwartz and Weaver, 1998).

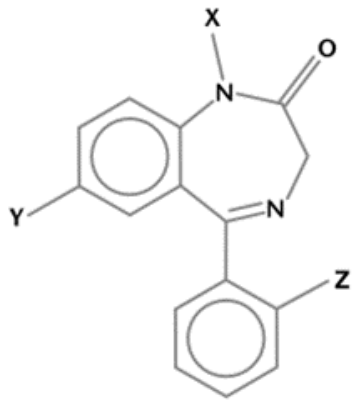


Figure 2.4: General structure of nimetazepam and related compounds

Due to its powerful effect, flunitrazepam is frequently utilised as a date-rape drug (Schwartz and Weaver, 1998) as it is very water soluble in drinks. When comparing clonazepam to flunitrazepam, the difference between them is the methyl group at the X position but a hydrogen at the same position in clonazepam. Clonazepam is marketed under the brand name Klonopin and is reported to be the third most prescribed benzodiazepine in the United States, which is behind alprazolam and lorazepam. Several other compounds including nitrazepam, flurazepam, halazepam and quazepam are tabulated in Table 2.1.

Table 2.1: Chemical structures of nimetazepam and related compounds

| Compounds | X | Y | Z |
|---|---|---|---|
| Nimetazepam (Erimin) | $-CH_3$ | $-NO_2$ | -H |
| Diazepam (Valium) | $-CH_3$ | -Cl | -H |
| Flunitrazepam (Rohypnol) | $-CH_3$ | $-NO_2$ | -F |
| Clonazepam (Klonopin) | -H | $-NO_2$ | -F |
| Nitrazepam (Mogadon) | -H | -H | $-NO_2$ |
| Flurazepam (Dalmane) | $-CH_2CH_2N(C_2H_5)_2$ | -Cl | -F |
| Halazepam (Pixapam) | $-CH_2CF_3$ | -Cl | -H |
| Quazepam (Doral) | $-CH_2CF_3$ | -Cl | F |

Source: Kuhar, P. D., J., M., & Liddle, H. (2012). Drugs of Abuse. New York: Marshall Cavendish Corporation.

When an additional hydroxyl group (-OH) is attached to the seven-membered ring in another group of benzodiazepines (Kuhar et al., 2012) from the basic structure of nimetazepam as shown in Figure 2.4, they can form the structure seen in lorazepam and its related compounds which has also been documented as having been used inappropriately as a form of drug associated with date rape (Grabel and Associates, 2022) although it is not as water soluble as flunitrazepam. The use of lorazepam with alcohol is particularly dangerous. By comparing the substituents in the positions of X, Y and Z, based on this structure in Figure 2.5, two other compounds, i.e., oxazepam and temazepam are also found to be potentially addictive and posed withdrawal symptoms.

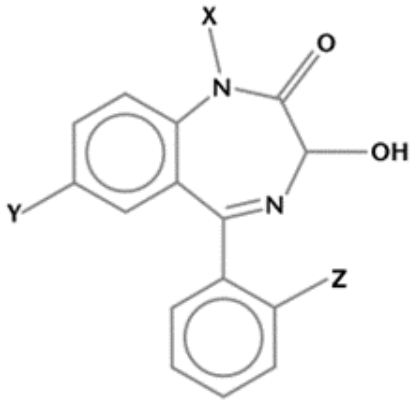


Figure 2.5: General structure of lorazepam and related compounds

Table 2.2: Chemical structures of lorazepam and related compounds

| Compounds | X | Y | Z |
|---|---|---|---|
| Lorazepam (Ativan, Temasta, Tavor) | -H | -Cl | -Cl |
| Oxazepam (Serax, Alepam) | -H | -Cl | -H |
| Temazepam (Restoril) | $-CH_3$ | -Cl | -H |

Source: Kuhar, P. D., J., M., & Liddle, H. (2012). Drugs of Abuse. New York: Marshall Cavendish Corporation.

From the basic structure of nimetazepam, an additional ring to the seven-membered ring can give rise to the structure as shown in Figure 2.6. Such structure provides increased potency (Kuhar et al., 2012). One such of the compound based on this structure is triazolam, first patented in 1970 which was believed to be 20-fold more effective than diazepam. In addition to alprazolam, triazolam was one of the drugs that were utilised in the practise of date rape (D. Walling, 2000; Johansen and Dahl-Sørensen, 2012). Different derivatives with a slight difference in the substituents at positions W, X, Y and Z give rise to alprazolam, etizolam and midazolam, as shown in Table 2.3.

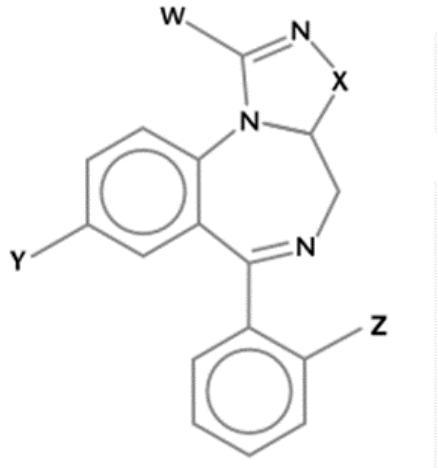


Figure 2.6: General structure of triazolam and related compounds

Table 2.3: Chemical structure of triazolam and related compounds

| Compounds | W | X | Y | Z |
|---|---|---|---|---|
| Triazolam (Halcion) | $-CH_3$ | -N- | -Cl | -Cl |
| Alprazolam (Xanax) | $-CH_3$ | -N- | -Cl | -H |
| Estazolam (ProSom) | -H | -N- | -Cl | -H |
| Midazolam (Versed) | $-CH_3$ | -CH- | -Cl | -F |

Source: Kuhar, P. D., J., M., & Liddle, H. (2012). Drugs of Abuse. New York: Marshall Cavendish Corporation.

As we can see from the various types of benzodiazepines, it is understandable that the street-level Erimin-5 tablets may or may not contain nimetazepam and are substituted with a variety of other chemicals as seen in Table 2.1 - 2.3. (UNODC, 2020). A complete understanding of potential compounds that could be used as nimetazepam replacements is crucial for forensic intelligence. As was previously noted, nimetazepam is a member of the benzodiazepine family of medicines that suppress the central nervous system and bring one down (John Roger and Michael McBay, 2005). This effect makes them good candidates to counteract the effects of as

stimulants of the amphetamine-type and this is why the use of Erimin-5 is also related to stimulant users.

### 2.4 Legal Status of Erimin-5 in Malaysia in Comparison with Other Countries

Since Erimin-5 is a trade name, the focus of forensic investigation regarding the drug's legal status should be on its active compounds present in the formulation. Legal Erimin-5 has been found to contain the restricted substance nimetazepam. According to the Convention on Psychotropic Substances of 1971, the compound is designated as a controlled substance in Schedule IV of the list of substances that fall under the purview of this convention (UNODC, 1971). Note that the Convention is a treaty ratified by the United Nations that aims to control psychoactive drugs (also known as substances that alter one's state of mind) by imposing import and export restrictions, as well as other rules, with the goals of restricting drug use to scientific and medical applications only.

There are four different schedules of controlled substances in this Convention. These schedules are named accordingly from most restrictive to least restrictive, with Schedule I including the most restrictive substances and Schedule IV including the least restrictive ones. In a nutshell, chemicals that fall under Schedule IV include hypnotics, tranquillizers (benzodiazepines), and analgesics, with nimetazepam being one of the compounds that fall within the benzodiazepine category (United Nations Office on Drugs and Crime (UNODC), 1971). The international regulation of benzodiazepines in accordance with the United Nations Convention on Psychotropic Substances of 1971 is broken down into more detailed categories in Table 2.4.

Table 2.4: The international control of benzodiazepines under the United Nations Convention on Psychotropic Substances of 1971

| Year of Scheduling Decision | Schedule | Substance Name | |
|---|---|---|---|
| 1984 | IV | Alprazolam | Haloxazolam |
| | | Bromazepam | Ketazolam |
| | | Camazepam | Loprazolam |
| | | Chlordiazepoxide | Lorazepam |
| | | Clobazam | Lormetazepam |
| | | Clonazepam | Medazepam |
| | | Clorazepate | Nimetazepam |
| | | Clotiazepam | Nitrazepam |
| | | Cloxazolam | Nordazepam |
| | | Delorazepam | Oxazepam |
| | | Diazepam | Oxazolam |
| | | Estazolam | Pinazepam |
| | | Ethyl loflazepate | Prazepam |
| | | Fludiazepam | Temazepam |
| | | Flurazepam | Tetrazepam |
| | | Halazepam | Triazolam |
| 1990 | IV | Midazolam | |
| 1995 | III | Flunitrazepam | |
| | IV | Brotizolam | |
| 2016 | IV | Phenazepam | |

(Source: United Nations Office on Drugs and Crime (UNODC). (2017). Non-medical use of benzodiazepines: a growing threat to public health? Global Smart Update, 18.)

UNODC use a structured classification of benzodiazepines, into six subgroups, namely 1,4-Benzodiazepines, oxazolobenzodiazepines, thienotriazolodiazepines, triazolobenzodiazepines, imidazolobenzodiazepines and thienodiazepines (UNODC, 2021). In the United States, nimetazepam is a Schedule IV controlled substance, as defined by Title 21, Part 1308 of the Drug Enforcement Administration's regulations (Code of Federal Regulations, 2022). In the United Kingdom, Schedule II of the

Misuse of Drugs Act 1974 lists nimetazepam, along with other restricted substances, as a Class C substance and is also scheduled in the Misuse of Drugs Regulation 2001 lists it as a Schedule 4 Part 1 controlled substance (UK Statutory Instruments, 2001). In Singapore, nimetazepam is a Schedule I, Class C prohibited substance, making it subject to rigorous regulation under the Misuse Drugs Act (Chapter 185) (Singapore Statue Online, 2001). Schedule I of the Act specifies which drugs fall into which categories (Class A, Class B, and Class C) (Singapore Statue Online, 2001).

In the republic, possessing nimetazepam has potential penalties of up to 10 years in prison, a fine of up to S$20,000, or both. As Singapore has very strict law enforcement on drugs, the maximum sentence for nimetazepam trafficking is ten years in prison and five canings. Importing or exporting nimetazepam without a licence carries a maximum sentence of 20 years in prison and 15 lashes with the cane (Central Narcotics Bureau, 2021). In Hong Kong, nimetazepam is regulated under Schedule I in chapter 134 Dangerous Drugs Ordinance (Customs and Excise Department, 2016).

In Malaysia, part III of the First Schedule of the Dangerous Drugs Act (1952) classifies nimetazepam as a controlled drug because of its high potential for abuse and addiction. Note that part IV of the Act classifies drugs with the lowest risk for abuse and addiction. Similar to Singapore, Malaysia's drug laws are extremely stringent, with severe penalties (Dangerous Drugs Act 1952, 1980). In brief, nimetazepam has been classified as a controlled substance with a low to moderate potential for misuse and addiction in most countries.

### 2.5 Trends of Abuse of Benzodiazepines

The College of American Pathologists listed the 2022 Novel Opioids and Benzodiazepines (NOB) drugs below, with the potential challenges that include a mix

of drugs. The two new drugs are 8-aminoclonazolam and alpha-hydroxyetizolam. The rising prevalence of benzodiazepine use, particularly in conjunction with polydrug usage, is a major cause for worry from the point of view of clinical settings. From 2000 to 2017, the number of drug overdose deaths in the United States involving opioids and benzodiazepines increased steadily but a small decrease was observed from 2017 to 2019 before a small spike from 2019 to 2020 (Figure 2.7) (National Institute on Drug Abuse, 2022).

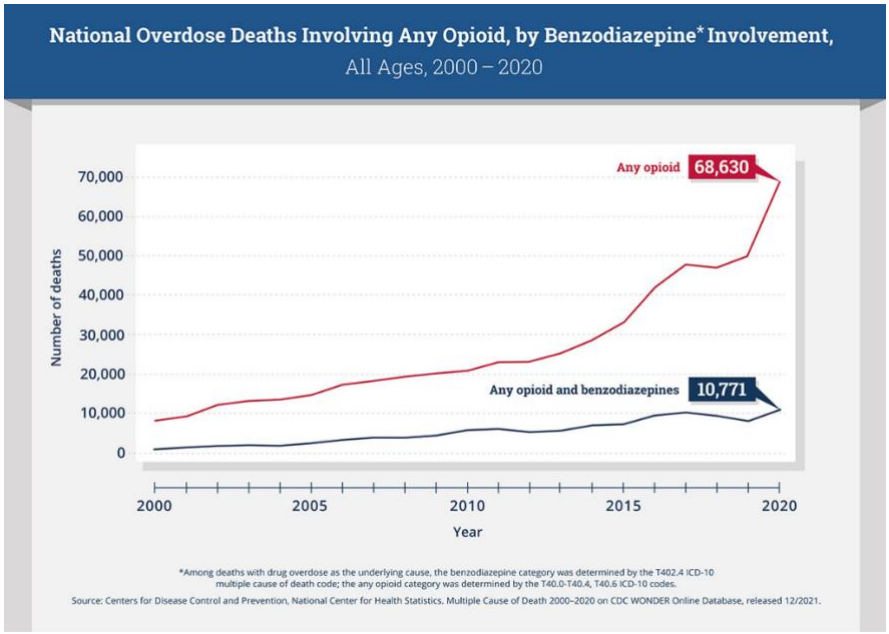


Figure 2.7: US drug overdose deaths involving opioids and benzodiazepines

The number of adults in the United States who filled a benzodiazepine prescription increased by almost 67% between 1996 and 2013 (from 8.1 million to 13.5 million), according to a study on prescriptions and overdose mortality conducted by Bachhuber et al. (2016). Researchers found no evidence of declining rates of fatal benzodiazepine overdoses, even though overall trends in such overdoses had levelled off. Acknowledging that prescription patterns and deaths from drug overdoses were shown to vary by demographic group, the authors also noted these differences (Bachhuber et al., 2016).

In several fatal cases involving the use of benzodiazepines, the use of alcohol or other substances was cited by various writers as a potential risk factor for deadly overdose in multiple fatal cases. It was proposed that some action be taken to reduce benzodiazepine dependence or make the medications safer (Bachhuber et al., 2016; Sun et al., 2017). In response to the heightened risk of combining benzodiazepines with other drugs, most notably opiates, the Centres for Disease Control and Prevention (CDC) devised and released updated recommendations for prescription opioids in 2016. Similarly, in the United Kingdom, as the general practice, benzodiazepines should only be described in the lowest effective dose for a maximum of 2-4 weeks of severe panic disorder or severe anxiety. It further notes that benzodiazepines should not be used if short-term mild anxiety (Kennedy and O'riordan, 2019). The linked risk of combining benzodiazepines and other drugs led to the updated recommendations. When at all possible, clinicians should refrain from giving benzodiazepines at the same time with opioids (Dowell et al., 2016).

As stated by Cole and Chiarello (1990), benzodiazepines are rarely used as party drugs, though it has been recreationally used. From the perspective of the recreational use of benzodiazepines, this problem has been there for a long time and is associated with a large number of cases of overdose-related death and intoxication globally, particularly those involving the use of opioids, alcohol and other drugs (UNODC, 2017). In the publication by UNODC (2021) on Current NPS Threats, a total of 38 benzodiazepines are under international control as of 2021 with another three scheduled to be included, i.e. clonazolam, diclazepam and flubromazolam at the end of 2021, making a total of 41 benzodiazepines under international control. It's possible that different regions of the world make use of different benzodiazepine types in their recreational drug use and this changes over the years. Between 2010 and 2014

for example, in the United States of America alone, alprazolam and diazepam were the benzodiazepines that were detected concomitantly the majority of the time (Warner et al., 2016).

Hedegaard et al. (2017) have revealed the regional differences in the specific drugs that are most frequently involved in drug overdose deaths in the United States (Hedegaard et al., 2019). In the findings, it was determined that diazepam, which had been among the top ten from 2011 to 2016, had dropped to the position of 12th in 2017, while clonazepam was positioned in 11$^{th}$ place in 2017. In the UNODC 2021 reports, the most common benzodiazepines on drugs report were flualprazolam (n=494), etizolam (n=371), flubromazolam (n=271) and clonazolam (n=152) (UNODC, 2021). The information on regional disparities in the drugs that are most frequently involved in drug overdose deaths could help the authorities in the planning of prevention and policy making (Hedegaard et al., 2019).

It is important to point out that during the course of time, the production of certain pharmaceutical benzodiazepine products may have changed or ceased entirely. At the same time, it's possible that some new kinds of benzodiazepines will be established and then abused as we have seen over the years. For example, nimetazepam, which was formerly sold under the brand name "Erimin," stopped production several years ago, unlicensed preparations of nimetazepam are still on the market in certain areas, particularly in Asian countries, and still maintain its name and packaging because users are already familiar with the name (UNODC, 2017).

### 2.6 Erimin-5 Cases in Malaysia

In Malaysia, Erimin-5 tablets, often known as "Happy," "Five," "Give me Five," or "Happy Five," are still being widely abused as can be seen in the nightclub

setting and seizure cases frequently reported in the news. One of the reasons is that the materials for making the tablets or even the manufactured tablets are widely available. The magnitude and the degree of problems of the Erimin-5 trafficking and usage problem in Malaysia can be estimated using the documented significant seizure occurrences that have occurred on multiple occasions.

In a recent case, a clandestine laboratory was dismantled where huge numbers of Erimin-5 pills were seized (Mokhtar, 2022). Among the large seizure, the Royal Malaysian Police and Royal Malaysian Customs at Port Klang discovered 2.5 million nimetazepam tablets hidden within a container that had been shipped from Taiwan. The drug traffickers often use Malaysia as a transit to where these nimetazepam tablets were allegedly planned for sale not only on the local market but also in the marketplaces of the neighbouring countries (Mohamad Radhi, 2017).

According to the Narcotics Crime Investigation Department of the Royal Malaysian Police, various nationwide operations in January 2021 alone resulted in the arrest of 9000 people. Among the total of RM 168 million worth of drugs of various types that were seized, the total amount of Erimin-5 that was seized was 1,847.47 kilogrammes, and it was valued at RM 142.31 million (Zolkepli, 2020). A quick internet search could compile various news that was issued by the law enforcement agencies on drug seizures, it is clear to say that the severity of the Erimin-5 is indeed present. Although the authorities have worked together to develop collective strategies that are more aggressive and effective. Still, drug traffickers are always looking for new strategies and methods of concealment to make their way.

As stated by UNODC, the drug market is a complex system. The benzodiazepine drug market is also extremely complicated, and as a result, it presents a variety of obstacles to regulating agencies and countries (UNODC, 2017). At one

extreme of the spectrum, the simultaneous use of alcohol, opioids and benzodiazepines is extremely hazardous to public health. Polydrug use has contributed to an increasing number of overdose deaths. In addition, there is a wide range of benzodiazepines accessible on the market which can come in a variety of forms, ranging from licit products to illicit drugs with unidentified pharmacological and toxicological side effects (UNODC, 2017).

In fact, there is still a shortage of data and information regarding benzodiazepine products in the market especially those distributed underground, both from a scientific perspective and from the perspective of intelligence for law enforcement. In addition, the pharmacological properties of some novel drugs such as alpha-hydroxyetizolam and 8-aminoclonazolam that belong to the class of benzodiazepines are still unclear. The contents of illicit or counterfeit tablets, particularly those manufactured by the clandestine chemist likely to be different from legitimate drugs. From this point of view, it is vital to conduct an additional study and proper profiling of the products to provide a better understanding of the composition and formulation pattern of these products.

The benefits of conducting more research can be broken down into two categories. Further research on the pharmaceuticals that are now accessible on the market can provide helpful information that can be used to establish successful policy responses and drug prescription regimes for medical usage that comes from legal sources. The information obtained from the research could, in addition to providing profile intelligence for source determination to link to drug-rings, help to raise awareness of the potential severe adverse effects and the dangers of acquiring the drugs and engaging in polydrug use (Mail, 2021). This is true both for abuse that is not intended for medical purposes and for counterfeit products.

From a forensic point of view, the successful identification of similarities and differences between drug samples can help to answer whether or not two or more drug samples are connected, this relationship provides a possible link between users or dealers, or networks of distribution, the sample comes from a particular geographic origin, or a particular clandestine laboratory, or the method of clandestine drug production and specific chemicals that were used (Mail, 2021).

## 2.7 Analytical Methods for Analysing Drugs

In the field of forensic drug analysis, there are well-established analytical methods that can be applied for the purpose of comparing and characterising different types of illegal drugs. Very useful sources have been provided by UNODC on recommended methods for the analysis of different classes of drugs and drug profiling. With careful analysis, forensic chemists are able to assist law enforcement personnel not only in establishing the identity of drugs and their concentration but also assist in locating sources of supply and manufacture of illegal drugs, establishing a relationship between seized samples based on a common feature, and identify specific analytes that may yield information such as the manufacturing pathway that was used (Sanger et al., 1979).

When a seizure of drugs is made, scientists also have to plan for the sampling strategies, sample storage, measures, extraction and analysis plan so that the most information can be obtained. In brief, a full physical characterisation of the materials should first be carried out. This is then normally followed by a full chemical analysis including drug extraction from the tabletted materials, presumptive testing, thin layer chromatography and subsequent confirmatory technique (M. D. Cole, 2003).

### 2.7.1 Physical Characterisation

The literature search revealed that Tillson and Johnson (1974) had established a systematic scheme for comparing illicit drugs, with its authentic drugs. Their work was among the earliest examples of systematic forensic drug comparison. In the initial step of the process of conducting a physical analysis, particularly on tablets, the determination of the gross features of the sample, including its shape, diameter, thickness, and weight was very important. This is then followed by a low-power microscope examination to inspect the minute "punch" markings made by punching machines.

Any accurate measurements of the table's small details, such as groove angle, width, and depth were found important prior to subsequent move on to the identification of the constituents such as by the use of optical crystallographic techniques (Tillson and Johnson, 1974). The study by Gomm (1975), has also provided extensive strategies that can be used for the physical inspection of tablets that are produced illicitly. Many techniques including methods for illicit tablet comparison using physical methods by these authors have formed the fundamental principles which are still applicable in the present.

Many other current available analytical methods, such as spectroscopy and are available in forensic chemistry laboratories. Among the methods are ATR-FTIR spectroscopy, Raman spectroscopy, X-ray fluorescence (XRF) spectroscopy, GC-MS methods, and HPLC methods. The physical analysis approach is known as the "ballistics method" which was utilised for drug identification (Tillson and Johnson, 1974). Simply because the scheme and principles employed in the physical examination of tablets are similar to those utilised in the physical examination of bullets.

In tablet analysis, the packaging material is an important source of data (Tillson and Johnson, 1974). It is vital to keep in mind that the product may be packaged in a different manner by wholesalers than by retailers for end users at the retail level especially since the product may be repackaged as well at the local market if it is produced elsewhere. This local packaging may or may not adhere to a completely different packaging regime. Illicit tablets may contain packaging materials that are aesthetically similar to those used for legal items because the users are always familiar with the original packaging. Due to very similar products, it may be difficult to identify the quality of counterfeits from that of real products, through comparisons of suspected counterfeit samples, particularly when the packing materials are connected. In addition, the advancement in printing technology has made it more difficult to differentiate between items, which means that forensic authentication is not as simple and uncomplicated (Dégardin et al., 2018).

Using data from XRF and Raman spectrometry, Dégardin et al. (2018) have authenticated a few components of the packaging of one medicinal product. Statistical grouping was carried out so that the findings of the visual assessment could be objectively supported. Dégardin and Roggo (2016) conducted a case study of different drug samples. The investigation began with an analysis of the packaging, which involved making a comparison to authentic samples and looking for indicators of modification. The samples were compared using capillary zone electrophoresis, UV-spectrophotometry, near-infrared and infrared spectroscopy, and near-infrared and infrared spectroscopy.

The authors discovered that 17 of the samples were fakes. This research suggested the utility of a defensible counterfeit analysis technique to create data for forensic intelligence (Dégardin and Roggo, 2016). In the UNODC manual for drug