European Monitoring Centre for Drugs and Drug Addiction

EU EARLY WARNING SYSTEM FORMAL NOTIFICATION

Date issued	4 May 2021	RCS ID	EU-EWS-RCS-FN-2021-0017
Issued by	EMCDDA	Transmitted by	Action on New Drugs Sector, EMCDDA
Subject	Formal notification of 1-(5-chloro-1*H*-indol-3-yl)propan-2-amine (5-chloro-alpha-methyltryptamine) by Slovenia as a new psychoactive substance under the terms of Regulation (EU) 2017/2101		

1. Read me first

This document provides formal notification of the analytical identification of 1-(5-chloro-1*H*-indol-3-yl)propan-2-amine (5-chloro-alpha-methyltryptamine) for the first time in Europe.

Please report any additional data you have on this substance to: ews@emcdda.europa.eu

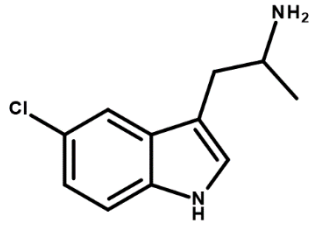
2. Data use restrictions

As with all formal notifications issued by the EU EWS remember that they may contain information that could be regarded as sensitive. Should you provide some of the information in this notification to other groups we would ask that you exercise your best judgment on what information needs to be provided. If you have any questions in this respect, please contact us.

3. Names of substance and other identifiers

- IUPAC name: 1-(5-chloro-1*H*-indol-3-yl)propan-2-amine
- Chemical names: 5-chloro-α-methyl-1*H*-indole-3-ethanamine; 1-(5-chloro-1*H*-indol-3-yl)-2-propanamine; 5-chloro-3-(2-aminopropyl)indole
- Common name: 5-chloro-alpha-methyltryptamine
- Other names: 5Cl-AMT; 5Cl-alpha MT; 5-chloro-α-MT; 5-chloro-αMT; 5-chloro-α-methyltryptamine; PAL-542
- Chemical formula: $C_{11}H_{13}ClN_2$
- Molecular weight: 208.69
- CAS Registry number: 712-07-2 (base); 1313013-10-3 (hydrochloride salt); 1313013-10-3 (*R*-isomer); 1313013-09-0 (*S*-isomer)
- InChIKey: QMKOQSCXSYPIPB-UHFFFAOYSA-N

Molecular structure



4. Substance classification

Tryptamine

5. Detection

Type: Collected sample
Case Report identifier: EDND-CR-2021-284

Details: 5-chloro-alpha-methyltryptamine was identified in 5 grams of white-off-white powder collected and delivered to the Slovenian National Forensic Laboratory on 9 February 2021. The substance was contained in a plastic zip-bag without any label and the hydrochloride salt form of 5-chloro-alpha-methyltryptamine was identified.

The substance was analytically confirmed using GC-MS, GC-MS-IR Condensed Phase, FTIR, IC, and LC-TOF by the National forensic laboratory, and by NMR in the Faculty of Chemistry and Chemical Technology. A purity of >97% was reported based on NMR analysis.

6. Chemistry and Analysis

Chemical classification: arylalkylamine; indole alkylamine; tryptamine

5-Chloro-alpha-methyltryptamine is the 5-chloro derivative of alpha-methyltryptamine (AMT), formally notified in 2003. AMT was critically reviewed by the Expert Committee on Drug Dependence (ECDD) in 2014 and was recommended for surveillance, mainly due to the lack of data regarding dependence, abuse, and risks to public health [1]. AMT is a structural isomer of *N*-methyltryptamine (NMT), 6-IT and 5-IT, formally notified in March 2020, 2016 and 2012 respectively.

5-Chloro-alpha-methyltryptamine also shares structural similarities with 5-Cl-DMT (5-chloro-*N,N*-dimethyltryptamine), formally notified in July 2020. 5-Chloro-alpha-methyltryptamine differs from 5-Cl-DMT due to the presence of a methyl substituent at the alpha carbon and due to the replacement of *N,N*-dimethylmethanamine present in 5Cl-DMT, with methanamine.

The synthesis of 5-chloro-alpha-methyltryptamine (*7b*) by nitro olefin formation followed by lithium ammonium hydride reduction has been reported [2]. An *in-vitro* assay analysed using hydrophilic interaction liquid chromatography-high resolution tandem mass spectrometry (HILIC-HR-MS/MS) has been developed and validated for the analysis of thirteen AMT analogs, including 5-chloro-alpha-methyltryptamine [3].

5-Chloro-alpha-methyltryptamine contains a stereogenic centre and therefore two possible enantiomers may exist.

7. Pharmacology and toxicology

Pharmacological classification: hallucinogen

5-Chloro-alpha-methyltryptamine (*compound 7b*) has been reported to be a potent dual dopamine (DA) – serotonin (5HT) releaser and the most selective dual DA/5HT releaser identified in a study of 25 tryptamines [2]. It was also found to be 36-fold weaker as a norepinephrine (NE) releaser [2]. 5-Chloro-alpha-methyltryptamine is reported as displaying a therapeutically relevant EC_{50} value as a DA (EC_{50} **=** 54.3 ± 1.8 Nm) and 5HT (EC_{50} at 5HT = 16.2 ± 2.2 nM) releaser [2].

In a study of thirteen AMT analogs and their potential to inhibit monoamine oxidase (MAO), 5-chloro-alpha-methyltryptamine was found to significantly inhibit MAO-A activity, with an IC_{50} value of 0.25 µM reported, similar to the IC_{50} value of 5-IT; and MAO-B activity, with an IC_{50} value of 82 µM reported [3]. 5-Chloro-alpha-methyltryptamine has been shown to inhibit the activity of several CYP isoenzymes, such as CYP2A6 and CYP2B6, and the authors note that this substance may cause clinically relevant interactions with those CYPs [3].

5-Chloro-alpha-methyltryptamine (PAL-542) was examined, with three other dopamine/serotonin releasers, as a potential treatment for cocaine addiction [4]. In the study, none of the compounds substituted for the discriminative stimulus effects of cocaine in rats and monkeys, while continuous treatment with 5-chloro-alpha-methyltryptamine, which had the greatest selectivity for DA/5HT vs. NE, failed to decrease cocaine choice [4]. The authors noted that 5-chloro-alpha-methyltryptamine in fact increased ‘cocaine self-administration at a dose that also reduced food-maintained responding’, an effect they stated was similar to that seen with fenfluramine [4].

8. Further information

Further information on this substance is available on the EDND profile:
https://ednd2.emcdda.europa.eu/ednd/substanceProfiles/1213

9. Acknowledgements

The Slovenian National Focal Point, the Slovenian National Forensic Laboratory and the Faculty of Chemistry and Chemical Technology are kindly acknowledged for the information and analytical data provided.

10. Attachments

None.

11. References

[1] Expert Committee on Drug Dependence. Critical Review Report: Alpha-methyltryptamine (AMT). Thirty-sixth Meeting, Geneva, 16-20 June 2014. https://www.who.int/medicines/access/controlled-substances/4_FollowUp36th_Summary_FV.pdf?ua=1

[2] Blough BE, et al. Alpha-ethyltryptamines as dual dopamine–serotonin releasers. Bioorganic & medicinal chemistry letters. 2014;24(19):4754-8.
[3] Wagmann L, et al. *In vitro* monoamine oxidase inhibition potential of alpha-methyltryptamine analog new psychoactive substances for assessing possible toxic risks. Toxicology letters. 2017;272:84-93.
[4] Banks ML, et al. Abuse-related effects of dual dopamine/serotonin releasers with varying potency to release norepinephrine in male rats and rhesus monkeys. Experimental and clinical psychopharmacology. 2014;22(3):274.