

KnowItAll DEA Controlled Substance Regulation System

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Introduction

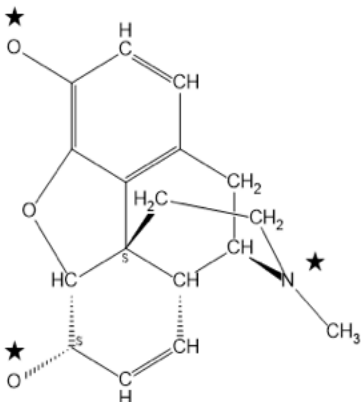


For organizations that deal with chemical substances in the United States, it is critical to comply with DEA regulations on controlled substances¹. Manually or electronically recording and recognizing hundreds of regulations is difficult, especially when regulations are changed or new regulations are introduced over time. Adding to the complexity, most of the regulations apply to classes of compounds (isomers, salts, ethers, esters, derivatives, salts of all mentioned, and exceptions) rather than one unambiguous chemical structure. Therefore, accurately expressing a regulation by an electronic “fuzzy” chemical structure is the ideal method.

Within the Wiley KnowItAll Spectroscopy and ChemWindow software, one can categorize chemical structures of controlled substances using property prediction in the Minelt application. This predictive model categorizes structures using a database of DEA regulation rules.

Method

A classification database was constructed in the KnowItAll system to correlate DEA regulations with chemical classes using fuzzy structures. Some DEA regulations were simple to represent by structure. For example, this is a structural representation of Morphine³. The fuzzy structure in Figure 1 expresses the ruling for citation “1308.12(b)(1)(ix).”



The chemical structure of Morphine is shown with several atoms marked with a star (★). These stars are placed next to the oxygen atom at the top left, the nitrogen atom on the right side, and the oxygen atom at the bottom left. The structure includes a pentacyclic ring system with a double bond, a hydroxyl group, and a methyl group on the nitrogen.

All Properties	Attachments	Preferred Properties	Substructs	Sel. Substructs	Original Data Files	
Name		Value				
Name		Morphine				
CAS Registry Number		57-27-2				
Comments		Substances, vegetable origin or chemical synthesis. Unless specifically excepted or unlisted in another schedule, any of the following substances whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis				
Controlled Drug Sample Type		Salts				
DEA Citation		21 CFR §1308.12 (b) (1) (ix)				
DEA Controlled Substances Code Number		9300				
DEA Schedule		Schedule II				

Figure 1. Morphine. A star next to an atom “locks it,” meaning only the salt (charged) form is acceptable. H-atoms attached to C-atoms prevent it from forming other covalent bonds. A stereochemical match can be enforced in a substructure match.

Most rulings, however, require quite a bit of interpretation in order to incorporate structural variations and exceptions. For example, “1308.11(b)(2)” lists Acetylmethadol⁴. However, the section “1308.11(b)” applies to “*Opiates*.” Unless specifically excepted or listed in another schedule, any opiates could be applicable. This is including their isomers, esters, ethers, salts, and salts of isomers, esters and ethers whenever the existence of these is possible within the specific chemical designation (for purposes of 3-methylthiofentanyl only, the term “isomer” includes the optical and geometric isomers).

If one treats all Acetylmethadol stereoisomers as Schedule I classifications, this would be incorrect. These classes of stereoisomers have to be excluded because they are regulated in other citations: S,S-isomer Levacetylmethadol "1308.12(c)(11)" (Schedule II); R,R-isomer α -acetylmethadol "1308.11(b)(7)" (Schedule I); S,R-isomer β -acetylmethadol "1308.11(b)(13)" (Schedule I). The DEA classification database has been constructed to manage this complexity to ensure accurate classification. See Figure 2.

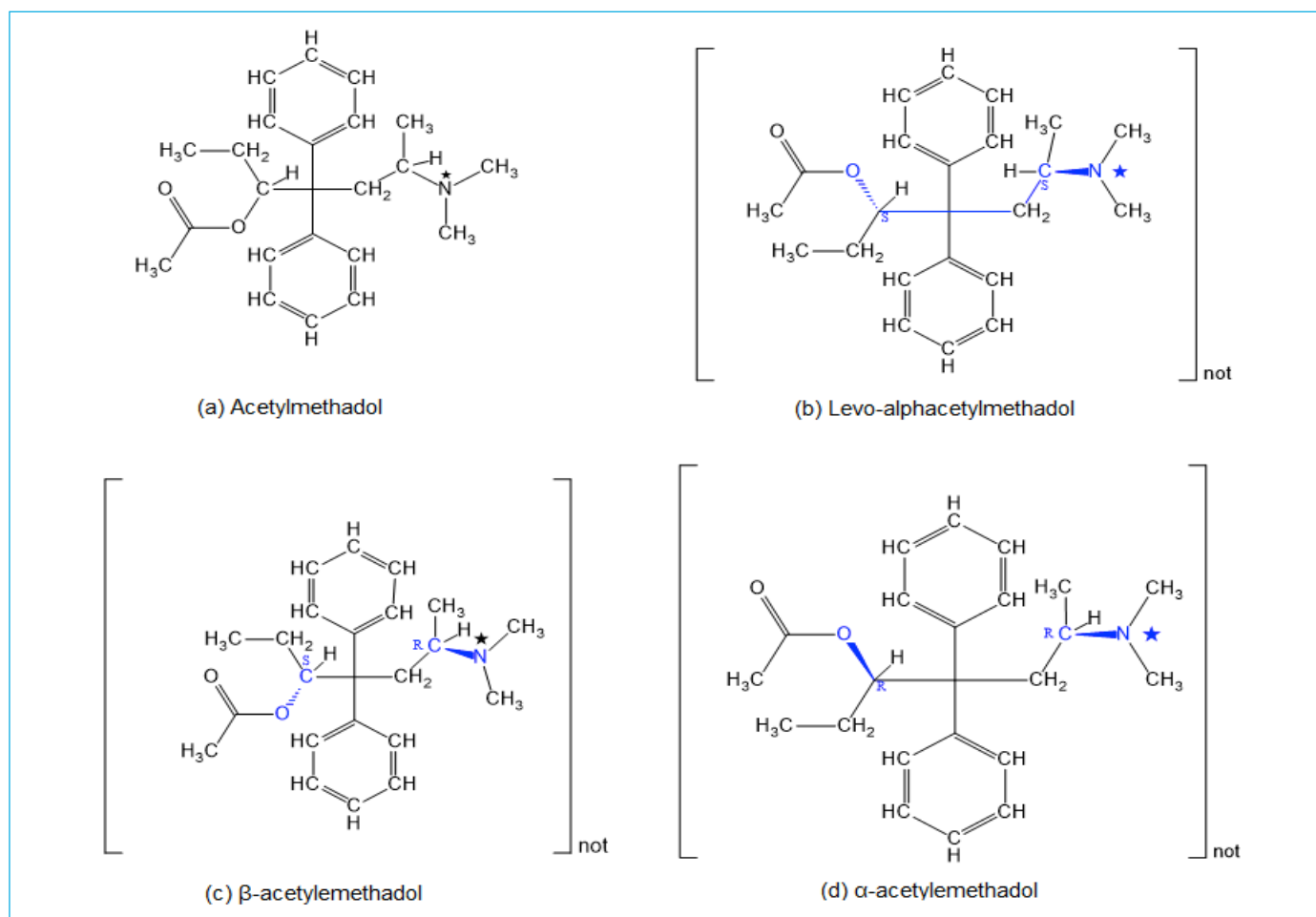


Figure 2. Ruling on Acetylmethadol. (a) Acetylmethadol includes unspecified stereochemical isomers, possible salts on Nitrogen, and no substituents on any Carbon. It excludes (b) S,S-isomer Levacetylmethadol, (c) S,R-isomer β -acetylmethadol, and (d) R,R-isomer α -acetylmethadol. The exclusion is expressed by "[]not."

Some regulations cannot be expressed by chemical structures alone. There are very few of these and are thus temporarily not in the scope of KnowItAll's Controlled Substance Regulation prediction system. For example, "1308.11(d)(58)," Marijuana Extract⁴.

Results and Discussion

Testing

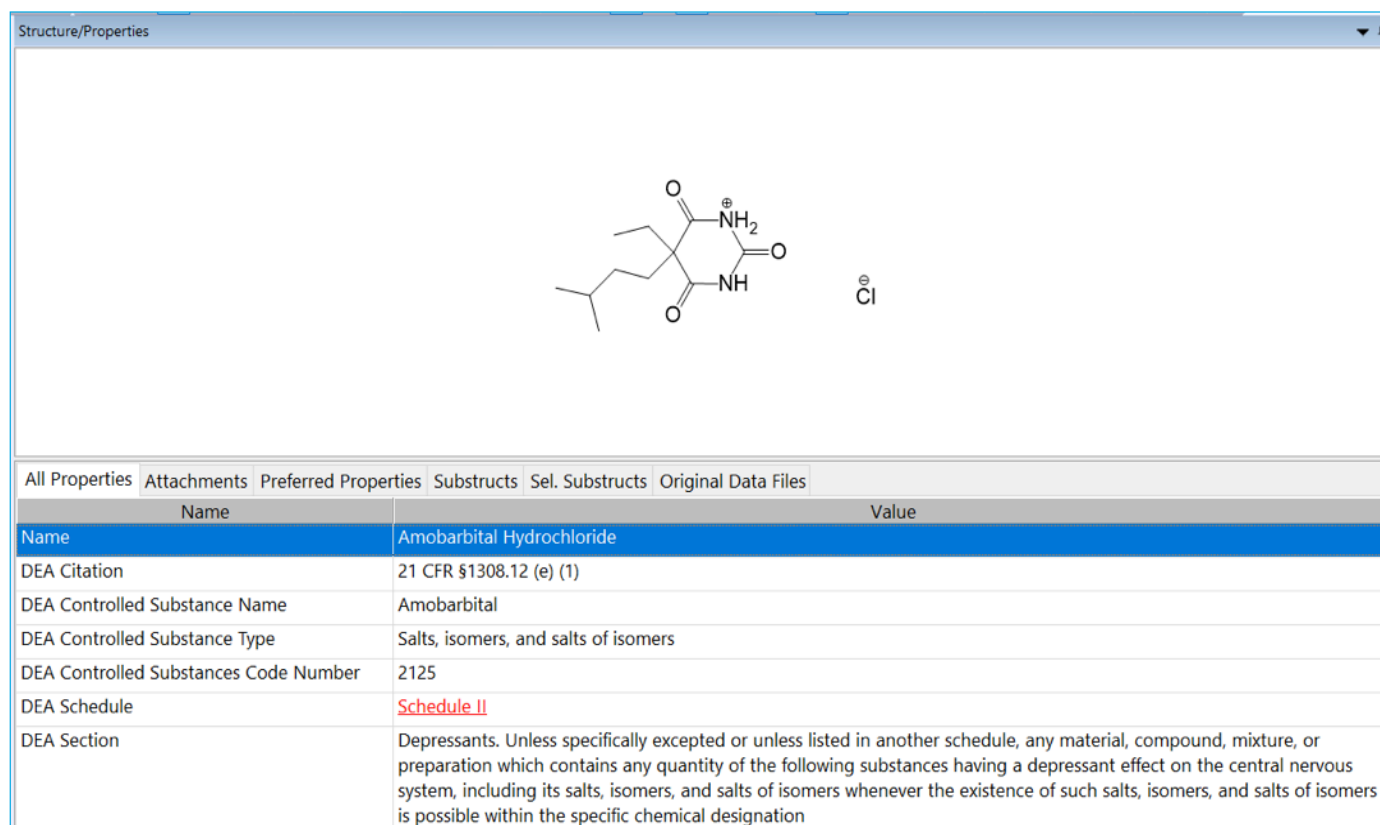
Test Structures

During the construction of the fuzzy structures, a test database was created alongside which contains enumerated unambiguous chemical structures for positive and negative scenarios in order to prove that KnowItAll can reliably classify these chemical structures

Test Database: Wiley Commercial Databases

Selective Wiley databases contain controlled substance schedules manually entered by experts or taken from commercial chemical providers and public websites such as Pubchem⁵. These databases were used to test the KnowItAll DEA Controlled Substance Regulation System and found false positives and negatives. These discrepancies were manually examined, which further confirmed the accuracy and reliability of the KnowItAll DEA Controlled Substance Regulation System.

A batch computing routine allows KnowItAll users to apply the KnowItAll DEA Controlled Substance Regulation System on user databases from within KnowItAll's Minelt application using a batch prediction feature. The DEA Citation, the DEA Controlled Substance Name, the DEA Controlled Substance Type, the DEA Controlled Substance Code Number, and the DEA Section are populated if the structure matches a ruling (Figure 3).



Structure/Properties	
Name	Value
Name	Amobarbital Hydrochloride
DEA Citation	21 CFR §1308.12 (e) (1)
DEA Controlled Substance Name	Amobarbital
DEA Controlled Substance Type	Salts, isomers, and salts of isomers
DEA Controlled Substances Code Number	2125
DEA Schedule	Schedule II
DEA Section	Depressants. Unless specifically excepted or unless listed in another schedule, any material, compound, mixture, or preparation which contains any quantity of the following substances having a depressant effect on the central nervous system, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation

Figure 3. DEA ruling produced for Amobarbital Hydrochloride.

Conclusion

DEA Controlled Substance Regulations can be expressed electronically by using KnowItAll's comprehensive fuzzy structure features. Batch predictions can be applied to internal chemical inventory databases for sanity checking as well as in drug design. Compliance is systematically assured, not in-house expertise dependent, so that the risk of accidental violation of DEA regulations is minimized.

References

1. PART 1308 - SCHEDULES OF CONTROLLED SUBSTANCES (usdoj.gov) Accessed on September 29, 2021.
2. KnowItAll Software (version 2021). John Wiley & Sons, Inc. Hoboken, NJ (2021). [Computer Software]
3. PART 1308 - Section 1308.12 Schedule II (usdoj.gov) Accessed on September 29, 2021.
4. PART 1308 - Section 1308.11 Schedule I (usdoj.gov) Accessed on September 29, 2021.
5. PubChem (nih.gov) Accessed on September 29, 2021.

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