ORPHINES NAMING GUIDE

Benzimidazol-2-ones, also known as "orphines", are a complex and rapidly emerging subclass of novel synthetic opioids. **NPS opioid naming schemes** are typically tailored to a prototypical drug (e.g., fentanyl, etonitazene), which helps indicate structure and biological effects while initiating the naming convention process. Consequently, the orphine analogues and orphine-related substances require distinct nomenclatures.

TRADITIONAL ORPHINE ANALOGUES

Traditional orphine nomenclature stems from the prototypical drug **brorphine**, which first emerged in 2020 as its name was coined among online gray market sites. This analyte now serves as the blueprint for a semi-systematic naming convention to denote different structural modifications that may occur on the tail and core moieties using "orphine" as the root of the naming convention (**Figure 1**).

- **Tail:** Modifications to the substituted benzyl moiety are denoted by adding a prefix to the orphine root with a hyphen (e.g., *o*-, *o*'-, *m*-, *m*'-, *p*-, or alpha-). Halogenated substitutions in the *para*- position are common. Substances with this modification are named with an abbreviated prefix to denote the substitution followed by the root "orphine" (e.g., **br**orphine, **chl**orphine). Alkyl substituents in the *para*- position follow a similar rule, though their prefixes are not abbreviated to avoid confusion with other existing drugs (i.e., **methyl**orphine vs. methorphan, **ethyl**orphine vs. etorphine). Any shared functional groups should be grouped using the appropriate substitution and numeric prefix to indicate the number of occurrences (e.g., di-, tri-, etc.). If multiple substituents are present, α- substitutions should be listed before those on the benzene ring and those on the benzene ring should be listed in order of priority following IUPAC rules preceding those in the *para*- position (e.g., **alpha-ethyl-*m*-chloro-methyl**orphine).
  - **Substitution Examples:**
  - Single:
    - The ***para***- position is assumed if not denoted, and these modifications are fixed at the front of the root "orphine" (i.e., *p*-bromo → **br**orphine [do not use *p*-bromo-orphine], *p*-methyl → **methyl**orphine [do not use *p*-methyl-orphine])
    - ***ortho***- and ***meta***- substitutions are specifically listed, and these modifications are explicitly listed in front of the root "-orphine" (e.g., ***m*-bromo**-orphine, ***o*-chloro**-orphine)
  - Multiple:
    - List positions with comma(s), use appropriate prefix(es), and group when possible (e.g., di-, tri-), using the *m*'- and *o*'- prefixes when there are multiple substitutions on opposite sides of the benzene ring (e.g., ***m*-bromo-chl**orphine, ***m'*-fluoro-*m*-chloro**-orphine)
    - If a *para*- position substituent is present, use shorthand naming (e.g., ***o*,*p*-dibr**orphine)
    - If no *para*- substituent is present, the functional groups will remain separated from the "-orphine" root (e.g., ***o*,*m*-dibromo**-orphine, ***o*-bromo-*m'*-chloro**-orphine)
  - α-Carbon:
    - Absence of the methyl group = **"desmethyl"** conjoined prefix (e.g., **desmethylbr**orphine)
    - Replacement of methyl group = **"alpha-[substituent]-"** (e.g., **alpha-ethyl-br**orphine)
  - Absence of Tail:
    - Use "**nor**-orphine" as the root

- **Core:** The core moiety is comprised of the benzimidazolone and piperidine ring systems of the orphine scaffold. Substitutions on the core are named before that of the tail and separated with a space from the root, which is dictated by what tail modifications have been made as described above. Substitutions at the nitrogen atom are denoted with an "*N*-" prefix while those on the carbon atoms are denoted using the appropriate number and substitution (e.g., #-, #'-). If there are multiple substitutions, these should be listed in order of the following priority: *N*-, benzimidazolone ring (#-), and piperidine ring (#'-). Shared functional groups should be grouped together using a numeric prefix to indicate the number of occurrences (e.g., di-, tri-, etc.).
  - **Substitution Examples:**
  - Single: **7-ethyl** orphine, ***N*-propionitrile br**orphine
  - Multiple: **5,6-dimethyl flu**orphine, **N-propionitrile-5-chloro desmethylbr**orphine

TRADITIONAL ORPHINES

NAMING SYSTEM

core tailorphine

SIMPLE & COMPLEX EXAMPLES

Tail Substitution:
***o/m/p/o'/m'/alpha-sub-*orphine**
Examples: *o*-flu**orphine**, **alpha-propyl-br**orphine

Core Substitution:
***N/#/#'-sub* orphine**
Examples: ***3'*-ethyl** orphine, ***N*-propionitrile** chlorphine

Core & Tail Substitutions:
***N/#/#'-sub o/m/p/o'/m'/alpha-sub-*orphine**
Examples: **5-fluoro alpha-ethyl-**orphine,
***N*-methyl desmethylchl**orphine

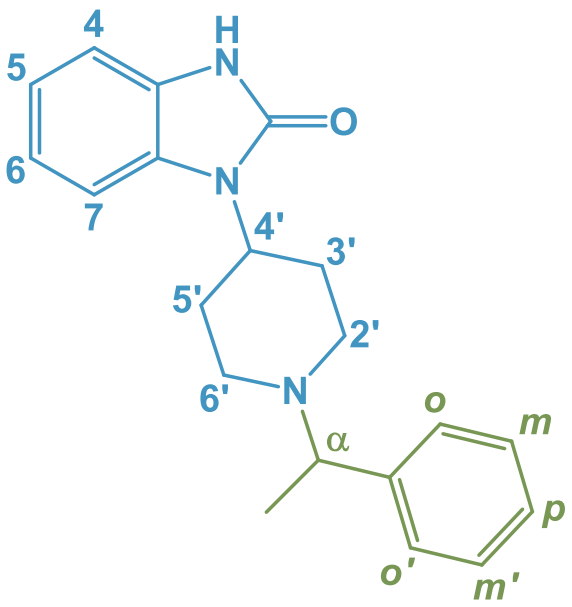
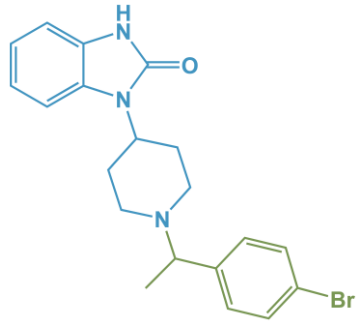
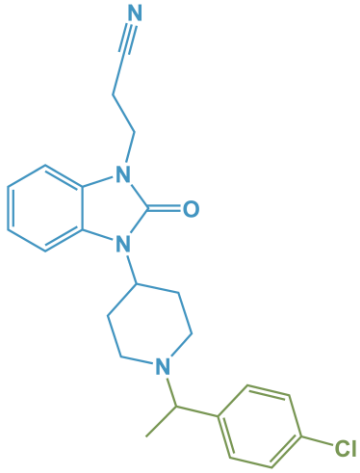
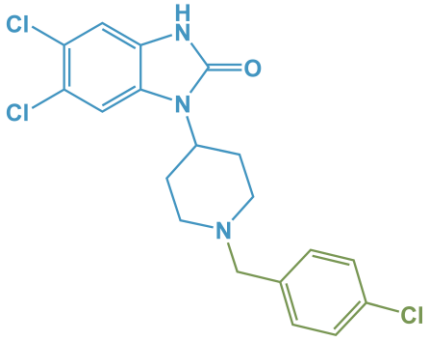


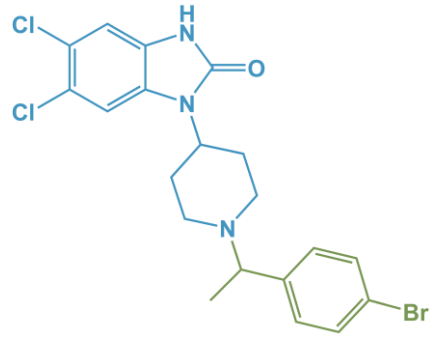
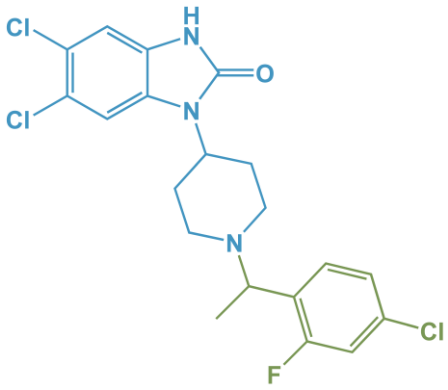
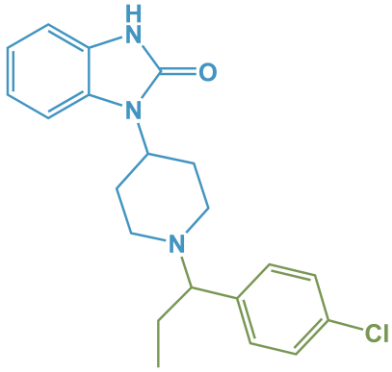
Figure 1: Numbering System for Traditional Orphine Scaffold

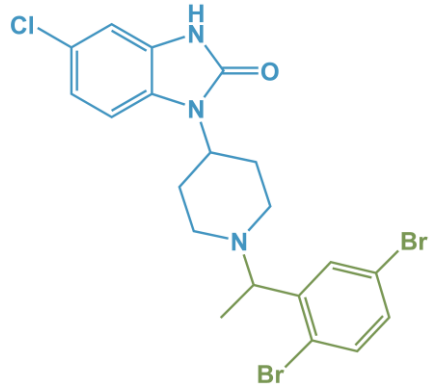
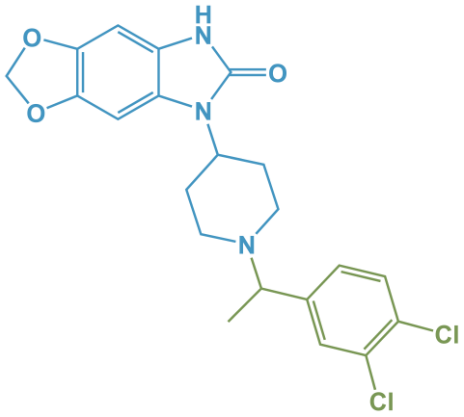
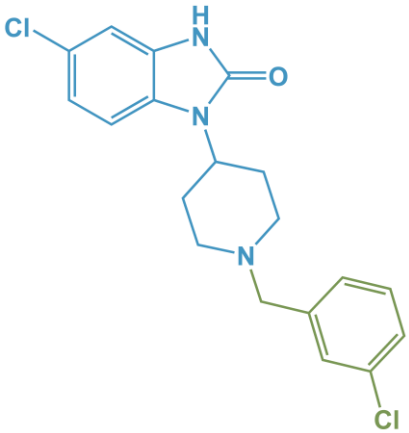
Note: *All components of the scheme may not be present within every molecule so the appropriate scheme should be selected for naming.*

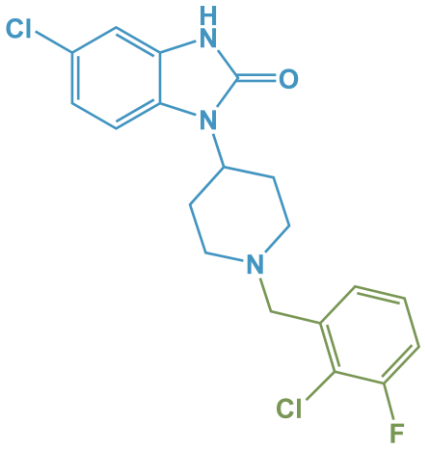
Definition: *Substitution = Replacing one atom (e.g., hydrogen) with another atom (e.g., fluorine, chlorine) or functional group.*

Table 1: Examples of Traditional Orphine Analogues

Structure	Preferred Name	Synonym(s)
	brorphine	N/A
	*N*-propionitrile chlorphine	cychlorphine
	5,6-dichloro desmethylchlorphine	SR-17018

Structure	Preferred Name	Synonym(s)
	5,6-dichloro brorphine	SR-14968
	5,6-dichloro *o*-fluoro-chlorphine	SR-14969
	alpha-ethyl-chlorphine	R-6555

Structure	Preferred Name	Synonym(s)
	5-chloro *o,m'*-dibromo-orphine	N/A
	5,6-methylenedioxy *m,p*-dichlorphine	N/A
	5-chloro desmethyl-*m*-chloro-orphine	N/A

Structure	Preferred Name	Synonym(s)
	5-chloro desmethyl-*o*-chloro-*m*-fluoro-orphine	N/A

SPIRO ORPHINE ANALOGUES

Spiro orphine analogue nomenclature stems from the emergence of **spirochlorphine**. This scaffold is noted by a phenyl-triazaspirodecanone moiety (**Figure 2**). Unlike traditional orphines, the piperidine and benzimidazolone rings are conjoined by sharing a carbon atom, or "spiro" conformation, rather than being connected via a single bond bridge. Despite structural differences, spiro orphine analogues follow a naming convention similar to that of the traditional orphine analogues.

- **Tail:** Modifications to the substituted benzyl moiety follow rules similar to those for traditional orphine analogues but instead using "spiro_orphine" as the root with substituent names inserted within the root (e.g., spiro**br**orphine, spiro**chl**orphine). As noted above, prefixes for halogenated substituents are abbreviated whereas alkyl chains are not.
  - **Substitution Examples:** *(following that of traditional orphine analogues)*
  - Single:
    - Modifications to this scaffold are denoted by inserting the substituent within the "spiro_orphine" root (e.g., spiro**br**orphine, spiro**methyl**orphine)
    - The ***para-*** position is assumed if not denoted (*p*-bromo → spiro**br**orphine)
    - ***ortho-*** and ***meta-*** substituents are specifically listed in front of the "spiroorphine" root (e.g., ***m*-bromo**-spiroorphine, ***o*-chloro**-spiroorphine)
  - Multiple:
    - List positions with comma(s), use appropriate prefix(es), insert appropriate *para-* substituent within "spiro_orphine" root, and group when possible (e.g., di, tri, etc.), using the *m'-* and *o'-* prefixes when there are multiple substitutions on opposite sides of the benzene ring (e.g., ***m*-bromo**-spiro**chl**orphine, ***m'*-fluoro-*m*-chloro**-spiroorphine)
    - If a *para-* position substituent is present, use shorthand naming (e.g., ***o,p*-**spiro**dibr**orphine)
    - If no *para-* substituents are present, the functional group will remain separated from the "-spiroorphine" root (e.g., ***o,m*-dibromo**-spiroorphine, ***o*-bromo-*m'*-chloro**-spiroorphine)
  - α-Carbon:
    - Absence of the methyl group = **"desmethyl"** conjoined prefix (e.g., **desmethyl**spiroorphine)
    - Replacement of methyl group = **"alpha-[substituent]-"** (e.g., **alpha-ethyl**-spiroorphine)
  - Absence of Tail:
    - Use "**nor**-spiroorphine" as the root
- **Core:** The core moiety is comprised of the phenyl-triazaspirodecanone. Modifications to this scaffold follow rules similar to those of traditional orphine analogues.
  - **Substitution Examples:**
  - Single: **4-bromo** spiroorphine; ***N*-methyl** spiro**br**orphine
  - Multiple: **3,4-difluoro** spiro**chl**orphine; ***N*-methyl-4-fluoro** spiro**flu**orphine

SPIRO ORPHINES

NAMING SYSTEM

core spiro[tail]orphine

SIMPLE & COMPLEX EXAMPLES

Tail Substitution:
***o/m/p/o'/m'/alpha*-spiro[sub]orphine**

Examples: *o*-spirobrorphine,
alpha-ethyl-spirochlorphine

Core Substitution:
***N*/#/#'-sub spiroorphine**

Example: 4-ethyl spiroorphine

Core & Tail Substitutions:
***N*/#/#'-sub *o/m/p/o'/m'/alpha*-spiro[sub]orphine**

Examples: 5-fluoro spirobrorphine,
N-methyl desmethylspirochlorphine

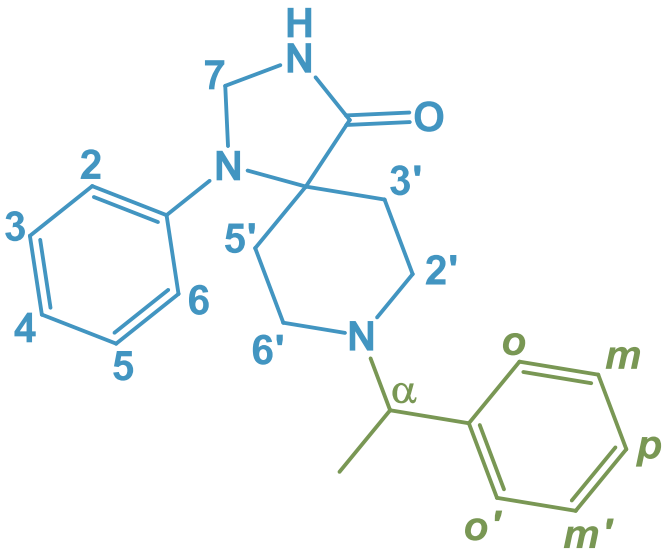
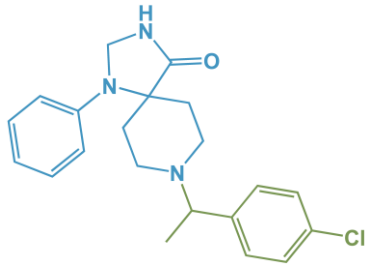
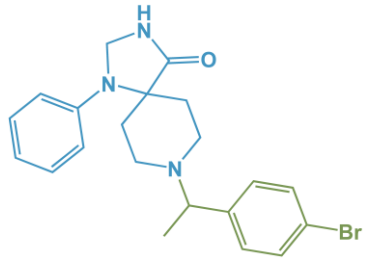
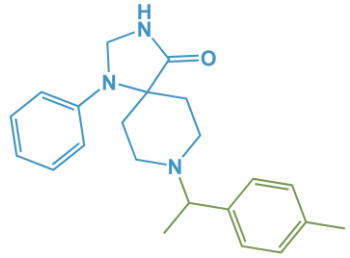
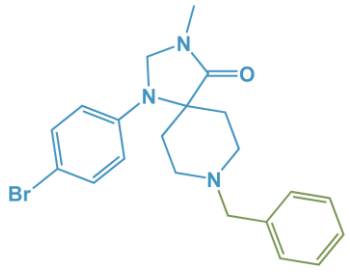
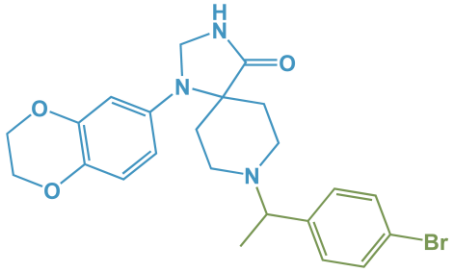


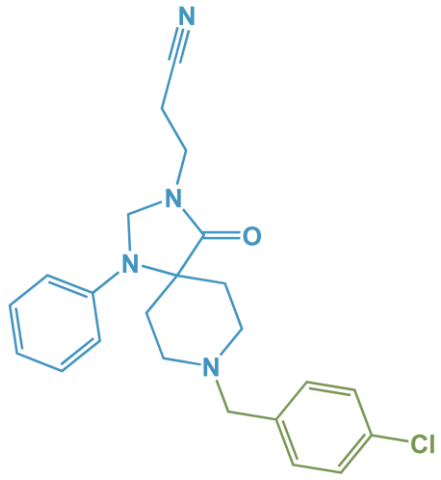
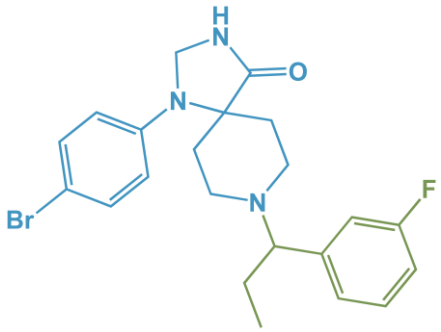
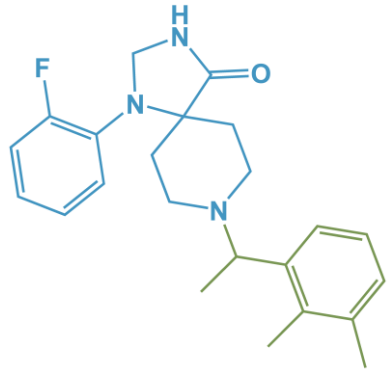
Figure 2: Numbering System for Spiro Orphines Scaffold

Note: *All components of the scheme may not be present within every molecule so the appropriate scheme should be selected for naming.*

Definition: *Substitution = Replacing one atom (e.g., hydrogen) with another atom (e.g., fluorine, chlorine) or functional group.*

Table 2: Examples of Spiro Orphine Analogues

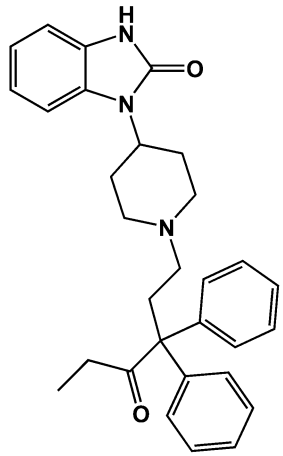
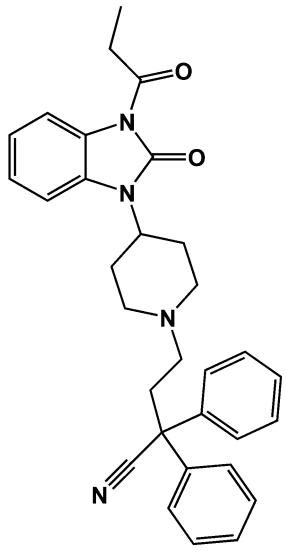
Structure	Preferred Name	Synonym(s)
	spirochlorphine	R-6890
	spirobrorphine	N/A
	spiromethylorphine	R-6372
	*N*-methyl-4-bromo desmethylspiroorphine	N/A
	3,4-ethylenedioxy spirobrorphine	N/A

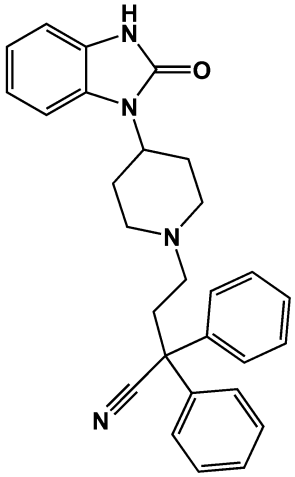
Structure	Preferred Name	Synonym(s)
	*N*-propionitrile desmethylspirochlorphine	N/A
	4-bromo alpha-ethyl-*m*-fluoro-spiroorphine	N/A
	2-fluoro *o,m*-dimethyl-spiroorphine	N/A

ZITRAMIDE ANALOGUES

Zitramides are structurally similar to orphine analogues but with previously developed names that have historical context. While these drugs share the orphine core, the benzyl tail is replaced with features contained within methadone analogues. Updates and guidance on the naming of new analogues in this subclass will be provided in the future, as needed. Select examples of known zitramide analogues are listed below in Table 3.

Table 3: Examples of Zitramide Analogues

Structure	Preferred Name	Synonyms
	etodezitramide	R-4837
	bezitramide	R-4845

Structure	Preferred Name	Synonyms
	despropionyl bezitramide	R-4618

About: With funding from the National Institute of Justice (NIJ), the Center for Forensic Science Research and Education (CFSRE) at the Fredric Rieders Family Foundation, in collaboration with Cayman Chemical, is developing and implementing standardized nomenclature and taxonomy in relation to novel psychoactive substance (NPS), with a focus on five main classifications: benzodiazepines, opioids, stimulants hallucinogens, cannabinoids, and miscellaneous. The goal of this specific initiative is to improve communications regarding NPS and help eliminate confusion by assigning preferred names and naming guides for future NPS.

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