WashU

Office of Technology Management

NEUROACTIVE STEROID ANESTHETIC COMPOUNDS

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T-004034

Technology Description

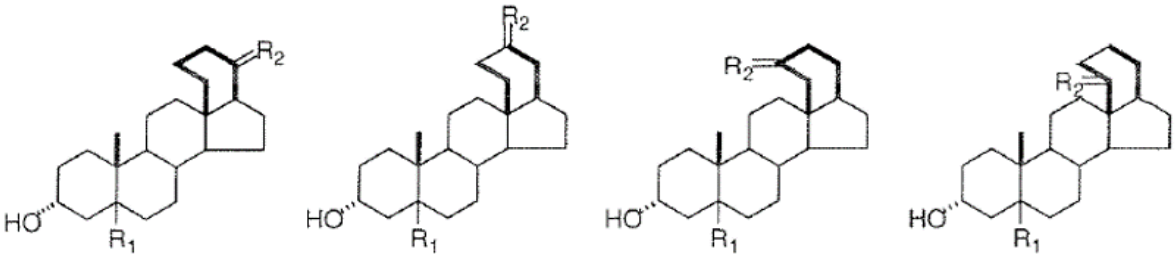
Researchers at Washington University have developed a range of steroid anesthetic agents that share known neurosteroid structures but are more potent. These compounds share the basic structure of neurosteroids alphaxalone, allopregnanolone, and ent-androsterone, but the structural modifications have resulted in synthetic non-natural steroids that possess better neuroactive properties.

Like propofol, these novel neurosteroids enhance the actions of GABA (gamma-aminobutyric acid) at $GABA_A$ receptors. But there is a significant opportunity to produce competitor compounds due to past critical shortages of propofol, as well as side effects like apnea and reduced respiration.

Studies on tadpoles, and for selected compounds on mice, have shown desirable anesthetic properties by a rapid onset of anesthesia, followed by a rapid and pleasant recovery. Besides use as anesthetics, these compounds are also expected to have potential as anxiolytics, analgesics, anticonvulsants, sleep enhancers, and antidepressants. Moreover, their reduced lipophilicity is expected to result in enhanced water solubility to facilitate parenteral formulation.

Neuroactive 17,18-cyclohexylsteroids (T-004034)

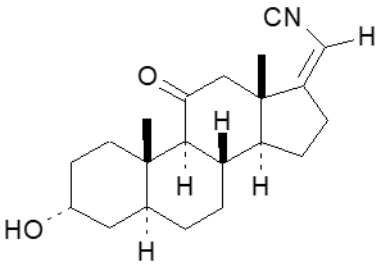
The researchers have synthesized neuroactive 13,24-cyclo-18,21-dinorcholanes and related pentacyclic steroids for use as anesthetic agents. *In vitro* studies have confirmed the mechanism of action- enhancing GABA activity at $GABA_A$ receptors. The anesthetic activity has been demonstrated *in vivo* in tadpoles.



R_1 = α-H or β-H R_2 = O; H_{ax}, CN_{eq}; H_{eq}, CN_{ax}; CHCN; $CHC(O)CH_3$.

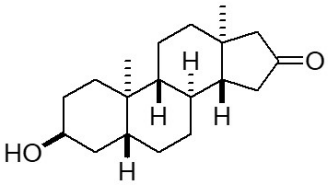
Neuroactive 17(20)-Z-vinylcyano-substituted steroids (T-010292, T-012294)

The researchers have synthesized steroid anesthetics based on the structure of alphaxalone but with more potency. The lead compound (6a) is shown below. Initial *in vivo* testing in both tadpoles and mice indicate that compound 6a functions similarly but more potently than alphaxalone.

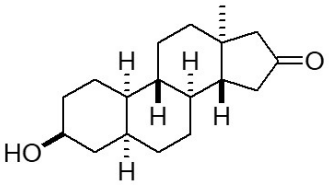


Neuroactive enantiomeric 13-, 15-, 16- and 17-substituted steroids (T-011272, T-011273, T-012325)

The researchers have synthesized a series of steroid anesthetics (examples shown below) based on both the structures of alphaxalone and ent-Androsterone. The lead compound MQ-35 was shown to be many times more potent *in vitro* at binding and activating $GABA_A$ receptors. *In vivo* studies showed MQ-35 to be 1.5 times more potent than alphaxolone in mice and 6 times more potent than ent-Androsterone in tadpoles.



MQ-35



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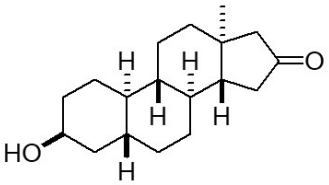

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Publications

- Stastna E, Krishnan K, Manion BD, Taylor A, Rath NP, … Covey DF. (2011). Neurosteroid Analogues. 16. A new explanation for the lack of anesthetic effects of Δ^{16}-alphaxalone and identification of a $\Delta^{17(20)}$ analogue with potent anesthetic activity. *Journal of Medicinal Chemistry,* 54(11): 3926-3934.
- Krishnan K, Manion BD, Taylor A, Bracamontes J, Steinbach JH, … Covey DF. (2012). Neurosteroid Analogues. 17. Inverted binding orientation of androsterone enantiomers at the steroid potentiation site on γ–aminobutyric acid type A receptors. *Journal of Medicinal Chemistry,* 55(3): 1334-1345.

Applications

- Short-acting intravenous anesthetics
  - Surgical anesthesia
  - Moderate/deep sedation for non-surgical procedures
- Potential anxiolytics, analgesics, anticonvulsants, sleep enhancers, antidepressants

Key Advantages

- Easier to formulate than propofol
- Similar to or more potent than existing neurosteroids

Patents

- US 7,781,421
- US 8,759,330

- US 9,388,210
- US 9,512,170
- US 9,765,110
- US 10,053,487
- US 10,160,783
- US 10,202,413

Related Web Links: Covey Profile & Lab