The importance of stereochemistery of drugs action

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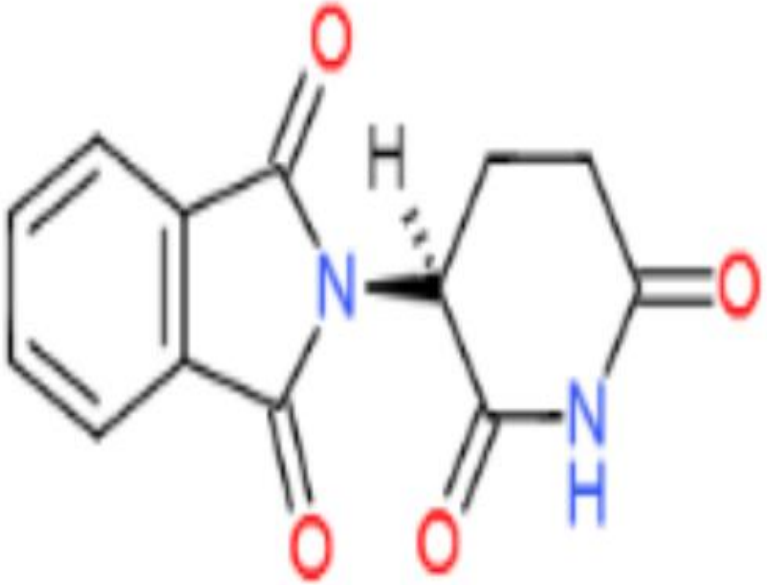
Did you know that **most newer antidepressants** (e.g., sertraline, mirtazapine) and **drugs for attention-deficit/hyperactivity disorder (ADHD) and sleep disorders** (e.g., atomoxetine, dexamfetamine, lisdexamfetamine, methylphenidate, modafinil, *etc.*) exhibit chirality? The same is true of **ketamine**, a veterinary tranquillizer turned miracle drug for treatment-resistant cases of depression.

: *Chirality*

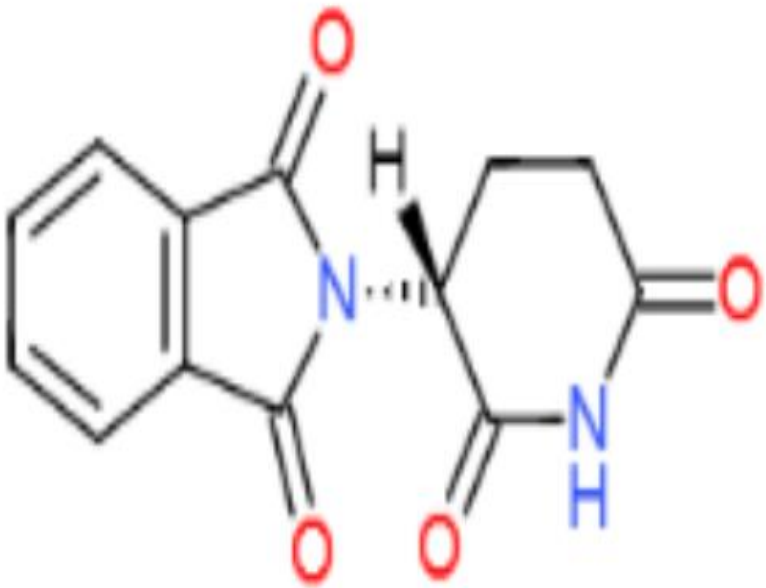
Chirality for those of you that do not belong to a field that requires first year university chemistry knowledge, is basically a fancy way of saying mirror image forms of the same drug molecule. They are created using They are assigned either (*R*) or (*S*) designations based on the CIP rules which we use to distinguish the two mirror image forms based on their orientation. We call these two mirror forms, **stereoisomers**. (*R*)-enantiomers are orientated to the right according to the CIP rules and (*S*)-enantiomers are orientated towards the left.

Impact of chirality on pharmacology: the thalidomide disaster

The **two stereoisomers** of a drug molecule often have **vastly different biological activities**. For example, **thalidomide** is an example that my chemistry professor from last year loved to mention. Ironically this professor is German and thalidomide was initially synthesized and marketed by a German pharmaceutical company. **Thalidomide** has two enantiomers: the (*S*)-enantiomer believed to be responsible for the birth defects caused by thalidomide whilst the (*R*)-enantiomer produces its therapeutic effects. Funnily enough it did not matter whether or not the (*R*)-enantiomer was served by itself or not as in the body it is quickly converted to the (*S*)-enantiomer too, hence negating any value from separating the two.



(S)-thalidomide



(R)-thalidomide

Antidepressants

All MAOIs except pirlindole, selegiline and tranylcypromine have no stereocentres. All TCAs except trimipramine are without stereocentres.

- **Bupropion**, comes as a racemate of the two enantiomers. A single enantiomer of bupropion was apparently under investigation in 2003, although this is according to just one source I have come across.[1]

Structure

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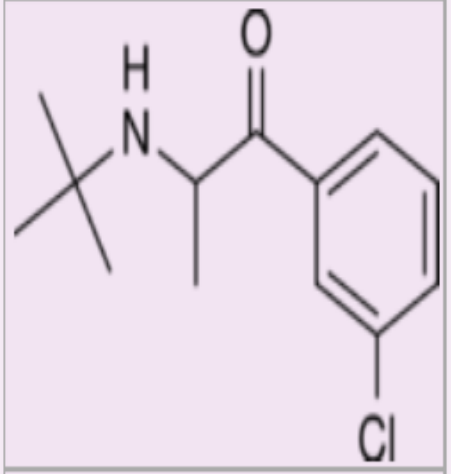

Bupropion's 2D structure

- **Citalopram**, it is sold as a racemate, which contains both enantiomers in equal quantities. (*S*)-citalopram is the active enantiomer whereas the (*R*)-enantiomer may even negate some of the therapeutic effects of the (*S*)-enantiomer. The racemic mixture of both (*R*)- and (*S*)-citalopram is also more likely to adversely affect the heart than the pure (*S*)-enantiomer.[1] It is a selective serotonin reuptake inhibitor.

Structure

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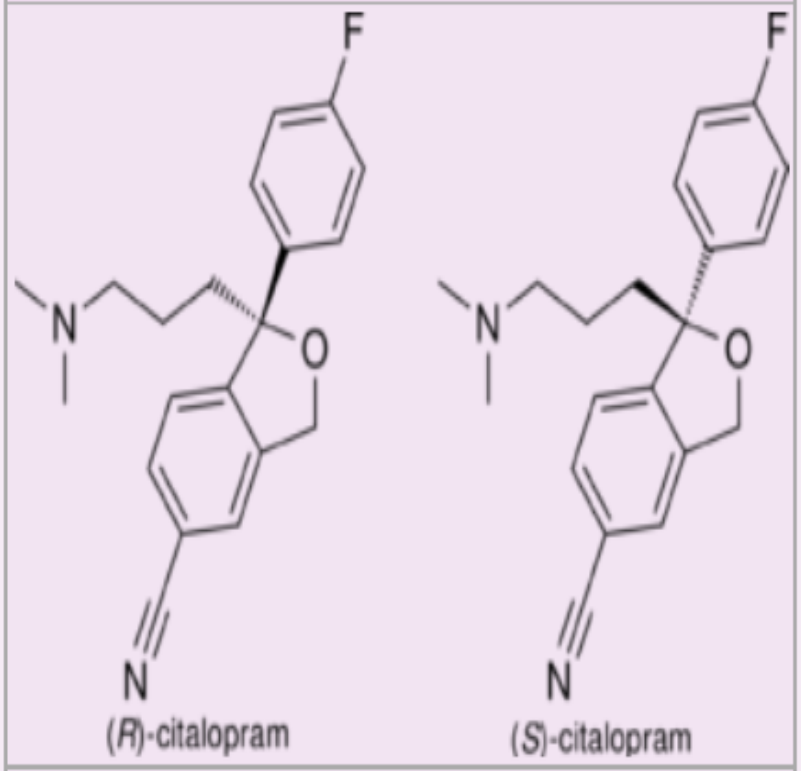

2D structure of the racemate of citalopram

- **Desvenlafaxine**, is a racemic mixture of both *R* and *S* with no convincing evidence of superior efficacy of either enantiomer. It is a serotonin-noradrenaline reuptake inhibitor and the chief active metabolite of venlafaxine.

Racemic structure

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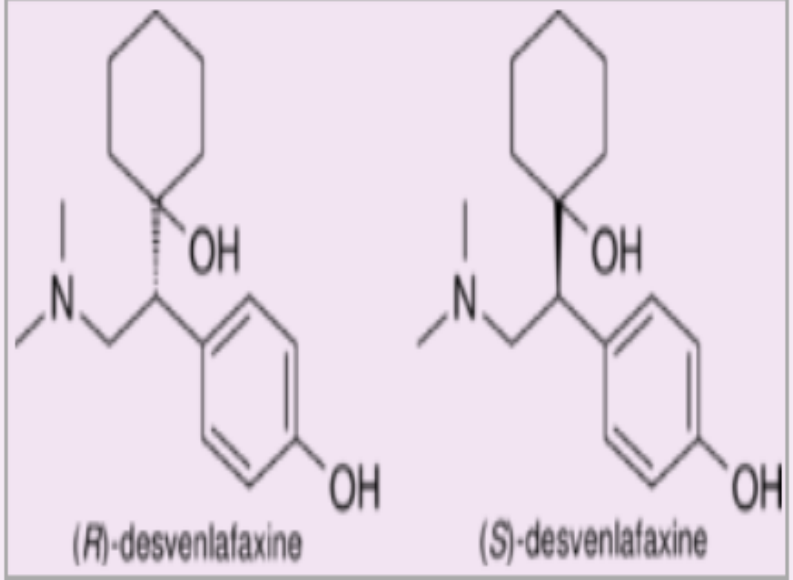

Structure of desvenlafaxine as a racemate

- **Fluoxetine**, both enantiomers are equally effective at increasing brain serotonin levels and hence also at relieving depression, but the (*R*)-enantiomer has more predictable pharmacokinetics. Pure (*R*)-fluoxetine was being developed as a treatment for depression until it was discovered that its effects on the heart were too significant for it to be of use, medically.[1] It is a selective serotonin reuptake inhibitor.

Structure

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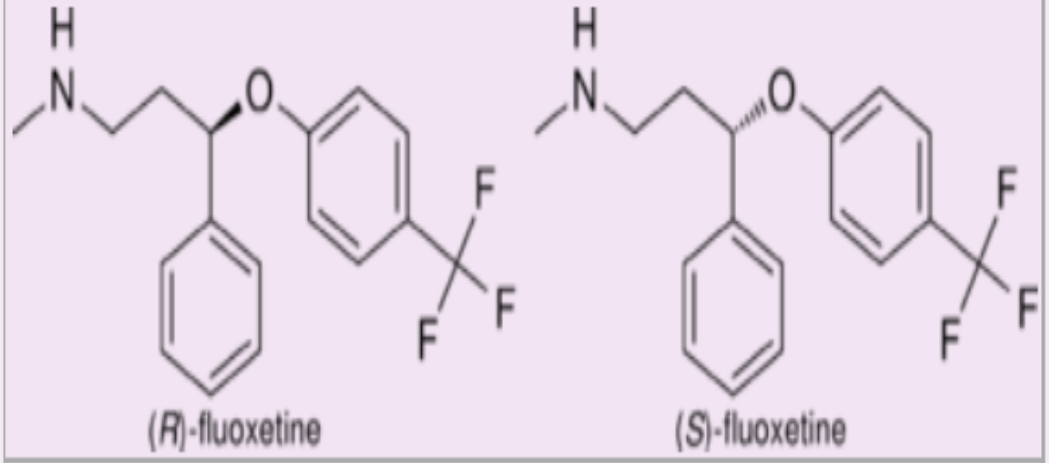

Racemic fluoxetine's 2D structure

- **Milnacipran**, the levorotatory (*l*-), (1*S*,2*R*)-stereoisomer is the more active enantiomer. Milnacipran is prepared as a racemate containing the *l*-(1*S*,2*R*)- and *d*-(1*R*,2*S*)-stereoisomers. It is a fairly balanced serotonin-noradrenaline reuptake inhibitor.

Structure

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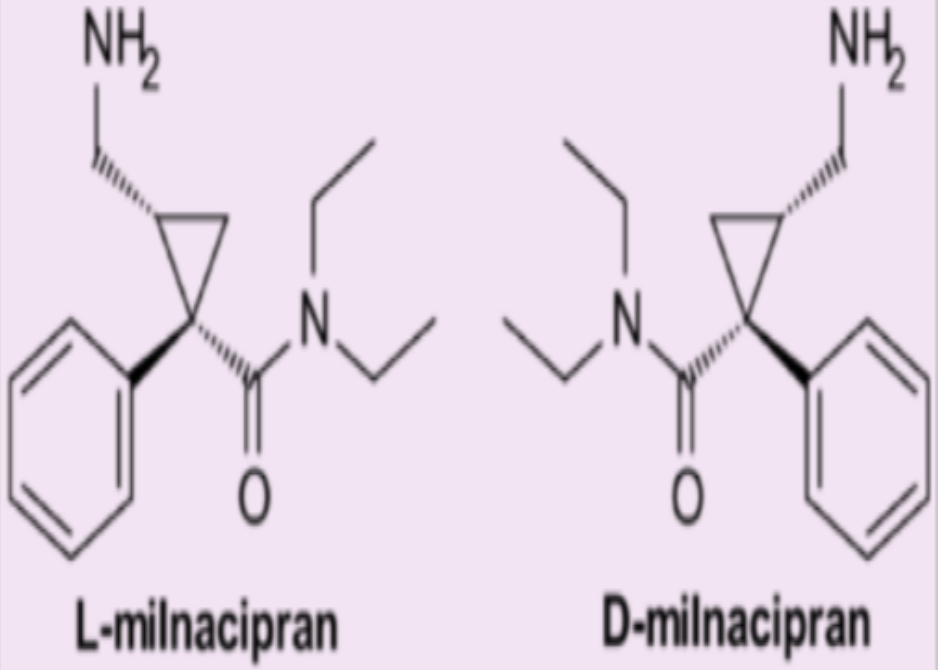

Milnacipran's 2D structure

- **Mirtazapine**, also comes as a racemic mixture of the two enantiomers. The *S*(+)-enantiomer is responsible for the drug's actions at the 5-HT_2 receptors, whereas the *R*(−)-enantiomer is responsible for its actions at the 5-HT_3 receptors. It too is a NaSSA.

Structure

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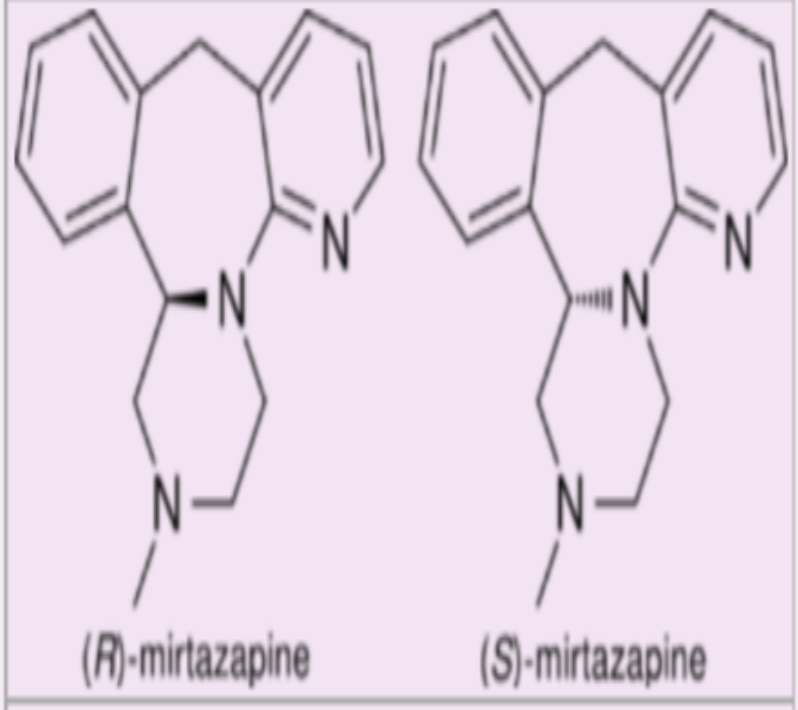

2D structure of racemic mirtazapine

- **Reboxetine**, both enantiomers are marketed, it serves as a noradrenaline reuptake inhibitor.

Structure

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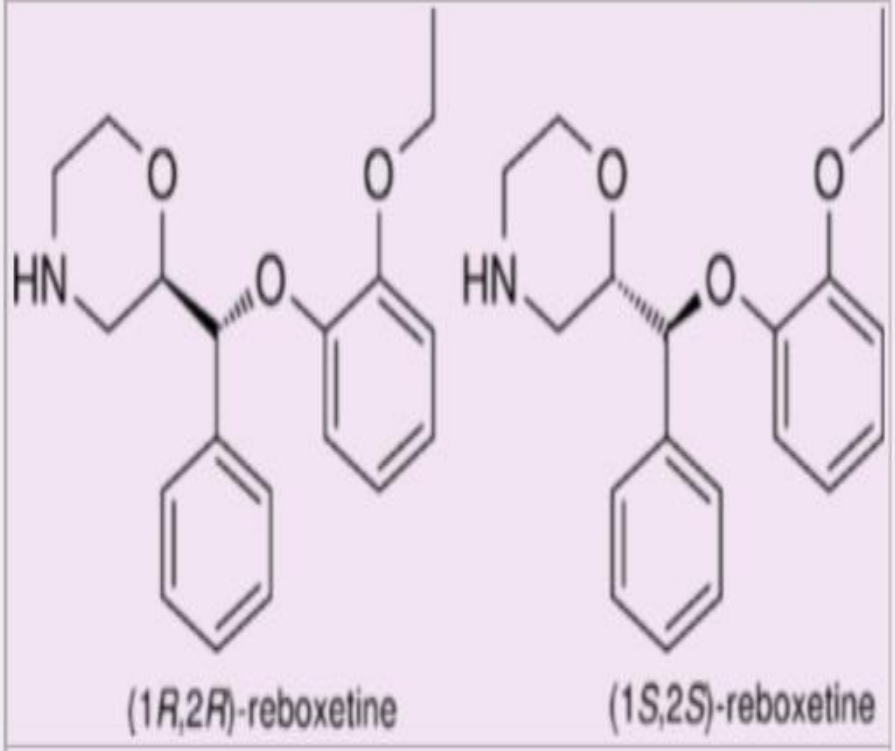

(1*R*,2*R*)-reboxetine (1*S*,2*S*)-reboxetine

Reboxetine's 2D structure

- **Venlafaxine**, comes as a racemic mixture, with no major difference between the two in as far as their biological effect is known. It inhibits the reuptake of serotonin and noradrenaline, with a significant preference for the former neurotransmitter.

Structure

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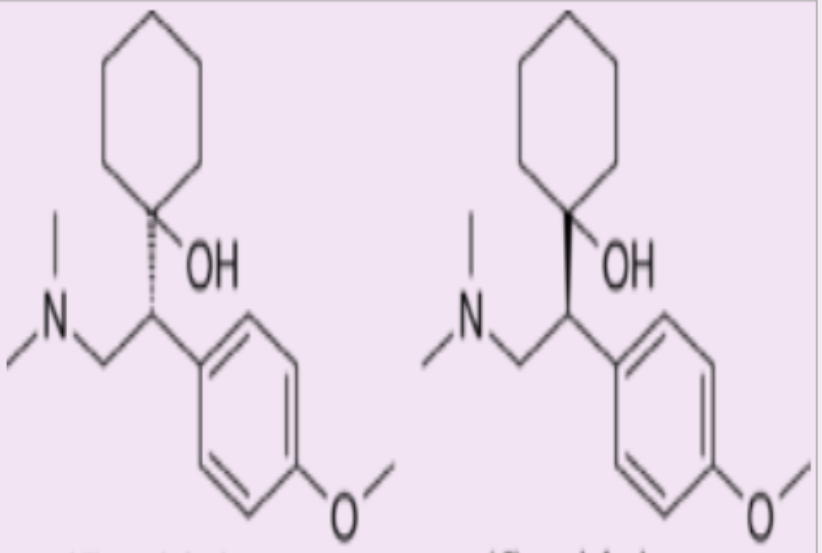

- **Tranylcypromine**, both the (1*R*,2*S*)(−) and (1*S*,2*R*)(+)-stereoisomers are present in the racemate. The (+)-enantiomer inhibits monoamine oxidase, whereas the (−)-enantiomer acts in a similar way to the amfetamines, to which it is chemically related. It is an irreversible monoamine oxidase inhibitor.[3]

Structure

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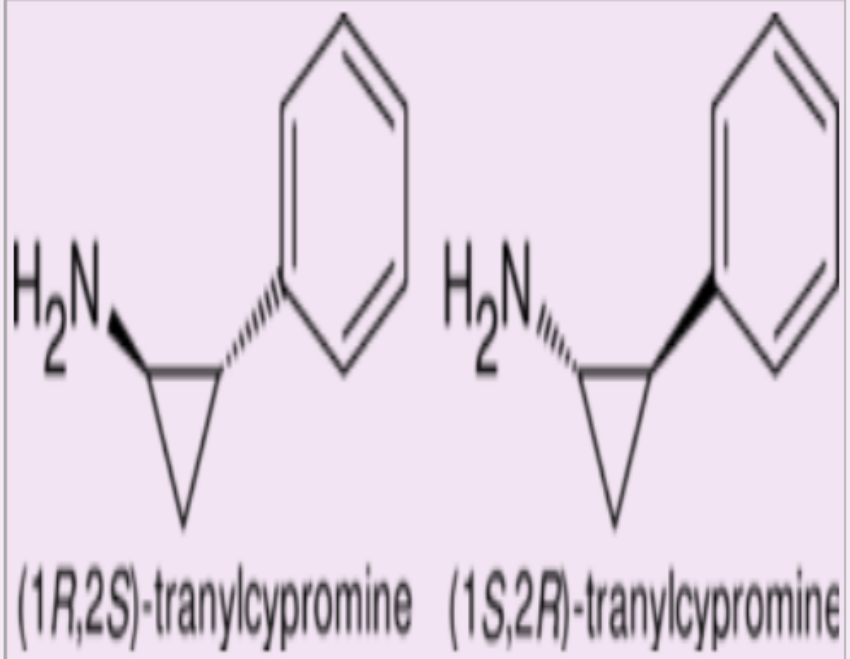

Tranylcypromine's 2D structure

- **Trimipramine**, comes as a racemate, there is no convincing evidence that either enantiomer is any more effective than the other. It is of the tricyclic antidepressant class.

Structure

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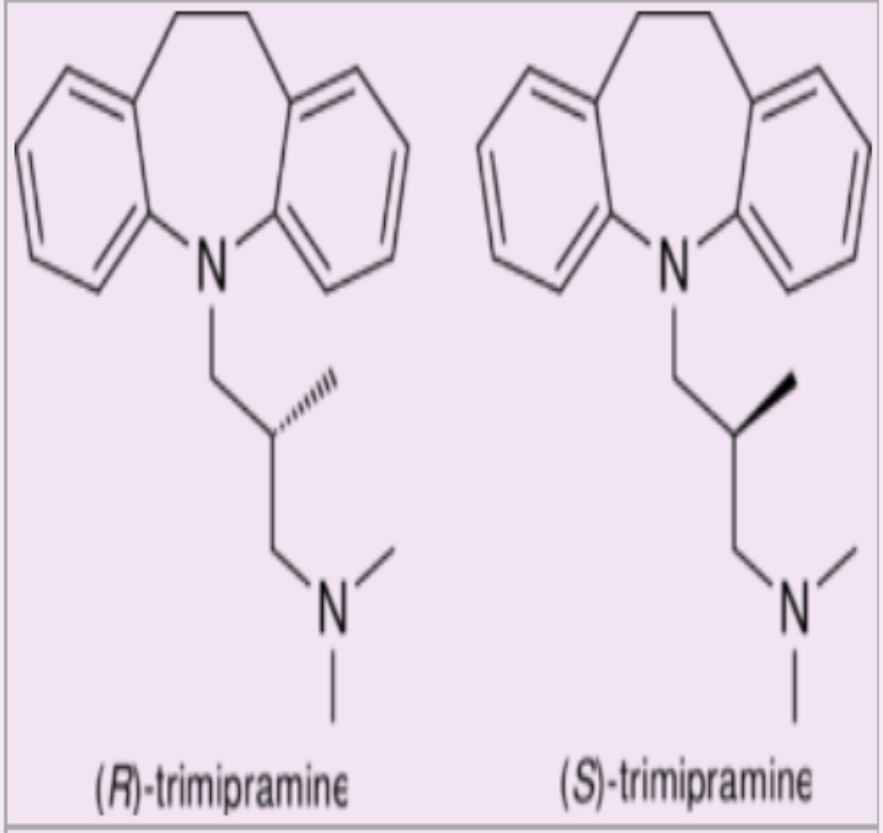

Trimipramine's 2D structure

ADHD and narcolepsy medicines

- **Amfetamine**, usually in the form of mixed amfetamine salts, is used in the management of ADHD in North America and a small handful of European countries. It comes as a mixture of the *R*(−)- and *S*(+)-enantiomers, approximately three-quarters are made up of the *S*(+)-enantiomer and the remaining quarter is made up of *R*(−)-amfetamine. The *S*(+)-enantiomer is significantly more active at inducing the release and inhibiting the reuptake of dopamine than the *R*(−)-enantiomer, although the *R*(−)-enantiomer produces more prominent peripheral effects like increased blood pressure and heart rate, constipation, dry mouth, *etc.*

Structure

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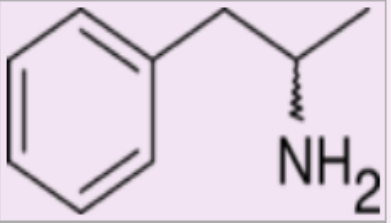

Amfetamine's 2D structure

- **Dexamfetamine** is the (*S*) enantiomer of amfetamine. It is a second-line treatment for ADHD in most of the developed world, including Australia, Canada, New Zealand, the UK and the U.S.A. It is also used in the management of narcolepsy.

Structure

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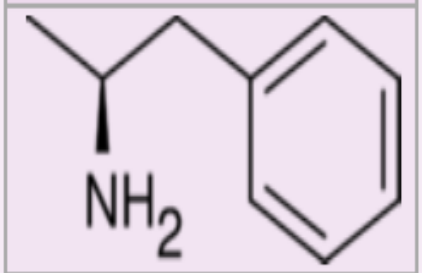

Dexamfetamine's 2D structure

- Dexmethylphenidate is the pure and more active *S*(+)-enantiomer of methylphenidate. Used solely in the management of ADHD and only available in select countries such as the U.S.A.

Structure

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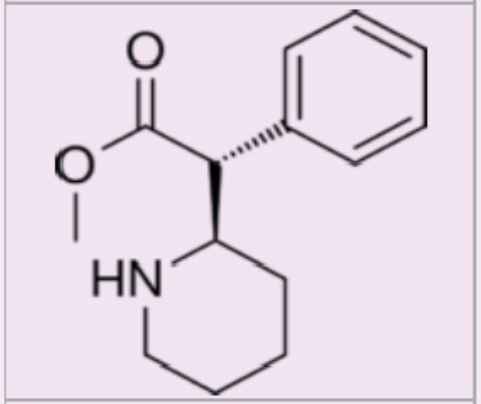

Dexmethylphenidate's 2D structure

- **Methylphenidate** is only stimulant medicine that is approved for the first-line treatment of ADHD; it is also used in the treatment of narcolepsy. It is available in virtually every developed country worldwide and is usually rather inexpensive. It is unlike the amfetamines in that it is solely a noradrenaline-dopamine reuptake inhibitor, with no appreciable ability to directly induce the release of these two neurotransmitters.

Structure

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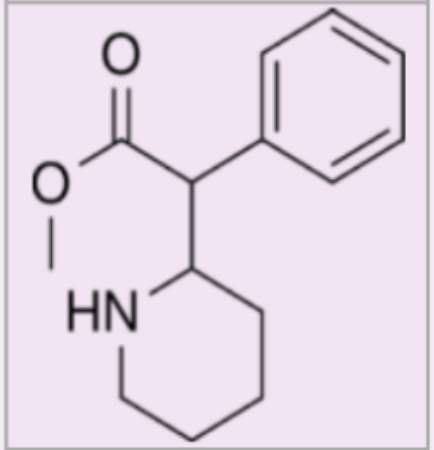

Methylphenidate's 2D structure

- **Metamfetamine** is only marketed in the U.S.A., where it as the pure *S*(+)-enantiomer, for the treatment of resistant cases of ADHD and obesity. Although the *R*(−)-enantiomer is also available for use in the management of nasal congestion (i.e., a runny nose) in the U.S.A.

Structure

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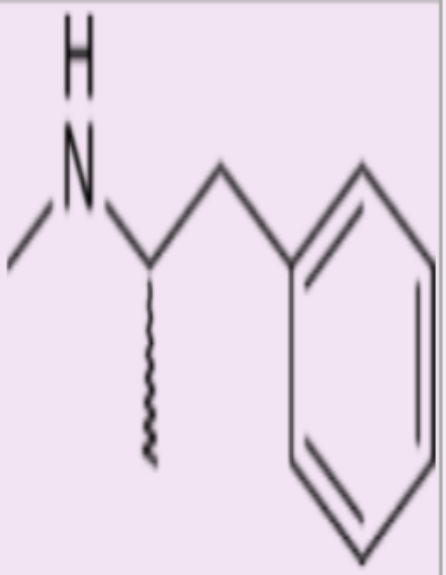

Metamfetamine's 2D structure

- **Modafinil** is used in the management of narcolepsy, primarily, although it can be used, usually as a third or fourth-line treatment, for the management of ADHD. The (*R*)-enantiomer is the more active form and is also marketed under the generic name of armodafinil. It is not technically a stimulant, as it does not usually produce euphoria, neither does it possess any significant abuse liability. Its exact mechanism of action is unknown but it is known to be a weak dopamine reuptake inhibitor.

Structure

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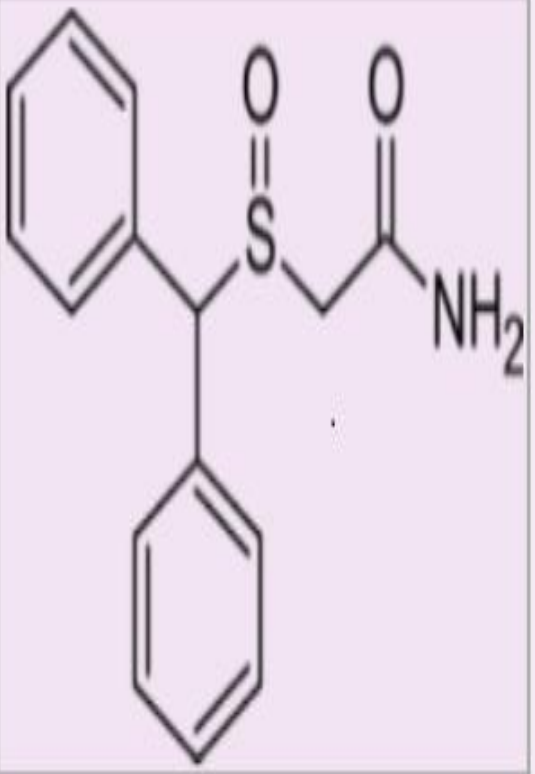

Modafinil's 2D structure

- **Atomoxetine** comes solely as the (*R*)-enantiomer. It is a significantly selective noradrenaline reuptake inhibitor, although a weak, yet clinically significant (most as far as the potential for it to contribute to serotonin syndrome) effect on serotonin reuptake is usually seen at clinically-utilized doses. It is a first-line treatment for the condition, along with methylphenidate.

Structure

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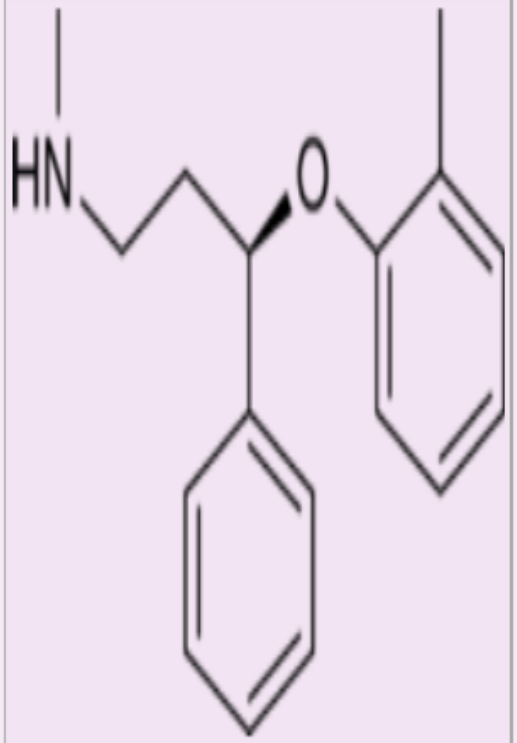

Atomoxetine's 2D structure