# New derivatives of 14,15-dihydro-20,21-dinoreburnamin-14-ol as potent antidepressants[1]

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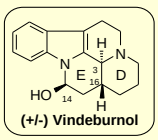
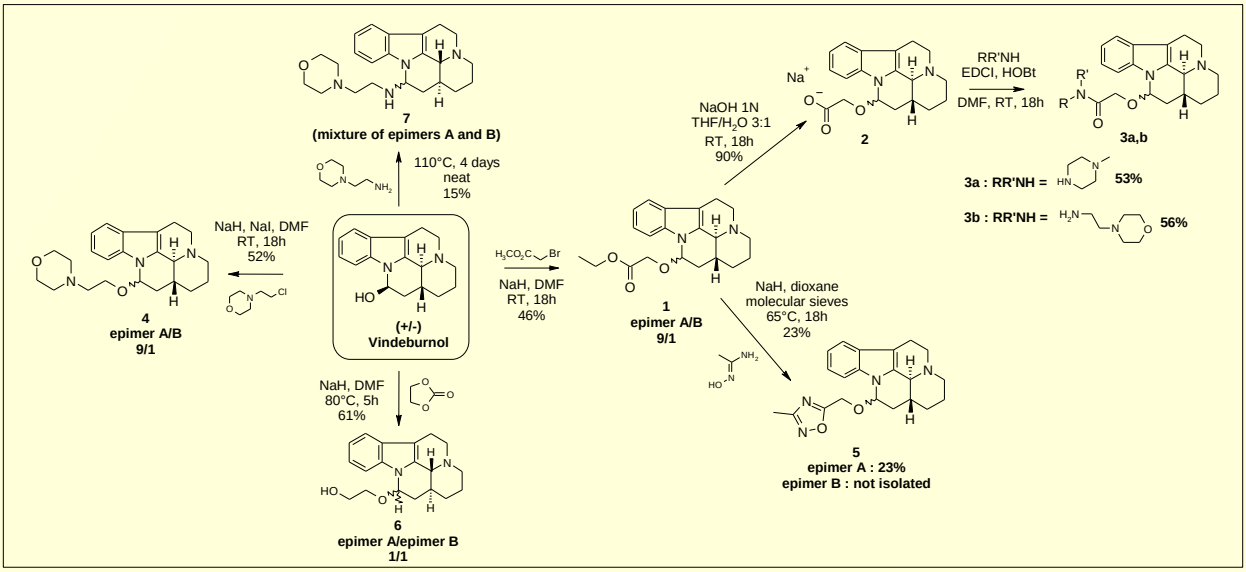
Derivatives of 20,21-dinoreburnamine including 14,15-dihydro-20,21-dinoreburnamin-14-ol (Vindeburnol) are already known for their vaso-expanding properties in the brain and for their effects on the regulation of tyrosine hydroxylase (TH) in the *locus coeruleus (LC)* which makes them of interest as antidepressants.[2]



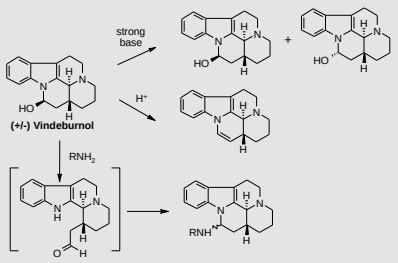

Only few C-14 analogues of Vindeburnol have been already described in the literature[3,4]. To enhance pharmacokinetics properties of Vindeburnol, C-14 modified derivatives have been synthesized. For this purpose, substituants have been attached at C-14 either as O-ethers of Vindeburnol or as secondary amines of 14-amino-vindeburnane.

## Synthesis of 14-modified derivatives of Vindeburnol




### Reactivity of Vindeburnol

- In presence of strong bases, Vindeburnol isomerizes in 14-position
  - ➢ *It explains the obtention of diastereomers A and B during O-alkylation step*
- In presence of acid, Vindeburnol is deshydrated
- In presence of primary amine, Vindeburnol leads to 14-amino derivatives thanks to the opening of the aminal moiety




### Stereochemistry of derivatives 1, 4 and 6

- The two diastereomers A and B present in the mixtures **1**, **4** and **6** obtained during the O-alkylation are separable by flash chromatography
- RMN studies of epimer A of **4** reveals that inversion of configuration occurs on C-14 during O-alkylation step
- Compounds A and B are racemates. In both cases, the corresponding enantiomers can be obtained by preparative chiral HPLC

## Conclusion

- New innovative derivatives of Vindeburnol have been synthesized
- Water solubility (>20mg/mL) is improved compared to Vindeburnol
- Addition of hydrophilic moieties on Vindeburnol do not prevent CNS selectivity: regulation of the TH is observed in the *LC*
- These new antidepressants are useful for major depressive disorders and for depressive patients resistant to classical treatment

## References

[1] "Derivatives of 14,15-dihydro-20,21-dinoreburnamenin-14-ol, and applications thereof" P. Ciapetti, L.Deyon-Jung, C.G. Wermuth, J.F Pujol and D. Weissmann. US20070022046
[2] "Long term effect of RU24722 on tyrosine hydroxylase in the rat locus coeruleus: differential effects of two enantiomeric forms"
O. Bourde, P. Schmitt, F. Robert, C. Thal and J.F. Pujol. Neurochem. Int., 1993; 23: 567-74
[3] "Blood oxygenating and cerebral vasoregulating 20,21-dinoreburnamenines" F. Clemence , I. Medici, R. Fournex US4501740
[4] « Dérivés vincaminiques déséthylés, leur synthèse et leur application en thérapeutique » J. Lefevre, G. Rossey. FR2475549