New derivatives of 14,15-dihydro-20,21-dinorebearnamin-14-ol as potent antidepressants

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Derivatives of 20,21-dinoreburnamine including 14,15-dihydro-20,21-dinorebearnamin-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. Only few C-14 analogues of Vindeburnol have been already described in the literature. To enhance pharmacokinetics properties of Vindeburnol, C-14 modified derivatives have been synthesized. For this purpose, substituents 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 dehydrated
- 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

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