Synthesis of chiral 4-pyrazolyl dihydropyridines and their enantiomeric separation

Rakesh Kumar,[a] Neha Yadav,[a] Jyoti Arora,[a] Ashok K Prasad[b]

[a] *Department of Chemistry, Bio-organic Laboratory, Kirori Mal College, University of Delhi, Delhi-110007, India*

[b] *Department of Chemistry, Bio-organic Laboratory, University of Delhi, Delhi-110 007, India*

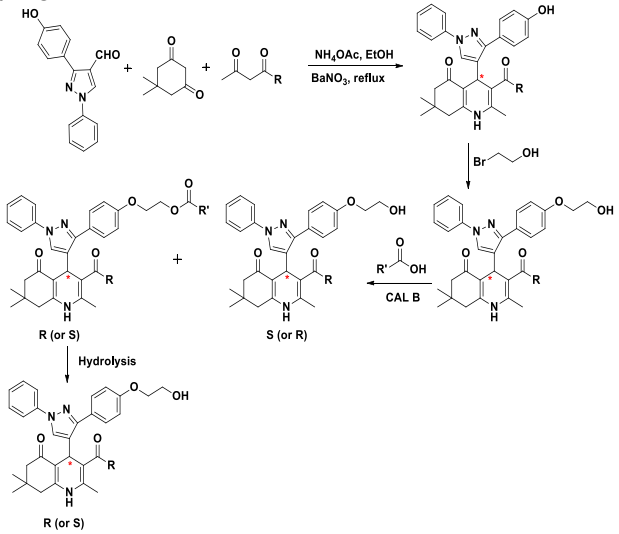
**e-mail* - rakeshkp@email.com

Keywords: Pyrazole, chiral dihydropyridine, enantiomer separation

INTRODUCTION

The 1,4-dihydropyridines are the most effective of the calcium antagonists or calcium channel blockers.[1] This class also includes compounds that have exactly the opposite action profile and are known as calcium agonists. There are even instances in which this reversal of activity is found between enantiomers.[2]

We herein report the efficient chiral synthesis of DHP derivatives. In contrast to the techniques used previously[3] in our enantioselective Hantzsch variant the chirality information is introduced using two different β-keto esters. The separation of respective enantiomers of 1a is achieved using enzymatic method and calcium channel antagonist activity of the synthesised pure enantiomers is under progress.

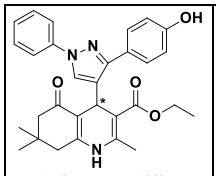
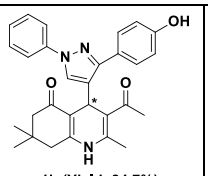
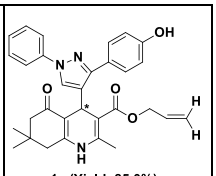
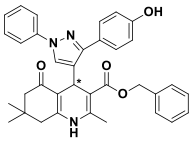
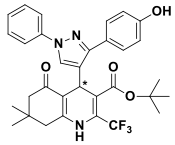
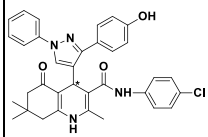
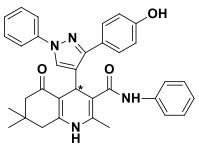
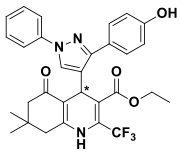
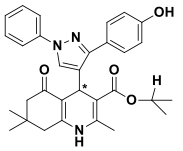


Scheme 1. Synthesis & enantiomeric separation of 4-pyrazolyl dihydropyridines

RESULTS AND DISCUSSION

- Various chiral 4-pyrazolyl dihydropyridines were synthesized (**Table 1**).
- We hybridized pyrazole with 1,4-dihydropyridine to enhance the biological activity of new scaffolds.
- The enantiomeric resolution of these chiral dihydropyridines involves lipase-catalysed esterification.
- The enantiomeric excess of 1a as calculated was 85% and for other derivatives, it is under progress.

Table 1. 4-Pyrazolyl dihydropyridines

 1a (Yield= 92.2%)	 1b (Yield=84.7%)	 1c (Yield=85.0%)
 1d (Yield=88.9%)	 1e (Yield=92.7%)	 1f (Yield=90.7%)
 1g (Yield=86.0%)	 1h (Yield=96.4%)	 1i (Yield=74.8%)

CONCLUSION

The chiral 4-pyrazolyl dihydropyridines were synthesized using mild reaction conditions, very simple and accessible starting materials, solvent as well as an inexpensive and non-toxic catalyst. The separation of enantiomers is also based on enzymatic method.

ACKNOWLEDGEMENTS

The authors would like to thank Defence Research and Development Organisation for their financial support.

REFERENCES

[1] Hadjebia, M.; Hashtroudib, M.; Bijanzadeh, H.R.; Balalaie, S. *Helvetica Chimica Acta* **2011**, *94*, 382-388.

[2] Rudong, S.; Velazquez, C.; Knaus, E.E. *J. Med. Chem.* **2004,** *47,* 254-261.

[3] Enders, D.; Miller, S.; Demir, A. S. *Tetrahedron Letters* **1988**, *29*, 6437-6440.