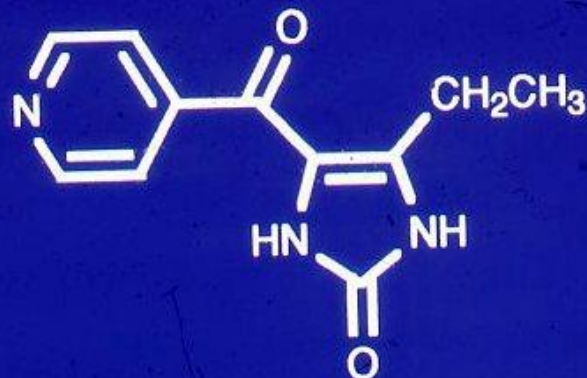


Pyridazin-3(2H)-ones via δ^2 isoxazoline intermediates: synthetic studies

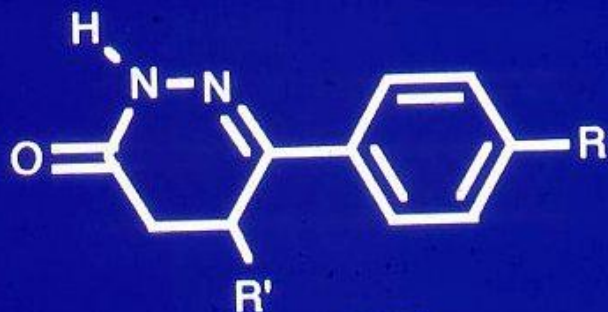
IV International Symposium on the
Chemistry and Pharmacology of Pyridazines
Bled, Slovenia, 28-30 Settembre 1994



Amrinone $R=H$, $R'=NH_2$
 Milrinone $R=CH_3$, $R'=CN$

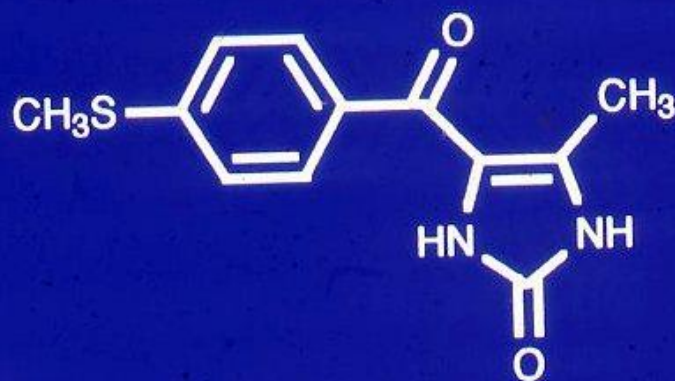


Piroximone

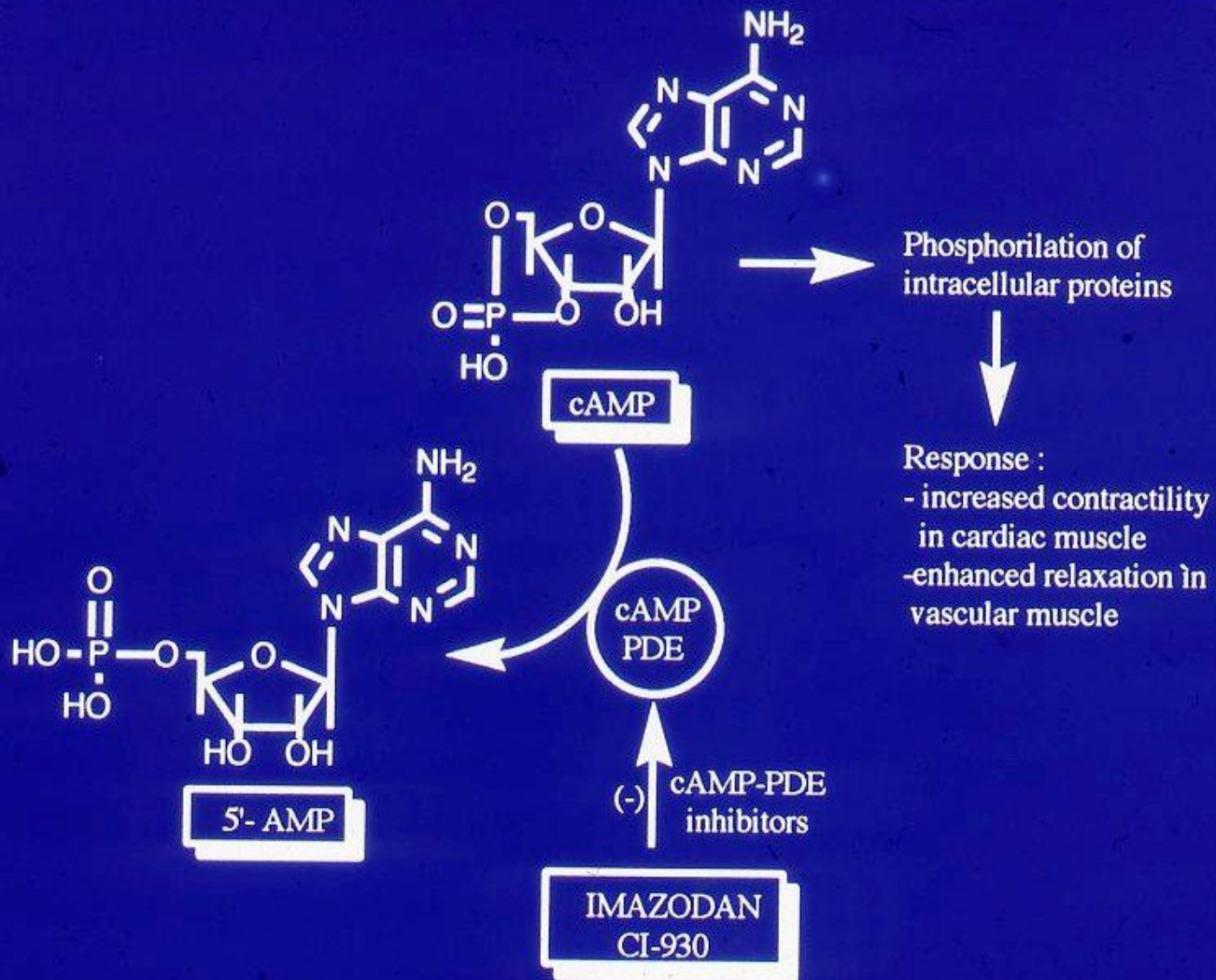


Imazodan $R=$ , $R'=H$

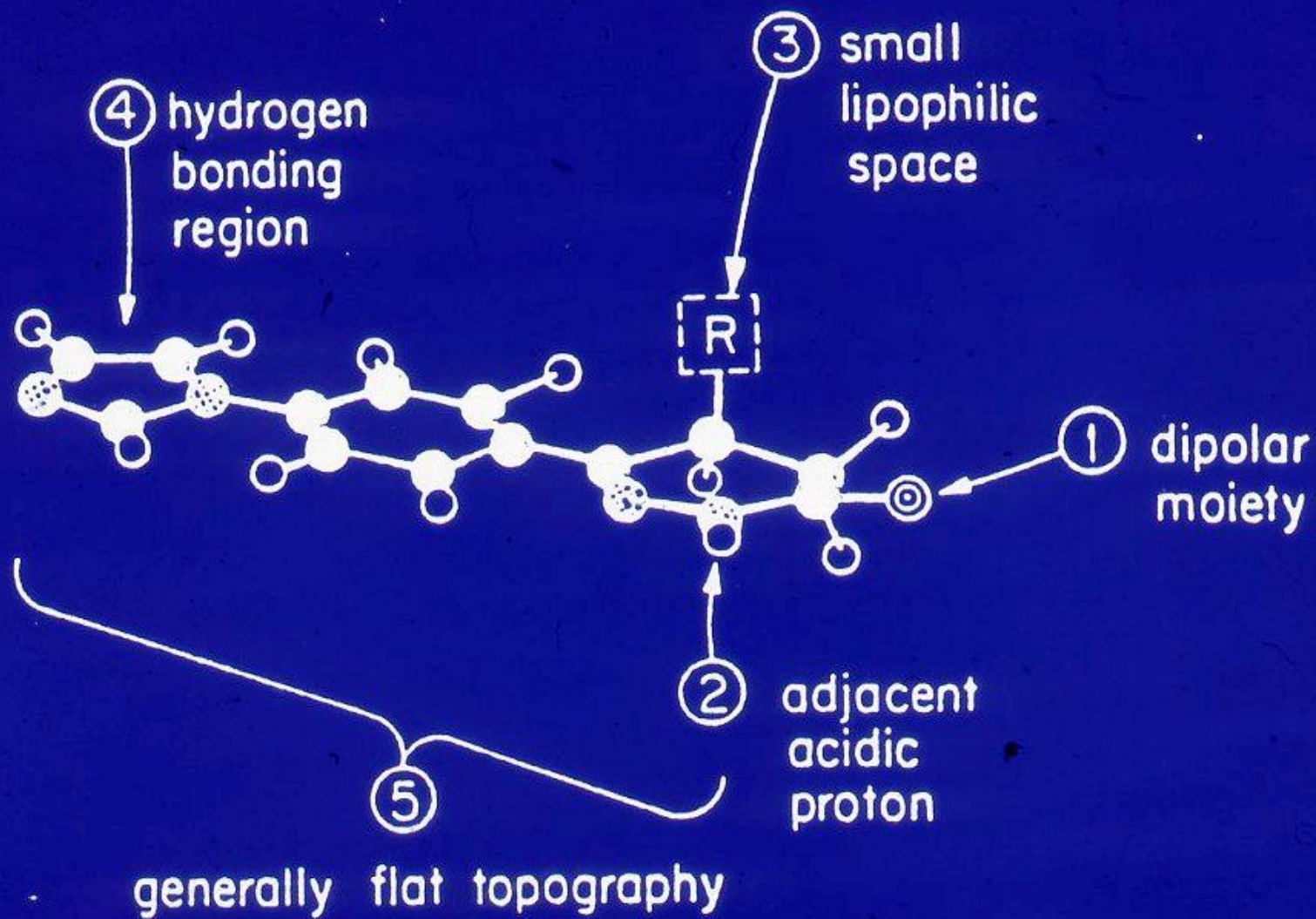
CI-930 $R=$ , $R'=CH_3$

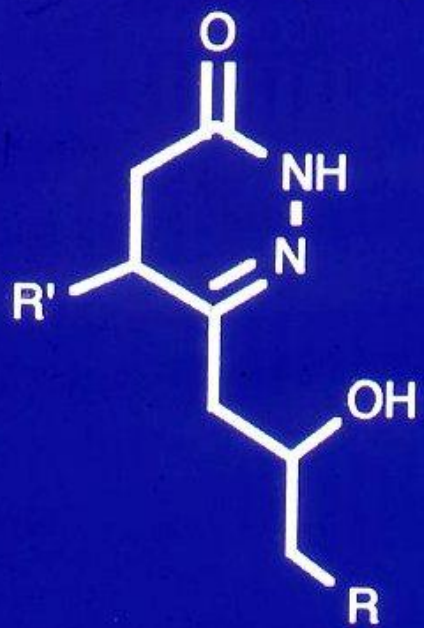


Enoximone

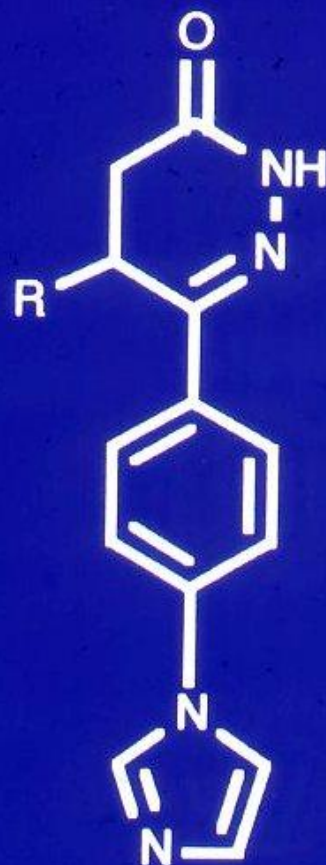


Hydrolysis of cAMP to 5'-AMP, catalyzed by PDE





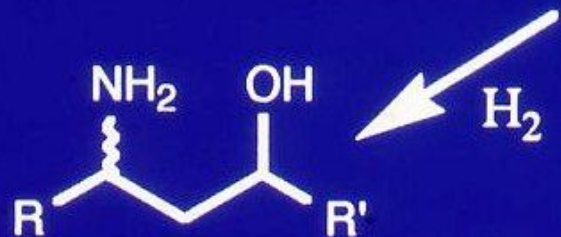
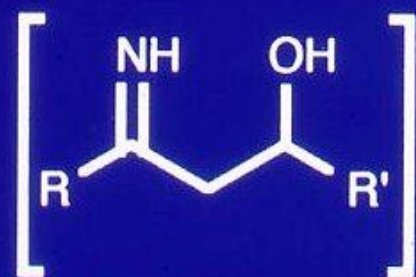
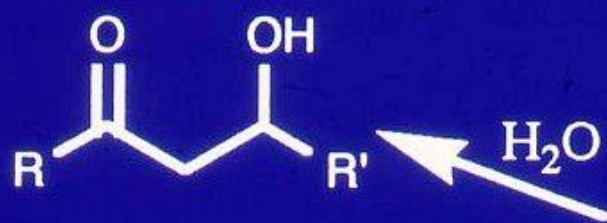
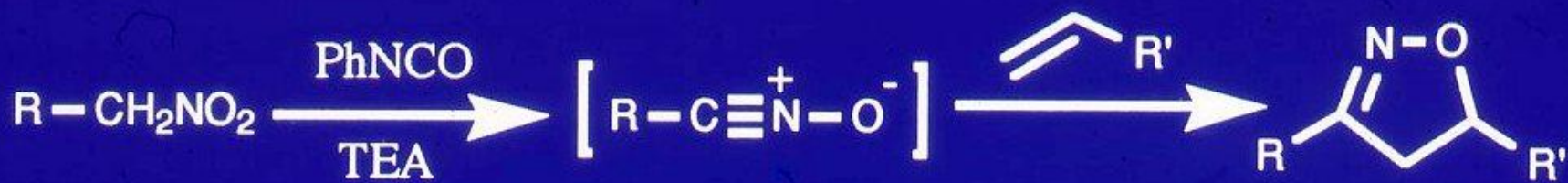
R' = H, Me
R = Aryl, Alkyl



R = H, Imazodan-91
R = CH₃, CI-930

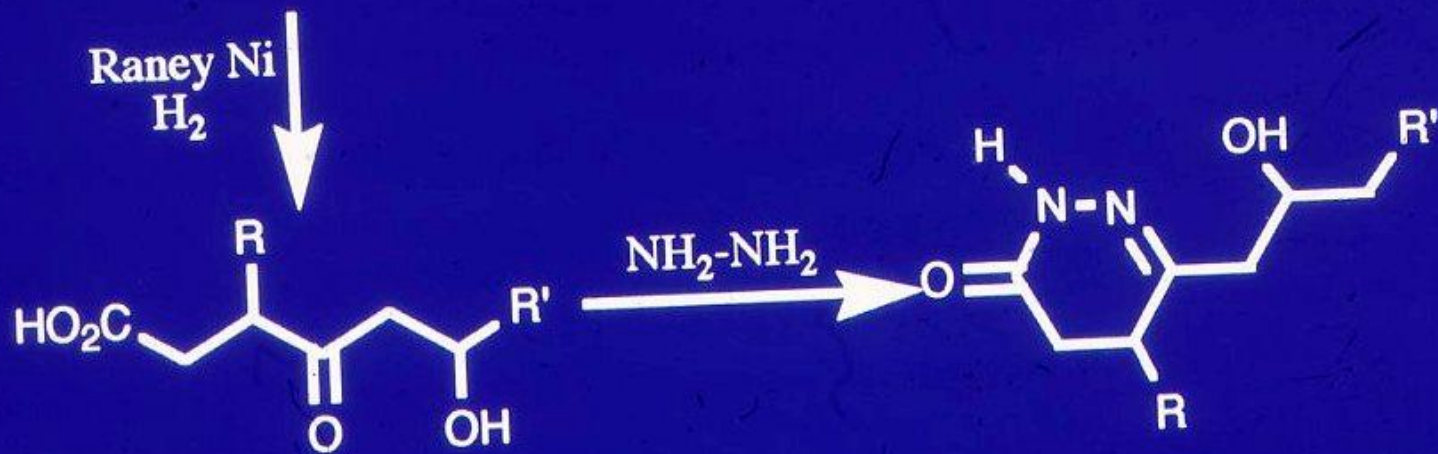
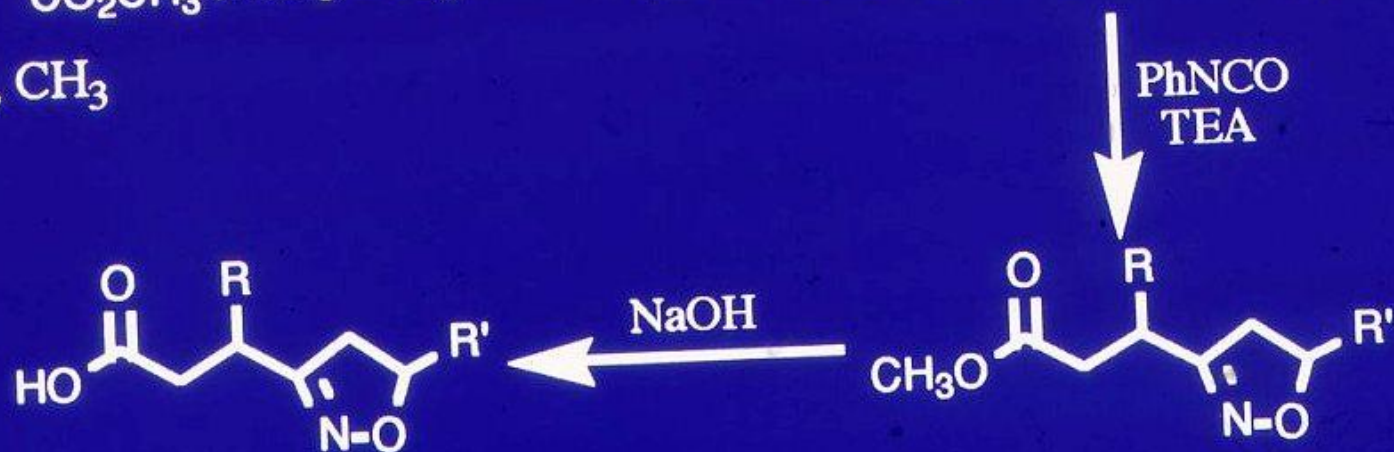


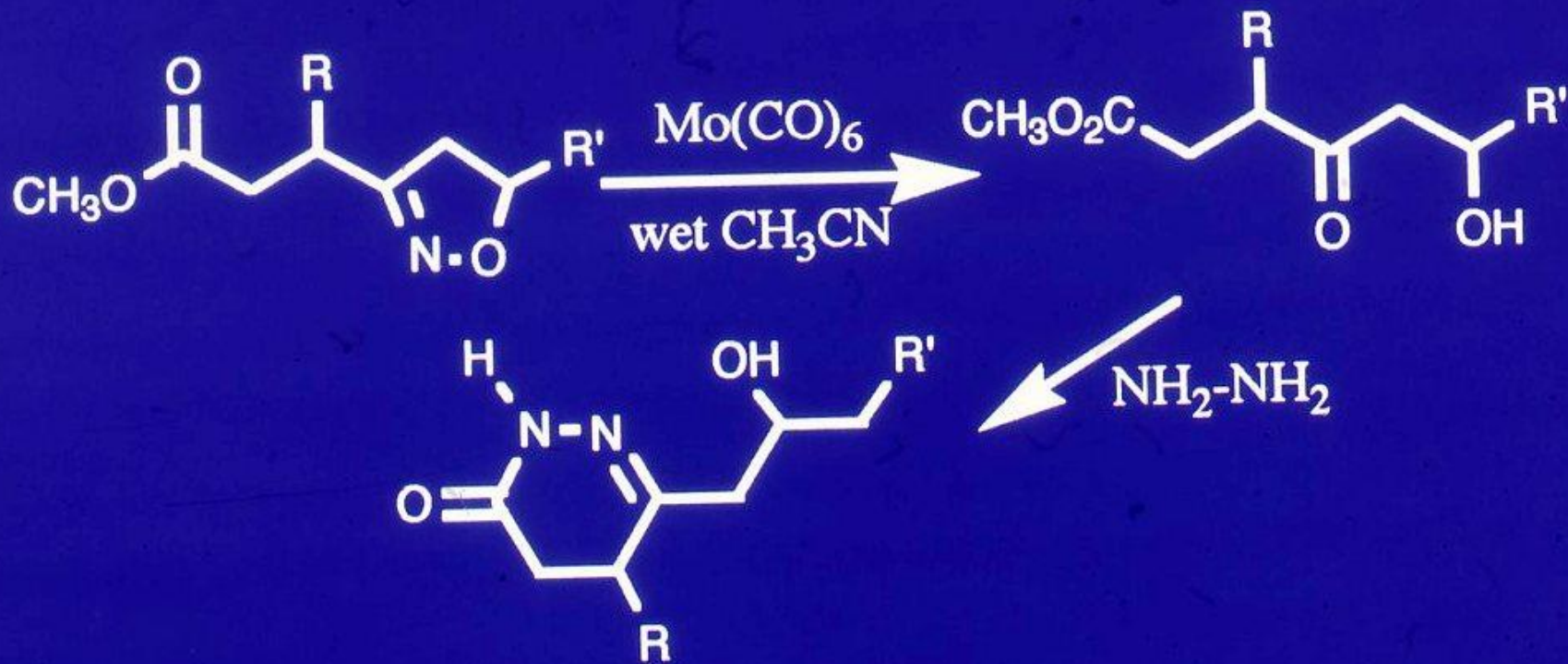
i : $\text{NH}_2\text{-NH}_2 \cdot \text{H}_2\text{O}, \Delta, \text{EtOH}$



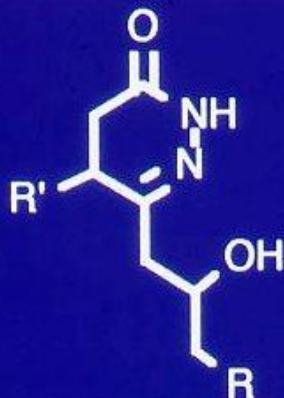


R = H, CH₃

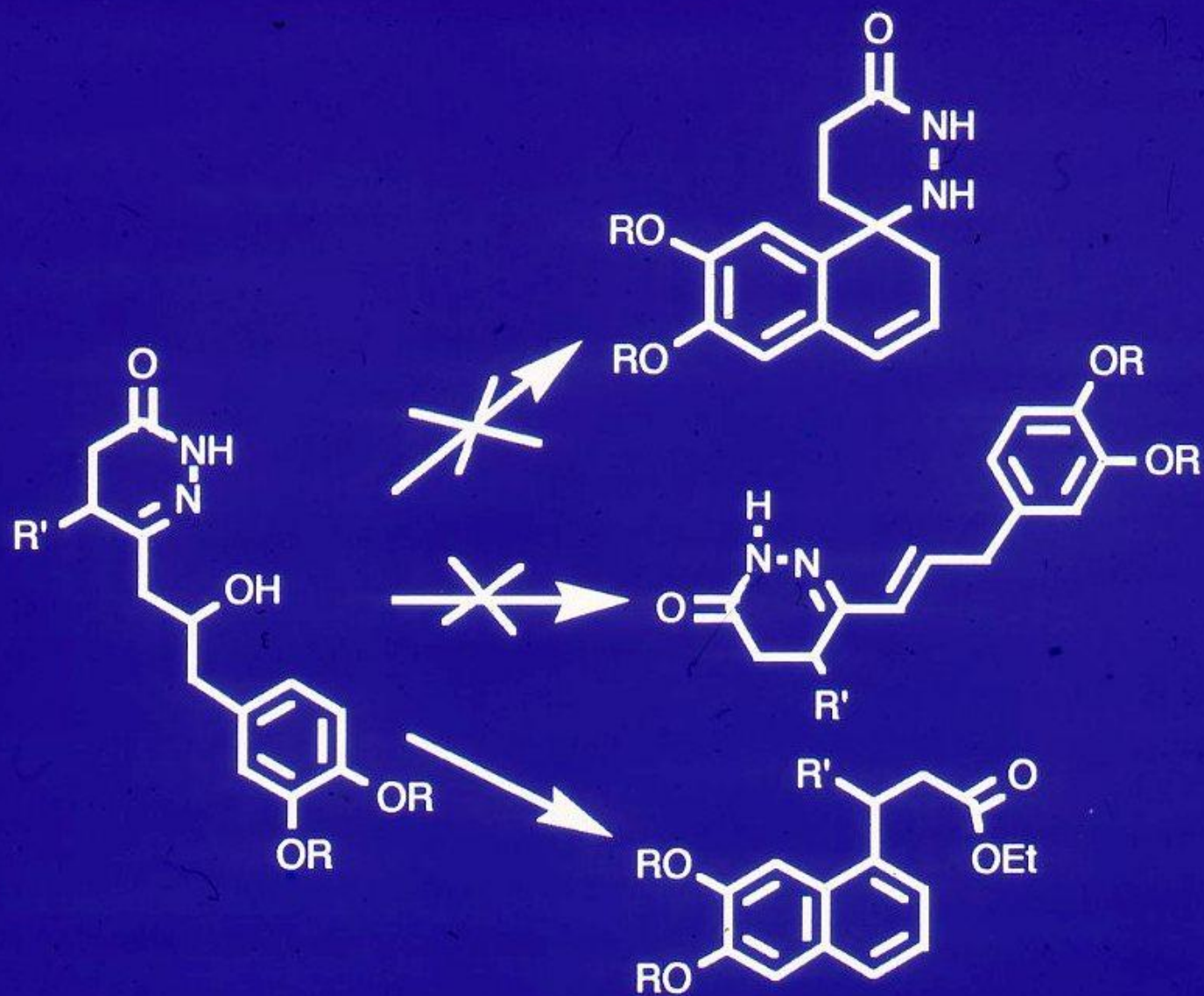


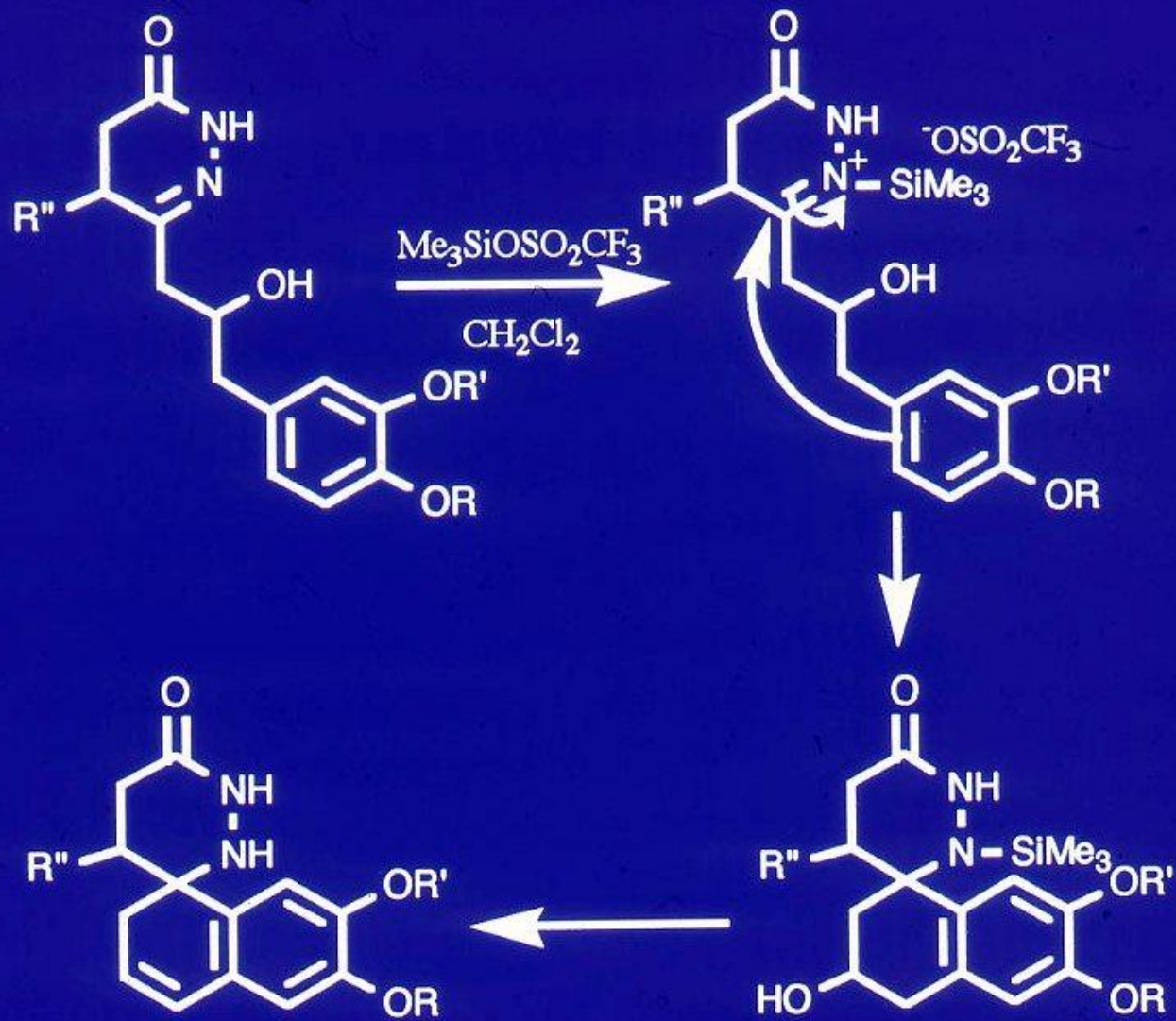


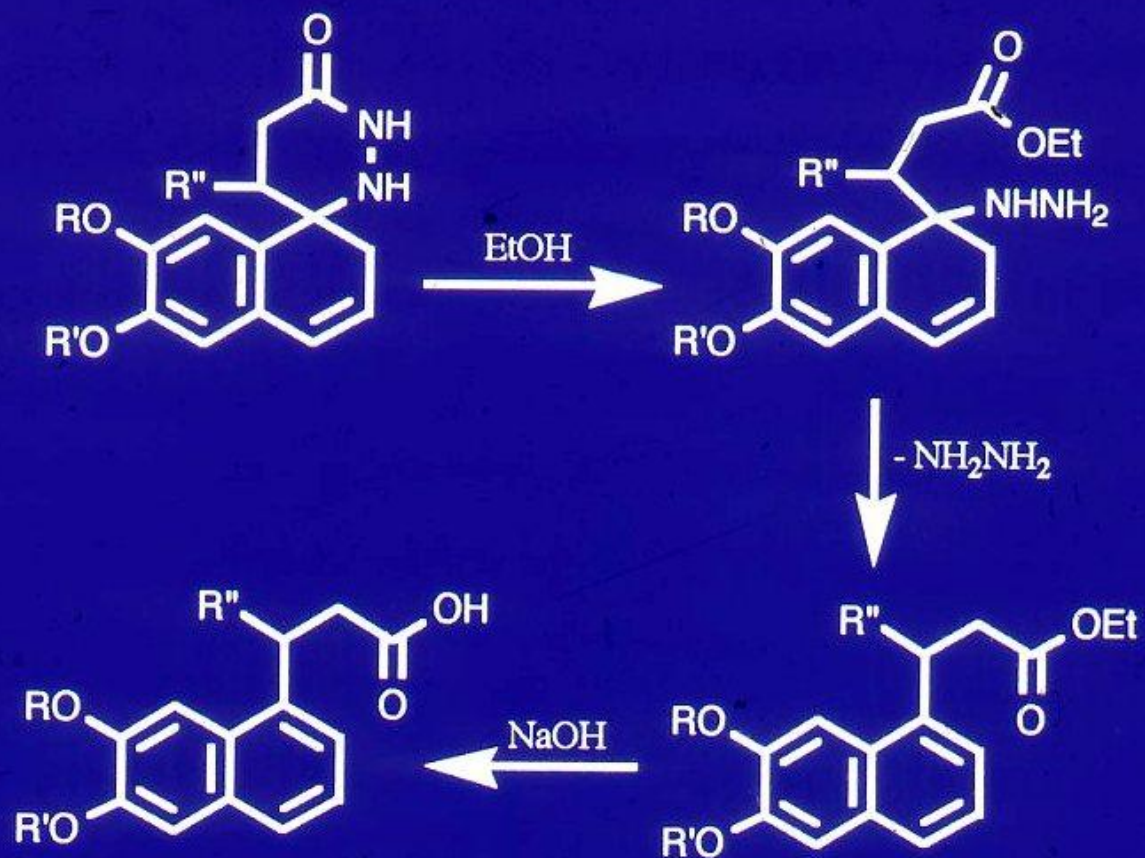
BIOLOGICAL EVALUATION



- 1) Preliminary studies designed to examine the inotropic and chronotropic effects of these compounds : $R = nC_4H_9$; $nC_{11}H_{23}$; CH_2Ph , $R'=H$, on isolated cardiac preparations from guinea pig hearts, showed no significant activity respect to the reference compounds.
- 2) Compounds $R = nC_{11}H_{23}$; $nC_{13}H_{27}$, $R'=H$ showed antithrombotic effect in mice treated with collagen and adrenalin (50% maxim protection).
- 3) The same compounds described in the entry 2) showed a decrease of blood pressure of about 20 mmHg for six hours at the dose of 6.25 mg/Kg. A lower degree of hypotensive effect was also presented by the compounds containing a benzyl or substituted benzyl chain.

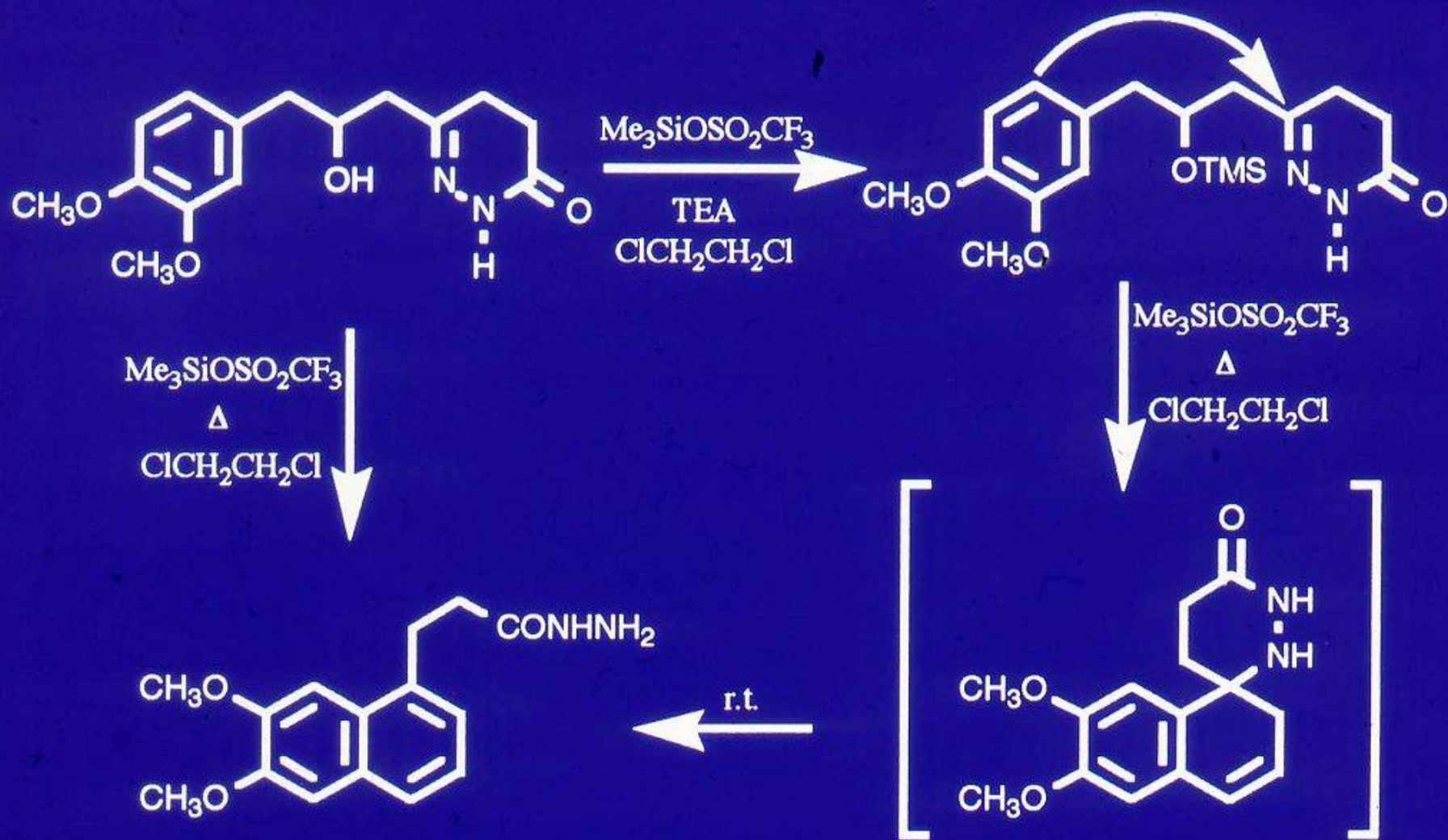






$R'' = \text{H}, \text{CH}_3$

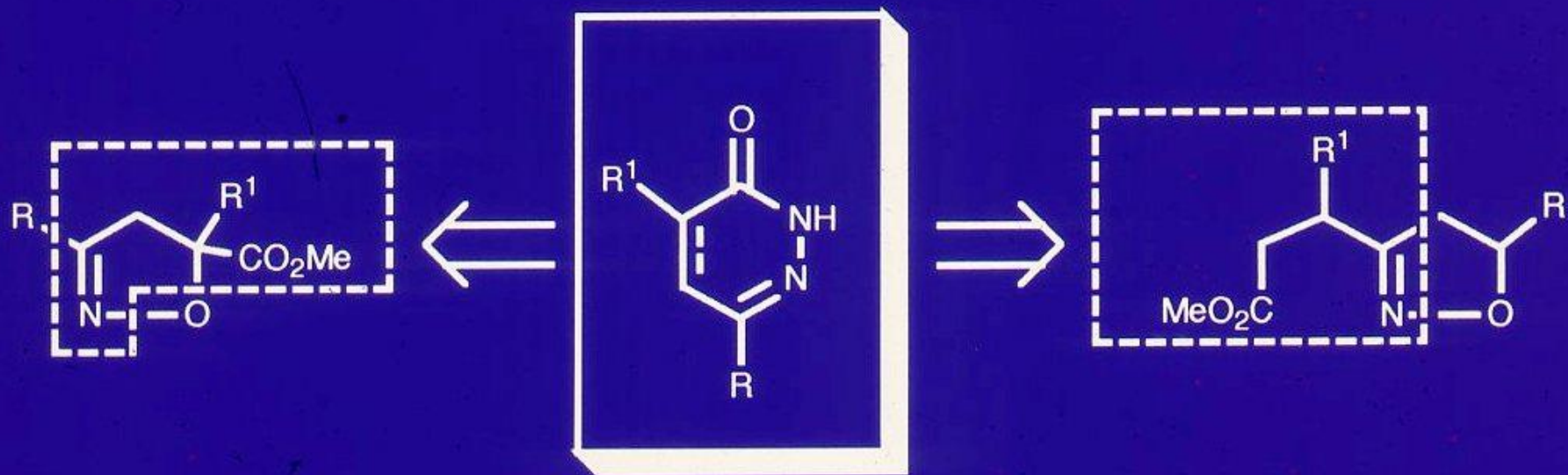
$R' = R = \text{CH}_3$; $R = R' = -\text{CH}_2-$; $R' = \text{CH}_3, R = \text{H}$

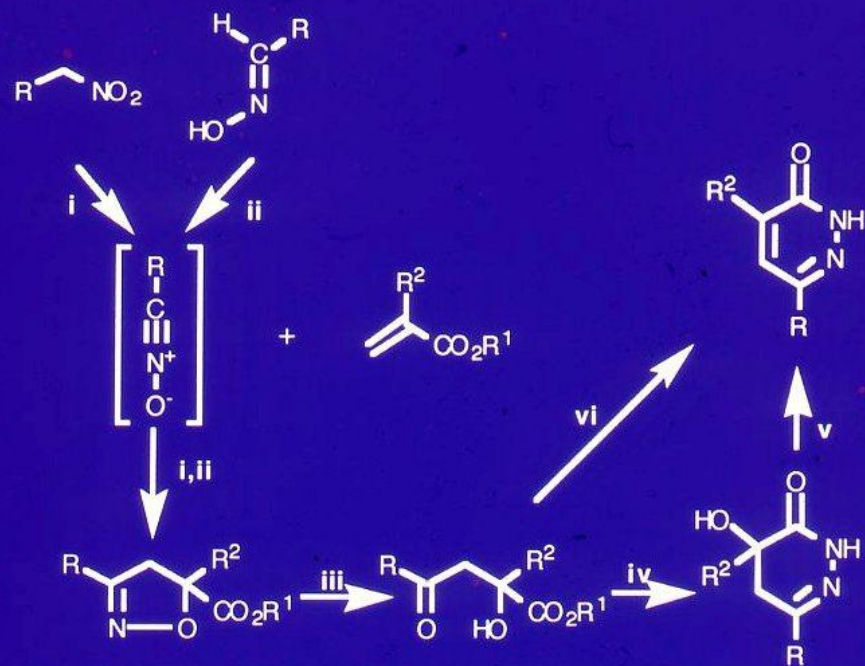


CONCLUSIONS

In conclusion, we have developed a new method to transform a 4,5 dihydro-pyridazin-3(2H)-one nucleus into α naphthalen-propionic acid derivative.

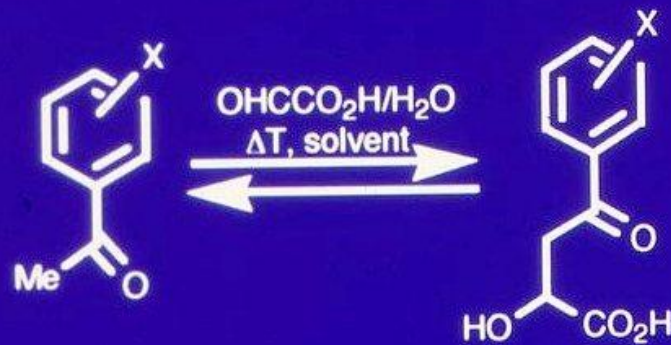
Further studies are in progress to support the proposed reaction mechanism. This methodology can be extended to the synthesis of antiinflammatory agents, like FANS propionic acid derivative.



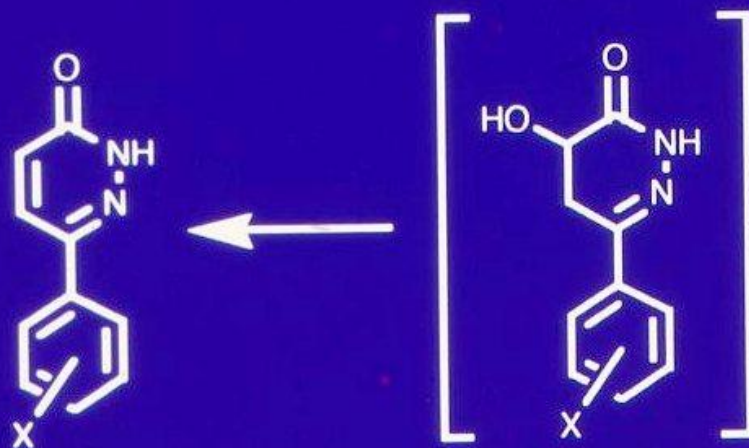


i: Ph-NCO, Ph-H, Et₃N; ii: NCS, Py, Et₃N, 65-80%; iii: Mo(CO)₆, MeCN/H₂C or H₂, Raney Ni, 77-90%; iv: NH₂-NH₂, EtOH, r.t., 77-93%; v: EtOH, HCl 10%, 75-84%; vi: NH₂-NH₂, EtOH, reflux, 95%.

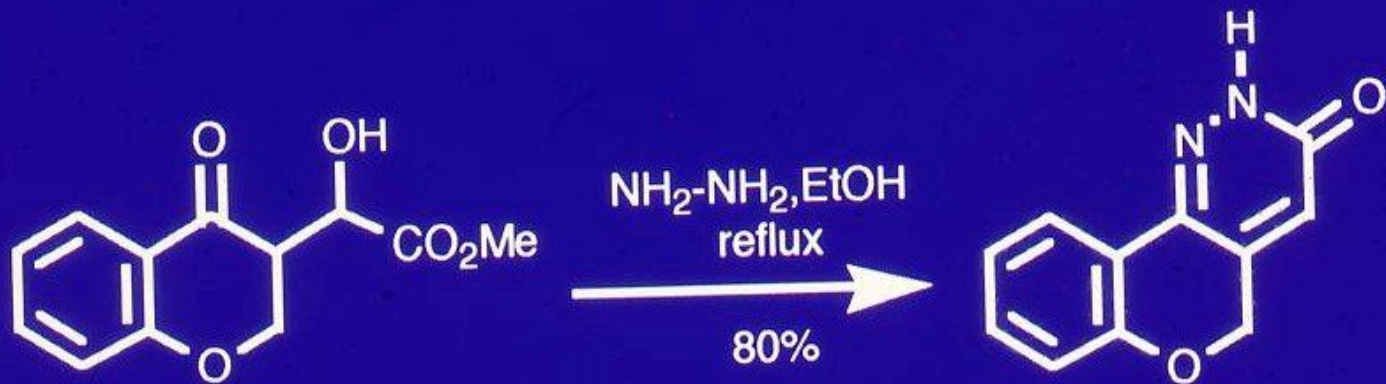
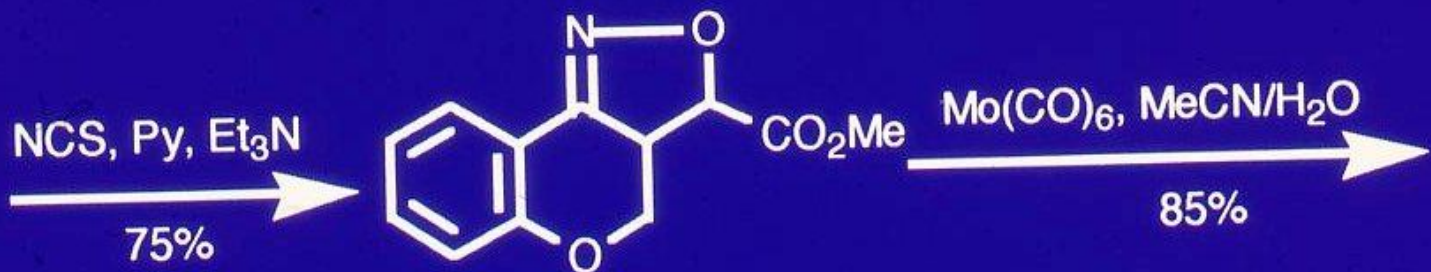
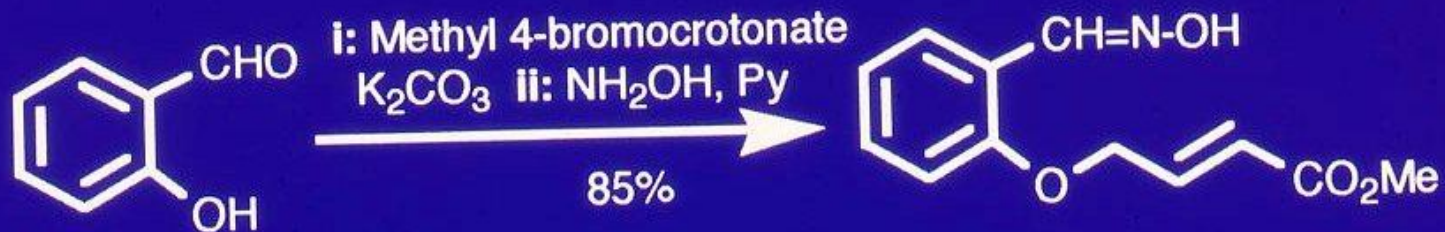
R	R ¹	R ²
Me	Et	H
n-Bu	Et	H
Et	Me	Me
4-pyridyl	Et	H
o-HO-Ph	Et	H
2-pyridyl	Et	H

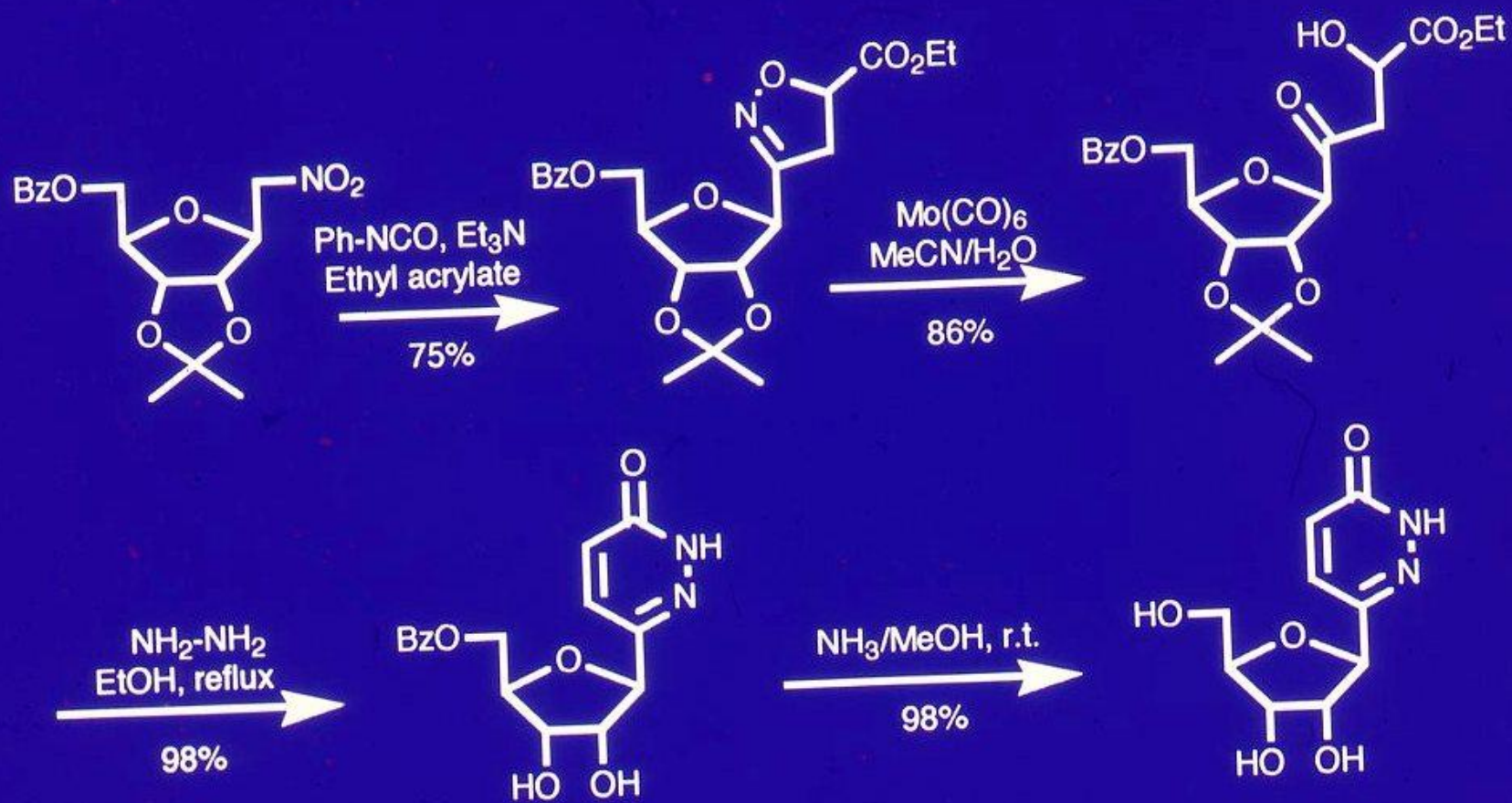


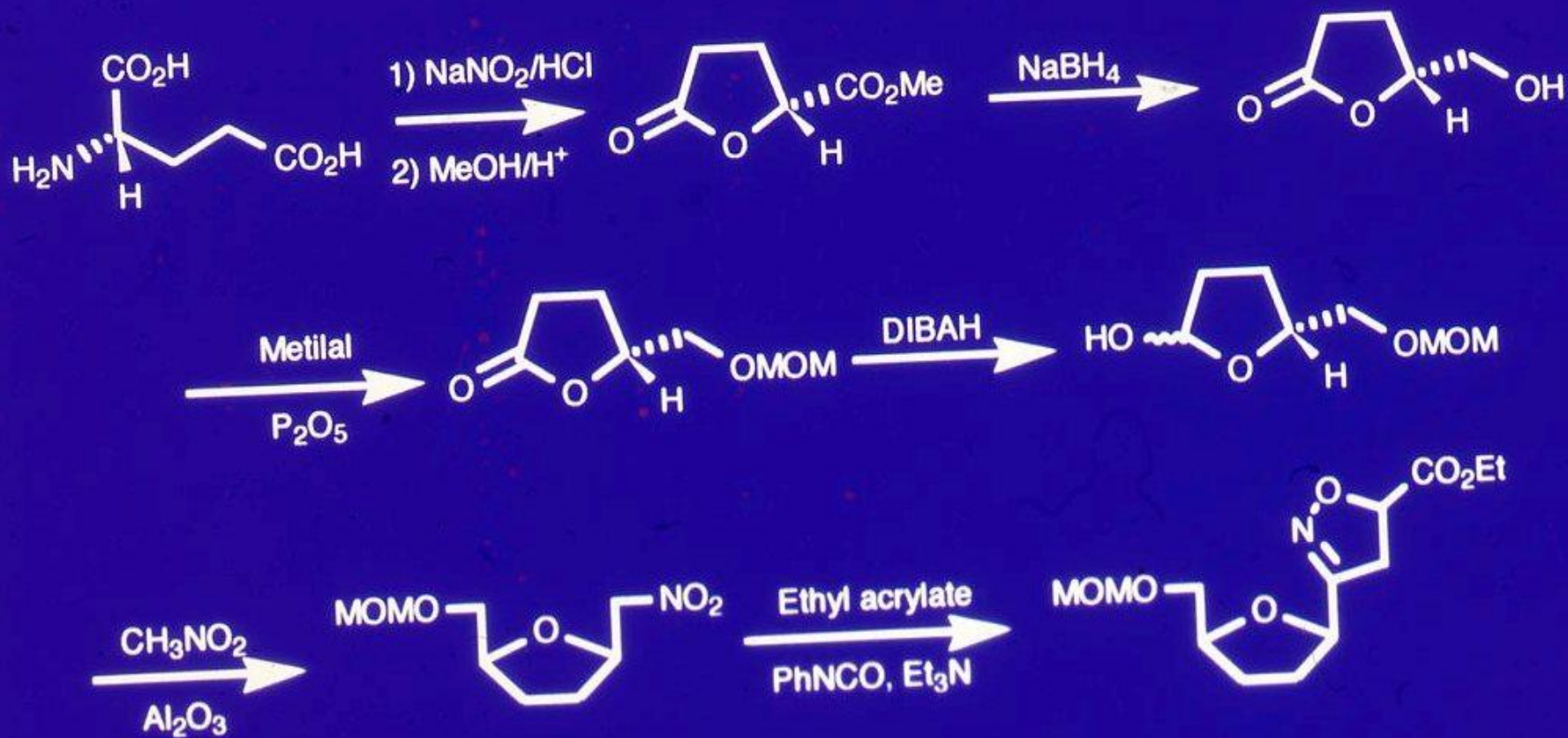
- i: $\text{H}_2\text{O}/\text{NH}_4\text{OH}$ to pH 8
ii: extraction of unreacted starting material
iii: N_2H_4 , ΔT

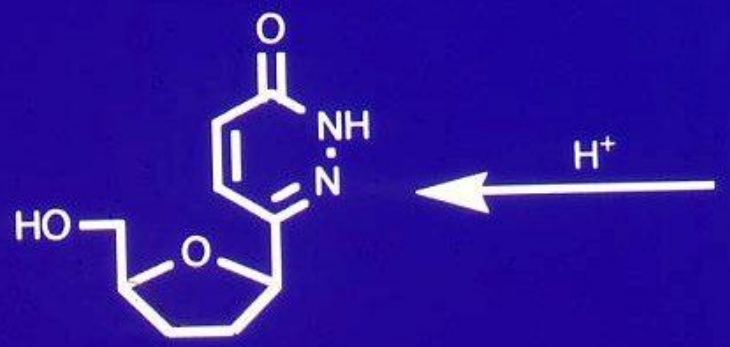
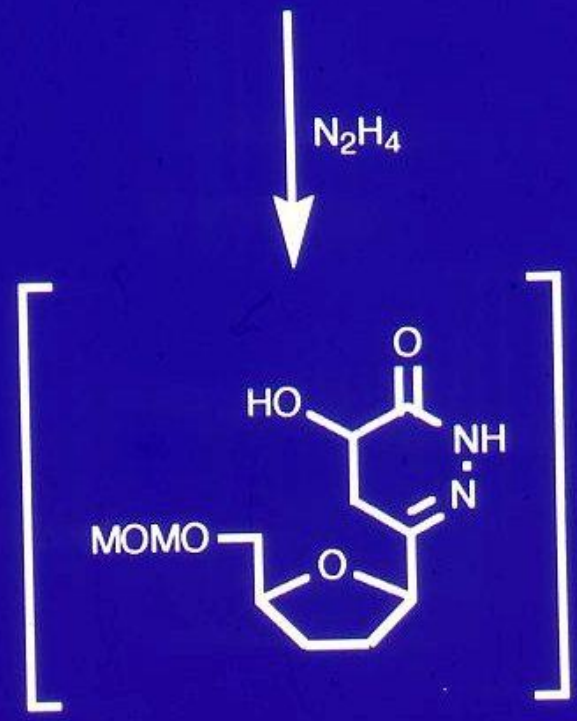
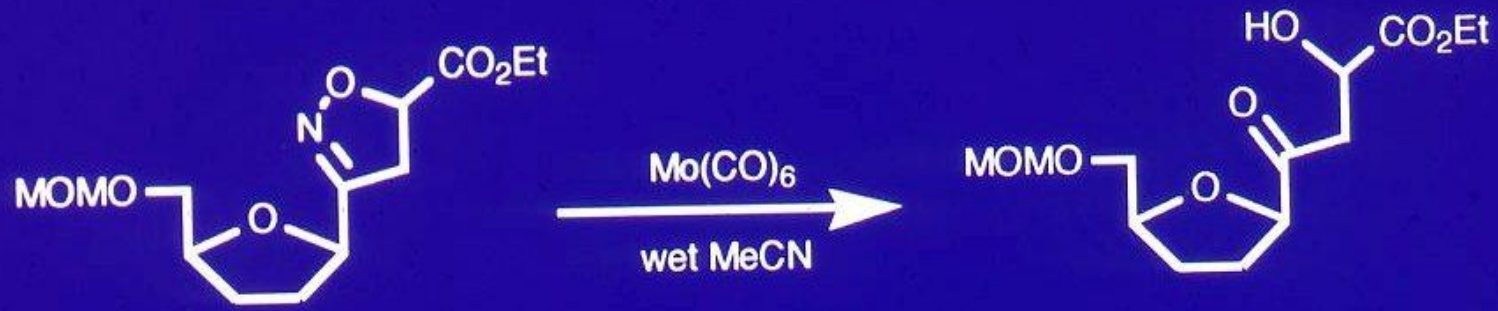


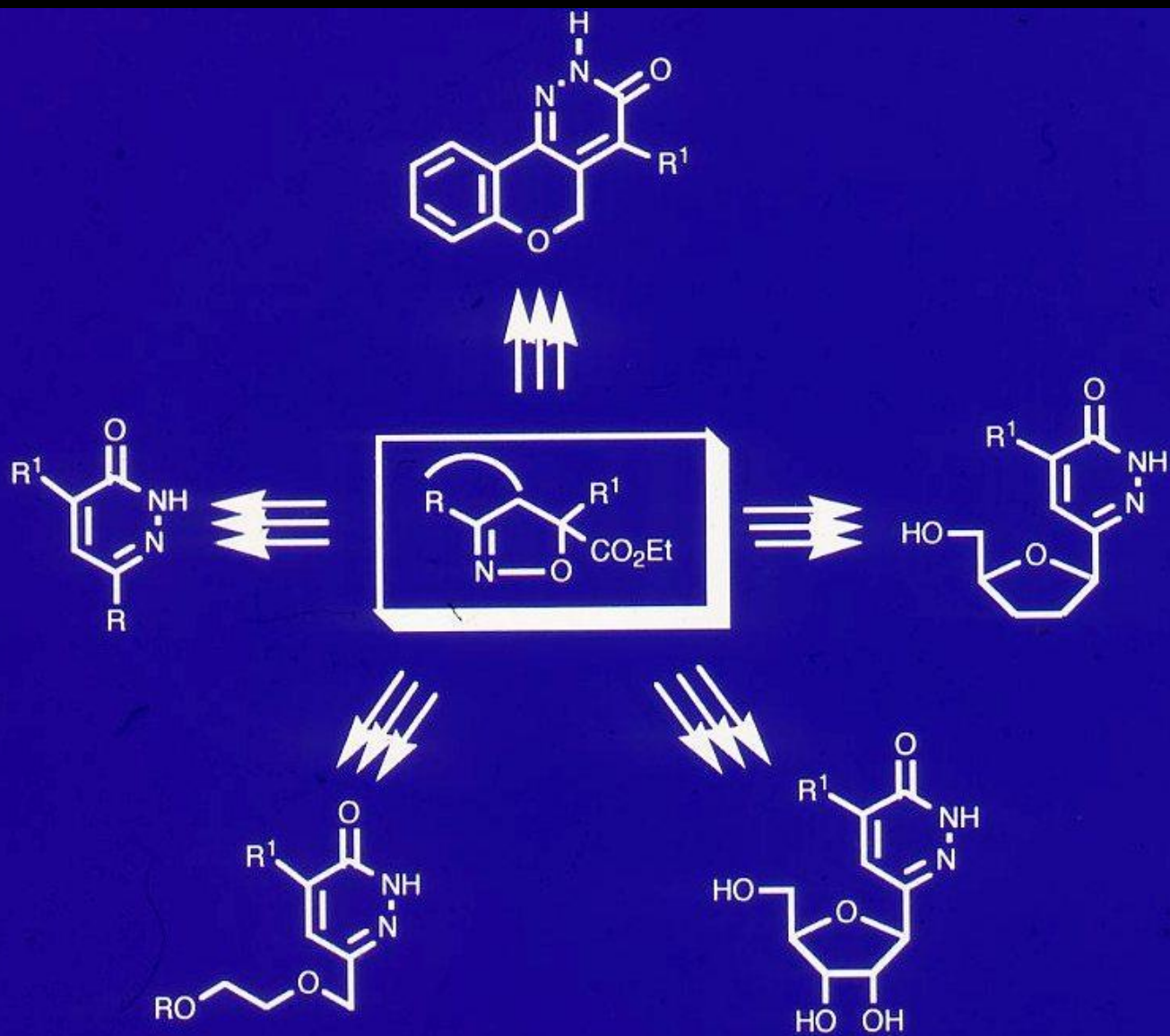
Coates, W.J.; McKillop, A. *Synthesis*, 1993,334

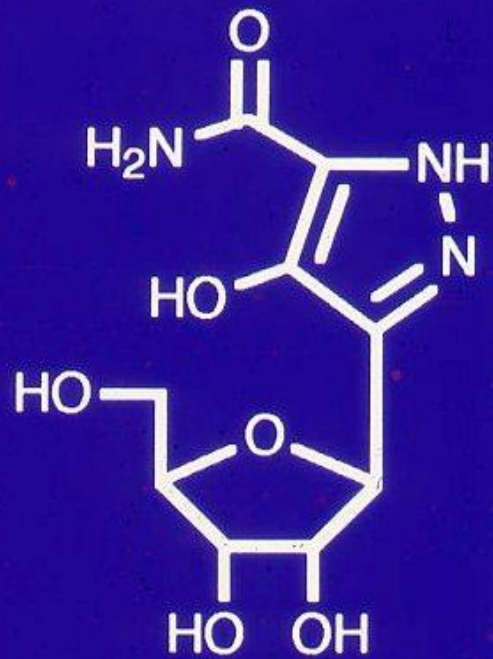




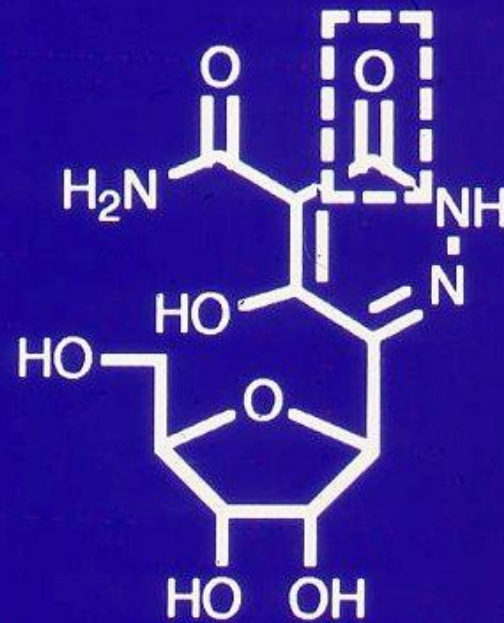






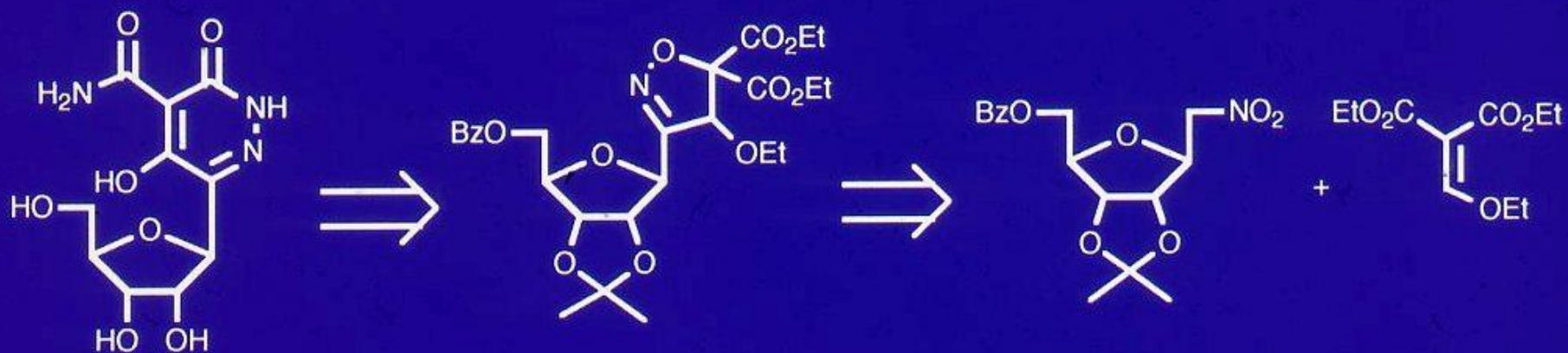


"Pyrazofurin"

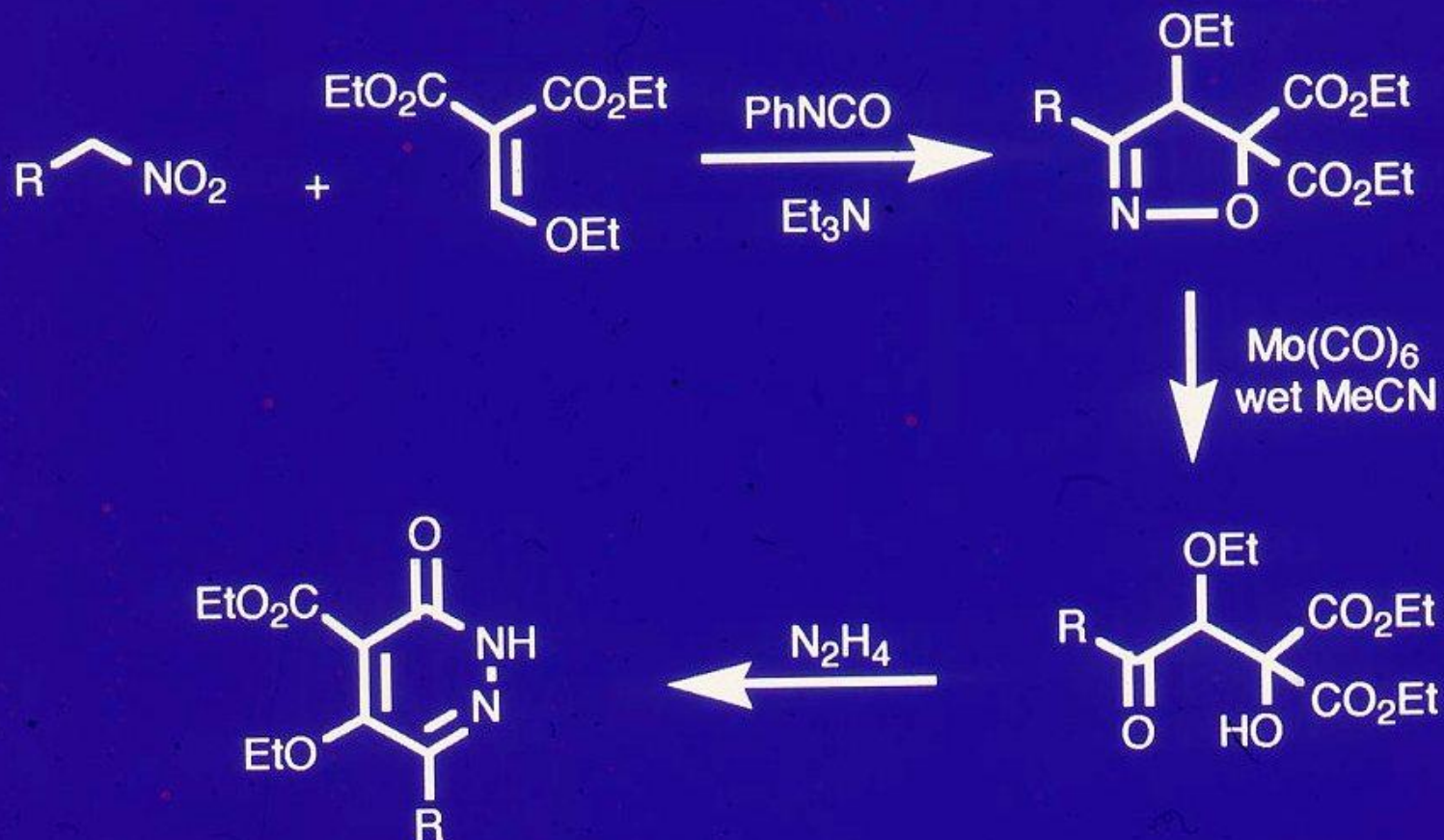


"Pyridazofurin"

RETROSYNTHETIC SCHEME FOR PYRIDAZOFURIN



MODEL STUDIES



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