Cardiotonics

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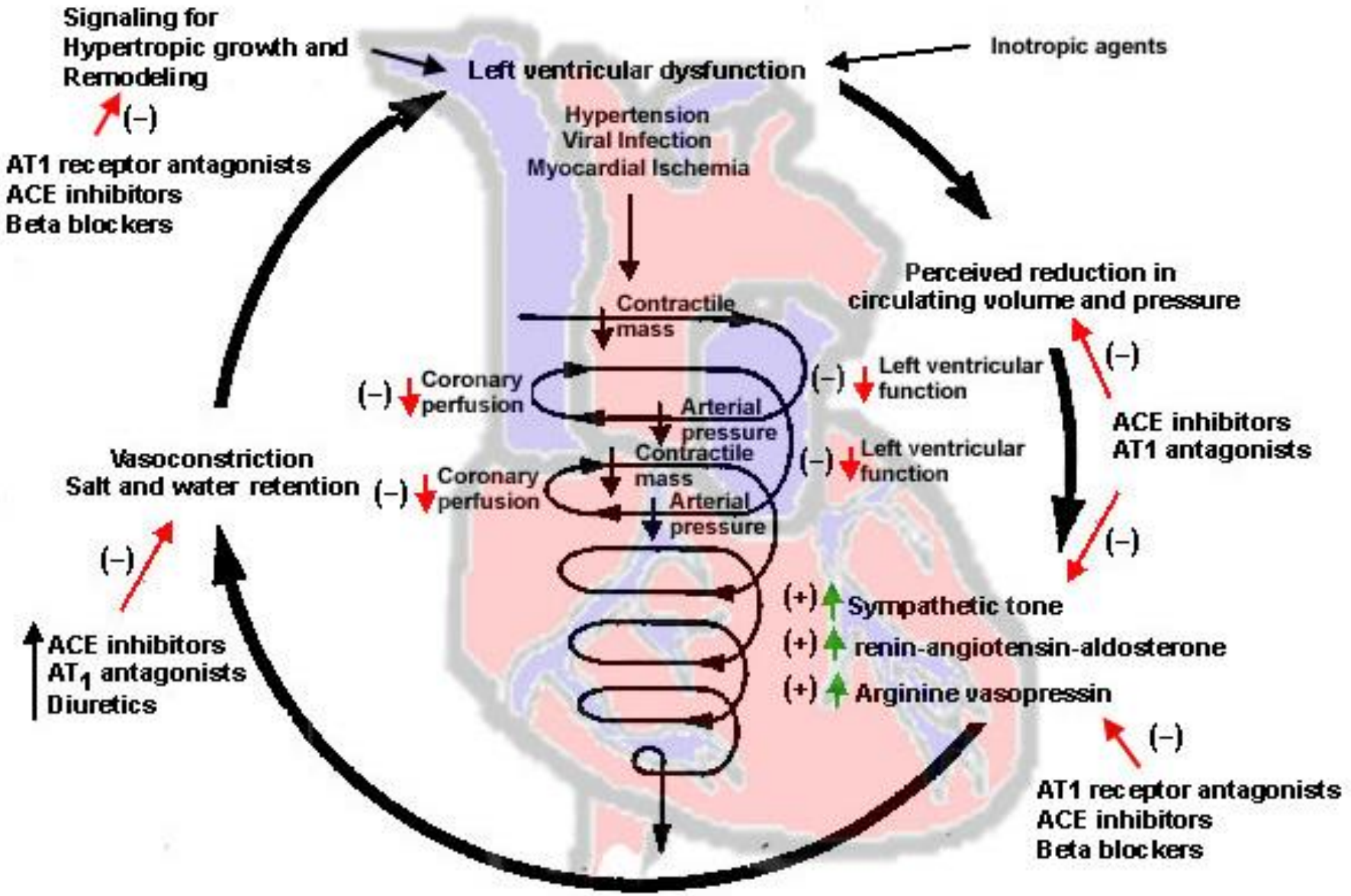
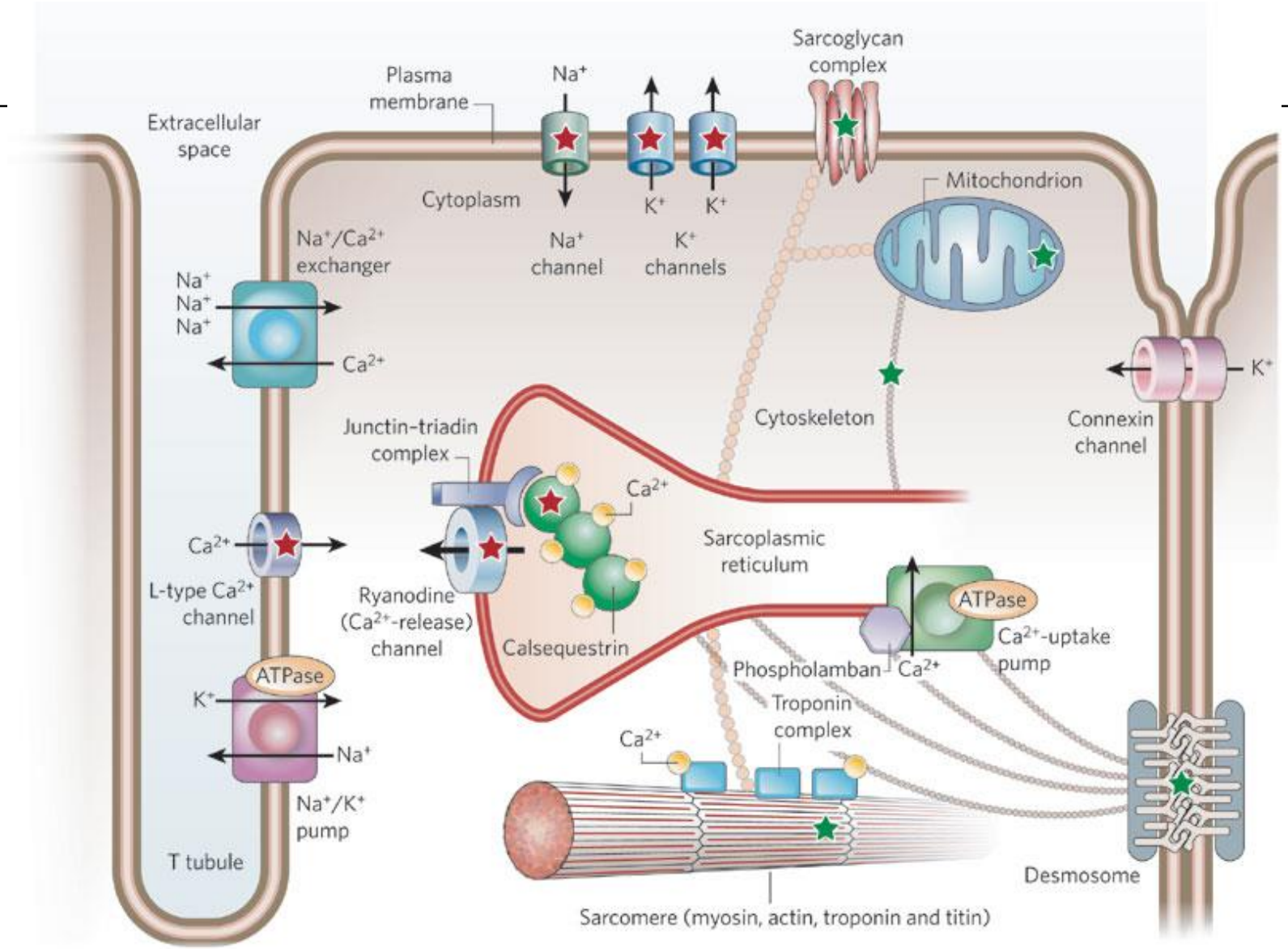
03.11.2014

Heart failure



Cardiomyocyte contraction

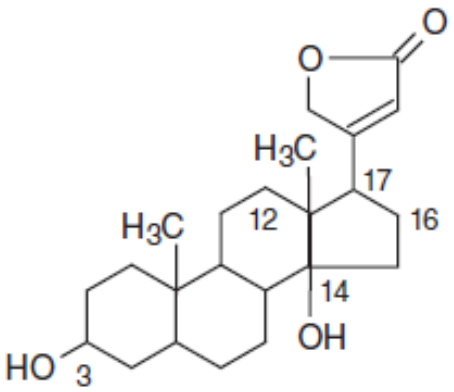


Therapy of heart failure: inotropic agents

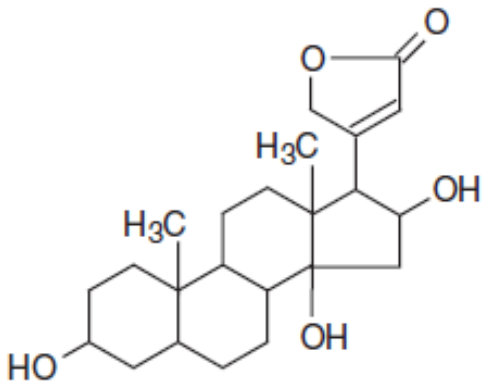
- cardioglycosides
- β-adrenergic agonists
- phosphodiesterase inhibitors
- Ca^{2+} channel senzitizers

Cardiac glycosides

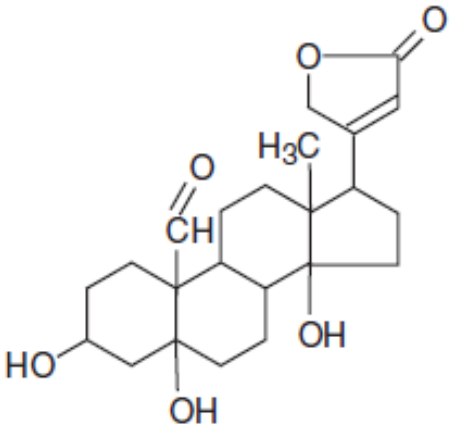
- Aglycons:



digitoxigenin

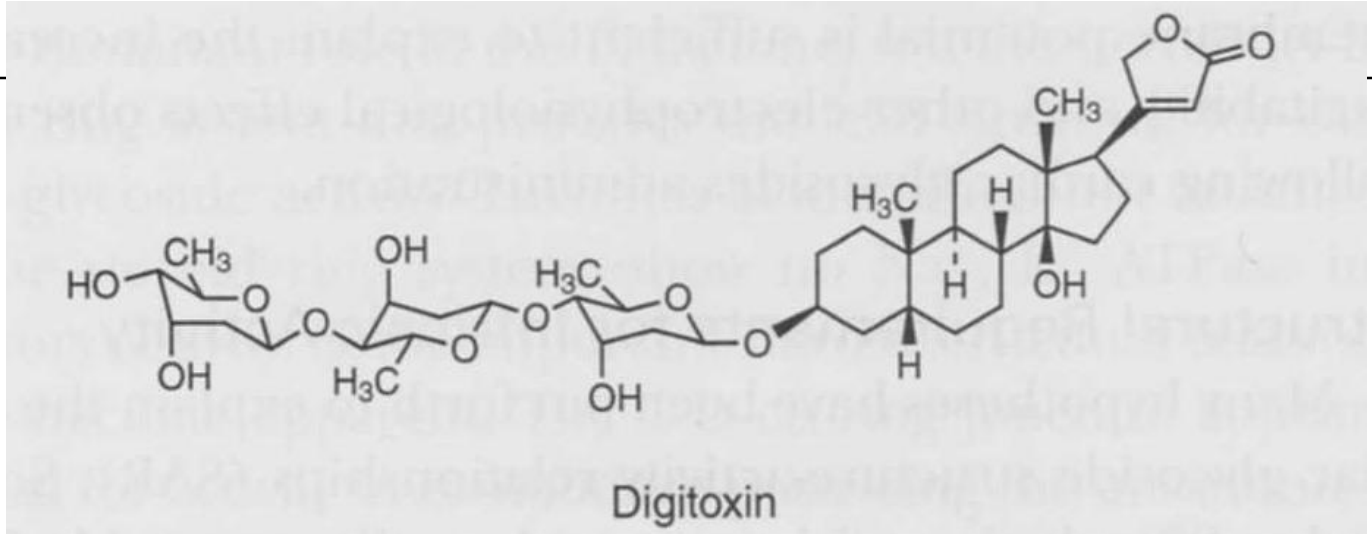


gitoxigenin

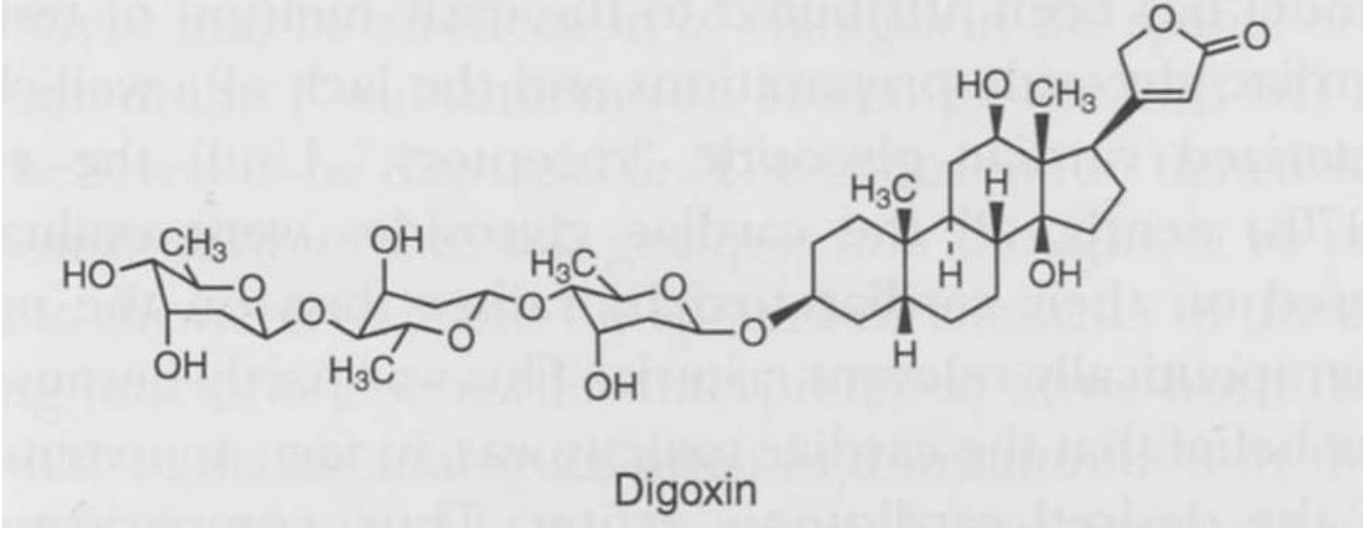


strophanthidin

Cardiac glycosides



Digitoxin



Digoxin

Cardiac glycosides – mechanism of action

- Na^+/K^+-ATPase inhibitors
- Na^+ ions intracelular retention
- due to ion substitution also Ca^{2+}intracelular retention
- positive inotropic effect

Cardiac glycosides used in therapy

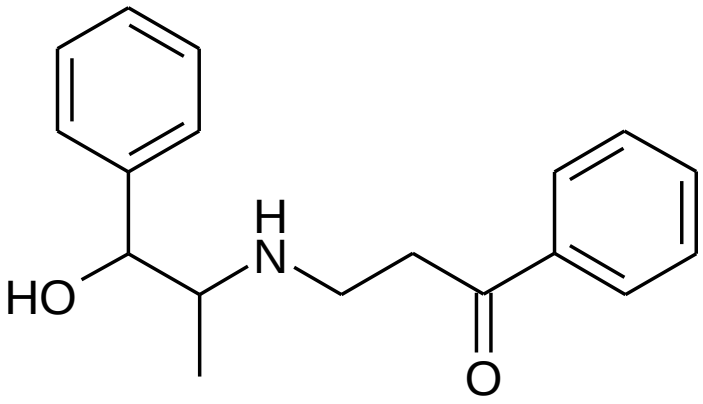
- Lanatosides A, B, C; purpureaglycosides A, B digitoxin, gitoxin, digoxin – secundary glycosides with cleavaged terminal sugar
- Ouabain, k-strophantoside
- Proscillaridine, meproscillarine (buffadienolides)

Cardiac glycosides

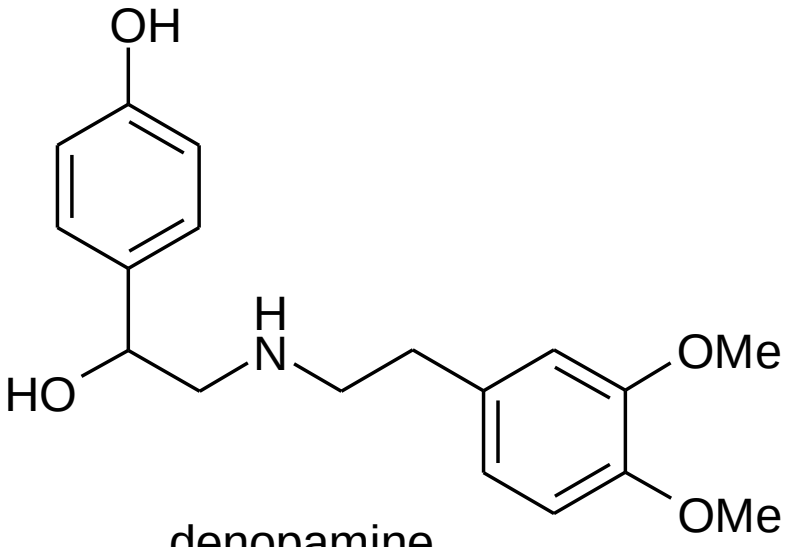
- narrow therapeutic-toxic window
- high plasma proteins binding
- monitoring during therapy necessary
- long-term administration increases mortality – therapeutic use in future questionable

β_1-adrenergic receptor agonists

- stimulation of adenylate-cyclase, increase of intracelular cAMP, positive inotropic effect

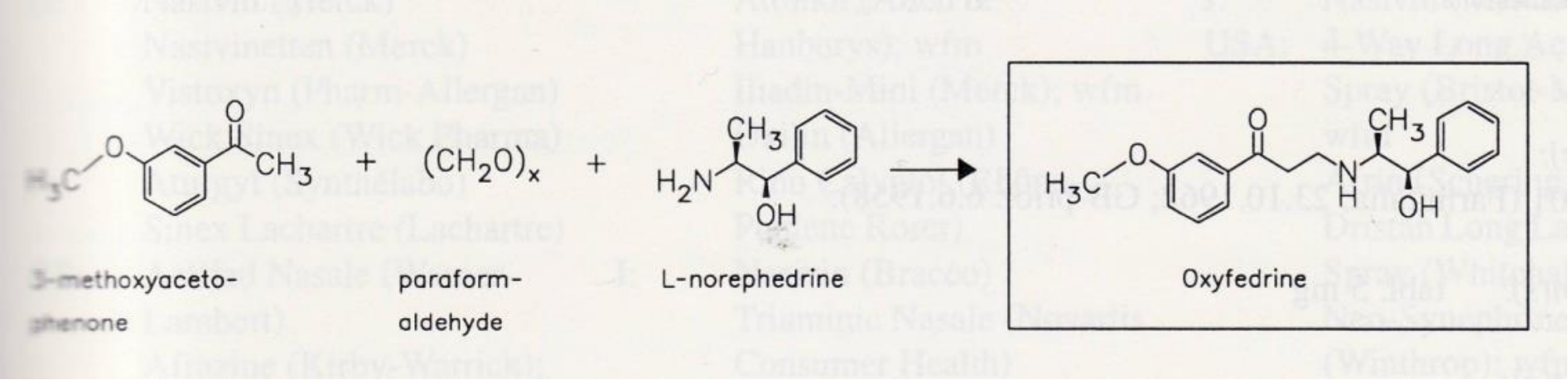


oxyfedrine

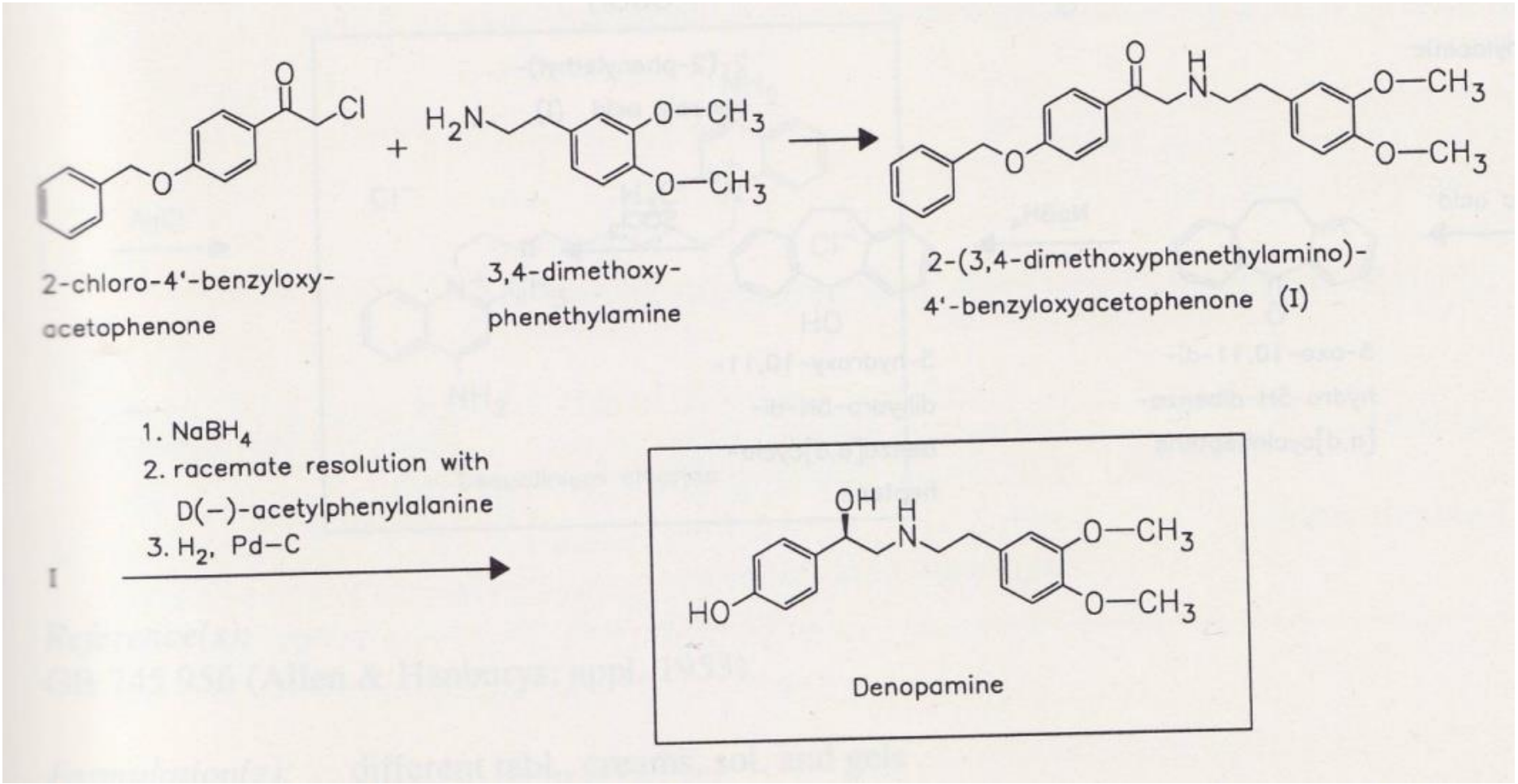


denopamine

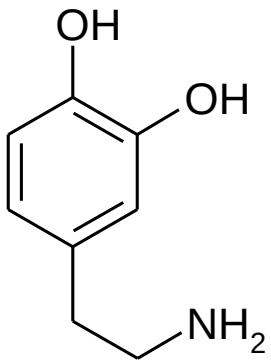
Oxyfedrine synthesis



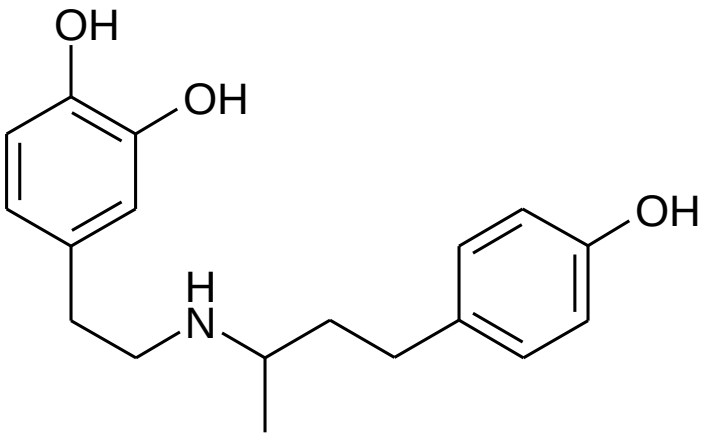
Denopamine synthesis



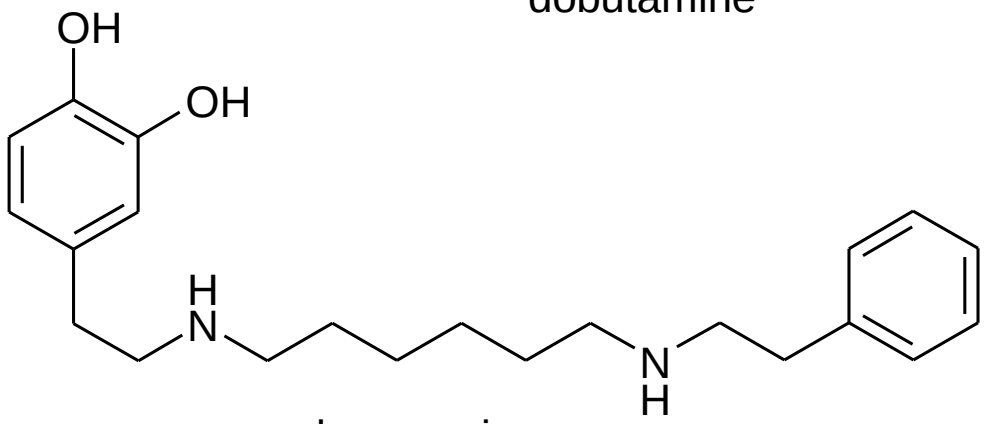
β_1-adrenergic receptor agonists



dopamine

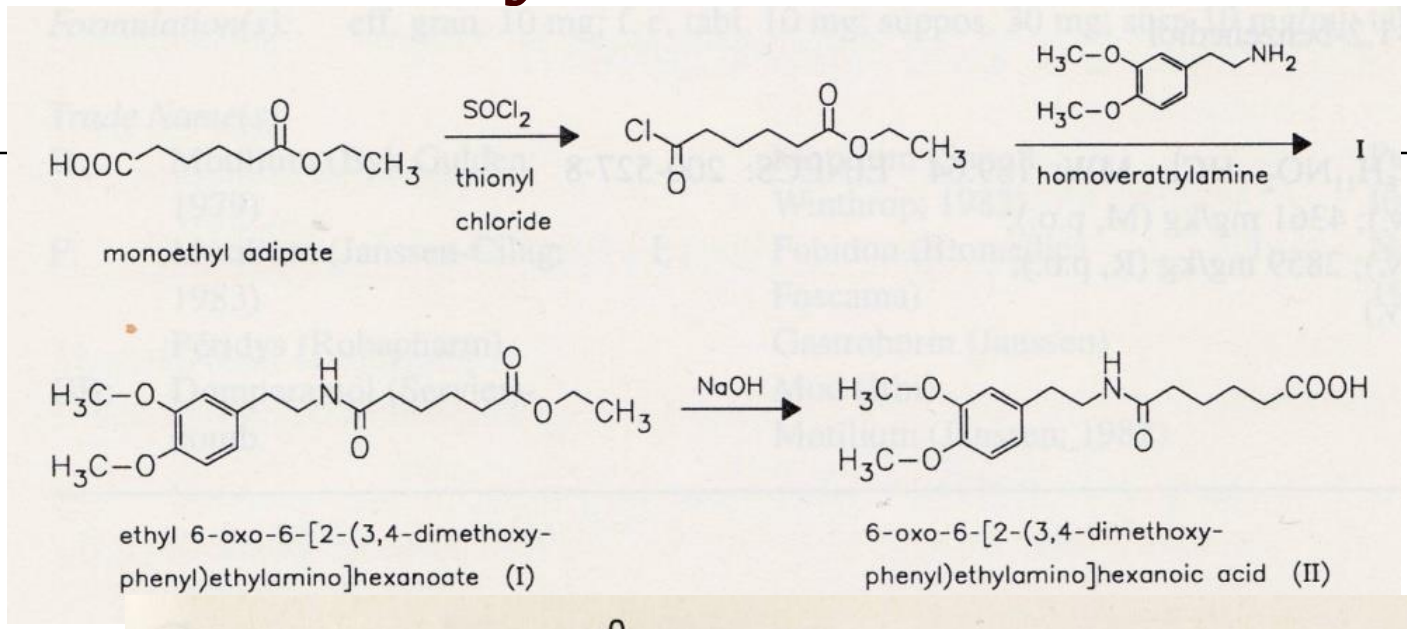


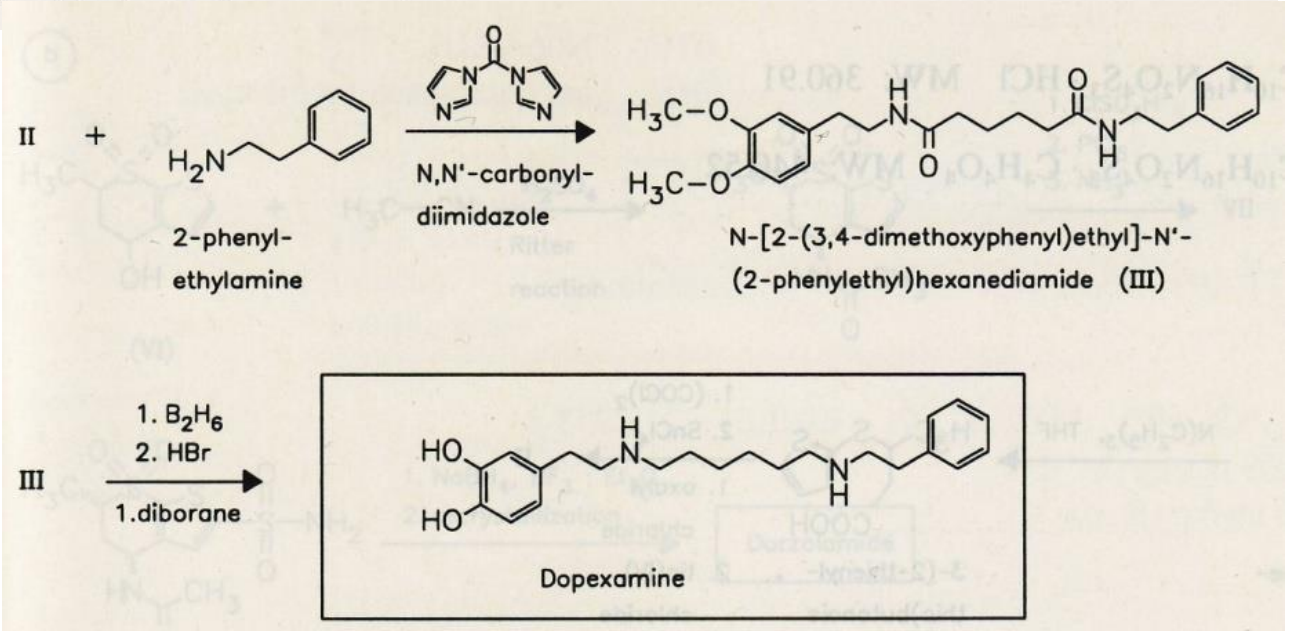
dobutamine



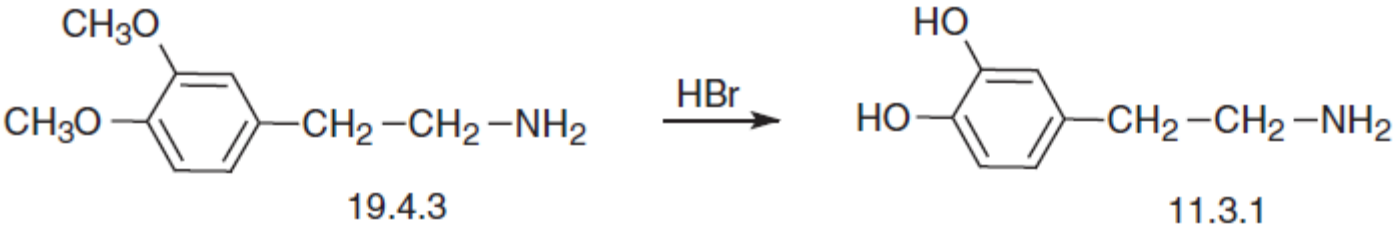
dopexamine

Dopexamine synthesis



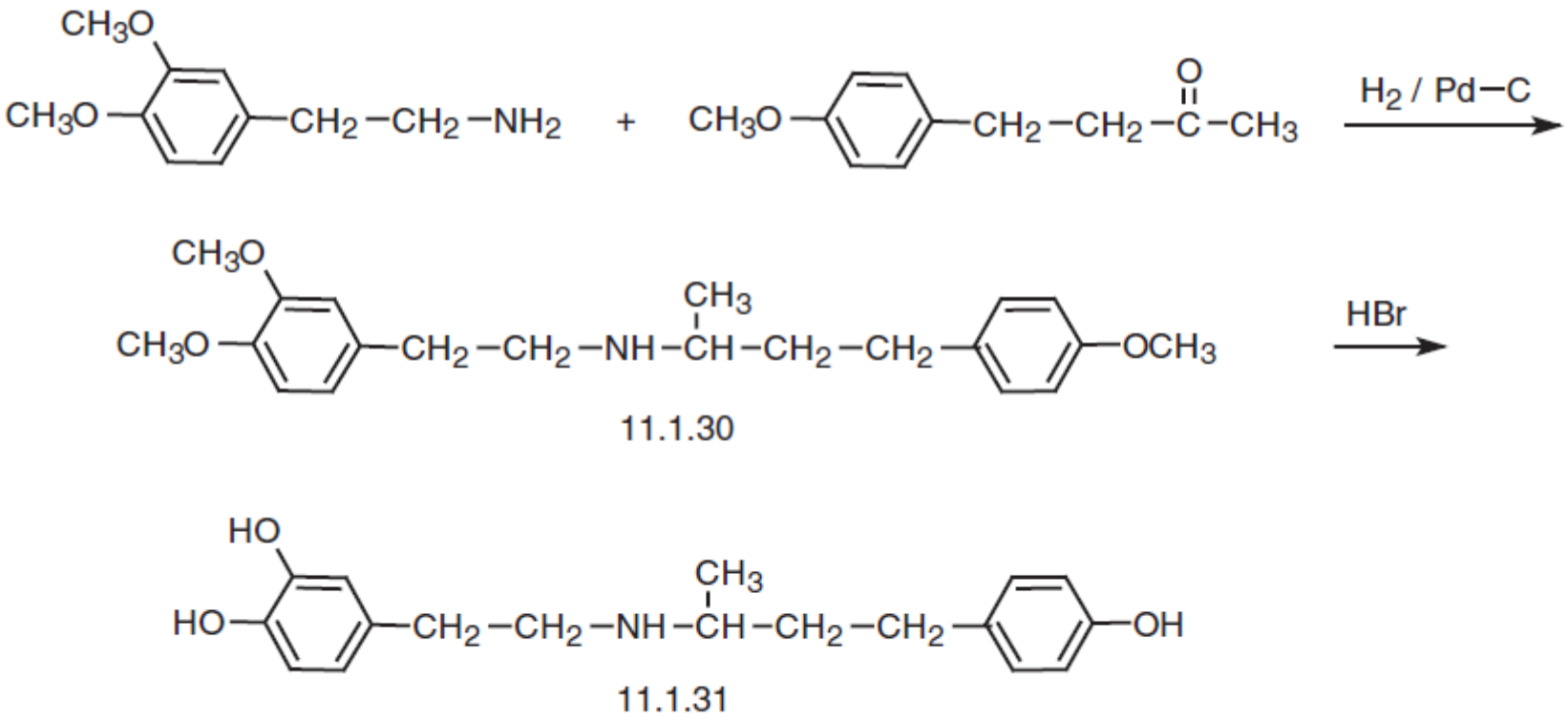


Dopamine synthesis



19.4.3 11.3.1

Dobutamine synthesis



Phosphodiesterase inhibitors

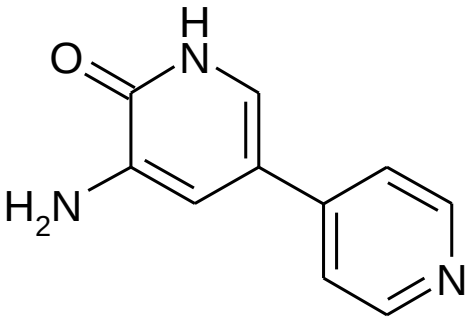
- xanthine derivatives
- bipyridine derivatives
- 3-pyridazinone derivatives
- chinolin-2-one derivatives

Xanthine derivatives

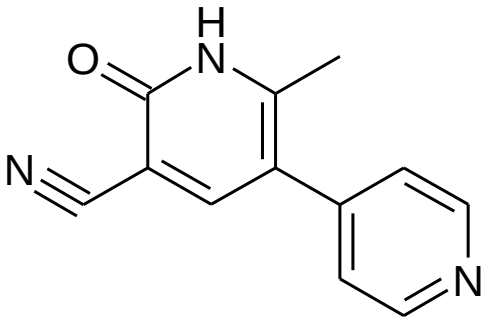
- Theophyline
- Aminophyline
- Etophyline

* see coronary vasodilatators presentation

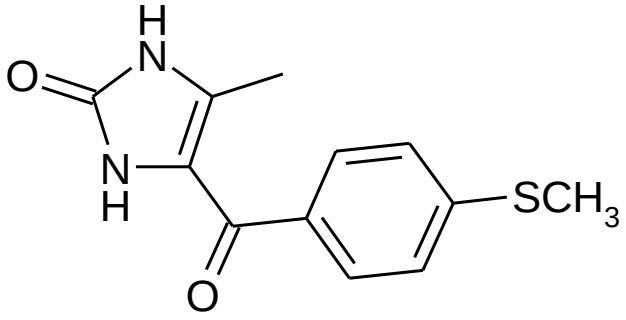
Bipyridine derivatives



Amrinon

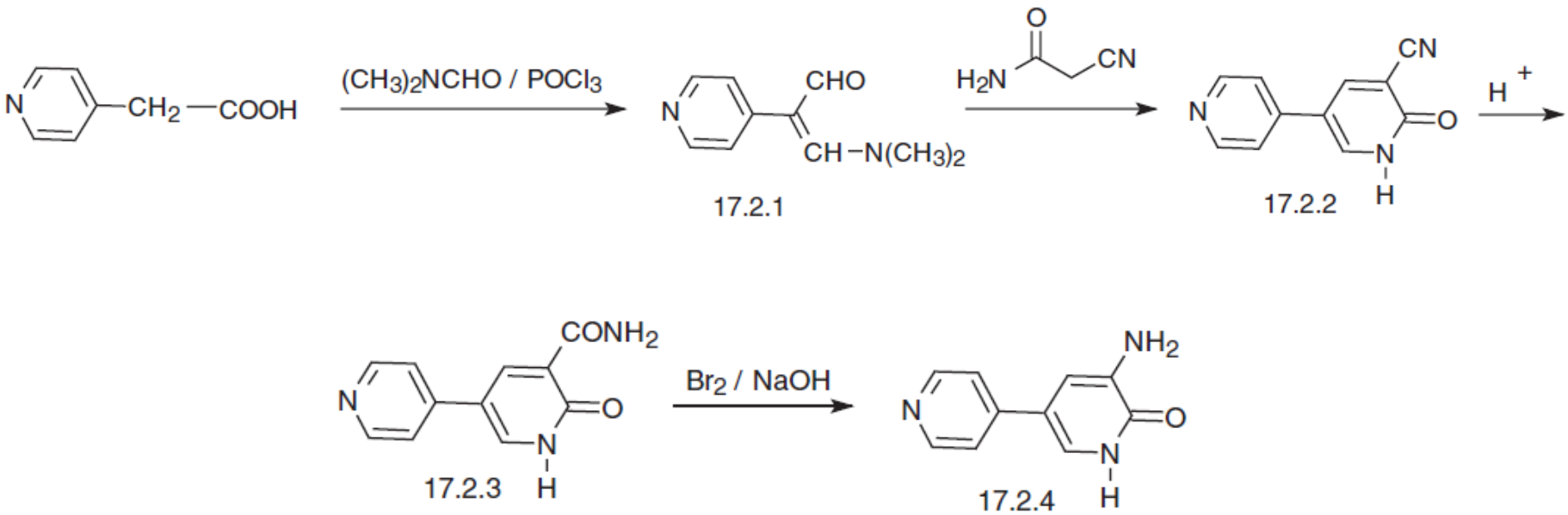


Milrinon

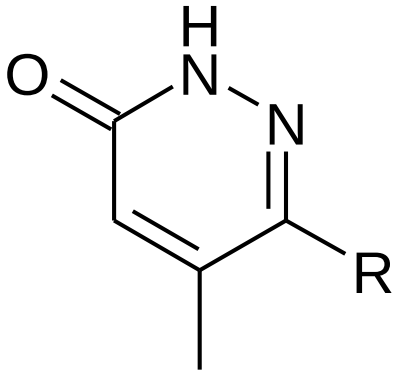


Enoximon

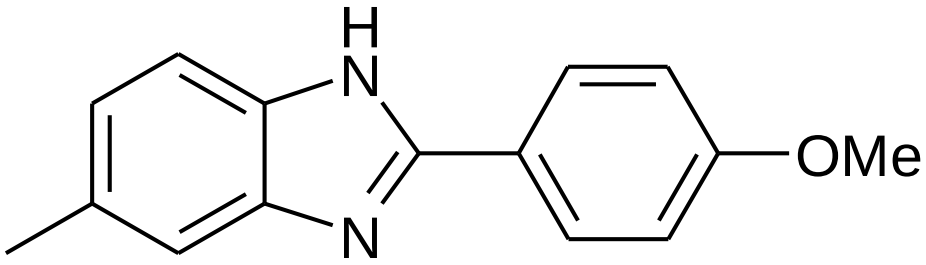
Amrinon synthesis



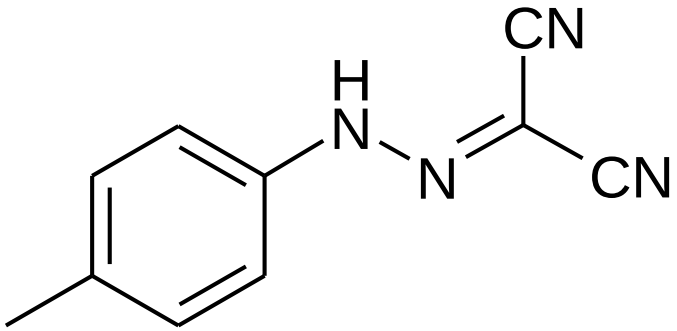
3-pyridazinone derivatives



R:

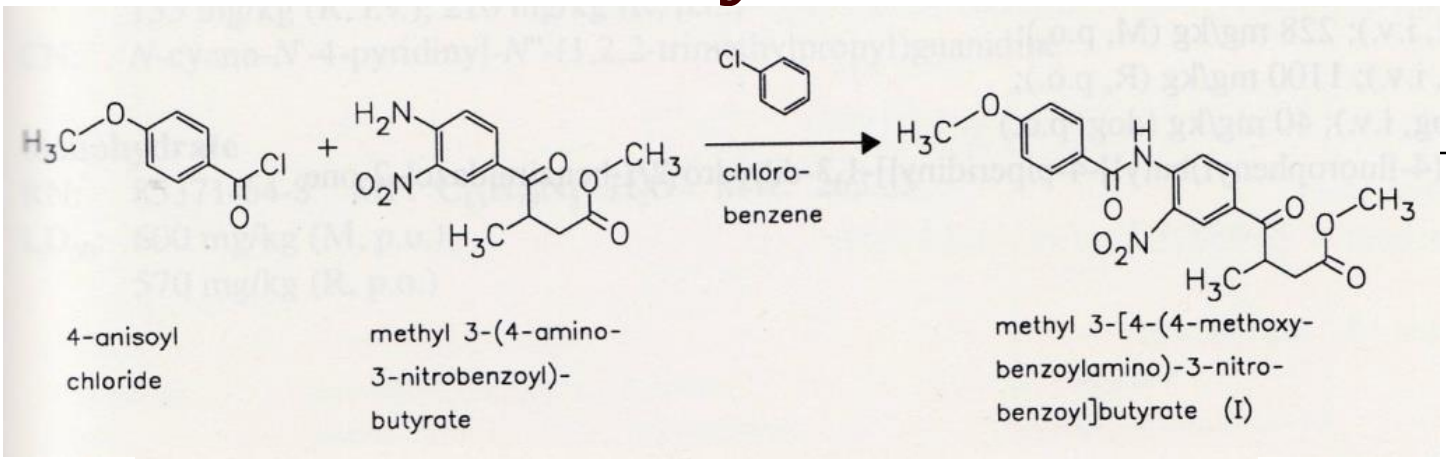


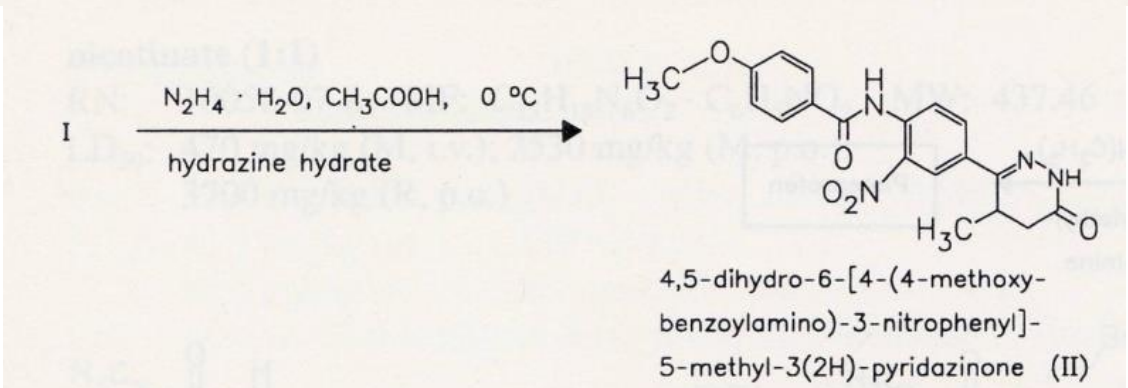
Pimobendan

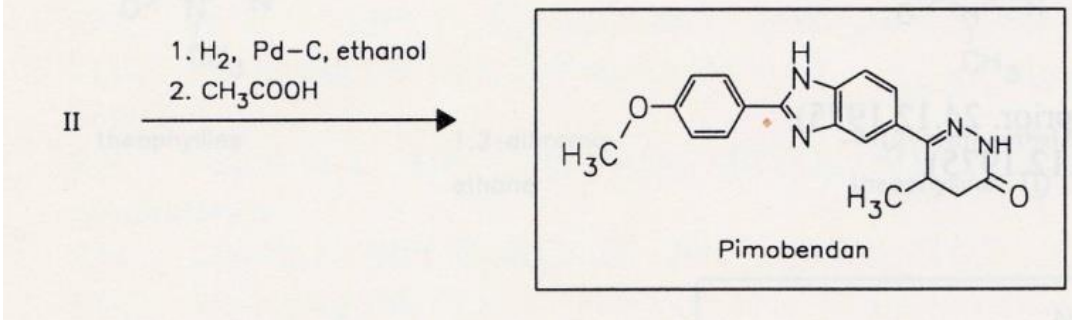


Simendan

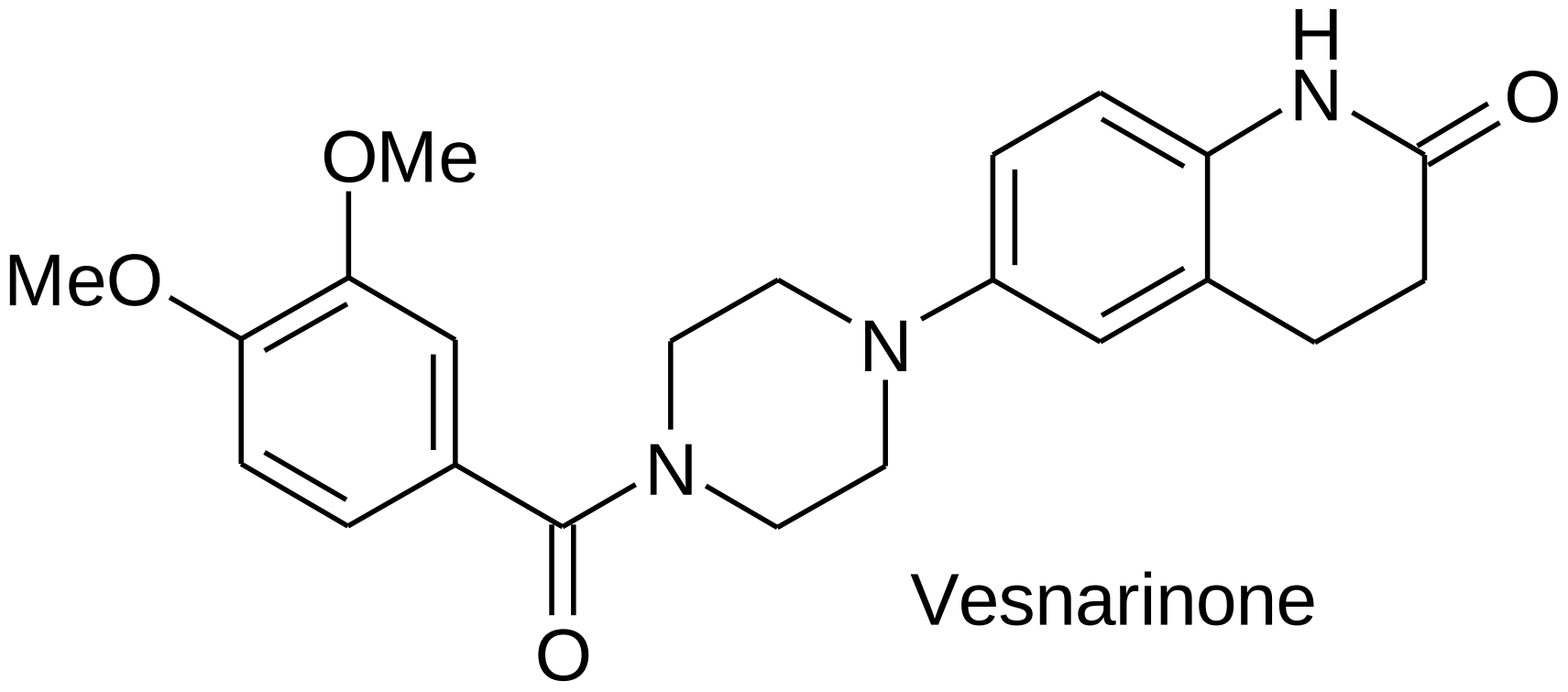
Pimobendan synthesis





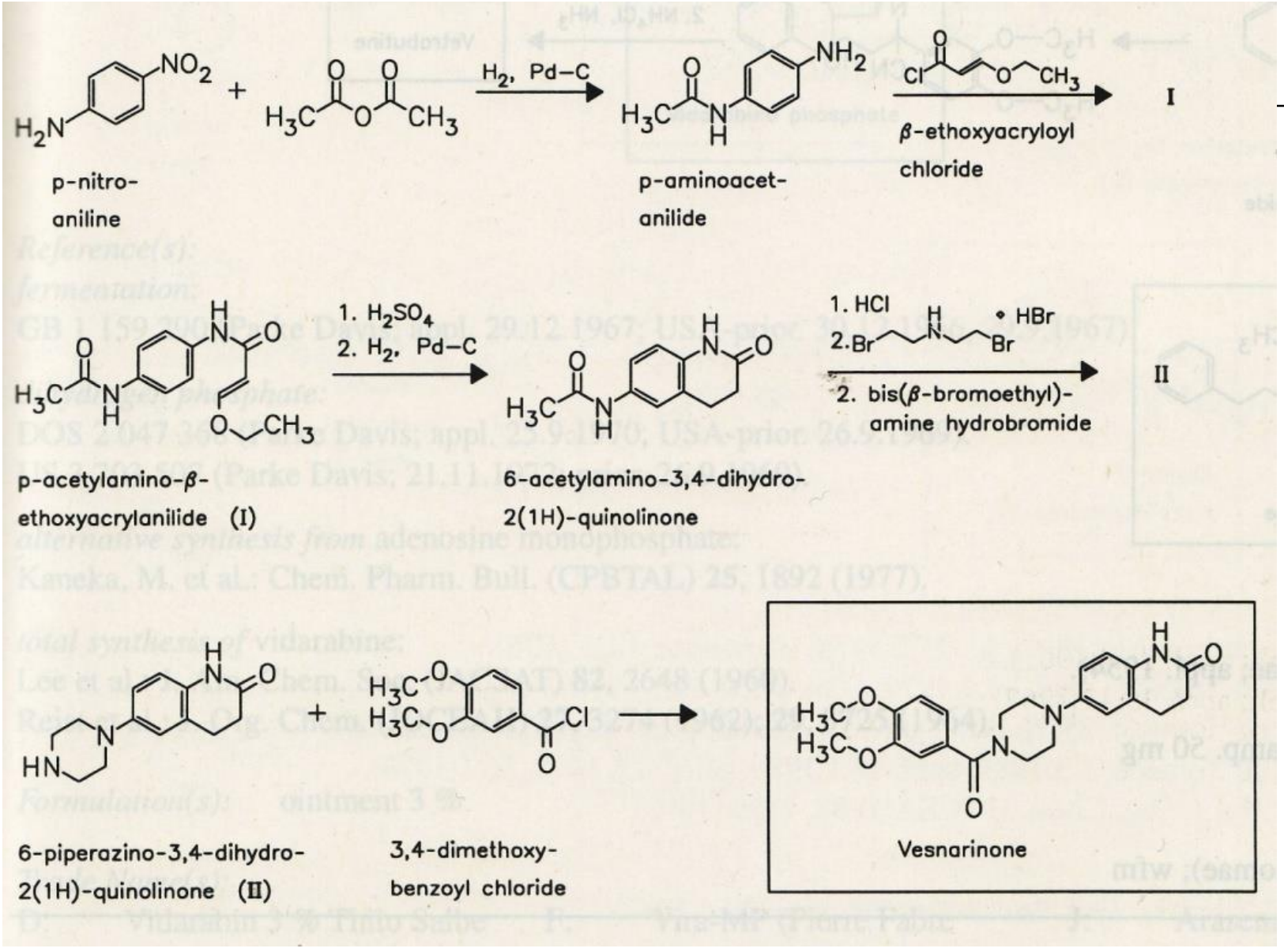


Chinolin-2-one derivatives



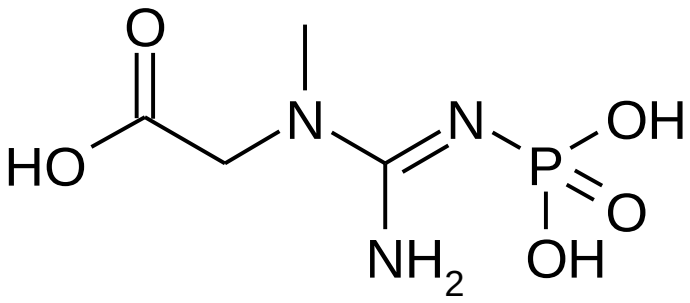
Vesnarinone

Vesnarinone synthesis

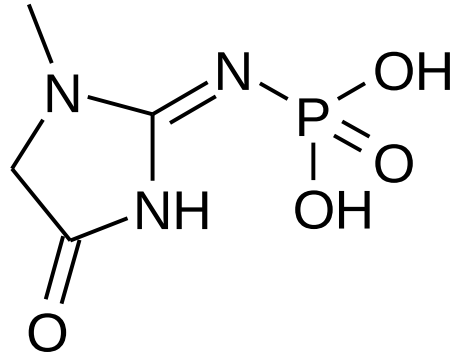


Cardioprotectives

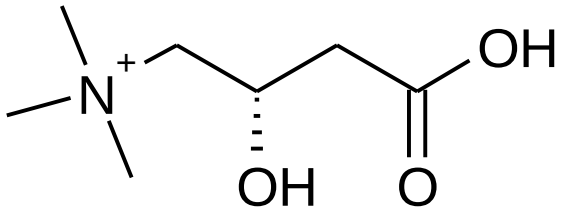
- detoxication of free radicals (NO, OO, OH)



phosphocreatin



phosphocreatinin



L-carnitin