Position Papers for Classes of NDSRIs

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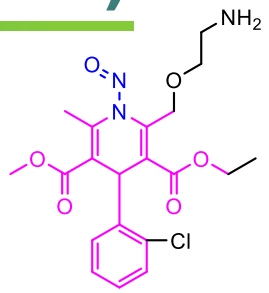
Position Papers for Class of NDSRIs

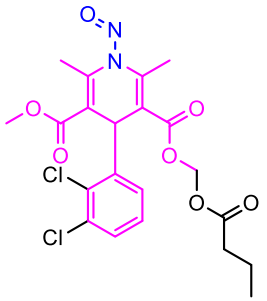
Nitrosamines of:

- Ca channel blockers (“-dipines”)
- β-blockers (“-ololS”) and β-agonists
- ACE inhibitors (“-prils”)

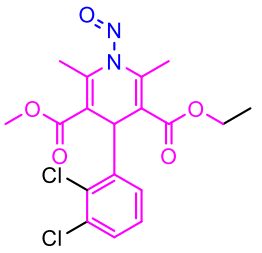
Nitroso-CCBs (“-dipines”)



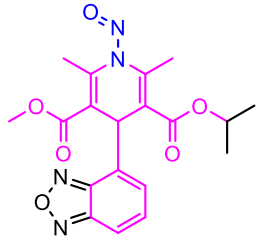
Nitroso-Amlodipine



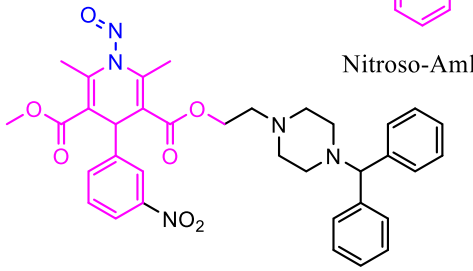
Nitroso-Clevidipine



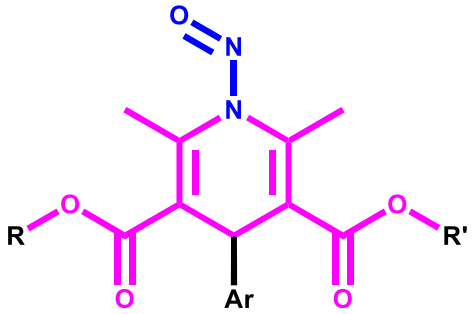
Nitroso-Felodipine

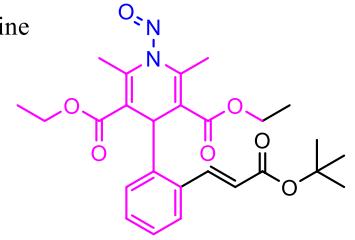


Nitroso-Isradipine

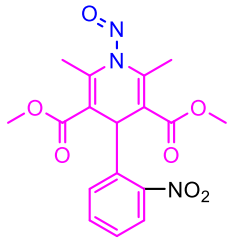


Nitroso-Manidipine

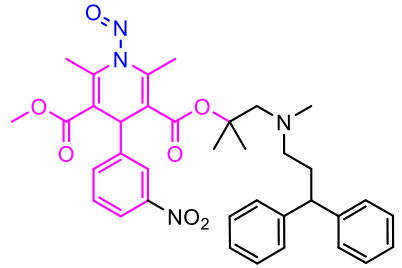




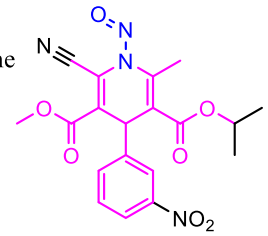
Nitroso-Lacidipine



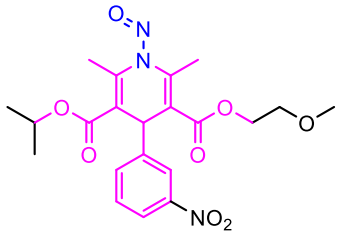
Nitroso-Nifedipine



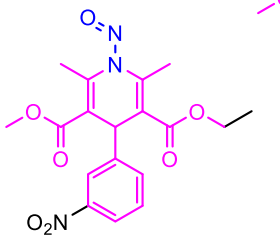
Nitroso-Lercanidipine



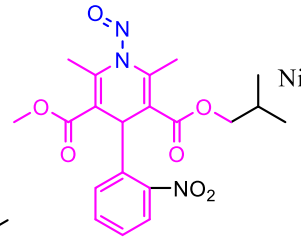
Nitroso-Nilvadipine



Nitroso-Nimodipine

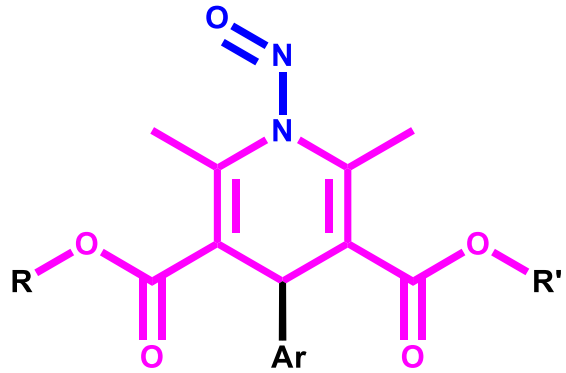


Nitroso-Nitrendipine



Nitroso-Nisoldipine

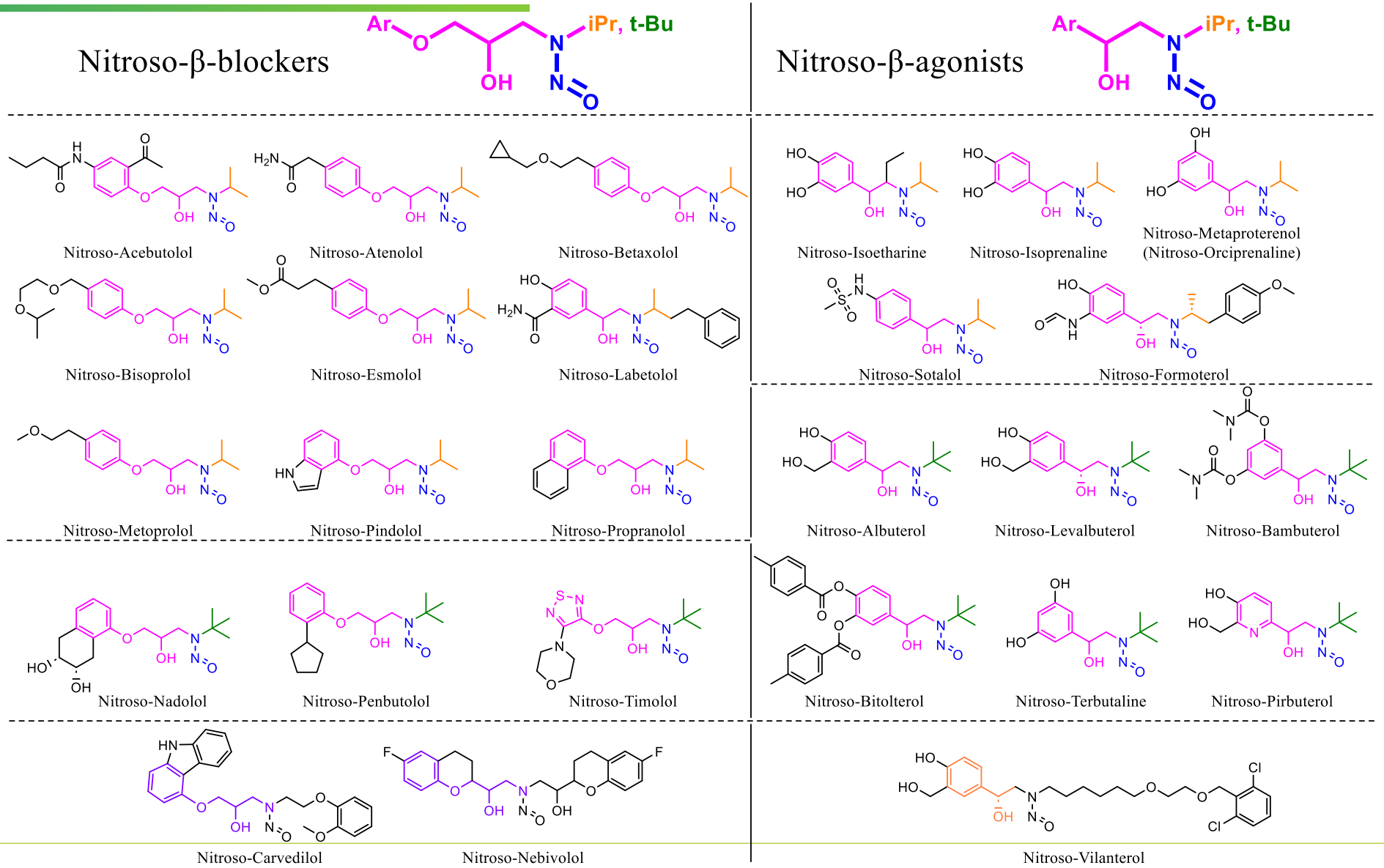
Nitroso-CCBs (“-dipines”)



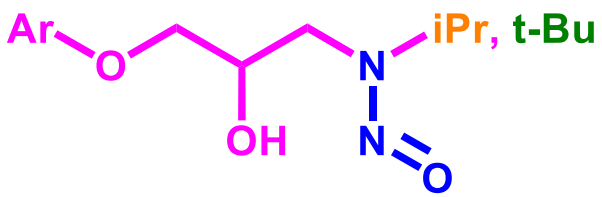
- Experimentally cannot nitrosate dihydropyridine
  - Preference to aromatization
  - Described in in earlier literature and validated recently
  - (Vendors mistakenly offer nitroso-CCBs)

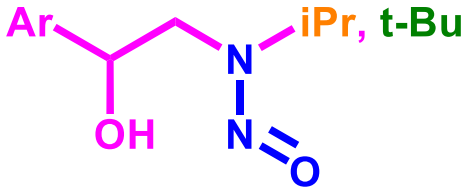
- No α-hydrogens
  - Even if they could form, they could not undergo α-hydroxylation

Nitrosamines of β-blockers (“-olols”) and β-agonists



Nitrosamines of β-blockers ("-ololS") and β-agonists

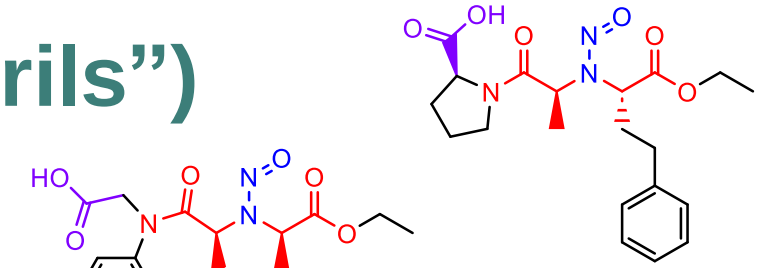




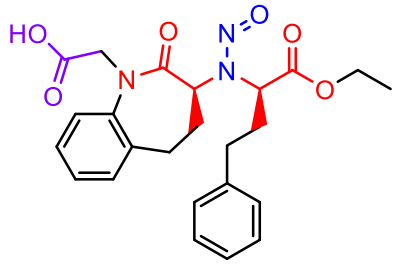
- Clastogenicity - considerably less potent than NDMA (Martinelli et al 1994)
- β-Hydroxyl – potency reducing (e.g. NDELA)
- Steric hindrance:
  - *i*Pr at α-position – strong potency reducing (Cross and Ponting 2021; Thomas et al. 2022; Ponting et al. 2022)
  - *tert*-Butyl at α-position – eliminates carcinogenicity; read across from methyl-*tert*-butylnitrosamine (NMTBA) and ethyl-*tert*-butylnitrosamine (EBNA)
  - Bulky groups also on the other side
- Carvedilol and nebivolol – read across from NDELA; alternative metabolic pathways
- Conflicting Ames test results
- Several TGR studies are currently ongoing
- Overall WoE indicates this class of NDSRIs should not be included in the Cohort of Concern

Martinelli et al 1994: https://doi.org/10.1016/0378-4274(94)90057-4
Cross and Ponting 2021: https://doi.org/10.1016/j.comtox.2021.100186
Thomas et al. 2022: https://doi.org/10.1021/acs.chemrestox.2c00199
Ponting et al. 2022: https://doi.org/10.1021/acs.jmedchem.2c01498

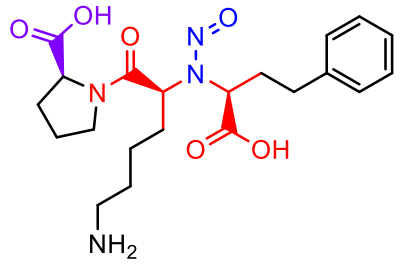
Nitroso-ACE inhibitors (“prils”)



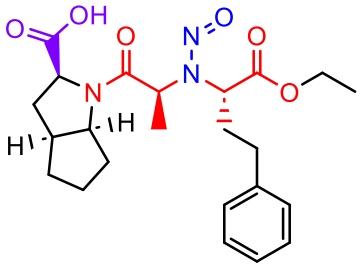
Nitroso-Enalapril



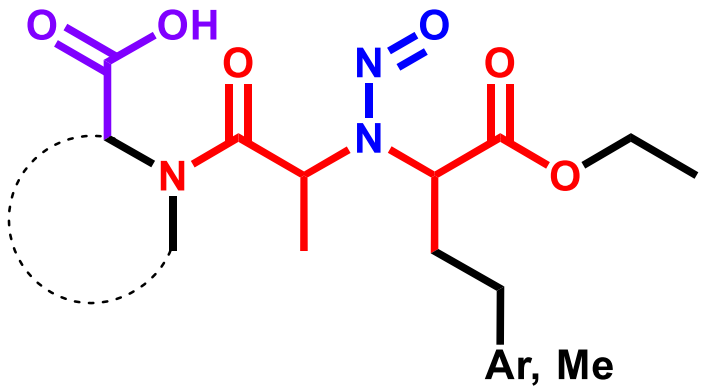
Nitroso-Benazepril

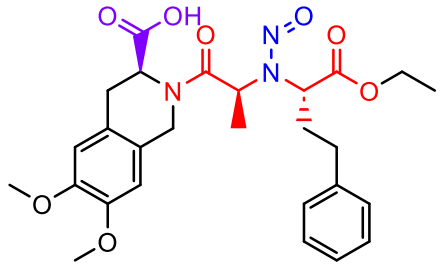


Nitroso-Lisinopril

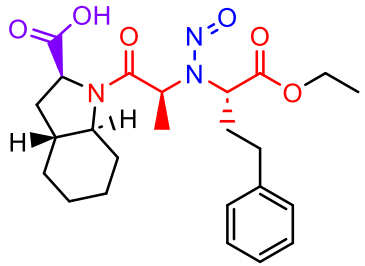


Nitroso-Ramipril

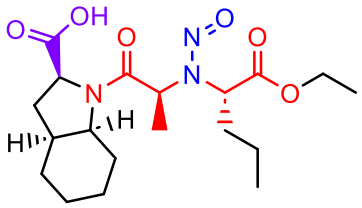




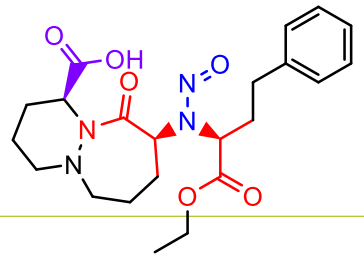
Nitroso-Moexipril



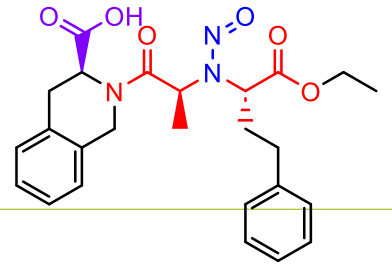
Nitroso-Trandolapril



Nitroso-Perindopril



Nitroso-Cilazapril

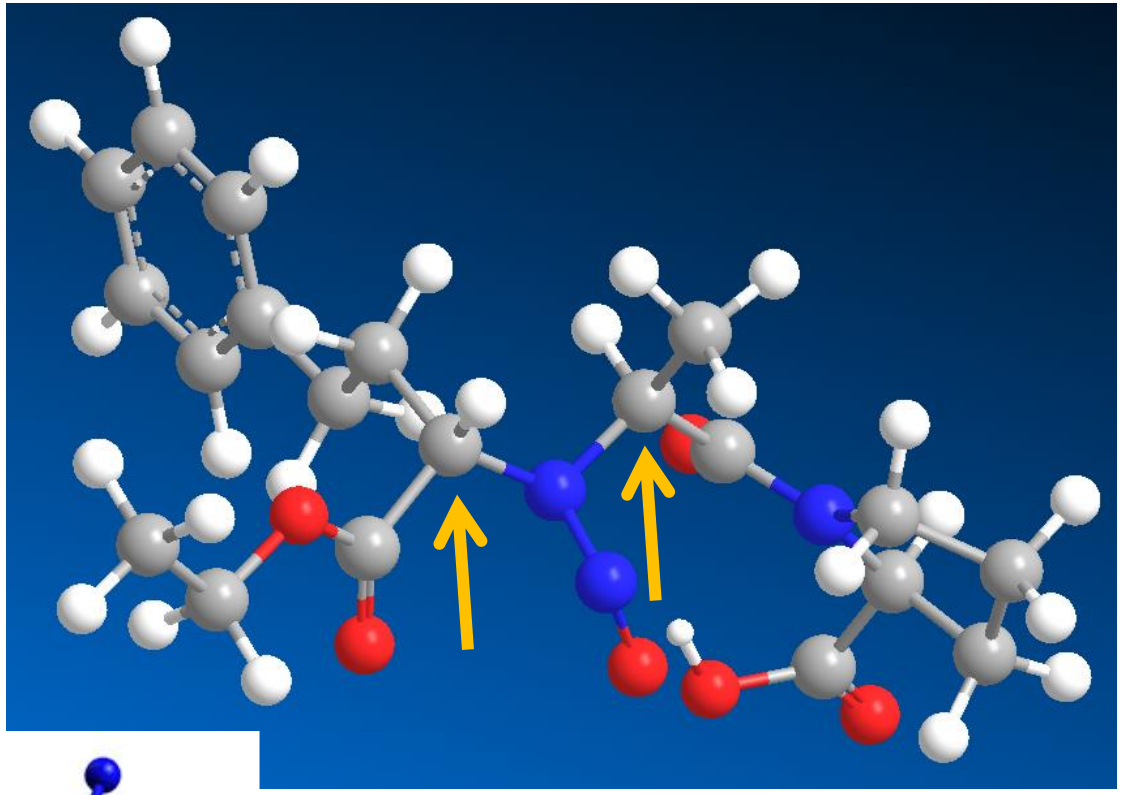


Nitroso-Quinapril

Nitroso-ACE inhibitors (“prils”)

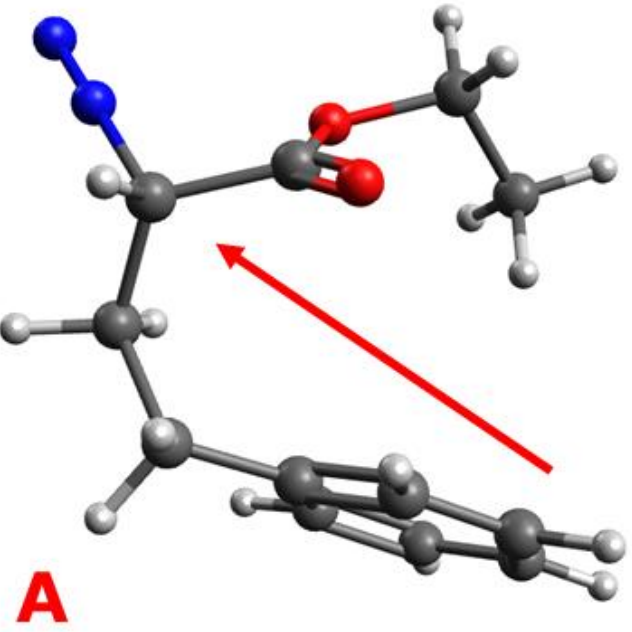
Nitroso-enalapril

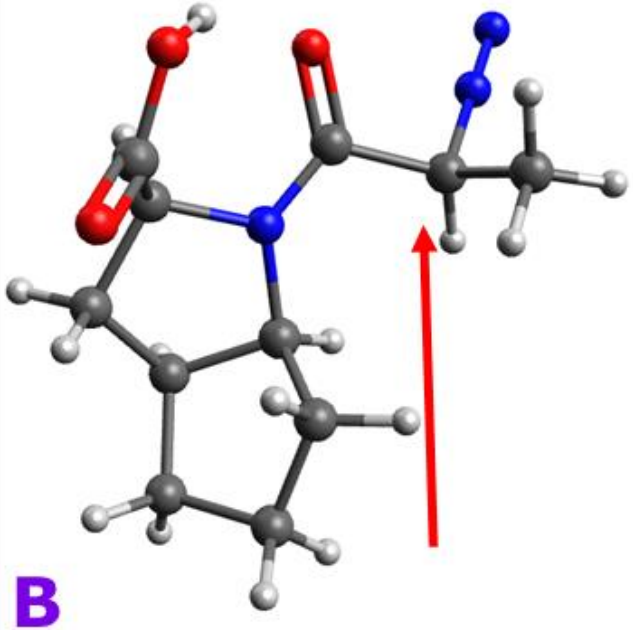
- Steric hindrance prohibits α-hydroxylation



Diazonium derivatives of ramipril

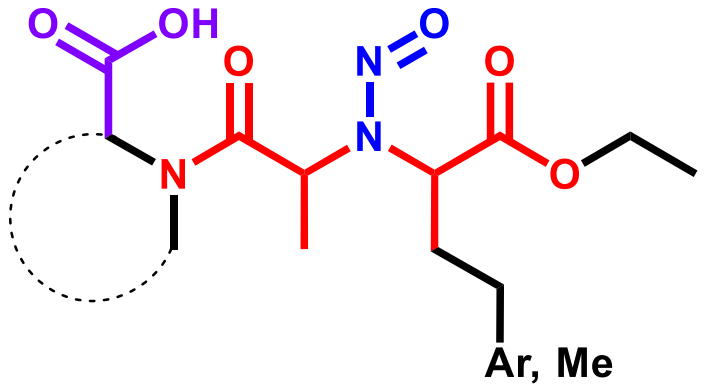
- steric hindrance around the diazonium ion would prohibit DNA binding





- Both possible Diazonium ions sterically protect the ion position
- DNA base do not fit into these grooves

Nitroso-ACE inhibitors ("prils")



- Considerable steric hindrance on both α-positions prohibit α-hydroxylation
- Quantum chemical calculations – low probability of α-hydroxylation
- Steric hindrance around putative diazonium ions would prohibit DNA binding
- Free carboxylate - carcinogenicity reducing (Ponting et al. 2022)
- Negative Ames tests (except for a few positives without S9) – Lhasa Complex Nitrosamines Data Sharing Initiative
- Several in vivo mutagenicity studies (TGR + duplex sequencing) are currently ongoing (some already found to be negative)
- Overall WoE indicates this class of NDSRIs should not be included in the Cohort of Concern

Ponting et al. 2022: https://doi.org/10.1021/acs.jmedchem.2c01498

Conclusions

Nitroso-CCBs (“-dipines”)

- do not form (aromatization preferential to nitrosation)
- Even if formed, no α-hydrogens thus no formation of diazonium ion
- Conclusion: no risk of formation

Nitrosamines of β-blockers (“-ololS”) and β-agonists

- SAR points to weak carcinogenic potency or non-carcinogenicity
- Conclusion: not to be included in CoC

Nitroso-ACE inhibitors (“prils”)

- Considerable steric hindrance
- Negative *in vitro* and *in vivo* data
- Conclusion: not to be included in CoC

Thank You תודה רבה

Questions?