Tyr-Pro-Ser-Lys-Pro-Asp-Asn-Pro-Gly-Glu-
Asp-Ala-Pro-Ala-Glu-Asp-Leu-Ala-Arg-Tyr-
Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-
Ile-Thr-Arg-Gln-Arg-Tyr-$NH_2$

# NEUROPEPTIDE Y (NPY)

Tatemoto et al., *Nature*, *296*, 659 (1982)

## NEUROPEPTIDE Y RECEPTORS

| Nomenclature | $Y_1$ | $Y_2$ |
|---|---|---|
| Potency order (endogenous ligands) | PYY≥NPY>>PP | PYY≥NPY>>PP |
| Selective agonists | [Pro$^{34}$]NPY | $NPY_{13-36}$ |
| | [Leu$^{31}$,Pro$^{34}$]NPY | $NPY_{18-36}$ |
| Selective antagonists | - | - |
| Radioligands | [$^{125}$I]- or [$^{3}$H]NPY | [$^{125}$I]- or [$^{3}$H]NPY |
| Predominant effectors | cAMP ↓ | cAMP ↓ |
| | | Ca channel ↓ (G) |
| Structural information | 384 aa human 7TM | - |
| | 382 aa rat 7TM | |

Other receptors/binding sites: A third receptor, $Y_3$, has been proposed.

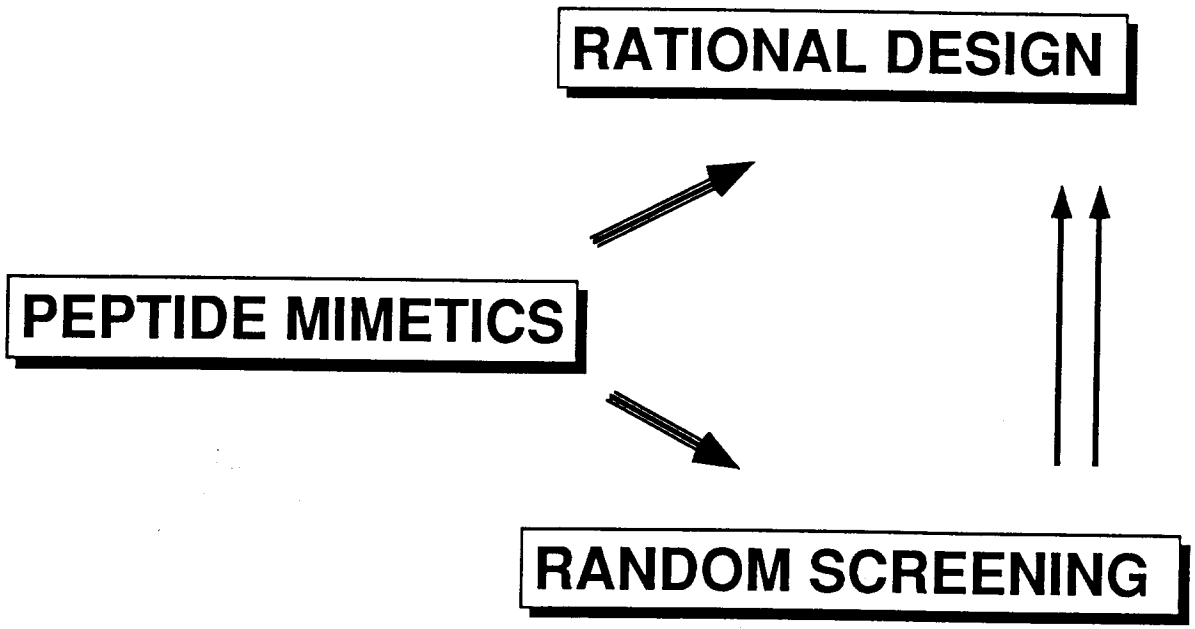
NPY, neuropeptide Y; PYY, peptide YY; PP, pancreatic polypeptide

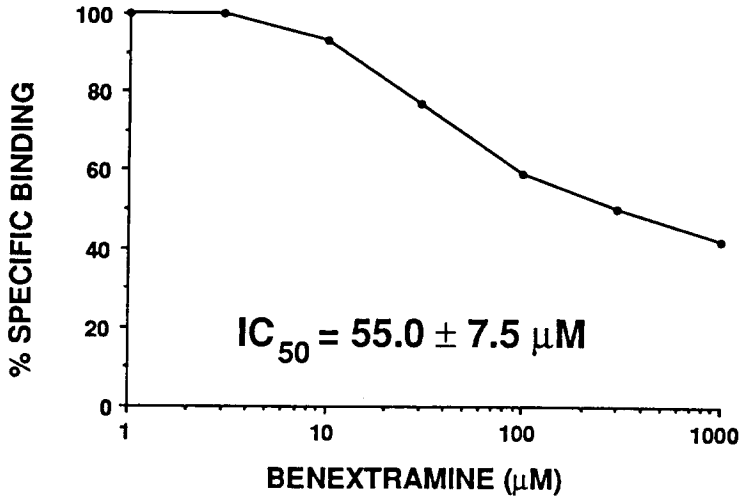
| RECEPTOR | PEPTIDE | TISSUE |
|---|---|---|
| $Y_1$ | [Pro$^{34}$]NPY=NPY=PYY>>$NPY_{13-36}$>>PP | blood vessels<br>cerebral cortex<br>hypothalamus |
| $Y_2$ | PYY≥NPY>$NPY_{13-36}$ >>[Pro$^{34}$]NPY, PP | nerve endings<br>renal tubular cells<br>hippocampus |
| $Y_3$ | NPY≥[Pro$^{34}$]NPY≥$NPY_{13-36}$ >>PYY, PP | brainstem<br>heart<br>adrenal medulla |

NPY, neuropeptide Y; PYY, peptide YY; PP, pancreatic polypeptide

## WHY PEPTIDE MIMETICS?

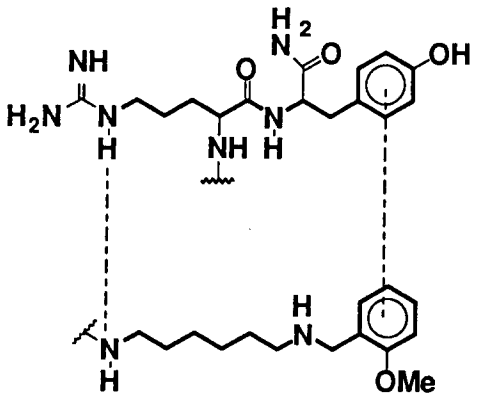
- Bioavailability
- Duration of action
- Cost






**Effects of varying concentrations of benextramine on the specific binding of [3H]NPY to rat brain membranes.**

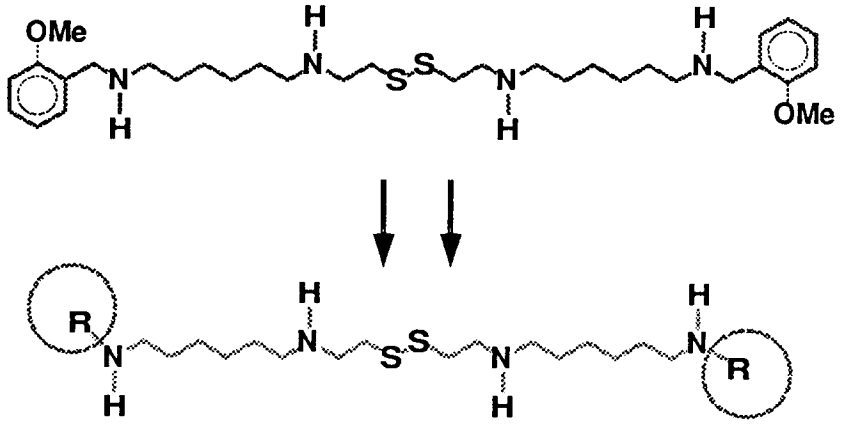
Doughty et al., *Eur. J. Pharmacol.*, *185*, 113 (1990)



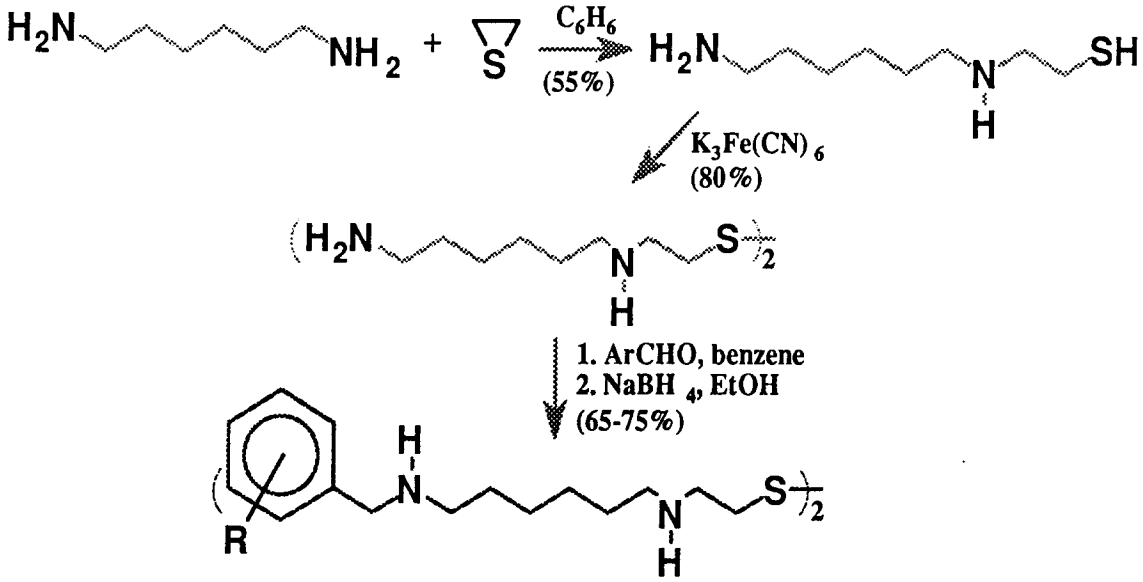

NPY

BENEXTRAMINE

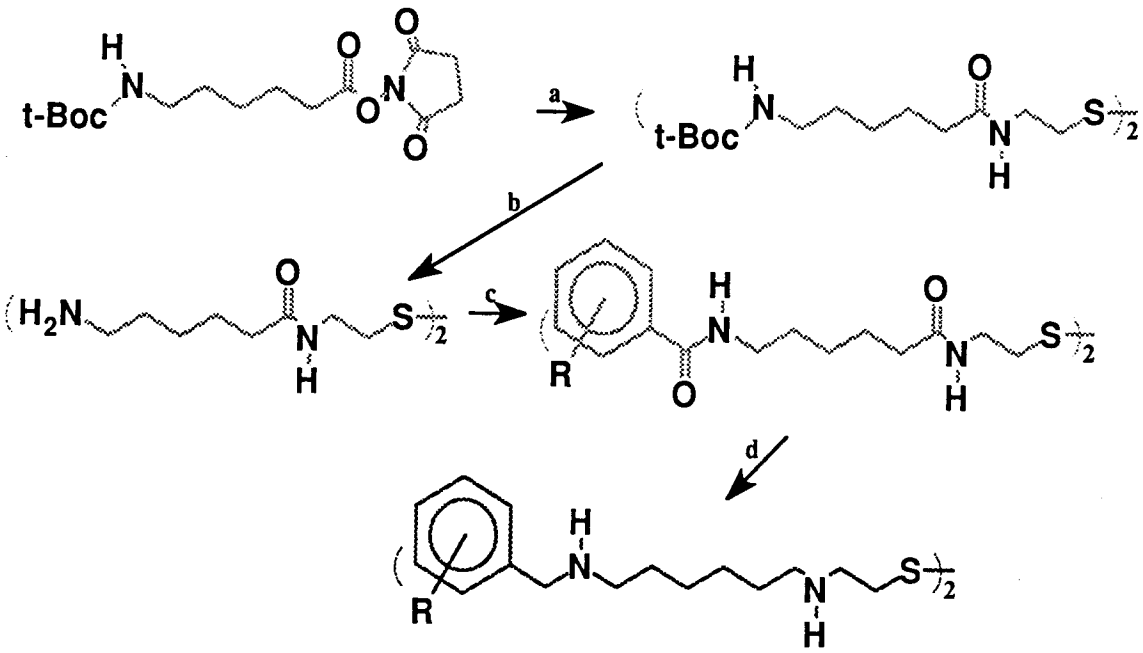
**Hypothetical structural relationships between benextramine's inner nitrogen and phenyl ring and NPY's Arg35 guanidinium group and Tyr36 phenolic ring**




R = H, aryl

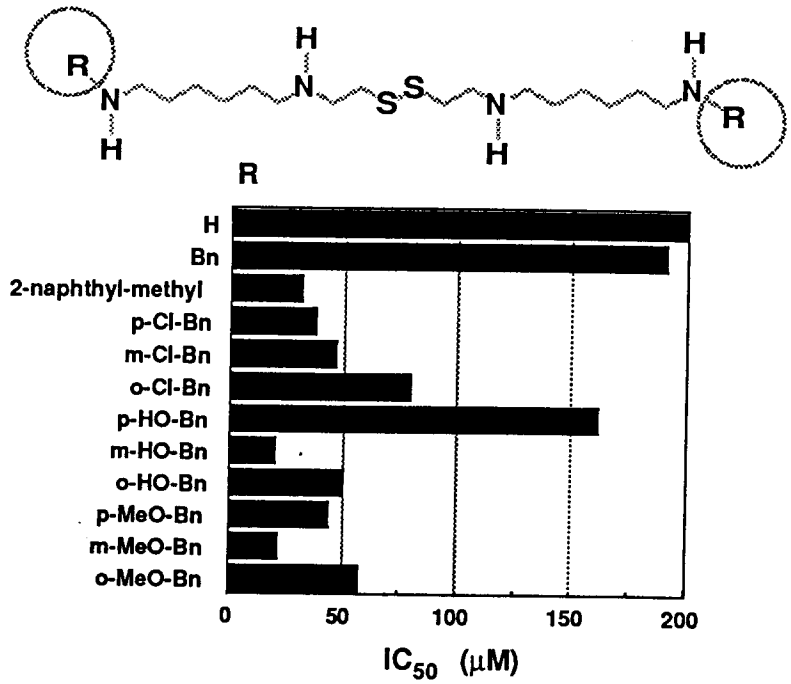



Melchiorre et al., *J. Med. Chem., 21*, 1126 (1978)



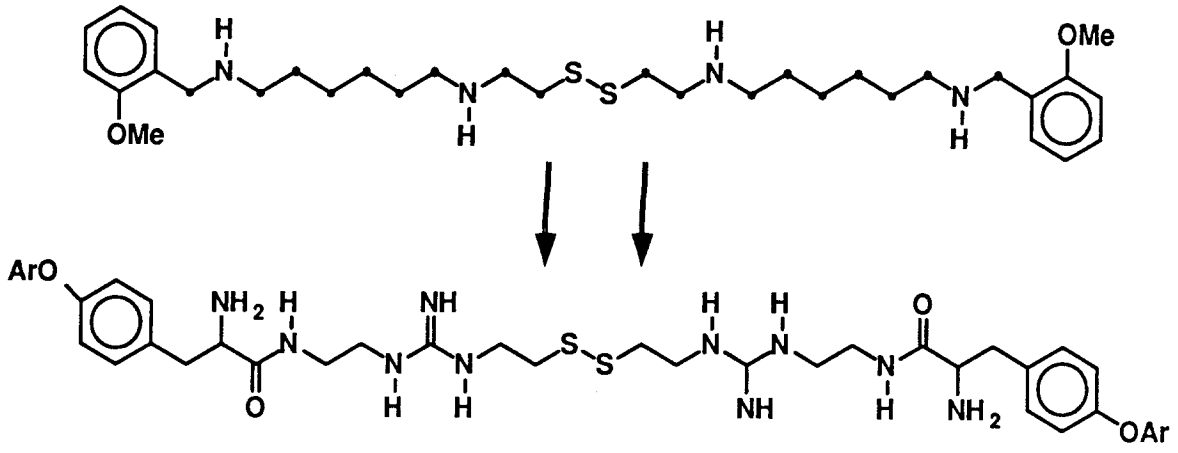

(a): cystamine; (b) 4N HCl; (c) aroyloxysuccinimides or ArCOCl; (d) diborane

Doughty et al., *J. Med. Chem.*, *36*, 272 (1993)



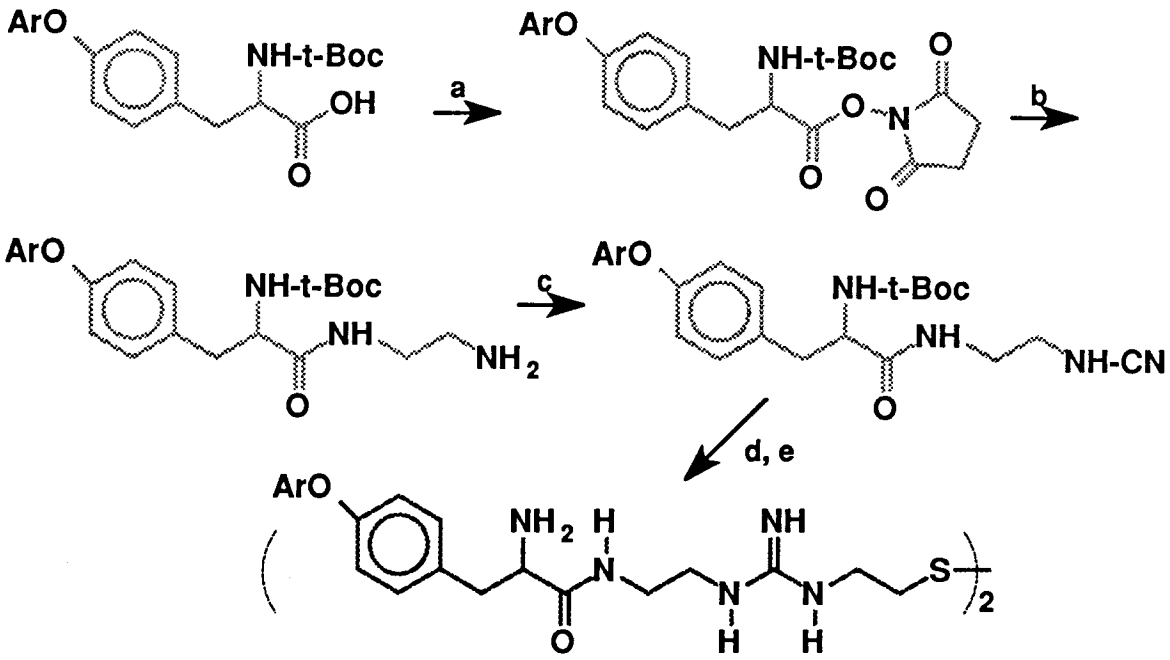

**Comparison of [3H]NPY inhibitory activity of benextramine (R = o-MeO-Bn) analogues in rat whole brain membranes.**

Doughty, Chaurasia & Li, *J. Med. Chem.*, *36*, 272 (1993)

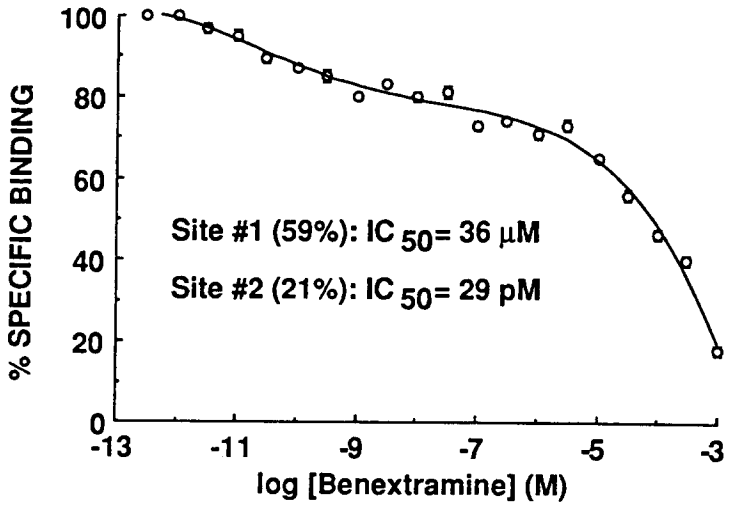


Ar = 2,6-dichlorobenzyl

Doughty et al., *Bioorg. Med Chem. Lett.*, *2*, 1497 (1992)

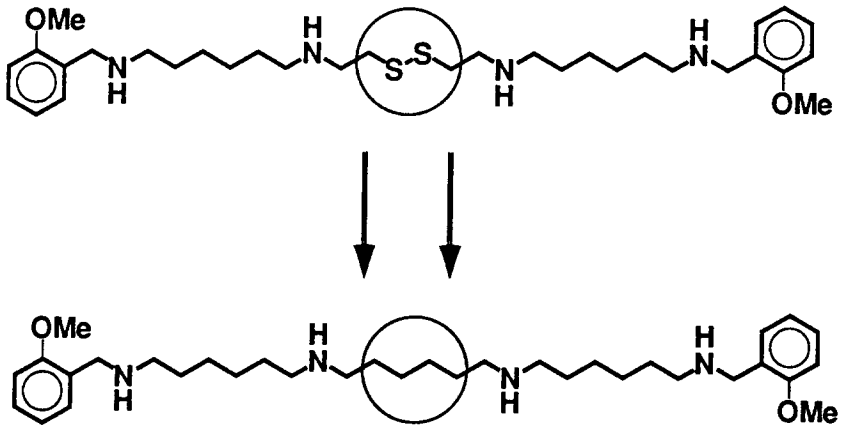


Ar = 2,6-dichlorobenzyl. (a) DCC, N-hydroxysuccinimide; (b) ethylenediamine (c) BrCN; (d) cystamine; (e) 50% trifluoroacetic acid/methylene chloride



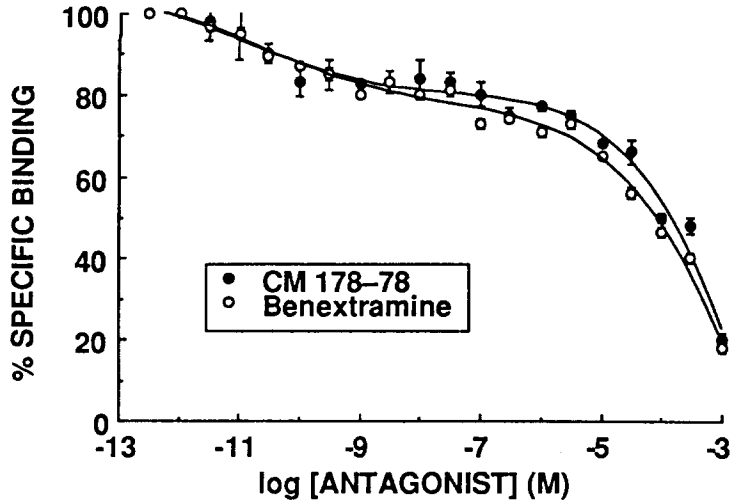

**Effects of varying concentrations of benextramine on the specific binding of [3H]NPY to rat brain membranes**

Melchiorre et al., *Eur. J. Pharmacol.*, in press.



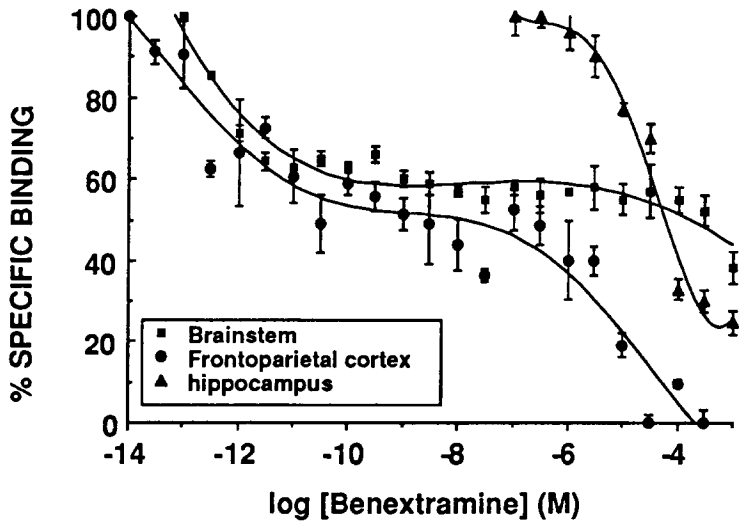

**CM 178-78**

**FROM PHARMACOLOGY TO DRUG DESIGN**



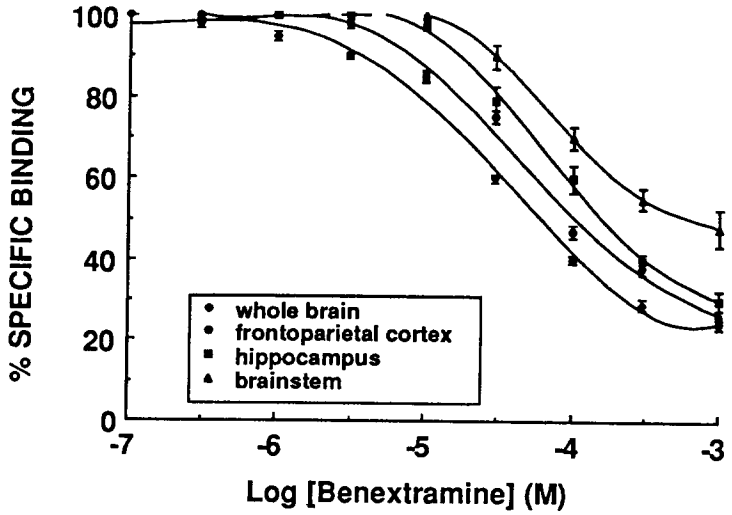

**Effects of varying concentrations of benextramine and CM 178-78 on the specific binding of [3H]NPY to rat brain membranes**

Melchiorre et al., *Eur. J. Pharmacol.*, in press.




**Effects of varying concentrations of benextramine on the specific binding of [3H]NPY to rat frontoparietal cortex (Y1), hippocampus (Y2) and brainstem (Y3) membranes**

Melchiorre et al., *Eur. J. Pharmacol.*, in press.



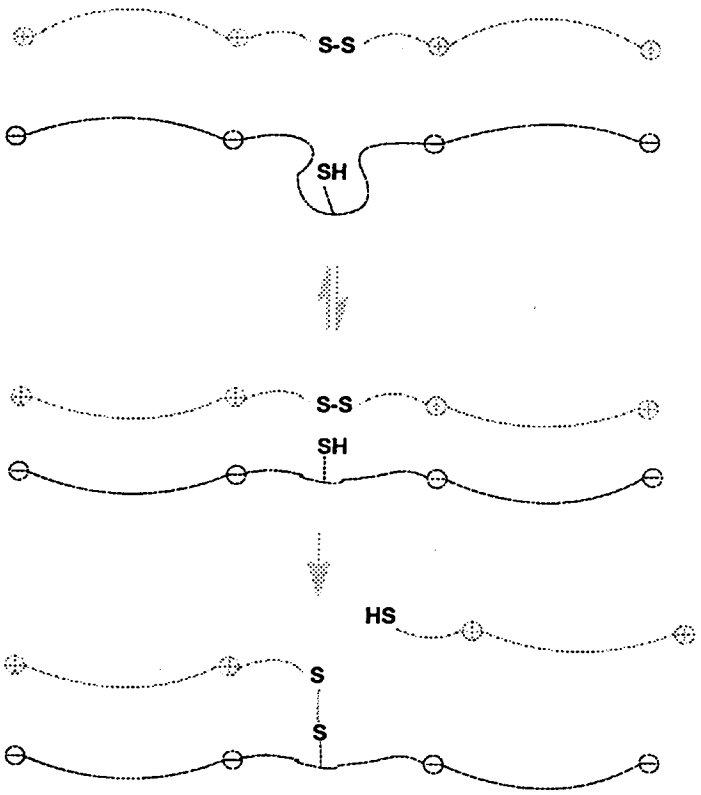

**Effects of varying concentrations of benextramine on the specific binding of [3H]NPY to rat whole brain, frontoparietal cortex (Y1), hippocampus (Y2) and brainstem (Y3) membranes, following pretreatment with 1 μM benextramine and 30 min washing.**

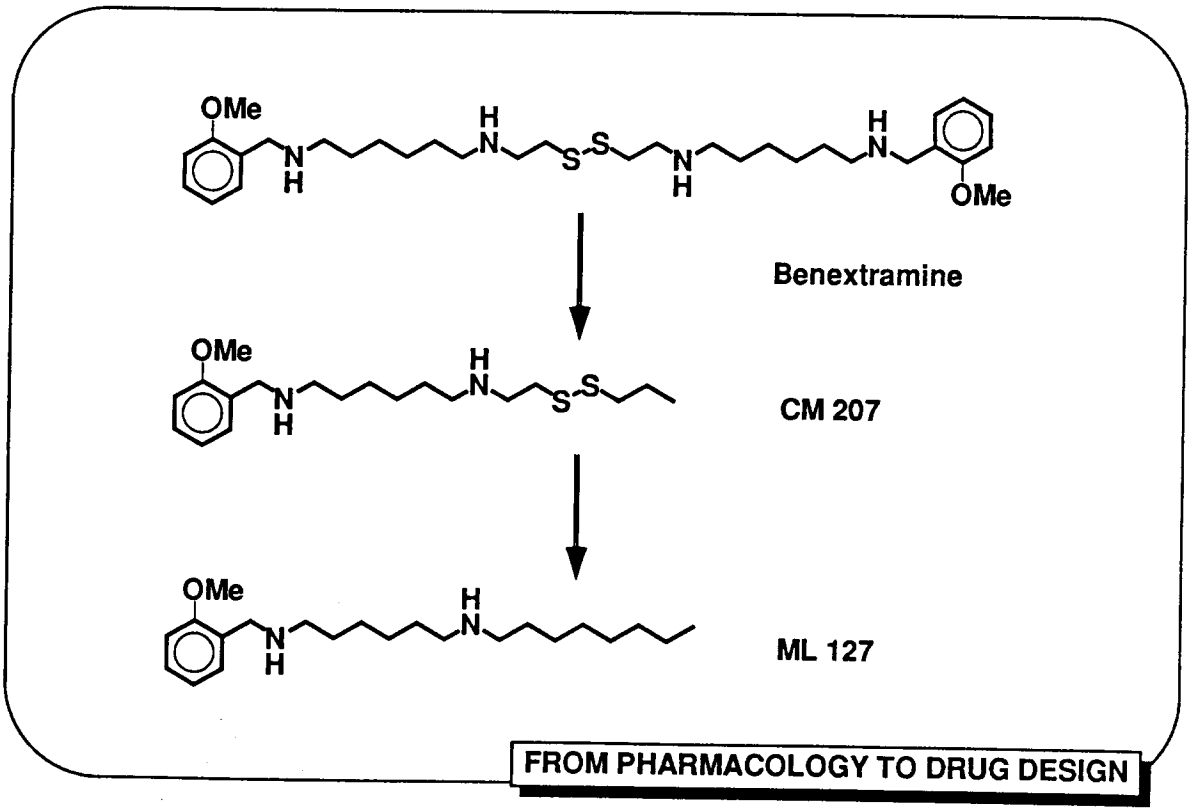
Melchiorre et al., *Eur. J. Pharmacol.*, in press.

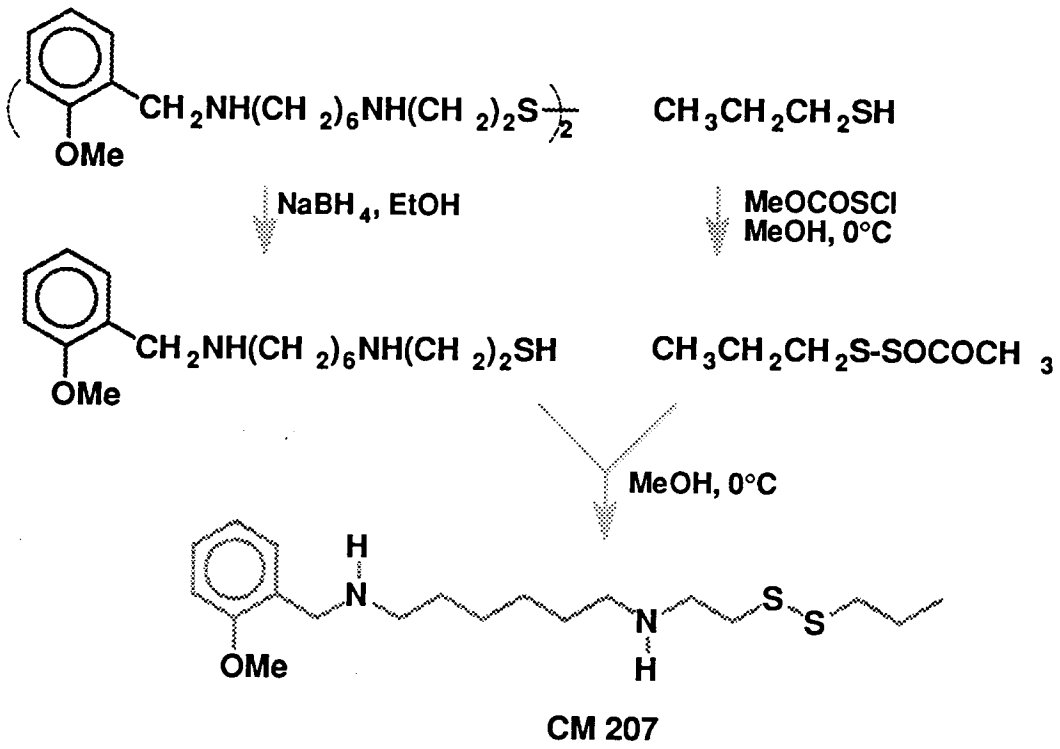
## POLYAMINES VS BENEXTRAMINE

1. REDUCED, IF ANY, AFFINITY FOR α-ADRENORECEPTORS AND MUSCARINIC RECEPTORS
2. IMPROVED AFFINITY AND SELECTIVITY FOR NPY RECEPTORS

FROM PHARMACOLOGY TO DRUG DESIGN

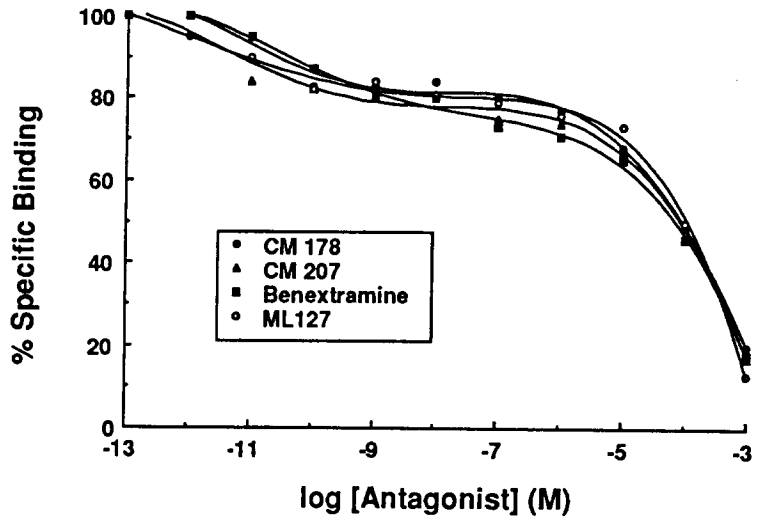

S-S
SH
S-S
SH
HS
S
S


OMe
H
N
S
S
N
H
N
H
OMe
Benextramine
OMe
H
N
S
S
CM 207
OMe
H
N
ML 127
FROM PHARMACOLOGY TO DRUG DESIGN




CM 207

Melchiorre et al., *Farmaco, Ed. Sci.*, *33*, 999 (1978)



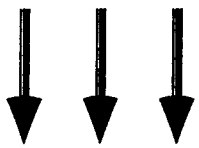

**Effects of varying concentrations of benextramine, CM 178, CM 207 and ML 127 on the specific binding of [3H]NPY to rat whole brain membranes.**

Melchiorre et al., unpublished results.

Activities of polyamines in displacing [$^3$H]NPY from specific binding sites in rat brain

| | site # 1 (low) | | site # 2 (high) | |
|---|---|---|---|---|
| Compound | $pIC_{50}$ | % Receptors | $pIC_{50}$ | % Receptors |
| Benextramine | 4.44 | 55 | 10.53 | 21 |
| CM 178 | 4.29 | 61 | 11.19 | 20 |
| CM 207 | 4.03 | 59 | 11.20 | 22 |
| ML 127 | 3.77 | 57 | 11.89 | 21 |

**SUBSTITUTED POLYAMINES**



**A first class of non-peptide, powerful and selective antagonists of neuropeptide Y receptors**