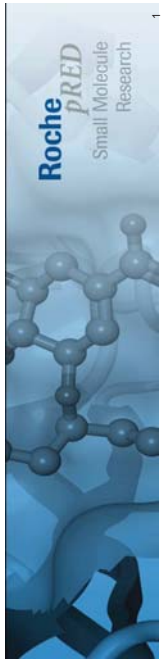
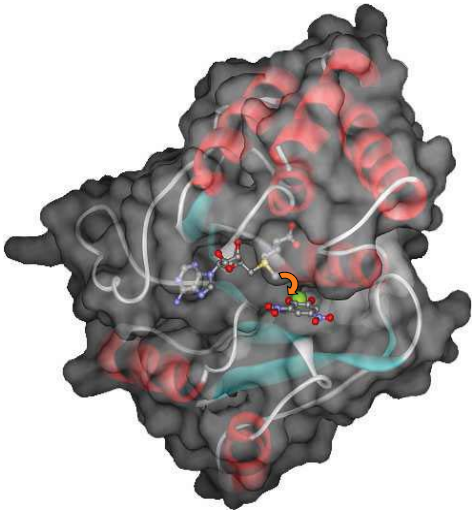
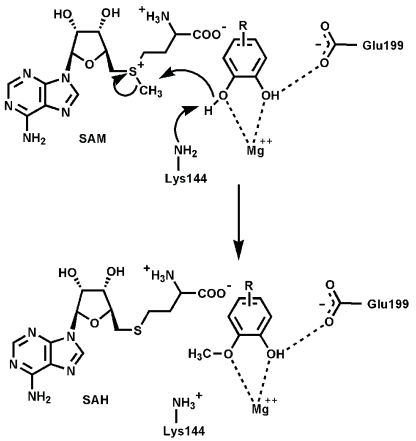
Adventures with COMT inhibition

Christian Lerner, pRED, Discovery Chemistry
F. Hoffmann-La Roche AG, Basel, Switzerland



The Target: Catechol *O*-Methyltransferase (COMT)





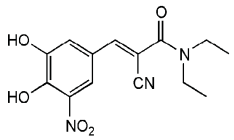
J. Vidgren, L. A. Svensson, A. Liljas, *Nature (London)* **1994**, *368*, 354-358

Catechol Substrates e.g.:

L-DOPA, dopamine, noradrenaline, adrenaline, catecholestrogens

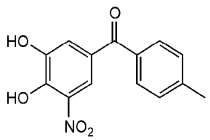
COMT inhibitors on the market for Parkinson

Monosubstrate Inhibitors



Entacapone (Comtan®)

- Novartis (Orion)
- short-lasting inhibitor
- does not enter the brain



Tolcapone (Tasmar®)

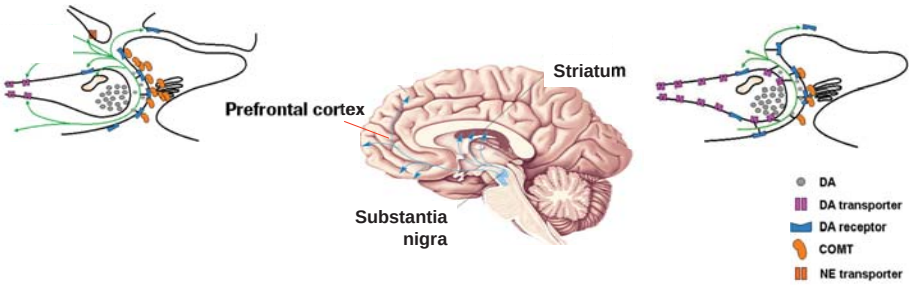
- Roche, licensed to Valeant
- long-lasting inhibitor
- inhibits brain COMT (B/P ~0.01)

Rationale for COMT inhibition in the brain

Hypofrontality in schizophrenia

In Schizophrenia:

- **Decreased dopamine** levels and dopaminergic transmission in **prefrontal cortex**
- **Increased dopamine** levels and dopaminergic transmission **in striatum**

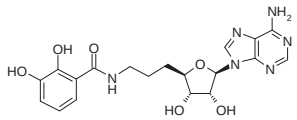


Source: D.R. Weinberger, NIH

Inhibition of COMT selectively restores dopaminergic transmission in the prefrontal cortex without worsening the exaggerated dopaminergic transmission in the striatum.

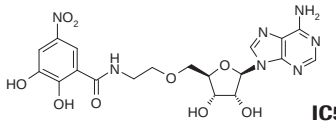
COMT bisubstrate inhibitors

The concept works



E. Pinard, Roche **1995**

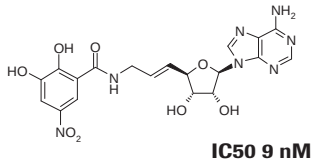
52% @ 100 µM



IC50 2 µM

B. Masjost, P. Ballmer, E. Borroni, G. Zürcher, F. K. Winkler, R. Jakob-Roetne, F. Diederich,

Chem. Eur. J. **2000,** *6*, 971.

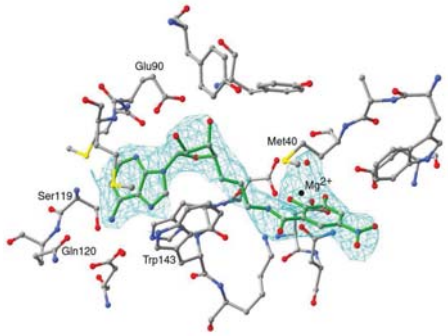


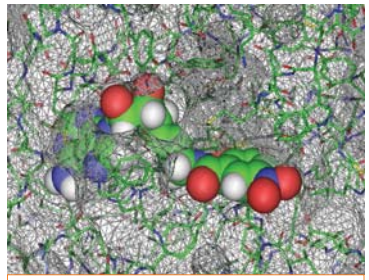
IC50 9 nM

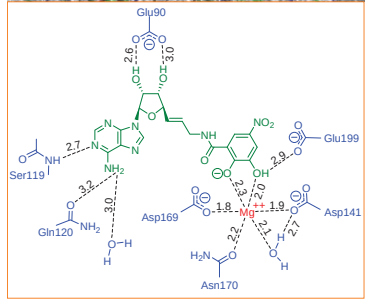
C. Lerner, A. Ruf, V. Gramlich, B. Masjost, G. Zürcher,R. Jakob-Roetne, E. Borroni, F. Diederich,
Angew. Chem. Int. Ed. **2001**, *40*, 4040.

Crystal Structure of COMT with Bisubstrate Inhibitor

Proof of bisubstrate inhibition

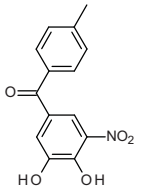




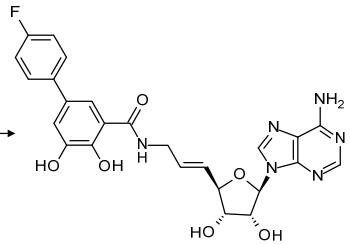


C. Lerner, A. Ruf, V. Gramlich, B. Masjost, G. Zürcher,R. Jakob-Roetne, E. Borroni, F. Diederich,
Angew. Chem. Int. Ed. **2001**, *40*, 4040.

Aim: Non-nitro COMT inhibitor active in the brain



Tolcapone
b/p = 0.01



Non-nitro nucleosidic bisubstrate inhibitors

R. Paulini, C. Lerner, R. Jakob-Roetne, G. Zürcher, E. Borroni, F. Diederich, *ChemBioChem* **2004**, *5*, 1270-1274.

logD 1.6
MW 522
ON 12
Hdon 7
PSA 154

ProtBind >99%
MAB h 37%
MAB r 23%

pH 1-10 stable
Lysa 64 ug/ml
pKa 6.9
Cyps > 50
GSH no flag

logD 2-3
MW <500
ON <10
Hdon 2-3
PSA <90

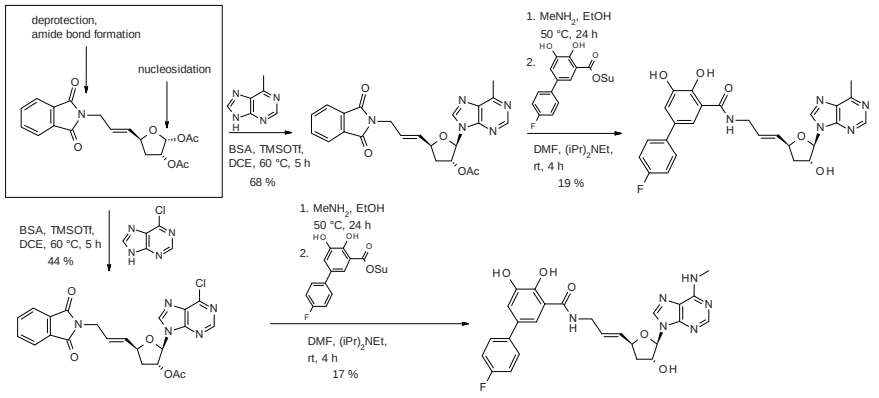
CNS drug profile

?

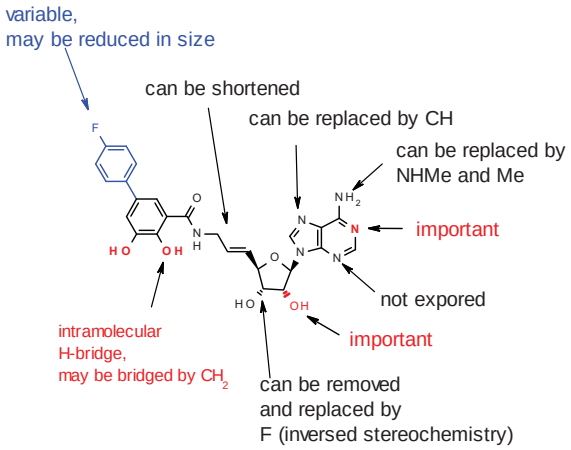
So far, no COMT inhibitor with good brain exposure is known

3'-Deoxynucleosides

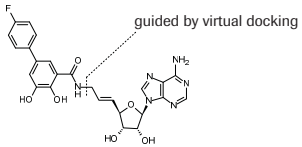
Nucleosidation, deprotection, coupling

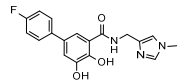


Nucleoside bisubstrate inhibitors
SAR summary

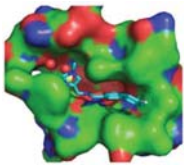


Non-nucleosidic bisubtrate inhibitors
Radical change of scaffold using parallel chemistry

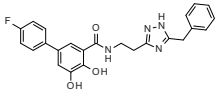




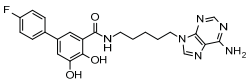
IC50 = 4.6 µM



X-ray available

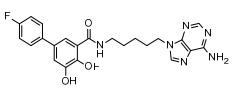


IC50 1.2 µM

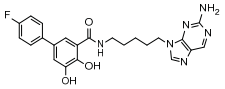


IC50 1.6 µM

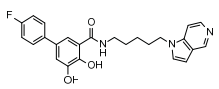
Open chain COMT bisubstrate inhibitors
Breakthrough in potency



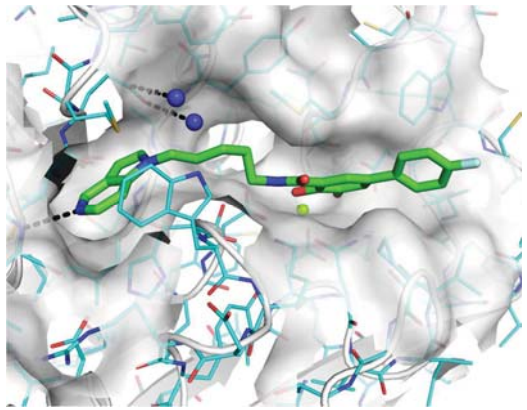
IC50 1.6 µM



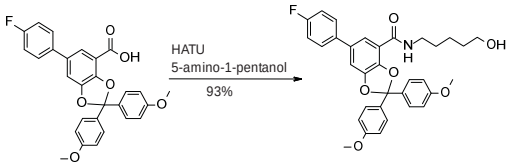
IC50 40 nM

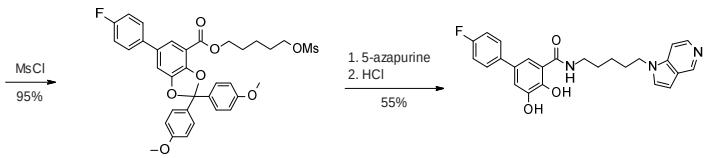


IC50 30 nM



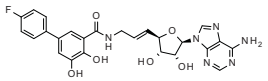
Open chain COMT bisubstrate inhibitors
Short 4 step synthesis





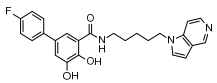
Non nucleosidic COMT bisubstrate inhibitors

Goals achieved for PSA and H-bond donors



IC50 15 nM

MW 522
pKa 6.9
PSA 155
Hdon 7 (1 intra)
logD 1.6

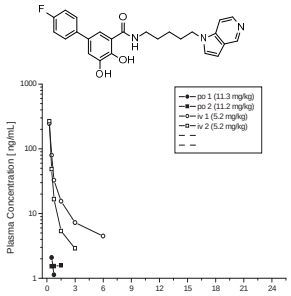


IC50 30 nM

MW 433
pKa 7.4 (calc)
PSA 69
Hdon 3 (1 intra)
logD 2.6

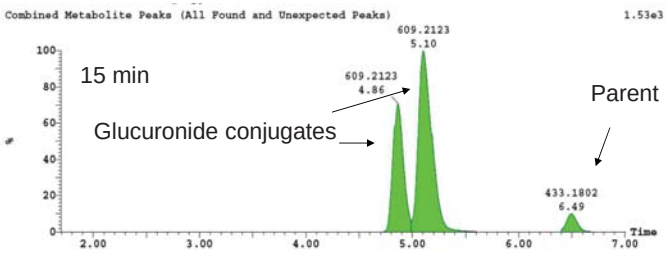
Problem to be solved

SDPK: fast glucuronidation, very high clearance



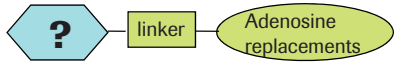
RAT

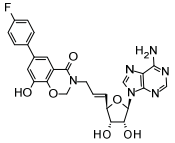
T½	0.2 - 1.8 h
CL	330 mL/min/kg (HIGH)
CLpred	62 mL/min/kg (high)
CLmic	110 µL/min/mg (high)
Vss	13.6 L/kg (HIGH)
F	0.3% (predicted 30%)
B/P	<0.17 (predicted 0.6)



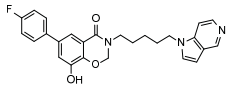
Search for catechol replacements

Discovery of a novel catechol site inhibitor

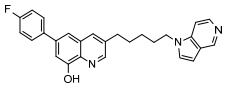




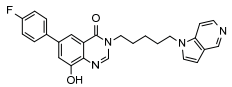
IC50 = 66 nM



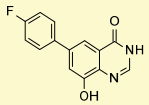
IC50 = 7.5 µM



IC50 = 4 µM



IC50 = 387 nM

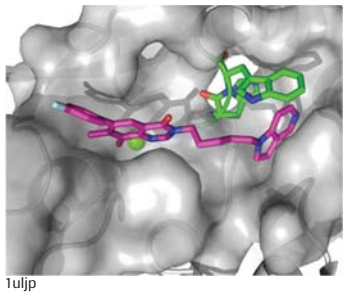


IC50 = 17 nM
MW = 256, LE = 0.6

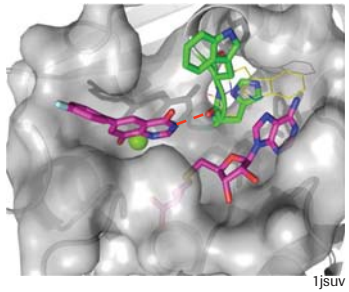
Hydroxyquinazolinone series

A novel lead structure to inhibit COMT

Essential H-bond to backbone



1uljp



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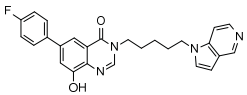
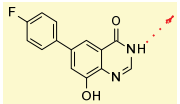


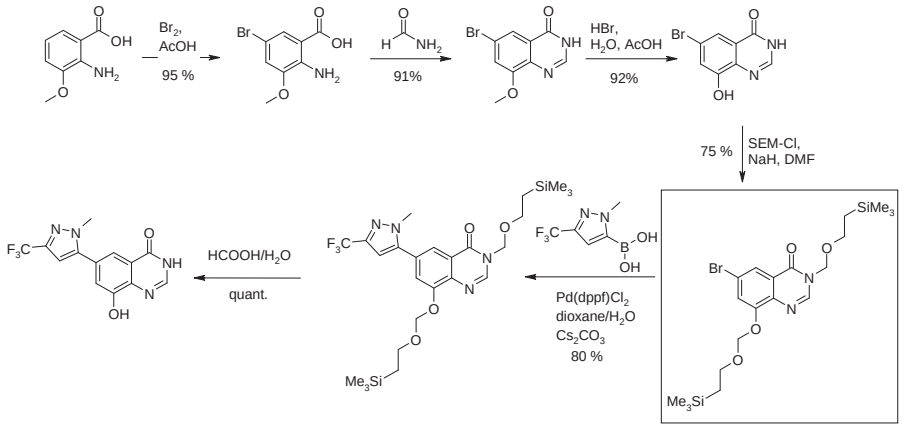
IC50 = 387 nM



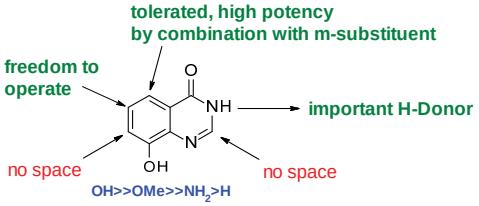
IC50 = 17 nM

Synthesis

Modification of exit vector in last steps

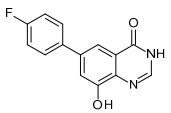


SAR summary Hydroxyquinazolinones

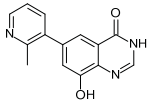


Properties of selected examples

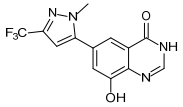
Acceptable, except for high hepatocyte clearance



IC50 17 nM
PSA54
Hdon 2
logD 2.7
pKa 8.0(a)
CYPs >50
PAMPA 52 % membr.
4 % accept.
Solubility LYSA < 1
MAB h 68%, r 20%
CL hepatocytes h 150
r 130



IC50 41 nM
PSA68
Hdon 2
clogP 1.1, logD na
pKa 4.9(b), 8.7(a)
CYPs >50
PAMPA 79 % membr.
14 % accept.
Solubility pSOL 100 µg/ml
MAB h 87%, r 59%
CL hepatocytes h 68
r 144

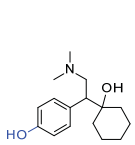


IC50 16 nM
PSA74
Hdon 2
logD 2.3
pKa 2.7(b), 7.6(a)
CYPs >50
PAMPA 22 % membr.
11 % accept.
Solubility LYSA 30 µg/ml
MAB h 84%, r 76%
CL hepatocytes h 137
r unstable

➢ stabilization of phenolic inhibitors = mission impossible ?

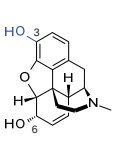
Marketed phenolic drugs

How are these phenoles stabilized ?



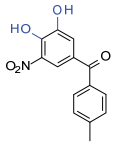
Desvenlafaxine

antidepressant (Wyeth)
F = 80%, t1/2 = 14-18 h
brain penetrant



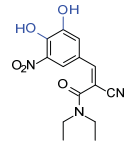
Morphine

analgesic
F = 25%, t1/2 = 2-3 h
morphine-6-glucuronide
active metabolite
brain penetrant



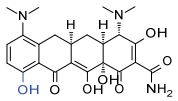
Tolcapone

COMT inhibitor (Roche/Valeant)
F = 65%, t1/2 = 2-3.5 h
limited (1%) brain penetration



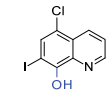
Entecapone

COMT inhibitor (Orion/Novartis)
F = 35%, t1/2 = 0.4-0.7 h



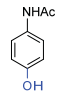
Minocycline

antibiotic
F = 100%, t1/2 = 11-22 h
brain penetrant !
B/P = 0.3



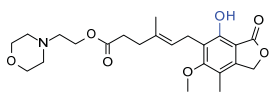
Clioquinol

antifungal
F = 8%, t1/2 = 7 h
brain penetrant



Paracetamol

analgesic
F = 100%, t1/2 = 1-4 h
brain penetrant



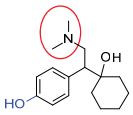
Cellcept (mycophenolic acid prodrug)

immunosuppressant (Syntex/Roche)
F = 94%, t1/2 = 16-18 h
glucuronidation and enterohepatic recycling
of the parent acid

▪ 8% of the structures in the top 200 pharma product list 2009 contain phenoles

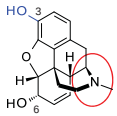
Marketed phenolic drugs

Presence of basic centers



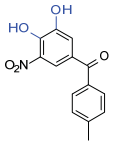
Desvenlafaxine

antidepressant (Wyeth)
F = 80%, t1/2 = 14-18 h
brain penetrant



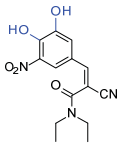
Morphine

analgesic
F = 25%, t1/2 = 2-3 h
morphine-6-glucuronide
active metabolite
brain penetrant



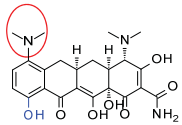
Tolcapone

COMT inhibitor (Roche/Valeant)
F = 65%, t1/2 = 2-3.5 h
limited (1%) brain penetration



Entecapone

COMT inhibitor (Orion/Novartis)
F = 35%, t1/2 = 0.4-0.7 h



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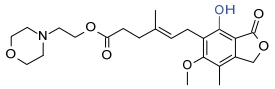
antibiotic
F = 100%, t1/2 = 11-22 h
brain penetrant !
B/P = 0.3

Clioquinol

antifungal
F = 8%, t1/2 = 7 h
brain penetrant

Paracetamol

analgesic
F = 100%, t1/2 = 1-4 h
brain penetrant



Cellcept (mycophenolic acid prodrug)

immunosuppressant (Syntex/Roche)
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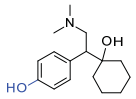
glucuronidation and enterohepatic recycling
of the parent acid

Marketed phenolic drugs

Increased acidity



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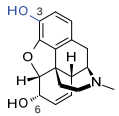
antidepressant (Wyeth)
F = 80%, t1/2 = 14-18 h
brain penetrant



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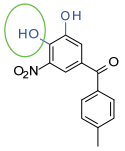
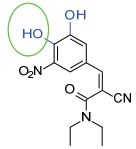
analgesic
F = 25%, t1/2 = 2-3 h
morphine-6-glucuronide
active metabolite
brain penetrant



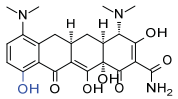
Tolcapone

COMT inhibitor (Roche/Valeant)
F = 65%, t1/2 = 2-3.5 h
limited (1%) brain penetration



Entecapone

COMT inhibitor (Orion/Novartis)
F = 35%, t1/2 = 0.4-0.7 h



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antibiotic
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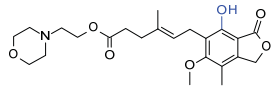
brain penetrant !
B/P = 0.3

Clioquinol

antifungal
F = 8%, t1/2 = 7 h
brain penetrant

Paracetamol

analgesic
F = 100%, t1/2 = 1-4 h
brain penetrant

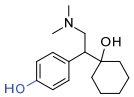


Cellcept (mycophenolic acid prodrug)

immunosuppressant (Syntex/Roche)
F = 94%, t1/2 = 16-18 h
glucuronidation and enterohepatic recycling
of the parent acid

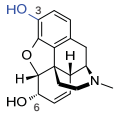
Marketed phenolic drugs

Steric hinderance



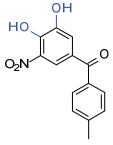
Desvenlafaxine

antidepressant (Wyeth)
F = 80%, t1/2 = 14-18 h
brain penetrant



Morphine

analgesic
F = 25%, t1/2 = 2-3 h
morphine-6-glucuronide
active metabolite
brain penetrant



Tolcapone

COMT inhibitor (Roche/Valeant)
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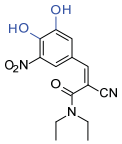
limited (1%) brain penetration



Entecapone

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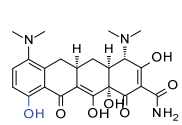
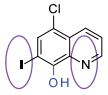


Minocycline

antibiotic
F = 100%, t1/2 = 11-22 h
brain penetrant !
B/P = 0.3

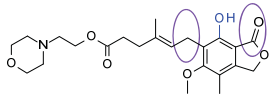


Clioquinol

antifungal
F = 8%, t1/2 = 7 h
brain penetrant

Paracetamol

analgesic
F = 100%, t1/2 = 1-4 h
brain penetrant



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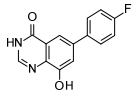
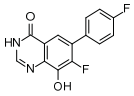
F = 94%, t1/2 = 16-18 h
glucuronidation and enterohepatic recycling
of the parent acid

Microsome incubations with UDP-glucuronic acid

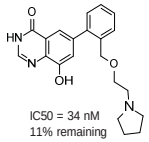
Glucuronidation problem solved ?



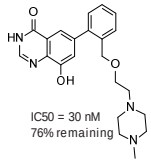
IC50 = 17 nM
7% remaining



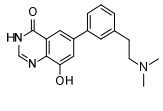
IC50 = 20 nM
0% remaining



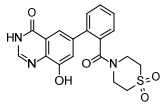
IC50 = 34 nM
11% remaining



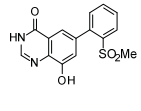
IC50 = 30 nM
76% remaining



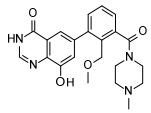
IC50 = 50 nM
74% remaining



IC50 = 730 nM
100% remaining



IC50 = 870 nM
79% remaining



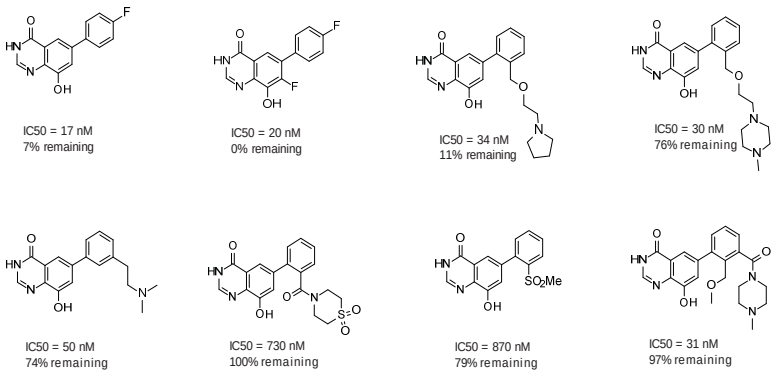
IC50 = 31 nM
97% remaining

after 30 min

- basic side chains and polar ortho-substituents stabilize molecules towards glucuronidation

Microsome incubations with UDP-glucuronic acid

Glucuronidation problem solved ?

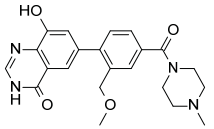


after 30 min

- basic side chains and polar ortho-substituents stabilize molecules towards glucuronidation

8-Hydroxy-quinazolinones

Key compounds

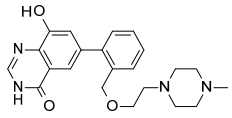


IC_{50} = 13 nM

MAB h100 r87
rHep CL 21 (FH 37%)
Plasma 100% (stable)
fu 54%

30 mg/kg po: after 15 min
exposure 0 - 7 ng/ml
20 mg/kg sc: after 30 min
exposure 1053 ng/ml

Weak liver COMT inhibition
No brain COMT inhibition



IC_{50} = 30 nM

MAB h93
rHep CL 35 (FH 26%)
Plasma 100% (stable)

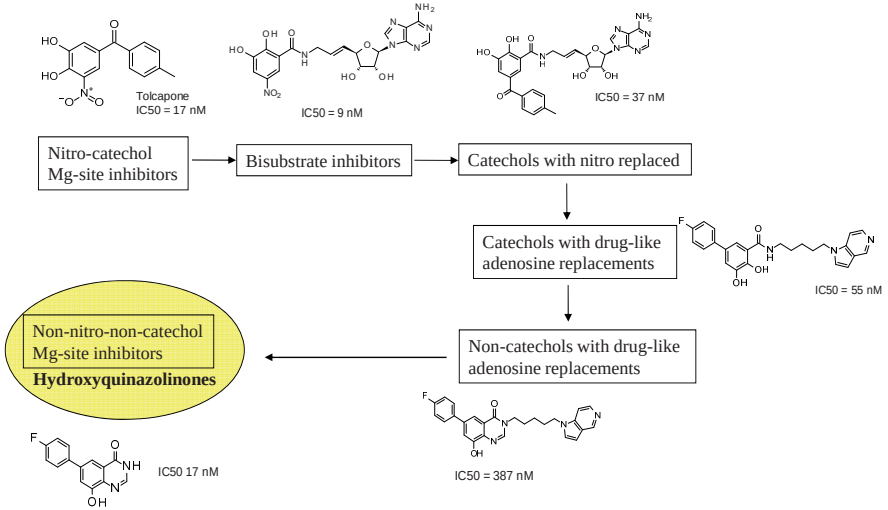
30 mg/kg po: after 15 min
exposure 450 ng/ml
34 ng/mL after 30 min
3.7 mg/kg iv: after 30 min
exposure 1000 ng/ml

Weak liver COMT inhibition
No brain COMT inhibition

High exposure reached after sc and iv administration,
but *ex vivo* only weak liver and no brain COMT inhibition observed.

Adventures with COMT

Journey from Nitrocatechols to Hydroxyquinazolines



Acknowledgements

Discovery Chemistry
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Peter Weber
Christian Lerner
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Bernd Büttelmann
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Caterina Bissantz (modeling)

DMPK
Rodolfo Gasser
Gerhard Zürcher
Martin Kapps

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Doris Roth (screening, assay development)
Pia Warga
Philippe Hartz
Alain Gast (screening)
Francis Hermann
Daniel Schlatter (protein supply)
Martin Weber
Daniela Hügin

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(nucleosidic bisubstrate inhibitors)