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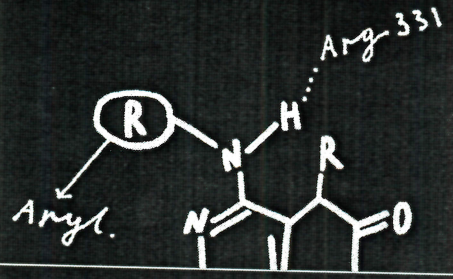
#RESEARCHNEVERSTOPS

Identification of novel, selective and developable D3 antagonists through the modification of the "amino" region



IASOC 2018

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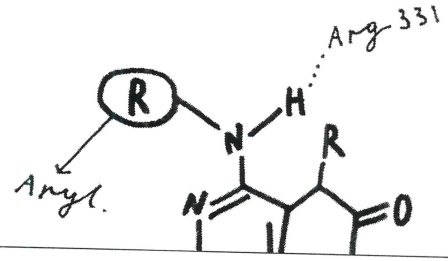
Synopsis

The target

The starting points

The quest for developability

The latest results



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Unmet Medical Needs in the Drug Dependence Area

Significant room for improvement exists

Efficacy	Safety	Comorbidity
Short-term quit rates and efficacy in long-term abstinence.	No CV, CNS and GI side effects.	Treatment of both drug and alcohol dependence.
Immediate effect on cravings and withdrawal symptoms.	Chronic administration with no tolerance effects.	Treatment of psychiatric comorbidities.
Use in abuse or dependence of multiple substances (cocaine, heroin, marijuana, alcohol, etc.).	No liver or kidney toxicity.	
More rapid onset of effect.	No abuse liability (non scheduling).	
Shorter overall treatment period.		

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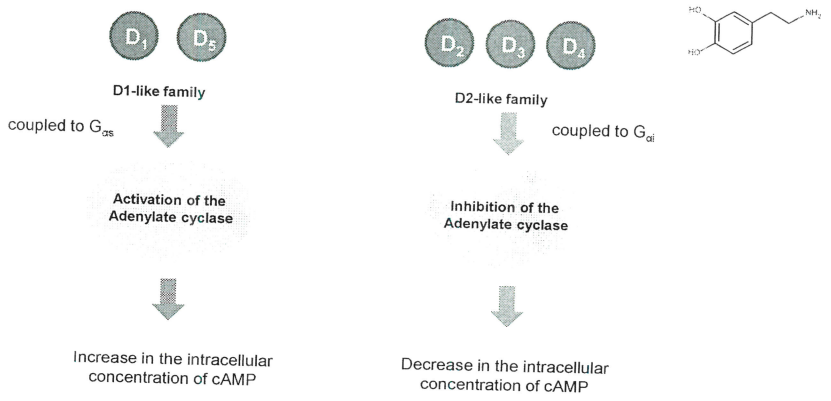
Dopamine (DA) receptor subtypes

Just a reminder...



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Distribution of the target

And expression in disease tissues

- Contrary to DA D1 and D2 receptors, DA D3 receptors are expressed preferentially in granule cells of the islands of Calleja and in medium-sized spiny neurons of the rostral and ventromedial shell of the NAc, regions in which the D2 receptors are scarcely expressed (Gurevitch and Joyce, 1999)
- The distribution of the D3 receptor in the human brain appears to follow a rather similar pattern to that observed in the rat brain (Hall et al., 1996; Shafer and Levant, 1998; Suzuki et al., 1998; Gurevich and Joyce, 1999)
- The density of DA D3 receptors is elevated one-to-threefold in the NAc and ventromedial subregions of the caudate-putamen in the brains of cocaine overdose fatalities compared with both age-matched, drug-free control subjects and cocaine overdose victims presenting pre-terminal excited delirium (Staley and Mash, 1996; Mash and Staley, 1999)
- The expression of DA D3 receptor mRNA in the human NAc is increased six-fold in cocaine overdose victims (Segal et al., 1997)

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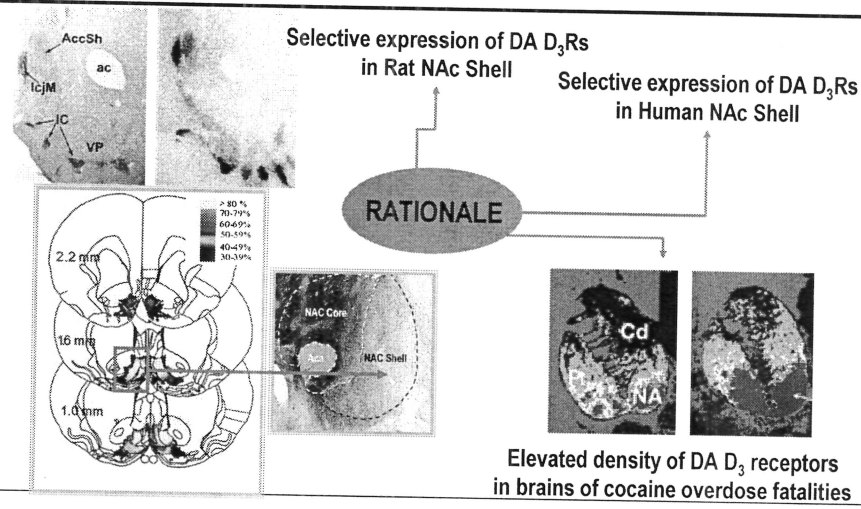
Selective DA D3 receptor antagonists

A target for drug dependence



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What selective DA D3 antagonists CAN do

- Prevent cue/drug/stress induced reinstatement of extinguished self-administration in rats
  - A model of induced-relapse
- Reduce time spent in the place of drug supply (CPP)
  - A model of drug-seeking behaviour specifically evoked by the incentive salience acquired by environmental cues
- Decrease the "break-point" in progressive ratio schedule paradigms for drugs in rodent
  - A model of incentive motivation
  - (how hard one is willing to work to obtain the drug once quit)
- Do not effect acquisition of drug dependence in rodents
  - Does not appear to directly effect initial rewarding properties

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What selective DA D3 antagonists WILL NOT do

- **do not** produce any significant effect on spontaneous locomotion and motor coordination
- **do not** induce catalepsies;
- **do not** alter sexual activity/motivation
- **do not** produce conditioned place aversion;
- **are not** negative reinforcers
- **are not** self-administered
- **do not** alter natural reinforcers
  - e.g. food, sucrose etc.

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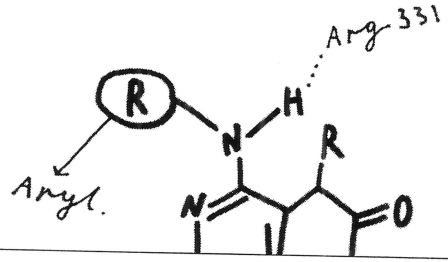

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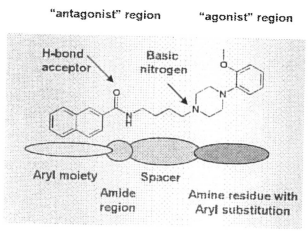
The starting points

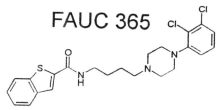
The "known" at the start of the project

- Some example of "selective" DA D3 receptor antagonists

BP 897



FAUC 365



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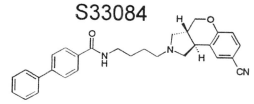

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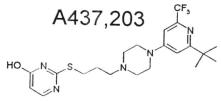

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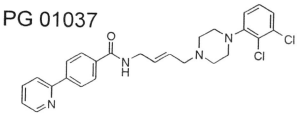
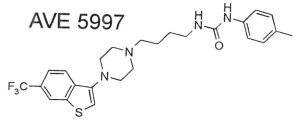
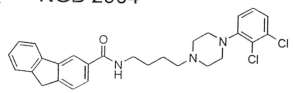


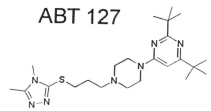
AVE 5997



NGB 2904



ABT 127



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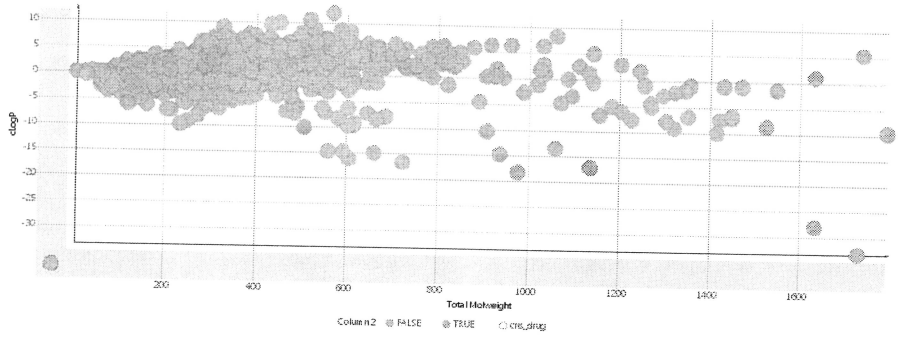
FDA Approved oral drugs chemical space

CNS vs non-CNS



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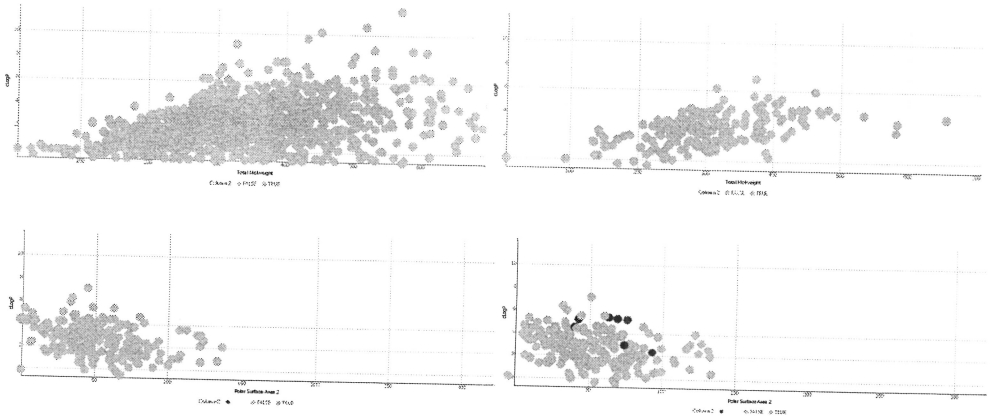
Cutting MW and focusing on other properties

non-CNS drugs vs CNS / CNS vs Unknows



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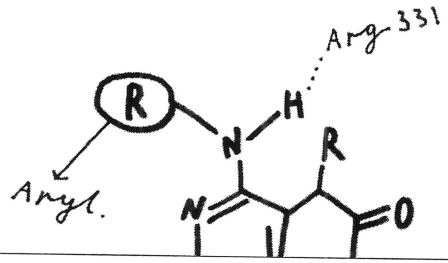

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The quest for developability

DA D3 receptor antagonists - the GSK evolution

SB-277011

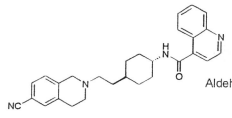
J. Pharmacol. Exp. Ther. **2000**, *294*, 1154-65

Potent and Selective DA D_3 antagonist

Robust activity in animal models

D_3(fpKi)/D_2 (fpKi)/ hERG (pIC_{50})

8.4/6.4/5.7



Aldehyde oxidase liability

Potential Isoquinolinium metabolite formation

SB-414796

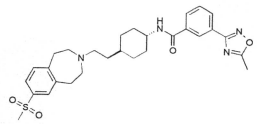
J. Med. Chem. **2003**, *46*, 4952–64

Potent and Selective DA D_3 antagonist

Robust activity in animal models

D_3(fpKi)/D_2 (fpKi)/ hERG (pIC_{50})

9.2/6.1/5.6



QTc prolongation in dog

Increased BP & HR in dog

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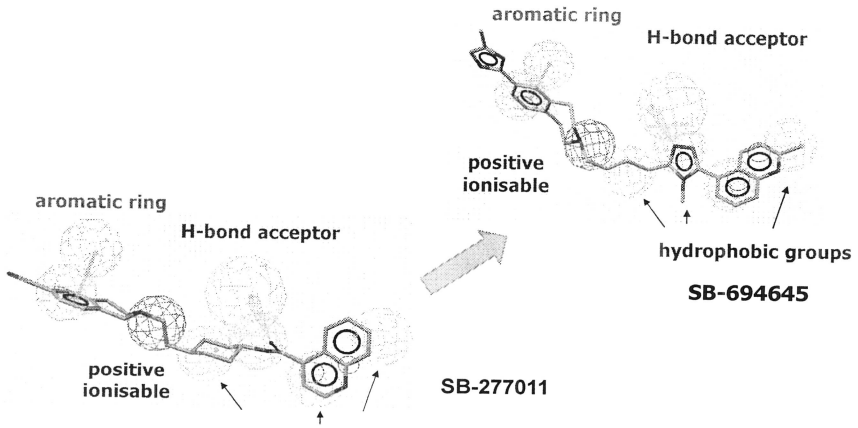
The identification of alternative templates

The DA D3 pharmacophore model –> scaffold "evolution"



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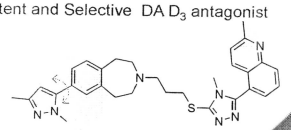
GSK Benzo-azepine scaffold

Scaffold evolution

Improvement of the BAZ system: the thiotriazole

J. Med. Chem **2007**, *50*, 5076-5089

Potent and Selective DA D_3 antagonist



D_3(fpKi)/D_2 (fpKi)/ hERG (pIC_{50})

8.8/6.5/5.7

Excellent Potency & Selectivity

Lower hERG inhibition & no QTc

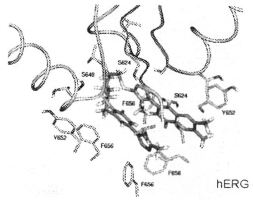
High brain penetration

No Cyp450 issue

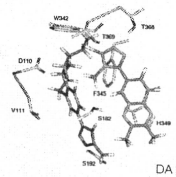
Good PK in rat and dog

Robust activity in animal models

Parallel SAR: DA D_3 and hERG, but . .



hERG channel model

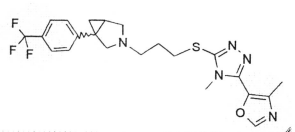


DA D3 receptor model

The GSK azabicyclo[3.1.0]hexane template

A metabolically stable and highly "developable" template

Potent and Selective DA D_3 antagonist

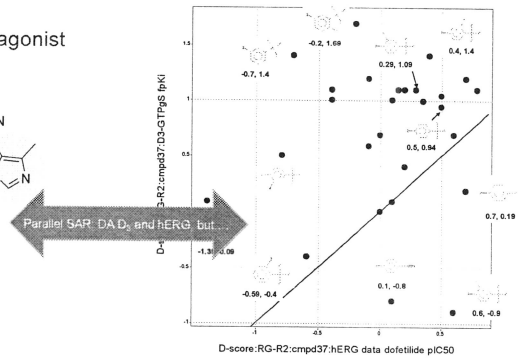


J. Med. Chem **2010**, *53*, 374-391

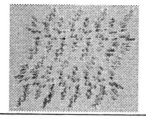
$D_3(fpKi)/D_2$ *(fpKi)/ hERG* (pIC_{50})

9.0/7.0/6.1

Excellent Potency & Selectivity
Low hERG inhibition & no QTc
High brain penetration
No Cyp450 issue
Good PK in preclinical species

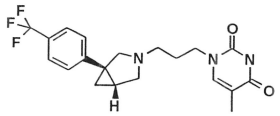


One enantiomer is more active
Than the other one



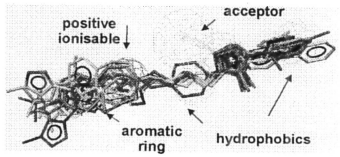
GSK work on the "right hand-side"

Are new cores tolerated?

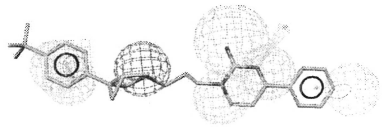


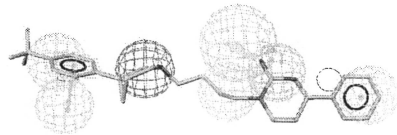
$D_3(fpKi)/D_2$ *(fpKi)/ hERG* (pIC_{50})

8.0/6.5/6.0



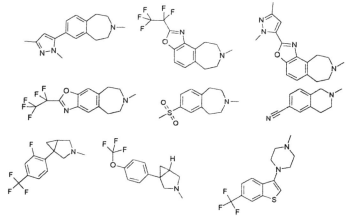
Fit ?

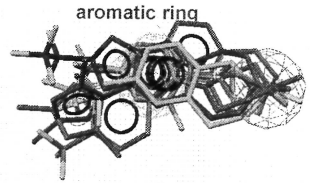


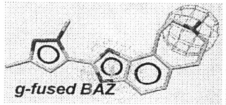


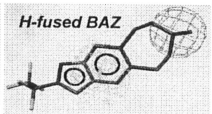
GSK work on the "left hand-side"

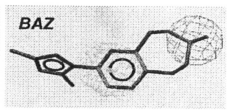
Can we change the "tail" of the system?

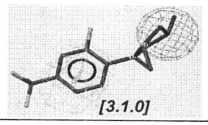


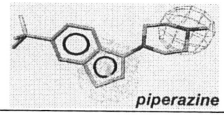


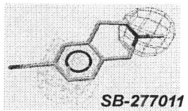






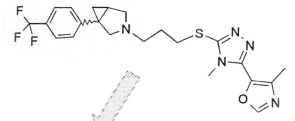






The GSK exploration of the amine portion

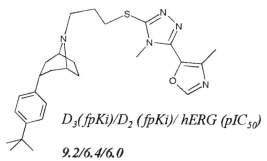
Is there room for maneuver?



J. Med. Chem. **2010**, *53*, 7129-7139

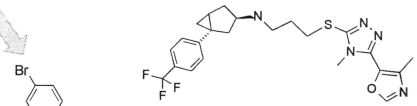
Excellent Potency & Selectivity

High brain penetration



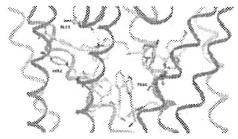
$D_3(fpKi)/D_2$ *(fpKi)/ hERG* (pIC_{50})

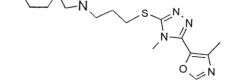
9.2/6.4/6.0



$D_3(fpKi)/D_2$ *(fpKi)/ hERG* (pIC_{50})

8.4/6.3/6.2





$D_3(fpKi)/D_2$ *(fpKi)/ hERG* (pIC_{50})

8.1/6.3/6.2

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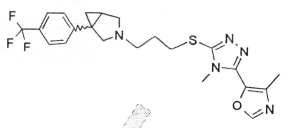
Additional GSK work in the amine region

Further templates are tolerated



J. Med. Chem. **2010**, *53*, 7129-7139

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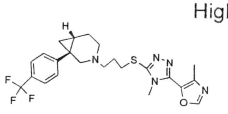
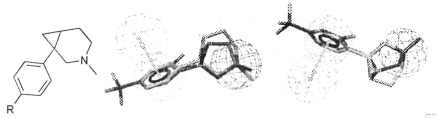
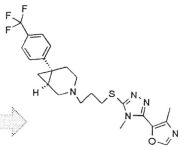


$D_3(fpKi)/D_2\ (fpKi)/\ hERG\ (pIC_{50})$

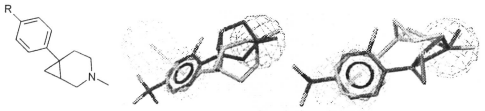
8.1/6.3/5.7

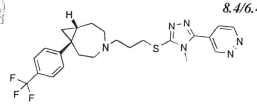




$D_3(fpKi)/D_2\ (fpKi)/\ hERG\ (pIC_{50})$

7.4/6.5/6.1





$D_3(fpKi)/D_2\ (fpKi)/\ hERG\ (pIC_{50})$

8.4/6.4/5.3

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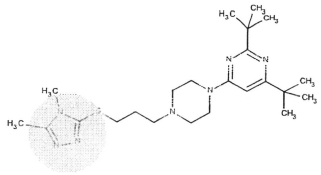
The turn of the tide

Clinical candidates

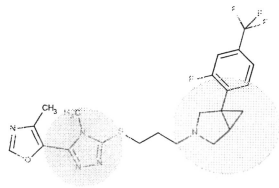


MW 445.6; 6 HBA; 0 HBD; 8 rot.bonds; PSA 64.2; clogP 5.3

ABT-127, 35th annual meeting neuroscience, Washington, 2005

The FASEB Journal. 2006;20:A1109

ABT-127 is a novel and orally efficacious dopamine D3-selective antagonist targeted for the treatment of schizophrenia (pre-clinical efficacious Cmax in a rat model of social interaction = 50 ng/mL) and is hypothesized to produce fewer cardiovascular effects than classical or atypical antipsychotics that target multiple receptors. ..... ABT-127 produced no increase in the QT-interval corrected for changes in heart rate (QTc) at any concentration tested (up to 3.36 µg/mL; 67-fold the Cmax). In contrast, both classical and atypical antipsychotics have been shown to produce dose-dependent hemodynamic and electrocardiographic effects (increases in QTc) in the same model and in patients.



MW 481.5; 4 HBA; 0 HBD; 8 rot.bonds; PSA 61.2; clogP 3.2

GSK598809, J. Med. Chem. 2010, 53, 374

J. Med. Chem. 2010, 53, 374

.....In agreement with our screening cascade, derivatives **27**,**28**, **32**, and **74** were all evaluated for their ability to determine QTc prolongation in vivo when assessed in the anesthetized guinea pig model. All of the compounds were administered intravenously in escalating doses from 0.5 to 15 mg/kg. Despite the very high exposure reached at the top dose of 15 mg/kg (Cmax=6237, 9577, 8322, and 8635 ng/mL for **27**, **28**, **32**, and **74**, respectively), the QTc interval was not significantly increased in the guinea pig model by any of the derivatives. Thus, there is a large window between the efficacy and the potential side effects that was obtained in preclinical species for these derivatives.

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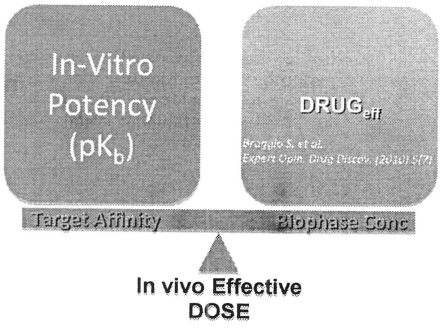
The concept of "Drug Efficiency"

The need of delivering the molecules to the target



Perspective

Expert Opinion

Drug efficiency: a new concept to guide lead optimization programs towards the selection of better clinical candidates

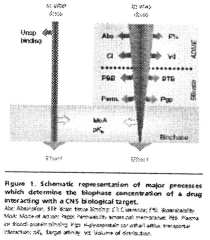


Figure 1. Schematic representation of major processes which determine the biophase concentration of a drug interacting with a CNS biological target.

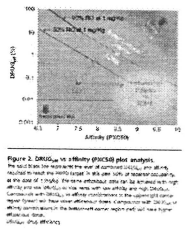


Figure 2. $DRUG_{eff}$ vs affinity (FSCSA) plot analysis.

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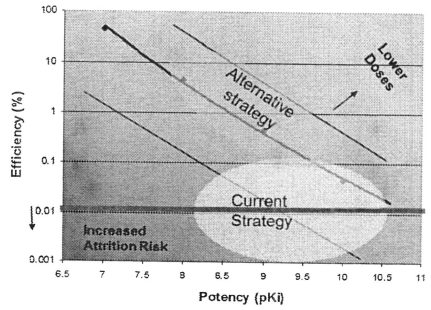
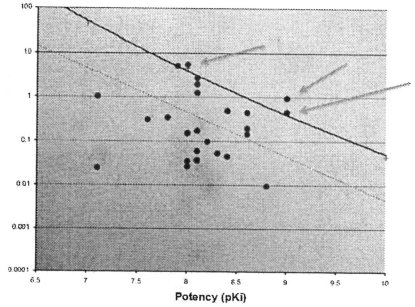
Applying developability and "drug efficiency"

J. Med. Chem. 2010, 53, 374





Some of the DA D3 antagonists reported in J. Med. Chem. 2010, 53, 374

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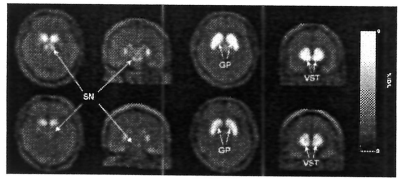
Effect of a selective DA D_3 antag. dosed in humans

The human PoC



[^{11}C]-(+)-PHNO integral images (summed over 10-90 min.) at baseline (top row) and after administration of 175 mg the compound (bottom row). Slices are selected to illustrate the marked change in SN, moderate change in GP and VST, and marginal change in dorsal striatal regions.

Laruelle M. et al – Biological Psychiatry (2010), 68(4), 392-399 and NeuroImage (2011), 54(1), 264-277

Neuropsychopharmacology (2012), 1–11
www.neuropsychopharmacology.org

Occupancy of Brain Dopamine D_3 Receptors and Drug Craving: A Translational Approach

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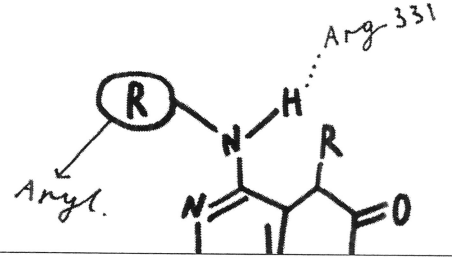
Synopsis

The target

The starting points

The quest for developability

The latest results



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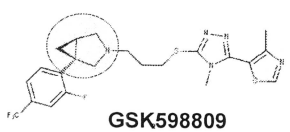
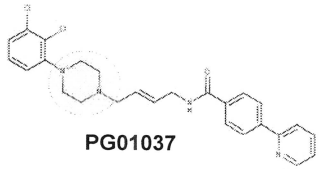
The latest results

2014 – the status of the art



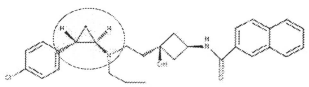
GSK598809



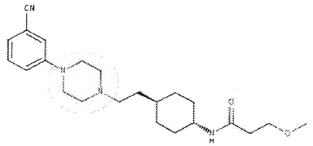
PG01037

J. Med. Chem **2010**, *53*, 374-391

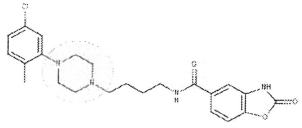
D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
9.0 / 7.0 / 6.1



CJ-1882



BioProjet 1.4979



YQA14

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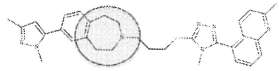
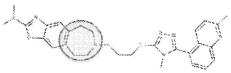
The compound with modified amino region

The GSK derivatives



J. Med. Chem **2007**, *50*, 5076-5089

D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
8.0/ 6.5 / 5.7



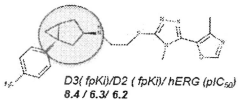
BMCL **2008**, *18*, 901-907

D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
9.0 / < 6.3 / 4.7

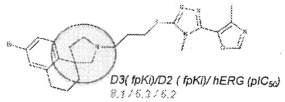
BMCL **2008**, *18*, 908-912

D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
9.0 / < 6.3 / 5.7

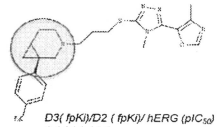
J. Med. Chem **2010**, *53*, 7129-7139



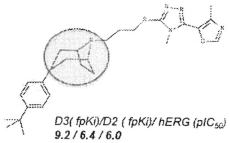
D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
8.4 / 6.3/ 6.2



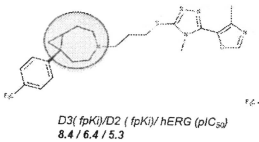
D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
8.1 / 6.3 / 6.2



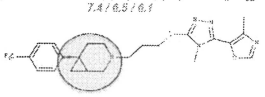
D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
8.1 / 6.3 / 5.7



D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
9.2 / 6.4 / 6.0



D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
8.4 / 6.4 / 5.3



D3(fpKi)/D2 (fpKi)/ hERG (pIC_{50})
7.4 / 6.5 / 6.1

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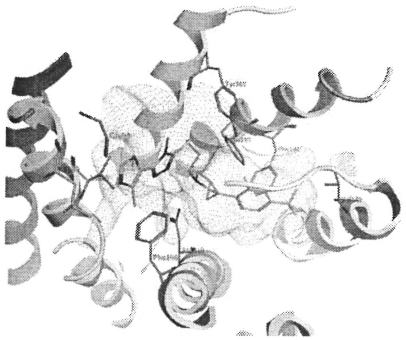
New alternative "amino region" scaffolds

New key info available & a request for novel templates

- Additional info available ?
  - Appropriate basicity to interact with $Asp^{3.32}$ in the orthosteric binding site (Science, 2010, 330, 1091).
  - Contribute to the overall selectivity of the molecule vs. the DA D2 receptor i.e. capability to direct the molecule in the SBP near the 2nd EL (Mol Pharmacol 84:854–864, December 2013)
- The needs ?
  - "Novelty" in a very complex IP environment
  - Further "developability" to be progressed up to clinical trials



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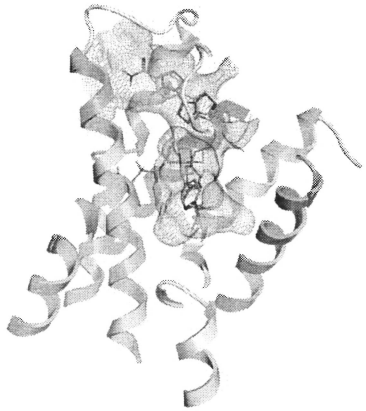
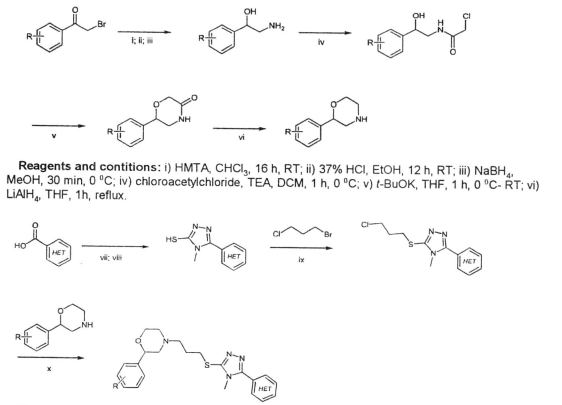
The morpholine scaffold

Keep it as simple as possible





Reagents and contitions: i) HMTA, $CHCl_3$, 16 h, RT; ii) 37% HCl, EtOH, 12 h, RT; iii) $NaBH_4$, MeOH, 30 min, 0 °C; iv) chloroacetylchloride, TEA, DCM, 1 h, 0 °C; v) *t*-BuOK, THF, 1 h, 0 °C- RT; vi) $LiAlH_4$, THF, 1h, reflux.

Reagents and contitions: vii) T3P in AcOEt, 4-methyl-3-thiosemicarbazide, DIPEA, DMF, 12h, RT; viii) 4M NaOH, 40 min, reflux; ix) K_2CO_3, methanol/acetone, 12 h, RT; x) Na_2CO_3, NaI, DMF, 12 h, 60 °C.

BMCL, 26 (2016) 1329–1332

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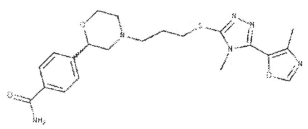
Some morpholine examples

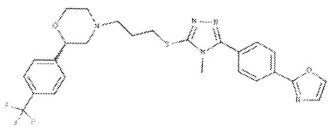
Good potency and selectivity over the hERG channel



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer (Unknown absolute stereochemistry)
7.8 / 4.9 / 5.2

D3(fpKi)
8.2

Δ D3 fpKi – hERG pIC_{50} = **1000 fold**



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer (Unknown absolute stereochemistry)
8.2 / 5.3 / 5.9

D3(fpKi)
8.5

Δ D3 fpKi – hERG pIC_{50} = **400 fold**

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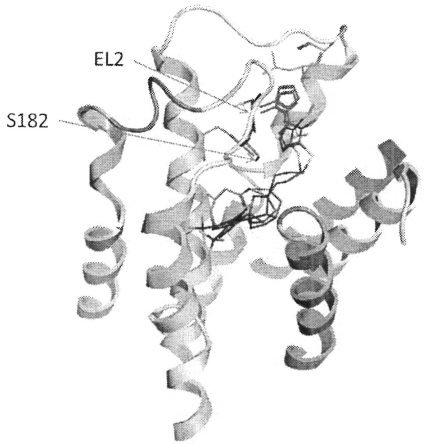
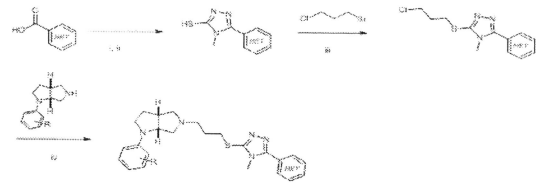
Octahydropyrrolo[2,3-b]pyrroles

Fused structures





i: 4-methyl-3-thiosemicarbazide, T3P in AcOEt, DIPEA, DMF, 0 °C–RT, Overnight; ii: NaOH, 70 °C, 1-4 h; iii: K_2CO_3, acetone/MeOH, RT, 3-12 h; iv: Na_2CO_3, NaI, DMF or CH_3CN, 60 °C, Overnight

BMC, 24 (2016) 1619–1636

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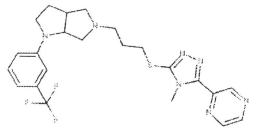
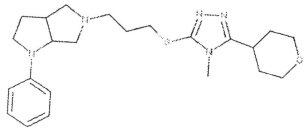
Octahydropyrrolo[2,3-b]pyrroles examples

Potency, selectivity and hERG therapeutic window

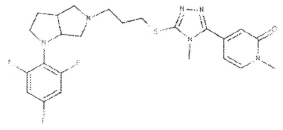


D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer (Unknown absolute stereochemistry)
9.7 / 7.5 / > 7
Δ D3 pKi – hERG pIC_{50} = **100 fold**



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer (Unknown absolute stereochemistry)
8.2 / 6.1 / 5.5
Δ D3 pKi – hERG pIC_{50} = **500 fold**

Blood Fub = 31% Brain Fub = 43%



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer (Unknown absolute stereochemistry)
8.4/ 6.0 / 5.2
Δ D3 pKi – hERG pIC_{50} = 1580 fold

Rat *in vivo* parameters:
Fa = 54%, Eh = 0.6. $T_{1/2}$ = 0.6 h, Vss = 2.6 l/kg, Clb = 73 ml/min/kg; F = 29%

Blood Fub = 22% Brain Fub = 42%

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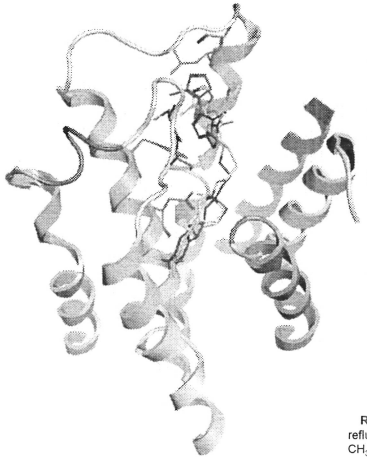
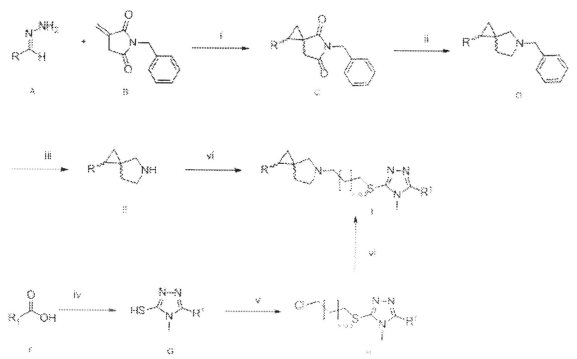
5-Azaspiro[2.4]heptanes

Potency, selectivity and hERG therapeutic window





Reagents and contitions: i: MnO_2, dioxane, RT; ii: 2M $LiAlH_4$ THF, reflux; iii: H_2, NH_4COOH, Pd/C, MeOH, reflux; iv: T3P in AcOEt, 4-methyl-3-thiosemicarbazide, NaOH; v: K_2CO_3/acetone, RT; vi: Na_2CO_3, NaI, DMF or CH_3CN, 60 °C.

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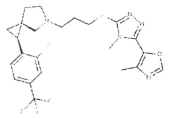
5-Azaspiro[2.4]heptanes examples

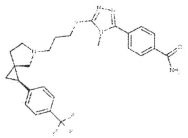
Spiro systems



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer (Unknown absolute stereochemistry)
8.2 / 6.0 / 6.3 *D3(fpKi)* 8.2
Δ D3 fpKi – hERG pIC_{50} = **80 fold**

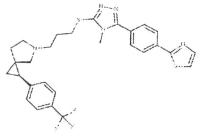
Rat *in vivo* parameters:
Fa = 70%, Eh = 0.3. $T_{1/2}$ = 2.3 h, Vss = 4.9 l/kg, Clb = 33 ml/min/kg; F = 49%

Blood Fub = 7.9% Brain Fub = 4.4%



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer
9.8 / 6.5 / 6.1 *D3(fpKi)* 9.4
Δ D3 fpKi – hERG pIC_{50} = 1260 fold

Blood Fub = 3.7% Brain Fub = 6.7%



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer
10.2 / 6.4 / 6.8 *D3(fpKi)* 9.7 *(0.06 nM or 60 pM in binding)*
Δ D3 fpKi – hERG pIC_{50} = 800 fold

Blood Fub = 1.2 % Brain Fub = 1.0%

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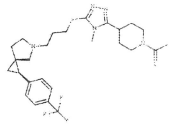
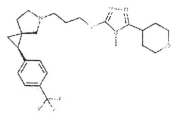
Further derivatives in the spyro system

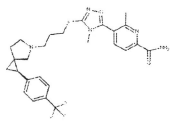
5-Azaspiro[2.4]heptanes examples



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer ***8.1 / 6.0 / 5.5*** *D3(fpKi)* 8.6
Δ D3 fpKi – hERG pIC_{50} = 1260 fold
Rat *in vivo* parameters:
Fa = 28%, Eh = 0.0. $T_{1/2}$ = 2.5 h, Vss = 6.0 l/kg, Clb = 40 ml/min/kg; F = 33%
Blood Fub = 12% Brain Fub = 20%



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer ***8.8 / 6.1 / 5.5*** *D3(fpKi)* 8.8
Δ D3 fpKi – hERG pIC_{50} = 2000 fold
Rat *in vivo* parameters:
Fa = 57%, Eh = 0.8. $T_{1/2}$ = 0.6 h, Vss = 3.7 l/kg, Clb = 87 ml/min/kg; F = 11%
Blood Fub = 9.8% Brain Fub = 18.8%



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer ***8.9 / 5.9 / 5.6*** *D3(fpKi)* 9.2
Δ D3 fpKi – hERG pIC_{50} = 3980 fold
Rat *in vivo* parameters:
Fa = 54%, Eh = 0.3. $T_{1/2}$ = 4.4 h, Vss = 5.5 l/kg, Clb = 21 ml/min/kg; F = 53%
Blood Fub = 7.8% Brain Fub = 19%

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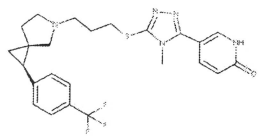
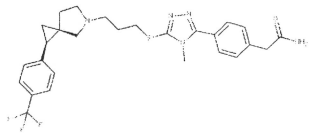
Additional spyro derivatives

5-Azaspiro[2.4]heptanes examples



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer 8.7 / 6.5 / 5.0
Δ D3 pKi – hERG pIC_{50} = 5000 fold

Blood Fub = 8% Brain Fub = 19%



D3(pKi)/D2 (pKi)/ hERG (pIC_{50})
Single enantiomer 9.1 / 6.3 / 5.1
Δ D3 pKi – hERG pIC_{50} = 10000 fold

Blood Fub = 5.2% Brain Fub = 14.1%

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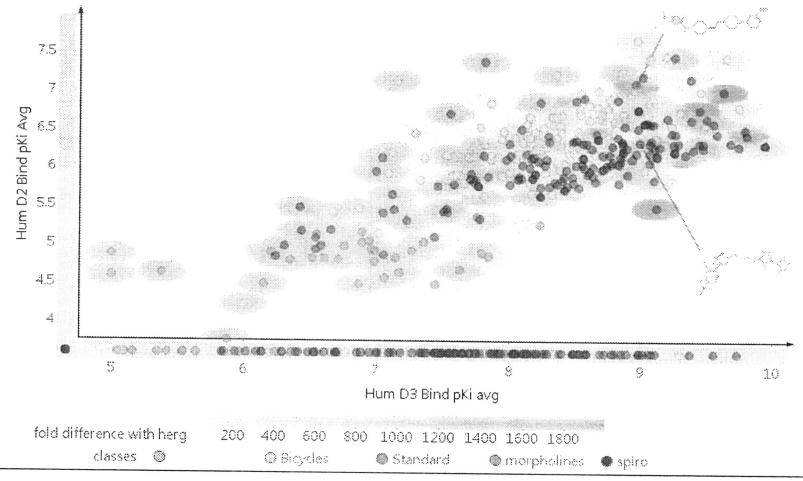
High selectivity and increased window vs hERG

Increasing potency and selectivity



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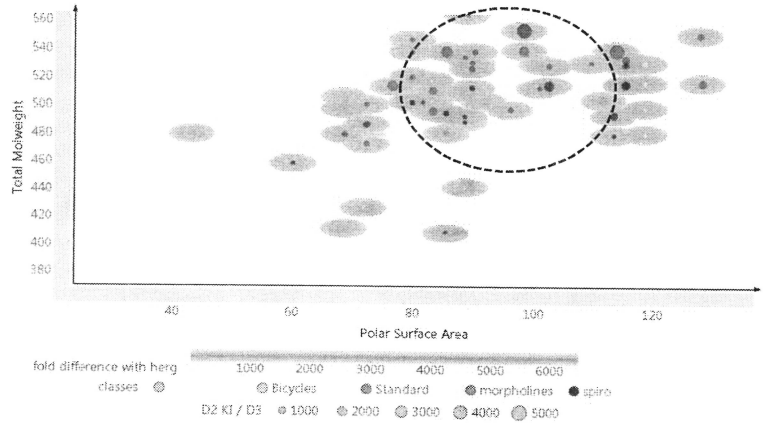
PSA – MW – Selectivity and hERG window

Being where we wanted to be...



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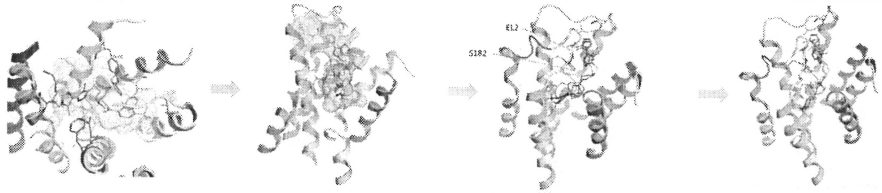
DA D3 antagonists

Improving "druggability" working on new modified "amino region"

6 months H2L and 9 months LO phase – series explored in parallel *ChemMedChem* **2017**, *12*, 1254 – 1260

# of examples included in the patent considering single enantiomers

≈ 40 ≈ 200 ≈ 250



GSK598809A

J. Med. Chem, **2010**, *53*, *374-391*

DA D3(fpKi) = 9.0
DA D2 (fpKi) = 7.0
hERG (pIC_{50}) = 6.1

Δ D3 fpKi – hERG pIC_{50} = 790 fold

Morpholine scaffold

BMCL, **2016**, *26*, *1329–1332*
WO 2017/064488

Ex
DA D3 (pKi) = 8.2
DA D2 (pKi) = 5.3
hERG (pIC_{50}) = 5.9
D3(fpKi) = 8.5

Δ D3 fpKi – hERG pIC_{50} = 400 fold

Octahydropyrrolo[2,3-b]pyrroles scaffold

BMC, **2016**, *24*, *1619–1636*
WO 2017/021920

Ex
DA D3 (pKi) = 8.4
DA D2 (pKi) = 6.0
hERG (pIC_{50}) = 5.2

Rat in vivo parameters:
Fa = 54%, Eh = 0.6. $T_{1/2}$ = 0.6 h, Vss = 2.6 l/kg,
Clb = 73 ml/min/kg; F = 29%
Blood Fub = 22% Brain Fub = 42%

Δ D3 pKi – hERG pIC_{50} = 1580 fold

5-Azaspiro[2.4]heptanes scaffold

J. Med. Chem., **2016**, *59*, *8549–8576*
WO 2016/067043

Ex
DA D3 (pKi) = 8.9
DA D2 (pKi) = 5.9
hERG (pIC_{50}) = 5.6
D3(fpKi) = 9.2

Rat in vivo parameters:
Fa = 54%, Eh = 0.3. $T_{1/2}$ = 4.4 h, Vss = 5.5 l/kg,
Clb = 21 ml/min/kg; F = 53%
Blood Fub = 7.8% Brain Fub = 19%

Δ D3 fpKi – hERG pIC_{50} = 3980 fold

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Conclusions

Never give up....

- Different series of "amino terminal" replacement identified
- From morpholines to spiro derivatives a range of parameters have been explored and carefully modified both in vitro and in vivo
- Huge therapeutic window over hERG was achieved

- We would like to acknowledge Indivior Inc. for supporting this last part of the project