Working at the interface between Medicinal Chemistry and Chemical Development

IASOC 2008, Ischia, Italy

Daniele Andreotti
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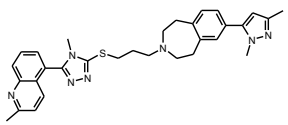
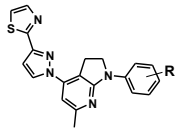
GlaxoSmithKline

Two examples

- Route optimization of preclinical/clinical candidates targeting D3 antagonist and CRF-1 antagonist.





- Development of a new methodology for regioselective preparation of substituted N-Methyl Pyrazole.
- Constructive interaction with Medicinal Chemistry and Chemical Development partners

A potent and selective dopamine D3 Receptor Antagonist

- **Drug Addiction**
  - Selective antagonism at DA D_3R attenuates drug-seeking behaviour and reduces the reinforcing efficacy of a wide range of drugs of abuse
  - Validation in 19 preclinical animal models: carried out across 6 International Research Centres, with compounds from 3 different chemical series, and demonstration of efficacy against 4 drugs of abuse including nicotine, alcohol, cocaine, and heroin

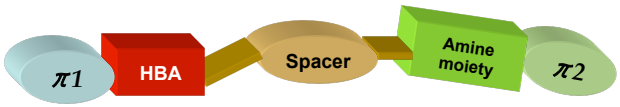
Worldwide Prevalence of Drug Addiction

- An estimated **1.2 billion smokers** worldwide comprising approximately 1/3 of the global population aged 15 or older.
  - WHO estimates that the worldwide number of smokers will continue to increase to **1.6 billion by 2025**.
- **76.3 million** (**32million**, top 7 Markets) adults diagnosed with **alcohol use disorders.**
- There are about **200 million users of illegal drugs** worldwide, which represent 3.4% of the world population.

For every dollar invested in drug treatment,
7 dollars are saved in health and social costs

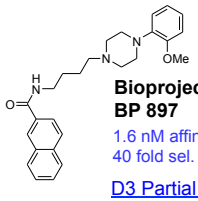
Uhl GR & Grow RW (2004) Arch Gen Psychiatry 61: 223-229
Andlin-Sobocki et al. (2005) Eur. J. Neurol. 12 (Suppl. 1): 1-27
World Health Organization (WHO), 2005.

General features for a selective D3 ligand



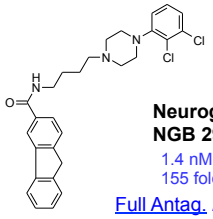
Pharm. & Therap. 2006, 112, 281

Historical examples:



Early 90's

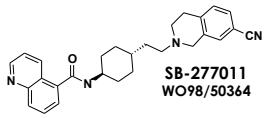
Bioproject
BP 897
1.6 nM affinity
40 fold sel. vs D_2
D3 Partial Agonist



Neurogen
NGB 2904
1.4 nM affinity
155 fold sel. vs D_2
Full Antag. / Poorly soluble

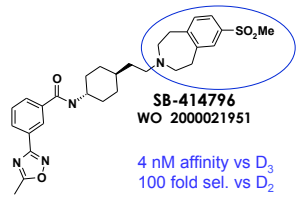
GSK main D3 Antagonist compounds Medicinal Chemistry: where we started from

From legacy GSK company:



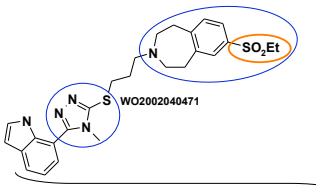
SB-277011
WO98/50364
10 nM affinity vs D_3
100 fold sel. vs D_2

Great validation tool but not developable

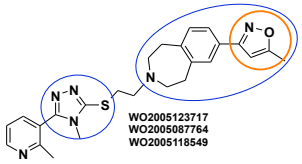


SB-414796
WO 2000021951
4 nM affinity vs D_3
100 fold sel. vs D_2

Thiotriazole-benzazepine Series:



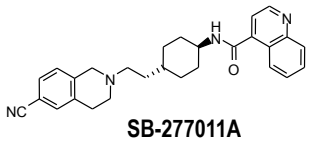
WO2002040471



WO2005123717
WO2005087764
WO2005118549

Very potent and selective compounds good developability characteristics

Target Validation with Tool Compound



SB-277011A

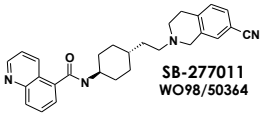
- Potent, competitive D_3 receptor antagonist (pKb 8.4, 80 fold functional selectivity over hD_2)
- 100-fold selective for hD_3 over hD_2 in radioligand binding assays
- 100-fold selective over 66 other receptors, ion channels and enzymes

- Lacks agonist activity at hD_2 and hD_3 receptors
- No effects on spontaneous locomotor activity (2-42 mg/kg p.o.)
- No effects on open field exploration (3-51mg/kg p.o.)
- Non-cataleptogenic up to 80 mg/kg p.o.

- No elevation of plasma prolactin at 93 mg/kg p.o.
- No proconvulsant effects up to 93 mg/kg p.o.

- Great validation tool, but not developable…
- Main issue is aldehyde oxidase liability.

GSK main D3 R Antagonist compounds Medicinal Chemistry: where we started from



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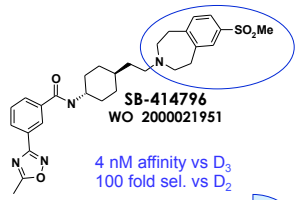

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Thiotriazole-benzazepine Series:

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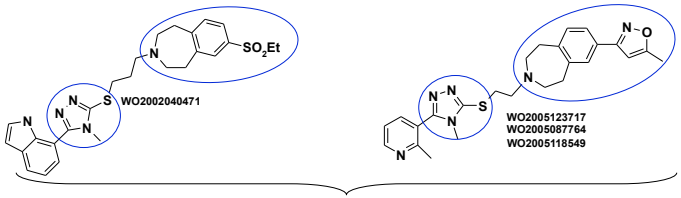
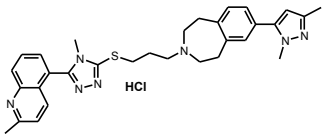


Very potent and selective compounds good developability characteristics



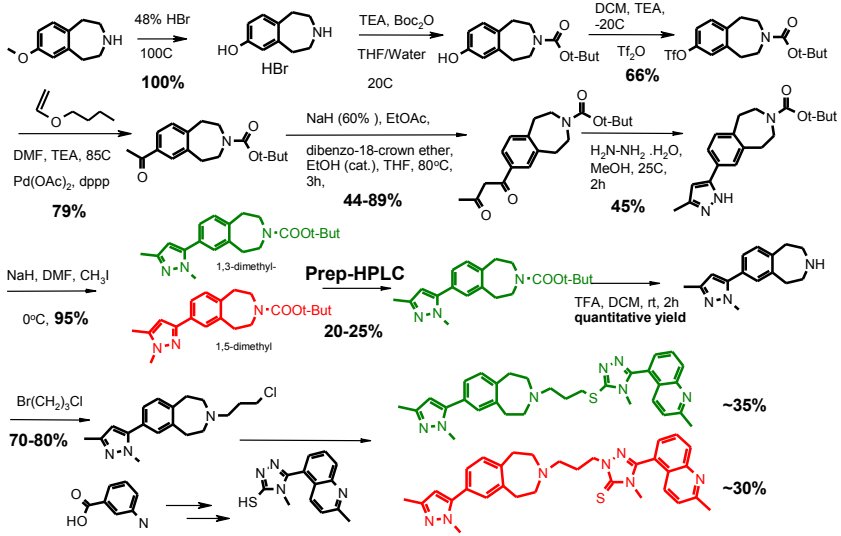
fpKi (D3/2) 8.8 / 6.5
H1 = 6.1
High selectivity over a wide panel of receptors

hERG IC50 0.43 µM
stable to P450

Clb 38ml/min/Kg
F% (15%) po in rat;
B:B 2.5

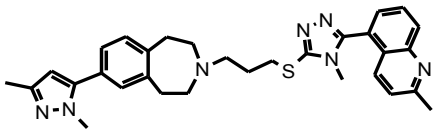
Journal of Medicinal Chemistry (2007), 50(21), 5076-5089

General route towards Thiotriazole-benzazepine

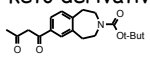


W2002/040471, WO2006/002928, WO2005/123717, WO2005/118549

Issues of Medicinal Chemistry route

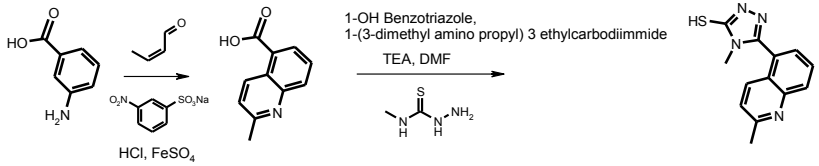


- High number of steps (11+2).
- Yields of many steps are quite low (30-40%) overall yield ~ **1-2%**.
- Several purifications by flash chromatography.
- Prep HPLC is needed to separate N-Methyl Pyrazole isomers.
- Poor N/S selectivity during alkylation of tiotriazole.
- Reproducibility problems with the preparation of the 1,3 di-keto derivative.



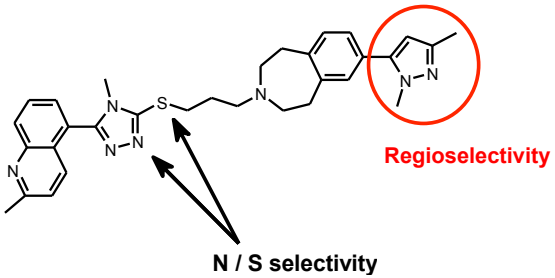
- ~700mg was the max scale of material produced.

Tiotriazole preparation

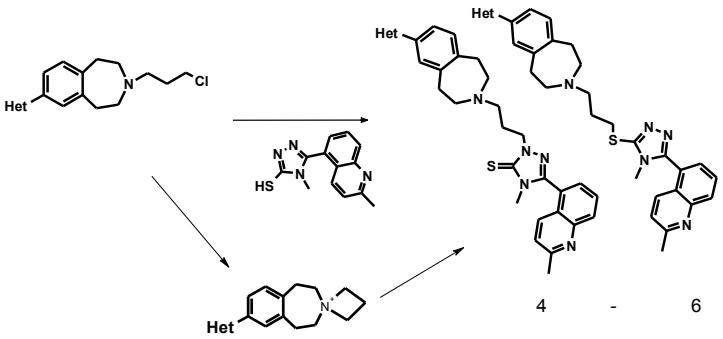


PCT Int. Appl., 2005087764

The chemical route exploited by Medicinal Chemist for SAR exploration was not viable for a scale-up.

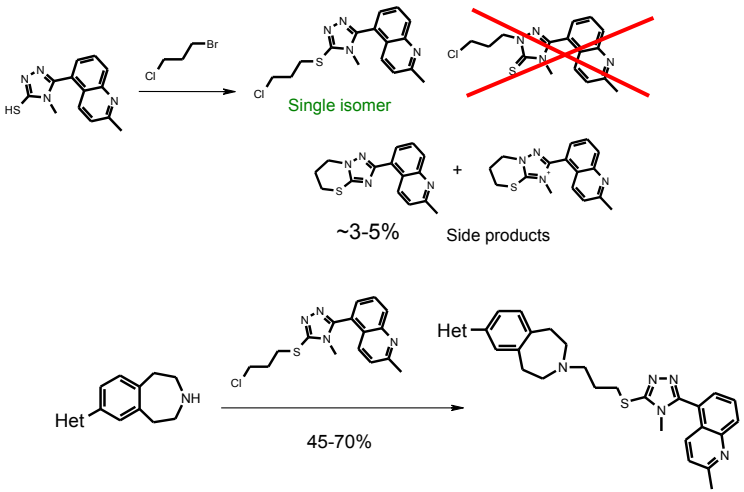


Alkylation step: poor N/S selectivity

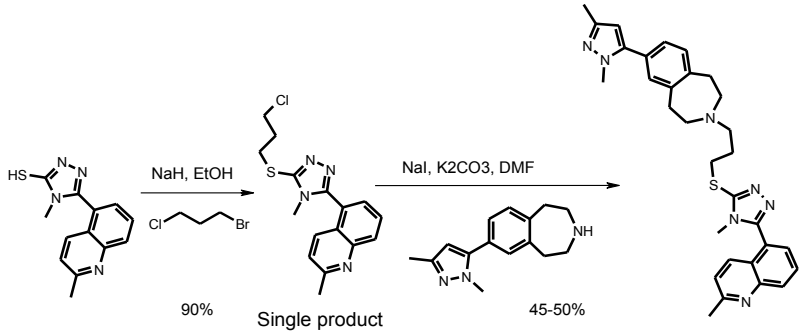


Observed by LCMS

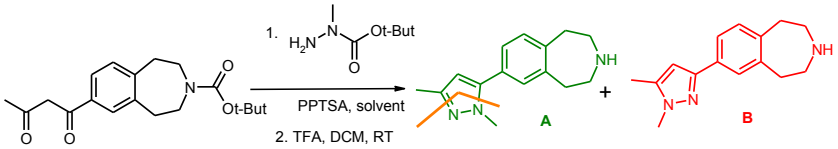
Alkylation step: improved N/S selectivity



Alkylation step: improved N/S Selectivity

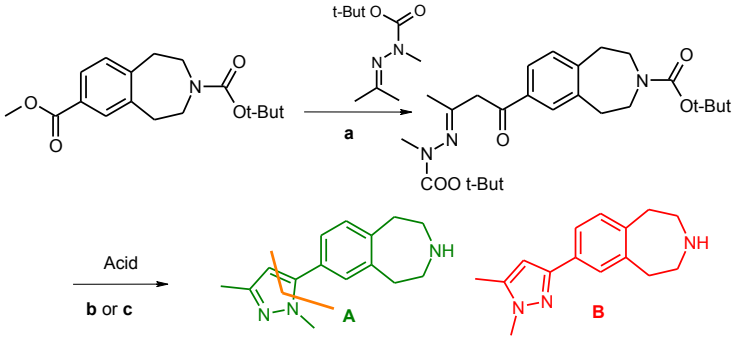


First attempt to improve N-Methyl Pyrazole formation



Solvent	A	B
Ethanol	85	15
DCM	90	10
Pyridine	**96**	**4**

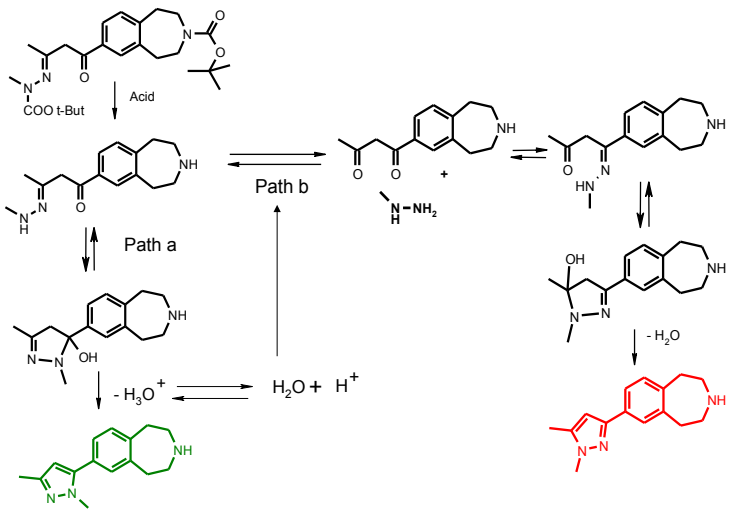
Second attempt



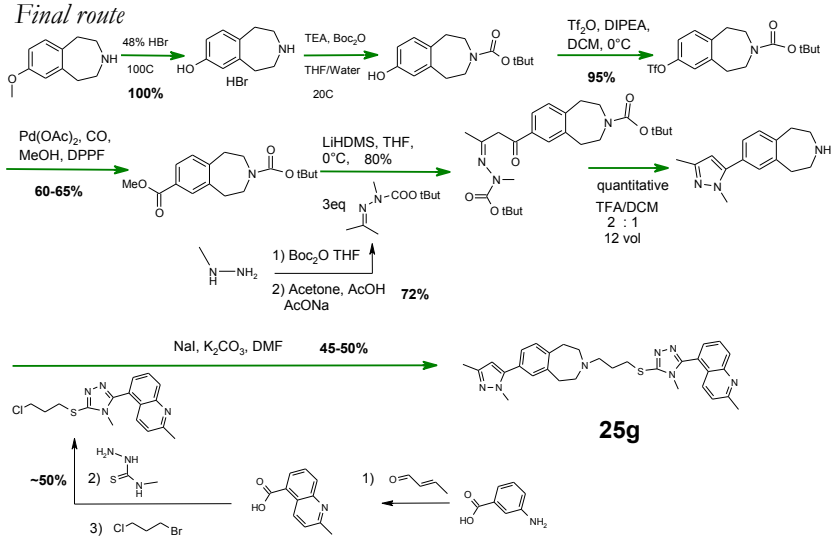
(a): LiHMDS (3eq), **9** (3eq), THF, 0ºC, 3h, 80%
(b): HCOOH, RT, 2h, quantit. conversion 85/15 **A/B** ratio
(c): TFA, DCM, RT, 2h, quantit. conversion to **A** single isomer

Acid	A	B
HCOOH	85	15
TFA	**100**	**0**

A possible explanation of the result



Final route



Overall Yield = **20% mol** (40%w/w) longest branch
N of Steps = 7+3+2

Amount produced = 25g
No problems of isolation

Andreotti et al. Synlett in press

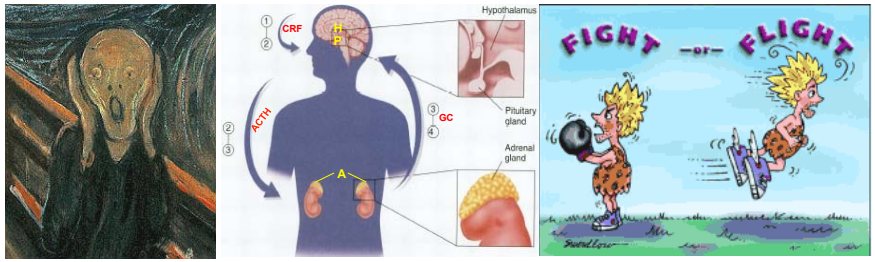
Conclusions

- DA D3 receptor antagonists show the highest promise for treatment of addiction, and might find application in schizophrenia, cognition and depression area.
- We have identified a potent and selective D3 antagonist and it represents a promising compound for the treatment of drug addiction.
- A viable chemical route has been identified to scale it up permitting a full Safety Assessment evaluation.
- A novel and regioselective method for the preparation of N-Methyl Pyrazole derivatives was identified.

A potent and selective (CRF-1) Corticotropin-Releasing Factor-1 Antagonists

- **Major depression**
  - In most cases, major depression is a recurrent lifelong illness, characterised by repeated exacerbation and remission periods.
  - Several lines of evidence associate **chronic stress** with **anxiety** and **depression** via the hyperactivation of the hypothalamus-pituitary-adrenal (HPA) axis triggered by the hypersecretion of the neuropeptide corticotropin-releasing factor (CRF). Which is considered one of the major biochemical modulators that coordinate the adaptive response of organisms to stress.
  - There are clinical evidences suggesting the association between hyperdrive of CRF and, the onset of anxiety and depressive disorders.
  - CRF exerts its biological functions through binding to two GPCR subfamily B 7-TM receptors: CRF type-1 (CRF1) and CRF type-2 (CRF2) receptor.
  - Onset of effect and tolerability of the current treatment (SSRI) still remains the main unmet medical needs.

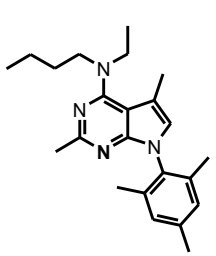
Role of CRF in mediating the stress response



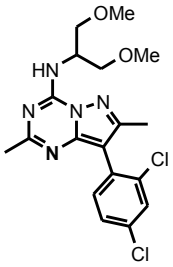
The stress hormone response:
When the brain perceives stress, the hypothalamus releases corticotropin-releasing factor (CRF) (1), which triggers the release of adrenocorticotropin (ACTH) (2) from the pituitary gland. ACTH (2) travels through the bloodstream and (along with signals from the brain sent through the nervous system) stimulates the adrenal glands to release cortisol and epinephrine into the bloodstream (3). Cortisol and epinephrine (3) help provide energy, oxy-gen, and stimulation to the heart, the brain, and other muscles and organs (4) to support the body's response to stress.

There is a link between Anxiety/Depression and the unbalancing of the stress response.

CP-154,5265 and DMP-6966 were amongst the first compounds showing high affinity along with interesting signs of in vivo activity in animal models of anxiety and depression.



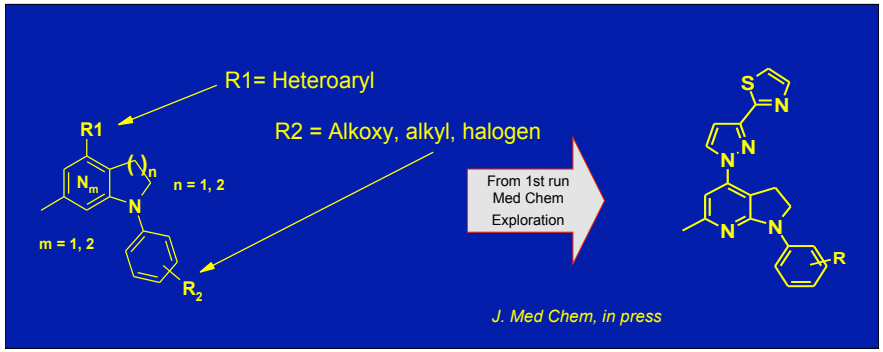
CP-154,526



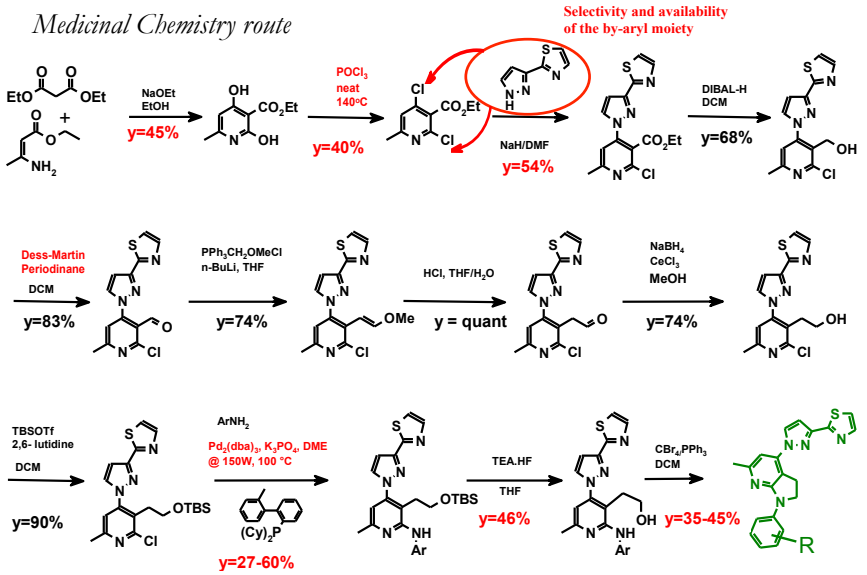
DMP-696

CRF1 Antagonists program

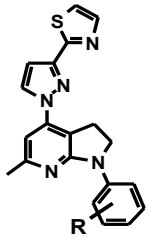
- *To identify novel CRF1 receptor antagonists in a highly competitive IP field (~350 patents issued).*
- *To find chemical series that would overcome the issues associated with already published compounds (poor PK, low brain penetration, etc..)*

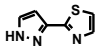


Medicinal Chemistry route

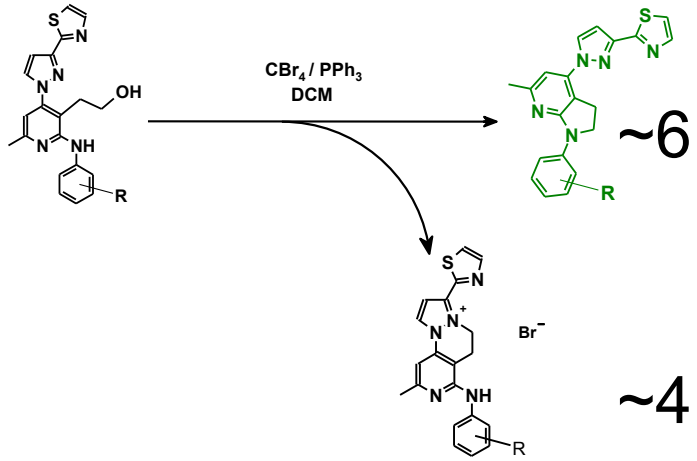


Issues of Medicinal Chemistry route



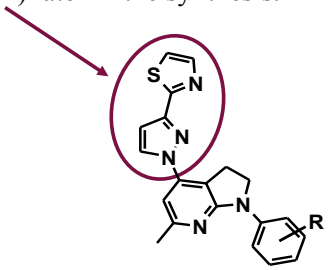
- Linear synthesis with high number of steps (12)
- Use of a few hazardous reagents
- Yields of many steps are quite low (30-40%), overall yield **0.2%**
- Several purifications by flash chromatography
- Biaryl moiety is not commercially available 
- Undesired side reaction on last step of the synthesis

Undesired side reaction on last step of the synthesis



In addition to that……

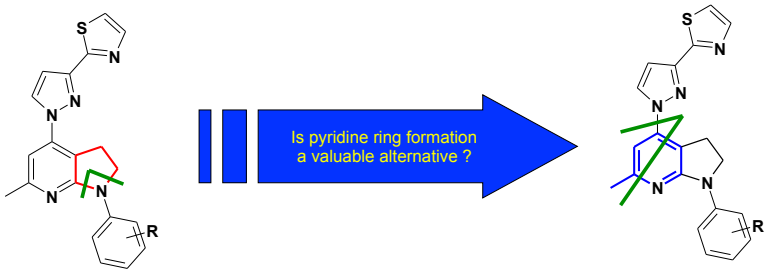
- The CRF-1 program team was seeking for a more flexible chemical route suitable for introducing different hetero-aromatic moieties (R1) later in the synthesis.



Novel approach

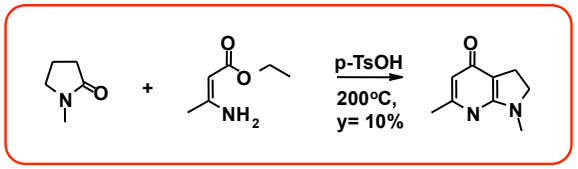
First strategy

New strategy



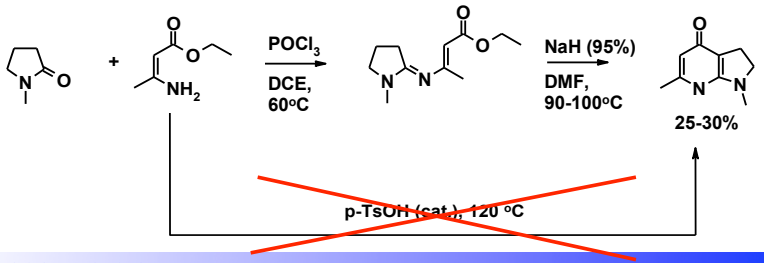
The main chemical issues are related to 5 member ring formation.

The novel approach : what we found in literature

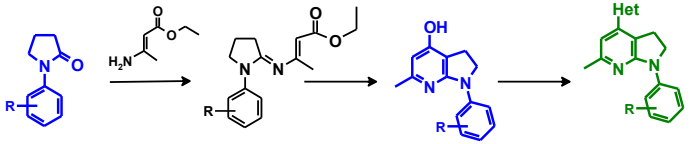


Chem.Heretocycl.Compd. Engl.Transl., *12*(6), **1976**, 672

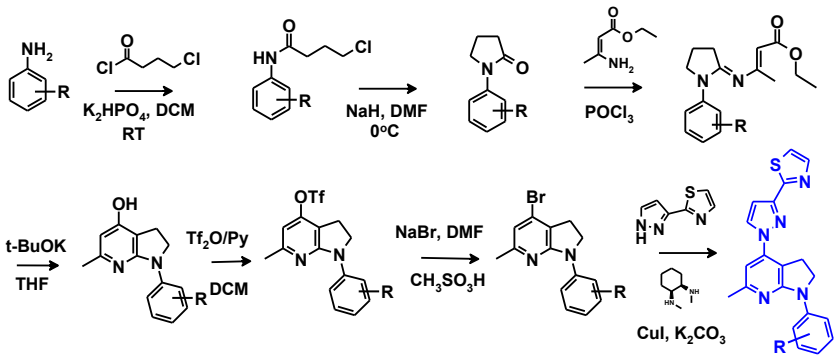
Preliminary exploration of the chemistry



A novel approach

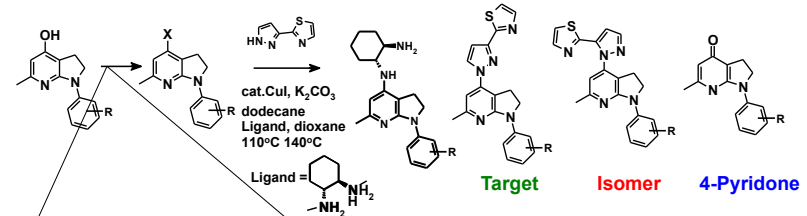


A novel approach



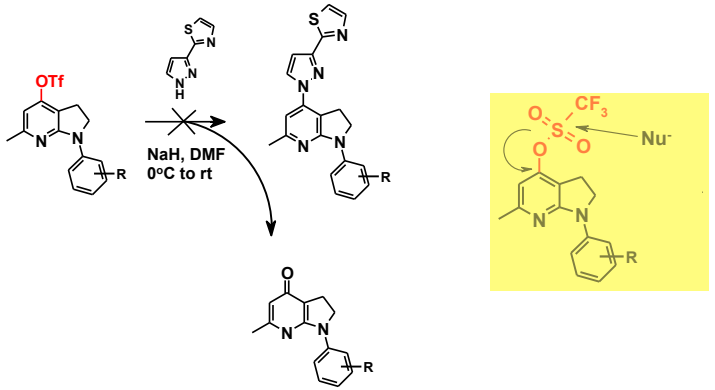
7 steps with overall yield 12%
From 20g to Kg scale

Cross Coupling

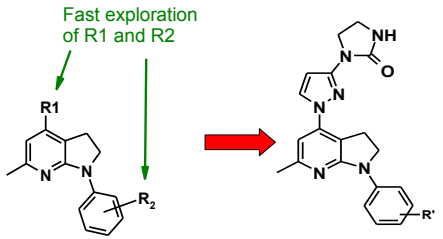


Reaction conditions to convert OH to X	X	Starting material	Target	Isomer	4-Pyridone
$POCl_3$, CH_3CN	Cl	√	--	--	--
1)Tf_2O, Py 2) NaBr, DMF	Br	--	√	1-2%	--
1)Tf_2O, Py 2) KI, DMF	I	--	√	5-8%	--
1)Tf_2O, Py	OTf	10%	--	--	√

Nucleophilic substitution

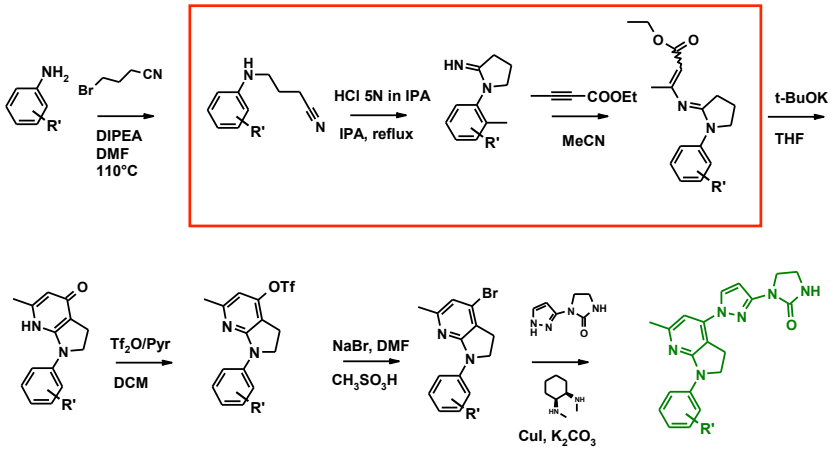


Fast exploration of the scaffold



Identified by CRF-1 Med Chem team

Optimised route applied to the scale-up of new compound

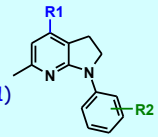


7 steps, Overall yield = 15-25%
From 50g to Kg scale

J. Med Chem, in press

Conclusions

- A more chemically viable route has been identified for preparing the target compound.
  - Shorter synthesis: 7 steps vs 12 steps (Overall yield ~15-25%)
  - Route reliability and robustness validated up Kg scale
  - Introduction of the biaryl moiety at the last step of the synthesis (R1)
  - Good availability of starting materials, eg anilines (R2)



- The new chemical route has permitted a fast and broad SAR exploration of the scaffold, further promising compounds have been identified.