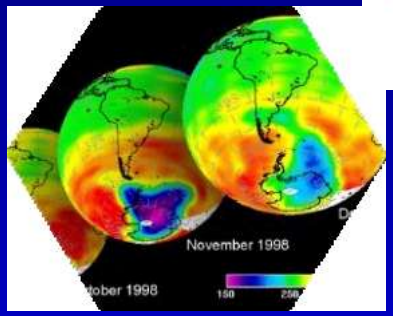
The Role of Chemists in the Discovery of New Medicines

Nottingham, 13th October 2011

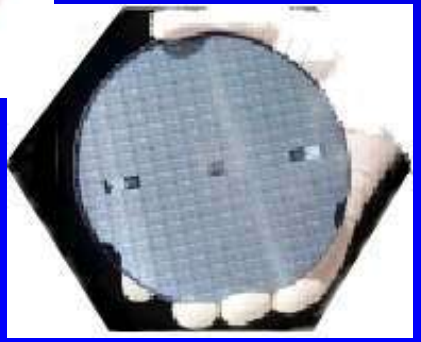
Dave Alker

What do you have that your great-grandparents didn't at your age i.e. ~1936?

- Effective medicines e.g. antibiotics, anti-cancer drugs
- Fast, reliable, safe cars….and good roads to drive on!
- Computers (30 years ago a BBC computer = 256 KB!)
- High-quality, varied and tasty food
- Man-made fibres, dyes, plastics
- Mobile phones……the list goes on and on
- ….and we take the key role of chemistry for granted!!



"Everything around us, whether man-made or natural, relates to chemistry"



Are you studying AS or A2 level chemistry?

YOU
ARE
SPECIAL!

IF YOU STUDY CHEMISTRY YOU ARE SPECIAL!

- You've started to build core knowledge, problem-solving skills and analytical thinking

- At AS level you will already know more chemistry than……

…..Wayne Rooney

……or Lady Gaga

- Don't forget even Harry Kroto, Nobel prize winner, all round smart dude, had to pass A levels!

- Don't be afraid to ask questions and always strive for understanding

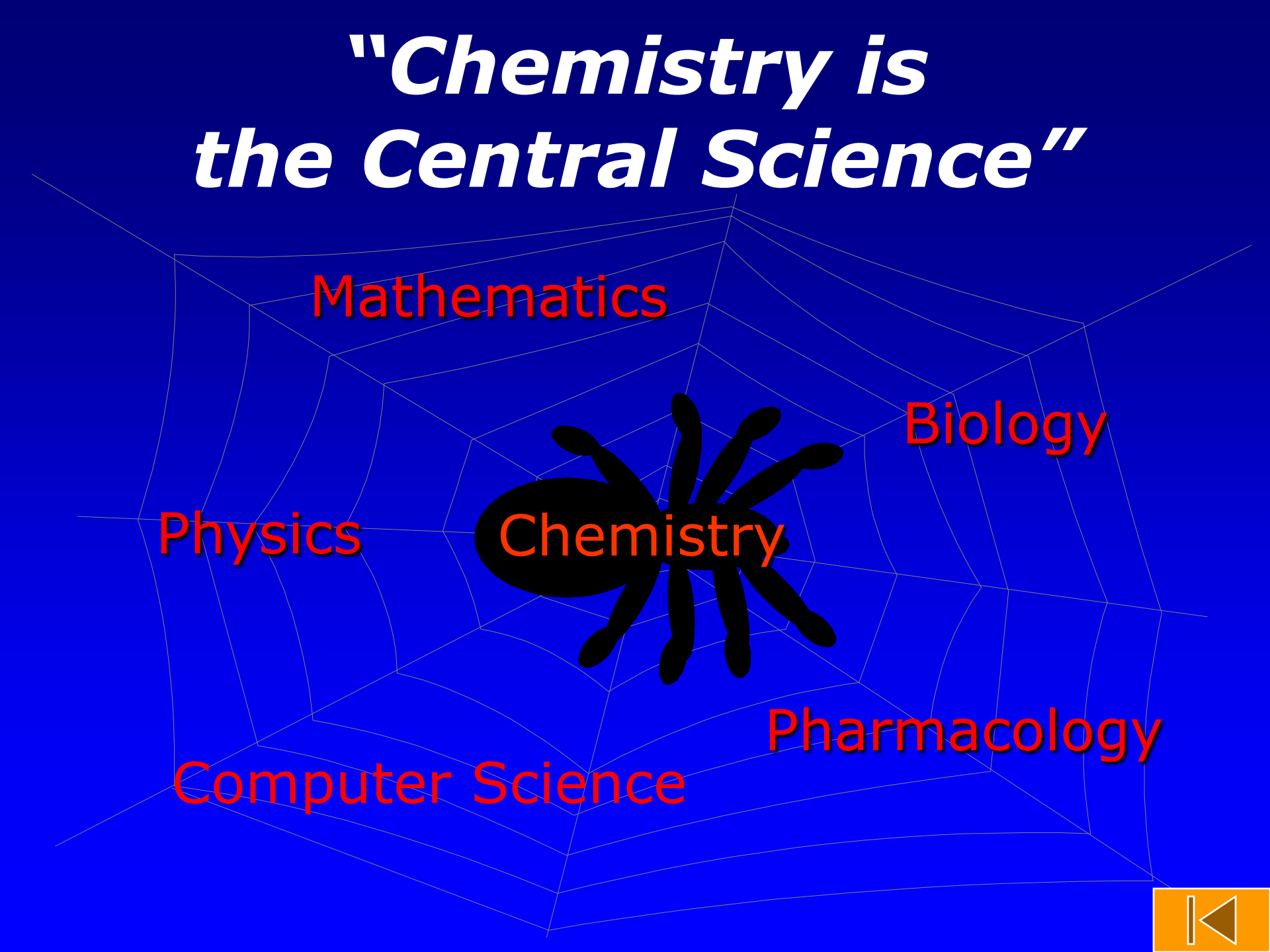
'GO FOR IT'

Why study chemistry??

- It's exciting, challenging, amazing……AND FUN
- Good training in analytical thinking, problem-solving and creativity/innovation
- Excellent background for many careers……R&D, manufacturing, teaching, sales, finance, law……even PM
- Range of sub-disciplines, multi-disciplinary interactions
- Chemists are employable and generally well paid compared to other graduates
- Even in a recession the UK needs good chemists

So how do you discover new medicines?

"Chemistry is the Central Science"



How do you decide what to work on?

- Medical Need – no effective therapy available or current drugs sub-optimal
- Prevalence - how many people suffer from the disease
- Tractability – can you understand and solve the issues?
- Funding
  - ROI important for pharma
  - Charities, academic research rely on grants

How do you decide how to work on it?

Develop a hypothesis: what molecular mechanism causes the disease?

In-house exploratory work

Literature

Conferences

Clinical data

Research collaborations

Why are chemists so important?

- All medicines are a molecule with defined biological and physicochemical properties

- The structure of a molecule defines its properties

- These molecular properties control the biological and physical profile of a compound

- For a new medicine, need to design a molecule with specific properties

- only a chemist can solve a project's problems and design a medicine!

Where do you start?

Competitor Compounds

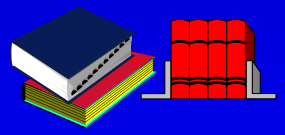
GSK
AstraZeneca
Merck

Natural Products

Endogenous Ligand

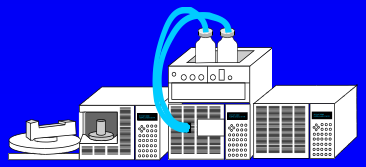
e.g. Natural peptide, hormone, etc.

Scientific Literature

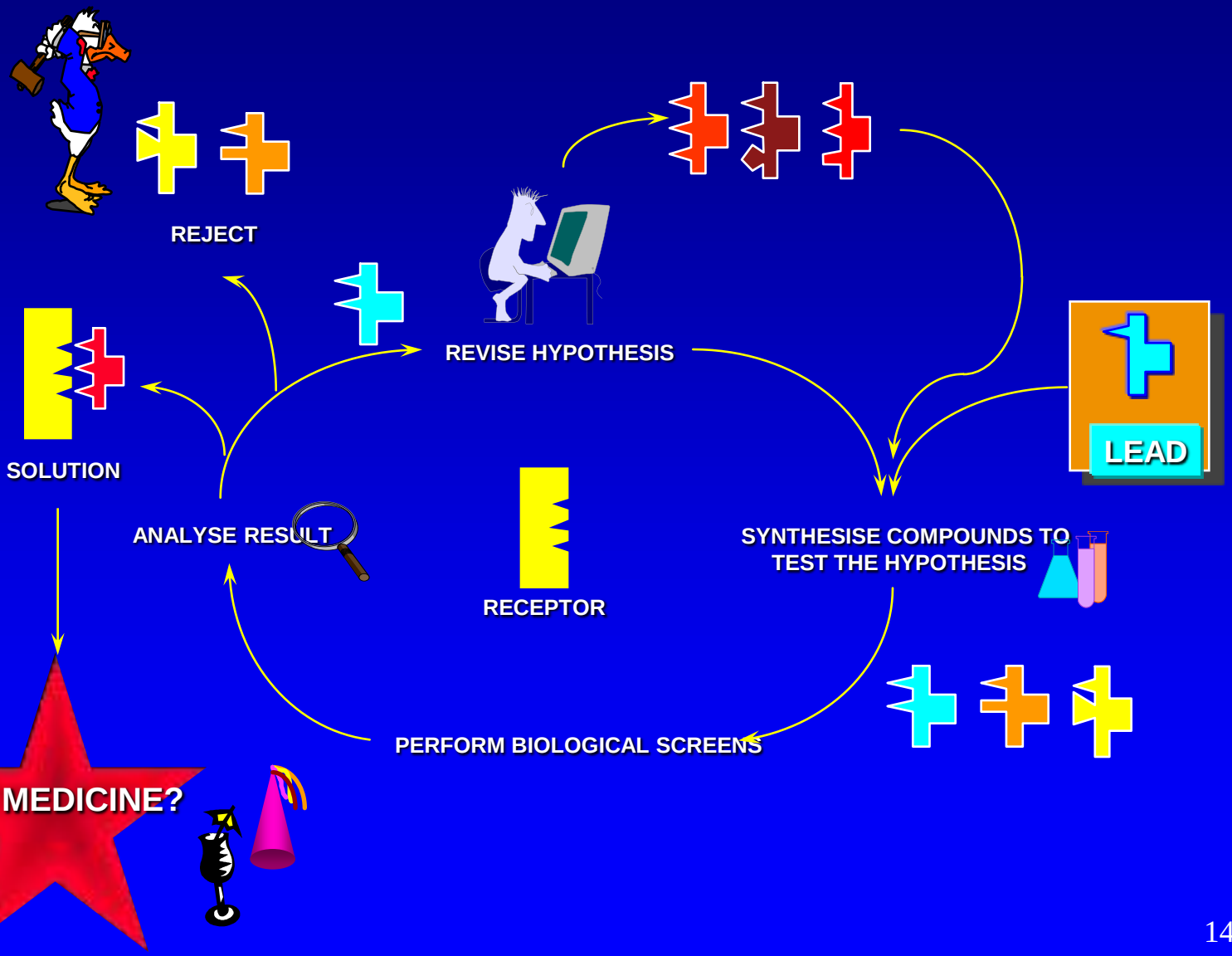


Random Screening of Compound File

Combinatorial Libraries



From Lead to Potential Medicine



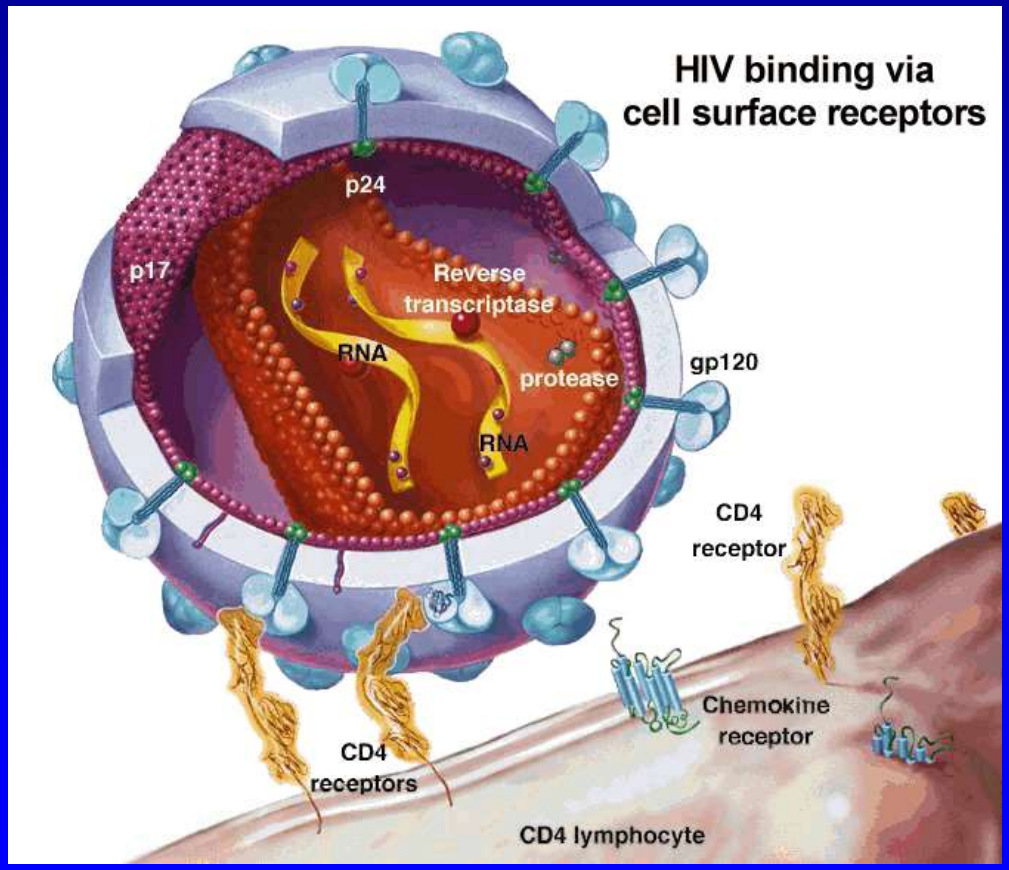
Maraviroc (Celesentri$^{R)}$;a new medicine for HIV/AIDS

A new treatment for HIV/AIDS?

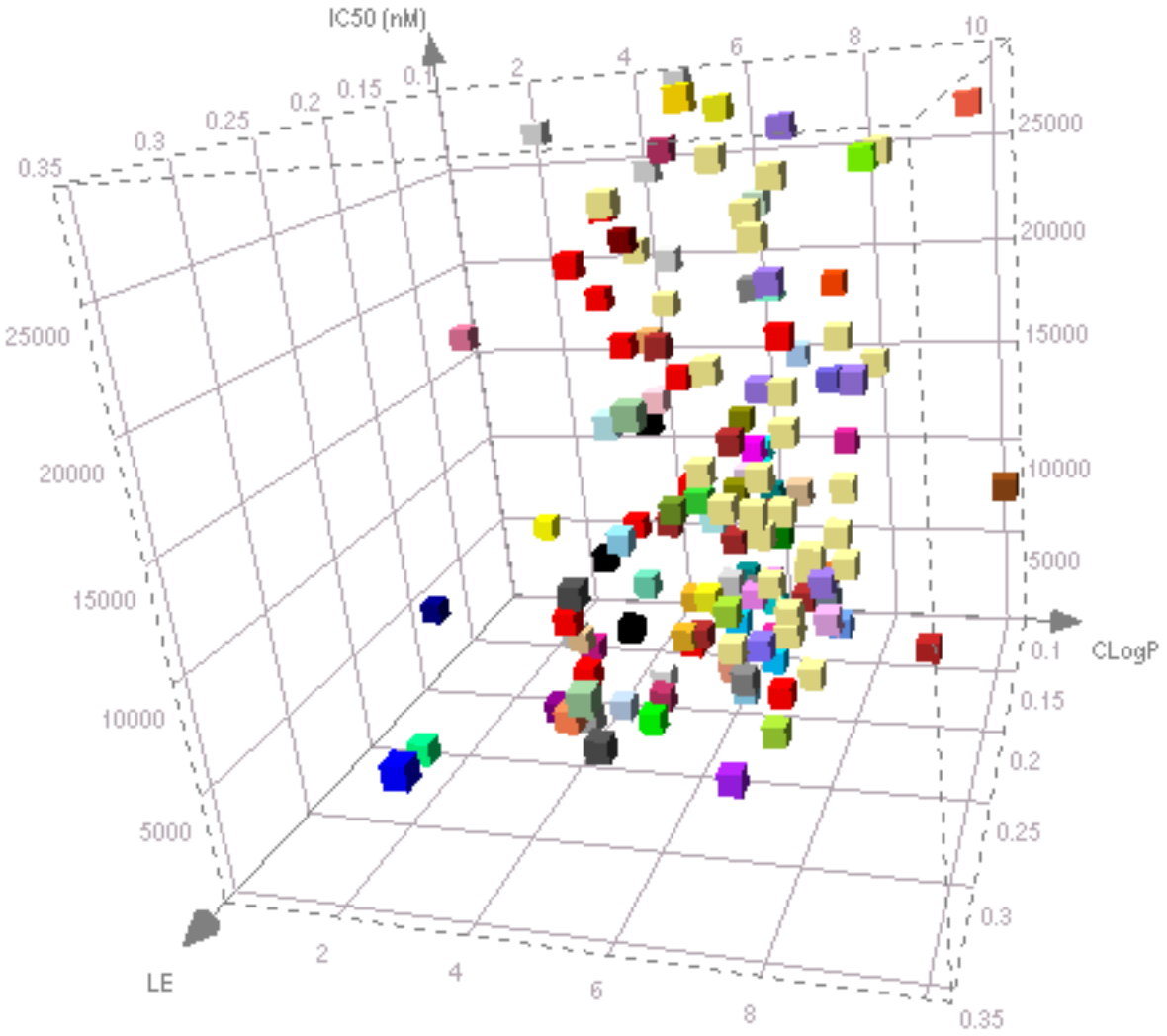
- In 30 years, 33 million have died from HIV/AIDS
- 33 million currently infected with HIV/AIDS (2009)
- 1.8 million deaths in 2009
- 1.5 million people infected in US
- Current therapies show serious side effects and growing resistance - new treatments were desperately needed!
- See http://www.avert.org/worldstats.htm

Why might a CCR-5 blocker work??

- it is a receptor on the cell surface by which HIV enters cells
- people without the genes to express CCR-5 don't get HIV

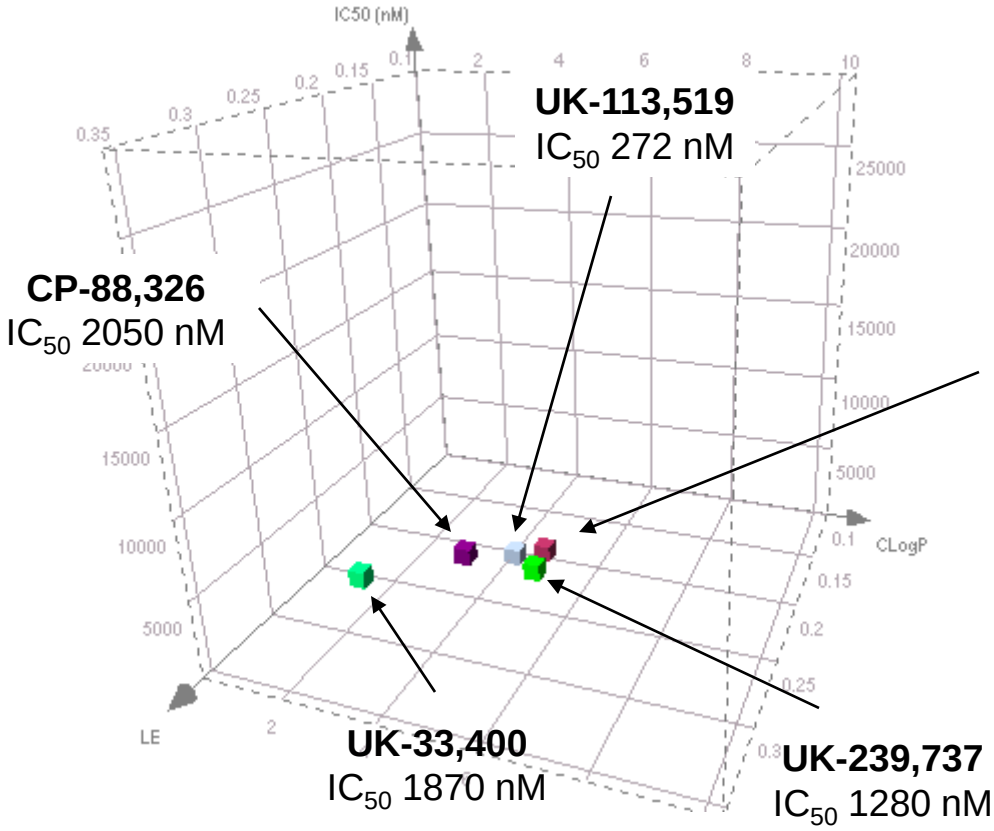


hit selection



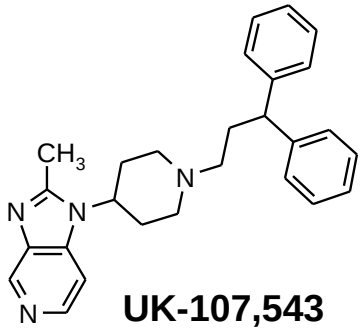
hit selection

LE >0.2
clogP <5
IC_{50} < 2500 nM



UK-113,519
IC_{50} 272 nM

CP-88,326
IC_{50} 2050 nM

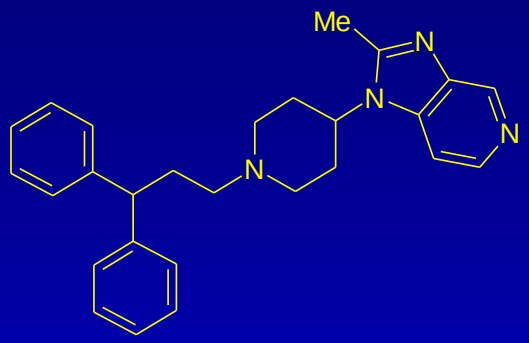


UK-107,543
IC_{50} 650 nM

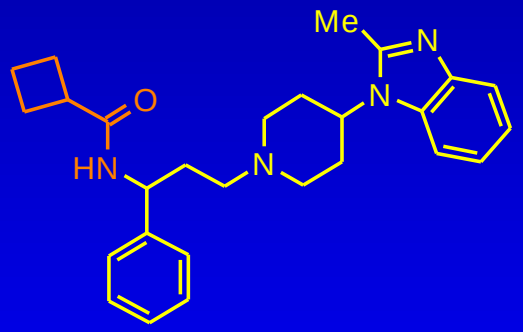
UK-33,400
IC_{50} 1870 nM

UK-239,737
IC_{50} 1280 nM

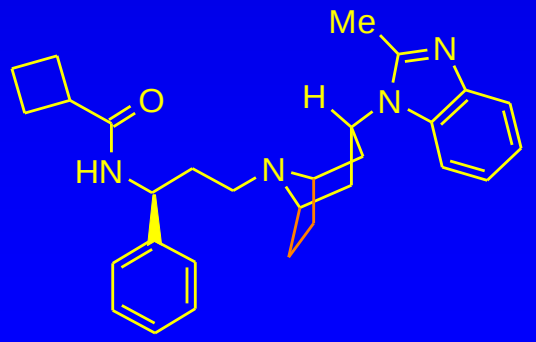
Early work – finding a chemical starting point



- high-throughput screen 'hit' UK-107,543
- IC_{50} = 650nM i.e. weak binder to the CCR-5 receptor

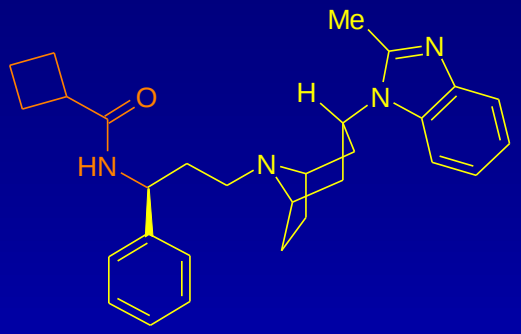


- increased binding to CCR-5 receptor
- stops HIV infecting cells in culture - AV_{90} = 73nM i.e. concentration which blocks 90% of HIV infection

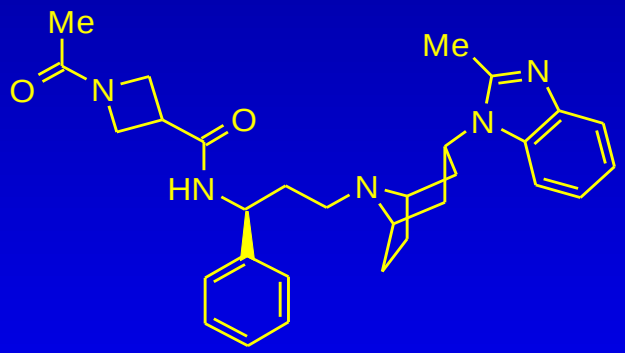


- a more conformationally rigid system i.e. less entropic loss upon binding - AV_{90} = 3nM

Solving problems through structural change

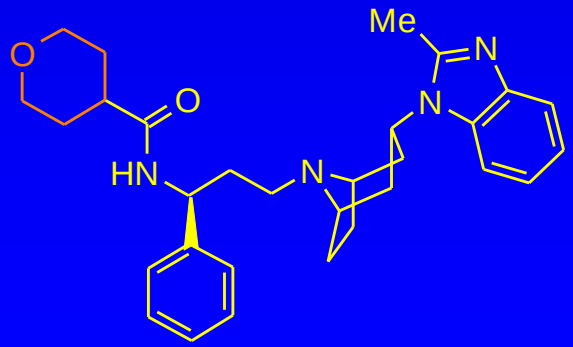


…but it also blocks a K^+ ion channel in the heart



- polar group removes ion channel activity and retains anti-viral activity AV_{90}=2nM

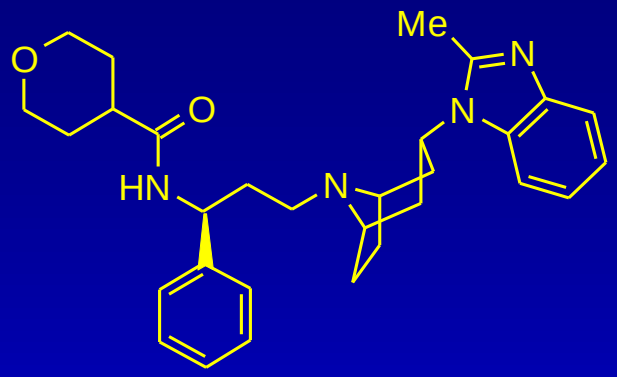
…but it is not absorbed!



- AV_{90}=0.6 nM
- no ion channel activity
- well absorbed

…but this is rapidly metabolised

After 965 compounds and 2.5 years…



- UK-396,794 unstable to metabolism
- logD window = 0-2
- $logD_{7.4}$ = 3.1

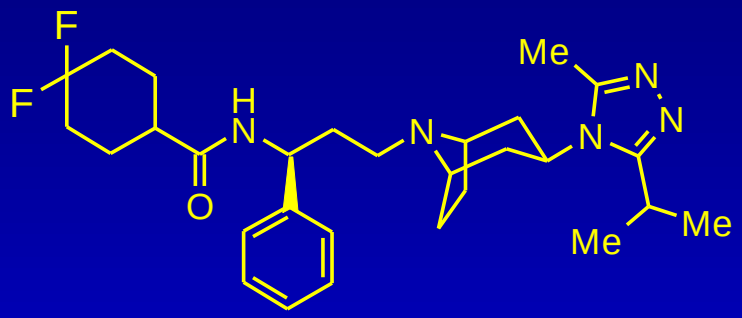
- Replacing benzimidazole with triazole reduces logD by 2 units
- 'Library' of ~ 80 compounds made to optimise amide substituent

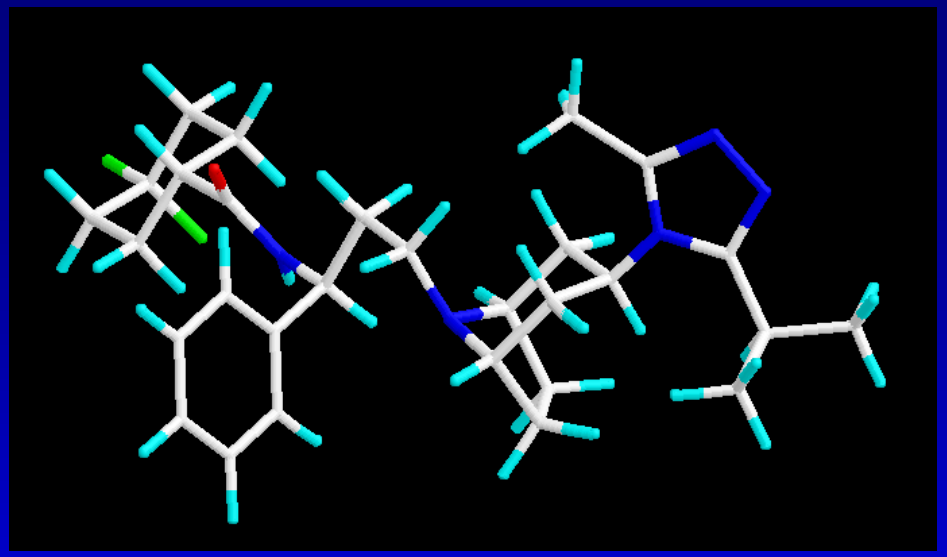
- AV_{90} = 1 nM
- no ion channel effects
- well absorbed
- metabolised slowly
- UK-427,857

Harnessing modern robotic technology

- 1983 - mixtures can be good not bad!!
- Robotic technology adapted from car industry
- 80 compounds made, purified and analysed in less than a week!

UK-427,857 = maraviroc = Celsentri



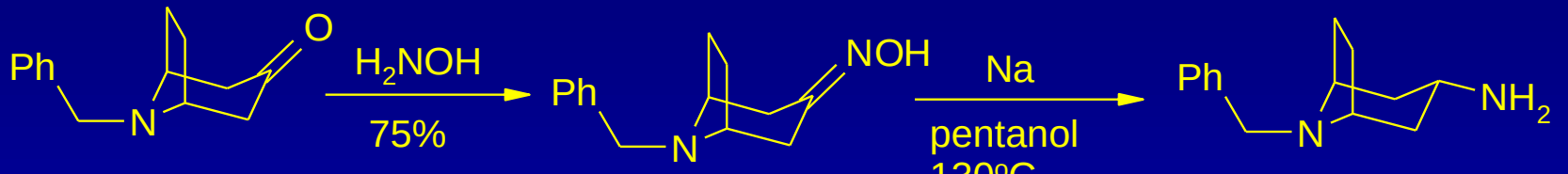


See http://en.wikipedia.org/wiki/Maraviroc

FDA approval 04/07, EC approval 09/07

Projected 2011 sales = $500million

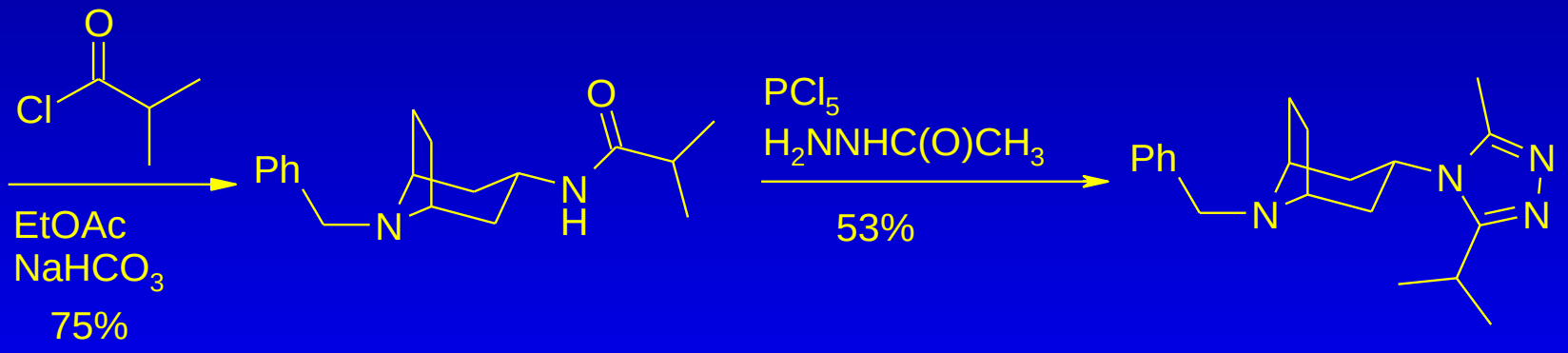
Synthesis – making the tropane



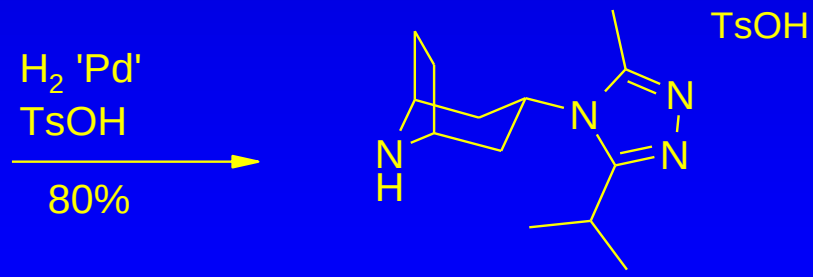
Bought in or prepared in 1 step

UK-182,975

Bought in from St-Andrews



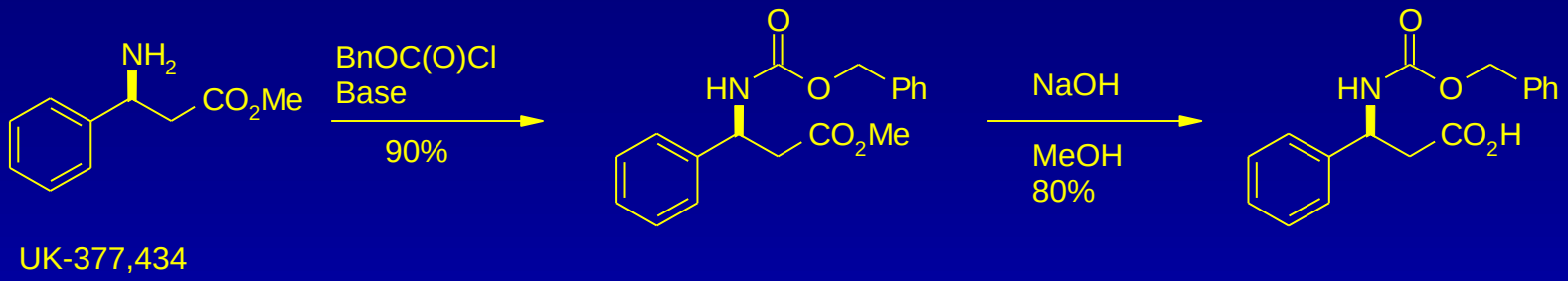
UK-408,026



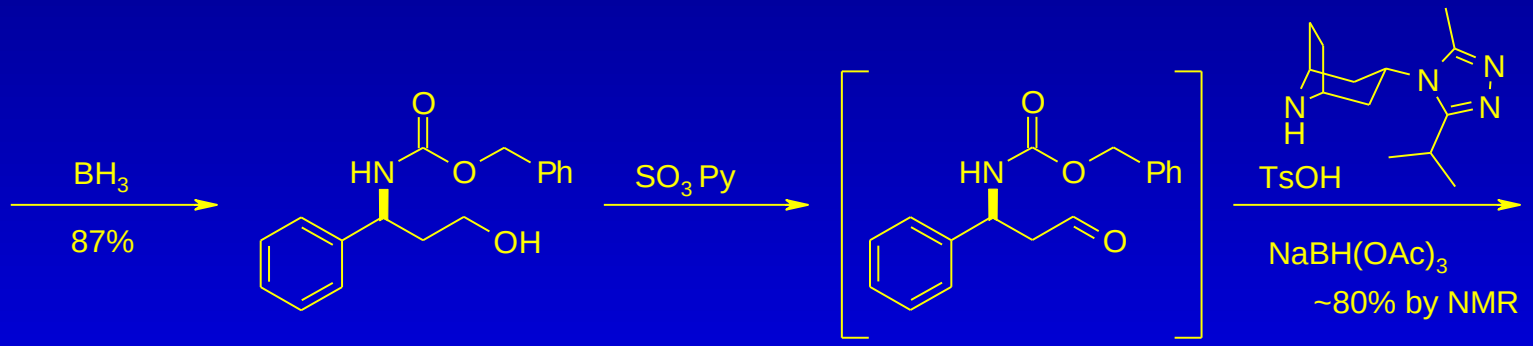
UK-408,027-15

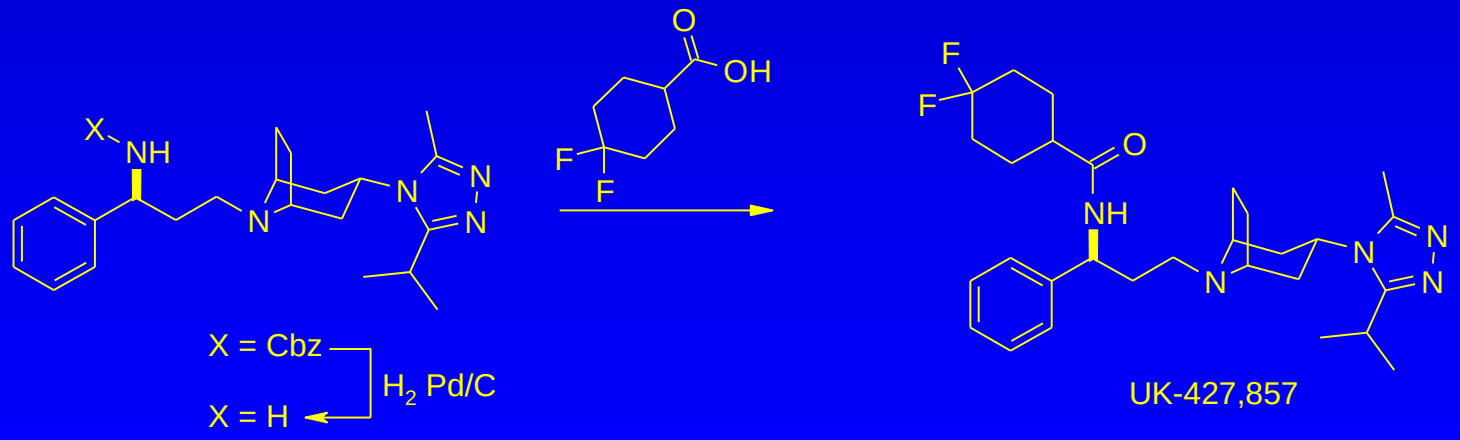
Overall yield from UK-182,975 =31%

Synthesis – putting it all together



UK-377,434





UK-427,857

Conclusions?

- Chemistry is fun and exciting
- You can make a difference
- You have important skills
- Make the most of them