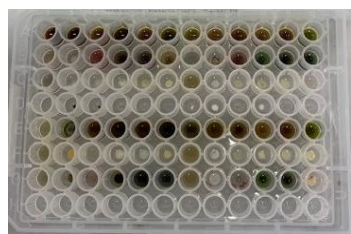


Biomimetic metabolite synthesis

Why do we need to synthesise Metabolites?

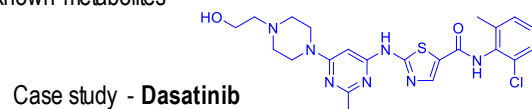
- Drug toxicity accounts for roughly 40% of clinical drug failures
- In 2008, the FDA released guidance for drug metabolite safety testing (MIST) recommending that all human disproportionate drug metabolites are assessed in safety studies
- We have developed a biomimetic chemical toolbox to generate drug metabolites *via* late stage oxidation/de-alkylation
- Putative metabolites of client APIs are identified in our screening panel and can be reproduced at scale, with detailed structure characterisation carried out by in house experts
- Synthesis of pharmacologically active metabolites can provide up front protection of patents at time of filing

Biomimetic Oxidation Screen



36 plate based reactions are run in parallel

- Successfully developed a late stage biomimetic oxidation screen utilising a minimum of 100 mg of client API
 - Scale up mg requirements dependent on reaction profile, with an estimate provided as part of the screening report
 - Biomimetic screen, analysis and draft report provided in < 2 weeks
- Late stage oxidation screen tested successfully on several approved drugs with known metabolites



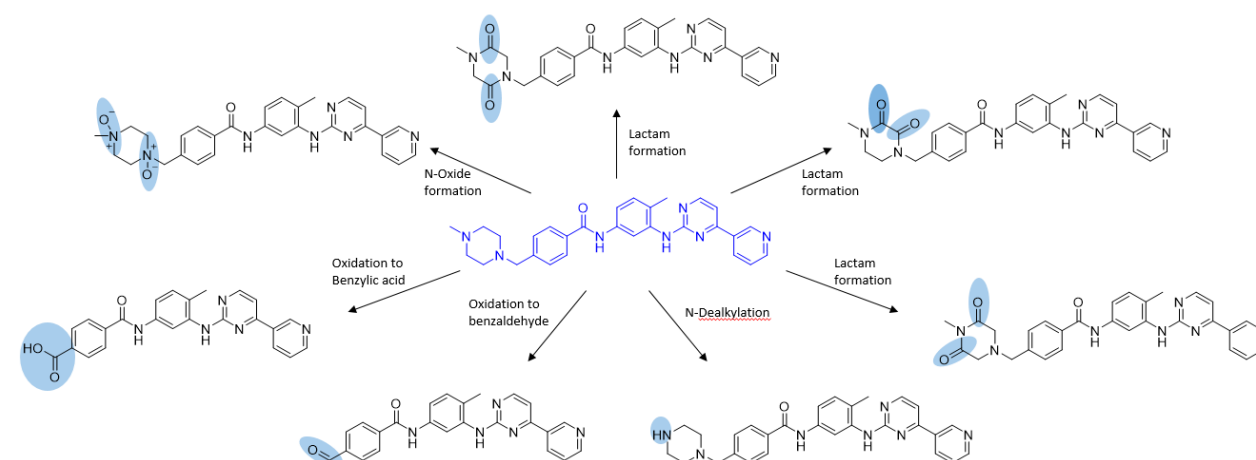
Well	1	2	3	4	5	6	7	8	9	10	11	12
A	O1a	O1b O1c	-	O1a O3	-	O3	O1a	O1a	O1b O1c	O3	-	O3
B	O2 O1a	O1b O2	O1c O2	O2 O3 O1a	O3	O1a O2	O1a O2	-	O1b O1c	O1b O2	-	-
C	O1a	O1b O1c	O1a	O1a	-	O1a	O1a	O1a	O1b	-	-	O1a

Analysis of reaction profiles and formation of putative metabolites. Key: O1 – O3 indicate addition of multiple +16 masses (potential oxidations), a-c indicate different retention times.

Biomimetic De-alkylation Screen

- Complementary synthetic de-alkylation protocol has been developed to mimic metabolic O/N de-alkylation
- De-alkylation chemistry can be run in parallel with the oxidation screen if client API has the appropriate structural features

Scale-up & Characterisation



Case study – Imatinib: Synthesis, isolation and full characterization of seven known metabolites of Imatinib

- All our metabolite synthesis methods are scalable to enable production of mg to g amounts of pure metabolites
 - A reaction optimisation phase is included as required in any scale up campaign
 - Typical optimisation and scale up campaign is completed in 4-6 weeks (5-50 mgs), 5-7 weeks (50-500 mgs)