Bio-orthogonal catalysis for cancer therapy

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Meeting 2
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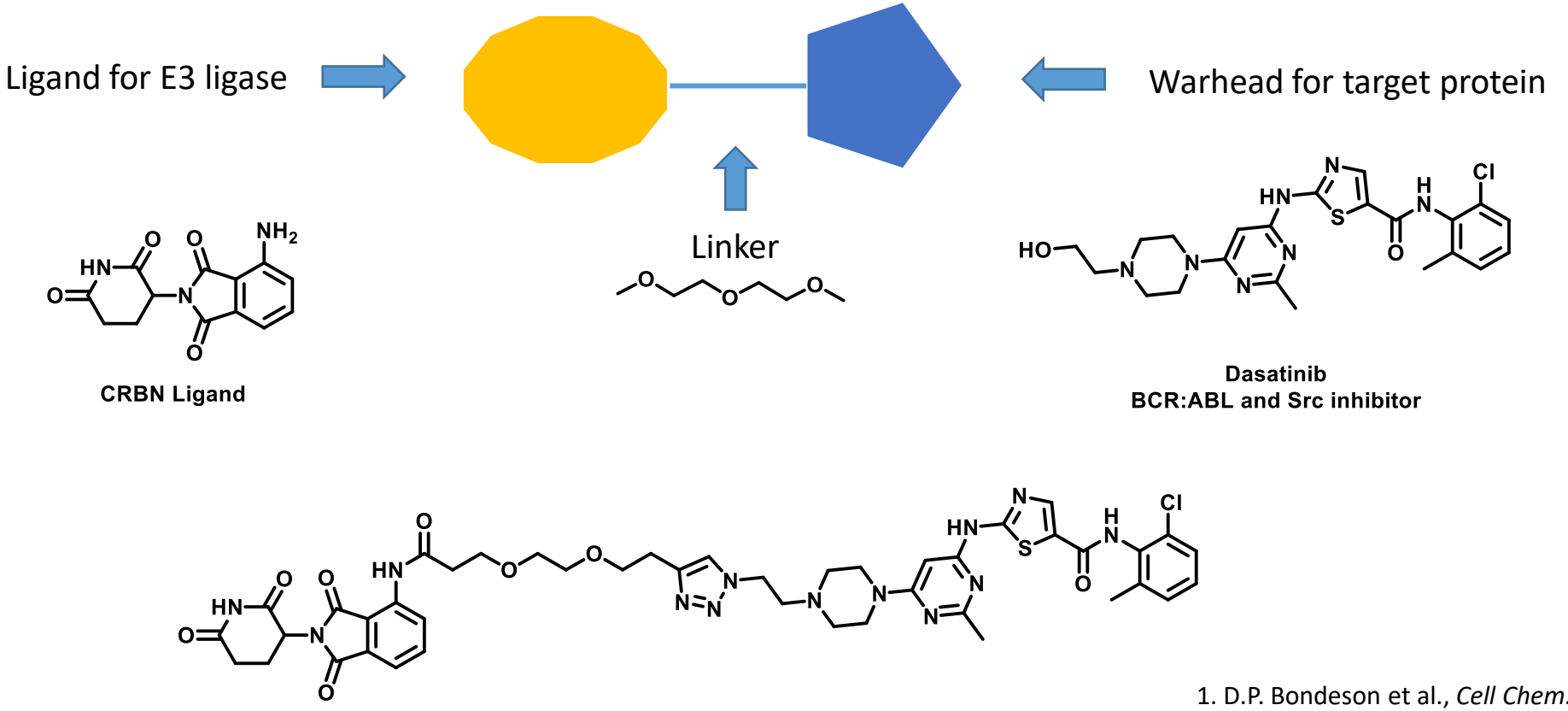
MARIE SKŁODOWSKA-CURIE ACTIONS

Innovative Training Networks (ITN) – Marie Skłodowska-Curie Actions
H2020-MSCA-ITN-2017 (THERACAT-765497)

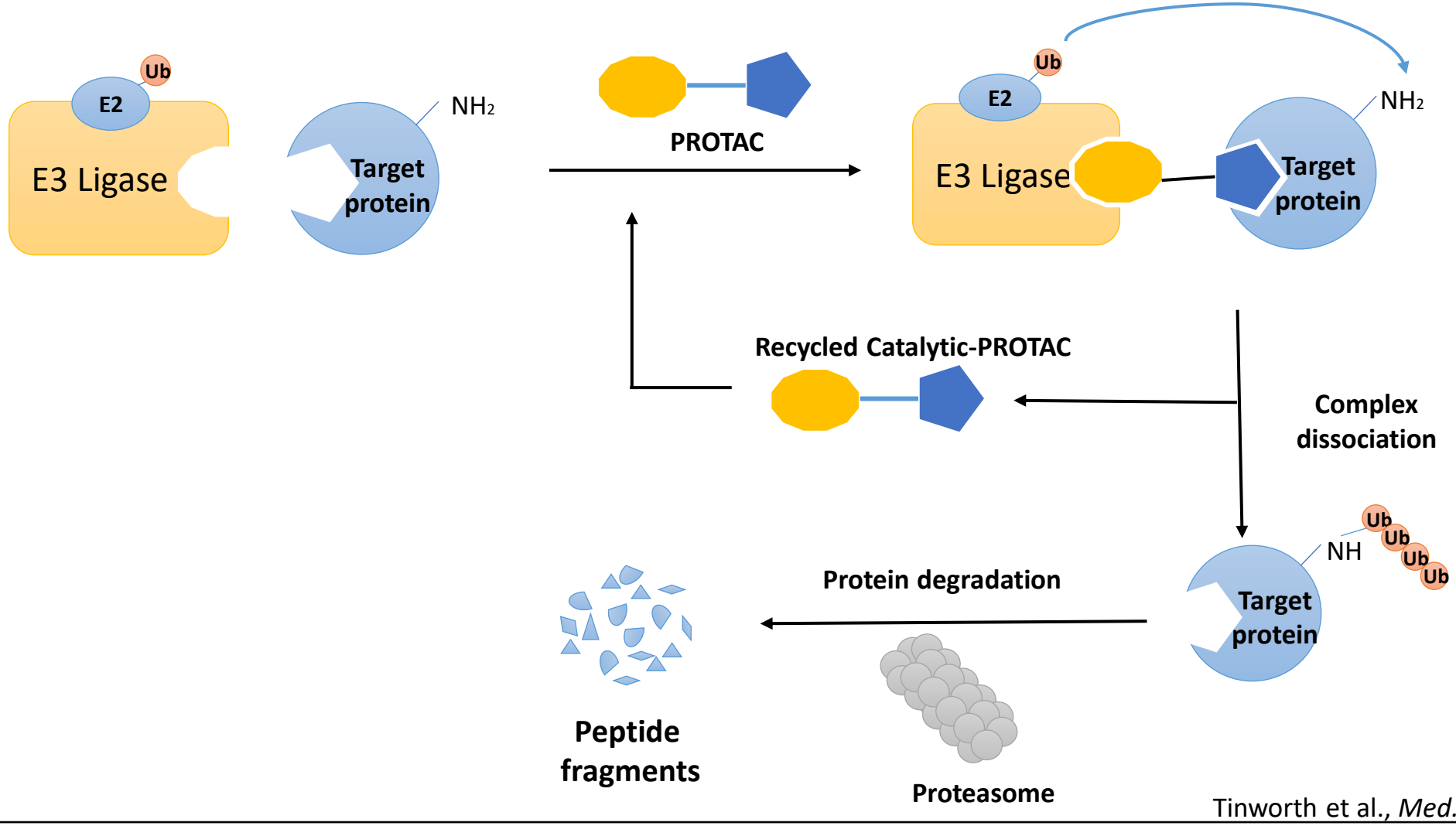
Key components of PROtein TArgetting Chimera (PROTAC)

PROTACs are bivalent ligands that hijack normal cellular processes to mediate the degradation of a target protein



1. D.P. Bondeson et al., *Cell Chem. Biol.*, 2018, **25**, 78–87.

PROTAC induced protein degradation

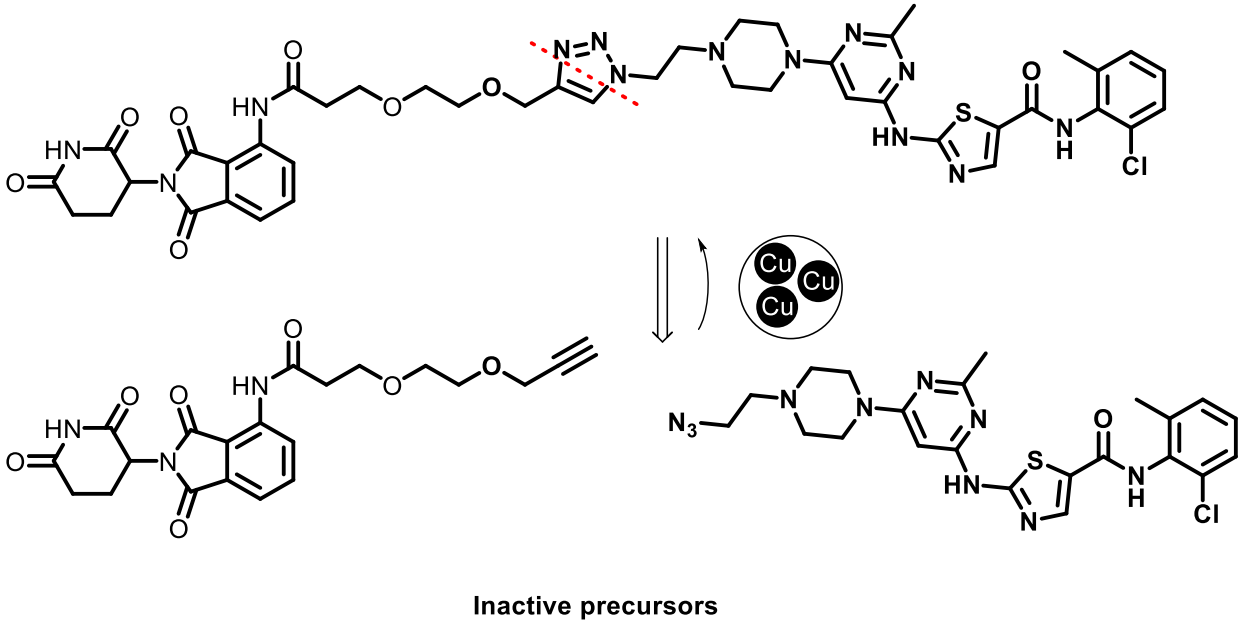


Tinworth et al., *Med.Chem.Comm*. 2016, **7,** 2206.

PROTACs as Therapeutics

Disadvantages of PROTACs

- Toxicity
- Poor PK

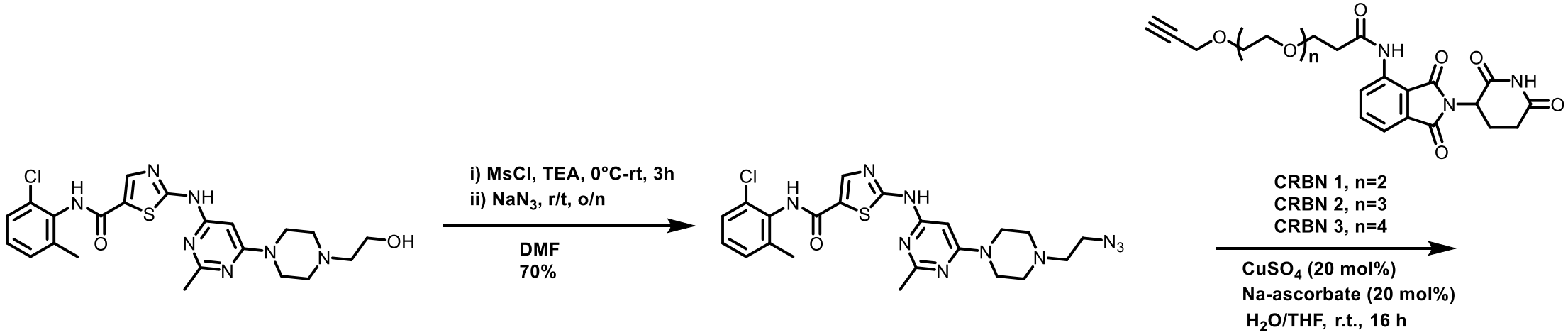


- Physiochemical properties determined by the structure of the drug dictates the PK profile of a drug
- Since their discovery in 2001 there has been no FDA approved PROTAC therapy
- Bio-orthogonal chemistry refers to any chemical reaction that can occur inside a living system without disrupting normal biochemical processes
- *In situ* drug synthesis allows for the controlled generation of a drug from inactive precursors inside an organism

Objectives

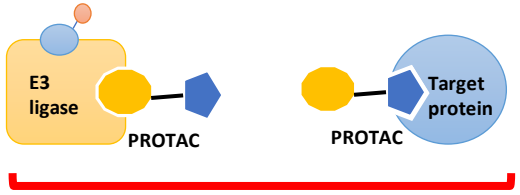
1. Synthesise library of Cu assembled PROTACs
2. Investigate PROTAC assembly study in cell culture

Synthesis of dasatinib library



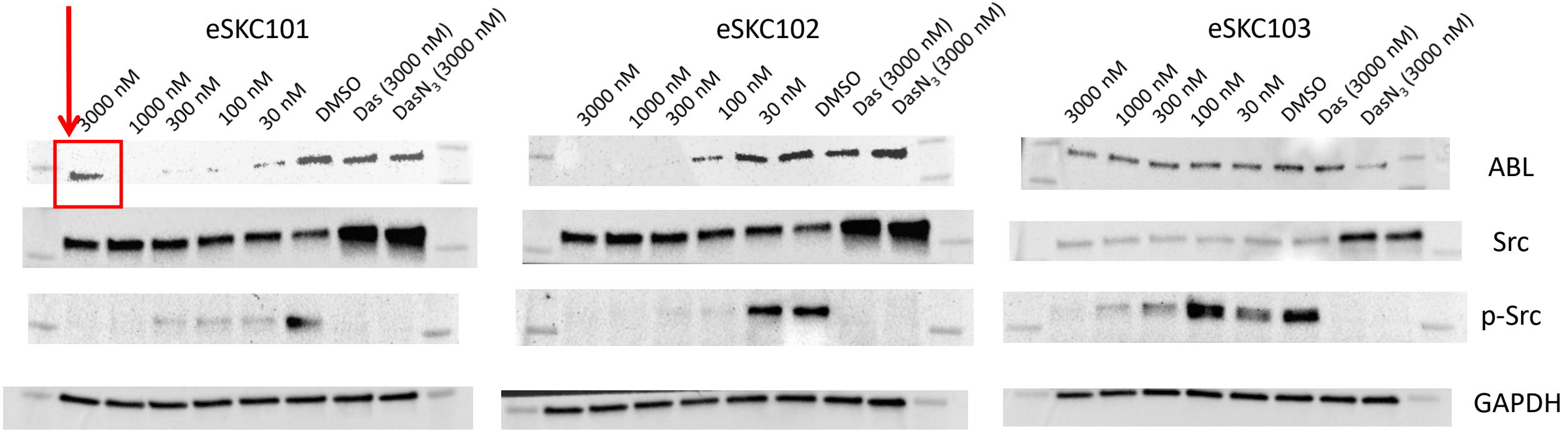
eSKC101, n=2, 25%
eSKC102, n=3, 50%
eSKC103, n=3, 25%

Dasatinib-based PROTACs induce degradation of ABL at low-nanomolar concentrations in MDA-MB-231



Cells were treated with increasing doses of the indicated compounds for 24 hr

Unproductive dimers



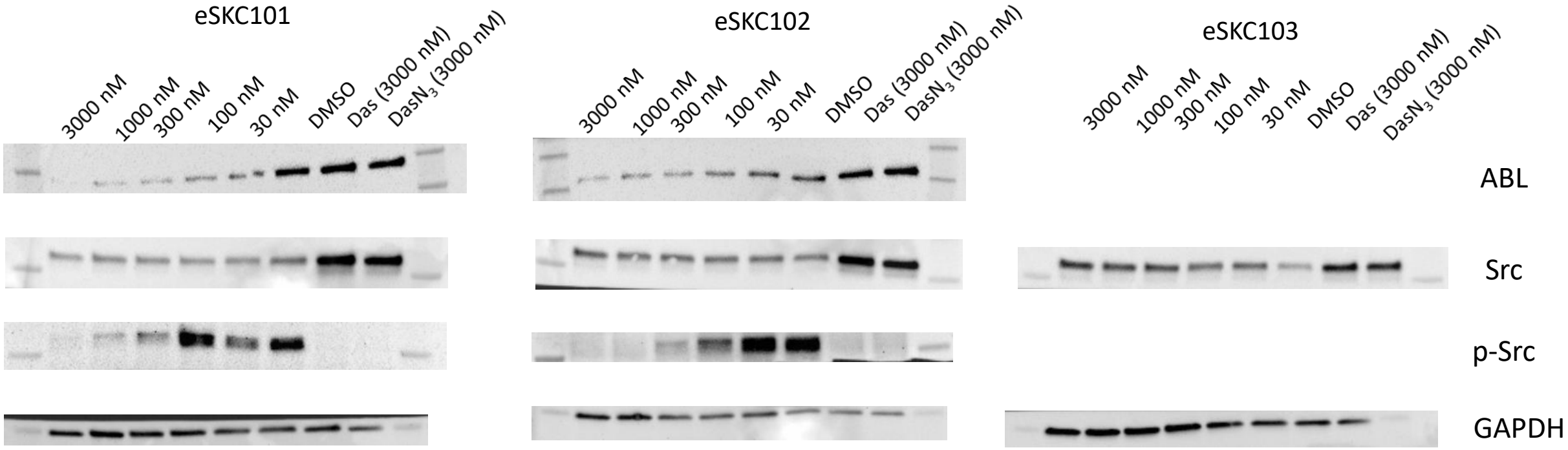
IC_{50} 557 nM

IC_{50} 414 nM

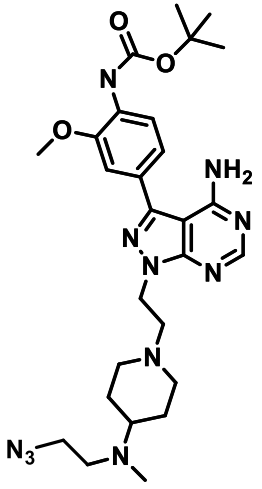
IC_{50} 232 nM

Dasatinib-based PROTACs induce degradation of ABL at low-nanomolar concentrations in MDA-MB-436

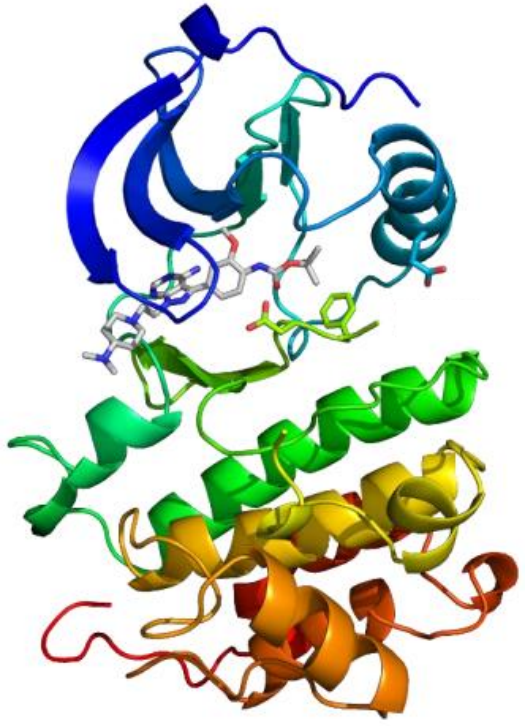
Cells were treated with increasing doses of the indicated compounds for 24 hr



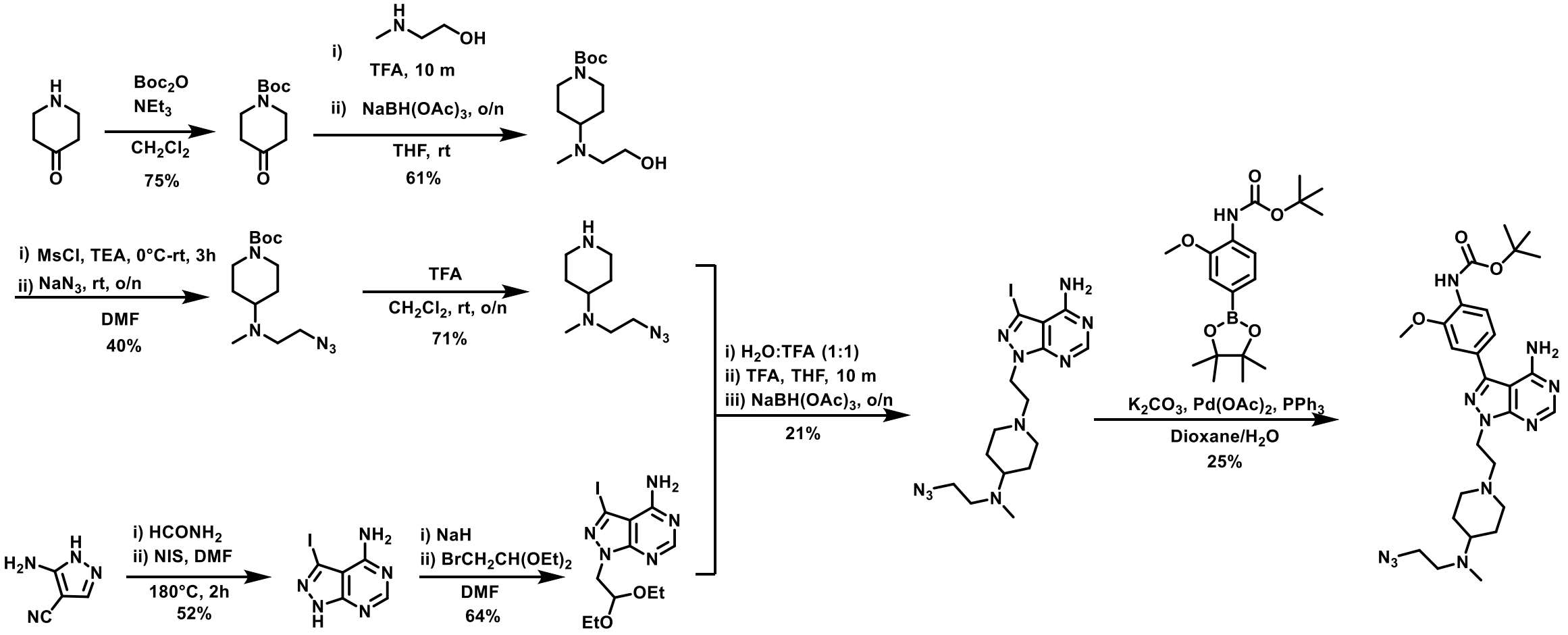
Design of eCF506 based PROTAC



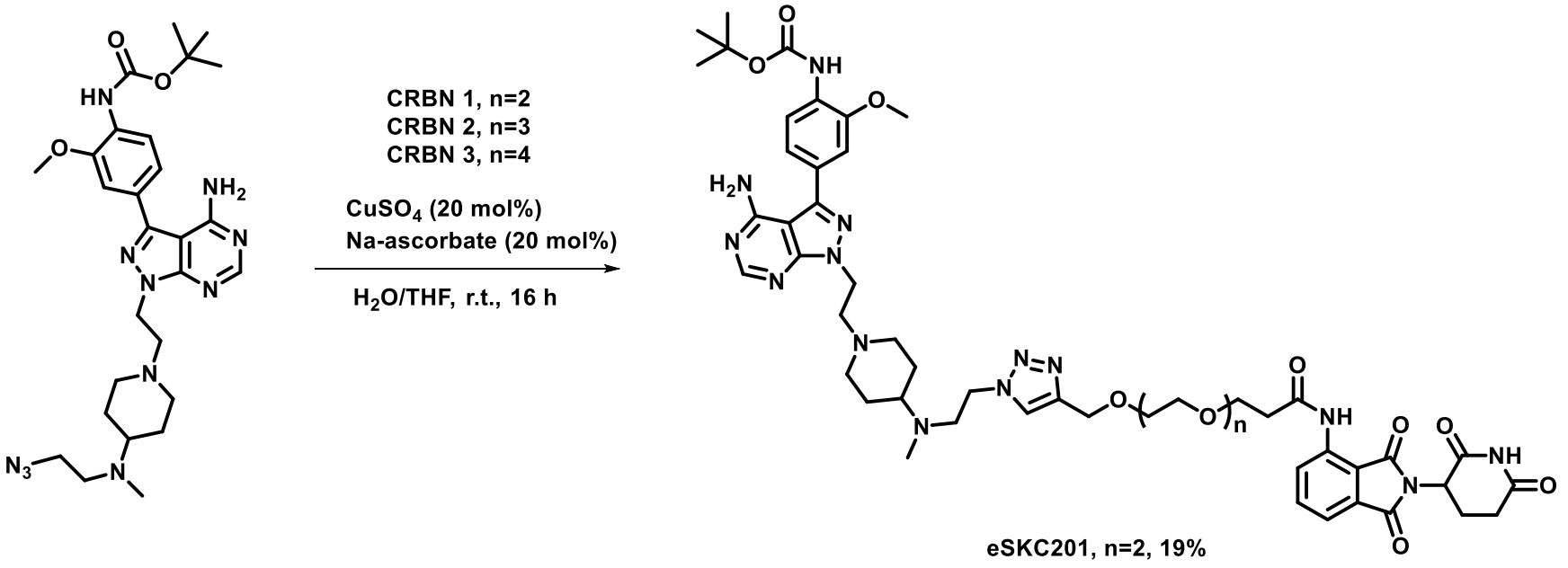
eCF506: Src selective inhibitor



Synthesis of eCF506 library



Synthesis of eCF506 library (Cond't.)

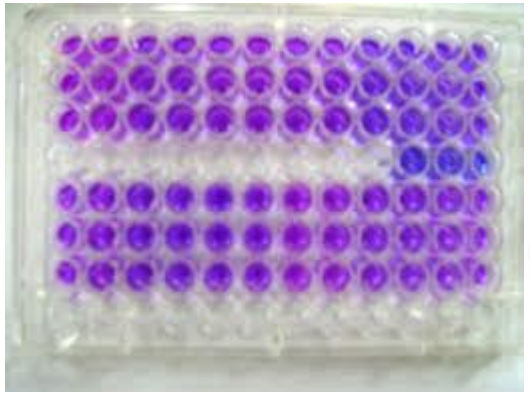


In summary

- Synthetic route established for dasatinib PROTAC series
- Synthetic route established for eCF506 PROTAC series
- Western blots and cell viability assays established
- ABL degradation observed for dasatinib PROTAC series at nanomolar concentraions
- Nanomolar IC_{50} observed for dasatinib PROTAC series in MDA-MB-231 cell line

Scientific and transversal skills training

Scientific skills

Transversal skills

1. Workshops
2. Network Training Events

Communication and dissemination

48th Scottish Regional Organic Division Meeting
University of St Andrews
9th January 2020

CBTDDC
Children's Brain Tumour Drug Delivery Consortium
Accelerating Progress in Drug Delivery

BRITISH PHARMACOLOGICAL SOCIETY

BIOORTHOGONAL & BIORESPONSIVE 2019

Acknowledgements

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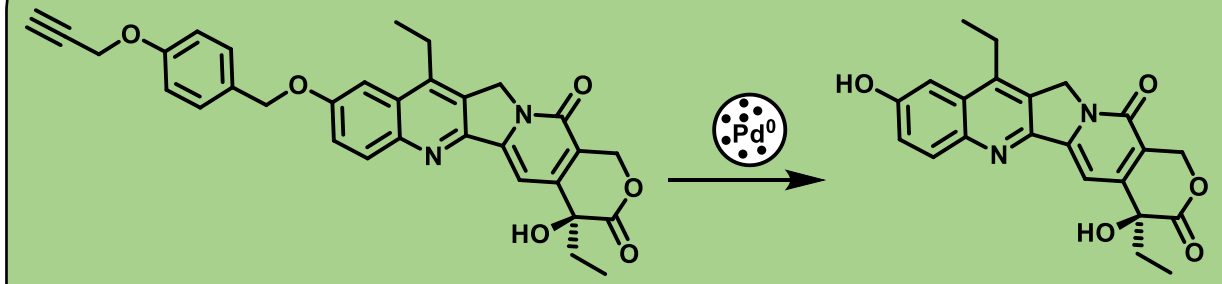
Prof Val Bruton

igmm INSTITUTE OF GENETICS & MOLECULAR MEDICINE
MRC Medical Research Council
CANCER RESEARCH UK
European Commission
Marie Skłodowska-Curie Actions

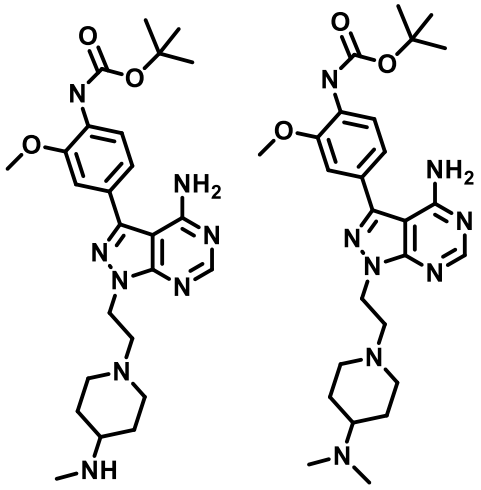
Future work

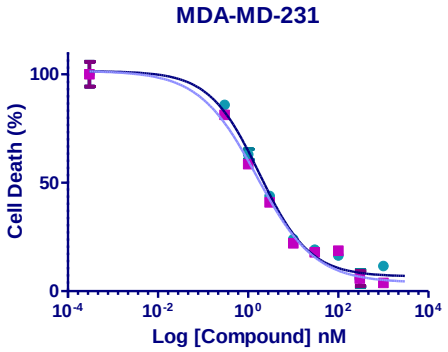
Caged Drugs



SN-38 Prodrug

SN-38
Topoisomerase I inhibitor





eCF606: 2.096 nM
eSKC201: 1.848 nM