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The Development of PI3K Inhibitors as Anticancer Drugs

Andrew James Marshall

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry

Auckland Cancer Society Research Centre
The University of Auckland

July 2010
Phosphatidylinositol 3-kinases (PI3Ks) are a lipid enzyme family that are vitally important regulators of intracellular signalling pathways which control cellular activities including cell survival, growth and proliferation. Deregulation of the PI3K signalling cascade has been observed in a broad range of human diseases including cancer, diabetes, thrombosis, immunity and inflammatory disorders. With the discovery of PI3K’s link to a variety of diseases, there has been a race to produce ATP competitive inhibitors as therapeutic agents against the Class I PI3K isoymes. Herein, compounds from two structurally distinct chemotypes were synthesised and their activity and specificity characterized against isolated Class PI3K enzymes and two cellular lines.

The aryl morpholine containing pyrido[1,2-α]pyrimidines probed the requirements of the Class IA PI3K active sites through modification of the pendant C9 position. Interestingly, no compound synthesised exhibited superior activity towards the p110β enzyme than TGX-221 (1.14). The second series of compounds probed the requirements of the thiazole-linked pyrazolo[1,5-α]pyridine 4.41B, identified through scaffold hopping studies using the novel p110α selective inhibitor PIK-75 (1.34). Although 4.41B was not synthetically accessible, analogues explored alternative linkers and substitution of the 2-methyl-5-nitrobenzene ring, to investigate the effect on p110α selectivity and potency. The sulfone-pyrazole linker group in (5.5) was found to be critical, with alternative linker groups in the thiazole series SO₂CH₂ 4.123, CH₂ 4.122, CHOH 4.114 and linker absent 4.108 ablating activity, while activity was retained by thiazole-CH₂SO₂ 4.124.

As the complexes between the pyrido[1,2-α]pyrimidine and pyrazolo[1,5-α]pyridine chemotypes with the active sites of p110β and p110α respectively are not known, docking simulations were performed using structural p110β models and p110α (pdb:2RD0) respectively to understand the molecular basis for the isoform selectivity exhibited by the two chemotypes. Suitable docking methods were obtained by first investigating the ability of three docking protocols GOLD, SURFLEX and AutoDock to find and correctly rank an experimentally derived conformation both retrospectively (rescoring), where the compounds were docked back into the p110γ crystal, and prospectively, where the ligands were docked into the apo p110α (2RD0).
Acknowledgments

I was very fortunate to work alongside my supervisor Associate Professor Gordon Rewcastle an active bench chemist and group leader. His boyish enthusiasm for chemistry, amazing memory and hard work, to make a difference for cancer patients was a real inspiration for me. Most of all Gordon has been a great friend, confident and chauffeur to my mother and me for many years.

It was a pleasure to work with Dr Jackie Kendall who always kind, ready to listen and encouraging and greatly supported my work on the thiazole linked-pyrazolo[1,5-α]pyridines.

I am indebted to Dr Jack Flanagan who shared and taught me how to use a bewildering array of computation tools, and who also spent countless hours of his time, helping me structure and correct the modelling and biological sides of the project into a cohesive whole.

Thanks to my main supervisor Professor Bill Denny who took me on, provided office and lab space in an incredible working environment with world class researchers, and a challenging project that became a component of a drug development program. I am also appreciative to Bill for securing a generous scholarship from the Maurice Wilkins Centre for Molecule Biodiscovery which made the generation of this work possible. I sincerely hope that I am not the last chemistry student for the next 20 years to work in the unique multidisciplinary organization of the ACSRC.

I am appreciative towards my fellow chemists on the PI3K project Swarna Gamage, Anna Giddens and Sophia Tsang for their helpful advice, and who did an amazing amount of work to meet commercial deadlines imposed by Pathway Therapeutics.

I am grateful to our amazing NMR technologists Dr Maruta Boyd, Dr Shannon Black and Dr Stephanie Maurer for their work on obtaining spectra, and assistance in interpreting spectra. I would also like to thank Dr Brian Palmer and Adrian Blaser for looking after the LCMS and element analysis services.

I am appreciative to Mr Wilson Sun for distilling solvent for column chromatography, finding and purchasing chemicals and the best possible price and maintaining a laboratory store second to none. Further, my thanks to Mr Sisira Kumara and Mrs Karin Tan for their analytic and preparative HPLC work on my compounds respectively.
Thanks to Professor Bruce Baguley who headed work on cancer biology aspect of the PI3K project, and whom provided many mornings of stimulated discussion whilst walking through Newmarket and the Auckland Domain. I would also like to thank Claire Mawson, Jo Yu for testing my insoluble compounds in laborious isolated enzyme assays, Steve Jamieson Emma Richardson, Wayne Joseph, Laura Broome and my mother Elaine, for cell culture work and Phil Kestell and Ripu Singh who conducted the pharmacology aspect of the project.

Thanks to our collaborators from the Department of Molecular Medicine and Pathology headed by Professor Peter Shepherd and the team consisting of Christina Buchanan, Claire Chaussade, Kitty Cho, Sharada Kolekar, Woo-Jeong Lee and Alisha Malik who conducting isolated enzyme assays.

I am grateful to my friends and colleges of the “Coffee Crew” Drs Amir Ashoorzadeh, Anna Giddens, Hamish Sutherland, Daniel Heinrich, Kit Tsang, Dani Lyons, Patrick O’Connor, Mrs Leigh-Anne Parish and Miss Charu Reddy, for the laughs and good times.

I would like to thank my close friends; Veeb and Karmon, Scott and Joe, Beau and Merita and Paul and Kim for their love, support and fun times over the long years.

A special thanks to my girlfriend Jessica Dunn who has loved, supported me, and put up with my moods over the years, and to her family (especially her father who took a keen interest in my studies).

Finally, a big thank you goes to my family, especially my mother, father, and brother Geoffrey for their love, support and encouragement over the years.
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This is to certify that:

1. the thesis comprises only my original work towards the PhD except where indicated below;
2. due acknowledgment has been made in the text to all other material used.

My project was part of an established and multi-disciplinary drug development program exploring inhibitors of PI3K, comprised of Chemistry, Biology (Prof. Bill Denny and Prof. Bruce Baguely, ACSRC) and Molecular Biology (Prof. Peter Sheperd, MMP). To indicate the rationale for exploring the sulfonyl-thiazole linker moiety in Chapters 4 and the observed SAR presented in Chapter 5, these Chapters include data from compounds not synthesised by the Author: Chapter 4 (Tables 4.1 and 4.2) and Chapter 5 (Table 5.1) present data from a series of compounds synthesised by Jackie Kendall (ACSRC). Furthermore, molecular modelling work conducted by Raphael Frederick (ACSRC) was included to illustrate a hypothetical binding mode for the series, presented in Chapter 4 (Figures 4.2 and 4.3).

Compounds synthesised in the PI3K program were screening against isolated enzyme panel consisting of p110α, p110β and p110δ. The IC\textsubscript{50} values are obtained from a kinase assay that measures radioactive phosphatidylinositol 3-phosphate (PIP), produced by the p110-p85 heterodimer phosphorylation of phosphatidylinositol (PI). Claire Mawson, Jo Yu (ACSRC), Kitty Cho, Sharada Kolekar, Woo-Jeong Lee and Alisha Malik (MMP) ran these assays under the supervision of Prof Peter Sheperd.

Cellular antiproliferative data were also obtained from two human tumour cell lines, by measuring radioactive thymidine incorporation. NZB5 is derived from a brain cancer, and has wild-type PI3K, while NZOV9 (an ovarian tumour cell line) contains mutation Y1021C in the p110α helical domain. Emma Richardson, Wayne Joseph, Laura Broome, and Elaine Marshall carried out the cellular assays, under the supervision of Prof. Bruce Baguely.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Ac:</td>
<td>Acetyl</td>
</tr>
<tr>
<td>AcOH:</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>APCI:</td>
<td>Atmospheric pressure chemical ionization</td>
</tr>
<tr>
<td>aq.:</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar:</td>
<td>Aromatic</td>
</tr>
<tr>
<td>Boc / BOC:</td>
<td>tert-Butyloxy carbonyl</td>
</tr>
<tr>
<td>br:</td>
<td>Broad</td>
</tr>
<tr>
<td>Bu:</td>
<td>Butyl</td>
</tr>
<tr>
<td>C:</td>
<td>Celsius</td>
</tr>
<tr>
<td>cat.:</td>
<td>Catalytic</td>
</tr>
<tr>
<td>cm:</td>
<td>Centimetre</td>
</tr>
<tr>
<td>Conc.:</td>
<td>Concentrated</td>
</tr>
<tr>
<td>COSY:</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>d:</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd:</td>
<td>Doublet of doublets</td>
</tr>
<tr>
<td>ddd:</td>
<td>Doublet of doublet of doublets</td>
</tr>
<tr>
<td>dil.:</td>
<td>Dilute</td>
</tr>
<tr>
<td>DIPEA:</td>
<td>Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP:</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF:</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO:</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>dq:</td>
<td>Doublet of quartets</td>
</tr>
<tr>
<td>dt:</td>
<td>Doublet of triplets</td>
</tr>
<tr>
<td>EDG:</td>
<td>Electron donating group</td>
</tr>
<tr>
<td>EDTA:</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EI:</td>
<td>Electron impact ionization</td>
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<tr>
<td>Et:</td>
<td>Ethyl</td>
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<td>EtOAc:</td>
<td>Ethyl acetate</td>
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<td>EtOH:</td>
<td>Ethanol</td>
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<tr>
<td>eV:</td>
<td>Electron volt</td>
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<td>g:</td>
<td>Gram</td>
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<tr>
<td>hr:</td>
<td>Hour</td>
</tr>
<tr>
<td>HPLC:</td>
<td>High performance liquid chromatography</td>
</tr>
</tbody>
</table>
HRMS: High resolution mass spectroscopy
HSQC: Heteronuclear single quantum coherence
Hz: Hertz
'Pr / i-Pr: iso-Propyl
LDA: Lithium diisopropylamide
LHMDS: Lithium hexamethyldisilazide
lit.: Literature
m.p.: Melting point
m: Multiplet (NMR)
m-CPBA: meta-Chloroperoxybenzoic acid
Me: Methyl
MeOH: Methanol
mg: Milligram
MHz: Megahertz
min: Minute
mmol: Millimol
Ms: Methanesulfonyl, Mesyl
"Bu / n-Bu: n-Butyl
NMR: Nuclear magnetic resonance
NO: Nitric oxide
NOE: Nuclear Overhauser effect
Ph: Phenyl
ppm: Part per million
Pr: Propyl
py: Pyridine
q: Quartet
qd: Quartet of Doublets
r.t.: Room temperature
s: Singlet (NMR)
T / temp.: Temperature
t: Triplet
TBAB: Tetrabutylammonium Bromide
'tBu / t-Bu: tert-Butyl
td: Triplet of doublets
TFA: Trifluoroacetic acid
THF: Tetrahydrofuran
Amino acids

<table>
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<tr>
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<th>Amino Acid</th>
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<tbody>
<tr>
<td>Ala (A)</td>
<td>Alanine</td>
</tr>
<tr>
<td>Arg (R)</td>
<td>Arginine</td>
</tr>
<tr>
<td>Asn (N)</td>
<td>Asparagine</td>
</tr>
<tr>
<td>Asp (D)</td>
<td>Aspartic acid</td>
</tr>
<tr>
<td>Cys (C)</td>
<td>Cysteine</td>
</tr>
<tr>
<td>Gln (Q)</td>
<td>Glutamine</td>
</tr>
<tr>
<td>Glu (E)</td>
<td>Glutamic acid</td>
</tr>
<tr>
<td>Gly (G)</td>
<td>Glycine</td>
</tr>
<tr>
<td>His (H)</td>
<td>Histidine</td>
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<td>Ile (I)</td>
<td>Isoleucine</td>
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<td>Leu (L)</td>
<td>Leucine</td>
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<td>Lysine</td>
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<td>Tyr (Y)</td>
<td>Tyrosine</td>
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<tr>
<td>Val (V)</td>
<td>Valine</td>
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Abbreviations (Molecular and Cellular biology)

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Akt/PKB:</td>
<td>v-akt murine thymoma viral oncogene homolog 1</td>
</tr>
<tr>
<td>ATM:</td>
<td>Ataxia telangiectasia mutated gene product</td>
</tr>
<tr>
<td>AML:</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>BAD:</td>
<td>Bcl2-antagonist of cell death</td>
</tr>
<tr>
<td>CDK:</td>
<td>Cyclin dependent kinase</td>
</tr>
<tr>
<td>CK2:</td>
<td>Casein kinase 2</td>
</tr>
<tr>
<td>cDNA:</td>
<td>Complimentary Deoxyribonucleic acid</td>
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</tbody>
</table>
DNA: Deoxyribonucleic acid
DNA-PK: DNA-dependent protein kinase
EGFR: Epidermal growth factor receptor
GBM: Glioblastoma multiforme
GPCR: G-protein-coupled receptor
GSK3: Glycogen synthesis kinase 3
HIF-1α: Hypoxia-inducible factor 1α
IRS: Insulin receptor substrate
mTOR: Mammalian target of rapamycin
MLCK: Myosin light chain kinase
n.d: Not determined
PAF: Platelet activated factor
PH: Pleckstrin homology
PI3K: Phosphatidylinositol 3-kinase
PI: Phosphatidylinositol
PIP: Phosphatidylinositol 4-phosphate
PIP₂: Phosphatidylinositol 4,5-bisphosphate
PIP₃: Phosphatidylinositol 3,4,5-trisphosphate
PKB/Akt: Protein kinase B
PKC: Protein kinase C
PIKK: PI3K-related kinase
PLK: Polo-like kinase
PTEN: Phosphatase and tensin homologue
PIK3CA: cDNA for the human p110α subunit of PI3K
PIK3CB: cDNA for the human p110β subunit of PI3K
PIK3CD: cDNA for the human p110δ subunit of PI3K
PIK3CG: cDNA for the human p110γ subunit of PI3K
PK: Pharmacokinetics
RAS: oncogenes causing Rat sarcoma
RTK: Receptor tyrosine kinase
VEGF: Vascular endothelial growth factor
Vps34: Vacuolar protein sorting 34