Thesis title:

SMALL MOLECULE INHIBITORS OF 
THE HEDGEHOG SIGNALLING PATHWAY 
AS CANCER SUPPRESSING AGENTS

Thesis submitted in fulfilment of the requirement for the award of the degree of

DOCTOR OF PHILOSOPHY

(BIOLOGICAL SCIENCES)

BY

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M.S.

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              Prof. Eileen A. McLaughlin
              Dr. Christopher P. Gordon

April 2016
Statements of originality and authorship

I hereby certify that this thesis contains no material which has been accepted for the award of any other degree or diploma in any University or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University’s Digital Repository, subject to the provisions of the Copyright Act 1968.

Furthermore, I hereby certify that the work embodied in this thesis contains published journal articles of which I am the first author. I have included as part of the thesis a written statement, endorsed by my primary supervisor, attesting to my contribution to the joint publications.

Nguyen Trieu Trinh
29 April 2016
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Statement of contribution

I hereby certify that this thesis is submitted in the form of a series of published/submitted papers of which I am the first author. I have included as part of the thesis a written statement from each senior co-author; and endorsed by the Faculty Assistant Dean of Research Training, attesting to my contribution to the following joint publications:


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Date: 02/11/2016
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Date: of Research
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Among various options to treat cancers, targeting the signalling pathways that are differentially expressed in specific cancer cells has developed as a promising approach. Whilst huge benefits of targeted therapies have been obtained with less severe side effects and higher survival rates than past experiences with traditional cytotoxic chemotherapy, the application of selective targeting is hindered and in part determined by the knowledge of the molecular biology of each cancer. Cancers are so diverse in nature expressing distinctive signalling pathways or components, whose biological elucidation is challenging but invaluable to the development of cancer treatment. In this respect, the Hedgehog Signalling Pathway (HSP) has become as an attractive target in a number of human cancers thanks to its unique mechanism of activity.

The HSP plays a pivotal role in the spatial and temporal regulation of cell proliferation and differentiation. Conversely aberrant Hh signalling is involved in Gorlin syndrome, basal cell carcinoma (the most common cancer in the world), and more than one third of all human medulloblastoma cases. In all of these cases, it is believed that deregulated Hh signalling leads to increased cell proliferation and tumour formation. Inhibition of the Hedgehog Signalling Pathway, is a recently validated anti-cancer drug target, with vismodegib (GDC-0449, Erivedge®) and sonidegib (LDE225, Odomzo®), approved by the U.S. Food and Drug Administration for treatment of early and advanced basal cell carcinomas.

We developed three new scaffolds of small molecule inhibitors of the HSP. The first scaffold consisted of 11 quinolone-2-(1H)-ones developed from a sequential Ugi-Knoevenagel reaction pathway (Chapter 3). These analogues not only express their anti-hedgehog activity through the significant inhibition of Gli2 at both gene and protein expression in SAG-activated Shh LIGHT 2 cells at 10 and 25 µM, respectively, but are able to suppress a panel of nine human HSP expressing cancer cells (GI50 from 2.9 to 18.0 µM). Whilst the exact mechanism remains to be determined, it is probable the inhibition observed is occurring downstream of Smo, due to its activity in the presence of SAG, a potent Smo activator.

Subsequent second and third generation analogues were developed on the quinolone-2-(1H)-one pharmacophore, which highlighted the importance of a C3-tethered indole moiety. These new scaffolds were built on tryptophan (9 analogues, Chapter 4) and benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amine derivatives (11 analogues, Chapter 4) displaying superior inhibitory activity against Gli protein expression with the best inhibitors displaying submicromolar IC50 (Chapter 4). Noteworthy, active compounds from the second and third libraries displayed inhibitory activity downstream of Smo, which circumvents the resistance issues experienced by the Smo inhibitors currently in use.
We discovered the fourth library of 1,3-thiazine-6-phenylimino-5-carboxylates in a multicomponent one pot synthesis (12 analogues, Chapter 5). These analogues display structural similarities to HPI-1, a non-selective Gli inhibitor, and thus may present themselves as HSP inhibitors. Current biological evaluation is going on to investigate their anti-hedgehog properties.

Additionally, using flow technique we have synthesised the potent Smo inhibitor LDE-225, as well as a number of aldehydes containing the furan-based biaryl motif (Chapter 2). This motif is available in biological active compounds, including the HSP inhibitors, and thus presents an opportunity to develop new scaffolds of HSP inhibitors.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>Carbon-13 nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>$^1$H</td>
<td>Proton nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>3CR</td>
<td>Three component reaction</td>
</tr>
<tr>
<td>4CR</td>
<td>Four component reaction</td>
</tr>
<tr>
<td>A2780</td>
<td>Human ovarian carcinoma cell line</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetate</td>
</tr>
<tr>
<td>Acetone-$d_6$</td>
<td>Deuterated acetone</td>
</tr>
<tr>
<td>ACN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>Ar</td>
<td>Aromatic</td>
</tr>
<tr>
<td>BCC</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>BCL2</td>
<td>B-cell CLL/lymphoma 2</td>
</tr>
<tr>
<td>BE2-C</td>
<td>Human neuroblastoma cell line</td>
</tr>
<tr>
<td>BM11</td>
<td>B lymphoma Mo-MLV insertion region 1 homolog</td>
</tr>
<tr>
<td>BRD4</td>
<td>Bromodomain-containing protein 4</td>
</tr>
<tr>
<td>bs</td>
<td>Broad singlet (NMR)</td>
</tr>
<tr>
<td>C3H10T1/2</td>
<td>Mouse mesenchymal cell line</td>
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<tr>
<td>CatCart™</td>
<td>Catalyst cartridges for use in ThalesNano flow reactors</td>
</tr>
<tr>
<td>CDC13</td>
<td>Deuterated chloroform</td>
</tr>
<tr>
<td>CK1</td>
<td>Casein kinase 1</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic myeloid leukaemia</td>
</tr>
<tr>
<td>CSC</td>
<td>Cancer stem cell</td>
</tr>
<tr>
<td>d</td>
<td>Doublet (NMR)</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublet (NMR)</td>
</tr>
<tr>
<td>Dhh</td>
<td>Desert hedgehog</td>
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<tr>
<td>DIPEA</td>
<td>Diisopropylamine</td>
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<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
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<tr>
<td>DMSO-$d_6$</td>
<td>Deuterated dimethyl sulfoxide</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>DU145</td>
<td>Human prostate carcinoma cell line</td>
</tr>
<tr>
<td>ELK1</td>
<td>ETS-like gene 1</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
</tbody>
</table>
**EtOH**  Ethanol
**FC**  FibreCat
**Fmoc**  Fluorenylmethyloxycarbonyl chloride
**g**  Gram
**GI**<sub>50</sub>  Concentration of drug that reduces cell growth by 50% relative to an untreated control
**Gli**,<sub>1,2,3</sub>  Glioma-associated oncogene homolog 1,2,3
**GLI**  Glioma-associated protein
**GSK3β**  Glycogen synthase kinase 3β
**h**  Hour
**H460**  Human lung carcinoma cell line
**HATU**  1-[(Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
**HCl**  Hydrochloric acid
**H-Cube Pro™**  Flow hydrogenation reactor
**HDAC**  Histone Deacetylase (HDACs) enzymes
**Hh**  Hedgehog
**Hhat**  Hedgehog acyltransferase
**Hip**  Hedgehog interacting protein
**HPI**  Hedgehog signalling pathway inhibitor
**HPLC**  High performance liquid chromatography
**HRMS**  High resolution mass spectra
**HSP**  Hedgehog signalling pathway
**HT29**  Human colorectal carcinoma cell line
**Hz**  Hertz
**IC**<sub>50</sub>  Concentration of a drug required to reduce enzyme/protein activity by 50%
**Ihh**  Indian hedgehog
**IR**  Infra-red
**J**  Coupling constant in Hz
**LRMS**  Low resolution mass spectra
**LXR**  Liver X receptor
**M**  Molar
**m**  Multiplet (NMR)
**MCF-7**  Human breast adenocarcinoma cell line
**MeOH**  Methanol
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>MHz</td>
<td>Mega Hertz</td>
</tr>
<tr>
<td>MIA-Paca-2</td>
<td>Human Pancreatic carcinoma cell line</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mL.min(^{-1})</td>
<td>Millilitre per minute</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
</tr>
<tr>
<td>MSX2</td>
<td>Homeobox msh-like</td>
</tr>
<tr>
<td>NANOG</td>
<td>Early embryo specific expression NK-type homeobox protein</td>
</tr>
<tr>
<td>NanoHHI</td>
<td>HPI-1 encapsulated by nanoparticles</td>
</tr>
<tr>
<td>NFkB</td>
<td>Nuclear factor kappa-light-chain-enhancer of activated B cells</td>
</tr>
<tr>
<td>NIH 3T3</td>
<td>Mouse embryo fibroblast cell line</td>
</tr>
<tr>
<td>nm</td>
<td>Nanometre</td>
</tr>
<tr>
<td>nM</td>
<td>Nanomolar</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>N-Myc</td>
<td>Myelocytomatosis viral oncogene homolog</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>PANC1</td>
<td>Human pancreatic carcinoma, epithelial-like cell line</td>
</tr>
<tr>
<td>Pd Tetrakis</td>
<td>Palladium Tetrakis catalyst</td>
</tr>
<tr>
<td>Pd(OH)(_2)/C</td>
<td>Palladium hydroxide/Carbon hydrogenation catalyst</td>
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<td>Pd/C</td>
<td>Palladium/Carbon hydrogenation catalyst</td>
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<tr>
<td>PdCl(_2)(PPh(_3))(_2)-DVB</td>
<td>Bis-triphenylphosphine CatCart™ catalyst</td>
</tr>
<tr>
<td>PDE4</td>
<td>Phosphodiesterase 4</td>
</tr>
<tr>
<td>PGF</td>
<td>Prostaglandin F</td>
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<tr>
<td>PI3/ALK/Mtor</td>
<td>Phosphoinositide 3-kinase pathway</td>
</tr>
<tr>
<td>PKA</td>
<td>Protein kinase A</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PTCH1</td>
<td>Hedgehog ligand receptor patched 1</td>
</tr>
<tr>
<td>Ptc(_h)(_1)</td>
<td>Gene of hedgehog ligand receptor patched</td>
</tr>
<tr>
<td>PTM</td>
<td>Post translational modification</td>
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<tr>
<td>q</td>
<td>Quartet (NMR)</td>
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<tr>
<td>RAS/RAF/MEK/ERK</td>
<td>Mitogen-activated protein kinases pathway</td>
</tr>
<tr>
<td>RP-HPLC</td>
<td>Reverse phase High performance liquid chromatography</td>
</tr>
<tr>
<td>Rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Rt</td>
<td>Retention time</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>RTK</td>
<td>Receptor tyrosine kinases</td>
</tr>
<tr>
<td>s</td>
<td>Singlet (NMR)</td>
</tr>
<tr>
<td>SAG</td>
<td>Smoothened agonist</td>
</tr>
<tr>
<td>Shh</td>
<td>Sonic hedgehog</td>
</tr>
<tr>
<td>SHH LIGHT2</td>
<td>Fibroblast reporter cell line</td>
</tr>
<tr>
<td>Smo</td>
<td>Smoothened protein</td>
</tr>
<tr>
<td>SNAIL</td>
<td>Zinc-finger transcription factors</td>
</tr>
<tr>
<td>SUFU</td>
<td>Suppressor of fused protein</td>
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<tr>
<td>SW480</td>
<td>Human colorectal carcinoma</td>
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<tr>
<td>t</td>
<td>Triplet (NMR)</td>
</tr>
<tr>
<td>TBAA</td>
<td>Tetrabutylammonium acetate</td>
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<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TCAM-2</td>
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<tr>
<td>TEA</td>
<td>Triethylamine</td>
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<td>TGF-β</td>
<td>Transforming growth factor β</td>
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<td>TLC</td>
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<tr>
<td>TM3</td>
<td>Murine testis Leydig cell line</td>
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<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet light</td>
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<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<td>Nuclear Ser/Thr phosphatase</td>
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<td>Wingless-related integration site</td>
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<tr>
<td>X-Cube™</td>
<td>Flow Reactor</td>
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<td>δ</td>
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