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QUINOLINE-TYPE COMPOUNDS:
ASYMMETRIC CATALYTIC REACTION
AND THEIR BIOLOGICAL ACTIVITIES

CHAN SAU HING

Ph.D

The Hong Kong Polytechnic University

2013
The Hong Kong Polytechnic University

Department of Applied Biology & Chemical Technology

Quinoline-type Compounds: Asymmetric Catalytic Reaction and Their Biological Activities

CHAN Sau Hing

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

April 2013
Certificate of Originality

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___________________
CHAN Sau Hing
Abstract of thesis entitled “Quinoline-type Compounds: Asymmetric Catalytic Reaction and Their Biological Activities”

Submitted by CHAN Sau Hing
For the degree of Doctor of Philosophy
at The Hong Kong Polytechnic University in April 2013

The dipyridinyl phosphine ligand \textbf{P-Phos} was proven to be effective for many catalytic reactions. Herein the iridium-complex catalyzed asymmetric hydrogenation of 8-hydroxyquinoline substrates with the newly synthesized dipyridinyl phosphine type ligands was investigated. The electronic properties of the dipyridinyl phosphine type ligands had a significant effect on the enantioselectivities of 8-substituted 1,2,3,4-tetrahydroquinoline compounds. High enantioselectivities were observed for most 8-substituted quinoline compounds with ligands containing the electron-donating OMe group at the \textit{para}-position with ee up to 96%. However, lower enantioselectivities were obtained with ligands containing the electron-withdrawing CF$_3$ group at the \textit{para}-position.

Asymmetric transfer hydrogenation could be an alternative method to produce optically active compounds. In this project, the efficiency of easily synthesized chiral quinoline-based ligand 1-((1R,2R)-2-aminocyclohexyl)-3-(quinolin-8-yl)urea has been
evaluated in the ruthenium catalyzed asymmetric transfer hydrogenation of aromatic ketones in isopropanol with ee up to 84%. This catalyst could be recovered and reused in room temperature ionic liquid and polyethylene glycol at least five times with no significant loss of enantioselectivities.

The quinoline derivatives and their possible cytotoxic potential towards human cancer cell lines were described in this project. 8-Hydroxy-2-quinolinecarbaldehyde, 2-methyl-1,2,3,4-tetrahydroquinolin-8-ol, 2-methyl-8-(4-(trifluoromethyl)benzyl)oxy)-1,2,3,4-tetrahydroquinoline, and 5,7-dibromo-2-methyl-1,2,3,4-tetrahydroquinolin-8-ol showed the best in vitro cytotoxicity against a plane of human cancer cell lines that include MDA231, T-47D, Hs578t, SaoS2, K562, SKHep, Hep3B, KYSE150, HKESC-3, HKESC-4 and MCF-7 with MTS_{50} range of 3.1-12.5μg/ml. The experimental results showed that these quinoline compounds were potential anti-tumor agents. Further in vivo results showed that the dosage of 5-10mg/kg/day (i.p. injection for 9 to 20 days) could completely abolish the growth of the Hep3B hepatocellular and KYSE150 esophageal tumor xenograft on athymic nude mice model compared with the control, with no damage to vital organs at the histological level.
Publications and Conference Papers

Paper


Patent


Conference

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**Abbreviations**

A549  Human Lung Adenocarcinoma Epithelial Cell Line  
BINAP  2,2’-Bis (diphenylphosphino)-1,1’-binaphthyl  
BMIMBF₄  1-Butyl-3-methylimidazolium tetrafluoroborate  
BMIMNTf₂  1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl) imide  
CDDP  Cisplatin  
CL-MeO-Biphep  5,5’-Dichloro-6,6’-dimethoxy-2,2’-bis(diphenylphosphino)-1,1’-biphenyl  
Difluorphos  5,5’-Bis(diphenylphosphino)-2,2,2’,2’-tetrafluoro-4,4’-bi-1,3-benzodioxole  
DMAP  4-Dimethylaminopyridine  
DMEM  Dulbecco’s Modified Eagle’s Medium  
DMPEG  Polyethylene Glycol Dimethyl Ether  
DMSO  Dimethyl Sulfoxide  
e  Enantiomeric Excess  
ESCC  Esophageal Squamous Cell Carcinomas  
ESI  Electron Spray Ionization (in mass spectrometry)  
FBS  Fetal Bovine Serum  
Hep3B  Human Hepatoma Cell Line  
HKESC-1  Esophageal Cancer Cell Line  
HKESC-4  Esophageal Cancer Cell Line  
Hs578t  Human Breast Cancer Cell Line  
Ip  Intraperitoneal  
[Ir(COD)Cl]₂  Chloro-1,5-cyclooctadiene Iridium(I) dimer  
K562  Human Erythroleukemia Cell Line  
KYSE150  Human Oesophageal Squamous Cell Carcinoma
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<td>LDA</td>
<td>Lithium Diisopropylamide</td>
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<tr>
<td>M/L</td>
<td>Metal to Ligand ratio</td>
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<td>MCF-7</td>
<td>Human Breast Adenocarcinoma Cell Line</td>
</tr>
<tr>
<td>MDA231</td>
<td>Human Breast Cancer Cell Line</td>
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<tr>
<td>MEM α</td>
<td>Minimum Essential Medium Alpha Medium with Non-essential Amino Acids</td>
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<td>MeO-Biphep</td>
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<td>NBS</td>
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<td>NIH3T3</td>
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<td>PBS</td>
<td>Phosphate Buffered Saline</td>
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Chapter 1

Introduction

1.1 Alkaloids

Alkaloids are a type of naturally occurring organic alkalis compounds that generally contain nitrogen, hydrogen, oxygen and carbon atoms.\textsuperscript{1,2} There can be divided into five classes according to the position of the N-atom in the main chemical structure: they are heterocyclic alkaloids, N-atom in exocyclic position alkaloids, prtrescine, spermidine and spermine alkaloids, peptide alkaloids, and terpene and steroid alkaloids.\textsuperscript{2}

1.2 Quinoline and Isoquinoline: Reaction, Synthesis and Biological Activities

Quinoline (1) and isoquinoline (2) derivatives represent the major class of heterocyclic alkaloids, and their chemical and pharmacological properties have always attracted both synthetic and biological chemists.\textsuperscript{3,4} Quinoline is a liquid with high boiling point and sweetish odour first isolated by Runge from coal tar in 1834; isoquinoline is a low-melting colourless solid and isolated from the same source in 1885 by Hoogewerff and Dorp.\textsuperscript{5,6} Many quinoline derivatives can also be isolated from plants that offer a broad spectrum of biological activities.\textsuperscript{2,7-11}
4-Hydroxy-6-methoxyquinoline-2-carboxylic acid (3) is the first known natural quinoline compound isolated from *Ephedra pachyclada ssp. sinaica* (麻黄). It is used in TCM with diaphoretic, diuretic, antitussive, anti-allergic, hypertensive, anti-viral and CNS stimulatory effects.\(^{12}\)

In 1820, quinine (4) was isolated from the bark of cinchona trees for the treatment of malaria and successfully replaced the crude bark, which had been used for centuries, as a standard drug for such purpose. This molecule has also played an important role in organic chemistry as a target for structural determination and enantioselective\(^ {13}\) and stereoselective\(^ {14}\) total syntheses. Nowadays, however, it has been replaced by much more potent synthetic quinoline-based drugs such as chloroquin (5), plasmoquin (6) and atebrin (7).\(^ {4,6,15,16}\) The quinoline skeleton has also contributed to many commercially available dyes.\(^ {6,17}\)
1.2.1 Quinoline Reactions

Quinoline displays chemical properties associated with a tertiary amine. It frequently shows properties of both benzenoid and pyridinoid compounds. Quinoline is a weak base and can react with acids to form water soluble salts. It also can undergo electrophilic substitution; the electron-rich nitrogen atom of quinoline is the main centre of attack by electrophiles for halogenation, nitration, sulfonation, acylation and alkylation reactions. Quinoline can also react with oxidizing, nucleophilic reducing or radical agents. Isoquinoline has many properties that resemble to those of quinoline. Figure 1-1 shows the typical chemical reaction of a quinoline compound. Isoquinoline has chemical reactions very similar to quinoline.

Figure 1-1. Typical chemical reactions of a quinoline compound
1.2.2 Quinoline/Isoquinoline Synthesis

The quinoline ring system constitutes a key structural component of pharmaceuticals, agrochemical, dyestuffs and materials. The continuous development in the synthesis of new quinoline derivatives is a challenge in research. The preparations of quinoline derivatives have been known since the late 1800s. Table 1-1 shows some examples of quinoline and isoquinoline synthesis. The quinoline skeleton and some ligands, pharmaceutical agents and functional materials that bear quinoline backbone have generally been synthesized by various well-known classical methods such as Combes (Scheme 1-1), Conrad-Limpach (Scheme 1-2), Skraup (Scheme 1-3), Doebner-von Miller (Scheme 1-4), Friedländer (Scheme 1-5) and Pfitzinger (Scheme 1-6) syntheses.3-6

Table 1-1. Examples of quinoline synthesis methods

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Synthesis of quinoline from Arylamines and 1,3-Dicarbonyl Compound</td>
<td>5,6</td>
</tr>
<tr>
<td>1a</td>
<td>Combes Synthesis</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>Conrad-Limpach-Knorr Synthesis</td>
<td>5,6</td>
</tr>
</tbody>
</table>

![Scheme 1-1](image1)

![Scheme 1-2](image2)
2 Synthesis of quinoline from ArylAmines and α, β-Unsaturated Carbonyl Compounds

| 2a | Skraup Synthesis | ![Scheme 1-3](image) |
| 2b | Doebner-Miller Synthesis | ![Scheme 1-4](image) |

3 Synthesis of quinoline from Ortho-Acylarylamines and Carbonyl Compounds

| 3a | Friedlander Synthesis | ![Scheme 1-5](image) |
| 3b | Pfitzinger Synthesis | ![Scheme 1-6](image) |

4 Synthesis of Quinolines by Forming the N-C-2 Bond

![Scheme 1-7](image)

**Isoquinoline Synthesis**

5 Isoquinolines from Aryl - aldehydes and Aminoacetal

| 5a | Pomeranz-Fritsch Synthesis | ![Scheme 1-9](image) |

6 Isoquinoline from arylethanamides

| 6a | Bischler-Napieralski Synthesis | ![Scheme 1-9](image) |
| 6b | Pictet-Gams Synthesis | ![Scheme 1-10](image) |
However, these modern quinoline synthesis methods are not applicable for substitution on the quinoline ring system. Recently, a new metal-catalyzed coupling cyclization or acid catalyzed cycloaddition of appropriate precursors could compete with classical quinoline syntheses in the efficacy and rapidity of quinoline construction. Arcadi and coworkers developed a new “green” approach to the Friedländer synthesis of quinolines through a Gold(III)-catalyzed sequential condensation/annulation reaction of o-amino aromatic carbonyls and ketones in 2003. In 2004, Yadav and coworkers demonstrated the same reaction under milder reaction conditions using a catalytic amount of bismuth triflate (Scheme 1-12).

In 2003, Levacher and co-workers described a new solid-phase synthesis of quinolines based on a Borsche modification of the Friedländer-type reaction between the resin-bound imine and ketones. The resin did not lose any activity after storage for
several weeks. Moreover, the polymer-bound aniline equivalent was easily recycled and could be reused with comparable performance.\textsuperscript{4,20} (Scheme 1-13)

Miller and coworker recently developed a rapid, high-yielding one-pot analogue of Friedländer synthesis, with conversion of $o$-nitrobenzaldehydes to quinolines in the presence of SnCl$_2$/ZnCl$_2$ in EtOH.\textsuperscript{4,21} (Scheme 1-14)

Cho and coworker demonstrated that $o$-aminobenzyl alcohol can be oxidatively cyclised with an array of ketones in dioxane at 80ºC in the presence of a ruthenium catalyst (Grubbs’ catalyst) and KOH to offer the corresponding quinoline derivatives in high yields.\textsuperscript{4,22} (Scheme 1-15). This reaction is a novel transition metal-catalyzed Friedländer quinoline synthesis. The reaction pathway seems to proceed via an initial
oxidative addition of ruthenium to O-H bond followed by β-hydrogen elimination to give o-aminobenzaldehyde.$^{4,22}$

\[
\text{NH}_2\text{OH} + \text{R} \xrightarrow{\text{RuCl}_2(=\text{CHPh})(\text{PCy}_3)_2} \xrightarrow{\text{KOH / dioxane / 80°C}} \text{NH}_2\text{O}
\]

Scheme 1-15

Strekowski and coworkers developed a facile route to synthesize substituted aminoquinolines via anionic cyclization of ketimines derived from o-(trifluoromethyl)aniline in which each fluorine of the CF\(_3\) group is successfully displaced by a series of internal nucleophilic processes using the strong base RNHLi. 2-Substituted 4-fluoroquinolines were also obtained from the reaction of o-(trifluoromethyl)aniline with lithium enolates derived from methyl ketones (Scheme 1-16).$^{4,23,24}$

\[
	ext{CF}_3\text{NH}_2\text{CF}_3\text{NPhPhO} \xrightarrow{\text{LiO}} \xrightarrow{\text{THF}} \text{NHR} \xrightarrow{\text{RNHLi, Et}_2\text{O, -5°C}} \text{NHR}
\]

Scheme 1-16
In 1999 Castells and coworkers described the palladium-catalyzed transfer hydrogenation/heterocyclization of \( \beta-(\alpha\text{-aminophenyl})-\alpha,\beta\text{-ynones} \) that yielded corresponding 2-arylquinolines under mild reaction conditions.\(^4\)\(^,\)\(^25\) When analogous starting materials were treated with various nucleophiles, 2,4-substituted quinolines were obtained (Scheme 1-17).\(^4\)\(^,\)\(^26\)

![Scheme 1-17](image)

**1.2.3 Biological Activities of Quinolines**

Quinoline and its fused heterocyclic derivatives with diverse pharmacological activity constitute an important class of compounds in the development of new drugs. Quinoline compounds have also been demonstrated to possess satisfactory biological activities, such as anticancer, antimycobacterial, antimicrobial, anticonvulsant, anti-inflammatory and cardiovascular activities.\(^3\)\(^,\)\(^27\)\(^-\)\(^30\)
1.2.3.1 Anti-cancer Activities of Quinoline Derivatives

A lot of quinoline compounds have been synthesized in recent years and their significance against different types of cancer activities that target different sites like topoisomerase I, telomerase, farnasyl transferase, Src tyrosine kinase, protein kinase CK-II etc has been reported (Figure 1-2).³

Vittorio and coworkers synthesized indole-fused 10H-indolo[3,2-b]quinoline bearing bis-dimethylaminoethyl chain (8) which is an alkaloid from the West African shrub Cryptolepis sanguinolenta. It was found to possess inhibitory activity against the telomerase enzyme with IC₅₀ of 16μM.³,³¹ Mikata and coworkers reported the synthesis of new derivatives of 2-phenyl quinoline with the [(2-aminoethyl)aminomethyl] group, (9) a type of compounds that showed ability to intercalate into double stranded DNA.³,³² Similarly pyridine-fused pyrido[3,2-g]quinoline derivative (10) showed strong binding to DNA.³,³³ Ronald and coworkers found that various pyrazolo[3,4-b]quinoline ribofuranosides (11) were able to inhibit the nucleotide exchange process on the oncogenic Ras gene and in most in vitro studies.³,³⁴ Charles and coworkers synthesized a series of 3-imidazolymethylaminophenylsulphonyltetrahydroquinolines (12) as farnesyl transferase inhibitors (FTI) with FTIC₅₀ of 0.13μM.³,³⁵ Mettey and coworkers reported that the compound 6-hydroxy-10-chlorobenzo[c]quinololizinum (13) showed
the most potent inhibition and good selectivity for CK-II with IC₅₀ of 0.005μM."}^{3,36}

Dalla and co-workers reported the high antiproliferative activity of 1-[4-(3H-pyrrolo[3,2- f]quinolin-9-ylamino)-phenyl]-ethanone hydrochloride (14). The compound can form an intercalative complex with DNA, inhibit DNA topoisomerase II and block the cell cycle in G2/M phases."}^{3,37}

![Chemical Structures]

**Figure 1-2.** Examples of quinoline compounds with anti-cancer activities

Kohn *et al.* showed that quinoline-phthalide derivative (15) exhibited a potent effect on the proliferation of all cell lines."}^{3,38} Kemnitzer and co-workers demonstrated that
the compound 1-(4-(1H-imidazol-1-yl)benzoyl)-3-cyanopyrrolo[1,2-a]quinoline (16) was highly active in human breast cancer cells T47D, human colon cancer cells HCT116, and hepatocellular carcinoma cancer cells SNU398.\textsuperscript{3,39} Recently, Serda and coworkers reported that quinoline-based thiosemicarbazones showed anti-tumor efficacy involving iron chelation mechanism.\textsuperscript{40} With reference to 5-FU, Ai and coworkers reported the synthesis of a series of pyrimido[5,4-c]quinoline-4-(3H)-one derivatives, which exhibited moderate anti-tumor activity against several selected human cancer cell lines including KB, CNE2, MGC-803, GLC-82, MDA-MB-453 and MCF-7.\textsuperscript{41} Zhang and coworkers reported the design and synthesis of a series of quinoline-3-carbonitrile derivatives and most of them showed excellent selective cytotoxicity toward SMMC-7721 cell line in comparison to Gefitinb in MTT assay.\textsuperscript{42}

\subsection*{1.2.3.2 Antimycobacterial Activities of Quinoline Derivatives}

Tuberculosis (TB) has become a global health problem because of a lack of proper therapeutic agents for its remedy.\textsuperscript{3} Various quinoline-containing molecules have recently been synthesized and tested for anti-TB activity all over the world. In 2008, Sriram and co-workers synthesized a series of 2-(sub)-3-fluoro/nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-\textit{a}]quinoline-6-carboxylic acid (17). The compounds were studied \textit{in vitro} against \textit{Mycobacterium tuberculosis}.
H37Rv (MTB) and multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB) with minimum inhibitory concentration (MIC) of 0.18 and 0.08 μM. They extended their work to synthesize various novel 6-nitroquinone-3-carboxylic acids derivatives (18) with MIC of 0.08 and 0.16 μM *in vitro* against MTB and MDR-TB, respectively. Jain and co-worker developed new 4-(adamantan-1-yl)-2-substituted quinolines derivatives (19) that showed the most potent analog with 99% inhibition at 1.00 μg/mL against drug-sensitive strain, and MIC of 3.125 μg/mL against isoniazid-resistant TB strain (Figure 1-3).

![Figure 1-3](image)

**Figure 1-3.** Examples of quinoline compounds with antimycobacterial activities

1.2.3.3 Antimicrobial Activities of Quinoline Derivatives

Over the last few decades there has been a dramatic increase in the prevalence of multi-drug resistant microbial infections. Discovering of new drugs for the treatment
of systemic mycoses remains an important and challenging task for medicinal chemists in infectious disease research.\textsuperscript{3}

Quinolones characterized by 1,4-dihydro-4-oxo-3-pyridine carboxylic acid and a fused benzene ring moiety is a class of quinoline antimicrobial agents. Ciprofloxacin (20), ofloxacin (21) and sparfloxacin (22) are some commercially available antimicrobial agents.\textsuperscript{3,46} In 2003, Sadana and co-workers synthesized 1-aryl/heteroaryl-5-methyl-1,2,4-triazolo[4,3-\textit{a}]quinoline derivatives (23) which exhibited MIC 10\mu g/ml against salmonella typhae.\textsuperscript{3,47} Singh and co-workers reported that quinoline derivatives 4-(4-pyrozolyl)-2-aminopyrimidines (24) had moderate activity against \textit{C. albicans, A. niger, Salmonella typhae}.\textsuperscript{3,48} A novel 2-amino-4-(8-quinolinol-5-yl)-1-(p-tolyl)-pyrrole-3-carbonitrile (25) synthesized by Abdel-Mohsen in 2005 showed moderate to good activity \textit{in vitro} against two strains of bacteria and fungi in 1998.\textsuperscript{3,49} Parikh and co-workers synthesized isoxazoline and cyanopyridines bearing 2-chloro-7-methoxyquinoline moiety (26) had attimicrobial activities against \textit{E.coli, S. aureus, A. niger} etc. (Figure 1-4).\textsuperscript{3,50}
1.2.3.4 Anticonvulsant Activities of Quinoline Derivatives

Recently various quinoline derivatives have been reported to possess anticonvulsant activities (Figure 1-5). Epilepsy is common chronic neurological disorder that involves spontaneous, intermittent, and abnormal electrical activities in the brain. Characterization of the anticonvulsant activity of a new compound is based on the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) tests.\(^3\) In 2009 Guo and co-workers reported a series of 5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives (27) with anticonvulsant activity evaluated by MES with effective dosage (ED\(_{50}\)) of 19.0 mg/kg.\(^3,51\) The same group synthesized a series of 7-alkoxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-1(2H)-one derivatives (28) with ED\(_{50}\) of 12.3 mg/kg.\(^3,52\) 8-(3’-(4’-phenylpiperazino)-2’-hydroxypropyloxy) quinoline
(29) synthesized by Muruganantham and coworkers showed potent inhibition against seizures by MES and scMet tests. In 2007, Guan and co-workers found that triazole derivatives showed stronger anticonvulsant effects, ED\textsubscript{50} of 27.4mg/kg and 22.0mg/kg by MES and PTZ tests for compound 5-(p-fluorophenyl)-4,5–dihydro-1,2,4-triazolo[4,3-a]quinoline (30). Kynurenic acid (31) derivatives analogue 4-urea-5,7-dichlorokynurenic acid was synthesized and subsequently screened in mice by Nichols and co-workers and it showed excellent anticonvulsant activity.

\[
\text{Figure 1-5. Examples of quinoline compounds with anticonvulsant activities}
\]

**1.2.3.5 Antiinflammatory Activities of Quinoline Derivatives**

Non-steroidal antiinflammatory drugs (NSAIDs) have a wide range of clinical use for the treatment of inflammatory and painful conditions that include rheumatoid arthritis, soft tissue and oral cavity lesions, respiratory tract infections and fever. Most NSAIDs act as nonselective inhibitors of COX-1, COX-2 and suppress TXA\textsubscript{2} formation and platelet aggregation. In 1995, 8-(phenylmethylene)tetrahydroquinoline analogue (32)
was synthesized by Calhoun and co-workers and evaluated for antiinflammatory activity both in vivo and in vitro; it showed totally inhibition of both 5-LOX and COX in rat polymorphonuclear leukocytes assay (PMN) at 50µM. The acidic function groups of novel substituted 1,2,3,4-tetrahydroquinoline derivatives (33-34) as disease modifying anti-rheumatic drugs (DMARD) was reported by Kohno and co-worker in 1997. The novel substituted 1,2,3,4-tetrahydroquinoline derivatives significantly suppressed the swelling of adjunct arthritic rat paw at dosages less than 25 mg/kg (acute/chronic). The ability to inhibit formation of Leukotrienes (a target for antiinflammatory drugs) via the 5-lipoxygenase enzyme was also studied. Dube and co-workers reported that substituted 2-cyanoquinoline derivatives (35) represented a distinct class of 5-LOX inhibitors and possessed in vitro and in vivo potency comparable to or superior than naphthalenic acid analogue. 4-alkoxy derivative 5-ethyl-4-methoxy-2-phenyl quinoline (36) was synthesized by Huang and co-workers as novel antiplatelet agents with an IC₅₀ of 0.08µM, which was about three fold more active than indomethacin. Moreover, various tetrazolo[1,5-α]quinoline derivatives (37) containing pyrimidine ring were reported to possess dual antiinflammatory and antibacterial activities (Figure 1-6).
**Figure 1-6.** Examples of quinoline compounds with antiinflammatory activities

### 1.3 Transition-metal Catalyzed Asymmetric Reactions

The term chiral is generally used to describe a molecule that is not superimposed on its mirror image similar to our pair of hands. Life itself depends on molecular chirality, because many biologically active molecules are chiral, such as naturally occurring amino acids, sugars, enzymes, proteins, hormones, nutrients, and fats. Optical and electronic processes are also with chiral molecules.\(^6\) Two mirror images of a chiral molecule are called enantiomers or optical isomers.\(^6\) There are big differences in the activity and property of each enantiomer, such as taste, smell, drug activity and bioactivity.\(^6\) The discovery of molecular chirality (handedness) in nature has greatly influenced the development of science and technology, especially in the
In the pharmaceutical industry, in year 2000 about 40% of all drug sales were sold as single enantiomer. However, the optically pure form of chiral compounds cannot be easily obtained. In the early days, biochemical and biological methods such as cell cultures, enzymes or whole microorganisms were used to make enantiomerically pure compounds from prochiral precursors. Until the early 1970s, resolution, transformation and derivatization of racemates were used to obtain optically active compounds. Asymmetric catalytic reaction is an ideal and powerful method to synthesize a wide spectrum of optically pure compounds, this method only requires a small amount of chiral substrate, reagent, solvent, or catalyst to produce large quantities of naturally and non-naturally occurring chiral materials. In 2001, Knowles, Noyori and Sharpless were awarded the chemistry Nobel prizes for their significant contribution and brilliant achievement in the transition-metal catalyzed asymmetric catalysis of prochiral olefins and ketones and their applications in industry. The catalyst asymmetric reaction is an important area not only in academia but also in industry.

1.3.1 Asymmetric Hydrogenation

Asymmetric hydrogenation is an economic and clean process to produce chiral products. It involves the asymmetric addition of hydrogen to chemical bonds such as
C=C, C=O, C=N or C=S in the presence of chiral transition metal catalysts. A wide spectrum of optically pure precursors and building blocks for biologically active compounds (such as pharmaceuticals, agrochemicals, flavors, and fragrances as well as the advanced materials) can be prepared simply by asymmetric hydrogenation.

Asymmetric hydrogenation was the first catalytic asymmetric technology to be operated at the industrial scale.

1.3.1.1 Asymmetric Hydrogenation of Heteroaromatic Compounds

Nowadays, the catalytic asymmetric hydrogenation of prochiral unsaturated compounds, such as functionalized and unfunctionalized olefins, ketones and imines have been intensively studied. However, the asymmetric hydrogenation of heteroaromatic compounds is relatively less explored. In contrast to functionalized alkenes and ketones, it is difficult to achieve high enantioselectivity for the hydrogenation of heteroaromatic compounds. This might be due to the following reasons: (1) the high stability of aromatic compounds usually requires high reaction temperature and pressures and thereby adversely affecting the enantioselective reduction; (2) deactivation and/or poisoning of catalysts by heteroaromatic compound containing nitrogen and sulfur atoms; (3) the lack of a secondary coordinating group in simple aromatic compounds.
Many optically pure heteroaromatic compounds and their derivatives are important building blocks and intermediates for the synthesis of biologically active compounds.

To develop highly effective catalytic systems for the synthesis of these chiral heteroaromatic compounds is still a challenge. A one-step enantioselective catalytic hydrogenation of the corresponding heteroaromatic compounds would be a very attractive approach. Recently, more and more catalytic asymmetric hydrogenation of heteroaromatic compounds has been reported.

1.3.1.1 Asymmetric Hydrogenation of Quinoline and Isoquinoline

Tetrahydroquinoline and isoquinoline derivatives are important organic synthetic intermediates, since many biologically active compounds and alkaloids contain this quinoline structure. Direct hydrogenation reaction is the most convenient and economical route to synthesize these tetrahydroquinoline and isoquinoline compounds.

In 2003, Zhou and co-workers reported the use of [Ir(COD)Cl]2/Mo-BIPHEP(38)/I2/toluene catalytic system for the asymmetric hydrogenation of 2-methylquinoline (Scheme 1-18) that led to high enantioselectivities to up to 94% as well as high yields. The same group also demonstrated using iridium complexes with chiral ferrocene-based S-P (39) and N-P
(40) derived ligands for the asymmetric hydrogenation of quinolines to up to 90% ee. In 2008 Bolm showed the use of iridium complexes of naphthalene-bridged N-P-type sulfoximine ligands (41) for the enantioselective hydrogenation of 2-methylquinoline with ee up to 92%. 

\[
\text{H}_2, [\text{Ir(COD)Cl}]_2 \xrightarrow{\text{Solvent, } L^*} \text{Ph}_2\text{N}^+\text{BARF}^-
\]

**Scheme 1-18.** Asymmetric hydrogenation of 2-methylquinoline

In 2005, comparably good results of the asymmetric hydrogenation of quinoline derivatives were subsequently achieved by Chan’s group using their air-stable and recyclable Ir/P-Phos (42a) catalytic system with ee up to 92%. Moreover, this catalyst could be effectively immobilized and reused in environmentally benign and cheap polymer liquid polyethylene glycol dimethyl ether (DMPEG), the enantioselectivity and reactivity of this catalyst can be retained in eight times. They also demonstrated the use of Ir/H8-BINAPO (43) catalyst and Ir complexes of the chiral diphosphinite ligands based on a 1,1′-spirobiindane backbone (R-Spiropo 44) was
highly effective for this reaction with up to 97% ee. In 2006, Chan’s group found that the iridium complex of chiral atropisomeric diphosphine ligand (PQ-Phos 45) could give tetrahydroquinolines in 93% ee. More recently, they also investigated the iridium catalysts with $C_2$-symmetric ligands such as XyIPPhos (42b), SYNPHOS (46), Cl-MeO-BIPHEP (47) and DifluorPhos (48) and found that they were highly effective for this type of reaction in DMPEG/hexane biphasic system with up to 92% ee.

In 2006, Reetz and coworkers found that a BINOL derived chiral diphosphonite ligand bearing an achiral diphenyl ether (50) was also effective in Ir-catalyzed asymmetric hydrogenation of quinolines with 73-96% ee. It was noted that iridium-catalyzed asymmetric hydrogenation of quinolines in the presence of iodine required high catalyst loading, which might be due to catalyst deactivated by forming an inactive dimer. In 2007, Fan and co-workers reported the use of chiral dendritic catalysts derived from BINAP ((S)-GnDenBINAP 51) for the asymmetric hydrogenation of quinoline with high enantioselectivities (ee up to 93%), significant catalytic activities (TOF up to 3450/h) and productivity (TON up to 43000), which might be due to the protection of active catalyst by the dendrimer. They also found that the third generation catalyst could be recovered and reused at least six times with no loss of enantioselectivity. Good results (up to 93% and 96% ee) were achieved by
Ratovelomanana-Vidal’s and Chan’s groups who employed SYNPHOS (46) or DifluorPhos (48) as the ligand.\textsuperscript{86,87} In 2008, Zhou and co-workers synthesis of PEG supported air-stable and recyclable tunable axial chiral bisphosphine ligand from (S)-MeO-Biphed (49) for the asymmetric hydrogenation of quinoline with ee up to 92%.\textsuperscript{88} Scheme 1-19 summarized the enantioselectivities of asymmetric hydrogenation of quinoline with a series of chiral ligands.

So far, I\textsubscript{2} as a crucial additive in the asymmetric hydrogenation of quinoline is undoubttable. Meanwhile, Zhou and co-workers demonstrated a new strategy for Ir/Segphos (52) catalyzed asymmetric hydrogenation of quinoline and isoquinoline by using alkyl chloroformates as the activating agent and Li\textsubscript{2}CO\textsubscript{3} as the base, which provided a new avenue for the hydrogenation of heteroaromatic compounds without the use of I\textsubscript{2} as additive (Scheme 1-20).\textsuperscript{89} Recently, Zhou and co-workers reported Ir-catalyzed asymmetric transfer hydrogenation of quionlines with Hantzsch esters as the hydrogen source using SegPhos (52) as ligand with up to 88% ee.\textsuperscript{90}
Scheme 1-19. Asymmetric hydrogenation of quinoline with various chiral ligands

Scheme 1-20. Asymmetric hydrogenation of quinoline and isoquinoline activated by alkyl chloroformates
More recently, Fan and coworkers developed a new kind air-stable highly effective phosphine-free chiral cationic Cp*Ir(OTf)(CF$_3$TsDPEN) (53) iridium complex for the asymmetric hydrogenation of quinoline with ee up to 99% at a high substrate-to-catalyst molar ratio.$^{91}$

1.3.2 Asymmetric Transfer Hydrogenation

Asymmetric reduction of carbonyl compounds that forms chiral alcohols and amines is an important transformation for the preparation of fine chemicals, agrochemicals, perfumes and pharmaceuticals.$^{92}$ Compared with the commonly used asymmetric hydrogenation processes that involve high hydrogen pressure or hazardous reducing reagents, transfer hydrogenation ia as a safe, simple, relatively environmental friendly and versatile method for the reduction of carbonyl compounds.$^{92-95}$ The process includes hydrogen abstraction from the reagent by means of a catalyst, followed by hydrogen addition to the unsaturated functional group of the substrate (Scheme 1-21).$^{94}$

\[
\text{DH}_2 + \text{A} \rightleftharpoons \text{D} + \text{AH}_2
\]

\(\text{DH}_2 = \text{Hydrogen donor; A = Hydrogen acceptor}\)

Scheme 1-21
A particular advantage of transfer hydrogenation is that the ligands employed are often stable to the reaction conditions and may be recovered after use. Recently, different types of unsaturated substrates such as ketones, α,β-unsaturated carbonyl compounds and imines have been successfully reduced by transfer hydrogenation in the presence of both homogeneous and heterogeneous catalysts.

1.3.2.1 Hydrogen Donors for Asymmetric Transfer Hydrogenation

2-Propanol (IPA) and formic acid are the most commonly hydrogen source in transfer hydrogenation. 2-Propanol is stable, easy to handle, nontoxic, environmentally friendly, inexpensive, and can easily dissolve in many organic compounds. During the transfer hydrogenation reaction, IPA is oxidized to acetone (Scheme 1-22), which makes the reduction of ketone by IPA a reversible process with the equilibrium being regulated by the oxidation potentials of the relevant carbine/ketone couples. This reversible process is the major drawback with IPA as the hydrogen donor in asymmetric transfer hydrogenation. In order to shift the complex to catalysis, sodium or potassium carbonates, hydroxides or alkoxide at various concentrations would be added into the reaction.
Formic acid is another well behaving, inexpensive reducing agent.\textsuperscript{95,97} The asymmetric transfer hydrogenation using this hydrogen donor is better than using IPA because the dehydrogenation of formic acid in open system is substantially irreversible due to the release of CO\textsubscript{2} (Scheme 1-23).\textsuperscript{98}

In fact, an azeotropic 5 : 2 mixture of formic acid and triethylamine (TEAF) is most frequently used as reducing agent in transfer hydrogenation reaction. It is miscible with many solvents to give a single phase at room temperature, and allows for high concentration of substrates and high conversions without back-reaction and racemization.\textsuperscript{95} However, there are some restrictions in the use of TEAF. Several complexes undergo fast decomposition on the attempted dissolution in formic acid and some lose completely their catalytic activity completely, and the reason may be due to the acid inhibit one activation step promoted by the base.\textsuperscript{98}
1.3.2.2 Ligands for Asymmetric Transfer Hydrogenation

Chiral phosphines are the most popular ligands in asymmetric catalytic reaction, and they have been employed in transfer hydrogenation with ruthenium, rhodium, and iridium catalysts. Besides a few tertiary monophosphines, chelating bidentate diphosphines like DIOP, CHIRAPHOS, NORPHOS, and BINAP have been mainly used.

It should be noted that unlike asymmetric hydrogenation, the most commonly used chiral ligands for enantioselective transfer hydrogenation contain nitrogen atoms, not phosphorus. The ligands used in asymmetric transfer hydrogenation have various combinations of nitrogen, oxygen, phosphorus and sulfur as the donor atoms. They can be bidentate, tridentate or tetradeutate. Scheme 1-24 show some examples of ligands with $\text{ee} \geq 90\%$ in the asymmetric transfer hydrogenation of acetophenone.
Scheme 1-24. Examples of ligands with ee ≥ 90% in the asymmetric transfer hydrogenation of acetophenone.\textsuperscript{100-103}

1.3.2.3 Asymmetric Transfer Hydrogenation with Hantzsch Esters

Recently, a new approach has been developed by List and co-workers,\textsuperscript{104-111} MacMillan and co-workers,\textsuperscript{112-115} Rueping and co-workers,\textsuperscript{116-118} and Zhao and co-workers\textsuperscript{119} that uses Hantzsch esters (64) (Figure 1-7) as hydrogen source for the highly enantioselective transfer hydrogenation in the presence of catalytic amounts of metal complexes or small organic molecules.\textsuperscript{120}
1.3.2.3.1 Reduction of C = C Bond

Li and co-worker demonstrated that the asymmetric transfer hydrogenation of α,β-unsaturated aldehydes (65) in the presence of 10 mol% of imidazolidinone salt (67) with Hantzsch ester 64b as the hydrogen source with ee up to 96% (Table 1-2, entry 1). At the same time, MacMillan and co-worker reported that imidazolidinone salt (68) catalyzed asymmetric transfer hydrogenation of α,β-unsaturated aldehydes with Hantzch ester 64a with good yield and excellent ee (up to 97%) (Table 1-2, Entry 2). Zhou and Cordova demonstrated the asymmetric transfer hydrogenation of aldehydes with 10 mol% chiral pyrrolidine (69) and Hantzch ester 64a as the hydrogen source to afford 66 with ee up to 97% (Table 1-2, Entry 3). In 2006, Mayer and co-worker also reported the same reaction with ammonium phosphate (70) as the catalyst with Hantzch ester 64b as hydrogen source reduced α,β-unsaturated aldehydes to their corresponding saturated aldehydes in moderate to good yields with excellent enantioselectivities (up to 99%) (Table 1-2, Entry 4).
Table 1-2. Asymmetric transfer hydrogenation of \( \alpha,\beta \)-unsaturated aldehydes with Hantzch Ester as hydrogen source.

![Chemical Structure]

<table>
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<th>Entry</th>
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<th>Ee %</th>
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</table>

1.3.2.3.2 Reduction of C = N Bond

Besides the transfer hydrogenation of C=C bonds, Hantzsch esters were also used to reduce C=N bonds such as imines and quinoline to their corresponding amines and tetrahydroquinolines.\(^{120}\) Recently, Rueping and co-workers found that chiral phosphoric acid (71a) was an effective catalyst for the transfer hydrogenation of
various aryl methyl ketimines with Hantzsch ester 64a in benzene at 60°C to give the desired amines with up to 84% ee.\textsuperscript{116} Subsequently, List and co-workers used a more sterically hindered phosphoric acid (71b) for the same transformation, and good to excellent yields and enantioselectivities were attained for a variety of aryl methyl ketimines in the presence of Hantzsch ester 64a in toluene at 35°C with up to 93% ee (Scheme 1-25).\textsuperscript{107}

Very recently, Rueping and co-workers demonstrated the transfer hydrogenation of quinolines by using Hantzsch ester 64a as the hydrogen source with excellent enantioselectivities of up to 99% ee in the presence of 2 mol% of phosphoric acid 71c (Scheme 1-26).\textsuperscript{117}
This method has been applied to synthesize several biologically active tetrahydroquinoline alkaloids such as (-)-angustureine, (+)-galipinine and (+)-cuspareine with high ee (Figure 1-8).120

\[ \text{Figure 1-8. Examples of tetrahydroquinoline synthesized by transfer hydrogination} \]

1.3.2.3 Reduction of C = O Bond

Hantzsch esters as the hydrogen source are not only able to use in the transfer-hydrogenation process in the presence of an organocatalyst, they can also reduce the carbonyl functional group with chiral metal complex.120

Recently, Yang and co-workers reported an enantioselective reduction of α-ketoesters by a chiral copper(II) bisoxazoline complex in the presence of 64c as the hydrogen source to yield the optically active α-hydroxy esters with up to 94% ee (Scheme 1-27).111

\[ \text{Scheme 1-27} \]
1.4 Quinoline-Based Ligands in Catalytic Reactions

The development of chiral ligands for transition metal catalyzed asymmetric reaction has been intensively pursued with the aim of obtaining efficient catalytic systems.\textsuperscript{121} In recent years, various $C_2$-symmetric and non-symmetric chiral ligands bearing phosphine, nitrogen and sulfur have been developed and used in numerous transition metal catalyzed reactions.\textsuperscript{122,123} Thus, a wide range of non-symmetric chiral NP- and NS-type compounds was found to be efficient ligands for catalytic asymmetric reaction base on their electronic and steric properties.\textsuperscript{123} However, the NP ligands derived from pyridine were reported in only few cases.\textsuperscript{124,125} Figure 1-9 showed some examples of quinoline-based ligands.

\textbf{Figure 1-9.} Examples of quinoline-based ligands
Buono and co-workers described a straightforward synthesis of new chiral P-pyridine and quinoline phosphine ligands (QUIPHOS 76) and successfully used it in asymmetric palladium-catalyzed allylic substitution reactions with up to 87% ee. (Scheme 1-28).\textsuperscript{122,123}

\[
\begin{array}{c}
\text{OAc} + \text{MeOOCCOOMe} \\
\text{[Pd(allyl)Cl]_2/76} \\
\text{BSA-Acetate salt} \\
16h \\
\end{array}
\rightarrow
\begin{array}{c}
\text{MeOOCCOOMe} \\
\text{up to 87\% ee} \\
\end{array}
\]

**Scheme 1-28**

QUIPHOS (76) can also catalyzed diels-alder reaction with ee up to 99\% (Scheme 1-29).\textsuperscript{126-128}

\[
\begin{array}{c}
\text{C}_{6}H_{5} \text{C}l_3, 4-7 h \\
\end{array}
\rightarrow
\begin{array}{c}
\text{up to 99\% ee} \\
\end{array}
\]

**Scheme 1-29**

Park and co-workers in 1999 synthesized several chiral phosphino(oxazlinyl)quinoline ligands (DPOQ 77), and employed them in the Ru(II)-catalyzed asymmetric intramolecular cyclopropanation reaction of diazo-alkenes with good reactivity and high thermal stability (Scheme 1-30).\textsuperscript{121}

\[
\begin{array}{c}
\text{[RuCl_2(p-cymene)]_2/77} \\
\text{CHCl_3, 4-7 h} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{up to 99\% ee} \\
\end{array}
\]

**Scheme 1-30**
Leitner and co-workers introduced a new family of bidentate chiral ligands that contained 2-alkyl-1,2-dihydroquinoline and had two different phosphorus donor sites connected to positions 1 and 8 of the heterocyclic backbone (78). It could be applied in asymmetric reactions such as asymmetric hydroformylation of styrene (Scheme 1-31) and enantioselective hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate with moderate to high ee.\textsuperscript{129}

\[
\text{C}_2\text{H}_4 \xrightarrow{[\text{Rh(acac})(\text{CO})_2]78/\text{H}_2/\text{CO}} \text{CHO} + \text{C}_8\text{H}_{12}\text{CHO}
\]

\textbf{Scheme 1-31}

In 2006, Zhou and co-workers synthesized a new class of modular conformationally rigid N,P-ligand (79) for iridium-catalyzed asymmetric hydrogenation of aryl alkene. Excellent enantioselectivity (up to 99% ee) was obtained (Scheme 1-32).\textsuperscript{130}

\[
\text{C}_6\text{H}_{12} \xrightarrow{[\text{Ir(COD)}\text{Cl}]_2/79/\text{DCM, 50 bar H}_2, \text{r.t. 16h}} \text{C}_8\text{H}_{12}
\]

\textbf{Scheme 1-32}

up to 99% ee

In 2006 four P,N-ligands (80-83) with different steric and electronic properties were synthesized by Sirbu and co-workers. The nickel complex of these ligands was highly active toward the oligomerization of ethylene at ambient temperature and in the presence of MAO as the cocatalyst.\textsuperscript{131}
In 2009 Scrivanti and co-worker reported that the palladium complex \([\text{PdCl}_2(\text{P-N})]\) containing the basic and sterically demanding 8-(di-tert-butylphosphinooxy)-quinoline ligand (P-N) (84) was a highly efficient catalyst for the Suzuki-Miyaura coupling of phenylboronic acid with aryl bromides or aryl chlorides in very high TOF number (Scheme 1-33).\(^{132}\)

\[
\text{Ar-Br/Cl} + \text{B(OH)}_2 \xrightarrow{\text{84}} \text{K}_2\text{CO}_3 \rightarrow \text{Ar}
\]

\textbf{Scheme 1-33}

Han and co-workers synthesized a new type of chiral phosphine-quinoline ligand bearing spiro[4,4]-1,6-nonadiene scaffold (85). High activity and moderate enantioselectivity were obtained for the asymmetric hydrogenation of alkene and imine derivatives with cationic iridium complex of 85 (Scheme 1-34).\(^{133}\)

\[
\text{[Ir(COD)Cl]}_2/85 \xrightarrow{\text{DME, 50 atm H}_2, \text{r.t., 24 h}} \text{HN}_{\text{Ar}}
\]

\textbf{Scheme 1-34}
1.5 Aims and Objectives

Chan et al. developed and synthesized a dipyridylphosphine ligand P-Phos family and successfully applied it in various types of asymmetric catalytic reaction. Recently, three new dipyridinyl phosphine type ligands have been synthesized. Following Chan’s work, our first objective is to explore our catalyst system with the newly synthesized dipyridinyl phosphine type ligands for asymmetric hydrogenation of 8-substituted quinoline derivatives.

Quinoline derivatives are important organic synthetic intermediates, and many biological active compounds and alkaloids contain this structure. However, only a few examples of quinoline skeleton as ligand for asymmetric catalytic reaction, especially for asymmetric transfer hydrogenation. In order to contribute to the asymmetric transfer hydrogenation with quinoline-based ligands, our second objective is to employ the quinoline-based ligand for the asymmetric transfer hydrogenation of ketone.

Quinoline compounds have been demonstrated to possess various types of biological activity, such as anti-cancer activities against human cancer cell lines. With reference to the anti-cancer activity of quinoline compounds, our third objective is to use the easily available compounds to prepare quinoline/tetrahydroquinoline compounds, and then study their anti-cancer activities and establish their quantitative
structure-activity relationship (QSAR). Also, we will identify the lead compounds for further drug development.
Chapter 2

Iridium-Catalyzed Asymmetric Hydrogenation of 8-Substituted Quinoline with Dipyridinyl Phosphine Type Ligands

Quinoline and its tetrahydroquinoline derivatives represent the major class of heteroaromatic compounds. The chemical and pharmacological properties of quinoline compounds, in particular 8-hydroxyquinoline derivatives, have always attracted both synthetic and biological chemists.\(^3,4,27\)

Asymmetric hydrogenation of heterocyclic compounds offers an effective, convenient and attractive reaction route to produce numerous partially saturated or saturated optically pure heterocyclic compounds and their derivatives.\(^73\) However, only a few successful examples of asymmetric hydrogenation of heterocyclic compounds have been reported. The search for new catalyst systems for this reaction is still a challenge. Recently, more and more catalytic asymmetric hydrogenation of heterocyclic compounds has been reported.\(^75-77,79-85,87,89-91,141\) For instance, Zhou\(^75-77,89,141\) and Chan\(^79-81,83\) have demonstrated that MeO-BIPHEP \((48)\),\(^75\) ferrocenyl-oxazoline derived N-P, S-P ligand,\(^76,77\) P-Phos \((42a)\)\(^79,83\) and H8-BINAPO \((43)\)\(^80\) as effective chiral ligands for iridium-catalyzed asymmetric hydrogenation of 2 or 2,6-substituted quinolines.
8-Hydroxyquinoline and their tetrahydroquinoline derivatives show strong biological activities,\textsuperscript{27,28} the search for effective catalysts for asymmetric hydrogenation of this type of substrates is highly desirable, as part of our continuing effort in catalytic asymmetric hydrogenation reaction. As a continuation of our patented work using atropisomeric dipyridinyl phosphine ligand, 2,2’-6,6’-tetramethoxy-bis (diphenylphosphino)-3,3’-bipyridine (\textbf{P-Phos, 42a}) and 2,2’,6,6’-tetramethoxy-bis (3,5-dimethylphenylphosphino)-3,3’-bipyridine (\textbf{Xyl-P-Phos, 42b}), as air stable and effective catalyst for asymmetric hydrogenation.\textsuperscript{79,135,136,142-145} Three new derivatives of dipyridinyl phosphine type ligands were synthesized by our group (see \textbf{42c-f} in Figure 2-1), and the asymmetric hydrogenation of quinolines was investigated and reported in this chapter.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{dipyridinyl_phosphine_structure.png}
\caption{The structure of the dipyridinyl phosphine type ligands}
\end{figure}

We have reported the preparation of chiral tetrahydroquinolines using Ir-catalyzed asymmetric hydrogenation and the tetrahydroquinoline products show possible
cytotoxic potential anti-cancer activity. In particular, we have reported that 1,2,3,4-tetrahydroquin-8-ol may be a potential cancer chemotherapeutic agent.30 Six dipyridinyl type ligands (42a-f) were examined in the asymmetric hydrogenation of 2-methyl-8-quinolinol (86a). All the catalysts were prepared via an in situ reaction of [Ir(COD)Cl]2 with the chiral ligands in THF (unless otherwise specified) with I2 as an additive, and the reactions were carried out for 20 hours at room temperature under hydrogen pressure. The results were shown in Table 2-1. It was noted that ligand 42d, which bear an electron-donating methoxy group, had the highest enantioselectivity of 96% (Table 2-1, Entry 4). However, only 66% ee was obtained with ligand 42c bearing a strong electron-withdrawing group. It is interesting to find out the steric hindrance of the phenyl groups on 3 and 3’ positions of ligand 42f is not favour for this reaction. This may be due to the two phenyl groups greatly increase the rigidity of the biheteroaryl system; then the rotation of the two P-phenyl groups should also be significantly restricted. The results shows that no enantioselectivity was observed and only 48% conversion (Table 2-1, Entry 6), and it was not examined for any further reactions.
Table 2-1. Asymmetric hydrogenation of 2-methyl-8-quinolinol (86a) with the dipyridinyl phosphine type ligands

![Chemical structure of 86a and 87a](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Ee(^b) (%)</th>
<th>Conv(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42a</td>
<td>94 (R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>42b</td>
<td>88 (R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>42c</td>
<td>66 (S)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>42d</td>
<td>96 (R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>42e</td>
<td>62 (S)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>42f</td>
<td>Nil</td>
<td>48</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 0.3 mmol 86a, [Ir(COD)Cl]_2 (0.0015 mmol), ligand (0.0032 mmol), I₂ (0.015 mmol), 1.5 ml THF as solvent at r.t., 700psi H\(_2\) for 20 h. \(^b\)The ee values were determined by HPLC with a Chiralpak OJ-H column. \(^c\)The conversion was determined by \(^1\)HNMR spectroscopy of the crude product.

The optimal reaction conditions for the asymmetric hydrogenation of quinoline with **P-Phos** (42a) and **Xyl-P-Phos** (42b) are according to our previous report.\(^{79,83}\)

Considering the importance of solvent effect in this type of reaction, a search for the best solvent for the ligands (42c-42e) was necessary. It can be seen from Table 2-2 that several organic solvents were examined; the solvents had a significant effect on both enantioselectivities and conversions. The use of protic solvents, such as methanol and ethanol, led to poor enantioselectivities for both ligands (Table 2-2, Entries 6-7, 12-13 and 18-19) and poor activities for ligands 42c and 42e (Table 2-2, Entries 6-7 and 18-19). This might be due to the poor solubility of the catalyst in these two protic
solvents. High enantioselectivities (92-96%) were obtained for ligand 42d with both selected organic solvents (Table 2-2, Entries 8-11), the best results were observed with THF as the reaction medium with 96% ee and over 99% conversion (Table 2-2, Entry 8). However, the effect of solvent was not significant for ligand 42c; low enantioselectivities were obtained for both used solvents (Table 2-2, Entries 3-7). Moreover, only 21% conversion was achieved with DCM as reaction medium (Table 2-2, Entry 4). Therefore, THF was the best choice of solvent for ligand 42e with 66% ee and >99% conversion (Table 2-2, Entry 3). A similar solvent effect was observed for ligand 42e, and THF was the best solvent in this study (Table 2-2, Entries 14-17). The experiment results showed that, THF was the best reaction medium for all ligands in the asymmetric hydrogenation of 8-substituted quinoline compounds. Therefore, THF was used to further study this reaction.
Table 2-2. Solvent effect of asymmetric hydrogenation of 2-methyl-8-quinolinol (86a) with the dipyridinyl phosphine type ligands\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Ee\textsuperscript{b} %</th>
<th>Conv\textsuperscript{c} %</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42a</td>
<td>THF</td>
<td>94</td>
<td>&gt;99</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>42b</td>
<td>THF</td>
<td>88</td>
<td>&gt;99</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>42c</td>
<td>THF</td>
<td>66</td>
<td>&gt;99</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>42c</td>
<td>DCM</td>
<td>60</td>
<td>21</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>42c</td>
<td>THF/DCM 1:1</td>
<td>65</td>
<td>82</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>42c</td>
<td>MeOH</td>
<td>61</td>
<td>12</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>42c</td>
<td>EtOH</td>
<td>63</td>
<td>25</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>42d</td>
<td>THF</td>
<td>96</td>
<td>&gt;99</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>42d</td>
<td>DCM</td>
<td>92</td>
<td>93</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>42d</td>
<td>THF/DCM 1:1</td>
<td>92</td>
<td>99</td>
<td>R</td>
</tr>
<tr>
<td>11</td>
<td>42d</td>
<td>Toluene</td>
<td>95</td>
<td>50</td>
<td>R</td>
</tr>
<tr>
<td>12</td>
<td>42d</td>
<td>MeOH</td>
<td>76</td>
<td>99</td>
<td>S</td>
</tr>
<tr>
<td>13</td>
<td>42d</td>
<td>EtOH</td>
<td>42</td>
<td>95</td>
<td>S</td>
</tr>
<tr>
<td>14</td>
<td>42e</td>
<td>THF</td>
<td>60</td>
<td>99</td>
<td>S</td>
</tr>
<tr>
<td>15</td>
<td>42e</td>
<td>DCM</td>
<td>13</td>
<td>53</td>
<td>S</td>
</tr>
<tr>
<td>16</td>
<td>42e</td>
<td>THF/DCM 1:1</td>
<td>28</td>
<td>98</td>
<td>S</td>
</tr>
<tr>
<td>17</td>
<td>42e</td>
<td>Toluene</td>
<td>14</td>
<td>39</td>
<td>S</td>
</tr>
<tr>
<td>18</td>
<td>42e</td>
<td>MeOH</td>
<td>13</td>
<td>36</td>
<td>R</td>
</tr>
<tr>
<td>19</td>
<td>42e</td>
<td>EtOH</td>
<td>8</td>
<td>59</td>
<td>R</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 0.3 mmol 86a, [Ir(COD)Cl]\textsubscript{2} (0.0015 mmol), ligand (0.0032 mmol), I\textsubscript{2} (0.015 mmol), 1.5 ml solvent at r.t., 700psi H\textsubscript{2} for 20 h. \textsuperscript{b}The ee values were determined by HPLC with a Chiralpak OJ-H column. \textsuperscript{c}The conversion was determined by \textsuperscript{1}H-NMR spectroscopy of the crude product.

The effect of substrate-to-catalyst (S/C) ratio on the asymmetric hydrogenation reaction of quinoline was also examined with the use of THF as reaction medium and the results were shown in Table 2-3. A change in S/C ratio had a slight effect on enantioselectivities for all ligands (Table 2-3, Entries 1-6). For ligand 42c, a large
A decrease in conversion resulted at a higher S/C ratio (Table 2-3, Entries 3-6).

Remarkably, this reaction could even be performed at an S/C ratio of 5000:1 without any significant losses in both enantioselectivities and conversion for ligand 42d. Both enantioselectivities and conversion were dropped at a higher S/C ratio for ligand 42e. In this reaction, the best result was obtained at an S/C ratio of 200:1 for all ligands.

Table 2-3. S/C ratio of asymmetric hydrogenation of 2-methyl-8-quinolinol (86a) with the dipyridinyl phosphine type ligands

<table>
<thead>
<tr>
<th>Entry</th>
<th>S/C Ratio</th>
<th>42c</th>
<th>42d</th>
<th>42e</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ee(^b) (conv)(^c)</td>
<td>Ee(^b) (conv)(^c)</td>
<td>Ee(^b) (conv)(^c)</td>
</tr>
<tr>
<td>1</td>
<td>100:1</td>
<td>64 (&gt;99)</td>
<td>94 (&gt;99)</td>
<td>60 (&gt;99)</td>
</tr>
<tr>
<td>2</td>
<td>200:1</td>
<td>65 (&gt;99)</td>
<td>95 (&gt;99)</td>
<td>62 (&gt;99)</td>
</tr>
<tr>
<td>3</td>
<td>500:1</td>
<td>59 (56)</td>
<td>91 (&gt;99)</td>
<td>44 (&gt;99)</td>
</tr>
<tr>
<td>4</td>
<td>1000:1</td>
<td>65 (55)</td>
<td>91 (&gt;99)</td>
<td>34 (93)</td>
</tr>
<tr>
<td>5</td>
<td>2000:1</td>
<td>63 (54)</td>
<td>91 (95)</td>
<td>35 (63)</td>
</tr>
<tr>
<td>6</td>
<td>5000:1</td>
<td>61 (31)</td>
<td>91 (95)</td>
<td>27 (60)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 0.15 mmol 86a, [Ir(COD)Cl]\(_2\) (0.03 μmol to 1.5 μmol), ligand (0.064 μmol to 3.2 μmol), I\(_2\) (0.015 mmol), 1.5 ml THF as solvent at r.t., 700psi H\(_2\) for 20 h. \(^b\)The ee values were determined by HPLC with a Chiralpak OJ-H column. \(^c\)The conversion was determined by \(^1\)H-NMR spectroscopy of the crude product.

The effects of hydrogen pressure and temperature on the hydrogenation reaction were then investigated. Table 2-4 showed that the conversion was relatively insensitive to changes in hydrogen pressure for all ligands, but the enantioselectivities decreased slightly at a lower pressure for all ligands (Table 2-4, Entries 1-3). The reaction with
ligand 42c was favorable at low temperature and higher enantioselectivities were obtained (Table 2-4, Entry 6). However, the conversion was dropped by around 10%.

Table 2-4. Pressure effect of asymmetric hydrogenation of 2-methyl-8-quinolinol (86a) with the dipyridinyl phosphine type ligands

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pressure (psi)</th>
<th>42c</th>
<th>42d</th>
<th>42e</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>61 (&gt;99)</td>
<td>93 (&gt;99)</td>
<td>34 (&gt;99)</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>64 (&gt;99)</td>
<td>93 (&gt;99)</td>
<td>43 (&gt;99)</td>
</tr>
<tr>
<td>3</td>
<td>500</td>
<td>62 (&gt;99)</td>
<td>94 (&gt;99)</td>
<td>57 (&gt;99)</td>
</tr>
<tr>
<td>4</td>
<td>700</td>
<td>65 (&gt;99)</td>
<td>95 (&gt;99)</td>
<td>60 (&gt;99)</td>
</tr>
<tr>
<td>5</td>
<td>1000</td>
<td>65 (&gt;99)</td>
<td>95 (&gt;99)</td>
<td>60 (&gt;99)</td>
</tr>
<tr>
<td>6</td>
<td>700, 0°C</td>
<td>67 (90)</td>
<td>95 (90)</td>
<td>Nil</td>
</tr>
</tbody>
</table>

*aReaction conditions: 0.3 mmol 86a, [Ir(COD)Cl]₂ (0.0015 mmol), ligand (0.0032 mmol), I₂ (0.015 mmol), 1.5 ml solvent at r.t./0°C for 20 h. bThe ee values were determined by HPLC with a Chiralpak OJ-H column. cThe conversion was determined by ¹H-NMR spectroscopy of the crude product.

I₂ is necessary additive for the asymmetric hydrogenation of quinoline, the substrate to I₂ (S/I₂) ratio was studied with ligand 42d and the results were shown in Table 2-5. At lower S/I₂ ratio the conversion was relatively unaffected by changes in the ratio (Table 2-5, Entries 1-3). The best results were obtained while S/I₂ ratio equal to 10 with 96% ee and over 99% conversions (Table 2-5, Entry 3). When S/I₂ ratio increased to 20, both conversion and enantioselectivity were reduced (Table 2-5, Entry 4). Further increasing the S/I₂ ratio
to 30 led to very sluggish reaction and no hydrogenated product would be detected even after 20 hrs (Table 2-5, Entry 5).

Table 2-5. S/I2 ratio of asymmetric hydrogenation of 2-methyl-8-quinolinol (86a) with ligand 42d

<table>
<thead>
<tr>
<th>Entry</th>
<th>S/I2</th>
<th>Ee (%)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>93</td>
<td>&gt;99</td>
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<tr>
<td>2</td>
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<td>&gt;99</td>
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<tr>
<td>3</td>
<td>10</td>
<td>96</td>
<td>&gt;99</td>
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<tr>
<td>5</td>
<td>30</td>
<td>Nil</td>
<td>0</td>
</tr>
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</table>

*Reaction conditions: 0.3 mmol 86a, [Ir(COD)Cl]2 (0.0015 mmol), 42d (0.0032 mmol), I2 (0.06-0.005 mmol), 1.5 ml solvent at r.t., 700psi H2 for 20 h. The ee values were determined by HPLC with a Chiralpak OJ-H column. The conversion was determined by 1H-NMR spectroscopy of the crude product.*

To verify the effectiveness of these catalyst systems in asymmetric hydrogenation of quinoline substrates, a series of 8-substituted quinoline compounds (86b-86o) were also hydrogenated under the optimized reaction conditions (Scheme 2-1), and the results were shown in Table 2-6. In brief, only ligand 42d provided the best enantioselectivities performance for most of tested 8-substituted quinolines compounds, while lower enantioselectivities were observed for most of the substrates with ligands 42c and 42e. For ligands 42a-b, moderate to high enantioselectivities were obtained.
The introduction of an alkyl group into the position 8 of 2-methyl-8-quinolinol led to lower enantioselectivities for all ligands except ligand 42e (Table 2-6, Entries 1-2). Only ligand 42a could promote good enantioselectivity for 8-OAc substituted quinoline compound with 84% ee; however, the conversion was lowered to 56%. High conversions but moderate enantioselectivities (60-76% ee) were obtained with ligands 42c and 42e. Only low enantioselectivity and conversion with ligand 42b (Table 2-6, Entry 3) can be observed.

Moderate to good enantioselectivities with high conversions were obtained for ligand 42a-b with all benzyl substituted 8-hydroxyl quinoline compounds regardless whether the benzyl group contains either electron donating or withdrawing functionality. Moreover, the position of the substitutes on the benzyl group on the enantioselectivities was varied (Table 2-6). A slightly lower ee (79%) was observed for 3,5-CF₃ substituted 8-benzyloxy quinoline compound for ligand 42a, which might be due to the steric hindrance of the two CF₃ groups (Table 2-6, Entry 15).

The tolerance of the hydroxyl group was well demonstrated by the successful hydrogenation of all tested 8-hydroxy substituted quinoline substrates with ligand 42d with up to 99% conversion and up to 96% ee (Table 2-6). On the contrary, high conversion but lower enanoselectivities were obtained for both of quinoline substrates for ligands 42e and 42e.
Table 2-6. Asymmetric hydrogenation of 8-substituted quinolinol with the dipyridinyl phosphine type ligands

![Diagram of the reaction](Image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>42a</th>
<th>42b</th>
<th>42c</th>
<th>42d</th>
<th>42e</th>
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<tr>
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<td>Ee (conv) %</td>
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<td>85(99)</td>
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</tr>
<tr>
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<td>87o</td>
<td>79(99)</td>
<td>71(99)</td>
<td>63(99)</td>
<td>85(94)</td>
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</tbody>
</table>

Reactions conditions: 0.3 mmol 86, [Ir(COD)Cl]₂ (0.0015 mmol), ligand (0.0032 mmol), I₂ (0.015 mmol), 1.5 ml THF as solvent at r.t., 700 psi H₂ for 20 h. The ee values were determined by HPLC with a Chiralpak OJ-H (87a, 87c, 87o), OD-H (87b, 87d, 87g-n), AD-H (87e-f) column. The chiral products produced by 42a, 42b and 42d are R configuration while 42c and 42e are S configuration. The conversion was determined by ¹H-NMR spectroscopy of the crude product.
The electronic properties of the structural difference between ligands can be affecting the enantioselectivities. The electronic effect can be represented by a Hammett relationship,\textsuperscript{146-155} between enantioselectivity and the electronic character (Hammett sigma constants) of the substituents. This electronic effect on enantioselectivities of our ligands appears to be significant in this iridium catalyzed asymmetric hydrogenation of quinoline.

Table 2-7 showed the relationship between the Hammett sigma constants and the enantioselectivities of asymmetric hydrogenation of 2-methyl-8-quinolinol. Ligand 42d with electron-donating methoxy group at the para-position of the phenyl group (Table 2-7, Entry 1) gave higher enantioselectivities for most of 8-substituted 1,2,3,4-tetrahydroquinoline products (Table 2-6). However, lower enantioselectivities were resulted with ligand 42c, which bears an electron-deficient CF\textsubscript{3} group at the same position of the phenyl group (Table 2-7, Entry 3 and Table 2-6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Functional group at the \textit{para}-position of phenyl group</th>
<th>Hammett sigma constants ((\sigma_p))\textsuperscript{156}</th>
<th>Ee %</th>
</tr>
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<tr>
<td>1</td>
<td>42d</td>
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<td>-0.27</td>
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</tr>
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<td>2</td>
<td>42a</td>
<td>-H</td>
<td>0.00</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>42c</td>
<td>-CF\textsubscript{3}</td>
<td>0.54</td>
<td>66</td>
</tr>
</tbody>
</table>
This approaches explained why the difference in catalytic behaviour between the dipyridinyl phosphine ligands in the asymmetric hydrogenation of 8-substituted quinoline compounds.
Chapter 3
Asymmetric Transfer Hydrogenation of Aromatic Ketone with Quinoline-Based Ligand

The stereoselective synthesis of optically pure secondary alcohols is a well studied topic in organic chemistry because of the significance of these intermediates in the synthesis of numerous biologically active molecules and the manufacture of pharmaceuticals and advanced materials. The catalytic asymmetric reduction is the most direct and effective method to provide these optically active alcohols.

Asymmetric transfer hydrogenation could be an alternative method to achieve our targeted purpose due to the simplicity of its techniques and mild reaction conditions. A particular advantage of asymmetric transfer hydrogenation is that the ligands employed are often indefinitely stable to the reaction conditions and may be recovered after use. Recently, different types of unsaturated substrates such as ketones, \(\alpha,\beta\)-unsaturated carbonyl compounds and imines have been successfully reduced by asymmetric transfer hydrogenation in the presence of both homogeneous and heterogeneous catalysts. Compared with the commonly used asymmetric hydrogenation processes that involve high hydrogen pressure or hazardous reducing reagents, transfer hydrogenation is a safe, simple, relatively
environmental friendly and versatile method for the reduction of carbonyl compounds.\textsuperscript{92-95}

Apart from the traditional chiral phosphine ligands, various $C_2$-symmetric and non-symmetric chiral ligands have been recently developed and used in numerous transition metal catalyzed reactions.\textsuperscript{122,123} However, ligands derived from pyridine were reported in only a few cases.\textsuperscript{124,125}

Asymmetric transfer hydrogenation of aromatic ketone with quinoline-based ligands was herein studied. Some chiral 1,2,3,4-tetrahydroquinoline compounds were employed as ligand for the asymmetric transfer hydrogenation of acetophenone. However, the reaction was very sluggish with only 25-42% conversion after 20 hrs and no enantioselectivities were detected.

![Scheme 3-1](image)

**Scheme 3-1.** Asymmetric transfer hydrogenation of acetophenone (88a) with quinoline-based ligands
Then two other quinoline-based ligands (90 & 91)\(^{159-162}\) were used for the asymmetric transfer hydrogenation of acetophenone (Scheme 3-1). 76% ee and 86% conversion were obtained with ligand 90; however, for ligand 91 only 31% ee and 43% conversion were obtained. Ligand 90 would be used for further reactions. The initial experiments employed Ru, Ir and Pd as metal precursors. The results were summarized in Table 3-1, although high conversion was resulted with [Ir(COD)Cl]\(_2\) as the metal precursor, very low enantioselectivities were obtained (Table 3-1, Entry 1). Both lower conversion and lower enantioselectivities were obtained with the Pd complex (Table 3-1, Entries 5-6).

Three ruthenium precursors were used for the reaction (Table 3-1, Entries 2-4). Very low enantioselectivity (4%) and conversion (14%) were obtained with [Ru(COD)Cl]\(_2\). For [RuCl\(_2\)(C\(_6\)H\(_6\))]\(_2\) precursor, only 40% enantioselectivity and 66% conversion were observed (Table 3-1, Entry 2). The best results were obtained using [Ru(\(\rho\)-cymene)Cl\(_2\)]\(_2\) as the metal precursor, and gave products with 76% ee and 86% conversion. Based on these preliminary results, the [Ru(\(\rho\)-cymene)Cl\(_2\)]\(_2\) and ligand 90 catalyst system was chosen for further study of this reaction.
Table 3-1. Asymmetric transfer hydrogenation of acetophenone (88a) using different metal precursors with ligand 90a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal Precursor</th>
<th>Ee b %</th>
<th>Conv c %</th>
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<tbody>
<tr>
<td>1</td>
<td>[Ir(COD)Cl]2</td>
<td>8</td>
<td>85</td>
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<tr>
<td>2</td>
<td>[RuCl2(C6H6)]2</td>
<td>40</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>[Ru(ρ-cymene)Cl]2</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>[Ru(COD)Cl]2</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Pd(CF3CO2)2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)2</td>
<td>21</td>
<td>2</td>
</tr>
</tbody>
</table>

aReaction conditions: 0.16 mmol 88a, metal precursor (0.0016 mmol), ligand (90) (0.0032 mmol), t-BuOK (0.1M), 1.5 ml IPA. b, cThe ee and conversion were determined by Wcot Fused Silica 25m x 0.25mm, coating Cp Chirasil-Dex CB column, N2 as carrier gas.

The effect of temperature for the asymmetric transfer hydrogenation with Ru/90 catalyst system was studied and summarized in Table 3-2. From the results, the reaction favours at lower temperature (Table 3-2, Entries 3-6). Up to 84% ee was obtained at -10°C, but the conversion was very low (34%) (Table 3-2, Entry 6). As a comparison, higher conversion could be obtained at higher temperature (Table 3-2, Entries 1-3). The best results with 83% ee and 77% conversion were obtained at 0°C (Table 3-2, Entry 5).
Table 3-2. Temperature effect of asymmetric transfer hydrogenation of acetophenone (88a)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature °C</th>
<th>Ee\textsuperscript{b} %</th>
<th>Conv\textsuperscript{c} %</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>54</td>
<td>87</td>
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<tr>
<td>2</td>
<td>r.t.</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>81</td>
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<td>77</td>
</tr>
<tr>
<td>6</td>
<td>-10</td>
<td>84</td>
<td>34</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 0.08 mmol 88a, [Ru(\textit{p}-cymene)Cl\textsubscript{2}]\textsubscript{2} (0.0016 mmol), ligand (90) (0.0064 mmol), t-BuOK (0.1M), 1.5 ml IPA. \textsuperscript{b}The ee and conversion were determined by Wcot Fused Silica 25m x 0.25mm, coating Cp Chirasil-Dex CB column, N\textsubscript{2} as carrier gas.

With the best reaction conditions, the effect of substrate-to-catalyst (S/C) ratio on the asymmetric transfer hydrogenation of ketone was also examined and the results were listed in Table 3-3. The change in S/C ratio had a slight effect on enantioselectivities (Table 3-3, Entries 1-6). Remarkably, this reaction could even be performed at an S/C ratio of 2000:1 without any significant loss in enantioselectivities. However, the conversion was dropped seriously at a higher S/C ratio. In this reaction, the best result was obtained at the S/C ratio of 100:1 with 84% ee and 77% conversion (Table 3-3, entry 2).
After studying the effect of S/C ratio for asymmetric transfer hydrogenation of acetophenone, the metal to ligand (M/L) ratio and concentration of base were also demonstrated, and the results were listed in Table 3-4. Changes in M/L ratio and concentration of base only affected the enantioselectivities of this reaction slightly (Table 3-4). The conversion dropped at lower M/L ratio and higher t-BuOK concentration. The best results were obtained with M/L ratio of 1:4 and 0.1M t-BuOK.

<table>
<thead>
<tr>
<th>Entry</th>
<th>S/C Ratio</th>
<th>Ee(^b) %</th>
<th>Conv(^c) %</th>
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</thead>
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<tr>
<td>1</td>
<td>50:1</td>
<td>83</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>100:1</td>
<td>84</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>200:1</td>
<td>83</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>500:1</td>
<td>83</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>1000:1</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
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<td>35</td>
</tr>
<tr>
<td>7</td>
<td>5000:1</td>
<td>57</td>
<td>20</td>
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\(^a\)Reaction conditions: 0.08 mmol 88a, [Ru(ρ-cymene)Cl\(_2\)]\(_2\) (0.016 - 1.6 umol), ligand (90) (0.064 - 6.4 umol), t-BuOK (0.1M), 1.5 ml IPA. \(^b\)The ee and conversion were determined by Wcot Fused Silica 25m x 0.25mm, coating Cp Chirasil-Dex CB column, N\(_2\) as carrier gas. Reaction at 0\(^\circ\)C.
Table 3-4. M/L ratio and concentration of base for the asymmetric transfer hydrogenation of acetophenone (88a) \(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>M/L Ratio</th>
<th>t-BuOK (M)</th>
<th>Ee(^b) %</th>
<th>Conv(^c) %</th>
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\(^a\)Reaction conditions: 0.16mmol 88a, [Ru(ρ-cymene)Cl]_2 (0.0016 mmol), ligand (90) (0.0032-0.0064 mmol), t-BuOK, 1.0 ml IPA. \(^b\)\(^c\)The ee and conversion were determined by Wcot Fused Silica 25m x 0.25mm, coating Cp Chirasil-Dex CB column, N\(_2\) as carrier gas. Reaction at 0°C.

Additives could play an important role in improving the enantioselectivity and reactivity of many asymmetric reactions.\(^{163-169}\) King \emph{et al}\(^{170}\) reported that acid additives could promote the reaction rates in ruthenium catalyzed hydrogenation of \(\beta\)-ketoesters. To determine the effect of additives on the asymmetric transfer hydrogenation of ketone with the Ru/90 catalyst system, we examined the hydrogenation transfer of acetophenone (88a) with a series of additives. Table 3-5 showed that the enantioselectivities was not improved by the addition of additives, but the conversions were decreased with all used additives. 84% ee and 77% conversion were obtained without any additive under optimized reaction conditions (Table 3-5, Entry 1). Therefore, additives were not used in the further reactions.
Table 3-5. Effect of additives in asymmetric transfer hydrogenation of acetophenone (88a)\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>Ee(^b) %</th>
<th>Conv(^c) %</th>
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</thead>
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<td>I(_2)</td>
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<td>21</td>
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\(^a\)Reaction conditions: 0.16 mmol 88a, [Ru(ρ-cymene)Cl\(_2\)]\(_2\) (0.0016 mmol), ligand (90) (0.0064 mmol), t-BuOK (0.1M), 1.5 ml IPA, 0.02mmol additive. \(^b\)^\(^c\)The ee and conversion were determined by Wcot Fused Silica 25m x 0.25mm, coating Cp Chirasil-Dex CB column, N\(_2\) as carrier gas. Reaction at 0°C. The steric hinderance and electronic features of substituents had significant influences on the catalytic activities. Under optimized reaction conditions, a series of substituted aromatic ketones were tested with the Ru/90 catalyst system and the results were listed in Table 3-6. In general, this catalyst system provided moderate to high conversions and moderate enantioselectivities to all substrates tested. Moderate to high conversions were obtained with most substituted aryl alkyl ketones.
(Table 3-6, entries 2-12). Consistent to the findings of Chan and coworkers, the positioning of the substituent on the aromatic ring of acetophenone had significant effect on the catalytic performances. Lower enantioselectivities were observed with the para-substituted acetophenone (Table 3-6, Entries 2, 4, 7). In contrast, the ortho- and meta-substitued acetophenone yielded moderate enantioselectivities (Table 3-6, Entries 3, 5-6, 8-9). This phenomenon might due to the steric hindrance of the substitutes which affect the approach of the carbonyl group to the catalyst. The introduction of an electron-donating group at the ortho-position increased the reactivity of the catalyst but decreased the enantioselectivities (Table 3-6, Entries 5 & 8). However, both conversion and enantioselectivities were reduced with an electron-donating group at the para position (Table 3-6, Entries 7 & 10). In contrast, enhanced conversions were obtained with electron-withdrawing group no matter which positions it located (Table 3-6, Entries 2-4 & 12).

Besides the substituted acetophenone, two substituted benzophenones were also examined with this catalyst system. Both lower conversion and enantioslectivities were obtained (Table 3-6, Entries 14-15). The reason for the disappointing results might be due to the bulkiness of the aromatic ring next to the active site.
Table 3-6. Asymmetric transfer hydrogenation of aromatic ketones

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Ee&lt;sup&gt;b&lt;/sup&gt; %</th>
<th>Conv&lt;sup&gt;c&lt;/sup&gt; %</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Ph (89a)</td>
<td>CH₃</td>
<td>84</td>
<td>77</td>
</tr>
<tr>
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<td>4-ClPh (89b)</td>
<td>CH₃</td>
<td>58</td>
<td>94</td>
</tr>
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<td>98</td>
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<td>6</td>
<td>3-OCH₃Ph (89f)</td>
<td>CH₃</td>
<td>72</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>4-OCH₃Ph (89g)</td>
<td>CH₃</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>2-CH₃Ph (89h)</td>
<td>CH₃</td>
<td>79</td>
<td>98</td>
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<td>9</td>
<td>3-CH₃Ph (89i)</td>
<td>CH₃</td>
<td>79</td>
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<tr>
<td>10</td>
<td>4-CH₃Ph (89j)</td>
<td>CH₃</td>
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<td>70</td>
</tr>
<tr>
<td>11</td>
<td>Ph (89k)</td>
<td>CH₂CH₃</td>
<td>78</td>
<td>70</td>
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<tr>
<td>12</td>
<td>4-CF₃Ph (89l)</td>
<td>CH₃</td>
<td>74</td>
<td>79</td>
</tr>
<tr>
<td>13</td>
<td>2'-naphthyl (89m)</td>
<td>CH₃</td>
<td>76</td>
<td>50</td>
</tr>
<tr>
<td>14</td>
<td>2-ClPh (89n)</td>
<td>Ph</td>
<td>66</td>
<td>52</td>
</tr>
<tr>
<td>15</td>
<td>4-CF₃Ph (89o)</td>
<td>Ph</td>
<td>57</td>
<td>68</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: 0.32 mmol 88, [Ru(p-cymene)Cl₂]₂ (0.0032 mmol), ligand (0.0128 mmol), t-BuOK (0.1M), 1.5 ml IPA. <sup>b</sup> The ee and conversion were determined by Wcot Fused Silica 25m x 0.25mm, Coating Cp Chiral-Aanalytical for substrate 89a-89l; for substrates 89m-89o, conversion was determined by CYCLOSIL-B [J & W scientific] 30m x 0.25mm x 0.25 um column, N₂ as carrier gas, ee was determined by HPLC OD-H column for substrate 89m-89n or OB-H column for substrate 89l. Chiral products 89a-89g, 89i-89m are R configuration; 89h, 89n-o are S configuration. Reaction at 0°C.

Scientists have interested in the immobilization and recycle of chiral catalyst. Herein, we examined the effectiveness of the immobilization and reused of our Ru/90 complexes for the asymmetric transfer hydrogenation of acetophenone (88a) using high viscous room temperature ionic liquids (RTILs) and
poly(ethyl glycol) (PEG). In order to facilitate the separation of a product from the reaction system, it is generally recognized that there should be distinct solubility difference between the catalysts and the products in the solvent systems. In this regard, two common imidazole ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate (BMIMBF₄) and 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl) imide (BMIMNTf₂), and three polymer solutions PEG (Mn = 200 & 300) and poly(ethyl glycol) dimethyl ether (DMPEG, Mn = 500) were chosen as solvents for the recycle reaction. In order to allow a good mixing between catalyst and substrate, isopropanol (IPA) was employed as co-solvent in this study. The results were summarized in Table 3-7. The reaction was run smoothly with moderated enantioselectivities for both RTILs and PEG polymer solution.

The recyclability of our Ru/90 catalyst in RTILs and PEG polymer solution was investigated by employing 88a as the model substrate. The results shown in Table 3-7 indicated that our Ru/90 catalyst could be recovered and reuse. Experiments were carried out to monitor the reaction in RTILs and PEG polymer solution. After 40 hrs of reaction, the IPA was dried and the products in RTILs and PEG polymer solution were extracted with hexane (3 x 2 ml). The combined hexane layer was concentrated in vacuum to give a crude product, which was analyzed with GC chiral column for enantioselectivities and conversion. Then the RTILs and PEG polymer solution layers
were recharged with IPA, substrate and base for another reaction cycle. The results showed that the catalyst activities remained the same even after 4 cycles. The conversions decreased after each cycle, and the decrease in conversion might due to a certain degree of catalyst deactivation or leaching in the course of experiment.

We also investigated the catalyst stability, the catalyst in RTILs and PEG were placed in a laboratory for 15 days after 5-cycle experiments. Then the catalysts were recharged with IPA, substrate and base for a new reaction cycle, the results (Table 3-7, Entry 6) showed that both activity and enantioselectivity decreased only slightly.

Table 3-7. Recycle and reuse of catalyst for asymmetric transfer hydrogenation of acetophenone (88a)

<table>
<thead>
<tr>
<th>Cycle</th>
<th>BMIMBF₄</th>
<th>BMIMNTf₂</th>
<th>DMPEG (M.W.=500)</th>
<th>PEG (M.W.=300)</th>
<th>PEG (M.W.=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eeᵇ (conv)ᶜ %</td>
<td>Eeᵇ (conv)ᶜ %</td>
<td>Eeᵇ (conv)ᶜ %</td>
<td>Eeᵇ (conv)ᶜ %</td>
<td>Eeᵇ (conv)ᶜ %</td>
</tr>
<tr>
<td>1</td>
<td>75(56)</td>
<td>72(55)</td>
<td>75(69)</td>
<td>79(37)</td>
<td>68(30)</td>
</tr>
<tr>
<td>2</td>
<td>74(45)</td>
<td>72(47)</td>
<td>75(65)</td>
<td>78(29)</td>
<td>65(26)</td>
</tr>
<tr>
<td>3</td>
<td>74(42)</td>
<td>72(32)</td>
<td>74(60)</td>
<td>78(22)</td>
<td>64(18)</td>
</tr>
<tr>
<td>4</td>
<td>74(34)</td>
<td>72(28)</td>
<td>73(58)</td>
<td>78(20)</td>
<td>64(13)</td>
</tr>
<tr>
<td>5</td>
<td>74(25)</td>
<td>68(26)</td>
<td>73(42)</td>
<td>75(17)</td>
<td>62(9)</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>73(25)</td>
<td>65(19)</td>
<td>72(30)</td>
<td>56(10)</td>
<td>54(4)</td>
</tr>
</tbody>
</table>

ᵇReaction conditions: 0.32 mmol 88a, [Ru(ρ-cymene)Cl₂]₂ (0.0032 mmol), ligand (0.0128 mmol), t-BuOK (0.1M), IL/PEG : IPA = 1 : 2, b, cThe ee and conversion were determined by Wcot Fused Silica 25m x 0.25mm, coating Cp Chiral-Sil-Dex CB column, N₂ as carrier gas. bIL/PEG with catalyst was placed in a laboratory 15 days before the reaction cycle. Reaction time : 40hrs.
Chapter 4

Anti-tumor Activity of Quinoline Compounds

Cancer is the second life threatening disease worldwide\(^{178}\) and development of anti-cancer drugs with high efficacy and minimal side-effects remains to be a challenge. The nitrogen-containing alkaloids, which were discovered in natural plants, are usually basic in nature and bear biological activities.\(^{7,10,11,179-182}\) Quinoline compounds are well known due to their broad biological activities,\(^{183}\) such as antifungal,\(^{184}\) antibacterial\(^{185}\) and HIV-1 replication inhibiting activities\(^{186}\) that have been made use of in traditional medicine. Recently, quinoline-based azolyalkylquinolines with differentazole groups, such as benzothiazole, tetrazole and 1,2,4-triazole have been synthesized and reported as potent anti-tumor agents against breast cancer cells \textit{in vitro}.\(^{187}\) 8-Hydroxyquinoline derivatives have been prepared and studied for treatment of neurodegenerative diseases such as Alzheimer’s disease.\(^{188}\) In addition, the derivatives have been reported to possess biological activities on the proliferation of rat mesenchymal stem cells (rMSCs).\(^{189}\) The anti-tumor applications of quinoline analogues have also been reported.\(^{27-30,190-193}\)

The anti-tumor activities of quinoline compounds have been investigated in this study. Preliminary results had shown that quinoline compounds have effective anti-tumor activities against a plane of human cancer cell lines (such as Hep3B, KYSE150,
HKESC-1, HKESC-4, MCF-7, T-47D and K562) and Hep3B hepatocellular and KYSE150 esophageal tumor xenograft in athymic nude mice model with no observable damages on the vital organs.\textsuperscript{27-30} Here, the simple quinoline derivatives (Figure 4-1) have aroused our interest because of their anti-tumor activity.

![Figure 4-1. Examples of quinoline derivatives](image)

### 4.1 Anti-tumor Activity of 8-Hydroxy Substituted Quinoline Derivatives

Firstly, a number of easily available substituted quinoline compounds were prepared to initiate the anti-tumor study with various types of cancer cell lines \textit{in vitro}. The preliminary screening with MTS ([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium]) assay,\textsuperscript{194,195} with cisplatin (CDDP) as positive reference, showed that pure 2-substituted quinoline moieties such as 2-methylquinoline (Figure 4-1, compound a), did not have any significant anti-tumor effect.

The introduction of the hydroxyl group at position 8 of a quinoline compound (92e) (Table 4-1, Entry 6 vs 2) showed a prominent positive anti-tumor effect against T47D
and K562 cancer cell lines in vitro, with the relative MTS activities being of 52.6 and 26.7 respectively at a concentration of 50μg/ml. Commercially available quinoline compounds with the hydroxyl group on positions 4, 6 and 7 (92b-92d) were also studied, but they only showed little activities (Table 4-1, Entries 3-5). The hydroxyl group at position 8 is necessary for the anti-tumor activity of quinoline compounds, because when this hydroxyl group was replaced by hydrogen, no significant anti-cancer effect was observed (Table 4-1, Entries 2).

Table 4-1. MTS assay of quinoline compounds.\(^{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Relative MTS Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100±6.5</td>
</tr>
<tr>
<td>2</td>
<td>92a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H H H H H H</td>
</tr>
<tr>
<td>3</td>
<td>92b</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>H H H OH H</td>
</tr>
<tr>
<td>4</td>
<td>92c</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>H H OH H</td>
</tr>
<tr>
<td>5</td>
<td>92d</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>H H OH H</td>
</tr>
<tr>
<td>6</td>
<td>92e</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>52.6 ± 2.4</td>
</tr>
<tr>
<td>7</td>
<td>CDDP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30.5 ± 4.8</td>
</tr>
</tbody>
</table>

\(^{a}\)Cisplatin (CDDP) is used as a positive reference. All the tested compounds and CDDP are at a concentration of 50μg/ml. Results are shown as mean ± SD from triplicate experiments.
A series of 8-hydroxyl substituted quinoline compounds were synthesized (Scheme 4-1) and employed as anti-tumor agents against a series of human cancer cell lines and the results are shown in Table 4-2. Most 8-hydroxyl substituted quinoline compounds showed positive relative MTS activities. Overall, the liver cancer cell line Hep3B was more sensitive to our tested quinoline compounds with lower relative MTS values.

![Reaction Scheme](image)

**Scheme 4-1.** Synthesis of 8-hydroxyl substituted quinoline compounds

The cytotoxicity of 8-hydroxyl substituted quinoline compounds was affected by the electronic properties and the position of substituted functional groups for different cancer cell lines. High cytotoxicity was found in compounds with electron-donating substituted groups for all tested human cancer cell lines (Table 4-2, Entries 4-5, 7). Compounds with electron-withdrawing substituted groups had lower cytotoxicity for all tested cancer cell lines (Table 4-2, Entries 8-10). The substituted group at position 3 could provide higher cytotoxicity than that at position 4. Higher cytotoxicity was for substrates 86e, 86h and 86o than 86f, 86g and 86m respectively for all cancer cell lines (Table 4-2, Entries 2 vs 3, 4 vs 5 and 10 vs 12 ).
Table 4-2. MTS assay of 8-hydroxysubstituted quinoline compounds\textsuperscript{a}

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Relative MTS Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hep3B</td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>86e</td>
<td>(\text{NO}_2)</td>
<td>61.7±14.5</td>
</tr>
<tr>
<td>3</td>
<td>86f</td>
<td>(\text{NO}_2)</td>
<td>111.3±2.6</td>
</tr>
<tr>
<td>4</td>
<td>86g</td>
<td>(\text{OMe})</td>
<td>32.0±1.7</td>
</tr>
<tr>
<td>5</td>
<td>86h</td>
<td>(\text{OMe})</td>
<td>20.9±3.0</td>
</tr>
<tr>
<td>6</td>
<td>86i</td>
<td>(\text{CN})</td>
<td>63.7±2.0</td>
</tr>
<tr>
<td>7</td>
<td>86j</td>
<td>(\text{Ph})</td>
<td>37.0±21.4</td>
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<tr>
<td>8</td>
<td>86k</td>
<td>(\text{OCF}_3)</td>
<td>77.7±13.0</td>
</tr>
<tr>
<td>9</td>
<td>86l</td>
<td>(\text{F})</td>
<td>81.1±6.9</td>
</tr>
<tr>
<td>10</td>
<td>86m</td>
<td>(\text{CF}_3)</td>
<td>87.8±7.3</td>
</tr>
<tr>
<td>11</td>
<td>86n</td>
<td>(\text{Cl})</td>
<td>63.9±14.0</td>
</tr>
<tr>
<td>12</td>
<td>86o</td>
<td>(\text{CF}_3)</td>
<td>41.4±0.8</td>
</tr>
<tr>
<td>13</td>
<td>CDDP</td>
<td></td>
<td>17.0±1.2</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Cisplatin (CDDP) is used as a positive reference. All the tested compounds and CDDP are at a concentration of \(50\mu\text{g/ml}\). Results are shown as mean ± SD from triplicate experiments.
4.1.1 Anti-tumor Activity of 8-Hydroxyquinoline-2-Carbaldehyde (93b)

Compounds with a hydroxyl group at position 8 but various functional groups at position 2 (Table 4-3, substrates 86a, 93a-93b) were also studied and different anti-tumor effects were detected (Table 4-3, Entries 2-4). For compound 8-hydroxyquinoline-2-carbaldehyde (93b) which bore a carboxyaldehyde group on position 2 together with a hydroxyl group on position 8, there was a nearly 4-fold increase in cytotoxicity in comparison with CDDP against T47D cell line (Table 4-3, Entries 4 & 6). Herein the carboxyaldehyde group showed the major influence for the anti-tumor activities when compared with the other two compounds that bore the methyl or nitrile group on position 2 (Table 4-3, substrates 86a & 93a). However, there wasn’t any significant anti-tumor effect for compound quinoline-2-carbaldehyde (93c) that only contained a carbaldehyde group on position 2 but not any hydroxyl group on position 8 in selective cancer cell lines (Table 4-3, Entry 5).
Table 4-3. MTS assay of quinoline compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>R₁</th>
<th>Relative MTS Activities</th>
</tr>
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<tbody>
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<td></td>
<td></td>
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<td>2</td>
<td>86a</td>
<td>CH₃</td>
<td>OH</td>
<td>46.5 ± 9.4</td>
</tr>
<tr>
<td>3</td>
<td>93a</td>
<td>CN</td>
<td>OH</td>
<td>72.9 ± 12.0</td>
</tr>
<tr>
<td>4</td>
<td>93b</td>
<td>CHO</td>
<td>OH</td>
<td>8.4 ± 3.5</td>
</tr>
<tr>
<td>5</td>
<td>93c</td>
<td>CHO</td>
<td>H</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>CDDP</td>
<td></td>
<td></td>
<td>30.5 ± 4.8</td>
</tr>
</tbody>
</table>

*Cisplatin (CDDP) is used as a positive reference. All the tested compounds and CDDP are at a concentration of 50μg/ml. Results are shown as mean ± SD from triplicate experiments.

To further demonstrate the anti-tumor effect of compound 93b, we studied its possible cytotoxic activity by means of MTS assay with various cancer cell lines together with a non-tumor mouse embryonic fibroblast cell line NIH3T3. As shown in Table 4-4, compound 93b showed very promising MTS₀ activity (50% reduction of MTS assay signal by the chemical treated cells as compared with the control), especially against Hep3B cells (MTS₀ = 6.25-12.5 μg/mL) (Table 4-2, Entry 8). Lung cancer cell line A549 showed most resistance with our compound 93b with MTS₀ greater than 50μg/ml (Table 4-4, Entry 1); the MTS₀ of other cancer cell lines ranged from 12.5-25μg/ml (Table 4-4, Entries 2-7).
Table 4-4. *In vitro* anti-tumor activity (MTS<sub>50</sub>) of 8-hydroxyquinoline-2-carbaldehyde (93b).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cell Line</th>
<th>MTS&lt;sub&gt;50&lt;/sub&gt; Range (μg/ml)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>A549</td>
<td>&gt;50</td>
</tr>
<tr>
<td>2</td>
<td>MDA231</td>
<td>12.5-25</td>
</tr>
<tr>
<td>3</td>
<td>T-47D</td>
<td>12.5-25</td>
</tr>
<tr>
<td>4</td>
<td>Hs578t</td>
<td>12.5-25</td>
</tr>
<tr>
<td>5</td>
<td>K562</td>
<td>12.5-25</td>
</tr>
<tr>
<td>6</td>
<td>SaoS2</td>
<td>12.5-25</td>
</tr>
<tr>
<td>7</td>
<td>SKHep1</td>
<td>12.5-25</td>
</tr>
<tr>
<td>8</td>
<td>Hep3B</td>
<td>6.25±0.034</td>
</tr>
<tr>
<td>9</td>
<td>NIH3T3</td>
<td>7.00±0.051</td>
</tr>
</tbody>
</table>

Figure 4-2 shows the dose-dependent cytotoxicity of compound 93b on human breast carcinoma cancer cell lines T47D, Hs578t and chronic myelogenous leukemia K562, the cytotoxicity increased with increasing compound concentrations.

Then various cancer cells were treated with compound 93b as presented in Table 4-4 and after 48 hours, morphological changes, including cell rounding, cell shrinkage
and loss of adherent property (for solid tumor cell lines), were recorded under a phase contrast microscope. The morphological changes were indicating the anti-tumor effect of the compound 93b. Seven of the eight cancer cell lines, including the breast carcinoma cell lines (T47D, MDAMB-231 and Hs578t) showed cell shrinkage, lost the adherent property and cell rounding (Figure 4-3). Normal growth was observed in the DMSO controls. The A549 lung cancer cells were the least affected.

![Figure 4-3. Morphological studies of the cytotoxic action of compound 93b on human cancer cell lines.](image)

As shown in Figure 4-4, the K562 leukemia cell line and the T47D breast cancer cell line were treated with compound 93b for 24 hours. Afterwards, cells were washed
with phosphate buffered saline and allowed to grow for 10 days and viable colonies formed in semi-solid methylcellulose were stained with MTT. Then the colonies were fixed and stained with methylene blue and photographed. Results showed that compound 93b could effectively exert its anti-tumor effect by inhibiting the anchorage-dependent clonogenicity potential of K562 and T47D cells in a dose dependent manner (Figure 4-4).

**Figure 4-4.** a) K562 colonies from vehicle control; b) K562 treated with compound 93b (50μg/ml) for 24 hrs; c) Percentages of colony formation inhibition of compound 93b on the K562 and T47D cancer cells using the anchorage dependent clonogenicity assay.

Compound 93b showed very prominent anticancer activities *in vitro* in our experiments. *In vivo* activity of compound 93b was also studied using the athymic nude mice hepatocellular carcinoma Hep3B xenograft tumor model. As shown in Figure 4-5, a near complete disappearance of tumor on the ninth day was observed in the mice that received daily intraperitoneal (i.p.) injection of compound 93b at the
dosage of 10mg/kg/day as compared with the vehicle control. None of the mice died during the treatment. A significant difference in the tumor volume was observed in mice from the treatment and control groups.

**Figure 4-5.** Athymic nude mice with Hep3B xenograft experiment for testing the *in vivo* anti-tumor effect of compound 93b and vehicle control. Arrows indicate the positions of the xenograft tumors. The tumor size was significantly reduced in the mice treated with compound 93b.

The relative changes in tumor volume in the mice that received compound 93b and those received the vehicle control are shown in Figure 4-6. There was a large increase in relative tumor volume in the control group’s nude mice, however, for the nude mice received compound 93b, the relative tumor volume decreased from day 5 and totally disappeared at day 9. Our compound 93b would effectively reduce the tumor size in this nude mice xenograft model.
Pathological investigation of vital organs (heart, liver, lung and kidney) of athymic nude mice treated with compound 93b, stained with haematoxylin and eosin (Figure 4-7) and tested with the liver-enzyme release under the therapeutic doses (Figure 4-8) did not demonstrate any observable toxicology or tissue damage. We also studied the toxicology of compound 93b, where C57 mice were treated with compound 93b up to 30mg/kg/day daily i.p. injection for an 8 continuous days as the treatment of nude mice xenograft experiment showed insignificant toxicity on the animals.

**Figure 4-6.** Relative changes of tumor volume (mm$^3$) of athymic nude mice with subcutaneous human hepatocellular carcinoma Hep3B xenografts cells treated with compound 93b or vehicle control. Both the control and treated groups consisted of five mice. Results are shown as mean ± SD of tumor volume.*P<0.05 (Student’s t-test).
Figure 4-7. Histological appearance of vital organs collected from an athymic nude mouse treated with compound 93b for 8 days showing no sign of tissue damage at the histological level. Original magnification: 200x.

Figure 4-8. Effects of 93b on the levels of serum markers for liver functions. No significant changes in serum marker levels were observed at various drug concentration.
Since compound 8-hydroxyquinoline-2-carbaldehyde (93b) showed very strong anti-tumor activities, a series of 8-hydroxyl substituted 2-carbaldehyde quinoline compounds were synthesized (Scheme 4-2) and employed as anti-tumor agents against a series of human cancer cell lines. The results were shown in Table 4-5. All the tested 8-hydroxyl 2-carbaldehyde substituted quinoline compounds showed positive anticancer activities. Compared with the 8-hydroxy substituted quinoline compounds (Table 4-2), the introduction of carboxaldehyde group increased the compounds anti-tumor activity (Table 4-5).

Scheme 4-2. Synthesis of 8-hydroxyl substituted 2-carbaldehyde quinoline compounds

The relative MTS activities were affected by the electronic properties and the position of substituted functional groups for all tested cancer cell lines. High cytotoxicity was observed in compounds with electron-donating substituted groups in all tested cancer cell lines (Table 4-5, Entries 2, 5-6, 8), while lower cytotoxicity was observed in compounds with electron-withdrawing substituted groups (Table 4-5, Entries 9-13).

The position of the substituted groups also affected the cytotoxicity of compounds. For compounds that contained the same substituted groups, higher cytotoxicity was
observed that substituted group at meta position than at para position in all human cancer cell lines (Table 4-5, Entries 3 vs 4, 5 vs 6).

**Table 4-5.** MTS assay of 8-substituted 2-carbaldehyde quinoline compounds$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Relative MTS Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hep3B</td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>94a</td>
<td>H</td>
<td>9.2±0.3</td>
</tr>
<tr>
<td>3</td>
<td>94b</td>
<td>3-NO$_2$</td>
<td>78.0±0.3</td>
</tr>
<tr>
<td>4</td>
<td>94c</td>
<td>4-NO$_2$</td>
<td>75.4±1.2</td>
</tr>
<tr>
<td>5</td>
<td>94d</td>
<td>4-OMe</td>
<td>12.0±0.3</td>
</tr>
<tr>
<td>6</td>
<td>94e</td>
<td>3-OMe</td>
<td>7.5±0.3</td>
</tr>
<tr>
<td>7</td>
<td>94f</td>
<td>4-CN</td>
<td>88.9±0.8</td>
</tr>
<tr>
<td>8</td>
<td>94g</td>
<td>3-Ph</td>
<td>7.2±0.2</td>
</tr>
<tr>
<td>9</td>
<td>94h</td>
<td>4-OCF$_3$</td>
<td>24.7±0.5</td>
</tr>
<tr>
<td>10</td>
<td>94i</td>
<td>4-F</td>
<td>15.8±1.1</td>
</tr>
<tr>
<td>11</td>
<td>94j</td>
<td>4-CF$_3$</td>
<td>19.5±0.5</td>
</tr>
<tr>
<td>12</td>
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<td>4-Cl</td>
<td>65.9±0.5</td>
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<tr>
<td>13</td>
<td>94l</td>
<td>3,5-CF$_3$</td>
<td>84.6±2.8</td>
</tr>
</tbody>
</table>

$^a$All tested compounds are at a concentration of 50μg/ml. Results are shown as mean ± SD from triplicate experiments.
4.1.2 Anti-tumor Activity of 8-Hydroxy Substituted 5,7-Dibromoquinoline Compounds

Our experimental results showed that with the hydroxyl group at position 8 of the quinoline compounds were necessary for their anti-tumor activities. Some 8-hydroxysubstituted 5,7-dibromoquinoline compounds (95a-i) were synthesized by addition of Br₂ into 2-methylquinolin-8-ol (86a) in MeOH (Scheme 4-3). Their anti-cancer activities against human cancer cell lines were then studied and the results are shown in Table 4-6.

Scheme 4-3. Synthesis of 8-hydroxysubstituted 5,7-dibromo-quinoline compounds

Overall, the human liver cancer cell line Hep3B was more sensitive for the bromo-substituted quinoline compounds, and the human lung cancer cell line A549 was more resistant to this type of compounds. The anti-tumor activities were affected by the compounds’ electronic properties and the position of substitutes. The best result was obtained for compound 2-(5,7-dibromo-2-methylquinolin-8-yloxy)-1-(4-fluorophenyl)ethanone (95e), which contained an electron-withdrawing fluoro group at the para position in all tested human cancer cell lines (Table 4-6, Entry 5). Relatively lower MTS activities were
observed in compounds that contained –OMe at *ortho* and *para* positions (95g & 95i) (Table 4-6, Entries 7 & 9). However, relatively higher MTS activities were observed in compounds that contained OMe at *meta* positions (95h) in both Hep3B and A549 cancer cell lines (Table 4-6, Entry 8). In contrast, the position of substitutes was less affected in HKESC-1 and KYSE150 cancer cell lines. (Table 4-6, Entries 7-9).

**Table 4-6.** MTS assay of 8-hydroxysubstituted 5,7-dibromo-quinoline compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Relative MTS Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hep3B</td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>95b</td>
<td></td>
<td>14.8±0.3</td>
</tr>
<tr>
<td>3</td>
<td>95c</td>
<td></td>
<td>32.5±2.7</td>
</tr>
<tr>
<td>4</td>
<td>95d</td>
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<td>66.2±3.2</td>
</tr>
<tr>
<td>5</td>
<td>95e</td>
<td></td>
<td>12.2±0.1</td>
</tr>
<tr>
<td>6</td>
<td>95f</td>
<td></td>
<td>22.9±1.1</td>
</tr>
<tr>
<td>7</td>
<td>95g</td>
<td></td>
<td>28.2±0.7</td>
</tr>
<tr>
<td>8</td>
<td>95h</td>
<td></td>
<td>44.2±0.7</td>
</tr>
<tr>
<td>9</td>
<td>95i</td>
<td></td>
<td>28.4±0.8</td>
</tr>
</tbody>
</table>

*aAll tested compounds are at a concentration of 40μg/ml. Results are shown as mean ± SD from triplicate experiments.*

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The MTS$_{50}$ of compound 95e was studied *in vitro* with four human cancer cell lines, the results are shown in Figure 4-9. Higher MTS$_{50}$ values were obtained for the human lung cancer cell line A549. The human liver cancer cell line Hep3B was more sensitive to this type of compound with lower MTS$_{50}$ values were observed.

![Figure 4-9. MTS$_{50}$ of 2-(5,7-dibromo-2-methylquinolin-8-yloxy)-1-(4-fluorophenyl)ethanone (95e). Results are shown as mean±SD for MTS$_{50}$ values.](image)

Then the *in vivo* activity of compound 95e was studied using an athymic nude mice hepatocellular carcinoma Hep3B xenograft tumor model. As shown in Figure 4-10, a tumor nearly stopped growth in mice that received compound 95e daily intraperitoneal (i.p.) injection dosage of 10mg/kg/day from Day 9 of the drug administration compared with the vehicle control. Moreover, no mice died during the treatment. It was noticed that significant differences in the tumor volume was
observed in mice from the two groups. It could be confirmed that our compound 95e could effectively reduce the tumor size in this nude mice model.

![Graph showing relative change in tumor volume](image)

**Figure 4-10.** Relative changes of tumor volume (mm³) of athymic nude mice with subcutaneous human hepatocellular carcinoma Hep3B xenografts cells treated with compound 95e and vehicle control. Both control and treated groups consisted of five mice. Results are shown as mean ± SD of tumor volume. **P<0.005 (Student t-test)**

Cell morphological changes were studied after the in vivo study. Various cancer cells (Hep3B, A549, HKESC-1, HKESC-4, KYSE150 and MCF-7) were treated with compound 95e at 50μg/ml after 48 hours incubation, and morphological changes including cell rounding, cell shrinkage and loss of adherent property were recorded under a phase contrast microscope to show the anti-tumor effect of the compound 95e. The entire tested cancer cell lines showed cell shrinkage and lost of adherent property
and cell rounding and normal growth was observed in the DMSO controls (Figure 4-11).

**Figure 4-11.** Morphological studies of the cytotoxic action of compound 95e on human cancer cell lines.

### 4.2 Anti-tumor Activity of 8-Substituted 1,2,3,4-Tetrahydroquinoline Derivatives

The pharmacological activities of tetrahydroquinoline compounds, such as Sumanireole maleate\(^{196-198}\) (an anti-depressant for Parkinson’s disease) and Vesnarinone\(^{199}\)(a positive inotropic agent) have attracted the attention of many scientists. The natural optically active 1-methyl 2-alkyl-substituted quinoline alkaloids
can be isolated from the plant *Galipea officinalis Hancock*, and the compound angustureine was first isolated by Jacquemond-Collet and his co-workers.\textsuperscript{200} The *G. officinalis* has been used in traditional herbal medicine to treat fever of dyspepsia, dysentery and chronic diarrhea.\textsuperscript{201} Chirality introduction via asymmetric catalysis may provide these organic compounds with beneficial biological activities, and this is particularly important for the relatively unexplored enantioselective tetrahydroquinoline derivatives.\textsuperscript{28,30}

Asymmetric hydrogenation is an efficient route to synthesize chiral compounds with chiral catalyst. Here chiral 1,2,3,4-tetrahydroquinolines compounds (both *R* and *S* isomers) were synthesized by the asymmetric hydrogenation method under our previous optimal reaction conditions (Scheme 4-4).\textsuperscript{79-81,83} The anti-tumor activities of these chiral compounds were studies both *in vitro* and *in vivo*.

![Scheme 4-4. Asymmetric synthesis of 8-substituted 1,2,3,4-tetrahydroquinolines](image)
4.2.1 Anti-tumor Activity of 1,2,3,4-Tetrahydro-2-methylquinolin-8-ol (87a)

1,2,3,4-tetrahydro-2-methylquinolin-8-ol (87a) was synthesized via asymmetric hydrogenation of 8-hydroxy-2-methylquinoline (86a) (Scheme 4-5). Then the anti-tumor activities were studied for possible cytotoxic activity by means of MTS assay with a series of human cancer cell lines, and the results are shown in Table 4-7. The tested cancer cell lines were relatively insensitive to the unsaturated substrate 8-hydroxy-2-methylquinoline (86a). Higher MTS$_{50}$ values (25-50 μg/ml) were obtained (Table 4-7, Entries 2-3, 5) in lung cancer cell line A549 and live cancer cell line SKHep1 with MTS$_{50}$ greater than 50μg/ml (Table 4-7, Entries 1, 4). On the other hand, the partially saturated compound 1,2,3,4-tetrahydro-2-methylquinolin-8-ol (87a) showed very promising MTS$_{50}$ activity regardless to compounds enantioselectivities, especially against Hep3B cells (MTS$_{50}$ < 3.1 μg/ml) (Table 4-7, Entry 5). The lung cancer cell line A549 showed most resistance to our compound 87a with an MTS$_{50}$ range of 12.5-25μg/ml (Table 4-7, Entry 1), the MTS$_{50}$ of other cancer cell lines ranged from 3.1-6.3μg/ml (Table 4-7, Entries 2-4).
Table 4-7. *In vitro* anti-tumor activity (MTS$_{50}$) of 8-hydroxy-2-methylquinoline (86a) and 1,2,3,4-tetrahydro-2-methylquinolin-8-ol (87a)$^a$.

![Scheme 4-5](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cancer Cell lines</th>
<th>MTS$_{50}$ (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>86a</td>
</tr>
<tr>
<td>1</td>
<td>A549</td>
<td>&gt;50</td>
</tr>
<tr>
<td>2</td>
<td>MDA231</td>
<td>25-50</td>
</tr>
<tr>
<td>3</td>
<td>SaoS2</td>
<td>25-50</td>
</tr>
<tr>
<td>4</td>
<td>SKHep1</td>
<td>&gt;50</td>
</tr>
<tr>
<td>5</td>
<td>Hep3B</td>
<td>25-50</td>
</tr>
</tbody>
</table>

$^a$Results are based on MTS assay. Three independent experiments were performed with triplicate and similar results were obtained.

Compound 87a showed strong anti-tumor activities *in vitro* in our experiments, and its *in vivo* activity was also studied using an athymic nude mice hepatocellular carcinoma Hep3B xenograft tumor model. As shown in the Figures 4-12 and 4-13, a significant retardation of tumor growth of the hepatocellular carcinoma Hep3B xenograft was observed in the mice that received compound 87a daily intraperitoneal (i.p.) injection dosage of 5mg/kg/day at Day 14 of the drug administration compared with the vehicle control. Moreover, no mice died during the treatment. It was noticed that significant differences in tumor volume was observed in mice from the two groups.
Figure 4-12. Athymic nude mice with Hep3B xenograft experiment for testing the \textit{in vivo} anti-tumor effect of compound \textbf{87a} (5mg/kg/day) and vehicle control. Arrows indicate the positions of the xenograft tumors. The tumor size was significantly reduced in the mice tested with compound \textbf{87a}.

![Vehicle Control](image1)

![Compound 87a](image2)

Figure 4-13. Relative changes in tumor volume (mm$^3$) of athymic nude mice with subcutaneous human hepatocellular carcinoma Hep3B xenografts treated with compound \textbf{87a} (5mg/kg/day) and vehicle control. Both control and treated groups consisted of five mice. Results are shown as mean ± SD of tumor volume.**$P<0.005$ (Student \textit{t}-test).
Then various cancer cells (Hep3B, A549, HKESC-1, HKESC-4, KYSE150 and MCF-7) were treated with compound 87a at 50μg/ml after 48 hours incubation, and morphological changes including cell rounding, cell shrinkage and loss of adherent property were recorded under a phase contrast microscope to show the anti-tumor effect of compound 87a. All six cancer cell lines showed cell shrinkage and loss of the adherent property, and cell rounding and normal growth were observed in the DMSO controls (Figure 4-14).

**Figure 4-14.** Morphological studies of the cytotoxic action of compound 87a on human cancer cell lines.
Pathological investigation of livers from athymic nude mice treated with compound 87a stained with haematoxylin and eosin (Figure 4-15) did not demonstrate any observable toxicity or tissue damage.

![Vehicle control vs Compound 87a](image)

**Figure 4-15.** Histological appearances of vital organs collected from athymic nude mice treated with compound 87a and vehicle control showing no sign of tissue damage at the histological level.

4.2.2 **Anti-tumor Activity of 2-Methyl-8-(4-(trifluoromethyl)benzyl)oxy)-1,2,3,4-tetrahydroquinoline (87m)**

1,2,3,4-tetrahydro-2-methylquinolin-8-ol (87a) showed strong anti-tumor activities. A series of 8-hydroxyl substituted 1,2,3,4-tetrahydroquinoline compounds were synthesized (Scheme 4-4) and employed as anti-tumor agents against a series of human cancer cell lines and the results are shown in Table 4-8. Most 8-hydroxyl substituted 1,2,3,4-tetrahydroquinoline compounds showed positive anticancer
activities. Overall, the liver cancer cell line Hep3B was more sensitive with high cytotoxicity to our tested compounds.

The cytotoxicity of the tested compounds was affected by the electronic properties of the substituted functional groups. High cytotoxicity was observed in compounds with electron-withdrawing substituted groups for most of the tested human cancer cell lines (Table 4-8, Entries 8-11), except the human esophageal cancer cell line KYSE150, in which relatively lower MTS activities were observed with electron-donating substituted groups (Table 4-8, Entries 4-7). Compound 2-methyl-8-(4-(trifluoromethyl)benzyl)cyclooctyl)-1,2,3,4-tetrahydroquinoline (87m) showed relatively strong anti-tumor activity in Hep3B liver cancer cell line.
Table 4-8. MTS assay of 8-substituted 1,2,3,4-tetrahydroquinoline compounds

![Structure of compound 87]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Relative MTS Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hep3B</td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>87e</td>
<td>NO₂</td>
<td>68.8±2.7</td>
</tr>
<tr>
<td>3</td>
<td>87f</td>
<td>NO₂</td>
<td>126.4±3.0</td>
</tr>
<tr>
<td>4</td>
<td>87g</td>
<td>OMe</td>
<td>55.4±11.4</td>
</tr>
<tr>
<td>5</td>
<td>87h</td>
<td>OMe</td>
<td>72.6±6.5</td>
</tr>
<tr>
<td>6</td>
<td>87i</td>
<td>CN</td>
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</tr>
<tr>
<td>7</td>
<td>87j</td>
<td>Ph</td>
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<td>87k</td>
<td>OCF₃</td>
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<tr>
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<td>87l</td>
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<td>41.2±1.7</td>
</tr>
<tr>
<td>10</td>
<td>87m</td>
<td>CF₃</td>
<td>20.4±2.4</td>
</tr>
<tr>
<td>11</td>
<td>87n</td>
<td>Cl</td>
<td>60.9±4.2</td>
</tr>
</tbody>
</table>

*All tested compounds are at a concentration of 50μg/ml. Results are shown as mean ± SD from triplicate experiments.

The *in vivo* activity of compound 87m was also studied using an athymic nude mice hepatocellular carcinoma Hep3B xenograft tumor model. As shown in Figures 4-16 and 4-17, a total disappearance of tumor growth of the hepatocellular carcinoma
Hep3B xenograft was observed in mice that received compound 87m daily intraperitoneal (i.p.) injection at the dosage of 10mg/kg/day at Day 13 of drug administration compared with the vehicle control. Moreover, no mice died during the treatment. It was noticed that significant difference in the tumor volume was observed in mice from the two groups. It can be confirmed that our compound 87m can effectively reduce the tumor size in this nude mice xenograft model.

![Figure 4-16.](image)

**Figure 4-16.** Athymic nude mice with Hep3B xenograft experiment for testing the *in vivo* anti-tumor effect of compound 87m or vehicle control. Arrows indicate the positions of the xenograft tumors. The tumor size was significantly reduced in the mice tested with compound 87m.
Figure 4-17. Relative changes of tumor volume (mm$^3$) of athymic nude mice with subcutaneous human hepatocellular carcinoma Hep3B xenografts cells treated with compound 87m or vehicle control. Both control and treated groups consisted of five mice. Results are shown as mean ± SD of tumor volume. **P<0.005 (Student’s t-test).

Cells morphological changes were also studied after the in vivo study. Various cancer cells (Hep3B, A549, HKESC-1, HKESC-4, KYSE150 and MCF-7) were treated with compound 87m at 50μg/ml after 48 hours incubation, morphological changes including cell rounding, cell shrinkage and loss of adherent property were recorded under a phase contrast microscope to show the anti-tumor effect of the compound 87m. Most cancer cell lines showed cell shrinkage and loss of the adherent property, and cell rounding and normal growth were observed in the DMSO controls; however, the A549 lung cancer cells were least affected. (Figure 4-18).
4.2.3 Anti-tumor Activity of 5,7-Dibromo-2-methyl-1,2,3,4-tetrahydroquinolin-8-ol (96a)

The chiral 5,7-dibromo-2-methyl-1,2,3,4-tetrahydroquinolin-8-ol (96a) was synthesized by asymmetric hydrogenation reaction of 5,7-dibromo-2-methylquinolin-8-ol (95a) with our previous optimal reaction conditions (Scheme 4-6).

Scheme 4-6. Synthesis of chiral compound (R/S)-96a
To demonstrate the anti-tumor effect of compound (R/S)-96a, we studied the MTS$_{50}$ with various human cancer cell lines, and the results are showed in Figure 4-19. Both (R)-96a and (S)-96a showed very promising MTS$_{50}$ (MTS$_{50}$ range of 4.3-9.5μg/ml) activities compared with CDDP. The figure indicated that the anti-tumor activities of $R$ emantiomer of compound 96a was better than $S$ emantiomer for most of cancer cell lines, except the lung cancer cell line A549. For the liver cancer cell line Hep3B, the anti-tumor activities were the same for both $R$ and $S$ emantiomers. The human esophageal cancer cell line KYSE150 was most sensitive to (R)-96a with MTS$_{50}$ lowered to 4.3μg/ml (Figure 4-19).

**Figure 4-19.** MTS$_{50}$ of compounds (R)-96a and (S)-96a of five cancer cell lines compared with CDDP.
The enantioselectivities effect on the anti-tumor activities of chiral compound 96a (both $R$ and $S$) was investigated. Both the $R$ and $S$ forms of chiral compound 96a with various ee values were prepared with their anti-tumor activities in five human cancer cell lines being examined with MTS assay. The MTS$_{50}$ values were slightly decreased with increasing in enantioselectivities of chiral compound ($R$)-96a in all tested human cancer cell lines. However, the results of the chiral compound ($S$)-96a were opposite with the MTS$_{50}$ values being slightly increased with decreasing in enantioselectivities in all tested human cancer cell lines. This might be due to the chemical structure of ($R$)-96a, which was more favorable for killing the cancer cells more effectively than ($S$)-96a.

The chiral compound ($R$)-96a showed very promising MTS$_{50}$ of 4.3μg/ml for the KYSE150 human esophageal cancer cell line (Figure 4-19). The in vivo activity of compound ($R$)-96a was studied using an athymic nude mice esophageal carcinoma KYSE150 xenograft tumor model. As shown in Figures 4-20 and 4-21, a total disappearance of tumor growth of the esophageal carcinoma KYSE150 xenograft was observed in the mice that received compound ($R$)-96a daily intraperitoneal (i.p.) injection at the dosage of 10mg/kg/day at Day 19 of drug administration compared with the vehicle control (Figures 4-21). Moreover, no mice died during the treatment. It was noticed that significant differences in the tumor volume was observed in mice
from the two groups (Figures 4-20). It can be confirmed that our compound \((R)-96a\) can effectively reduce the tumor size in this nude mice xenograft model.

**Figure 4-20.** Athymic nude mice with KYSE150 esophageal xenograft experiment for testing the *in vivo* anticancer effect of compound \((R)-96a\) and vehicle control. Arrows indicate the positions of the xenograft tumors. The tumor size was significantly reduced in the mice treated with compound \((R)-96a\).

**Figure 4-21.** Relative changes of tumor volume (mm\(^3\)) of athymic nude mice with subcutaneous human esophageal carcinoma KYSE150 xenografts cells treated with compound \((R)-96a\) or vehicle control. Both the control and treated groups consisted of five mice. Results are shown as mean ± SD of tumor volume. **P<0.005 (Student’s *t*-test).
Then various cancer cells (Hep3B, A549, HKESC-1, HKESC-4, KYSE150 and MCF-7) were treated with compound 96a at 50μg/ml after 48 hours incubation, morphological changes including cell rounding, cell shrinkage and loss of adherent property were recorded under a phase contrast microscope to show the anti-tumor effect of compound 96a. All six cancer cell lines showed cell shrinkage and loss of the adherent property and cell rounding. Normal growth was observed from the DMSO controls (Figure 4-22).

**Figure 4-22.** Morphological studies of the cytotoxic action of compound 96a on human cancer cell lines.
4.3 Anti-tumor Activity of Carbaldehyde Quinoline Dimer

Our study showed that compound 8-hydroxyquinoline-2-carbaldehyde (93b) has very promising MTS$_{50}$ activity in human cancer cell lines. Here the dimer compounds of 8-hydroxyquinoline-2-carbaldehyde (93b) which contained a carbon chain of different length had been synthesized (Scheme 4-7).$^{185}$

![Scheme 4-7. Synthesis of Carbaldehyde Quinoline Dimer](image)

The anti-tumor activities of the synthesized carbaldehyde quinoline dimer compounds against various human cancer cell lines were studied, and the results are shown in Table 4-9. The anti-tumor activities were weaker for all tested carbaldehyde quinoline dimer compounds compared with their monomer compound 93b in all human cancer cell lines. This might be due to the bulkiness of dimer and the length of carbon chain affects the dimer compounds’ anti-tumor activities.

The anti-cancer activities of carbaldehyde quinoline dimer compounds were affected by the number of carbon of the carbon chain. Higher MTS activities were obtained for dimer compounds that contained carbon in the odd number, such as compounds 98b, 98d and 98f, which contained 3, 5 and 7 carbons respectively in all tested human
cancer cell lines. The results were comparable with their monomer compound 93b (Table 4-9, Entries 4, 6 & 8 vs Entry 2). However, for dimer compounds that contained carbon in the even number, such as compounds 98c, 98e, 98g and 98h which contained 4, 6, 8 and 10 carbons respectively, the anti-tumor activities were weaker (Table 4-9, Entries 5, 7 & 9-10).

The MT$_{50}$ of dimer compounds of 98b, 98d and 98f were studied with five human cancer cell lines, the results are shown in Figure 4-23. Overall, higher MT$_{50}$ values were obtained for the A549 human lung cancer cell line for these three compounds. The human liver cancer cell line Hep3B was more sensitive to this carbaldehyde quinoline dimer compound and lower MT$_{50}$ values were observed. The most prominent anti-tumor effect was obtained with the dimer compound that contained five carbons in the carbon chain.
Table 4-9. MTS assay of Carbaldehyde Quinoline Dimer

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>No. of n</th>
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</tr>
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<td></td>
<td></td>
<td></td>
<td>Hep3B</td>
</tr>
<tr>
<td>1</td>
<td>Control</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>93b</td>
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<td>4.0±0.3</td>
</tr>
<tr>
<td>3</td>
<td>98a</td>
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<tr>
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<td>98b</td>
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<td>98c</td>
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<td>98d</td>
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<td>98e</td>
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<tr>
<td>9</td>
<td>98g</td>
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<td>47.5±3.9</td>
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<tr>
<td>10</td>
<td>98h</td>
<td>10</td>
<td>13.2±0.2</td>
</tr>
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</table>

*All testing compounds are at a concentration of 40μg/ml. Results are shown as mean ± SD from triplicate experiments.*

Figure 4-23. MTS_{50} of carbaldehyde quinoline dimer 98.
4.4 Anti-tumor Activity of Quinolinium Derivatives

We observed that the solubility of compound 8-hydroxyquinoline-2-carbaldehyde (93b) was not optimal in physiological saline that acted as drug vehicle. To solve this problem, compound 99 (salt of 93b) was synthesized (Scheme 4-8).

![Scheme 4-8. Synthesis of compound 99](image)

The *in vitro* MTS assay was performed on the Hep3B cell line and the anti-tumor activities of compound 99 were comparable to those of compound 93b with MTS$_{50}$ ranging from 12.5-25μg/ml. Figures 4-24 and 4-25 show the *in vivo* experiment of compound 99, almost complete disappearance of hepatocellular carcinoma Hep3B xenograft was observed in mice that received compound 99 at Day 13 of drug administration. No mice died during the treatment.

Then the mice treated with compound 99 were further allowed to live for ten more days to see if there was any relapse in the tumor. Interestingly, no relapse was detected.
Figure 4-24. Athymic nude mice with Hep3B xenograft experiment for testing the in vivo anti-tumor effect of compound 99 and vehicle control. Arrows indicate the positions of the xenograft tumors. The tumor size was significantly reduced in the mice treated with compound 99.

Figure 4-25. Relative changes of tumor volume (mm$^3$) treated with compound 99 compared with vehicle control.
Then compound 99 was also tested using our preliminary *in vivo* chemically induced hepatoma animal model. We observed that no change in the total number of tumor in both the vehicle and compound 99 treated mice was detected. However, there was no growth in tumor size in the compound 99 treated mice was detected but significant enlargement of tumor size was found in the vehicle control mice. Further haematoxylin and eosin staining of the tumor showed extensive necrotic features (Figure 4-26).

![Figure 4-26](image)

**Figure 4-26.** Pathological investigation of liver from athymic nude mice treated with compound 99 and vehicle control.

Other anti-tumor active quinoline compounds are similar to 93b, that the solubility was not optimal in physiological saline. In order to solve this practical issue, the salt of those anti-cancer active quinoline compounds (100-103) were synthesized (Scheme
4-9). Preliminary *in vitro* experiment showed that the anticancer activities of those quinoline salt compounds were still comparable to those of their organic compounds.

Scheme 4-9. Synthesis of Quinolinium Derivatives (100-103)
4.5. Effect of Quinoline Compounds on In Vitro Cell Migration Rate of KYSE150 Cancer Cell Line

An in vitro migration assay of five quinoline compounds was performed using human esophageal cancer cell line KYSE150; the results are shown in Table 4-10. The KYSE150 cell layers were wounded and cultured for up to 48 hours in the presence of quinoline compounds and the vehicle control. The cells began to migrate over the wounded area and covered near half of the wounded area by 24 hours and covered all the wound area by 48 hours for the vehicle control sample (Table 4-10, Entry 1). However, when the quinoline compounds were subjected to the wound migration assay, cell migration was significantly inhibited even after 48 hours (Table 4-10, Entries 2-6), especially for compounds 95e and (R)-96a (Table 4-10, Entries 3 & 6). The migration was less inhibited for compounds 93b and 87a (Table 4-10, Entries 2 & 4).
Table 4-10. Effect of quinoline compounds on *in vitro* cell migration rate of KYSE150 cancer cell line. Original magnification: 100x.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>0 hr</th>
<th>24 hrs</th>
<th>48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle Control</td>
<td><img src="vehicle_control_0hr.png" alt="Image" /></td>
<td><img src="vehicle_control_24hrs.png" alt="Image" /></td>
<td><img src="vehicle_control_48hrs.png" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td>93b</td>
<td><img src="93b_0hr.png" alt="Image" /></td>
<td><img src="93b_24hrs.png" alt="Image" /></td>
<td><img src="93b_48hrs.png" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td>95c</td>
<td><img src="95c_0hr.png" alt="Image" /></td>
<td><img src="95c_24hrs.png" alt="Image" /></td>
<td><img src="95c_48hrs.png" alt="Image" /></td>
</tr>
<tr>
<td>4</td>
<td>87a</td>
<td><img src="87a_0hr.png" alt="Image" /></td>
<td><img src="87a_24hrs.png" alt="Image" /></td>
<td><img src="87a_48hrs.png" alt="Image" /></td>
</tr>
<tr>
<td>5</td>
<td>87m</td>
<td><img src="87m_0hr.png" alt="Image" /></td>
<td><img src="87m_24hrs.png" alt="Image" /></td>
<td><img src="87m_48hrs.png" alt="Image" /></td>
</tr>
<tr>
<td>6</td>
<td>(R)-96a</td>
<td><img src="R-96a_0hr.png" alt="Image" /></td>
<td><img src="R-96a_24hrs.png" alt="Image" /></td>
<td><img src="R-96a_48hrs.png" alt="Image" /></td>
</tr>
</tbody>
</table>
The most involved molecular mechanism of the drug actions will further identify with eDNA microarray analysis. The total RNA extracte from the cancer cell treated with our quinoline compounds with reference to the MTS_{50} value and vehicle control after 48 hours. Then the samples will performe in the Genome Research Centre of the University of Hong Kong using the Human Genome U133 Plus 2.0 arrays (Affymetrix)\textsuperscript{29,202} to identify the differentially expressed genes in cancer cells after the treatment with our quinoline compounds.
Chapter 5
Experimental Section

Part I: Chemistry

5.1 General procedures

All reactions were performed under an inert atmosphere (e.g. dry nitrogen atmosphere) unless otherwise stated. The preparation of samples and the set-up of the high pressure reactor were either carried out in a nitrogen-filled continuous purge Innovative Technology glovebox or using standard Schlenk-type techniques. All solvents used were dried with standard methods and distilled before use unless otherwise stated. The hydrogenation reactions were performed in 50 ml stainless-steel autoclaves purchased from Parr Company.

All reactions were monitored by thin layer chromatography (TLC) on Merck aluminum-coated plate of silica gel 60 F 254, unless otherwise stated, and visualized under ultra-violet light (254 nm), or through spraying with acidic ammonium molybdate (VI), basic potassium permanganate, 5% (w/v) dodecaphosphomolybdic acid in ethanol or 5% (w/v) ninhydrin in ethanol and subsequent heating, or by placing in iodine vapor.

Flash column chromatography was carried out on 230-400 mesh (0.04-0.063 mm) silica gel (NA SILICA GEL).
NMR spectra were recorded on a Varian Oxford AS 500/400 MHz Fourier transform spectrometer using CDCl₃ as solvent unless otherwise specified. As internal reference for ¹H NMR and ¹³C NMR spectra, residual protic solvent in CDCl₃ (δ_H 7.26 ppm, s; δ_C 77.7 ppm, t) were used respectively; a positive value of the chemical shift denotes a resonance downfield from TMS. Coupling constants were recorded in hertz (Hz). Multiplicities were recorded as the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Melting points were determined using a BUCHI Melting Point B-545 and Stuart Melting Point Apparatus SMP30 in capillaries sealed under atmosphere. Mass analysis was performed on a Fisons VG platform or Electrospray Ionization-Quadrupole-Time of Flight (ESI-Q-TOF) mass spectrometer. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter at room temperature. High performance liquid chromatography (HPLC) analysis was performed using Agilent 1100 LC with a variety of optically active column and Gas chromatography (GC) analysis was conducted on a HP 5890 series II system.
5.2 Synthesis of Quinoline Compounds

5.2.1 Synthesis of 8-Substituted Quinoline Compounds

![Reaction Scheme](image)

To a solution of 2-methyl-8-quinolinol (478 mg, 3 mmol), alkyl halide or benzyl halide (RX, 3 mmol, where X = Br⁻ or Cl) and K₂CO₃ were stirred in 10ml DMF. The reaction was run at room temperature and monitored by TLC. After the reaction was completed, the mixture was washed with Na₂CO₃, extracted with chloroform (3 x 20 ml), and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to give the pure product (n-Hexane/EA = 5/1).

8-Butoxy-2-methylquinoline (86b)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 1-bromobutane (323 μl, 3 mmol) and isolated as a pale yellow solid, ¹H-NMR (500 MHz, CDCl₃): δ 1.02 (t, 3H, J = 7.5 Hz), 1.54-1.59 (m, 2H), 1.99-2.05 (m, 2H), 2.78 (s, 3H), 4.24 (t, 2H, J = 7.5 Hz), 7.04 (d, 1H, J = 7.5 Hz), 7.28-7.38 (m, 3H), 7.99 (d, 1H, J = 8.0 Hz);
\(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 14.56, 19.86, 26.37, 31.49, 69.38, 109.56, 119.83, 122.97, 126.23, 128.27, 136.57, 140.57, 154.96, 158.57; HRMS (ESI): Calcd. for C\(_{14}\)H\(_{18}\)NO [M+H]\(^+\), 216.1388; found 216.1398; Melting Point = 52.2-54.1\(^\circ\)C; Yield = 70.5%.

8-(Benzyloxy)-2-methylquinoline (86d)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and benzyl bromide (357 \(\mu\)l, 3 mmol,) and isolated as a white solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.82 (s, 3H), 5.47 (s, 2H), 7.00 (d, 1H, \(J = 7.5\) Hz), 7.27-7.38 (m, 6H), 7.53 (d, 2H, \(J = 8.0\) Hz), 7.99 (d, 1H, \(J = 8.5\) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 26.42, 71.41, 111.13, 120.43, 123.11, 126.11, 127.43, 128.19, 128.33, 129.12, 136.63, 137.91, 140.72, 154.47, 158.74; HRMS (ESI): Calcd. for C\(_{17}\)H\(_{16}\)NO [M+H]\(^+\), 250.1232; found 250.1231; Melting Point = 91.0-91.7\(^\circ\)C; Yield = 96.9%.

8-(3-Nitrobenzyloxy)-2-methylquinoline (86e)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 3-nitrobenzyl bromide (648 mg, 3 mmol) and isolated as a white solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.82 (s, 3H), 5.52 (s, 2H), 7.00 (d, 1H, \(J = 7.5\) Hz), 7.32 (q, 2H, \(J = 9.0\) Hz), 7.39 (d, 1H, \(J = 8.0\) Hz), 7.54 (t, 1H, \(J = 7.5\) Hz), 7.89 (d, 1H, \(J = 7.5\) Hz), 8.02 (d, 1H, \(J = 8.5\) Hz), 8.07 (d, 1H, \(J = 8.5\) Hz), 8.17 (d, 1H, \(J = 8.5\) Hz), 8.27 (d, 1H, \(J = 8.5\) Hz), 8.51 (d, 2H, \(J = 8.5\) Hz), 10.23 (s, 1H).
Hz), 8.16 (d, 1H, \( J = 8.5 \) Hz), 8.44 (s, 1H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 26.46, 70.61, 111.58, 121.41, 122.61, 123.42, 126.08, 128.53, 130.23, 133.58, 136.79, 140.27, 140.74, 149.12, 154.03, 159.19; HRMS (ESI): Calcd. for C\(_{17}\)H\(_{15}\)N\(_2\)O\(_3\) [M+H]\(^+\), 295.1083; found 295.1078; Melting Point = 94.4-95.2\(^\circ\)C; Yield = 80.1 \%

**8-(4-Nitrobenzyloxy)-2-methylquinoline (86f)**

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 4-nitrobenzyl bromide (648 mg, 3 mmol) and isolated as a brown solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \( \delta \) 2.83 (s, 3H), 5.55 (s, 2H), 6.95 (d, 1H, \( J = 7.5 \) Hz), 7.29-7.40 (m, 3H), 7.71 (d, 2H, \( J = 8.5 \) Hz), 8.04 (d, 1H, \( J = 8.5 \) Hz), 8.24 (d, 2H, \( J = 9.0 \) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 26.45, 70.39, 111.23, 121.31, 123.44, 124.48, 126.05, 127.94, 128.51, 136.82, 140.61, 145.54, 148.10, 153.87, 159.15; HRMS (ESI): Calcd. for C\(_{17}\)H\(_{15}\)N\(_2\)O\(_3\) [M+H]\(^+\), 295.1083; found 295.1089; Melting Point = 144.1-145.7\(^\circ\)C; Yield = 50 \%

**8-(4-Methoxybenzyloxy)-2-methylquinoline (86g)**

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 4-methoxybenzyl chloride (470 mg, 3 mmol) and isolated as a pale brown solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \( \delta \) 2.80 (s, 3H), 3.80 (s, 3H), 5.38 (s, 2H), 6.90 (d, 2H, \( J = 8.5 \) Hz), 7.10 (d, 2H, \( J = 8.5 \) Hz), 7.20 (d, 2H, \( J = 9.0 \) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 26.45, 70.39, 111.23, 121.31, 123.44, 124.48, 126.05, 127.94, 128.51, 136.82, 140.61, 145.54, 148.10, 153.87, 159.15; HRMS (ESI): Calcd. for C\(_{17}\)H\(_{15}\)N\(_2\)O\(_3\) [M+H]\(^+\), 295.1083; found 295.1089; Melting Point = 144.1-145.7\(^\circ\)C; Yield = 50 \%.
(d, 1H, $J = 8.0$ Hz), 7.03 (d, 1H, $J = 7.0$ Hz), 7.26-7.34 (m, 3H), 7.45 (d, 2H, $J = 8.5$ Hz), 8.00 (d, 1H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 26.28, 55.92, 71.25, 111.09, 114.57, 120.38, 123.18, 126.21, 128.37, 129.31, 129.84, 133.85, 136.75, 140.69, 154.54, 158.79, 159.80, 159.87; HRMS (ESI): Calcd. for C$_{18}$H$_{18}$NO$_2$ [M+H]$^+$, 280.1338; found 280.1343; Melting Point = 130.8-131.5$^\circ$C; Yield = 67.3 %.

8-(3-Methoxybenzyloxy)-2-methylquinoline (86h)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 3-methoxybenzyl bromide (603 mg, 3 mmol) and isolated as a white solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.81 (s, 3H), 3.79 (s, 3H), 5.44 (s, 2H), 6.84 (d, 1H, $J = 8.0$ Hz), 7.01 (d, 1H, $J = 8.0$ Hz), 7.08-7.11 (m, 2H), 7.15-7.38 (m, 4H), 8.01 (d, 1H, $J = 8.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 26.42, 55.90, 71.43, 111.20, 112.85, 113.99, 119.71, 120.53, 123.21, 126.21, 128.39, 130.25, 136.74, 139.67, 140.73, 154.52, 158.81, 160.53; HRMS (ESI): Calcd. for C$_{18}$H$_{18}$NO$_2$ [M+H]$^+$, 280.1338; found 280.1337; Melting Point = 104.1-104.8$^\circ$C; Yield = 86 %.

4-((2-Methylquinolin-8-yloxy)methyl)benzonitrile (86i)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and $\alpha$-bromo-$\rho$-tolunitrile (588 mg, 3 mmol) and isolated as a white solid, $^1$H-NMR (500
MHz, CDCl$_3$): $\delta$ 2.81 (s, 3H), 5.49 (s, 2H), 6.93 (d, 1H, $J = 8.0$ Hz), 7.28-7.39 (m, 3H), 7.63-7.67 (m, 4H), 8.03 (d, 1H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 26.47, 45.45, 70.59, 111.19, 112.16, 119.47, 121.24, 123.44, 126.09, 127.91, 128.53, 133.09, 136.84, 140.64, 143.53, 153.95, 159.15; HRMS (ESI): Calcd. for C$_{18}$H$_{15}$N$_2$O \[M+H\]^+ 275.1184; found 275.1187; Melting Point = 124.1-125.3°C; Yield = 85.7 %.

8-(Biphenyl-3-ylmethoxy)-2-methylquinoline (86j)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 3-phenylbenzyl bromide (741 mg, 3 mmol) and isolated as a white solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.82 (s, 3H), 5.53 (s, 2H), 7.05 (d, 1H, $J = 7.5$ Hz), 7.26-7.35 (m, 4H), 7.41-7.46 (m, 3H), 7.51-7.54 (m, 2H), 7.59-7.61 (m, 2H), 7.78 (s, 1H), 8.01 (d, 1H, $J = 8.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 26.43, 71.66, 111.29, 120.60, 123.23, 126.22, 126.35, 126.50, 127.17, 127.88, 128.00, 128.42, 129.39, 129.66, 136.75, 138.54, 140.76, 141.63, 142.15, 154.57, 158.86; HRMS (ESI): Calcd. for C$_{23}$H$_{20}$NO \[M+H\]^+ 326.1545; found 326.1557; Melting Point = 89.8-99.4°C; Yield = 85.7 %.
8-(4-(Trifluoromethoxy)benzyl)oxy)-2-methylquinoline (86k)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 4-trifluoromethoxybenzyl bromide (765 mg, 3 mmol) and isolated as a white solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.81 (s, 3H), 5.44 (s, 2H), 6.99 (d, 1H, \(J = 6.5\) Hz), 7.22 (d, 2H, \(J = 7.5\) Hz), 7.29-7.37 (m, 3H), 7.56 (d, 2H, \(J = 9.0\) Hz), 8.01 (d, 1H, \(J = 8.5\) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 26.44, 70.73, 111.17, 120.88, 121.75, 121.76, 123.33, 126.16, 128.47, 129.07, 136.65, 136.79, 140.71, 149.35, 154.28, 159.00; HRMS (ESI): Calcd. for C\(_{18}\)H\(_{15}\)NO\(_2\)F\(_3\) [M+H]\(^+\), 334.1055; found 334.1056; Melting Point = 103.9-104.6\(^\circ\)C; Yield = 73.1 %.

8-(4-Fluorobenzyl)oxy)-2-methylquinoline (86l)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 4-fluorobenzyl bromide (567 mg, 3 mmol) and isolated as a white solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.80 (s, 3H), 5.40 (s, 2H), 6.99 (d, 1H, \(J = 6.5\) Hz), 7.05 (t, 2H, \(J = 6.5\) Hz), 7.28-7.35 (m, 3H), 7.48-7.51 (m, 2H), 8.01 (d, 1H, \(J = 8.5\) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 26.42, 70.91, 111.19, 116.03, 116.20, 120.73, 123.27, 126.16, 128.44, 129.46, 129.53, 133.59, 136.77, 140.73, 154.36, 158.92, 164.00; HRMS (ESI):
Calcd. for C_{17}H_{15}NOF [M+H]^+, 268.1138; found 268.1144; Melting Point = 130-130.6°C; Yield = 80.5%.

8-(4-(Trifluoromethyl)benzyloxy)-2-methylquinoline (86m)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 4-trifluoromethylbenzyl bromide (717 mg, 3 mmol) and isolated as a white solid, 

^1H-NMR (500 MHz, CDCl₃): δ 2.82 (s, 3H), 5.50 (s, 2H), 6.95 (d, 1H, J = 8.0 Hz), 7.28-7.37 (m, 3H), 7.61-7.65 (m, 4H), 8.02 (d, 1H, J = 8.5 Hz); ^13C-NMR (125 MHz, CDCl₃): δ 26.46, 70.75, 111.17, 120.99, 123.38, 126.19, 127.60, 128.49, 130.41, 130.67, 136.81, 140.67, 142.09, 154.14, 159.06; HRMS (ESI): Calcd. for C_{18}H_{15}NOF₃ [M+H]^+, 318.1106; found 318.1118; Melting Point = 130.8-131.5°C; Yield = 82%.

8-(4-Chlorobenzyloxy)-2-methylquinoline (86n)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 4-chlorobenzyl bromide (617 mg, 3 mmol) and isolated as a white solid, 

^1H-NMR (500 MHz, CDCl₃): δ 2.81 (s, 3H), 5.41 (s, 2H), 6.96 (d, 1H, J = 6.5 Hz), 7.27-7.36 (m, 5H), 7.45 (d, 2H, J = 8.5 Hz), 8.01 (d, 1H, J = 8.5 Hz); ^13C-NMR (125 MHz, CDCl₃): δ 26.43, 70.78, 111.19, 120.79, 123.29, 126.13, 128.44, 128.95, 129.38, 134.07, 136.44, 136.77, 140.69, 154.24, 158.95; HRMS (ESI): Calcd. for
C\textsubscript{17}H\textsubscript{15}NOCl [M+H]\textsuperscript{+}, 284.0842; found 284.0841; Melting Point = 118.7-119°C; Yield = 90.5 %.

**8-(3,5-Bis(trifluoromethyl)benzyloxy)-2-methylquinoline (86o)**

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (478 mg, 3 mmol) and 3,5-bis(trifluoromethyl)benzyl bromide (921 mg, 3 mmol) and isolated as a white solid, \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 2.81 (s, 3H), 5.51 (s, 2H), 7.03 (d, 1H, \(J = 7.5\) Hz), 7.33-7.35 (m, 2H), 7.42 (d, 1H, \(J = 8.0\) Hz), 7.83 (s, 1H), 8.03 (d, 1H, \(J = 8.0\) Hz), 8.08 (s, 2H); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 26.37, 71.07, 112.44, 119.98, 121.91, 122.43, 122.69, 123.43, 125.40, 126.14, 127.91, 128.65, 132.41, 132.73, 136.81, 140.98, 154.24, 159.31; HRMS (ESI): Calcd. for C\textsubscript{19}H\textsubscript{14}NOF\textsubscript{6} [M+H]\textsuperscript{+}, 386.0980; found 386.0974; Melting Point = 101.9-110.3°C; Yield = 90.0%.

**5.2.2 Synthesis of 2-Methylquinolin-8-yl Acetate (86c)**

\[\text{2-Methylquinolin} \xrightarrow{\text{Acetic Anhydride, EtOH, Et}_3\text{N, DMAP, DCM}} \text{2-Methylquinolin-8-yl Acetate}\]

Scheme 5-2

120
To a solution of 2-methyl-8-quinolinol (477 mg, 3 mmol), 10 ml EtOH, acetic anhydride (4.5 ml, 47 mmol) and 10 ml triethylamine were stirred in 10 mL DCM with one crystal DMAP. The reaction was run at room temperature and monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (hexane/EA = 5/1) to give a pure product as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.50 (s, 3H), 2.73 (s, 3H), 7.30 (d, 1H, $J$ = 9.0 Hz), 7.40 (d, 1H, $J$ = 7.5 Hz), 7.46 (t, 1H, $J$ = 8.0 Hz), 7.67 (d, 1H, $J$ = 8.5 Hz), 8.05(d, 1H, $J$ = 9.0 Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 21.66, 26.39, 31.58, 121.96, 122.89, 125.32, 126.23, 128.44, 136.65, 141.31, 147.67, 160.06, 170.64; HRMS (ESI): Calcd. for C$_{12}$H$_{12}$NO$_2$ [M+H]$^+$, 202.0868; found 202.0870; Yield = 91.1%.

5.2.3 Synthesis of 8-Substituted 2-Quinolinecarboxaldehyde

$$\begin{align*}
\text{SeO}_2, \text{dioxane, H}_2\text{O} & \xrightarrow{\text{reflux}} \\
\text{OR} & \Rightarrow \text{OR} \quad \text{CHO}
\end{align*}$$

Scheme 5-3

Substituted 8-hydroxy-2-methylquinoline (3.1 mmol), selenium dioxide (435mg, 3.95 mmol), 150 ml of pre-dried 1,4-dioxane, and 0.5 ml of water were mixed and stirred
in a 500 ml round bottom flask. The resulting solution was then refluxed for 24 h. The reaction was monitored until completion using TLC method. The reaction mixture was then filtered off, the selenium metal was then washed with dichloromethane, and the combined filtrates were then evaporated off under reduced pressure. The crude product was then purified with sublimation under reduced pressure or by silica gel chromatography to yield a pure product.

8-Hydroxyquinoline-2-carbaldehyde (93b)

Prepared according to the general procedure described above from 2-methyl-8-quinolinol (493 mg, 3.1 mmol) and isolated as a yellow solid, $^1$H-NMR (500 MHz, C$_6$D$_6$): $\delta$ 6.80-6.82 (m, 1H), 7.09 (d, 2H, $J = 4.0$ Hz), 7.36 (d, 1H, $J = 9.0$ Hz), 7.66 (d, 1H, $J = 9.0$ Hz ), 8.05 (s, 1H), 9.82 (s, 1H);

$^{13}$C-NMR (125 MHz, C$_6$D$_6$): $\delta$ 111.26, 117.78, 117.94, 130.43, 130.81, 137.27, 137.99, 150.44, 153.64, 192.03; HRMS (ESI): Calcd. for C$_{10}$H$_8$NO$_2$ [M+H]$^+$, 174.0555; found 174.0562; Melting point $= 98.0$-99.7$^\circ$C ; Yield $= 74.5$ %.

8-(Benzyloxy)quinoline-2-carbaldehyde (94a)

Prepared according to the general procedure described above from 8-(benzyloxy)-2-methylquinoline (773 mg, 3.1 mmol) and isolated as a brown solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.46 (s, 2H), 7.13 (d, 1H, $J = 8.0$ Hz), 7.31 (t, 1H, $J = 7.5$ Hz), 7.37-7.43 (m, 3H), 7.49-7.55 (m, 3H), 8.03 (d, 1H, $J =$
8.5 Hz), 8.22 (d, 1H, \( J = 8.5 \) Hz), 10.31 (s, 1H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \)
71.73, 111.68, 118.41, 120.56, 127.73, 128.63, 129.30, 132.01, 137.18, 137.83,
140.93, 152.18, 155.81, 194.48; HRMS (ESI): Calcd. for C\(_{17}\)H\(_{14}\)NO\(_2\) [M+H]\(^+\),
264.1025; found 264.1015; Melting Point = 92.0-93.0\(^\circ\)C; Yield = 92.3%.

8-(3-Nitrobenzyloxy)quinoline-2-carbaldehyde (94b)

Prepared according to the general procedure described above from 2-methyl-8-(3-nitrobenzyloxy)quinoline (912 mg, 3.1 mmol) and isolated as a pale yellow solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \( \delta \) 5.54 (s, 2H), 7.16 (d, 1H, \( J = 7.5 \) Hz), 7.52 (d, 1H, \( J = 7.5 \) Hz), 7.58 (q, 2H, \( J = 8.5 \) Hz), 7.93 (d, 1H, \( J = 7.5 \) Hz), 8.08 (d, 1H, \( J = 8.5 \) Hz), 8.19 (d, 1H, \( J = 8.5 \) Hz), 8.29 (d, 1H, \( J = 8.5 \) Hz), 8.48 (s, 1H), 10.30 (s, 1H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 70.28, 111.58, 118.23, 121.01, 122.28, 123.24, 129.67, 129.94, 131.68, 133.17, 137.54, 139.05, 140.47, 148.74, 151.94, 154.88, 193.84; HRMS (ESI): Calcd. for C\(_{17}\)H\(_{13}\)N\(_2\)O\(_4\) [M+H]\(^+\), 309.0875; found 309.0863; Melting Point = 179.0-180.5\(^\circ\)C; Yield = 75.3%.

8-(4-Nitrobenzyloxy)quinoline-2-carbaldehyde (94c)

Prepared according to the general procedure described above from 2-methyl-8-(4-nitrobenzyloxy)quinoline (912 mg, 3.1 mmol) and isolated as a pale yellow solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \( \delta \) 5.57 (s, 2H), 7.11 (d, 1H, \( J = 7.5 \) Hz), 7.51-7.57 (m, 2H), 7.75 (d, 2H, \( J = 8.5 \) Hz), 8.09 (d, 1H,
$J = 8.0 \text{ Hz}$, 8.26 (d, 2H, $J = 8.0 \text{ Hz}$), 8.31 (d, 1H, $J = 8.5 \text{ Hz}$), 10.31 (s, 1H);

$^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 70.50, 111.72, 118.62, 121.31, 124.49, 128.00, 130.00, 132.05, 137.93, 140.76, 144.58, 148.25, 152.30, 155.12, 194.12; HRMS (ESI): Calcd. for C$_{17}$H$_{13}$N$_2$O$_4$ [M+H]$^+$, 309.0875; found 309.0862; Melting Point = 198.0-199.0°C; Yield = 46.6%.

8-(4-Methoxybenzyloxy)quinoline-2-carbaldehyde (94d)

Prepared according to the general procedure described above from 8-(4-methoxybenzyloxy)-2-methylquinoline (866 mg, 3.1 mmol) and isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 3.79 (s, 3H), 5.37 (s, 2H), 6.91 (d, 2H, $J = 8.5 \text{ Hz}$), 7.15 (d, 1H, $J = 7.5 \text{ Hz}$), 7.42 (d, 1H, $J = 8.0 \text{ Hz}$), 7.46 (d, 2H, $J = 8.0 \text{ Hz}$), 7.52 (t, 1H, $J = 8.0 \text{ Hz}$), 8.03 (d, 1H, $J = 8.5 \text{ Hz}$), 8.22 (d, 1H, $J = 8.5 \text{ Hz}$), 10.29 (s, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 56.02, 71.70, 111.83, 114.82, 118.51, 120.58, 129.26, 129.64, 130.38, 132.14, 137.95, 141.09, 152.27, 156.02, 160.25, 194.65; HRMS (ESI): Calcd. for C$_{18}$H$_{15}$NO$_3$Na [M+Na]$^+$, 316.0950; found 316.0938; Melting Point = 100.0-103.9°C; Yield = 88.4%.

8-(3-Methoxybenzyloxy)quinoline-2-carbaldehyde (94e)

Prepared according to the general procedure described above from 8-(3-methoxybenzyloxy)-2-methylquinoline (866 mg, 3.1 mmol) and isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 3.79 (s,
3H), 5.45 (s, 2H), 6.85 (d, 1H, $J = 8.0$ Hz), 7.12 (t, 3H, $J = 8.5$ Hz), 7.29 (t, 1H, $J = 7.5$ Hz), 7.43 (d, 1H, $J = 8.0$ Hz), 7.51 (t, 1H, $J = 8.0$ Hz), 8.04 (d, 1H, $J = 8.5$ Hz), 8.25 (d, 1H, $J = 8.5$ Hz), 10.31 (s, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 55.88, 71.63, 111.75, 113.19, 114.12, 118.45, 119.83, 120.60, 130.27, 130.38, 132.04, 137.86, 138.86, 140.95, 152.21, 155.80, 160.61, 194.51; HRMS (ESI): Calcd. for C$_{18}$H$_{16}$NO$_3$ [M+H]$^+$, 294.1130; found 294.1118; Melting Point = 85.6-87.0°C; Yield = 94.2%.

4-((2-Formylquinolin-8-yl oxy)methyl)benzonitrile (94f)

Prepared according to the general procedure described above from 4-((2-methylquinolin-8-yl oxy)methyl)benzonitrile (850 mg, 3.1 mmol) and isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.52 (s, 2H), 7.10 (d, 1H, $J = 7.5$ Hz), 7.51 (d, 1H, $J = 8.0$ Hz), 7.55 (t, 1H, $J = 8.5$ Hz), 7.69 (s, 4H), 8.08 (d, 1H, $J = 8.5$ Hz), 8.29 (d, 1H, $J = 8.5$ Hz), 10.30 (s, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 70.82, 111.81, 112.58, 118.73, 119.27, 121.35, 128.06, 130.14, 132.16, 133.20, 138.04, 140.88, 142.72, 152.40, 155.30, 194.27; HRMS (ESI): Calcd. for C$_{18}$H$_{13}$N$_2$O$_2$ [M+H]$^+$, 289.0977; found 289.0968; Melting Point = 206.8-207.6°C; Yield = 77.8%.
8-(Biphenyl-3-ylmethoxy)quinoline-2-carbaldehyde (94g)

Prepared according to the general procedure described above from 8-(biphenyl-3-ylmethoxy)-2-methylquinoline (1.009 g, 3.1 mmol) and isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.55 (s, 2H), 7.19 (d, 1H, $J = 8.0$ Hz), 7.35 (t, 1H, $J = 7.0$ Hz), 7.42-7.49 (m, 4H), 7.53-7.61 (m, 5H), 7.81 (s, 1H), 8.07 (d, 1H, $J = 8.5$ Hz), 8.27 (d, 1H, $J = 8.0$ Hz), 10.33 (s, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 71.90, 111.83, 118.51, 120.70, 126.54, 126.63, 127.51, 127.83, 128.13, 129.45, 129.81, 130.30, 132.09, 137.81, 137.90, 141.01, 141.50, 142.34, 152.26, 155.91, 194.53; HRMS (ESI): Calcd. for C$_{23}$H$_{18}$NO$_2$ [M+H]$^+$, 340.1338; found 340.1345; Melting Point = 130.7-132.0 $^\circ$C; Yield = 96.7%.

8-(4-(Trifluoromethoxy)benzyloxy)quinoline-2-carbaldehyde (94h)

Prepared according to the general procedure described above from 2-methyl-8-(4-(trifluoromethoxy)benzyloxy)quinoline (1.033 g, 3.1 mmol) and isolated as a pale brown solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.45 (s, 2H), 7.14 (d, 1H, $J = 7.5$ Hz), 7.25 (d, 2H, $J = 8.5$ Hz), 7.48 (d, 1H, $J = 8.0$ Hz), 7.55 (t, 1H, $J = 7.5$ Hz ), 7.59 (d, 2H, $J = 8.5$ Hz), 8.06 (d, 1H, $J = 8.5$ Hz), 8.27 (d, 1H, $J = 8.5$ Hz), 10.30 (s, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 70.99, 111.75, 118.61, 120.99, 121.87, 129.27, 130.23, 132.13, 135.95, 137.96, 140.97, 149.65,
152.34, 155.63, 194.43; HRMS (ESI): Calcd. for C_{18}H_{13}NO_{2}F_{3} [M+H]^+, 348.0848; found 348.0851; Melting Point = 128.0-130.0°C; Yield = 92.7%.

**8-(4-Fluorobenzyloxy)quinoline-2-carbaldehyde (94i)**

Prepared according to the general procedure described above from 8-(4-fluorobenzyloxy)-2-methylquinoline (829 mg, 3.1 mmol) and isolated as a pale yellow solid, ^1H-NMR (500 MHz, CDCl\textsubscript{3}): δ 5.40 (s, 2H), 7.06 (t, 2H, J = 8.5 Hz), 7.13 (d, 1H, J = 8.0 Hz), 7.44 (d, 1H, J = 8.5 Hz), 7.50-7.54 (m, 2H), 8.03 (d, 1H, J = 8.5 Hz), 8.24 (d, 1H, J = 8.5 Hz), 10.28 (s, 1H); ^13C-NMR (100 MHz, CDCl\textsubscript{3}): δ 71.13, 111.71, 116.11, 116.32, 118.47, 120.77, 129.63, 129.71, 130.19, 132.04, 132.89, 137.87, 140.91, 152.21, 155.66, 161.93, 164.39, 194.40; HRMS (ESI): Calcd. for C_{17}H_{13}NO_{2}F [M+H]^+, 282.0930; found 282.0920; Melting Point = 129.0-130.9°C; Yield = 96.7%.

**8-(4-(Trifluoromethyl)benzyloxy)quinoline-2-carbaldehyde (94j)**

Prepared according to the general procedure described above from 2-methyl-8-(4-(trifluoromethyl)benzyloxy)quinoline (984 mg, 3.1 mmol) and isolated as a pale brown solid, ^1H-NMR (500 MHz, CDCl\textsubscript{3}): δ 5.52 (s, 2H), 7.11 (d, 1H, J = 8.0 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.54 (t, 1H, J = 8.0 Hz), 7.66 (q, 3H, J = 5.5 Hz), 8.06 (d, 1H, J = 8.5 Hz), 8.27 (d, 1H, J = 8.5 Hz), 10.30 (s, 1H); ^13C-NMR (100 MHz, CDCl\textsubscript{3}): δ 70.96, 111.74, 118.61, 121.08, 126.29,
126.33, 127.78, 130.18, 131.04, 132.11, 137.96, 140.90, 141.34, 152.33, 155.47, 194.35; HRMS (ESI): Calcd. for C_{18}H_{13}NO_{2}F_{3} [M+H]^+ 332.0898; found 332.0883; Melting Point = 127.5-129.0°C; Yield = 97.1%.

8-(4-Chlorobenzyloxy)quinoline-2-carbaldehyde (94k)

Prepared according to the general procedure described above from 8-(4-chlorobenzyloxy)-2-methylquinoline (880 mg, 3.1 mmol) and isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.42 (s, 2H), 7.10 (d, 1H, $J = 8.0$ Hz), 7.35 (d, 2H, $J = 8.5$ Hz), 7.46 (t, 2H, $J = 8.0$ Hz), 7.52 (t, 1H, $J = 8.0$ Hz), 8.04 (d, 1H, $J = 8.5$ Hz), 8.25 (d, 1H, $J = 8.5$ Hz), 10.29 (s, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 71.02, 111.73, 118.51, 120.86, 129.12, 129.50, 130.18, 132.05, 134.46, 135.69, 137.90, 140.89, 152.24, 155.56, 194.38; HRMS (ESI): Calcd. for C$_{17}$H$_{13}$NO_{2}Cl [M+H]^+ 298.0635; found 298.0624; Melting Point = 159.6-160.4°C; Yield = 76.3%.

8-(3,5-Bis(trifluoromethyl)benzyloxy)quinoline-2-carbaldehyde (94l)

Prepared according to the general procedure described above from 8-(3,5-bis(trifluoromethyl)benzyloxy)-2-methylquinoline (1.194 g, 3.1 mmol) and isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.54 (s, 2H), 7.19 (d, 1H, $J = 7.5$ Hz), 7.55 (d, 1H, $J = 8.0$ Hz), 7.60 (t, 1H, $J = 8.0$ Hz), 7.87 (s, 1H), 8.07-8.11 (m, 3H), 8.30 (d, 1H, $J = 8.5$ Hz), 10.27 (s, 1H);
13C-NMR (100 MHz, CDCl₃): δ 70.80, 112.41, 118.75, 121.82, 122.71, 125.29, 127.89, 130.15, 132.19, 132.58, 132.91, 133.24, 138.06, 140.16, 141.02, 152.51, 155.38, 194.23; HRMS (ESI): Calcd. for C₁₉H₁₂NO₂F₆ [M+H]⁺, 400.0772; found 400.0782; Melting Point = 150.4-150.9 °C; Yield = 91.7%.

5.2.4 Synthesis of 8-Subsitituted 5,7-Dibromo-2-Methylquinoline

2-Methyl-8-quinolinol (1.6 g, 10 mmol) was dissolved in 150 mL MeOH. 1 ml Br₂ in MeOH was added into the solution dropwise. After the reaction was completed, Na₂SO₃ was added and the product was extracted with DCM to give a crude product. The crude product was purified by silica gel column chromatography to give a pure product as a pink solid, 5,7-dibromo-2-methylquinolin-8-ol (95a).

To a solution of 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol), bromo-ketone (2 mmol) and K₂CO₃ were stirred in 10 ml DMF. The reaction was run at room temperature and monitored by TLC. After the reaction was completed, the mixture was washed with Na₂CO₃, extracted with EA, and then dried over anhydrous sodium
sulfate. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to give a pure product.

5,7-Dibromo-2-methylquinolin-8-ol (95a)

\[ \begin{align*}
\text{\textsuperscript{1}H-NMR} (500 \text{ MHz, CDCl}_3): & \quad \delta 2.75 (s, 3\text{H}), 7.39 (d, 1\text{H}, J = 8.5 \text{ Hz}), 7.79 (s, 1\text{H}), 8.26 (d, 1\text{H}, J = 8.5 \text{ Hz}); \\
\text{\textsuperscript{13}C-NMR} (125 \text{ MHz, CDCl}_3): & \quad \delta 25.41, 104.24, 110.65, 124.61, 125.48, 133.30, 136.65, 138.64, 149.77, 159.47; \\
\text{HRMS (ESI): Calcd. for C}_{10}\text{H}_8\text{NOBr}_2 [M+H]^+:} & \quad 315.8973; \text{ found 315.8981;}
\end{align*} \]

Melting Point = 126.9-128.5°C; Yield = 64.4%.

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-phenylethanone (95b)

\[ \begin{align*}
\text{Prepared according to the general procedure described above from 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol) and 2-bromoacetophenone (298 mg, 2 mmol) and isolated as a pale gray solid,} \\
\text{\textsuperscript{1}H-NMR} (500 \text{ MHz, CDCl}_3): & \quad \delta 2.54 (s, 3\text{H}), 5.79 (s, 2\text{H}), 7.30 (d, 1\text{H}, J = 9.0 \text{ Hz}), 7.48 (t, 2\text{H}, J = 8.0 \text{ Hz}), 7.58 (t, 1\text{H}, J = 7.0 \text{ Hz}), 7.89 (s, 1\text{H}), 8.13 (d, 2\text{H}, J = 8.0 \text{ Hz}), 8.27 (d, 1\text{H}, J = 9.0 \text{ Hz}); \\
\text{\textsuperscript{13}C-NMR} (125 \text{ MHz, CDCl}_3): & \quad \delta 25.54, 77.05, 115.78, 116.18, 123.95, 126.88, 129.04, 129.30, 133.23, 134.08, 134.63, 135.67, 136.65, 142.63, 151.55, 159.92, 195.13; \\
\text{HRMS (ESI): Calcd. for C}_{18}\text{H}_{14}\text{NO}_2\text{Br}_2 [M+H]^+:} & \quad 433.9391; \text{ found 433.9398; Melting Point = 128.4-128.6°C; Yield = 87.7%}. 
\end{align*} \]
2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-p-tolylethanone (95c)

Prepared according to the general procedure described above from 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol) and 2-bromo-4'-methylacetophenone (426 mg, 2 mmol) and isolated as a pale brown solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.40 (s, 3H), 2.55 (s, 3H), 5.76 (s, 2H), 7.26-7.30 (m, 3H), 7.89 (s, 1H), 8.02 (d, 2H, $J = 8.0$ Hz), 8.27 (d, 1H, $J = 9.0$ Hz);

$^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 22.39, 25.57, 76.99, 115.81, 116.14, 123.93, 126.87, 129.11, 129.98, 133.14, 133.21, 136.63, 142.69, 144.91, 151.63, 159.92, 194.75;

HRMS (ESI): Calcd. for C$_{19}$H$_{16}$NO$_2$Br$_2$ [M+H]$^+$, 447.9548; found 447.9549; Melting Point = 131.9-133.0$^\circ$C; Yield = 95.4%.

1-(4-Bromophenyl)-2-(5,7-dibromo-2-methylquinolin-8-yloxy)ethanone (95d)

Prepared according to the general procedure described above from 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol) and 2,4'-dibromoacetophenone (556 mg, 2 mmol) and isolated as a pale gray solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.58 (s, 3H), 5.65 (s, 2H), 7.33 (d, 1H, $J = 9.0$ Hz), 7.64 (d, 2H, $J = 8.5$ Hz), 7.91 (s, 1H), 8.10 (d, 2H, $J = 8.5$ Hz), 8.31 (d, 1H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 25.59, 77.33, 116.00, 116.60, 124.11, 127.03, 129.31, 130.96, 132.64, 133.30, 134.58, 136.85, 142.70, 151.49, 160.15, 194.65;
HRMS (ESI): Calcd. for C_{18}H_{13}NO_{2}Br_3 [M+H]^+ 511.8496; found 511.8508; Melting Point = 189.3-189.7°C; Yield = 26.4 %.

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(4-fluorophenyl)ethanone (95e)

Prepared according to the general procedure described above from 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol) and 2-bromo-4'-fluoroacetophenone (424 mg, 2 mmol) and isolated as a pale yellow solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.58 (s, 3H), 5.67 (s, 2H), 7.17 (t, 2H, \(J = 9.0\) Hz), 7.33 (d, 1H, \(J = 8.5\) Hz), 7.91 (s, 1H), 8.25-8.31 (m, 3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 25.58, 77.27, 115.99, 116.37, 116.54, 124.06, 126.99, 132.07, 132.14, 132.24, 133.27, 136.79, 142.73, 151.51, 160.10, 165.57, 167.60, 193.95; HRMS (ESI): Calcd. for C_{18}H_{13}NO_{2}Br_2F [M+H]^+ 451.9297; found 451.9306; Melting Point = 136.9-138.4°C; Yield = 80.5%.

1-(Biphenyl-4-yl)-2-(5,7-dibromo-2-methylquinolin-8-yloxy)ethanone (95f)

Prepared according to the general procedure described above from 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol) and 2-bromo-4'-phenylacetophenone (550 mg, 2 mmol) and isolated as a pale yellow solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.53 (s, 3H), 5.72 (s, 2H), 7.23 (d, 1H, \(J = 8.5\) Hz), 7.41 (t, 1H, \(J = 7.5\) Hz), 7.57 (t, 2H, \(J = 7.5\) Hz), 7.65 (d, 2H, \(J = 7.0\)Hz), 7.73 (d, 2H, \(J = 8.0Hz\)), 7.86 (s, 1H), 8.17 (d, 2H, \(J = 8.0Hz\)), 8.26 (d, 1H, \(J = 8.5Hz\));
\(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 25.64, 77.27, 116.02, 116.40, 124.05, 127.01, 127.96, 127.98, 128.98, 129.66, 129.79, 133.33, 134.48, 136.79, 140.55, 142.81, 146.78, 151.69, 160.10, 194.93; HRMS (ESI): Calcd. for C\(_{24}\)H\(_{18}\)NO\(_2\)Br\(_2\) [M+H]\(^+\), 509.9704; found 509.9716; Melting Point = 177.2-179.0\(^\circ\)C; Yield = 75.8%.

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(4-methoxyphenyl)ethanone (95g)

Prepared according to the general procedure described above from 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol) and 2-bromo-4'-methoxyacetophenone (458 mg, 2 mmol) and isolated as a brown solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.51 (s, 3H), 3.80 (s, 3H), 5.65 (s, 2H), 6.89 (d, 2H, \(J = 8.5\) Hz), 7.26 (d, 1H, \(J = 8.5\) Hz), 7.82 (s, 1H), 8.07 (d, 2H, \(J = 7.0\) Hz), 8.22 (d, 1H, \(J = 8.5\) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 25.45, 56.00, 76.79, 114.34, 115.68, 116.05, 123.85, 126.75, 128.51, 131.24, 133.03, 136.51, 142.59, 151.51, 159.85, 163.01, 164.24, 193.55; HRMS (ESI): Calcd. for C\(_{19}\)H\(_{16}\)NO\(_3\)Br\(_2\) [M+H]\(^+\), 463.9497; found 463.9509; Melting Point = 122.0-122.5\(^\circ\)C; Yield = 69.5%.

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(3-methoxyphenyl)ethanone (95h)

Prepared according to the general procedure described above from 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol) and 2-bromo-3'-methoxyacetophenone (458 mg, 2 mmol) and isolated as a pale gray solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.57 (s, 3H), 3.85 (s, 3H), 5.80 (s, 2H), 6.89 (d, 2H, \(J = 8.5\) Hz), 7.26 (d, 1H, \(J = 8.5\) Hz), 7.82 (s, 1H), 8.07 (d, 2H, \(J = 7.0\) Hz), 8.22 (d, 1H, \(J = 8.5\) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 25.64, 77.27, 116.02, 116.40, 124.05, 127.01, 127.96, 127.98, 128.98, 129.66, 129.79, 133.33, 134.48, 136.79, 140.55, 142.81, 146.78, 151.69, 160.10, 194.93; HRMS (ESI): Calcd. for C\(_{24}\)H\(_{18}\)NO\(_2\)Br\(_2\) [M+H]\(^+\), 509.9704; found 509.9716; Melting Point = 177.2-179.0\(^\circ\)C; Yield = 75.8%.
7.12-7.14 (m, 1H), 7.31 (d, 1H, \( J = 8.5 \) Hz), 7.39 (t, 1H, \( J = 8.0 \) Hz), 7.64-7.65 (m, 1H), 7.69 (d, 1H, \( J = 7.5 \) Hz), 7.91 (s, 1H), 8.29 (d, 1H, \( J = 9.0 \) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 25.59, 56.14, 77.06, 113.28, 115.85, 116.19, 120.66, 121.51, 123.98, 126.92, 130.33, 133.28, 136.72, 136.94, 142.67, 151.55, 159.96, 160.54, 194.95; HRMS (ESI): Calcd. for C\(_{19}\)H\(_{16}\)NO\(_3\)Br\(_2\) [M+H]\(^+\), 463.9497; found 463.9498; Melting Point = 131.0-132.3\(^\circ\)C; Yield = 48.4%.

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(2-methoxyphenyl)ethanone (95i)

Prepared according to the general procedure described above from 5,7-dibromo-2-methylquinolin-8-ol (624 mg, 2 mmol) and 2-bromo-2'-methoxyacetophenone (458 mg, 2 mmol) and isolated as a pale gray solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \( \delta \) 2.50 (s, 3H), 3.86 (s, 3H), 5.84 (s, 2H), 6.95 (d, 1H, \( J = 8.5 \) Hz), 7.02 (t, 1H, \( J = 8.0 \) Hz), 7.26 (d, 1H, \( J = 9.0 \) Hz), 7.47 (t, 1H, \( J = 7.0 \) Hz), 7.88 (s, 1H), 7.96 (d, 1H, \( J = 8.0 \) Hz), 8.24 (d, 1H, \( J = 9.0 \) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 25.52, 56.15, 80.27, 112.09, 115.30, 121.47, 123.69, 126.75, 131.66, 133.19, 134.93, 136.45, 142.55, 151.84, 159.41, 159.81, 195.64; HRMS (ESI): Calcd. for C\(_{19}\)H\(_{16}\)NO\(_3\)Br\(_2\) [M+H]\(^+\), 463.9497; found 463.9494; Melting Point = 152.6-153.7\(^\circ\)C; Yield = 36.5%.
5.3 Synthesis of Quinoline Dimer

A mixture of 2-methylquinolin-8-ol (2.4 g, 15 mmol) and dihaloalkyl (X = Br− or Cl, 5 mmol) in ACN was added with K$_2$CO$_3$ (2.28 g, 16.5 mmol) and refluxed overnight. Then the ACN was removed and hydrolysed with water. The organic product was extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to give a pure quinoline dimer product.

Quinoline dimer (3.1 mmol.), selenium dioxide (435 mg, 3.95 mmol), 150 ml of pre-dried 1,4-dioxane, and 0.5 ml of water were mixed and stirred in a 500 ml round bottom flask. The resulting solution was then refluxed for 24 h. The reaction was monitored until completion using TLC method. The reaction mixture was then filtered off, the selenium metal washed with dichloromethane (DCM), and the combined filtrates were evaporated off under reduced pressure. The crude product was then purified with silica gel chromatography to yield a pure carbaldehyde quinoline dimer product.
Bis(2-methylquinolin-8-yloxy)methane (97a)

Prepared according to the general procedure described above from 2-methylquinolin-8-ol (2.4 g, 15 mmol) and dibromomethane (351 μl, 5 mmol) isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): δ 2.76 (s, 6H), 6.37 (s, 2H), 7.26 (d, 2H, $J = 8.0$ Hz), 7.39 (d, 2H, $J = 7.5$ Hz), 7.44 (d, 2H, $J = 8.0$ Hz), 7.73 (d, 2H, $J = 8.0$ Hz), 7.99 (d, 2H, $J = 8.5$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 26.31, 94.68, 116.13, 122.54, 123.03, 126.37, 128.44, 136.76, 140.97, 153.03, 158.97; HRMS (ESI): Calcd. for C$_{21}$H$_{19}$N$_2$O$_2$ [M+H]$^+$, 331.1452; found 331.1447; Melting Point = 123.8-124.2°C; Yield = 12.4%.

1,3-Bis(2-methylquinolin-8-yloxy)propane (97b)

Prepared according to the general procedure described above from 2-methylquinolin-8-ol (2.4 g, 15 mmol) and 1,3-dibromopropane (511 μl, 5 mmol) isolated as a pale red solid,$^1$H-NMR (500 MHz, CDCl$_3$): δ 2.64-2.66 (m, 2H), 2.74 (s, 6H), 4.54 (t, 4H, $J = 6.5$ Hz), 7.13 (d, 2H, $J = 7.0$ Hz), 7.22 (d, 2H, $J = 8.0$ Hz), 7.26-7.31 (m, 4H), 7.93 (d, 2H, $J = 8.0$ Hz); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 26.13, 29.34, 66.66, 110.30, 120.11, 122.94, 126.25, 128.22, 136.60, 140.47, 154.66, 158.48; HRMS (ESI): Calcd. for C$_{23}$H$_{23}$N$_2$O$_2$ [M+H]$^+$, 359.1760; found 359.1743; Melting Point = 91.0-92.3°C; Yield = 45.2%.
1,4-Bis(2-methylquinolin-8-yloxy)butane (97c)

Prepared according to the general procedure described above from 2-methylquinolin-8-ol (2.4 g, 15 mmol) and 1-bromo-4-chlorobutane (576 µl, 5 mmol) isolated as a pale yellow solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.29-2.32 (m, 4H), 2.77 (s, 6H), 4.40 (t, 4H, \(J = 6.0\) Hz), 7.08 (d, 2H, \(J = 7.5\) Hz), 7.29 (d, 2H, \(J = 8.5\) Hz), 7.31-7.36 (m, 4H), 7.99 (d, 2H, \(J = 8.5\) Hz);

\(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 26.27, 26.48, 69.46, 109.80, 119.93, 122.99, 126.28, 128.27, 136.64, 140.45, 154.83, 158.54; HRMS (ESI): Calcd. for C\(_{24}\)H\(_{25}\)N\(_2\)O\(_2\) [M+H]\(^+\), 373.1916; found 373.1915; Melting Point = 178.9-179.6\(^\circ\)C; Yield = 22.7%.

1,5-Bis(2-methylquinolin-8-yloxy)pentane (97d)

Prepared according to the general procedure described above from 2-methylquinolin-8-ol (2.4 g, 15 mmol) and 1,5-diiodopentane (1.62 g, 5 mmol) isolated as a pale yellow solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.78-1.82 (m, 2H), 2.12-2.18 (m, 4H), 2.77 (s, 6H), 4.28 (t, 4H, \(J = 7.0\) Hz), 7.03 (d, 2H, \(J = 7.0\) Hz), 7.27 (d, 2H, \(J = 8.5\) Hz), 7.31-7.37 (m, 4H), 7.99 (d, 2H, \(J = 8.5\) Hz); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 23.08, 26.15, 29.15, 53.95, 69.35, 109.64, 119.82, 122.83, 126.11, 128.13, 136.46, 140.37, 154.74, 158.39; HRMS (ESI): Calcd. for C\(_{25}\)H\(_{27}\)N\(_2\)O\(_2\) [M+H]\(^+\), 387.2073; found 387.2065; Melting Point = 109.8-110.7\(^\circ\)C; Yield = 91.8%.
1,6-Bis(2-methylquinolin-8-yloxy)hexane (97e)

Prepared according to the general procedure described above from 2-methylquinolin-8-ol (2.4 g, 15 mmol) and 1,6-dibromohexane (1.22 g, 5 mmol) isolated as a white solid,

\[ ^1H\text{-NMR (500 MHz, CDCl}_3\text{): } \delta 1.63-1.66 (m, 4H), 2.06-2.09 (m, 4H), 2.76 (s, 6H), 4.24 (t, 4H, } J = 7.0 \text{ Hz), 7.01 (d, 2H, } J = 7.5 \text{ Hz), 7.25 (d, 2H, } J = 8.5 \text{ Hz), 7.31 (d, 2H, } J = 8.0 \text{ Hz), 7.35 (t, 2H, } J = 8.0 \text{ Hz), 7.96 (d, 2H, } J = 8.5 \text{ Hz); } ^{13}\text{C-NMR (100 MHz, CDCl}_3\text{): } \delta 26.29, 26.51, 29.44, 69.52, 109.66, 119.88, 122.96, 126.22, 128.26, 136.56, 140.53, 154.89, 158.55; \text{HRMS (ESI): Calcd. for C}_{26}\text{H}_{29}\text{N}_2\text{O}_2 [M+H]^+, 401.2229; found 401.2227; Melting Point = 142.3-143.1{^\circ}\text{C}; \text{Yield = 41.8 \%.} \]

1,7-Bis(2-methylquinolin-8-yloxy)heptane (97f)

Prepared according to the general procedure described above from 2-methylquinolin-8-ol (2.4 g, 15 mmol) and 1,7-dibromoheptane (1.29 g, 5 mmol) isolated as a pale yellow solid,

\[ ^1H\text{-NMR (500 MHz, CDCl}_3\text{): } \delta 1.51-1.58 (m, 6H), 2.01-2.05 (m, 4H), 2.76 (s, 6H), 4.22 (t, 4H, } J = 7.0 \text{ Hz), 7.01 (d, 2H, } J = 7.5 \text{ Hz), 7.26 (d, 2H, } J = 8.5 \text{ Hz), 7.29-7.36 (m, 4H), 7.97 (d, 2H, } J = 8.5 \text{ Hz); } ^{13}\text{C-NMR (100 MHz, CDCl}_3\text{): } \delta 26.29, 26.56, 29.39, 29.87, 69.66, 109.73, 119.88, 123.00, 126.29, 128.30, 136.68, 140.47, 154.90, 158.57; \]
HRMS (ESI): Calcd. for C\textsubscript{27}H\textsubscript{31}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+}, 415.2386; found 415.2383; Melting Point = 131.1-131.8°C; Yield = 43.0%.

1,8-Bis(2-methylquinolin-8-yloxy)octane (97g)

Prepared according to the general procedure described above from 2-methylquinolin-8-ol (2.4 g, 15 mmol) and 1,8-dibromooctane (1.36 g, 5 mmol) isolated as a pale yellow solid, \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 1.44-1.46 (m, 4H), 1.51-1.54 (m, 4H), 1.99-2.04 (m, 4H), 2.77 (s, 6H), 4.21 (t, 4H, \(J = 7.0\) Hz), 7.02 (d, 2H, \(J = 7.5\) Hz), 7.27 (d, 2H, \(J = 8.5\) Hz), 7.30 (d, 2H, \(J = 7.0\) Hz), 7.35 (t, 2H, \(J = 7.5\) Hz), 7.98 (d, 2H, \(J = 8.5\) Hz); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 26.29, 26.56, 29.46, 30.00, 69.77, 109.80, 119.90, 123.07, 126.37, 128.34, 136.80, 140.44, 154.92, 158.64; HRMS (ESI): Calcd. for C\textsubscript{28}H\textsubscript{33}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+}, 429.2542; found 429.2528; Melting Point = 127.8-130.3°C; Yield = 37.3%.

1,10-Bis(2-methylquinolin-8-yloxy)decane (97h)

Prepared according to the general procedure described above from 2-methylquinolin-8-ol (2.4 g, 15 mmol) and 1,10-dibromodecane (1.5 g, 5 mmol) isolated as a pale yellow solid, \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 1.32-1.38 (m, 8H), 1.45-1.50 (m, 4H), 1.96-2.02 (m, 4H), 2.73 (s, 6H), 4.18 (t, 4H, \(J = 7.0\) Hz), 7.02 (d, 2H, \(J = 7.5\) Hz), 7.26 (d, 2H, \(J = 8.5\) Hz).
6.99 (d, 2H, J = 7.0 Hz), 7.23 (d, 2H, J = 8.5 Hz), 7.30 (d, 2H, J = 7.5 Hz), 7.33 (t, 2H, J = 8.0 Hz), 7.94 (d, 2H, J = 8.5 Hz); 13C-NMR (100 MHz, CDCl₃): δ 26.35, 26.61, 29.46, 30.06, 30.11, 69.76, 109.67, 119.87, 123.00, 126.27, 128.32, 136.61, 140.61, 155.00, 158.59; HRMS (ESI): Calcd. For C₃₀H₃₇N₂O₂ [M+H]⁺, 457.2855; found 457.2851; Melting Point = 122.2-123.1°C; Yield = 21.5%.

8,8′-Methylenebis(oxy)diquinoline-2-carbaldehyde (98a)

Prepared according to the general procedure described above from bis(2-methylquinolin-8-yloxy)methane (1.024 g, 3.1 mmol) and isolated as a pale yellow solid, ¹H-NMR (500 MHz, CDCl₃): δ 6.47 (s, 2H), 7.59 (d, 2H, J = 8.0 Hz), 7.64 (t, 2H, J = 8.5 Hz), 7.83 (d, 2H, J = 7.5 Hz), 8.02 (d, 2H, J = 8.5 Hz), 8.27 (d, 2H, J = 8.5 Hz), 10.21 (s, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 30.34, 116.39, 118.49, 122.94, 130.33, 132.05, 138.12, 141.15, 152.50, 154.10, 194.15; HRMS (ESI): Calcd. for C₂₁H₁₅N₂O₄[M+H]⁺, 359.1032; found 359.1029; Melting Point = 189.3-191.3°C; Yield = 66.2%.

8,8′-(Propane-1,3-diylbis(oxy))diquinoline-2-carbaldehyde (98b)

Prepared according to the general procedure described above from 1,3-bis(2-methylquinolin-8-yloxy)propane (1.111 g, 3.1 mmol) and isolated as a brown solid, ¹H-NMR (500 MHz, CDCl₃): δ 2.72-2.77 (m, 2H), 4.67 (t, 4H, J = 6.0 Hz), 7.27 (d, 2H, J = 8.0 Hz), 7.42 (d, 2H, J =
8.5 Hz), 7.56 (t, 2H, J = 8.5 Hz), 8.00 (d, 2H, J = 8.5 Hz), 8.21 (d, 2H, J = 8.5 Hz), 10.20 (s, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 29.53, 30.36, 66.78, 111.05, 118.41, 120.45, 130.41, 131.98, 137.82, 140.86, 152.07, 156.21, 194.37; HRMS (ESI): Calcd. for C\(_{23}\)H\(_{19}\)N\(_2\)O\(_4\)[M+H]\(^+\), 387.1345; found 387.1360; Melting Point = 167.5-168.8\(^\circ\)C; Yield = 27.5%.

**8,8'-(Butane-1,4-diylbis(oxy))diquinoline-2-carbaldehyde (98c)**

![Chemical Structure](image)

Prepared according to the general procedure described above from 1,4-bis(2-methylquinolin-8-yl)butane (1.155 g, 3.1 mmol) and isolated as a pale yellow solid. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.37 (s, 4H), 4.50 (s, 4H), 7.16 (d, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 8.5 Hz), 7.52 (t, 2H, J = 8.0 Hz), 7.95 (d, 2H, J = 8.5 Hz), 8.16 (d, 2H, J = 8.5 Hz), 10.15 (s, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 26.66, 30.36, 69.72, 110.42, 118.30, 120.15, 130.33, 131.89, 137.69, 140.64, 151.91, 156.16, 194.37; HRMS (ESI): Calcd. for C\(_{24}\)H\(_{21}\)N\(_2\)O\(_4\)[M+H]\(^+\), 401.1501; found 401.1510; Melting Point = 203.1-203.5\(^\circ\)C; Yield = 50.1%.

**8,8'-(Pentane-1,5-diylbis(oxy))diquinoline-2-carbaldehyde (98d)**

![Chemical Structure](image)

Prepared according to the general procedure described above from 1,5-bis(2-methylquinolin-8-yl)pentane (1.197 g, 3.1 mmol) and isolated as a brown solid. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\)
1.87-1.93 (m, 2H), 2.18-2.24 (m, 4H), 4.34 (t, 4H, J = 7.0 Hz), 7.13 (d, 2H, J = 7.5 Hz), 7.42 (d, 2H, J = 8.5 Hz), 7.56 (t, 2H, J = 8.5 Hz), 8.01 (d, 2H, J = 8.5 Hz), 8.23 (d, 2H, J = 8.0 Hz), 10.23 (s, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 23.50, 29.34, 30.31, 69.84, 110.45, 118.39, 120.15, 130.38, 132.01, 137.82, 140.78, 152.07, 156.23, 194.40; HRMS (ESI): Calcd. for C$_{25}$H$_{23}$N$_2$O$_4$[M+H]$^+$, 415.1658; found 415.1668; Melting Point = 107.8-109.1°C; Yield = 45.3%.

8,8'-(Hexane-1,6-diylbis(oxy))diquinoline-2-carbaldehyde (98e)

Prepared according to the general procedure described above from 1,6-bis(2-methylquinolin-8-yloxy)hexane (1.242 g, 3.1 mmol) and isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): δ 1.75 (s, 4H), 2.13 (s, 4H), 4.31 (t, 4H, J = 7.0 Hz), 7.13 (d, 2H, J = 8.0 Hz), 7.42 (d, 2H, J = 8.0 Hz), 7.57 (t, 2H, J = 8.0 Hz), 8.00 (d, 2H, J = 9.0 Hz), 8.23 (d, 2H, J = 8.0 Hz), 10.22 (s, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 26.43, 29.44, 69.75, 110.31, 118.32, 120.02, 130.35, 131.95, 137.74, 140.70, 151.97, 156.23, 194.35; HRMS (ESI): Calcd. for C$_{26}$H$_{25}$N$_2$O$_4$[M+H]$^+$, 429.1814; found 429.1822; Melting Point = 173.3-173.5°C; Yield = 82.4%.

8,8'-(Heptane-1,7-diylbis(oxy))diquinoline-2-carbaldehyde (98f)

Prepared according to the general procedure
described above from 1,7-bis(2-methylquinolin-8-yloxy)heptanes (1.284 g, 3.1 mmol) and isolated as a brown solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.54-1.64 (m, 6H), 2.02-2.08 (m, 4H), 4.25 (t, 4H, \(J = 7.0\) Hz), 7.09 (d, 2H, \(J = 7.5\) Hz), 7.39 (d, 2H, \(J = 8.0\) Hz), 7.54 (t, 2H, \(J = 8.5\) Hz), 7.98 (d, 2H, \(J = 8.0\) Hz), 8.20 (d, 2H, \(J = 8.5\) Hz), 10.24 (s, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 26.56, 29.43, 29.76, 69.89, 110.35, 118.32, 119.99, 130.38, 131.95, 137.78, 140.70, 151.96, 156.21, 194.39; HRMS (ESI): Calcd. for C\(_{27}\)H\(_{27}\)N\(_2\)O\(_4\)[M+H]\(^+\), 443.1971; found 443.1987; Melting Point = 100.0-101.7\(^\circ\)C; Yield = 67%.

\(8,8'\)-(Octane-1,8-diylbis(oxy))diquinoline-2-carbaldehyde (98g)

Prepared according to the general procedure described above from 1,8-bis(2-methylquinolin-8-yloxy)octane (1.329 g, 3.1 mmol) and isolated as a pale yellow solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.47 (s, 4H), 1.57 (s, 4H), 2.00-2.06 (m, 4H), 4.25 (t, 4H, \(J = 7.0\) Hz), 7.10 (d, 2H, \(J = 8.0\) Hz), 7.39 (d, 2H, \(J = 8.0\) Hz), 7.55 (t, 2H, \(J = 8.0\) Hz), 7.98 (d, 2H, \(J = 8.5\) Hz), 8.20 (d, 2H, \(J = 8.5\) Hz), 10.24 (s, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 26.53, 29.46, 29.88, 30.27, 69.95, 110.36, 118.29, 119.96, 130.38, 131.96, 137.75, 140.75, 151.98, 156.24, 194.38; HRMS (ESI): Calcd. for C\(_{28}\)H\(_{29}\)N\(_2\)O\(_4\)[M+H]\(^+\), 457.2127; found 457.2135; Melting Point = 154.0-155.7\(^\circ\)C; Yield = 66.3%.
8,8’-(Decane-1,10-diylbis(oxy))diquinoline-2-carbaldehyde (98h)

Prepared according to the general procedure described above from 1,10-bis(2-methylquinolin-8-yl)oxy)decane (1.416 g, 3.1 mmol) and isolated as a pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): δ 1.34-1.4 (m, 8H), 1.50-1.56 (m, 4H), 1.99-2.05 (m, 4H), 4.25 (t, 4H, $J = 7.0$ Hz), 7.11 (d, 2H, $J = 8.0$ Hz), 7.39 (d, 2H, $J = 8.0$ Hz), 7.55 (t, 2H, $J = 8.0$ Hz), 7.99 (d, 2H, $J = 8.5$ Hz), 8.21 (d, 2H, $J = 8.5$ Hz), 10.25 (s, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 26.59, 29.48, 29.97, 30.04, 70.01, 110.36, 118.29, 119.93, 130.38, 131.96, 137.75, 140.75, 151.99, 156.28, 194.41; HRMS (ESI): Calcd. for C$_{30}$H$_{33}$N$_2$O$_4$[M+H]$^+$, 485.2440; found 485.2460; Melting Point = 131.2-132.0°C; Yield = 79.7%.

5.4 Synthesis of Quinolinium Derivatives

To a stirred solution of quinoline/1,2,3,4-tetrahydroquinoline (3 mmol) in dichloromethane (20 ml), freshly prepared hydrochloride gas was bubbled at room temperature. The precipitate was collected by filtration to give the designed product.
2-Formyl-8-hydroxyquinolinium chloride (99)

Prepared according to the general procedure described above from 8-hydroxyquinoline-2-carbaldehyde (520 mg, 3 mmol) and isolated as a yellow solid.

$^1$H-NMR (500 MHz, DMSO-$d_6$): $\delta$ 3.92 (s, 1H), 7.28 (d, 1H, $J = 7.5$ Hz), 7.55 (d, 1H, $J = 8.5$ Hz), 7.65 (t, 1H, $J = 8.0$ Hz), 8.00 (d, 1H, $J = 8.5$ Hz), 8.55 (d, 1H, $J = 8.0$ Hz), 10.18 (s, 1H); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): $\delta$ 113.79, 118.19, 118.85, 131.63, 131.76, 138.70, 139.21, 151.33, 155.45, 194.43; Melting point = 184.1-185.0°C; yield = 96.5%.

101 Prepared according to the general procedure described above from 2-methyl-1,2,3,4-tetrahydroquinolin-8-ol (490 mg, 3 mmol) and isolated as a pale yellow solid, $^1$H NMR (500 MHz, DMSO-$d_6$) : $\delta$ 1.46 (d, 3H, $J = 6.5$), 1.78-1.86 (m, 1H), 2.03-2.06 (m, 1H), 2.78-2.90 (m, 2H), 3.41-3.46 (m, 1H), 6.73 (d, 1H, $J = 7.5$), 7.00 (d, 1H, $J = 8.0$), 7.16 (t, 1H, $J = 8.0$), 10.59 (s, 1H) , 11.06
(s, 1H); ¹³C-NMR (125 MHz, DMSO-δ₆): δ 18.77, 25.72, 27.23, 51.32, 114.25, 129.91, 120.74, 129.40, 133.23, 151.87; Melting point = 251.8-252.6°C; yield = 92.8%.

103 Prepared according to the general procedure described above from 5,7-dibromo-2-methyl-1,2,3,4-tetrahydroquinolin-8-ol (963 mg, 3 mmol) and isolated as a pale yellow solid.¹H NMR (500 MHz, DMSO-δ₆): δ 1.28 (d, 3H, J = 6.0), 1.57-1.65 (m, 1H), 1.92-1.98 (m, 1H), 2.48-2.68 (m, 2H), 3.31-3.36 (m, 1H), 6.26 (bs, 4H), 7.35 (s, 1H); ¹³C-NMR (125 MHz, DMSO-δ₆): δ 20.39, 27.67, 28.16, 48.84, 109.93, 115.71, 126.14, 128.06, 131.52, 144.51; Melting Point = 198.1-198.5°C; yield = 91.2%.
5.5 Synthesis of Dipyridinyl Phosphine type Ligands\(^ {134,136,203-205}\)

\[
\text{MeO} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{OMe} \end{array} \xrightarrow{\text{NBS}} \xrightarrow{\text{CH}_3\text{CN, rt, 4d, 98\%}} \text{MeO} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{Br} \end{array}
\]

1. LDA, THF, -78 °C, 1 h
2. Ar₂PCl, -78 °C, 12 h
3. \text{H}_2\text{O}_2, \text{Acetone, 0}^\circ\text{C}

\[
\begin{array}{c} \text{MeO} \end{array} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{Br} \end{array} \xrightarrow{\text{Ar}_2\text{PCl}} \xrightarrow{\text{H}_2\text{O}_2, \text{Acetone, 0}^\circ\text{C}} \text{MeO} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{Me} \end{array}
\]

B₁: Ar = 4-\text{CF}_3\text{C}_6\text{H}_4;
B₂: Ar = 4-\text{CH}_3\text{OC}_6\text{H}_4;
B₃: Ar = \text{Pr};
B₄: Ar = \text{Ph}

\[
\begin{array}{c} \text{MeO} \end{array} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{Br} \end{array} \xrightarrow{\text{B₄} \ Pd(PPh}_3)_4, \text{PhB(OH)}_2} \xrightarrow{\text{Acetone, 0}^\circ\text{C}} \text{MeO} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{O} \end{array}
\]

1. t-BuLi, THF, -78 °C
2. \text{I}_2
3. \text{Cu, DMF, 148 °C, 12 h}

For C₂ and C₃
1. (-)-\text{L}-\text{DBTA} or (+)-\text{D}-\text{DBTA}
2. fractional crystallization
3. 10% aqueous NaOH

or for C₁ and C₄: HPLC separation

\[(R)-\text{C} \text{ and } (S)-\text{C}\]

\[
\begin{array}{c} \text{MeO} \end{array} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{PAr}_2 \end{array} \xrightarrow{\text{HSiCl}_3, \text{TEA}} \xrightarrow{\text{toluene, reflux, 19 h}} \text{MeO} \begin{array}{c} \text{N} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{O} \end{array} \begin{array}{c} \text{O} \end{array}
\]

(R)-\text{C₁: } \text{Ar} = 4-\text{CF}_3\text{C}_6\text{H}_4, \text{ R} = \text{H};
(R)-\text{C₂: } \text{Ar} = 4-\text{CH}_3\text{OC}_6\text{H}_4, \text{ R} = \text{H};
(R)-\text{C₃: } \text{Ar} = \text{Pr}, \text{ R} = \text{H};
(R)-\text{C₄: } \text{Ar} = \text{Ph}, \text{ R} = \text{Ph};

\text{Scheme 5-8}

5.5.1 Synthesis of 3-bromo-2,6-dimethoxypyridine (A)

2,6-Dimethoxypyridine (10 ml, 75.5 mmol) was dissolved in 200 ml ACN at room temperature. N-Bromosuccinimide (NBS) (13.4 g, 75.5 mmol) was added to the above
solution. The reaction mixture was stirred at room temperature in darkness for 4 days. Solvent was removed after reaction completed and column chromatography gave the product (A) as colorless oil. \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 3.91 (s, 3H), 4.00 (s, 3H), 6.23 (d, 1H, \(J = 8.28\) Hz), 7.64 (d, 1H, \(J = 8.32\) Hz). \(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 53.5, 54.0, 95.1, 102.5, 143.4, 158.2, 161.9; HRMS (ESI): Calcd. for C\(_7\)H\(_8\)BrNO\(_2\)[M+H]\(^+\), 217.9817, found: 217.9808, Yield = 98%.

5.5.2 Synthesis of B1-B3

3-Bromo-2,6-dimethoxypyridine (A) (436 mg, 2.0 mmol) in THF (10 ml) was added to freshly prepared lithium diisopropylamide (LDA) (Pr\(_2\)NH (0.5 ml, 3.52 mmol) in THF (8 ml) was cooled to -30°C, then n-butyllithium (1.6 M, 2.0 mL, 3.2 mmol) was added dropwise. The reaction mixture was stirred at -30°C for 30 minutes at -78°C. After the addition completed, the mixture was stirred at -78°C for 2 hours. Then substituted phosphine chloride solvents in THF (10 ml) was added to the above mixture at -78°C and slowly warmed to room temperature overnight. The reaction was worked up with 2 ml water and the solvent was removed under reduced pressure. The organic product was extracted with DCM and concentrated to give crude products which were used for the next step without further purification.
To a stirred solution of crude products in acetone (15 ml), 1.0 ml of ca. 35% hydrogen peroxide was added slowly at 0°C. The reaction mixture was monitored by TLC and the product was extracted with DCM. The combined extract was washed with brine and dried over anhydrous Na$_2$SO$_4$. The filtrate was concentrated under reduced pressure. Column chromatography gave pure products.

**3-Bromo-2,6-dimethoxy-4-di(4-trifluoromethylphenyl)phosphinoylpyridine (B1)**

Prepared according to the general procedure described above from bis(4-trifluoromethylphenyl)phosphine chloride (3.0 g, 8.44 mmol) and isolated as white solid, $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 3.92 (s, 3H), 4.02 (s, 3H), 6.31 (d, 1H, $J = 13.6$ Hz), 7.74-7.77 (m, 4H), 7.83-7.88 (m, 4H), $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 53.8, 103.6, 103.7, 122.0, 124.7, 125.59, 125.63, 125.71, 125.75, 132.4, 132.5, 134.26, 134.29, 134.5, 134.6, 134.62, 135.5, 144.6, 145.6, 163.6, 163.7; $^{31}$P-NMR (160 MHz, CDCl$_3$): $\delta$ 24.99; HRMS (ESI): Calcd. for C$_{21}$H$_{15}$BrF$_6$NO$_3$P[M+H]$^+$, 553.9955, found: 553.9933; Yield = 65%.

**3-Bromo-2,6-dimethoxy-4-di(4-methoxyphenyl)phosphinoylpyridine (B2)**

Prepared according to the general procedure described above from bis(4-methoxyphenyl)phosphine chloride (616 mg, 2.2 mmol) and isolated as white solid, $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 3.84 (s, 6H), 3.88 (s, 3H), 3.99 (s, 3H), 6.34 (d, 1H, $J = 13.12$ Hz), 6.95-6.98 (dd, 4H, $J_1 = 2.4$ Hz, $J_2 = 8.88$ Hz), 7.58-7.63 (m, 4H);
\(^{13}\)C-NMR (400 MHz, CDCl\(_3\)): \(\delta 53.9, 54.8, 55.3, 98.6, 98.7, 108.0, 108.1, 114.1, 114.2, 121.3, 122.5, 133.8, 133.9, 146.4, 147.4, 159.7, 159.8, 161.6, 161.7, 162.7;\)

\(^{31}\)P-NMR (160 MHz, CDCl\(_3\)): \(\delta 29.67;\) HRMS (ESI): Calcd. for C\(_{21}\)H\(_{21}\)BrNO\(_3\)P[M+H]+, 478.0419, found: 478.0428; Yield = 60%.

3-Bromo-2,6-dimethoxy-4-diisopropylphosphinoylpyridine (B3)

Prepared according to the general procedure described above from diisopropylphosphine chloride (840 mg, 5.5 mmol) and isolated as white solid,

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 0.95-1.01\) (dd, 6H, \(J_1 = 7.24\) Hz, \(J_2 = 16.68\) Hz), 1.32-1.37 (dd, 6H, \(J_1 = 7.04\) Hz, \(J_2 = 15.4\) Hz), 2.62-2.73 (m, 2H), 3.93 (s, 3H), 4.01 (s, 3H), 7.11 (d, 1H, \(J = 10.6\) Hz), \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta 16.18, 16.21, 16.99, 17.03, 26.4, 27.1, 54.1, 54.8, 95.2, 108.8, 147.7, 158.9, 162.3;\) \(^{31}\)P-NMR (160 MHz, CDCl\(_3\)): \(\delta 53.9;\) HRMS (ESI): Calcd. for C\(_{13}\)H\(_{22}\)BrNO\(_3\)P[M+H]+, 350.0521, found: 350.0529; Yield = 71%.

5.5.3 Synthesis of C1-C3

A mixture of B and Cu powder (334 mg, 5.21 mmol) in dried DMF (15 ml) was stirred at 140°C for 12 hours. Then DMF was evaporated under reduced pressure. CHCl\(_3\) was added and the mixture was refluxed for a few minutes. Insoluble solid was removed through celite and was washed with CHCl\(_3\). The combined filtrate was
concentrated. Column chromatography gave the pure product.

2,2’,6,6’-Tetramethoxy-bis-[di(4-trifluoromethylphenyl)phosphinoyl]-3,3’-bipyridine (C1)

Prepared according to the general procedure described above from B1 (1.108 g, 2 mmol) and isolated as white solid, $^1$H-NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 3.30 (s, 6H), 3.86 (s, 6H), 6.06 (d, 2H, $J$ = 13.96 Hz), 7.65-7.68 (q, 4H), 7.72-7.75 (q, 4H), 7.76-7.82 (m, 8H); $^{13}$C-NMR (100 MHz, CD$_2$Cl$_2$): $\delta$ 52.7, 53.2, 104.3, 104.4, 111.77, 111.82, 111.85, 111.89, 121.9, 122.0, 124.65, 124.69, 124.77, 124.81, 124.85, 124.89, 124.98, 125.01, 132.2, 132.3, 132.4, 132.99, 133.02, 133.32, 133.34, 134.9, 135.9, 136.3, 137.4, 143.5, 144.5, 160.5, 160.7, 161.7, 161.9; $^{31}$P-NMR (160 MHz, CD$_2$Cl$_2$): $\delta$ 25.65; HRMS (ESI): Calcd. for C$_{42}$H$_{30}$F$_{12}$N$_2$O$_6$P$_2$[M+H]$^+$, 949.1466, found: 949.1470; Yield = 62%.

2,2’,6,6’-Tetramethoxy-bis-[di(4-methoxyphenyl)phosphinoyl]-3,3’-bipyridine (C2):

Prepared according to the general procedure described above from B2 (623 mg, 1.30 mmol) and isolated as white solid, $^1$H-NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 3.36 (s, 6H), 3.78 (s, 6H), 3.81 (s, 6H), 3.83 (s, 6H), 6.12 (d, 2H, $J$ = 13.52 Hz), 6.84-6.87 (dd, 4H, $J_1$ = 2.24 Hz, $J_2$ = 8.88 Hz), 6.90-6.93 (dd, 4H, $J_1$ = 2.16 Hz, $J_2$ = 8.8 Hz), 7.47-7.55 (m, 8H); $^{13}$C-NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 52.6, 52.9, 54.8, 54.9, 104.3, 104.4, 113.14,
113.19, 113.27, 113.32, 122.7, 123.8, 124.3, 125.4, 133.3, 133.4, 133.6, 133.7, 145.3, 146.3, 160.3, 160.4, 161.0, 161.2, 161.81, 161.83; $^{31}$P-NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 27.58. HRMS (ESI): Calcd. for C$_{42}$H$_{42}$N$_2$O$_{10}$P$_2$[M+H]$^+$, 797.2393, found: 797.2364; Yield = 69%.

**2,2',6,6'-Tetramethoxy-bis-(diisopropylphosphinoyl)-3,3'-bipyridine (C3):**

Prepared according to the general procedure described above from B3 (1.4 g, 4 mmol) and isolated as white solid, $^1$H-NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 1.09-1.19 (m, 24H), 2.18-2.28 (m, 2H), 2.36-2.46 (m, 2H), 3.76 (s, 6H), 3.93 (s, 6H), 6.26 (s, 1H), 6.29 (s, 1H); $^{13}$C-NMR (100 MHz, CD$_2$Cl$_2$): $\delta$ 15.30, 15.31, 15.51, 15.53, 15.86, 15.89, 16.1, 16.2, 25.8, 26.3, 26.4, 27.0, 52.8, 52.9, 101.1, 101.2, 114.3, 114.4, 144.3, 145.1, 160.70, 160.76, 160.83, 160.9; $^{31}$P-NMR (160 MHz, CD$_2$Cl$_2$): $\delta$ 49.67; HRMS (ESI): Calcd. for C$_{26}$H$_{43}$N$_2$O$_6$P$_2$[M+H]$^+$, 541.2596, found: 541.2595; Yield = 47%.

**5.5.4 Synthesis of 42c-42e**

(R)-C (0.66 mmol) was dissolved in dried toluene (40 ml) and the mixture was degassed. Triethylamine (1.7 ml, 12 mmol) was added under N$_2$ and followed by the addition of trichlorosilane (1.2 ml, 12 mmol). The reaction mixture was stirred and heated at 100°C for 1 hour, and then refluxed overnight. After the mixture was cooled to room temperature, 20 ml of 10% aqueous NaOH solution was carefully added. The
mixture was then stirred at 80°C until the organic and aqueous layers were clear. The aqueous layer was separated and extracted with toluene. The combined organic layer was washed with 20 ml of 10% NaOH solution and brine and then dried over anhydrous Na₂SO₄. The organic layer was concentrated under reduced pressure to give a pure product.

(R)-2,2',6,6'-Tetramethoxy-4,4'-bis[di(4-trifluoromethylphenyl)phosphino]-3,3'-bipyridine ((R)-42c)

Prepared according to the general procedure described above from (R)-C1 (629 mg, 0.66 mmol) and isolated as a white solid, ¹H-NMR (400 MHz, CDCl₃): δ 3.36 (s, 6H), 3.86 (s, 6H), 5.97 (t, J = 2.1 Hz, 2H), 7.28-7.38 (m, 8H), 7.57 (d, J = 7.28 Hz, 8H), ¹³C-NMR (100 MHz, CDCl₃): δ 52.9, 53.4, 105.0, 113.6, 113.8, 114.0, 122.5, 122.6, 124.9, 124.96, 125.0, 125.03, 125.25, 125.27, 125.27, 125.34, 125.4, 130.9, 131.1, 131.2, 131.5, 133.4, 133.5, 133.6, 134.6, 134.7, 134.8, 139.0, 139.1, 139.2, 140.4, 140.5, 140.6, 151.96, 152.01, 152.05, 160.8, 160.9, 160.92, 162.8, ³¹P-NMR (160 MHz, CD₂Cl₂): -12.91; HRMS (ESI): Calcd. for C₄₂H₃₀F₁₂N₂O₄P₂ [M+H]⁺, 917.1567; found: 917.1609; [α]D³¹ = -49° (c 1, CHCl₃); Yield = 98%.

(R)-2,2’,6,6’-Tetramethoxy-4,4’-bis[di(4-methoxyphenyl)phosphino]-3,3’-bipyridine ((R)-42d)
Prepared according to the general procedure described above from (R)-C2 (529 mg, 0.66 mmol) and isolated as a white solid, $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 3.34 (s, 6H), 3.783 (s, 6H), 3.785 (s, 6H), 3.81 (s, 6H), 6.01 (t, $J = 1.6$ Hz, 2H), 6.79-6.85 (m, 8H), 7.13-7.18 (m, 8H), $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 52.9, 53.2, 55.11, 55.14, 104.6, 113.6, 113.66, 113.7, 114.02, 114.05, 114.08, 126.58, 126.62, 126.66, 127.77, 127.83, 127.9, 134.8, 134.9, 135.1, 135.8, 135.9, 136.0, 155.1, 155.2, 155.3, 160.0, 160.1, 160.5, 160.55, 160.6, 162.1, $^{31}$P-NMR (160 MHz, CD$_2$Cl$_2$): -15.48; HRMS (ESI): Calcd. for C$_{42}$H$_{42}$N$_2$O$_8$P$_2$ [M+H]$^+$; 765.2495; found: 765.2526; $\left[\alpha\right]_{D}^{21} = +47^o$ (c 1, CHCl$_3$); Yield = 98%.

(R)-2,2',6,6'-Tetramethoxy-4,4'-bis[diisopropylphosphino]-3,3'-bipyridine

((R)-42e)

Prepared according to the general procedure described above from (R)-C3 (360 mg, 0.66 mmol) and isolated as a white solid, $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.91-0.97 (m, 12H), 1.02-1.11 (m, 12H), 1.78-1.85 (m, 2H), 2.05-2.13 (m, 2H), 3.79 (s, 6H), 3.96 (s, 6H), 6.47 (d, $J = 1.2$ Hz, 2H), $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 18.7, 19.5, 20.3, 22.6, 24.8, 24.84, 53.1, 53.3, 103.2, 116.4, 116.6, 116.7, 153.3, 153.36, 153.4, 153.5, 160.5, 161.5, $^{31}$P-NMR (160 MHz, CD$_2$Cl$_2$): -3.21; HRMS (ESI): Calcd. for C$_{26}$H$_{43}$N$_2$O$_4$P$_2$ [M+H]$^+$; 509.2698; found: 509.2707; $\left[\alpha\right]_{D}^{21} = +140^o$ (c 1, CHCl$_3$); Yield = 98%.
5.6 Iridium Catalyzed Asymmetric Hydrogenation of Quinoline

A mixture of \([\text{Ir(COD)Cl}]_2\) (1mg, 0.0015 mmol) and ligands (0.0032 mmol) in 1.0ml dried solvent was stirred at room temperature for 30 min. in a glovebox or on a bench. The mixture was transferred with a gas-tight syringe to a stainless steel autoclave, which contains a mixture of I\(_2\) (4 mg, 0.015 mmol) and quinoline substrate (0.3 mmol) in 1ml solvent. The hydrogenation reaction was performed at room temperature under H\(_2\) for 20 hours unless otherwise specified. After careful releasing the hydrogen gas, aqueous sodium carbonate solution (2 ml) was added, and the mixture was stirred for 15 min. The aqueous layer was then extracted with EA \((3 \times 2 \text{ ml})\). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford a crude product. The substrate conversion was determined by \(^1\text{H}-\text{NMR}\) spectroscopy of the crude product. The enantiomeric excesses (ee) were determined by HPLC after purification on silica gel \((\text{n-hexane/EA} = 5/1)\) with a chiral column (OJ-H, OD-H or AD-H).

\[
\text{Ir(COD)Cl}_2, \text{H}_2, \text{L}^*, \text{I}_2, \text{solvent, rt}
\]

\[
\begin{align*}
\text{OR} & \quad \text{86} \\
\text{Ir(COD)Cl}_2, \text{H}_2 & \quad \text{L}^*, \text{I}_2, \text{solvent, rt} \\
\text{OR} & \quad \text{87}
\end{align*}
\]

Scheme 5-9
(+)-1,2,3,4-Tetrahydro-2-methylquinolin-8-ol (87a)

![Chemical Structure]

| Chemical Structure | Pale yellow solid, $^1$H-NMR (500 MHz, DMSO-$d_6$): δ 1.15 (d, 3H, $J = 6.5$ Hz), 1.40-1.46 (m, 1H), 1.81-1.85 (m, 1H), 2.49 (s, 1H), 2.57-2.70 (m, 1H), 2.71-2.74 (m, 1H), 3.25-3.38 (m, 1H), 4.42 (s, 1H), 6.28 (t, 1H, $J = 7.5$ Hz), 6.37 (d, 1H, $J = 7.5$ Hz), 6.46 (d, 1H, $J = 7.5$ Hz), 8.98 (s, 1H); $^{13}$C-NMR (125 MHz, DMSO-$d_6$): δ 23.28, 26.87, 30.81, 47.09, 112.43, 116.04, 120.68, 121.23, 134.67, 144.08; HRMS (ESI): Calcd. for C$_{10}$H$_{14}$NO [M+H]$^+$, 164.1075; found 164.1080; $[^{18}\alpha]_D = +189$ (c 0.0063, CHCl$_3$), 95% ee; HPLC (OJ-H, elute: Hexane / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 ml/min), $t_1 = 22.3$ min (major), $t_2 = 24.7$ min (minor). |

(+)-8-Butoxy-1,2,3,4-tetrahydro-2-methylquinoline (87b)

| Chemical Structure | Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): δ 0.99 (t, 3H, $J = 7.5$ Hz), 1.26 (d, 3H, $J = 6.0$ Hz), 1.47-1.54 (m, 2H), 1.60-1.64 (m, 1H), 1.79-1.81 (m, 2H), 1.93-1.95 (m, 1H), 2.73-2.76 (m, 1H), 2.84-2.88 (m, 1H), 3.40-3.42 (m, 1H), 3.94-4.01 (m, 2H), 4.14 (bs, 1H), 6.55 (t, 1H, $J = 7.5$ Hz), 6.61 (t, 2H, $J = 7.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 14.59, 20.05, 23.28, 27.05, 30.77, 32.14, 47.35, 68.48, 108.88, 116.43, 121.76, 121.94, 135.26, 146.09; HRMS (ESI): Calcd. for C$_{14}$H$_{22}$NO [M+H]$^+$, 220.1701; found 220.1698; $[^{18}\alpha]_D = +139$ (c 0.0076, CHCl$_3$), 95% ee; HPLC (OJ-H, elute: Hexane / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 ml/min), $t_1 = 22.3$ min (major), $t_2 = 24.7$ min (minor). |
CHCl₃), 94% ee; HPLC (OD-H, elute: Hexane / i-PrOH = 99 / 1, detector: 254 nm, flow rate: 0.5 ml/min), t₁ = 10.70 min (minor), t₂ = 9.54 min (major).

**2-Methyl-1,2,3,4-tetrahydroquinolin-8-yl acetate (87c)**

Pale yellow solid, ¹H-NMR (500 MHz, CDCl₃): δ 1.05 (d, 3H, J = 6.0 Hz), 2.27 (s, 3H), 2.29-2.44 (m, 3H), 2.45-2.62 (m, 1H), 4.81 (q, 1H, J = 6.5 Hz), 7.02 (d, 1H, J = 8.5 Hz), 7.10 (d, 1H, J = 7.5 Hz), 7.21 (t, 1H, J = 8.0 Hz), 13C-NMR (125 MHz, CDCl₃): δ 21.44, 23.49, 26.16, 32.74, 53.02, 119.23, 120.45, 126.63, 128.15, 135.78, 152.21, 171.66; HRMS (ESI): Calcd. for C₁₂H₁₆NO [M+H]⁺, 206.1181; found 206.1184; 84 % ee; HPLC (OJ-H, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), t₁ = 7.48 min (minor), t₂ = 13.48 min (major).

**(+)-8-(Benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87d)**

White solid, ¹H-NMR (500 MHz, CDCl₃): δ 1.25 (d, 3H, J = 6.5 Hz), 1.62-1.67 (m, 1H), 1.94-1.97 (m, 1H), 2.76-2.79 (m, 1H), 2.86-2.90 (m, 1H), 3.40-3.43 (m, 1H), 4.21 (bs, 1H), 5.08 (q, 2H, J = 6 Hz), 6.56 (t, 1H, J = 8.0 Hz), 6.68 (q, 2H, J = 8.0 Hz), 7.35(t, 1H, J = 7.0 Hz), 7.42 (t, 2H, J = 8.0 Hz), 7.46 (d, 2H, J = 7.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ 23.25, 27.04, 30.70, 47.34, 71.04, 109.63, 116.31, 121.96, 122.50, 128.29, 128.57, 129.20, 135.47, 138.06, 145.88; HRMS (ESI): Calcd. for C₁₇H₂₀NO [M+H]⁺, 254.1545; found 254.1542;
\([\alpha]^8_D = +321 \ (c \ 0.0048, \text{CHCl}_3), \ 93\% \ ee; \ HPLC \ (\text{OD-H}, \ \text{elute: Hexane} / i-\text{PrOH} = 90 / 10, \ \text{detector: 254 nm, flow rate: 1.0ml/min}) \), \ t_1 = 5.4 \ (\text{min (minor)}), \ (R) \ t_2 = 6.7 \ (\text{min (major)}).

\((-\))\-8-(3-Nitrobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87e)

Pale brown solid, \(^1\)H-NMR (500 MHz, \text{CDCl}_3): \delta 1.28 \ (d, 3H, \ J = 6.5 \text{ Hz}), \ 1.62-1.67 \ (m, 1H), \ 1.96-2.00 \ (m, 1H), \ 2.77-2.81 \ (m, 1H), \ 2.87-2.91 \ (m, 1H), \ 3.42-3.48 \ (m, 1H), \ 4.17 \ (bs, 1H), \ 5.16 \ (q, 2H, \ J = 13 \text{ Hz}), \ 6.56 \ (t, \ 1H, \ J = 7.5 \text{ Hz}), \ 6.65 \ (d, 2H, \ J = 8.0 \text{ Hz}), \ 6.70 \ (d, 1H, \ J = 7.5 \text{ Hz}), \ 7.58 \ (t, 1H, \ J = 8.0 \text{ Hz}), \ 7.78 \ (d, 1H, \ J = 7.5 \text{ Hz}), \ 8.20 \ (d, 1H, \ J = 8.0 \text{ Hz}), \ 8.32 \ (s, 1H); \ ^{13}\text{C-NMR} \ (125 \text{ MHz, CDCl}_3): \delta 23.17, \ 26.97, \ 30.51, \ 47.31, \ 69.70,109.65, \ 116.28, \ 122.27, \ 122.83, \ 122.99, \ 123.47, \ 130.17, \ 133.92, \ 135.37, \ 140.14, \ 145.15, \ 148.98; \ HRMS (ESI): \ Calcd. \ for \ C_{17}H_{19}N_2O_3 \ [\text{M+H}]^+, \ 299.1396; \ found \ 299.1405; \ \([\alpha]^8_D = +33 \ (c \ 0.003, \ \text{CHCl}_3), 93\% \ ee; \ HPLC \ (\text{AD-H}, \ \text{elute: Hexanes} / i-\text{PrOH} = 99 / 1, \ \text{detector: 254 nm, flow rate: 1.0 mL / min}) \), \ t_1 = 14.0 \ (\text{min (minor)}), \ t_2 = 15.5 \ (\text{min (major)}).

\((-\))\-8-(4-Nitrobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87f)

Pale brown solid, \(^1\)H-NMR (500 MHz, \text{CDCl}_3): \delta 1.29 \ (d, 3H, \ J = 6.5 \text{ Hz}), \ 1.62-1.69 \ (m, 1H), \ 1.96-2.01 \ (m, 1H), \ 2.76-2.81 \ (m, 1H), \ 2.86-2.93 \ (m, 1H), \ 3.43-3.47 \ (m, 1H), \ 4.16 \ (br, 1H), \ 5.18 \ (q, 2H, \ J = 13 \text{ Hz}), \ 6.55 \ (t, 1H, \ J = 7.5 \text{ Hz}), \ 6.61 \ (d, 2H, \ J = 7.5 \text{ Hz}), \ 6.70 \ (d, 1H, \ J = 7.5 \text{ Hz}), \ 7.60 \ (d,
2H, $J = 8.5$ Hz), 8.24 (d, 2H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 23.18, 26.95, 30.50, 47.32, 69.60, 109.54, 116.30, 122.29, 122.97, 124.37, 128.27, 135.31, 145.08, 145.44, 148.08; HRMS (ESI): Calcd. for C$_{17}$H$_{19}$N$_2$O$_3$ [M+H]$^+$, 299.1396; found 299.1405; $\left[\alpha\right]_{D}^{18} = +76$ (c 0.0032, CHCl$_3$), 91% ee; HPLC (AD-H, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), $t_1 = 9.5$ min (minor), $t_2 = 11.6$ min (major).

(+)-8-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87g)

Pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.28 (d, 3H, $J = 6.0$ Hz), 1.65-1.71 (m, 1H), 1.98-2.00 (m, 1H), 2.80-2.83 (m, 1H), 2.90-2.94 (m, 1H), 3.41-3.46 (m, 1H), 3.89 (s, 1H), 4.23 (br, 1H), 5.03 (q, 2H, $J = 11$ Hz), 6.52 (t, 1H, $J = 8.0$ Hz), 6.71 (d, 1H, $J = 7.5$ Hz), 6.75 (d, 1H, $J = 8.0$ Hz), 6.98 (d, 2H, $J = 9.0$ Hz), 7.42 (d, 2H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 23.18, 26.98, 30.65, 47.25, 55.86, 70.71, 109.54, 114.51, 116.25, 121.80, 122.34, 129.99, 130.01, 135.38, 145.88, 160.02; HRMS (ESI): Calcd. for C$_{18}$H$_{22}$NO$_2$ [M+H]$^+$, 284.1651; found 284.1657; $\left[\alpha\right]_{D}^{18} = +277$ (c 0.0033, CHCl$_3$), 88% ee; HPLC (OD-H, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), $t_1 = 6.6$ min (minor), $t_2 = 9.2$ min (major).
(+)-8-(3-Methoxybenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87h)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.26 (d, 3H, $J = 6.5$ Hz), 1.63-1.68 (m, 1H), 1.93-1.98 (m, 1H), 2.77-2.79 (m, 1H), 2.87-2.91 (m, 1H), 3.41-3.43 (m, 1H), 3.85 (s, 1H), 4.23 (bs, 1H), 5.05 (q, 2H, $J = 11.5$ Hz), 6.56 (t, 1H, $J = 8.0$ Hz), 6.68 (t, 2H, $J = 8.5$ Hz), 6.90 (d, 1H, $J = 7.5$ Hz), 7.03 (t, 2H, $J = 8.0$ Hz), 7.33 (t, 1H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 22.86, 26.63, 30.29, 46.93, 55.50, 70.56, 109.27, 113.31, 113.67, 115.91, 120.07, 121.55, 122.12, 139.84, 135.06, 139.26, 145.44, 160.04; HRMS (ESI): Calcd. for C$_{18}$H$_{22}$NO$_2$, 284.1651; found 284.1657 [M+H]$^+$; $[\alpha]^o_D = +543$ (c 0.0028, CHCl$_3$), 92% ee; HPLC (OD-H, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), $t_1 = 6.5$ min (minor), $t_2 = 8.1$ min (major).

(+)-4-((1,2,3,4-Tetrahydro-2-methylquinolin-8-yloxy)methyl)benzonitrile (87i)

White solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.28 (d, 3H, $J = 6.5$ Hz), 1.62-1.68 (m, 1H), 1.97-2.00 (m, 1H), 2.77-2.80 (m, 1H), 2.87-2.91 (m, 1H), 3.42-3.47 (m, 1H), 4.20 (bs, 1H), 5.14 (q, 2H, $J = 13.5$ Hz), 6.55 (t, 1H, $J = 8.0$ Hz), 6.61 (d, 2H, $J = 8.0$ Hz), 6.70 (d, 1H, $J = 7.5$ Hz), 7.55 (d, 2H, $J = 8.0$ Hz), 7.68 (d, 2H, $J = 8.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 23.16, 26.90, 30.47, 47.25, 69.80, 109.50, 112.15, 116.24, 119.28, 122.17, 122.86, 128.20, 132.92, 135.26, 143.38, 145.09; HRMS (ESI): Calcd. for C$_{18}$H$_{19}$N$_2$O [M+H]$^+$,
279.1497; found 279.1510; $\left[\alpha\right]_D^{18} = +294 \ (c \ 0.0012, \ CHCl_3), \ 85\% \ ee; \ HPLC$

(OD-H, elute: Hexanes / i-ProOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min),

t_1 = 12.2 \ min \ (minor), \ t_2 = 20.5 \ min \ (major).

(+)-8-(Biphenyl-3-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroquinoline (87j)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.30 (d, 3H, $J = 6.0$ Hz), 1.66-1.74 (m, 1H), 1.98-2.03 (m, 1H), 2.81-2.86 (m, 1H), 2.91-2.98 (m, 1H), 3.44-3.50 (m, 1H), 4.30 (bs, 1H), 5.18 (q, 2H, $J = 11.5$ Hz), 6.64 (t, 1H, $J = 8.0$ Hz), 6.74 (d, 1H, $J = 7.5$ Hz), 6.79 (d, 1H, $J = 8.5$ Hz), 7.43 (t, 1H, $J = 8.0$ Hz), 7.48-7.55 (m, 4H), 7.64 (d, 1H, $J = 7.5$ Hz), 7.69 (d, 2H, $J = 7.0$ Hz), 7.75 (s, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 23.20, 27.00, 30.64, 47.28, 71.10, 109.73, 116.32, 121.92, 122.55, 127.06, 127.19, 127.35, 127.80, 128.04, 129.41, 129.62, 135.45, 138.54, 141.48, 142.10, 145.85; HRMS (ESI): Calcd. for C$_{23}$H$_{24}$NO [M+H]$^+$, 330.1858; found 330.1874; $\left[\alpha\right]_D^{18} = +131 \ (c \ 0.009, \ CHCl_3), \ 92\% \ ee; \ HPLC$ (OD-H, elute: Hexanes / i-ProOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), $t_1 = 7.1$ min (minor), $t_2 = 8.5$ min (major).
(+)-8-(4-(Trifluoromethoxy)benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87k)

Pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.29 (d, 3H, $J = 6.0$ Hz), 1.65-1.71 (m, 1H), 1.97-2.02 (m, 1H), 2.80-2.83 (m, 1H), 2.89-2.94 (m, 1H), 3.43-3.48 (m, 1H), 4.22 (bs, 1H), 5.09 (q, 2H, $J = 12.0$ Hz), 6.60 (t, 1H, $J = 7.5$ Hz), 6.71 (t, 2H, $J = 8.5$ Hz), 7.29 (d, 2H, $J = 7.5$ Hz), 7.50 (d, 2H, $J = 9.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 23.19, 27.01, 30.62, 47.35, 70.10, 109.61, 116.34, 121.70, 122.12, 122.17, 122.74, 129.60, 135.41, 136.75, 145.57, 149.49; HRMS (ESI): Calcd. for C$_{18}$H$_{19}$NO$_2$F$_3$ [M+H]$^+$, 338.1368; found 338.1367; $[\alpha]_{D}^{20} = +30$ (c 0.0039, CHCl$_3$), 91% ee; HPLC (OD-H, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), $t_1 = 5.0$ min (minor), $t_2 = 6.8$ min (major).

(+)-8-(4-Fluorobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87l)

Pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.28 (d, 3H, $J = 6.0$ Hz), 1.65-1.69 (m, 1H), 1.98-2.00 (m, 1H), 2.79-2.83 (m, 1H), 2.89-2.94 (m, 1H), 3.42-3.47 (m, 1H), 4.22 (br, 1H), 5.06 (q, 2H, $J = 11.5$ Hz), 6.60 (t, 1H, $J = 7.5$ Hz), 6.71 (d, 2H, $J = 8.0$ Hz), 7.12 (t, 2H, $J = 8.5$ Hz), 7.45 (t, 2H, $J = 8.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 23.19, 26.99, 30.62, 47.31, 70.29, 109.57, 115.96, 116.22, 122.01, 122.59, 130.06, 130.13, 133.72, 133.75, 135.37, 145.66,
164.09; HRMS (ESI): Calcd. for C_{17}H_{19}NOF [M+H]^+, 272.1451; found 272.1458;

\([\alpha]_D^{18} = +74\ (c\ 0.0042,\ CHCl_3),\ 92%\ ee;\) HPLC (OD-H, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), \(t_1 = 5.4\) min (minor), \(t_2 = 7.1\) min (major).

\((+)-8-(4-(Trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline\)

\((87m)\)

White solid, \(^1\)H-NMR (500 MHz, CDCl₃): \(\delta\ 1.30\ (d,\ 3H,\ J = 6.0\ Hz),\ 1.63-1.72\ (m,\ 1H),\ 1.95-1.98\ (m,\ 1H),\ 2.75-2.79\ (m,\ 1H),\ 2.85-2.90\ (m,\ 1H),\ 3.39-3.43\ (m,\ 1H),\ 4.17\ (bs,\ 1H),\ 5.13\ (q,\ 2H,\ J = 12.5\ Hz),\ 6.54\ (t,\ 1H,\ J = 8.0\ Hz),\ 6.68\ (d,\ 1H,\ J = 8.0\ Hz),\ 6.72\ (d,\ 1H,\ J = 7.5\ Hz),\ 7.55\ (d,\ 2H,\ J = 8.0\ Hz),\ 7.66\ (d,\ 2H,\ J = 8.5\ Hz);\) \(^{13}\)C-NMR (125 MHz, CDCl₃): \(\delta\ 23.22,\ 27.02,\ 30.61,\ 47.37,\ 70.11,\ 109.58,\ 116.35,\ 122.20,\ 122.83,\ 125.89,\ 126.16,\ 128.14,\ 130.70,\ 135.39,\ 142.11,\ 145.44;\) HRMS (ESI): Calcd. for C_{18}H_{19}NOF₃ [M+H]^+, 322.1419; found 322.1417; \([\alpha]_D^{18} = +60\ (c\ 0.002,\ CHCl_3),\ 91%\ ee;\) HPLC (OD-H, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), \(t_1 = 5.4\) min (minor), \(t_2 = 7.7\) min (major).
(+)-8-(4-Chlorobenzyl oxy)-1,2,3,4-tetrahydro-2-methylquinoline (87n)

White solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.27 (d, 3H, $J = 6.5$ Hz), 1.62-1.68 (m, 1H), 1.95-2.00 (m, 1H), 2.77-2.80 (m, 1H), 2.86-2.93 (m, 1H), 3.42-3.44 (m, 1H), 4.18 (bs, 1H), 5.05 (q, 2H, $J = 12.0$ Hz), 6.56 (t, 1H, $J = 7.5$ Hz), 6.68 (dd, 2H, $J = 8.0$ Hz), 7.39 (s, 4H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 22.87, 26.64, 30.26, 46.96, 69.84, 109.20, 115.94, 121.69, 122.29, 128.99, 129.21, 133.97, 135.02, 136.13, 145.20; HRMS (ESI): Calcd. for C$_{17}$H$_{19}$NOCl [M+H]$^+$, 288.1155; found 288.1161; $[\alpha]^D_{18}$ = +254 ($c$ 0.0024, CHCl$_3$), 92% ee; HPLC (OD-H, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL / min), $t_1$ = 5.5 min (minor), ($t_2$ = 7.4 min (major).

8-(3,5-Bis(trifluoromethyl)benzyl oxy)-2-methyl-1,2,3,4-tetrahydroquinoline (87o)

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.26 (d, 3H, $J = 6.5$ Hz), 1.60-1.66 (m, 1H), 1.95-1.98 (m, 1H), 2.76-2.79 (m, 1H), 2.85-2.91 (m, 1H), 3.41-3.44 (m, 1H), 4.13 (bs, 1H), 5.17 (q, 2H, $J = 13.0$ Hz), 6.56 (t, 1H, $J = 7.5$ Hz), 6.65 (d, 1H, $J = 8.0$ Hz), 6.71 (d, 1H, $J = 7.5$ Hz) 7.87 (s, 1H), 7.91 (s, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 23.19, 27.09, 30.62, 47.44, 70.01, 110.14, 116.46, 119.90, 122.59, 123.41, 125.32, 128.16, 132.65, 135.64, 140.81, 145.27; HRMS (ESI): Calcd. for C$_{19}$H$_{18}$NOF$_6$[M+H]$^+$, 390.1293;
found 390.1306; 85% ee; HPLC (OJ-H, elute: Hexanes / i-PrOH = 99 / 1, detector: 254 nm, flow rate: 1.0 mL / min), \( t_1 = 6.74 \) min (minor), \( t_2 = 7.61 \) min (major).

### 5.7-Dibromo-2-methyl-1,2,3,4-tetrahydroquinolin-8-ol (96a)

Pale yellow solid, \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \( \delta \) 1.29 (d, 3H, \( J = 6.5 \) Hz), 1.59-1.66 (m, 1H), 1.93-1.97 (m, 1H), 2.48-2.60 (m, 1H), 2.63-2.68 (m, 1H), 3.32-3.34 (m, 1H), 7.37 (s, 1H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 22.75, 27.89, 30.17, 46.90, 107.32, 116.76, 120.83, 120.97, 135.93, 138.33; HRMS (ESI): Calcd. for C\(_{10}\)H\(_{12}\)NOBr \([\text{M+H}]^+\), 319.9286; found 319.9261; 75% ee; HPLC (OJ-H, elute: Hexanes / i-PrOH = 99 / 1, detector: 254 nm, flow rate: 1.0 mL / min), \( t_1 = 19.08 \) min (minor), \( t_2 = 20.45 \) min (major)

### 5.7 Synthesis of Quinoline-Based Ligand\(^{161,162}\)

![Scheme 5-10](image-url)
1-((1R,2R)-2-aminocyclohexyl)-3-(quinolin-8-yl)urea (90)

To a stirred solution of 8-aminoquinoline (0.5 g, 3.47 mmol) and triethylamine (0.97 ml, 6.94 mmol) in THF (20 ml), the mixture was cooled to 0°C under nitrogen atmosphere, then phenylchloroformate (0.46 ml, 3.68 mmol) was added dropwise over 5 minutes into the mixture. The resulting solution was stirred at ambient temperature over 12 h to generate a heterogeneous mixture. The solvent was removed in vacuo and the solid obtained was diluted with EA (25 ml) and sat. aq. NaHCO₃ (1:1; 25 ml). The organic layer was separated and the aqueous layer was extracted with EA (10 ml). The combined organic layers were washed with brine (20 ml), dried over anhydrous MgSO₄ and concentrated to 5 ml. The resulting precipitate was filtered and washed with hexanes (10 ml) to provide Phenyl-quinolin-8-yl-carbamate as a white solid.

To a solution of Phenyl-quinolin-8-yl-carbamate (0.579 g, 2.19 mmol) in DMSO (5 ml) was added tert-butyl (1R, 2R)-2-aminocyclohexylcarbamate (0.469 g, 2.19 mmol) in portions over 5 minutes. It was subsequently stirred at room temperature for 5 hours. The reaction mixture was diluted with EA (25 ml) and washed with water (20 ml), 1 M NaOH (20 ml), brine (10 ml). The solution was then concentrated under reduced pressure to a volume of 5 ml. The precipitated solid was filtered and washed with ether (10 ml), hexane (10 ml) and dried in vacuo to provide tert-butyl
(1R,2R)-2-(3-quinolin-8-ylureido)cyclohexylcarbamate and de-protect the amine group to obtain the ligand 90. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$: 1.12-1.37 (m, 4H), 1.54 (br m, 3H), 1.68-1.71 (m, 2H), 1.95-2.02 (m, 1H), 2.07-2.10 (m, 1H), 2.39-2.44 (m, 1H), 3.43-3.50 (m, 1H), 5.59 (d, 1H, $J = 7.0$ Hz), 7.32-7.35 (m, 2H), 7.46 (t, 1H, $J = 8.0$ Hz), 8.07 (dd, 1H, $J = 1.3$, 8.3 Hz), 8.51 (dd, 1H, $J = 1.3$, 7.8 Hz), 8.68 (dd, 1H, $J = 1.5$, 4.5 Hz), 9.12 (br s, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$: 26.75, 26.84, 34.8, 37.1, 57.5, 58.7, 116.4, 120.9, 122.8, 129.1, 129.6, 137.7, 137.8, 139.8, 149.2, 157.4; HRMS (ESI): Calcd. for C$_{16}$H$_{21}$N$_4$O [M+H]$^+$, 285.1715, found 285.1703.

5.8 Ruthenium Catalyzed Asymmetric Transfer Hydrogenation of Ketone

To a 10 ml vial, [Ru(p-cymene)Cl$_2$]$_2$ (1mg, 0.0016 mmol) and ligand (0.0032 mmol) were stirred in 0.5ml dry isopropyl alcohol (IPA) for 15 min in room temperature under N$_2$. Then freshly prepared 0.1M KO$_2$Bu in IPA solution was added to the catalyst complex with vigorous stirring followed by added the ketone substrates. The mixture was stirred for 20 hours. Then the mixture was quenched with 5% acetic acid in IPA, and passed through a short pad of silica gel. The conversion and ee were monitored by GC with a chiral Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column.
For asymmetric transfer hydrogenation in room temperature ionic liquid/PEG, the procedures were the same as stated above except that the catalyst was generated \textit{in situ} in 0.5 ml ionic liquid/PEG. After 20 hours of reaction, the IPA was evaporated under vacuum and the products in ionic liquid/PEG layer were extracted with hexane (3 x 1 ml). The combined hexane layer was concentrated in vacuum to give a crude product which was analyzed with the same method as described above. The ionic liquid/PEG phase was then simply recharged with substrate and KO'Bu solution to another cycle under the same reaction conditions.

![Scheme 5-11](image)

**1-Phenylethanol (89a)**

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.51 (d, 3H, $J = 6.5$ Hz), 4.91 (q, 1H, $J = 6.5$ Hz), 7.29 (d, 1H, $J = 7.0$ Hz), 7.34-7.39 (m, 4H);

$^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 25.74, 70.93, 126.02, 128.03, 129.08, 146.45; HRMS (ESI): Calcd. for C$_8$H$_{10}$ONa [M+Na]$^+$, 154.0629; found 145.0634; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 110°C isothermal), (Substrate) $t_o = 4.2$ min, ($R$) $t_1 = 10.1$ min, ($S$) $t_2 = 11.2$ min.
**1-(4-Chlorophenyl)ethanol (89b)**

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.43 (d, 3H, $J = 6.5$ Hz), 2.52 (s, 1H), 4.82 (q, 1H, $J = 6.5$ Hz.), 7.25-7.30 (m, 4H);

$^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 25.84, 70.26, 127.43, 127.45, 129.18, 133.61, 144.87;

HRMS (ESI): Calcd. for C$_8$H$_9$ONaCl [M+Na]$^+$, 179.0240; found 179.0223; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 135°C isothermal), (Substrate) $t_o = 4.8$ min, ($R$) $t_1 = 10.2$ min, ($S$) $t_2 = 11.3$ min.

**1-(3-Bromophenyl)ethanol (89c)**

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.43 (d, 3H, $J = 6.5$ Hz), 2.73 (s, 1H), 3.87-3.79 (m, 1H), 4.79 (q, 1H, $J = 6.5$ Hz.), 7.18 (t, 1H, $J = 7.5$ Hz), 7.24 (d, 1H, $J = 7.5$ Hz), 7.36-7.38 (m, 1H), 7.49-7.50 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 25.79, 70.22, 123.16, 124.65, 129.16, 130.69, 131.01, 148.73; HRMS (ESI): Calcd. for C$_8$H$_9$ONaBr [M+Na]$^+$, 222.9734; found 222.9743; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 130°C isothermal), (Substrate) $t_o = 7.3$ min, ($R$) $t_1 = 20.0$ min, ($S$) $t_2 = 22.3$ min.
1-(4-Bromophenyl)ethanol (89d)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$, 1.43 (d, 3H, $J$ =6.5 Hz), 2.43 (s, 1H), 4.81 (q, 1H, $J$ =6.5 Hz), 7.21 (d, 2H, $J$ =8.0 Hz), 7.44 (d, 2H, $J$ =8.0 Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 25.83, 70.32, 121.73, 127.78, 127.79, 132.14, 132.16, 145.39; HRMS (ESI): Calcd. for C$_8$H$_8$Br [M+H-H$_2$O]$^+$, 182.9809; found 182.9808; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 130°C isothermal), (Substrate) $t_0 = 9.0$ min, ($R$) $t_1 = 21.5$ min, ($S$) $t_2 = 24.5$ min.

1-(2-Methoxyphenyl)ethanol (89e)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$1.50 (d, 3H, $J$ = 7.0 Hz), 3.84 (s, 3H), 5.11 (q, 1H, $J$ = 6.5 Hz), 6.88 (d, 1H, $J$ = 8.0 Hz), 6.95-6.98 (m, 1H), 7.23-7.27 (m, 1H), 7.35-7.37 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 23.52, 55.79, 66.77, 110.95, 121.33, 126.60, 128.77, 134.14, 156.99; HRMS (ESI): Calcd. for C$_9$H$_{12}$O$_2$Na [M+Na]$^+$, 175.0735; found 175.0733; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 110°C isothermal), (Substrate) $t_0 = 13.8$ min, ($R$) $t_1 = 40.1$ min, ($S$) $t_2 = 35.7$ min.
1-(3-Methoxyphenyl)ethanol (89f)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): δ 1.46 (d, 3H, $J = 6.5$ Hz), 2.56 (s, 1H), 3.79 (s, 3H), 4.82 (q, 1H, $J = 6.5$ Hz), 6.79-6.81 (m, 1H), 6.92-6.93 (m, 2H), 7.23-7.26 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 25.37, 55.43, 70.42, 111.17, 113.05, 117.97, 129.72, 147.93, 159.95; HRMS (ESI): Calcd. for C$_9$H$_{12}$O$_2$Na [M+Na]$^+$, 175.0735; found 175.0744; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 115°C isothermal), (Substrate) $t_o$ = 11.5 min, (R) $t_1 = 32.0$ min, (S) $t_2 = 35.5$ min.

1-(4-Methoxyphenyl)ethanol (89g)

Pale yellow solid, $^1$H-NMR (500 MHz, CDCl$_3$): δ 1.44 (d, 3H, $J = 6.5$ Hz), 2.38 (s, 1H), 3.78 (s, 3H), 4.80 (q, 1H, $J = 6.5$ Hz), 6.84-6.87 (m, 2H), 7.25-7.28 (m, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 25.61, 55.86, 70.43, 114.40, 127.27, 138.69, 159.48; HRMS (ESI): Calcd. for C$_9$H$_{12}$O$_2$Na [M+Na]$^+$, 175.0735; found 175.0746; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 120°C isothermal), (Substrate) $t_o$ = 14.0 min, (R) $t_1 = 21.1$ min, (S) $t_2 = 23.1$ min.
1-o-Tolylethanol (89h)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.46 (d, 3H, $J = 6.0$ Hz), 2.35 (s, 1H), 5.09 (q, 1H, $J = 6.5$ Hz), 7.14 (d, 1H, $J = 7.5$ Hz), 7.17-7.2 (m, 1H), 7.23-7.26 (m, 1H), 7.51 (d, 1H, $J = 8.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 19.49, 24.50, 67.30, 125.12, 126.94, 127.70, 130.92, 134.78, 144.49; HRMS (ESI): Calcd. for C$_9$H$_{12}$ONa [M+Na]$^+$, 159.0786; found 159.0801; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp ChiralSil-Dex CB DF = 0.25 column, 130°C isothermal), (Substrate) $t_0 = 3.2$ min, (R) $t_1 = 7.5$ min, (S) $t_2 = 9.1$ min.

1-m-Tolylethanol (89i)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.49 (d, 3H, $J = 6.5$ Hz), 2.38 (s, 3H), 4.85 (q, 1H, $J = 6.5$ Hz), 7.10 (d, 1H, $J = 7.5$ Hz), 7.16-7.20 (m, 2H), 7.24-7.27 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 22.09, 25.74, 71.02, 123.08, 126.75, 128.82, 129.04, 138.75, 146.46; HRMS (ESI): Calcd. for C$_9$H$_{12}$ONa [M+Na]$^+$, 159.0786; found 159.0789; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp ChiralSil-Dex CB DF = 0.25 column, 110°C isothermal), (Substrate) $t_0 = 6.9$ min, (R) $t_1 = 16.0$ min, (S) $t_2 = 18.0$ min.
1-p-tolylethanol (89j)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 1.48 (d, 3H, $J = 6.5$ Hz), 2.36 (s, 3H), 4.85 (q, 1H, $J = 6.5$ Hz), 7.17 (d, 2H, $J = 8.0$ Hz), 7.26 (d, 2H, $J = 8.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 21.73, 25.69, 70.83, 125.93, 126.10, 129.66, 129.87, 137.74, 143.51; HRMS (ESI): Calcd. for C$_8$H$_9$ONaBr $[M+Na]^+$, 222.9734; found 222.9743; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 110°C isothermal), (Substrate) $t_0 = 7.6$ min, ($R$) $t_1 = 13.9$ min, ($S$) $t_2 = 16.1$ min.

1-Phenylpropan-1-ol (89k)

Pale yellow oil, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 0.91 (t, 3H, $J = 8.0$ Hz), 1.71-1.84 (m, 2H), 4.55 (t, 1H, $J =7.0$ Hz), 7.27-7.37 (m, 5H);

$^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 10.72, 32.42, 76.48, 126.60, 127.98, 128.91, 145.23; HRMS (ESI): Calcd. for C$_9$H$_{12}$ONa $[M+Na]^+$, 159.0786; found 159.0797; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 105°C isothermal), (Substrate) $t_0 = 8.8$ min, ($R$) $t_1 = 22.1$ min, ($S$) $t_2 = 24.8$ min.
1-(4-(Trifluoromethyl)phenyl)ethanol (89l)

Pale yellow oil, \(^1^H\)-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.49 (d, 3H, \(J = 6.5\) Hz), 4.94 (q, 1H, \(J = 6.5\) Hz), 7.47 (d, 2H, \(J = 8.5\) Hz), 7.60 (d, 2H, \(J = 8.0\) Hz); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 26.03, 70.48, 121.60, 123.76, 125.93, 126.19, 128.09, 130.28, 150.37; HRMS (ESI): Calcd. for C\(_9\)H\(_9\)OF\(_3\)Na [M+Na]\(^+\), 213.0503; found 213.0544; Capillary GC (Wcot Fused Silica 25m x 0.25mm, Coating Cp Chirasil-Dex CB DF = 0.25 column, 125\(^\circ\)C isothermal), (Substrate) \(t_0 = 3.0\) min, (\(R\)) \(t_1 = 7.5\) min, (\(S\)) \(t_2 = 8.8\) min.

1-(Naphthalen-2-yl)ethanol (89m)

White solid, \(^1^H\)-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.58 (d, 3H, \(J = 6.5\) Hz), 2.33 (bs, 1H), 5.04 (q, 1H, \(J = 6.5\) Hz), 7.46-7.52 (m, 3H), 7.79 (s, 1H), 7.82-7.85 (m, 3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 25.75, 71.09, 124.44, 124.48, 126.42, 126.77, 128.31, 128.58, 128.92, 133.53, 133.94, 143.84; HRMS (ESI): Calcd. for C\(_{12}\)H\(_{12}\)ONa [M+Na]\(^+\), 195.0786; found 195.0792; conversion was determined by Capillary GC (CYCLOSIL-B [J \& W scientific] 30m x 0.25mm x 0.25um column, 230\(^\circ\)C isothermal), (Substrate) \(t_0 = 6.3\) min, (Product) \(t_1 = 8.2\) min.

Ee value was determined by HPLC (Daicel Chiralcel OD-H column, elute: Hexanes / \(i\)-PrOH = 98 / 2, detector: 254 nm, flow rate: 1.0 mL / min), (\(R\)) \(t_1 = 30.0\) min, (\(S\)) \(t_2 = 33.0\) min.
2-Chlorophenyl(phenyl)methanol (89n)

White solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.51 (s, 1H), 6.23 (bs, 1H), 7.22-7.41 (m, 8H), 7.62 (d, 1H, $J = 8.0$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 73.33, 127.59, 127.77, 128.44, 128.69, 129.15, 129.42, 130.21, 133.16, 141.63, 142.88; HRMS (ESI): Calcd. for C$_{13}$H$_{11}$ONaCl $[M+Na]^+$, 241.0396; found 241.0404; conversion was determined by capillary GC (CYCLOSIL-B [J & W scientific] 30m x 0.25mm x 0.25um column, 230°C isothermal), (Substrate) $t_0 = 8.5$ min, (Product) $t_1 = 14.5$ min. Ee value was determined by HPLC (Daicel Chiralcel OD-H column, elute: Hexanes / i-PrOH = 90 / 10, detector: 254 nm, flow rate: 1.0 mL/min), (R) $t_1 = 8.5$ min, (S) $t_2 = 10.3$ min.

Phenyl(4-(trifluoromethyl)phenyl)methanol (89o)

White solid, $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.47 (s, 1H), 5.87 (s, 1H), 7.27-7.33 (m, 1H), 7.35-7.37 (m, 4H), 7.51(d, 2H, $J = 8.0$ Hz), 7.60 (d, 2H, $J = 8.5$ Hz); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 76.42, 123.69, 126.04, 126.07, 126.10, 126.13, 127.31, 127.34, 128.78, 129.46, 143.81, 148.18; HRMS (ESI): Calcd. for C$_{14}$H$_{10}$F$_3$ $[M+H-H_2O]^+$, 235.0735; found 235.0729; conversion was determined by capillary GC (CYCLOSIL-B [J & W scientific] 30m x 0.25mm x 0.25um column, 230°C isothermal), (Substrate) $t_0 = 3.9$ min, (Product) $t_1 = 7.9$ min. Ee value was determined by HPLC (Daicel Chiralcel OB-H column, elute: Hexanes /
\( i\text{-PrOH} = 90 / 10, \text{detector: 254 nm, flow rate: 1.0 mL / min}, (R) t_1 = 7.6 \text{ min}, (S) t_2 = 10.2 \text{ min}.\)

**Part II: Biology**

**5.9 General procedures**

ESCC cell lines of Hong Kong Chinese origin (HKESC-1 and HKESC-4) and breast cancer cell line MCF-7 were cultivated in 80% minimum essential medium alpha medium with non-essential amino acids (MEM\(\alpha\)) with 20% fetal bovine serum (FBS), 1% penicillin. ESCC cell lines of Japanese origin (KYSE 150) was cultivated in 45% RPMI 1640, 45% Ham’s F12 medium with 10% FBS and 1% penicillin. Liver cancer cell line (Hep3B) was cultivated in 85% Dulbecco's modified eagle medium (DMEM) with 20% FBS and 1% penicillin. Lung cancer cell line (A549) was cultivated in 95% DMEM with 5% FBS and 1% penicillin. All mediums were stored in refrigerator at 4°C and warmed to 37°C before use unless otherwise specified.

All cancer cell lines were cultivated in an incubator at 37°C with 5% carbon dioxide (CO\(\text{2}\)) unless otherwise stated. All the liquid nitrogen cell stocks were prepared by freezing the cells in the freezing medium which containing 70% of corresponding cell line’s medium, 20% of FBS and 10% of DMSO first at -20°C for 3 hours and then
-80°C overnight and finally stored in a -180°C liquefied nitrogen tank unless otherwise stated.

All culture mediums, trypsin and FBS were purchased from commercial suppliers and used without further treatment. Commercial purchased working MTS solution was diluted four times with phosphate buffered saline (PBS) before use unless otherwise stated.

All pipette tubes, centrifuge tubes, cultivate flask and PBS solution were sterilized before use unless otherwise stated.

All subcultivation was processed in ESCO class II biohazard safety cabinet unless otherwise stated.

Centrifugation was carried out using eppendorf centrifuge 5804R unless otherwise stated.

Absorbance of MTS product was measured by Bio-Rad microplate reader at 490nm wavelength unless otherwise stated.

5.10 In Vitro Cytotoxicity MTS Assay

Cells subjected to [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium] (MTS) assay\textsuperscript{194,195} were harvested from an incubation flask by trypsinization.
Then, the cells with 100ul medium were seeded in the 96-wells microtitre plates (5x10^3-10 x10^3 cells per well) and placed in the incubator for 24 hours. Compounds were prepared in varies concentrations in dimethylsulfoxide (DMSO)/MeOH/saline were added and incubated for another 48 hours. Untreated controls received either total complete medium or 0.1% of DMSO/MeOH. Cisplatinum (CDDP) was the positive reference. Then the medium in each well was removed and 100µl of working MTS solution was added to each well. The plate was then wrapped with aluminium foil and incubated for 2-2.5 hours at 37°C with 5% CO₂ incubator. Afterwards, the possible antiproliferative or cytotoxicity of those compounds was examined by measuring the absorbance of formazan products using a microplate reader (Bio-Rad) at 490nm. Each treatment was performed in triplicate and the results were shown as mean ± standard derivation (SD) when compared with the untreated vehicle controls unless otherwise specified.

5. 11 In Vivo Athymic Nude Mice Xenograft Experiment

Athymic nude mice purchased from the Chinese University of Hong Kong and The Hong Kong Polytechnic University with average body weight of 25g were injected subcutaneously with the human hepatocellular carcinoma (HCC) cell line Hep3B or esophageal carcinoma (ESCC) cell line KYSE150. They were housed in a sterile environment.
condition. Tumor size was daily measured by electronic calliper. When tumor size reached a mean volume of about 150mm$^3$ (where tumor volume was calculated by the formula $(\text{length} \times \text{width} \times \text{width})/2$), the mice were randomly divided into two groups, each group consisted of five mice. Compounds at a concentration of 5-10mg/Kg body weight/day were administrated by intraperitoneal (Ip) injection for 8-20 consecutive days. The control group received only the drug carrier.

5. 12 Morphological Changes Assay

When the cell culture reached 70% confluence, was fed with medium containing the tested compounds at 50μl/ml in DMSO/MeOH/saline and its corresponding MTS$_{50}$ concentration and the untreated controls received either total complete medium or 0.1% of DMSO/MeOH. Morphology of cells was observed under inverted microscopy before treatmen with the tested compounds. Morphological changes were recorded by photography before treatment with the tested compounds, and after 24 hours and 48 hours of incubation under an inverted microscope.

5.13 Cell Migration Assay

Cancer cells were seeded in a 6-well plate with their corresponding mediums and grown to confluence. After removing the Culture medium and washing with PBS,
monolayers were scratched with a plastic pipette tip to create a cell-free area (wound) approximately 2 mm in width according to the previous methods\textsuperscript{207}. Then cultures were washed twice in PBS to remove cell debris and a marked area of the wound was photographed under phase-contrast microscopy. Culture medium with MTS\textsubscript{50} of tested compound was added into the plate and incubated for 24hrs or 48hrs, while the control sample received only culture medium. Cells migration from the leading edge was photographed and counted at 0hr, 24hrs and 48hrs.
Chapter 6

Conclusion

The iridium catalysts with chiral dipyridinyl phosphine type ligands were found to be effective for the asymmetric hydrogenation of 8-hydroxy substituted quinolines with enantioselectivities up to 96%. The electronic properties of the dipyridinyl phosphine type ligands had significant effect on the enantioselectivities, high enantioselectivities were observed for most of the 8-hydroxy substituted quinolines with ligands containing the electron-donating OMe group.

The ruthenium catalyzed asymmetric transfer hydrogenation of aromatic ketones with quinoline-based ligand 90 was studied with ee up to 84%. The catalyst could also be recycled and reused in RTILs and PEG for at least five reaction cycles.

The cytotoxic potentials of quinoline derivatives against the human cancer cell lines were studied. Quinoline compounds 2-methyl-1,2,3,4-tetrahydroquinolin-8-ol (87a), 2-methyl-8-(4-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydroquinoline (87m), 8-hydroxy-2-quinolinecarbaldehyde (93b), and 5,7-dibromo-2-methyl-1,2,3,4-tetrahydroquinolin-8-ol (96a) showed remarkable cytotoxicity with MTS_{50} ranging from 3.1 to 12.5μg/ml. In vivo athymic nude mice tumor-xenograft experiments with subcutaneous Hep3B/KYSE150 tumor confirmed the anti-tumor activity that the tumor has shrunk at a dosage of 5-10mg/kg/day when
administrated intraperitoneally with no observable toxicity in the vital organs at the histological level.
Chapter 7

Recommendations and Future Work

1. To study other asymmetric catalytic reactions with the newly synthesized dipyridinyl phosphine type ligands.

2. To synthesize more quinoline-based ligands and study their asymmetric catalytic reactions.

3. To continue development of quinoline compounds and chiral quinoline compounds as anti-tumor agents; and to study their biological anti-tumor mechanism and toxicity.

4. To identify more lead compounds for development of new drugs.
Appendix

($^1$H, $^{13}$C and MS spectra)
8-Butoxy-2-methylquinoline (86b)

$^1$H-NMR (CDCl$_3$, 500MHz)

8-Butoxy-2-methylquinoline (86b)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
8-Butoxy-2-methylquolinol (86b)

HRMS

2-Methylquolinol-8-yl acetate (86c)

$^1$H-NMR (CDCl$_3$, 500MHz)

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8-(Benzyloxy)-2-methylquinoline (86d)

1H-NMR (CDCl₃, 500MHz)

8-(Benzyloxy)-2-methylquinoline (86d)

13C-NMR (CDCl₃, 125MHz)
Single Mass Analysis

Tolerance = 100.0 PPM / DBE: min = -1.5, max = 30.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
8 formula(e) evaluated with 1 results within limits (all results up to 1000) for each mass

Elements Used:
C: 0-17  H: 0-1000  N: 0-1  O: 0-1

Chan Sau Hing, CD05a
HR07_C516_9 72 (1.362) AM (Cen4, 80.00, H1, 1000.0, 3.00, 1.00); Sm (SG, 2x3.00); Sb (15,10.00); Cn (72,77) TCF MS ES+

Minimum:

Maximum:

Mass Calc. Mass mDa PPM DBE i-FIT Formula

250.1231 250.1232 -0.4 10.5 0.4 C17 H16 N O

8-(3-Nitrobenzyloxy)-2-methylquinoline (86e)

1H-NMR (CDCl3, 500MHz)

8-(Benzyloxy)-2-methylquinoline (86d)

HRMS


Elemental Composition Report

**Single Mass Analysis**

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions
16 formula(s) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:

C: 0.17 H: 0.1000 N: 0.2 O: 0.3

11C NMR (CDCl3, 125MHz)

8-(3-Nitrobenzyloxy)-2-methylquinoline (86e)

HRMS
8-(4-Nitrobenzyloxy)-2-methylquinoline (86f)

$^1$H-NMR (CDCl$_3$, 500MHz)

8-(4-Nitrobenzyloxy)-2-methylquinoline (86f)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
Elemental Composition Report

**Single Mass Analysis**

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
16 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0.17  H: 0.1000  N: 0.2  O: 0.3

Chen, B. Y. H., Q070a
HR07_0C24_B 143 (2.93%) AM (Cen,4, 80.00, Ht,10000.0,0.00,1.00), Sm (Sc, 2x3.00): Cn (138:159)

**8-(4-Nitrobenzyloxy)-2-methylquinoline (86f)**

HRMS

**8-(4-Methoxybenzyloxy)-2-methylquinoline (86g)**

$^1$H-NMR (CDCl$_3$, 500MHz)
8-(4-Methoxybenzoyloxy)-2-methylquinoline (86g)

Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
10 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-18  H: 0-1000  N: 0-1  O: 0-2

Chin Sau Hing, Q077a
HR97_1024_7 110 (2.048) AM (Cen,4, 80.00, Hi,10000.0,0.00,1.00); Sm (SG, 2x2.00); Sb (10,10.00); Cm (104:141) 260.1343

Least Significant Figure: 3

Minimum:  5.0  10.0  -1.3
Maximum:  50.0

Mass  Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
260.1343  280.1338  0.5  1.6  10.5  0.9  C18 H18 N O2
8-(3-Methoxybenzyl-0xy)-2-methylquinoline (86h)

1H-NMR (CDCl₃, 500MHz)

13C-NMR (CDCl₃, 125MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
10 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-18 H: 0-1000 N: 0-1 O: 0-2

Czhan Sau Ming, G078a
HR07_1024_B 140 (2.771) AM (Carb, 4, 80.00, Ht,10000.0,0.00,1.00), Sm (BG, 2c3.00); Cm (B7:166)

C10 H10 N O2

HRMS (TOF MS ES+) m/z 6.82e3

Micromass GTQF-2

N O CN 4-((2-Methylquinolin-8-yloxy)methyl)benzonitrile (86i)
1H-NMR (CDCl3, 500MHz)

N O Me 8-(3-Methoxybenzyl)oxy-2-methylquinoline (86h)
HRMS

4-((2-Methylquinolin-8-yloxy)methyl)benzonitrile (86i)
1H-NMR (CDCl3, 500MHz)
NOCN4-((2-Methylquinolin-8-yloxy)methyl)benzonitrile (86i)

13C-NMR (CDCl3, 125MHz)

Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
10 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-18 H: 0-1000 N: 0-2 O: 0-1

4-((2-Methylquinolin-8-yloxy)methyl)benzonitrile (86i) HRMS
8-(Biphenyl-3-ylmethoxy)-2-methylquinoline (86j)

$^1$H-NMR (CDCl$_3$, 500MHz)

8-(Biphenyl-3-ylmethoxy)-2-methylquinoline (86j)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0.23   H: 0-1000   N: 0-2   O: 0-1

Chun Sau Hing, QIOKa
HR07_1224_10 359 (7.409 AM (CenA, 60.00, Ht,10000.0,0.00,1.00); Sm (SG, 2x3.00); Cm (398:435)
326.1557

\[ \text{8-(Biphenyl-3-ylmethoxy)-2-methylquinoline (86j)} \]

1H-NMR (CDCl3, 500MHz)

\[ \text{8-(4-(Trifluoromethoxy)benzoxyl)-2-methylquinoline (86k)} \]

HRMS
8-(4-(Trifluoromethoxy)benzyloxy)-2-methylquinoline (86k)

**Single Mass Analysis**

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

28 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:

C: 0-13 H: 0-1000 N: 0-1 O: 0-2 F: 0-3

**Elemental Composition Report**

**Page 1**

![Elemental Composition Report](image-url)
8-(4-Fluorobenzyloxy)-2-methylquinoline (86l)

\[^{1}H\text{-NMR (CDCl}_3, 500MHz)}

![NMR Spectrum of 8-(4-Fluorobenzyloxy)-2-methylquinoline (86l)]

\[^{13}C\text{-NMR (CDCl}_3, 125MHz)}

![NMR Spectrum of 8-(4-Fluorobenzyloxy)-2-methylquinoline (86l)]
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
12 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-17 H: 0-1000 N: 0-1 O: 0-1 F: 0-1

Chan Sai Hing, Q082a
HR67_1024_12 01 (1.696) AM (Cen,4, 80.00, Ht,13000.0,0.00,1.00); Srm (SG, 2x3.00); Cm (01:133)

8-(4-Fluorobenzyloxy)-2-methylquinoline (86l)
HRMS

8-(4-Fluorobenzyloxy)-2-methylquinoline (86l)
HRMS

8-(4-Fluorobenzyloxy)-2-methylquinoline (86l)
HRMS
**Elemental Composition Report**

**Single Mass Analysis**

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0

Selected filters: None

Monoisotopic Mass, Even Electron ions

20 formula(e) evaluated with 1 results within limits (all results up to 1000) for each mass

Elements Used:

C: 0-18  H: 0-1000  N: 0-1  O: 0-1  F: 0-3

Chan Sau Hing, CD83a

HR07_024_13 02 (1.526) AM (Cen4, 0.600, Ht,10000,0,0,0,0,1.00); Sm (3G, 2x3.00); Cm (01:107)

HRMS (ES+):

m/z 318.1118

Minimum: 318.1118

Maximum: 318.1196

Calc. Mass: 318.1122

mDa: 0.2

PPM: 0.5

DBE: 1-FIT

Formula: C18H15N F3
8-(4-Chlorobenzyloxy)-2-methylquinoline (86n)

**1H-NMR (CDCl₃, 500MHz)**

**13C-NMR (CDCl₃, 125MHz)**

---

203
Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
12 formula(e) evaluated with 1 results within limits (all results up to 1000) for each mass
Elements Used:
C: 0-17 H: 0-1000 N: 0-1 O: 0-1 Cl: 0-1

Chan Sau Hing, Q084a
HR07_1024_14A 10 (0.1% AM (Cam, 4, 80.60, HI,10000.00,0,0,1.00); Sm (SG, Zk3.00); Cn (1:12)
294 0941

Minimum: -1.5
Maximum: 50.0

Mass Calc. Mass mDa PPM DBE 1-FIT Formula
264.0841 264.0842 -0.1 -0.4 10.5 0.2 C17 H15 N O Cl

1H-NMR (CDCl3, 500MHz)
8-(3,5-Bis(trifluoromethyl)benzyloxy)-2-methylquinoline (86o)

\[ ^{13}\text{C-NMR (CDCl}_3, 100\text{MHz)} \]

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DEE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
165 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-19  H: 0-14  N: 0-3  O: 0-3  F: 0-6  Na: 0-1
Kiss-Depth 30000201 HS 312 31 (3.5853) Cm (Cn,10, 50,0, Ar); 6m (5G, 2x5,0); 1m 86; 10,0,0; Cm (31,34)

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<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DEE</th>
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</table>
8-Hydroxyquinoline-2-carbaldehyde (93b)

1H-NMR (C₆D₆, 500MHz)

8-Hydroxyquinoline-2-carbaldehyde (93b)

13C-NMR (C₆D₆, 125MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 100.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
7 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0.10  H: 0.1000  N: 0.1  O: 0.2

HN CHO
OBn
8-(Benzyloxy)quinoline-2-carbaldehyde
(94a)

1H-NMR (CDCl3, 500MHz)

8-Hydroxyquinoline-2-carbaldehyde (93b)
HRMS

8-(Benzyloxy)quinoline-2-carbaldehyde (94a)
$^1$H-NMR (CDCl3, 500MHz)
Elemental Composition Report

Single Mass Analysis

Tolerance = 10.0 PPM / DBE: min = -100.0, max = 1000.0

Selected filters: None

Monoisotopic Mass, Even Electron Ion
65 formula(e) evaluated with 1 result(s) within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0.17  H: 0.14  N: 0.4  O: 0.5  Na: 0.1

Kern:Dept-253032011 HS SIS 2(0.402) AM (Top,10, H1:10000,0.00,1.00). Srm (Min, 2x3.00)

264.1015

 sto 69.5

M. Imun:  100.0
Maxiumum:  10.0  1000.0

Mass   Calc. Mass   mDa   PPM   DBE   i-FIT   Formula
264.1015  264.1025  -1.0  -3.8  11.5  0.2  C17 H14 N O2
8-(3-Nitrobenzyloxy)quinoline-2-carbaldehyde

$^1$H-NMR (CDCl$_3$, 500MHz)

8-(3-Nitrobenzyloxy)quinoline-2-carbaldehyde $^1$C-NMR (CDCl$_3$, 100MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron lens
25 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
O: 0-19 H: 0-13 N: 0-3 D: 0-4 Na: 0-1

Kin Dependent: 3323201H HS S19 27 (0.509) Cn (Cn,10, 00, 00, A); Sm (Sg, 2c3, 00); Sb (1c, 10, 00); Cn (21, 37)

TOF MS ES+


8-(3-Nitrobenzyloxy)quinoline-2-carbaldehyde

HRMS

1H-NMR (CDCl3, 500MHz)

8-(4-Nitrobenzyloxy)quinoline-2-carbaldehyde

HRMS

1H-NMR (CDCl3, 500MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Molecular Mass, Even Electron Ions
80 formula(s) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-17  H: 0-13  N: 0-3  O: 0-10  Na: 0-1

Kin-Det 62002011 HS 51 29 (0.527) Cn (Cen,10, 80.00, Ar); Sm (2G, 2x3.00); Sb (10,10.00 ); Cn (27,21)

TOF-MS ES-

309.0862  2.70e3

1  ppm:
Maximum: 5.0 10.0  1000.0

Mass  Calc. Mass  mDa  PPM  DBE  1-PIT  Formula
309.0862  309.0875  -1.3  -4.2  12.8  153.3  C17 H13 N2 O4

8-(4-Nitrobenzyloxy)quinoline-2-carbaldehyde (94c)
8-(4-Methoxybenzyloxy)quinoline-2-carbaldehyde (94d)

$^1$H-NMR (CDCl$_3$, 500MHz)

$^{13}$C-NMR (CDCl$_3$, 100MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
17 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-18 H: 0-15 N: 0-3 O: 0-3 Na: 0-1

Kin Dp2: 23302011 HS 52 26 (0.027) Cr (Cen,10, 60.00, Ar); Sm (C1, 2x0.00); Sn (2x10.00); Cm (26:35)

TOF MS ES+ 1.13e+4

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<th>Calc. Mass</th>
<th>MDa</th>
<th>ppm</th>
<th>DBE</th>
<th>i-FIT</th>
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<td>11.5</td>
<td>75.9</td>
<td>C18 H15 N O3 Na</td>
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8-(4-Methoxybenzyloxy)quinoline-2-carbaldehyde
(94d)

8-(3-Methoxybenzyloxy)quinoline-2-carbaldehyde
(94e)

1H-NMR (CDCl3, 500MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
28 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-19  H: 0-16  N: 0-3  O: 0-3  Na: 0-1

Measured: 294.1118  

3.63e3

Calculated: 294.1118  

5.0 ppm DBE 1-FIT

C18 H16 N O3
4-((2-Formylquinolin-8-yloxy)methyl)benzonitrile (94f)

1H-NMR (CDCl₃, 500MHz)

4-((2-Formylquinolin-8-yloxy)methyl)benzonitrile (94f)

13C-NMR (CDCl₃, 100MHz)
**Elemental Composition Report**

**Single Mass Analysis**

Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0

Selected filters: None

**Monoisotopic Mass, Even Electron Ions**

31 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
- C: 0-19
- H: 0-15
- N: 0-3
- O: 0-3
- Na: 0-1

Kin-Dep: 230030111 I3 314 28 (0.227) Cn (C3n,16, 90.00, Ar, 3n (3G, 2xG0), 3b (10, 10.00), Cn (19.46)

**TOF MS ES+**

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<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
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<td>C16 H13 N2 O2</td>
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**HRMS**

8-(Biphenyl-3-ylmethoxy)quinoline-2-carbaldehyde (94g)

[1H-NMR (CDCl3, 500MHz)]
8-(Biphenyl-3-ylmethoxy)quinoline-2-carbaldehyde
(94g)

Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
33 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-23  H: 0-18  N: 0-3  O: 0-3  Na: 0-1

Km-Oct: 29322211 HS S3 27 (0.039) Cr (Can: 10, 89.00, Al); Sm (SG, 2x3.00); Eb (10,10.00); Cm (22:43)

TOF MS ES+

Mass Calc. Mass aDa PPM DBE i-PIT Formula
340.1345 340.1338 0.7 2.1 15.5 117.4 C23 H18 N O2
8-(4-(Trifluoromethoxy)benzyloxy)quinoline-2-carbaldehyde (94h)

$^{1}$H-NMR (CDCl$_3$, 500MHz)

8-(4-(Trifluoromethoxy)benzyloxy)quinoline-2-carbaldehyde (94h)

$^{13}$C-NMR (CDCl$_3$, 100MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
77 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-18  H: 0-13  N: 0-3  O: 0-3  F: 0-3  Na: 0-1
Kin-Dip: 23332011 HS S4 26 (0.527) Cr (Can, 10, 80.00, Ar); Sm (SG, 2x3.00); Sn (10, 10.00); Crn (22.33)
TOF MS ES+

8-(4-(Tetrafluorophenyl)benzyloxy)quinoline-2-carbaldehyde (94i)

1H-NMR (CDCl₃, 500MHz)

8-(4-Fluorobenzyloxy)quinoline-2-carbaldehyde (94h)
HRMS

8-(4-(Fluorobenzyloxy)quinoline-2-carbaldehyde (94i)

1H-NMR (CDCl₃, 500MHz)
**Elemental Composition Report**

**Single Mass Analysis**
Tolerance = 5.0 PPM  /  DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
130 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-18  H: 0-13  N: 0-3  O: 0-3  F: 0-3  Na: 0-1

Kubilay-2030211 H5 S6 27 (0.50): Cn (Cen,10, 80.00, x); Sn (3G, 2x3.00); Sb (10,10.00); Cn (22:35)
TOF MS ES+ 282.0920

**Mass**  
Calc. Mass  mDa  PPM  DBE  i-PID  Formula
282.0920  282.0910  -1.0  -3.5  11.5  53.6  Cl7 H13 N C2 F

**8-(4-Fluorobenzyloxy)quinoline-2-carbaldehyde**

**HRMS**
8-(4-(Trifluoromethyl)benzyl)oxy)quinoline-2-carbaldehyde (94j)

$^1$H-NMR (CDCl$_3$, 500MHz)

8-(4-(Trifluoromethyl)benzyl)oxy)quinoline-2-carbaldehyde (94j)

$^{13}$C-NMR (CDCl$_3$, 100MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
77 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-18  H: 0-13  N: 0-3  O: 0-3  F: 0-3  Na: 0-1

Kin-Dup: 2332011 HS-B: 28 (0.527) Cn (Cen,10, 80.00, At); Sm (Sg, 2X3.00); Sb (10,10.00); Cn (22,34)

TOF MS ES+: 332.0893

Mass     Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
332.0893  332.0896  -1.5  -4.5  11.5  125.4  C13 H13 N O2 F3

8-(4-Chlorobenzyloxy)quinoline-2-carbaldehyde (94k)

H-NMR (CDCl3, 500MHz)

\[
\text{\chem{\begin{array}{c}
\text{CHO} \\
\text{N} \\
\text{O} \\
\text{Cl} \\
\text{C} \\
\end{array}}}
\text{8-(4-Chlorobenzyloxy)quinoline-2-carbaldehyde (94k)}}
\]

\[^{1}H\text{-NMR (CDCl}_3, 500MHz)\]
8-(4-Chlorobenzyloxy)quinoline-2-carbaldehyde

\(^{13}\)C-NMR (CDCl\textsubscript{3}, 100MHz)

Elemental Composition Report

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

8-(4-Chlorobenzyloxy)quinoline-2-carbaldehyde

HRMS
**1H-NMR (CDCl3, 500MHz)**

8-(3,5-Bis(trifluoromethyl)benzyloxy)quinoline-
2-carbaldehyde (94I)

**13C-NMR (CDCl3, 100MHz)**

8-(3,5-Bis(trifluoromethyl)benzylxy)quinoline-
2-carbaldehyde (94I)
8-(3,5-Bis(trifluoromethyl)benzyloxy)quinoline-2-carbaldehyde (94l)

HRMS

5,7-Dibromo-2-methylquinolin-8-ol (95a)

$^1$H-NMR (CDCl$_3$, 500MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
33 formula(e) evaluated with 1 results within limits (all results up to 1000) for each mass
Elements Used:
C: 0-12  H: 0-1000  N: 0-1  O: 0-3  Br: 0-2

Chen Sen Hsing, Q091a
HR08_0810_8.13 (0.2400) AM (Top4, H1,0000,0,00,1,00); Sm (SG, 2x3.00); Crm (10:17)

315.8981 0.8 2.5 6.5 0.2 C10 H8 N O Br2
2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-phenylethanone (95b)

\[ \text{\textsuperscript{1}H-NMR (CDCl}_3\text{, 500MHz)} \]

\[ \text{\textsuperscript{13}C-NMR (CDCl}_3\text{, 125MHz)} \]
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:

Chan Sau Hing, G125a
QT_ESP_HR_WLM_2020_0722_2_101 (1.881) AM (Cen/4, 80.00, H=100250.0,3.00,1.00); Sm (G3, 2x3.00); Cm (G6:127)  TOF MS: ES+
435.9385

Minimum:                                      -1.5
Maximum:                                      100.0  10.0   60.0
Mass   Calc. Mass   mDa      PPM   DBE   i-FIT   Formula
433.9398 433.9391   0.7      1.6  11.5    0.9   Cl18 H14 N O2 Br2
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:

HRMS

Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
447.9549  447.9548  0.1  0.2  11.5  0.1  C19 H16 N O2 Br2
1-(4-Bromophenyl)-2-(5,7-dibromo-2-methylquinolin-8-yloxy)ethanone (95d)

13C-NMR (CDCl3, 125MHz)

1H-NMR (CDCl3, 500MHz)
Elemental Composition Report

**Single Mass Analysis**

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
33 formula(e) evaluated with 1 results within limits (all results up to 1000) for each mass

Elements Used:
C: 0-19  H: 0-1000  N: 0-1  O: 0-2  Br: 0-3

Chen Seu Hing, G127a
QIT_ESP_FR_WLM_2009_0722_4A 219.4.070 AM (Cen. 3.8000. H. 10000. 0.000. 0.000); Sm (SG. 2.933); Cn (167-233) TDF MS ES+

![Chemical Structure](attachment:image.png)

Minimum:
100.0  10.0  -1.5

Maximun:
500.0  60.0

**Mass**
Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
511.8509  511.8496  1.2  2.3  11.5  0.5  C18 H13 N O2 Br3

![NMR Spectrum](attachment:image.png)
Elemental Composition Report

Single Mass Analysis

Tolerance = 10.0 PPM
DDE: min = -1.5, max = 6.0
Selected filters: None

Molecular Mass: Even Electron Ion
41 formula(e) evaluated with results within limits (all results up to 0.0001 for each mass)
Elements used: C: 0.18 O: 0.2 Br: C: 0.18
H: 0.10 N: 0.2 O: 0.2 Br: C: 0.18

HRMS

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(4-fluorophenyl)ethanone (95e)

C13H7Br2N2O3

13C-NMR (CDCl3, 125MHz)
1-(Biphenyl-4-yl)-2-(5,7-dibromo-2-methylquinolin-8-yloxy)ethanone (95f)

\[ \text{C-NMR (CDCl}_3, 125\text{MHz)} \]

1H-NMR (CDCl3, 500MHz)
**Single Mass Analysis**

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
35 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-24   H: 0-1000   N: 0-1   O: 0-3   Br: 0-2

Chan Sau Hing, Q129a
GT_ESP_HR_WLM_2009_0722_8 226 (4.260) AM (Cen, 4, 80.00, H, 10000.0, 0.00, 1.00); Sm (SG, 2x3.00); Cm (200.238) TCI MS ES+ 1.4503

Minimum:
100.0 0.0 60.0

Mass    Calc. Mass    mDa    PPM    DBE    i-FIT    Formula
509.9716  509.9704  1.2    2.4    15.5    0.1    C24 H18 N O2 Br2

Std proton
Q139a

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(4-methoxyphenyl)ethanone (95g)

1H-NMR (CDCl3, 500MHz)
2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(4-methoxyphenyl)ethanone (95g)

**Elemental Composition Report**

**Single Mass Analysis**
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
28 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-19  H: 0-1000  N: 0-1  O: C-3  Br: 0-2

Chen Sau Hing, Q:130a
QT_ESP_FR_WM, 2009_0722_7 97 (1.567) AM (C4n, 40.00, Ht,100000,0,0,0,130); Sm (SG, 3x3.00); Cm (54:103)  TOF MS ES+ 8.55e3

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2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(3-methoxyphenyl)ethanone (95h)

**1H-NMR (CDCl₃, 500MHz)**

![1H-NMR Spectrum](image)

**13C-NMR (CDCl₃, 125MHz)**

![13C-NMR Spectrum](image)
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
28 formula(s) evaluated with 1 results within limits (all results up to 1000) for each mass
Elements Used:
C: 0-19  H: 0-1000  N: 0-1  O: 0-3  Br: 0-2

Channeling Ring, QT_ESP_HR_VLM_2009_0722_8 75 (1.396) AM (Caa, 4, 60.00, HT, 1000.0, 0.00, 1.00); Sm (SG, 2x3.00); Cm (88.167) TOF MS ES +  4.3963

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(3-methoxyphenyl)ethanone (95i)

MassCalc. Mass mDa PPM DBE 1-FIT Formula
463.9498 463.9497 0.1 0.2 11.5 0.6 C19 H16 N 03 Br2

2-(5,7-Dibromo-2-methylquinolin-8-yloxy)-1-(2-methoxyphenyl)ethanone (95i)

1H-NMR (CDCl3, 500MHz)
**Elemental Composition Report**

**Single Mass Analysis**

Tolerance = 10.0 PPM  /  DBE: min = -1.5, max = 60.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

28 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:

C: 0-19  H: 0-1000  N: 0-1  O: 0-3  Br: 0-2

Mass  Calc. Mass  m/z  PPM  DBE  i-FIT  Formula

463.9494  463.9497  -0.3  -0.6  11.5  1.4  C19 H16 N C3 Br2
Bis(2-methylquinolin-8-yloxy)methane (97a)

\[\text{1H-NMR (CDCl}_3, 500\text{MHz)}\]

\[\text{13C-NMR (CDCl}_3, 100\text{MHz)}\]
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
36 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-21 H: 0-1000 N: 0-2 O: 0-2 Na: 0-1

Penny Chor, C134a

1H-NMR (CDCl3, 500MHz)

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBR</th>
<th>i-FIT</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>331.1452</td>
<td>331.1447</td>
<td>0.5</td>
<td>1.5</td>
<td>13.5</td>
<td>0.1</td>
<td>C21 H19 N2 O2</td>
</tr>
</tbody>
</table>

1,3-Bis(2-methylquinolin-8-yloxy)propane (97b)

Bis(2-methylquinolin-8-yloxy)methane (97a)

HRMS
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monosotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-23  H: 0-23  N: 0-3  O: 0-2  Na: 0-1

1,3-Bis(2-methylquinolin-8-yloxy)propane
(97b)

HRMS

Calc. Mass 359.1743

Mass 359.1760

Mda 1.7

PPM -4.7

DBE 13.5

i-FIT 46.8

Formula C23 H23 N2 O2

Page 1
1,4-Bis(2-methylquinolin-8-yloxy)butane

$^1$H-NMR (CDCl$_3$, 500MHz)

1,4-Bis(2-methylquinolin-8-yloxy)butane

$^{13}$C-NMR (CDCl$_3$, 100MHz)
1.4-Bis(2-methylquinolin-8-yloxy)butane (97c) HRMS

1.5-Bis(2-methylquinolin-8-yloxy)pentane (97d) 1H-NMR (CDCl₃, 500MHz)
**Elemental Composition Report**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

![Chemical Structure](image)

1,5-Bis(2-methylquinolin-8-yloxy)pentane

![13C-NMR (CDCl3, 100MHz)](image)

**Data**

- **Tolerance**: 5.0 PPM
- **DBE**: min = -100.0, max = 1000.0
- **Selected filters**: None

**Monoisotopic Mass, Even Electron Ions**

14 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

**Elements Used**:

- C: 0-25
- H: 0-27
- N: 0-3
- O: 0-1

**Isotopic Distribution**

![Isotopic Distribution Graph](image)

**Minimum**:

- 341.3081

**Maximum**:

- 387.2065

**Mass**

- **Calc. Mass**: 387.2073
- **mDa**: 0.0
- **PPM**: -2.1
- **DBE**: 13.5
- **i-FIT**: 59.0
- **Formula**: C25 H27 N2 C2
1,6-Bis(2-methylquinolin-8-yloxy)hexane

(97e)

$^1$H-NMR (CDCl$_3$, 500MHz)

1,6-Bis(2-methylquinolin-8-yloxy)hexane

(97e)

$^{13}$C-NMR (CDCl$_3$, 100MHz)
1,6-Bis(2-methylquinolin-8-yloxy)hexane

(97e)

HRMS

1,7-Bis(2-methylquinolin-8-ylxyloxy)heptane

(97f)

1H-NMR (CDCl₃, 500MHz)
1,7-Bis(2-methylquinolin-8-yloxy)heptane

(97f)

$^{13}$C-NMR (CDCl$_3$, 100MHz)

Elemental Composition Report

Single Mass Analysis
Tolerance = 20.0 PPM  /  DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0.27  H: 0.31  N: 0.3  O: 0.2

KIN-DEPT-05052010 HS S1646 (0.661) AM (Cen,10, 80.00, Ar,5000.0,0.00,1.00); Sm (SG, 2x3.00); Sb (10,10.00 ); Cm (31:38)

TOF MS ES+: 415.2383

Minimum: 5.0  20.0  -100.0

Mass  Calc Mass  mDa  PPM  DBE  I-FIT  Formula
415.2383  415.2386  -0.3  -0.7  13.5  200.1  C27 H31 N2 O2
1,8-Bis(2-methylquinolin-8-yloxy)octane (97g)

$^1$H-NMR (CDCl$_3$, 500MHz)

1,8-Bis(2-methylquinolin-8-yloxy)octane (97g)

$^{13}$C-NMR (CDCl$_3$, 100MHz)

248
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monisotopic Mass, Even Electron Ions
13 'formula(e)' evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-28 H: 0-33 N: 0-3 O: 0-2 Na: 0-1
KIN-DEPT-350 spectrometer: HS S17 45 (0.843) AM (Top, 5, H1,10000, 0.00, 1.00); Sm (SG, 2x3 00); Sb (10,10 00): Cn (40:54)

TOF MS ESI+

Minimum:
Maximum:

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<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>DPM</th>
<th>DBE</th>
<th>i-PIT</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>429.2528</td>
<td>429.2542</td>
<td>-1.4</td>
<td>-3.3</td>
<td>13.5</td>
<td>1.0</td>
<td>C28 H33 N2 O2</td>
</tr>
</tbody>
</table>

1,10-Bis(2-methylquinolin-8-yloxy)decane (97h)
1H-NMR (CDCl3, 500MHz)

1,8-Bis(2-methylquinolin-8-yloxy)octane (97g)
HRMS
Elemental Composition Report

**Single Mass Analysis**

Tolerance = 5.0 PPM / DBE: min = -5.0, max = 100.0

Selected fillers: None

Monoisotopic Mass, Even Electron Ions

17 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:

- C: 0-30
- H: 0-100
- N: 0-2
- O: 0-2

Ferry GmbH, 13C, 21a dimer, C11810

DEPT PENTHR HR 2008_1209_5 144 (2.853) AM (Cen4, 80.00, H4, 100.00, 0.00, 0.00); Sm (SG, 3x3.00); Cn (142:191) TOF MS ES+

HRMS

\[ \text{M} = 457.2851 \]

\[ \text{M} + 1 = 458.2856 \]

\[ \text{M} + 2 = 459.2859 \]

Minimum: 437.1932

Maximum: 459.2914

Mass Calc. Mass mDa PPM DBE i-FIT Formula

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>i-FIT</th>
<th>Formula</th>
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<tr>
<td>457.2851</td>
<td>457.2855</td>
<td>-0.4</td>
<td>-0.9</td>
<td>13.5</td>
<td>0.2</td>
<td>C30 H37 N2 C2</td>
</tr>
</tbody>
</table>
8,8'-Methylenebis(oxy)diquinoline-2-carbaldehyde (98a)

$^1$H-NMR (CDCl$_3$, 500MHz)

8,8'-Methylenebis(oxy)diquinoline-2-carbaldehyde (98a)

$^{13}$C-NMR (CDCl$_3$, 100MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 1.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
245 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-30  H: 0-33  N: 0-5  O: 0-6  Na: 0-1
KIN-DEPT-13052910 HS S3-2-45 (0.642) AM (Top, 5, H,10000.0,0.00,1.00), Sm (Mn, 2x3.00), Crn (42.43)
TOF MS ES+

Minimum:                  5.0   1.0   1000.0
Maximum:                  5.0   1.0   1000.0

Mass  Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
359.1029  359.1032  -0.3  -0.8  15.5  2773073.3  C21 H15 N2 O4

8,8'-Methylenebis(oxy)diquinoline-2-carbaldehyde (98b)

^{1}H-NMR (CDCl{\textsubscript{3}}, 500MHz)

---

8,8'-(Propane-1,3-diylbis(oxy))diquinoline-2-carbaldehyde (98b)

---

1H-NMR (CDCl{\textsubscript{3}}, 500MHz)
8,8'-(Propane-1,3-diylbis(oxy))diquinoline-2-carbaldehyde (98b)

$^{13}$C-NMR (CDCl$_3$, 100MHz)

Elemental Composition Report

**Single Mass Analysis**

Tolerance = 10.0 ppm / DBE: min = -100.0, max = 100.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions

138 formula(e) evaluated with 1 result within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-23  H: 0-33  N: 0-5  O: 0-6  Na: 0-1

KIN-DEPT: 13009210 HS SB 2.40 (0.749) AM (Cen, 10, 80.00, Ar, 5300.0, 0.00, 1.60); Sm (SG, 2x3.00); Sb (10, 10.00); Cn (34.40)

TOF MS ES+

<table>
<thead>
<tr>
<th>m/z</th>
<th>387.1340</th>
<th>389.1447</th>
</tr>
</thead>
</table>

Minimum: 387.1340  1.5  3.9  15.5  9.6  C23 H19 N2 O4

Maximum: 389.1447  5.0  10.0  100.0

Mass  Calc. Mass  mDa  PPM  DBE  1-FIT  Formula
8,8'-(Butane-1,4-diylbis(oxy))diquinoline-2-carbaldehyde (98c)

$^1$H-NMR (CDCl$_3$, 500MHz)

13C-NMR (CDCl$_3$, 100MHz)

Std Carbon
G149a_C

Sample
G416_d

Sample
G416_f

Sample
G416_e
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
104 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-24  H: 0-25  N: 0-5  O: 0-6  Na: 0-1

1H-NMR (CDCl3, 500MHz)

8.8'-(Butane-1,4-diylbis(oxy))diquinoline-2-carbaldehyde (98c)

HRMS

8.8'-(Pentane-1,5-diylbis(oxy))diquinoline-2-carbaldehyde (98d)

1H-NMR (CDCl3, 500MHz)
Elemental Composition Report

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
100 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0.25  H: 0.26  N: 0.5  O: 0.6  Na: 0.1

KIN-DEPT-130; 2610 HS SSB 45 (0.842) AM (Cen, 10, 80.00, Ar, 5000.0, 0.00, 1.00); Sm (SG, 2x3.00); Sb (10, 16.00); Crn (41, 52)
TOF MS ES+


Minimum:
<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBR</th>
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<th>Formula</th>
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<tbody>
<tr>
<td>415.1668</td>
<td>415.1658</td>
<td>1.0</td>
<td>2.4</td>
<td>15.5</td>
<td>51.1</td>
<td>C25 H23 N2 O4</td>
</tr>
</tbody>
</table>
8,8’-(Hexane-1,6-diylbis(oxy))diquinoline-2-carbaldehyde (98e)

$^1$H-NMR (CDCl$_3$, 500MHz)

8,8’-(Hexane-1,6-diylbis(oxy))diquinoline-2-carbaldehyde (98e)

$^{13}$C-NMR (CDCl$_3$, 100MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
94 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0.26  H: 0.25  N: 0.5  O: 0.6  Na: 0.1

KIN-DEPT.13002010 HS SP 44 (0.824) AM (Con,10, 80.08, Ar,5003.0.00,1.00); Sm (5G, 2c3.00); Sb (16,10.00); Cm (41:64)

TOF MS ES+

Minimum: 429.1822
Maximum: 429.1814

Mass Calc. Mass mDa PPM DBE i-FIT Formula
429.1822 429.1814 0.8 1.9 15.5 8.1  C25 H25 N2 O4

8.8'-(Hexane-1,6-diylbis(oxy))diquinoline-2-carbaldehyde (98e)

HRMS

8.8'-(Heptane-1,7-diylbis(oxy))diquinoline-2-carbaldehyde (98f)

1H-NMR (CDCl3, 500MHz)
## Elemental Composition Report

**Single Mass Analysis**

Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0

Selected filters: None

8,8'-(Heptane-1,7-diylbis(oxy))diquinoline-2-carbaldehyde (98f)

8.8'-{(Heptane-1,7-diylbis(oxy))diquinoline-2-carbaldehyde (98f)}

**HRMS**

**1H-NMR (CDCl3, 100MHz)**

**259**
8,8'-((Octane-1,8-diylbis(oxy))diquinoline-2-carbaldehyde (98g)

$^1$H-NMR (CDCl$_3$, 500MHz)

13C-NMR (CDCl$_3$, 100MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
101 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-29  H: 0-29  N: 0-5  O: 0-6  Na: 0-1

KIN-DEPT-13092010 HS S11 46 (0.861) AM (Cen,10, 80.00, Ar,5000.0,0.00,1.00); Sm (SC, 2x3.00); Sb (10,10.00); Crn (41.56)
T0F MS E5+

Minimum:
Maximum:

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<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>i-FIT</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
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<td>457.2127</td>
<td>0.8</td>
<td>1.7</td>
<td>15.5</td>
<td>38.2</td>
<td>C28 H29 N2 O4</td>
</tr>
</tbody>
</table>

8,8′-(Octane-1,8-diylbis(oxy))diquinoline-2-carbaldehyde (98g)

HRMS

8,8′-(Decane-1,10-diylbis(oxy))diquinoline-2-carbaldehyde (98h)

\[^1\text{H-NMR (CDCl}_3, 500\text{MHz)}\]

261
**Elemental Composition Report**

**Single Mass Analysis**
Tolerance = 5.0 PPM / DBE: min = -100.0, max = 1000.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions

109 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-30  H: 0-33  N: 0-5  O: 0-6  Ne: 0-1

KIN-DEPT-13020101 HS S12 46 (0.831) AM (Cen 10, 60.00, Ar, 5000.0, 0.00, 1.00); Sm (G3, 2x3.00); Sb (10, 10.00); Cm (41.59)

**HRMS**

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>DBE</th>
<th>i-FIT</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>485.2460</td>
<td>485.2460</td>
<td>2.0</td>
<td>4.1</td>
<td>15.5</td>
<td>1.6</td>
<td>C30 H33 N2 O4</td>
</tr>
</tbody>
</table>
2-Formyl-8-hydroxyquinolinium chloride

\[ \text{\(N+CHO\)} \text{OH H Cl-}\]

\(2-\text{Formyl-8-hydroxyquinolinium chloride (99)}\)

\[ ^1\text{H-NMR (DMSO-d_6, 500MHz)} \]

\[ ^{13}\text{C-NMR (DMSO-d_6, 125MHz)} \]
### 1. H-NMR (DMSO-d$_6$, 500MHz)

![1H-NMR spectrum](image)

- **Chemical Shifts:**
  - 0.74 ppm
  - 1.29 ppm
  - 1.021 ppm
  - 2.05 ppm
  - 1.02 ppm

### 13C-NMR (DMSO-d$_6$, 125MHz)

![13C-NMR spectrum](image)

- **Chemical Shifts:**
  - 115.88 ppm
  - 133.238 ppm
  - 129.460 ppm
  - 128.352 ppm
  - 124.254 ppm
  - 123.816 ppm
  - 118.614 ppm
  - 114.195 ppm
  - 51.292 ppm
  - 51.332 ppm
  - 41.206 ppm
  - 40.673 ppm
  - 40.654 ppm
  - 40.628 ppm
  - 40.617 ppm
  - 37.207 ppm
  - 27.327 ppm
  - 25.806 ppm
  - 23.698 ppm
  - 18.650 ppm
  - 16.738 ppm

---

**Std protein**

**GSSic_c_H**

**SAMPLE**

- **Name:** apol
- **Date:** Jan 13 2008
- **Solvent:** DMSO-d$_6$
- **Spectrometer:** Varian INOVA 500 MHz
- **Temperature:** 300 K
- **Protein Concentration:** 20 mM
- **Sample Code:** apol

**Acquisition Parameters**

- **FID:** 5000 Hz
- **Processing:** 32 scans, 2 ppm, 2.024 MHz
- **Display:** 1.2 ppm

**1H-NMR Spectrum**

- **Resonances:**
  - 0.74 ppm
  - 1.29 ppm
  - 1.021 ppm
  - 2.05 ppm
  - 1.02 ppm

---

**Std Carben**

**GSSic_c_C**

**SAMPLE**

- **Name:** apol
- **Date:** Jan 13 2008
- **Solvent:** DMSO-d$_6$
- **Spectrometer:** Varian INOVA 500 MHz
- **Temperature:** 300 K
- **Protein Concentration:** 20 mM
- **Sample Code:** apol

**Acquisition Parameters**

- **FID:** 5000 Hz
- **Processing:** 32 scans, 2 ppm, 2.024 MHz
- **Display:** 1.2 ppm

**13C-NMR Spectrum**

- **Resonances:**
  - 115.88 ppm
  - 133.238 ppm
  - 129.460 ppm
  - 128.352 ppm
  - 124.254 ppm
  - 123.816 ppm
  - 118.614 ppm
  - 114.195 ppm
  - 51.292 ppm
  - 51.332 ppm
  - 41.206 ppm
  - 40.673 ppm
  - 40.654 ppm
  - 40.628 ppm
  - 40.617 ppm
  - 37.207 ppm
  - 27.327 ppm
  - 25.806 ppm
  - 23.698 ppm
  - 18.650 ppm
  - 16.738 ppm

---

264
1,2,3,4-Tetrahydro-2-methylquinolin-8-ol (87a)

$\text{H-NMR(DMSO-d}_6, 500\text{MHz})$

13C-NMR(DMSO-d$_6$, 125MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
5 formula(e) evaluated with 1 result(s) within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-10  H: 0-1000  N: 0-1  O: 0-1

Chan Sau Hing, C02:1b
H-F08_0422_1 15 (0.265) AM (Tet,4, Ht,1CH200,0.0,0.01,1.00); Sm (5G, 2x0.00); Cm (14:29)

1H-NMR (CDCl3, 500MHz)

Minimum: 5.0  10.0 50.0

Mass  Calc. Mass  mDa  PPM  DBR  i-PIT  Formula
164.1080  164.1075  0.5  3.0  4.5  0.3  C10 H14 N O

8-Butoxy-1,2,3,4-tetrahydro-2-methylquinolin-8-ol (87a)
HRMS

1H-NMR (CDCl3, 500MHz)

8-Butoxy-1,2,3,4-tetrahydro-2-methylquinolin-8-ol (87b)

1H-NMR (CDCl3, 500MHz)
**Elemental Composition Report**

**Single Mass Analysis**

Tolerance = 100.0 PPM / DBE: min = -1.5, max = 60.0

Selected filters: None

- Monoisotopic Mass, Even Electron Ions
- 14 formula(s) evaluated with 1 results within limits (all results (up to 1000) for each mass)

**Elements Used:**
- C: 0-17
- H: 0-1000
- N: 0-1
- O: 0-1

Chen Bau Hing, Q395b
HR07_0516_6A 151 (2.847) AM (Top.4, Mt:1000.0,0.0,0.0,0.00,0.00); Smg (SG, 2x3.00); Sb (15,10.00); Cm (141:172) 220.1698

**HRMS**

8-Butoxy-1,2,3,4-tetrahydro-2-methylquinoline (87b)

8-Butoxy-1,2,3,4-tetrahydro-2-methylquinoline (87b)

**Minimum:**

- 220.1698

**Maximum:**

- 220.1701

**Mass**  | **Calc. Mass** | **mDa** | **PPM** | **DBE** | **i-FIT** | **Formula**
---|---|---|---|---|---|---
220.1698 | 220.1701 | -0.3 | -1.4 | 4.5 | 0.7 | Cl4 H22 N O
2-Methyl-1,2,3,4-tetrahydroquinolin-8-yl acetate (87c)

$^1$H-NMR (CDCl$_3$, 500MHz)

2-Methyl-1,2,3,4-tetrahydroquinolin-8-yl acetate (87c)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Odd and Even Electron Ions
18 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-12  H: 0-1000  N: 0-1  O: 0-2  Ne: 0-1
Chn Sau Hing, CO44b

8-(Benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87d)
1H-NMR (CDCl3, 500MHz)

Minimum:
Maximum:

Mass  Calc. Mass  mDa  DPM  DBE  i-FIT  Formula
206.1184   206.1181  0.3   1.5   5.5   0.4  C12 H16 N O2

8-(Benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87d)
1H-NMR (CDCl3, 500MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 100.0 PPM
Selected filters: None

Monoisotopic Mass, Even Electron Ions
5 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-17  H: 0-1000  N: 0-1  O: 0-1

Chao Sau Hing, Q042b
HR07_0516_10_75 (1.419) AM (Con) 4.80.00, H: 1.0000.0, 0.00.1.000; Sm (SC, 2.00); Sb (15.10.00); Cm (75,75) TDF MS ES+ 120,142

Minimum:       -1.5
Maximum:       5.0  100.0  60.0
Mass     Calc. Mass mDa  PPM  DBE  i-FIT  Formula
254.1542  254.1545  -0.3  -1.2  8.5  0.7  C17 H20 N O
8-(3-Nitrobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87e)

$^1$H-NMR (CDCl$_3$, 500MHz)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 60.0
Selected filers: None

Monoisotopic Mass, Even Electron Ions
16 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-17  H: 0-100  N: 0-2  O: 0-3

Chen Sau Hing, Q075b
HR06_0303_11238 (4.483) AM (Top, 4, Ht, 10000, 0.0, 60, 1.00), Sm (SG, 3x0.00), Cm (224.246)
296.1405

8-(3-Nitrobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87e)

HRMS

8-(4-Nitrobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87f)

1H-NMR (CDCl3, 500MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 80.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-17 H: 0-100 N: 0-2 O: 0-3

HRMS (TOF) ES+
1.41e3

Minimum: 500.0 50.0 50.0
Maximum: 299.1345 299.1396 0.9 3.0 9.5 9.6 Cl7 H19 N2 O3
**8-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87g)**

**1H-NMR (CDCl₃, 500MHz)**

**13C-NMR (CDCl₃, 125MHz)**

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**Std proton Q7TH_B**

Sample: 87g

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**Std Carbon Q7TH_C**

Sample: 87g

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275
Elemental Composition Report

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 80.0 8-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87g)
Selected filters: None

Monoisotopic Mass, Even Electron Ions
7 formula(e) evaluated with 1 results within limits (all results up to 1000) for each mass
Elements Used:
C: 0-13  H: 0-100  N: 0-1  O: 0-2
Chan Sau Hing, C077b
HRMS 0303_1210 (3.957) AM (Top,4, Hi,10000,0,0,90,1.00); Snr (SG, 3x3.00); Sb (10,10.00 ); Cm (210.246)
264.1557

Minimum: 500.0 50.0 -1.5
Maximum: 500.0 50.0

Mass  Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
284.1657  284.1651  0.6  2.1  8.5  0.4  C18 H22 N O2

8-(3-Methoxybenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87h)
1H-NMR (CDCl3, 500MHz)

276
Elemental Composition Report

**Single Mass Analysis**

Tolerance = 50.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
7 formula(s) evaluated with 1 results within limits (all results up to 1000) for each mass

**Elements Used:**

C: 0-18  H: 0-100  N: 0-1  O: 0-2

Chan Sau Hirg. Q178D
HR6_0303_14_194 (3.658) AM (Top,4; Ht,1000;0.6,0.60,1,60); Sm (5G, 3x3.00); Cm (170,195) 284.1657

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**Minimum:**

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**4-((1,2,3,4-Tetrahydro-2-methylquinolin-8-yloxy)methyl)benzonitrile (87i)**

**1H-NMR (CDCl₃, 500MHz)**

**13C-NMR (CDCl₃, 125MHz)**
**Elemental Composition Report**

**Single Mass Analysis**
- Tolerance = 50.0 PPM / DBE: min = -1.5, max = 60.0
- Selected filters: None

Monoisotopic Mass, Even Electron Ions
- 1) formula(s) evaluated with 1 results within limits (all results (up to 1000) for each mass)

**Elements Used:**
- C: 0-18
- H: 0-100
- N: 0-2
- O: 0-1

**Micromass QTOF-2**
- HR08_0303_15 47 (0.891) AV (Cen,4, 80.00, Ht,10000.0,0.00,0.00,1.00); Sm (SG, 3x3.00); Sb (10,10.00); Cm (47.60) 270.1510

**Minimum:**
- 1H-NMR (CDCl3, 500MHz)

- Mass Calc. Mass mDa PPM DBE i-FIT Formula
- 279.1510 279.1497 1.3 4.7 10.5 0.3 C18 H19 N2 O

**8-(Biphenyl-3-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroquinoline (87j)**

**1H-NMR (CDCl3, 500MHz)**

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*Image and additional information related to the chemical structures and spectra have been excluded.*

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279
8-(Biphenyl-3-ylmethoxy)-2-methyl-1,2,3,4-tetrahydroquinoline (87j)

**Elemental Composition Report**

**Single Mass Analysis**

Tolerance = 50.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
8 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0.23  H: 0.100  N: 0.1  O: 0.1

Chen Sau Hing, Q38lib micromass QTOF-2
HR00_0304_1 64 (1.211) AM (Cen,4, 80.00, H+1,10003.0,0.00,1.60); 6m (50, 2.53.30); Om (50.67) 330.1874 0.50 330.1874

Relative Abundance%

Minimum: 500.0  50.0  -1.5
Maximum: 500.0  50.0  60.0

Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
330.1874  330.1858  1.6  4.8  12.5  0.3  C23 H24 N O
**8-(4-(Trifluoromethoxy)benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87k)**

**1H-NMR (CDCl₃, 500MHz)**

**13C-NMR (CDCl₃, 125MHz)**
**Elemental Composition Report**

**Single Mass Analysis**
Tolerance = 50.0 PPM  /  DBE: min = -1.5, max = 60.0

Selected filters: None

Monoisotopic Mass, Even Electron Ions
25 formula(s) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-18  H: 0-100  N: 0-1  O: 0-2  F: 0-3

8-(4-(TFFluoromethoxy)benzylxyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87k)

HRMS

**1H-NMR (CDCl3, 500MHz)**

**8-(4-(Fluorobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87l)**
Elemental Composition Report

Single Mass Analysis
Tolerance = 50.0 PPM  /  DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
8 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-17  H: 0-100  N: 0-1  O: 0-1  F: 0-1

Chan Sau Hing, Q082b
HR08_0394_3 101 (1.007) AM (Top,4, Hi,10000,0,0,0,0,1,00); Sn (SG, 2x3.60); Cm (100:125)

8-(4-Fluorobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87l)

HRMS

8-(4-Fluorobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87l)

8-(4-Fluorobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87l)
8-(4-(Trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87m)

1H-NMR (CDCl₃, 500MHz)

8-(4-(Trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87m)

13C-NMR (CDCl₃, 125MHz)

std proton
Q03m_H

8-(4-(Trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87m)

8-(4-(Trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87m)
Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 60.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
17 formula(s) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-18  H: 0-100  N: 0-1  O: 0-1  F: 0-3

Chan Sau Hing, Q83b
HR08_C934_1.271 (5.134) AM (Top,4,Hi;10000.0,0.06,1.00); Sm (SS, 2x3.00); Cm (268.291)
322.1417

Minimum: 
Maximum: 500.0  10.0  60.0

Mass  Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
322.1417  322.1419  -0.2  -0.6  8.5  0.4  C18 H19 N O F3

8-(4-(Trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydro-
2-methylquinoline (87m)

1H-NMR (CDCl3, 500MHz)
**8-(4-Chlorobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87n)**

**Elemental Composition Report**

**Single Mass Analysis**

Tolerance = 60.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
9 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-17  H: 0-100  N: 0-1  O: 0-1  Cl: 0-1

Chen Sau-Hung, Q04b
HR03_0304_2 62 (1.73) AM |Cen,4, 80.00, H1,120(0.00.00.1.00)| Sm (SG, 2x3.00), Cm (34.65)

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**HRMS**

8-(4-Chlorobenzyloxy)-1,2,3,4-tetrahydro-2-methylquinoline (87n)
8-(3,5-Bis(trifluoromethyl)benzyl oxy)-2-methyl-1,2,3,4-tetrahydroquinoline (87o)

$^1$H-NMR (CDCl$_3$, 500MHz)

8-(3,5-Bis(trifluoromethyl)benzyl oxy)-2-methyl-1,2,3,4-tetrahydroquinoline (87o)

$^{13}$C-NMR (CDCl$_3$, 100MHz)
Elemental Composition Report

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
599 formulae evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-19 H: 0-18 N: 0-3 O: 0-4 F: 0-6 Na: 0-1 K: 0-1

Kin-Det: C12H1S1 N10 127 (2.356) CH (Con4, 60.00, A9) Sn (80, 2x3.00) Sb (60, 10.40, 00) Cm (?127.152)

TOF MS ES+

N
HOH
Br

5,7-Dibromo-2-methyl-1,2,3,4-tetrahydroquinoline (87a)
1H-NMR (DMSO-d6, 500MHz)

8-(3,5-Bis(trifluoromethyl)benzyloxy)-2-methyl-1,2,3,4-tetrahydroquinolin-8-ol (87a)

HRMS

5,7-Dibromo-2-methyl-1,2,3,4-tetrahydroquinoline-8-ol (96a)

1H-NMR (DMSO-d6, 500MHz)
Elemental Composition Report

**Single Mass Analysis**
Tolerance = 50.0 PPM  /  DEE: min = -1.5, max = 50.0
Selected filters: None

Monoisotopic Mass, Even Electron Ions
13 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:
C: 0-10  H: 0-1000  N: 0-1  O: 0-1  Br: 0-2

Penny Chan. CO9f1b
HR8g_0714_4.413 (7.669) AM (Cm2, 80.00, H,100000.00,0.00,1.00); Sm (SG, 2x3.03); Cm (397.425)

Minimum: 5.0
Maximum: 50.0

Mass Calc. Mass mDa PPM DEE i-FIT Formula
319.9261 319.9266 -2.5 -7.8 4.5 111.8 C10 H12 N O Br2
1-Phenylethanol (89a)

1H-NMR (CDCl₃, 500MHz)

1-Phenylethanol (89a)

13C-NMR (CDCl₃, 125MHz)
**1-(4-Chlorophenyl)ethanol (89b)**

**1H-NMR (CDCl3, 500MHz)**

![1H-NMR Spectrum](image)

**13C-NMR (CDCl3, 125MHz)**

![13C-NMR Spectrum](image)
1-(4-Bromophenyl)ethanol (89d)

^1^H-NMR (CDCl$_3$, 500MHz)

13C-NMR (CDCl$_3$, 125MHz)
1-(2-Methoxyphenyl)ethanol (89e)

$^{1}H$-NMR (CDCl$_3$, 500MHz)

$^{13}C$-NMR (CDCl$_3$, 125MHz)
1-(3-Methoxyphenyl)ethanol (89f)

$^1$H-NMR (CDCl$_3$, 500MHz)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
1-(4-Methoxyphenyl)ethanol (89g)

$^1$H-NMR (CDCl$_3$, 500MHz)

13C-NMR (CDCl$_3$, 125MHz)
1-o-Tolylethanol (89h)

$^1$H-NMR (CDCl$_3$, 500MHz)

$^{13}$C-NMR (CDCl$_3$, 125MHz)

I-o-Tolylethanol (89h)
1-m-Tolylethanol (89i)

1H-NMR (CDCl₃, 500MHz)

13C-NMR (CDCl₃, 125MHz)
$\text{1-H-NMR (CDCl}_3, 500\text{MHz)}$

$\text{13-C-NMR (CDCl}_3, 125\text{MHz)}$
1-Phenylopropan-1-ol (89k)

**1H-NMR (CDCl₃, 500MHz)**

![NMR Spectrum](image1)

**13C-NMR (CDCl₃, 125MHz)**

![NMR Spectrum](image2)
**1-(4-(Trifluoromethyl)phenyl)ethanol (89l)**

**1H-NMR (CDCl₃, 500MHz)**

**13C-NMR (CDCl₃, 125MHz)**
1-(Naphthalen-2-yl)ethanol (89m)

$^1$H-NMR (CDCl$_3$, 500MHz)

1-(Naphthalen-2-yl)ethanol (89m)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
Cl OH

(2-Chlorophenyl)(phenyl)methanol (89n)

$^1$H-NMR (CDCl$_3$, 500MHz)

Cl OH

(2-Chlorophenyl)(phenyl)methanol (89n)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
Phenyl(4-(trifluoromethyl)phenyl)methanol (89o)

$\text{Ph}_3\text{C}$

$\text{OH}$

Phenyl(4-(trifluoromethyl)phenyl)methanol (89o)

$^1$H-NMR (CDCl$_3$, 500MHz)

Phenyl(4-(trifluoromethyl)phenyl)methanol (89o)

$^{13}$C-NMR (CDCl$_3$, 125MHz)
Reference


50. Khunt, R. C.; Datta, N. J.; Bharmal, F. M.; Mankad, G. P.; Parikh, A. R. 


84. Reetz, M. T.; Li, X. G. *Chemical Communications* 2006, 2159-2160.


156. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley-Interscience: New York, **1979**.


205. Lam, K. H., The Hong Kong Polytechnic University, *2004*.
