Enantioselective Synthesis of Mefloquine Analogs and Their Derivatives

by

Akira Nakamura

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This thesis was presented

by

Akira Nakamura

It was defended on

November 20th, 2009

and approved by

Dr. Dennis P. Curran, Department of Chemistry

Dr. Toby Chapman, Department of Chemistry

Thesis Director: Dr. Peter Wipf, Department of Chemistry

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Mefloquine is a clinically useful anti-malarial compound active against strains of the *Plasmodium* parasite. The behavioral effects of each of the enantiomers of mefloquine were assessed. Clear quantitative differences were observed between the two enantiomers. The (+)-(11*R*,12*S*)-enantiomer showed higher activity against *Plasmodium falciparum*. Another study revealed that the (-)-(11*S*,12*R*)-enantiomer specifically binds to adenosine A_{2A} receptors more strongly than the (+)-(11*R*,12*S*)-enantiomer, in the central nervous system. Progress has been made toward the enantioselective synthesis of (+)-(11*R*,12*S*)-8-chloromefloquine analog. An enantiometically pure product was obtained by using hydrozirconation followed by a zinc-palladium catalyzed Negishi cross-coupling reaction and a Sharpless dihydroxylation as key steps.

A series of mefloquine analogs have been developed to facilitate future structure-activity relationships and the development of new antimalaria agents. A recent study suggested an increase in the potency with electron-withdrawing groups at both the 2- and 8-positions of the quinoline ring. According to this concept, six new 8-position derivatives were synthesized via a palladium mediated coupling reaction.

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LIST OF ABBREVIATIONS

Ac……..acetyl

AIBN……..2,2'-azobisisobutyronitrile

Bn……...benzyl

Boc…….tert-butoxycarbonyl

CuTc.....copper(I) thiophene-2-carboxylate

Cp……..cyclopentadienyl

Cy……..cyclohexyl

DEAEA….2-diethylaminoethylamine

DIAD…….diisopropyl azodicarboxylate

DMAP……4-dimethylaminopyridine

DMA……..dimethylacetamide

DMF……..dimethylformamide

DMP……..2,2-dimethoxypropane

dpppe……1,5-bis(diphenylphosphino)pentane

dppf……...1,1'-bis(diphenylphosphino)ferrocene

MS…….molecular sieve

NMP……..*N*-methyl-2-pyrrolidone, *N*-methylpyrrolidone

Pd_2dba_3…..palladium dibenzylideneacetone

PPA……polyphosphoric acid

py……...pyridine

rt…….room temperature

SFC……super fluid chromatography

THF……tetrahydrofurane

TFA……trifluoroacetic acid

TMS…….. trimethylsilyl

Ts……4-toluene sulfonic

μW …….microwave

WRAIR…. Walter Reed Army Institute of Research

1.0 INTRODUCTION

Falciparum malaria is an infectious disease caused by *Plasmodium falciparum*, a protozoan parasite, transmitted by the female Anopheles mosquitoes. *P. falciparum* is one of the most dangerous infections and often leads to death unless diagnosed early. Approximately 300 million cases of *falciparum* malaria occur, and more than a million people, mainly children, die each year.[1] This major public health problem is aggravated by the widespread resistance to one or more anti-malarial drug in the last three decades. The mechanisms by which the parasite is chemoresistant to antimalarials generally involve chromosomal mutations.[2]

Quinine was the first effective treatment for malaria caused by *P. falciparum*, appearing in chemotherapeutics in the 17th century. It remained the antimalarial drug of choice until the 1940s when other drugs replaced it. Since then, many anti-malarial drugs were developed to protect U.S. troops from malaria, particularly during World War II. Chloroquine, primaquine, proguanil, amodiaquine, sulfadoxine and pyrimethamine were all developed during this time (Figure 1).[3] Chloroquine is very cheap and, until recently, was very effective, which made it the antimalarial drug of choice for many years in most parts of the world. However, resistance of Plasmodium falciparum to chloroquine probably arises through the sequential accumulation of mutations and has spread recently from Asia to Africa, making the drug ineffective against the most dangerous Plasmodium strain. Predicting the emergence and spread of resistance to current

antimalarials and newly introduced compounds is necessary for planning malaria control and instituting strategies.[4,5]

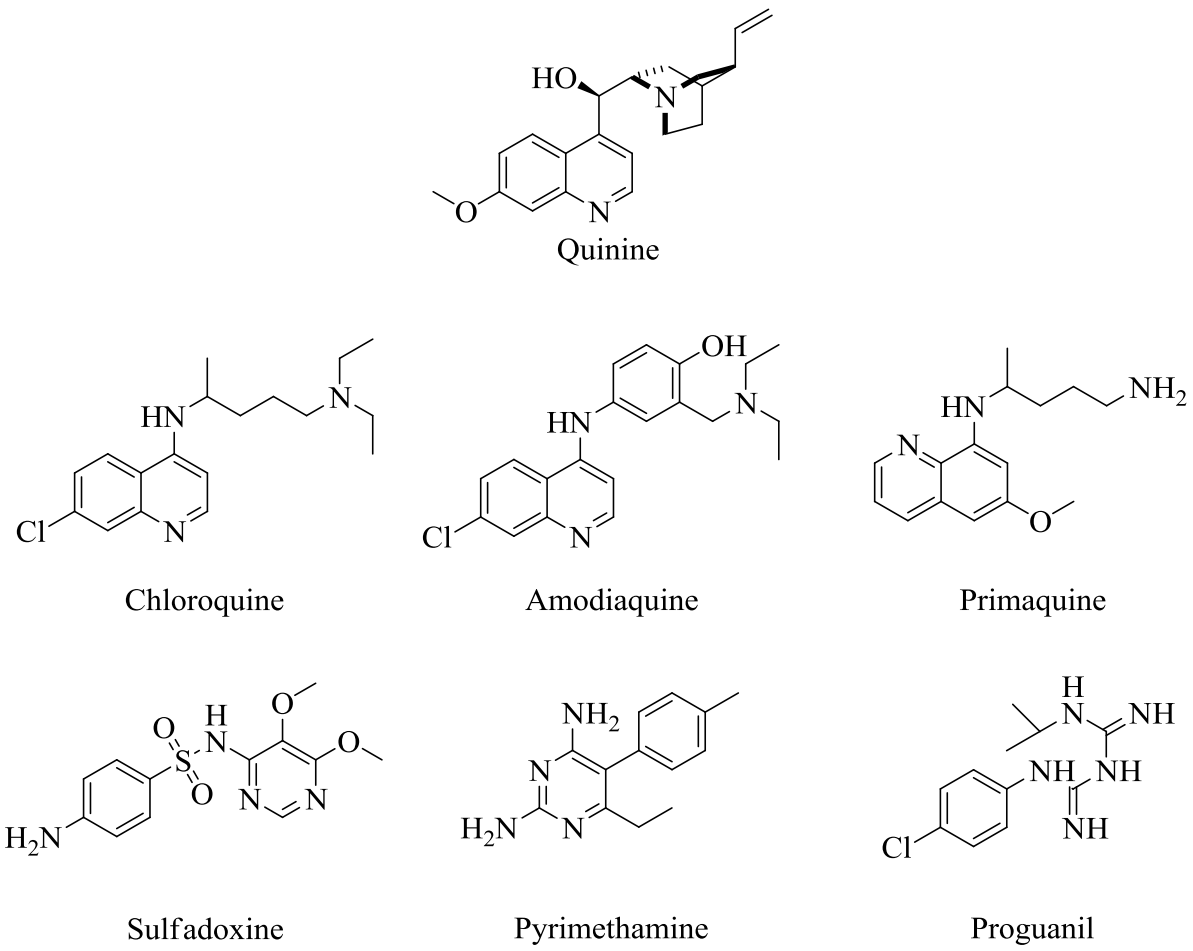


Figure 1. Classical anti-malaria drugs

Mefloquine, a clinically useful anti-malarial compound which is chemically related to quinine and active against strains of the *Plasmodium* parasite, is a product of the US Army's antimalarial research program. It was developed during the Vietnam War, in the beginning of the 1970s, to protect American soldiers from the multi-drug resistant *falciparum* malaria, especially from chloroquine-resistant *Plasmodium falciparum*.[6] Mefloquine has a high cure rate after a

single dose of 250 mg, once a week, and is also efficient in preventing falciparum malaria when taken regularly. It is a very potent blood schizonticide with a long half-life. Its mechanism of action is thought to involve forming toxic heme complexes that damage parasitic food vacuoles.[7] However, resistance to mefloquine began to appear in Asia in 1985, around the time the drug became generally available. Nevertheless, mefloquine is still one of the most effective anti-malarial therapies.

2.0 ENANTIOSELECTIVE SYNTHESIS OF MEFLOQUINE ANALOGS

2.1 INTRODUCTION

The pharmacological activities of each enantiomer of mefloquine were studied and clear quantitative differences were observed. Both of the pure mefloquine enantiomers were shown to be more effective against Plasmodium falciparumI than the racemic mixture, and, furthermore, the (+)-(11*R*,12*S*)-enantiomer showed the highest activity. In 1993, it was reported by Walter Reed Army Institute of Research (WRAIR) that (+)-(11*R*,12*S*)-enantiomer was 1.81 times more active than the (-)-enantiomer against chloroquine sensitive parasites (Sierra Leone D-6 clone) and also 1.69 times more active against chloroquine resistant (Indochina W-2 clone).[9] The actual IC_{50} values were 34.4, 23.4 and 42.3 nM for racemic, (+)-enantiomer and (-)-enantiomer, respectively, against the D-6 clone, and 3.87, 4.09 and 6.61 nM against the W-2 clone. The WRAIR study concluded that the structure of the quinoline ring system containing the piperidine ring was important to differentiate the potency of each enantiomer because none of the enantiomers of acyclic analogs at the piperidine ring site nor any other aromatic system containing the piperidine ring displayed significant differences of activity among their respective enantiomers. Another study, reported in 2002, indicated a similar difference in activity between the two enantiomers against chloroquine resistant strains of *Plasmodium flaciparum* PF.IBS2,

confirming that the (+)-(11*R*,12*S*)-mefloquine enantiomer was more potent than the (-)-enantiomer (Figure 2).[10]

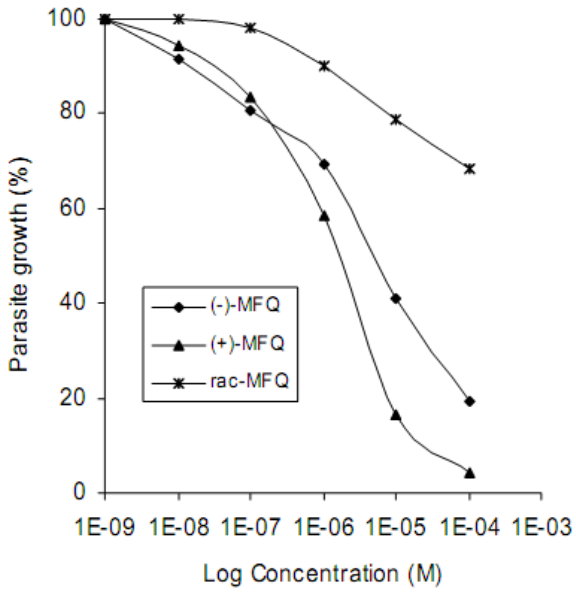
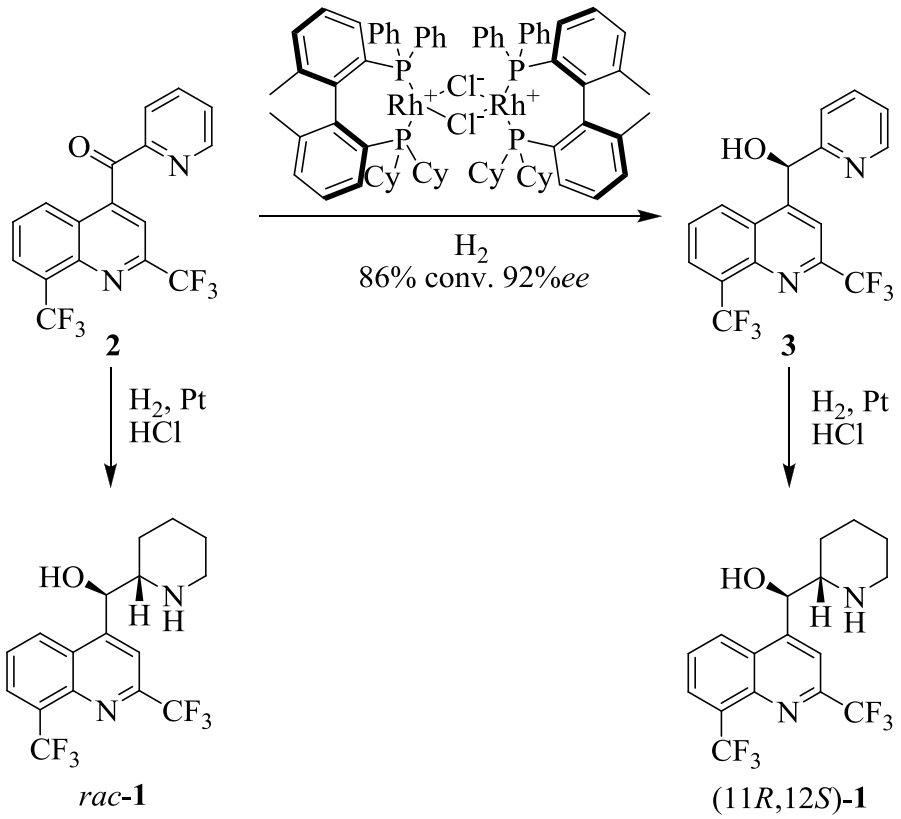


Figure 2. In vitro activity of *rac*- and (±)-mefloquine against *plasmodium falciparum* PF.IBS2[10]

The difference in side-effects for each enantiomer was also investigated. Remarkable differences of adverse effects between the two enantiomers were reported; for example, mice dosed with the (-)-enantiomer of mefloquine displayed clonic seizures, increased reactivity and reduced body weight after 48 h, though none of these effects were observed in mice treated with the (+)-enantiomer.[7] The difference in psychotropic effects was explained by a specific binding of the (-)-enantiomer to adenosine A_{2A} receptors in the central nervous system, with an affinity of 100 times that of the (+)-enantiomer.[11] Nevertheless, exclusive racemic mefloquine is being sold under Roche's trade name Lariam, maybe due to the lower cost and the convenience of the manufactural process for the racemic material.

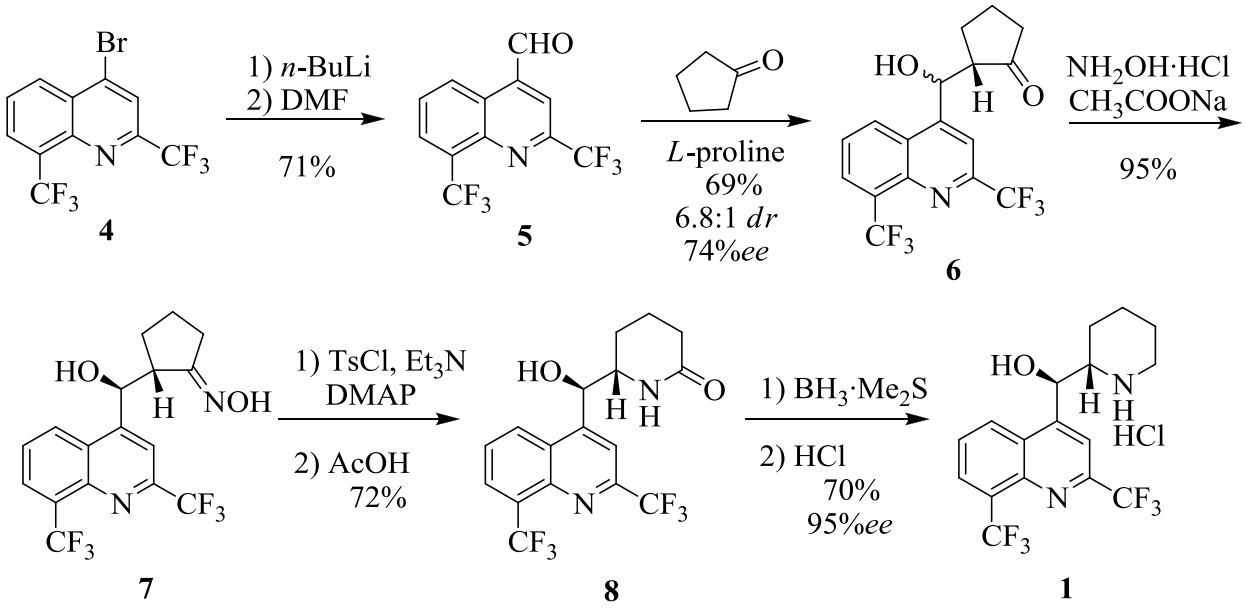
2.2 CLASSIC AND RECENT MEFLOQUINE SYNTHESES

As part of a search for superior anti-malarial drugs, α-dialkylaminomethyl-4-quinolinemethanols were first synthesized in 1946 by Lutz et. al.[12] Since the first synthesis of 2,8-bis(trifluoromethyl)quinolin-4-yl-(2-piperidyl)methanol, mefloquine, was reported in 1971, several synthetic routes have been developed for the preparation of (±)-mefloquine.[13] A popular method was, to first constract ketone **2** or the corresponding racemic alcohol, and then selectively reduce the pyridine ring to furnish (±)-mefloquine **1** (Scheme 1).[14] Chiral resolution methods were developed by Carroll's group for accessing enantiometically pure (+)-(11*R*,12*S*)-mefloquine **1**, and its absolute configuration was determined by comparison of CD spectra of the four optical isomers with the CD spectra of the stereoisomers of ephedrine and cinchona alkaloids in 1974.[15]



Scheme 1. Racemic and asymmetric hydrogenation methods

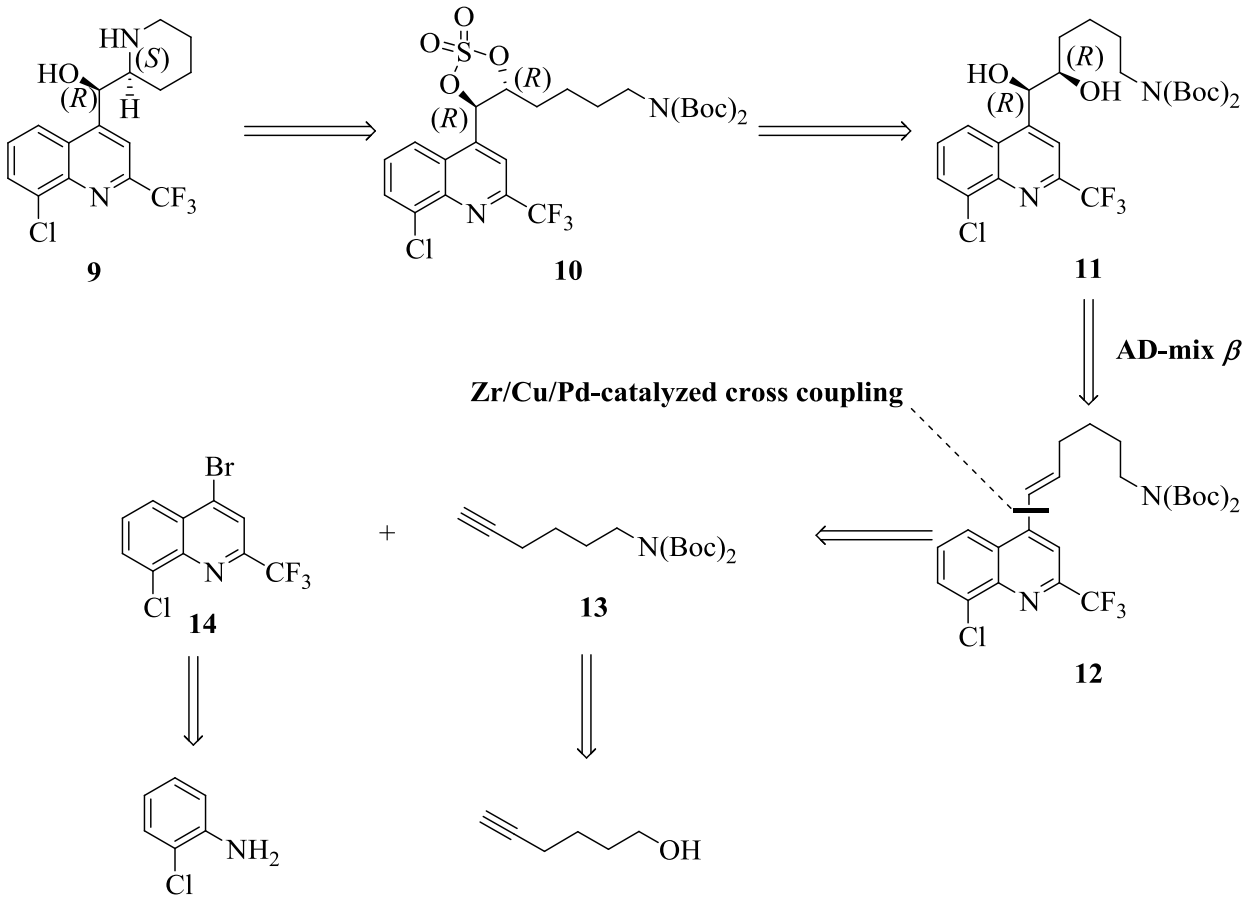
In 1993, the first asymmetric synthesis of (+)-(11*R*,12*S*)-mefloquine was reported by a Roche group using an enantioselective rhodium-catalyzed hydrogenation of α-pyridyl ketone **2** to give the α-pyridyl alcohol **3** in moderate enantiomeric excess.[16] Later, Schmid's group achieved 92%*ee* by using a modified chiral catalyst and subsequent heterogeneous hydrogenation of the pyridine nucleus provided (11*R*,12*S*)-mefloquine **1** (Scheme 1).[17]



Scheme 2. A recent asymmetric synthesis of (11*R*,12*S*)-mefloquine

In 2008, the Zhi-Xiang group reported a new enantioselective synthesis of mefloquine using a proline-catalyzed aldol reaction and a Beckmann rearrangement as key steps (Scheme 2).[18] The synthesis started from the common intermediate 4-bromoquinoline **4**. The corresponding aldehyde **5** was generated by halogen-metal exchange and formylation with DMF. The proline-catalyzed asymmetric direct aldol reaction provided a 6.8:1 ratio mixture of diastereomers **6**. The enantiomeric purity of the desired *syn*-aldol **6** was checked by chiral HPLC analysis to be 74%*ee*. Treatment of **6** with hydroxylamine hydrochloride and sodium acetate gave oxime **7** in quantitative yield. A Beckmann rearrangement under standard conditions afforded the desired lactam **8**. Finally, (11*R*,12*S*)-mefloquine **1** was obtained by the reduction of lactam **8** with borane-dimethyl sulfide complex. The high *ee*, 95%, was explained by a kinetic resolution through an amino alcohol-catalyzed enantioselective reduction of the lactam with borane.[19] The overall yield of this synthesis was 14% over the 7 steps.

2.3 OUR APPROACH TO MEFLOQUINE ANALOGS



Scheme 3. Retrosynthetic analysis of (11*R*,12*S*)-mefloquine analogs **9**

An enantioselective synthesis strategy of the target (11*R*,12*S*) **9** is illustrated in the retrosynthetic format in Scheme 3. Two stereocenters can be established from diol **11** via a cyclic sulfate opening, and the chiral diol **11** could be prepared by a Sharpless asymmetric dihydroxylation of a *trans*-olefin **12**. Alkenylzirconocenes have been useful intermediates since they are easily obtained by hydrozirconation reactions of alkynes.[20] The olefin **12** would be obtained through further palladium-catalyzed cross-coupling reactions of the alkenylzirconocene and 4-

bromoquinoline **14**.[21] Each of the coupling components **13** and **14** can be prepared in 2 steps from commercially available compounds.

2.4 RESULTS AND DISCUSSION

The synthesis of intermediate **14** began with the PPA mediated condensation and subsequent cyclization of *o*-chloroaniline and ethyl 4,4,4-trifluoroacetoacetate to generate **15** in 60% yield (Table 1, entry 1).[22] The reaction worked well on a 5 g scale; however, the yield decreased to 30% on >10 g scale. Another quinolone synthesis method that was tested first formed the trifluoroacetoacetanilide intermediate in the presence of catalytic amounts of *p*TsOH under reflux conditions, followed by an in situ cyclization under vigorous conditions.[23] Unfortunately, the yield did not increase significantly in spite of these attempted optimizations (Table 1, entry 2 to 7).

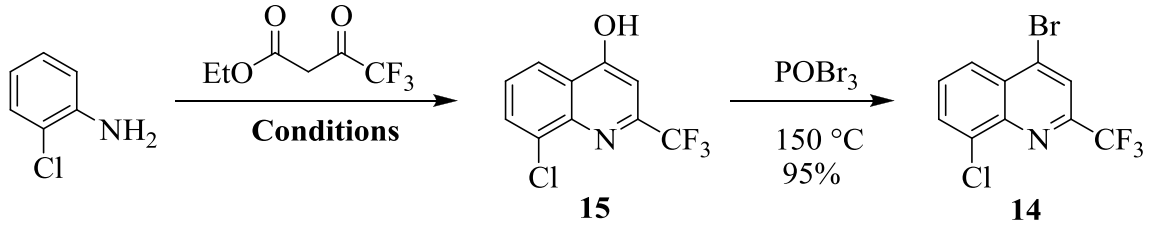
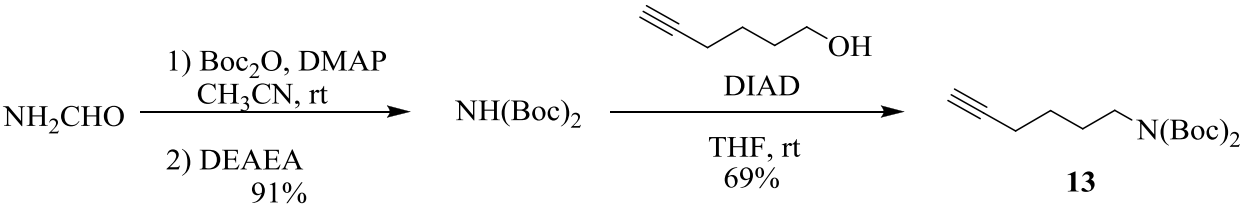


Table 1. Synthesis of intermediate quinoline **15**

Entry	Additive / Solvent	Conditions	Yield[%]
1	PPA	150 °C, 6 h	60
2	*p*TsOH, PhH / Ph_2O	100 °C, 8 h then 230 °C, 14 h	34
3	*p*TsOH, PhH / Ph_2O	100 °C, 8 h then 250 °C, 30 h	12
4	*p*TsOH, PhH / Ph_2O	100 °C, 8 h then 210 °C, 8 h	43
5	*p*TsOH, PhH / Ph_2O	100 °C, 8 h then 250 °C, 0.5 h[a]	36
6	*p*TsOH, Ph_2O	250 °C, 1 h[a]	30
7	*p*TsOH, PhH / PhPh	100 °C, 8 h then 210 °C, 14 h	33

[a] Irradiated in microwave.

Quinolone **15** was then reacted with $POBr_3$ at 150 °C, forming the corresponding 4-bromo-8-chloro-2-trifluoromethylquinoline **14** in 95% yield.



Scheme 4. Synthesis of intermediate **13**

Di-*t*-butyl iminodicarbonate was prepared by a literature procedure.[24] Treatment of formamide with 2 equivalents of di-*t*-butyl dicarbonate in the presence of catalytic amounts (10 mol%) of 4-dimethylaminopyridine (DMAP) generated di-Boc-formamide. Addition of 2-

diethylaminoethylamine (DEAEA) cleaved the formyl group to provide di-*t*-butyl iminodicarbonate. The 91% yield was better than the reported 80%. The Mitsunobu reaction of 5-hexyl-1-ol and di-*t*-butyl iminodicarbonate with diisopropyl azodicarboxylate (DIAD) formed intermediate **13** in 69% yield.[25]

Several conditions were explored for the cross-coupling reaction of fragments **16** and **14** (table 2). First, alkenylzirconocene **16** was generated *in situ* by hydrozirconation of fragment **13** with 1.1 equivalent of Schwartz's reagent in THF at room temperature. *In situ* transmetalation with CuCl afforded the corresponding copper species. Subsequently, the cross-coupling was expected to proceed with bromoquinoline **14** in the presence of a catalytic amount of $Pd(PPh_3)_4$.[21] however, target olefin **12** was not isolated and a quantitative amount of bromoquinoline **14** was recovered, even when the temperature was increased to reflux (Table 2, entry 1). The solvent system was found to be critical for the reaction and 30% of (*E*)-olefin **12** was isolated when a 1:2 mixture of THF and NMP was used as a solvent (Table 2, entry 2). Alternative copper sources were also investigated, and copper(I) thiophene-2-carboxylate (CuTc) gave a slightly better 40% yield of olefin **12** (Table 2, entry 4).

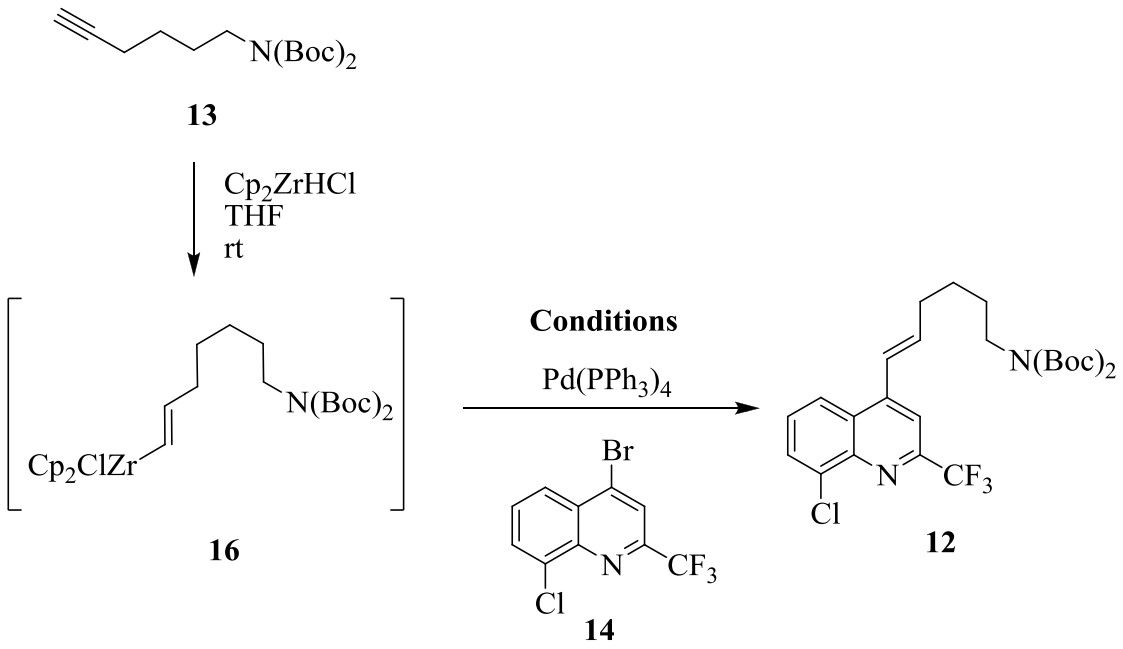
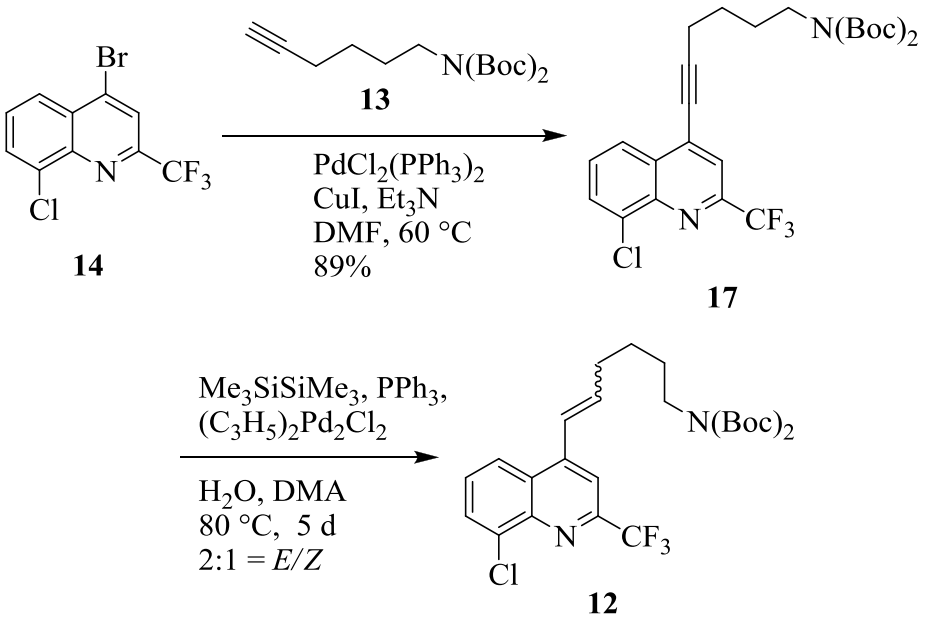


Table 2. Zr/M/Pd coupling conditions for *E*-olefin **12**

Entry	Additive (1.1 eq)	Solvent	Temp.	Time [h]	Yield of **12** [%]
1	CuCl	THF	rt to reflux	8	NR
2	CuCl	1:2 THF/NMP	rt	14	30
3	CuCl	1:2 THF/NMP	0	48	NR
4	CuTc	1:2 THF/NMP	rt	24	40
5	$ZnCl_2$	THF	rt to reflux	8	NR
6	$ZnCl_2$	1:2 THF/NMP	rt	14	25
7	$ZnCl_2$	1:2 THF/NMP	rt	14	NR
8	$ZnCl_2$	1:2 THF/NMP	0	48	NR
9	$ZnCl_2$	1:2 THF/NMP	50	14	NR
10	$ZnCl_2$	1:1 THF/NMP	rt	14	50
11	$ZnCl_2$	2:1 THF/NMP	rt	14	52

In a similar protocol, Negishi reported the palladium catalyzed cross-coupling with alkenyizirconocenes *via* sequential transmetalation with $ZnCl_2$.[26, 27] THF turned out to be an

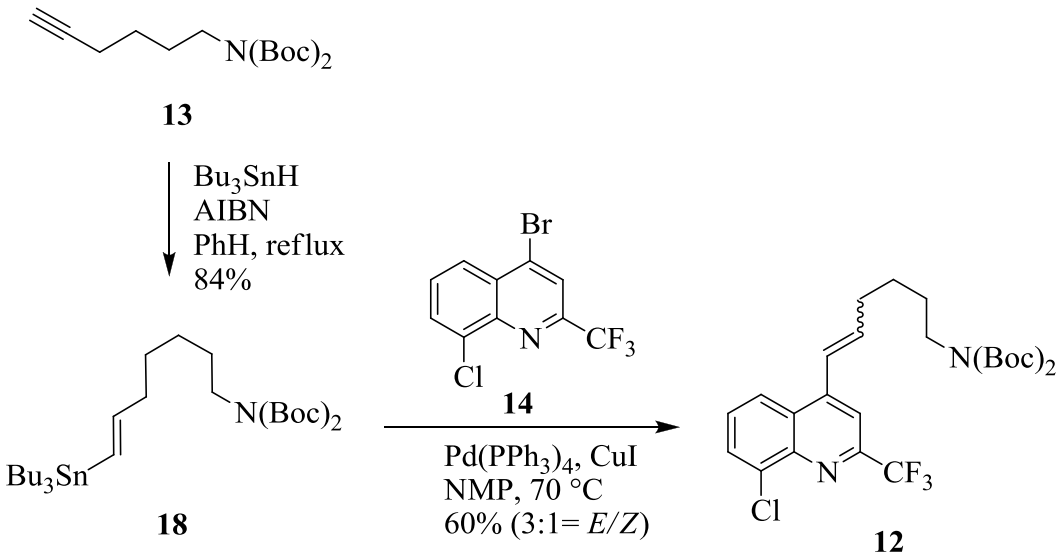
ineffective solvent (Table 2, entry 5). However, 25% of the target (*E*)-olefin **12** was isolated in a 1:2 ratio of the THF/NMP solvent system at room temperature (Table 2, entry 6). The reaction temperature was found to be equally important as the solvent system (Table 2, entries 7 to 9). Finally, 52% of (*E*)-olefin **12** were obtained by using a 2:1 ratio of THF/NMP at room temperature (Table 2, entry 11).



Scheme 5. Synthesis of intermediate **12** by alkyne reduction

Since the yield of the Zr/Cu/Pd or the Zr/Zn/Pd cross-coupling was not sufficient, another approach to form the (*E*)-olefin **12** was employed (Scheme 4). In 2005, Hayashi found a combination of hexamethyldisilane and deuterium oxide could be used as a deuterium transfer reagent for alkynes in the presence of a catalytic amount of a palladium complex to give (*E*)-olefines predominantly.[28] For example, they reported that a quantitative amount of stilbene was isolated in a >99:1 *E*/*Z* selectivity when diphenylacetylene was used as a starting material.

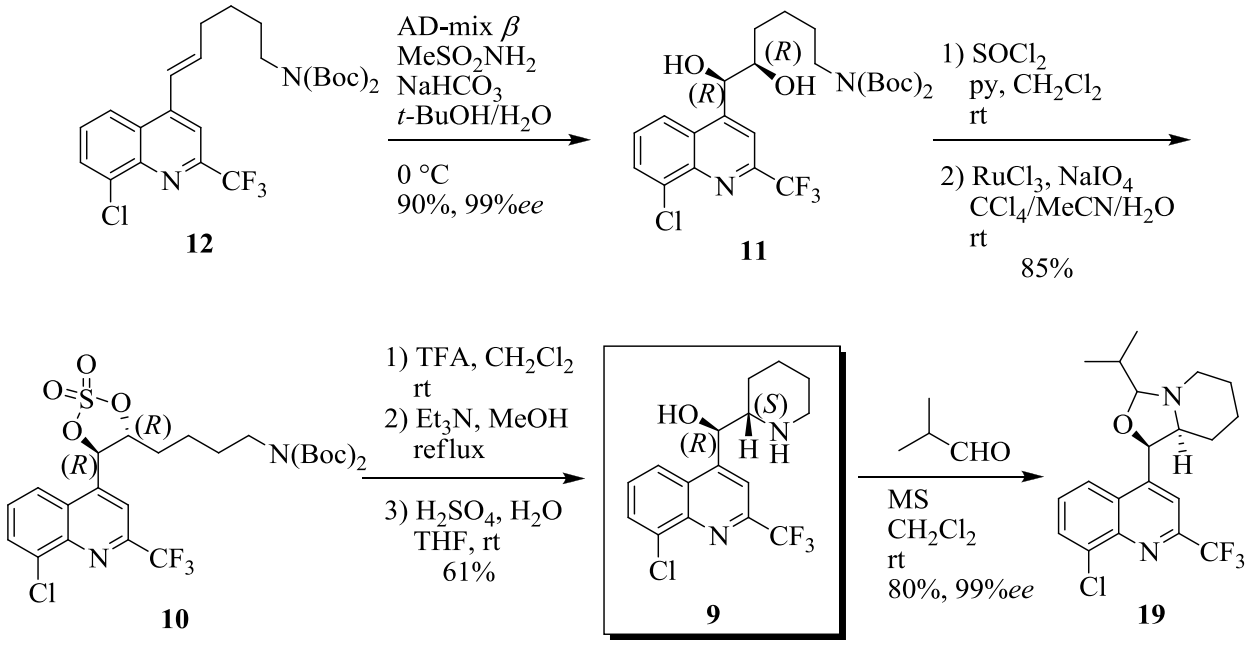
Intermediate **17** was obtained in 89% yield via standard Sonogashira reaction of fragments **13** and **14**. Then, following a procedure by Hayashi, the formation of (*E)*-alkene **12** was expected to result from the isomerization of the corresponding (*Z*)-derivative. Unfortunately, the isomerization occurred only partly after 5 days under thermal conditions and resulted in a 2:1 ratio mixture of (*E*/*Z*)-**12** according to a ^{1}H NMR analysis of the crude material.



Scheme 6. Synthesis of intermediate **12** by Stille coupling

Alternatively, a Stille coupling was also used to form **12** (Scheme 6). Remarkably, when (*E*)-stannane **18**, prepared in 84% yield from **13** by a standard protocol,[29] was heated in NMP in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI, a 3:1 ratio of *E/Z* mixture of olefin **12** was isolated in 60% yield. Isomerization during Stille couplings is precedented but in most cases this effect is observed with *tri*-substituted alkenyl stannanes.[30, 31]

In a similar fashion, a Suzuki coupling could be applied to form (*E*)-olefine **12**. However, deprotection of the Boc-group occurred when intermediate **13** was treated with catecholborane in THF at room temperature.



Scheme 7. Synthesis of (11*R*,12*S*)-8-chloro mefloquine analog **9**

The Sharpless asymmetric dihydroxylation of olefin **12** by AD-mix β proceeded very well to generated diol **11** in 90% yield and 99%*ee* based on chiral HPLC analysis comparing to the corresponding racemic diol.[32] Diol **11** was treated with $SOCl_2$ in the presence of excess pyridine to avoid the deprotection of the Boc-groups by the HCl generated *in situ.* The corresponding cyclic sulfite was formed quite cleanly, and the crude material was oxidized by a catalytic amount of $RuCl_3$ at room temperature to give sulfate **10** in 85% yield over 2 steps.[33] Finally, the deprotection of **10** with TFA, followed by opening of the cyclic sulfate by the primary amine in the presence of Et_3N formed the desired two stereocenters. Acidic hydrolysis with sulfuric acid generated the mefloquine analog **9** in 61% yield over 3 steps.[33] To determine the enentiomeric excess, **9** was treated with isobutyraldehyde in the presence of molecular

sieves to generate **19**. An *ee* of 99% was detected by SFC analysis in comparison to the corresponding racemic **19**, prepared in the next chapter.

2.5 CONCLUSION

The enantioselective synthesis of the mefloquine analog **19** was achieved in 14% overall yield and 11 steps with excellet enantiomeric selectivity. The key step for generating the *E*-olefin intermediate was a Zr/Zn/Pd cross-coupling reaction. This process proceeded under mild conditions after optimization of the solvent system. Accordingly, this method may find general use in the synthesis of *E*-olefins from aryl halides.

3.0 LIBRARY SYNTHESIS OF MEFLOQUINE ANALOGS

3.1 INTRODUCTION

Currently, many anitimalarial drugs are available for therapy, but the rate of expansion of drug-resistant malaria strains is likely to limit future treatment options. Mefloquine resistance has grown in South Asia as well as East Africa within the 6 years that mefloquine has been introduced as a treatment for regular *falciparum* induced malaria.[8] Therefore, the development of next-generation mefloquine analogs is required to address the emerging resistance.

From a screening program carried out at the WRAIR, an initial SAR for quinoline ring modified mefloquine analogs has emerged.[34] These analogs have been used to analyze the three-dimensional interaction between the drug and its target, which can facilitate the design of new antimalarial drugs. The study concluded that electronic features rather than steric factors were the primary effectors of antimalarial potency. Based on the results of a biological assay and a computational calculation, the group also proposed to increase the potency with electron-withdrawing groups such as CF_3- or phenyl or phenyl ether groups substituted by a halogen- or CF_3- function at both the 2- and 8-positions of the quinoline ring. Various analogs with halogen, phenyl or functionalized arene groups at the 2-position were synthesized; replacement of CF_3- by a 4-CF_3-benzene group increased antimalarial activity by about 20%.

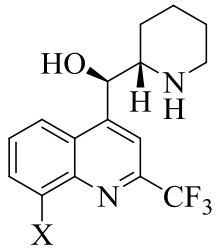


Table 3. Antimalarial activity of C8-mefloquine analogs[34]

Compound		Activity[a]
Mefloquine	X = -CF_3	1
WR228974	X = -Cl	0.03
WR117107	X = -F	NC[b]
WR073879	X = -CH_3	NC

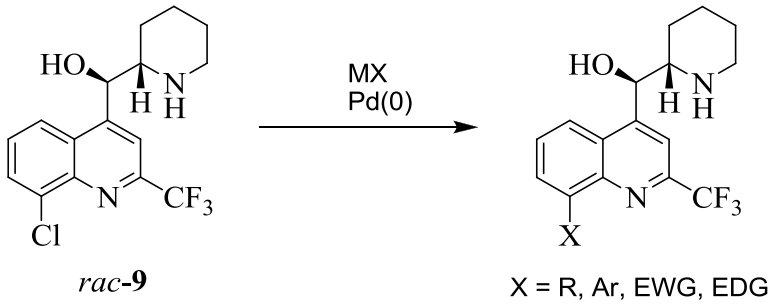
[a] The in vivo activity of the test compound is expressed in terms of the molar ratio of the 50% curative dose of mefloquine hydrochloride to that of the test compound. [b] Not curative.

So far, only three C8-mefloquine analogs were synthesized and tested for biological activity (Table 3). The purpose of this project is to recognize a trend toward improved antimalarial potency by building a library of 8-position analogs of mefloquine. The result of these biological studies would provide further information about the steric environment, lipophilicity, electronic properties and hydrogen bonding donating and accepting effects, that are crucial to achieve antimalarial efficacy.

3.2 SYNTHETIC STRATEGY

Aryl bromides have been of interest for chemists as precursors of other functionalized arenes, providing an entry point to a wide variety of compounds through metal-catalyzed couplings reactions or other substitution processes. Because of their moderate accessibility and reactivity,

these building blocks have been commonly used in medicinal chemistry as starting materials for library synthesis.[35] In contrast, aryl chlorides have generally been considered to be unreactive for metal-catalyzed cross-coupling reactions, but the recent development of new catalysts has allowed an expansion of their utility as synthetic intermediates. Indeed, these systems have been used in Stille[36] or Suzuki reactions[37] using palladium catalysis and in cross-coupling reactions with Grignard[38] or organozinc reagents[39] using nickel catalysis. Thus, the synthetic approach to C8-analogs involved the use of this new aryl chloride chemistry (Scheme 8).



rac-**9**

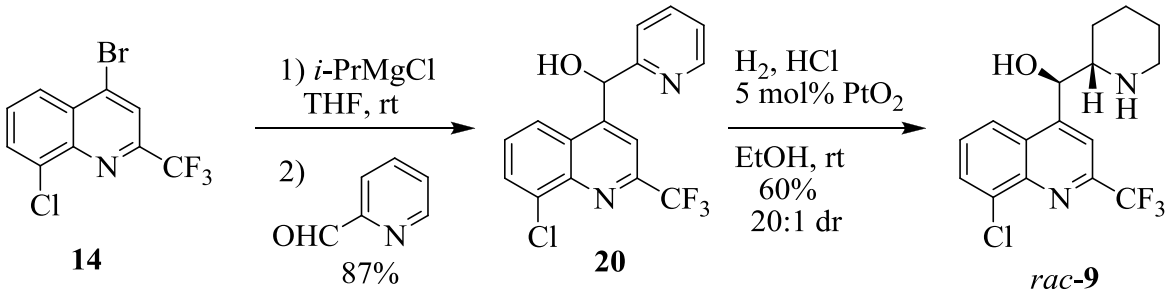
Scheme 8. Synthetic approach to C8-analogs

3.3 RESULT AND DISCUSSION

3.3.1 Racemic synthesis of 9

As shown in chapter 2, the enantioselective synthesis was accomplished but was not sufficiently scalable, and therefore the classical racemic synthesis, reported by Lutz, was chosen to prepare intermediate **9** on scale.[14] Intermediate **20** was obtained in 87% yield; first, the corresponding Grignard reagent was generated by treating **14** with 1.5 equivalent of *iso*-propyl magnesium

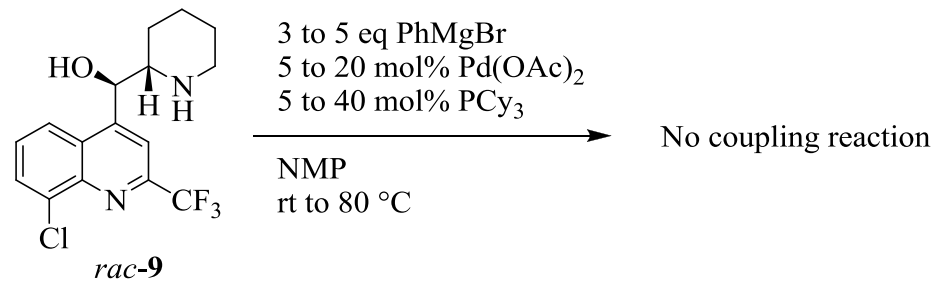
chloride and then the reagent was quenched with 2-pyridinecarboxaldehyde (Scheme 9). Hydrogenation of **20** in the presence of a Brønsted acid and a catalytic amount of platinum oxide gave mefloquine analog **9**. However, the product was found to be a 5:1 mixture of diastereomer according to ^{1}H NMR analysis. A clearly related 5.7:1 ratio of diastereomers was obtained in quantitative yield when naphthylpyridyl alcohol was hydrogenated with platinum oxide at room temperature.[40] Several solvents were tested for recrystallization, and finally a 60% yield of a 20:1 ratio diastereomers of *rac*-**9** was obtained on gram scale by recrystallization using MeOH.



Scheme 9. Classical racemic synthesis of intermediate *rac*-**9**

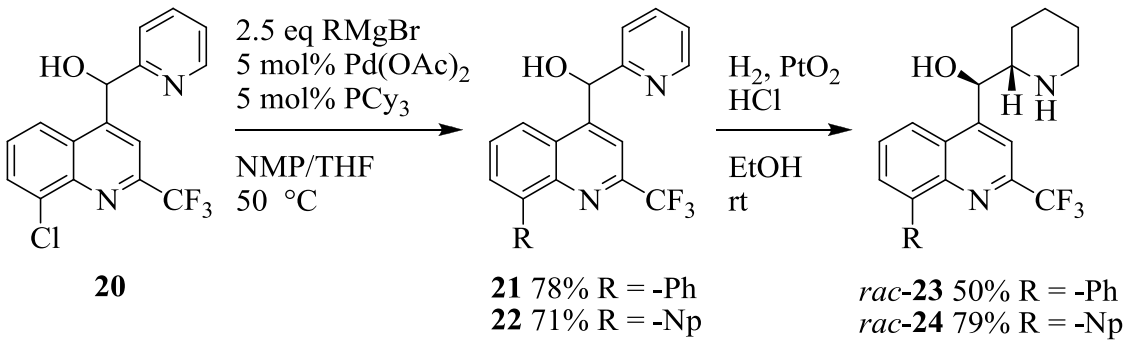
3.3.2 Kumada coupling

In 2002, the Beller group developed a novel method for the palladium-catalyzed cross-coupling of alkyl chlorides and Grignard reagents which provided good to excellent yields at room temperature.[41] As a result of the high reactivity of the palladium catalyst system, we explored the Kumada coupling for the coupling of intermediate *rac*-**9** (Scheme 10).



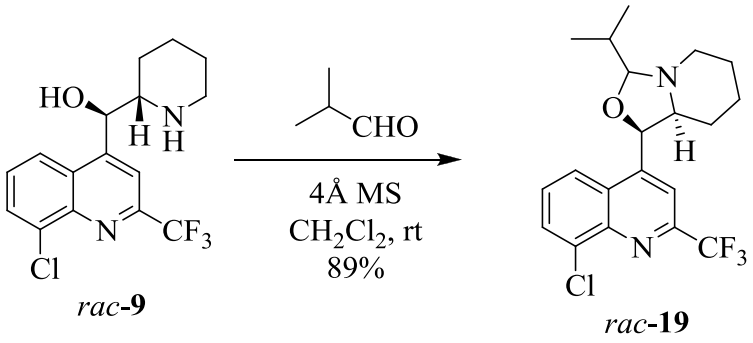
Scheme 10. Initial attempt of applying the Kumada coupling

Initial attempts aimed to react *rac*-**9** and a THF solution of phenyl magnesium bromide in the presence of catalytic amounts of $Pd(OAc)_2$ and PCy_3 in NMP; however, the starting material was recovered even after increasing the reaction temperature and also the amounts of Grignard reagent, $Pd(OAc)_2$ and PCy_3. The failure of this reaction can be potentially attributed to the chelate effect between the amino alcohol and the palladium catalyst. When the coordination sites of mefloquine were studied, a strongly chelating site was detected and the structure of the N,O-chelate complex of mefloquine with palladium(II) was determined by X-ray diffraction analysis.[42]



Scheme 11. Application of Kumada coupling reaction to form C8 analogs

In contrast to the results obtained for the Kumada coupling reaction of *rac*-**9**, coupling products **21** and **22** were isolated 78% and 71% yield, respectively, by reaction with 2.5 equivalents of Grignard reagent. The preparation of the Grignard reagents followed a genereal protocol; The alkyl or aryl bromide and magnesium turnings were heated at reflux in THF for 1 h under the inert condition. The concentration of these reagents was determined by a titration technique using salicylaldehyde phenylhydrazone as an indicater.[43] The hydrogenation of coupling products **21** and **22** generated the corresponding C8-mefloquine analogs *rac*-**23** and *rac*-**24** in 50% and 79% yield (Scheme 11).



Scheme 12. Formation of the oxazolidine

Another approach was also investigated to overcome the chelating problem by installing an oxazolidine. The oxazolidine ring could easily be prepared by the reaction of 2,2-dimethoxypropane (DMP) and *rac*-**9** in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*TsOH).[44] Unfortunately, the pure oxazolidine was not obtained after a simple work-up and decomposition was observed during the purification by chromatography on silica gel. On the other hand, the desired oxazolidine *rac*-**19** was isolated in 89% yield by treatment of *rac*-**9** with an excess of isobutyraldehyde in the presence of 4Å MS at room temperature (Scheme 12).[45] It is

interesting to note that the oxazolidine *rac*-**19** was formed as a single diastereomer according to the ^{1}H NMR.

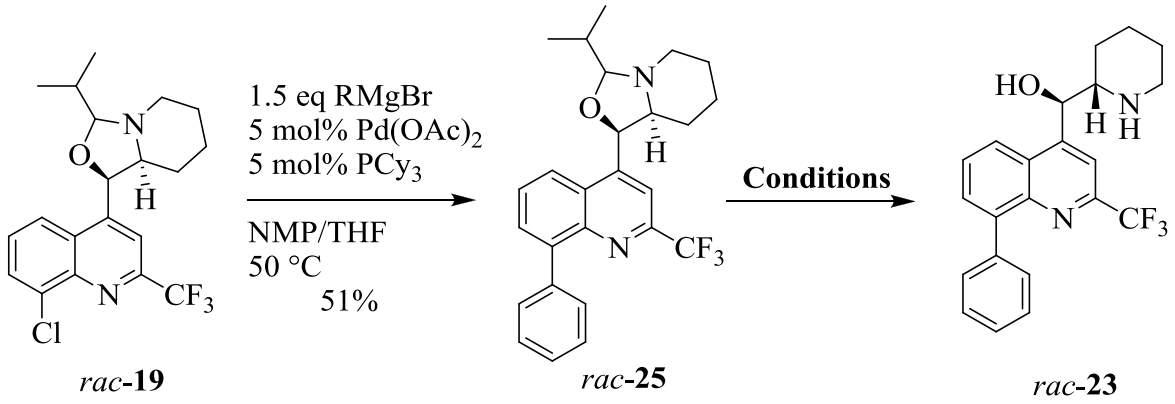


Table 4. Deprotection conditions of oxazolidine *rac*-**25**

Entry	Additive	Solvent	Temp.	Time	Result[a]
1	*p*TsOH	MeOH	rt	3 d	NR
2	HCl	MeOH	rt	3 d	NR
3	$FeCl_3$-SiO_2	$CHCl_3$	rt	1 d	NR
4	HCl, 1,3-propanedithiol	CF_3CH_2OH	rt	12 h	quant.
5	*p*TsOH, neopentylglycol	MeOH	rt	18 h	quant.

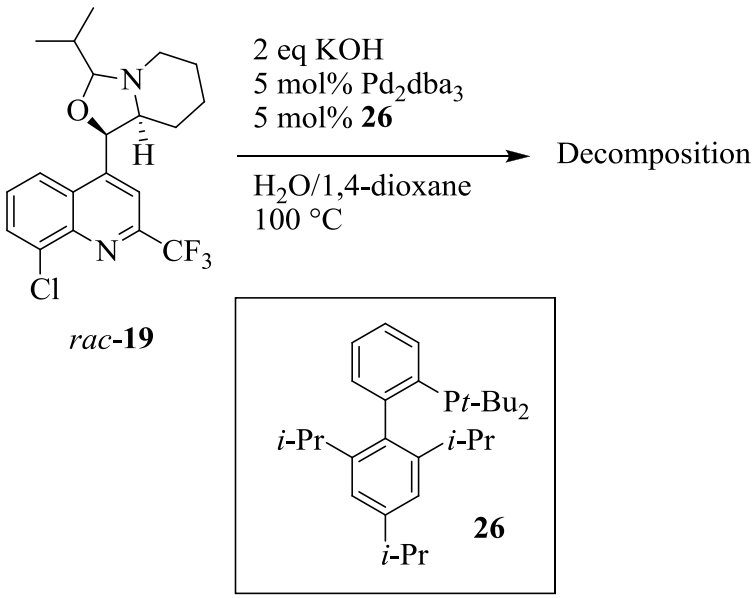
[a] Based on TLC analysis.

As mentioned previously, Kumada couplings were successfully performed in the absence of the amino alcohol group (Scheme 10). The purification by chromatography was found to be very difficult because of the similar polarity of the starting material *rac*-**19** and the coupling product *rac*-**25**, even though the coupling products were easily observed in the crude ^{1}H NMR and TLC analyses. Therefore, the seemingly straightforward deprotection was applied without further purification, but the conventional protocols were unsuccessful (Table 5, entry 1 and 2).[46,47] The $FeCl_3$-SiO_2 reagent has been well established for the cleavage of acetals in

chloroform at room temperature.[48] The reaction was supposed to be finished in a couple of hours, but most of the starting material was recovered after 1 day (Table 5, entry 3). In contrast, Corey's protocol using HCl and 1,3-propanedithiol in trifluoroethanol as a solvent, worked well at room temperature (Table 5, entry 4).[49] Finally, the deprotection was successful in a mixture of *p*TsOH and neopentylglycol (2,2-dimethyl-1,3-propanediol) in methanol (Table 5, entry 5), and provided the desired C8 analog *rac*-**22** in quantitative yield.

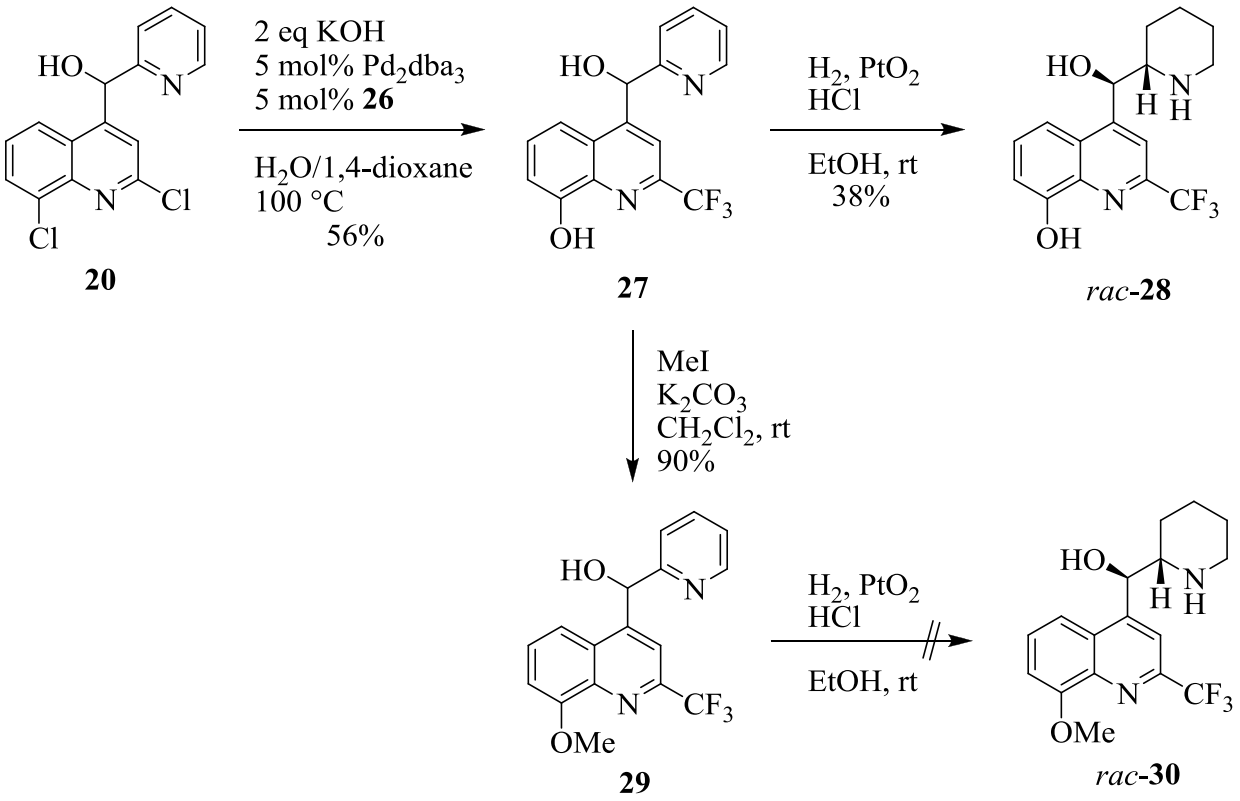
3.3.3 Phenol synthesis from arylchoride

Phenols are widespread in nature and are common products in synthetic chemistry. Aryl halides would be suitable precursors to phenols but, generally, reactions that convert aryl halides to phenols in the absence of a catalyst require strongly basic conditions, high temperatures, and elevated pressures.[50] In 2006, Buchward reported a palladium-catalyzed formation of C-O bonds was an effective method for the construction of phenols from aryl halides in the presence of bulky, monodentate phosphine ligands.[51] Intermediate *rac*-**19** was treated with KOH in the presence of a catalytic amount of Pd_2dba_3 and *tert*-butyl X-phos ligand **26** in a mixture of degassed water and 1,4-dioxane (Scheme 12); however, no desired phenol was isolated even though all starting material *rac*-**19** was consumed, implying that the oxazolidine ring was not significantly stable to relatively strong base under thermal conditions.

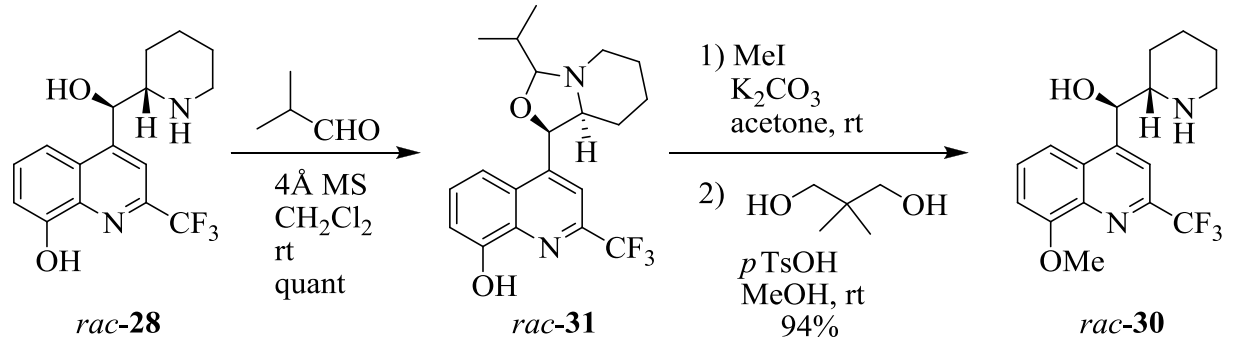


Scheme 13. Initial attempt at phenol synthesis from *rac*-**19**

In contrast, the Buchward protocol worked well using intermediate **20** under slightly harsher conditions. Conversion was accomplished in the microwave at 120 °C after only 30 min to afford the corresponding phenol **27** in 56% yield (Scheme 14). Subsequently, the hydrogenation with PtO_2 furnished the C8-hydroxy analog *rac*-**28** in 38% yield after recrystalization. At this stage, the C8-methoxy analog was considered to be easily accessible from the corresponding intermediate **29** which was obtained in 90% yield by selective methylation of phenol **27**; however, the hydrogenation of **29** always gave messy products. An overreduction of the quinoline ring was reported as the absence of C2-CF_3- substitution decreased the selectivity of the protonation of the pyridine vs the quinoline ring.[13] The absence of selectively in the presence of the methoxy group on the quinoline ring is reflective of the increase of electron density in the quinoline, which leads to diminished steric interactions and a redistribution of electronic effects.



Scheme 14. Synthesis of C8-O mefloquine derivatives



Scheme 15. Synthesis of the C8-methoxy analog *rac*-**30**

The synthetic strategy was slightly modified to first prepare oxazolidine *rac*-**31** from phenol *rac*-**28** (Scheme 15). Oxazolidine *rac*-**31** was sufficiently pure after a simple work-up and

could be used in the next reaction without any purification. Methylation and deprotection provided a quantitative yield of the desired C8-methoxy analog *rac*-**30**.

3.3.4 Nitrile synthesis

Aryl nitriles represent important ingredients for the preparation of dyes, pesticides, agrochemicals, medicines, and bioactive natural products. A variety of synthetic methods for the preparation of aryl nitriles have been developed. The most direct method is the metal catalyzed cyanation of aryl halides.[52] Another well-known protocol is the Rosenmund-von Braun reaction; an aryl halide reacts with copper cyanide to give an aryl nitrile. However, these reactions require relatively high temperatures of up to 150–250 °C, which is incompatible with sensitive substrates. The process is also limited to aryl bromides and iodides. Several metal-catalyzed cross-coupling reactions have been reported, but these methodologies were not applicable for aryl chlorides due to the low reactivity of sp^2-carbon linked chlorides.[53]

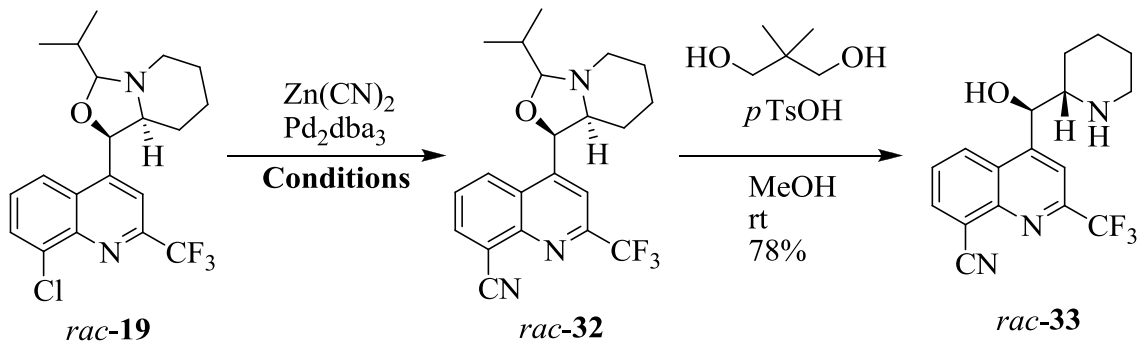


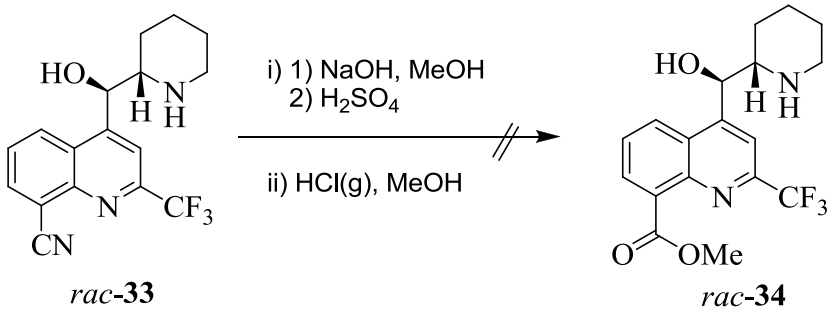
Table 5. Conditions for nitrile coupling

Entry	Ligand	Solvent	Temp.[°C]	Time [min]	Yield of *rac*-**19** [%]
1	dppf	DMF	160[a]	30	0[b]
2	S-phos	NMP	160[a]	30	0[b]
3	S-phos	NMP	140[a]	30	25
4	S-phos	NMP	130[a]	30	.47
5	S-phos	NMP	130	60	38
6	S-phos	NMP	110	60	0[c]

[a] Irradiated in microwave. [b] *rac*-**19** was consumed but no *rac*-**32** was isolated. [c] *rac*-**19** was recovered.

In 2000, the first successful palladium catalyzed cyanation coupling of aryl chlorides was published by the DuPont Company.[54] Following the reported protocol, intermediate *rac*-**19** was treated with 0.6 equivalent of zinc cyanide in the presence of a catalytic amount of Pd_2dba_3 and 1,1'-bis(diphenylphosphino)ferrocene (dppf) in DMF at 160 °C under microwave conditions for 30 min (Table 5, entry 1). The reaction was repeated twice, but no target cyanide *rac*-**32** was isolated. An alternative, more efficient protocol was reported by the Merck Company in 2006.[55] They found that the 2-(2',6'-dimethoxybiphenl-yl)dicyclohexylphosphine (S-phos) ligand was a more effective promoter of the cyanation of aryl chlorides than dppf or 1,5-bis(diphenylphosphino)pentane (dpppe) under either microwave-assisted or thermal conditions. However, only a baseline spot was found by TLC analysis of a reaction performed at 160 °C

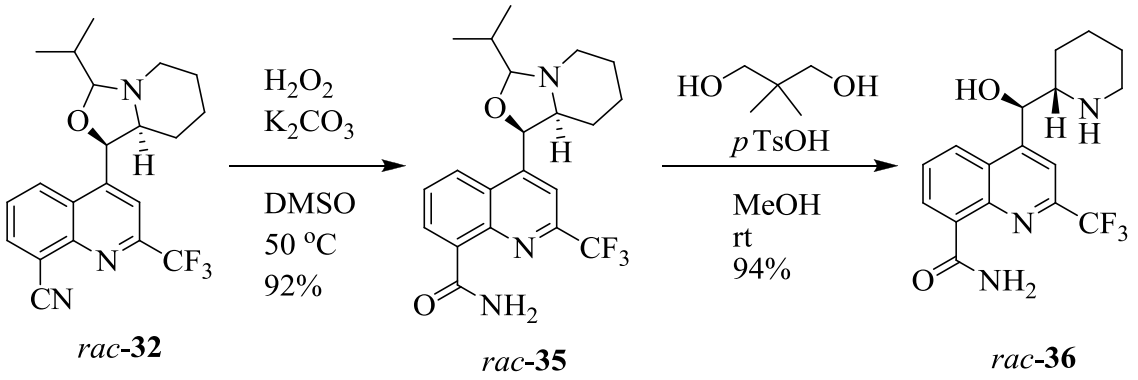
under microwave conditions (Table 5, entry 2). In contrast, 25% of nitrile *rac*-**32** was isolated under milder conditions (Table 5, entry 3). Finally, nitrile *rac*-**32** was prepared in 47% yield by heating a reaction mixture at 130 °C for 30 min in the microwave (Table 5, entry 4). The coupling also proceeded under thermal conditions, but the resulting yield was lower (Table 5, entry 5). The deprotection of nitrile *rac*-**32** gave the C-8 nitrile analog *rac*-**33** in 78% yield.



rac-**33** *rac*-**34**

Scheme 16. Hydrolysis of nitrile *rac*-**33**

Acid- or base-catalyzed hydration of a nitrile is a method frequently used for the preparation of the corresponding carboxylic acids or esters, occurring in two steps through an intermediate amide. The selective hydrolysis of a nitrile to an amide is difficult to achieve, because the amide is often more easily hydroyzed than the nitrile.[57] Classical methods for the nitrile hydrolysis were applied to *rac*-**33**,[56, 58] however, two of these general methods resulted in messy reaction mixture (Scheme 16).



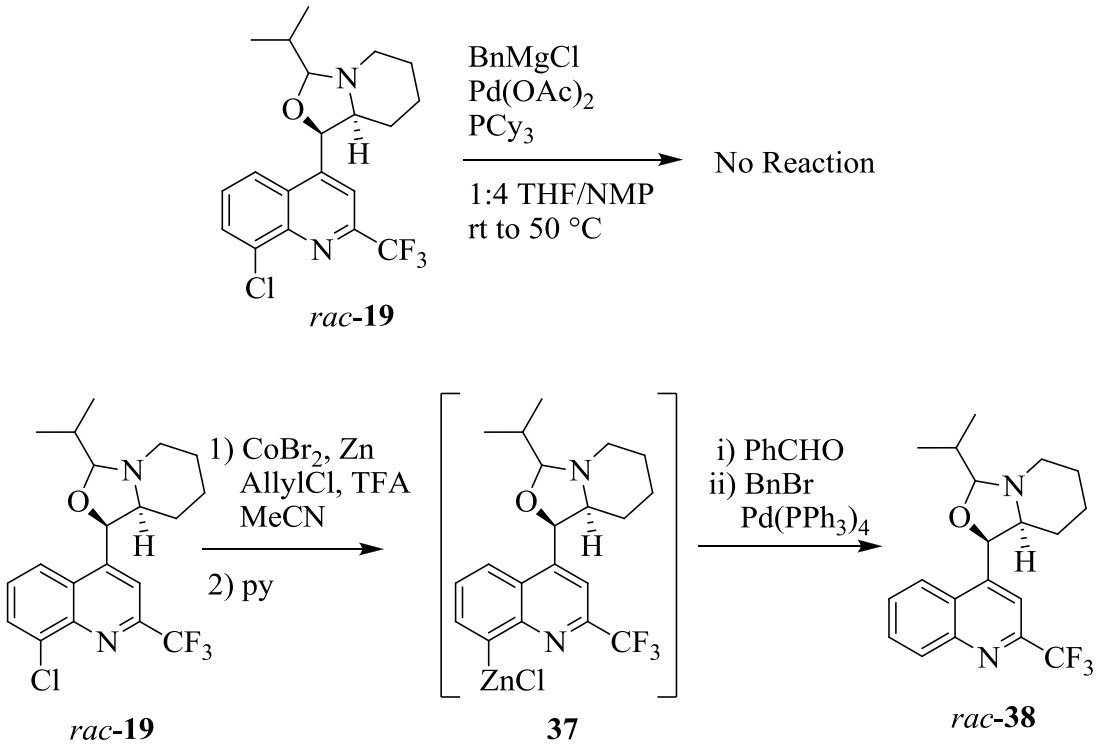
Scheme 17. Synthesis of C8-amide *rac*-**36**

The conversion of nitriles to the corresponding primary amides can also be performed with hydrogen peroxide under basic conditions.[57] Actually, this reaction proceeded very well for nitrile *rac*-**32** at 50 °C, even though no reaction occurred at room temperature, and the primary amide *rac*-**35** was isolated in 92% yield. The deprotection of *rac*-**35** afforded the C8-primary amide analog *rac*-**36** in 94% yield. Further attempts to generate the C8-carboxy acid or ester failed.

3.3.5 Negishi coupling

In an attempt to synthesize C8-benzyl analogs, the Kumada coupling protocol was applied to intermediate *rac*-**19** using commercially available benzyl magnesium chloride at room temperature or 50 °C, but no reaction was observed (Scheme 18). The stability of benzyl magnesium chloride in NMP could be the problem with this process. In 2005, the Gosmini group reported a method for the preparation of an aryl zinc species from the corresponding aromatic chlorides in a mixture of acetonitrile and pyridine, using cobalt catalysis. A subsequent Negishi reaction allowed the preparation of the desired coupling product in modest yield.[59] Intermediate *rac*-**19** was treated with commercially available zinc dust activated by traces of TFA in the

presence of $CoBr_2$ (0.33 equiv) in acetonitrile–pyridine at room temperature. The resulting organozinc species was quenched with benzaldehyde or applied to the Negishi coupling with benzyl bromide. Unfortunately, in both cases, the corresponding *rac*-**38** was isolated as the major product. Most likely, the stability of the organozinc intermediate **37** is inefficient in these reactions.

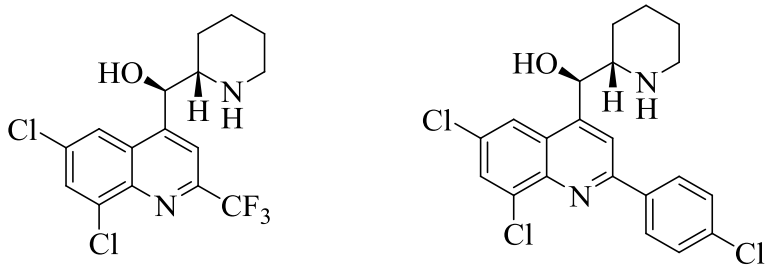


Scheme 18. Attempt toward the synthesis of a C8-benzyl analog

3.4 SELECTIVE COUPLING OF BIS-CHLOROQUINOLINE SYSTEM

3.4.1 Regioselectivity of quinoline

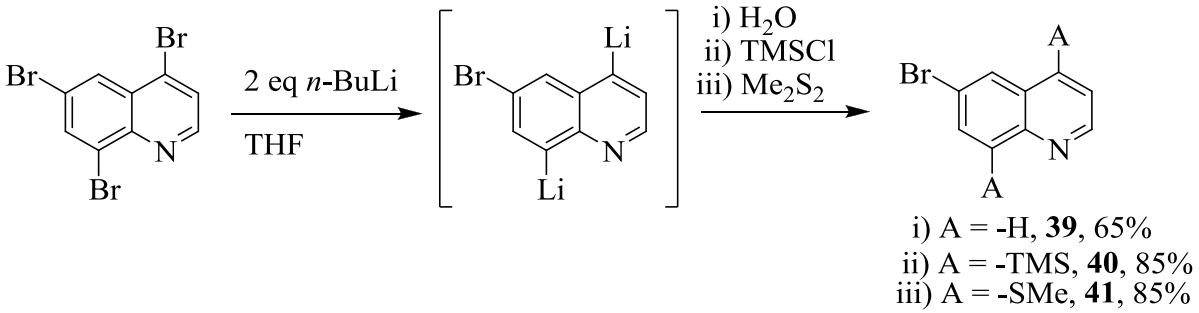
Bis- and trichloromefloquine analogs of WR226253 and WR007936 have curative antimalarial activity in vivo, showing lower IC_{50}'s for several *P. flaciparum* strains and lower neurotoxicity than mefloquine (Figure 3).[60] It is therefore worthwhile to develop analogs for next-generation anti-malarial drugs.



WR226253 WR007936

Figure 3. Bis-chloro and trichloromefloquine analogs

The regioselective preparation of bis-halo-quinolines is of great interest since they are useful starting materials for a number of polyfunctionalized quinolines. Therefore, the regioselective synthesis of these compounds can be valuable for the development of multifunctionalized quinoline derivatives. Some precedence has been reported regarding the regioselectivities of C2 versus C4 or C4 versus C8 sites of dihaloquinolines.[61]



Scheme 19. Regioselective metalation of tribromoquinoline

In 2008, the regioselective metalation of 4,6,8-tribromoquinoline was demonstrated via a lithium–halogen exchange reaction.[61] Treatment of 4,6,8-tribromoquinoline with 2 equivalents of *n*-BuLi followed by quenching with electrophiles, water, trimethylsilyl chloride (TMSCl), or dimethyl disulphide (Me_2S_2), proceeded regioselectively at C4 and C8 sites and afforded the corresponding 4,8-disubstituted-6-bromoquinolines (Scheme 19).

3.4.2 Selective Kumada coupling

Following the procedure developed previously for the Kumada coupling of aryl chlorides, the regioselectivity of the bischloroquinoline **42** was explored as a test substrate. When 2.5 equivalents of PhMgBr were used, the crude ^{1}H NMR showed a 1:3 ratio of mono-coupling product **43** and bis-coupling product **44** (Table 6, entry 1). Several conditions were tested but the products were mixtures of mono- and bis-coupled quinolines (Table 6, entry 2 to 4). According to these results, a secondary cross-coupling reaction could be applied before consumption of the starting materials at room temperature. Fortunately, the differential reactivity of starting material **42** and mono-coupling product **43** was apparent when the reaction was performed at 0 °C (Table 6, entry 6). Finally, only the mono-coupling product **43** was generated when the reaction was

quenched after 4 h (Table 6, entry 7). However, because of the similar polarities, the product and starting material could not be well separated.

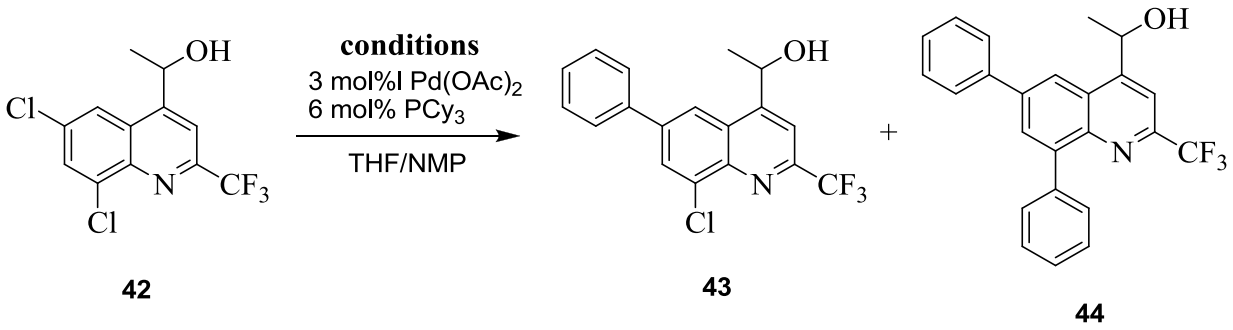
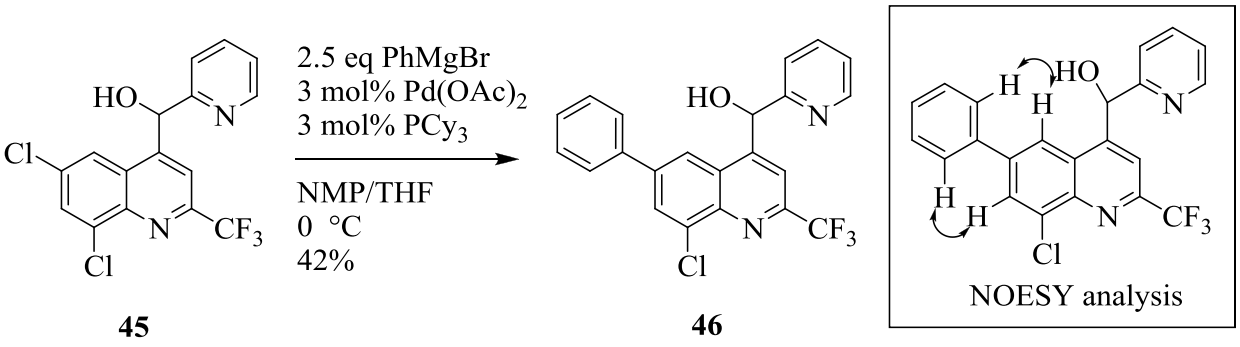


Table 6. Conditions for selective Kumada coupling

Entry	Additive	Temp.	Tiem[h]	Result[a]		
				42	**43**	**44**
1	2.5 eq PhMgBr	rt	24	0	1	3
2	1.2 eq PhMgBr	rt	24	4	2	1
3	2.0 eq PhMgBr	rt	24	2	1	1
4	2.0 eq PhMgBr	rt	12	3	2	1
5	4.0 eq PhMgBr	rt	3	0	0	1[b]
6	2.5 eq PhMgBr	0 °C	6	1	4	1
7	2.5 eq PhMgBr	0 °C	4	2	3	0

[a] Relative ratio of coupling products **43**, **44** and starting material **42** were determined by ^{1}H NMR of the crude mixture. [b] Only isolated **44** in 83% yield.

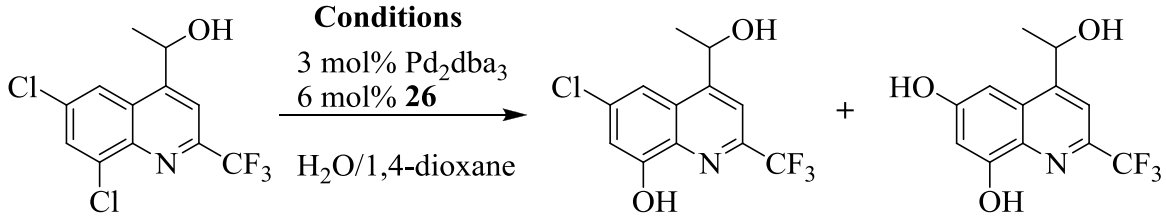
The optimized conditions found above were applied to bischloro-mefloquine precursor **42**, and a 47% yield of the mono-coupling product **43** was achieved (Scheme 20). The coupling site was determined by NOESY analysis, showing couplings both C6 and C8 protons on quinoline ring with *ortho*-protons on the benzene ring.



45 **46**

Scheme 20. Regioselective Kumada coupling

3.4.3 Selective phenol synthesis



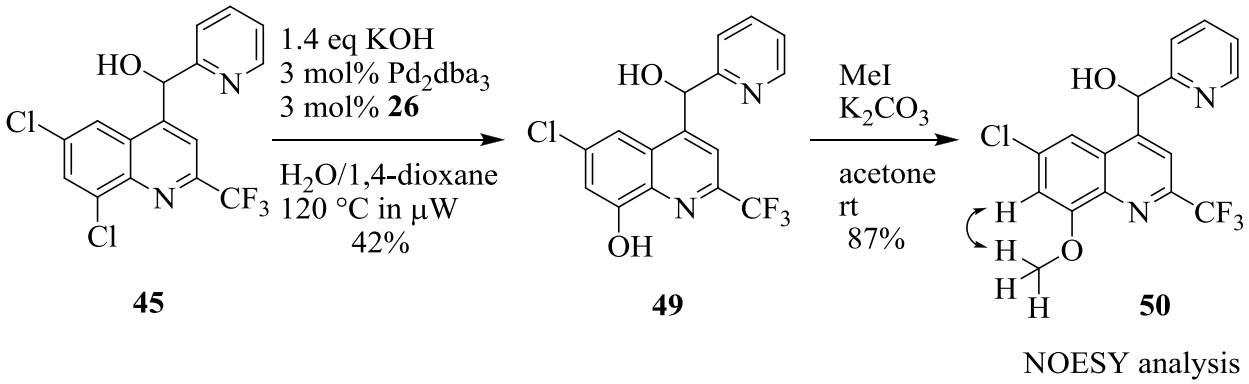
42 **47** **48**

Table 7. Conditions for selective phenol synthesis

Entry	Additive	Temp.[°C][a]	Time [h]	Result[c]		
				42	**47**	**48**
1	1.5 eq KOH	100[b]	30	1	1	0
2	3.0 eq KOH	150	0.5	0	0	1[d]
3	1.0 eq KOH	120	0.5	1	1	0
4	1.2 eq KOH	120	0.5	1	2	0
5	1.5 eq KOH	120	0.5	0	5	2
6	1.4 eq KOH	120	0.5	0	1[e]	0

[a] Irradiated in microwave. [b] heated in an oil bath. [c] Relative ratio of coupling products **47**, **48** and starting material **42** was determined by ^{1}H NMR of the crude mixture. [d] Only isolated **48** in 68% yield. [e] Only isolated **47** in 80% yield.

The regioselectivity of the phenol synthesis that was previously used was also investigated (Table 7). Initially, reflux conditions were tested because the regioselectivity under thermal conditions might be superior to microwave irradiation (Table 7, entry 1). After 30 h, a 1:1 ratio of starting material **42** and mono-hydroxy quinoline **47** was isolated. Under microwave conditions, the dihydroxy quinoline **48** was predominantly generated in the presence of an excess amount of KOH (Table 9, entry 2), and a 1:1 ratio of starting material **39** and mono-hydroxy quinoline **48** was observed with 1 equivalent of KOH (Table 7, entry 3). The best selectivity was found at 120 °C under microwave conditions with 1.4 equivalents of KOH providing 80% of the mono-hydroxy quinoline **47**.



45 **49** **50**

Scheme 21. Regioselective phenol synthesis

These successfully optimized conditions were applied to the bischloromefloquine precursor **45** as well (Scheme 21). Even though the yield was decreased compared to the test reaction, 42% of C8 hydroxy **49** was isolated. The NOESY spectrum of the corresponding methoxy **50**, prepared in 95% yield from **49**, confirmed the site of the palladium-catalyzed phenol synthesis: the methoxy proton is only correlated with the C7 hydrogen and significant correlation is also observed between the C5 hydrogen and the benzyl hydrogen.

3.5 BIOLOGICAL ANALYSIS

The in vitro antimalarial activities were comparing mefloquine and C8-substituted analogs. The 90% inhibitory concentrations (IC_{90}) against *P. falciparum* C2A (Pf C2A), a multi-drug resistant strain, using mefloquine, chloroquine and pyrimethanmine, were evaluated by Dow et al. at WRAIR by using the labeled hypoxanthine assay of Desjardins et al.[62] as modified by Milhous et al.[63] (Table 8)[64]. None of new analogs were found to be active, suggesting that a strong electron withdrawing group on the quinoline is required for antimalarial activity.

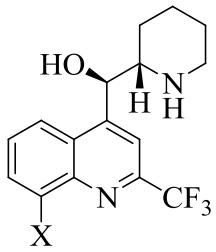


Table 8. Biological assay results of C8 analogs supplied by WRAIR

	X	IC_{90} [ng/mL]
$-CF_3$	Mefloquine	68-158
-Ph	*rac*-**23**	448
-Np	*rac*-**24**	250
-OH	*rac*-**28**	485
-OMe	*rac*-**30**	274
-CN	*rac*-**33**	440

3.6 CONCLUSION

Six new C8-substituted mefloquine analogs were synthesized by recently developed palladium cross couplings of chlorides **19** and **20**. It was found to be more convenient to prepare the mefloquine analogs from **19** because of the easier product purification, but the oxazolidine system was not stable enough under harsh conditions.

The preliminary results of the regioselective coupling reaction for a mefloquine derivative precursor are promising for multifunctionalized analogs. Unfortunately, the yields of the reaction are low, less than 50%, but an interesting observation was made. The C6 chloride site was found to be more active toward the Kumada coupling, whereas, in contrast, the C8 chloride site was active in the phenol synthesis, even though both reactions are thought to proceed by similar palladium-catalyzed mechanisms. The two different transformation of the bischloroquinoline developed previously, followed by a platinum-catalyzed reduction, could quickly provide a wide variety of bisfunctionalized mefloquine analogs.

4.0 EXPERIMENTAL

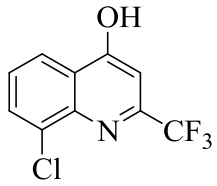
4.1 GENERAL

All moisture-sensitive reactions were performed under an atomosphere of argon gas and all glassware was dried in an oven at 140 °C prior to use. THF was distilled over sodium / benzophenone ketyl, NMP was distilled over CaH_2 and CH_2Cl_2 was purified using an alumina filtration system. Reactions were monitored by TLC analysis (EM Science pre-coated silica gel 60 F254 plates, 250 μm layer thickness) and visualization was accomplished with a 254 nm UV light and by staining with a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 2.0 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution) and a ninhydrin solution (0.3 g of ninhydrin and 3 mL of AcOH in 100 mL of *n*-BuOH). Chromatography on SiO_2 was used to purify the crude reaction mixtures. Microwave reactions were performed on a Biotage Initiator microwave reactor. Melting points were determined on a Nicolet Avatar 360 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 300 instrument unless otherwise noted. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra were recorded at 300 MHz or 500 MHz and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number of protons, and coupling constant(s). ^{13}C NMR spectra were recorded at 75 MHz using a proton-decoupled pulse sequence with a d_1 of 3 sec, and are tabulated by observed peak. Mass spectra

were obtained on a Micromass Autospec double focusing instrument. Infrared spectra were obtained on a Smiths Detection IdentifyIR FT-IR spectrometer (ATR). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 25 °C. Enantiomeric excess were determined by HPLC analysisi using AD-H column (0.46 cmϕ X 25 cm): tris (3,5-dimethylphenylcarbamate) derivative of amylose coated on silica-gel or by SFC analysis on a Mettler Toledo-MiniGram instrument using chiralpac IA column (0.46 cmϕX 25 cm): tris (3,5-dimethylphenylcarbamate) derivative of amylose immobilized on silica-gel.

4.2 EXPERIMENTAL PROCEDURE

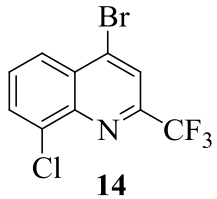
4.2.1 Enantioselective Synthesis of Mefloquine Analogs



15

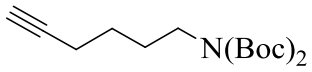
8-Chloro-2-(trifluoromethyl)quinoline-4(1H)-one (15). To a vigorously stirred solution of 2-chloroaniline (3.18 g, 24.4 mmol) in polyphosphoric acid (50 g) was added ethyl 4,4,4-trifluoroacetoacetate (4.54 g, 24.4 mmol) over 5 min at 100 °C under Ar. The reaction mixture was heated to 150 °C for 10 h. After cooling to room temperature, the oily mixture was neutralized with a 5% NaOH solution. The precipitate formed was isolated by vacuum filtration, washed with water and then re-dissolved in a 10% NaOH solution. The basic yellow solution was filtered and then 6 N HCl was added until a pH of 4.5 was achieved. The white precipitate

was collected and recrystalized from EtOH/water to afford **15** (4.02 g, 60%) as a white solid: Mp 134-135 °C; IR (neat) 3245, 3133, 2335,1838, 1515, 1280, 1135 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.57 (bs, 1 H), 8.28 (d, 1 H, *J* = 8.4 Hz), 7.78 (dd, 1 H, *J* = 7.8, 1.2 Hz), 7.39 (t, 1 H, *J* = 7.8 Hz), 6.67 (s, 1 H); ^{13}C NMR (acetone-d_6, 175 MHz) δ 164.3, 149.6, 145.7, 134.2, 123.3, 128.0, 123.9, 122.5 (q, J_{CF} = 273.0 Hz), 122.4, 102.1; MS (EI) *m/z* 247 (M^+, 100), 219 (23), 199 (70), 75 (23); HRMS (EI) *m/z* calcd for $C_{10}H_5ClF_3NO$ 247.0012, found 247.0023.



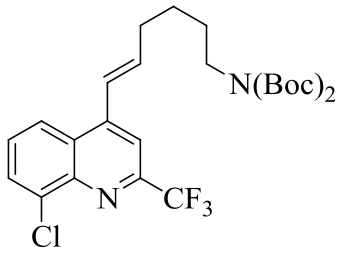
14

4-Bromo-8-chloro-2-(trifluoromethyl)quinoline (14). A mixture of **15** (2.21 g, 8.93 mmol) and $POBr_3$ (2.61 g, 8.93 mmol) was stirred at 150 °C for 30 min under Ar. After cooling to room temperature, the reaction mixture was diluted with water and CH_2Cl_2. The organic layer was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by chromatography on SiO_2 (1:9, EtOAc/Hexane) to afford **14** (2.62 g, 95%) as a white solid: Mp 68-69 °C; IR (neat) 3096, 3064, 1452, 1323,1258, 1182, 1198, 1129, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (dd, 1 H, *J* = 8.4, 1.2 Hz), 8.10 (s, 1 H), 8.01 (dd, 1 H, *J* = 4.5, 1.2 Hz), 7.70 (t, 1 H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.9 (q, J_{CF} = 36.0 Hz), 144.0, 136.3, 135.2, 131.9, 129.8, 129.7, 125.9, 122.0 (d, J_{CF} = 2.3 Hz), 120.8 (q, J_{CF} = 273.8 Hz); MS (EI) *m/z* 313 (25), 311 (M+1, 100), 309 (85), 242 (24); HRMS (EI) *m/z* calcd for $C_{10}H_4BrClF_3N$ 308.9168, found 308.9157.



13

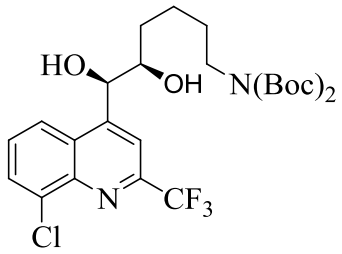
***N*-5-Hexyn-1-yl-*N*,*N*-di-*t*-butycarbamate (13).** To a solution of 5-hexyn-1-ol (6.00 g, 59.3 mmol), triphenylphosphine (31.4 g, 119 mmol) and di-*t*-butyl iminodicarbonate (14.2 g, 65.2 mmol) in dry THF (400 mL) cooled in an ice bath was added DIAD (24.8 mL, 119 mmol), and the reaction mixture was stirred at room temperature for 14 h, and concentrated under reduced pressure. The resulting oil was diluted with CH_2Cl_2, washed with a 10% of hydroxyperoxide solution and water, dried ($MgSO_4$) and concentrated under reduced pressure. The yellow syrup was purified by chromatography on SiO_2 (1:9 Et_2O/Hexane) to afford **13** (12.2 g, 69%) as colorless oil: IR (neat) 3295, 2982, 2937, 1735, 1690, 1366, 1133, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.24 (s, 1 H), 3.50 (t, 2 H, *J* = 7.2 Hz), 2.13 (td, 1 H, *J* = 6.9, 2.7 Hz), 1.87 (d, 1 H, *J* = 2.7 Hz), 1.68-1.55 (m, 2 H), 1.50-1.47 (m, 1 H), 1.51 (s, 18 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.6, 84.1, 82.1, 68.6, 45.8, 28.2, 28.1, 25.7, 18.2.; HRMS (TOF MS ES+) *m/z* calcd for $C_{16}H_{27}NO_4Na$ (M+Na) 320.1838, found 320.1812.



12

***N*-(*E*)-6-(8-chloro-2-(trifluoromethyl)quinolin-4-yl)hex-5-en-*N*,*N*-di-*t*-butylcarbamate (12).** A dry flask wrapped with aluminum foil was charged with Cp_2ZrHCl (57 mg, 0.222 mmol) and dry THF (0.5 mL), and **13** (60 mg, 0.202 mmol) was added via a syringe at room temperature. After stirring for 1 h, a homogeneous pale yellow solution resulted. A

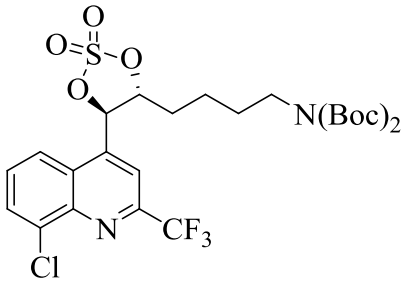
solution of anhydrous $ZnCl_2$ (33 mg, 0.242 mmol) in dry NMP (0.5 mL) was added via a syringe. After stirring for 10 min, a mixture of **14** (69 mg, 0.222 mmol) and $Pd(PPh_3)_4$ (11 mg, 0.0101 mmol) dissolved in NMP (0.5 mL) was added, and then the combined mixture was stirred at room temperature for 14 h. The reaction was quenched with water and CH_2Cl_2. The organic layer was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (3:7, CH_2Cl_2/Hexane then 1:4, EtOAc/Hexane) to afford 27 mg (25%) of **12** as a colorless oil: IR (neat) 2976, 2932, 1729, 1690, 1454, 1366, 1267, 1178, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, 1 H, *J* =8.7 Hz), 7.90 (dd, 1 H, *J* = 7.2, 1.2 Hz), 7.79 (s, 1 H), 7.56 (t, 1 H, *J* = 8.1 Hz), 7.10 (d, 1 H, *J* = 15.6), 6.59 (dt, 1 H, *J* = 15.6, 6.9 Hz), 3.64 (t, 2 H, *J* = 6.9 Hz), 2.43 (td, 2 H, *J* = 6.6 Hz), 1.75-1.55 (m, 4 H), 1.51 (s, 9 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 153.0, 148.3 (q, J_{CF} = 34.5 Hz), 146.8, 144.3, 140.5, 135.2, 130.8, 128.3, 128.1, 124.4, 122.9, 121.7 (q, J_{CF} = 273.8 Hz), 114.0 (d, J_{CF} = 2.3 Hz), 82.4, 46.2, 33.3, 28.7, 28.3, 26.1; MS (EI) *m/z* 528 [M^+] (60), 372 (70), 355 (60), 260 (77), 258 (94), 114 (100), ; HRMS (EI) *m/z* calcd for $C_{26}H_{32}ClF_3N_2O_4$ 528.2003, found 528.1987.



11

(-)-(1*R*,2*R*)-6-*N*,*N*-di-t-butylcarbamic-1-(8-chloro-2-(trifluoromethyl)quinolin-4-yl)hexane-1,2-diol (11). To a solution of **12** (22 mg, 0.0416 mmol) and methanesulfoneamide (6.0 mg, 0.0624 mmol) in a 1:1 mixture of *t*-BuOH and water (1 mL) was added AD-mix *β* (77 mg). After stirring at 0 °C for 24 h, the reaction mixture was quenched with saturated aqueous

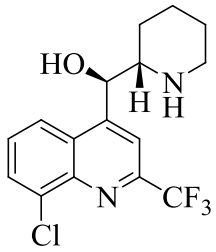
$Na_2S_2O_4$ and then extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude yellow oil was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford **11** (22 mg, 90%) as white foam. The ee (99%) was determined by HPLC using an AD-H column (3%, *i*-PrOH/Hex): $[\alpha]_D$ -28.6 (c 0.35, CH_3OH); IR (neat) 3409, 2987, 2935, 1768, 1729, 1690, 1367, 1183, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (s, 1 H), 7.91 (d, 1 H, *J* = 7.2 Hz), 7.89 (d, 1 H, *J* = 8.4 Hz), 7.58 (dd, 1 H, *J* = 8.7, 7.2 Hz), 5.30 (t, 1 H, *J* = 4.2 Hz), 3.80 (m, 1 H), 3.72 (d, 1 H, *J* = 4.8 Hz), 3.53 (t, 2 H, *J* = 6.3 Hz), 2.71 (d, 1 H, *J* = 6.0 Hz), 1.70-1.25 (m, 6 H), 1.45 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 151.2, 128.2 (q, J_{CF} = 35.3 Hz), 143.9, 135.7, 130.7, 128.6, 128.0, 122.0, 121.6 (q, J_{CF} = 273.8 Hz), 116.0, 82.7, 74.8, 72.4, 46.0, 33.5, 28.8, 28.2, 23.0; HRMS (TOF MS ES+) *m/z* calcd for $C_{26}H_{34}ClF_3N_2O_5Na$ (M+Na) 585.1955, found 585.1921.



10

(+)-(1*R*,2*R*)-6-*N*,*N*-di-t-butylcarbamic-1-(8-chloro-2-(trifluoromethyl)quinolin-4-yl)hexane-1,2-*O*-sulfate (10). To an ice-cooled stirred solution of **11** (40.0 mg, 0.0710 mmol) and pyridine (23.0 ul, 0.284 mmol) in CH_2Cl_2 (1 mL) was added thionyl choride (7.9 mL, 0.107 mmol). The reaction mixture was stirred at room temperature for 20 min, and then diluted with CH_2Cl_2 and water. The organic layer was extracted with CH_2Cl_2, washed with brine and concentrated under reduced pressure. The crude cyclic sulfite was dissolved in a mixture of water (0.5 mL), CH_3CN (0.25 mL), and CCl_4 (0.5 mL). Sodium periodate (23.0 mg, 0.106 mmol)

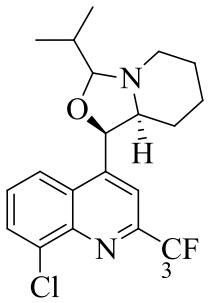
and $RuCl_3$ hydrate (7.1 mg, 0.00710 mmol) were added, and the resulting mixture was vigorously stirred at room temperature for 20 h. The reaction mixture was diluted with ethyl ether and filtered through a Celite pad. The filtered organic layer was washed with water and saturated $NaHCO_3$ solution followed by brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford **10** (38.0 mg, 85%) as a white solid: $[\alpha]_D$ +9.0 (c 0.10, CH_3OH); Mp 138-139 °C; IR (neat) 2982, 2937, 1698, 1392, 1366, 1245, 1210, 1118 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 8.44 (d, 1 H, *J* = 8.7 Hz), 8.31 (s, 1 H), 8.20 (dd, 1 H, *J* = 7.5, 0.9 Hz), 7.94 (dd, 1 H, *J* = 8.7, 7.5 Hz), 6.94 (d, 1 H, *J* = 8.1 Hz), 5.48 (ddd, 1 H, *J* = 10.4, 7.3, 3.0 Hz), 3.49 (t, 2 H, *J* = 6.8 Hz), 2.81 (m, 2 H), 2.34-2.24 (m, 1 H), 1.60-1.15 (m, 1 H), 1.43 (s, 18 H), 1.35-1.29 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.0, 148.6 (q, J_{CF} = 36.5 Hz), 144.5, 140.8, 136.7, 131.8, 130.3, 127.2, 121.1 (q, J_{CF} = 273.8 Hz), 121.0, 116.4 (d, J_{CF} = 1.5 Hz), 88.4, 83.2, 82.6, 45.3, 31.3, 28.2, 28.1, 22.6; HRMS (TOF MS ES+) *m/z* calcd for $C_{26}H_{32}ClF_3N_2O_8SNa$ (M+Na) 647.1442, found 647.1368.



9

(+)-(11*R*,12*S*)-8-Chloro2-(trifluoromethyl)quinolin-4-yl-(2-piperidyl)methanol (9). A solution of **10** (30.0 mg, 0.0480 mmol) in CH_2Cl_2 (0.5 mL) was treated with TFA (18.0 uL, 0.0981 mmol). After stirring at room temperature for 12 h, the solvent was removed under reduced pressure. Methanol (0.5 mL) and triethylamine (14.0 uL, 0.0960 mmol) were added to

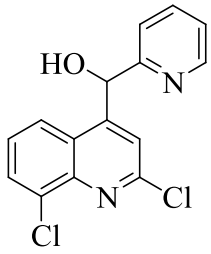
the crude solid and the reaction mixture was heated at reflux for 2 h. After cooling to room temperature, the solution was concentrated under reduced pressure. The gray residue was dissolved in THF (1 mL), followed by adding a drop of sulfuric acid and water. After stirring for 1 h at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ and diluted with EtOAc. The organic layer was extracted with EtOAc, washed several times with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by chromatography on SiO_2 (1:9, MeOH/ CH_2Cl_2) to afford **9** (10.0 mg, 60%) as a white solid: $[\alpha]_D$ +30.0 (c 0.10, CH_3OH); Mp 203-205 °C; IR (neat) 3096, 2935, 2853, 2717, 1453, 1362, 1261, 1181, 1129, 1107 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 8.35 (d, 1 H, J = 8.7 Hz), 8.14 (s, 1 H), 8.05 (dd, 1 H, J = 7.5, 1.2 Hz), 7.73 (dd, 1 H, J = 8.4, 7.5 Hz), 5.58 (d, 1 H, J = 4.2 Hz), 3.42 (bs, 2 H), 3.08-2.95 (m, 2 H), 2.59 (td, 1 H, J = 12.0, 2.7 Hz), 1.75-1.65 (m, 1 H), 1.55-1.40 (m, 1 Hz), 1.40-1.10 (m, 3 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 154.2, 148.3 (q, J_{CF} = 36.0 Hz), 144.5, 135.4, 131.6, 129.5, 129.3, 124.5, 122.8 (q, J_{CF} = 272.3 Hz), 116.5, 73.1, 62.1, 47.6, 27.0, 26.8, 25.0; HRMS (TOF MS ES+) *m/z* calcd for $C_{16}H_{17}ClF_3N_2O$ (M+H) 345.0982, found 345.0974.



19

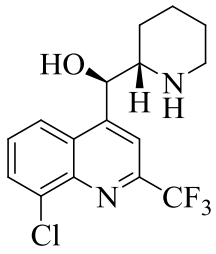
(1*R*,8a*S*)-1-(8-Chloro-2-(trifluoromethyl)quinolin-4-yl)-3-isopropylhexahydro-1H-oxazolo[3,4-a] pyridine (19). Distilled isobutyraldehyde (1.41 mL, 34.8 mmol) was added into a solution of *rac*-**9** (1.20 g, 3.48 mmol) in dry CH_2Cl_2 (35 mL) in the presence of 4 Å molecular sieves. The reaction mixture was stirred at room temperature for 20 h. After filtering and washing the flask with more CH_2Cl_2, the combined organic solutions were evaporated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford **19** (1.24 g, 89%) as a white solid. The ee (99%) of **19** prepared from (11*R*, 12*S*)-**9** was determined by SFC using a Chiral IB column (6% MeOH): Mp 263-265 °C (decomp.); IR (neat) 2945, 2786, 1456, 1264, 1183, 1131, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.29 (s, 1 H), 7.92 (d, 1 H, *J* = 9.0 Hz), 7.90 (d, 1 H, *J* = 7.5 Hz), 7.56 (t, 1 H, *J* = 8.1 Hz), 5.86 (d, 1 H, *J* = 8.7 Hz), 3.85 (s, 1 H), 3.04 (d, 1 H, *J* = 10.2 Hz), 2.79 (ddd, 1 H, *J* = 11.1, 8.4, 2.1 Hz), 2.10-1.93 (m, 2 H), 1.65-1.50 (m, 2 H), 1.40-1.30 (m, 2 H), 1.24 (d, 3 H, *J* = 6.9 Hz), 1.18 (d, 3 H, *J* = 6.9 Hz), 1.16-1.12 (m, 1 H), 0.36 (qd, 1 H, *J* = 12.0, 3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.6, 148.3 (q, J_{CF} = 35.3 Hz), 143.7, 135.6, 130.4, 128.5, 128.1, 122.0, 121.8 (q, J_{CF} = 274.5 Hz), 116.8 (d, J_{CF} = 1.5 Hz), 99.5, 74.6, 67.2, 47.9, 28.9, 26.7, 24.3, 24.1, 19.2, 15.4; HRMS (EI) *m/z* calcd for $C_{20}H_{22}ClF_3N_2O$ 398.1373, found 398.1367.

4.2.2 C8-Mefloquine Analogs



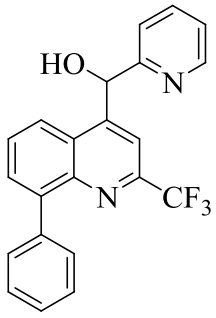
20

General Procedure A. (8-Chloro-2-(trifluoromethyl)quinolin-4-yl)(pyridin-2-yl)methanol (20). A solution of **14** (1.80 mg, 5.80 mmol) in dry THF (60 mL) under Ar was reacted with a 2 M solution of *i*-PrMgCl in THF (3.19 mL, 6.38 mmol) at 0 °C. After stirring for 1 h, 2-pyridinecarboxyaldehyde (0.613 mL, 6.38 mmol) was added and the resulting mixture was allowed to warm to room temperature over 30 min. The reaction mixture was quenched with water and diluted with EtOAc. The organic layer was extracted with EtOAc, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by chromatography on SiO_2 (3:7, EtOAc/Hexane) to afford **20** (1.71 g, 87%) as a white solid: Mp 142-143 °C; IR (neat) 3075, 2831, 2686, 1595, 1454, 1265, 1181, 1111, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.66 (d, 1 H, *J* =4.8 Hz), 8.14 (dd, 1 H, *J* = 8.4, 0.9 Hz), 7.94 (s, 1 H), 7.92 (dd, 1 H, *J* =7.5, 1.2 Hz), 7.63 (td, 1 H, *J* = 7.8, 1.8 Hz), 7.56 (dd, 1 H, *J* = 7.8, 8.4 Hz), 7.29 (dd, 1 H, *J* = 7.2, 5.1 Hz), 7.05 (d, 1 H, *J* = 7.8 Hz), 6.50 (s, 1 H), 5.54 (bs, 1 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 162.1, 154.5, 149.6, 148.6 (q, J_{CF} = 34.5 Hz), 144.6, 138.2, 135.3, 131.5, 129.4, 129.1, 125.2 123.8, 122.7 (q, J_{CF} = 273.0 Hz), 122.4, 116.1, 74.0; MS (EI) *m/z* 338 (M^+, 50), 321 (22), 108 (46), 86 (66), 84 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{10}ClF_3N_2O$ 338.0434, found 338.0440.



rac-**9**

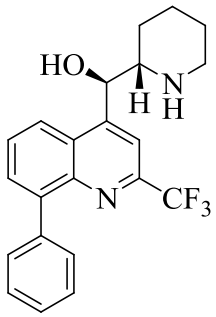
General Procedure B. (±)-8-Chloro-2-(trifluoromethyl)quinolin-4-yl-(2-piperidyl)methanol (*rac*-9). To a solution of **20** (200 mg, 0.590 mmol) in EtOH (6 mL) were added successively concentrated HCl (49 uL, 0.590 mmol) and PtO_2 (7.0 mg) and then the reaction mixture was hydrogenated at 5 bar for 3 h at room temperature. After removal of the insolubles by filtration through Celite packed with CH_2Cl_2, the filtrate was washed with saturated $NaHCO_3$, water and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. The gray solid was purified by chromatography on SiO_2 (1:10, MeOH/CH_2Cl_2) to afford product (184 mg, 90%) as a gray solid. The diastreomer ratio was 5:1 as determined by ^{1}H NMR



21

General Procedure C. (8-Phenyl-2-(trifluoromethyl)quinolin-4-yl)(pyridin-2-yl)methanol (21). A mixture of **20** (80.0 mg, 0.236 mol), palladium acetate (1.6 mg, 0.00708 mmol), and tricyclohexylphosphine (4.0 mg, 0.0141 mmol) was dissolved in dry NMP (2 mL) under Ar, then Grignard reagent (0.437 mL of 1.35 M solution) generated from bromobenzene was added by syringe. The reaction mixture was stirred at 50 °C for 6 h. After cooling to room

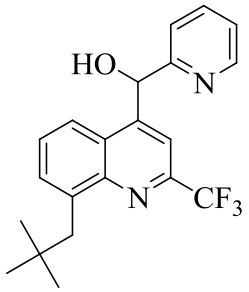
temperature, the reaction was quenched with saturated NH_4Cl and diluted with EtOAc. The organic layer was extracted with EtOAc, washed with water several times, dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford **21** (70.0 mg, 78%) of as a pink solid: Mp 117-118 °C; IR (neat) 3347, 2961, 1632, 1550, 1444, 1358, 1288, 1202 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.67 (d, 1 H, *J* = 4.8 Hz), 8.20 (d, 1 H, *J* = 6.6 Hz), 7.89 (s, 1 H), 7.86 (dd, 1 H, *J* = 7.2, 1.5 Hz), 7.77-7.68 (m, 2 H), 7.63 (td, 1 H, *J* = 7.8, 1.5 Hz), 7.53-7.40 (m, 3 H), 7.29 (dd, 1 H, *J* = 7.2, 5.4 Hz), 7.11 (d, 1 H, *J* = 7.8 Hz), 6.56 (s, 1 H), 5.59 (bs, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 150.5, 148.6, 147.4 (q, J_{CF} = 35.3 Hz), 145.5, 142.3, 138.8 137.7 131.3, 131.2, 128.7, 127.4, 123.6, 123.5, 121.8 (q, J_{CF} = 273.8 Hz), 121.6, 115.4 (d, J_{CF} = 1.5 Hz), 72.4; HRMS (TOF MS ES+) *m/z* calcd for $C_{22}H_{15}F_3N_2ONa$ (M+Na) 403.1034, found 403.0999.



rac-**23**

(±)-(8-Phenyl-2-(trifluoromethyl)quinolin-4-yl)(piperidin-2-yl)methanol (*rac*-23). According to general procedure B, to a solution of **21** (70.0 mg, 0.184 mmol) in EtOH (2 mL) were added successively 6 N HCl (15.0 uL, 0.184 mmol) and PtO_2 (2.0 mg, 0.00920 mmol) and then hydrogenated at ballon pressure for 6 h at room temperature. After removal of the insolubles by filtration through Celite, the filtrate was diluted with water and ether. The organic layer was washed with sat. $NaHCO_3$ solution and brine, then dried ($MgSO_4$) and concentrated in vacuo.

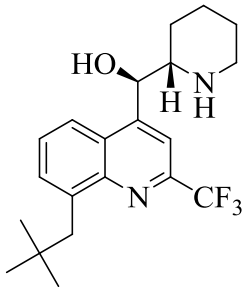
The residue was purified by chromatography on SiO_2 (10% MeOH/DCM), then purified by Preparative TLC (10% MeOH/DCM) to afford *rac*-**23** (35.0 mg, 49%) of product as a white solid; Mp 230-232 °C; IR (neat) 3207, 2926, 2853, 1442, 1264, 1180, 1131, 1109 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 8.44 (d, 1 H, J = 8.5 Hz), 8.11 (s, 1 H), 7.81 (d, 1 H, J = 7.0 Hz), 7.80-7.63 (m, 2 H), 7.47-7.40 (m, 3 H), 6.07 (s, 1 H), 4.98 (bs, 2 H), 3.41-3.32 (m, 2 H), 3.00-2.85 (m, 1 H), 1.74-1.63 (m, 3 H), 1.32-1.29 (m, 3 H), 0.87-0.83 (m, 1 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 153.0, 147.3 (d, J_{CF} = 33.8 Hz), 145.7, 142.8, 140.0, 132.1, 131.9, 129.4, 128.7, 128.4, 128.1, 124.4, 123.0 (d, J_{CF} = 273.0 Hz), 115.4, 72.7, 61.7, 47.4, 26.7, 26.3, 24.9.



22

(8-Neopentyl-2-(trifluoromethyl)quinolin-4-yl)(pyridin-2-yl)methanol (22). According to general procedure C, a mixture of **20** (100 mg, 0.295 mol), palladium acetate (4.2 mg, 0.00886 mmol), and tricyclohexylphosphine (5.0 mg, 0.0177 mmol) was dissolved in dry NMP (2 mL) under Ar, then Grignard reagent prepared from 1-bromo-2,2-dimethylpropane (0.53 mL of 1.4 M solution) was added. The reaction mixture was stirred at 50 °C for 6 h. The crude oil was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford **22** (78.0 mg, 71%) as a white solid: Mp 124-126 °C; IR (neat) 3340, 2950, 2863, 1681, 1593, 1470, 1362, 1178, 1133 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 8.48 (d, 1 H, J = 7.8 Hz), 8.33 (dd, 1 H, J = 8.1, 1.8 Hz), 8.15 (s, 1 H), 7.77 (td, 1 H, J = 7.8, 1.8 Hz), 7.70-7.60 (m, 2 H), 7.25 (ddd, 1 H, J = 7.5,

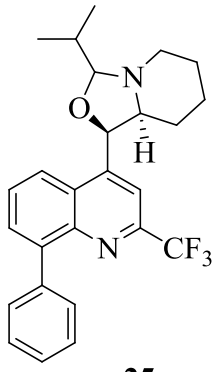
4.8, 1.2 Hz), 6.68 (d, 1 H, J = 3.9 Hz), 5.80 (d, 1 H, J = 4.5 Hz), 3.34, 3.23 (AB, 2 H, J = 12.3 Hz), 0.91 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 150.2, 148.5, 147.3, 146.5 (q, J_{CF} = 34.5 Hz), 141.2, 137.7, 132.3, 128.1, 127.5, 127.0, 123.4, 122.2, 122.0 (q, J_{CF} = 273.8 Hz), 121.6, 114.8, 72.3, 43.7, 33.2, 30.0; HRMS (TOF MS ES+) *m/z* calcd for $C_{21}H_{21}F_3N_2O$ 375.1684, found 375.1653.



rac-**24**

(±)-(8-Neopentyl-2-(trifluoromethyl)quinolin-4-yl)(piperidin-2-yl)methanol (*rac*-24). According to general procedure B, to a solution of **22** (50.0 mg, 0.134 mmol) in EtOH (1.5 mL) were added 6 N HCl (11 uL, 0.134. mmol) and PtO_2 (1.5 mg, 0.00668 mmol) and then the reaction mixture was hydrogenated at ballon pressure at room temperature for 5 h. The gray solid was purified by chromatography on SiO_2 (1:9, MeOH/CH_2Cl_2) to afford *rac*-**24** (40.0 mg, 79%) as a gray solid; Mp 215-117 °C; IR (neat) 3100, 2937, 2868, 2667, 1461, 1360, 1274, 1183, 1135, 1103 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 7.97 (s, 1 H), 7.89 (dd, 1 H, J = 8.1, 1.8 Hz), 7.76-7.57 (m, 2 H), 5.45 (d, 1 H, J = 3.3 Hz), 3.35, 3.24 (AB, 2 H, J = 12.3 Hz), 3.17-3.05 (m, 2 H), 2.73 (td, 1 H, J = 12.0, 2.7 Hz), 1.70-1.60 (m, 2 H), 1.60-1.50 (m, 2 H), 1.40-1.23 (m, 3 H), 1.18-1.05 (m, 1 H), 0.93 (s, 9 H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 153.1, 145.9, 144.5 (q, J_{CF} = 34.5 Hz), 139.4, 132.2, 127.9 (q, J_{CF} = 273.0 Hz), 126.7, 122.4, 121.9, 113.8, 71.6, 61.2, 46.5, 42.8,

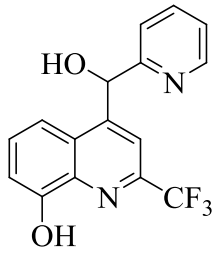
32.7, 29.7, 26.3, 26.1, 24.0; HRMS (TOF MS ES+) *m/z* calcd for $C_{21}H_{27}F_3N_2ONa$ (M+Na) 403.1973, found 403.1994.



rac-**25**

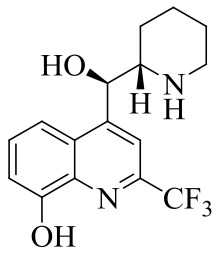
(±)-3-Isopropyl-1-(8-phenyl-2-(trifluoromethyl)quinolin-4-yl)hexahydro-1H-oxazolo pyridine (*rac*-25). According to general procedure C, a mixture of *rac*-**19** (50.0 mg, 0.125 mol), palladium acetate (0.8 mg, 0.00376 mmol), and tricyclohexylphosphine (2.1 mg, 0.00752 mmol) was dissolved in dry NMP (1.2 mL) under Ar, then Grignard reagent prepared from bromobenzene (0.125 mL of 2 M solution, 0.251 mmol) was added. The reaction mixture was stirred at 50 °C for 6 h. The crude oil was purified by chromatography on SiO_2 (1:20, EtOAc/Hexane) to afford *rac*-**25** (28.0 mg, 51%) as yellow oil: IR (neat) 2928, 2850, 1461, 1260, 1178, 1131, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1 H), 8.09 (dd, 1 H, *J* = 8.4, 1.2 Hz), 7.85 (dd, 1 H, *J* = 4.5, 1.5 Hz), 7.80-7.77 (m, 2 H), 7.70 (dd, 1 H, *J* = 8.4, 4.2 Hz), 7.53-7.42 (m, 3 H), 5.94 (d, 1 H, *J* = 8.4 Hz), 3.87 (d, 1 H, *J* = 2.1 Hz), 3.06 (d, 1 H, *J* = 10.5 Hz), 2.83 (ddd, 1 H, *J* = 11.1, 8.7, 2.4 Hz), 2.15-1.95 (m, 2 H), 1.65-1.55 (m, 2 H), 1.49-1.35 (m, 2 H), 1.25 (d, 3 H, *J* = 6.9 Hz), 1.19 (d, 1 H, *J* = 7.5 Hz), 1.00-0.85 (m, 1 H), 0.47 (, 1 H, *J* = Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.6, 147.3 (d, J_{CF} = 36.0 Hz), 144.8, 142.3, 139.0, 131.3, 130.9, 128.0, 128.0, 127.7, 127.6, 122.4, 122.0, 115.8, 99.5, 67.3, 48.1, 29.0, 26.8, 24.4, 24.2, 19.2,

15.5.; MS (EI) 440 (M^+, 42), 397 (100), 381 (98), 355 (63), 325 (42), 321 (95), 293 (40), 140 (70), 125 (60); *m/z* HRMS (EI) *m/z* calcd for $C_{26}H_{27}F_3N_2O$ 440.2075, found 440.2068.



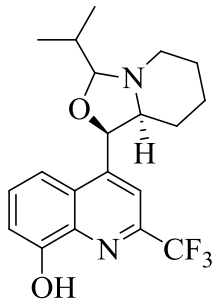
27

General procedure D. 4-(Hydroxy(pyridin-2-yl)methyl)-2-(trifluoromethyl)quinolin-8-ol (27). A mixture of **20** (100 mg, 0.295 mmol), tris(dibenzylideneacetone)dipalladium (5.5 mg, 0.00590 mmol), 2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1',1'-biphenyl (6.5 mg, 0.00646 mmol) and KOH (22.6 mg, 0.354 mmol) was added to a microwave tube and then flushed with Ar. A 1:1 mixture of degassed water and dioxane (3 mL) was added and the resulting mixture was irradiated at 120 °C for 30 min in the microwave. After cooling to room temperature, the reaction mixture was acidified with dilute aqueous HCl. The resulting solution was extracted with EtOAc, dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford **27** (56 mg, 56%) as a white solid: Mp 123-124 °C; IR (neat) 3384, 3295, 3032, 2617, 1508, 1472, 1366, 1191, 1129, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.66 (d, 1 H, *J* = 4.8 Hz), 8.14 (s, 1 H), 7.93 (s, 1 H), 7.70 (d, 1 H, *J* = 4.2 Hz), 7.65-7.55 (m, 2 H), 7.35-7.23 (m, 1 H), 7.10 (d, 1 H, *J* = 7.8 Hz), 6.51 (d, 1 H, *J* = 3.6 Hz), 5.55 (s, 1 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 162.3, 154.8, 154.0, 149.6, 146.0 (q, J_{CF} = 34.5 Hz), 138.8, 138.1, 130.9, 128.3, 123.8, 123.8, 122.9 (q, J_{CF} = 273.0 Hz), 122.4, 116.0, 115.6 (d, J_{CF} = 2.3 Hz), 112.6, 74.0; MS (EI) 320 (M^+, 42), 303 (15), 108 (90), 84 (100); *m/z* HRMS (EI) *m/z* calcd for $C_{16}H_{11}F_3N_2O_2$ 320.0773, found 320.0783.



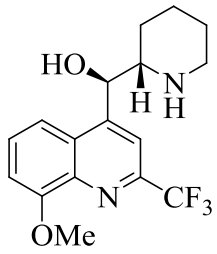
rac-**28**

(±)-4-(Hydroxy(piperidin-2-yl)methyl)-2-(trifluoromethyl)quinolin-8-ol (*rac*-29). According to general procedure B, to a solution of **27** (70.0 mg, 0.219 mmol) in EtOH (2 mL) were added 6 N HCl (18.2 uL, 0.219 mmol) and PtO_2 (2.5 mg, 0.0109 mmol) and then the reaction mixture was hydrogenated at ballon pressure at room temperature for 6 h. The crude solid was purified by chromatography on SiO_2 (1:9, MeOH/CH_2Cl_2) to afford *rac*-**28** (30.0 mg, 38%) as a yellow solid: Mp 232-235 °C; IR (neat) 3265, 3082, 2948, 2868, 1351, 1260, 1170, 1118 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.91 (s, 1 H), 7.69 (d, 1 H, J = 8.1 Hz), 7.60 (dd, 1 H, J = 8.4, 7.5 Hz), 7.23 (d, 1 H, J = 7.2 Hz), 5.76 (bs, 1 H), 5.27 (d, 1 H, J = 4.2 Hz), 3.34 (bs, 2 H), 2.92 (d, 1 H, J = 12.0 Hz), 2.85-2.75 (m, 1 H), 2.43, 1.73-1.60 (m, 1 H), 1.48-1.37 (m, 4 H), 1.37-1.10 (m, 1 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.3, 152.7, 143.8 (d, J_{CF} = 33.8 Hz), 137.9, 129.6, 127.7, 121.8 (d, J_{CF} = 273.0 Hz), 114.5, 113.9, 112.5, 71.7, 61.1, 46.5, 26.2, 26.1, 24.1; HRMS (TOF MS ES+) *m/z* calcd for $C_{16}H_{17}F_3N_2O_2$ (M+H) 327.1320, found 327.1310.



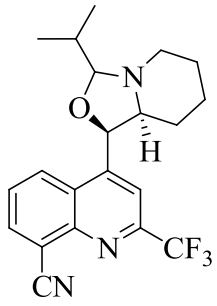
rac-**31**

(±)-4-(3-Isopropylhexahydro-1H-oxazolopyridin-1-yl)-2-(trifluoromethyl)quinolin-8-ol (*rac*-31). Distilled isobutyraldehyde (12.0 uL, 0.306 mmol) was added into a solution of **30** (20.0 mg, 0.0613 mmol) in dry CH_2Cl_2 (1 mL) in the presence of 4 Å molecular sieves, then the solution was stirred at room temperature for 20 h. After passing through short silica column and concentrating under reduced puressure, *rac*-**31** (23.0 mg, 94%) was isolated as pale yellow oil. The crude *rac*-**31** was pure enough and used next step without further purification: IR (neat) 3422, 2937, 2794, 1513, 1472, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.25 (s, 1 H), 8.15 (bs, 1 H), 7.56 (t, 1 H, *J* = 8.0 Hz), 7.45 (d, 1 H, *J* = 8.5 Hz), 7.25 (d, 1 H, *J* = 7.5 Hz), 5.84 (d, 1 H, *J* = 8.5 Hz), 3.85 (d, 1 H, *J* = 1.5 Hz), 3.04 (d, 1 H, *J* = 10.0 Hz), 2.79 (ddd, 1 H, *J* = 6.6, 5.4, 1.2 Hz), 2.11-2.03 (m, 1 H), 1.99 (ddd, 1 H, *J* = 7.5, 6.0, 1.5 Hz), 1.63-1.55 (m, 2 H), 1.43-1.35 (m, 2 H), 1.24 (d, 3 H, *J* = 7.0 Hz), 1.18 (d, 3 H, *J* = 7.0 Hz), 1.15-1.10 (m, 1 H), 0.39 (qd, 1 H, *J* = 6.9, 2.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.3, 150.6, 145.5 (d, J_{CF} = 35.0 Hz), 137.3, 129.8, 127.6, 121.8 (d, J_{CF} = 273.8 Hz), 116.5, 113.5, 110.8, 99.6, 74.7, 67.3, 48.0, 29.0, 26.6, 24.4, 24.1, 19.2, 15.4; MS (EI) *m/z* 379 (10), 338 (75), 337 (M-*i*-Pr, 100), 309 (72), 139 (90), 124 (89); HRMS (EI) *m/z* calcd for $C_{17}H_{16}F_3N_2O_2$ [M-(*i*-Pr)] 337.1164, found 337.1166.



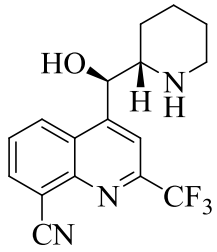
rac-**30**

(±)-(8-Methoxy-2-(trifluoromethyl)quinolin-4-yl)(piperidin-2-yl)methanol (*rac*-30). To a solution of **31** (15 mg, 0.0394 mmol) and K_2CO_3 (5.4 mg, 0.0394 mmol) dissolved in CH_2Cl_2 (0.5 mL) was added MeI (7.4 uL, 0.118 mmol) by a syringe. After stirring at room temperature for 8 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with saturated NH_4Cl and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude oil was dissolved in MeOH (0.3 mL), followed by the addition of 2,2-dimethyl-1,3-propanediol (21.2 mg, 0.197 mmol) and *p*TsOH (7.5 mg, 0.0394 mmol). The reaction mixture was stirred at room temperature for 14 h. After diluting with ether and water, the organic layer was extracted, washed with saturated $NaHCO_3$ solution and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (first EtOAc to remove 2,2-dimethyl-1,3-propanediol then 1:4, MeOH/CH_2Cl_2) to afford *rac*-**30** (8 mg, 60%) as a white solid: IR (neat) 3327, 2932, 2855, 1604, 1437, 1178, 1131, 1109 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 8.07 (s, 1 H), 7.83 (d, 1 H, J = 8.7 Hz), 7.62 (dd, 1 H, J = 8.4, 8.1 Hz), 7.27 (d, 1 H, J = 7.8 Hz), 5.69 (d, 1 H, J = 3.3 Hz), 4.30 (bs, 2 H), 4.04 (s, 3 H), 3.28 (d, 2 H, J = 11.1 Hz), 2.76 (td, 1 H, J = 11.7, 2.7 Hz), 1.78-1.67 (m, 1 H), 1.65-1.40 (m, 1 H), 1.35-1.15 (m, 1 H), 0.92-0.83 (m, 1 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 157.5, 52.1, 146.3 (d, J_{CF} = 33.8 Hz), 140.4, 130.0, 128.8, 123.1 (d, J_{CF} = 272.3 Hz), 116.0, 115.7, 109.8, 72.5, 61.5, 56.4, 26.6, 24.8, 23.4.



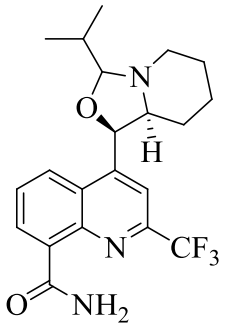
rac-**32**

(±)-4-(3-Isopropylhexahydro-1H-oxazolopyridin-1-yl)-2-(trifluoromethyl)quinoline-8-carbonitrile (*rac*-32). A mixture of *rac*-**19** (100 mg, 0.251 mmol), zinc cyanide (17.8 mg, 0.150 mmol), Pd_2dba_3 (7.0 mg, 0.00752 mmol) and *S*-Phos (6.2 mg, 0.0150 mmol) was dissolved in dry NMP (2.5 mL) under Ar. The reaction mixture was irradiated at 130 °C for 30 min in the microwave. The resulting solution was quenched with saturated NH_4Cl and diluted with EtOAc. The organic layer was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford *rac*-**32** (46 mg, 47%) as a white solid: Mp 127-128 °C; IR (neat) 2950, 2812, 2235, 1470, 1269, 1174, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.34 (s, 1 H), 8.28 (dd, 1 H, *J* = 8.7, 0.6 Hz), 8.21 (dd, 1 H, *J* = 7.2, 0.9 Hz), 7.73 (dd, 1 H, *J* = 7.2, 7.2 Hz), 5.86 (d, 1 H, *J* = 8.4 Hz), 3.86 (d, 1 H, *J* = 2.4 Hz), 3.05 (d, 1 H, *J* = 10.5 Hz), 2.82 (ddd, 1 H, *J* = 11.1, 8.7, 2.1 Hz), 2.15-1.95 (m, 2 H), 1.65-1.55 (m, 2 H), 1.40-1.25 (m, 2 H), 1.23 (d, 3 H, *J* = 6.9 Hz), 1.17(d, 1 H, *J* = 7.2 Hz), 0.97 (d, 1 H, *J* = 6.6 Hz), 0.35 (qd, 1 H, *J* = 11.7, 3.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.0, 149.8 (q, J_{CF} = 35.3 Hz), 146.3, 136.4, 128.0, 127.5, 127.2, 121.4, 117.8, 116.6, 115.1, 99.7, 74.4, 67.1, 47.9, 28.9, 26.8, 24.3, 24.1, 19.1, 15.4; MS (EI) *m/z* 389 [M^+] (21), 347 (85), 346 (100), 318 (86), 319 (57), 318 (91), 139 (77), 124 (75); HRMS (EI) *m/z* calcd for $C_{21}H_{22}F_3N_3O$ 389.1715, found 389.1706.



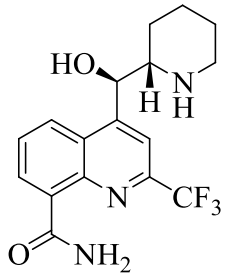
rac-**33**

(±)-4-(Hydroxy(piperidin-2-yl)methyl)-2-(trifluoromethyl)quinoline-8-carbonitrile (*rac*-33). According to general procedure B, a mixture of *rac*-**32** (30.0 mg, 0.0770 mmol), 2,2-dimethyl-1,3-propanediol (40.0 mg, 0.385 mmol) and *p*-TsOH (23.0 mg, 0.116 mmol) in MeOH (1 mL) was stirred at room temperature for 14 h. After diluting with Ether and water, the organic layer was extracted, washed with saturated $NaHCO_3$ solution and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by chromatography on SiO_2 (first EtOAc then 1:4, MeOH/CH_2Cl_2) to afford *rac*-**33** (22.0 mg, 85%) as a white solid; Mp 239-241 °C; IR (neat) 3258, 2924, 2851, 2725, 2334, 1600, 1366, 1267, 1185, 1137, 1114 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 8.85 (d, 1 H, J = 8.7 Hz), 8.29 (dd, 1 H, J = 7.2, 1.2 Hz), 8.21 (s, 1 H), 7.65 (dd, 1 H, J = 8.4, 7.5 Hz), 6.15 (d, 1 H, J = 2,7 Hz), 3.98 (bs, 2 H), 3.45-3.35 (m, 2 H), 2.97 (td, 1 H, J = 11.7, 3.9 Hz), 1.80-1.60 (m, 2 H), 1.40-1.20 (m, 4 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 153.1, 149.5 (d, J_{CF} = 34.5 Hz), 138.0, 130.3, 129.0, 127.3, 122.5 (d, J_{CF} = 273.0 Hz), 117.2, 116.9, 114.9, 70.1, 61.1, 46.3, 32.4, 24.3, 23.2, 14.4; HRMS (EI) *m/z* calcd for $C_{17}H_{15}F_3N_3$ (M-OH) 318.1218, found 318.1206.



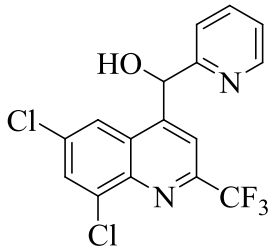
rac-**35**

(±)-4-(3-Isopropylhexahydro-1H-oxazolopyridin-1-yl)-2-(trifluoromethyl)quinoline-8-carboxamide (*rac*-35). To a solution of *rac*-**32** (55.0 mg, 0.141 mmol) in DMSO (1.5 mL) were added K_2CO_3 (58.6 mg, 0.424 mmol) and 30% H_2O_2 (48 uL, 0.424 mmol) and then the reaction mixture was kept stirring at 60 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with water and EtOAc. The organic layer was extracted, washed several times with water and brine, dried ($MgSO_4$) and then concentrated under reduced pressure. The crude oil was purified by chromatography on SiO_2 (3:7, EtOAc/Hex) to afford *rac*-**35** (52 mg, 90%) as a pink solid: Mp 220-222 °C; IR (neat) 3345, 3164, 2940, 2794, 1677, 1569, 1424, 1180, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.48 (bs, 1 H), 8.95 (dd, 1 H, *J* = 7.2, 1.2 Hz), 8.31 (s, 1 H), 8.20 (d, 1 H, *J* = 7.8 Hz), 7.80 (t, 1 H, *J* = 7.8 Hz), 6.26 (bs, 1 H), 5.92 (d, 1 H, *J* = 8.7 Hz), 3.87 (d, 1 H, *J* = 2.1 Hz), 3.05 (d, 1 H, *J* = 9.9Hz), 2.83 (ddd, 1 H, *J* = 11.1, 8.7, 2.1 Hz), 2.15-1.95 (m, 2 H), 1.65-1.55 (m, 2 H), 1.45-1.30 (m, 2 H), 1.25 (d, 3 H, *J* = 6.9 Hz), 1.18 (d, 3 H, *J* = 7.2 Hz), 1.15-1.10 (m, 1 H), 0.36 (qd, 1 H, *J* = 12.0, 3.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0, 152.0, 146.9 (q, J_{CF} = 36.0 Hz), 144.3, 135.3, 130.2, 128.1, 127.4, 127.2, 121.7 (d, J_{CF} = 272.3 Hz), 115.9, 99.6, 74.7, 67.2, 48.0, 28.9, 26.9, 24.3, 24.1, 19.2, 15.5; HRMS (TOF MS ES+) *m/z* calcd for $C_{21}H_{25}F_3N_3O_2$ (M+H) 408.1899, found 408.1864.



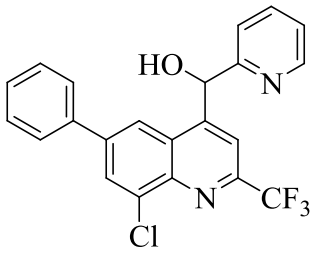
rac-**36**

(±)-4-(Hydroxy(piperidin-2-yl)methyl)-2-(trifluoromethyl)quinoline-8-carboxamide (*rac*-36). According to general procedure F, a reaction mixture of *rac*-**35** (20.0 mg, 0.0491 mmol), 2,2-dimethyl-1,3-propanediol (25.8 mg, 0.245 mmol) and *p*-TsOH (8.4 mg, 0.0736 mmol) in MeOH (0.5 mL) was stirred at room temperature for 14 h. After diluting with Ether and water, the organic layer was extracted, washed with saturated $NaHCO_3$ solution and brine, then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography (first EtOAc then 1:9, MeOH/CH_2Cl_2) to afford *rac*-**36** (16.0 mg, 92%) as a white solid: IR (neat) 3258, 2924, 2850, 1668, 1565, 1428, 1263, 1181, 1127 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 9.29 (bs, 1 H), 8.56 (d, 1 H, J = 8.7 Hz), 8.54 (d, 1 H, J = 6.0 Hz), 8.04 (s, 1 H), 8.00 (bs, 1 H), 7.90 (t, 1 H, J = 7.8 Hz), 5.96 (bs, 1 H), 5.37 (d, 1 H, J = 4.2 Hz), 3.31 (bs, 2 H), 2.95-2.75 (m, 2 H), 2.41 (t, 1 H, J = 10.7 Hz), 1.72-1.65 (m, 1 H), 1.50-1.35 (m, 1 H), 1.30-1.10 (m, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.4, 155.0, 145.2 (d, J_{CF} = 33.8 Hz), 143.6, 133.1, 132.1, 128.2, 127.8, 127.0, 121.8 (d, J_{CF} = 273.0 Hz), 114.7, 71.8, 61.6, 46.4, 26.6, 25.9, 24.0; HRMS (EI) *m/z* calcd for $C_{17}H_{18}F_3N_3O_2$ 353.1351, found 353.1353.



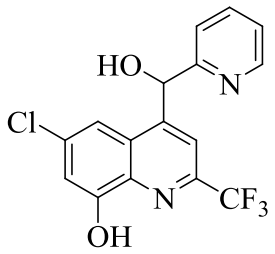
45

6-Chloro-4-(hydroxy(pyridin-2-yl)methyl)-2-(trifluoromethyl)quinolin-8-ol (45). According to general procedure A, 2-bromo-6,8-bischloro-2-(trifluoromethyl)quinolin (2.00 g, 5.80 mmol) was dissolved in dry THF (60 mL) under Ar, and then a 2 M solution of *i*-PrMgCl in THF (3.18 mL, 6.38 mmol) was added at 0 °C. After stirring for 1 h, 2-pyridinecarboxyaldehyde (0.613 mL, 6.38 mmol) was added and the resulting mixture was allowed to warm to room temperature over 30 min. The crude residue was purified by chromatography on SiO_2 (3:7, EtOAc/Hexane) to afford **45** (1.42 g, 65%) as a yellow solid: Mp 135-136 °C; IR (neat) 3400, 3088, 1593, 1448, 1185, 1139, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.69 (dd, 1H, J = 4.8, 0.9 Hz), 8.18 (d, 1H, J = 2.1 Hz), 7.90 (d, 1H, J = 2.4 Hz), 7.89 (s, 1H), 7.06 (d, 1H, J = 8.1 Hz), 7.32 (dd, 1H, J = 7.2, 4.8 Hz), 7.06 (d, 1H, J = 8.1 Hz), 6.40 (s, 1H), 5.42 (d, 1H, J = 2.7 Hz); ^{13}C NMR (acetone-d_6, 75 MHz) δ 162.0, 154.2, 149.7, 148.9 (q, J_{CF} = 34.5 Hz), 143.3, 138.3, 136.6, 134.3, 131.8, 129.4, 124.6, 123.9, 122.6 (q, J_{CF} = 262.5 Hz), 122.3, 117.2 (d, J_{CF} = 2.3 Hz), 73.9; MS (EI) 374 (45), 373 (35), 372 (M^+, 72), 371 (45), 353 (20), 355 (22), 108 (94), 79 (100); *m/z* HRMS (EI) *m/z* calcd for $C_{16}H_{10}ClF_3N_2O_2$ 372.0044, found 372.0033.



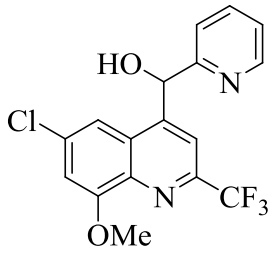
46

(8-Chloro-6-phenyl-2-(trifluoromethyl)quinolin-4-yl)(pyridin-2-yl)methanol (46). According to general procedure B, a mixture of **45** (80.0 mg, 0.214 mol), palladium acetate (1.4 mg, 0.00642 mmol), tricyclohexylphosphine (3.6 mg, 0.0128 mmol) was dissolved in dry NMP (1.5 mL) under Ar. After cooling to 0 °C, Grignard reagent prepared from bromobenzene (0.429 mL of 1.25 M solution in THF) was added by syringe. The reaction mixture was kept stirring at 0 °C for 12 h. The crude solid was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford **46** (37.0 mg, 42%) as a white solid: IR (neat) 3450, 3071, 2926, 2855, 1593, 1457, 1277, 1183, 1134 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.69 (d, 1 H, *J* = 5.0 Hz), 8.33 (d, 1 H, *J* = 2.0 Hz), 8.20 (d, 1 H, *J* = 1.5 Hz), 7.94 (s, 1 H), 7.65 (td, 1 H, *J* = 7.5, 1.5 Hz), 7.62 (d, 2 H, *J* = 7.0 Hz), 7.51 (t, 2 H, *J* = 7.5 Hz), 7.46 (d, 1 H, *J* = 7.5 Hz), 7.31 (dd, 1 H, *J* = 7.0, 5.0 Hz), 7.10 (d, 1 H, *J* = 8.0 Hz), 6.54 (s, 1 H), 5.49 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.7, 151.2, 148.9, 148.2 (q, J_{CF} = 35.3 Hz), 143.7, 141.6, 138.9, 137.8, 135.9, 130.4, 129.4, 128.9, 128.5, 127.7, 123.7, 121.6 (q, J_{CF} = 273.8 Hz), 121.5, 120.9, 116.9, 72.5; HRMS (EI) *m/z* calcd for $C_{22}H_{15}ClF_3N_2O$ (M+H) 415.0825, found 415.0819.



49

6-Chloro-4-(hydroxy(pyridin-2-yl)methyl)-2-(trifluoromethyl)quinolin-8-ol (49). A mixture of **45** (80.0 mg, 0.214 mmol), tris(dibenzylideneacetone)dipalladium (5.9 mg, 0.00643 mmol), 2-di-t-butylphosphino-2',4',6'-tri-i-propyl-1',1'-biphenyl (6.0 mg, 0.0129 mmol) and KOH (19.1 mg, 0.300 mmol) was added to a microwave tube. A 1:1 mixture of degassed water and dioxane (2 mL) was added and the resulting mixture was irradiated at 120 °C for 30 min in the microwave. The crude solid was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford **49** (32.0 mg, 42%) as a white solid: Mp 131-133 °C; IR (neat) 3403, 3075, 1595, 1505, 1275, 1183, 1137 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.67 (d, 1 H, J = 4.8 Hz), 8.19 (s, 1 H), 7.92 (s, 1 H), 7.70 (d, 1 H, J = 2.1 Hz), 7.66 (td, 1 H, J = 7.8, 1.8 Hz), 7.31 (dd, 1 H, J = 6.9, 4.8 Hz), 7.26 (d, 1 H, J = 2.1 Hz), 7.10 (d, 1 H, J = 8.1 Hz), 6.40 (s, 1 H), 5.53 (d, 1 H, J = 3.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.1, 154.0 150.8, 148.8, 145.9 (d, J_{CF} = 35.3 Hz), 137.8, 136.8, 136.7, 128.0, 123.8, 121.4 (d, J_{CF} = 273.0 Hz), 117.3, 114.0, 112.9, 71.7; MS (EI) 356 (46), 355 (40), 354 (M^+, 89), 353 (45), 319 (40), 108 (89), 79 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{10}ClF_3N_2O_2$ 354.0383, found 354.0379.



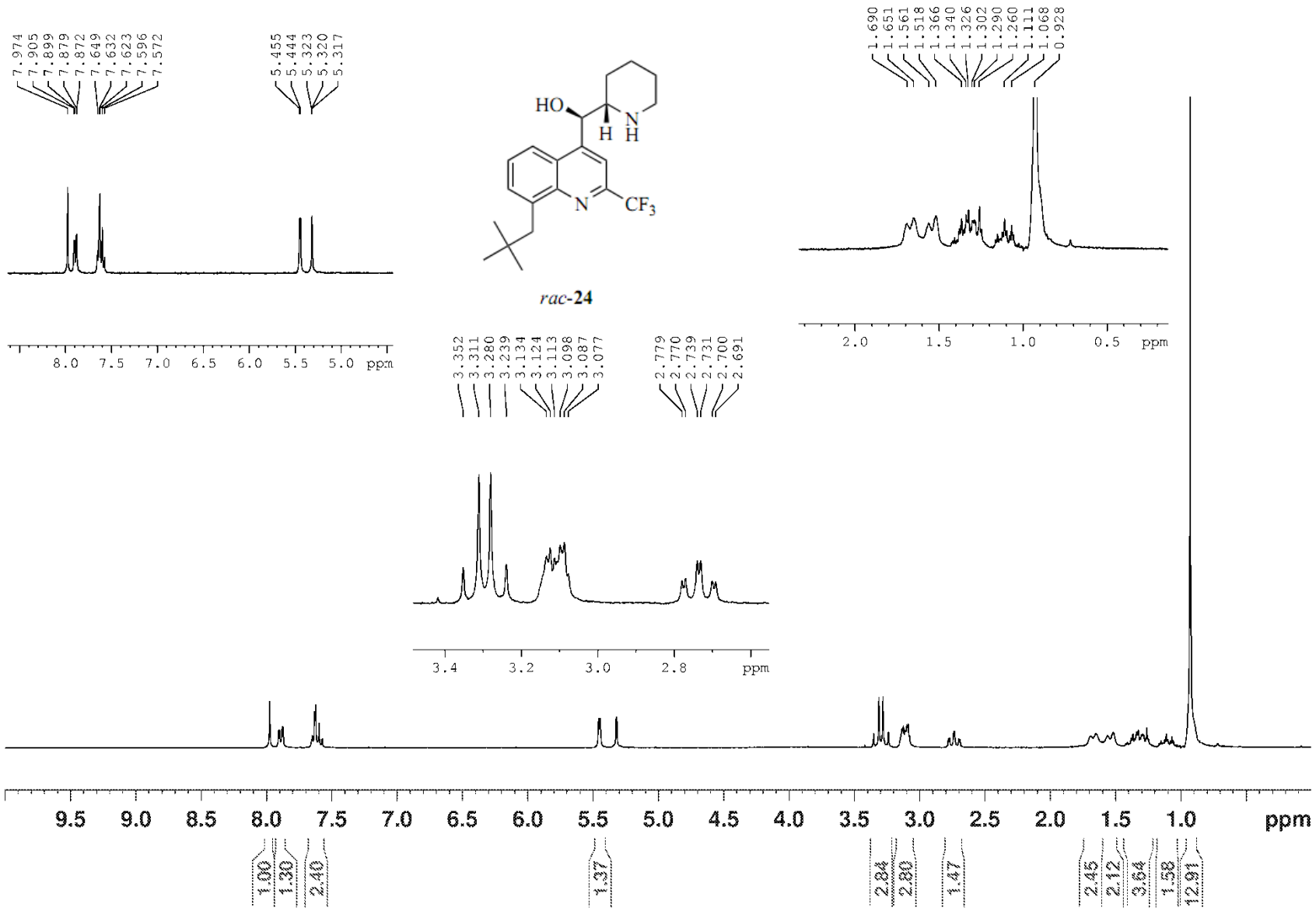
50

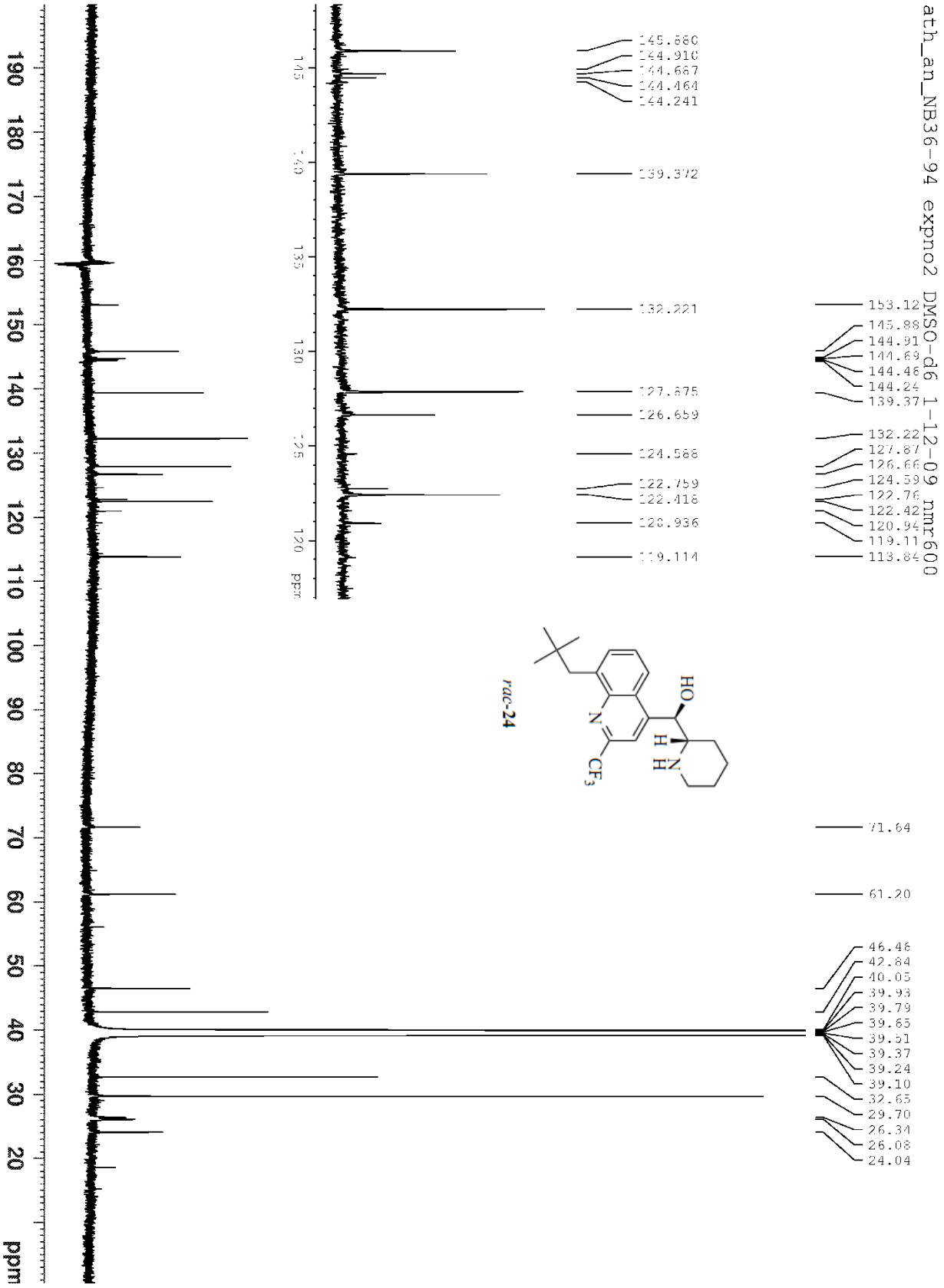
(6-Chloro-8-methoxy-2-(trifluoromethyl)quinolin-4-yl)(pyridin-2-yl)methanol (50). To a solution of **45** (20.0 mg, 0.0564 mmol) and K_2CO_3 (11.7 mg, 0.0846 mmol) in CH_2Cl_2 (0.5 mL) was added MeI (10.5 uL, 0.169 mmol) by a syringe. After stirring at room temperature for 8 h, the reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with saturated NH_4Cl and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude solid was purified by chromatography on SiO_2 (1:4, EtOAc/Hexane) to afford 50 (18.0 mg, 87%) as a white solid: Mp 155-156 °C; IR (neat) 3400, 2922, 2851, 1595, 1540, 1256, 1180, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.66 (d, 1 H, *J* = 4.5 Hz), 7.89 (s, 1 H), 7.77 (d, 1 H, *J* = 2.0 Hz), 7.65 (td, 1 H, *J* = 7.5, 1.5 Hz), 7.30 (dd, 1 H, *J* = 7.5, 5.0 Hz), 7.08-7.04 (m, 2 H), 6.39 (s, 1 H), 5.53 (bs, 1 H), 4.10 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.4, 157.2, 149.8, 148.7, 147.4 (q, J_{CF} = 35.3 Hz), 138.8, 137.7, 135.7, 128.7, 123.7, 121.6 (q, J_{CF} = 273.8 Hz), 121.4, 117.2, 115.0, 110.5, 72.0, 56.9; MS (EI); *m/z* 370 ($[M+2]^+$, 65), 369 (70), 368 (M^+, 100), 367 (77), 260 (63), 108 (93); HRMS (EI) *m/z* calcd for $C_{17}H_{12}ClF_3N_2O_2$ 368.0539, found 368.0528.

APPENDIX A

SELECTED ^{1}H AND ^{13}C NMR DATA FOR COMPOUNDS *rac*-**24** and *rac*-**36**

NB36-94 CD2Cl2 301b 1H NMR

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144.91
144.69
144.46
144.24
139.37
132.22
127.87
126.66
124.59
122.76
122.42
120.94
119.11
113.84
71.64
61.20
46.46
42.84
40.05
39.93
39.79
39.65
39.51
39.37
39.24
39.10
32.65
29.70
26.34
26.08
24.04
145.880
144.910
144.667
144.464
144.241
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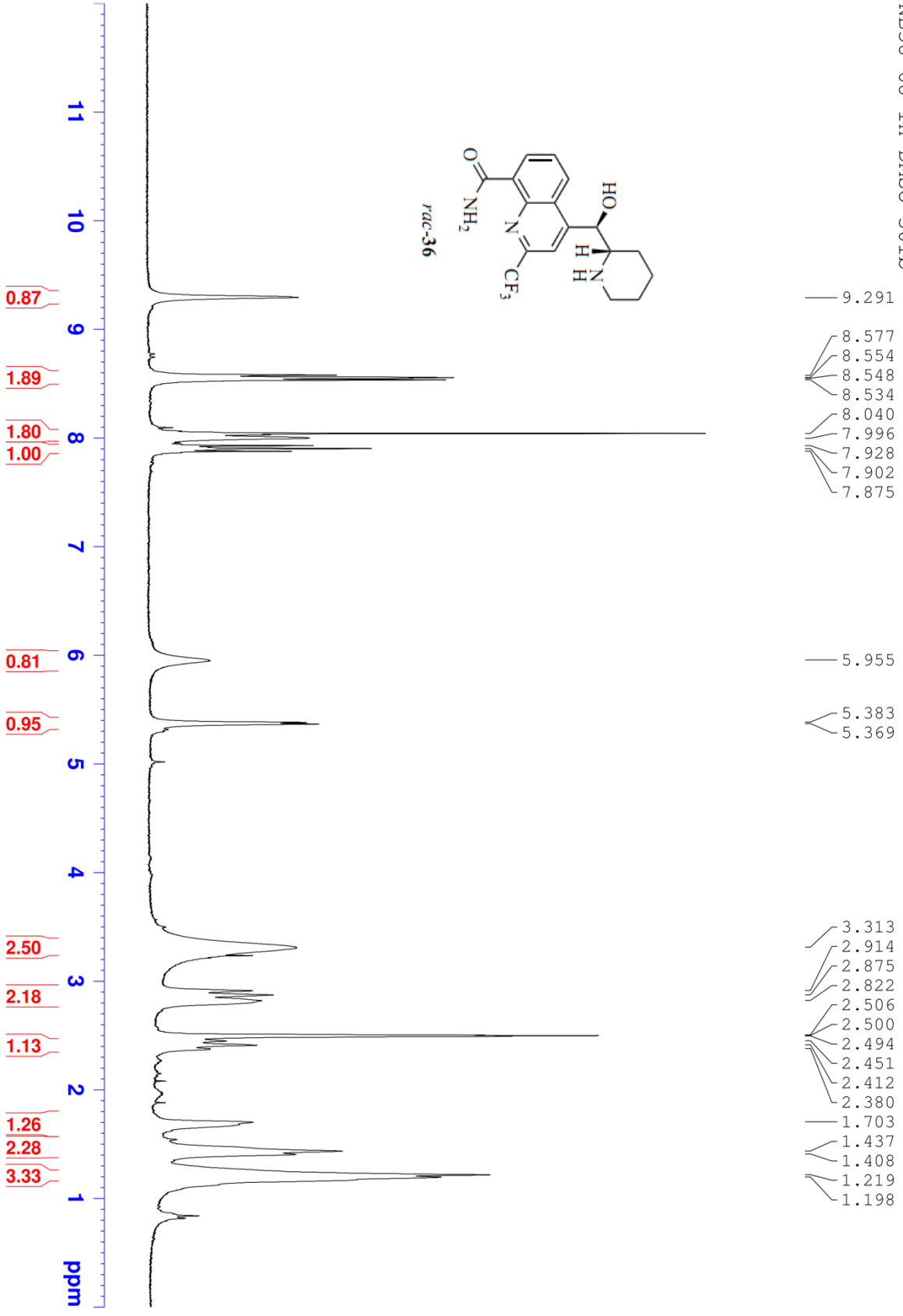
132.221
127.675
126.659
124.588
122.759
122.418
120.936
119.114
ppm
rac-24


NB38-68 1H DMSO 301b
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9.291
8.577
8.554
8.548
8.534
8.040
7.996
7.928
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7.875
5.955
5.383
5.369
3.313
2.914
2.875
2.822
2.506
2.500
2.494
2.451
2.412
2.380
1.703
1.437
1.408
1.219
1.198
0.87
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1.00
0.81
0.95
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1.13
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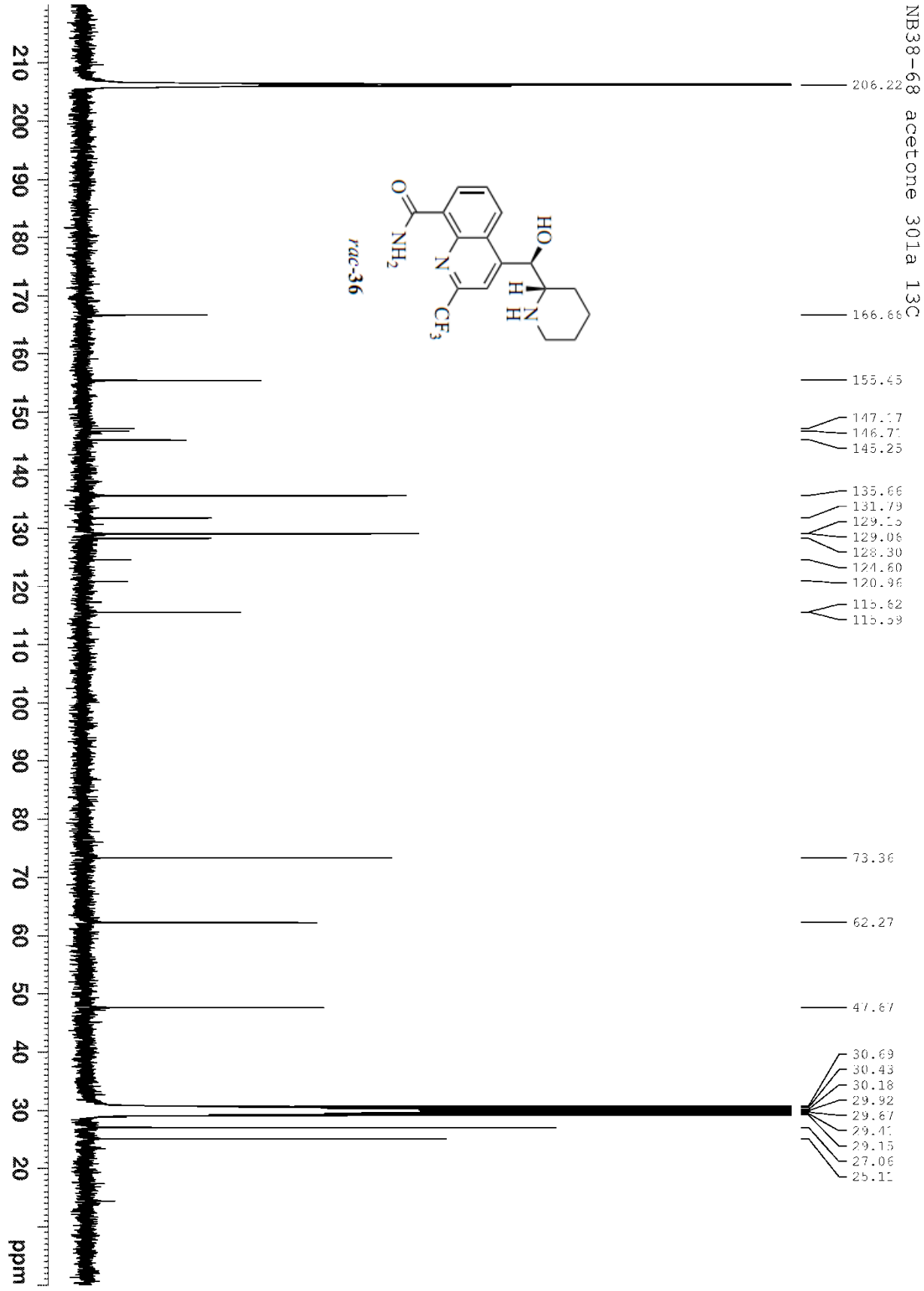
2.28
3.33
ppm


NB38-68 acetone 301a 13C
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155.45
147.17
146.71
145.25
135.66
131.79
129.06
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120.96
73.36
62.27
47.67
30.69
30.43
30.18
29.92
29.67
29.15
27.06
25.11
ppm
rac-36

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