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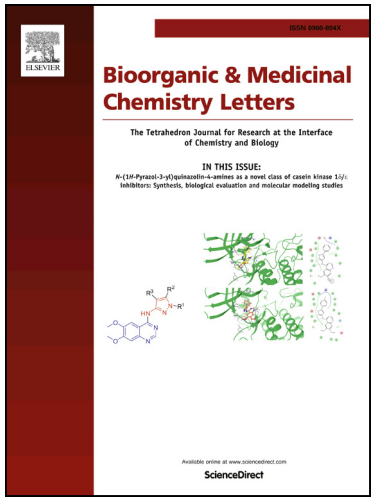

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The Synthesis of 2,3,6-Trisubstituted 1-oxo-1,2-dihydroisoquinolines as Potent $CRTh_2$ Antagonists

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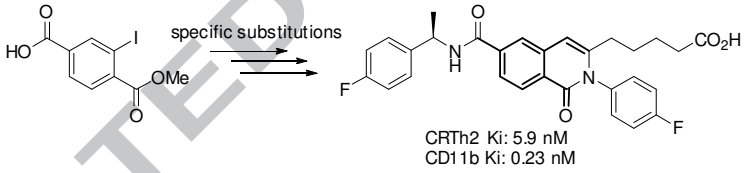
Graphic Abstract of Content



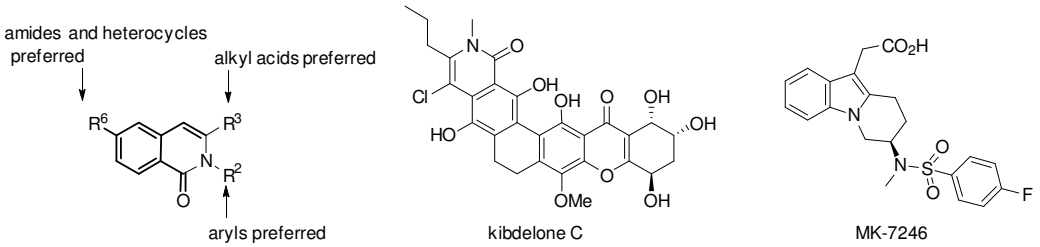
Abstract

New synthetic methods were developed for the preparation of 2,3,6-trisubstituted 1-oxo-1,2-dihydroisoquinolines as $CRTh_2$ antagonists. The isoquinolinone core could be constructed before the introduction of substitution groups or synthesized through a catalytic intramolecular cyclization reaction with desired substitution groups properly installed. These synthetic strategies have helped to accelerate the SAR development of this series, and potent lead compounds were identified in both the $CRTh_2$ receptor binding assay and the CD11b biomarker assay.

Keywords: 1-oxo-1,2-dihydroisoquinoline, isoquinolinone, intramolecular cyclization, $CRTh_2$ antagonists, asthma, respiratory diseases

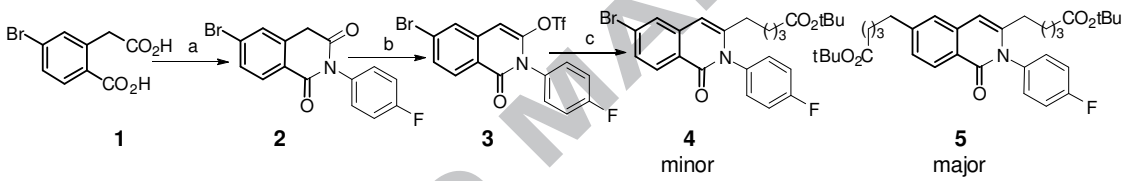
Heterocyclic compounds continue to play very important role in modern drug discovery due to their contribution to specific interactions with the targeted proteins and desirable physicochemical properties.[1] Depending on the targeted interactions and program needs, different heterocyclic compounds can be designed. In a recent effort in the $CRTh_2$ (chemoattractant receptor-homologous molecule expressed on Th_2 cells) antagonist program, we became interested in the synthesis of 2,3,6-trisubstituted 1-oxo-1,2-dihydroisoquinolines (also known as isoquinolinones, Figure 1). The isoquinolinone cores not only are important pharmacophores in biologically active compounds[2] (Figure 1) but also versatile building blocks to access more complex derivatives.[3] There were numerous methods reported for the preparation of isoquinolinones with most of them involving an intramolecular cyclisation reaction employing benzamides.[4] However, most of these methods were not suitable for the purpose of our program. We would like to have diversified modifications of R2, R3 and R6 in a convergent way to evaluate the SAR in a short period of time considering the competitive landscape of the program. In the past decade, small molecule $CRTh_2$ antagonist discovery research has attracted much attention from the pharmaceutical industry due to the role of $CRTh_2$ receptors in mediating the biological actions of prostaglandin D2 (PGD2) and potential applications of these antagonists in the treatment allergic inflammatory diseases such as asthma, atopic dermatitis and allergic rhinitis.[5] Several $CRTh_2$ antagonists have advanced to clinical trials from several companies including **MK-7246**.[6] As a potential backup series, we are interested in the development of structurally different and novel isoquinolinone series. The challenge here is how to efficiently construct the isoquinolinone core to accelerate the SAR development of this series. Herein we report our synthetic efforts to prepare 1-oxo-1,2-dihydroisoquinolines to facilitate specific 2,3,6-trisubstitutions, and the evaluation of these analogs as $CRTh_2$ antagonists for the treatment of asthma.

Figure 1. 1-oxo-1,2-dihydroisoquinoline core, its derivative, and structure of MK-7246.



Based on previous SAR,[7] R2 as an aryl group and R3 as an alkyl acid were important for activity, and more options were available for R6 substitutions such as amides and heterocycles (Figure 1). How to install these substitutions will impact the SAR development. We first chose to focus the synthetic efforts on the construction of the isoquinolinone core before the introduction of substitution groups. This would be the most efficient from an SAR development point of view if we could modify the substitutions with the common core installed. With this design principle in mind, we thought the bifunctional isoquinolinone core (**3**) would be a good starting point to modify R3 and R6 while maintaining R2 as 4-fluorophenyl. Compound **3** was synthesized from diacid **1** in two steps with good yields. However, no good selectivity between the bromide and triflate could be achieved when we tried to introduce a R3 alkyl group through the Suzuki coupling reaction and the major product isolated was the bis-alkylated product **5** (Scheme 1).

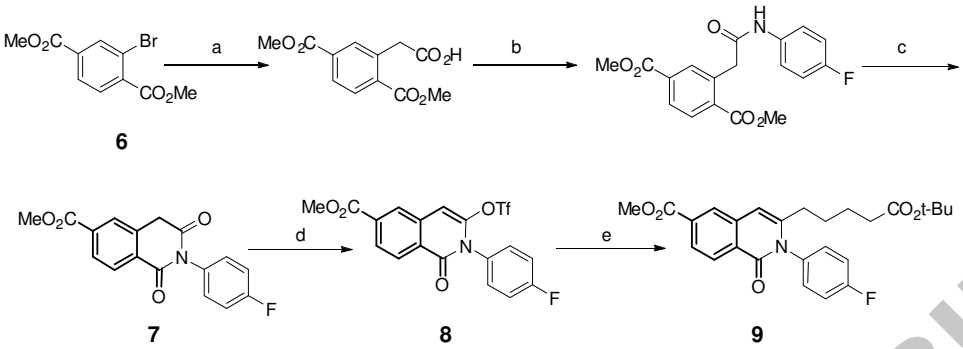
Scheme 1. Chemistry attempts to synthesize isoquinolinone core with R3 and R6 diversification.



Reagents and conditions: a. p-TSA (cat.), 4-FPhNH$_2$, toluene, 140 ^{o}C, 67%; b. 2-ClPyNTf$_2$, LHMDS, THF, -78 ^{o}C, 64%; c. tert-butyl pent-4-enoate, 9-BBN, Pd$_2$(dba)$_3$, butyldi-1-adamantylphosphine, K$_3$PO$_4$, THF, 75 ^{o}C.

To avoid the selectivity issue and to quickly evaluate R3 SAR, we decided to fix R6 as an ester (amide precursor) and R2 as 4-fluorophenyl (**9**) at this point. In this regard, triflate **8** was chosen as the key intermediate which was synthesized readily from compound **6** as demonstrated in Scheme 2. Through this effort, we were able to prepared advanced intermediate **9** to establish R3 SAR and identified the pentanoic acid side chain as the optimum substitution.

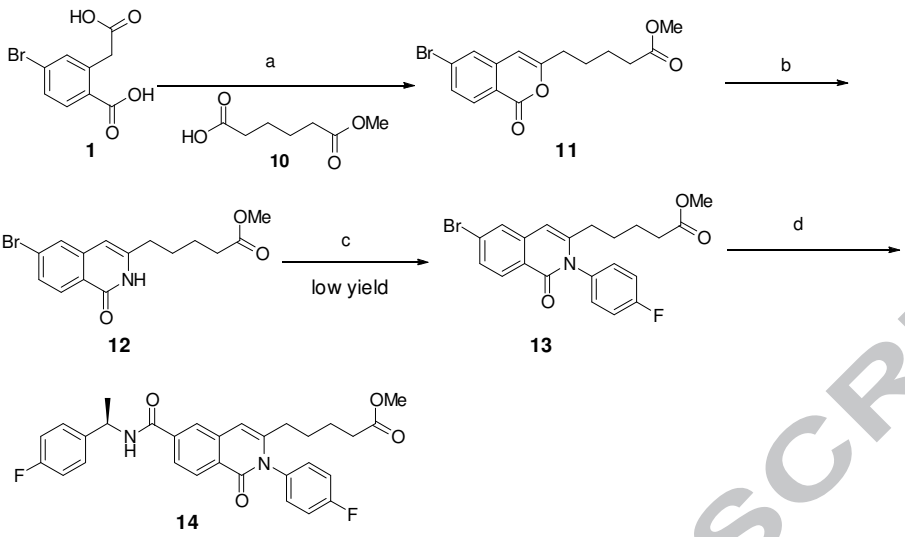
Scheme 2. Isoquinolinone core synthesis with variation at R3 and R6.



Reagents and conditions: a. allyl tributyltin, $Pd(PPh_3)_4$, LiCl, dioxane, 80 ^oC, 98%; ozone, DCM/MeOH, -78 ^oC, 100%; sodium chlorite, sodium phosphate monobasic monohydrate, 2-methylbut-1-ene, water/butanol, 93%; b. 4-$FPhNH_2$, EDC, HOBt, $EtN(iPr)_2$, DMF, 90%; c. NaH, THF, 0 ^oC, 97%; d. 2-[N,N-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine, NaH, THF, 0 ^oC, 73%; e. tert-butyl pent-4-enoate, 9-BBN, $Pd_2(dba)_3$, butyldi-1-adamantylphosphine, K_3PO_4, THF, 75 ^oC, 84%.

With the best R3 group identified, we next looked into the synthetic strategy to build the isoquinolinone core so that R2 and R6 could be introduced sequentially while fixing R3 as pentanoic acid. Compound **12** was chosen as the key intermediate in this case. It was prepared from compound **1** in two steps in good yield. Compound **12** could be converted to the final product through the Chan-Lam N-arylation[8] to introduce R2 (**13**) and subsequent one pot amide formation reaction to give R6 substitutions (Scheme 3). Through this route, we were able to establish baseline SAR at R2 and R6 positions. However, the low yield of the Chan-Lam N-arylation (~5% in this case) hampered the effort to produce the key intermediate in sufficient quantity to support broad SAR development and scale up.

Scheme 3. Isoquinolinone core synthesis with R2 and R6 diversification.

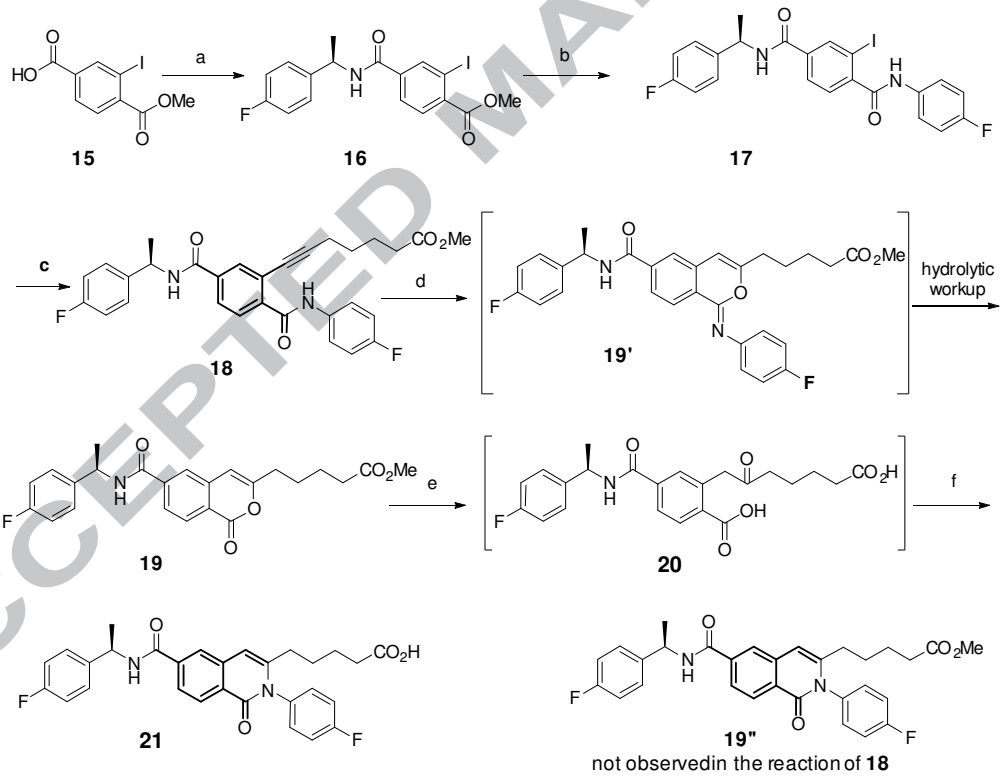


Reagents and conditions: a. **10**, Hunig's base, CDI, MeCN, 90 ^{o}C, 15%; b. NH_3/MeOH (7 M), 84%; c. 4-fluorophenylboronic acid, copper(II) acetate, pyridine, DCM, 50 ^{o}C, 5%; d. (R)-1-(4-fluorophenyl)ethylamine, $Pd(OAc)_2$, molybdenum hexacarbonyl, DBU, THF, 160 ^{o}C, 45%.

At this point, the above chemistry served the purpose to carry out initial SAR of this series. But more efficient chemistry was needed to further expand the SAR scope and scale up lead compounds for downstream characterizations. We decided to explore the possibility of constructing the isoquinolinone ring after R2, R3 and R6 functional groups were strategically placed. To achieve this, we chose to employ an intramolecular cyclization reaction of *ortho*-alkynylbenzamides using transition metal catalysts. Although similar methods were reported in the literature as an important strategy for the direct synthesis of isoquinolinones,[4,9] the application of these methods were limited for two main reasons. The first reason was poor regioselectivity due to competitive cyclization processes that can occur through either the *5-exo* or *6-endo* cyclization. The second reason was potential lack of chemoselectivity due to competitive nuecleophicity of the oxygen and nitrogen atoms of the amide moieties.[10] Moreover, a cyclization reaction involving arylbenzamides was not reported, which was a key functional feature (R2) of the current series. To test this idea, alkyne **18** was prepared from iodide **15** in 3 steps with high yields through sequential amide formation (**16** and **17**) and alkyne coupling reaction. When compound **18** was subjected to a Pd mediated cyclisation reaction (benzylbis(triphenylphosphine)palladium(II) chloride), the product isolated was 1H-isochromen-1-one derivative **19** instead of the desired N-cyclized product **19''**. This product might have been

derived from the hydrolysis of O-attacked product **19'** (Scheme 4) which slowly decomposed to the hydrolyzed product **19** under mild acidic conditions or on silica gel. Although it could be isolated by manipulating workup conditions, crude intermediate **19'** was directly hydrolyzed to **19** by treating the reaction mixture with ethyl acetate and 1 N HCl (Scheme 4) upon workup to facilitate the synthesis. Use of different catalysts such as $AuClPPh_3$ in the presence of silver trifluoromethanesulfonate[11] failed to change the chemoselectivity, and provided the same product in comparable yield (75%). Interestingly, this arylbenzamide cyclization reaction was highly regioselective and the 5-exo cyclization product was minimized. If any of this product could be detected, it could not be isolated in synthetically useful amount. While this was a disappointing result, we were able to convert compound **19** to the desired product **21** in two steps without isolating ketodiacidic product **20**.

Scheme 4. Isoquinolinone core synthesis through intramolecular cyclization.

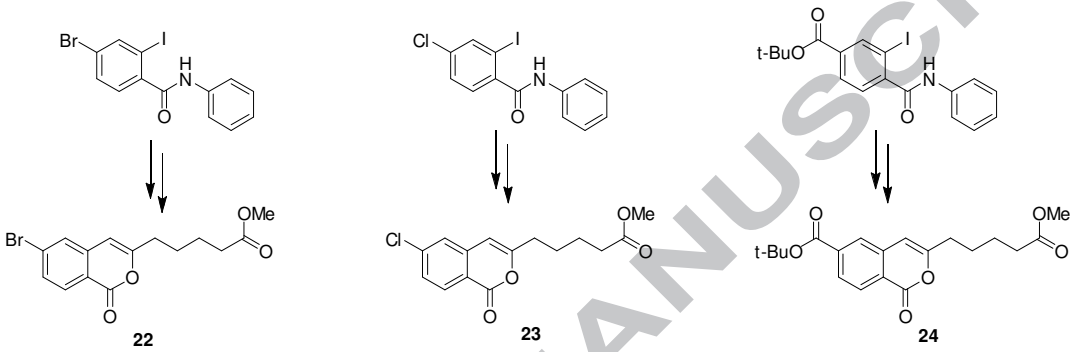


Reagents and conditions: a. (R)-1-(4-fluorophenyl)ethylamine, EDC, HOBt, Hunig's base, DMF, 98%; b. 4-$FPhNH_2$, LHMDS, THF, 0 ^oC, 25%; c. methyl hept-6-ynoate, CuI, $PdCl_2(PPh_3)_2$, NEt_3/DMF, 82%; d. benzylbis(triphenylphosphine)palladium(II) chloride, NEt_3, THF, 80 ^oC,

work up with EtOAc/1 N HCl, 80%; e. $LiOH.H_2O$, THF/water, 100%; f. 4-$FPhNH_2$, HOAc, 90 ^oC, 50%.

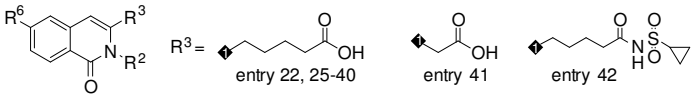
With this process worked out, we were able to apply it to the synthesis of a few key intermediates (Figure 2, **22**-**24**) which were employed in the preparation of compounds with diversified R2, R3 and R6 substitution patterns to assist SAR development.

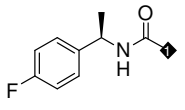
Figure 2. The preparation of 1H-isochromen-1-ones.



With efficient chemistry worked out and key intermediates synthesized, a series of compounds were prepared with diversified R2, R3 and R6 groups. Their binding activity (competitive binding) against the $CRTh_2$ receptor was summarized in Table 1. As can be seen, both electronic withdrawing and donating group substituted aryls were acceptable at R2 position (compounds **21, 25**-**30**, Table 1) with 4-fluorophenyl group as one of the best (compound **21**). R6 substitution could tolerate numerous functional groups including amides and heterocycles (compounds **31**-**40**, Table 1) and a number of very potent compounds were identified (compounds **31** and **32**). Although a shortened side chain at R3 was not tolerated (compound **41**, Table 1), acylsulfonamides with the proper alkyl linkage gave comparable activity to the acids at the R3 position (compound **42**, Table 1).

Table 1. SAR summary of 2,3,6-trisubstituted 1-oxo-1,2-dihydroisoquinolines as $CRTh_2$ antagonists.



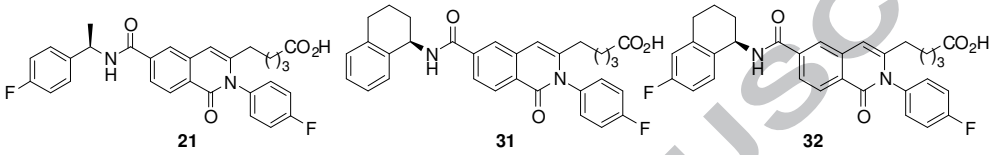
No.	R^6	R^2	Ki (nM)	No.	R^6	R^2	Ki (nM)
21			5.9	**34**			14
25			703	**35**			21
26			49	**36**			11
27			8.5	**37**			26
28			13	**38**			22
29			19	**39**			7.8
30			9.2	**40**			13
31			5.8	**41**			4920
32			6.5	**42**			15
33			24				

Data represented the average values of duplicates or triplicates.[12]

To further evaluate the potential application of these compounds in modulating CRTh2 activity in an endogenous setting, three compounds (**21**, **31**, and **32**) were evaluated in the CD11b

activation assay, a biomarker indicative of pharmacodynamic efficacy of $CRTh_2$ antagonists.[13,14] All three compounds showed excellent inhibition of CD11b activation with compound **21** the most potent with a Ki of 0.23 nM. These biological results warrant further characterization of these compounds in PK/PD studies and ancillary profilings as lead $CRTh_2$ antagonists for the treatment of asthma.

Figure 3. Activity of lead 2,3,6-trisubstituted 1-oxo-1,2-dihydroisoquinolines in the CD11b assay.



In summary, new synthetic methods were developed for the preparation of 2,3,6-trisubstituted 1-oxo-1,2-dihydroisoquinolines as $CRTh_2$ antagonists. The isoquinolinone core could be constructed before the introduction of substitution groups or could be synthesized through an intramolecular cyclization reaction with substitution groups properly installed. These synthetic strategies have helped to accelerate the SAR development of this series. Lead compounds were identified with potent activity in both the $CRTh_2$ binding assay and the CD11b biomarker assay. Further characterization of these lead compounds is ongoing and the results will be reported in due courses.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/xxxx/xxxxxxx.

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