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SHORT COMMUNICATION

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Breaking and Making of Rings: A Method for the Preparation of 4-Quinolone-3-carboxylic Acid Amides and the Expensive Drug Ivacaftor

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A simple and convenient method to access 4-quinolone-3-carboxylic acid amides from indole-3-acetic acid amides through one-pot oxidative cleavage of the indole ring followed by condensation (Witkop–Winterfeldt type oxidation) was explored. The scope of the method was confirmed with more than 20 examples and was successfully applied to the synthesis of the drug Ivacaftor, the most expensive drug on the market.

Introduction

Quinolones are present in several biologically active natural products and many blockbuster drugs. More precisely, 4-quinolone-3-carboxylic acid derivatives are among the most common frameworks, and they appear in several marketed drugs, in particular, in many synthetic antibiotic drugs, such as Ciprofloxacin, Levofloxacin, and Moxifloxacin.[1] The recently approved Vertex drug Ivacaftor[2] used for the treatment of cystic fibrosis also contains a 4-quinolone-3-acid amide core structure. Another drug called Orkambi is a combination of Ivacaftor and Lumacaftor, and it just obtained FDA approval for expanded therapeutic potential in treating cystic fibrosis. In addition, this class of compounds is associated with a variety of biological activities, including antitumor, antiviral, and antiparasitic activities and cannabinoid receptor 2 modulation.[1,3] Selected compounds with their biological activities are listed in Figure 1. Therefore, the 4-quinolone-3-carboxylic acid motif can be regarded as a "privileged structure" in medicinal chemistry. Considering the widespread nature of this class of compounds, we expected many synthetic routes to access them. To our surprise, all the reported methods fall into only three routes for this valuable scaffold, and they are listed in Scheme 1.[1,3,4] Though these methods, along with some improvements, have been used for the synthesis of quinolonecarboxylic acid derivatives, they suffer from harsh conditions such as high temperature (> 200 °C) and removal of high-boiling solvents is difficult. As part of the total synthesis program in our group, we recently utilized ozonolysis for the oxidative cleavage of indole rings towards solomonamide natural products.[5] Ozonolysis is a powerful tool for the synthesis of numerous interesting bioactive natural products and pharmaceutical agents.[6] The recent advancements in technologies and experimental approaches for ozonolysis have allowed the large-scale production of drugs and useful building blocks at the industrial scale.[7] The prospects of 4-quinolone-3-carboxylic acid derivatives in drug discovery and the existing harsh conditions for their synthesis prompted us to develop a simple and mild method

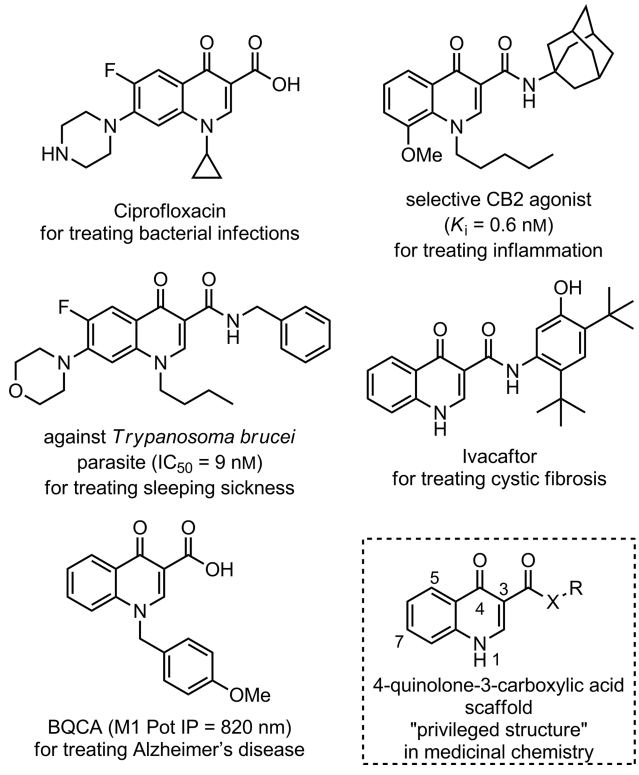

Figure 1. Selected compounds with their biological activities.

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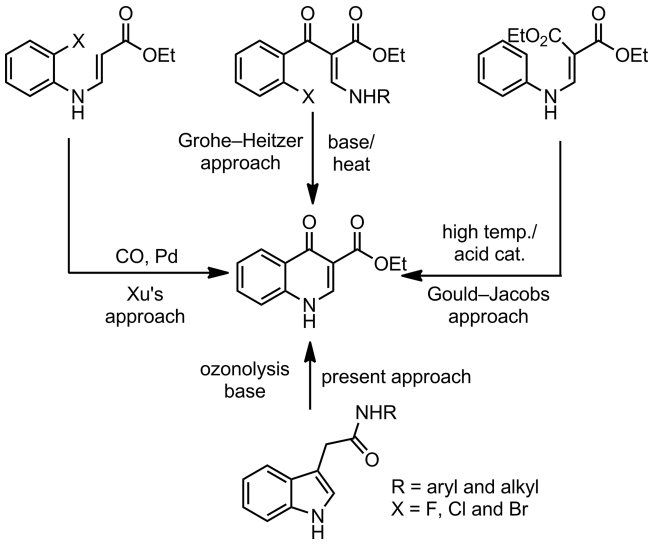
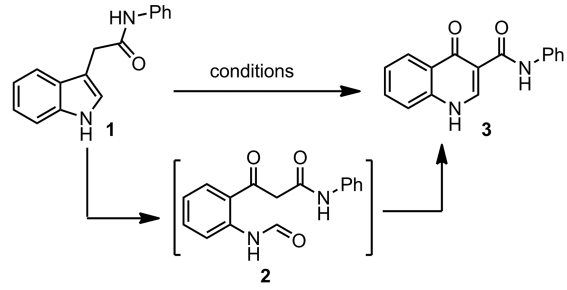
that is similar to the underexplored Witkop–Winterfeldt oxidation (WWO).[8] This reaction involves oxidative cleavage of the C2–C3 double bond of the indole skeleton (Witkop oxidation) followed by an aldol-type condensation (Camps cyclization) to form a quinolone ring system. Although WWO has great potential, it is mostly restricted to polycyclic substrates, which results in quinolones embedded within polycyclic systems.[9] A few years ago, an excellent compilation of the literature on WWO was published in a review article by Breinbauer.[10] Herein, we disclose a new method to produce the title compounds.



Scheme 1. Approaches to quinolone-3-carboxylic acid derivatives.

Results and Discussion

To begin, we chose indol-3-ylacetic acid phenylamide (**1**)[11] as a substrate for optimization. We tried various conditions, and they are compiled in Scheme 2. Ozonolysis of compound **1** in CH_2Cl_2 with an excess amount of pyridine (Py, ca. 10 equiv.)[12] gave only oxidatively cleaved product **2**.[13] Encouragingly, the addition of an external base [e.g., Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)] resulted in desired 4-quinolone-3-carboxylic acid amide **3** along with compound **2** (Scheme 2, Entries 2–4), which is in agreement with literature data.[14] On doubling the amount of base (Scheme 2, Entry 5), the desired product ratio was increased. To our delight, ozonolysis in a mixture of CH_2Cl_2/MeOH (5:1) under similar conditions improved the yield (58%; Scheme 2, Entry 7). No significant improvement was observed by changing the quenching reagents, for example, dimethyl sulfide (Me_2S), or by using an inorganic base such as $NaHCO_3$. After these trials, we settled with ozonolysis in CH_2Cl_2/MeOH, followed by the addition of pyridine and stirring at room temperature for 3 h followed by the addition of *N*,*N*-diisopropylethylamine (DIPEA) to obtain the desired products.



Entry	Conditions	Yield [%][a] 3	2
1	O_3, CH_2Cl_2, Py (10 equiv.)	0	70
2	O_3, CH_2Cl_2, Py (3 equiv.), Et_3N (3 equiv.)	30	35
3	O_3, CH_2Cl_2, Py (3 equiv.), DBU (3 equiv.)	25	33
4	O_3, CH_2Cl_2, Py (3 equiv.), DBN (3 equiv.)	20	42
5	O_3, CH_2Cl_2, Py (3 equiv.), Et_3N (6 equiv.)	45	20
6	O_3, CH_2Cl_2/MeOH, Py (3 equiv.), Et_3N (6 equiv.)	55	15
7	O_3, CH_2Cl_2/MeOH, Py (3 equiv.), DIPEA (6 equiv.)	58	10
8	O_3, CH_2Cl_2/MeOH, Me_2S (3 equiv.), Et_3N (6 equiv.)	48	trace
9	O_3, CH_2Cl_2/MeOH, Me_2S (3 equiv.), DIPEA (6 equiv.)	50	trace
10	O_3, CH_2Cl_2/MeOH, Py, $NaHCO_3$ (6 equiv.)	20	40

O_3, –78 °C, 15 min, then pyridine, –78 °C to r.t. (3 h), then DIPEA, r.t., 18 h.
[a] Isolated yields.

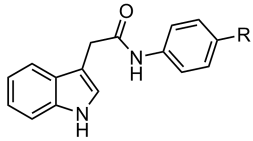
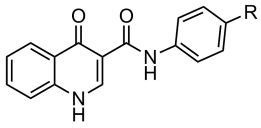
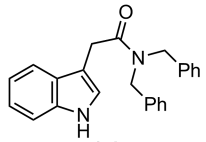
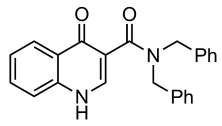
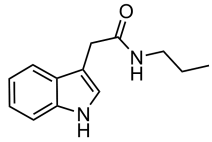
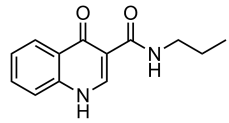
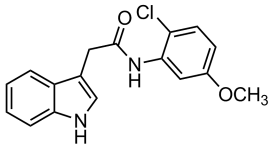
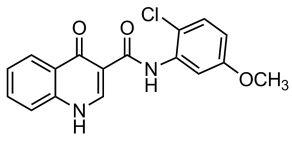
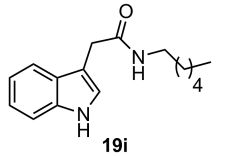
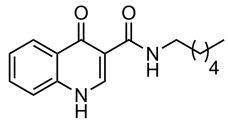
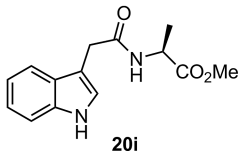
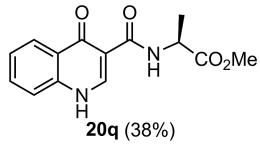
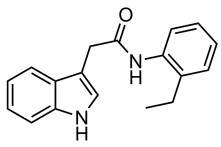
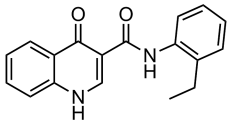
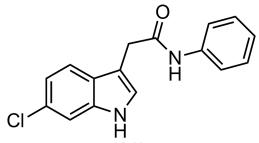
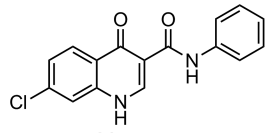
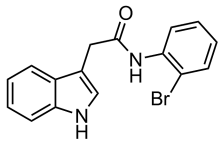
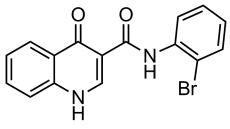
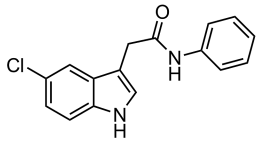
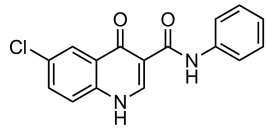
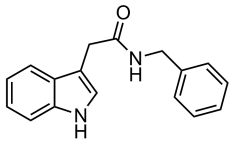
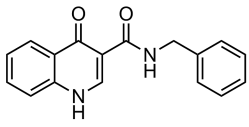
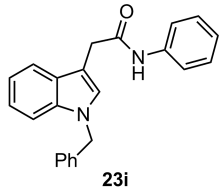
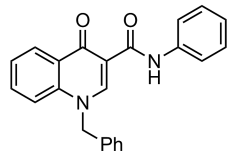
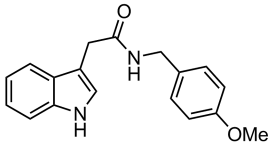
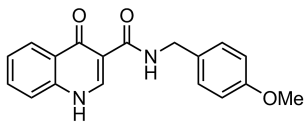
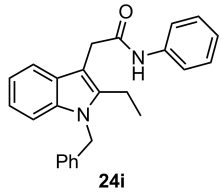
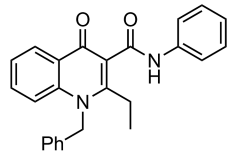
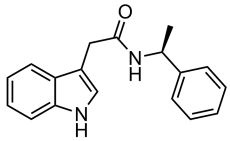
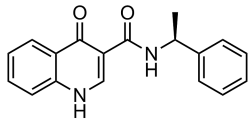
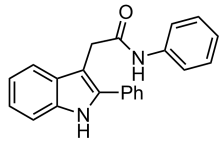
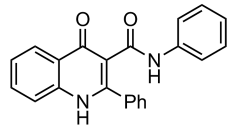
Scheme 2. Reaction optimization by using ozonolysis.

Having the optimized conditions in hand, we then decided to test the scope of the method with various indolylacetic acid amides.[15] All the results along with the yields of the isolated products are summarized in Table 1. The initial 10 entries (see compounds **4** to **13**) are compounds with substituted aniline moieties, and all of them were well tolerated. Benzylamides, including chiral phenethylamide and dibenzylamide, also worked well under the reaction conditions (see compounds **14**–**17**). Notably, compound **17q** was the initial lead compound in the Vertex program on cystic fibrosis.[16] Aliphatic amides with short chains and long chains also underwent smooth conversion to provide the corresponding 4-quinolone-3-carboxylic acid amides in moderate yields (see compounds **18** and **19**). We also included the amide of alanine methyl ester to increase the scope of the method, which gave us slightly inferior yields (see compound **20**). Chloro substitution on the indole ring was also well tolerated (see compounds **21** and **22**).

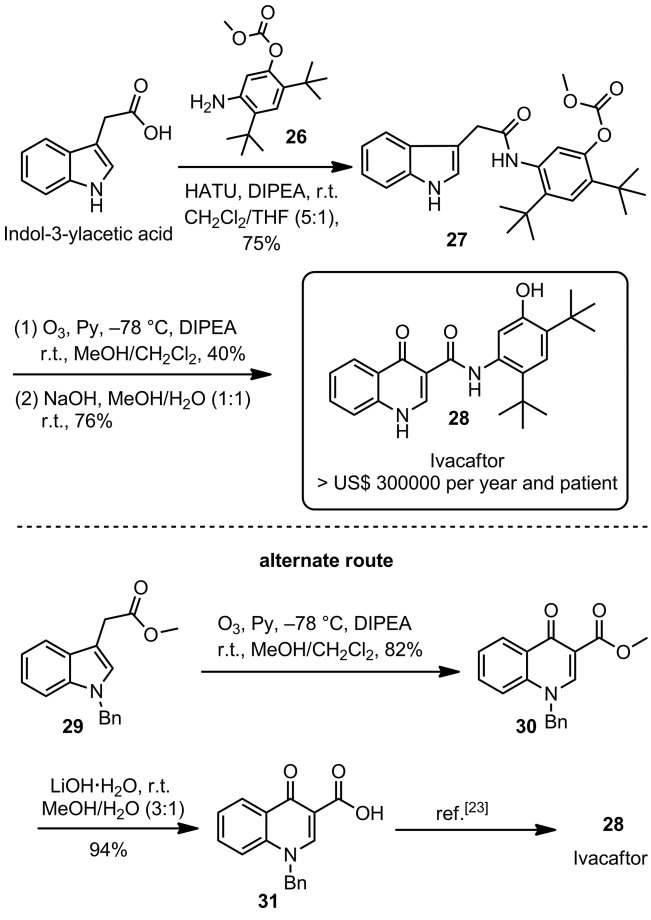
Substrates with *N*-benzyl substitution also underwent smooth conversion under the optimized conditions (see compound **23**). However, 2-substituted indol-3-ylacetic acid amides (see compounds **24i** and **25i**) did not give the desired quinolones (see compounds **24q** and **25q**), and this can probably be explained by the reactivity difference between alkyl-/arylamides and formamide.

As a direct application of the present method, the synthesis of Ivacaftor,[2,17] the most expensive and only drug available on the market for treating the genetic disorder cystic

Table 1. Scope of the method.

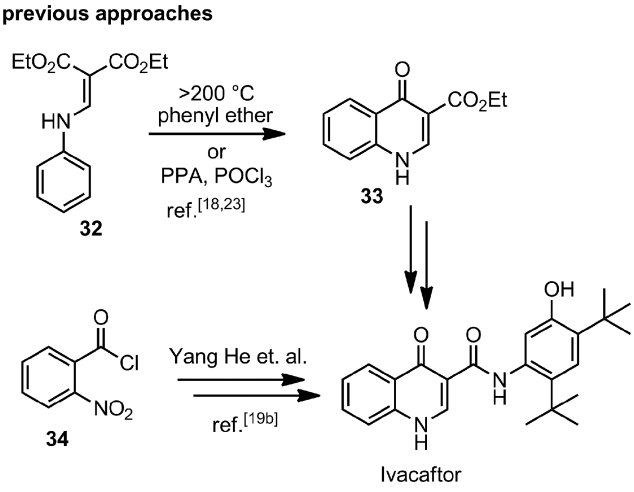
Indol-3-ylacetic acid amide	Quinolone-3-carboxylic acid amide (yield)	Indol-3-ylacetic acid amide	Quinolone-3-carboxylic acid amide (yield)
 **4i**: R = F **5i**: R = Cl **6i**: R = Me **7i**: R = Et **8i**: R = Pr **9i**: R = *i*Pr **10i**: R= OCF_3	 **4q**: R = F (56%) **5q**: R = Cl (51%) **6q**: R = Me (57%) **7q**: R = Et (51%) **8q**: R = Pr (55%) **9q**: R = *i*Pr (46%) **10q**: R= OCF_3 (57%)	 **17i**	 **17q** (43%)
		 **18i**	 **18q** (47%)
 **11i**	 **11q** (54%)	 **19i**	 **19q**(51%)
		 **20i**	 **20q** (38%)
 **12i**	 **12q** (58%)	 **21i**	 **21q** (48%)
 **13i**	 **13q** (47%)	 **22i**	 **22q** (52%)
 **14i**	 **14q** (58%)	 **23i**	 **23q** (55%)
 **15i**	 **15q** (53%)	 **24i**	 **24q** (0%)
 **16i**	 **16q** (53%)	 **25i**	 **25q** (0%)

fibrosis, was undertaken (Scheme 3). Indol-3-ylacetic acid was coupled with known 5-amino-2,4-di-*tert*-butylphenyl methyl carbonate (**26**)[18] by using 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) as a peptide coupling agent to afford corresponding amide **27** in 75% yield. Upon subjecting compound **27** to ozonolysis under the optimized conditions, the desired 4-quinolone-3-carboxylic acid amide was furnished in moderate yield, and on deprotection[18] by using methanolic NaOH solution at room temperature it afforded Ivacaftor (**28**). The spectroscopic data were compared with the reported data, and they were found to be identical in all respects.[19] In an alternate route, indolylacetic acid ester **29**[20] was subjected to ozonolysis under the same conditions to yield corresponding quinolone ester **30**[21] in excellent yield (82%). Ester hydrolysis of compound **30** under basic conditions gave known 4-quinolone-3-carboxylic acid **31**[22] in 94% yield; this compound was previously converted into Ivacaftor through amine coupling followed by debenzylation.[23] For comparison purposes, the known methods for the synthesis of Ivacaftor are shown in Scheme 4, and they suffer from drawbacks such as high temperature, the use of strong acid, and so on.



Scheme 3. Synthesis of Ivacaftor.

Therefore, the present method is better than the existing methods, and furthermore, two reactions (breaking and making of rings) take place in a single operation under mild conditions.



Scheme 4. Selected previous approaches to Ivacaftor. PPA = polyphosphoric acid.

Conclusions

Thus, we developed a simple, short, and convenient method for the preparation of 4-quinolone-3-carboxylic acid derivatives starting from commercially available indol-3-ylacetic acid by using one-pot oxidative cleavage of indole and condensation as the key steps. This method has great potential for the synthesis of several biologically active compounds, in particular quinolone-based antibiotic drugs. In addition, the generality of the method was established with a variety of substrates, and it was successfully applied to the synthesis of the drug Ivacaftor.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for all key intermediates and final products.

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