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A Consolidated and Continuous Synthesis of Ciprofloxacin from a Vinylogous Cyclopropyl Amide

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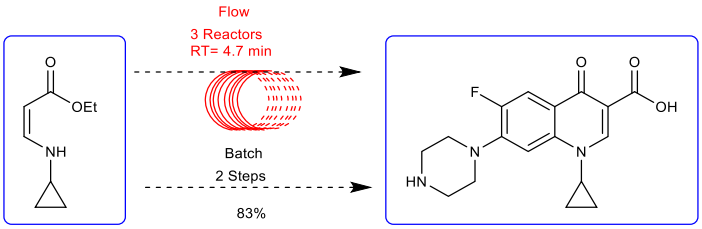
Supporting Information



ABSTRACT: Ciprofloxacin is a broad-spectrum antibiotic that is recognized as one of the World Health Organization's Essential Medicines. It is particularly effective in the treatment of Gram-negative bacterial infections associated with urinary, respiratory and gastrointestinal tract infections. A streamlined and high yielding continuous synthesis of ciprofloxacin has been developed, which employs a chemoselective C-acylation step that precludes the need for intermediate isolations, extractions or purifications. The end-to end process has a residence time of 4.7 minutes with a 15.8 g/hr throughput at laboratory scale and an overall isolated yield of 83%.

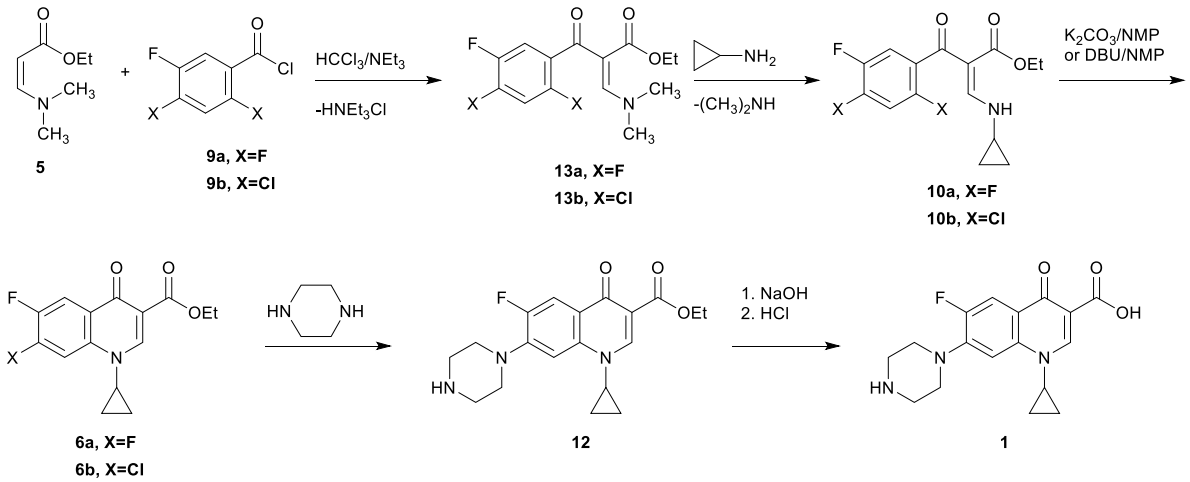
INTRODUCTION

Access to affordable medications continues to be one of the most significant challenges in global health care management. For many of these treatments, synthesis of the active pharmaceutical ingredient (API) represents the most technically demanding and financially important element in the preparation of these materials. In many cases, the API cost accounts for up to 60-75% of the total drug product cost.[1–3] These API processes often evolve from medicinal chemistry routes in an effort to expedite commercialization of the drug product, thus providing an opportunity to apply new and more cost effective synthetic approaches for the preparation of these compounds.[2,4–8]

Our research group has applied the principles of process intensification to develop streamlined approaches to API production of essential medicines as defined by the World Health Organization (WHO). This approach involves utilizing low-cost raw materials, developing high yielding convergent chemical synthesis and novel manufacturing platforms.[2,8–10] In this body of work, we report an improved continuous preparation of ciprofloxacin (**1**).

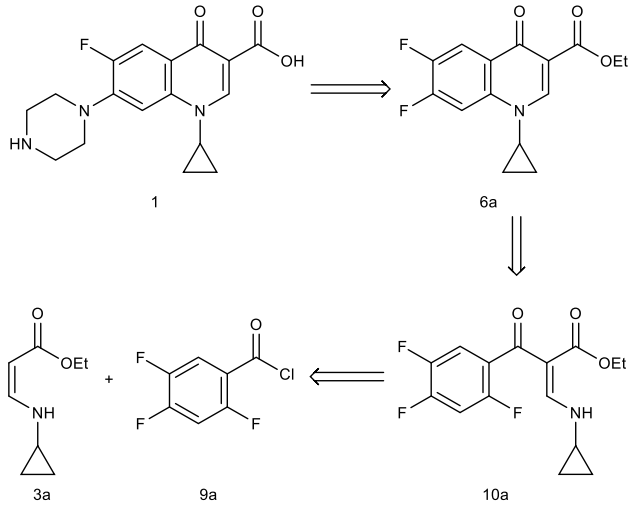
Ciprofloxacin (**1**) is the most widely prescribed of the fluoroquinolone class of antibiotics and is employed in the treatment of urinary tract, respiratory tract and gastrointestinal infections.[11–15] Since its discovery by Bayer AG nearly four decades ago,[12] limited advances has been made to the general synthetic scheme for the preparation of this important medication. One of the more efficient methods for the preparation of ciprofloxacin (**1**) that has been published relies on a multi-stage one pot batch synthesis with seven chemical

Scheme 1. Current synthetic route to ciprofloxacin



transformations (Scheme 1)[17–19] and an overall yield of 49%. Recently, Lin and coworkers reported a continuous ciprofloxacin process with an overall yield of 60%.[19] Both of these processes employ a common synthetic strategy that utilizes dimethylaminoacrylate (**5**) as a starting material.

Scheme 2. Our retrosynthetic strategy to ciprofloxacin



We were able to take advantage of the ability of lithiated secondary enamines to give the desired C-acylated product (Figure 1).[19] In this application using LiHMDS as the base, a high yielding chemoselective C-acylation product **10a** (Scheme 2) was exclusively produced and upon gradual warming to room temperature, gave the ring-closed precursor **6a** in a 94% yield. Furthermore, this approach precludes the formation of a key side-product **4** that is produced when **5** (Scheme 1) is employed as a starting material (Figure 2).[18,19] By consolidating this multi-step reaction sequence into a minimal number of high yielding unit operations, the preparation and conversion of the quinolone intermediate (**6a**) into the API can be readily applied to both batch and continuous operations.

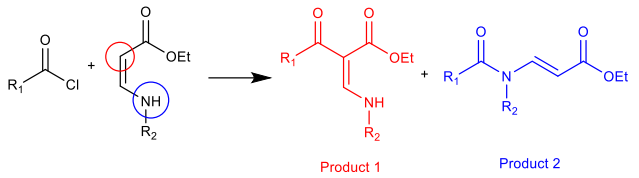
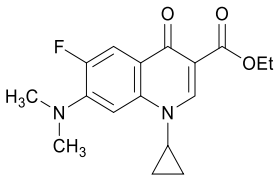


Figure 1. Competitive C-acylation and N-acylation

Herein we report an alternative, more convergent and higher yielding approach for the synthesis of ciprofloxacin (**1**) (Scheme 2) that relies on the early stage insertion of the cyclopropylamine moiety via a chemo-selective addition of the corresponding vinylogous amide **3a**, which was prepared from a more affordable and cost-effective vinyl ether.



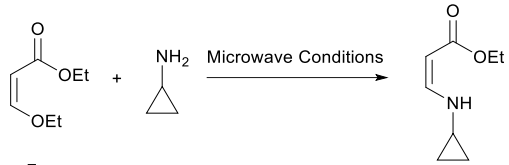
4

Figure 2. Major ciprofloxacin by-product

RESULTS AND DISCUSSION

The development of a viable synthetic route for the vinylogous amide **3a** represented the initial challenge towards streamlining the API process. We elected to evaluate a range of reaction conditions using the corresponding vinyl ether (**7**) and cyclopropylamine as starting materials with the knowledge that the poor electrophilic character of the ethyl ethoxyacrylate[20–22] may impede the conversion to **3a**. Initial screening studies were carried out with microwave heating under autogenous pressure and a broad range of solvents. All experiments were conducted in septum-sealed reaction vessels with the single-mode cavity dedicated Biotage Initiator reactor. All reaction temperatures were measured externally on the outside vessel wall by an IR sensor, as permitted only by the conventional setup of the above MW reactor. The results of these experiments are summarized in Table 1. The reaction proceeded in ethanol albeit with only 35% conversion (Table 1, entry 1). The transformation failed to proceed when poor microwave absorbing solvent such as toluene and THF were used (Table 1, entry 3 and 4). The desired product was obtained in good yields when the reactions were microwave heated to 150 °C in DMSO or DMF (Table1, entries 7 and 8).

Table 1. Synthesis of vinylogous amides in microwave[a]

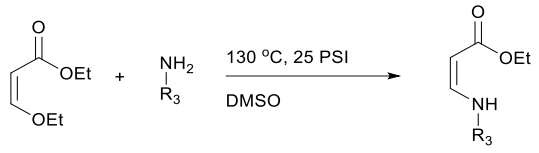


Entry	Solvent	Temp (°C)	Time (min)	Conv. (%)[b]
1	EtOH	78	90	35
2	-	60	30	0
3	Toluene	90	30	0
4	THF	90	30	0
5	ACN	140	60	38
6	DMF	150	30	87
7	DMF	150	60	100 (96)[c]
8	DMSO	150	60	99 (96)[c]

[a]Reaction conditions: **7** (1.0 equiv.), cyclopropylamine (3.0 equiv.). The aminations were carried out in a septum-sealed vial using the Biotage Initiator Microwave Reactor. [b]Conversions are determined by HPLC. [c]Isolated yield.

The nucleophilic displacement was successfully reproduced when the reaction vessel was pressurized to 25 PSI with argon and traditional thermal heating at 130 °C to give **3a** in a high yield (96%). We also applied this methodology to various substrates with the goal of producing corresponding vinylogous amides. The method worked well with selected amines as shown in Table 2.

Table 2. Synthesis of vinylogous amides in batch[a]



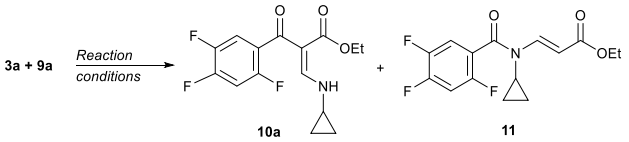
7 8a-d 3a-d

Amines	R_3	Conv. (%)[b]	Product (%)
8a	cyclopropyl	100	**3a** (96)[c]
8b	propyl	96	**3b** (94)
8c	benzyl	89	**3c** (85)
8d	cyclohexyl	91	**3d** (87)

[a]Reaction conditions: **7** (1.0 equiv.), **amine** (3.0 equiv.), DMSO. All reactions were carried out at 130 °C, at 25 PSI with argon. [b]Conversions are determined by HPLC. [c]Isolated yield.

We then proceeded to react **3a** with 2,4,5-trifluorobenzoyl chloride. Previous attempts to achieve selective C-acylation using n-BuLi as a base have been reported, yielding a mixture of N-acylation and C-acylation in a ratio of 6:1 respectively[19]. A screen of the bases confirmed the difficulty of the chemoselective alkylation (Table 3, entry 1-4). However, in our hands the desired alkylation was achieved when bulkier lithiated non-nucleophilic bases were used (Table 3, entry 5 and 6). A complete conversion with exclusively C-acylation was achieved in the presence of LiHMDS with a 96% isolated yield (Table 3, entry 6). In addition, we were able to demonstrate the selective C-acylation of the vinylogous amine when LiHMDS was used when the R = propyl, benzyl and cyclohexyl in good yield (Scheme 3).

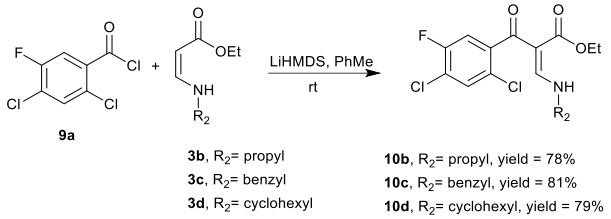
Table 3. C-acylation optimization[a]



Entry	Base	Temp (°C)	**10a**:**11** ratio	Conv. (%)[b]
1	Et_3N	90	1:7	10.5
2	Pyridine	rt	1:13	5
3	DBU	90	1:10	6
4	DIPEA	90	1:10	6
5	LDA	rt	>100:1	83
6	LiHMDS	rt	>100:1	100 (96%)[c]
7	NaH	0	1:60	2

[a]Reaction conditions: **3a** (1.0 equiv.), 2,4,5-trifluorobenzoyl chloride (1.2 equiv.), base (1.2 equiv.), toluene, [b]Conversions are determined by HPLC. [c]Isolated yield. rt (room temperature).

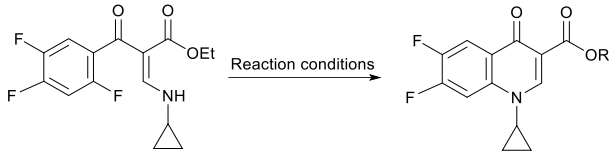
Scheme 3. Selective C-acylation vinylogous amide **3b-d**.



[a]Reaction conditions: **3b-d** (1.0 equiv.), **9a** (1.1 equiv.). LiHMDS (1.1 equiv.), -78 °C to rt

Previous reports suggest that **10a** cyclizes in the presence of an additional equivalent of strong bases (Table 4, entry 1-4).[17,19] When **10a** was treated with LiHMDS, **6a** was prepared with a near quantitative yield (Table 4, entry 5). We additionally sought to consolidate the acylation to **10a** and the intramolecular ring closing to **6a** into a single step. By treating **9a** and **3a** with a slight excess of LiHMDS we were able to obtain the quinolone (**6a)** in a 94% isolated yield (Scheme 4).

Table 4. Intramolecular ring closing to **6a**[a]



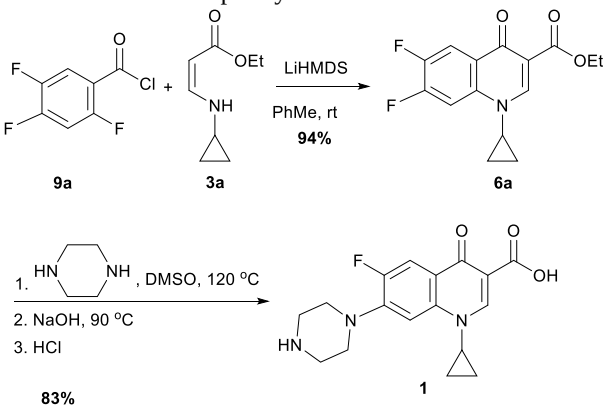
Entry	Base	Temp (°C)	Solvent	R	Conv. (%)[b]
1	DBU	90	DMSO	Et	98
2	K_2CO_3	90	DMSO	Et	98
3	NaH	90	DMSO	Et	96
4	LiOH	90	DMSO	H	98 [c]
5	LiHMDS	rt	Toluene	Et	98 (95[c])

[a]Reaction conditions: **10a** (1.0 equiv.), base (1-4) (3 equiv.), LiHMDS (1.1 equiv.). [b]Conversions are determined by HPLC. [c]Isolated yield.

With the preparation of the quinolone (**6a**) optimized, we set out to complete the synthesis of (**1**). The piperazine coupling was carried out at 120 °C in DMSO to give the ciprofloxacin ester (**12**) with a 94% conversion. The ester was then hydrolysed in the presence of NaOH, followed by a pH adjustment to afford ciprofloxacin (**1**) (Scheme 4). With all steps optimized, the process was telescoped into a one-pot synthesis as shown in Scheme 4. The telescope batch synthesis (Scheme 4) provided a final yield of 83% after crystallization, which proposes to reduce the number of unit operations compared to the existing batch process.

Based on these findings, we envisioned a telescoped continuous process over a three reactor platform with no intermediate isolations, separations or purifications. Lin and co-workers have previously reported a continuous method for the preparation of **1** over five reactors with a total residence time of

Scheme 4. Telescoped synthesis of **1**



[a]Reaction conditions: **3a** (1.0 equiv.), **9a** (1.1 equiv.). LiHMDS (2.2 equiv.), -78 °C to rt, 2 h; piperazine (4 equiv.), H_2O, 90 °C, NaOH (4 equiv.).

9 mins.[19] Using this alternative streamlined synthetic approach, we carried out the acylation step by reaction of the lithiated **3a** with **9a** over a 2 mL reactor coil. The direct conversion to the quinolone (**6a**) was achieved in 1 min with a 92% yield in a 2 mL reactor coil (Scheme 5). However, the production of **6a** resulted in clogging when toluene was used as a solvent. By substituting THF as the solvent, we were able to solubilize both reactants and products to give a 95% isolated yield of **6a** while retaining a 1 min residence time.

Since we had previously found that the condensation of **6a** with piperazine required heating to 120 °C, we preheated the piperazine to this temperature in DMSO prior to mixing with the output from reactor I which was preheated to 60 °C. The subsequent mixture was fed into a 10 mL reactor coil (reactor II). The reaction temperature was raised to 140 °C, at 75 PSI with a residence time of 2.5 minutes to give a 96% conversion to **12**. The hydrolysis of **12** was carried out in an additional 10 mL reactor coil (reactor III) with 1 M sodium hydroxide at 120 °C followed by pH adjustment to give **1** in 83% isolated yield and an overall throughput of 15.8 g/hr. A summary of the total continuous synthesis of **1** is provided in Scheme 5.

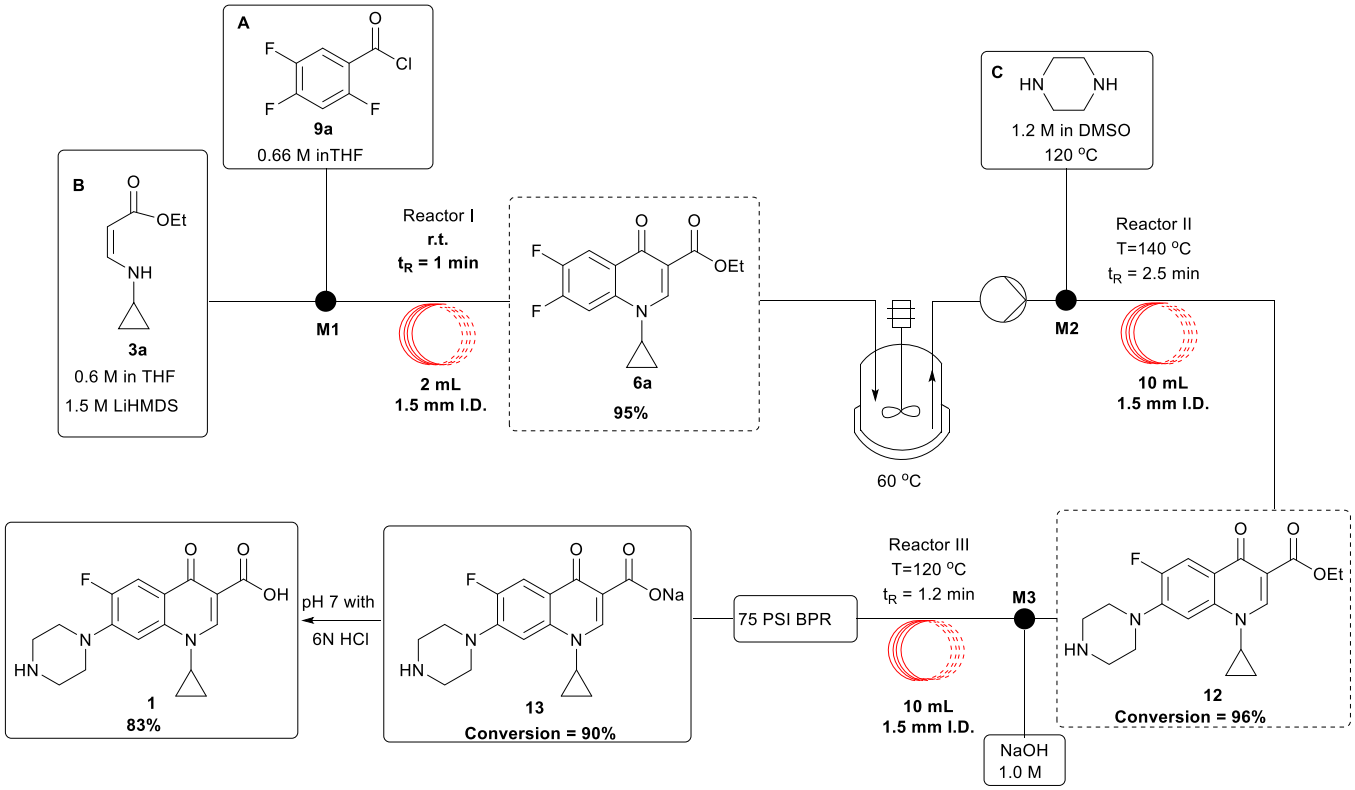
CONCLUSION

In summary, we have developed an improved synthetic route to ciprofloxacin employing a strategy based on the early stage insertion of the cyclopropyl amine moiety via a chemoselective addition of the corresponding vinylogous amide (**3a**). As a result, we were able to consolidate the acylation and the S_NAr into a single step, leading to an 83% overall yield of the API. Furthermore, we successfully transitioned our streamlined synthesis into a continuous process over only four unit operations with a 4.7 min residence time and a 15.8 g/hr throughput in our laboratory unit.

EXPERIMENTAL SECTION

General Information and Method. Experiments involving moisture and/or air sensitive compounds were performed under a positive pressure of argon in oven-dried glassware equipped with a rubber septum inlet. Dried solvents and liquids were transferred by oven-dried syringes or hypodermic syringes cooled to ambient temperature. Reactions mixtures were stirred in a round-bottom flask with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents/compounds was removed in high vacuo by means of an oil pump and subsequent purging with argon. Solvents were removed in vacuo under pressure and heated with water bath at 30-40 °C using rotary evaporator with aspirator. All experiments were monitored with High Performance Liquid Chromatography (HPLC) analysis. UV detection was monitored at 254 nm, 210 nm and 280 nm at the same time.

Scheme 5. Continuous synthesis of ciprofloxacin **(1)**



HPLC samples were dissolved in HPLC grade acetonitrile unless otherwise stated.
Columns for flash chromatography contained silica gel 200-300 mech. Columns were equilibrated using appropriate solvent system.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) and proton-decoupled carbon (^{13}C{1H} NMR) (600 and 150 MHz, respectively) were recorded in $CDCl_3$ or in DMSO-d_6 or otherwise stated on Bruker FT-NMR spectrometer. NMR data were processed using MestReNova 10.0 software package. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS. In order to measure and assign the $J_{19F\text{-}13C}$ coupling constants for compounds 6a, 10a, 10b, 10c, and 10d, complete spectral assignments were obtained by detailed analysis of ^{1}H 1D, ^{13}C {^{1}H} 1-D, COSY, ^{1}H-^{13}C HSQC, and ^{1}H-^{13}C HMBC experiments. The $J_{19F\text{-}13C}$ coupling constants were measured from the ^{13}C {^{1}H} 1-D spectra acquired using 32 k data points defining the FID processed using 0.3 Hz line broadening and zero filled to 256k to provide a reasonably fine digital resolution of 0.14 Hz for 256k points spread over 240 ppm at 150 Hz/ppm.

The names of the products were generated using PerkinElmer ChemBiodraw Ultra v.12.0.2 software package. HPLC chromatograms were recorded on Agilent Technologies 1260 Infinity instrument with a Poroshell 120 EC-C18 column (4.6 x 50 mm, 2.7 µm). High resolution mass spectra were obtained through the Virginia Commonwealth University Chemical and Proteomic Mass Spectrometry Core Facility using an Orbitrap Velos mass spectrometer from Thermo Electron Corporation. Microwave reactions were carried out in Biotage Initiator. Continuous flow experiments were carried out using the E-series flow reactor instrument purchased from Vapourtec Ltd. PFA tubing (1/8" O.D. x 1/16" I.D.) was used for all reactor coils in flow experiments.

Materials. All commercial reagents were purchased and used without further purification. All reaction solvents used: tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), toluene (PhMe) were taken from a "Grubbs-style" solvent dispensing system purchased from Pure Process Technology. All other anhydrous solvents used were purchased from Sigma-Aldrich with Sure Seal. Analytical and preparative thin layer chromatography (TLC) was performed using Analtech Uniplate™ Silica Gel GF (250 micron) precoated glass plates or Merck KGaA Silica Gel 60 F254. Spots were detected by 254 nm UV lamp.

Experimental Procedures

Synthesis of Ethyl-3-(cyclopropylamino)acrylate (3a) in microwave. To a solution of ethyl-3-ethoxyacrylate (**7**) (6.94 mmoles) was added cyclopropylamine (**8a**) (20.82 mmol) in 2 mL Biotage reaction vial. The mixture was diluted with 0.5 mL of DMF and the septum-sealed reaction vial was irradiated by microwave at 150 ^{o}C for 1 h. The reaction was monitored by HPLC. Upon completion of the reaction, the reaction mixture was diluted with 10 mL of water and extracted with dichloromethane (3 x 25 mL), washed with brine (10 mL) and dried over sodium sulfate, filtered under gravity. The solvent was removed under pressure to yield the product as a yellow oil (1.03 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$, Mixture of (E/Z) Isomers (5:1); integrals represent the major isomer): δ 7.44 (q, 1H), 5.06 (s, 1H) 5.01 (d, J = 13.0 Hz, 1H), 4.12 (q, 2H), 2.39 (s, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.71 (quint, 2H), 0.52 (m, 2H);^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 169.4, 152.1, 149.5, 87.5, 83.1, 58.8, 14.5, 6.5. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}NO_2$ 156.0916; found 156.1002.

Synthesis of the amino acrylate (3a-d) from the vinyl ether in batch (General Procedure A). To a solution of ethyl-3-ethoxyacrylate (**7**) (5 g, 34.72 mmol) dissolved in DMSO (30 mL) in a 250-mL round-bottom pressure flask was added the appropriate amine (**8a-d**) (3 equiv.). The vessel was pressurized to 25 PSI under argon and heated to 130 ^{o}C for 4-6 h. After cooling to room temperature, the reaction mixture was diluted in dichloromethane (30 mL) and washed with water (2 x 10 mL), brine (10 mL) dried over sodium sulfate. The combined organic layer was further purified by flash column chromatography (5:1 Hex/EtOAc). The purity was determined by HPLC.

Ethyl-3-(cyclopropylamino)acrylate (**3a**). Prepared following the general procedure A from ethyl-3-ethoxyacrylate (**7**) (15 g, 104.16 mmol) and cyclopropylamine (**8a**) (17.81 g, 312.48 mmol) to give a yellow oil (15.5 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$, Mixture of (E/Z) Isomers (5:1); integrals represent the major isomer): δ 7.44 (q, 1H), 5.06 (s, 1H) 5.01 (d, J = 12.8 Hz, 1H), 4.12 (q, J = 7.2, 2H), 2.39 (s, 1H), 1.25 (t, J = 7.2 Hz, 3H), 0.71 (q, 2H), 0.52 (m, 2H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 169.4, 152.1, 149.5, 87.5, 83.4, 58.8, 14.5, 6.5. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}NO_2$ 156.0916; found 156.1002.

Ethyl-3-(propylamino)acrylate (**3b**). Prepared following the general procedure A from ethyl-3-ethoxyacrylate (**7**) (5 g, 34.72 mmol) and propylamine (**8b**) (6.15 g, 104.16 mmol) to give a yellow oil (5.13 g, 94%)**.** ^{1}H NMR (600 MHz, $CDCl_3$, Mixture of (E/Z) Isomers (3.8:1); integrals represent the major isomer): δ 7.78 (s, 1H), 6.57 (q, J = 7.0, 1H), 4.38 (d, J = 7.8 Hz, 1H), 4.07 (q, J = 7.0 Hz, 2H), 3.07 (q, J = 6.7 Hz, 2H), 1.52 (q, J = 7.1 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H), 0.89 (q, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 171.0, 152.4, 81.3, 58.6, 50.4, 24.5, 14.6, 11.0. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_8H_{16}NO_2$ 158.1103; found 158.1160.

Ethyl-3-(phenylamino)acrylate (**3c**). Prepared following the general procedure A from ethyl-3-ethoxyacrylate (**7**) (5 g, 34.72 mmol) and benzylamine (**8c**) (11.15 g, 104.16 mmol)**.** Further purification with flash column chromatography (5:1:0.1 Hex/EtOAc/Et_3N) gave a yellow oil (6.05 g, 85%)**.** ^{1}H NMR (600 MHz, $CDCl_3$, Mixture of (E/Z) Isomers (3:1); integrals represent the major isomer): δ 8.07 (s, 1H), 7.29 (m, 2H), 7.22 (m, 3H), 6.64 (q, J = 13.1 Hz, 8.2 Hz, 1H), 4.48 (d, J = 13.3 Hz, 1H,), 4.19 (d, J = 6.1 Hz, 2H), 4.08 (m, 2H), 1.2 (q, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.8, 152.1, 138.5, 128.7 (2C), 127.5, 127.1 (2C), 82.9, 58.7, 52.1, 14.5, 14.5. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{16}NO_2$ 206.1103; found 206.1156.

Ethyl-3-(cyclohexylamino)acrylate (**3d**). Prepared following the general procedure A from ethyl-3-ethoxyacrylate (**7**) (5 g, 34.72 mmol) and cyclohexylamine (**8d**) (10.32 g, 104.16 mmol)**.** Further purification with flash column chromatography (5:1:0.1 Hex/EtOAc/Et_3N) gave a white solid (5.97 g, 87%)**.** ^{1}H NMR (600 MHz, $CDCl_3$, Mixture of (E/Z) Isomers (5:1); integrals represent the major isomer): δ 7.89 (s, 1H), 6.74 (q, 1H) , 4.47 (d, 1H, J = 8.0 Hz), 4.14 (p, 2H), 3.05 (m, 1H), 1.92 (t, J = 6.0 Hz, 2H), 1.78 (m, 2H), 1.65 (t, J = 15.0 Hz , 2H), 1.32

(q, 2H), 1.29 (t, J = 7.2 Hz , 3H), 1.21 (p, 2H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.9, 150.4, 81.2, 58.5, 56.7, 34.2 (2C), 25.3 (2C), 24.6, 14.6. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{11}H_{20}NO_2$ 198.1416; found 198.1469.

Synthesis of 10a-d (General Procedure B). A 1 M solution of lithium bis(trimethylsilyl)amide was prepared by dissolving lithium bis(trimethylsilyl)amide (8.4 g) in toluene in a 50 mL volumetric flask under an argon atmosphere. The solution of lithium bis(trimethylsilyl)amide (1.1 equiv.) was charged to an oven dried three necked equipped with a stirring bar was charged under. The solution was cooled to -78 ° C and followed by a slow addition of the acrylate (**3**) (1 equiv.). The resulting bright yellow solution was stirred for 30 min followed by the dropwise addition of 2,4,5-trifluorobenzoyl chloride (1.1 equiv.). The mixture was allowed to warm to room temperature and stirred for 1h. After the completion of the reaction, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and diluted in 30 mL of dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4. The organic solvent was removed under pressure. The resulting yellowish oil was further purified by flash column chromatography (5:1 Hex/EtOAc) to afford the desired product.

Ethyl-3-(cyclopropylamino)-2-(2,4,5-trifluorobenzoyl) acrylate (**10a**). Prepared following the general procedure B from Ethyl-3-(cyclopropylamino)acrylate (**3a**) (2 g, 12.9 mmol), LiHMDS (14.2 mmol) and 2,4,5-trifluorobenzoyl chloride (**9a**) (2.76 g, 14.19 mmol). Flash column chromatography (5:1 Hex/EtOAc) gave a yellow oil (3.99 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (s,1H), 7.33 (q, 1H), 7.00 (q, 1H), 5.80 (d, J = 14.2 Hz, 1H), 4.20 (q, 2H), 2.76 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.92 (br, 3H), 0.60 (br, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ. 167.4, 165.7, 154.4 ($^1J_{19F\text{-}13C}$ = 250.9 Hz, $^2J_{19F\text{-}13C}$ = 9.8 Hz, $^4J_{19F\text{-}13C}$ = 2.69 Hz), 152.3 ($^1J_{19F\text{-}13C}$ = 257.1 Hz, $^2J_{19F\text{-}13C}$ = 26.2 Hz, $^3J_{19F\text{-}13C}$ = 13.0 Hz), 147.4 ($^1J_{19F\text{-}13C}$ = 248.8 Hz, $^3J_{19F\text{-}13C}$ = 12.4 Hz, $^4J_{19F\text{-}13C}$ = 3.9 Hz), 142.0, 120.3, 118.4 ($^2J_{19F\text{-}13C}$ = 20.8 Hz, $^3J_{19F\text{-}13C}$ = 4.7 Hz, $^3J_{19F\text{-}13C}$ = 1.6 Hz), 106.6 ($^2J_{19F\text{-}13C}$ = 27.9 Hz, $^2J_{19F\text{-}13C}$ = 21.2 Hz), 103.3, 60.6, 27.7, 14.6, 6.9, 4.5.

Ethyl-2-(2,4-dichloro-5-fluorobenzoyl)-3-(propylamino)acrylate (**10b**). Prepared following the general procedure B from ethyl-3-(propylamino)acrylate (**3b**) (5 g, 31.8 mmol), LiHMDS (35 mmol) and 2,4,5-trifluorobenzoyl chloride (**9a**) (7.96 g, 35 mmol). Flash column chromatography (5:1 Hex/EtOAc) gave a yellow solid (8.64 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.14 (d, J = 14.1 Hz, 1H), 7.38 (d, J = 6.3 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 4.00 (q, 2H), 3.43 (q, 2H), 1.73 (q, 2H), 1.01 (m, 6H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 191.0, 166.7, 161.5, 156.9 ($^1J_{19F\text{-}13C}$ = 250.1 Hz), 142.9 ($^3J_{19F\text{-}13C}$ = 5.9 Hz), 130.8, 125.6 ($^4J_{19F\text{-}13C}$ = 3.7 Hz), 121.3 ($^2J_{19F\text{-}13C}$ = 19.3 Hz), 115.5 ($^2J_{19F\text{-}13C}$ = 23.6 Hz), 100.5, 60.1, 52.5, 24.0, 14.2, 11.3. The NMR data shows evidence of one major and two minor isomers/conformers. The values for δ_H, δ_C, and $J_{19F\text{-}13C}$ are reported for the major isomer/conformer only. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}Cl_2FNO_3$ 348.0491; found 348.0513.

Ethyl-3-(benzylamino)-2-(2,4-dichloro-5-fluorobenzoyl)acrylate (**10c**). Prepared following the general procedure B from ethyl-3-(phenylamino)acrylate (**3c**) (5 g, 24.4 mmol), LiHMDS (26.8 mmol) and 2,4,5-trifluorobenzoyl chloride (**9a**) (6.10 g, 26.8 mmol). Flash column chromatography (5:1 Hex/EtOAc) gave a white solid (7.83 g, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.24 (d, J = 13.9 Hz, 1H), 7.40 (m, 4H), 7.30 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 8.7 Hz, 1H), 4.63 (d, J = 6.1 Hz, 2H), 4.01 (q, 2H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 191.3, 166.5, 161.3, 156.8 ($^1J_{19F\text{-}13C}$ = 212.8 Hz), 142.8 ($^3J_{19F\text{-}13C}$ = 6.0 Hz), 135.7, 130.8, 129.5 (2C), 128.8, 127.8 (2C), 125.6 ($^4J_{19F\text{-}13C}$ = 4 Hz), 121.4 ($^2J_{19F\text{-}13C}$ = 18.9 Hz), 115.5 ($^2J_{19F\text{-}13C}$ = 23.8 Hz), 101.1, 60.2, 58.3, 54.4, 14.2. The NMR data shows evidence of one major and one minor isomer. The values for δ_H, δ_C, and $J_{19F\text{-}13C}$ are reported for the major isomer only. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{17}Cl_2FNO_3$ 396.0491; found 396.0510.

Ethyl-3-(cyclohexylamino)-2-(2,4-dichloro-5-fluorobenzoyl)acrylate (**10d**). Prepared following the general procedure B from ethyl-3-(phenylamino)acrylate (**3d**) (5 g, 25.36 mmol), LiHMDS (27.9 mmol) and 2,4,5-trifluorobenzoyl chloride (**9a**) (6.10 g, 27.9 mmol). Flash column chromatography (5:1 Hex/EtOAc) gave a yellow solid (7.78 g, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.09 (s, 1H), 8.19 (d, J = 14.3 Hz, 1H), 7.38 (d, J = 6.4 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 4.00 (q, 2H), 3.35 (br, 1H), 2.02 (m, 2H), 1.83 (m, 2H), 1.65 (m, 1H), 1.47 (q, 2H), 1.39 (q, 2H), 1.25 (m, 1H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 190.8 ($^4J_{19F\text{-}13C}$ = 1.2 Hz), 166.7, 159.3, 156.9 ($^1J_{19F\text{-}13C}$ = 249.6 Hz), 143.0 ($^3J_{19F\text{-}13C}$ = 5.9 Hz), 130.7, 125.6 ($^4J_{19F\text{-}13C}$ = 3.7 Hz), 121.2 ($^2J_{19F\text{-}13C}$ = 19.0 Hz), 115.4 ($^2J_{19F\text{-}13C}$ = 23.5 Hz), 100.2, 60.0, 59.3, 33.8, 25.2, 24.6, 14.2. The NMR data shows evidence of one major and one minor isomer. The values for δ_H, δ_C, and $J_{19F\text{-}13C}$ are reported for the major isomer only. HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}Cl_2FNO_3$ 388.0804; found 388.0816.

Synthesis of Ethyl 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (6a). An oven dried three necked round bottom flask equipped with a stirring bar was charged under argon with lithium bis(trimethylsilyl)amide in toluene (1 M) (70.54 mL, 70.54 mmol) and cooled to -78 °C and followed by a slow addition of the acrylate (**3a**) (5 g, 32.2 mmol). The resulting bright yellow solution was stirred for 30 min followed by the dropwise addition of 2,4,5-trifluorobenzoyl chloride (6.89 g, 35.48 mmol) over 10 min. The mixture was allowed to slowly warm to room temperature over an 1 h and stirred for an additional 1 h. After the completion of the reaction, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and diluted in 60 mL of dichloromethane. The organic layer was washed with brine and dried over Na_2SO_4. The organic solvent was removed under pressure. The resulting yellowish oil was further purified by flash column chromatography (1.25:1 Hex/EtOAc) to afford a yellow powder (8.9 g, 94%). All spectra collected and recorded were in agreement with previously reported data.[18,19] ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.26 (dd, 1H), 7.73 (dd, 1H), 4.39 (q, 2H), 3.45 (m, 1H), 1.41 (t, J = 7.1 Hz, 3H), 1.37 (m, 2H), 1.16 (m, 2H); ^{13}C{1H} NMR (150 MHz, $CDCl_3$) δ 173.1 ($^4J_{19F\text{-}13C}$ = 1.9 Hz), 165.7, 153.7 ($^1J_{19F\text{-}13C}$ = 255.8 Hz, $^2J_{19F\text{-}13C}$ = 14.8 Hz), 149.3, 149.0 ($^1J_{19F\text{-}13C}$ = 251.2 Hz, $^2J_{19F\text{-}13C}$ = 13.5 Hz), 137.9 ($^3J_{19F\text{-}13C}$ = 9.5 Hz. $^4J_{19F\text{-}13C}$ = 6.2 Hz), 126.1 ($^3J_{19F\text{-}13C}$ = 4.9 Hz, $^4J_{19F\text{-}13C}$ = 2.3 Hz), 115.8 ($^2J_{19F\text{-}13C}$ = 18.8 Hz, $^4J_{19F\text{-}13C}$ = 2.2 Hz), 111.3, 105.8 ($^2J_{19F\text{-}13C}$ = 22.7 Hz), 61.5, 35.1, 14.7, 8.6 (2C).

Synthesis of ciprofloxacin (1). An oven dried three necked round bottom flask equipped with a stirring bar was charged under argon with lithium bis(trimethylsilyl)amide in toluene (1

M) (70.54 mL, 70.54 mmol) and toluene and cooled to -78 °C and followed by a slow addition of the acrylate (**3a**) (5 g, 32.2 mmol). The resulting bright yellow solution was stirred for 30 min followed by the dropwise addition of 2,4,5-trifluorobenzoyl chloride (6.89 g, 35.48 mmol) over 10 min. The mixture was allowed to slowly warm to room temperature over an 1h and stirred for an additional 1 h. Upon completion of the reaction, the reaction mixture was diluted with DMSO (30 mL) followed by the addition of piperazine (11 g, 128 mmol) and the mixture was heated to 120 °C over 2 h. After complete consumption of **6a**, the temperature was lowered to 90 °C and the reaction mixture was charged with NaOH (2.6 g, 65 mmol). The reaction mixture was stirred over 1 h, cooled to room temperature, diluted with 30 mL of water followed by addition of 4 N HCl to adjust the pH to 7. Ciprofloxacin was allowed to gradually precipitate in a 4 °C fridge. The solid was filtered, washed three with water and dried to afford (8.84 g, 83%) of yellow solid. All spectra collected and recorded were in agreement with previously reported data.[18,19] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.90 (d, *J* = 13.4 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 3.86 (m, 1H), 3.25 (t, *J* = 5.0 Hz, 4H), 2.92 (t, *J* = 5.0 Hz, 4H), 1.34 (q, 2H), 1.20 (q, 2H). ^{13}C{1H} NMR (150 MHz, DMSO-d_6) δ 176.6, 166.4, 152.6, 148.3, 146.2, 139.7, 118.7, 111.4, 111.2, 107.1, 106.5, 51.2, 45.8 (2C), 36.3, 8.03 (2C).

Synthesis of ciprofloxacin in flow. Solutions A-B were prepared in oven-dried 50 mL screw cap volumetric flasks under an argon atmosphere. Without any precautions, solution C were prepared in a 100 mL volumetric flask. Back pressure was regulated with a back-pressure regulator (BPR). Mixing was done by combining two streams into a tee (IDEX Health & Science P-712).

The sequence was run on two Vapourtec E-series units with each Vapourtec E series flow reactor equipment consisting of two peristaltic pumps for reagents and solvents delivery. The Vapourtec using were equipped with one 2 mL and two 10 mL PFA reactors (1/8" O.D. x 1/16" I.D.) that was utilized in the flow chemistry experiments. All reactors were primed with anhydrous THF before each experiment. Reactor II was pre-heated to 140 °C and Reactor II was pre-heated to 120 °C. The Vapourtec Pump A was used to pump the stock of 2,4,5-trifluorobenzoyl chloride (0.66 M) and Vapourtec Pump B was used to pump the stock of the acrylate (**8a**) and LiHMDS mixture in THF (0.6 M). Solutions A and B were mixed at a T-piece (M1) (IDEX Health and Science, P-726) and pumped through Reactor I (1/8" O.D. x 1/16" I.D., 2 mL) and streamed into a continuous stir tank reactor heated at 60 °C. The heated mixture was then pumped out through pump C meeting a preheated solution of piperazine (1.2 M) in DMSO preheated (120 °C) at a second T-piece (M2). The collective flow mixture was allowed to pump into Reactor II (1/8" O.D. x 1/16" I.D., 10 mL). The output from Reactor II was connected to a third T-piece (M3) meeting a solution of 1.0 M of NaOH. The collective flow mixture was allowed to pump in Reactor III (1/8" O.D. x 1/16" I.D., 10 mL). A 75 PSI back pressure regulator (BPR) (IDEX Health and Science, P-785) was connected after Reactor III. After approximately three total system residence times, the output flow from Reactor III was collected for 10 min (80 mL). The output was allowed to cool to room temperature was followed by the addition of 4 N HCl to adjust the pH to 7. Ciprofloxacin was allowed to gradually precipitate in a 4 °C fridge. The solid was filtered, washed three with water and dried to afford 4.7 g (83% overall) of yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.90 (d, *J* = 12 Hz, 1H), 7.55 (d, *J* = 12 Hz, 1H), 3.86 (m, 1H), 3.25 (t, *J* = 12 Hz, 4H), 2.92 (t, *J* = 12 Hz, 4H), 1.34 (q, 2H), 1.20 (q, 2H). ^{13}C{1H} NMR (150 MHz, DMSO-d_6) δ 176.6, 166.4, 152.6, 148.3, 146.2, 139.7, 118.7, 111.4, 111.2, 107.1, 106.5, 51.2, 45.8 (2C), 36.3, 8.0 (2C).

ASSOCIATED CONTENT

Supporting Information

Copies of 1H, 13C{1H} NMR spectra

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REFERENCES

(1) Pinheiro, E.; Vasan, A.; Yong, J.; Lee, E.; Marc, J.; Perriens, J. Examining the Production Costs of Antiretroviral Drugs. *AIDS* **2006**, No. 20, 1745–1752.

(2) Ott, D.; Kralisch, D.; Denčić, I.; Hessel, V.; Laribi, Y.; Perrichon, P. D.; Berguerand, C.; Kiwi-Minsker, L.; Loeb, P. Life Cycle Analysis within Pharmaceutical Process Optimization and Intensification: Case Study of Active Pharmaceutical Ingredient Production. *ChemSusChem* **2014**, *7* (12), 3521–3533.

(3) Bumpas, J.; Betsch, E. "Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines." **2009**.

(4) Verghese, J.; Kong, C. J.; Rivalti, D.; Yu, E. C.; Krack, R.; Alcázar, J.; Manley, J. B.; McQuade, D. T.; Ahmad, S.; Belecki, K.; Gupton, F. B. Increasing Global Access to the High-Volume HIV Drug Nevirapine through Process Intensification. *Green Chem.* **2017**, *19* (13), 2986–2991.

(5) Dach, R.; Song, J. J.; Roschangar, F.; Samstag, W.; Senanayake, C. H. The Eight Criteria Defining a Good Chemical Manufacturing Process. *Org. Process Res. Dev.* **2012**, *16* (0), 1697–1706.

(6) Goldbach, M.; Danieli, E.; Perlo, J.; Kaptein, B.; Litvinov, V. M.; Blümich, B.; Casanova, F.; Duchateau, A. L. L. Preparation of Grignard Reagents from Magnesium Metal under Continuous Flow Conditions and On-Line Monitoring by NMR Spectroscopy. *Tetrahedron Lett.* **2016**, *57* (1), 122–125.

(7) Chemical Process Research and Development in the 21st Century: Challenges, Strategies, and Solutions from a Pharmaceutical Industry Perspective. *Acc. Chem. Res.* **2009**, *42* (5), 671–680.

(8) Caron, S.; Thomson, N. M. Pharmaceutical Process Chemistry: Evolution of a Contemporary Data-Rich Laboratory Environment. *J. Org. Chem.* **2015**, *80* (6), 2943–2958.

(9) Yu, E.; Mangunuru, H. P. R.; Telang, N. S.; Kong, C. J.; Verghese, J.; Gilliland, S. E.; Ahmad, S.; Dominey, R. N.; Gupton, B. F. High-Yielding Continuous-Flow Synthesis of Antimalarial Drug Hydroxychloroquine. *Beilstein J. Org. Chem.* **2018**, *14*, 583–592.

(10) Korwar, S.; Amir, S.; Tosso, P. N.; Desai, B. K.; Kong, C. J.; Fadnis, S.; Telang, N. S.; Ahmad, S.; Roper, T. D.; Gupton, B. F. The Application of a Continuous Grignard Reaction in the Preparation of Fluconazole. *European J. Org. Chem.* **2017**, *2017* (44), 6495–6498.

(11) Kong, C. J.; Fisher, D.; Desai, B. K.; Yang, Y.; Ahmad, S.; Belecki, K.; Gupton, B. F. High Throughput Photo-Oxidations in a Packed Bed Reactor System. *Bioorg. Med. Chem.* **2017**.

(12) Emmerson, A. M. The Quinolones: Decades of Development and Use. *J. Antimicrob. Chemother.* **2003**, *51* (90001), 13–20.

(13) Mitscher, L. A. Bacterial Topoisomerase Inhibitors: Quinolone and Pyridone Antibacterial Agents. *Chem. Rev.* **2005**, *105* (2), 559–592.

(14) Aldred, K. J.; Kerns, R. J.; Osheroff, N. Mechanism of Quinolone Action and Resistance. *Biochemistry* **2014**, *53* (10), 1565–1574.

(15) Linder, J. A.; Huang, E. S.; Steinman, M. A.; Gonzales, R.; Stafford,

R. S. Fluoroquinolone Prescribing in the United States: 1995 to 2002. *Am. J. Med.* **2005**, *118* (3), 259–268.
(16) Andriole, V. T. The Quinolones : Past , Present , and Future. **2005**, *41* (Suppl 2), 113–119.
(17) Grohe, K.; Heitzer, H. Cycloaracylation of Enamines. I. Synthesis of 4-Quinolone-3-Carboxylic Acids. *Liebigs Ann. Chem.* **1987**, No. 1, 29–37.
(18) Schwalbe, T.; Kadzimirsz, D.; Jas, G. Synthesis of a Library of Ciprofloxacin Analogues by Means of Sequential Organic Synthesis in Microreactors. *QSAR Comb. Sci.* **2005**, *24* (6), 758–768.
(19) Lin, H.; Dai, C.; Jamison, T. F.; Jensen, K. F. A Rapid Total Synthesis of Ciprofloxacin Hydrochloride in Continuous Flow. *Angew. Chemie - Int. Ed.* **2017**, 8870–8873.
(20) Bartoli, G.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. A Versatile Route to β-Enamino Esters by Acylation of Lithium Enamines with Diethyl Carbonate or Benzyl Chloroformate. *Tetrahedron* **1995**, *51* (31), 8613–8622.
(21) Lavrard, H.; Larini, P.; Popowycz, F. Superacidic Cyclization of Activated Anthranilonitriles into 2-Unsubstituted-4-Aminoquinolines. *Org. Lett.* **2017**, *19* (16), 4203–4206.
(22) Girling, P. R.; Batsanov, A. S.; Shen, H. C.; Whiting, A. A Multicomponent Formal [1+2+1+2]-Cycloaddition for the Synthesis of Dihydropyridines. *Chem. Commun.* **2012**, *48* (40), 4893–4895.