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Flow Synthesis in Hot Water: Synthesis of the Atypical Antipsychotic Iloperidone

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Abstract: Inductively heated steel reactors continuously perform organic transformations in water under high temperature conditions, utilizing the unique physiochemical properties of water at subcritical conditions. We demonstrated the power of this set-up in the continuous synthesis of the atypical antipsychotic drug iloperidone, in which we performed four out of five steps under aqueous conditions.

Introduction

High temperature/high pressure reactions have recently attracted increased interest because the emergence of new enabling technologies for organic synthesis allow us to create technical devices and chemical environments that facilitate this type of chemistry.[1] Traditionally, flash vacuum pyrolysis (FVP) has been used, in which precursor molecules are exposed under gas-phase conditions to short thermal shocks at high temperatures.[2] In contrast, flow reactors are an ideal tool for performing high temperature/high pressure transformations in solution phase, provided that pressure resistant reactors are utilized that can rapidly be heated to temperatures around and well above 200 °C.[3] It was shown by us[4] and others[5] that the scope of synthetic applications is much broader for such continuous set-ups than for those of FVP. Indeed, under such conditions, fluids including aqueous solutions as well as reaction mixtures become near- or supercritical.[6]

In previous years we introduced inductive heating to organic synthesis and disclosed that this technique can ideally be combined with continuous flow processes.[4,7] During inductive heating, an externally located medium (15–100 MHz) or high frequency (100–800 MHz) electromagnetic field induces heat in conductive materials or alternatively in superparamagnetic nanostructured particles. The latter usually serve as a fixed bed material in flow devices, whereas copper or steel reactors can directly be heated under these conditions. This fast heating technique broadens the scope of synthetic high temperature applications because residence times in flow devices and thus the time of exposure under high temperature conditions can be controlled by means of the flow rate.

Synthesis under supercritical or subcritical conditions is highly attractive with water as the solvent of choice. From an industrial perspective, the cost issues and the safety and environmental concerns make water an interesting alternative to traditional organic solvents.[8] In selected cases, the solvent water provides unique reactivity properties for organic compounds or promotes accelerated reaction rates.[9] When water is used under superheated conditions (>100 °C) its properties change drastically. The dielectric constant (ε') drops from 78.5 at 25 °C to 27.5 at 250 °C, and therefore it shows a similar solubility for organics as do acetonitrile or methanol. Furthermore, the ion product increases with temperature. The dissociation constant of (pK_w) decreases from 14 at 25 °C to a minimum of 11.2 at 250 °C. Above that temperature the pK_w increases again.[8] Consequently, the solvent can act simultaneously as an acid and a base, without the need for neutralization or catalyst regeneration when terminating the reaction.[10] Solubility problems can be overcome by organic co-solvents forming aqueous suspensions that dissolve starting materials as well as products, and such mixtures can ideally be handled in microfluidic reactors. Principally, the phase boundary is already enlarged in mircofluidic devices but reaction rates are still not sufficient in water under conventional conditions. Under high temperature/high pressure conditions the solvent system can be brought to a point close to critical conditions, removing almost completely the phase boundary and at the same time raising the solubility of organic compounds in the aqueous phase leading to hugely increased reaction rates.[6,11] In this context, pioneering work on the utilization of subcritical water in organic synthesis was published by the groups of Ikushima and Polikaoff.[10,12]

In this report, we disclose the first applications of aqueous suspensions conducted in an inductively heated high-temperature and high-pressure flow environment. We also disclose an improved way to measure and control the temperature inside the reactor in the presence of an external oscillating electromagnetic field. Finally, we demonstrate that this set-up is well suited for the synthesis of the commercially used atypical antipsychotic drug iloperidone.

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Results and Discussion

Reactor design

So far, we had encountered difficulties to reliably and accurately determine and control the temperature inside the reactor in the presence of an external electromagnet field. A permanently installed IR-pyrometer has been one option. Alternatively, we now show that direct temperature measurements inside the reactor can be realized for inductively heated reactors under medium frequencies conditions using a thermocouple (K-element) connected to a T-joint located inside a 1/4" flow reactor (Figure 1). Gratifyingly, the error of these measurements compared to self-heating of the thermocouple inside the oscillating magnetic field was below 1% (for details see the Supporting Information).

Heating profiles of water in a Steel 316 reactor (1/4", length of 14 cm, 1.5 mL volume) at different flow rates (1.0, 2.0, and 5.0 mL min^{-1}) at 4.5 MPa were conducted for different energy inputs of the external inductor. Noteworthy, the limiting factor for heating beyond 270 °C is the boiling point of water at 4.5 MPa, a pressure that is determined by the choice of the backpressure regulator (Figure 2).

The difference of heating profiles at 1.0 and 2.0 mL min^{-1} is marginal. Only at high flow rates of around 5.0 mL min^{-1} are higher power inputs needed to heat water up to 300 °C. Still, this is achieved within 20 seconds and with a relative inductor power input of only 30% (300‰ PWM = pulse width modulation).

Next, the AC-generator was equipped with a computer-controlled on/off-switch to control the temperature, either by the signal transmitted from the thermocouple being located in the solvent stream in the last quarter segment of the reactor or the signal transmitted from the IR-pyrometer, which measures the temperature on the reactor surface. In Figure 3 the heating profiles for temperatures preset at 100, 150, 200, and 250 °C, respectively, at 50% maximum energy input are listed. Water was pumped through the reactor at a flow rate of 1.0 mL min^{-1} and the heating was controlled either by the thermocouple or by the IR-pyrometer. Remarkably, the desired temperature was reached within 30 s in all cases. Thermocontrol with the thermocouple revealed some overheating of the reactor surface, for which the larger heat capacity of water compared with steel is responsible. In contrast, when we performed the thermocontrol with the IR-pyrometer, the set temperature of the stream is reached after prolonged time, because overheating does not occur.

If a 1/8" steel reactor is heated under high frequency conditions, it became necessary to coil up the tube to reach adequate reactor volumes being exposed to the inductor. The void volume of this reactor was 1.2 mL (60 cm length) and the heating profile at a flow rate of 1.0 mL min^{-1} at 100, 150, 200, and 250 °C set temperature was determined (Figure 4, top graph). Again, the IR-pyrometer was linked to the computer-controlled AC generator. For reaching 100 or 150 °C, respectively, 30% of the maximum power input was applied and for reaching 200 or 250 °C, respectively, 50% of the maximum power input was applied. In all cases, the set temperature was reached within 20 seconds. The heating profile of water at a flow rate of 0.5, 1.0, 2.0, 3.0, and 5.0 mL min^{-1} at different temperatures (RT to 200 °C) revealed that the flow rate has only a minimal effect on the heating rate under high frequency conditions (Figure 4, bottom graph).

To evaluate the effect of these harsh conditions on the reactor material, we opened the reactors after these test runs and then cut in half. Although the reactor surface had changed colour due to slight oxidation, no substantial corrosion was observed even after 36 h of operation time.

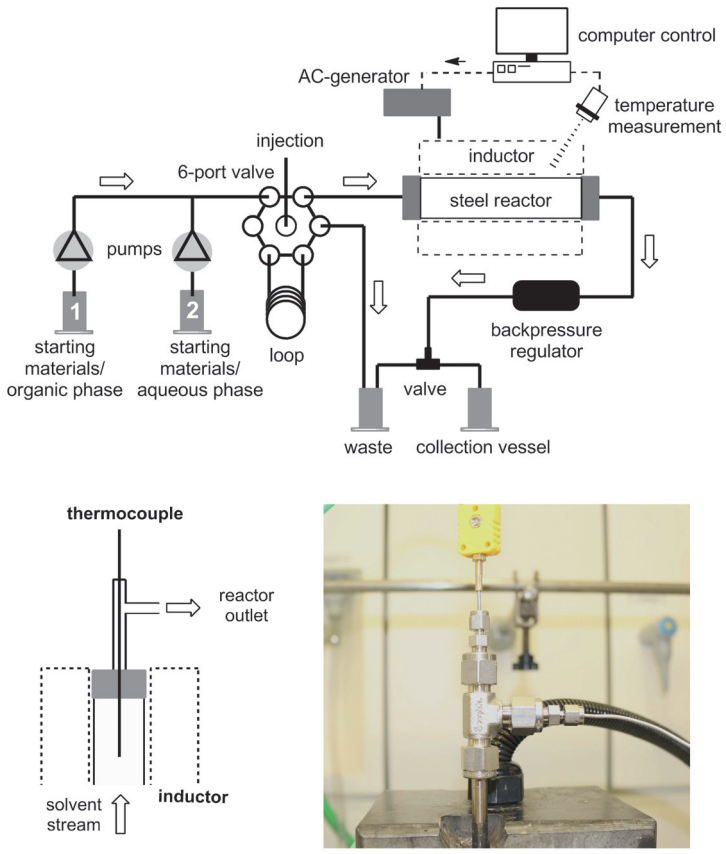
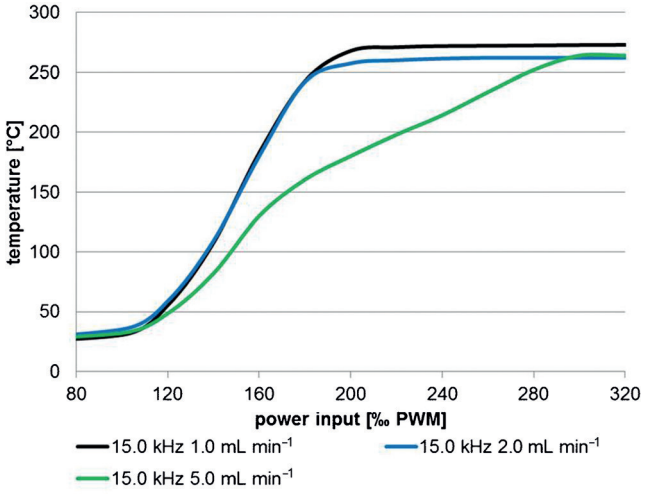


Figure 1. Set-up for inductive heating under continuous flow conditions in an aqueous suspension under high temperature/high pressure conditions (top) and K-element for temperature measurements inside flow reactors (bottom).

Organic synthesis under high pressure/high temperature conditions

With a reliable computer-assisted temperature control in hand, we tested selected organic transformations under high temperature aqueous conditions under flow conditions. The Brönstedt- or Lewis acid-promoted trimerization of 4-methoxy-3-butene-2-one **1** in water is known to yield triacetyl benzene **2** at around 150 °C.[13] We found that this reaction also



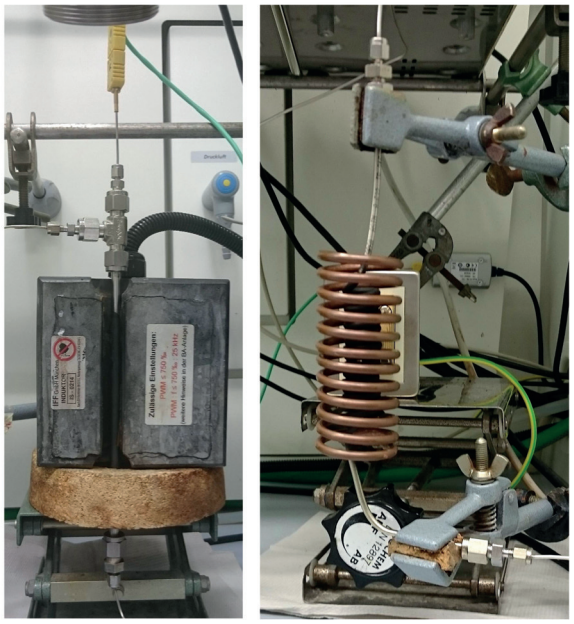


Figure 2. Temperature versus power input for a 1/4" steel reactor at 15.0 kHz; the temperature was measured at the outlet of the reactor using the K-element (top); 1/4" steel reactor encased in middle frequency inductor (bottom left); 1/8" coil reactor encased in high frequency inductor (bottom right).

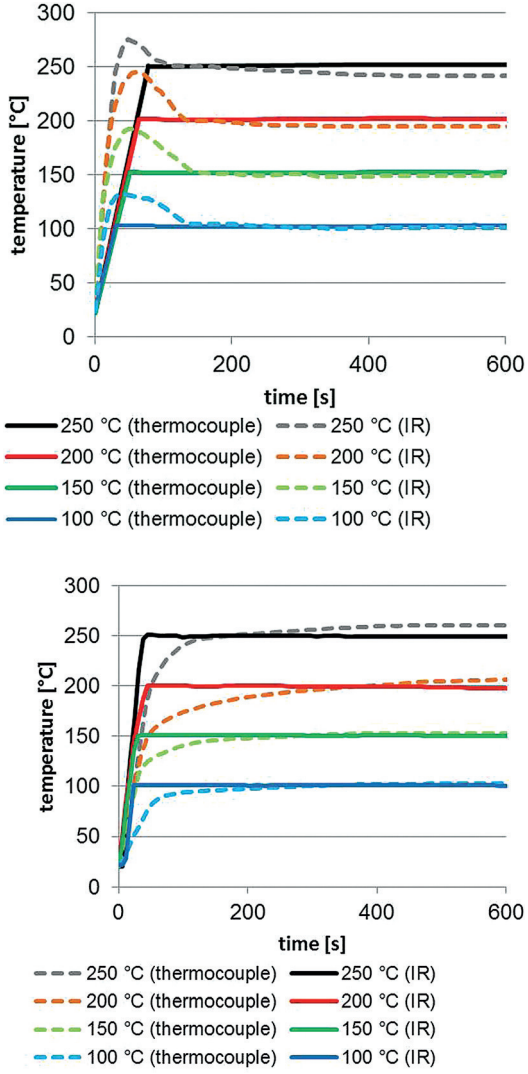
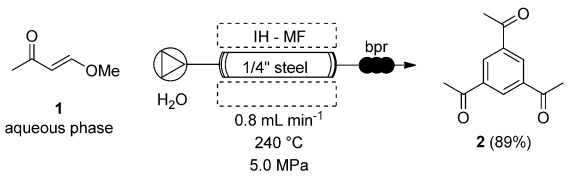


Figure 3. Temperature profile over time for differently preset temperatures; temperatures determined by thermocouple (top) and by IR-pyrometer (bottom) [1/4" steel reactor at 15.0 kHz, 100, 150, 200, 250 °C temperature set].



Scheme 1. Continuous preparation of triacetyl benzene **2** in water under near supercritical conditions (**1**/H_2O = 1:10, toluene was added to the reaction mixture at the outlet of the reactor to dissolve the product; threefold with respect to H_2O; the pumps were operated with pure water).

smoothly proceeds in an aqueous suspension with toluene in the absence of any acid under high temperature conditions.[14] Triacetyl benzene **2** was isolated in 89% yield at 240 °C in less than 2 min residence time and in the absence of a phase-transfer catalyst. Noteworthy, most byproducts remain in the aqueous phase, and a simple extraction was sufficient to collect the pure product (Scheme 1).

Ketone **1** was also employed in a multicomponent reaction with benzaldeyhdes and benzyl amines to yield dihydropyridines.[15] The use of a Lewis acid such as scandium triflate was necessary and reaction times were reported to vary between 2 to 20 days, providing the product in 13–86% yield. We found that under aqueous high temperature conditions, dihydropyridine **5** can be prepared under flow conditions from ketone **1**, benzaldehyde **3**, and benzylamine **4** in the absence of a Lewis acid.

At temperatures above 200 °C, substantial polymerization and formation of a polar byproduct was observed. However,

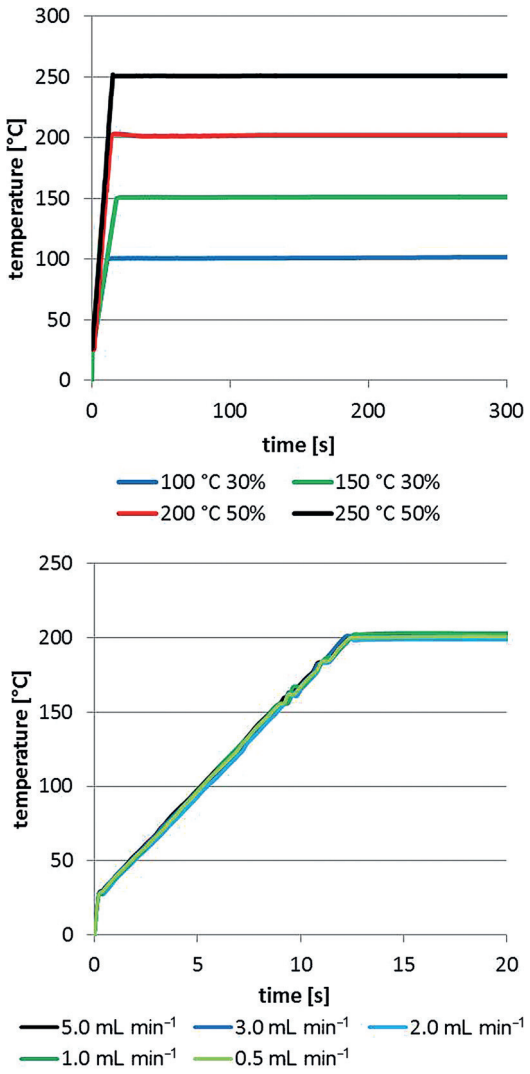
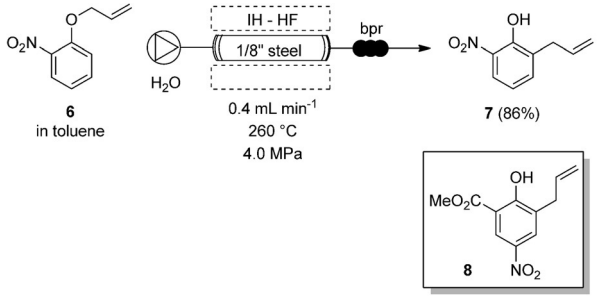


Figure 4. Temperature over time for different preset temperatures (1/8" steel reactor at 300.0 kHz and preset temperatures at 100, 150, 200 and 250 °C) and flow rates (0.5, 1.0, 2.0, 3.0 and 5.0 mL min^{-1}); determined with an IR-pyrometer.

the reaction proceeded smoothly at 180 °C with full conversion, and we isolated dihydropyridine **5** in 81% yield (Scheme 2). Remarkably, the residence time was well below eight minutes.

Thirdly, we investigated the electronically disfavored Claisen rearrangement of allyl ether **6**, which proceeds in very low yields after long reaction times. In previous work we demonstrated that inductive heating at high frequencies significantly accelerates the formation of phenol **8** (91%, 4 min residence time).[4b] We found that this type of rearrangement also proceeds well in high temperature aqueous media under flow conditions to yield phenol **7** isolated in 86% yield (Scheme 3). Remarkably, the residence time was about 3 min.



Scheme 3. Claisen rearrangement of **6** in aqueous medium (toluene/H_2O = 1:5; pumps were operated with pure water; inner reactor diameter = 1/16", 60 cm length).

In essence we encountered no major influence of the pressure (2.0 to 8.0 MPa) on the yields of these three reactions. The pressure only needs to be high enough to prevent evaporation of the solvent within the reactor.

Having established the principles of continuous synthesis in water at high temperature conditions using water as solvent, we extended our studies to the synthesis of a pharmaceutically relevant goal. Iloperidone **9** is an atypical antipsychotic that is used for the treatment of schizophrenia. It was commercialized in 2009 under the name Fanapt® (Figure 5).

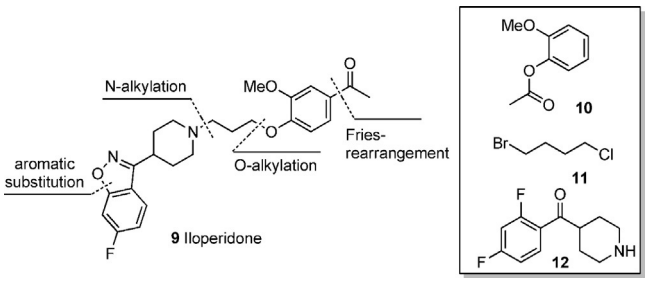
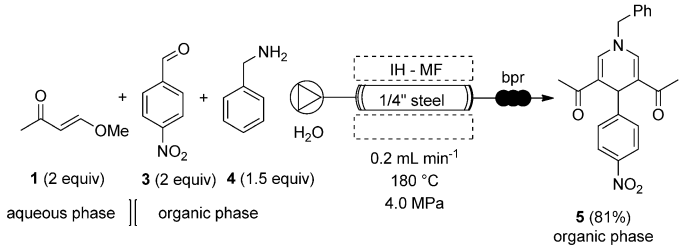
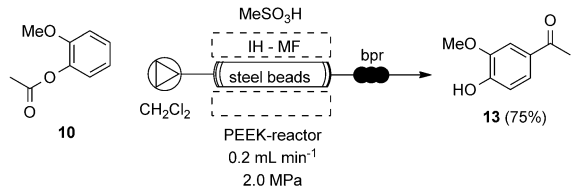


Figure 5. Synthetic plan towards iloperidone **9**.



Scheme 2. Synthesis of dihydropyridine **5** in an aqueous suspension (toluene/H_2O = 4:3; pumps were operated with pure water).

The multistep flow synthesis is based on two aromatic building blocks **10** and **12** that are connected with 3-bromo-1-chloropropane **11**. The first step, the Fries rearrangement of aryl acetate **10** is the only reaction that could not work in water but dichloromethane was the solvent of choice. The rearrangement was conducted in the presence of methane sulfonic acid (3.2 equiv) in a flow reactor made of polyether ether ketone (PEEK) (Scheme 4). The choice of reactor material hampered its operation above a pressure of



Scheme 4. Fries rearrangement of acetate **10** under flow conditions.

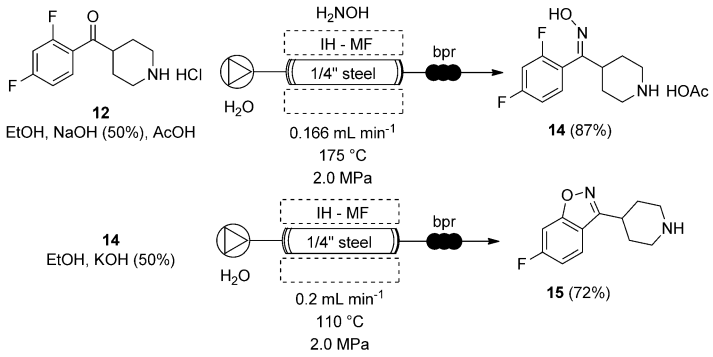
2.0 MPa. The reactor was filled with steel beads (0.8 mm) that were heated under medium frequency conditions while the starting material **10** was passed through the reactor. The flow rate was 0.2 mL min^{-1} (15 min residence time) to yield the desired acetophenone **13** in 75% (7.3 mmol product h^{-1}).

The western fragment was elaborated by first transforming ketone **12** into the corresponding oxime **14** and an intramolecular aromatic nucleophilic substitution occurred in the following (Scheme 5). Oxime **14** was prepared in an acidic aqueous medium; the product was isolated in 87% yield by simple filtration of the solid material, which only formed at the reactor outlet because the pressure had dropped. The process was conducted with a 1/4"-reactor at a flow rate of 0.166 mL min^{-1} and 175 °C, which corresponds to a residence time of 9 min. Then, oxime **14** underwent ring closure at 110 °C in the presence of potassium hydroxide (50 wt% in water) to yield benzisoxazole **15** in 72% yield, again at a flow rate of 0.2 mL min^{-1} (7.5 min residence time).

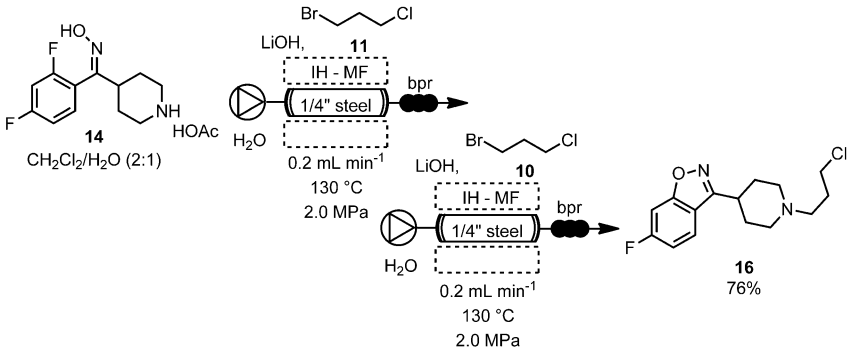
Unfortunately, though both processes require similar flow rates, these two steps could not be telescoped because the in situ masking of the secondary amine as acetate is necessary for oxime formation. Therefore, we investigated the coupling of the ring closure with the alkylation process. Thus, oxime **14** was *N*-alkylated with 3-bromo-1-chloropropane **11**, and intramolecular subsitution as well as nucleophilic substitution took place under these conditions. However, the multistep process required optimization because ring closure and alkylation did not lead to full transformation in a single pass. Therefore, we first performed the ring closure in the presence of 3-bromo-1-chloropropane **11**, which provided a mixture of the benzisoxazole **15** and the desired alkylation product **16**. The reaction mixture was mixed with a second portion of 3-bromo-1-chloropropane **11** at the outlet of the reactor, and the mixture was submitted to the flow system again, which increased the degree of conversion (Scheme 6).

At the same time it was possible to switch the organic solvent to CH_2Cl_2 to increase the solubility of the salts. Under these conditions, 1.2 M LiOH-solution was sufficient for initiating the ring closure compared with the reaction in 13 M KOH-solution mentioned above (Scheme 5). The reaction was carried out at a flow rate of 0.2 mL min^{-1} (15 min residence time) at 130 °C. We also envisaged and studied the *O*-alkylation of phenol **13** first, but all such attempts only yielded inseparable product mixtures.

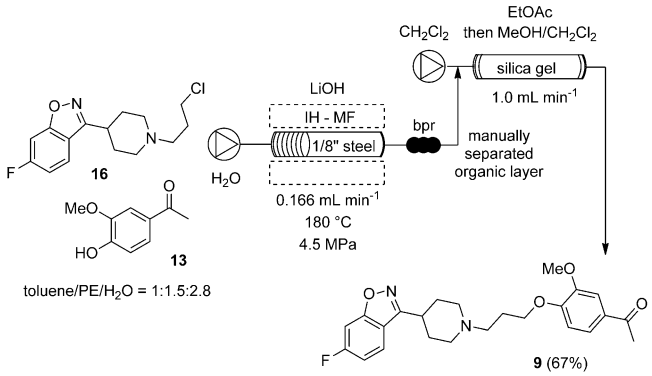
Finally, the *N*-alkylated product **16** was coupled with phenol **10** to yield iloperidone **9** in 78% yield (Scheme 7). Decomposition of the *N*-alkylation product **16** was suppressed when using the 1/8"-reactor, which was heated to 180 °C under high frequency conditions. For purification, we developed a "catch and release" protocol. After formation, iloperidone **9** was loaded and trapped on silica gel, which was used as fixed bed material in a steel pipe cartridge. Next, this cartridge was washed with EtOAc and finally release of **9** was achieved by flushing the silica gel with 2% MeOH in CH_2Cl_2. We collected the target molecule after concentration in vacuo.



Scheme 5. Oxime formation and intramolecular, nucleophilic substitution in aqueous media and formation of benzisoxazole **15**.



Scheme 6. Telescoped cyclization/N-alkylation in aqueous media.



Scheme 7. Iloperidone **9** formation and purification by a "catch and release" protocol.

Conclusions

We have disclosed the first applications of continuously operated organic transformations in high temperature aqueous media using inductively heated steel reactors. This set-up allows us to rapidly achieve high temperature/high pressure conditions. We studied selected examples such as the trimerization of 4-methoxy-3-butene-2-one and its use in a multicomponent reaction towards dihydropyridines, in which water as a solvent reveals its unique properties at near supercritical conditions by acting as an acidic promoter. To showcase this technology, we implemented it in a process for preparing the neurolepticum iloperidone **9**. Importantly, four out of five steps could be carried out in an aqueous medium under high temperature/high pressure continuous flow conditions. We are certain that inductive heating in combination with flow reactors has great potential to open up many other avenues for organic synthesis under pyrolytic solution phase conditions.[16]

Experimental Section

General information

^{1}H NMR spectra were recorded with a Bruker Avance-400 (400 MHz) with DPC console and Bruker DRX-500 (500 MHz) with DRX-console at room temperature. Multiplicities are described with the following abbreviations: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; b: broad.

^{13}C NMR spectra were recorded at 100 MHz with a Bruker Avance-400 and at 125 MHz with a Bruker DRX-500. Chemical shifts of ^{1}H- and ^{13}C NMR spectra are reported in δ (ppm) relative to TMS as the internal standard. Multiplicities are described with the following abbreviations: s: singlet (due to quaternary carbon), d: doublet (methine), t: triplet (methylene), q: quartet (methyl), m: multiplet. All coupling constants *J* are expressed in Hertz. Supporting ^{1}H-^{1}H correlation (COSY) and ^{1}H-^{13}C correlation (HSQC, HMBC) experiments were performed for interpretation of mutaproducts spectra.

Mass spectra were recorded with a type QTOF premier (MICROMASS) spectrometer (ESI mode) in combination with a Waters Acquity S2 UPLC system equipped with a Waters Acquity UPLC BEH C18 1.7 μm (SN 01473711315545) column (solvent A: water + 0.1 % (v/v) formic acid, solvent B: MeOH + 0.1 % (v/v) formic acid; flow rate = 0.4 mL min^{-1}; gradient (*t* [min]/solvent B [%]): 0/5; 2.5/95; 6.5/95; 6.6/5; 8/5). Ion mass signals (*m/z*) are reported as values in atomic mass units. Retention times (t_R) are given in the experimental part.

Flash column chromatography was performed using MACHEREY-NAGEL silica gel (grain size 40–63 μm).

Commercially available reagents and solvents were used as received or purified by conventional methods prior to use, described in the literature.[17] For thin-layer chromatography precoated silica gel 60 F254 plates (MERCK, Darmstadt) were used and the spots were visualized with UV light at 254 nm or alternatively by staining with ninhydrine or permanganate solutions.

Flow synthesis components

HPLC-pumps: Solvent or reaction mixture pumping was performed by HPLC PUMP K-120, K-1001, Smartline Pump 100 and Azura P 4.1S from Knauer (Berlin, Germany).

Tubing and capillaries*:* Standardly, steel capillaries with 1/16" outer diameter and 1.0 mm inner diameter made of stainless steel 316 from Techlab GMBH (Braunschweig, Germany) was used in all systems. Additional, PTFE-tubing from Bohlender GMBH (Grünsfeld, Germany) with 0.8 × 1.6 × 0.4 was used in room-pressured areas.

Injection valve: Starting materials were injected to the pressurized system via a Rheodyne® 6-way valve from Idex Corporation (Lake Forest, USA).

Temperature measurement*:* The temperature of inductively heated system was measured with a digital IR pyrometer CTLLTCF3 with laser light tag from Optris GMBH (Berlin, Germany) or a NiCr-Ni type K thermocouple from B + B Thermo-Technik GMBH (Donaueschingen, Germany). For accurate temperature measurement, the reactor was coated with temperature stable black varnish and the emission factor was set to 0.95.

Inductor/Generator medium frequency*:* The generator for medium frequency was acquired from IFF GMBH (Ismaning, Germany). The water-cooled device allows a stepless adjustment of the frequency in the range of 8 to 25 kHz with a maximum power output of 10.0 kW. Pulse width modulation is possible steplessly from 100 to 1000 promille. The prototype inductor provided following features of performance: 368 μH, N = 20 w, pack = 2.9 mm^2.

Inductor/Generator high frequency*:* The high frequency generator HU 2000+ and the compatible inductor were acquired from Himmel (Tübingen, Germany). Both devices are water-cooled and allow a maximum power output of 2.0 kW at 280–310 and 780–850 kHz. The power output is adjustable between 5–100 % in 0.1 % steps.

Back pressure modules*:* For pressure regulation in-line back pressure modules, BPR Assembly from Upchurch Scientific (Oak Harbor, USA) with different cartridges 250 psi (1.72 MPa), 500 psi (3.45 MPa), 750 psi (5.17 MPa) and 1000 psi (6.90 MPa) were used.

Reactors*:* PEEK-reactors were fabricated in the workshop of the institute of technical chemistry at the Leibniz University Hannover. Ketron PEEK rods 1000 Natur (1 m, Ø 25 mm) were purchase from Arthur Krüger KG (Barsbüttel, Germany). Steel reactors and fittings made of stainless steel 316 from Swagelok (Salon, Ohio USA) were acquired from BEST FLUID GMBH (Hamburg, Germany) with 1/8" × 0.028", 1/4" × 0.049" and 3/8" × 0.049" measurements.

Computer software*:* The computer assisted reaction control was realized with LabView 2014, 14.0 32-bit from National Instruments (Austin, USA).

Computer hardware*:* Digital and analog input and output was performed with a USB-6001 from National Instruments (Austin,

USA) and a Photomos 1A 2500 MA 60V AQV252G from Panasonic Corporation (Kadoma, Japan).

Procedures and analytical data

The numerical assignment for the spectra signals are displayed in the Supporting Information.

Triacetylbenzene (**2**): *Synthesis in a flow system: Trans*-4-methoxy-3-butene-2-one (100 μL, 1.0 mmol, 1.0 equiv, 1.0 M) was dissolved in distilled water (1.0 mL). The solution was injected in front of toluene (3.0 mL) into the loop and pumped through a 1/4"-steel reactor ($V=1.5$ mL) with distilled water at 0.8 mL min^{-1}. The reactor was heated by a medium frequency field to 240 °C and pressurized to 4.5 MPa. The collected reaction solution was extracted with toluene (3×5 mL), the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Drying in high vacuum gave the target molecule as colorless crystals (60 mg, 0.29 mmol, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3=7.26$ ppm): $\delta=$ 8.70 (s, 3H), 2.71 ppm (s, 9H).

Dihydropyridine (**5**): *Synthesis in a flow system: Trans*-4-methoxy-3-butene-2-one (100 μL, 1.0 mmol, 1.0 equiv, 0.5 M), 4-nitrobenzaldehyde (150 mg, 1.0 mmol, 2 equiv), and benzylamine (75 μL, 0.75 mmol, 1.5 equiv) were dissolved in toluene (2.0 mL) and distilled water (1.5 mL) was added. The mixture was injected into the loop and pumped through a 1/4"-steel reactor ($V=1.5$ mL) with distilled water at 0.2 mL min^{-1}. The reactor was heated by a medium frequency field to 180 °C and pressurized to 4.5 MPa. The collected reaction solution was extracted with toluene (3× 15 mL), the combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by using flash chromatography (petroleum ether/ethyl acetate = 3:1–1:1) gave the target molecule as a yellow oil (152 mg, 0.40 mmol, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3=7.26$ ppm): $\delta=$ 8.08–7.99 (m, 2H), 7.51–7.38 (m, 5H), 7.32 (dd, $J=$ 11.1, 9.6 Hz, 2H), 7.22 (s, 2H), 5.29 (s, 1H), 4.72 (s, 2H), 2.14 ppm (s, $J=$ 5.5 Hz, 6H).

2-Allyl-6-nitrophenol (**7**): *Synthesis in a flow system:* 1-(Allyloxy)-2-nitrobenzene (50 mg, 0.28 mmol, 1.0 equiv) were dissolved in toluene (0.2 mL) and distilled water (1.0 mL). The mixture was injected into the loop and pumped through a 1/8" steel reactor ($V=1.2$ mL) with distilled water at 0.4 mL min^{-1}. The reactor was heated by a high frequency field (300 kHz) to 260 °C and pressurized to 4.5 MPa. The collected reaction solution was extracted with ethyl acetate (3×15 mL), the combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by using flash chromatography (petroleum ether→petroleum ether/ethyl acetate = 99:1–98:2) gave the target molecule as a yellow oil (43 mg, 0.24 mmol, 86 %). ^{1}H NMR (400 MHz, DMSO, $CD_2HSOCD_3=2.49$ ppm): $\delta=$ 10.95 (s, 1H), 7.99 (dd, $J=$ 8.6, 1.7 Hz, 1H, H-3), 7.46 (dd, $J=$ 7.3, 1.1 Hz, 1H, H-5), 6.92 (dd, $J=$ 8.5, 7.4 Hz, 1H, H-4), 6.06–5.90 (m, 1H, H-8), 5.14 (t, $J=$ 1.3 Hz, 1H, H-9), 5.11 (dq, $J=$ 8.3, 1.5 Hz, 1H, H-9), 3.48 ppm (d, $J=$ 6.6 Hz, 2H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$, $CHCl_3=77.16$ ppm): $\delta=$ 153.4 (C-1), 137.6 (C-5), 135.2 (C-8), 133.7 (C-2), 131.5 (C-6), 123.2 (C-3), 119.6 (C-4), 116.9 (C-9), 33.8 ppm (C-7); HRMS (LCT): *m/z* calcd for $C_9H_{10}N_1O_3^+$: 180.0655 $[M+H]^+$, found: 180.0656.

1-(4-Hydroxy-3-methoxyphenyl)ethan-1-one (**13**): *Synthesis in a round-bottom flask*: 2-Methoxyphenylacetate (250 μL, 1.70 mmol, 1.0 equiv, 0.68 M) was added to a mixture of 2.0 mL CH_2Cl_2, methane sulfonic acid (440 μL, 6.73 mmol, 4.0 equiv) and phosphor(V)-oxide (62 mg, 0.43 mmol, 0.25 equiv) and stirred for 16 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed three times with bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether→ petroleum ether/ethyl acetate 1:9 to 3:7) gave the target molecule as slightly brown crystals (208 mg, 1.25 mmol, 74 %).

Synthesis in a flow system: 2-Methoxyphenylacetate (250 μL, 1.70 mmol, 1.0 equiv, 0.81 M) was dissolved in a mixture of CH_2Cl_2 (1.5 mL) and methane sulfonic acid (350 μL, 5.39 mmol, 3.2 equiv). The solution was injected into the loop and pumped through a PEEK-reactor filled with steel bead (0.8 mm) at a flow rate of 0.2 mL min^{-1} CH_2Cl_2. The reactor was heated by a medium frequency inductor at 360‰ PWM and pressurized to 2.1 MPa. The reaction mixture was washed three times with bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by using flash chromatography (petroleum ether→petroleum ether/ethyl acetate = 1:9 to 3:7) gave the target molecule as slightly brown crystals (213 mg, 1.28 mmol, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$, $CHCl_3=7.26$ ppm): $\delta=7.52$ (td, $J=$ 4.4, 1.9 Hz, 1H), 6.98–6.88 (m, 1H), 6.39 (s, 1H), 3.92 (s, 2H), 2.54 (s, 2H) ppm; T_{mp}: 113.5 °C; HRMS (EI): *m/z* calcd $C_9H_{10}O_3^+$: 166.0630 $[M+H]^+$; found: 166.0626.

(2,4-Difluorophenyl)(piperidin-4-yl)methanone oxime acetate (**14**): *Synthesis in a round-bottom flask*: Hydroxylamine hydrochloride (240 mg, 3.45 mmol, 1.5 equiv) was dispersed in a mixture of ethanol (2.4 mL) and distilled water (0.5 mL). Sodium hydroxide (230 mg, 5.75 mmol, 2.5 equiv) was added to the mixture and stirred for 10 min at room temperature. Subsequently, 4-(2,4-difluorbenzoyl)piperidinehydrochloride (600 mg, 2.29 mmol, 1.0 equiv, 0.66 M) and acetic acid (0.5 mL, 8.7 mmol, 3.8 equiv) were added. The reaction mixture was stirred for 6 h at 90 °C then cooled down and stirred additionally for one hour at room temperature. The precipitated solid was filtered off and washed with ethanol (2×1.0 mL). Drying under high vacuum gave the product as colorless crystals (640 mg, 2.13 mmol, 93 %).

Synthesis in a flow system: 4(2,4-Difluorbenzoyl)piperidiehydrochloride (1.2 g, 4.58 mmol, 1.0 equiv, 0.66 M) and hydroxylamine hydrochloride (480 mg, 6.90 mmol, 1.5 equiv) were dissolved in a mixture of CH_2Cl_2 (5.4 mL) and sodium hydroxide (0.62 mL) solution (50 % in water, 11.46 mmol, 2.5 equiv). Acetic acid (1.0 mL, 17.6 mmol, 3.8 equiv) was added and the solution was injected into the loop and pumped through a 1/4" steel reactor ($V=1.5$ mL) with distilled water at 0.166 mL min^{-1}. The reactor was heated by a medium frequency field to 175 °C and pressurized to 2.0 MPa. The reaction solution was stored for one hour at room temperature after the reaction and the precipitated solid was filtered off. The remaining solution was stored for additional 16 h and the precipitated solid was filtered off. The combined solids were washed with ethanol (2× 3.0 mL). Drying under high vacuum gave the product as colorless crystals (1.2 g, 4.00 mmol, 87 %). ^{1}H NMR (400 MHz, DMSO, $CD_2HSOCD_3=2.49$ ppm): $\delta=$ 7.29–7.21 (m, 2H, H-5,6), 7.11 (td, $J=$ 8.5, 2.5 Hz, 1H, H-2), 2.96 (d, $J=$ 12.3 Hz, 2H, H-10), 2.57–2.44 (m, 3H, H-8,10), 1.82 (s, 3H, H-14), 1.71–1.61 (m, 2H, H-9), 1.37 ppm (qd, $J=$ 12.3, 3.9 Hz, 2H, H-9); ^{13}C NMR (100 MHz, DMSO, $CD_2HSOCD_3=40.45$ ppm): $\delta=$ 174.1 (C-13), 163.04 (dd, $J=$ 246.7, 12.1 Hz, C-3), 159.52 (dd, $J=$ 247.8, 12.4 Hz, C-1), 154.57 (d, $J=$ 3.2 Hz, C-7), 131.32 (dd, $J=$ 10.2, 6.4 Hz, C-5), 119.70 (dd, $J=$ 19.2, 4.2 Hz, C-6), 112.34 (dd, $J=$ 21.3, 4.1 Hz, C-4), 104.79 (t, $J=$ 26.2 Hz, C-2), 45.4 (C-10), 41.7 (C-8), 29.7 (C-9), 23.6 ppm (C-14); T_{mp}: decomposition at 210 °C; HRMS (LCT): *m/z* calcd for $C_{12}H_{15}F_2N_2O^+$: 241.1152 $[M-OAc]^+$; found: 241.1149.

6-Fluoro-3-(piperidin-4-yl)benzo[d]isoxazole (**15**): *Synthesis in a round-bottom flask*: (2,4-Difluorophenyl)piperidine-4-ylmethanonoxim acetate (100 mg, 0.33 mmol, 1.0 equiv, 0.66 M) was dissolved in potassium hydroxide-solution (0.5 mL, 50 % in water, 5.35 mmol, 20 equiv). The mixture was stirred for 1 h at 110 °C then diluted

with distilled water (3.0 mL) and the aqueous layer was extracted with toluene (3×5.0 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Recrystallization from diethyl ether gave the target molecule as colorless crystals (20.3 mg, 0.092 mmol, 28%).

Synthesis in a flow system: (2,4-Difluorophenyl)piperidine-4-ylmethanonoxim acetate (500 mg, 1.67 mmol, 1.0 eq, 0.21 M) was dissolved in ethanol (6.0 mL) and potassium hydroxide (2.0 mL) solution (50% in water, 21.60 mmol, 12.9 equiv) was added. The solution was injected into the loop and pumped through a 1/4" steel reactor ($V=1.5$ mL) with distilled water at 0.2 mL min^{-1}. The reactor was heated by a medium frequency field to 110 °C and pressurized to 2.0 MPa. The collected reaction solution was extracted with toluene (3×25 mL), the combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Recrystallization from diethyl ether gave the target molecule as colorless crystals (323 mg, 1.46 mmol, 88%). ^{1}H NMR (400 MHz, DMSO, $CD_2HSOCD_3=2.49$ ppm): $\delta=8.41$ (s, 1H, H-11), 8.05 (dd, $J=8.8$, 5.3 Hz, 1H), 7.69 (dd, $J=9.1$, 2.1 Hz, 1H), 7.34–7.27 (dd, $J=8.8$, 2.1 Hz, 1H), 3.44 (tt, $J=11.4$, 3.8 Hz, 1H), 3.28 (d, $J=12.7$ Hz, 2H), 2.95 (td, $J=12.4$, 2.8 Hz, 2H), 2.10 (dd, $J=13.5$, 2.6 Hz, 2H), 1.99 ppm (ddd, $J=15.7$, 12.8, 3.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO, $CD_2HSOCD_3=40.45$ ppm): $\delta=164.3$ (dd, $J=131.1$, 116.9 Hz, C-3), 164.0 (d, $J=14.2$ Hz, C-1), 161,6 (C-7) 124.6 (d, $J=11.3$ Hz, C-5), 117.9 (d, $J=1.2$ Hz, C-6), 113.6 (d, $J=25.3$ Hz, C-4), 98.4 (d, $J=27.4$ Hz, C-2), 44.0 (C-10), 32.6 (C-8), 28.4 ppm (C-9); T_{mp}: 119.3 °C; HRMS (LCT): *m/z* calcd $C_{12}H_{14}FN_2O^+$ 221.1090 $[M+H]^+$; found: 221.1091.

3-(1-(3-Chloropropyl)piperidin-4-yl)-6-fluorobenzo[d]isoxazole (**16**): *Synthesis in a flow system:* 6-Fluor-3-(piperidin-4-yl)benzo[*d*]-isoxazole (200 mg, 0.91 mmol, 1.0 equiv, 0.061 M) and 1-bromo-3-chloropropane (167 μL, 1.82 mmol, 2.0 equiv) were dissolved in a mixture of CH_2Cl_2 (10.0 mL) and distilled water (5.0 mL) and lithium hydroxide solution (0.9 mL, 1.2 M, 1.09 mmol, 1.2 equiv) was added. The solution was injected into the loop and pumped through a 1/4" steel reactor (V=1.5 mL) with distilled water at 0.5 mL min^{-1}. The reactor was heated by a medium frequency inductor to 125 °C (125‰ PWM) and pressurized to 2.0 MPa. The collected reaction solution was extracted with ethyl acetate (3× 10 mL), the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Purification via flash chromatography (petroleum ether→petroleum ether/ethyl acetate 1:9 to 3:7) gave the target molecule as slightly yellow crystals (180 mg, 0.61 mmol, 67%).

Synthesis in a flow system (2 steps): (2,4-Difluorophenyl)piperidine-4-ylmethanonoximacetate (400 mg, 1.33 mmol, 1.0 equiv, 0.21 M) and 1-bromo-3-chloropropane (230 μL, 2.33 mmol, 1.75 equiv) were dissolved in CH_2Cl_2 (4.0 mL) and lithium hydroxide-solution (2.8 mL, 1.2 M, 3.30 mmol, 2.5 equiv) was added. The solution was injected into the loop and pumped through a 1/4" steel reactor (V=1.5 mL) with distilled water at 0.2 mL min^{-1}. The reactor was heated by a medium frequency field to 130 °C and pressurized to 2.0 MPa. 1-bromo-3-chloropropane (230 μL, 2.33 mmol, 1.75 equiv) and lithium hydroxide solution (1,1 mL, 1.2 M, 1.33 mmol, 1.0 equiv) were added to the collected solution and the mixture was injected a into the loop for a second run at the same conditions. The collected reaction solution was extracted with ethyl acetate (3× 30 mL), the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by using flash chromatography (petroleum ether→petroleum ether/ethyl acetate 1:9 to 3:7) gave the target molecule as slightly yellow crystals (300 mg, 1.01 mmol, 76%). ^{1}H NMR (400 MHz, DMSO, $CD_2HSOCD_3=2.49$ ppm): $\delta=7.68$ (dd, $J=8.7$, 5.1 Hz, 1H, H-5), 7.23 (dd, $J=8.5$, 2.1 Hz, 1H, H-2), 7.04 (td, $J=8.8$, 2.1 Hz, 1H, H-4), 3.62 (t, $J=6.5$ Hz, 2H, H-13), 3.12–2.99 (m, 3H, H-8,10), 2.53 (t, $J=7.1$ Hz, 2H, H-11), 2.23–2.09 (m, 2H, H-10), 2.09–2.02 (m, 4H, H-9), 1.98 ppm (q, $J=6.8$ Hz, 2H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$, $CHCl_3=77.16$ ppm): $\delta=164.2$ (d, $J=250.6$ Hz, C-3), 164.0 (d, $J=13.6$ Hz, C-1), 161.18 (d, $J=0.8$ Hz, C-7), 122.7 (d, $J=11.1$ Hz, C-5), 117.4 (d, $J=1.3$ Hz, C-6), 112.4 (d, $J=23.3$ Hz, C-4), 97.5 (d, $J=26.7$ Hz, C-2), 55.8 (C-11), 53.7 (C-10), 43.4 (C-13), 34.7 (C-8), 30.7 (C-9), 30.2 ppm (C-12); T_{mp}: slow decomposition starting at 170 °C; HRMS (LCT): *m/z* calcd for $C_{15}H_{19}FN_2OCl^+$: 297.1170 $[M+H]^+$; found: 297.1168.

Iloperidone (1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-phenyl]ethanone) (**9**): *Synthesis in a flow system (purification by flash chromatography):* 3-(1-(3-Chloropropyl)piperidin-4-yl)-6-fluorobenzo[d]isoxazole (120 mg, 0.40 mmol, 1.2 equiv) was dissolved in CH_2Cl_2 (1.5 mL) and 4-acyl-2-methoxyphenol (56 mg, 0.34 mmol, 1.0 equiv) and lithium hydroxide solution (850 μL, 1.2 M, 1.01 mmol, 3.0 equiv) were added. The solution was injected into the loop and pumped through a 1/4" steel reactor ($V=1.5$ mL) with distilled water at 0.2 mL min^{-1}. The reactor was heated by a medium frequency field to 180 °C and pressurized to 4.5 MPa. The collected reaction solution was extracted with CH_2Cl_2 (3×15 mL), the combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by using flash chromatography (ethyl acetate→ethyl acetate/methanol 1:0 to 95:5) gave the target molecule as slightly yellow crystals (112 mg, 0.27 mmol, 78%).

Synthesis in a flow system (catch and release purification): 3-(1-(3-Chloropropyl)piperidin-4-yl)-6-fluorobenzo[d]isoxazole (200 mg, 0.67 mmol, 1.0 equiv) was dissolved in toluene (1.0 mL), and 4-acyl-2-methoxyphenol (111 mg, 0.67 mmol, 1.0 equiv), lithium hydroxide-solution (2.8 mL, 1.2 M, 3.37 mmol, 5.0 equiv) and 1.5 mL petroleum ether were added. The mixture was injected into the loop and pumped through a 1/8" steel reactor ($V=1.2$ mL) with distilled water at 0.1 mL min^{-1}. The reactor was heated by a high frequency field to 180 °C and pressurized to 4.5 MPa. The reactor was flushed with additional CH_2Cl_2 (3.0 mL) after the reaction and CH_2Cl_2 (5.0 mL) was added to the reaction mixture. The organic layer was separated from the aqueous layer, injected into a loop and pumped through a 1/4" steel reactor ($V=2.5$ mL) filled with silica gel at 1.0 mL min^{-1} with ethyl acetate. The product was washed with ethyl acetate (20 mL) and then released by pumping a mixture of ethyl acetate/methanol 98:2 (8 mL) through the plug silica. Concentration in vacuo gave the target molecule as slightly yellow crystals (184 mg, 0.43 mmol, 64%). ^{1}H NMR (400 MHz, DMSO, not calibrated because DMSO signal was overlayed): $\delta=7.98$ (dd, $J=8.7$, 5.3 Hz, 1H, H-5), 7.66 (dd, $J=9.1$, 1.9 Hz, 1H, H-2), 7.60 (dd, $J=8.4$, 1.9 Hz, 1H, H-18), 7.44 (d, $J=1.8$ Hz, 1H, H-16), 7.26 (td, $J=9.3$, 2.1 Hz, 1H, H-4), 7.07 (d, $J=8.4$ Hz, 1H, H-19), 4.11 (t, $J=6.3$ Hz, 2H, H-13), 3.83 (s, 3H, H-15′), 3.18–3.05 (m, 1H, H-8), 2.98 (d, $J=11.2$ Hz, 2H, H-10), 2.52 (s, 3H, H-17″), 2.54–2.44 (m, 2H, H-11), 2.11 (t, $J=10.9$ Hz, 2H, H-10), 2.06–1.74 ppm (m, 6H, H-9, 11, 12); ^{13}C NMR (100 MHz, DMSO, $CD_2HSOCD_3=40.45$ pp): $\delta=197.2$ (C-17′), 164.5 (d, $J=247.8$ Hz, C-3), 163.9 (d, $J=14.2$ Hz, C-1), 162.3 (C-7), 153.4 (C-14), 149.6 (C-15), 130.7 (C-17), 124.6 (d, $J=11.4$ Hz, C-5), 124.0 (C-18), 118.16 (d, $J=1.1$ Hz, C-6), 113.3 (d, $J=25.3$ Hz, C-4), 112.6 (C-19), 111.3 (C-16), 98.2 (d, $J=27.3$ Hz, C-2), 67.7 (C-13), 56.4 (C-15′), 55.5 (C-11), 53.9 (C-10), 34.4 (C-8), 31.1 (C-9,12), 27.2 ppm (C-17″); T_{mp}: 120–122 °C; HRMS (LCT): *m/z* calcd for $C_{24}H_{28}FN_2O_4^+$: 427.2028 $[M+H]^+$; found: 427.2026.

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