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Development of an Efficient Large-Scale Synthesis for a 4*H*-imidazo[5,1-*c*][1,4] benzoxazine-3-carboxamide Derivative for Depression and Anxiety

Nicola Giubellina,* Paolo Stabile, Gilles Laval, Alcide D. Perboni, Zadeo Cimarosti, Pieter Westerduin, and Jason W. B. Cooke

Chemical Development, GlaxoSmithKline Medicine Research Centre, Via Fleming 4, 37135 Verona, Italy

Abstract:

The development and scale-up of an optimized synthesis for a novel drug candidate for depression and anxiety is presented. The updated synthesis represents a convergent and efficient four-stage approach to the API, overcoming high cost of goods (COG), general lack of convergence, and low yield of previous routes. A lower cost of goods resulted from using 3-nitrosalicylaldehyde as a starting material and introducing the expensive side chain (2-methyl-5-(piperazin-1-yl)quinoline) at a later stage. Green chemistry principles were applied when a direct amidation enabled a straightforward conversion of the 4*H*-imidazo[5,1-*c*][1,4]benzoxazine-3-carboxylate to the corresponding amide in the last step. In addition, the total number of stages was reduced from seven to four, and solvent usage was greatly minimized. The modified synthesis was demonstrated on a kilogram pilot scale, allowing the isolation of the API in 17% overall yield with the required purity.

Introduction

Neuroscience drugs will be playing a paramount role in the treatment of depression in the coming years.[1] Depression is a chronic, recurring, and potentially life-threatening illness that affects up to 20% of the population across the globe.[2] It is one of the top 10 causes of morbidity and mortality worldwide.[3] Although today's treatments for depression are generally safe and effective, they are far from ideal, in addition to the need to administer the drugs for weeks or months to observe clinical benefit.[3]

Selective serotonin reuptake inhibitors (SSRIs) have a widespread utility in the treatment of depression and other mental illnesses, but their therapeutic use showed latency in the onset of clinically meaningful effects. It was identified that approaches based on inhibition of serotonin reuptake in conjunction with antagonism of 5-HT_1 autoreceptors offer advantages over the current antidepressants in terms of a faster onset of therapeutic effect and improved efficacy.[4] Candidate 6-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}-4*H*-imidazo[5,1-*c*][1,4]benzoxazine-3-carboxamide **11** is a presynaptic inhibitor 5-HT_1 receptor antagonist selected for the cure of depression and anxiety that reached early phase II trials.[5]

The original medicinal chemistry synthesis and the subsequent process development campaigns followed a linear synthetic strategy (Scheme 1). Process development of the medicinal chemistry route (10 steps) followed a fit for purpose (design for delivery) strategy to afford substantial improvements, resulting in a more scalable process. This was run successfully for the preparation of kilogram quantities of active pharmaceutical ingredient (API) to cover phase I studies. While this process was suitable for the preparation of the initial supplies of API, it was found to be inefficient for further scale-up. The route suffers from low yields over a linear sequence, used toxic reagents (*e.g.*, osmium tetroxide), and high loading of metal catalysts, and introduced an expensive intermediate, 5-(1-piperazinyl)quinaldine **5**, in the early steps. The promising results of the first dose in man have led the Chemical Development team to look into the discovery of an alternative route to supply material for phase II.

Results and Discussion

The alternative route selection was tackled by synthetic chemists that envisioned several synthetic strategies toward the API, out of which the route with the use of 2-hydroxy-3-nitrobenzaldehyde **17** as a starting material was evaluated in full (Scheme 2). **17** gives the possibility of modulating the nitrophenol into a benzoxazine-3-one in a few steps that can eventually provide the imidazolylcarboxylate ring.[5,6] In addition, homologation of the aldehyde **16** would easily give access to the piperazinylquinoline side of the molecule. The last stage encompasses the hydrolysis of the carboxylic ester **13**, followed by a coupling reaction to the desired tricyclic carboxamide **11**.

Process Development for Stage One: Synthesis of 1,4-Benzoxazine-3-one 16. *O*-Alkylation of 3-nitrosalicylaldehyde **17** with ethyl bromoacetate proceeded smoothly in tetrahydrofuran at reflux.[7]

Initially, the reaction conditions included tetrahydrofuran and diisopropylethylamine (DIPEA) for the first step. Accordingly,

* Author to whom correspondence may be sent. Telephone: +39 045 8218053. Fax: +39 045 8218117. E-mail: Nicola.2.Giubellina@gsk.com.

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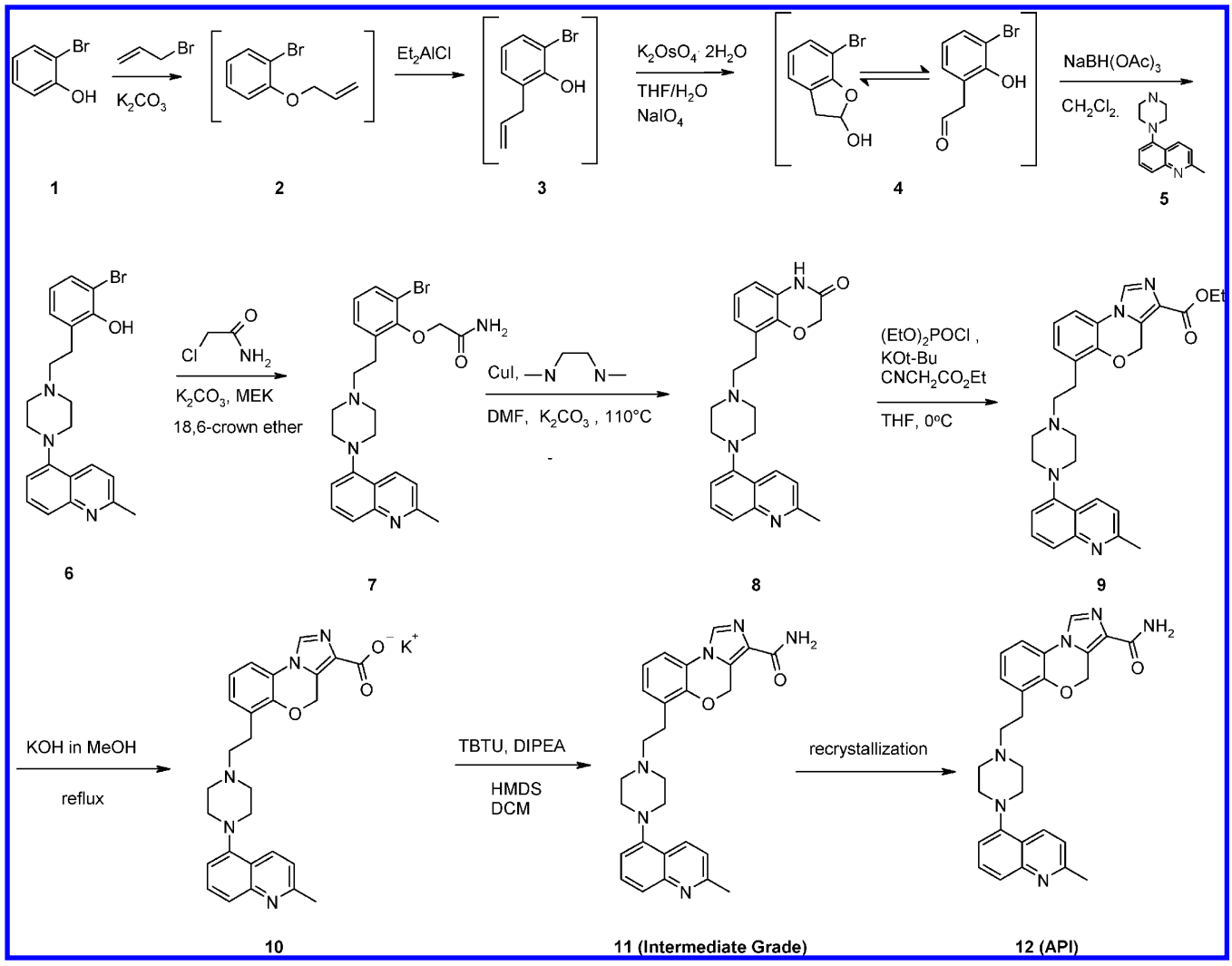
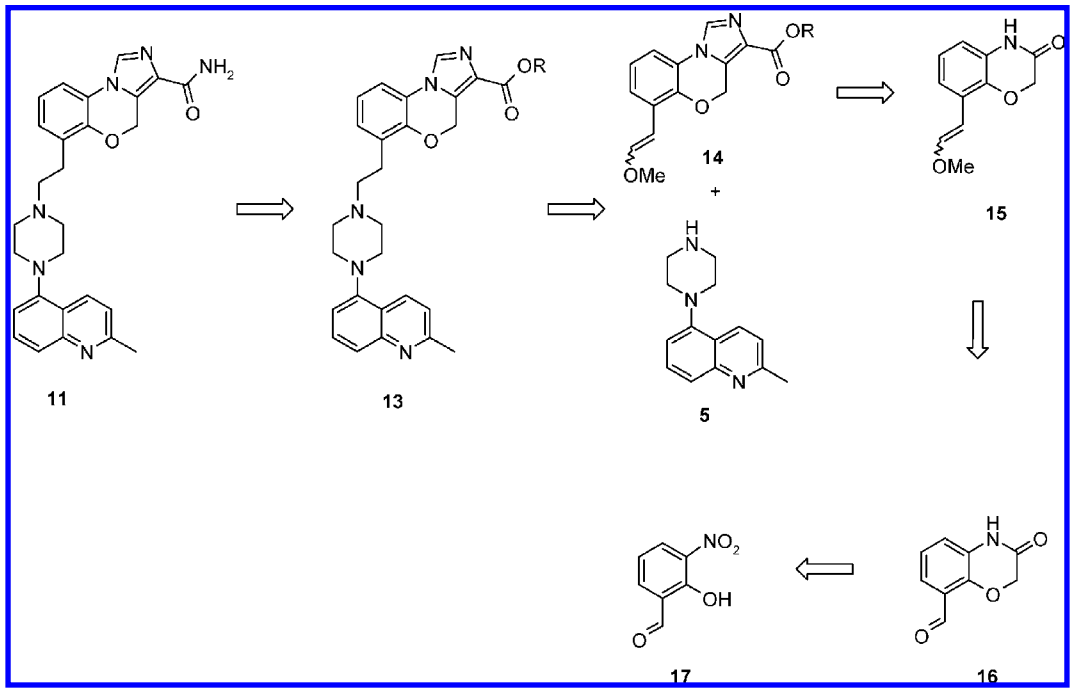
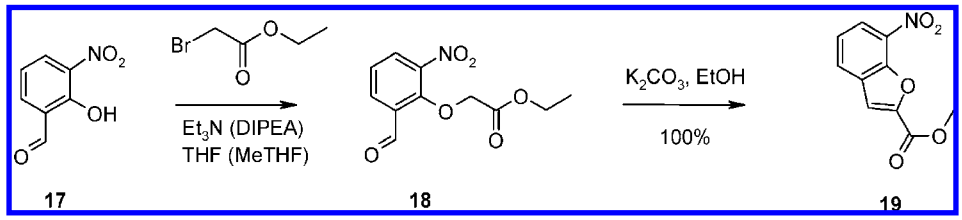
Scheme 1. **First scale-up route of the API 6-{2-[4-(2-methyl-5-quinolinyl)-1-piperazinyl]ethyl}-4*H*-imidazo[5,1-*c*][1,4]benzoxazine-3-carboxamide 12**



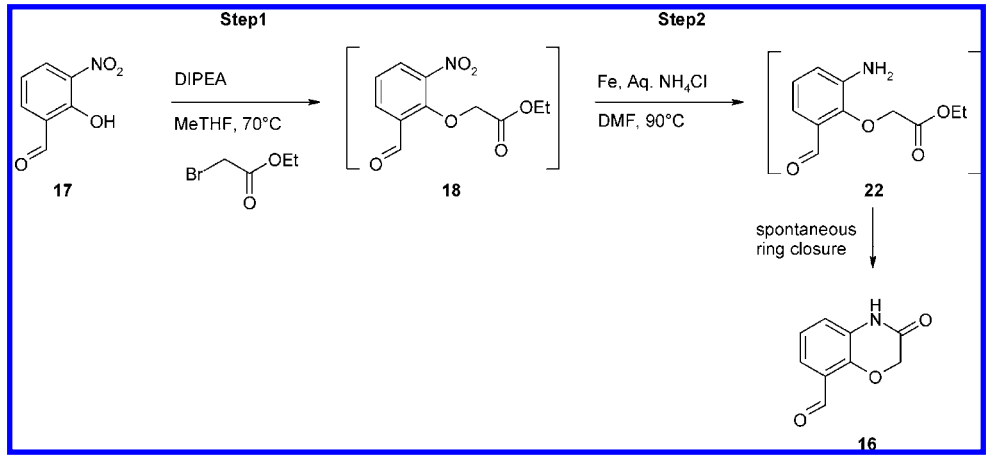
Scheme 2. **Retrosynthetic approach toward the intermediate grade 11**



Scheme 3. **Alkylation reaction of 3-nitrosalicylaldehyde 17 with ethylbromoacetate, and formation of benzofuran 19[7]**



Scheme 4. **Stage one: telescoped procedure for 3-oxo-1,4-benzoxazine-8-carbaldehyde 16**



the selected alkylation conditions were run on a small scale and then were reproduced in a 2-L glass reactor with complete conversion to the ester intermediate **18** in high yields (Scheme 3). Further process development included the replacement of tetrahydrofuran with 2-methyltetrahydrofuran (MeTHF) with no impact on the reaction profile and yields.[8] While the initial process included partition between hydrochloric acid and ethylacetate, MeTHF was used during the aqueous washes because it is only partially soluble in water, thus simplifying the process. Fine-tuning of the reaction temperature, equivalents of reagents, and amount of solvents led to the isolation of the phenoxy derivative **18** in 95% a/a (area/area, HPLC) or higher, with no need for further purification.

Assuming that basic conditions and protic solvents might allow the undesired cyclization of the nitrophenoxyacetate **18** to the benzofuran **19** (Scheme 3),[7] the *O*-acetylation reaction conditions were studied in non-protic media (THF, MeTHF) and a few bases (DIPEA, Et_3N) in order to evaluate the formation of this side product **19**. Under no circumstances did the reaction give the undesired benzofuran side product, **19**. The best reaction conditions included *N*,*N*-diisopropylethylamine (1.9 equiv) as a base and THF or MeTHF (3 vol) as a solvent at 70 °C for 30 min. Those conditions gave the phenoxyacetate **18** in 98% yield and 99% a/a (HPLC).

The nitrophenoxyacetate **18** was submitted to reduction to give 1,4-benzoxazine-3-one **16** that results from the amino group formation followed by *in situ* lactamization (Scheme 4).[9] In order to gain access to the amino compound **22** a few reducing agents were screened, including palladium on carbon,[10,11] tin(II) chloride,[12] and iron.[13]

Catalytic hydrogenation reactions were carried out in methanol with various amounts of palladium catalyst. Unfortunately, they furnished the 4-hydroxybenzoxazine-3-one **21** as the major reaction product through intramolecular oxime cyclization with the acetate moiety. Tin(II) chloride reductions[12] were strongly dependent on the acid concentration, leading to mixtures of acetic acid derivative **20**, benzoxazine-3-one **16**, and compound **21** in various ratios according to the reaction conditions. As an example, the amount of the undesired cyclized derivative **21** increased in tin(II) chloride dihydrate with concentrated hydrochloric acid in THF, and *N*-hydroxybenzoxazine **21** was isolated in 76% yield (Figure 1).

Complete conversion of the nitrophenoxyacetate **18** to benzoxazine-3-one **16** was observed with iron powder in acidic media. When acetic acid was applied, the major product of the synthesis was **16**, which was isolated in poor yield because of the rather difficult workup. It was found that ammonium chloride was the best proton source because it prevented the hydrolysis of the ester, allowing the ring closure in high yield. Reduction of nitrobenzaldehyde **18** with iron powder in hot DMF and aqueous ammonium chloride gave complete conver-

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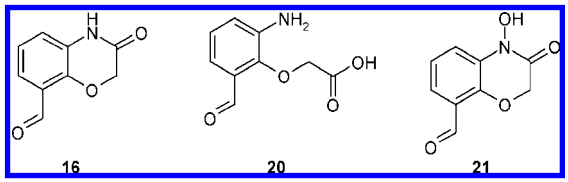


Figure 1. **Products of the reduction of the nitrophenoxyacetate 18.**

sion to benzoxazine-3-one **16** (HPLC analysis). However the isolated yield was not satisfactory, mainly due to low solubility of benzoxazine-3-one **16** in DMF at room temperature. Indeed, the iron reduction is producing large amounts of inorganic byproducts, i.e., iron and ammonium salts, which may initiate the crystallization of the benzoxazine-3-one **16**. Thus, the inorganic byproducts were removed by filtration, and the waste cake was washed with hot DMF to ensure a good recovery of the aldehyde. The filtration and waste cake washing were performed at temperatures above 60 °C to prevent loss of the aldehyde by crystallization, leading to a satisfactory mass balance of the reaction. Then, an experiment was run on a 100-g scale to evaluate the scalability of the two-step procedure (Scheme 4). At this time the ester **18** was isolated and used as crude for the synthesis of benzoxazinone **16**. The iron was added to the hot mixture of **18** in DMF and ammonium chloride, and then brought to 90 °C. After complete conversion in 30 min and filtration, DMF washes (24 volumes) allowed the isolation of benzoxazinone **16** as a green solid, which we speculated to have fairly high residual iron content. This solid was suspended in DMF (8 vol) and hydrochloric acid 37 wt %/wt (2 vol) and dissolved at 65 °C, kept for 2 h, and recrystallized at room temperature. Upon filtration, the crystals were analyzed by means of inductively coupled plasma (ICP) to determine the residual iron content as 5297 ppm (0.74 wt %/wt).

This first attempt to scale up these reactions in a batch unit highlighted the known concerns about the difficult and very exothermic nitro-group reductions. In fact, there was a thermal runaway of the reduction step that is only controlled by the reflux of the solvent mixture (undetected in experiments on small scale). On the basis of previous observations and the fact that reduction of nitroaromatic compounds is recognized to be exothermic,[14] it was found that a chemical reaction hazard exists for this reaction step and the reaction should not be scaled up without further investigation. This prompted us to look into the current synthesis conditions using reaction calorimetry.[15] In addition, large volumes of DMF, slow cake filtration, and a high level of residual iron in the isolated dry crystals **16** were still problems.

A process improvement allowed the telescoping of steps one and two (Scheme 4), namely the alkylation and reduction reactions, isolating the aldehyde **16** with yield and purity comparable to that obtained in the two-stage process with the isolation of the intermediate **18**: 68% overall yield and 98% a/a as compared to 67% yield and 98% a/a in the telescoped process. As a result, the first step was performed with MeTHF and **18** was not isolated. Solvent swap to DMF (3 vol) gave a mixture ready for step two (reduction). Indeed, safe control of the process was obtained via implementation of a reverse addition of the nitrobenzaldehyde **18** to the slurry of aqueous ammonium chloride, Celite and iron in DMF at 90 °C.[16] Experiments revealed that the method of addition of the nitro derivative to the slurry of ammonium chloride in DMF was critical for the good outcome of the reaction. In fact slow addition via syringe pump failed to give complete conversion of the nitro derivative to the amine, while portionwise addition gave complete conversion. In addition, it was found that the filtration of the slurry of step two ran smoothly when Celite[17] (0.3 wt referred to **17**) was added as a filter aid directly into the reaction mixture.[18] The volume of DMF used in the hot filtration of the solid byproducts was lowered from 24 vol to 4 vol. Having implemented those changes on a 500-g scale-up experiment resulted in the alkylated compound **18** in 96% a/a (HPLC, 3% residual starting material), and the benzoxazine-3-one **16** was isolated in 97% a/a (HPLC) and 69% yield (Scheme 4).

Pilot Scale for Stage One. After having established a fairly good process understanding of the critical parameters for stage one (Scheme 4), a 10-kg-scale reaction was implemented at a pilot scale. The telescoped alkylation procedure resulted in the ester **18** in 98% a/a after workup, isolated as a DMF solution (4 volumes). As part of the engineering controls for the nitro group reduction, mechanical safeguards included the addition of the previous DMF solution (4 volumes) through the head tank, which was charged in four portions in order to prevent full accidental mischarge of the starting nitro derivative **18** solution in DMF that could result in a hazardous situation. As an additional precaution, during the addition of the nitro derivative to the hot iron−Celite−DMF mixture, the reactor temperature was set at 75 °C in jacket control (Figure 2). In this way, the nitro derivative solution **18** was added in 10 portions through the reactor head tank, resulting in a controlled process, and with a complete conversion to the desired benzoxazine-3-one **16**. Thus, step two gave benzoxazine-3-one **16** in 98% a/a (7.1 kg, 67% yield), as brown crystals. ICP for the iron content was only 246 ppm, confirming that the iron content on the isolated benzoxazine-3-one **16** was influenced by the amount of DMF used in the waste cake washes, and that the use of hydrochloric acid as antisolvent in the final recrystallization was beneficial to achieve this result.

Process Development for Stage Two: Synthesis of Imidazo[5,1-*c*][1,4]benzoxazine-3-carboxylate 9. Stage two gave access to the tricyclic ester imidazo[5,1-*c*][1,4]benzoxazine-3-carboxylate **9**, including a Wittig reaction, an esterification, an imidazole formation, a hydrolysis, and a reductive amination (Scheme 5). Those reactions were at first conducted as separated steps, and the products **26**, **27**, and **9** were isolated (Scheme 5). Similar results were obtained at laboratory scale while telescoping the previously mentioned steps, and tricyclic ester **9** was isolated with comparable purity and yield. Initial attempts to synthesize the vinylether **25** *via* the Horner−Wadsworth−

(14) Duggan, P. J. *Hazards XIII: Process Safety: The Future; Institute of Chemical Engineers Symposium Series 141*; Zeneca Specialties: Manchester, U.K., 1997; pp 285−291.
(15) Hazard data will follow as a separate paper in due course.
(16) Grimm, J.; Liu, F.; Stefanick, S.; Sorgi, K. L.; Maryanoff, C. A. *Org. Process Res. Dev.* **2003**, *7*, 1067.
(17) Celite 545 (particle size 0.02−0.1 mm), purchased from Merck.
(18) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, 2000; p 216.

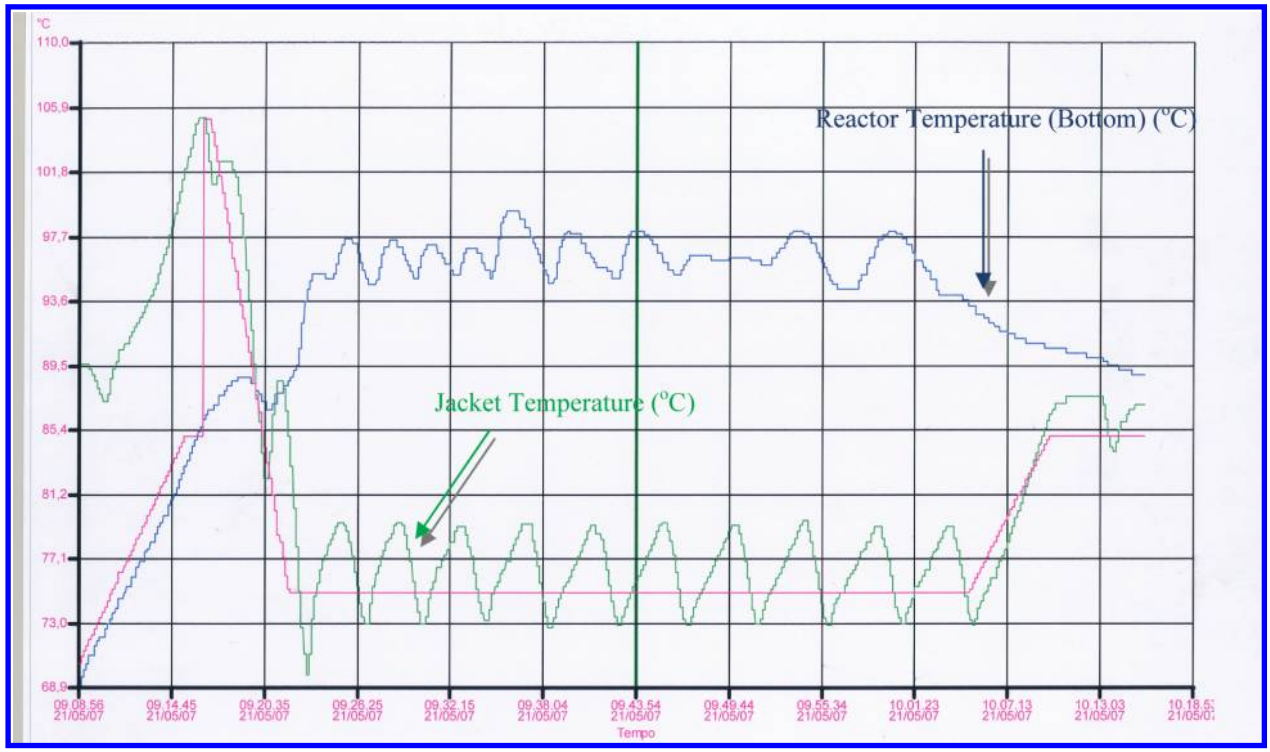
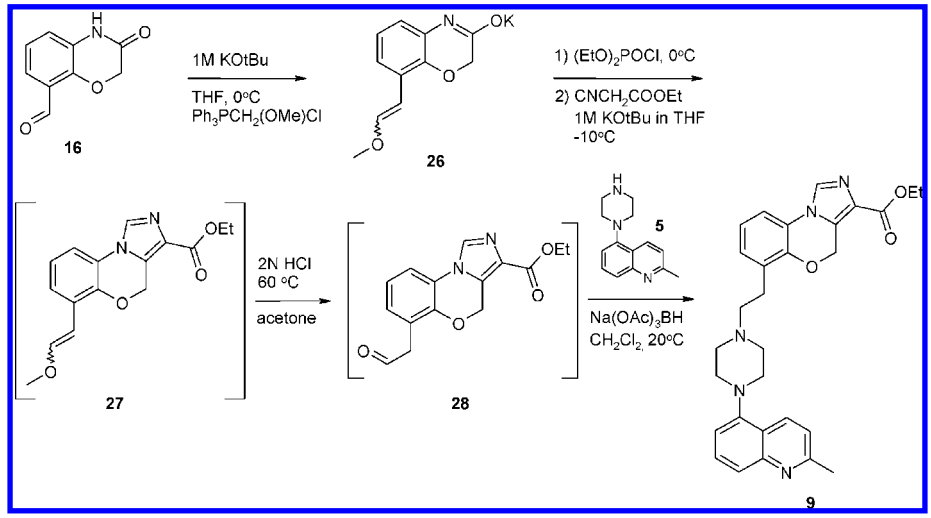
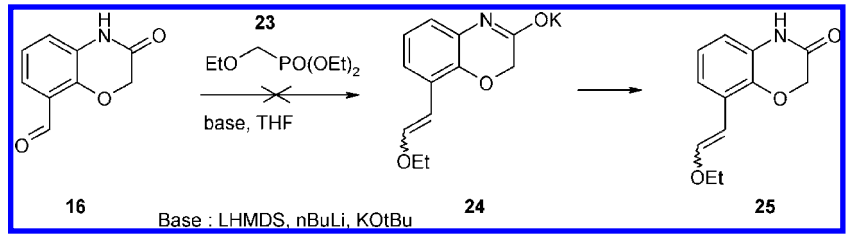


Figure 2. **Reactor temperature profiles for the reduction of the nitrobenzaldehyde 18 to benzoxazine-3-one 16 (stage one).**

Scheme 5. **Initial conditions for stage two for the synthesis of imidazo[5,1-*c*][1,4]benzoxazine-3-carboxylate 9**



Scheme 6. **Horner−Wadsworth−Emmons reaction of diethylphosphonate 23 and arylaldehyde 16**



Emmons reaction failed to give the desired compound **25** (Scheme 6). As an example, the diethyl(ethoxymethyl)phosphonate **23**, generated via an Arbuzov reaction of the trialkylphosphite and (bromoethoxy)methane, was reacted in THF in various bases (lithium hexamethyldisilazane, *n*-butyllithium, potassium *tert*-butoxide) at low temperature leading to complex reaction mixtures out of which the vinylether **25** was isolated in poor yields or not recovered.

The Wittig reaction was superior in terms of reaction profile and conversion of the arylaldehyde **16** to the methylether **26** (Scheme 5). The previously illustrated arylaldehyde **16** was submitted to Wittig reaction with (methoxymethyl)(triph-

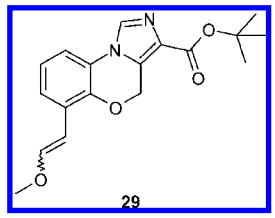


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Figure 3. ***tert*-Butyl 6-[2-methoxyethenyl]-4*H*-imidazo[5,1-*c*][1,4]benzoxazine-3-carboxylate 29, major side product of stage two.**

enyl)phosphonium chloride and 2 equiv of potassium *tert*-butoxide in THF to give the vinylether **26** as (3:1) *E*/*Z* isomer mixture. Unfortunately, the triphenylphosphine oxide (TPPO), side product of the Wittig step, could not be removed at this point and was only separated during the last recrystallization of tricyclic compound **9** in acetone, thus making the analysis of the process with HPLC (at 220 nm) more difficult because of the high absorbance of the triphenylphosphine oxide. Chlorodiethylphosphate, ethylisocyanoacetate, and an additional equivalent of potassium *tert*-butoxide were added at low temperature (0 to −10 °C) to the previously isolated vinylether **26** to facilitate the synthesis of the imidazobenzoxazine-3-carboxylate intermediate **27**, according to known literature conditions.[19] After workup, the solution of **27** was treated with 2N hydrochloric acid to reveal the aldehyde **28**, final reductive amination gave piperazinylquinaldine derivative **9** in 22% overall yield (92% a/a by HPLC) after recrystallization from acetone. As highlighted before, the triphenylphosphine oxide was partially removed during the latter acetone recrystallization of the imidazo[5,1-*c*][1,4]benzoxazine-3-carboxylate derivative **9**.

First attempts at scale-up of the stage two process depicted in Scheme 5 gave a poorly reproducible process and overall yields were ranging from 13% to 28% yield. One of the main drawbacks of the synthesis shown in Scheme 5 was the very large volume of solvents and reagents used (134 vol in relation to the compound **16**). Ethyl acetate (bp 76.5 °C) was used during the workup for the isolation of methylether **27**, followed by a tedious solvent swap to run the next hydrolysis step in acetone (bp 56 °C). Finally, variable amounts of the *tert*-butyl ester derivative **29** (Figure 3) were formed along with the desired methylether derivative **27** in the imidazole formation step. Thus, the development focused on the consistency and robustness of stage two (Scheme 5).

It was found that the first step could be carried out at room temperature (instead of 0 °C) in MeTHF as solvent. It was also demonstrated that MeTHF could be used as both extraction solvent for the workup of the second step and solvent in the biphasic acidic hydrolysis of the vinylether **27** (step two/three). Potassium *tert*-butoxide (1.6 M) was also used instead of 1 M solution in THF in the first step, thus lowering the total volumes of the process.

Step two was carried out at −10 °C, which simplified the operations and reduced the processing time required in the plant. To lower the total volumes of the process and to avoid the formation of side product **29** (Figure 3), 21 wt % sodium ethoxide in ethanol was introduced as a base in place of 1 M solution of potassium *tert*-butoxide in THF. As a result, the *tert*-butyl derivative **29** was only detected in trace quantities in the reaction mixture. The crude reaction mixture resulting from step two/three (Scheme 7) was treated with aqueous $NaHCO_3$ and extracted with MeTHF. After two distillations, the solution of methylether **27** in MeTHF was directly treated with aqueous 2 N hydrochloric acid at 60 °C to afford arylacetaldehyde **28**. This avoided the solvent swap from ethylacetate to acetone, and the overall process was simplified by using only 78 vol vs 134 vol and affording tricyclic ethyl ester **9** (96% a/a by HPLC) in 34% yield on 5-g scale. The sequence was then scaled up in the Verona kilo-lab facility on a 200-g scale and the API precursor **9** was obtained in 35% yield with good HPLC purity (95.4% a/a).

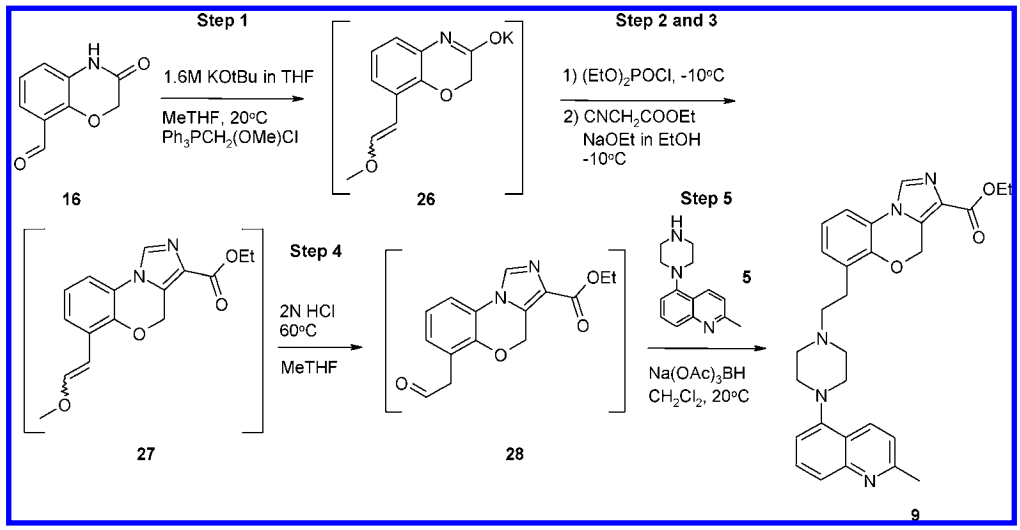
The synthesis described in Scheme 7 was finally scaled up in the Verona pilot plant to prepare 5.75 kg of ethyl 6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl)]ethyl}-4*H*-imidazo[5,1-*c*]-[1,4]benzoxazine-3-carboxylate **9**. Despite the fact that the yield (29%) was lower than the one obtained in the kilo-lab experiment, the quality of the material (94% a/a by HPLC) was in the expected range. The quality of the 21 wt % sodium ethoxide in ethanol was suspected to be the principal cause of the lower yield: tarry material was in fact present in the pilot batch. Unfortunately, the base was released for use on the basis of its certificate of analysis, and no use test was performed. In order to have a scalable process, stage two was modified as follows: the Wittig reaction was carried out at 20 °C instead of −10 °C; 1.6 M potassium *tert*-butoxide solution in THF was used in step one instead of 1 M potassium *tert*-butoxide in THF; MeTHF replaced THF as a reaction solvent in step one (Scheme 7), and it was used during the workup of step three instead of ethylacetate and for step four (hydrolysis); 21 wt %/wt sodium ethoxide in ethanol replaced potassium *tert*-butoxide in THF in step three to avoid the formation of the *tert*-butyl ester side product **29**; the total amount of solvents was reduced from 134 vol to 78 vol; the extraction in acidic water of step four with removal of the TPPO was studied to give a higher recovery of material by working at pH 2 or lower.

The previously mentioned route (Scheme 1) allowed the synthesis of the intermediate grade **11** from the ester **9** in a two-step process (Scheme 8). On a plant scale the ethyl ester **9** was converted in the presence of potassium hydroxide to the corresponding potassium carboxylate **10**, and the latter was then reacted with hexamethyldisilazane (HMDS) and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′*N*′-tetramethyluronium tetrafluoroborate (TBTU) to give **11** (IG) in high overall yield (∼98 wt %/wt).

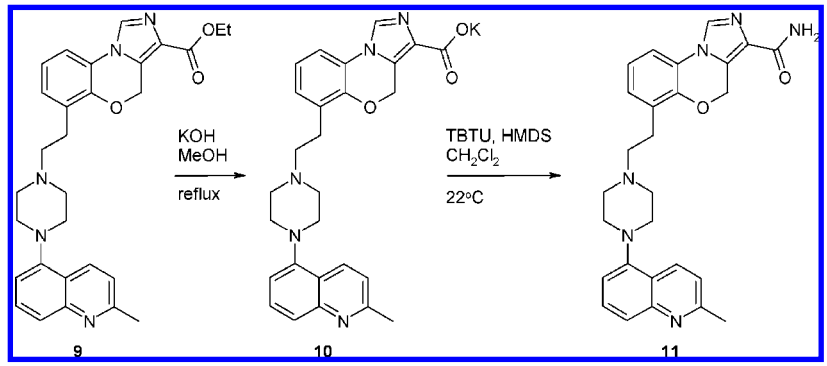
The main drawback of the approach shown in Scheme 8 was the high value of residue on ignition (∼17 wt %/wt) in the intermediate grade **11** due to the coprecipitation of the potassium tetrafluoroborate side product along with the tricyclic amide **11**. After a tedious and poorly efficient recrystallization to remove the inorganic impurity, the carbamide **11** was recovered in modest yield (∼57 wt %/wt). Moreover, hydrolysis and amide coupling were required to isolate intermediate **11**. Therefore, a new and straightforward synthesis of **11** starting from **9** was investigated. First attempts to directly transform the ethyl ester **9** into **11** were carried out on a laboratory scale with 7 N ammonia in methanol under microwave irradiation (Scheme

(19) Erker, T.; Handler, N. *J. Heterocycl. Chem.* **2002**, *39*, 645.

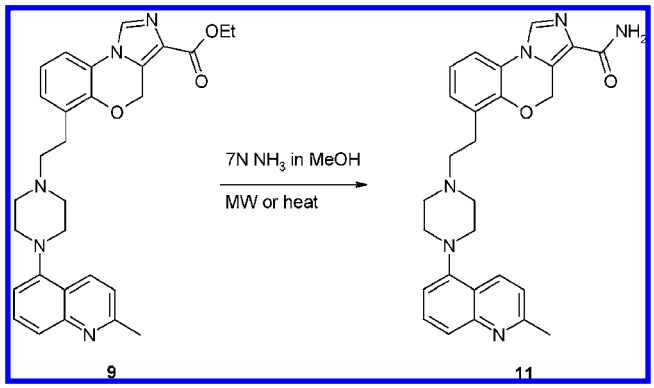
Scheme 7. **Pilot scale-up of stage two, five-step synthesis of imidazo[5,1-*c*][1,4]benzoxazine-3-carboxylate 9**



Scheme 8. **Synthesis of 11 via TBTU coupling**



Scheme 9. **Attempted direct amidation of ester 9 with ammonia in methanol**



9). Pure **11** was recovered in only modest yield (38%). On the other hand, the reaction was extremely slow under conventional heating (less than 2% a/a of **11** by HPLC at 150 °C after 1.5 h, while increasing the temperature to 175 and 190 °C under pressure led only to complex reaction mixtures).

High temperature and high pressure made the latter approach (Scheme 9) not easily applicable for the scale-up. Because of that, a facile and extremely convenient methodology for the synthesis of **11** was found to overcome the issues described above.

Direct amidation of esters with amides in the presence of methoxide ion is a pretty well-known transformation.[20] The preparation of primary amides requires the use of formamide as the amidation reagent. In search of a straightforward synthesis of the primary amide **11** from the ethyl ester **9**, the latter direct transformation looked extremely attractive for its simplicity and convenience, since atmospheric pressure and low temperatures are employed. The formamide-induced amidation of **9** was initially carried out in the presence of two equiv of 21 wt % sodium ethoxide in ethanol as the base. Formamide (10 vol) was used as the solvent of the reaction. The mixture was magnetically stirred for 23 h at 60 °C, cooled to room temperature, and diluted with methanol (10 vol), and the desired product was directly collected by filtration in 73% yield.

A variety of alkoxide bases was screened: powder potassium *tert*-butoxide, 30 wt % sodium methoxide in methanol, 21 wt % sodium ethoxide in ethanol, and 1 M potassium *tert*-butoxide in THF. All the bases were effective, affording **11** in high yield and purity. Sodium methoxide (30 wt %) in methanol was finally chosen as the base, to effect volume reduction of the reaction mixture. Amide **11** was collected by filtration at room temperature after dilution of the reaction mixture with methanol. The resulting sluggish filtration was overcome by the use of a mixture of formamide/methanol (Table 1). Two equivalents of 30 wt % sodium methoxide in methanol was used in this series of experiments. In addition, when using methanol as a cosolvent, reactions were more than 7 times faster (3 h instead of 22−30 h). Moreover, the filtration times were significantly lower, as expected.

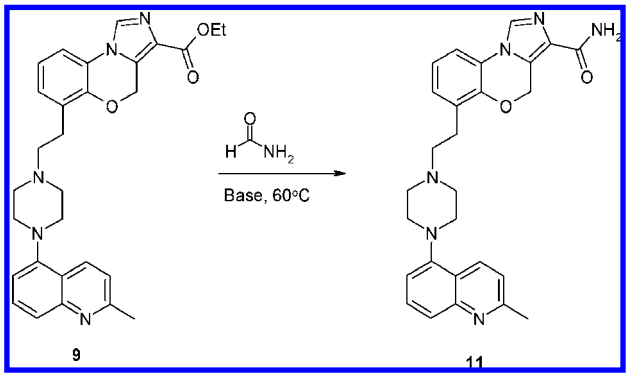
(20) Allred, E. L.; Hurwitz, M. D. *J. Org. Chem.* **1965**, *30*, 2376.

Table 1. **Effect of the presence of different amounts of methanol in the reaction mixture on the filtration time; filter porosity was 20 μm (2-g scale of 9)**

entry	formamide/ MeOH (v/v)	filtration time (min)	**11**, yield (%)	HPLC (%a/a)
1	10/0	22	80.1	96.5
2	4/1	10	69.1[a]	96.2
3	5/5	3.5	82.0	97.0
4	1/4	4	84.2	97.2

[a] Lower yield was obtained due to loss of material passing through the filter during the filtration step.

Scheme 10. **Direct conversion of the ester 9 into amide 11**



A second series of experiments was then carried out to investigate the effect of different amounts of base (30 wt % sodium methoxide in methanol) on the efficiency of the reaction. A mixture of formamide/methanol (1:4) was used as the solvent. An excess of base is required to maximize the recovery of **11**.

The optimized reaction conditions were then scaled up on 800-g scale. Therefore, tricyclic ester **9** was reacted at 60 °C in a mixture formamide/methanol (1:4) (10 vol) in the presence of two equiv of 30 wt % sodium methoxide in methanol. After diluting with methanol and cooling to room temperature, the desired intermediate grade **11** was isolated in good yield (86%) and high purity (98% a/a by HPLC).

In conclusion, process development and scale-up synthesis of **11** was accomplished (Scheme 11) by a new route that represents an efficient and economical process starting from the easily accessible 3-nitrosalicylaldehyde. The overall yield was improved from 8% (Scheme 1) to 17% (Scheme 11), and the number of stages to the API was lowered by almost half (from 7 to 4), thus reducing number and quantity of solvents and the cycle times. Finally, the route performed well at a pilot scale, and no major issues were identified, confirming that the novel approach is feasible for future deliveries and can be considered for manufacturing.

General Remarks

NMR spectra were recorded on 600 MHz Varian Inova 600 for ^{1}H NMR. HPLC analysis of the intermediates and reaction monitoring was carried out on Agilent Series 1200 (Agilent). Generic acidic HPLC method used: column type Luna C18; mobile phase A: 0.05% TFA/water and B: 0.05% TFA/acetonitrile; gradient: 0 min 100% A to 8 min 95% B; flow 1 mL/min; column temperature 40 °C; detector UV DAD @220 nm. Mass spectra analyses were performed on an Agilent 1100 LC/MS, with the mass spectrometer operating in positive electrospray ion mode. Commercially available reagents and solvents were purchased from ordinary chemical suppliers and used without purification.

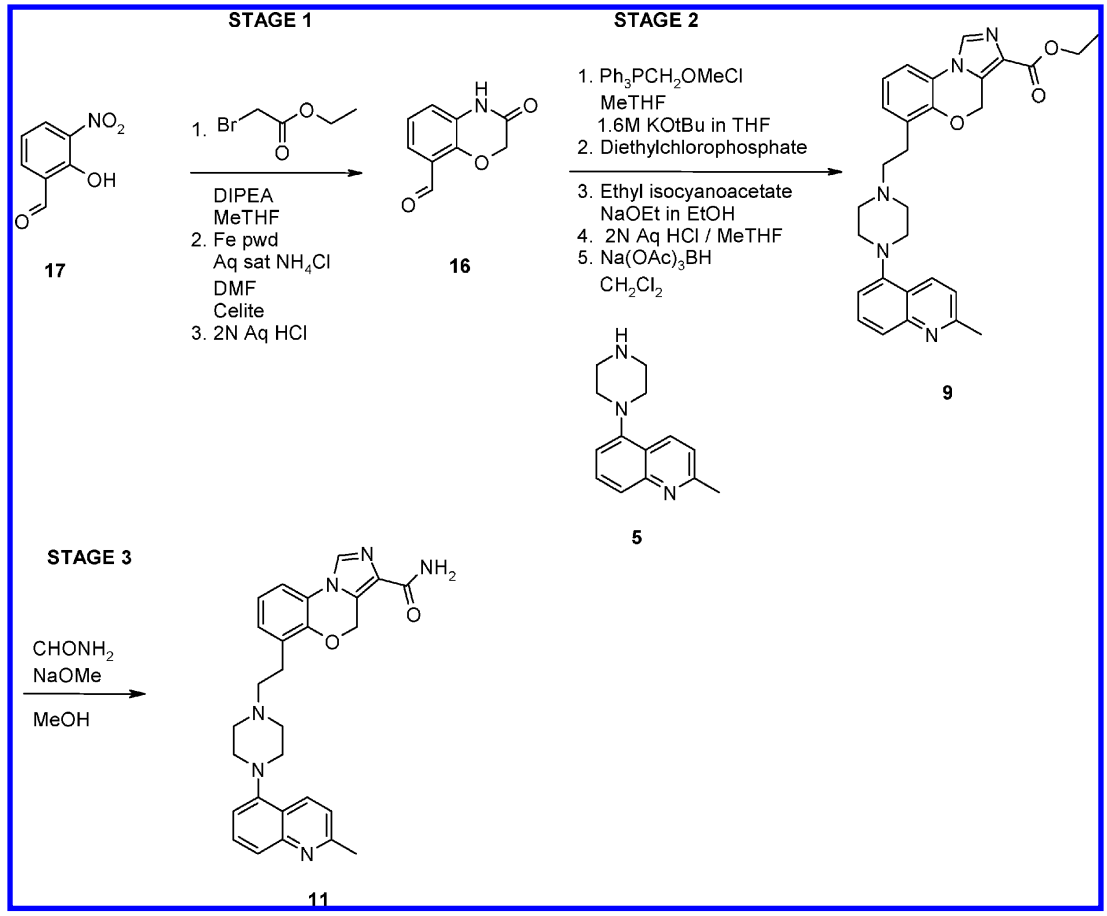
Observed retention times were as follows: 3-nitrosalicylaldehyde **17** (2.99 min), nitrobenzaldehyde **18** (4.28 min), benzoxazine-8-carbaldehyde **16** (2.63 min), imidazo[5,1-*c*]-[1,4]benzoxazine-3-carboxylate **9** (3.02 min), imidazo[5,1-*c*]-[1,4]benzoxazine-3-carboxamide **11** (2.67 min).

3-Oxo-3,4-dihydro-*2H*-1,4-benzoxazine-8-carbaldehyde (16). *Step One.* To a suspension of 3-nitrosalicylaldehyde (10 kg, 1 wt, 1 equiv) in MeTHF (3 vol) at 20 °C, DIPEA (2 vol, 1.92 equiv) is added followed by ethylbromoacetate (0.8 vol, 1.2 equiv). The mixture is stirred at reflux (ca. 80 °C, internal temperature) for 30 min. The reaction mixture is cooled to room temperature in 20 min, MeTHF (2 vol) is added followed by water (5 vol). After 5 min at room temperature, the organic phase is collected and the aqueous phase is back-extracted with MeTHF (2 vol). The combined organic phases are washed with 2 M hydrochloric acid (5 vol) and water (5 vol). The organic phase is concentrated under vacuum to 2.5 vol and DMF (3 vol) is added. The resulting mixture is concentrated under vacuum to 4 vol and is called Solution 1, this is used for the next step without further purification.

Step Two. Celite (0.3 wt) and iron powder-325mesh (0.8 wt, 2.4 equiv) is successively added to a vigorously stirred solution of DMF (3 vol) and aqueous ammonium chloride (1 vol) at 20 °C. The resulting suspension is warmed to 85 °C (internal temperature) over 40 min. Solution 1 is added portionwise over 20−30 min (jacket controlled, jacket temp 75 °C) maintaining the internal temperature below 100 °C. At the end of the addition the reaction mixture is stirred at 85 °C for 30 min. DMF (10 vol) is added at 80 °C. The suspension is filtered at 80 °C and the cake is washed with DMF (4 vol) at 80 °C. The filtrate is concentrated under vacuum to 3 vol and then 2 M aqueous hydrochloric acid (5 vol) is added at 40 °C. The resulting suspension is stirred at 40 °C for 1 h then diluted with water (5 vol) and stirred at 5 °C for 5 h. The resulting suspension is filtered and the cake is washed with water (3× 3 vol). The cake is dried on the filter for 1 h and then in the vacuum oven at 50 °C for 20 h to give 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-8-carbaldehyde **16** (7.1 kg, 67%th yield, 71 wt %/wt) as a brown solid. ^{1}H NMR (600 MHz, d_6-DMSO) δ 4.75 (s, 2H), 7.07 (t, 1H), 7.17 (dd, 1H), 7.33 (dd, 1H), 10.28 (s, 1H), 10.94 (s, 1H).

Ethyl 6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl)]ethyl}-*4H*-imidazo[5,1-*c*][1,4]benzoxazine-3-carboxylate (9). 3-Oxo-3,4-dihydro-2*H*-1,4-benzoxazine-8-carbaldehyde **16** (7.0 kg, 1 wt) and methoxymethyl-triphenylphosphonium chloride (1.1 equiv, 2.13 wt) are suspended at 18 °C in MeTHF (4 vol). Potassium *tert*-butoxide (1.6 N) in THF (2.4 equiv, 8.4 vol) is added dropwise over 30 min, keeping the temperature below 30 °C during the addition. The reaction mixture is stirred for 30 min at 18 °C, and then it is cooled to −10 °C. Diethylchlorophosphate (1.4 equiv, 1.14 vol) is added in 10 min, maintaining the temperature below −3 °C. The reaction mixture is stirred at −10 °C for 15 min, and then ethylisocyanoacetate (1.1 equiv, 0.68 vol) is added. Sodium ethoxide (21 wt %) in EtOH (1.2 equiv, 2.5 vol) is added dropwise in 20 min, keeping the

Scheme 11. **Optimized synthesis of 11**



temperature below −3 °C. The reaction mixture is stirred at −10 °C for 30 min. Sodium hydrogencarbonate (5 wt %/wt) (5 vol) is added, and the mixture is concentrated to 11 vol. The residue is diluted with MeTHF (5 vol) and concentrated to 11 vol. The residue is diluted in MeTHF (5 vol) and concentrated to 11 vol. The crude is diluted with 5 wt %/wt $NaHCO_3$ (5 vol), and the separated aqueous phase is back-extracted with MeTHF (5 vol). The organics are combined. Hydrochloric acid (2 N, 5 vol) is added, and the mixture is stirred at 60 °C (internal temperature) for 1 h. The mixture is cooled down to 18 °C. Toluene (5 vol) is added. The organic phase is extracted with 2 N hydrochloric acid (5 vol). The combined aqueous phases are diluted with 13% Na_2CO_3 (6 vol) (target: pH 1.5 to 2) and extracted with dichloromethane (2 × 5 vol). The combined organics are washed with water (3 vol). The resulting dichloromethane solution is called Solution A.

Piperazinylquinaldine **5** (6.3 kg, 0.7 equiv, 0.9 wt) and sodium triacetoxyborohydride (1 equiv, 1.2 wt) are suspended in dichloromethane (6 vol). The mixture is allowed to stir at room temperature for 10 min. Solution A is added dropwise over 60 min, and the resulting mixture is stirred for 20 min at room temperature. $NaHCO_3$ (5%, 5 vol) is added, and the resulting mixture is stirred for 30 min at room temperature. The dichloromethane solution is evaporated to 5 vol. Acetone (15 vol) is added and the mixture evaporated to 10 vol. The suspension is diluted with acetone (10 vol) and the mixture evaporated to 10 vol. The suspension is stirred at room temperature for 15 h. The solid is collected by filtration, washed with acetone (2 vol), and dried at 40 °C under reduced pressure (5.75 kg, 29%th, 82 wt %/wt). ^{1}H NMR (600 MHz, d_6-DMSO) δ 1.31 (t, 3H), 2.63 (s, 3H), 2.64 (m, 2H), 2.75 (m, 4H), 2.87 (t, 2H), 3.03 (m, 4H), 4.27 (q, 2H), 5.55 (s, 2H), 7.10 (m, 2H), 7.24 (dd, 1H), 7.38 (d, 1H), 7.59 (m, 2H), 7.77 (dd, 1H), 8.35 (d, 1H), 8.60 (s, 1H).

6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl)]ethyl}-*4H*-imidazo[5,1-c][1,4]benzoxazine-3-carboxamide (11). Sodium methoxide in methanol (30 wt %) (2 equiv, 0.77 vol, 0.73 wt) was added at room temperature to a vigorously stirred mixture of **9** (800 g, 1 wt) in formamide/methanol 1:4 (10 vol). The reaction mixture was heated up to 60 °C and stirred for 3 h. Methanol (5 vol) was added, and the resulting mixture was stirred for 1 h at 60 °C and then cooled down to room temperature over 1 h and stirred overnight. The mixture is filtered, and the cake is washed with methanol (3 × 2.5 vol) and dried at 40 °C under reduced pressure (644 g, 86%th, 80 wt %/wt). ^{1}H NMR (600 MHz, CD_3COOD) δ 2.98 (s, 3H), 3.29 (dd, 2H), 3.54 (m, 4H), 3.55 (m, 6H), 5.66 (s, 2H), 7.14 (t, 1H), 7.30 (dd, 1H), 7.50 (d, 1H), 7.66 (dd, 1H), 7.79 (d, 1H), 7.97 (t, 1H), 8.00 (d, 1H), 8.39 (s, 1H), 9.06 (d, 1H).

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