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An Isoxazole Strategy for the Synthesis of Fully Substituted Nicotinates

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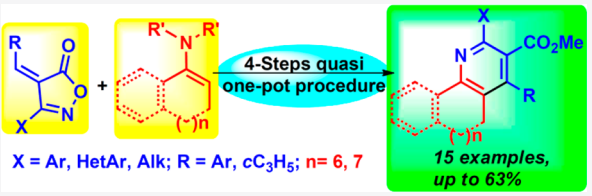
ABSTRACT: A four-step quasi one-pot procedure for the preparation of fully substituted nicotinates from ketone enamines and 4-methylideneisoxazol-5-ones has been developed. The reaction sequence involves (1) reaction of 4-methylideneisoxazol-5-ones with ketone enamines with the formation of isoxazole-5-ols, (2) their O-methylation with diazomethane, (3) hydrogenative cleavage of the O−N bond in 5-methoxyisoxazoles under action of $Mo(CO)_6/H_2O$ and simultaneous isomerization and condensation of the formed enamines, with the formation of dihydropyridines, and (4) aromatization of the latter.



Nicotinate is one of the most important pyridine-containing frameworks found in natural products[1] and is widely exploited in pharmaceutical[2] and agro chemistries.[3] Various biological activities of nicotinates have led to the development of a plethora of methods for their synthesis.[4] However, only a few methods for the preparation of polysubstituted nicotinates were published in the literature (Scheme 1).[5] New synthetic strategies for the preparation of substituted nicotinates and, in particular, 5,6,7,8-tetrahydroquinoline-3-carboxylates, which are showing new biological activity,[6] still need to be developed for the mentioned reasons.

Taking all this into account and based on our experience in the use of isoxazoles as valuable synthetic blocks for the preparation of nitrogen heterocycles,[7] we postulated that fully substituted nicotinates and, in particular, 5,6,7,8-tetrahydroquinoline-3-carboxylates, can be synthesized using the reaction sequence shown in Scheme 2. The scheme involves (1) Michael addition of enamines **2** to 4-methylideneisoxazol-5-ones **1**, (2) methylation of hydroxyisoxazole **3**, (3/4) catalytic hydrogenative cleavage of the O−N bond in isoxazole **4**, followed by intramolecular condensation to give dihydropyridine **6**, and (5) dehydrogenative aromatization of dihydropyridine **6**.

Although the direct condensation of 4-methylideneisoxazol-5-ones **1** with enamines (Scheme 1, step 1) has not been studied, nevertheless it was postulated in the amine-catalyzed reactions of 4-methylideneisoxazol-5-ones with ketones.[8] Methylation of isoxazol-5-oles, which are in an equilibrium with the corresponding isoxazol-5-ones, using diazomethane is well-known[7] as well as hydrogenative cleavage of the O−N bond in isoxazole **4** under action $Mo(CO)_6/H_2O$.[9] Further, since $Mo(CO)_6$ can catalyze *Z*/*E*-isomerization of (*Z*)-*β*-aminoacrylates,[9a] which is necessary for condensation of **5** into **6**, it was not unreasonable to assume that this condensation can proceed directly under the conditions of hydrogenative cleavage of the O−N bond of isoxazole **4**. Taking into account that mixtures of isomers will be formed on the 1−4 steps (Scheme 2), most of which will be becoming to the desired product, we decided to try implementing the reaction sequence leading from isoxazolones **1a**−**1c** and enamine **2a** to target nicotinates **7a**−**7c** without isolation and purification of intermediate products **3**−**6**. The use of such a so-called "quasi one-pot" procedure[10] with chromatographic purification only after the final reaction step allows operating costs to be kept to a minimum. Having obtained target products **7a**−**7c** in low yield after the first experiments and based on our experience in isoxazolone chemistry, we decided to examine step 2 more closely and found that under the normal methylation conditions (diazomethane, THF/Et_2O, 0 °C), in addition to O-methylation of compound **3**, N-methylation also occurs (∼1:1 ratio). We found that it is possible to shift the reaction toward the formation of the desired O-methylation product **4** by lowering the temperature to −20 °C (∼2:1 ratio). The unseparated N-methylation **4′** product does not interfere with further reaction of **4**. Finally, using conditions shown in Table 1, nicotinates **7a**−**7o** were synthesized in 20−63% yield (72−91% average yield on each step) by this quasi one-pot procedure.

When pure isoxazole **4i** (Scheme 3), isolated in one of the experiments of the optimization stage, was introduced into further reactions of the sequence, nicotinate **7i** was obtained in 77% yield.

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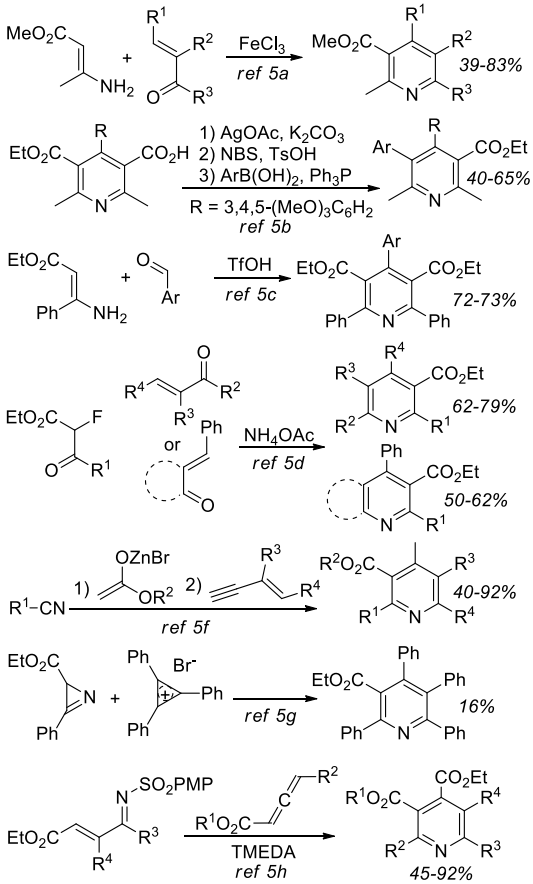
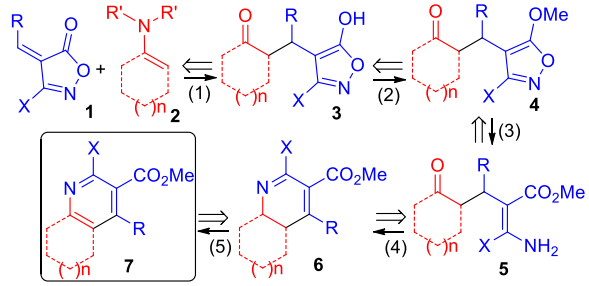
Scheme 1. Reported Synthetic Approaches to Fully Substituted Nicotinates



Scheme 2. Retrosynthesis of Fully Substituted Nicotinates from Isoxazolones 1 and Enamines 2[a]



[a](1) Michael addition, (2) O-methylation, (3) hydrogenative cleavage of the isoxazole O−N bond, (4) intramolecular condensation, and (5) aromatization.

The procedure tolerates 4-methylideneisoxazol-5-ones containing aryl, hetaryl, and alkyl groups at the isoxazolone core and electron-donating and electron-withdrawing substituted aryl and cyclopropyl group at the C=C double bond. Enamines derived from morpholine and cyclohexanone, cycloheptanone, tetralones, and propiophenone were successfully used in the reactions, while use of enamines derived from acetophenone, ethyl acetoacetate, hept-4-one, and 1,3-diarylethanone led to too complex reaction mixtures.

The developed sequence is also applied for the preparation of 5,6,7,8-tetrahydroquinolines by omitting the methylation step (Scheme 2, step 2). In this case, the intermediate isoxazol-5-ol **3b** undergoes hydrogenative cleavage of the O−N bond under action of $Mo(CO)_6/H_2O$ and additionally decarboxylation (cf. Fe/acid catalyzed decarboxylation[8c]), followed by isomerization of the intermediate enamine and condensation (Scheme 4) to give 5,6,7,8-tetrahydroquinoline **8**.

Synthesized 5,6,7,8-tetrahydroquinoline-3-carboxylates and 5,6-dihydrobenzo[*h*]quinoline-3-carboxylate were aromatized on Pd/C to the corresponding quinoline-3-carboxylate **9** and benzo[*h*]quinoline-3-carboxylates **10** (Scheme 5).

All new compounds were characterized by ^{1}H, ^{13}C NMR, and HRMS methods. Moreover, the structures of **4i**, **7b**, and **7c** were also confirmed by single-crystal X-ray diffraction analysis. Compounds **7**−**10** are nonhygroscopic crystalline solids, which are stable under an air atmosphere for a long time at rt.

In conclusion, fully substituted nicotinates can easily be prepared by a four-step quasi one-pot procedure from ketone enamines and 4-methylideneisoxazol-5-ones, without isolation of the intermediates. The procedure makes use of a chromatographic purification only after the last step of the reaction sequence, resulting in a minimization of operational effort and a maximization of yield.

EXPERIMENTAL SECTION

General Information and Methods. Melting points were determined on a melting point apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were recorded on a NMR spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane (TMS, δ = 0.00). ^{1}H NMR spectra were calibrated according to the residual peak of $CDCl_3$ (7.26 ppm) and DMSO-d_6 (2.50 ppm). For all new compounds, ^{13}C{^{1}H} and ^{13}C DEPT-135 spectra were recorded and calibrated according to the peak of $CDCl_3$ (77.00 ppm) and DMSO-d_6 (39.51 ppm). Electrospray ionization (ESI) mass spectra were recorded on a mass spectrometer, HRMS-ESI-QTOF. Single-crystal X-ray data were collected by means of a diffractometer. Crystallographic data for the structures **4i** (CCDC 2053525), **7b** (CCDC 2053526), and **7c** (CCDC 2053527) have been deposited with the Cambridge Crystallographic Data Centre. Thin-layer chromatography (TLC) was conducted on aluminum sheets with 0.2 mm silica gel with a fluorescent indicator. Some solvents were distilled and dried prior to use. Acetonitrile was distilled from P_2O_5, then distilled from anhydrous K_2CO_3, and stored over 3 Å sieves. Toluene was distilled from Na with benzophenone and stored over Na. Other solvents were used without purification.

Starting 3-(aryl/heteroaryl)isoxazol-5(4*H*)-ones **11** were commercially available or prepared by the well-studied reaction of hydroxylamine with β-keto esters.[11] Aryl/alkyl aldehydes **12** were commercially available. Physical and spectral data of oxazolones: 4-(4-methoxybenzylidene)-3-phenyl-5(4*H*)-one **1a**,[12] 4-(4-bromobenzylidene)-3-phenyl-5(4*H*)-one **1b**,[12] 4-(4-nitrobenzylidene)-3-phenyl-5(4*H*)-one **1c**,[13] 4-(4-methylbenzylidene)-3-(4-nitrophenyl)isoxazol-5(4*H*)-one **1d**,[9] 4-(4-methoxybenzylidene)-3-methylisoxazol-5(4*H*)-one **1g**,[14] and 4-(3,4-dimethoxybenzylidene)-3-(thiophen-2-yl)-isoxazol-5(4*H*)-one **1h**;[9] and enamines: 4-(cyclohex-1-en-1-yl)-morpholine **2a**,[15] 4-(cyclohept-1-en-1-yl)morpholine **2b**,[16] 4-(3,4-dihydronaphthalen-1-yl)morpholine **2c**,[17] and 4-(1-phenylprop-1-en-1-yl)morpholine **2e**,[18] prepared according to the published procedures, were in agreement with previously reported values.

Synthesis of Starting Materials. *3-(Quinolin-2-yl)isoxazol-5(4H)-one/3-(quinolin-2-yl)isoxazol-5-ol (**11b**).* Compound **11b** was prepared following the published procedure[19] from methyl 3-oxo-3-(quinolin-2-yl)propanoate (4.25 g, 18.5 mmol) and $NH_2OH\cdot HCl$ (3.22 g, 46.3 mmol) in MeOH (30 mL) in 3.30 g (84% yield) as a rose solid: mp 184−185 °C (dec., MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.52 (d, 1H, J = 8.6 Hz), 8.04−8.10 (m, 3H), 7.82−7.86 (m, 1H), 7.68−7.71 (m, 1H), 5.92 (br. s, 0.7 H), 4.38 (br. s, 0.7 H).

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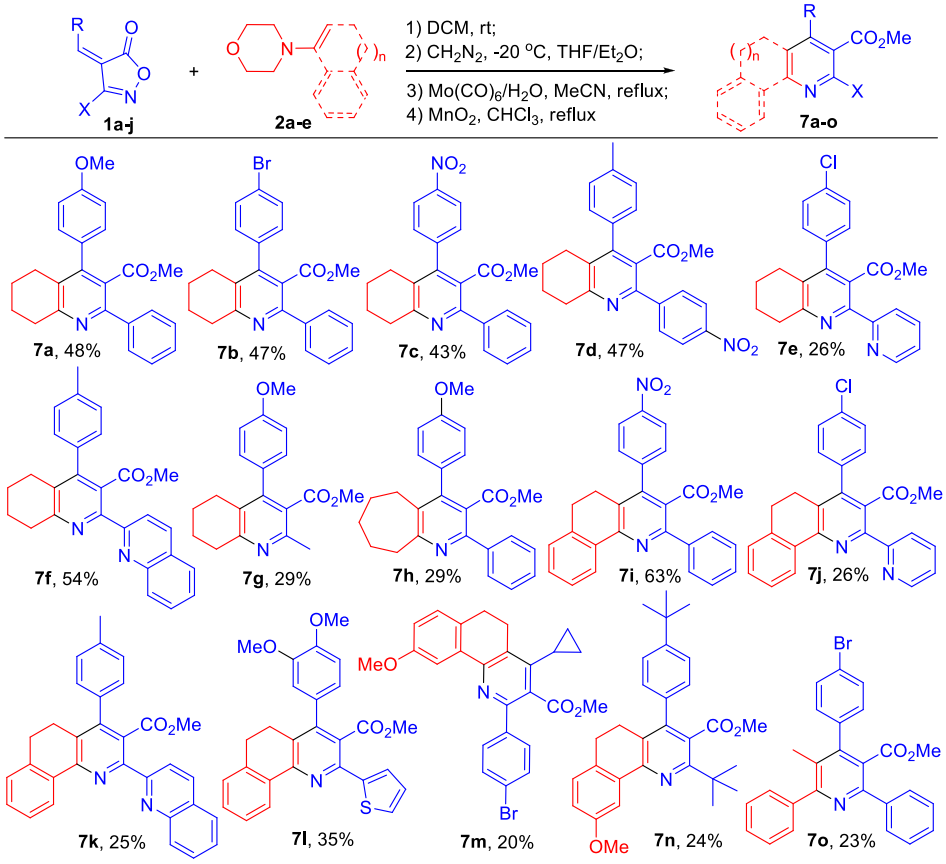
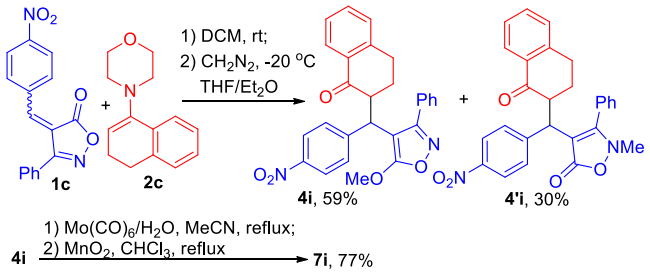
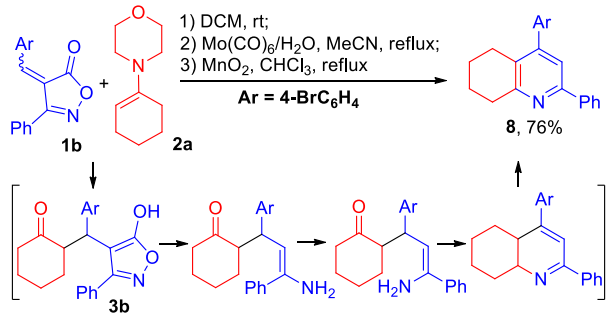
Table 1. Synthesis of Fully Substituted Nicotinates 7 by Quasi One-Pot Procedure



Scheme 3. Synthesis of Nicotinate 7i with Isolation of Intermediate Isoxazole 4i



Scheme 4. Synthesis of 5,6,7,8-Tetrahydroquinoline 8

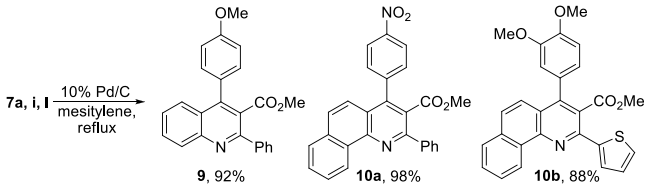


HRMS (ESI) m/z: 235.0478 calcd for $C_{12}H_8N_2NaO_2^+$ $[M + Na]^+$; found 235.0475. The product was used without further purification.

*4-(4-Chlorobenzylidene)-3-(pyridin-2-yl)isoxazol-5(4H)-one (**1e**).* Compound **1e** was prepared following the published procedure[9] from methyl 3-(pyridin-2-yl)isoxazol-5(4*H*)-one **11a** (1.236 g, 7.6 mmol) and 4-chlorobenzaldehyde **12a** (1.342 g, 9.6 mmol) in MeOH (18 mL) with a few drops of morpholine for 0.5 h in 1.35 g (62% yield) as a bright yellow solid: mp 142−144 °C (dec., MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.15 (s, 1H), 8.74−8.76 (m, 1H), 8.35 (d, 2H, J = 8.6 Hz), 8.09 (d, 1H, J = 8.0 Hz), 7.85−7.89 (m, 1H), 7.49 (d, 2H, J = 8.6 Hz), 7.44−7.49 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 168.2 (C), 159.3 (C), 155.1 (CH), 149.2 (CH), 148.7 (C), 140.3 (C), 137.2 (CH), 135.4 (CH), 131.3 (C), 129.2 (CH), 125.2 (CH), 123.0 (CH), 117.1 (C). HRMS (ESI) m/z: 307.0245 calcd for $C_{15}H_9ClN_2NaO_2^+$ $[M + Na]^+$; found 307.0236.

*4-(4-Methylbenzylidene)-3-(quinolin-2-yl)isoxazol-5(4H)-one (**1f**).* Compound **1f** was prepared following the published procedure[9] from 3-(quinolin-2-yl)isoxazol-5(4*H*)-one **11b** (849 mg, 4.0 mmol) and 4-methylbenzaldehyde **12b** (720 mg, 6.0 mmol) in MeOH (10 mL) with a few drops of morpholine for 0.5 h in 889 mg (71% yield) as a green solid: mp 199−200 °C (MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.57 (s, 1H), 8.37 (d, 2H, J = 8.2 Hz), 8.28 (d, 1H, J = 8.6 Hz), 8.16−8.20 (m 2H), 7.89 (d, 2H, J = 8.1 Hz), 7.79−7.82 (m, 1H), 7.63−7.67 (m 1H), 7.35 (d, 2H, J = 8.2 Hz), 2.47 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 168.6 (C), 159.2 (C), 157.6 (CH), 149.1 (C), 147.3 (C), 145.7 (C), 137.1 (CH), 134.7 (CH), 130.8 (C), 130.2 (CH), 129.8 (CH), 129.7 (CH), 128.2 (C), 128.0 (CH), 127.8 (CH), 119.6 (CH), 115.5 (C), 22.1 (CH_3). HRMS

Scheme 5. Aromatization of 5,6,7,8-Tetrahydroquinoline and 5,6-Dihydrobenzo[*h*]quinoline-3-carboxylates



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(ESI) m/z: 315.1128 calcd for $C_{20}H_{15}N_2O_2^+$ $[M + H]^+$; found 315.1136.

*3-(4-Bromophenyl)-4-(cyclopropylmethylene)isoxazol-5(4H)-one (**1i**).* Compound **1i** was prepared following the modified published procedure[9] from 3-(4-bromopheny)isoxazol-5(4*H*)-one **11c** (720 mg, 3.0 mmol) and cyclopropanecarbaldehyde **12c** (350 mg, 5.0 mmol) in *i*PrOH (7 mL) with a few drops of morpholine under Ar atmosphere for 30 min in 590 mg (67% yield) as a beige solid: mp >140 °C (dec. without melt, *i*-PrOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, 2H, J = 8.3 Hz), 7.40 (d, 2H, J = 8.3 Hz), 6.46 (d, 1H, J = 11.5 Hz), 3.27−3.36 (m, 1H), 1.45−1.50 (m, 2H), 1.01−1.04 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 169.7 (C), 166.0 (CH), 160.2 (C), 132.5 (CH), 129.6 (CH), 126.3 (C), 125.6 (C), 118.4 (C), 14.8 (CH), 13.8 (CH_2). HRMS (ESI) m/z: 313.9787 calcd for $C_{13}H_{10}BrNNaO_2^+$ $[M + Na]^+$; found 313.9790.

*3-(tert-Butyl)-4-(4-(tert-butyl)benzylidene)isoxazol-5(4H)-one (**1j**).* Compound **1j** was prepared following the published procedure[9] from 3-(*tert*-butyl)isoxazol-5(4*H*)-one **11d** (800 mg, 5.7 mmol) and 4-(*tert*-butyl)benzaldehyde **12d** (1.379 g, 8.5 mmol) in MeOH (5 mL) with a few drops of morpholine for 2 h in 573 mg (35% yield) as a bright yellow solid: mp 103−104 °C (MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, 2H, J = 8.4 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.83 (s, 1H), 1.46 (s, 9H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 169.1 (C), 168.8 (C), 158.0 (C), 151.0 (CH), 133.8 (CH), 129.5 (C), 125.9 (CH), 117.1 (C), 35.4 (C), 34.7 (C), 30.9 (CH_3), 28.7 (CH_3). HRMS (ESI) m/z: 286.1802 calcd for $C_{18}H_{24}NO_2^+$ $[M + H]^+$; found 286.1803.

*4-(7-Methoxy-3,4-dihydronaphthalen-1-yl)morpholine (**2d**).* Compound **2d** was prepared following the published procedure[17] from 6-methoxy-1,2,3,4-tetrahydro-1-naphthalenone (12.6 g, 71 mmol) in toluene (30 mL), morpholine (37 mL, 430 mmol), and $TiCl_4$ (3.5 mL, 36 mmol) in toluene (5 mL) for 2 weeks in 8.64 g (50% yield) as a beige solid: bp 172−173 °C (2−3 × 10^{-3} Torr), mp 32−33 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.35 (m, 1H), 6.72−6.75 (m, 1H), 6.72 (s, 1H), 5.16 (t, 1H, J = 4.7 Hz), 3.81−3.86 (m, 4H), 3.81 (s, 3H), 2.81−2.83 (m, 4H), 2.63−2.67 (m, 2H), 2.19−2.24 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.5 (C), 147.3 (C), 140.0 (C), 124.9 (C), 124.5 (CH), 113.6 (CH), 110.9 (CH), 105.1 (CH), 67.2 (CH_2), 55.2 (CH_3), 51.3 (CH_2), 29.0 (CH_2), 22.4 (CH_2). HRMS (ESI) m/z: 246.1489 calcd for $C_{15}H_{20}NO_2^+$ $[M + H]^+$; found 246.1492.

General Procedure A for Preparation of Nicotinates 7 by QuasiOne-Pot Procedure.

Step 1. Alkylidenisoxazolone **1** (1 mmol) and enamine **2** (2−3 mmol, 2−3 equiv) were dissolved in dichloromethane and stirred at rt until full conversion of isoxazolone **1** (TLC control; in most cases it takes about 12 h). The solvent was evaporated in vacuo, and the residue was dissolved in 1% aq KOH, the water layer was separated, washed with diethyl ether, and acidified to pH 1−2 (to pH 5 for compounds containing pyridine moiety). Sodium chloride (7−15 g) was added to the water layer, and the product was extracted with ethyl acetate (8−15 × 15−20 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated in vacuo. The residue, containing hydroxyisoxazole **3**, was used without further purification.

Step 2. A solution of hydroxyisoxazole **3** in THF was slowly added to a solution of diazomethane in diethyl ether, freshly prepared from 1-methyl-1-nitrosourea (3 mmol, 3 equiv) and 40% aq KOH (10 mmol) at −20 °C. The reaction mixture was stirred at −20 °C for 20 min and then at rt for 1 h, and the excess of diazomethane was quenched with acetic acid and the solvents were evaporated in vacuo to give the residue, containing 5-methoxyisoxazole **4**.

Step 3. Water (1−2 drops) and $Mo(CO)_6$ (0.5 mmol, 0.5 equiv) was added to a solution, containing 5-methoxyisoxazole **4** in acetonitrile, and the mixture was refluxed for 7 h (heating in an oil bath). The solvent was evaporated in vacuo, and the residue was suspended in chloroform and filtered through Celite.

Step 4. Manganese (IV) oxide (5−6 mmol, 5−6 equiv) was added to the chloroform solution of **6**, obtained in the previous step, and the mixture was refluxed for 3 h (heating in an oil bath), the inorganic material was filtered off, the solvent was evaporated, the residue was dissolved in a minimum volume of chloroform and purified by chromatography on silica gel (light petroleum/ethyl acetate (v/v) + 0.5% NEt_3). After evaporation of the solvents, the product was washed with pentane and air-dried.

*2-((5-Methoxy-3-phenylisoxazol-4-yl)(4-nitrophenyl)methyl)-3,4-dihydronaphthalen-1(2H)-one (**4i**) and 2-methyl-4-((4-nitrophenyl)(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)-3-phenylisoxazol-5(2H)-one (**4′i**).* Compounds **4i** and **4′i** were prepared following general procedure A (steps 1 and 2) from (step 1) arylidenisoxazolone **1c** (294 mg, 1 mmol) and enamine **2c** (430 mg, 2 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (20 mL) and THF (20 mL).

4i. 268 mg (59% yield, after column chromatography on silica (light petroleum/ethyl acetate, 15:1−7:1 (v/v) + 0.5% NEt_3) as a colorless solid: mp 149−150 °C (light petroleum/ethyl acetate). R_f = 0.35 (light petroleum/ethyl acetate 3:1 (v/v) + 0.5% NEt_3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, 2H, J = 8.7 Hz), 7.92−7.95 (m, 1H), 7.45−7.49 (m, 1H), 7.37−7.41 (m, 1H), 7.28−7.35 (m, 7H), 7.20 (d, 1H, J = 7.7 Hz), 4.46 (d, 1H, J = 8.6 Hz), 4.21 (s, 3H), 3.55−3.61 (m, 1H), 2.87−3.01 (m, 2H), 1.96−2.04 (m, 1H), 1.51−1.61 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 198.0 (C), 168.6 (C), 165.7 (C), 149.5 (C), 146.7 (C), 142.9 (C), 133.4 (CH), 132.6 (C), 129.47 (CH), 129.44 (C), 129.1 (CH), 128.7 (CH), 128.51 (CH), 128.48 (CH), 127.5 (CH), 126.8 (CH), 123.8 (CH), 93.4 (C), 58.3 (CH_3), 49.4 (CH), 38.6 (CH), 28.0 (CH_2), 27.1 (CH_2). HRMS (ESI) m/z: 477.1421 calcd for $C_{27}H_{22}N_2NaO_5^+$ $[M + Na]^+$; found 477.1421.

4′i. 135 mg (30% yield, after column chromatography on silica (light petroleum/ethyl acetate, 15:1−7:1 (v/v) + 0.5% NEt_3) as a colorless solid: mp 221−222 °C (light petroleum/ethyl acetate). R_f = 0.30 (light petroleum/ethyl acetate 3:1 (v/v) + 0.5% NEt_3). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 2H, J = 8.7 Hz), 7.93 (d, 1H, J = 7.7 Hz), 7.49−7.57 (m, 5H), 7.42−7.46 (m, 3H), 7.26−7.30 (m, 1H), 7.17 (d, 1H, J = 7.7 Hz), 4.06−4.15 (m, 2H), 3.13 (s, 3H), 2.99−3.07 (m, 1H), 2.81−2.87 (m, 1H), 1.85−1.91 (m, 1H), 1.49 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 199.0 (C), 170.4 (C), 165.2 (C), 149.6 (C), 146.9 (C), 143.3 (C), 133.3 (CH), 132.8 (C), 131.0 (CH), 129.3 (CH), 129.0 (CH), 128.61 (CH), 128.56 (CH), 127.4 (C), 127.3 (CH), 126.5 (CH), 124.1 (CH), 104.7 (C), 47.6 (CH), 40.8 (CH_3), 39.5 (CH), 28.7 (CH_2), 27.8 (CH_2). HRMS (ESI) m/z: 455.1601 calcd for $C_{27}H_{23}N_2O_5^+$ $[M + H]^+$; found 455.1609.

*Methyl 4-(4-methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (**7a**).* Compound **7a** was prepared following general procedure A from (step 1) arylidenisoxazolone **1a** (279 mg, 1 mmol) and enamine **2a** (500 mg, 3 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (20 mL) and THF (8 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (15 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (50 mL) in 178 mg (48% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−6:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 126−127 °C (light petroleum/ethyl acetate). R_f = 0.28 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60−7.62 (m, 2H), 7.34−7.42 (m, 3H), 7.14 (d, 2H, J = 8.5 Hz), 6.94 (d, 2H, J = 8.5 Hz), 3.84 (s, 3H), 3.34 (s, 3H), 3.06 (t, 2H, J = 6.4 Hz), 2.48 (t, 2H, J = 6.3 Hz), 1.87−1.93 (m, 2H), 1.73−1.78 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 169.1 (C), 159.2 (C), 158.4 (C), 152.8 (C), 147.8 (C), 140.0 (C), 129.5 (CH), 129.2 (C), 128.9 (C), 128.33 (CH), 128.31 (CH), 128.25 (CH), 127.2 (C), 113.7 (CH), 55.2 (CH_3), 51.8 (CH_3), 33.3 (CH_2), 27.2 (CH_2), 22.82 (CH_2), 22.77 (CH_2). HRMS (ESI) m/z: 374.1751 calcd for $C_{24}H_{24}NO_3^+$ $[M + H]^+$; found 374.1755.

*Methyl 4-(4-bromophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (**7b**).* Compound **7b** was prepared following general procedure A from (step 1) arylidenisoxazolone **1b** (328 mg, 1 mmol) and enamine **2a** (500 mg, 3 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (20 mL) and

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THF (10 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (15 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (52 mL) in 201 mg (47% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−8:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 149−150 °C (light petroleum/ethyl acetate). R_f = 0.39 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59−7.61 (m, 2H), 7.56 (d, 2H, J = 8.4 Hz), 7.37−7.42 (m, 3H), 7.10 (d, 2H, J = 8.4 Hz), 3.34 (s, 3H), 3.07 (t, 2H, J = 6.5 Hz), 2.44 (t, 2H, J = 6.3 Hz), 1.88−1.94 (m, 2H), 1.73−1.79 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 168.8 (C), 158.7 (C), 153.0 (C), 146.8 (C), 139.8 (C), 135.7 (C), 131.5 (CH), 130.0 (CH), 128.6 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 126.6 (C), 122.3 (C), 51.9 (CH_3), 33.3 (CH_2), 27.2 (CH_2), 22.70 (CH_2), 22.66 (CH_2). HRMS (ESI) m/z: 444.0570 calcd for $C_{23}H_{20}BrNO_2^+$ $[M + Na]^+$; found 444.0575.

*Methyl 4-(4-nitrophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (**7c**).* Compound **7c** was prepared following general procedure A from (step 1) arylidenisoxazolone **1c** (294 mg, 1 mmol) and enamine **2a** (500 mg, 3 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (20 mL) and THF (10 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (15 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (57 mL) in 168 mg (43% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−6:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 170−171 °C (light petroleum/ethyl acetate). R_f = 0.25 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.30 (d, 2H, J = 8.6 Hz), 7.59−7.60 (m, 2H), 7.37−7.43 (m, 5H), 3.32 (s, 3H), 3.09 (t, 2H, J = 6.4 Hz), 2.41 (t, 2H, J = 6.2 Hz), 1.89−1.95 (m, 2H), 1.76−1.80 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 168.5 (C), 159.1 (C), 153.5 (C), 147.6 (C), 145.9 (C), 143.8 (C), 139.6 (C), 129.5 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.0 (C), 125.9 (C), 123.6 (CH), 52.1 (CH_3), 33.3 (CH_2), 27.2 (CH_2), 22.60 (CH_2), 22.55 (CH_2). HRMS (ESI) m/z: 389.1496 calcd for $C_{23}H_{21}N_2O_4^+$ $[M + H]^+$; found 389.1495.

*Methyl 2-(4-nitrophenyl)-4-(p-tolyl)-5,6,7,8-tetrahydroquinoline-3-carboxylate (**7d**).* Compound **7d** was prepared following general procedure A from (step 1) arylidenisoxazolone **1d** (308 mg, 1 mmol) and enamine **2a** (500 mg, 3 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (20 mL) and THF (18 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (11 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (70 mL) in 187 mg (47% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−8:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 158−159 °C (light petroleum/ethyl acetate). R_f = 0.39 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, 2H, J = 8.6 Hz), 7.79 (d, 2H, J = 8.6 Hz), 7.24 (d, 2H, J = 7.8 Hz), 7.09 (d, 2H, J = 7.8 Hz), 3.34 (s, 3H), 3.06 (t, 2H, J = 6.4 Hz), 2.51 (t, 2H, J = 6.2 Hz), 2.40 (s, 3H), 1.89−1.93 (m, 2H), 1.73−1.79 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 168.5 (C), 159.0 (C), 150.3 (C), 148.6 (C), 147.8 (C), 146.3 (C), 138.0 (C), 133.3 (C), 130.6 (C), 129.4 (CH), 129.1 (CH), 128.0 (CH), 127.2 (C), 123.5 (CH), 52.1 (CH_3), 33.3 (CH_2), 27.3 (CH_2), 22.62 (CH_2), 22.60 (CH_2), 21.3 (CH_3). HRMS (ESI) m/z: 425.1472 calcd for $C_{24}H_{22}N_2NaO_4^+$ $[M + Na]^+$; found 425.1468.

*Methyl 4-(4-chlorophenyl)-2-(pyridin-2-yl)-5,6,7,8-tetrahydroquinoline-3-carboxylate (**7e**).* Compound **7e** was prepared following general procedure A from (step 1) arylidenisoxazolone **1e** (285 mg, 1 mmol) and enamine **2a** (500 mg, 3 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (28 mL) and THF (9 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (8 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (50 mL) in 98 mg (26% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−8:1 + 0.5% NEt_3, (v/v)) as a beige solid: mp 176−177 °C (light petroleum/ethyl acetate). R_f = 0.33 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.53−8.54 (m, 1H), 8.28 (d, 1H, J = 7.8 Hz), 7.77−7.81 (m, 1H), 7.40 (d, 2H, J = 8.3 Hz), 7.25−7.26 (m, 1H), 7.16 (d, 2H, J = 8.3 Hz), 3.50 (s, 3H), 3.06 (t, 2H, J = 6.4 Hz), 2.42 (t, 2H, J = 6.3 Hz), 1.88−1.94 (m, 2H), 1.72−1.78 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.0 (C), 158.0 (C), 155.9 (C), 150.1 (C), 148.3 (CH), 147.3 (C), 136.7 (CH), 135.0 (C), 134.0 (C), 130.3 (C), 129.9 (CH), 128.5 (CH), 126.5 (C), 123.4 (CH), 122.4 (CH), 51.8 (CH_3), 33.3 (CH_2), 27.3 (CH_2), 22.69 (CH_2), 22.66 (CH_2). HRMS (ESI) m/z: 379.1208 calcd for $C_{22}H_{20}ClN_2O_2^+$ $[M + H]^+$; found 379.1215.

*Methyl 4-(p-tolyl)-5,6,7,8-tetrahydro-[2,2′-biquinoline]-3-carboxylate (**7f**).* Compound **7f** was prepared following general procedure A from (step 1) arylidenisoxazolone **1f** (314 mg, 1 mmol) and enamine **2a** (500 mg, 3 mmol) in DCM (15 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (25 mL) and THF (14 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (8 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (50 mL) in 219 mg (54% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−8:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 188−189 °C (light petroleum/ethyl acetate). R_f = 0.38 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.47 (d, 1H, J = 8.6 Hz), 8.25 (d, 1H, J = 8.6 Hz), 7.97 (d, 1H, J = 8.4 Hz), 7.83 (d, 1H, J = 8.0 Hz), 7.64 (m, 1H), 7.50−7.53 (m, 1H), 7.24 (d, 2H, J = 7.8 Hz), 7.13 (d, 2H, J = 7.8 Hz), 3.56 (s, 3H), 3.11 (t, 2H, J = 6.4 Hz), 2.49 (t, 2H, J = 6.3 Hz), 2.41 (s, 3H), 1.90−1.96 (m, 2H), 1.73−1.79 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.4 (C), 157.8 (C), 155.9 (C), 149.8 (C), 128.8 (C), 147.1 (C), 137.5 (C), 136.5 (CH), 133.5 (C), 131.0 (C), 129.5 (CH), 129.4 (CH), 128.9 (CH), 128.3 (CH), 127.9 (C), 127.5 (CH), 127.2 (C), 126.7 (CH), 120.1 (CH), 51.6 (CH_3), 33.3 (CH_2), 27.4 (CH_2), 22.8 (CH_2), 22.8 (CH_2), 21.3 (CH_3). HRMS (ESI) m/z: 431.1730 calcd for $C_{27}H_{24}N_2NaO_2^+$ $[M + Na]^+$; found 431.1730.

*Methyl 4-(4-methoxyphenyl)-2-methyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (**7g**).* Compound **7g** was prepared following general procedure A from (step 1) arylidenisoxazolone **1g** (217 mg, 1 mmol) and enamine **2a** (500 mg, 3 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (20 mL) and THF (10 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (11 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (50 mL) in 91 mg (29% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−5:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 113−114 °C (light petroleum/ethyl acetate). R_f = 0.24 (light petroleum/ethyl acetate 5:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.06−7.09 (m, 2H), 6.90−6.92 (m, 2H), 3.83 (s, 3H), 3.51 (s, 3H), 2.94 (t, 2H, J = 6.4 Hz), 2.51 (s, 3H), 2.41 (t, 2H, J = 6.2 Hz), 1.83−1.88 (m, 2H), 1.66−1.71 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.3 (C), 159.1 (C), 157.9 (C), 151.1 (C), 147.3 (C), 129.4 (CH), 129.2 (C), 127.8 (C), 127.3 (C), 113.6 (CH), 55.2 (CH_3), 51.9 (CH_3), 33.1 (CH_2), 27.0 (CH_2), 22.81 (CH_2), 22.75 (CH_2), 22.5 (CH_3). HRMS (ESI) m/z: 334.1414 calcd for $C_{19}H_{21}NNaO_3^+$ $[M + Na]^+$; found 334.1424.

*Methyl 4-(4-methoxyphenyl)-2-phenyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-3-carboxylate (**7h**).* Compound **7h** was prepared following general procedure A from (step 1) arylidenisoxazolone **1a** (279 mg, 1 mmol) and enamine **2b** (545 mg, 3 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (21 mL) and THF (10 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (12 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (55 mL) in 112 mg (29% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−8:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 124−125 °C (light petroleum/ethyl acetate). R_f = 0.36 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62−7.63 (m, 2H), 7.35−7.42 (m, 3H), 7.13 (d, 2H, J = 8.5 Hz), 6.94 (d, 2H, J = 8.5 Hz), 3.85 (s, 3H), 3.34 (s, 3H), 3.18−3.20 (m, 2H), 2.62−2.65 (m, 2H), 1.85−1.88 (m, 2H), 1.76−1.79 (m, 2H), 1.57−1.60 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.5 (C), 164.6 (C), 159.1 (C), 151.8 (C), 146.8 (C), 140.0 (C), 134.8 (C), 129.8 (CH), 129.5 (C), 128.3 (CH), 128.3 (CH), 128.3 (CH), 127.4 (C), 113.6 (CH), 55.2 (CH_3), 51.9 (CH_3), 39.6 (CH_2), 32.2 (CH_2), 29.6 (CH_2), 27.5 (CH_2), 26.4 (CH_2). HRMS (ESI) m/z: 388.1907 calcd for $C_{25}H_{26}NO_3^+$ $[M + H]^+$; found 388.1913.

*Methyl 4-(4-nitrophenyl)-2-phenyl-5,6-dihydrobenzo[h]quinoline-3-carboxylate (**7i**).* Compound **7i** was prepared following general procedure A from (step 1) arylidenisoxazolone **1c** (279 mg, 1

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mmol) and enamine **2c** (430 mg, 2 mmol) in DCM (10 mL) for 3 d; (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (25 mL) and THF (17 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (9 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (68 mL) in 275 mg (63% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−8:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 198−199 °C (light petroleum/ethyl acetate). R_f = 0.44 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)).

Compound **7i** also was prepared following the general procedure A (steps 3 and 4) from (step 3) isoxazole **4i** (156 mg, 0.34 mmol) and $Mo(CO)_6$ (47 mg, 0.18 mmol) in MeCN (8 mL); (step 4) MnO_4 (181 mg, 2.1 mmol) in $CHCl_3$ (30 mL). The chloroform solution was filtered, the solvent was evaporated, and the residue was washed with cold MeOH to give a product in 115 mg (77% yield, after washing with methanol). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.49−8.51 (m, 1H), 8.32−8.35 (m, 2H), 7.73−7.75 (m, 2H), 7.44−7.50 (m, 5H), 7.36−7.40 (m, 2H), 7.22−7.24 (m, 1H), 3.38 (s, 3H), 2.87−2.90 (m, 2H), 2.66−2.70 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 168.7 (C), 154.1 (C), 153.3 (C), 147.8 (C), 145.1 (C), 143.6 (C), 139.7 (C), 138.0 (C), 133.9 (C), 130.0 (CH), 129.8 (CH), 128.9 (CH), 128.39 (CH), 128.38 (CH), 127.7 (CH), 127.4 (C), 127.3 (CH), 126.7 (C), 126.2 (CH), 123.6 (CH), 52.2 (CH_3), 27.6 (CH_2), 25.2 (CH_2). HRMS (ESI) *m*/*z*: 437.1496 calcd for $C_{27}H_{21}N_2O_4^+$ $[M + H]^+$; found 437.1482.

*Methyl 4-(4-chlorophenyl)-2-(pyridin-2-yl)-5,6-dihydrobenzo[h]-quinoline-3-carboxylate (**7j**).* Compound **7j** was prepared following general procedure A from (step 1) arylidenisoxazolone **1e** (285 mg, 1 mmol) and enamine **2c** (430 mg, 2 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (30 mL) and THF (16 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (10 mL); (step 4) MnO_4 (450 mg, 5.2 mmol) in $CHCl_3$ (56 mL) for 7 h in 109 mg (26% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−6:1 + 0.5% NEt_3, (v/v)) as a beige solid: mp 190−191 °C (light petroleum/ethyl acetate). R_f = 0.31 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.52−8.56 (m, 3H), 7.84−7.88 (m, 1H), 7.23−7.45 (m, 9H), 3.58 (s, 3H), 2.85−2.89 (m, 2H), 2.68−2.72 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.1 (C), 155.8 (C), 152.3 (C), 150.5 (C), 148.1 (CH), 146.5 (C), 138.1 (C), 136.7 (CH), 134.7 (C), 134.3 (C), 134.2 (C), 130.1 (CH), 129.80 (C), 129.7 (CH), 128.5 (CH), 127.7 (CH), 127.3 (C), 127.2 (CH), 125.8 (CH), 123.6 (CH), 122.5 (CH), 51.9 (CH_3), 27.7 (CH_2), 25.3 (CH_2). HRMS (ESI) *m*/*z*: 427.1208 calcd for $C_{26}H_{20}ClN_2O_2^+$ $[M + H]^+$; found 427.1211.

*Methyl 2-(quinolin-2-yl)-4-(p-tolyl)-5,6-dihydrobenzo[h]-quinoline-3-carboxylate (**7k**).* Compound **7k** was prepared following general procedure A from (step 1) arylidenisoxazolone **1f** (220 mg, 0.7 mmol) and enamine **2c** (325 mg, 1.5 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (255 mg, 2.5 mmol) in Et_2O (25 mL) and THF (20 mL); (step 3) $Mo(CO)_6$ (105 mg, 0.4 mmol) in MeCN (9 mL); (step 4) MnO_4 (365 mg, 4.2 mmol) in $CHCl_3$ (45 mL) in 79 mg (25% yield), after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1−8:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 213−214 °C (light petroleum/ethyl acetate). R_f = 0.36 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.71 (d, 1H, *J* = 8.6 Hz), 8.59 (d, 1H, *J* = 7.6 Hz), 8.31 (d, 1H, *J* = 8.6 Hz), 7.99 (d, 1H, *J* = 8.4 Hz), 7.89 (d, 1H, *J* = 8.0 Hz), 7.66−7.70 (m, 1H), 7.52−7.56 (m, 1H), 7.42−7.46 (m, 1H), 7.35−7.39 (m, 1H), 7.24−7.29 (m, 3H), 7.21 (d, 2H, *J* = 8.0 Hz), 3.64 (s, 3H), 2.44 (s, 3H), 2.85−2.90 (m, 2H), 2.75−2.80 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.5 (C), 155.8 (C), 152.2 (C), 150.3 (C), 148.0 (C), 147.0 (C), 138.3 (C), 137.8 (C), 136.5 (CH), 134.4 (C), 133.3 (C), 130.5 (C), 129.6 (CH), 129.5 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 128.1 (C), 128.0 (C), 127.7 (CH), 127.6 (CH), 127.1 (CH), 126.8 (CH), 125.8 (CH), 120.2 (CH), 51.7 (CH_3), 27.8 (CH_2), 25.4 (CH_2), 21.3 (CH_3). HRMS (ESI) *m*/*z*: 457.1911 calcd for $C_{31}H_{25}N_2O_2^+$ $[M + H]^+$; found 457.1910.

*Methyl 4-(3,4-dimethoxyphenyl)-2-(thiophen-2-yl)-5,6-dihydrobenzo[h]quinoline-3-carboxylate (**7l**).* Compound **7l** was prepared following general procedure A from (step 1) arylidenisoxazolone **1h** (245 mg, 0.8 mmol) and enamine **2c** (345 mg, 1.6 mmol) in DCM (12 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (20 mL) and THF (10 mL); (step 3) $Mo(CO)_6$ (106 mg, 0.4 mmol) in MeCN (8 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (50 mL) in 124 mg (35% yield), after column chromatography on silica (light petroleum/ethyl acetate, 10:1−8:1−3:1 + 0.5% NEt_3, (v/v)) as a light yellow solid: mp 166−167 °C (light petroleum/ethyl acetate). R_f = 0.35 (light petroleum/ethyl acetate 3:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.47 (d, 1H, *J* = 7.4 Hz), 7.34−7.44 (m, 4H), 7.20−7.22 (m, 1H), 7.06−7.08 (m, 1H), 6.94−6.96 (m, 1H), 6.81−6.84 (m, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 3.59 (s, 3H), 2.83−2.87 (m, 2H), 2.73−2.76 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.3 (C), 152.7 (C), 148.9 (C), 148.7 (C), 147.0 (C), 145.9 (C), 144.0 (C), 138.2 (C), 134.0 (C), 129.7 (CH), 128.6 (C), 128.4 (C), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 126.0 (CH), 125.6 (CH), 125.5 (C), 121.2 (CH), 112.0 (CH), 110.9 (CH), 56.0 (CH_3), 55.9 (CH_3), 52.4 (CH_3), 27.8 (CH_2), 25.2 (CH_2). HRMS (ESI) *m*/*z*: 480.1240 calcd for $C_{27}H_{23}NNaO_4S^+$ $[M + Na]^+$; found 480.1240.

*Methyl 2-(4-bromophenyl)-4-cyclopropyl-9-methoxy-5,6-dihydrobenzo[h]quinoline-3-carboxylate (**7m**).* Compound **7m** was prepared following general procedure A from (step 1) isoxazolone **1i** (292 mg, 1 mmol) and enamine **2d** (490 mg, 2 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (32 mL) and THF (9 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (5 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (48 mL) in 93 mg (20% yield), after column chromatography on silica (light petroleum/ethyl acetate, 30:1−15:1 + 0.5% NEt_3, (v/v)) as a light yellow solid: mp 133−134 °C (light petroleum/ethyl acetate). R_f = 0.36 (light petroleum/ethyl acetate 15:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.29 (d, 1H, *J* = 8.6 Hz), 7.53−7.57 (m, 4H), 6.86−6.89 (m, 1H), 6.76−6.78 (m, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.13−3.17 (m, 2H), 2.90−2.94 (m, 2H), 2.00−2.07 (m, 1H), 0.98−1.03 (m, 2H), 0.52−0.56 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.9 (C), 160.8 (C), 152.8 (C), 152.5 (C), 146.6 (C), 140.2 (C), 139.3 (C), 131.4 (CH), 130.6 (C), 130.0 (CH), 128.2 (C), 127.5 (CH), 127.2 (C), 122.8 (C), 112.7 (CH), 112.6 (CH), 55.3 (CH_3), 52.3 (CH_3), 28.0 (CH_2), 24.8 (CH_2), 12.8 (CH), 6.5 (CH_2). HRMS (ESI) *m*/*z*: 486.0675 calcd for $C_{25}H_{22}BrNNaO_3^+$ $[M + Na]^+$; found 486.0673.

*Methyl 2-(tert-butyl)-4-(4-(tert-butyl)phenyl)-9-methoxy-5,6-dihydrobenzo[h]quinoline-3-carboxylate (**7n**).* Compound **7n** was prepared following general procedure A from (step 1) arylidenisoxazolone **1j** (285 mg, 1 mmol) and enamine **2d** (490 mg, 2 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (30 mL) and THF (8 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (5 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (50 mL) in 110 mg (24% yield), after column chromatography on silica (light petroleum/ethyl acetate, 50:1−30:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 201−202 °C (light petroleum/ethyl acetate). R_f = 0.65 (light petroleum/ethyl acetate 30:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.37 (d, 1H, *J* = 8.6 Hz), 7.41 (d, 2H, *J* = 8.2 Hz), 7.17 (d, 2H, *J* = 8.2 Hz), 6.91 (dd, 1H, *J* = 8.6, 2.4 Hz), 6.71 (d, 1H, *J* = 2.4 Hz), 3.85 (s, 3H), 3.33 (s, 3H), 2.76−2.79 (m, 2H), 2.61−2.64 (m, 2H), 1.48 (s, 9H), 1.35 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 170.7 (C), 160.7 (C), 160.5 (C), 150.9 (C), 150.6 (C), 147.0 (C), 140.0 (C), 134.0 (C), 128.5 (CH), 128.1 (C), 127.3 (CH), 126.1 (C), 125.5 (C), 124.8 (CH), 112.7 (CH), 112.6 (CH), 55.3 (CH_3), 51.4 (CH_3), 39.5 (C), 34.6 (C), 31.3 (CH_3), 30.3 (CH_3), 28.3 (CH_2), 25.0 (CH_2). HRMS (ESI) *m*/*z*: 458.2690 calcd for $C_{30}H_{36}NO_3^+$ $[M + H]^+$; found 458.2690.

*Methyl 4-(4-bromophenyl)-5-methyl-2,6-diphenylnicotinate (**7o**).* Compound **7o** was prepared following general procedure A from (step 1) arylidenisoxazolone **1b** (328 mg, 1 mmol) and enamine **2e** (600 mg, 3 mmol) in DCM (10 mL); (step 2) *N*-nitroso-*N*-methylurea (310 mg, 3 mmol) in Et_2O (28 mL) and THF (8 mL); (step 3) $Mo(CO)_6$ (133 mg, 0.5 mmol) in MeCN (7 mL); (step 4) MnO_4 (435 mg, 5 mmol) in $CHCl_3$ (51 mL) in 104 mg (23% yield), after column chromatography on silica (light petroleum/ethyl acetate,

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30:1−20:1−10:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 128−129 °C (light petroleum/ethyl acetate). R_f = 0.50 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.68−7.69 (m, 2H), 7.59−7.61 (m, 4H), 7.37−7.48 (m, 6H), 7.19 (d, 2H, J = 8.3 Hz), 3.40 (s, 3H), 2.11 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 168.8 (C), 159.9 (C), 152.9 (C), 148.1 (C), 140.4 (C), 139.5 (C), 136.3 (C), 131.6 (CH), 130.2 (CH), 129.2 (CH), 128.7 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.5 (C), 127.4 (C), 122.5 (C), 52.1 (CH_3), 17.8 (CH_3). HRMS (ESI) m/z: 480.0570 calcd for $C_{26}H_{20}BrNNaO_2^+$ $[M + Na]^+$; found 480.0575.

*4-(4-Bromophenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline (**8**).* Compound **8** was prepared following general procedure A (steps 1, 3, and 4) from (step 1) arylidenisoxazolone **1b** (164 mg, 0.5 mmol) and enamine **2a** (250 mg, 1.5 mmol) in DCM (8 mL); (step 3) $Mo(CO)_6$ (79 mg, 0.3 mmol) in MeCN (12 mL); (step 4) MnO_4 (230 mg, 2.5 mmol) in $CHCl_3$ (30 mL) in 139 mg (76%) yield, after column chromatography on silica (light petroleum/ethyl acetate, 20:1−15:1, (v/v)) as a colorless solid: mp 127−128 °C (light petroleum/ethyl acetate). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96−7.98 (m, 2H), 7.59 (d, 2H, J = 8.3 Hz), 7.43−7.46 (m, 2H), 7.37−7.40 (m, 1H), 7.36 (s, 1H), 7.22 (d, 2H, J = 8.3 Hz), 3.09 (t, 2H, J = 6.5 Hz), 2.63 (t, 2H, J = 6.2 Hz), 1.91−1.97 (m, 2H), 1.74−1.80 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.9 (C), 154.5 (C), 149.0 (C), 139.6 (C), 138.6 (C), 131.5 (CH), 130.3 (CH), 128.7 (CH), 128.6 (CH), 128.2 (C), 126.8 (CH), 122.0 (C), 118.8 (CH), 33.3 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 23.0 (CH_2). HRMS (ESI) m/z: 364.0695 calcd for $C_{21}H_{19}BrN^+$ $[M + H]^+$; found 364.0700.

General Procedure B for Preparation of Quinolines 9 and 10. Pyridine **7** (10 mg) and Pd/C 10 wt % (3 or 5 mg, 30/50 wt %) were refluxed in mesitylene (heating in an oil bath) until full conversion of the starting material (TLC control, hexanes/diethyl ether 20:1 + 0.5% NEt_3, (v/v)), the inorganic material was filtered off and the product was purified by chromatography on silica gel (light petroleum/ethyl acetate + 0.5%). After evaporation of the solvents, the product was washed with pentane and air-dried.

*Methyl 4-(4-methoxyphenyl)-2-phenylquinoline-3-carboxylate (**9**).* Compound **9** was prepared following general procedure B from pyridine **7a** (24 mg) and Pd/C (12 mg, 50 wt %) in mesitylene (3 mL) for 74 h in 22 mg (92% yield, after column chromatography on silica (light petroleum/ethyl acetate, 30:1−5:1 + 0.5% NEt_3, (v/v)) as a colorless solid: mp 125−126 °C (pentane). R_f = 0.31 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, 1H, J = 8.4 Hz), 7.73−7.79 (m, 3H), 7.68 (d, 1H, J = 8.4 Hz), 7.44−7.51 (m, 4H), 7.34 (d, 2H, J = 8.7 Hz), 7.04 (d, 2H, J = 8.7 Hz), 3.90 (s, 3H), 3.43 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 169.0 (C), 159.8 (C), 155.8 (C), 148.0 (C), 147.1 (C), 140.2 (C), 130.6 (CH), 130.4 (CH), 129.9 (CH), 128.9 C(CH), 128.5 (CH), 128.5 (CH), 127.6 (C), 127.2 (C), 127.0 (CH), 126.6 (CH), 125.9 (C), 113.8 (CH), 55.3 (CH_3), 52.1 (CH_3). HRMS (ESI) m/z: 392.1257 calcd for $C_{24}H_{19}NNaO_3^+$ $[M + Na]^+$; found 392.1259.

*Methyl 4-(4-nitrophenyl)-2-phenylbenzo[h]quinoline-3-carboxylate (**10a**).* Compound **10a** was prepared following general procedure B from pyridine **7i** (40 mg) and Pd/C (12 mg, 30 wt %) in mesitylene (4 mL) for 51 h in 38 mg (98% yield, after column chromatography on silica (light petroleum/ethyl acetate, 30:1−5:1 + 0.5% NEt_3, (v/v)) as a beige solid: mp 192−193 °C (light petroleum/ethyl acetate). R_f = 0.41 (light petroleum/ethyl acetate 8:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.46−9.48 (m, 1H), 8.40−8.42 (m, 2H), 7.88−7.93 (m, 3H), 7.76−7.80 (m, 3H), 7.63−7.65 (m, 2H), 7.50−7.56 (m, 3H), 7.30 (d, 1H, J = 9.1 Hz), 3.45 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 168.7 (C), 154.2 (C), 148.0 (C), 146.5 (C), 144.6 (C), 142.9 (C), 140.1 (C), 133.8 (C), 131.2 (C), 130.6 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 126.6 (C), 125.4 (CH), 123.5 (CH), 122.2 (C), 122.1 (CH), 52.4 (CH_3),. HRMS (ESI) m/z: 457.1159 calcd for $C_{27}H_{18}N_2NaO_4^+$ $[M + Na]^+$; found 457.1179.

*Methyl 4-(3,4-dimethoxyphenyl)-2-(thiophen-2-yl)benzo[h]-quinoline-3-carboxylate (**10b**).* Compound **10b** was prepared following general procedure B from pyridine **7l** (17 mg) and Pd/C (2.3 mg, 30 wt %) in mesitylene (2 mL) for 35 h in 15 mg (88% yield, after column chromatography on silica (light petroleum/ethyl acetate, 10:1−3:1 + 0.5% NEt_3, (v/v)) as a beige solid: mp 164−165 °C (light petroleum/ethyl acetate). R_f = 0.33 (light petroleum/ethyl acetate 3:1 + 0.5% NEt_3, (v/v)). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.42 (d, 1H, J = 7.9 Hz), 7.86−7.88 (m, 1H), 7.69−7.79 (m, 3H), 7.47−7.53 (m, 3H), 7.12−7.14 (m, 1H), 6.96−7.03 (m, 3H), 3.99 (s, 3H), 3.89 (s, 3H), 3.66 (s, 3H). ^1H NMR ($CDCl_3$, 400 MHz): δ 169.3 (C), 149.2 (C), 148.7 (C), 146.8 (C), 146.20 (C), 146.15 (C), 144.5 (C), 133.9 (C), 131.1 (C), 129.1 (CH), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.8 (C), 127.6 (CH), 127.3 (CH), 126.4 (CH), 125.4 (CH), 125.3 (C), 123.4 (C), 123.0 (CH), 122.2 (CH), 112.9 (CH), 110.9 (CH), 56.0 (CH_3), 55.9 (CH_3), 52.5 (CH_3). HRMS (ESI) m/z: 478.1083 calcd for $C_{27}H_{21}NNaO_4S^+$ $[M + Na]^+$; found 478.1081.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00286.

X-ray diffraction experimental data and NMR spectra of new compounds (PDF)

Accession Codes

CCDC 2053525−2053527 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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