Concise Synthesis of Vesnarinone and its Analogues Using Pd-Catalyzed C-N Bond forming Reactions

Yi Yang See,[a,b] Tuan Thanh Dang,[a] Anqi Chen,[a] and Abdul Majeed Seayad *[a]

Abstract: An efficient and concise synthesis of Vesnarinone and its analogues from readily available starting materials is reported using catalytic C-N bond forming reactions. In this protocol, a homogeneous Pd-catalyzed Buchwald-Hartwig amination and a supported Pd nanoparticles catalyzed aminocarbonylation were utilized as the two key reactions to achieve an overall yield of 73%. Synthesis of sixteen analogues was also reported in up to 89% overall yield.

Introduction

Vesnarinone (**1a**) was initially developed by Otsuka pharmaceutical company as a positive inotropic drug for the treatment of congestive heart failure.[1] In addition, biological studies have revealed that Vesnarinone also possesses interesting properties such as anti-cancer[2] and anti-inflammatory[3] activities. The first synthesis of Vesnarinone and its pharmacological evaluations was reported by Tominaga and co-workers in six stoichiometric steps in 23% overall yield.[4] In this synthesis, hazardous reagents such as metal hydrides, conc. mineral acids, alkyl halides and acid chlorides were used, thus making the synthesis unattractive from a green and sustainable perspective. Although there were subsequent improvements of the route,[5] the length of the route and the nature of chemistry were not significantly changed.

In light of our recent work on sustainable amide synthesis based on supported palladium nanoparticles catalyzed amino-carbonylation of aryl halides,[6] we envisioned that catalytic aminocarbonylation could be utilized to create one of the C-N bonds, the amide bond, towards achieving a more efficient and environmentally benign route to Vesnarinone and its analogues. Accordingly, we report herein a concise, *three-step* synthesis of Vesnarinone and its analogues utilizing palladium catalyzed C-N bond forming cross coupling reactions[7] such as aminocarbonylation[8] and Buchwald-Hartwig amination[9] as the key reactions.

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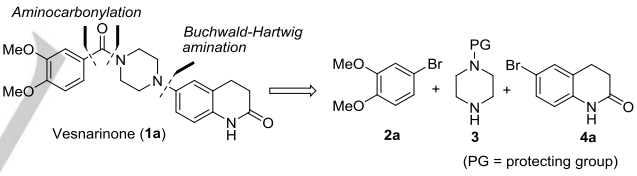
Results and Discussion

A retrosynthetic analysis of Vesnarinone outlined in Scheme 1 highlights the strategy of catalytic coupling of the three readily available components, i.e. 4-bromoveratrole (**2a**), *N*-protected piperazine (**3**) and bromoquinolinone (**4a**), via catalytic aminocarbonylation and Buchwald-Hartwig amination reactions.

This strategy involving two catalytic C-N cross coupling reactions would be more efficient than the previous approach in which the central piperazine ring was constructed through nitration, reduction and cyclization by nucleophilic substitution reactions.[4] Using a suitably mono-protected piperazine **3**, two approaches could be explored for the C-N cross coupling on the two nitrogen atoms using the two aryl bromide fragments **2a** and **4a** via aminocarbonylation[8] and Buchwald-Hartwig amination reaction[9] respectively in two different sequences.

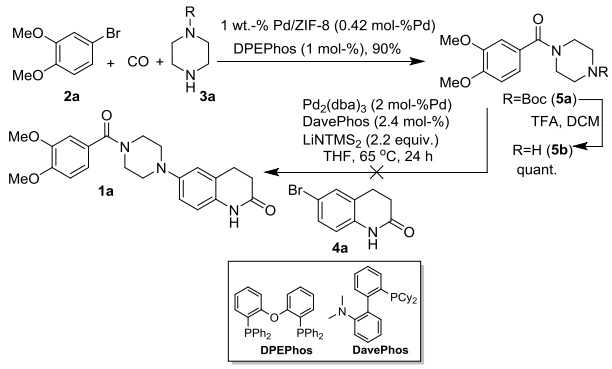


Scheme 1. Retrosynthetic analysis of Vesnarinone.

In the first approach, aminocarbonylation followed by Buchwald-Hartwig amination was investigated (Scheme 2). The aminocarbonylation of mono *N*-Boc protected piperazine (**3a**) with commercially available **2a** using our recently developed recyclable Pd nanoparticles supported on ZIF-8 (PdNP/ZIF-8) [6a] as a catalyst in the presence of DPEPhos as a ligand proceeded smoothly, providing the desired amide product **5a** in 90% isolated yield. It is especially noteworthy that the reaction required only 0.25 mo-l% of Pd loading at 120 ^{o}C and 10 bar carbon monoxide, despite lower reactivity of the aryl bromide. Removal of the Boc protecting group by treatment with TFA in dichloromethane[10] provided the amide **5b** in nearly quantitative yield.

In the second step, coupling of the amide **5b**, with commercially available bromoquinolinone (**4a**) was examined using a C-N coupling protocol reported by Buchwald and co-workers.[11] Disappointingly, this reaction did not yield the expected Vesnarinone product even after significant efforts in screening of the reaction conditions. Debrominated quinolinone was isolated

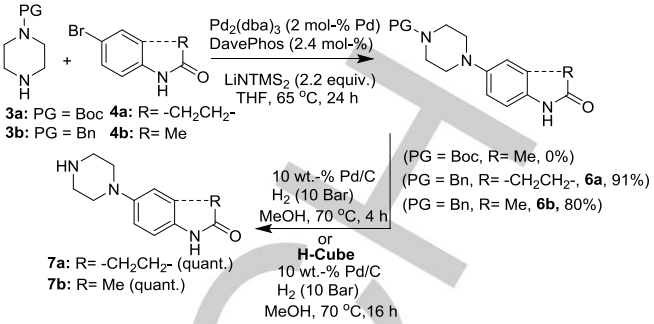
as the only side product with the remaining unconverted amide **5b** recovered.



Scheme 2. Synthesis strategy of Vesnarinone via aminocarbonylation, amination sequence.

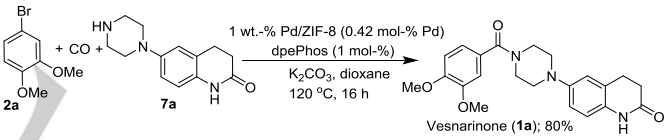
Since the cyclic amide, bromoquinolinone (**4a**), failed to undergo C-N coupling with the *N*-amide protected piperazine **5b** under the reported condition, the second approach, i.e., Buchwald-Hartwig coupling followed by aminocarbonylation was investigated. The investigation began with 4-bromoacetanilide (**4b**), which would not only serve as a readily available model compound to establish the coupling conditions but also enable access to acetamide analogues of Vesnarinone, which would be useful for structure-activity relationship studies. When *N*-Boc protected piperazine (**3a**) was used for the Buchwald-Hartwig coupling reaction, no product was formed, but 67% of the debrominated product of (**4b**) was isolated after the reaction (Scheme 3). However, up to 80% amination product **6b** was obtained when *N*-benzyl protected piperazine (**3b**) was used as the coupling partner using $Pd_2(dba)_3$ and DavePhos ligand in the presence of $LiNTMS_2$ as the base.[11] These conditions were successfully applied to the amination of bromoquinolinone (**4a**), providing the desired coupling product **6a** in 91% isolated yield.

The debenzylation of the arylated piperazines **6a** and **6b** was initially examined by the Sam and Spicer procedure[11] using ammonium formate and Pd/C catalyst, but this was met with difficulties. Although complete conversion was achieved, the deprotected products were contaminated with unidentified polar impurities which were inseparable from the polar *N*-aryl piperazines **7a** and **7b**. After screening a number of debenzylation conditions,[9] quantitative yield of **7a** and **7b** were obtained using Pd/C catalyst (10 mol-% of Pd) under 20 bar of hydrogen in methanol at 70 °C for 4 h, without any detectable impurities. Alternatively, the debenzylation of the arylated piperazines **6a** and **6b** could be readily carried out in an H-Cube flow hydrogenation system using Pd/C catalyst at 10 bar of hydrogen at 70 °C under recirculation mode for 16 h to give **7a** and **7b** in quantitative yields. Piperazines **7a** and **7b** prepared using these procedures were subjected to the next aminocarbonylation step without further purification.



Scheme 3. C-N coupling reaction and benzyl deprotection.

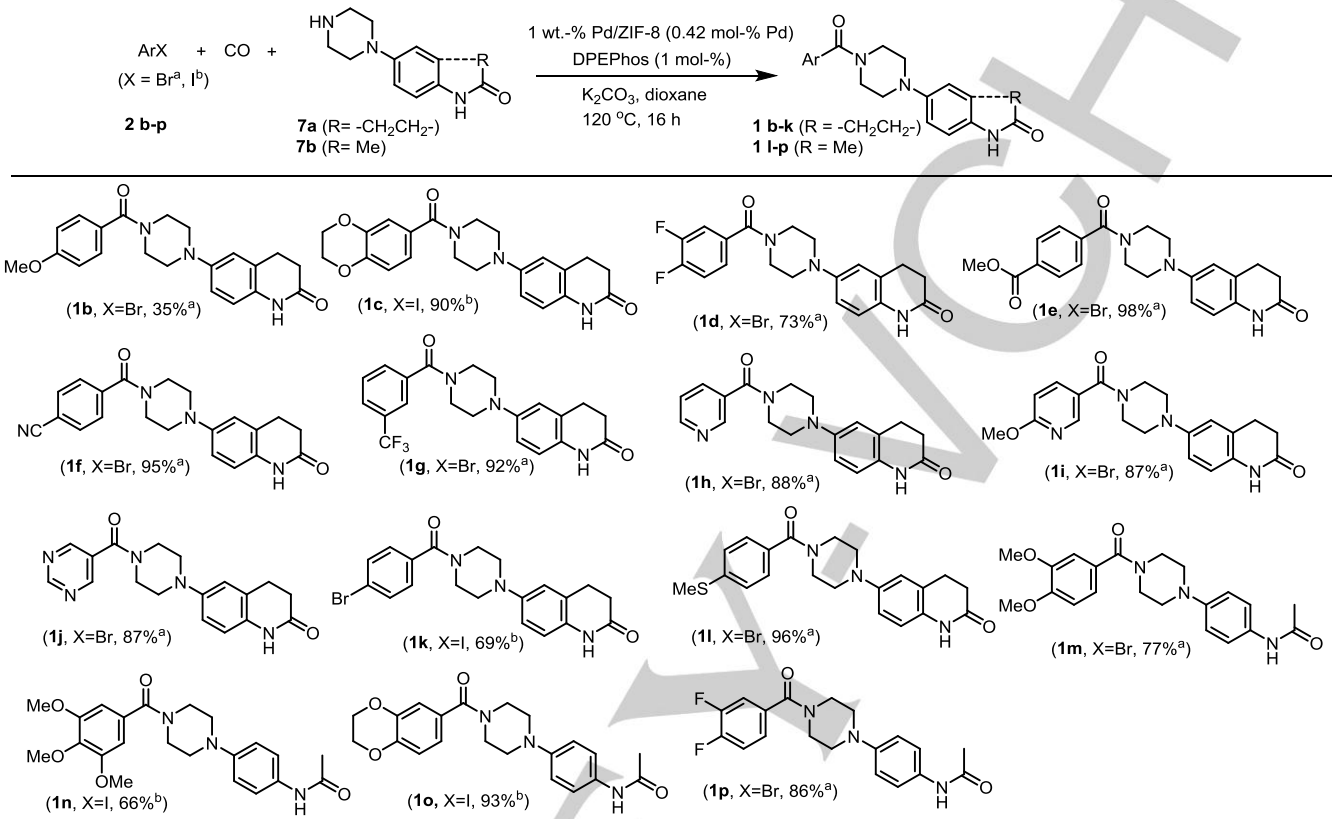
Aminocarbonylation of 4-bromoveratrole (**2a**) with the acyclic piperazine derivative **7b** using the heterogeneous PdNP/ZIF-8 catalyst[5a] readily gave the desired amide product in 76% isolated yield in toluene at 130 °C and 10 bar CO for 12 h. Unfortunately, the cyclic piperazine **7a** failed to yield the corresponding product (Vesnarinone) under the optimized aminocarbonylation condition. We recognized this reactivity difference could be due to the low solubility of piperazine **7a** in toluene. Accordingly, a number of solvents, including, DMF, diglyme and dioxane, were screened and dioxane was found to be the most suitable solvent, providing Vesnarinone (**1a**) in 80% isolated yield (Scheme 4).



Scheme 4. Completion of Vesnarinone synthesis by aminocarbonylation.

With the optimized aminocarbonylation conditions in hand, a series of Vesnarinone analogues bearing either the quinolinone or a *p*-acetamidophenyl motif were synthesized by aminocarbonylation reaction of **7a** and **7b** with a variety of functionalized aryl bromides and iodides (Table 1). As we have reported earlier **6a**, **6c** a phosphine ligand such as DPEPhos is needed for the aminocarbonylation of aryl bromides catalysed by PdNP/ZIF-8 and no ligand is necessary for more reactive aryl iodides. Good to excellent isolated yields were obtained for methoxy (**1b, 1m** and **1n**), cyclic ether (**1c** and **1o**), and fluoro (**1d** and **1p**) substituted products from the corresponding aryl bromides or iodides. Electron withdrawing substituents such as ester (**1e**), nitrile (**1f**), and trifluoromethyl (**1g**) functionalities were well tolerated, giving the corresponding amide products in up to 98% yields. In addition, the analogues containing N-heteroaromatic (**1h-1j**) and 4-methylthiophenyl groups were also conveniently obtained by the PdNP/ZIF-8 catalyzed aminocarbonylation in up to 88% yield without causing deactivation of the catalyst.

Table 1. Synthesis of Vesnarinone analogues.



Reaction conditions: [a]ArBr (0.7 mmol, 1.4 equiv.), **7a** (or **7b**) (0.5 mmol), K_2CO_3 (1.0 mmol, 2 equiv.), CO (10 bar), PdNP/ZIF-8 (1 wt.-%, 24.0 mg, 0.25 mol-% Pd), DPEPhos (5.4 mg, 1.0 mol-%), dioxane (8.0 mL). [b]ArI (0.7 mmol, 1.4 equiv.), **7a** (or 7b) (0.5 mmol), K_2CO_3 (1.0 mmol, 2 equiv.), CO (10 bar), PdNP/ZIF-8 (1 wt.-%, 24.0 mg, 0.25 mol-% Pd), dioxane (8.0 mL).

Notably, when *p*-iodobromobenzene was used as a substrate in the absence of a phosphine ligand, the mono-aminocarbonylated product having the bromide substituent **1k** was obtained in 69% yield. This would enable further functionalization by various coupling reactions to access diverse and more complex Vesnarinone analogues for biological and structure-activity relationship studies.

Similar to our previous observations,[6a] PdNP/ZIF-8 catalyst is highly stable under the present aminocarbonylation conditions, recyclable and offers very low palladium leaching (<3 ppm), which is very important for both the catalyst recovery and to ensure that the palladium residue is within the allowed limits of pharmaceutical products.[13]

Conclusions

In conclusion, we have developed an efficient, catalytic route for the synthesis of Vesnarinone (73% overall yield) and its analogues (up to 89% overall yield) using homogeneous palladium catalyzed Buchwald-Hartwig amination and a heterogeneous Pd nanoparticles catalyzed aminocarbonylation reactions as the key steps. This concise route not only provided convenient access to valuable compounds for the exploration of novel therapeutic applications but also demonstrated the potential use of catalytic C-N cross coupling reactions in the synthesis of pharmaceutically relevant compounds having amide and amine functionalities.[14] In addition, the use of a stable and low-leaching heterogeneous Pd-catalyzed aminocarbonylation at the end of the synthesis strategy would be beneficial considering the stringent regulation of metal residues in active pharmaceutical ingredients (API).

Experimental Section

General information

Commercially available reagents were used as received without further purification. For chromatographic purifications, technical-grade solvents were used. Reactions were monitored by thin layer chromatography (TLC) using Merck Silica Gel 60 F254 plates. The chromatographic purification of the products was performed on silica gel. NMR-spectra were measured in the given solvent on a Bruker Avance 400 (400 MHz, ^{1}H-NMR; 101MHz, ^{13}C-NMR). Chemical shifts δ are given in parts per million (ppm) relative to tetramethylsilane (TMS) for ^{1}H- and ^{13}C-NMR spectra and also calibrated against the solvent residual peak. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q

= quartet, m = multiplet, br = broad signal or as a combination of them. Coupling constants (*J*) are given in Hertz (Hz). HRMS was measured on Thermo Finnigan MAT95XP model instrument using ESI-TOF. A 25 mL Parr (Hastelloy-C) reactor (5500) with 4848 controller having facilities for temperature control, monitoring pressure and rpm was used for performing the aminocarbonylation reaction.

Procedure for the preparation of PdNP/ZIF-8 catalyst:

Following the reported procedure,[6a] potassium tetrachloropalladate(II) (17.3 mg, 0.053 mmol) was first dissolved in deionized water (40 mL) to give a yellow solution, to which ZIF-8 (500 mg) was added and stirred vigorously at room temperature for 30 minutes until fully suspended. This rapidly stirring murky orange suspension was added with 1 wt.-% of aqueous polyvinyl alcohol (PVA) (2.0 ml, 99% hydrolyzed) in one portion, followed by an aqueous solution of hydrazine (1.0 mL in 30 mL water, excess) dropwise slowly over 1 h. The resulting dark suspension was filtered over a fine porosity frit, washed successively with water (2 x 10 mL), methanol (1 x 10 mL) and diethyl ether (1 x 10 mL) and dried under vacuum for 24 h at 90 ˚C. Pd/ZIF-8 was obtained as a grey powder (495 mg) and was stored without any strict inert conditions.

General procedures and characterization of compounds

***tert*-Butyl 4-(3,4-dimethoxybenzoyl)piperazine-1-carboxylate (5a):** 4-bromoveratrole (1.085 g, 5.0 mmol), tert-butyl piperazine-1-carboxylate (1.395 g, 7.5 mmol, 1.5 equiv.), 1 wt.-% Pd/ZIF-8 (100 mg, 0.19 mo-l% of Pd), DPEphos (27 mg, 0.05 mmol, 1.0 mo-l%) and anhydrous potassium carbonate (1.035 g, 7.5 mmol, 1.5 equiv.) were added to a Parr reactor followed by dry toluene (12.0 mL) under air. The reactor was then quickly purged with dry N_2 (3 times), followed by CO (3 times). The CO pressure was then adjusted to 6 bar and the reaction was conducted at 120 ˚C for 12 h. After the reaction, the reactor was cooled to room temperature and purged with N_2 (3 times). The solvent was removed in vacuum and the residue dry loaded onto a silica column and eluted with 1:1 ethyl acetate/petroleum ether to give the compound (**5a**) as a white solid (1.575 g, 90%). IR (film): ν = 1685.6, 1621.8, 1515.3, 1424.5, 1246.6, 1176.8, 822.2 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.97 (m, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.58 (s, 4H), 3.45 (s, 4H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.6, 154.7, 150.6, 149.2, 127.8, 120.2, 111.1, 110.7, 80.4, 56.1, 43.8, 28.5. HRMS (ESI TOF): Calcd. for $C_{18}H_{27}N_2O_5[M+H]^+$: 351.1920; found: 351.1916.

1-(3,4-Dimethoxybenzoyl)piperazine (5b): *tert*-Butyl 4-(3,4-dimethoxybenzoyl)piperazine-1-carboxylate (350 mg, 1.0 mmol) was dissolved in DCM (20 mL) and cooled in ice. Trifluoroacetic acid (2.0 mL, excess) was added drop wise and the reaction was allowed to warm to room temperature under stirring overnight. The solvent was then removed in vacuum and washed with saturated sodium bicarbonate (20 mL). After adjusting the pH of the aqueous phase to >10, it was extracted with ethyl acetate until there was no more product in the aqueous phase as determined by TLC and UV visualization. The combined organic extracts were dried using anhydrous magnesium sulfate, filtered, the solvent was removed, the residue dry loaded onto a silica column and eluted with 1:1 ethyl acetate/petroleum ether to give the titled compound (**5b**) as a foamy pale yellow solid (249.6 mg, quantitative yield). IR (film): ν = 1678.4, 1515.9, 1440.8, 1207.0, 1134.9, 802.2, 724.7 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.02 – 6.95 (m, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.41 (br, s, 4H). 2.69 (br, s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 45.6, 55.6, 111.0, 111.2, 119.8, 128.2, 148.4, 149.7, 168.9. HRMS (ESI TOF): Calcd. for $C_{13}H_{19}N_2O_3$ $[M+H]^+$: 251.1396; found: 251.1395.

N-[4-(4-Benzylpiperazin-1-yl)phenyl]acetamide (6b):[15] 4-bromoacetanilide (3.17 g, 14.8 mmol), tris(dibenzylideneacetone)dipalladium (135.6 mg, 0.1 mmol, 2.0 mo-l% Pd) and DavePhos (140mg, 0.24 mmol, 2.4 mo-l%), were added to a Schlenk tube, evacuated and refilled with argon (3 times). N-Benzyl piperazine (3.13mL, 17.8 mmol, 1.2 equiv.) was then added via syringe followed by a 1.06M THF solution of LHMDS (32.5 mL, 32.6 mmol, 2.2 equiv.). The resulting red-brown solution was heated to 65 ˚C and the reaction was carried out for 24 h. After cooling the reaction mixture to room temperature, it was quenched by the addition of 2N aqueous HCl solution (20 mL) followed by stirring at room temperature for 5 min. The mixture was then basified by the addition of aqueous saturated sodium hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (4 x 50 mL). The organic layers were combined, dried over anhydrous magnesium sulfate and the solvent removed in vacuum. The yellow residue was purified on a silica column using ethyl acetate. The target product (**6b**) was obtained as a yellow solid (3.66 g, 80%). IR (film): ν = 1654.3, 1515.6, 1224.2, 825.3, 749.8, 694.9 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.13 (m, 7H), 7.05 (s, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 3.58 (s, 2H), 3.37 – 2.97 (m, 4H), 2.84 – 2.40 (m, 4H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.2, 148.6, 137.9, 130.4, 129.4, 128.4, 127.3, 121.6, 116.8, 63.2, 53.2, 49.7, 24.5. HRMS (ESI TOF): Calcd. for $C_{19}H_{24}N_3O$ $[M+H]^+$: 310.1919; found: 310.1920.

6-(4-Benzylpiperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (6a):[4a] 6-Bromo-3,4-dihydro-1H-quinolin-2-one (2.911g, 12.9 mmol), tris(dibenzylideneacetone)dipalladium (119 mg, 0.1 mmol, 2.0 mo-l% Pd), DavePhos (122mg, 0.24 mmol, 2.4 mo-l%), was added to a Schlenk tube and was evacuated and refilled with Ar (3 times). N-benzyl piperazine (2.75mL, 15.5 mmol, 1.2 equiv.) was then added via syringe followed by a 1.06 M THF solution of LHMDS (28.5 mL, 28.5 mmol, 2.2 equiv.). The red-brown solution was then heated to 65 ˚C and the reaction was carried out for 24 h. After cooling the reaction mixture to room temperature, it was quenched by the addition of 2N aqueous HCl solution (20 mL) followed by stirring at room temperature for 5 min. The mixture was then basified by the addition of aqueous saturated sodium hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (4 x 50 mL). The organic layers were combined, dried over anhydrous magnesium sulfate and the solvent removed in vacuum. The yellow residue was purified on a silica column using ethyl acetate. The target product (**6a**) was obtained as a yellow solid (3.768 g, 91%). IR (film): ν = 1669.0, 1509.1, 1388.3, 1236.6, 958.9, 738.9 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.93 (s, 1H), 7.32 – 7.39 (m, 5H), 6.75 (m, 3H), 3.61 (s, 2H), 3.20 – 3.11 (m, 1H), 2.93 (dd, *J* = 8.5, 6.5 Hz, 2H), 2.71 – 2.56 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.7, 147.7, 137.9, 130.5, 129.3, 128.4, 127.3, 124.6, 116.5, 116.2, 115.6, 63.1, 53.2, 50.0, 30.9, 26.0. HRMS (ESI TOF): Calcd. for $C_{20}H_{24}N_3O$ $[M+H]^+$: 322.1919; found: 322.1921.

***N*-[4-(Piperazin-1-yl)phenyl]acetamide (7b):**[15] *N*-[4-(4-Benzylpiperazin-1-yl)phenyl]acetamide (3.09 g, 10 mmol), 10 wt.-% palladium on carbon (1.64 g, 10% Pd) and methanol (10 mL) was added into a Parr reactor. The reactor was purged with dry N_2 (3 times), followed by H_2 (3 times). The H_2 pressure was then adjusted to about 20 bar and the reaction was carried out at 70 ˚C for 4 h. After the reaction, the reactor was cooled to room temperature and the reaction mixture filtered over a plug of Celite. The resulting filtrate was evaporated to dryness in vacuum to give the product (**7b**) as a pale yellow solid (2.08g, 95%). IR (film): ν = 1662.8, 1603.8, 1543.7, 1514.7, 1254.3, 904.5, 823.9 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ = 7.40 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 3.31 (m, 4H), 3.09 (m, 4H), 2.98 (m, 4H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ = 171.3, 149.9, 132.6, 122.5, 117.9, 51.5, 46.5, 23.6. HRMS (ESI TOF): Calcd. for $C_{12}H_{18}N_3O$ $[M+H]^+$: 220.1444; found: 220.1449.

6-(Piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (7a):[4a]

Procedure 1: N-[4-(4-Benzylpiperazin-1-yl)phenyl]acetamide (3.21 g, 10 mmol), 10 wt.-% palladium on carbon (1.64 g, 10% Pd) and methanol (10 mL) were charged into a Parr reactor. The reactor was purged with dry N_2 (3 times), followed by H_2 (3 times). The H_2 pressure was then adjusted to 20 bar and the reaction mixture heated to 70 ˚C for 4 h. The reactor was cooled to room temperature and the resulting reaction mixture filtered over a plug of Celite. The filtrate was evaporated to dryness in vacuum to give the product (**7a**) after column purification using 1:1 was a

pale yellow solid (2.19g, 95%). IR (film): ν = 1668.6, 1508.8, 1375.4, 1234.5, 949.0, 850.2, 824.4, 666.3 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ = 7.7 (s, 1H), 7.07 – 6.17 (m, 3H), 3.17 – 2.98 (m, 8H), 2.92 (dd, J = 8.5, 6.5 Hz, 4H), 2.60 (dd, J = 8.5, 6.5 Hz, 1H), 1.78 (s, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ = 171.5, 148.3, 130.5, 124.7, 116.6, 116.1, 115.7, 51.4, 46.3, 31.0, 26.1. HRMS (ESI TOF): Calcd. for $C_{13}H_{18}N_3O$ $[M+H]^+$: 232.1450; found: 232.1450.

Procedure 2: Debenzylation was also carried out in "H-Cube" hydrogenation reactor (from Thales Nano™) using 10 wt.-% Pd/C Catcart column. First, H-Cube reactor was purged with MeOH for 20 min with a rate of 1.0 mL/min. A solution of 6a (200mg, 0.62 mmol) in MeOH (200 mL) was purged through the system (1.0 mL/min) using full H_2 mode (~ 10bar) at 70 °C. The reaction was at circulation mode overnight and was monitored by TLC. The final reaction mixture was collected and solvent was removed under vacuum to give the product after a short column purification(143.8 mg, quantitative yield).

General procedure for the aminocarbonylation of piperazines and aryl bromide

Piperazine (0.5 mmol), anhydrous potassium carbonate (138 mg, 1.0 mmol, 2.0 equiv.), DpePhos (5.4 mg, 0.01 mmol, 2.0 mo-l%), 1 wt.-% Pd/ZIF-8 (24.0 mg, 0.45 mo-l% of Pd) and aryl bromide (0.7 mmol, 1.4 equiv.) were added to the Parr reactor, followed by dry dioxane (6.5 mL). The reactor was then closed and purged with dry N_2 (3 times), followed by CO (3 times). The CO pressure was then adjusted to 10 bar and the reaction was carried out at 120 ˚C for 18 h. After reaction, the reactor was cooled to room temperature and purged with N_2 (3 times). The solvent was removed under vacuum, the dry residue was loaded onto a silica column and eluted with ethyl acetate or 5% MeOH in DCM.

General procedure for the aminocarbonylation of piperazines and aryl iodide

Piperazine (0.5 mmol), anhydrous potassium carbonate (138 mg, 1.0 mmol, 2.0 equiv.), 1 wt.-% Pd/ZIF-8 (24.0 mg, 0.45 mo-l% of Pd) and aryl iodide (0.7 mmol, 1.4 equiv.) were added to the Parr reactor, followed by dry dioxane (6.5 mL). The reactor was then closed and purged with dry N_2 (3 times), followed by CO (3 times). The CO pressure was then adjusted to 10 bar and the reaction was conducted at 120 ˚C for 18 h. After the reaction, the reactor was cooled to room temperature and purged with N_2 (3 times). The solvent was removed under vacuum, the dry residue was loaded onto a silica column and eluted with ethyl acetate or 5% MeOH in DCM.

Vesnarinone (1a): [4a] Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 4-bromoveratrole (0.7 mmol), compound (**1a**) was isolated as a white solid (158.0 mg, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.86 (s, 1H), 7.06 – 6.94 (m, 2H), 6.92 – 6.65 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.84 – 3.74 (m, 4H), 3.12 (s, br, 2H), 2.91 (dd, J = 8.2, 6.8 Hz, 1H), 2.59 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.6, 170.4, 150.7, 149.2, 146.9, 131.7, 127.8, 124.8, 120.4, 117.5, 116.6, 116.3, 111.2, 110.7, 56.14, 56.11, 51.0, 30.8, 25.9.

6-(4-(4-Methoxybenzoyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (1b): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 1-methoxy-4-bromobenzene (0.7 mmol), compound (**1b**) was isolated as a white solid (65.8 mg, 36%). IR (film): ν = 1660.9, 1514.3, 1233.8, 1225.9, 1136.8, 816.5, 731.9, 695.5 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.81 (m, 2H), 6.72 (m, 1H), 3.84 (s, 3H), 3.82 (s, br, 4H), 3.14 (s, br, 4H), 2.93 (dd, J = 8.5, 6.5 Hz, 1H), 2.61 (dd, J = 8.5, 6.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.4, 170.6, 161.1, 147.0, 131.7, 129.4, 127.7, 124.9, 117.6, 116.6, 116.2, 114.0, 55.5, 51.3, 30.8, 29.8, 26.0. HRMS (ESI TOF): Calcd. for $C_{21}H_{24}N_3O_3$ $[M]^+$: 366.1818; found: 366.1803.

6-[4-(2,3-Dihydro-1,4-benzodioxine-6-carbonyl)piperazin-1-yl]-1,2,3,4-tetrahydroquinolin-2-one (1c): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 6-iodo-2,3-dihydro-1,4-benzodioxine (0.7 mmol), compound (**1c**) was isolated as a white solid (177.0 mg, 90%). IR (film): ν = 1671.9, 1628.8, 1508.5, 1436.9, 1286.6, 1066.8, 889.9, 730.5 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.21 (s, br, 1H), 7.02 – 6.66 (m, 6H), 4.27 (s, 4H), 3.79 (s, br, 4H), 3.12 (s, br, 4H), 2.93 (dd, J = 8.5, 6.5 Hz, 1H), 2.69 – 2.49 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.3, 170.1, 145.3, 143.6, 128.7, 124.9, 120.9, 118.0, 117.5, 116.83, 117.0, 116.6, 116.2, 64.6, 64.5, 51.0, 30.8, 26.0. HRMS (ESI TOF): Calcd. for $C_{22}H_{24}N_3O_4$ $[M+H]^+$: 394.1761; found: 394.1759.

6-[4-(3,4-Difluorobenzoyl)piperazin-1-yl]-3,4-dihydro-1H-quinolin-2-one (1d): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 4-bromo-1,2-difluorobenzene (0.7 mmol), compound (**1d**) was isolated as a white solid (135.8 mg, 73%). IR (film): ν = 1669.9, 1649.5, 1508.4, 1420.7, 1294.1, 1193.1, 832.4, 751.1 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.34 – 7.16 (m, 3H), 6.87 – 6.77 (m, 1H), 6.69 (d, J = 8.4 Hz, 1H), 3.79 (s, 4H), 3.14 (t, J = 5.1 Hz, 4H), 2.94 (dd, J = 8.5, 6.5 Hz, 2H), 2.65 – 2.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.7, 168.21 (d, J = 1.8 Hz), 151.4 (dd, J = 250, 10 Hz), 150.3 (dd, J = 250, 10 Hz), 146.9, 132.4 (t, J = 4.7 Hz), 131.7, 124.8, 123.9 (dd, J = 6.7, 3.9 Hz), 117.7 (d, J = 17.7 Hz), 117.5, 117.1 (d, J = 18.4 Hz), 116.6, 116.4, 50.8, 47.7, 42.6, 30.8, 25.9. HRMS (ESI TOF): Calcd. for $C_{20}H_{19}F_2N_3O_2$ $[M+H]^+$: 372.1524; found: 372.1520.

Methyl-4-(4-(2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)piperazine-1-carbonyl)benzoate (1e): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and methyl-4-bromobenzoate (0.7 mmol), compound (**1e**) was isolated as a white solid (194.5 mg, 99%). IR (film): ν = 1725.8, 1673.9, 1620.3, 1509.6, 1440.9, 1276.3, 1246.1, 835.6, 764.7, 749.9, 732.7 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 60˚C) δ = 8.53 (s, br, 1H), 8.11 (tt, J = 3.4, 1.5 Hz, 2H), 7.64 (dq, J = 7.9, 1.8 Hz, 1H), 7.56 – 7.47 (m, 1H), 6.81 – 6.71 (m, 2H), 3.93-3.48 (s, br, 4H), 3.13 (s, br, 4H), 2.91 (dd, J = 8.6, 6.4 Hz, 2H), 2.61 (dd, J = 8.6, 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.5, 169.5, 166.4, 136.0, 131.7, 131.1, 130.7, 129.0, 128.3, 124.9, 117.6, 116.6, 116.3, 52.5, 50.9, 47.8, 42.3, 30.8, 26.0. HRMS (ESI TOF): Calcd. for $C_{22}H_{23}N_3O_4$ $[M+H]^+$: 394.1761; found: 394.1757.

4-(4-(2-Oxo-1,2,3,4-tetrahydroquinolin-6-yl)piperazine-1-carbonyl)benzonitrile (1f): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 4-bromobenzonitrile (0.7 mmol), compound (**1f**) was isolated as a pale yellow solid (171.7 mg, 95%). IR (film): ν = 1667.6, 1636.3, 1507.9, 1434.7, 1388.8, 1235.4, 1018.3, 848.2, 762.8 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 60˚C) δ = 8.17 (s, br, 1H), 7.78 – 7.71 (m, 2H), 7.57 – 7.50 (m, 2H), 6.84 – 6.74 (m, 2H), 6.71 (d, J = 8.4 Hz, 1H), 3.25-4.12 (m, br, 4H), 3.13 (m, br, 4H), 2.92 (dd, J = 8.5, 6.5 Hz, 2H), 2.71 – 2.40 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.6, 168.4, 147.0, 140.1, 132.6, 131.6, 127.9, 124.8, 118.1, 117.5, 116.6, 116.3, 113.9, 50.8, 47.7, 42.5, 30.8, 26.0. HRMS (ESI TOF): Calcd. for $C_{21}H_{21}N_4O_2$ $[M+H]^+$: 361.1659; found: 361.1660.

6-(4-(4-(Trifluoromethyl)benzoyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (1g): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one and 1-bromo-3-(trifluoromethyl)benzene, compound (**1g**) was isolated as a pale yellow solid (185.2 mg, 92%). IR (film): ν = 1670.1, 1637.7, 1509.3, 1423.9, 1331.9, 1239.1, 1165.7, 1113.5, 811.2 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.47 (s, br, 1H), 7.74 – 7.68 (m, 2H), 7.66 – 7.54 (m, 2H), 6.79 (m, br, 2H), 6.74 (d, J = 8.3 Hz, 1H), 3.77 (m, br, 4H), 3.26 – 3.04 (m, 4H), 2.93 (dd, J = 8.5, 6.6 Hz, 1H), 2.61 (dd, J = 8.5, 6.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.3, 168.8, 146.3, 136.3, 131.2 (q, J = 33 Hz), 130.4, 129.2, 126.7 (q, J = 3 Hz), 124.8, 124.1(q, J = 4 Hz), 123.6 (q, J = 271

Hz), 117.6, 116.6, 116.1, 50.8, 47.7, 42.1, 30.7, 25.8.HRMS (ESI TOF): Calcd. for $C_{21}H_{21}F_3N_3O_2$ $[M+H]^+$: 404.1586; found: 404.1588.

6-(4-Nicotinoylpiperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (1h): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 3-bromopyridine (0.7 mmol), compound (**1h**) was isolated as a pale yellow solid (147.8 mg, 88%). IR (film): ν = 1673.9, 1636.2, 1512.7, 1440.8, 1239.5, 1012.2, 708.2 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.70 (m, 2H), 8.48 (s, br, 1H), 7.80 (dt, J = 7.8, 1.9 Hz, 1H), 7.46 – 7.32 (m, 1H), 6.89 – 6.59 (m, 3H), 4.21-3.25 (m, br, 4H), 3.12 (m, 4H), 2.93 (dd, J = 8.5, 6.5 Hz, 1H), 2.61 (dd, J = 8.5, 6.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.4, 167.9, 151.1, 148.1, 146.9, 135.3, 131.7, 131.6, 124.9, 123.7, 117.6, 116.6, 116.3, 50.8, 47.7, 42.3, 30.8, 26.0. HRMS (ESI TOF): Calcd. for $C_{19}H_{21}N_4O_2$ $[M+H]^+$: 337.1659; found: 337.1659.

6-(4-(6-Methoxynicotinoyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (1i): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 5-bromo-2-methoxypyridine (0.7 mmol), compound (**1i**) was isolated as a white solid (159.2 mg, 87%). IR (film): ν = 1667.6, 1616.8, 1600.6, 1500.3, 1427.5, 1373.3, 1293.6, 1238.8, 1021.3, 848.9 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.85 (s, br, 1H), 8.29 (dd, J = 2.5, 0.8 Hz, 1H), 7.69 (dd, J = 8.6, 2.4 Hz, 1H), 6.91 – 6.58 (m, 4H), 3.96 (s, 3H), 3.78 (dd, J = 5.8, 3.6 Hz, 4H), 3.12 (m, 4H), 2.92 (dd, J = 8.5, 6.5 Hz, 1H), 2.71 – 2.51 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.7, 168.4, 165.1, 146.9, 146.5, 138.4, 131.7, 124.8, 124.4, 117.5, 116.6, 116.3, 111.1, 53.9, 50.9, 30.8, 26.0. HRMS (ESI TOF): Calcd. for $C_{20}H_{23}N_4O_3$ $[M+H]^+$: 367.1765; found: 367.1759.

6-(4-(Pyrimidine-5-carbonyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (1j): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 5-bromopyrimidine (0.7 mmol), compound (**1j**) was isolated as a white solid (146.6 mg, 87%). IR (film): ν = 1672.9, 1636.8, 1509.3, 1403.5, 1293.6, 1240.8, 847.1, 629.7 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.30 (s, 1H), 8.85 (s, 2H), 8.03 (s, 1H), 6.85 (m, 2H), 6.72 (d, J = 8.4 Hz, 1H) 4.26-3.48 (m, br, 4H), 3.17 (s, br, 4H), 2.94 (dd, J = 8.6, 6.4 Hz, 2H), 2.66 – 2.57 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.1, 165.3, 159.7, 155.7, 131.8, 129.6, 125.0, 117.8, 116.8, 116.2, 50.9, 30.8, 26.0. HRMS (ESI TOF): Calcd. for $C_{18}H_{20}N_5O_2$ $[M+H]^+$: 338.1612; found: 338.1607.

6-[4-(4-Bromobenzoyl)piperazin-1-yl]-3,4-dihydro-1H-quinolin-2-one (1k): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 4-iodo-bromobenzene (0.7 mmol), compound (**1k**) was isolated as a white solid (142.2 mg, 69%). IR (film): ν = 1666.6, 1641.5, 1507.9, 1434.2, 1234.1, 1009.9, 862.0 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.29 (s, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 6.87 (m, 2H), 6.74 (d, J = 8.5 Hz, 1H), 3.82 (m, 4H), 3.14 (m, br, 4H), 2.94 (dd, J = 8.6, 6.5 Hz, 2H), 2.61 (dd, J = 8.5, 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.3, 169.5, 134.3, 132.0, 129.0, 125.0, 124.5, 118.0, 116.9, 116.3, 31.3, 30.8, 26.0. HRMS (ESI TOF): Calcd. for $C_{20}H_{21}BrN_3O_2$ $[M+H]^+$: 414.0812; found: 414.0804.

6-(4-(4-(Methylthio)benzoyl)piperazin-1-yl)-3,4-dihydroquinolin-2(1H)-one (1l): Following the general procedure and starting from 6-(piperazin-1-yl)-3,4-dihydro-1H-quinolin-2-one (0.5 mmol) and 4 (4-bromophenyl)(methyl)sulfane (0.7 mmol), compound (**1l**) was isolated as a pale yellow solid (177.2 mg, 93%). IR (film): ν = 1668.9, 1625.7, 1508.4, 1427.0, 1235.6, 1191.5, 829.1 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.6 (s, br, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 7.1 Hz, 1H), 7.29 (m, 2H), 6.77 (d, J = 8.3 Hz, 1H), 3.83 (s, 4H), 2.95 (dd, J = 8.5, 6.6 Hz, 2H), 2.63 (dd, J = 8.5, 6.5 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.5, 170.2, 141.7, 131.7, 130.4, 128.0, 125.96, 126.0, 125.1, 124.9, 117.7, 116.7, 116.3, 51.1, 47.1, 42.1, 30.8, 25.9, 15.4. HRMS (ESI TOF): Calcd. for $C_{21}H_{23}SN_3O_2$ $[M+H]^+$: 382.1584; found: 382.1580.

N-{4-[4-(3,4-Dimethoxybenzoyl)piperazin-1-yl]phenyl}acetamide (1m): Following the general procedure and starting from N-[4-(4-benzylpiperazin-1-yl)phenyl]acetamide and 4-bromoveratrole, compound (**1m**) was isolated as a white solid (149.4 mg, 76%). IR (film): ν = 1655.0, 1613.4, 1517.6, 1427.2, 1268.6, 1144.9, 1015.1, 816.4, 770.1 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, J = 8.5 Hz, 2H), 7.05 – 6.97 (m, 2H), 6.97 – 6.90 (m, 1H), 6.88 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.81 (s, br, 4H), 3.16 (s, br, 4H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.5, 168.4, 150.8, 149.3, 127.8, 121.6, 120.4, 117.9, 111.2, 110.8, 56.2, 56.1, 50.9, 24.5. HRMS (ESI TOF): Calcd. for $C_{21}H_{26}N_3O_4$ $[M+H]^+$: 384.1918; found: 394.1902.

***N*-(4-(4-(3,4,5-Trimethoxybenzoyl)piperazin-1-yl)phenyl)acetamide (1n):** Following the general procedure and starting from *N*-[4-(4-benzylpiperazin-1-yl)phenyl]acetamide (0.5 mmol) and 5-iodo-1,2,3-trimethoxybenzene (0.7 mmol), compound (**1n**) was isolated as a pale yellow solid (136.3 mg, 66%). IR (film): ν = 1655.4, 1614.8, 1518.3, 1434.9, 1269.6, 1145.3, 816.2 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7, 80 (s, br, 1H), 7.39 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 6.653(s, 2H), 3.85 (s, 3H), 3.84 (s, 6H), 3.79 – 3.68 (m, 4H), 3.13 (m, 4H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 168.6, 153.5, 147.1, 139.5, 132.1, 130.8, 121.6, 117.6, 104.6, 61.0, 56.4, 50.6, 24.3. HRMS (ESI TOF): Calcd. for $C_{22}H_{28}N_3O_5$ $[M+H]^+$: 414.2029; found: 414.2023.

***N*-{4-[4-(2,3-Dihydro-1,4-benzodioxine-6-carbonyl)piperazin-1-yl]phenyl}acetamide (1o):** Following the general procedure and starting from N-[4-(4-benzylpiperazin-1-yl)phenyl]acetamide (0.5 mmol) and 6-iodo-2,3-dihydro-1,4-benzodioxine (0.7 mmol), compound (**1o**) was isolated as a white solid (177.7 mg, 93%). IR (film): ν = 1655.2, 1625.8, 1604.1, 1509.1, 1431.7, 1294.6, 1065.9, 824.9 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.77 (s, br, 1H), 7.39 (d, J = 8.7 Hz, 1H), 6.99 – 6.83 (m, 5H), 4.26 (m, 4H), 3.77 (s, br, 4H), 3.11 (s, br, 4H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.1, 168.6, 147.1, 145.3, 143.5, 132.2, 128.5, 121.6, 120.9, 117.7, 117.4, 116.9, 64.6, 64.4, 50.6, 24.3. HRMS (ESI TOF): Calcd. for $C_{21}H_{24}N_3O_4$ $[M+H]^+$: 382.1767; found: 382.1778.

N-{4-[4-(3,4-Difluorobenzoyl)piperazin-1-yl]phenyl}acetamide (1p): Following the general procedure and starting from N-[4-(4-benzylpiperazin-1-yl)phenyl]acetamide and 4-bromo-1,2-difluorobenzene, compound (**1p**) was isolated as a white solid (154.4 mg, 86%). IR (film): ν = 1659.7, 1630.7, 1604.3, 1517.3, 1442.9, 1314.8, 1296.6, 1022.6, 825.4, 748.4 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43 (d, J = 8.5 Hz, 1H), 7.39 – 7.15 (m, 4H), 6.95 (m, br, 2H), 3.81 (s, br, 4H), 3.17 (s, br, 4H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.4, 168.3 (d, J = 1.8 Hz), 151.6 (dd, J = 250, 10 Hz), 150.5 (dd, J = 250, 10 Hz), 146.8, 132.3 (t, J = 4.7 Hz), 124.0 (dd, J = 6.7, 4.0 Hz), 121.6, 118.1, 117.9, 117.8, (d, J = 18.4 Hz), 117.2 (d, J = 18.5 Hz), 50.9, 24.5. HRMS (ESI TOF): Calcd. for $C_{19}H_{20}F_2N_3O_2$ $[M+H]^+$: 360.1518; found: 360.1512.

Supporting Information (see footnote on the first page of this article): ^1H NMR and ^{13}C NMR spectra for all compounds.

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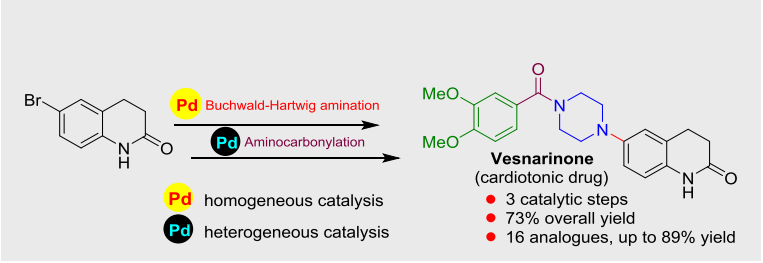

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Concise Synthesis of Vesnarinone and its Analogues Using Pd-Catalyzed C-N Bond forming Reactions

Key topic: Catalytic C-N coupling

Efficient and concise synthesis of Vesnarinone is achieved in three catalytic steps utilising palladium catalysed C-N coupling reactions such as Buchwald-Hartwig amination and aminocarbonylation as the key reactions. Very high overall yields were also obtained for several Vesnarinone analogues. Use of stable and very low metal leaching PdNP/ZIF-8 catalyst for the final aminocarbonylation step ensures negligible Pd residues in the final product.