Supporting Information

Phenyl Ether- and Aniline-Containing 2-Aminoquinolines as Potent and Selective Inhibitors of Neuronal Nitric Oxide Synthase

Maris A. Cinelli[1], Huiying Li[2], Anthony V. Pensa[1], Soosung Kang[1], Linda J. Roman[3], Pavel Martásek[3,4], Thomas L. Poulos[2]*, and Richard B. Silverman[1]*

General Procedure for Synthesis of Phenols Containing Boc-Protected Methylamines. *Step 1*. Methylamine in THF (2 eq.) was diluted with $CHCl_3$ (5-10 mL), and the requisite hydroxybenzaldehyde (1 eq.) was added in a solution of $CHCl_3$/MeOH (typically 5:1-10:1). Anhydrous Na_2SO_4 (~2-3 g/mmol) was added, and the mixture was stirred rapidly under argon at room temp for 90 min. Glacial AcOH (10 μL/0.100 g starting material) and additional anhydrous Na_2SO_4 (~1 g/mmol) was added. The mixture was stirred for a total of 4-4.5 h to overnight at room temp, and the Na_2SO_4 was filtered from the mixture. The filtrate was concentrated, and the residue was diluted with MeOH (10 mL/mmol), and cooled to 0 ˚C. $NaBH_4$ (1.4-1.5 eq.) was added, and the mixture was warmed to room temp and stirred for 20 min. The mixture was concentrated, and the residue was partitioned between EtOAc and sat. aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc until no residual amine was extracted (as measured by TLC, typically 3 x). For poorly soluble amines, some MeOH was added to improve organic solubility. The organic layer was washed with sat. aq. NaCl and dried. Concentration afforded the intermediate secondary amine. *Step 2*. The amine was immediately diluted in THF (10 mL/mmol) and Boc_2O (1.1-1.3 eq.) was added as a solution in minimal THF. The mixture was stirred until TLC indicated consumption of the starting amine (typically overnight), and then concentrated. The residue was partitioned between EtOAc and sat. aq. $NaHCO_3$ (or H_2O), and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and sat. aq. NaCl, dried over anhydrous sodium sulfate, and evaporated. The desired Boc-protected amines were obtained after purification by flash column chromatography (described below for individual compounds) and drying in vacuo.

2-(3-Methoxyphenyl)-*N*,*N*-dimethylethan-1-amine (28).

3-Methoxyphenethylamine (**27**, 0.302 g, 2.00 mmol) was diluted in anhydrous DMF (10 mL), and a mixture of formalin (0.42 mL) and formic acid (0.22 mL) was added. The mixture was heated at 60 ˚C for 15 min to drive off CO_2, and was then heated at reflux for 5 h. The mixture was cooled, poured into cold H_2O (40 mL), basified to pH 12 with 6 N NaOH, and extracted with EtOAc (3 x 40 mL). The organic layers were washed with 5% aq. NaCl (3 x 50 mL) and sat. aq. NaCl (50 mL), dried over anhydrous sodium sulfate, and concentrated to yield the product as a dark orange oil (0.358 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.20 (td, *J* = 7.6, 0.8 Hz, 1 H), 6.81-6.79 (m, 1 H), 6.76-6.74 (m, 2 H), 3.80 (s, 3 H), 2.79 (dd, *J* = 9.5, 6.7 Hz, 2 H), 2.58 (t, *J* = 7.9 Hz, 2 H), 2.34 (s, 6 H).

3-(2-(Dimethylamino)ethyl)phenol (29). Compound **28** (0.339 g, 1.89 mmol) was diluted in AcOH (3 mL), and HBr (48% in H_2O, 2 mL) was added. The mixture was heated to reflux for 22 h, cooled, and concentrated to 1/4th the original volume. The residue was diluted with H_2O (20 mL) and washed with EtOAc (3 x 10 mL). The aqueous layer was basified by the addition of K_2CO_3, and the aqueous layers were extracted with EtOAc (3 x 15 mL). The organic layers were washed with sat. aq. NaCl, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash column chromatography, eluting with a gradient of EtOAc to 36% MeOH in EtOAc, to yield **29** as a pale-pink solid (0.206 g, 66%) after trituration with 5% EtOAc in hexanes. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.14 (t, *J* = 7.7 Hz, 1 H), 6.69-6.67 (m, 3 H), 2.82 (dd, *J* = 10.2, 6.1 Hz, 2 H), 2.71-2.68 (m, 2 H), 2.38 (s, 6 H); the phenol proton is not visible due to broadening into the baseline.

***tert*-Butyl (3-Hydroxyphenethyl)(methyl)carbamate (32).** Compound **31** (0.225 g, 1.36 mmol) was diluted in AcOH (2 mL), and HBr (48% in H_2O, 2.2 mL) was added. The mixture was heated to reflux for 4 h, cooled, and concentrated. The residue was azeotroped with toluene and ethanol to remove AcOH and dried in vacuo (in a desiccator with P_2O_5) to yield an orange crystalline solid. The solid was suspended in anhydrous THF, and Et_3N (1 eq., 0.189 mL) was added, followed by Boc_2O (0.327 g, 1.5 mmol) as a solution in anhydrous THF (3 mL). The cloudy mixture was stirred overnight for 18 h, concentrated, and worked up as in Step 2 of the General Procedure. Purification of the residue by flash column chromatography, eluting with a gradient of hexanes to 40% EtOAc in hexanes, afforded **32** as a colorless syrup (0.276 g, 81%). The spectral data for this compound are consistent with those reported in the literature.[1]

3-((Dimethylamino)methyl)phenol (34). Dimethylammonium hydrochloride (1.00 g, 12.3 mmol) was diluted in $CHCl_3$ (15 mL, with 0.5 mL MeOH added to ensure solubility), and Et_3N (1.16 g, 11.48 mmol, 1.6 mL) was added. The mixture was stirred for 5 min before aldehyde **33** (0.500 g, 4.12 mmol) was added as a solution in 16:1 $CHCl_3$/MeOH (8 mL). The solution became yellow, anhydrous Na_2SO_4 (~2 g) was added, and the mixture was stirred at room temp for 90 min. $NaBH(OAc)_3$ (1.22 g, 5.74 mmol) was added, and the mixture was stirred for 20 h. MeOH (5 mL) was added, and the mixture was filtered. The solids were dissolved in sat. aq. $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The filtrate and the organic phase were combined, washed with sat. aq. $NaHCO_3$ (30 mL) and sat. aq. NaCl (30 mL). The organic layers were dried over anhydrous sodium sulfate, concentrated, and purified by flash column chromatography, eluting with a gradient of EtOAc to 30% MeOH in EtOAc, to yield the

product as an off-white waxy solid (0.319 g, 51%). The spectral data for this compound are consistent with those reported in the literature.[2]

***tert*-Butyl (3-Hydroxybenzyl)(methyl)carbamate (35).** This was prepared from aldehyde **33** (0.500 g, 4.12 mmol), methylamine (2 M in THF, 4.1 mL, 8.24 mmol) and $NaBH_4$ (0.203 g, 5.36 mmol), using the General Procedure, Step 1. After workup and isolation, the crude intermediate amine (0.453 g) was Boc-protected with Boc_2O (0.762 g, 3.63 mmol), using the General Procedure, Step 2. Following workup and purification by flash column chromatography, eluting with a gradient of 5% EtOAc in hexanes to 30% EtOAc in hexanes, **35** was obtained as a chalky white solid (0.614 g, 63%): mp 92-93 ˚C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.18 (t, J = 7.8 Hz, 1 H), 6.77-6.72 (m, 3 H), 5.30 (br s, 1 H), 4.37 (s, 2 H), 2.81 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.5, 156.2, 139.6, 129.7, 119.5, 114.4, 114.1, 80.1, 52.2, 34.0, 28.5; ESIMS *m/z* (rel. intensity) 236 (MH^-, 62), 473 ($2\,MH^-$, 100).

3-(3-(Dimethylamino)prop-1-yn-1-yl)phenol (39). 3-Iodophenol (**38**, 0.440 g, 2 mmol), *N,N*-dimethylpropargylamine (0.332 g, 4 mmol), CuI (0.037 g, 10 mol%), and $(PPh_3)_4Pd$ (0.112 g, 5 mol%) were diluted in anhydrous THF (10 mL) and Et_3N (8 mL), and the mixture was stirred under argon for 20 h at room temp. The mixture was concentrated, and the residue was partitioned between EtOAc and 2 N HCl (20 mL each). The aqueous layer was washed with EtOAc (2 x 10 mL), and the EtOAc layer was extracted with 2 N HCl (2 x 10 mL). The aqueous layers were basified with 3 N NaOH to pH 10 and extracted with EtOAc (4 x 70 mL). The organic layers were washed with sat. aq. NaCl (50 mL), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash column chromatography (SiO_2), eluting with a gradient of EtOAc to

12% MeOH in EtOAc, to yield crude **39** as a colorless solid (0.290 g, 83%), which was used in the following step without further purification: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.14 (t, *J* = 7.9 Hz, 1 H), 7.00 (d, *J* = 1.2 Hz, 1 H), 6.95 (d, *J* = 7.6 Hz, 1 H), 6.82 (dt, *J* = 8.2, 1.1 Hz, 1 H), 3.53 (s, 2 H), 2.47 (s, 6 H); the phenol proton is not visible due to broadening into the baseline.

3-(3-(Dimethylamino)propyl)phenol (**40**). Compound **39** (0.290 g, 1.65 mmol) was diluted in MeOH (10 mL) and a catalytic amount of 10% Pd/C (0.030 g) was added. The mixture was hydrogenated with a hydrogen-filled balloon for 18 h at room temp. The catalyst was filtered off through a pad of Celite, and the filtrate was concentrated. The residue was triturated with hexanes to yield **40** as a flocculent, colorless solid (0.231 g, 78%) that was collected by filtration: mp 101.5-103 ˚C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.11 (t, *J* = 7.8 Hz, 1 H), 6.66-6.63 (m, 2 H), 6.56 (t, *J* = 1.8 Hz, 1 H), 2.55 (t, *J* = 7.7 Hz, 2 H), 2.45-2.42 (m, 2 H), 2.32 (s, 6 H), 1.88-1.82 (m, 2 H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 157.2, 143.2, 129.5, 119.7, 115.5, 113.7, 59.0, 44.9, 33.7, 28.5; ESIMS *m/z* (rel. intensity) 180 (MH^+, 100).

4-((Dimethylamino)methyl)phenol (44). Dimethylammonium hydrochloride (1.00 g, 12.3 mmol) was diluted in $CHCl_3$ (14 mL, with 0.5 mL MeOH added to ensure solubility), and Et_3N (1.16 g, 11.48 mmol, 1.6 mL) was added. The mixture was stirred for 5 min before aldehyde **43** (0.5 g, 4.1 mmol) was added as a solution in 1:1 $CHCl_3$/MeOH (4 mL). The solution became yellow, anhydrous Na_2SO_4 (~3 g) was added, and the mixture was stirred at room temp for 90 min. $NaBH(OAc)_3$ (1.22 g, 5.74 mmol) was then added, and the mixture was stirred for 20 h. MeOH (5 mL) was added, and the mixture was filtered. The solids were dissolved in 1:1 sat. aq. $NaHCO_3$/H_2O (30

mL) and extracted with CH_2Cl_2 (3 x 30 mL), and then EtOAc (3 x 50 mL). The filtrate and the organic phases were separately washed with sat. aq. NaCl (30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, concentrated, and purified by flash column chromatography, eluting with a gradient of EtOAc to 20% MeOH in EtOAc, to yield the product as an cream-colored crystalline solid (0.319 g, 51%) after washing with hexanes. The spectral data for this compound are consistent with those reported in the literature.[2]

***tert*-Butyl (4-Hydroxybenzyl)(methyl)carbamate (45).** This was prepared from aldehyde **43** (0.500 g, 4.12 mmol), methylamine (2 M in THF, 4.1 mL, 8.24 mmol) and $NaBH_4$ (0.203 g, 5.36 mmol) using the General Procedure, Step 1. After workup and isolation, the crude intermediate amine (0.497 g) was Boc-protected with Boc_2O (0.870 g, 3.99 mmol) using the General Procedure, Step 2. Following workup and purification by flash column chromatography, eluting with a gradient of 5% EtOAc in hexanes to 30% EtOAc in hexanes, **45** was obtained as a colorless waxy solid (0.715 g, 73%): mp 122-123 ˚C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.08 (d, J = 8.1 Hz, 2 H), 6.79 (d, J = 8.0 Hz, 2 H), 5.30 (br s, 1 H), 4.34 (s, 2 H), 2.79 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.3, 155.4, 129.5, 128.9, 115.5, 80.1, 51.9, 33.8, 28.5; ESIMS *m/z* (rel. intensity) 236 (MH^-, 64), 473 ($2MH^-$, 100).

***N*,*N*-Dimethyl-1-(3-nitrophenyl)methanamine (47).** Dimethylammonium hydrochloride (1.69 g, 20.7 mmol) was diluted in anhydrous CH_2Cl_2 (30 mL), and MeOH (0.4 mL) was added to affect solution. Et_3N (2.87 mL, 20.7 mmol) was added, and to the resulting clear solution, bromide **46** (0.895 g, 4.14 mmol) was added dropwise as a solution in CH_2Cl_2 (6 mL). The mixture was stirred for 2.5 h at room temp, and then H_2O

(40 mL) was added. The layers were separated and the organic layers were washed with H_2O (4 x 70 mL), sat. aq. NaCl (50 mL), and dried over anhydrous sodium sulfate and concentrated. The residue was diluted with ether (5 mL), filtered to remove particulate matter, and reconcentrated to yield **47** as a clear, yellow-orange oil (0.680 g, 91%). The spectral data for this compound are consistent with those reported in the literature.[3]

3-((Dimethylamino)methyl)aniline (48). Amine **47** (0.340 g, 1.89 mmol) was diluted in MeOH (8 mL). Raney nickel (~0.5 g) was added, and the mixture was hydrogenated with a hydrogen-filled balloon for 40 min at room temp. The mixture was decanted from the nickel, filtered through a 0.4 μM syringe filter, and concentrated. The resulting residue was suspended in ether (5 mL), refiltered, concentrated, and dried in vacuo at 60 ˚C to yield **48** as a pale yellow syrup (0.228 g, 80%). The spectral data for this compound are consistent with those reported in the literature.[4]

***tert*-Butyl Methyl(3-nitrobenzyl)carbamate (49).** Methylamine in THF (10.3 mL, 2 M, 20.7 mmol) was diluted with CH_2Cl_2 (20 mL). Bromide **46** (0.895 g, 4.14 mmol) was added dropwise as a solution in CH_2Cl_2 (6 mL), and the mixture was stirred at room temp for 17 h. The mixture was filtered, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), and Boc_2O (0.993 g, 4.55 mmol) was added as a solution in CH_2Cl_2 (5 mL). The mixture was stirred at room temp for 6 h and was washed with sat. aq. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic layers were washed with H_2O and sat. aq. NaCl (30 mL each), dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash column chromatography, eluting with a gradient of hexanes to 20% EtOAc in

hexanes, to yield **49** as a colorless syrup (0.947 g, 86%). The spectral data for this compound are consistent with those reported in the literature.[5]

***tert*-Butyl (3-Aminobenzyl)(methyl)carbamate (50).** Amine **49** (0.340 g, 1.27 mmol) was diluted in MeOH (10 mL). Raney nickel (~0.5 g) was added, and the mixture was hydrogenated with a hydrogen-filled balloon for 40 min at room temp. The mixture was decanted from the nickel, filtered through a 0.4 μM syringe filter, and concentrated. The resulting residue was purified by flash column chromatography, eluting with a gradient of 15% EtOAc in hexanes to 40% EtOAc, in hexanes to yield **50** as a pale yellow oil (0.208 g, 69%). The spectral data for this compound are consistent with those reported in the literature.[6]

***tert*-Butyl (2-Fluoro-5-hydroxybenzyl)(methyl)carbamate (54).** This was prepared from aldehyde **51** (0.500 g, 3.57 mmol), methylamine (2 M in THF, 3.6 mL, 7.2 mmol) and $NaBH_4$ (203 mg, 5.36 mmol) using the General Procedure, Step 1. After workup and isolation, the crude intermediate amine was Boc-protected with Boc_2O (0.856 g, 3.93 mmol) using the General Procedure, Step 2. Following workup and purification by flash column chromatography, eluting with a gradient of 5% EtOAc in hexanes to 35% EtOAc in hexanes, **54** was obtained as a clear, colorless syrup that crystallized upon standing (0.709 g, 78%): mp 82.5-84.5 ˚C. ^{1}H NMR (500 MHz; $CHCl_3$): δ 6.89 (t, J = 9.1 Hz, 1 H), 6.74-6.68 (m, 2 H), 4.43 (s, 2 H), 2.85 (s, 3 H), 1.47 (s, 9 H); the phenol proton is not visible due to broadening into the baseline; ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.4, (155.7 + 153.9, 1 C), 152.8, 125.2, (116.09 + 115.90, 1 C), 115.6, (115.2 + 114.2, 1 C), 80.5, (46.3 + 45.1, 1 C), 34.3, 28.5; ESIMS *m/z* (rel. intensity) 254 (MH^-, 40), 509 ($2MH^-$).

***tert*-Butyl (2-Chloro-5-hydroxybenzyl)(methyl)carbamate (55).** This was prepared from aldehyde **52** (0.250 g, 1.60 mmol), methylamine (2 M in THF, 1.6 mL, 3.2 mmol) and $NaBH_4$ (0.085 g, 2.24 mmol) using the General Procedure, Step 1. After workup and isolation, the crude intermediate amine was Boc-protected with Boc_2O (0.384 g, 1.76 mmol) using the General Procedure, Step 2. Following workup and purification by flash column chromatography, eluting with a gradient of 5% EtOAc in hexanes to 35% EtOAc in hexanes, **55** (~90% purity) was obtained as an off-white solid (0.382 g, 88%) that was used without further purification: ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.19 (d, J = 8.9 Hz, 1 H), 6.71-6.70 (M, 2 H), 4.48 (s, 2 H), 2.88 (s, 3 H), 1.46 (s, 9 H); the phenol proton is not visible due to broadening into the baseline; ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.3, 156.0, 135.9, 130.4, 122.8, 115.6, 113.4, 80.7, (50.5 + 49.2, 1 C), 34.9, 28.4; ESIMS *m/z* (rel. intensity) 270/272 (MH^-, 60/26), 541/543 ($2MH^-$).

(*RS*)-*tert*-Butyl (1-(3-Hydroxyphenyl)ethyl)(methyl)carbamate (56). This was prepared from 3-hydroxyacetophenone (**53**, 0.750 g, 5.52 mmol), methylamine (2 M in THF, 6.96 mL) and sodium $NaBH_4$ (0.315 g, 8.30 mmol) using the General Procedure, Step 1. After workup and isolation, the crude intermediate amine was Boc-protected with Boc_2O (1.32 g, 6.07 mmol) using the General Procedure, Step 2. Following workup and purification by flash column chromatography, eluting with a gradient of hexanes to 25% EtOAc in hexanes, **56** was obtained as a white solid (0.434 g, 31%): mp 64-66 ºC. ^{1}H NMR (500 MHz; DMSO-d_6): ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.6, 156.2, 142.7, 129.5, 118.4, 114.4, 80.1, 53.5, 52.2, 28.5, 16.9, 16.0. ESIMS *m/z* (rel. intensity) 274 (MNa^+, 30).

***tert*-Butyl ((5-hydroxypyridin-3-yl)methyl)(methyl)carbamate (59).** This was prepared from aldehyde **57** (0.1 g, 7.28 mmol), methylamine (2 M in THF, 7.28 mL, 14.56 mmol) and $NaBH_4$ (0.420 g, 11.1 mmol) using the General Procedure, Step 1. After workup and isolation, crude intermediate amine **58** (0.450 g, 2.96 mmol) was diluted in AcOH (4 mL), and 9 mL HBr (48% in H_2O) was added. The mixture was heated to 130 ˚C overnight. The mixture was concentrated and dried in vacuo over P_2O_5 to yield an orange solid, which was diluted in THF (with a few drops of MeOH added to aid solubility). Et_3N (0.823 mL, 5.9 mmol) was added, and the mixture was sonicated until a white precipitate formed and then Boc-protected with Boc_2O (0.774 g, 3.55 mmol) using the General Procedure, Step 2. Following workup and purification by flash column chromatography, eluting with a gradient of 30% EtOAc in hexanes to 80% EtOAc in hexanes, **59** was obtained as a colorless syrup (0.135 g, 19%); the crude product was confirmed by TLC, ^{1}H-NMR and ESIMS and used without further characterization.

Table S1. Crystallographic data collection and refinement statistics

Data set[7]	nNOS-**6**	nNOS-**7**	nNOS-**8**	nNOS-**9**
Data collection				
PDB code	5AD4	5AD5	5AD6	5AD7
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions□ □ a, b, c (Å)	51.7 111.8 164.4	51.7 110.9 165.1	51.27 111.9 164.5	52.0 112.2 164.9
Resolution (Å)	1.98 (2.07-1.98)	1.90 (1.96 -1.90)	2.01 (2.08-2.01)	1.95 (2.02-1.95)
Rmerge	0.240 (3.409)	0.135 (2.325)	0.264 (2.422)	0.151 (2.367)
Rpim	0.082 (1.610)	0.103 (1.756)	0.095 (1.183)	0.121 (1.892)
CC ½	0.996 (0.479)	0.992 (0.402)	0.996 (0.601)	0.989 (0.415)
I / σI	10.3 (0.7)	6.0 (0.8)	9.3 (0.9)	149.8 (2.2)
No. unique reflections	65,436	75,185	65,044	71,279
Completeness (%)	99.9 (98.8)	99.9 (100.0)	99.5 (99.5)	99.9 (100.0)
Redundancy	9.2 (5.2)	4.9 (4.9)	8.6 (4.9)	4.3 (4.4)
Refinement				
Resolution (Å)	1.98	1.90	2.01	1.95
No. reflections used	48,512 [8]	74,815	50,933 [8]	70,705
R_{work} / R_{free}[9]	0.202/0.266	0.196/0.239	0.192/0.251	0.187/0.230
No. atoms				
Protein	6683	6679	6677	6671
Ligand/ion	177	175	175	173
Water	288	269	434	325
R.m.s. deviations				
Bond lengths (Å)	0.008	0.007	0.008	0.008
Bond angles (deg)	1.23	1.17	1.24	1.15

Data set [7]	nNOS-**10**	nNOS-**15**	nNOS-**17**	nNOS-**20**
Data collection				
PDB code	5AD8	5AD9	5ADA	5ADB
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions a, b, c (Å)	51.9 111.9 164.3	51.7 111.6 164.1	51.9 111.4 164.3	51.7 111.0 165.1
Resolution (Å)	1.91 (1.93-1.91)	2.30 (2.42-2.30)	1.98 (2.05-1.98)	2.05 (2.13-2.05)
Rmerge	0.084 (>1.000)	0.141 (2.111)	0.097 (2.350)	0.126 (3.719)
Rpim	0.047 (>1.000)	0.105 (1.541)	0.066 (1.569)	0.111 (3.276)
CC ½	n/a (0.348)	0.995 (0.360)	0.998 (0.506)	0.997 (0.300)
I / σI	22.3 (1.0)	8.2 (0.8)	10.7 (0.7)	8.0 (0.5)
No. unique reflections	74,044	40,566	67,370	60,428
Completeness (%)	98.2 (88.1)	94.7 (88.4)	100.0 (100.0)	99.7 (97.4)
Redundancy	4.5 (3.3)	4.8 (5.0)	6.0 (6.1)	4.1 (4.1)
Refinement				
Resolution (Å)	1.91	2.30	1.98	2.05
No. reflections used	73,553	40,513	67,180	44,328[8]
R_{work} / R_{free} [9]	0.190/0.232	0.199/0.260	0.193/0.236	0.193/0.255
No. atoms				
Protein	6668	6674	6674	6674
Ligand/ion	171	175	178	175
Water	301	212	318	204
R.m.s. deviations				
Bond lengths (Å)	0.007	0.009	0.008	0.008
Bond angles (deg)	1.15	1.24	1.17	1.23

Data set [7]	nNOS-**21**	nNOSDM-**9**	nNOSDM-**20**
Data collection			
PDB code	5ADC	5ADD	5ADE
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions □ □ a, b, c (Å)	51.8 110.9 164.7	51.8 110.8 165.1	51.6 111.6 164.2
Resolution (Å)	2.10 (2.19-2.10)	2.10 (2.19-2.10)	2.10 (2.19-2.10)
Rmerge	0.133 (1.552)	0.104 (1.182)	0.098 (1.200)
Rpim	0.098 (1.141)	0.092 (1.018)	0.078 (0.991)
CC ½	0.992 (0.412)	0.986 (0.560)	0.997 (0.552)
I / σI	5.9 (0.8)	7.5 (1.0)	6.8 (0.8)
No. unique reflections	53,918	56,311	56,289
Completeness (%)	96.1 (98.3)	99.7 (99.9)	99.9 (100.0)
Redundancy	4.2 (4.1)	3.9 (3.9)	4.1 (4.1)
Refinement			
Resolution (Å)	2.10	2.10	2.10
No. reflections used	53,806	56,198	36,009 [8]
R_{work} / R_{free} [9]	0.199/0.253	0.187/0.231	0.183/0.248
No. atoms			
Protein	6674	6682	6678
Ligand/ion	173	173	175
Water	251	354	236
R.m.s. deviations			
Bond lengths (Å)	0.008	0.008	0.008
Bond angles (deg)	1.12	1.14	1.25

Data set[7]	HnNOS-**17**	HnNOS-**20**	HnNOS-**21**
Data collection			
PDB code	5ADF	5ADG	5ADI
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions □ □ a, b, c (Å)	52.4 122.2 164.7	52.3 122.4 165.0	52.2 122.8 164.4
Resolution (Å)	1.97 (2.03-1.97)	1.98 (1.98-1.98)	2.20 (2.30-2.20)
Rmerge	0.088 (1.273)	0.094 (0.712)	0.132 (1.695)
Rpim	0.066 (0.957)	0.086 (0.645)	0.099 (1.298)
CC ½	0.996 (0.453)	0.998 (0.569)	0.989 (0.301)
I / σI	9.8 (0.9)	509.6 (2.1)	8.1 (0.9)
No. unique reflections	75,883	74,501	54,717
Completeness (%)	99.7 (99.6)	100.0 (100.0)	100.0 (100.0)
Redundancy	4.8 (4.7)	3.8 (3.9)	4.9 (5.0)
Refinement			
Resolution (Å)	1.97	1.98	2.20
No. reflections used	75,788	74,375	54,597
R_{work} / R_{free}[9]	0.182/0.225	0.191/0.204	0.185/0.237
No. atoms			
Protein	6705	6708	6705
Ligand/ion	167	196	187
Water	532	646	393
R.m.s. deviations			
Bond lengths (Å)	0.007	0.007	0.007
Bond angles (deg)	1.15	1.09	1.14

Data set [7]	eNOS-**7**	eNOS-**8**	eNOS-**9**	eNOS-**17**
Data collection				
PDB code	5ADJ	5ADK	5ADL	5ADN
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions a, b, c (Å)	57.6 105.8 156.3	58.0 106.4 157.1	58.0 106.3 157.4	57.7 106.1 155.7
Resolution (Å)	2.22 (2.26-2.22)	1.81 (1.85-1.81)	2.21 (2.24-2.21)	2.00 (2.08-2.00)
Rmerge	0.074 (>1.000)	0.082 (3.157)	0.122 (2.336)	0.096 (1.754)
Rpim	0.042 (0.916)	0.056 (2.226)	0.056 (1.123)	0.066 (1.215)
CC ½	n/a (0.381)	0.999 (0.260)	0.998 (0.278)	0.997 (0.444)
I / σI	21.7 (1.0)	12.0 (0.5)	9.7 (0.7)	9.6 (1.0)
No. unique reflections	48,102	89,217	49,484	63,225
Completeness (%)	99.7 (96.4)	99.2 (95.6)	99.3 (97.2)	97.8 (99.8)
Redundancy	4.8 (3.4)	5.5 (4.9)	5.5 (4.9)	4.7 (4.6)
Refinement				
Resolution (Å)	2.22	1.81	2.21	2.00
No. reflections used	48,025	88,058	48,832	63,184
R_{work} / R_{free} [9]	0.164/0.210	0.164/0.193	0.160/0.206	0.165/0.203
No. atoms				
Protein	6426	6520	6445	6478
Ligand/ion	201	201	217	208
Water	188	502	337	444
R.m.s. deviations				
Bond lengths (Å)	0.009	0.007	0.009	0.008
Bond angles (deg)	1.20	1.20	1.21	1.20

Data set [7]	eNOS-**20** with acetate	eNOS-**20** without acetate
Data collection		
PDB code	5FJ2	5FJ3
Space group	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions□ □ a, b, c (Å)	57.7 106.0 156.2	57.7 106.4 156.2
Resolution (Å)	2.05 (2.13-2.05)	2.20 (2.30-2.20)
Rmerge	0.125 (1.932)	0.086 (1.993)
Rpim	0.060 (0.931)	0.064 (1.499)
CC ½	0.997 (0.300)	0.998 (0.295)
I / σI	9.9 (0.8)	9.0 (0.3)
No. unique reflections	61,015	49,537
Completeness (%)	99.8 (98.3)	99.7 (100.0)
Redundancy	5.1 (5.0)	4.9 (5.0)
Refinement		
Resolution (Å)	2.05	2.20
No. reflections used	60,827	49,448
R_{work} / R_{free} [9]	0.173/0.221	0.180/0.230
No. atoms		
Protein	6434	6418
Ligand/ion	201	193
Water	433	236
R.m.s. deviations		
Bond lengths (Å)	0.007	0.009
Bond angles (deg)	1.15	1.15

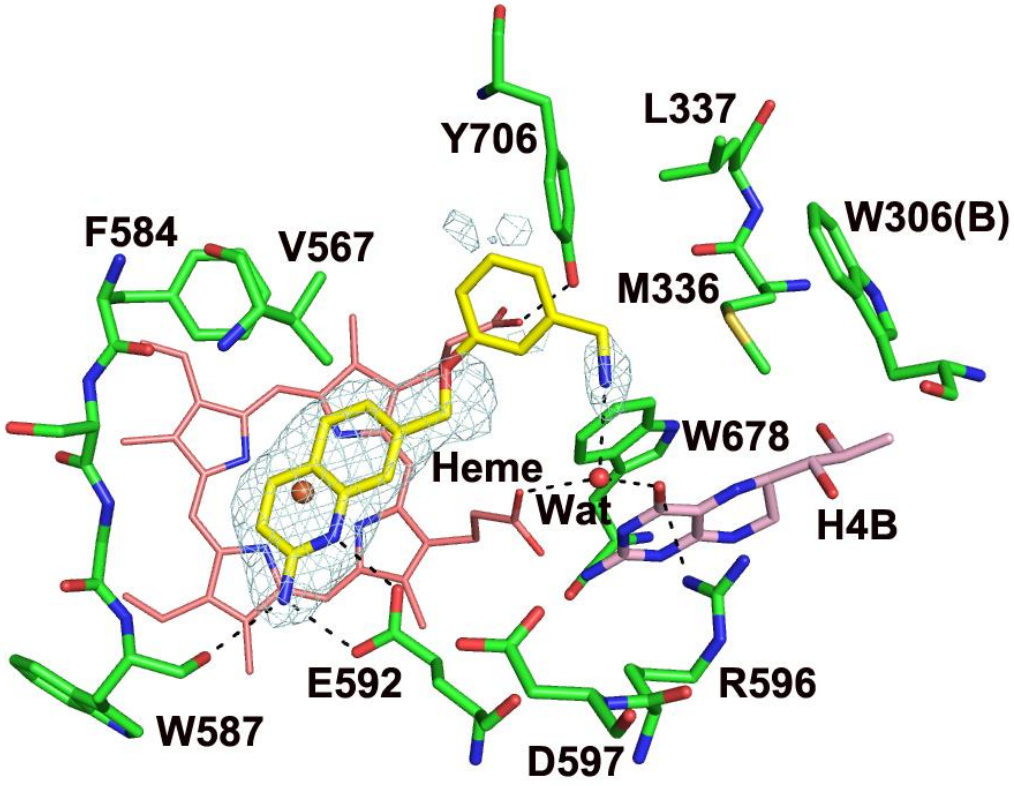

Figure S1. Active site structure of **10** bound to rat nNOS. The omit Fo – Fc density map for the inhibitor is shown at the 2.5 σ contour level. The methylamine of **10** makes a H-bond with a water bridging H_4B and heme. Major hydrogen bonds are shown as dashed lines.

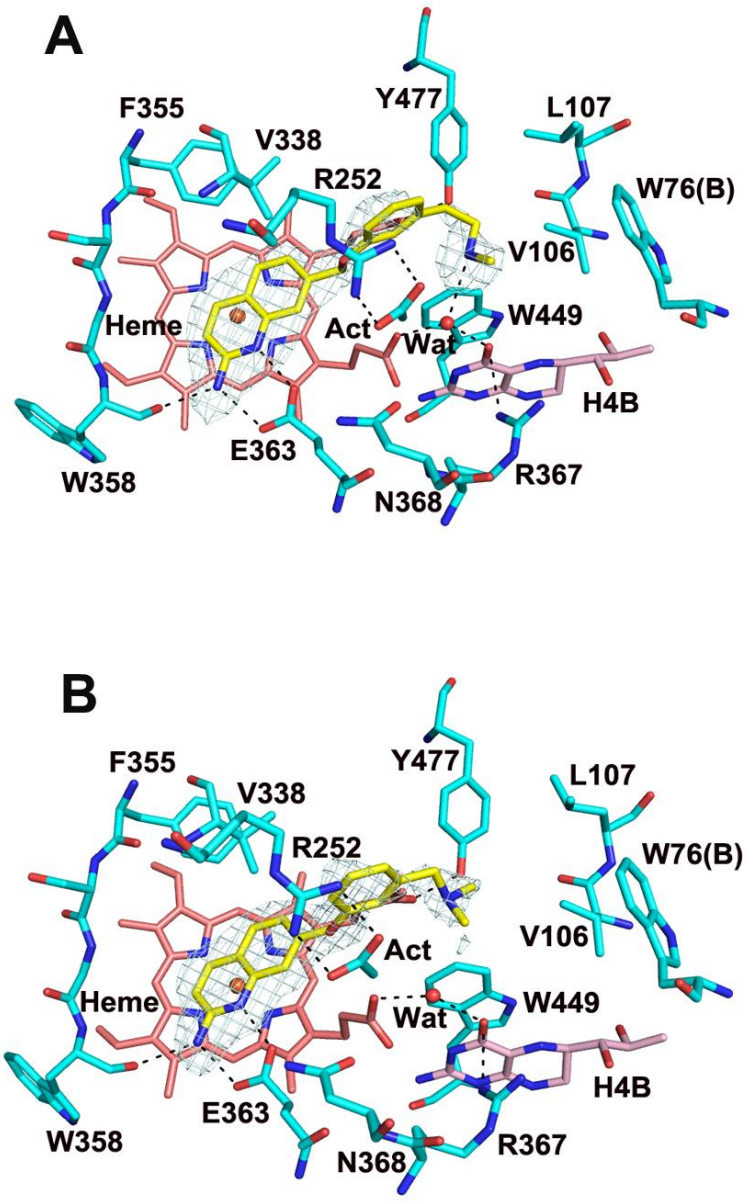

Figure S2. Active site structure of **7** (A) or **8** (B) bound to bovine eNOS. The omit Fo – Fc density map for the inhibitor is shown at the 2.5 σ contour level. The alkylamine of **7** makes a H-bond with the water bridging H_4B and heme. Major hydrogen bonds are shown as dashed lines.

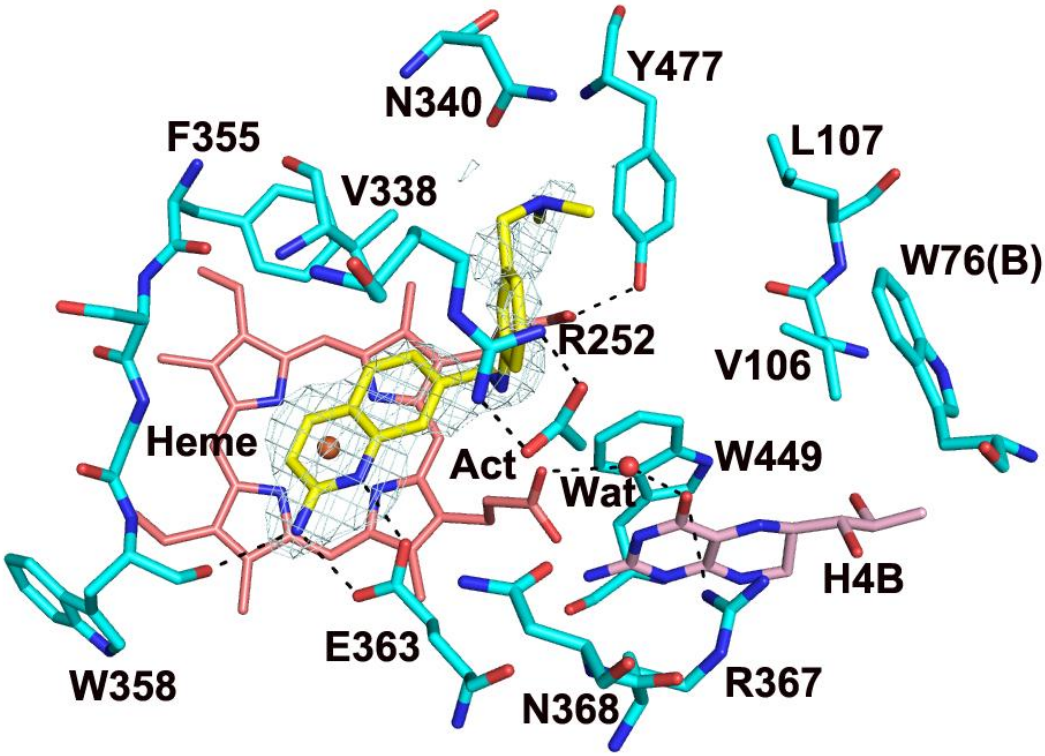

Figure S3. Active site structure of **17** bound to bovine eNOS. The omit Fo – Fc density map for the inhibitor is shown at the 2.5 σ contour level. The alkylamine of **17** is approaching Asn340. Major hydrogen bonds are shown as dashed lines.

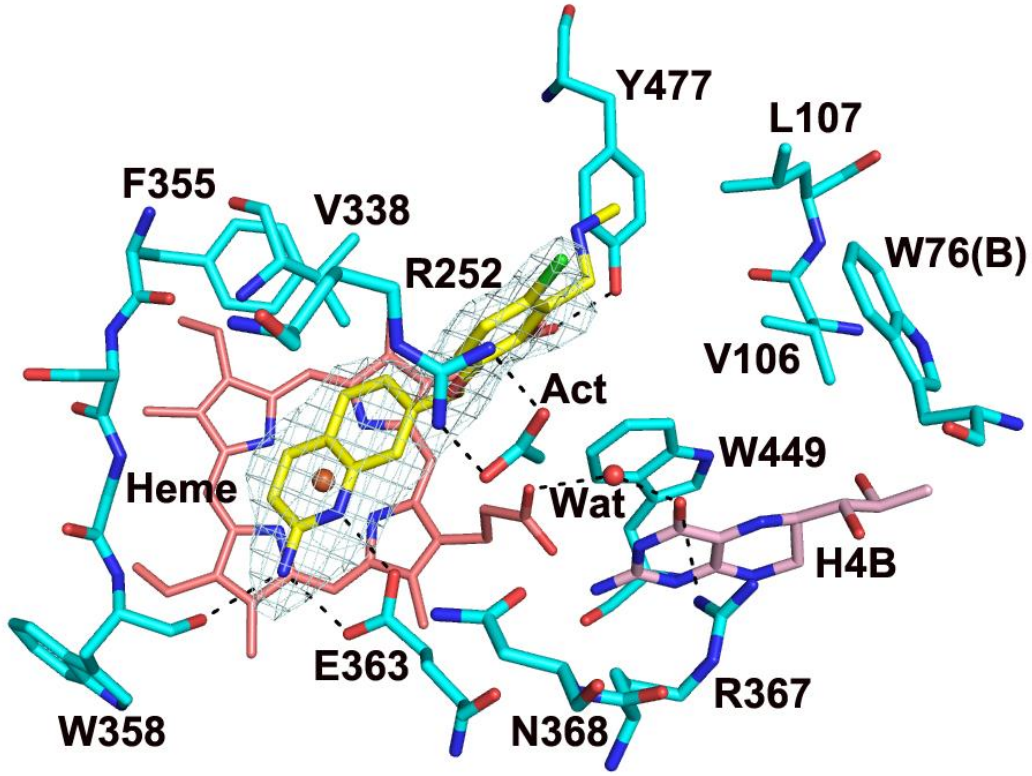

Figure S4. Active site structure of **20** bound to bovine eNOS. The omit Fo – Fc density map for the inhibitor is shown at the 2.5 σ contour level. The alkylamine of **20** has weaker density. Major hydrogen bonds are shown as dashed lines.

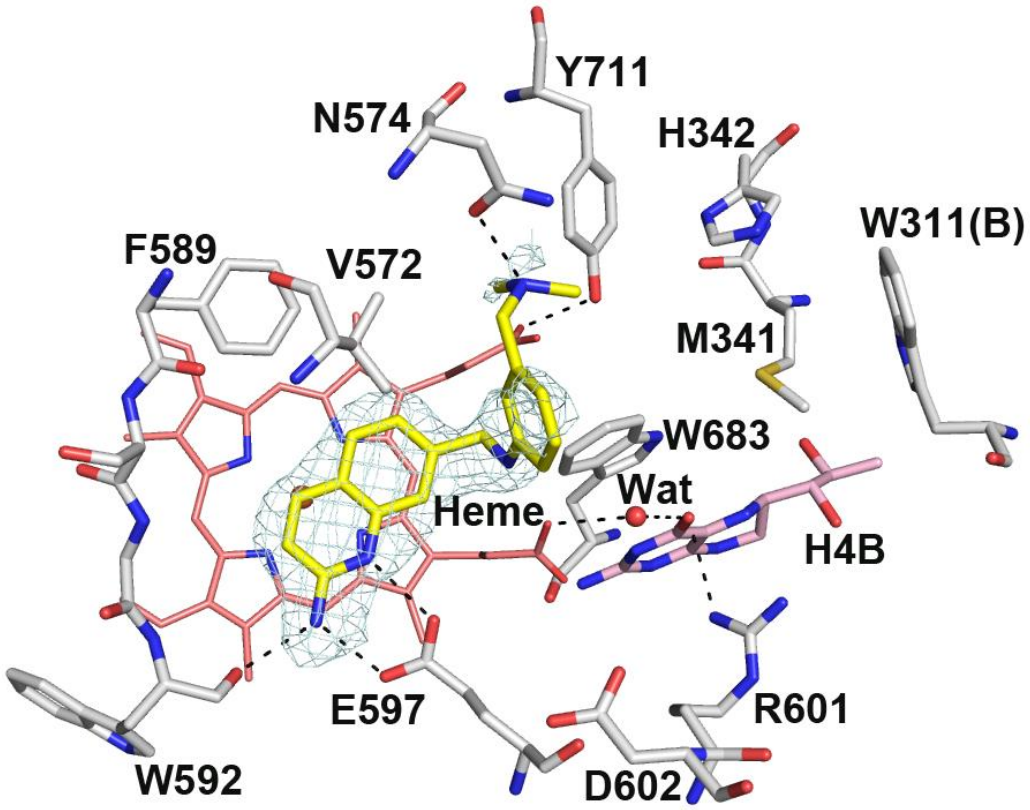

Figure S5. Active site structure of **17** bound to human nNOS. The omit Fo – Fc density map for the inhibitor is shown at the 2.5 σ contour level. The alkylamine of **17** makes a H-bond with Asn574. Major hydrogen bonds are shown as dashed lines.

Notes and References

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(7) See Figure 3 for the inhibitors' chemical structures.

(8) The diffraction anisotropy correction was performed using the online server (http://services.mbi.ucla.edu/anisoscale/).

(9) R_{free} was calculated with the 5% of reflections set aside throughout the refinement. The set of reflections for the R_{free} calculation were kept the same for all data sets of each isoform according to those used in the data of the starting model.