Supporting Information

N-Phenylphenylglycines as Novel Corticotropin Releasing Factor Receptor Antagonists.

Valentina Molteni,[†] Julie Penzotti,[†] Dean M. Wilson,[†] Andreas P. Termin,[†] Long Mao,[†] Christine M. Crane,[†] Fred Hassman,[†] Tao Wang,[†] Harvey Wong,[‡] Keith J. Miller,[‡] Scott Grossman,[‡] and Peter D. J. Grootenhuis[†*]

[*] To whom the correspondence should be addressed. Phone: 858-404-6676
fax: 858-404-6713. E-mail: Peter_Grootenhuis@sd.vrtx.com

Experimental section

Binding Assay. The cloned human CRH_1 binding assay was performed as previously described.[1]

Pharmacokinetic Studies. Pharmacokinetics studies were performed as previously described.[2]

Computational Methods. Our pharmacophore descriptors have been described in detail previously.[3] In summary, our pharmacophore space included all 2-, 3-, and 4-point pharmacophores predetermined by interfeature distance bins and 6 feature types: hydrogen-bond acceptors and donors, hydrophobes, negative and positive ionizable groups, and aromatic groups. The distance bin widths ranged from 0.5 Å at shorter distances (minimum distance 1.6 Å) to 2.0 Å at longer distances (maximum distance 13.2 Å). To eliminate edge effects, the distance bins were fuzzy, such that inter-feature distances that fell within 20% of the bin width from the bin boundary were categorized in both of the adjacent bins. The resulting "potential" pharmacophore space contained approximately 12 million pharmacophores. These descriptors have been used in a machine learning approach to develop ensemble models[3,4] and to derive pharmacophore spaces for library design from compound screening data or from structural data for a drug target.[5-7]

To map the pharmacophores, a full conformational model was generated for each compound or racemate using the program CONAN.[8] For a racemic mixture such as 1 or a compound with unspecified stereochemistry, the conformational model included conformers for all possible stereoisomers. A molecular "signature" was then created for each compound or racemate by recording the presence or absence of each of the 2-, 3-, and 4-point pharmacophores in any of a compound's conformers in a single bit string. Thus in the case of a racemic mixture, pharmacophores that could be matched by any of the stereoisomers were recorded in the same signature.

Chemistry. Reactions were carried out under ambient atmosphere and temperature unless noted otherwise. Solvents and reagents were obtained from commercial sources and used without further purification. Flash chromatography was performed using EM Science silica gel 60 (0.040-0.063 mm) and ethyl acetate / hexane mixtures as indicated. Thin layer chromatography (TLC) utilized EM Science precoated silca gel 60 F254 plates and ethyl acetate / hexane mixtures. Analytical and preparative HPLC experiments utilized a PE Sciex LC/MS system with Shimadzu SCL-10A system controller, Shimadzu SPD-10A UV-VIS detector, Shimadzu LC-8A pumps, Gilson 215 autosampler, API 150 EX mass spectrometer, and PE Sciex Sample Control 1.5 software running on a Macintosh G3 (OS 8.6). HPLC gradients were acetonitrile (0.035% TFA) / water (0.05% TFA). Analytical HPLC columns were YMC CombiScreen ODS-A (50 x 4.6 mm), preparitve columns were YMC YMC-Pack ODS-A (75 x 30 mm). The SFC supercritical fluid chromatograph instrument used in the experiments are: Berger SFC form Berger Instrument, Newark, DE for the analytical experiments and a Gilson SFC (SF3) from Gilson, Inc. from Middleton, WI for the semi-preparative experiments. Both SFC instruments were interfaced with a PE-Sciex 150EX mass spectrometer. SFC gradients were 20% methanol (0.1% DMA)/80% CO_2. Analytical SFC columns were 4.6 x 150 mm Chiralcel AD, 4.6 x 150 mm Chiralcel OD, 4.6 x 150 mm Chiralcel AS and 4.6 x 150 mm Chiralcel OJ, form Daicel Chemical industries, Ltd.. Preparative columns were

Chiralcel AD, from Daicel Chemical Industries, Ltd. (10 X 150mm). NMR spectra were obtained using either Varian 300 MHz or 400 MHz instruments. Chemical shifts are reported in ppm relative to internal solvent signals, and multiplicities are denoted as s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; br,broad; m, multiplet. Coupling constants are reported in Hertz (Hz).

General procedure to prepare N-phenyl-phenylglycines. To a magnetically stirred solution of glyoxylic acid monohydrate (1 mmol) and amine 1 (1 mmol) in toluene (1 ml) was added the boronic acid (1.5 mmol). The reaction was heated at 70° C for 12 h. The solvent was evaporated and the residue was redissolved in DMSO (1ml). To the solution were added, diisopropylamine (1 mmol), HATU (1 mmol) and amine 2 (1 mmol). The solution was stirred at r.t. for 12 h. The product was isolated by preparative LC/MS (gradient acetonitrile from 10 to 90%) upon addition of 1ml of MeOH. The compounds were charactherized by ^{1}H NMR, LC/MS (gradient acetonitrile 10 to 90%) and HRMS.

2-(2-Bromo-phenyl)-2-(2-chloro-4-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-acetamide (1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53-6.53 (m, 10H), 6.18 (d, 1H, J = 8.0 Hz), 5.28 (s, 1H), 3.90 (m, 1H), 3.49 (m, 1H), 3.02 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (300 MHz, CD_3OD) δ = 172.0, 150.14, 148.41, 139.89, 137.61, 133.165, 130.0, 129.43, 128.69, 128.49, 128.23, 128.11, 124.96, 124.13, 119.54, 112.61, 61.14, 39.43, 34.28, 19.01; r. t. 2.35 min; MS (EI) *m/z* 459.3, 460.3 $[MH]^+$; HRMS calcd for $C_{22}H_{21}BrClN_3O$ 457.0557, found 457.0560. **(1A)** r.t. (chiral SFC) 8.69 min. **(1B)** r.t. (chiral SFC) 11.76 min.

2-(2-Chloro-4-methyl-phenylamino)-2-(2-chloro-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50-6.85 (m, 10H), 6.38 (d, 1H, J = 8.0 Hz), 5.39 (s, 1H), 3.78 (m, 1H), 3.59 (m, 1H), 3.06 (m, 2H), 2.19 (s, 3H); r. t. 2.33 min; MS (EI) *m/z* 414.3 $[MH]^+$; HRMS calcd for $C_{22}H_{21}Cl_2N_3O$ 413.1062, found 413.1073.

2-(2-Chloro-4-methyl-phenylamino)-2-(2-fluoro-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (3). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52-6.86 (m, 10H), 6.43 (d, 1H, J = 8.0 Hz), 5.27 (s, 1H), 3.76 (m, 1H), 3.56 (m, 1H), 3.07 (m, 2H), 2.19 (s, 3H); r. t. 2.28 min; MS (EI) *m/z* 398.3 $[MH]^+$.

2-(2-Chloro-4-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-(2-vinyl-phenyl)-acetamide (4). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54-6.87 (m, 11H), 6.36 (d, 1H, J = 8.4 Hz), 5.62 (d, 1H, J = 16.8 Hz), 5.36 (d, 1H, J = 10.8 Hz), 5.03 (s, 1H), 3.8 (m, 1H), 3.48 (m, 1H), 2.99 (m , 2H), 2.32 (s, 3H); r. t. 2.38 min; MS (EI) *m/z* 406.3 $[MH]^+$.

2-(2-Chloro-4-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-o-tolyl-acetamide (5). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57-6.88 (m, 10H), 6.42 (d, 1H, J = 8.4 Hz), 4.93 (s, 1H), 3.8 (m, 1H), 3.62 (m, 1H), 3.10 (m, 2H), 2.37 (s, 3H), 2.25 (s, 3H); r. t. 2.33 min; MS (EI) *m/z* 394.1 $[MH]^+$.

2-(2-Chloro-4-methyl-phenylamino)-2-(2-isopropyl-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (6). ^{1}H NMR (300 MHz, CD_3OD) δ = 8.42-6.90 (m, 10H), 6.45 (d, 1H, J = 8.4 Hz), 5.07 (s, 1H), 3.52 (m, 2H), 3.2 (m, 1H), 3.02 (m, 2H), 2.23 (s, 3H), 1.21 (d, 6H); r. t. 2.50 min; MS (EI) *m/z* 422.3 $[MH]^+$.

2-(2-Chloro-4-methyl-phenylamino)-2-(2-methoxy-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (7). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35-6.80 (m, 10H), 6.22 (d, 1H, J = 8.4 Hz), 5.28 (s, 1H), 3.88 (s, 3H), 3.42 (m, 2H), 3.0 (m, 2H), 2.16 (s, 3H); r. t. 2.32 min; MS (EI) *m/z* 410.1 $[MH]^+$; HRMS calcd for $C_{23}H_{24}ClN_3O_2$ 409.1557, found 409.1556.

2-(2-Chloro-4-methyl-phenylamino)-2-(3-chloro-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (8). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.59-6.89 (m, 10H), 6.36 (d, 1H, J = 8.1 Hz), 4.69 (s, 1H), 3.70 (m, 2H), 3.01 (m, 2H), 2.24 (s, 3H); r. t. 2.40 min; MS (EI) *m/z* 414.1 $[MH]^+$; HRMS calcd for $C_{22}H_{21}Cl_2N_3O$ 413.1062, found 413.1074.

2-(2-Chloro-4-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-m-tolyl-acetamide (9). ^{1}H NMR (300 MHz, CD_3OD) δ = 8.39-6.80 (m, 10H), 6.35 (d, 1H, J = 8.4 Hz), 4.83 (s, 1H), 3.75 (m, 1H), 3.49 (m, 1H), 2.97 (m, 2H), 2.33 (s, 3H), 2.17 (s, 3H); r. t. 2.35 min; MS (EI) *m/z* 394.1 $[MH]^+$; HRMS calcd for $C_{23}H_{24}ClN_3O$ 393.1608, found 393.1614.

2-(2-Chloro-4-methyl-phenylamino)-2-(3-methoxy-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (10). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24-6.70 (m, 10H), 6.22 (d, 1H, J = 8.4 Hz), 4.61 (s, 1H), 3.67 (s, 3H), 3.56 (m, 1H), 3.28 (m, 1H), 2.83 (m, 2H), 2.07 (s, 3H); r. t. 2.27 min; MS (EI) *m/z* 410.1 $[MH]^+$; HRMS calcd for $C_{23}H_{24}ClN_3O_2$ 409.1557, found 409.1561.

2-(2-Chloro-4-methyl-phenylamino)-2-(4-chloro-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (11). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25-6.70 (m, 10H), 6.21 (d, 1H, J = 8.0 Hz), 4.69 (s, 1H), 3.55 (m, 1H), 3.34 (m, 1H), 2.85 (m, 2H), 2.08 (s, 3H); r. t. 2.40 min; MS (EI) *m/z* 414.1 $[MH]^+$; HRMS calcd for $C_{22}H_{21}Cl_2N_3O$ 413.1062, found 413.1062.

2-(2-Chloro-4-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-p-tolyl-acetamide (12). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23-6.78 (m, 10H), 6.23 (d, 1H, J = 8.0 Hz), 4.64 (s, 1H), 3.60 (m, 1H), 3.40 (m, 1H), 2.85 (m, 2H), 2.26 (s, 3H), 2.11 (s, 3H); r. t. 2.35 min; MS (EI) *m/z* 394.1 $[MH]^+$; HRMS calcd for $C_{23}H_{24}ClN_3O$ 393.1608, found 393.1608.

2-(2-Chloro-4-methyl-phenylamino)-2-(2,5-dimethoxy-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (13). ^{1}H NMR (300 MHz, CD_3OD) δ = 8.43-6.72 (m, 9H), 6.30 (d, 1H, J = 8.4 Hz), 5.27 (s, 1H), 3. 85 (s, 3H), 3.78 (m, 1H), 3.69 (s, 3H), 3.50 (m, 1H), 3.00 (m, 2H), 2.16 (s, 3H); r. t. 2.33 min; MS (EI) *m/z* 440.3 $[MH]^+$; HRMS calcd for $C_{24}H_{26}ClN_3O_3$ 439.1663, found 439.1657.

2-(2-Chloro-4-methyl-phenylamino)-2-(2,6-dimethoxy-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (15). ^{1}H NMR (300 MHz, CD_3OD) δ = 8.50-6.54 (m, 10H), 5.64 (s, 1H), 3. 82 (s, 6H), 3.63 (m, 2H), 3.08 (m, 2H), 2.18 (s, 3H); r. t. 2.32 min; MS (EI) *m/z* 440.3 $[MH]^+$; HRMS calcd for $C_{24}H_{26}ClN_3O_3$ 439.1663, found 439.1659.

2-(2-Chloro-4-methyl-phenylamino)-2-phenyl-N-(2-pyridin-4-yl-ethyl)-acetamide (16). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.64-6.37 (m, 12H), 5.58 (s, 1H), 3.71 (m, 1H), 3.60 (m, 1H), 3.02 (m, 2H), 2.23 (s, 3H); r. t. 2.23 min; MS (EI) *m/z* 380.1 $[MH]^+$; HRMS calcd for $C_{22}H_{22}ClN_3O$ 379.1451, found 379.1462.

2-(2-Bromo-phenyl)-2-(2-chloro-phenylamino)-N-(2-pyridin-4-yl-ethyl)-acetamide (17). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50-6.81 (m, 11H), 6.45 (d, 1H, J = 8.0 Hz), 5.38 (s, 1H), 3.81 (m, 1H), 3.57 (m, 1H), 3.08 (m, 2H); r. t. 2.25 min; MS (EI) *m/z* 444.1, 446.1 $[MH]^+$; HRMS calcd for $C_{21}H_{19}BrClN_3O$ 443.0400, found 443.0413.

2-(2-Bromo-phenyl)-2-[(2-chloro-phenyl)-methyl-amino]-N-(2-pyridin-4-yl-ethyl)-acetamide (18). ^{1}H NMR (300 MHz, CD_3OD) δ = 8.50-6.97 (m, 12H), 5.48 (s, 1H), 3.70 (m, 2H), 3.02 (m, 2H), 2.58 (s, 3H); r. t. 2.23 min; MS (EI) *m/z* 458.1, 460.1 $[MH]^+$; HRMS calcd for $C_{22}H_{21}BrClN_3O$ 457.0557, found 457.0572.

2-(2-Bromo-phenyl)-2-(2,4-dichloro-phenylamino)-N-(2-pyridin-4-yl-ethyl)-acetamide (19). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55-6.68 (m, 10H), 5.96 (d, 1H, J = 8.4 Hz), 4.98 (s, 1H), 3.18 (m, 1H), 3.42 (m, 1H), 2.67 (m , 2H); r. t. 2.43 min; MS (EI) *m/z* 480.1 $[MH]^+$; HRMS calcd for $C_{21}H_{18}BrCl_2N_3O$ 457.0010, found 457.0560.

2-(2-Bromo-phenyl)-2-(2-chloro-4-methyl-phenylamino)-N-(2-pyridin-2-yl-ethyl)-acetamide (20). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15-6.48 (m, 10H), 5.95 (d, 1H, J = 7.6 Hz), 4.94 (s, 1H), 3.40 (m, 1H), 3.29 (m, 1H), 2.77 (m, 2H), 1.82 (s, 3H); r. t. 2.38 min; MS (EI) *m/z* 460.1 $[MH]^+$.

2-(2-Bromo-phenyl)-2-(2-chloro-4-methyl-phenylamino)-N-(2-pyridin-3-yl-ethyl)-acetamide (21). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12-6.43 (m, 10H), 5.94 (d, 1H, J = 7.6 Hz), 4.91 (s, 1H), 3.31 (m, 1H), 3.18 (m, 1H), 2.59 (m, 2H), 1.80 (s, 3H); r. t. 2.37 min; MS (EI) *m/z* 460.1 $[MH]^+$.

2-(2-Bromo-phenyl)-2-(2-chloro-4-methyl-phenylamino)-N-phenethyl-acetamide (22). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50-6.31 (m, 10H), 6.18 (d, 1H, J = 8.1 Hz), 5.24 (s, 1H), 3.60 (m, 2H), 2.78 (m, 2H), 2.19 (s, 3H); r. t. 3.74 min; MS (EI) *m/z* 457.1, 459.1 $[MH]^+$.

2-(2-Bromo-phenyl)-2-(2-chloro-4-methyl-phenylamino)-N-[2-(1H-imidazol-4-yl)-ethyl]-acetamide (23). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (s, 1H), 7.21 (d, 1H, J = 8.0 Hz), 6.9 (m, 3H), 6.69 (s, 1H), 6.56 (s, 1H), 6.45 (d, 1H, J = 8 Hz), 5.96 (d, 1H, J = 7.2 Hz), 4.94 (s, 1H), 3.27 (m, 1H), 3.14 (m, 1H), 2.52 (m, 2H), 1.79 (s, 3H); r. t. 2.35 min; MS (EI) *m/z* 447.1 $[MH]^+$; HRMS calcd for $C_{20}H_{20}BrClN_4O$ 446.0509, found 446.0518.

2-(2-Bromo-phenyl)-2-(2-chloro-4-methyl-phenylamino)-N-[2-(4-fluoro-phenyl)-ethyl]-acetamide (24). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.58-6.44 (m, 10H), 6.35 (d, 1H, J = 8.1 Hz), 5.25 (s, 1H), 3.66 (m, 1H), 3.47 (m, 1H), 2.74 (m, 2H), 2.19 (s, 3H); r. t. 3.73 min; MS (EI) *m/z* 474.9, 476.9 $[MH]^+$; HRMS calcd for $C_{23}H_{21}BrClN_3O$ 474.0510, found 474.0524.

2-(2-Bromo-phenyl)-2-(2-chloro-4-methyl-phenylamino)-N-pyridin-4-ylmethyl-acetamide (25). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20-6.54 (m, 10H), 6.11 (d, 1H, J = 7.2 Hz), 5.17(s, 1H), 3.99 (s, 2H), 1.85 (s, 3H); r. t. 2.40 min; MS (EI) *m/z* 445.1, 446.1 $[MH]^+$; HRMS calcd for $C_{21}H_{19}BrClN_3O$ 443.0400, found 443.0384.

2-(2-Bromo-phenyl)-2-(2-chloro-4-methyl-phenylamino)-N-(3-hydroxy-4-methoxy-phenyl)-acetamide (27). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28-6.44 (m, 9H), 6.15 (d, 1H, J = 8.4 Hz), 5.10 (s, 1H), 3.47 (s, 3H), 1.83 (s, 3H); r. t. 3.28 min; MS (EI) *m/z* 475.1 $[MH]^+$; HRMS calcd for $C_{22}H_{20}BrClN_2O_3$ 474.0346, found 474.0349.

2-(2,4-Dichloro-phenylamino)-2-(2-ethyl-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (28). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.60-6.80 (m, 10H), 6.46 (d, 1H, J = 8.7 Hz), 4.97 (s, 1H), 3.67 (q, 2H), 3.04 (m, 2H),2.72 (m, 2H), 1.20 (t, 3H); r. t. 2.44 min; MS (EI) *m/z* 428.1 $[MH]^+$; HRMS calcd for $C_{23}H_{23}Cl_2N_3O$ 427.1218 , found 427.1213.

2-(2,4-Dichloro-phenylamino)-2-(2,6-dimethyl-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (29). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18-6.62 (m, 9H), 5.96 (d, 1H, J = 8.4 Hz), 4.91 (s, 1H), 3.34 (m, 1H), 3.16 (m, 1H), 2.67 (m, 2H), 2.00 (s, 6H); r. t. 2.53 min; MS (EI) *m/z* 428.1 $[MH]^+$; HRMS calcd for $C_{23}H_{23}Cl_2N_3O$ 427.1218, found 427.1206.

2-(2,4-Dichloro-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-o-tolyl-acetamide (30). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.43 (d, 2H, J = 5.9 Hz), 7.30 (m, 4H), 7.10 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.5 Hz), 6.99 (d, 2H, J = 5.9 Hz), 6.78 (m, 1H), 6.47 (d, 1H, J = 8.5 Hz), 5.13

(d, 1H, J = 2.8 Hz), 4.98 (d, 1H, J = 2.8 Hz), 3.65 (m, 1H), 3.45 (m, 1H), 2.75 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 170.98, 149.99, 147.75, 141.602, 136.99, 136.11, 131.76, 129.18, 129.04, 128.09, 127.15, 126.96, 124.28, 123.38, 120.54, 112.89, 60.69, 39.80, 35.09, 19.60; r. t. 2.5 min; MS (EI) *m/z* 414.3 $[MH]^+$. **(30A)** r.t. (chiral SFC) 5.08 min. **(30B)** r.t. (chiral SFC) 6.42 min; HRMS calcd for $C_{22}H_{21}Cl_2N_3O$ 413.1062, found 413.1053.

2-(2,4-Dichloro-phenylamino)-2-(4-fluoro-2-methyl-phenyl)-N-(2-pyridin-4-yl-ethyl)-acetamide (31). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.15-6.52 (m, 9H), 5.96 (d, 1H, J = 8.0 Hz), 4.62 (s, 1H), 3.32 (m, 1H), 3.23 (m, 1H), 2.70 (m , 2H), 1.99 (s, 3H); r. t. 2.43 min; MS (EI) *m/z* 432.1 $[MH]^+$.

2-(2,4-Dichloro-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-(2-trifluoromethyl-phenyl)-acetamide (33). ^1H NMR (300 MHz, $CDCl_3$) δ = 8.50-6.36 (m, 10H), 6. 25 (d, 1H, J = 8.7 Hz), 5.20 (s, 1H), 3.80 (m, 1H), 3.57 (m, 1H), 3.02 (m , 2H); r. t. 2.41 min; MS (EI) *m/z* 468.1 $[MH]^+$; HRMS calcd for $C_{22}H_{18}Cl_2F_3N_3O$ 467.0779, found 467.0775.

2-(2-Fluoro-4-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-o-tolyl-acetamide (34). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.10-6.10 (m, 11H), 4.61 (s, 1H), 3.34 (m, 1H), 3.53 (m, 1H), 2.67 (m, 2H), 2.01 (s, 3H), 1.89 (s, 3H); r. t. 2.18 min; MS (EI) *m/z* 378.1 $[MH]^+$; HRMS calcd for $C_{23}H_{24}FN_3O$ 377.1903, found 377.1901.

2-(4-Chloro-2-trifluoromethyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-o-tolyl-acetamide (35). δ = 8.48-7.22 (m, 10H), 6.50 (d, 1H, J = 8.0 Hz), 5.13 (s, 1H), 3.79 (m, 1H), 3.51 (m, 1H), 3.02 (m, 2H), 2.38 (s, 3H); r. t. 2.50 min; MS (EI) *m/z* 448.1 $[MH]^+$; HRMS calcd for $C_{23}H_{21}ClF_3N_3O$ 447.1325, found 447.1335.

2-(4-Methyl-2-trifluoromethyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-2-o-tolyl-acetamide (36). ^1H NMR (400 MHz, $CDCl_3$) δ = 8.06-6.08 (m, 10H), 6.06 (d, 1H, J = 8.8 Hz), 4.73 (s, 1H), 3.37 (m, 1H), 3.18 (m, 1H), 2.65 (m, 2H), 2.00 (s, 3H), 1.83 (s, 3H); r. t. 2.40 min; MS (EI) *m/z* 429.1 $[MH]^+$; HRMS calcd for $C_{24}H_{24}F_3N_3O$ 427.1871, found 427.1900.

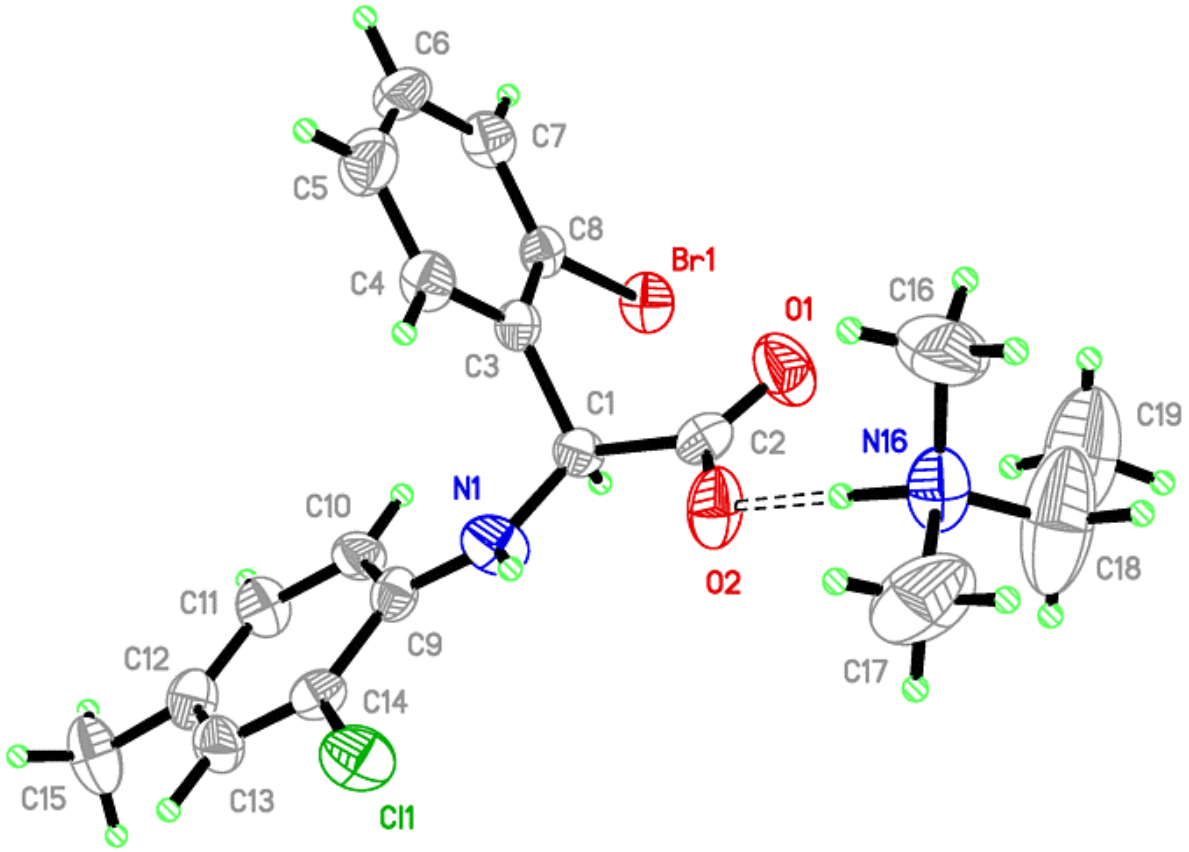
2-(2,4-Dichloro-phenylamino)-N-(3-hydroxy-4-methoxy-phenyl)-2-o-tolyl-acetamide (37). ^1H NMR (400 MHz, $CDCl_3$) δ = 6.62-5.98 (m, 9H), 5.78 (d, 1H, J = 8.0 Hz), 4.36 (s, 1H), 3.00 (s, 3H), 1.59 (s, 3H); r. t. 3.33 min; MS (EI) *m/z* 431.1 $[MH]^+$; HRMS calcd for $C_{22}H_{20}Cl_2N_2O_3$ 430.0851, found 430.0861.

2-(2,4-Dichloro-phenylamino)-N-(3,4-dimethoxy-phenyl)-2-o-tolyl-acetamide (38). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.10 (d, 1H, J = 6.8 Hz), 7.01-6.90 (m, 5H), 6.78 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 6.69 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 6.50 (d, 1H, J = 8.8 Hz), 6.29 (d, 1H, J = 8.8 Hz), 4.88 (s, 1H), 3.51 (s, 3H), 3.5 (s, 3H), 2.11 (s, 3H); r. t. 3.52 min; MS (EI) *m/z* 445.3 $[MH]^+$; HRMS calcd for $C_{23}H_{22}Cl_2N_2O_3$ 444.1007, found 444.1008.

2-(2,4-Dichloro-phenylamino)-N-(3-hydroxy-phenyl)-2-o-tolyl-acetamide (39). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.06-6.24 (m, 11H), 4.87 (s, 1H), 2.06 (s, 3H); r. t. 3.32 min; MS (EI) *m/z* 401.1 $[MH]^+$; HRMS calcd for $C_{21}H_{18}Cl_2N_2O_2$ 400.0745, found 400.0782.

N-(3-Acetylamino-phenyl)-2-(2-bromo-phenyl)-2-(2,4-dichloro-phenylamino)-acetamide (40). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.46-6.6 (m, 10H), 6.16 (d, 1H, J = 8.8 Hz), 5.21 (s, 1H), 1.76 (s, 3H); r. t. 3.33 min; MS (EI) *m/z* 508.1 $[MH]^+$; HRMS calcd for $C_{22}H_{18}BrCl_2N_3O_2$ 504.9959, found 504.9984.

Crystal Data for Ac1A dimethyl-ethyl amine.



CRYSTAL DATA: $C_{38}H_{48}Br_2Cl_2N_4O_4$, from ethylacetate/pentane, colorless, plate, ~0.300 x 0.300 x 0.050mm, monoclinic , P21 , a = 7.0696(11) A, b = 8.9830(13) A, c = 16.047(2) A, beta = 92.632(3) deg, Vol = 1018.0(3) A^3, Z = 1, T = -100.degC, Formula weight = 855.52, Density = 1.395mg/m^3, mu(Mo) = 2.16mm^{-1}

DATA COLLECTION: Bruker SMART 1K CCD system, MoKalpha radiation, standard focus tube , anode power = 50kV x 40mA, crystal to plate distance = 4.9mm, 512 x 512 pixels/frame, hemisphere data aquisition , total scans = 4, total frames = 1330, oscillation/frame = -0.30deg, exposure/frame = 8.0 sec/frame, maximum detector swing angle = -28.0deg, beam center = (254.93,252.33), in plane spot width = 1.19, omega half width = 1.13, SAINT integration, hkl min/max = (-9, 8, -11, 11, -20, 18), data input to shelx = 6455, unique data = 4186, two-theta range = 2.54 to 56.50deg, completeness to two-theta 56.50 = 92.80%, R(int-xl) = 0.0367, SADABS correction applied.

RESOLUTION AND REFINEMENT: Structure solved using XS(Shelxtl), refined using shelxtl software package, refinement by full-matrix least squares on F^2, scattering factors from Int. Tab. Vol C Tables 4.2.6.8 and 6.1.1.4, number of data = 4186, number of restraints = 1, number of parameters = 238, data/parameter ratio = 17.59, goodness-of-fit on F^2 = 0.92, R indices[I>4sigma(I)] R1 = 0.0442, wR2 = 0.0899, R indices(all data)

R1 = 0.0787, wR2 = 0.0997, max difference peak and hole = 0.543 and -0.590 e/A^3, refined flack parameter = 0.065(12) , All hydrogen atoms except those involved in hydrogen bonding have been idealized as riding hydrogens. The rotation of the methyl groups are refined.

RESULTS: This study determines the structure of N-phenyl-acetic acid-dimethyl-ethyl amine for pharmaceutical research(GPCR). The asymmetric unit contains one molecule and one dimethyl-ethyl amine molecule as shown in figure 1 with thermal ellipsoids drawn to the 50% probability level. The amine is hydrogen bonded to O2. The absolute configuration is determined with this study. The flack parameter refined to 0.07(1) indictating the correct enantiomeric setting.

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 00314. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(1)	-6379(1)	-6106(1)	-1901(1)	38(1)
Cl(1)	2324(2)	-2168(2)	-3186(1)	47(1)
O(1)	-2251(6)	-5825(6)	-706(2)	60(1)
O(2)	367(5)	-4641(5)	-1026(2)	46(1)
N(1)	-795(7)	-4004(5)	-2552(3)	40(1)
C(1)	-2126(7)	-4876(6)	-2083(3)	30(1)
C(2)	-1265(7)	-5166(6)	-1189(3)	34(1)
C(3)	-2613(6)	-6353(6)	-2502(3)	27(1)
C(4)	-1265(7)	-7072(6)	-2961(3)	35(1)
C(5)	-1632(10)	-8441(8)	-3355(4)	50(2)
C(6)	-3386(9)	-9088(7)	-3290(3)	45(2)
C(7)	-4762(7)	-8388(6)	-2845(3)	37(1)
C(8)	-4380(6)	-7019(6)	-2464(3)	28(1)
C(9)	-1250(8)	-3323(6)	-3287(4)	30(1)
C(10)	-3005(8)	-3459(6)	-3710(3)	34(1)
C(11)	-3418(7)	-2726(6)	-4458(3)	37(1)
C(12)	-2099(7)	-1837(6)	-4830(3)	38(1)
C(13)	-306(7)	-1694(6)	-4423(3)	36(1)
C(14)	85(6)	-2395(6)	-3680(3)	30(1)
C(15)	-2587(7)	-985(11)	-5618(3)	58(2)
N(16)	-2062(7)	-135(7)	-435(3)	49(1)
C(16)	-2663(13)	-1731(9)	-491(5)	94(3)
C(17)	-3810(10)	727(10)	-391(5)	85(3)
C(18)	-981(11)	445(14)	-1127(4)	107(4)
C(19)	831(11)	-40(13)	-1248(5)	116(3)

Table 2. Bond lengths [A] and angles [deg] for 00314.

Br(1)-C(8)	1.898(5)
Cl(1)-C(14)	1.749(5)
O(1)-C(2)	1.219(6)
O(2)-C(2)	1.262(6)
N(1)-C(9)	1.355(7)
N(1)-C(1)	1.459(6)
C(1)-C(3)	1.519(7)
C(1)-C(2)	1.555(7)
C(3)-C(8)	1.389(6)
C(3)-C(4)	1.391(6)
C(4)-C(5)	1.401(8)
C(5)-C(6)	1.378(9)
C(6)-C(7)	1.384(8)
C(7)-C(8)	1.395(7)
C(9)-C(10)	1.392(7)
C(9)-C(14)	1.427(7)
C(10)-C(11)	1.388(7)
C(11)-C(12)	1.383(7)
C(12)-C(13)	1.405(7)
C(12)-C(15)	1.505(8)
C(13)-C(14)	1.365(7)
N(16)-C(17)	1.463(8)
N(16)-C(18)	1.472(9)
N(16)-C(16)	1.497(9)
C(18)-C(19)	1.375(10)
C(9)-N(1)-C(1)	124.0(5)
N(1)-C(1)-C(3)	112.3(4)
N(1)-C(1)-C(2)	109.3(4)
C(3)-C(1)-C(2)	109.4(4)
O(1)-C(2)-O(2)	126.5(5)
O(1)-C(2)-C(1)	117.1(5)
O(2)-C(2)-C(1)	116.3(5)
C(8)-C(3)-C(4)	117.6(5)
C(8)-C(3)-C(1)	122.9(4)
C(4)-C(3)-C(1)	119.6(4)
C(3)-C(4)-C(5)	122.0(5)
C(6)-C(5)-C(4)	119.0(6)
C(5)-C(6)-C(7)	120.3(6)
C(6)-C(7)-C(8)	120.0(5)
C(3)-C(8)-C(7)	121.1(4)
C(3)-C(8)-Br(1)	121.7(4)
C(7)-C(8)-Br(1)	117.2(4)
N(1)-C(9)-C(10)	123.7(5)
N(1)-C(9)-C(14)	120.9(5)
C(10)-C(9)-C(14)	115.4(5)
C(11)-C(10)-C(9)	121.8(5)
C(12)-C(11)-C(10)	121.9(5)
C(11)-C(12)-C(13)	117.6(5)
C(11)-C(12)-C(15)	121.6(5)

C(13)-C(12)-C(15)	120.8(5)
C(14)-C(13)-C(12)	120.4(5)
C(13)-C(14)-C(9)	122.9(5)
C(13)-C(14)-Cl(1)	119.0(4)
C(9)-C(14)-Cl(1)	118.1(4)
C(17)-N(16)-C(18)	108.6(6)
C(17)-N(16)-C(16)	105.7(6)
C(18)-N(16)-C(16)	116.8(7)
C(19)-C(18)-N(16)	120.9(8)

Symmetry transformations used to generate equivalent atoms:

Table 3. Anisotropic displacement parameters (A^2 x 10^3) for 00314.

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Br(1)	24(1)	50(1)	40(1)	0(1)	4(1)	-1(1)
Cl(1)	28(1)	54(1)	59(1)	2(1)	0(1)	-12(1)
O(1)	65(2)	73(4)	40(2)	16(2)	-13(2)	-30(3)
O(2)	30(2)	77(3)	31(2)	-5(2)	-4(2)	-6(2)
N(1)	24(3)	48(3)	46(3)	9(2)	-14(2)	-13(2)
C(1)	30(3)	30(3)	29(3)	3(2)	-6(2)	-4(2)
C(2)	33(3)	32(3)	36(3)	-7(3)	-1(3)	-2(2)
C(3)	26(2)	31(4)	23(2)	0(2)	-1(2)	1(2)
C(4)	26(3)	42(3)	37(3)	-1(3)	6(2)	-2(2)
C(5)	51(4)	54(5)	46(4)	-11(3)	15(3)	-4(3)
C(6)	65(4)	33(3)	36(4)	-8(3)	-7(3)	-6(3)
C(7)	30(3)	44(3)	36(3)	1(3)	-2(2)	-10(3)

C(8)	24(2)	34(3)	25(3)	0(2)	-3(2)	-2(2)
C(9)	31(3)	32(3)	26(3)	-3(2)	-2(2)	3(3)
C(10)	32(3)	33(3)	36(3)	1(3)	-2(3)	-8(2)
C(11)	30(3)	45(3)	34(3)	7(3)	-6(2)	4(2)
C(12)	35(3)	44(3)	36(3)	-4(2)	3(2)	6(2)
C(13)	33(3)	40(3)	37(3)	0(2)	12(2)	-1(2)
C(14)	21(2)	30(3)	37(3)	-6(2)	-2(2)	-2(2)
C(15)	57(3)	81(4)	36(3)	17(4)	5(2)	7(5)
N(16)	33(3)	74(4)	38(3)	2(3)	1(2)	7(3)
C(16)	153(10)	47(5)	78(6)	-20(4)	-27(6)	10(5)
C(17)	59(5)	93(6)	103(6)	34(5)	-1(4)	24(4)
C(18)	51(5)	213(12)	58(5)	29(6)	7(4)	-1(6)
C(19)	90(7)	193(10)	66(5)	28(6)	14(5)	-16(7)

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 00314.

	x	y	z	U(eq)
H(1)	160(60)	-3900(50)	-2370(30)	10(13)
H(1A)	-3294	-4299	-2040	36
H(4A)	-83	-6632	-3007	42
H(5A)	-706	-8905	-3656	60
H(6A)	-3646	-9999	-3546	54
H(7A)	-5941	-8831	-2800	44
H(10A)	-3925	-4059	-3486	41
H(11A)	-4615	-2834	-4716	44
H(13A)	620	-1118	-4661	44
H(15A)	-3673	-1429	-5901	87
H(15B)	-1534	-1013	-5974	87
H(15C)	-2866	30	-5482	87
H(16A)	-3206	-2022	22	140
H(16B)	-1582	-2344	-587	140
H(16C)	-3587	-1850	-943	140
H(17A)	-3512	1769	-366	128

H(17B)	-4452	446	100	128
H(17C)	-4614	531	-877	128
H(18A)	-1723	249	-1638	129
H(18B)	-922	1518	-1063	129
H(19A)	1281	401	-1747	174
H(19D)	833	-1104	-1303	174
H(19B)	1645	245	-779	174
H(16)	-1130(70)	100(60)	190(30)	39(14)

Table 5. Torsion angles [deg] for 00314.

C(9)-N(1)-C(1)-C(3)	71.6(7)
C(9)-N(1)-C(1)-C(2)	-166.7(5)
N(1)-C(1)-C(2)-O(1)	176.7(5)
C(3)-C(1)-C(2)-O(1)	-60.0(6)
N(1)-C(1)-C(2)-O(2)	-0.7(6)
C(3)-C(1)-C(2)-O(2)	122.7(5)
N(1)-C(1)-C(3)-C(8)	-146.8(4)
C(2)-C(1)-C(3)-C(8)	91.6(5)
N(1)-C(1)-C(3)-C(4)	31.7(6)
C(2)-C(1)-C(3)-C(4)	-89.9(5)
C(8)-C(3)-C(4)-C(5)	-1.8(8)
C(1)-C(3)-C(4)-C(5)	179.6(5)
C(3)-C(4)-C(5)-C(6)	0.4(9)
C(4)-C(5)-C(6)-C(7)	0.4(9)
C(5)-C(6)-C(7)-C(8)	0.3(9)
C(4)-C(3)-C(8)-C(7)	2.5(7)
C(1)-C(3)-C(8)-C(7)	-178.9(5)
C(4)-C(3)-C(8)-Br(1)	-177.1(4)
C(1)-C(3)-C(8)-Br(1)	1.4(6)
C(6)-C(7)-C(8)-C(3)	-1.8(8)
C(6)-C(7)-C(8)-Br(1)	177.8(4)
C(1)-N(1)-C(9)-C(10)	-4.6(9)
C(1)-N(1)-C(9)-C(14)	175.3(5)
N(1)-C(9)-C(10)-C(11)	179.2(5)
C(14)-C(9)-C(10)-C(11)	-0.7(8)
C(9)-C(10)-C(11)-C(12)	1.0(8)
C(10)-C(11)-C(12)-C(13)	-0.1(8)
C(10)-C(11)-C(12)-C(15)	-176.9(6)
C(11)-C(12)-C(13)-C(14)	-1.0(7)
C(15)-C(12)-C(13)-C(14)	175.8(5)
C(12)-C(13)-C(14)-C(9)	1.4(8)
C(12)-C(13)-C(14)-Cl(1)	-179.1(4)
N(1)-C(9)-C(14)-C(13)	179.6(5)
C(10)-C(9)-C(14)-C(13)	-0.5(8)
N(1)-C(9)-C(14)-Cl(1)	0.1(7)
C(10)-C(9)-C(14)-Cl(1)	-180.0(4)
C(17)-N(16)-C(18)-C(19)	172.0(10)
C(16)-N(16)-C(18)-C(19)	-68.6(11)

Symmetry transformations used to generate equivalent atoms.

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