# Design and synthesis of potent, selective and orally bioavailable $I_{Ks}$ blockers

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**Supporting Information:**

| Cpd# | Formula | MW | Purity (HPLC) | Mass spec (m/z) | Mp | Analysis | Method |
|---|---|---|---|---|---|---|---|
| 8 | $C_{18}H_{29}NO_2$ | 291.44 | 99% | 292 $(M+H)^+$ | | | A |
| 9 | $C_{18}H_{29}NO_2$ | 291.44 | 99% | 292 $(M+H)^+$ | | | A |
| 10 | $C_{19}H_{31}NO_2$ | 305.46 | 86% | 306 $(M+H)^+$ | 74-76 | CHN | A |
| 11 | $C_{18}H_{29}NO_2$ | 291.44 | 99% | 292 $(M+H)^+$ | | | A |
| 12 | $C_{17}H_{27}NO_2$ | 277.41 | 99% | 278 $(M+H)^+$ | | | A |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 13 | $C_{17}H_{27}NO_2$ | 277.41 | 99% | 278 $(M+H)^+$ | | | A |
| 14 | $C_{21}H_{35}NO_2$ | 333.52 | 93% | 334 $(M+H)^+$ | | | A |
| 15 | $C_{20}H_{32}N_2O_2$ | 332.49 | 99% | 333 $(M+H)^+$ | | | A |
| 16 | $C_{21}H_{33}NO_2$ | 331.50 | 97% | 332 $(M+H)^+$ | 77-78 | CHN | A |
| 17 | $C_{20}H_{31}NO_2$ | 317.48 | 97% | 318 $(M+H)^+$ | 82-83 | CHN | A |
| 18 | $C_{20}H_{31}NO_2$ | 317.48 | 99% | 318 $(M+H)^+$ | 71-72 | CHN | A |
| 19A | $C_{21}H_{33}NO_2$ | 331.50 | 92% | 332 $(M+H)^+$ | 68-69 | CHN | A |
| 19B | $C_{21}H_{33}NO_2$ | 331.50 | 95% | 332 $(M+H)^+$ | 69-70 | CHN | A |
| 20A | $C_{22}H_{35}NO_2$ | 354.54 | 96% | 355 $(M+H)^+$ | 117-118 | CHN | A |
| 20B | $C_{22}H_{35}NO_2$ | 354.54 | 99% | 355 $(M+H)^+$ | 118-119 | CHN | A |
| 21 | $C_{21}H_{33}NO_2$ | 331.50 | 99% | 332 $(M+H)^+$ | | | A |
| 22 | $C_{22}H_{35}NO_2$ | 354.54 | 99% | 355 $(M+H)^+$ | 109-110 | CHN | A |
| 23 | $C_{17}H_{27}NO_2$ | 277.41 | 99% | 278 $(M+H)^+$ | | | B |
| 24 | $C_{20}H_{33}NO$ | 303.49 | 99% | 304 $(M+H)^+$ | | | B |
| 25 | $C_{20}H_{23}NO_2$ | 309.41 | 99% | 310 $(M+H)^+$ | | | B |
| 26 | $C_{20}H_{25}NO$ | 295.43 | 90% | 296 $(M+H)^+$ | | | B |
| 27 | $C_{19}H_{23}NO_2$ | 297.40 | 90% | 298 $(M+H)^+$ | | | B |
| 28 | $C_{19}H_{23}NO$ | 281.40 | 99% | 282 $(M+H)^+$ | | | B |
| 29 | $C_{21}H_{25}NO$ | 307.44 | 99% | 308 $(M+H)^+$ | | | B |
| 30 | $C_{21}H_{24}N_2O$ | 320.43 | 99% | 321 $(M+H)^+$ | | | B |
| 31 | $C_{21}H_{23}N_3O_2$ | 349.43 | 99% | 350 $(M+H)^+$ | 169-170 | CHN | C |
| 32 | $C_{19}H_{27}N_3O_2$ | 329.44 | 99% | 330 $(M+H)^+$ | 95-97 | CHN | C |
| 33A | $C_{21}H_{29}N_3O_2$ | 355.48 | 99% | 356 $(M+H)^+$ | 74-76 | CHN | C |
| 33B | $C_{21}H_{29}N_3O_2$ | 355.48 | 99% | 356 $(M+H)^+$ | 74-76 | CHN | C |
| 34A | $C_{18}H_{23}N_3O_2$ | 313.43 | 97% | 314 $(M+H)^+$ | 155-156 | CHN | C |
| 34B | $C_{18}H_{23}N_3O_2$ | 313.43 | 98% | 314 $(M+H)^+$ | 155-156 | CHN | C |
| 35A | $C_{20}H_{27}N_3O_2$ | 341.46 | 99% | 342 $(M+H)^+$ | 88-90 | CHN | C |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 35B | $C_{20}H_{27}N_3O_2$ | 341.46 | 99% | 342 $(M+H)^+$ | 88-90 | CHN | C |
| 36A | $C_{21}H_{27}N_3O_2$ | 354.47 | 99% | 354 $(M+H)^+$ | 116-117 | CHN | C |
| 36B | $C_{21}H_{27}N_3O_2$ | 354.47 | 99% | 354 $(M+H)^+$ | 116-117 | CHN | C |
| 37A | $C_{20}H_{24}F_3N_3O_2$ | 395.43 | 94% | 396 $(M+H)^+$ | 100-101 | | C |
| 37B | $C_{20}H_{24}F_3N_3O_2$ | 395.43 | 95% | 396 $(M+H)^+$ | 100-101 | | C |
| 38A | $C_{21}H_{29}N_3O_2$ | 355.48 | 95% | 356 $(M+H)^+$ | | | D |
| 38B | $C_{21}H_{29}N_3O_2$ | 355.48 | 99% | 356 $(M+H)^+$ | | | D |
| 39A | $C_{20}H_{24}F_3N_3O_2$ | 395.43 | 95% | 396 $(M+H)^+$ | 116-118 | CHN | E |
| 39B | $C_{20}H_{24}F_3N_3O_2$ | 395.43 | 99% | 396 $(M+H)^+$ | 116-118 | CHN | E |

Synthetic procedures:

**Method A** (General procedure for high throughput amide synthesis):

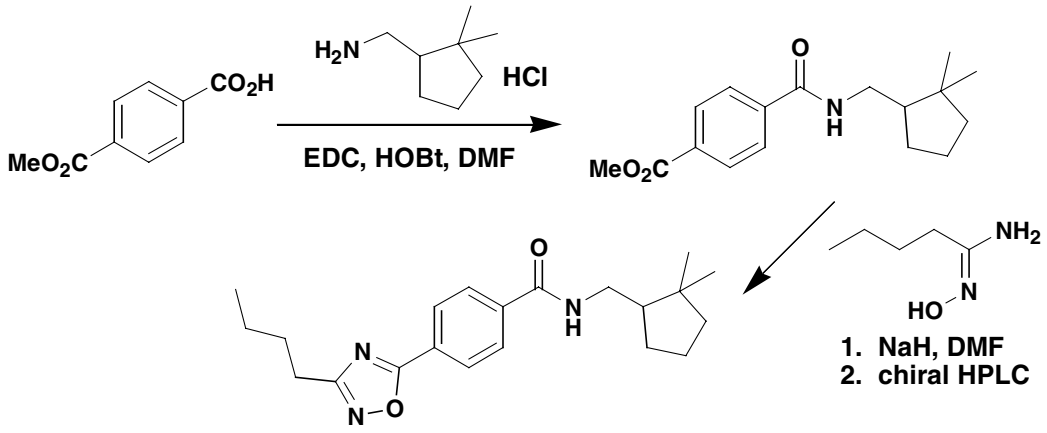
The amine(1.0 eq) was dissolved in dichloromethane and triethylamine (2 eq) was added. A solution of 4-(hexyloxy)benzoyl chloride (1.0 eq) was added and the reaction was allowed to stand overnight. The reaction mixture was purified by either SCX resin cartridge, silica gel chromatography or preparative reverse phase HPLC.

**Method B** (General procedure for high throughput amide synthesis):

The acid (1.0 eq.) was dissolved in dichloromethane and a solution of 3,3-dimethyl butyl amine (1.1 eq.) was added. A solution of dimethylaminopyridine (0.1 eg) in diclorormethane was added followed by addition of a solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide

hydrochloride (1.1 eq). The reaction was allowed to stand overnight. The reaction was purified by either SCX resin cartridge, silica gel chromatography or preparative reverse phase HPLC.

**Method C** (The procedure for the preparation of (S)-4-(3-Butyl-1,2,4-oxadiazol-5-yl)-N-[(2,2-dimethylcyclopentyl) methyl]benzamide (**33S**) and (R)-4-(3-Butyl-1,2,4-oxadiazol-5-yl)-N-[(2,2-dimethylcyclopentyl)methyl]benzamide (**33R**) is exemplary for the preparation of compounds **31**-**37**):




A. Preparation of 4-(methoxycarbonyl)-N-[(2,2-dimethylcyclopentyl)methyl]benzamide:

A solution of *mono*-methylterephthalate (180 mg, 1.0 mmol) in 4 mL of dimethylformamide under argon at room temperature was treated with 2,2-dimethylcyclopentylmethylamine hydrochloride (163 mg, 1.0 mmol), ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (297 mg, 1.0 mmol) and hydroxybenzotriazole monohydrate (135 mg, 1.0

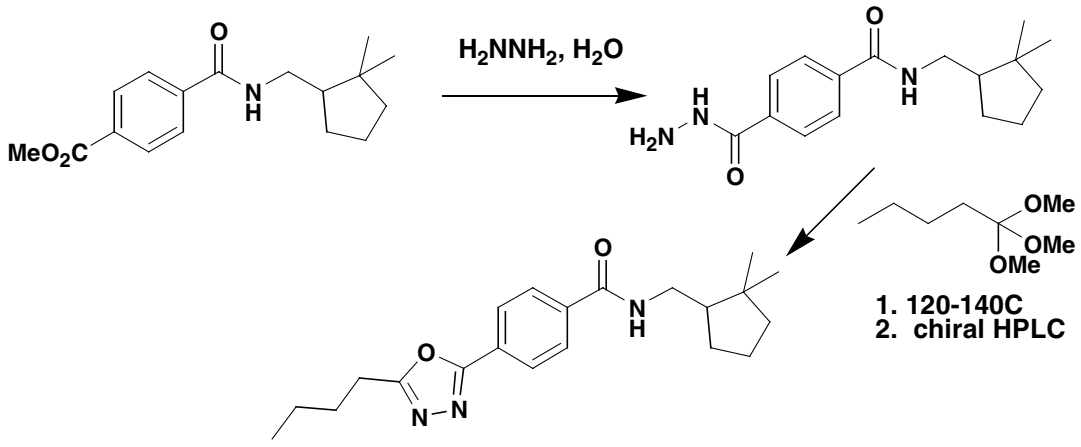
mmol). After stirring overnight, the reaction mixture was diluted with ethyl acetate and washed with 10% citric acid, water and brine. The dried ($MgSO_4$) organic fraction was concentrated, and the residue was flash chromatographed on 100 mL of EM-60 silica gel, eluting with ethyl acetate/hexanes (1:4) to give 282 mg (97 %) of product. mp 80-81 °C; $^1$H-NMR ($CDCl_3$) δ 8.08 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 6.16 (br s, 1H), 3.94 (s, 3H), 3.50-3.65 (m, 1H), 3.18-3.35 (m, 1H), 1,85-2.03 (m, 1H), 1.56-1.85 (m, 2H), 1.37-1.56 (m, 4H), 1.09 (s, 3H), 0.88 (s, 3H); $^{13}$H NMR ($CDCl_3$) δ 174.0, 173.9, 173.8, 166.6, 166.3, 138.8, 132.6, 129.8, 126.9, 52.4, 49.2, 42.1, 41.7, 40.6, 29.4, 28.6, 22.0, 21.3 (some peaks doubled); MS (ESI) *m/z* 290 ($MH^+$).

B. Preparation of (S)-4-(3-butyl-1,2,4-oxadiazol-5-yl)-N-[(2,2-dimethylcyclopentyl) methyl]benzamide (**33S**) and (R)-4-(3-Butyl-1,2,4-oxadiazol-5-yl)-N-[(2,2-dimethylcyclopentyl)methyl]benzamide (**33R**):

A solution of 4-(Methoxycarbonyl)-N-[(2,2-dimethylcyclopentyl)methyl]benzamide (56 mg, 0.20 mmol) and N-hydroxypentamidine (30 mg, 0.25 mmol) in 0.75 mL of dimethylformamide under argon at 0-5 °C was treated with sodium hydride (18 mg, 60 % in oil., 0.44 mmol) and allowed to stir at room temperature for 3 h. The mixture was diluted with ethyl acetate then washed with water and brine. The organic fraction was dried ($MgSO_4$) and concentrated *in vacuo* to give 74 mg of a solid. Chiral chromatography on a 50x500 mm Chiralpak AD column, eluted with 10% 2-propanol, hexane at 50 mL/min. gave individual enantiomers, each >99 % optically pure. (mp, MS, NMR of individual enantiomers are identical) mp 74-76 °C; $^1$H NMR ($CDCl_3$) δ8.18 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 6.21 (br s, 1H), 3.51-3.65

(m, 1H), 3.20-3.36 (m, 1H), 2.82 (t, J = 7.6 Hz, 2H), 1.86-2.04 (m, 1H), 1.56-1.86 (m, 5H), 1.35-1.56 (m, 5H), 1.10 (s, 3H), 0.97 (t, J = 7.3 Hz, 3H), 0.89 (s, 3H). $^{13}$H NMR ($CDCl_3$) δ 174.9, 172.0, 166.8, 138.9, 128.7, 128.0, 127.1, 49.6, 42.5, 42.2, 41.0, 29.9, 29.6, 29.0, 26.3, 22.7, 22.5, 21.8, 14.1; MS (ESI) *m/z* 356 ($MH^+$); (S)-4-(3-Butyl-1,2,4-oxadiazol-5-yl)-N-[(2,2-dimethylcyclopentyl) methyl]benzamide (**33S**), 30.7 mg, 43 %, $[\alpha]_D$ = +17.3° (c 0.11, $CHCl_3$); Anal. Calc'd. for $C_{21}H_{29}N_3O_2 \bullet 0.3C_6H_{14}$: C, 71.81; H, 8.78, N, 11.02. Found: C, 71.85; H, 8.69; N, 11.09. (R)-4-(3-Butyl-1,2,4-oxadiazol-5-yl)-N-[(2,2-dimethylcyclopentyl)methyl]-benzamide (**33R**), 30.9 mg, 43 %, $[\alpha]_D$ = -20.0° (c 0.12, $CHCl_3$); Anal. Calc'd for $C_{21}H_{29}N_3O_2$: C, 70.96; H, 8.22, N, 11.82. Found: C, 70.71; H, 8.28; N, 11.69.

**Method D** (Synthesis of 4-(5-butyl-1,3,4-oxadiazol-2-yl)-N-[(2,2-dimethylcyclopentyl)methyl]-benzamide, **38A** and **38B**).



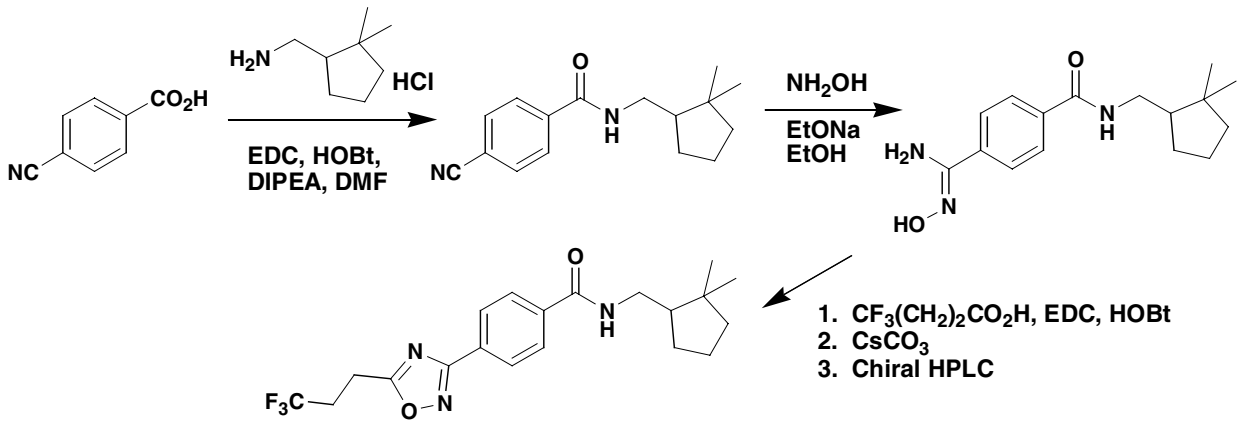

A. Preparation of 4-(hydrazinocarbonyl)-N-[(2,2-dimethylcyclopentyl)methyl]benz-amide:

The 4-(methoxycarbonyl)-N-[(2,2-dimethylcyclopentyl)methyl]benz-amide (275 mg) was treated with hydrazine monohydrate and heated at 120°C for 2 hours. The reaction mixture was diluted with water, saturated with potassium carbonate and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give the title compound (270 mg) as a white solid which was used in the next reaction without isolation.

B. Preparation of 4-(5-butyl-1,3,4-oxadiazol-2-yl)-N-[(2,2-dimethylcyclopentyl)methyl]-benzamide (**38A** and **38B**)

The 4-(hydrazinocarbonyl)-N-[(2,2-dimethylcyclopentyl)methyl]benzamide (270 mg) was dissolved in trimethyl orthovalerate (3 mL), heated at 120°C for 2 hours. The excess trimethyl orthovaerate was removed by purging with a stream of nitrogen at 140°C. The residue was heated at 140°C for 1.5 hours, diluted with dichloromethane, washed with 10% potassium carbonate and the organic layer was dried (magnesium sulfate) and concentrated. The crude product was subjected sequentiallty to flash chromatography (silica gel/hexane-EtOAc 1:1) and chiral preparative HPLC (Chirapak AD column/hexane-isopropanol-triethylamine 80:20:0.2) to give the two enantiomers: (+)-enantiomer A (104 mg, $[\alpha]_D$ = +22° C = 0.36, dichloromethane; m/e 355) and the (-)-enantiomer B (100 mg, $[\alpha]_D$ = -19.5° C = 0.36, dichloromethane; m/e 355) as white solids.

**Method E** (Preparation of N-[(2,2-dimethylcyclopentyl)methyl]-4-[5-(3,3,3-trifluoropropyl)-1,2,4-oxadiazole-3-yl]benzamide **39A** and **39B**):




A. Preparation of 4-(cyano)-N-[(2,2-dimethylcyclopentyl)methyl] benzamide:

A mixture of 4-cyanobenzoic acid (1.47 g, 10.0 mmol), 2,2-dimethylcyclopentylmethylamine hydrochloride (1.64 mg, 10.0 mmol), ethyl-3-(3-dimethylamino)-propyl carbodiimide hydrochloride (2.97 g, 10.0 mmol) and hydroxybenzotriazole monohydrate (1.35 g, 10.0 mmol) in 20 nmL of dimethyl formamide under argon at 0-5° C was treated with diisopropylethylamine (1.8 mL, 1.33g, 10.3 mmol). After 10 min the ice bath was removed and the reaction was stirred for 16 hr at room temperature. The reaction mixture was diluted with ethyl acetate and washed with 10 percent citric acid, water and brine. The dried ($MgSO_4$) organic fraction was concentrated to give 2.5 g of a white solid. Crystallization from ethyl acetate/hexane gave 2.07 g of product, mp 156-158.5° C. Additional product was obtained from the mother liquors by flash chromatography on silica gel (20%ethylacetate, hexane) for a total of 2.44 g (93 %). MS (ESI) *m/z* 257 ($MH^+$); Anal. Calc'd. for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86, N, 10.93. Found: C, 74.87; H, 7.99; N, 10.79.

B. Preparation of 4-amino(hydroxyimino)methyl]-N-[2,2-dimethylcyclopentyl)-methyl]benzamide:

To freshly prepared sodium ethoxide in ethanol (from 36 mg,1.56 mgatom sodium metal in 3 mL of absolute ethanol) were added hydroxylamine hydrochloride (102 mg, 1.47 mmol) and two drops of water, followed by 4-(cyano)-N-[(2,2-dimethylcyclopentyl)methyl] benzamide (378 mg, 1.47 mmol). After stirring for two days at room temperature, the mixture was cooled in an ice bath, and the solids were filtered and washed with a small amount of cold ethanol. The combined filtrate and washings were concentrated and the residue redissolved in ethanol, cooled in an ice bath, and the solids filtered and washed with a small amount of cold ethanol. The combined filtrate and washings were concentrated *in vacuo* to give 430 mg (100%) of a white solid. mp 70-85°; MS (ESI) *m/z* 288 ($M-H^-$); $^1$H NMR ($CDCl_3$) δ 7.54 (d, J = 5.9 Hz, 2H), 7.41 (d, J = 5.9 Hz, 2H), 6.55-6.75 (br s, 1H), 5.05-5.35 (br s, 2H), 3.30-3.50 (m, 1H), 3.05-3.25 (m, 1H), 1,25-1.90 (m, 7H), 0.98 (s, 3H), 0.78 (s, 3H); $^{13}$H NMR ($CDCl_3$) δ 167.3, 152.7, 136.3, 134.6, 127.3, 126.2, 77.3, 49.1, 42.2, 41.8, 40.6, 29.5, 28.6, 22.1, 21.4.

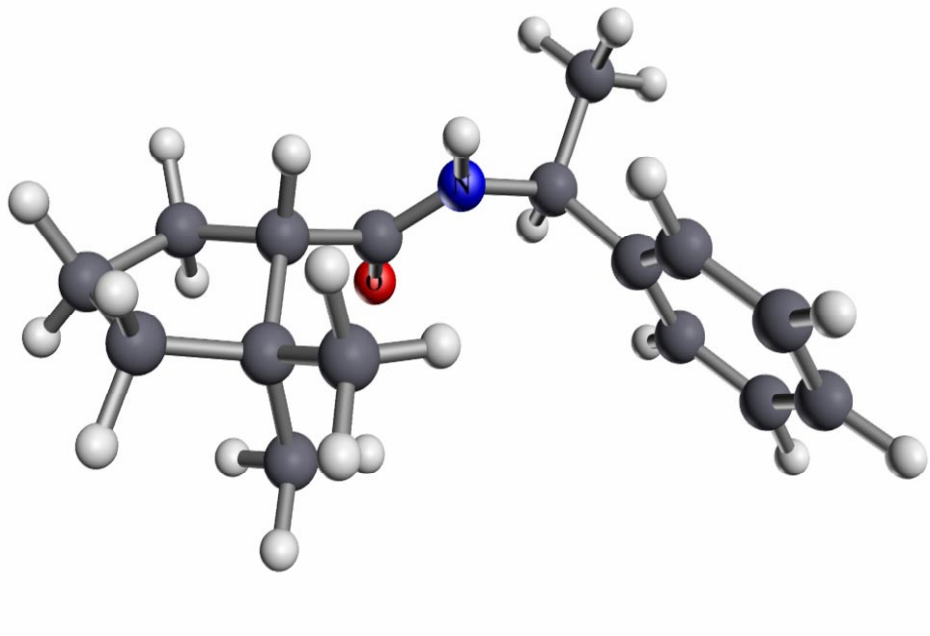
C. Preparation of (S)-N-[(2,2-dimethylcyclopentyl)methyl]-4-[5-(3,3,3-trifluoropropyl)-1,2,4-oxadiazole-3-yl]benzamide (**39A** and **39B**):

A solution of (4-N-hydroxyamidinyl) 2,2-dimethylcyclopentylmethyl benzamide (289 mg, 1.0 mmol) and ethyl 4,4,4-trifluorobutyrate (200 mg, 1.17 mmol) in 3 mL of dimethylformamide under argon at room temperature was treated with sodium hydride (50 mg, 60 % in mineral oil., 1.25 mmol). After stirring for 16 hr, the reaction mixture was diluted with ethyl acetate

and washed with water and brine, dried ($MgSO_4$) and concentrated to give 250 mg. Flash chromatography on silica gel, eluting with 20% ethyl acetate, hexane gave 220 mg of racemic product. Chiral chromatography on 50x500 mm Chirapak AD column, eluting with 15% 2-popanol, hexane at 50 ml/minute gave individual enantiomers, each >99 % optically pure. (mp, m/s, NMR of individual enantiomers are identical) mp 116-118°; MS (ESI) *m/z* 396 ($MH^+$); $^1$H NMR ($CDCl_3$) δ 8.13 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 6.13 (br s, 1H), 3.50-3.65 (m, 1H), 3.15-3.35 (m, 3H), 2.65-2.85 (m, 2H), 1.95-2.00 (m, 1H), 1.35-1.80 (m, 6H), 1.10 (s, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.89 (s, 3H). $^{13}$C NMR ($CDCl_3$) δ 178.1, 168.9, 167.6, 138.4, 128.6, 128.4, 77.0, 50.2, 43.1, 42.7, 41.5, 31.6, 30.4, 29.6, 23.0, 22.3, 22.1, 21.0. (**39A**) 88.7 mg (22.4 %); $[\alpha]_D$ = +16.8° (c = 0.88, $CHCl_3$); Anal. Calc'd. for $C_{20}H_{24}F_3N_3O_2$: C, 60.75; H, 6.12, N, 10.63; F, 14.41. Found: C, 60.57; H, 6.22; N, 10.48; F, 14.02. (**39B**) 86.2 mg (21.8 %); $[\alpha]_D$ = -16.9° (c = 0.96, $CHCl_3$); Anal. Calc'd. for $C_{20}H_{24}F_3N_3O_2$: C, 60.75; H, 6.12, N, 10.63; F, 14.41. Found: C, 60.87; H, 6.21; N, 10.45; F, 14.10.

Crystallographic data and details of refinement:

Compound **51**:



| | |
|---|---|
| Temperature, °C | -30 |
| Solvent | $CCl_4$/hexanes |
| a, angstrom | 6.901(1) |
| b, angstrom | 9.827(2) |
| c, angstrom | 21.699(5) |
| V, angstrom $^3$ | 1471.5(9) |
| Space Group | $P2_12_12_1$ |
| $d_{obs,}$ g-cm$^{-3}$ | 1.08 (@ 22°C) |
| $d_{calc}$, g-cm$^{-3}$ | 1.107 (@ -30°C) |
| Formula | $C_{16}H_{23}NO$ |
| Fw | 245.37 |
| Z | 4 |
| Habit | colorless rods |

| | |
|---|---|
| m, $cm^{-1}$ | 5.0 |
| Instrument | CAD4/Rigaku Rotating Anode |
| λ, Angstrom | 1.5418 |
| 2θmax, ° | 140 |
| $N_{ref}$[a] | 1660 |
| $N_{uni}$[b] | 1660 |
| $N_{obs}$[c] | 1460 |
| $N_{var}$[d] | 164 |
| ERRWT[e] | 2.14 |
| R | 0.042 |
| $R_w$ | 0.059 |
| $R_{enatiomer}$ | 0.042 |
| $R_{w\ enatiomer}$ | 0.059 |

[a]Total number of measured reflections within (2q)max. [b]Total number of symmetry-independent measured reflections. [c]Total number of "observed" reflections with $I \geq 3s(I)$ used in least-squares refinement. [d]Number of variables in least-squares refinements. [e]Error in an observation of unit weight.

Table of Positional Parameters and Their Estimated Standard Deviations for **51** at -30°C.

| Atom | x | y | z | B(A2) |
|---|---|---|---|---|
| O1 | 0.0456(3) | 0.9565(2) | 0.71764(7) | 3.93(4) |
| C1 | 0.1273(4) | 0.7491(2) | 0.66443(9) | 2.85(4) |

| | | | | |
|---|---|---|---|---|
| C2 | 0.3519(4) | 0.7340(2) | 0.6616(1) | 3.49(5) |
| C3 | 0.3751(6) | 0.6823(4) | 0.5953(1) | 6.53(8) |
| C4 | 0.2213(6) | 0.7503(4) | 0.5568(1) | 7.07(9) |
| C5 | 0.0716(5) | 0.8082(3) | 0.6013(1) | 4.50(6) |
| C6 | 0.0552(4) | 0.8306(2) | 0.71876(9) | 2.62(4) |
| N7 | 0.0083(3) | 0.7571(2) | 0.76859(7) | 2.87(3) |
| C8 | -0.0442(4) | 0.8179(2) | 0.82766(9) | 2.76(4) |
| C9 | -0.2350(4) | 0.7583(3) | 0.8507(1) | 3.89(5) |
| C10 | 0.1144(3) | 0.8000(2) | 0.87535(9) | 2.62(4) |
| C11 | 0.1784(4) | 0.9097(2) | 0.9101(1) | 3.70(5) |
| C12 | 0.3138(4) | 0.8924(3) | 0.9567(1) | 4.46(6) |
| C13 | 0.3865(4) | 0.7667(3) | 0.9694(1) | 4.25(6) |
| C14 | 0.3275(4) | 0.6558(3) | 0.9343(1) | 4.23(5) |
| C15 | 0.1927(4) | 0.6723(2) | 0.8875(1) | 3.29(4) |
| C16 | 0.4272(5) | 0.6275(3) | 0.7070(1) | 4.96(6) |
| C17 | 0.4565(5) | 0.8672(3) | 0.6727(2) | 6.85(9) |
| H11 | 0.058 | 0.651 | 0.671 | 3.7* |
| H31 | 0.519 | 0.719 | 0.578 | 7.8* |
| H32 | 0.374 | 0.575 | 0.593 | 7.8* |
| H41 | 0.272 | 0.825 | 0.526 | 7.8* |
| H42 | 0.146 | 0.669 | 0.529 | 7.8* |
| H51 | -0.076 | 0.781 | 0.589 | 5.3* |
| H52 | 0.083 | 0.919 | 0.602 | 5.3* |
| H71 | 0.012 | 0.654 | 0.765 | 3.7* |
| H81 | -0.060 | 0.926 | 0.821 | 3.5* |
| H91 | -0.274 | 0.806 | 0.894 | 4.9* |
| H92 | -0.350 | 0.779 | 0.818 | 4.9* |
| H93 | -0.222 | 0.651 | 0.858 | 4.9* |
| H111 | 0.120 | 1.010 | 0.900 | 4.6* |
| H121 | 0.363 | 0.982 | 0.983 | 5.5* |
| H131 | 0.487 | 0.754 | 1.008 | 5.1* |
| H141 | 0.389 | 0.556 | 0.943 | 5.3* |

| | | | | |
|---|---|---|---|---|
| H151 | 0.144 | 0.585 | 0.860 | 4.1* |
| H161 | 0.581 | 0.621 | 0.704 | 5.7* |
| H162 | 0.385 | 0.656 | 0.753 | 5.7* |
| H163 | 0.362 | 0.530 | 0.696 | 5.7* |
| H171 | 0.610 | 0.855 | 0.670 | 7.4* |
| H172 | 0.412 | 0.940 | 0.635 | 7.4* |
| H173 | 0.415 | 0.912 | 0.716 | 7.4* |

Starred atoms were refined isotropically. Parameters without errors were not refined. Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as:(4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)]

Table of General Displacement Parameter Expressions - U's

| Name | U(1,1) | U(2,2) | U(3,3) | U(1,2) | U(1,3) | U(2,3) |
|---|---|---|---|---|---|---|
| O1 | 0.080(1) | 0.0262(7) | 0.0436(8) | 0.0045(9) | 0.0127(9) | 0.0038(7) |
| C1 | 0.048(1) | 0.0301(9) | 0.0305(9) | 0.001(1) | -0.0021(9) | -0.0006(9) |
| C2 | 0.047(1) | 0.040(1) | 0.046(1) | 0.007(1) | 0.003(1) | -0.001(1) |
| C3 | 0.097(2) | 0.101(2) | 0.051(1) | 0.043(2) | 0.015(2) | -0.003(2) |
| C4 | 0.123(3) | 0.109(2) | 0.036(1) | 0.048(2) | 0.014(2) | 0.007(2) |
| C5 | 0.079(2) | 0.061(1) | 0.030(1) | 0.022(2) | -0.003(1) | 0.003(1) |
| C6 | 0.042(1) | 0.0274(9) | 0.0298(8) | 0.002(1) | -0.0021(9) | 0.0020(8) |
| N7 | 0.056(1) | 0.0260(8) | 0.0274(7) | 0.0015(9) | -0.0003(8) | -0.0008(7) |
| C8 | 0.047(1) | 0.0294(9) | 0.0286(9) | 0.004(1) | 0.001(1) | -0.0020(8) |
| C9 | 0.039(1) | 0.060(1) | 0.050(1) | -0.001(1) | 0.000(1) | 0.001(1) |
| C10 | 0.037(1) | 0.034(1) | 0.0281(9) | -0.0028(9) | 0.0040(9) | 0.0024(9) |
| C11 | 0.061(1) | 0.037(1) | 0.042(1) | -0.010(1) | -0.002(1) | -0.001(1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C12 | 0.059(1) | 0.066(2) | 0.044(1) | -0.022(1) | -0.006(1) | -0.005(1) |
| C13 | 0.036(1) | 0.088(2) | 0.037(1) | -0.001(1) | -0.000(1) | 0.003(1) |
| C14 | 0.050(1) | 0.065(1) | 0.046(1) | 0.022(1) | -0.002(1) | 0.001(1) |
| C15 | 0.047(1) | 0.042(1) | 0.036(1) | 0.010(1) | -0.001(1) | -0.002(1) |
| C16 | 0.055(1) | 0.060(2) | 0.074(2) | 0.010(1) | -0.014(1) | 0.010(1) |
| C17 | 0.055(2) | 0.053(2) | 0.152(3) | -0.012(2) | 0.020(2) | -0.000(2) |

The form of the anisotropic displacement parameter is: exp [-2PI2{h2a2U(1,1) + k2b2U(2,2) + l2c2U(3,3) + 2hkabU(1,2) + 2hlacU(1,3) + 2klbcU(2,3)}] where a,b, and c are reciprocal lattice constants.

Table of Bond Distances in Angstroms

| Atom 1 | Atom 2 | Distance | Atom 1 | Atom 2 | Distance |
|---|---|---|---|---|---|
| O1 | C6 | 1.239(3) | N7 | C8 | 1.460(3) |
| C1 | C2 | 1.558(4) | C8 | C9 | 1.525(3) |
| C1 | C5 | 1.536(3) | C8 | C10 | 1.516(3) |
| C1 | C6 | 1.510(3) | C10 | C11 | 1.387(3) |
| C2 | C3 | 1.534(4) | C10 | C15 | 1.392(3) |
| C2 | C16 | 1.527(4) | C11 | C12 | 1.387(4) |
| C2 | C17 | 1.514(4) | C12 | C13 | 1.362(4) |
| C3 | C4 | 1.507(5) | C13 | C14 | 1.391(4) |
| C4 | C5 | 1.525(5) | C14 | C15 | 1.387(4) |
| C6 | N7 | 1.340(3) | | | |

Table of Bond Angles in Degrees

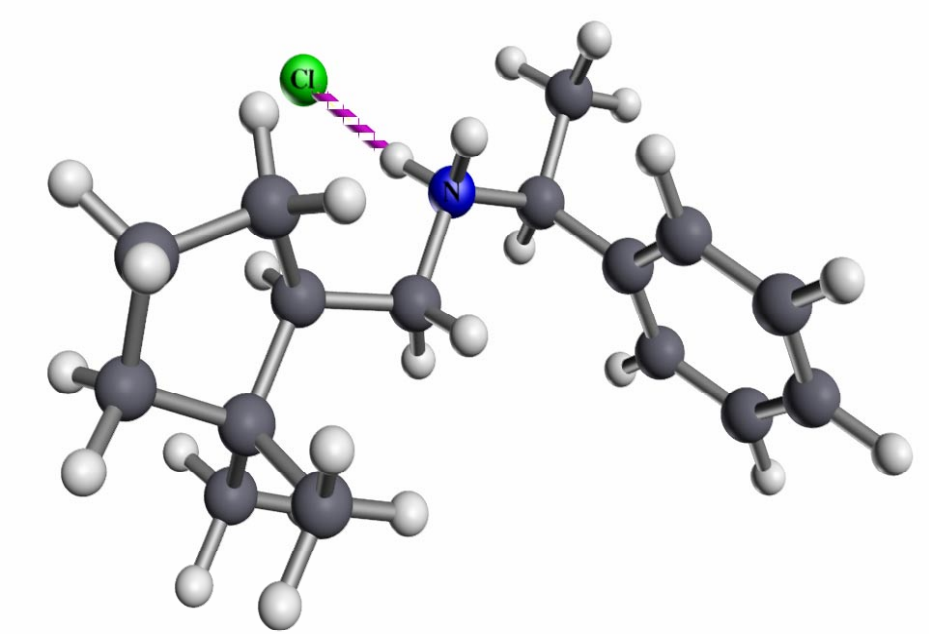
| Atom 1 | Atom 2 | Atom 3 | Angle | Atom 1 | Atom 2 | Atom 3 | Angle |
|---|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| C2 | C1 | C5 | 104.5(2) | C1 | C6 | N7 |
| 115.1(2) | | | | | | |
| C2 | C1 | C6 | 114.1(2) | C6 | N7 | C8 |
| 123.2(2) | | | | | | |
| C5 | C1 | C6 | 114.4(2) | N7 | C8 | C9 |
| 110.2(2) | | | | | | |
| C1 | C2 | C3 | 99.9(2) | N7 | C8 | C10 |
| 111.9(2) | | | | | | |
| C1 | C2 | C16 | 112.2(2) | C9 | C8 | C10 |
| 110.8(2) | | | | | | |
| C1 | C2 | C17 | 112.7(2) | C8 | C10 | C11 |
| 120.7(2) | | | | | | |
| C3 | C2 | C16 | 110.0(2) | C8 | C10 | C15 |
| 120.9(2) | | | | | | |
| C3 | C2 | C17 | 112.7(3) | C11 | C10 | C15 |
| 118.3(2) | | | | | | |
| C16 | C2 | C17 | 109.1(2) | C10 | C11 | C12 |
| 121.1(2) | | | | | | |
| C2 | C3 | C4 | 107.4(3) | C11 | C12 | C13 |
| 120.5(3) | | | | | | |
| C3 | C4 | C5 | 106.9(2) | C12 | C13 | C14 |
| 119.4(2) | | | | | | |
| C1 | C5 | C4 | 104.7(2) | C13 | C14 | C15 |
| 120.4(3) | | | | | | |
| O1 | C6 | C1 | 122.1(2) | C10 | C15 | C14 |
| 120.3(2) | | | | | | |
| O1 | C6 | N7 | 122.7(2) | | | |

Numbers in parentheses are estimated standard deviations in the least significant digits.

Orthorhombic crystals from carbontetrachloride and hexanes. a= 6.901(1), b= 9.827(2), c=21.699(5) angstrom; space group= $P2_12_12_1$, Z=4; $d_{calc}$=1.107 g-cm$^{-3}$(@-30 °C), $d_{obs}$=1.08 g-cm$^{-3}$(@22 °C). R= 0.042 for 1460 observed intensities ($I \geq 3s(I)$).

Amine hydrochloride from LAH reduction of compound **52:**




Crystallographic Data and Details of Refinement at -28˚C.

| | |
|---|---|
| Temperature, ˚C | -28 |
| Solvent | Methanol |
| a, Å | 7.217(1) |
| b, Å | 11.757(2) |
| c, Å | 18.607(2) |
| V, Å$^3$ | 1578.8(7) |

| | |
|---|---|
| Space Group | $P2_12_12_1$ |
| dobs, g-cm$^{-3}$ | 1.116 (@ 22˚C) |
| dcalc, g-cm$^{-3}$ | 1.127 (@ -28˚C) |
| Formula | $C_{16}H_{27}N^+ \bullet Cl^-$ |
| fw | 267.85 |
| Z | 4 |
| Habit | colorless rods |
| μ, cm-1 | 20.2 |
| Instrument | CAD4/sealed x-ray tube |
| λ, Å | 1.5418 |
| 2θmax, ˚ | 140 |
| Nref[a] | 1739 |
| Nuni[b] | 1739 |
| Nobs[c] | 1635 |
| Nvar[d] | 164 |
| ERRWT[e] | 2.34 |
| R | .040 |
| $R_w$ | .059 |
| $R_{enatiomer}$ | .052 |
| $R_{w\ enatiomer}$ | .077 |

[a]Total number of measured reflections within (2θ)max. [b]Total number of symmetry-independent measured reflections. [c]Total number of "observed" reflections with $I \geq 3\sigma(I)$ used in

least-squares refinement. [d]Number of variables in least-squares refinements. [e]Error in an observation of unit weight.

Table of Positional Parameters and Their Estimated Standard Deviations at -28°C.

| Atom | x | y | z | B(A2) |
|---|---|---|---|---|
| Cl1 | 0.98077(9) | 0.87984(5) | 0.49146(4) | 3.50(1) |
| C1 | 0.9660(4) | 0.6158(2) | 0.3598(1) | 2.67(4) |
| C2 | 1.0505(4) | 0.5573(2) | 0.2928(1) | 2.74(4) |
| C3 | 0.9490(4) | 0.6198(3) | 0.2319(1) | 3.54(5) |
| C4 | 0.7517(5) | 0.6420(4) | 0.2593(2) | 4.91(8) |
| C5 | 0.7605(5) | 0.6300(4) | 0.3414(2) | 5.04(7) |
| C6 | 1.0029(4) | 0.5536(2) | 0.4299(1) | 2.89(5) |
| N7 | 0.9203(3) | 0.6139(2) | 0.4927(1) | 2.62(4) |
| C8 | 0.9949(4) | 0.5742(2) | 0.5645(1) | 2.84(4) |
| C9 | 0.8930(4) | 0.6363(3) | 0.6246(1) | 3.56(5) |
| C10 | 0.9835(4) | 0.4458(2) | 0.5717(1) | 3.00(5) |
| C11 | 1.1455(5) | 0.3862(3) | 0.5881(2) | 4.17(6) |
| C12 | 1.1354(7) | 0.2680(3) | 0.5972(2) | 5.63(8) |
| C13 | 0.9705(8) | 0.2109(3) | 0.5881(2) | 5.84(9) |
| C14 | 0.8132(6) | 0.2699(3) | 0.5714(2) | 4.68(7) |
| C15 | 0.8180(4) | 0.3879(3) | 0.5632(1) | 3.51(5) |
| C16 | 1.2587(5) | 0.5726(4) | 0.2879(2) | 5.03(8) |
| C17 | 1.0022(7) | 0.4311(2) | 0.2896(2) | 4.99(8) |
| H11 | 1.034 | 0.697 | 0.369 | 3.7* |
| H31 | 1.020 | 0.698 | 0.219 | 4.6* |
| H32 | 0.946 | 0.567 | 0.184 | 4.6* |
| H41 | 0.707 | 0.728 | 0.244 | 6.2* |
| H42 | 0.654 | 0.582 | 0.237 | 6.2* |
| H51 | 0.681 | 0.560 | 0.360 | 6.5* |

| | | | | |
|---|---|---|---|---|
| H52 | 0.708 | 0.708 | 0.368 | 6.5* |
| H61 | 0.944 | 0.469 | 0.427 | 3.8* |
| H62 | 1.151 | 0.547 | 0.438 | 3.8* |
| H71 | 0.947 | 0.697 | 0.488 | 3.6* |
| H72 | 0.783 | 0.602 | 0.492 | 4.0* |
| H81 | 1.141 | 0.593 | 0.569 | 3.8* |
| H91 | 0.946 | 0.607 | 0.676 | 4.4* |
| H92 | 0.914 | 0.726 | 0.619 | 4.4* |
| H93 | 0.747 | 0.617 | 0.621 | 4.4* |
| H111 | 1.275 | 0.431 | 0.593 | 5.4* |
| H121 | 1.261 | 0.222 | 0.611 | 7.2* |
| H141 | 0.679 | 0.224 | 0.563 | 6.1* |
| H151 | 0.693 | 0.436 | 0.550 | 4.6* |
| H161 | 1.311 | 0.529 | 0.239 | 6.4* |
| H162 | 1.296 | 0.661 | 0.284 | 6.4* |
| H163 | 1.327 | 0.535 | 0.334 | 6.4* |
| H171 | 1.059 | 0.393 | 0.242 | 6.1* |
| H172 | 1.052 | 0.388 | 0.337 | 6.1* |
| H173 | 0.850 | 0.422 | 0.288 | 6.1* |

Starred atoms were refined isotropically. Parameters without errors were not refined. Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: (4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac(cos beta)*B(1,3) + bc(cos alpha)*B(2,3)]

Table of General Displacement Parameter Expressions - U's

| Name | U(1,1) | U(2,2) | U(3,3) | U(1,2) | U(1,3) | U(2,3) |
|---|---|---|---|---|---|---|
| ---- | ------ | ------ | ------ | ------ | ------ | ------ |
| Cl1 | 0.0340(3) | 0.0394(3) | 0.0596(3) | -0.0009(3) | -0.0048(3) | 0.0025(3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C1 | 0.036(1) | 0.033(1) | 0.032(1) | 0.001(1) | 0.003(1) | 0.002(1) |
| C2 | 0.036(1) | 0.034(1) | 0.033(1) | 0.001(1) | 0.002(1) | -0.000(1) |
| C3 | 0.049(1) | 0.052(1) | 0.034(1) | 0.009(1) | 0.004(1) | 0.007(1) |
| C4 | 0.048(2) | 0.097(3) | 0.041(1) | 0.017(2) | -0.002(1) | 0.011(2) |
| C5 | 0.042(1) | 0.105(2) | 0.044(1) | 0.025(2) | 0.004(1) | 0.011(2) |
| C6 | 0.041(1) | 0.039(1) | 0.030(1) | 0.006(1) | 0.001(1) | -0.0003(9) |
| N7 | 0.0302(9) | 0.035(1) | 0.0345(9) | -0.0008(8) | 0.0025(8) | 0.0001(9) |
| C8 | 0.039(1) | 0.039(1) | 0.030(1) | -0.000(1) | -0.000(1) | -0.0022(9) |
| C9 | 0.051(2) | 0.048(1) | 0.037(1) | -0.001(1) | 0.006(1) | -0.009(1) |
| C10 | 0.048(1) | 0.041(1) | 0.025(1) | 0.005(1) | 0.000(1) | 0.0013(9) |
| C11 | 0.054(2) | 0.061(2) | 0.043(1) | 0.017(2) | -0.003(1) | 0.004(1) |
| C12 | 0.091(3) | 0.058(2) | 0.065(2) | 0.031(2) | 0.002(2) | 0.011(2) |
| C13 | 0.127(3) | 0.041(1) | 0.053(2) | 0.009(2) | 0.016(2) | 0.010(1) |
| C14 | 0.085(2) | 0.046(2) | 0.047(1) | -0.010(2) | 0.008(2) | 0.006(1) |
| C15 | 0.051(2) | 0.041(1) | 0.041(1) | -0.006(1) | 0.003(1) | 0.005(1) |
| C16 | 0.038(1) | 0.107(3) | 0.046(1) | 0.005(2) | 0.007(1) | -0.009(2) |
| C17 | 0.106(3) | 0.037(1) | 0.046(1) | 0.002(2) | 0.002(2) | -0.004(1) |

The form of the anisotropic displacement parameter is: exp [-2PI2{h2a2U(1,1) + k2b2U(2,2) + l2c2U(3,3) + 2hkabU(1,2) + 2hlacU(1,3) + 2klbcU(2,3)}] where a,b, and c are reciprocal lattice constants.

Table of Bond Distances in Angstroms

| Atom 1 | Atom 2 | Distance | Atom 1 | Atom 2 | Distance |
|---|---|---|---|---|---|
| C1 | C2 | 1.548(3) | N7 | C8 | 1.513(3) |
| C1 | C5 | 1.531(4) | C8 | C9 | 1.524(4) |
| C1 | C6 | 1.519(3) | C8 | C10 | 1.518(4) |
| C2 | C3 | 1.536(4) | C10 | C11 | 1.397(5) |
| C2 | C16 | 1.516(4) | C10 | C15 | 1.384(4) |

| | | | | | |
|---|---|---|---|---|---|
| C2 | C17 | 1.526(4) | C11 | C12 | 1.401(5) |
| C3 | C4 | 1.535(5) | C12 | C13 | 1.377(7) |
| C4 | C5 | 1.535(4) | C13 | C14 | 1.367(7) |
| C6 | N7 | 1.491(3) | C14 | C15 | 1.395(4) |

Table of Bond Angles in Degrees

| Atom 1 | Atom 2 | Atom 3 | Angle | Atom 1 | Atom 2 | Atom 3 | Angle |
|---|---|---|---|---|---|---|---|
| C2 | C1 | C5 | 104.5(2) | C6 | N7 | C8 | 113.8(2) |
| C2 | C1 | C6 | 114.1(2) | N7 | C8 | C9 | 109.2(2) |
| C5 | C1 | C6 | 114.4(2) | N7 | C8 | C10 | 111.4(2) |
| C1 | C2 | C3 | 101.2(2) | C9 | C8 | C10 | 112.7(2) |
| C1 | C2 | C16 | 112.8(2) | C8 | C10 | C11 | 118.3(3) |
| C1 | C2 | C17 | 111.9(2) | C8 | C10 | C15 | 121.7(3) |
| C3 | C2 | C16 | 111.8(2) | C11 | C10 | C15 | 120.0(3) |
| C3 | C2 | C17 | 109.1(2) | C10 | C11 | C12 | 118.7(3) |
| C16 | C2 | C17 | 109.8(3) | C11 | C12 | C13 | 120.9(4) |
| C2 | C3 | C4 | 106.2(2) | C12 | C13 | C14 | 119.9(3) |
| C3 | C4 | C5 | 106.0(3) | C13 | C14 | C15 | 120.6(4) |
| C1 | C5 | C4 | 105.8(2) | C10 | C15 | C14 | 119.9(3) |
| C1 | C6 | N7 | 112.0(2) | | | | |