2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone.

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone, was prepared according to the method of Example 228, starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 4-fluorophenyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 330 mg, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.47 (s, 3H), 6.90-7.03 (m, 6H), 7.22-7.31 (m, 2H), 7.49-7.54 (m, 1H), 7.60-7.68 (m, 1H), 8.02 (s, 1H). MS (APCI+) m/z 439 $(M+H)^+$.

Example 206H

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 10, substituting 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 251 mg, 82%) mp 80-100 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.59 (s, 3H), 3.25 (s, 3H), 7.13-7.34 (m, 5H), 7.45 (s, 1H), 7.52-7.69 (m, 2H), 7.81 (d, J=8.4 Hz, 1H), 7.81-7.90 (m, 1H), 8.27 (s, 1H). MS (APCI+) m/z 471 (M+H) and m/z 488 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}F_3N_2O_3S$: C, 61.27; H, 3.64; N, 5.95. Found: C, 61.53; H, 3.92; N, 5.67.

Example 207

2-(3-Chlorophenyl)-4-(4-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 207A

2-(3-Chlorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 194A, substituting 3-chlorophenyl hydrazine·HCl in place of 4-fluorophenyl hydrazine·HCl (yield: 24.8 g, 88%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53-7.57 (m, 3H), 7.67-7.70 (m, 1H), 8.29 (s, 1H). MS (DCI/NH_3) m/z 365 $(M+H)^+$ and m/z 382 $(M+NH_4+)^+$.

Example 207B

2-(3-Chlorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 194B, substituting 2-(3-chlorophenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (yield: 12.4 g, 95%) ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.21 (s, 3H), 7.58-7.62 (m, 3H), 7.73-7.76 (m, 1H), 8.28 (s, 1H). MS (DCI/NH_3) m/z 317 $(M+H)^+$ and m/z 334 $(M+NH_4+)^+$.

Example 207C

2-(3-Chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 6 starting with 2-(3-chlorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone in place of 2-benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone and substituting 4-(methylthio)benzeneboronic acid in place of 4-fluorobenzeneboronic acid (yield: 3.3 g, 68%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.54 (s, 3H), 4.03 (s, 3H), 7.40 (d, J=9.0 Hz, 2H), 7.50-7.64 (m, 5H), 7.73-7.77 (m, 1H), 8.18 (s, 1H). MS (DCI/NH_3) m/z 359 $(M+H)^+$.

Example 207D

2-(3-Chlorophenyl)-4-methyl-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone.

2-(3-Chlorophenyl)-4-(4-fluorophenyl)-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone, was prepared according to the method of Example 228, starting with 2-(3-chlorophenyl)-4-methoxy-5-[3-methyl-4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 4-fluorophenyl magnesium bromide in place of cyclohexylmagnesium

chloride (yield: 180 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.56 (s, 3H), 7.28-7.45 (m, 6H), 7.58-7.63 (m, 1H), 7.71-7.74 (m, 1H), 7.82 (s, 1H). MS (APCI+) m/z 343 $(M+H)^+$ and m/z 360 $(M+NH_4)^+$.

Example 207E

2-(3-Chlorophenyl)-4-methyl-5-[4-(methylsulfonylphenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 10, substituting 2-(3-chlorophenyl)-4-methyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone for 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 125 mg, 67%). mp 164-168. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.13 (s, 3H), 7.37-7.46 (m, 2H), 7.61 (m, 3H), 7.71-7.74 (m, 1H), 7.81 (s, 1H), 8.13 (d, J=8.7 Hz, 2H). MS (APCI+) m/z 343 $(M+H)^+$ and m/z 360 $(M+NH_4)^+$.

Example 207F

2-(3-Chlorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chlorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 194F, substituting 2-(3-chlorophenyl)-4-methyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 90 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (s, 3H), 4.33 (s, 2H), 7.40-7.47 (m, 2H), 7.66 (ddd, J=2.4, 2.4, 7.2 Hz, 1H), 7.76-7.78 (m, 1H), 7.81 (d, J=8.7 Hz, 2H), 7.86 (s, 1H), 8.17 (d, J=8.7 Hz, 2H). MS (APCI−) m/z 453 $(M+H)^+$ and m/z 470 $(M+NH_4)^+$.

Example 207G

2-(3-Chlorophenyl)-4-(4-fluorophenoxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 194G, substituting 2-(3-chlorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-bromomethyl-5-[4-(methylsulfonyl)phenyl]-

3(2H)-pyridazinone (yield: 30 mg, 31%). mp 50-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11 (s, 3H), 4.94 (s, 2H), 6.78-6.85 (m, 2H), 6.91-6.99 (m, 2H), 7.39-7.48 (m, 2H), 7.64 (ddd, J=7.5, 1.9, 1.9 Hz, 1H), 7.71-7.77 (m, 3H), 7.93 (s, 1H), 8.08 (d, J=8.7 Hz, 2H). MS (APCI+) m/z 485 $(M+H)^+$.

Example 208

2-(3-Chlorophenyl)-4-(benzoyloxymethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 207 substituting benzoic acid in place of 4-fluorophenol (yield: 33 mg, 34%). mp 50-70 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (s, 3H), 5.36 (s, 2H), 7.36-7.48 (m, 4H), 7.52-7.59 (m, 1H), 7.61-7.68 (m, 3H), 7.75-7.78 (m, 1H), 7.83-7.88 (m, 2H), 7.89 (s, 1H), 8.02 (d, J=8.7 Hz, 2H). MS (APCI+) m/z 495 $(M+H)^+$.

Example 209

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 193, substituting 1-bromo-3-methylbutane in place of 4-fluorobenzyl bromide (yield 80 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J=7.5 Hz, 6H), 1.3-1.6 (m, 3H), 2.52 (m, 2H), 3.14 (3 H, s) 4.85 (q, J=9 Hz, 2H), 7.55 (d, J=9 Hz, 2H) 7.67 (s, 1H), 8.1 (d, J=9 Hz, 2H). MS (DCI/NH_3), m/z 403 $(M+H)^+$. Anal. calc. for $C_{18}H_{21}F_3N_2O_3S.0.25\ H_2O$: C, 53.12; H, 5.32; N, 6.88. Found C, 52.90; H, 5.14; N, 6.43.

Example 210

2-(2,2,2-Trifluoroethyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 210A

4-fluoro-3-methylbenzeneboronic acid:

5-Bromo-2-fluorotoluene (6 g, 31.7 mmol) was dissolved in dry THF (50 mL) and cooled to -78 C under N_2. n-BuLi (14 mL, 2.5M solution in THF) was added slowly using a dry syringe. Cloudiness appeared. The reaction was stirred for 40 minutes at -78 °C. Triisopropyl borate (22 mL, 95 mmol) was slowly added while stirring. The reaction was allowed to warm to room temperature. Stirring continued for an additional 2 hours. A pale yellow, cloudy solution formed. (TLC (1:2 ethyl acetate /hexanes)) indicated disappearance of the starting material. The reaction was quenched by adding 10% aqueous NaOH (200 mL). After stirring for 45 minutes, 10% citric acid solution (300 mL) was added until, pH ~5.0. The product was extracted with ethyl acetate (500 mL). The organic phase was washed with brine and dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to provide an off white solid (yield: 4.1 g, 84%).

Example 210B

2-(2,2,2-trifluoroethyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The boronic acid (231 mg, 1.5 mmol), prepared in example 210A, 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (500 mg, 1.36 mmol), tetrakis-(triphenylphosphine)-palladium(0) (47 mg, 0.041 mmol), and CsF (413 mg, 2.72 mmol) were stirred at reflux in DME (20 mL) under N_2 for 5 hours. TLC (1:1 hexanes/ethyl acetate) indicated that all the starting material was consumed. Volatiles were removed in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. An off white powder was obtained (yield: 275 mg, 46%). mp 88-91 °C; ^1H NMR (300 MHz, $CDCl_3$, a mixture of rotamers) δ 2.2, 2.25 (2d, J=1.5 Hz, 3H) 3.05, 3.09 (2 s, 3H) 4.78-4.92 (m, 2H) 6.61-6.8 (m, 1H) 6.82-6 98 (m, 1H) 7.35 (d, J=9 Hz, 1H) 7.78 (d, J=9 Hz, 1H) 7.86-8.09 (m, 4H). MS (DCI/NH_3), m/z 441 $(M+H)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_3S.0.5\ H_2O$. C, 53.45; H, 3.81; N, 6.23. Found C, 53.17, H, 3.65; N, 5.88.

Example 211

2-(2,2,2-Trifluoroethyl)-4-(3,5-dichlorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (150 mg, 0.409 mmol) (Example 193E) was dissolved in anhydrous DME (8 mL) and heated to reflux with 3,5-dichlorobenzeneboronic acid in presence of CsF (150 mg, 0.98 mmol) and tetrakis(triphenylphosphine)-palladium (17.38 mg, 0.015 mmol) for 6 hours. After cooling to room temperature the reaction mixture was diluted with water and extracted with ethyl acetate (100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The compound was purified on a silica gel column, eluting with 30% ethyl acetate in pentanes, to provide the title compound (yield: 110 mg, 58%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 4.88 (q, J=9 Hz, 2H), 7.06 (d, J=1.5 Hz, 9 Hz, 2H), 7.31 (t, J=1.5 Hz, 1H), 7.36 (d, J=9 Hz, 2H), 7.94 (s, 1H), 7.96 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 496 $(M+NH_4)^+$. Anal. calc for $C_{19}H_{13}Cl_2F_3N_2O_3S$: C, 47.81; H, 2.75; N, 5.87. Found: C, 47.77; H, 2.75; N, 5.65

Example 212

2-(2,2,2-Trifluoroethyl)-4-(3-ethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 3-ethoxyphenylboronic acid for 3,5-dichlorobenzeneboronic acid (yield: 155 mg, 86%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J=7.5 Hz, 3H), 3.06 (s, 3H), 3.90 (q, J=7.5 Hz, 2H), 4.88 (q, J=9 Hz, 2H), 6.65 (d, J=7.5 Hz, 1H), 6.75 (t, J=1.5 Hz, 1H), 6.85 (dd, J=1.5 Hz, 9 Hz, 1H), 7.15 (t, J=9 Hz, 1H), 7.38 (d, J=9 Hz, 2H), 7.88 (d, J=9 Hz, 2H), 7.90 (s, 1H). MS (DCI/NH_3) m/z 470 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{19}Cl_2F_3N_2O_4S$. C, 55.75; H, 4.23; N, 6.19. Found. C, 55.62; H, 4.30; N, 5.99

Example 213

2-(2,2,2-Trifluoroethyl)-4-(4-trifluoromethylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 4-(trifluoromethyl)benzeneboronic acid in place of 3,5-dichlorobenzeneboronic acid (yield: 85 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08 (s, 3H), 4.90 (q, J=9 Hz, 2H), 7.35 (t, J=9 Hz, 4H), 7.58 (d, J=9 Hz, 2H), 7.90 (d, J=9 Hz, 3H). MS (DCI/NH_3) m/z 494 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{14}F_6N_2O_3S$. C, 50.42; H, 2.96; N, 5.88. Found. C, 50.20; H, 3.02; N, 5.70

Example 214

2-(2,2,2-Trifluoroethyl)-4-(3-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 3-nitrobenzeneboronic acid in place of 3,5-dichlorobenzeneboronic acid (yield: 40 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 4.92 (q, J=9 Hz, 2H), 7.36 (d, J=9 Hz, 2H), 7.45-7.60 (m, 2H), 7.91 (d, J=9 Hz, 2H), 7.95 (s, 1H), 8.05 (m, 1H), 8.15-8.21 (m, 1H). MS (DCI/NH_3) m/z 471 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{14}Cl_2F_3N_3O_5S$.0.5 EtOAc: C, 50.70; H, 3.64; N, 8.44. Found: C, 50.61; H, 3.58, N, 8.53

Example 215

2-(2,2,2-Trifluoroethyl)-4-(2-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 2-methylbenzeneboronic acid in place of 3,5-dichlorolbenzeneboronic acid (yield: 45 mg, 27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05, 2.12 (2s, 3H), 3.01 (s, 3H), 4.75-5.05 (m, 2H), 6.88 (d, J=9 Hz, 1H), 7.03-7.25 (m, 3H), 7.31 (d, J=9 Hz, 2H), 7.85 (d, J=9 Hz, 2H), 7.95 (s, 1H). MS (DCI/NH_3) m/z 440 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_3S$: C, 55.10; H, 4.27; N, 6.42. Found: C, 55.17; H, 4.18; N, 6.10

Example 216

2-(2,2,2-Trifluoroethyl)-4-(4-vinylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211, substituting 4-vinylbenzeneboronic acid in place of 3,5-dichlorobenzeneboronic acid (yield: 56 mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06, 3.08 (2s, 3H), 4.78-4.95 (m, 2H), 5.30 (t, J=6 Hz, 1H), 5.65, 5.75(2d, J=18 Hz, 1H), 6.58-6.92 (m, 1H), 7.1-7.4 (m, 6H), 7.75-8.08 (m, 3H). MS (DCI/NH_3) m/z 452 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{17}F_3N_2O_3S$: C, 58.06; H, 3.94; N, 6.45. Found: C, 57.82; H, 4.01; N, 6.09

Example 217

2-(2,2,2-Trifluoroethyl)-4-[3-(trifluoromethyl)phenyl]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211 , substituting 3-trifluoromethylbenzeneboronic acid in place of 3,5-dichlorobenzeneboronic acid (yield: 120 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03, 3.08 (2s, 3H), 4.75-4.98 (m, 2H), 7.30-7.60 (m, 6H), 7.75-8.10 (m, 3H). MS (DCI/NH_3) m/z 494 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{14}F_6N_2O_3S$: C, 50.42; H, 2.96; N, 5.88. Found: C, 50.38; H, 2.97; N, 5.74

Example 218

2-(2,2,2-Trifluoroethyl)-4-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211 , substituting 3-fluoro-4-methoxybenzeneboronic acid in place of 3,5-dichlorobenzeneboronic acid (yield: 32 mg, 18%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05, 3.09 (2s, 3H), 3.85, 3.87 (2s, 3H), 4.78-4.90 (m, 2H), 6.60-7.10 (m, 3H), 7.30-8.15 (m,

5H). MS (DCI/NH_3) m/z 474 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_4S.0.5\ H_2O$: C, 51.61; H, 3.68; N, 6.01. Found: C, 51.52; H, 3.65; N, 5.93

Example 219

2-(2,2,2-Trifluoroethyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211 substituting 3-fluoro-4-methylbenzeneboronic acid in place of 3,5-dichlorobenzeneboronic acid (yield: 58 mg, 33%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.21, 2.25 (2d, J=1.5 Hz, 3H), 3.50, 3.55 (2s, 3H), 4.75-4.95 (m, 2H), 6.56-7.15 (m, 3H), 7.30-8.10 (m, 5H). MS (DCI/NH_3) m/z 458 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_3S.0.5\ H_2O$: C, 53.45; H, 3.81; N, 6.23. Found: C, 53.14; H, 3.80; N, 5.97

Example 220

2-(2,2,2-Trifluoroethyl)-4-(3,5-difluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 211 , substituting 3,5-difluoro-4-methoxybenzeneboronic acid in place of 3,5-dichlorobenzeneboronic acid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.9, 3.1 (2s, 3H), 3.92, 4.01 (2s, 3H), 4.78-4.95 (m, 2H), 6.25-6.80 (m, 1H), 7.30-7.5 (m, 2H), 7.7-8.15 (m, 4H). MS (DCI/NH_3) m/z 492 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{15}F_5N_2O_4S$: C, 50.64; H, 3.19; N, 5.90. Found: C, 50.542; H, 3.41; N, 5.67

Example 221

2-(2,2,2-Trifluoroethyl)-4-(1-oxo-1,3-dihydro-2-benzofuran-5-yl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

6-Bromophthalide (300 mg, 1.40 mmol, Teppema et al Recl. Trav. Chim. Pays-Bays, (1923) 42, 47) and hexamethylditin (326 µL, 1.55 mmol) were dissolved in toluene (5 mL), degassed with a nitrogen stream for 5 minutes, treated with $(Ph_3P)_4Pd$ (79 mg) and

heated at reflux for 1 hour. The reaction was cooled and directly purified by chromatography on a Biotage 40S column (pretreated with hexanes-TEA 400:1 then rinsed with hexanes) eluted with 4:1 hexanes-ethyl acetate. The product fractions were combined and evaporated to provide 6-(trimethyltin)phthalide (yield: 362 mg, 87%).

The tin reagent (180 mg, 0.61 mmol), prepared above, and 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 193E, (223 mg, 0.61 mmol) were dissolved in dry toluene (10 mL), degassed with an nitrogen stream for 5 minutes, treated with $(Ph_3P)_4Pd$ (34 mg) and heated at reflux for 1 day. The reaction was cooled and directly purified by chromatography on a Biotage 40S column eluted with 4:1 hexanes-ethyl acetate. The product fractions were combined and evaporated to provide the title compound along with the 4-(1,3-dihydro-1-oxo-6-isobenzofuranyl)-isomer in a 9:1 ratio Further manipulations to attempt to remove the minor isomer (ie chromatography, recrystallization from ethyl acetate-hexanes) failed (yield: 176 mg, 62%). mp 237-239 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 4.91 (q, J=8 Hz, 2H), 5.30 (s, 2 H, major isomer), 5.33 (s, 2 H, minor isomer), 7.20 (dd, J=1 Hz, 7 Hz, 1H), 7.36 (d, J=8 Hz, 2H), 7.52 (s, 1H), 7.79 (d, J=7 Hz, 1H), 7.92 (d, J=8 Hz, 2H), 7.96 (s, 1H). MS (DCI/NH_3) m/z 482 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{15}F_3N_2O_5S$: C, 54.31; H, 3.26; N, 6.03. Found: C, 54.15; H, 3.12; N, 5.76.

Example 222

2-(2,2,2-Trifluoroethyl)-4-(2-propenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A suspension of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (200 mg, 0.546 mmol), prepared according to the method of Example 193E, in THF (27 mL) was cooled to -78 °C. A solution of isopropenylmagnesium bromide (2.8 mL, 0.5 M in THF, Aldrich) was added. The reaction was warmed to room temperature and stirred for 30 minutes. The reaction was quenched at 0 °C by the addition of saturated ammonium chloride solution and partitioned between ethyl acetate and additional ammonium chloride solution. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide a reddish

brown solid. The crude material was dissolved in methylene chloride and adsorbed onto silica gel (2 g). Solvent was removed under reduced pressure, the adsorbed silica gel layered over an Extract-Clean Cartridge® (Alltech, packing: 5 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of 40 mL of the following mixtures: hexanes, 8:1 hexanes/acetone, 4:1, 2:1, and 1:1. Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5sil column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min over 50 minutes. Fractions containing the title product were combined and concentrated under reduced pressure to provide a pale yellow solid (yield: 99.3 mg, 49%). mp 192-195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J=17.4 Hz, 2H), 7.76 (s, 1H), 7.55 (d, 2H, J=17.4 Hz), 5.23 (br s, 1H), 4.84 (m, 3H), 3.11 (s, 3H), 1.98 (s, 3H). MS (DCI/NH_3) m/z 373 $(M+H)^+$, m/z 390 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{15}F_3N_2O_3S$: C, 51.61; H, 4.06; N, 7.52. Found: C, 51.72; H, 4.24; N, 7.35.

Example 223

2-(2,2,2-Trifluoroethyl)-4-(2-buten-2-yl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 222 substituting 1-methyl-1-propenylmagnesium bromide in place of isopropenylmagnesium bromide to provide a mixture of geometric isomers (~3:1 ratio) as an off-white solid (yield: 44.8 mg, 21%). mp 175-180 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J=18.0 Hz, 1.5H), 8.01 (d, J=18.0 Hz, 0.5H), 7.29 (s, 0.75H), 7.28 (s, 0.25H), 7.56 (d, J=17.4 Hz, 1.5H), 7 51 (d, J=17.4 Hz, 0.5H), 5.55 (m, 0.75H), 5.33 (m, 0.25H), 5.86 (q, J=17.4 Hz, 2H), 3.12 (s, 2.25H), 3.11 (s, 0.75H), 2.88 (m, 2H), 2.85 (m, 1H), 1.27 (m, 3H). MS (DCI/NH_3) m/z 387 $(M+H)^+$, m/z 404 $(M+NH_4)^+$, m/z 421 $(M-2NH_4-H)^-$. Anal. calc. for $C_{17}H_{17}F_3N_2O_3S$. C, 52.85; H, 4.43; N, 7.25. Found: C, 53.16, H, 4.68; N, 6.92.

Example 224

2-(2,2,2-Trifluoroethyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 224A

3-Fluorobenzyl magnesium bromide.

3-Fluorobenzyl bromide (613 μL, 5 mmol), followed by dibromoethane (10 μL), was added dropwise to an oven-dried flask containing small pieces of magnesium ribbon (134 mg, 5.5 mmol) and diethyl ether (12 mL). Gas evolution was noted followed by gentle reflux of the ether. The reaction was stirred until gas evolution ceased and most of the magnesium had dissolved. The resulting pale yellow solution of 3-fluorobenzylmagnesium bromide was used directly in the next reaction.

Example 224B

2-(2,2,2-Trifluoroethyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

A suspension of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (200 mg, 0.546 mmol), prepared according to the method of Example 193E, in THF (10 mL) was cooled to 0 °C. A solution of 3-fluorobenzyl magnesium bromide (4.0 mL, ~0.42 M in diethyl ether), prepared above was added. The reaction was stirred at 0 °C for 3 hours, quenched by the addition of saturated ammonium chloride solution, and partitioned, between ethyl acetate and additional ammonium chloride solution. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide a yellow oil. The crude material was dissolved in methylene chloride and adsorbed onto silica gel (2 g). Solvent was removed under reduced pressure, the silica gel with the product adsorbed was layered over an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of 60 mL of each of the following mixtures: hexanes, 8:1 hexanes/acetone, 4:1, 2:1, and 1:1. Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5 sil

silica column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min. for 50 minutes. Fractions containing the title product were combined and concentrated under reduced pressure to provide a pale yellow solid (yield: 130.9 mg, 54%). mp 58-62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J=18.0 Hz, 2H), 7.73 (s, 1H), 7.47 (d, J=17.4 Hz, 2H), 7.18 (m, 1H), 6.88 (m, 1H), 6.76 (br d, J=15.6 Hz, 1H), 6.68 (br d, J=18.6 Hz, 1H), 4.86 (q, J=17.4 Hz, 2H), 3.93 (s, 2H), 3.12 (s, 3H) MS (DCI/NH_3) m/z 441 $(M+H)^+$, m/z 458 $(M+NH_4)^+$, m/z 475 $(M+2NH_4-H)^+$. Anal. calc. for $C_{20}H_{16}F_4N_2O_3S$: C, 54.54; H, 3.66; N, 6.36. Found: C, 54.52; H, 3.81; N, 6.17.

Example 225

2-(2,2,2-Trifluoroethyl)-4-(1-cyclohexenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 225A

1-Cyclohexenyltriflate.

n-Butyllithium (2.5M in hexanes, 2.20 mL, 5.50 mmol) was added to a solution of diisopropylamine (0.77 mL, 5.50 mmol) in THF (20 mL) at-78 °C. The resulting pale yellow solution was warmed to 0 °C for 30 minutes then was cooled to -78 °C. Cyclohexanone (0.52 mL, 5.0 mmol) was added and the nearly colorless solution was warmed to 0 °C for 1 hour. N-Phenyltrifluoromethanesulfonimide (1.79 g, 5.5 mmol) was added as a solid. The solution was stirred at room temperature for 12 hours. The reaction mixture was then partitioned between diethyl ether and saturated sodium bicarbonate solution. The ether layer was washed with water then brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (20:1 hexanes/ethyl acetate) to provide the triflate as a pale yellow oil (yield: 0.73 g, 64%).

Example 225B

1-Cyclohexenyltrimethyltin.

A solution of 1-cyclohexenyltriflate (412 mg, 1.79 mmol), prepared according to the method of Example 225A, and LiCl (380 mg, 8.95 mmol) in THF (9 mL) was deoxygenated by bubbling a stream of N_2 through the solution. Hexamethylditin (339 µL, 1.61 mmol) and tetrakis(triphenylphosphine)palladium(0) (414 mg, 0.36 mmol) were added and the reaction heated at reflux for 12 hours. The reaction was cooled to room temperature and partitioned between diethyl ether and saturated sodium bicarbonate solution. The ether layer was washed with water then brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was dissolved in hexanes (1 mL) and loaded onto an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) which had been wetted with 10% triethylamine in hexanes. The cartridge was eluted with hexanes and fractions containing the triflate combined and concentrated under reduced pressure to provide 1-cyclohexenyltrimethyltin as a clear oil (yield: 150 mg, 34%).

Example 225C

2-(2,2,2-Trifluoroethyl)-4-(1-cyclohexenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

A solution of 1-cyclohexenyltrimethyltin (150 mg, 0.61 mmol), prepared according to the method of Example 225B, and 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (172 mg, 0.47 mmol), prepared according to the method of Example 193E, in anhydrous N-methylpyrrolidinone (1 mL) was deoxygenated with nitrogen. Dichlorobis(triphenylphosphine) palladium(II) (6 6 mg, 0.009 mmol) and [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (7.7 mg, 0.009 mmol) were added and the reaction heated at 80 °C for 16 hours. The reaction mixture was cooled to room temperature and partitioned between diethyl ether and water. The ether was washed with two additional portions water then brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was dissolved in acetone and adsorbed onto silica gel (1 g). Solvent was removed under

reduced pressure, the adsorbed silica gel layered over an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of the following mixtures: hexanes (60 mL), 8.1 hexanes/acetone (80 mL), 4:1 hexanes/acetone (150 mL). Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5 sil silica column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min. over 50 minutes. Fractions containing the title product were combined and concentrated under reduced pressure to provide a pale yellow foam (yield: 95.0 mg, 49%). mp 75-81 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J=17.4 Hz, 2H), 7.76 (s, 1H), 7.55 (d, J=17.4 Hz, 2H), 5.51 (br s, 1H), 4.83 (br q, J=16.2 Hz, 3H), 3.11 (s, 3H), 2.18 (br, 2H), 1.96 (br, 2H), 1.70-1.50 (m, 4H). MS (DCI/NH_3) m/z 413 $(M+H)^+$, m/z 430 $(M+NH_4)^+$, m/z 447 $(M+2NH_4-H)^+$. Anal. calc. for $C_{19}H_{19}F_3N_2O_3S$: C, 55.33; H. 4.64; N, 6.79. Found: C, 55.53; H, 4.71; N, 6.55.

Example 226

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

Example 226A

3-Fluoro-4-(methylthio)benzeneboronic acid.

3-Fluoro-4-(methylthio)benzeneboronic acid was prepared according to the method of Example1, substituting 4-bromo-2-fluorothioanisole in place of 4-bromothioanisole.

Example 226B

2-Benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone

2-Benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone is prepared according to the method of Example 83B starting with 2-benzyl-4,5-dibromo-3(2H)-pyridazinone, in place of 2-(2,2,2-trifluoroethyl)-4,5-dibromo-3(2H)-pyridazinone and substituting methanol in place of isopropanol.

Example 226C

2-Benzyl-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone

3-Fluoro-4-(methylthio)benzeneboronic acid and 2-benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone were coupled according to the method of Example 83C to provide 2-benzyl-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone as a yellow solid (yield: 4.98 g, 91%). ^{1}H NMR (300 MHz, CDCl3) ? 7.76 (s, 1H), 7.47 (m, 2H), 7.39-7.21 (m, 7H), 5.34 (s, 2H), 4.13 (s, 3H), 2.51 (s, 3H). MS (DCI/NH3) m/z 357 $(M+H)^+$, m/z 374 $(M+NH4)^+$.

Example 226D

3-Methylbutylmagnesium bromide

An oven-dried flask containing small pieces of magnesium ribbon (134 mg, 5.5 mmol) was charged with diethyl ether (12 mL). 1-Bromo-3-methylbutane (600 µL, 5 mmol) was added dropwise, followed by dibromoethane (10 µL). The reaction required heating at gentle reflux before gas evolution was observed. The reaction was refluxed for 3 hours and cooled to room temperature. The pale gray solution of 3-methylbutylmagnesium bromide was used in the next reaction.

Example 226E

2-Benzyl-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone

A solution of 2-benzyl-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone (500 mg, 1.40 mmol), prepared according to the method of Example 226C, in THF (20 mL) was cooled to-78 °C. 3-Methylbutylmagnesium bromide (5 mL, 1.96 mmol), prepared in Example 226D, was added, dropwise Upon completion of the addition, the reaction mixture was placed in an ice bath. After 2.5 hours, the reaction was quenched by adding saturated ammonium chloride solution. The crude reaction mixture was partitioned between ethyl acetate and additional ammonium chloride solution. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated

under reduced pressure to provide a yellow oil (yield: 550 mg, 99%). ^{1}H NMR (300 MHz, CDCl3) δ 7.67 (s, 1H), 7.49 (m, 2H), 7.39-7.25 (m, 4H), 7.02 (m, 2H), 5.35 (s, 2H), 2.57-2.49 (m, 2H), 2.52 (s, 3H), 1.62-1.36 (m, 3H), 0.83 (d, 6H, J=12.0 Hz). MS (DCI/NH3) m/z 397 $(M+H)^+$, m/z 414 $(M+NH4)^+$. MS (DCI/NH_3) m/z 397 $(M+H)^+$, m/z 414 $(M+NH_4)^+$.

Example 226F

4-(3-Methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone.

2-Benzyl-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone (550 mg, 1.39 mmol), prepared in Example 226E, was debenzylated according to the method of Example 11 to provide 4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone as a pale yellow solid (yield: 375 mg, 88%). ^{1}H NMR (300 MHz, CDCl3) δ 7.65 (s, 1H), 7.34 (dd, 1H, J=16.2, 16.2 Hz), 7.11-6.98 (m, 2H), 2.60-2.50 (m, 2H), 2.54 (s, 3H), 1.65-1.37 (m, 3H), 0.83 (d, 6H, J=12.0 Hz). MS (DCI/NH3) m/z 307 $(M+H)^+$, m/z 324 $(M+NH4)^+$ MS (DCI/NH_3) m/z 307 $(M+H)^+$, m/z 324 $(M+NH_4)^+$.

Example 226G

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone.

4-(3-Methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone (375 mg, 1.23 mmol), prepared in Example 226F, was alkylated according to the method of Example 20 to provide 2-(2,2,2-trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone as a clear oil (yield: 331 mg, 69%). ^{1}H NMR (300 MHz, CDCl3) δ 7.67 (s, 1H), 7.34 (dd, 1H, J=16.8, 16.8 Hz), 7.11-6.98 (m, 2H), 4.82 (dd, 2H, J=17.4, 17.4 Hz), 2.60-2.51 (m, 2H), 2.53 (s, 3H), 1.61-1.32 (m, 3H), 0.85 (d, 6H, J=12.0 Hz). MS (DCI/NH3) m/z 389 $(M+H)^+$, m/z 406 $(M+NH4)^+$. MS (DCI/NH_3) m/z 389 $(M+H)^+$, m/z 406 $(M+NH_4)^+$.

Example 226H

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone.

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone (331 mg, 0.85 mmol), prepared in Example 226G, was oxidized according to the method of Example 5 using only one equivalent of MCA to provide 2-(2,2,2-trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone as an off-white solid (yield: 240 mg, 69%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, 1H, J=15.0, 15.0 Hz), 7.67 (s, 1H), 7.37 (dd, 1H, J=17.4, 3.0 Hz), 7.11 (dd, 1H, J=18.6, 3.0 Hz), 4.84 (dd, 2H, J=17.4, 17.4 Hz), 2.91 (s, 3H), 2.53 (m, 2H), 1.60-1.35 (m, 3H), 0.57 (d, 6H, J=12.0 Hz). MS (DCI/NH3) m/z 405 $(M+H)^+$, m/z 422 $(M+NH4)^+$. MS (DCI/NH_3) m/z 405 $(M+H)^+$, m/z 422 $(M+NH_4)^+$.

Example 226I

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (240 mg, 0.594 mmol), prepared in Example 226H, was converted to the sulfonamide according to the procedure of Example 68 to provide the title compound as a white solid (yield: 109 mg, 44%). mp 153-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, J=15.0, 15.0 Hz, 1H), 7.74 (s, 1H), 7.27-7.19 (m, 2H), 5.14 (br s, 2H), 4.83 (q, J=18.0 Hz, 2H), 2.52 (m, 2H), 1.55 (m, 1H), 1.41 (m, 2H), 0.85 (d, J=12.6 Hz, 6H). MS (ESI (-)) m/z 420 $(M-H)^-$. Anal. calc. for $C_{17}H_{19}F_4N_3O_3S$. C, 48 45; H, 4.54, N, 9.97. Found: C, 48.24; H, 4.56; N, 9.80.

Example 227

2-(2,2,2-Trifluoroethyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by adding 1.0 M benzylmagnesium chloride in ether (0.53 mL, 0.53 mmol) to a THF (20 mL) solution of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (150 mg, 0.41 mmol), prepared

according to the method of Example 193E, at 0 °C, then allowing the mixture to warm to room temperature over 2 hours. After an aqueous work-up, the crude material was purified by column chromatography (silica gel, 65:35 hexanes/ethyl acetate) and crystallized from ethyl acetate/hexanes to provide white, crystalline product (yield: 74 mg, 43%). mp 112-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 3.94 (s, 2H), 4.85 (q, J=12 Hz, 2H), 6.99 (dd, J=7.5 Hz, 3 Hz, 2H), 7.2 (m, 3H), 7.48 (d, J=9 Hz, 2H), 7.72 (s, 1H), 8.06 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 423 $(M+H)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_3S$: C, 56.86; H, 4.05; N, 6.63. Found: C, 56.60; H, 4.13; N, 6.57.

Example 228

2-(4-Fluorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 194C, (200 mg, 0.51 mmol) in THF (8 ml) was cooled to -78 °C and treated with cyclohexylmagnesium chloride, 2 M solution in ether (0.31 ml, 0,7 mmol). The reaction mixture was stirred at -78 °C for 2 hours and then was warmed up to room temperature by removing the cooling bath. Stirred at room temperature for 2 hours water (50 ml) was added to the reaction mixture and extracted with ethyl acetate (50 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting methyl sulfide compound was purified by flash chromatography (SiO_2, eluting with 9:1 hexanes:ethyl acetate) to provide the desired product (yield: 128 mg, 69%). MS (DCI/NH_3) m/z 395 $(M+H)^+$, 412 $(M+NH_4)^+$.

The methyl sulfide compound, prepared above, (122 mg, 0.3 mmol) in CH_2Cl_2 (10 ml) at 0 °C, was treated with CH_3CO_3H (0.3 ml, 1 mmol). The reaction was complete in 2 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine respectively. The resulting crude residue was purified by flash chromatography (SiO_2, eluting with 1:1 hexanes:ethyl acetate) to provide the desired product (yield: 110 mg, 93%). mp 231-233 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.1 (m, 3H), 1.6 (m, 6H), 2.15 (m, 2H), 7.35 (t, 2H), 7.65 (m, 2H), 7.73 (dd, 2H) 7.93 (s, 1H), 8.1 (d, 2H). MS

(DCI/NH_3) m/z 427 $(M+H)^+$, 444 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{23}FN_2O_3S.0.75\ H_2O$: C, 64.77; H, 5.44; N, 6.57. Found: C, 62.86; H, 5.53; N, 5.78.

Example 229

2-(4-Fluorophenyl)-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , substituting p-tolylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 90 mg, 39%). mp 242-244 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.25 (s, 3H), δ 3.25 (s, 3H), 7.1 (t, 4H), 7.35 (t, 2H), 7.5 (d, J=9 Hz, 2H), 7.7 (dd, 2H) 7 9 (d, J=9 Hz, 2H), 8.2 (s, 1H). MS (DCI/NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_3S.0.5\ H_2O$: C, 66.34; H, 4.41, N, 6.45. Found: C, 64.61: H, 4.57; N, 6.10.

Example 230

2-(4-Fluorophenyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , substituting benzylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 179 mg, 81%). mp 180-182 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 7.0 (d, 2H), 7.2 (m, 3H), 7.35 (t, 2H), 7.65 (m, 2H), 7.72 (d, 2H) 8.05 (m, 3H). MS (DCI/NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}FN_2O_3S.0.5\ H_2O$: C, 66.34; H, 4.41; N, 6.45. Found: C, 66.48; H, 4.17, N, 6 36.

Example 231

2-(4-Fluorophenyl)-4-(phenylethynyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , substituting phenylacetylene magnesium bromide in place of cyclohexylmagnesium chloride (yield: 150 mg, 55.5%). mp 203-204 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 7.4 (m, 8H), 7.7 (m, 2H), 8.16 (m, 4H) ; 8.35 (s, 1H). MS (DCI/NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{17}FN_2O_3S$: C, 67.56; H, 3.86; N, 6.30. Found: C, 67.63, H, 3.86, N, 6.30.

Example 232

2-(3,4-Difluorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 245 mg, 80%). mp 80-83 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.1 (m, 3H), 1.6 (m, 6H), 2.15 (m, 2H), 7.5 (m, 1H), 7.6 (m, 2H), 7.7 (d, 2H), 7.78 (m, 2H), 7.93 (s, 1H), 8.1 (d, 2H). MS (DCI/NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{22}F_2N_2O_3S$: C, 62.15; H, 4.99; N, 6.30. Found: C, 62.65; H, 5.25; N, 5.97.

Example 233

2-(3,4-Difluorophenyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting benzylmagnesium bromide in place of cyclohexylmagnesium chloride (yield 206 mg, 66%). mp 166-168 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 3.9 (s, 2H), 7.0 (d, 2H), 7.2 (m, 3H), 7.6 (m, 2H), 7.72 (d, 2H), 7.8 (d, 1H), 8.05 (d, 2H), 8.12 (s, 1H). MS (DCI/NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}F_2N_2O_3S$: C, 63.71; H, 4.01; N, 6.19. Found: C, 63.53; H, 4.33; N, 5.76.

Example 234

2-(3,4-Difluorophenyl)-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-

pyridazinone and substituting p-tolylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 140 mg, 56%) . mp 190-192 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 2H), δ 3.25 (s, 3H), 7.1 (s, 4H), 7.5 (m, 4H), 7.89 (m, 3H), 8.05 (d, 2H), 8.23 (s, 1H). MS (DCI/NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{24}F_2H_{18}N_2O_3S$: C, 63.71; H, 4.01; N, 6.19. Found: C, 63.69; H, 4.29; N, 5.96.

Example 235

2-(3,4-Difluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 4-fluoro-3-methylbenzenemagnesium bromide in place of cyclohexylmagnesium chloride (yield: 180 mg, 72.5%) . mp 166-168 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 3H), δ 3.25 (s, 3H), 7.01 (m, 2H), 7.25 (d, 1H), 7.6 (m, 4H), 7.9 (m, 3H), 8.26 (s, 2H). MS (DCI/NH_3) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{24}F_3H_{17}N_2O_3S$: C, 61.27; H, 3.64; N, 5,95. Found: C, 61.47; H, 3.84; N, 5.67.

Example 236

2-(3,4-Difluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-vinyl-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting vinyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 85 mg, 31.8%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 3H), δ 3.3 (s, 3H), 5.7 (dd, 1H), 6.4 (dd, 1H), 6.7 (dd, 1H) 7.01 (m, 2H), 7.5 (m, 1H), 7.65 (m, 1H), 7.8 (m, 3H), 8.1 (s, 3H). MS (DCI/NH_3) m/z 389 $(M+H)^+$, 406 $(M+NH_4)^+$.

Example 237

2-(3,4-Difluorophenyl)-4-(2-thienyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 2-thienylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 66 mg, 28%). mp 189-191 °C ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 6.95 (m, 2H), 7.55 (m, 1H), 7.7 (m, 5H), 7.85 (m, 1H), 8.03 (d, J=9 Hz, 2H), 8.13 (s, 1H). MS (DCI/NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{14}F_2N_2O_3S_2$: C, 56.75; H, 3.17; N, 6.30. Found: C, 56.92, H, 3.92, N, 5.79.

Example 238

2-(3,4-Difluorophenyl)-4-(1-propynyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting methylacetylenemagnesium bromide in place of cyclohexylmagnesium chloride (yield: 65 mg, 24%) . mp 149-150 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.1 (s, 3H), 3.3 (s, 3H), 7.51 (m, 1H), 7.65 (m, 1H), 7.8 (m, 1H), 8.1 (m, 4H) : 8.3 (s, 1H). MS (DCI/NH_3) m/z 463M+H)$^+$, 480 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{14}F_2N_2O_3S$.0.25 H2O: C, 59.94, H, 3.52; N, 7.00. Found. C, 59.49: H, 3.63; N, 6.34

Example 239

2-(3,4-Difluorophenyl)-4-t-butyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting t-butylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 60 mg, 24%). mp 158-161 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21, (s, 9H), 3.3 (s, 3H), 7.51 (m, 1H), 7.45 (m, 1H), 7.75 (m, 4H),

8.02 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 419 $(M+H)^+$, 436 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{20}F_2N_2O_3S$: C, 60.27; H, 4.82; N, 6.69. Found: C, 60.15; H, 5.10; N, 6.39

Example 240

2-(2,2,2-Trifluoroethyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 193D, in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, (yield: 120 mg, 53%). mp 215-218 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.1 (tt, J=9 Hz, J=4.5 Hz, 2H), 1.25 (tt, J=9 Hz, 4.5 Hz, 1H), 1.49 (d, J=12 Hz, 2H), 1.63 (d, J=12 Hz, 1H), 1.75 (dt, J=12 Hz, 3 Hz, 2H), 2.21 (qd, J=9 Hz, 4.5 Hz, 2H), 2.51 (tt, J=12 Hz, 3 Hz, 1H), 3.17 (s, 3H), 4.83 (q, J=12 Hz, 2H), 7.49 (d, J=9 Hz, 2H), 7.6 (s, 1H), 8.09 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 415 $(M+H)^+$. Anal. calc. for $C_{19}H_{21}F_3N_2O_3S$: C, 55.06; H, 5.1; N, 6.75. Found: C, 55.08; H, 5.10; N, 6.70.

Example 241

2-(3-Chlorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chlorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 207C, and substituting 3-fluorobenzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 180 mg, 55%). mp 142-143 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.98 (s, 2H), 6.75 (br d, J=9 Hz, 1H), 6.82 (br d, J=9 Hz, 1H), 6.88 (br t, J=9 Hz, 1H), 7.15-7.23 (m, 1H), 7.37-7.47 (m, 2H), 7.54 (d, J=9 Hz, 2H), 7.63 (dt, J=9 Hz, 2 Hz, 1H), 7.75 (t, J=2 Hz, 1H), 7.82 (s, 1H), 8.10 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{18}ClF_3N_2O_3S.0.5\ H_2O$: C, 60.38; H, 3.88; N, 5.87. Found: C, 60.62; H, 3.89; N, 5.82.

Example 242

2-(4-Fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(4-Fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 194C, and substituting 3-fluorobenzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10, to provide the title compound (yield: 450 mg, 66.8%). mp 176-178 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.95 (s, 2H), 6.75 (br d, J=9 Hz, 1H), 6.82 (br d, J=9 Hz, 1H), 6.88 (br t, J=9 Hz, 1H), 7.14-7.23 (m, 3H), 7.54 (d, J=9 Hz, 2H), 7.67 (dd, J=9 Hz, 6 Hz, 2H), 7.81 (s, 1H), 8.10 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 516 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{19}F_2N_2O_5S.H_2O$: C, 61.28; H, 4.04; N, 5.96. Found: C, 61.24; H, 4.09; N, 5.77.

Example 243

2-(3,4-Difluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3,4-Difluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, and substituting 3-fluorobenzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 390 mg, 68%). mp 161-163 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.95 (s, 2H), 6.74 (br d, J=9 Hz, 1H), 6.82 (br d, J=9 Hz, 1H), 6.89 (br t, J=9 Hz, 1H), 7.15-7.33 (m, 2H), 7.48-7.57 (m, 1H), 7.53 (d, J=9 Hz, 2H), 7.59-7.67 (m, 1H), 7.83 (s, 1H), 8.10 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 471 $(M+H)^+$,

488 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}F_3N_2O_3S.0.5\ H_2O$: C, 60.13, H, 3.65; N, 5.85. Found: C, 60.08; H, 3.81; N, 5.54.

Example 244

2-(3-Chlorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chlorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 207C, and substituting 4-fluoro-3-methylphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 620 mg, 57%). mp 228-230 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.06 (s, 3H), 6.83-6.93 (m, 2H), 7.19 (br d, J=9 Hz, 1H), 7.37-7.47 (m, 2H), 7.40 (d, J=9 Hz, 2H), 7.65 (dt, J=7 Hz, 3 Hz, 1H), 7.68 (t, J=3 Hz, 1H), 7.91 (d, J=9 Hz, 2H), 7.98 (s, 1H). MS (DCI/NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}ClFN_2O_3S$. C, 61.54; H, 3.85; N, 5.99. Found: C, 61.39; H, 3.84; N, 5.82.

Example 245

2-(4-Fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(4-Fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 194C, and substituting 4-fluoro-3-methylphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 590 mg, 74.4%). mp 245-247 °C. ^1H NMR (300

MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.07 (s, 3H), 6.87 (m, 2H), 7.21 (m, 3H), 7.41 (d, J=9 Hz, 2H), 7.68 (m, 2H), 7.92 (d, J=9 Hz, 2H), 7.97 (s, 1H). MS (DCI/NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{18}F_2N_2O_3S.0.5\ H_2O$: C, 62.47; H, 3.90; N, 6.08. Found: C, 62.11; H, 4.11; N, 5.81.

Example 246

2-(3-Chloro-4-fluorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 246A

2-(3-Chloro-4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone

The title compound is prepared according to the method of Example 194A, substituting 3-chloro-4-fluorophenyl hydrazine·HCl in place of 4-fluorophenyl hydrazine.HCl (yield: 9.1 g, 9%). ^1H NMR (300 MHz, $CDCl_3$) 7.22 (d, J=9 Hz, 1H), 7.53-7.58 (m, 1H), 7.73 (dd, J=9 Hz, 3 Hz, 1H), 7.94 (s, 1H). MS (DCI/NH_3) m/z 383 $(M+H)^+$, 400 $(M+NH_4)^+$

Example 246B

2-(3-Chloro-4-fluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone.

The title compound is prepared according to the method of Example 194B, substituting 2-(3-chloro-4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (yield: 5.6 g, 84%). ^1H NMR (300 MHz, $CDCl_3$) 4.32 (s, 3H), 7.22-7.30 (m, 1H), 7.45-7.55 (m, 1H), 7.64-7.74 (m, 1H), 7.94 (d, J=9 Hz, 1H). MS (DCI/NH_3) m/z 335 $(M+H)^+$, 352 $(M+NH_4)^+$.

Example 246C

2-(3-Chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound is prepared according to the method of Example 6 starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone in place of 2-benzyl-

5-methoxy-4-bromo-3(2H)-pyridazinone and substituting 4-(methylthio)benzeneboronic acid in place of 4-fluorobenzeneboronic acid (yield: 3.2 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 4.13 (s, 3H), 7.25 (t, J=9 Hz, 1H), 7.35 (d, J=9 Hz, 2H), 7.52 (d, J=9 Hz, 2H), 7.55-7.64 (m, 1H), 7.78 (dd, J=9 Hz, 3 Hz, 1H), 7.93 (s, 2H). MS (DCI/NH_3) m/z 377 $(M+H)^+$, 394 $(M+NH_4)^+$.

Example 246D

2-(3-Chloro-4-fluorophenyl)-4-cyclohexyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound is prepared starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone by treatment of the methoxy-sulfide compound with cyclohexylmagnesium chloride according to the method of Example 228 to provide the cyclohexyl sulfide compound.

Example 246E

2-(3-Chloro-4-fluorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The methyl sulfide compound was oxidized according to the method of Example 10 to provide the title compound (yield: 150 mg, 53%). mp 180-181 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02-1.36 (m, 2H), 1.49-1.68 (m, 4H), 1.75 (br d, J=12 Hz, 2H), 2.28 (dq, J=12 Hz, 3 Hz, 2H), 2.57 (tt, J=12 Hz, 3 Hz, 1H), 3.17 (s, 3H), 7.25 (t, J=9 Hz, 1H), 7.53 (d, J=9 Hz, 1H), 7.53-7.61 (m, 2H), 7.69 (s, 1H), 7.78 (dd, J=9 Hz, 3 Hz, 1H), 8.12 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 461 $(M+H)^+$, 478 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{22}ClFN_2O_3S$: C, 60.01; H, 4.78; N, 6.09. Found. C, 59.85; H, 4.97; N, 5.79.

Example 247

2-(3-Chloro-4-fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246C, and substituting 4-fluoro-3-methylphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 118 mg, 53.7%). mp 207-208 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (br s, 3H), 3.08 (s, 3H), 6.81-6.93 (m, 2H), 7.15-7.30 (m, 2H), 7.41 (d, J=9 Hz, 2H), 7.60-7.68 (m, 1H), 7.85 (dd, J=9 Hz, 3 Hz, 1H), 7.93 (d, J=9 Hz, 2H), 7.99 (s, 1H). MS (DCI/NH_3) m/z 487 $(M+H)^+$, 504 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}ClF_2N_2O_3S.0.25\ H_2O$: C, 58.75; H, 3.52; N, 5.72. Found: C, 58.74; H, 3.60; N, 5.32.

Example 248

2-(3-Chloro-4-fluorophenyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-benzyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246C, and substituting benzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 110 mg, 38.4%). mp 164-166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11 (s, 3H), 3.99 (s, 2H), 7.01-7.06 (m, 2H), 7.17-7.28 (m, 4H), 7.53 (d, J=9 Hz, 2H), 7.59-7.66 (m, 1H), 7.81 (s, 1H), 7.82 (dd, J=6 Hz, 3 Hz, 1H), 8.09 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}ClFN_2O_3S$: C, 61.54; H, 3.85; N, 5.99. Found: C, 61.40; H, 3.82; N, 5.54.

Example 249

2-(3-Chloro-4-fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246C, and substituting 3-fluorobenzylmagnesium chloride in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 33 mg, 15%). mp 101-103 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3 15 (s, 3H), 3.95 (s, 2H), 6.73 (br d, J=9 Hz, 1H), 6.81 (br d, J=9 Hz, 1H), 6.88 (br t, J=9 Hz, 1H), 7.15-7.28 (m, 2H), 7.51 (d, J=9 Hz, 2H), 7.53 (ddd, J=9 Hz, 3 Hz, 1.5 Hz, 1H), 7.83 (dd, J=6 Hz, 3 Hz, 1H), 7.83 (s, 1H), 8.10 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 487 $(M+H)^+$, 504 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}ClF_2N_2O_3S$: C, 58.75; H, 3.52; N, 5.62. Found: C, 58.50; H, 3.65; N, 5.29.

Example 250

2-(4-Fluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(4-Fluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 194C, and substituting 3-fluoro-4-methylphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 540 mg, 73%). mp 245-248 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (br s, 3H), 3.05 (s, 3H), 6.83 (dd, J=9 Hz, 1.5 Hz, 1H), 6.96 (dd, J=9 Hz, 1.5 Hz, 1H), 7 06 (t, J=9 Hz, 1H), 7.18 (t, J=9 Hz, 2H), 7.41 (d, J=9 Hz, 2H), 7.65-7.72 (m, 2H), 7.91 (d, J=9 Hz, 2H), 7.95 (s, 1H). MS (DCI/NH_3) m/z 452 $(M+H)^+$, 470 $(M+NH_4)^+$.

Anal. calc. for $C_{24}H_{18}F_2N_2O_3S$: C, 63.86; H, 3.99; N, 6.21. Found: C, 63.49; H, 4.13; N, 5.98.

Example 251

2-(3-Chloro-4-fluorophenyl)-4-(3,5-difluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-(3,5-difluoro-4-methoxyphenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228, starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246C, and substituting 3,5-difluoro-4-methoxyphenylmagnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 590 mg, 65.7%). mp 195-197 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (s, 3H), 4.12 (s, 3H), 6.81 (br d, J=9 Hz, 2H), 7.27 (t, J=9 Hz, 1H), 7.43 (d, J=9 Hz, 2H), 7.60-7.67 (m, 1H), 7.83 (br d, J=9 Hz, 1H), 7.98 (d, J=9 Hz, 2H), 7.98 (s, 1H). MS (DCI/NH_3) m/z 487 $(M+H)^+$, 504 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{16}ClF_3N_2O_3S.0.5\ H_2O$: C, 54.44; H, 3.12; N, 5.30. Found: C, 54.50; H, 3.12; N, 5.15.

Example 252

2-(3-Chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3-Chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 228 , starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, prepared in Example 246C, and substituting 1-(3-methylbutyl)magnesium bromide in place of cyclohexylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 425 mg, 54.4%). mp 102-104 °C. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 0.85 (d, J=9 Hz, 6H), 1.41-1.62 (m, 1H), 2.50-2.63 (m, 2H), 3.30 (s, 3H), 7.22-7.38 (m, 3H), 7.57-7.64 (m, 1H), 7.72 (br s, 1H), 7.80 (br d, J=6 Hz, 1H), 8.15 (t, J=9 Hz, 1H). MS (DCI/NH_3) m/z 467 $(M+H)^+$, 484 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}ClF_2N_2O_3S$: C, 56.65; H, 4.51; N, 6.01 Found: C, 56.25; H, 4.49; N, 6.06.

Example 253

2-(4-Fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The sulfide from Example 242, 2-(4-fluorophenyl)-4-(3-fluorobenzyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, was oxidized to the methyl sulfoxide with one equivalent of meta-chloroperoxybenzoic acid according to the procedure in Example 69B to provide the sulfinyl compound.

The sulfoxide was converted to the title sulfonamide according to the method of Example 68 (yield: 120 mg, 31%). mp 199-202 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.92 (s, 2H), 6.85 (br t, J=9 Hz, 2H), 6.99 (br t, J=9 Hz, 1H), 7.26 (q, J=7 Hz, 1H), 7.35 (t, J=9 Hz, 2H), 7.50 (s, 2H), 7.62-7.71 (m, 4H), 7.95 (d, J=9 Hz, 2H), 8.11 (s, 1H). MS (DCI/NH_3) m/z 454 $(M+H)^+$, 471 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}F_2N_3O_3S$: C, 60.86; H, 3.75; N, 9.27. Found: C, 60.99; H, 3.76; N, 9.02.

Example 254

2-(3,4-Difluorophenyl)-4-(phenylethynyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 245 mg, 80%) and substituting phenylethynylmagnesium bromide in place of cyclohexylmagnesium chloride (yield: 195 mg, 61%). mp 211-213 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 7.46 (m, 5H), 7.65 (m, 2H), 8.18 (t, 4H) ; 8.4 (s, 1H). MS (DCI/NH_3) m/z 463M+H)$^+$, 480 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{16}F_2N_2O_3S$: C, 64.56; H, 3.49; N, 6.06. Found: C, 64.49; H, 3.68; N, 5.86.

Example 255

2-(3,4-Difluorophenyl)-4-(3,4-difluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

3,4-Difluorobenzyl bromide (0.1 ml, 0.8 mmol) in ether (10 ml) was treated with magnesium turnings (19.4 mg, 0.81 mmol) and the reaction mixture was refluxed for 1 hour. The reaction mixture was cooled and added to a solution of 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (0.25 g, 0.7 mmol) in THF (10 ml) at -78 °C. The reaction mixture was stirred at room temperature for 18 hours. Water (50 ml) was added to the reaction mixture and extracted with ethyl acetate (50 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting crude residue was purified by flash chromatography (SiO_2, eluting with 9:1 hexanes:ethyl acetate) to provide 120 mg of desired product and some starting material.

The methylthio compound (120 mg, 0.3 mmol) from above in CH_2Cl_2 (10 ml) at 0 °C, was treated with CH_3CO_3H (0.3 ml, 1 mmol). The reaction was complete in 2 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine respectively. The resulting crude residue was purified by flash chromatography (SiO_2, eluting with 1:1 hexanes:ethyl acetate) to provide the desired product (yield: 44 mg, 13%). mp 177-179 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 3.9 (s, 2H). 6.85 (m, 1H), 7.15 (m, 1H), 7.25 (m, 2H), 7.6 (m, 7H), 8.15 (m, 3H). MS (DCI/NH_3) m/z 489 $(M+H)^+$, 506 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{16}F_4N_2O_3S.0.25\ H_2O$: C, 59.01; H, 3.30; N, 5.74. Found: C, 58.16; H, 3.56; N, 4.51.

Example 256

2-(3,4-Difluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-

pyridazinone (yield: 245 mg, 80%) and substituting 1-bromo-3-methylbutane in place of cyclohexylmagnesium chloride (yield: 198 mg, 48%). mp 55-58 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 3.3 (s, 3H), 7.51 (m, 1H), 7.65 (m, 1H), 7.75 (d, J=9 Hz, 2H), 7.81 (m, 1H) 8.05 (s, 1H), 8.12 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 433 $(M+H)^+$, 450 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_3S.0.25\ H_2O$: C, 61.10; H, 5.13; N, 6.48. Found: C, 61.09: H, 5.23; N, 6.36.

Example 257

2-(3-Chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 starting with 2-(3-chloro-4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone from Example 246C in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 1-bromo-3-methylbutane in place of cyclohexylmagnesium chloride (yield: 256 mg, 88%). mp 55-58 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 3.3 (s, 3H), 7.62 (m, 2H), 7.75 (d, 2H), 7.93 (dd, 1H), 8.05 (s, 1H), 8.12 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}FN_2O_3SCl.0.25\ H_2O$: C, 58.86; H, 4.94; N, 6.24 . Found: C, 59.23; H, 5.12; N, 6.00.

Example 258

2-(3,4-Difluorophenyl)-4-(3-methylbutyl)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, procedure starting with 2-(3,4-difluorophenyl)-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 1-bromo-3-methylbutane in place of cyclohexylmagnesium chloride (yield: 100 mg, 20%) . mp 119-121 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 3.4 (s,

3H), 7.51 (m, 1H), 7.8 (m, 2H), 7.81 (m, 2H). MS (DCI/NH_3) m/z 451 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}F_3N_2O_3S$: C, 58.66: H, 4.7; N, 6.22.

Example 259

2-[4-Fluoro-3-(methylthio)phenyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred solution of 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (315 mg, 0.69 mmol), Example 182, in DMF (10 ml) at room temperature was treated with sodium thiomethoxide (51 mg, 0.7 mmol). The reaction mixture was stirred at room temperature for 3.15 hours. The reaction was poured into water (75 ml) and extracted into ethyl acetate. The organic layer was washed two times with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting crude residue was purified using flash chromatography (SiO_2, eluting with (15:1 CH_2Cl_2:diethyl ether) to provide the desired product (yield: 30 mg, 8%) . mp 105-107 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.55 (s, 3H), 3.23 (s, 3H), δ 7.15 (m, 2H), 7.3 (m, 2H), 7.55 (m, 5H), 7.9 (d, 2H), 8.25 (s, 1H). MS (DCI/NH_3) m/z 485 $(M+H)^+$, 502 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}F_2N_2O_3S_2$: C, 59.49: H, 3.74; N, 5.78.

Example 260

2-Benzyl-4-(4-fluorophenyl)-5-[4-(trifluoromethylsulfonyl)phenyl]-3(2H)-pyridazinone:

Example 260A

2-Benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared starting with 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and oxidizing the sulfide according to the procedure in example 69B

Example 260B

Bis(4-(5-(2-benzyl-4-(4-fluorophenyl)-3(2H)-pyridazinone)phenyl)disulfide:

A heterogeneous solution of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (1.0 g, 2.39 mmol) in trifluoroacetic anhydride (10 mL, 70.8 mmol) was rapidly stirred at reflux for 2 hours with a bath temperature of 40-43 °C. The reaction solution was cooled to 23 °C, concentrated in vacuo, and azeotroped with toluene (2 x 5-7 mL). The resultant yellow/orange oil was cooled to 0 °C, and methanol/triethylamine (1:1, 6 mL) was slowly added, along the interior wall of the reaction vessel with rapid stirring. The bright red-orange solution was stirred for 10 minutes at 0 °C, the cooling bath removed, and the reaction mixture stirred an additional 1.5 hours warming to 23 °C. The mixture was cooled back to 0 °C, and a saturated NH_4Cl solution (200 mL) slowly added followed by enough aqueous 1 M HCl to adjust the solution to pH 1-2. The cooling bath was removed and the solution stirred overnight. The mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with water and brine, and concentrated in vacuo. The resultant yellow/brown oil (0.89 g) was a mixture of predominantly the mono-sulfide and desired di-sulfide. Subsequent rapid stirring of a portion of the crude reaction mixture (360 mg) in benzene (100 mL) with I_2 (648 mg, 2.55 mmol) at 23 °C for 30 minutes completed the conversion of the mono-sulfide to the di-sulfide. (Chem. Pharm. Bull., 1992, 40, 2842) The mixture was treated with a 0.1 M $Na_2S_2O_3$ solution to consume the excess I_2. This solution was extracted with ethyl acetate, and the ethyl acetate layers dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2/hexanes and concentrated in vacuo to provide the of product (yield: 347 mg, 90% for partial conversion). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 4H), 6.91 (dd, J=8.8, 8.8 Hz, 4H), 7.02 (d, J=8.7 Hz, 4H), 7.11-7.20 (m, 4H), 7.28-7.39 (m, 10H), 7.54 (dd, J=6.9, 1.5 Hz, 4H), 7.83 (s, 2H).

Example 260C

2-Benzyl-4-(4-fluorophenyl)-5-[4-(trifluoromethylthio)phenyl]-3(2H)-pyridazinone:

A rapidly stirred mixture of bis[4-{5-[2-benzyl-4-(4-fluorophenyl)-3(2H)-pyridazinone]}-phenyl]-disulfide (140 mg, 0.181 mmol), potassium trifluoroacetate (55 mg, 0.361 mmol), and sulfolane (1.5 mL) was immersed in a 180 °C pre-heated oil bath.

The oil bath was heated to increase the temperature to 210 °C. and the reaction flask was promptly removed from the oil bath after 10 minutes from the point of first immersion. During the course of the reaction, the mixture changed from colorless and heterogeneous to deep, blood red and homogeneous. After cooling to 23 °C. the mixture was diluted with ethyl acetate and washed with aqueous 1 M HCl. water, and brine. The ethyl acetate solution was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes 1:4) to provide the product (yield: 17 mg, 41%). (Tetrahedron Lett.., 1996, 37, 9057) ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 2H), 6.94 (dd, J=8.2, 8.2 Hz, 2H), 7.11-7.20 (m, 4H), 7.31-7.42 (m, 3H), 7.52-7.61 (m, 4H), 7.86 (s, 1H). MS (APCI+) m/z 457 $(M+H)^+$ and m/z 474 $(M+NH_4)^+$

Example 260D

2-Benzyl-4-(4-fluorophenyl)-5-[4-(trifluoromethylsulfonyl)phenyl]-3(2H)-pyridazinone:

A solution of 2-benzyl-4-(4-fluorophenyl)-5-[4-(trifluoromethylthio)phenyl]-3(2H)-pyridazinone (100 mg, 0.219 mmol), 3-chloroperoxybenzoic acid (380 mg, 1.3 mmol, 57-86%), and methylene chloride (5 mL) was brought to reflux at a bath temperature of 55 °C. After 1.75 hours, 3.5 hours, 5 hours, and 6 hours, the reaction was not complete and additional 3-chloroperoxybenzoic acid (380 mg, 1.3 mmol, 57-86%) was added each time. With the reaction completed after 7.75 hours, the mixture was cooled to 23 °C and concentrated in vacuo. The residue was diluted with ethyl acetate and carefully shaken with a $NaHSO_3$ solution, 3 times, for several minutes to consume the excess 3-chloroperoxybenzoic acid. The ethyl acetate solution was subsequently washed with a saturated Na_2CO_3 solution (3x), water, and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed (flash silica gel, ethyl acetate/methylene chloride/hexanes 1:2:7) to provide of product (yield: 93 mg, 87%). (J. Med. Chem.., 1990, 33, 2569) mp 80-115 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 5.36 (s, 2H), 7.11 (dd, J=9.0, 9.0 Hz, 2H), 7.18-7.26 (m, 2H), 7.29-7.46 (m, 5H), 7.66 (d, J=8 7 Hz, 2H), 8.10 (d, J=8.7 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 489 $(M+H)^+$ and m/z 506

$(M+NH_4)^+$. Anal. calc. for $C_{24}H_{16}F_4N_2O_3S$: C, 59.02; H, 3.30; N, 5.74. Found: C, 59.30, H, 3.48; N, 5.59.

Example 261

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (150 mg, 0.41 mmol), prepared in Example 193E, and neopentyl alcohol (43 mg, 0.49 mmol) were dissolved in DMF (2 mL) and NaH (25 mg, 0.62 mmol, 60% in mineral oil) was added with shaking and left overnight. The reaction mixture was carefully quenched with saturated NH_4Cl solution, diluted with ethyl acetate and extracted with 1 N HCl, twice, then water, 3 times, and then dried over $MgSO_4$. After filtration of the drying agent and concentration of the filtrate in vacuo, the residue was purified by chromatography on silica gel (Biotage 40S) eluted with 2:1 hexanes-ethyl acetate. The product fractions were combined and evaporated to provide the title compound (yield: 137 mg, 76%). mp 145-146 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76 (s, 9H), 3.28 (s, 3H), 4.06 (s, 2H), 5.02 (q, J=9 Hz, 2H), 7.88 (d, J=8 Hz, 2H), 8.04 (d, J=8 Hz, 2H), 8.13 (s, 1H). MS (DCI/NH_3) m/z 419 $(M+H)^+$, 436 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{21}F_3N_2O_4S$: C, 51.67, H, 5.06; N, 6.69. Found: C, 51.47; H, 5.12; N, 6.48.

Example 262

2-(2,2,2-Trifluoroethyl)-4-(4-methoxyphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-methoxyphenol in place of neopentyl alcohol (yield: 130 mg, 54%). mp 194-195 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.24 (s, 3H), 3.26 (s, 3H), 5.00 (q, J=9 Hz, 2H), 6.88 (d, J=8 Hz, 2H), 7.09 (d, J=8 Hz, 2H), 7.37 (d, J=8 Hz, 2H), 8.03 (d, J=8 Hz, 2H), 8.33 (s, 1H). MS (ESI-) m/z 439 $(M-H)^-$. Anal. calc. for $C_{19}H_{17}F_3N_2O_4S$: C, 54.79; H, 3.91; N, 6.39. Found: C, 55.04; H, 4.00; N, 6.11.

Example 263

2-(2,2,2-Trifluoroethyl)-4-(2-fluoro-5-trifluoromethylphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-fluoro-5-trifluoromethylphenol in place of neopentyl alcohol (yield: 155 mg, 89%). mp 133-135 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.28 (s, 3H), 5.03 (q, J=9 Hz, 2H), 7.10-7.53 (m, 2H), 7.72 (dd, J=1 Hz, 7 Hz 1H), 7.92 (d, J=8 Hz, 2H), 8.07 (d, J=8 Hz, 2H), 8.38 (s, 1H). MS (DCI/NH_3) m/z 528 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{13}F_7N_2O_4S$: C, 47.66; H, 3.09; N, 5.05. Found. C, 47.68; H, 2.95; N, 5.16.

Example 264

2-(2,2,2-Trifluoroethyl)-4-(4-cyanophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-cyanophenol in place of neopentyl alcohol (yield: 109 mg, 71%). mp 179-181 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 5.02 (q, J=9 Hz, 2H), 7.25 (d, J=9 Hz, 2H), 7.81 (d, J=9 Hz, 2H), 7.86 (d, J=8 Hz, 2H), 8.03 (d, J=8 Hz, 2H), 8.37 (s, 1H). MS (DCI/NH_3) m/z 467 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{14}F_3N_3O_4S$: C, 53.45; H, 3.14; N, 9.35. Found. C, 53.19; H, 3.01; N, 9.09.

Example 265

2-(2,2,2-Trifluoroethyl)-4-(3-pyridyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 3-hydroxypyridine in place of neopentyl alcohol (yield: 120 mg, 69%). mp 191-193 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 5.01 (q, J=9 Hz, 2H), 7.36 (dd, J=3 Hz, 8 Hz, 1H), 7.55 (ddd, J=1 Hz, 3 Hz, 8 Hz, 1H), 7.88 (d, J=8 Hz, 2H), 8.04 (d, J=8 Hz, 2H), 8.31 (dd, J=1 Hz, 5 Hz, 1H), 8.36 (s, 1H), 8.38 (d, J=3 Hz, 1H). MS

(DCI/NH_3) m/z 426 $(M+H)^+$, 443 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{14}F_3N_3O_4S$: C, 50.82; H, 3.32; N, 9.88. Found: C, 50.95; H, 3.57; N, 9.71.

Example 266

2-(2,2,2-Trifluoroethyl)-4-(4-n-propylphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-(n-propyl)phenol in place of neopentyl alcohol (yield: 147 mg, 77%). mp 152-153 °C ^1H NMR (300 MHz, DMSO-d_6) δ 0.87 (t, J=7 Hz, 3H), 1.54 (h, J=7 Hz, 2H), 3.25 (s, 3H), 5.00 (q, J=9 Hz, 2H), 6.88 (d, J=9 Hz, 2H), 7.09 (d, J=9 Hz, 2H), 7.87 (d, J=8 Hz, 2H), 8.02 (d, J=8 Hz, 2H), 8.32 (s, 1H). MS (DCI/NH_3) m/z 484 $(M+H)^+$. Anal. calc. for $C_{22}H_{21}F_3N_2O_4S$: C, 56.33; H, 4.54; N, 6.01. Found: C, 56.23; H, 4.75; N, 5.79.

Example 267

2-(2,2,2-Trifluoroethyl)-4-[4-(methylsulfonyl)phenoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-(methylsulfonyl)phenol in place of neopentyl alcohol (yield: 115 mg, 56%). mp 212-213 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.21 (s, 3H), 3.27 (s, 3H), 5.03 (q, J=9 Hz, 2H), 7.31 (d, J=9 Hz, 2H), 7.83-7.89 (m, 4H), 8.04 (d, J=8 Hz, 2H), 8.40 (s, 1H). MS (DCI/NH_3) m/z 520 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_6S_2$: C, 47.81; H, 3.41; N, 5.58. Found: C, 47.92; H, 3.18; N, 5.52.

Example 268

2-(2,2,2-Trifluoroethyl)-4-(4-phenylphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-phenylphenol in place of neopentyl alcohol (yield: 105 mg, 51%). mp 163-165 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 5.02 (q, J=9 Hz, 2H), 7.10 (d, J=8

Hz, 2H), 7.33 (br t, J=7 Hz, 1H), 7.44 (t, J=7 Hz, 2H), 7.57-7.63 (m, 4H), 7.92 (d, J=8 Hz, 2H), 8.04 (d, J=8 Hz, 2H), 8.37 (s, 1H). MS (DCI/NH_3) m/z 518 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{19}F_3N_2O_4S$: C, 60.00; H, 3.83; N, 5.60. Found: C, 60.18; H, 3 66; N, 5.52.

Example 269

2-(2,2,2-Trifluoroethyl)-4-[2-(methylthio)ethoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-(methylthio)ethanol in place of neopentyl alcohol (yield: 105 mg, 61%). mp 103-105 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 2.01 (s, 3H), 2.72 (t, J=7 Hz, 2H), 3.29 (s, 3H), 4.59 (t, J=7 Hz, 2H), 5.03 (q, J=9 Hz, 2H), 7.91 (d, J=8 Hz, 2H), 8.04 (d, J=8 Hz, 2H), 8.15 (s, 1H). MS (DCI/NH_3) m/z 423 $(M+H)^+$, 440 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{17}F_3N_2O_4S_2$: C, 45.49; H, 4.06; N, 6.33. Found: C, 45.83; H, 4.11; N, 6.42.

Example 270

2-(2,2,2-Trifluoroethyl)-4-(phenylmethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting benzyl alcohol in place of neopentyl alcohol (yield: 137 mg, 76%). mp 121-123 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.28 (s, 3H), 5.06 (q, J=9 Hz, 2H), 5.48 (s, 2H), 7.20-7.25 (m, 2H), 7.27-7.81 (m, 3H), 7.76 (d, J=8 Hz, 2H), 7.98 (d, J=8 Hz, 2H), 8.12 (s, 1H). MS (DCI/NH_3) m/z 456 $(M+H)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_4S$: C, 54,79; H, 3.91; N, 6.39. Found: C, 55.10; H, 3.91; N, 6.13.

Example 271

2-(2,2,2-Trifluoroethyl)-4-(2-furylmethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-(hydroxymethyl)furan in place of neopentyl alcohol (yield: 101 mg, 58%)

mp 113-115 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.28 (s, 3H), 5.07 (q, J=9 Hz, 2H), 5.52 (s, 2H), 6.41 (dd, J=2 Hz, 3 Hz, 1H), 6.45 (d, J=4 Hz, 1H), 7.62 (d, J=2 Hz, 1H), 7.69 (d, J=8 Hz, 2H), 7.97 (d, J=8 Hz, 2H), 8.13 (s, 1H). MS (DCI/NH_3) m/z 446 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{15}F_3N_2O_5S$: C, 50.66; H, 3.80; N, 6.21. Found: C, 51.02; H, 3.71; N, 6.23.

Example 272

2-(2,2,2-Trifluoroethyl)-4-[2-(3,4-dimethoxyphenyl)ethoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-(3,4-dimethoxyphenyl)ethanol in place of neopentyl alcohol (yield: 118 mg, 56%). mp 133-134 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.82 (t, J=7 Hz, 2H), 3.28 (s, 3H), 3.63 (s, 3H), 3.70 (s, 3H), 4.68 (t, J=7 Hz, 2H), 5.01 (q, J=9 Hz, 2H), 6.61 (dd, J=2 Hz, 8 Hz, 1H), 6.74 (d, J=2 Hz, 1H), 6.77 (d, J=8 Hz, 1H), 7.74 (d, J=8 Hz, 2H), 7.93 (d, J=8 Hz, 2H), 8.11 (s, 1H). MS (DCI/NH_3) m/z 530 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}F_3N_2O_6S$: C, 53.90; H, 4.52; N, 5 47. Found: C, 53.87; H, 4.48; N, 5.45.

Example 273

2-(2,2,2-Trifluoroethyl)-4-[2-(4-morpholino)ethoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-(2-hydroxyethyl)morpholine in place of neopentyl alcohol (yield: 111 mg, 59%). mp 147-148 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.23 (m, 4H), 2.46 (t, J=5 Hz, 2H), 3.28 (s, 3H), 3.40 (m, 4H), 4.60 (t, J=5 Hz, 2H), 5.02 (q, J=8 Hz, 2H), 7.96 (d, J=8 Hz, 2H), 8.03 (d, J=8 Hz, 2H), 8.17 (s, 1H). MS (DCI/NH_3) m/z 462 $(M+H)^+$. Anal. calc. for $C_{19}H_{22}F_3N_3O_5S$: C, 49.45; H, 4.81; N, 9.11. Found: C, 49.59; H, 4.80; N, 8.88.

Example 274

2-(2,2,2-Trifluoroethyl)-4-[2-(1-piperidinyl)ethoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 1-(2-hydroxyethyl)piperidine in place of neopentyl alcohol (yield: 103 mg, 55%). mp 117-118 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (br s, 6H), 2.20 (br s, 4H), 2.41 (t, J=4 Hz, 2H), 3.28 (s, 3H), 4.60 (t, J=5 Hz, 2H), 5.02 (q, J=9 Hz, 2H), 7.97 (d, J=8 Hz, 2H), 8.03 (d, J=8 Hz, 2H), 8.15 (s, 1H). MS (DCI/NH_3) m/z 460 $(M+H)^+$. Anal. calc. for $C_{20}H_{24}F_3N_3O_4S$: C, 52.28; H, 5.26; N, 9.15. Found: C, 52.22; H, 5.08; N, 8.94.

Example 275

2-(2,2,2-Trifluoroethyl)-4-[4-(carboxamido)phenoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-hydroxybenzamide in place of neopentyl alcohol (yield: 50 mg, 26%). mp > 250 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H), 5.02 (q, J=8 Hz, 2H), 7.08 (d, J=9 Hz, 2H), 7.30 (s, 1H), 7.82 (d, J=9 Hz, 2H), 7.88 (d, J=8 Hz, 2H), 7.92 (s, 1H), 8.03 (d, J=8 Hz, 2H), 8.47 (s, 1H). MS (DCI/NH_3) m/z 468 $(M+H)^+$, 485 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{16}F_3N_3O_5S$: C, 51.39; H, 3.45; N, 8.99. Found. C, 51.31; H, 3.28; N, 8.77.

Example 276

2-(2,2,2-Trifluoroethyl)-4-(1-indanyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 1-indanol in place of neopentyl alcohol (yield: 84 mg, 44%). mp 113-114 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.07-2.14 (m, 1H), 2.22-2.35 (m, 1H), 2.73 (dd, J=5 Hz, 7 Hz, 2H), 3.24 (s, 3H), 5.00-5.22 (m, 2H), 6.48 (dd, J=2 Hz, 6 Hz, 1H), 7.12-7.24 (m, 2H), 7.21-7.28 (m, 2H), 7.44 (d, J=8 Hz, 2H), 7.87 (d, J=8 Hz, 2H), 8.09 (s, 1H). MS (DCI/NH_3) m/z 482 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{19}F_3N_2O_4S$: C, 57.19; H, 4.48; N, 5.80. Found: C, 57.36; H, 4.30; N, 5.78.

Example 277

2-(2,2,2-Trifluoroethyl)-4-[4-(acetamido)phenoxy)]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 4-acetamidophenol in place of neopentyl alcohol (yield: 45 mg, 23%). mp 215-216 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.02 (s, 3H), 3.26 (s, 3H), 5.02 (q, J=8 Hz, 2H), 6.61-6.65 (m, 1H), 7.17-7.20 (m, 2H), 7.34 (br s, 1H), 7.88 (d, J=9 Hz, 2H), 8.03 (d, J=8 Hz, 2H), 8.36 (s, 1H), 9.97 (s, 1H). MS (DCI/NH_3) m/z 499 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{18}F_3N_3O_5S$: C, 52.39; H, 3.77; N, 8.73. Found: C, 52.57; H, 4.02; N, 8.37.

Example 278

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 2-methylpropanol in place of neopentyl alcohol (yield: 111 mg, 50%). mp 108-110 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.77 (d, J=6.4 Hz, 6H), 1.52 (sept, J=6.4 Hz, 1H), 3.28 (s, 3H), 4.17 (d, J=6 Hz, 2H), 5.02 (q, J=9 Hz, 2H), 7.88 (d, J=9 Hz, 2H), 8.04 (d, J=9 Hz, 2H), 8.14 (s, 1H). MS (DCI/NH_3) m/z 405 $(M+H)^+$, 422 $(M+NH_4)^+$. Anal. calc. for $C_{17}H_{19}F_3N_2O_4S$ C, 50.49; H, 4.74; N, 6.93. Found: C, 50.69, H, 4.89; N, 6.75.

Example 279

2-(2,2,2-Trifluoroethyl)-4-(1-methylcyclopropylmethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 1-methylcyclopropanemethanol in place of neopentyl alcohol (yield: 360 mg, 75.5%). mp 98-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.35 (dt, J=40 Hz, 5 Hz, 4H), 0.91 (s, 3H), 3.11 (s, 3H), 4.32 (s, 2H), 4.82 (q, J=8.5 Hz, 2H), 7.80 (d, J=8.5 Hz, 2H), 7.84 (s,

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1H), 8.06 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 417 $(M+H)^+$, m/z 434 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{19}F_3N_2O_4S$: C, 51.92; H, 4.60; N, 6.73. Found: C, 51.87; H, 4.72; N, 6.69.

Example 280

2-(2,2,2-Trifluoroethyl)-4-(3,3-dimethylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 261, substituting 3,3-dimethyl-1-butanol in place of neopentyl alcohol (yield: 270 mg, 67.4%). mp 83-85 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.56 (t, J=8 Hz, 2H), 4.60 (t, J=8 Hz, 2H), 4.83 (q, J=8.5 Hz, 2H), 7.73 (d, J=8.5 Hz, 2H), 7.81 (s, 1H), 8.05 (d, J=8.5 Hz, 2H). MS (DCI/NH_3) m/z 433 $(M+H)^+$, m/z 450 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{23}F_3N_2O_4S$: C, 52.77; H, 5.36; N, 6.48. Found: C, 52.95; H, 5.29; N, 6.35.

Example 281

2-(3,4-Difluorophenyl)-4-(4-chlorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of 2-benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (187 mg, 0.5 mmol), prepared in Example 78, p-chlorophenol (129 mg, 0.5 mmol) and NaH (60% oil suspension) (40 mg, 1 mmol) in THF (25 mL) was refluxed at 50 °C for 3 hours and then concentrated in vacuo. The residue was partitioned between water and ethyl acetate. The acetate layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide 2-benzyl-4-(4-chlorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 200 mg, 82%).

The above derivative was dissolved in toluene (25 mL) and was treated with $AlBr_3$ (400 mg, 1.5 mmol) for 20 minutes at 80 °C. The mixture was cooled to room temperature and poured into ice-10% citric acid-ethyl acetate. The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo to provide crude desbenzyl derivative. This compound was immediately dissolved in pyridine (50 mL) and was treated with 3,4-

difluorobromobenzene (0.17 mL, 1.5 mmol), Cu (20 mg) and K_2CO_3 (100 mg, 1.5 mmol) at reflux for 16 hours. After the mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate and was washed with water, 10% citric acid and brine. Purification by column chromatography (silica gel, 1:1 hexanes-ethyl acetate) provided the title compound (yield: 73 mg, 30%). mp 192-194 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.22 (s, 3H), 7.13 (m, 2H), 7.35 (m, 2H), 7.50 (m, 1H), 7.60 (m, 1H), 7.75 (m, 1H), 7.87 (d, J=9 Hz, 2H), 8.05 (d, J=9 Hz, 2H), 8.41 (s, 1H). MS (APCI+) m/z 488 $(M+H)^+$ and (APCI-) m/z 523 $(M+Cl)^-$.

Example 282

2-(3,4-Difluorophenyl)-4-(4-bromophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 281 , substituting p-bromophenol in place of p-chlorophenol (yield: 54 mg, 20%). mp 196-199 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.25 (s, 3H), 7.09 (d, J=9 Hz, 2H), 7.47 (d, J=9 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.78 (m, 1H), 7.89 (d, J=9 Hz, 2H), 8.05 (d, J=9 Hz, 2H), 8.41 (s, 1H). MS (APCI+) m/z 533 $(M+H)^+$ and (APCI-) m/z 569 $(M+Cl)^-$.

Example 283

2-(2,2,2-Trifluoroethyl)-4-(cyclopentylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of NaH (26 mg, 1.1 mmol) in acetonitrile (3.0 mL), under nitrogen, was added cyclopentyl mercaptan (120 µL, 1.1 mmol) dropwise via syringe. The resulting solution was flushed with nitrogen for a period of 20 minutes; after which 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 193E, (200 mg, 0 52 mmol) was added in one portion. The solution was stirred for an additional 20 minutes at which time, all the 4-bromo pyridazinone was consumed. The solution was analyzed by TLC (1:1, ethyl acetate-Hex). Water (5 mL) was carefully added and the reaction partitioned between ethyl acetate (125 mL) and saturated saline (50

mL). The organic layer is washed with saturated saline (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Silica gel chromatography (20% ethyl acetate-80% hexanes) provided a pale yellow solid (yield: 202 mg. 83.1%). mp 149-151 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.34 (m, 2H), 1.62-1.54 (m, 4H). 1.93-1.88 (m, 2H), 3.13 (s, 3H), 4.40-4.35 (m, 1H), 4.85 (q, J=8.2 Hz, 2H). 7.58 (d, J=8.5 Hz, 2H), 7.66 (s, 1H), 8.06 (d, J=8.4 Hz, 2H). MS (DCI/NH_3) m/z 432 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{19}F_3N_2O_3S_2$: C, 49.99; H, 4.43; N, 6.48. Found: C, 50.15; H, 4.39; N, 6.45.

Example 284

2-(2,2,2-Trifluoroethyl)-4-(1H-1,2,4-triazole-3-ylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283 , substituting 1H-1,2,4-triazole-3-thiol in place of cyclopentyl mercaptan (yield: 164 mg, 93%). mp 197-200 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 4.84 (q, J=8.1 Hz, 2H), 7.41 (s, 1H), 7.68 (d, J=6.8 Hz, 2H), 7.83 (s, 1H), 8.00 (d, J=7.1 Hz, 2H), 8.05 (s, 1H). MS (DCI/NH_3) m/z 431 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{15}H_{12}F_3N_2O_3S_2$: C, 41.76; H, 2.80 ; N, 16.23. Found: C, 41.68; H, 2.85; N, 15.99.

Example 285

2-(2,2,2-Trifluoroethyl)-4-phenylmethylthio-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283 , substituting benzyl mercaptan in place of cyclopentyl mercaptan (yield: 141 mg, 76%). mp 108-111 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 3H). 4.38 (s, 2H), 4.87 (q, J=Hz, 2H). 7.10-7.06 (m, 2H), 7.22-7.20 (m, 5H). 7.59 (s, 1H). 7.95 (d, J=8.5 Hz, 2H). MS (DCI/NH_3) m/z 454 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{17}F_3N_2O_3S_2$, 0.75 EtOAc: C, 53.06; H, 4.45 ; N, 5.38. Found: C, 53.55; H, 4.16; N, 5.84.

Example 286

2-(2,2,2-Trifluoroethyl)-4-(4-fluorophenylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 283 , substituting 4-fluorophenylmethyl mercaptan in place of cyclopentyl mercaptan (yield: 184 mg, 73.5%). mp 182-185 °C. ^{1}H NMR (300 MHz. $CDCl_3$) δ 3.08 (s, 3H). 4.82 (q, J=8.5 Hz, 2H), 6.87-6.81 (m, 2H). 7.19-7.11 (m, 2H). 7.48 (d. J=9.0 Hz, 2H). 7.68 (s, 1H). 7.93 (d, J=8.5 Hz, 2H). MS (DCI/NH_3) m/z 458 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{14}F_4N_2O_3S_2$: C, 49.78: H, 3.08 : N, 6.11. Found: C. 49.89 ; H, 3.18 ; N, 5.86

Example 287

2-(2,2,2-Trifluoroethyl)-4-(cyclohexylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 283 , substituting cyclohexyl mercaptan in place of cyclopentyl mercaptan (yield: 189 mg, 78%). mp 165-167 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28-1.17 (m, 5H). 1.64-1.56 (m, 3H). 1.82-1.79 (m, 2H), 3.13 (s, 3H), 4.08-4.05 (m, 1H). 4.86 (q, J=8.5 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H). 7.67 (s, 1H). 8.06 (d. J=8.5 Hz, 2H). MS (DCI/NH_3) m/z 446 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{21}F_3N_2O_3S_2$: C, 51.11; H. 4.74 : N, 6.27. Found: C, 51.39 ; H, 4.72 ; N, 5.91.

Example 288

2-(2,2,2-Trifluoroethyl)-4-(3-chloro-4-fluorophenylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 283 , substituting 3-chloro-4-fluorothiophenol in place of cyclopentyl mercaptan (yield: 190 mg, 65%). mp 142-145 °C. ^{1}H NMR (300 MHz. $CDCl_3$) δ 3.18 (s. 3H), 4.85 (q. J=8.4 Hz, 2H), 6.96 (ov. t, J=8.5 Hz, 1H). 7.14-7.10 (m, 1H), 7.18 (dd. J=2.1, 6.5 Hz. 1H,), 7.53 (d, J=8.4 Hz, 2H), 7.77 (s, 1H), 7.96 (d. J=8.0 Hz, 2H). MS (CI) m/z 493 $(M+1)^+$, $(M+NH_4)^+$.

Anal. calc. for $C_{19}H_{13}ClF_4N_2O_3S_2.0.25\ C_6H_6.H_2O$: C, 47.36 ; H, 2.92; N, 5.41. Found: C, 47.88 ; H, 2.95; N, 5.24.

Example 289

2-(2,2,2-Trifluoroethyl)-4-(2,2,2-trifluoroethylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283, substituting 2,2,2-trifluoroethyl mercaptan in place of cyclopentyl mercaptan (yield: 175 mg, 66%). mp 155-158 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 3H), 3.98 (q, J=9.8 Hz, 2H), 4.86 (q, J=8.1 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H), 7.75 (s, 1H), 8.10 (d, J=8.4 Hz, 2H). MS (DCI/NH_3) m/z 446 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{15}H_{12}F_6N_2O_3S_2$: C, 40.36 ; H, 2.71; N, 6.28. Found: C, 40.50; H, 2.72; N, 6.01.

Example 290

2-(2,2,2-Trifluoroethyl)-4-(tert-butylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283 , substituting tert-butyl mercaptan in place of cyclopentyl mercaptan (yield: 212 mg, 85%). mp 186-189 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 3.13 (s, 3H), 4.87 (q, J=8.1 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H), 7.67 (s, 1H), 8.05 (d, J=8.1 Hz, 2H). MS (ESI) m/z 420 $(M+H)^+$, $(M+Na)^+$. Anal. calc. for $C_{17}H_{19}F_3N_2O_3S_2$: C, 48.56 ; H, 4.55; N, 6.66. Found: C, 50.15; H, 4.39; N, 6.45.

Example 291

2-(2,2,2-Trifluoroethyl)-4-(4-acetamidophenylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283 , substituting 4-acetamidothiophenol in place of cyclopentyl mercaptan (yield: 100 mg, 37%). mp 191-193 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.08 (s, 3H), 4.83 (q,

J=8.2 Hz, 2H), 7.00 (d, J=8.8 Hz, 2H), 7.19 (d, J=8.8 Hz, 2H), 7.31 (d, J=8.1 Hz, 2H), 7.58 (s, 1H), 7.78 (d, J=8.1 Hz, 2H). MS (CI) m/z 497 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{18}F_3N_3O_4S_2.0.25H_2O$. 0.25 C_6H_6: C, 52.83; H, 4.06; N, 7.70. Found: C, 52.97; H, 3.85; N, 7.65.

Example 292

2-(2,2,2-Trifluoroethyl)-4-(2-propylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283 , substituting isopropyl mercaptan in place of cyclopentyl mercaptan (yield: 180 mg, 81%). mp 165-167 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J=6.8 Hz, 6H), 3.13 (s, 3H), 4.33 (p, J=6.8 Hz, 1H), 4.86 (q, J=8.5 Hz, 2H), 6.59 (d, J=8.5 Hz, 2H), 7.68 (s, 1H), 8.07 (d, J=8.1 Hz, 2H). MS (DCI/NH_3) m/z 406 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{17}F_3N_2O_3S_2$, 0.75H_2O. C, 45.76 ; H, 4.4; N, 6.67. Found: C, 45.91; H, 3.98; N, 6.46.

Example 293

2-(2,2,2-Trifluoroethyl)-4-(2-methylprop-1-ylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 283 , substituting 2-methyl-1-propyl mercaptan in place of cyclopentyl mercaptan (yield: 100 mg, 83%). mp 135-138 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J=6.4 Hz, 6H), 1.67-1.60 (m, 1H), 3.00 (d, J=6.7 Hz, 2H), 3.14 (s, 3H), 4.84 (q, J=8.5 Hz, 2H), 7.61 (d, J=8.4 Hz, 2H), 7.67 (s, 1H), 8.08 (d, J=8.5 Hz, 2H). MS (DCI/NH_3) m/z 420 $(M+H)^+$, $(M+NH_4)^+$. Anal. calc. for $C_{17}H_{19}F_3N_2O_3S_2$: C, 48.56 ; H, 4.55; N, 6.66. Found: C, 47.86; H, 4.57; N, 6.51.

Example 294

2-(2,2,2-Trifluoroethyl)-4-amino-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared according to Example 193E, (500 mg, 1.36 mmol) was dissolved in DMF (10 mL) and treated with NaN_3 (100 mg, 1 5 mmol). After 2 hours at room temperature, the reaction was diluted with ethyl acetate and washed with water. 4 times, and dried over $MgSO_4$. After filtration of the drying agent and concentration of the filtrate in vacuo, the residue was purified by chromatography on silica gel (Biotage 40S) eluted with 2:1 hexanes-ethyl acetate. The product fractions were combined and evaporated to provide the azido intermediate, 2-(2,2.2-Trifluoroethyl)-4-azido-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 481 mg, 95%).

The 4-azido-compound above (39 mg, 0.105 mmol) was dissolved in THF (3 mL) and MeOH (2 mL) and treated with excess $NaBH_4$. After 15 minutes, the reaction was quenched with saturated NH_4Cl solution and the product was extracted into ethyl acetate. The organic layer was washed with water, 3 times, and dried over $MgSO_4$. Filtration of the drying agent and evaporation of the solvent provided the title compound (yield: 26 mg, 71%). mp > 260 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.26 (s, 3H). 4.93 (q, J=9 Hz, 2H), 6.71 (s, 2H), 7.72 (s, 1H), 7.76 (d, J=8 Hz, 2H), 8.02 (d, J=8 Hz, 2H). MS (ESI-) m/z 346 $(M-H)^-$. Anal. calc. for $C_{13}H_{12}F_3N_3O_3S$: C, 44.96; H, 3.48; N, 12.10. Found: C, 44.59; H, 3.52; N, 11.93.

Example 295

2-(2,2,2-Trifluoroethyl)-4-(3-methoxypropylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (200 mg, 0.546 mmol), prepared according to the method of Example 193E, and 3-methoxypropylamine (145 mg, 1.64 mmol) in pyridine (4 mL) was heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, mixed with silica gel (2 g), and the solvent removed under reduced pressure. The adsorbed silica gel was layered over an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of 60 mL of each of the

following mixtures: hexanes, 8:1 hexanes/acetone, 4:1, 2:1, and 1:1. Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5 sil silica column, 20 mm x 25 cm). The column was eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min over 50 minutes. Fractions containing product were combined and concentrated under reduced pressure to provide the product as off-white crystals (yield: 215 mg, 95%). mp 110-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J=18.0 Hz, 2H), 7.55 (d, 2H, J=18.0 Hz), 7.48 (s, 1H), 6.57 (br t, 1H, J=9.0 Hz), 4.81 (q, J=17.4 Hz, 2H), 3.33 (t, J=12.0 Hz, 2H), 3.28 (s, 3H), 3.12 (s, 3H), 2.76 (dt, J=12.0, 12.0 Hz, 2H), 1.65 (tt, J=12.0, 12.0, Hz, 2H). MS (DCI/NH_3) m/z 420 $(M+H)^+$, m/z 437 $[M+NH_4]^+$. Anal. calc. for $C_{17}H_{20}F_3N_3O_4S$: C, 48.68; H, 4.81; N, 10.02. Found: C, 48.74; H, 4.69; N, 9.84.

Example 296

2-(2,2,2-Trifluoroethyl)-4-(cyclopentylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting cyclopentylamine in place of 3-methoxypropylamine to provide brown crystals (yield: 195 mg, 86%). mp 134-139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J=18.0 Hz, 2H), 7.56 (d, J=18.0 Hz, 2H), 7.45 (s, 1H), 6.12 (br d, J=16.8 Hz, 1H), 4.79 (q, J=17.4 Hz, 2H), 3.33 (br m, 1H), 3.12 (s, 3H), 1.64-1.23 (br m, 8H). MS (DCI/NH_3) m/z 416 $(M+H)^+$, m/z 433 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{20}F_3N_3O_3S$: C, 52.04; H, 4.85; N, 10.11. Found: C, 52.40; H, 4.93; N, 10.03.

Example 297

2-(2,2,2-Trifluoroethyl)-4-(cyclobutylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting cyclobutylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 206 mg, 94%). mp 169-172 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J=17.4 Hz, 2H),

7.54 (d, J=17.4 Hz, 2H), 7.45 (s, 1H), 6.28 (br d, J=16.2 Hz, 1H), 4.81 (q, J=17.4 Hz, 2H), 3.42 (m, 1H), 3.13 (s, 3H), 1.79 (m, 4H), 1.64 (m, 1H), 1.39 (m, 1H). MS (DCI/NH_3) m/z 402 $(M+H)^+$, m/z 419 $(M+NH_4)^+$. Anal calc. for $C_{17}H_{18}F_3N_3O_3S.0.25\ CH_3COCH_3$: C, 51.25; H, 4.72; N, 10.10; found: C, 51.38; H, 4.68; N, 10.25.

Example 298

2-(2,2,2-Trifluoroethyl)-4-(3,4-dimethoxyphenethylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting 3,4-dimethoxyphenethylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 206 mg, 94%). mp 163-165 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J=18.0 Hz, 2H), 7.52 (d, J=18.0 Hz, 2H), 7.45 (s, 1H), 6.75 (d, J=16.2 Hz, 1H), 6.50 (m, 2H), 6.16 (br d, J=11.4 Hz, 1H), 4.79 (q, J=17.4 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.11 (s, 3H), 2.91 (dt, J=12.6, 12.6 Hz, 2H), 2.60 (t, J=13.8 Hz, 2H). MS (DCI/NH_3) m/z 529 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{29}F_3N_3O_5S$. C, 54.01; H, 4.73; N, 8.21. Found: C, 54.30; H, 4.69; N, 8.16.

Example 299

2-(2,2,2-Trifluoroethyl)-4-(cyclohexylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting cyclohexylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 103 mg, 42%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J=18.0 Hz, 2H), 7.58 (d, J=18.0 Hz, 2H), 7.44 (s, 1H), 6.06 (br d, J=18.6 Hz, 1H), 4.81 (q, J=18.0 Hz, 2H), 3.11 (s, 3H), 2.70 (m, 1H), 1.66-1.48 (m, 4H), 1.42 (m, 1H), 1.07 (m, 3H), 0.76 (m, 2H). MS (DCI/NH_3) m/z 430 $(M+H)^+$, m/z 447 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{22}F_3N_1O_3S$: C, 53.14; H, 5.16; N, 9.78. Found: C, 52.86, H, 5.06, N, 9.52.

Example 300

2-(2,2,2-Trifluoroethyl)-4-[2-(1-piperidinyl)ethylamino]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting 2-(1-piperdinyl)ethylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 210 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J=18.0 Hz, 2H), 7.56 (d, J=18.0 Hz, 2H), 7.49 (s, 1H), 6.91 (br, 1H), 4.82 (q, J=18.0 Hz, 2H), 3.13 (s, 3H), 2.64 (br, 2H), 2.32 (br, 4H), 1.58 (br, 6H), 1.42 (br, 2H). MS (DCI/NH_3) m/z 459 $(M+H)^+$. Anal. calc. for $C_{19}H_{22}F_3N_3O_3S$. C, 52.39; H, 5.50; N, 12.22. Found: C, 52.64; H, 5.59; N, 12.00.

Example 301

2-(2,2,2-Trifluoroethyl)-4-(2-tetrahydrofurfurylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting tetrahydrofurfurylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 150 mg, 64%). mp 128-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J=18.0 Hz, 2H), 7.56 (d, J=18.0 Hz, 2H), 7.47 (s, 1H), 6.48 (br t, J=9.0 Hz, 1H), 4.81 (q, J=18.0 Hz, 2H), 3.84 (m, 2H), 3.72 (m, 1H), 3.12 (s, 3H), 2.83 (m, 1H), 2.64 (m, 1H), 1.84 (m, 3H), 1.34 (m, 1H). MS (DCI/NH_3) m/z 432 $(M+H)^+$, m/z 449 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{20}F_3N_3O_3S$: C, 50.11; H, 4.67; N, 9.74. Found: C, 50.25; H, 4.68; N, 9.68.

Example 302

2-(2,2,2-Trifluoroethyl)-4-(cyclopropylmethylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting cyclopropylmethylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 130 mg, 59%). mp 145-146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J=18.0 Hz, 2H), 7.53 (d, J=18.0 Hz, 2H), 7.48 (s, 1H), 6.20 (br, 1H), 4.82 (q, J=18.0 Hz, 2H), 3.12 (s, 3H), 2.45 (br d, J=13.2 Hz, 2H), 0.88 (m, 1H), 0.51 (m, 2H), 0.10 (m, 2H). MS

(DCI/NH_3) m/z 402 $(M+H)^+$, m/z 419 $(M+NH_4)^+$. Anal. calc. for $C_{17}H_{18}F_3N_3O_3S$. C, 50.87; H, 4.52; N, 10.47. Found: C, 51.00; H, 4.52; N, 10.44.

Example 303

2-(2,2,2-Trifluoroethyl)-4-(2,3-dihydro-1H-inden-1-ylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting 1-indanylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 82 mg, 32%). mp 155-158 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J=18.0 Hz, 2H), 7.68 (d, J=18.0 Hz, 2H), 7.49 (s, 1H), 7.27-7.14 (m, 4H), 6.30 (br d, J=18.0 Hz, 1H), 4.81 (q, J=18.0 Hz, 2H), 4.57 (m, 1H), 3.09 (s, 3H), 2.89 (m, 1H), 2.60 (m, 1H), 1.85 (m, 1H), 1.68 (m, 1H). MS (ESI (-) m/z 462 $(M-H)^-$. Anal. calc. for $C_{22}H_{20}F_3N_3O_3S$: C, 57.01; H, 4.35; N, 9.07. Found: C, 57.30; H, 4.45; N, 8.86.

Example 304

2-(2,2,2-Trifluoroethyl)-4-(1-piperidinyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting piperidine in place of 3-methoxypropylamine to provide an off-white solid (yield: 180 mg, 79%). mp 160-161 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J=18.0 Hz, 2H), 7.58 (s, 1H), 7.46 (d, J=18.0 Hz, 2H), 4.80 (q, J=18.0 Hz, 2H), 3.13 (s, 3H), 2.96 (m, 4H), 1.65-1.52 (m, 6H). MS (DCI/NH_3) m/z 416 $(M+H)^+$. Anal. calc. for $C_{18}H_{20}F_3N_3O_3S.H_2O$: C, 52.04; H, 4.85; N, 10.11. Found: C, 52.21; H, 5.02; N, 9.75.

Example 305

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxypropylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting 3-hydroxypropylamine in place of 3-methoxypropylamine to provide a white solid (yield:

109.6 mg, 50%). mp 152-154 °C. ^{1}H NMR (300 MHz, CDCl3) δ 8.02 (d, J=18.0 Hz, 2H), 7.56 (d, J=18.0 Hz, 2H), 7.48 (s, 1H), 6.48 (br, 1H), 4.79 (q, J=17.4 Hz, 2H), 3.63 (t, J=12.0 Hz, 2H), 3.12 (s, 3H), 2.81 (dt, J=12.0, 12.0 Hz, 2H), 1.65 (tt, J=12.0, 12.0 Hz, 2H). MS (DCI/NH_3) m/z 406 $(M+H)^+$, m/z 423 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{18}F_3N_3O_4S$: C, 47.41; H, 4.48; N, 10.37. Found: C, 47.53; H, 4.33, N, 10.27.

Example 306

2-(2,2,2-Trifluoroethyl)-4-[3-(1H-imidazol-1-yl)propylamino]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting 1-(3-aminopropyl)imidazole in place of 3-methoxypropylamine. The reaction mixture was concentrated to dryness and the residue purified using RP-HPLC (Rainin Dynamax C-18 column, 60 Å pore size, 21.4 mm i.d.). The column was eluted with a linear gradient consisting of 20% acetonitrile (containing 0.1% TFA)/80% water (containing 0.1% TFA) to 100% acetonitrile (containing 0.1% TFA) at 15 mL/min over 70 minutes. The peak corresponding to the title product was collected and lyophilized to provide a tan hygroscopic foam (yield: 70.2 mg, 28%). ^{1}H NMR (300 MHz, DMSO) δ 8.95 (br s, 1H), 7.97 (d, J=16.8 Hz, 2H), 7.66 (d, J=16.2 Hz, 2H), 7.61 (s, 1H), 7.58 (d, J=15.0 Hz, 2H), 6.99 (br t, 1H, J=13.2 Hz), 4.97 (dt, J=18.0, 18.0 Hz, 2H), 3.97 (t, J=13.2 Hz, 2H), 3.28 (s, 3H), 2.69 (m, 2H), 1.81 (tt, J=13.2, 13.2 Hz, 2H). MS (DCI/NH_3) m/z 456 $(M+H)^+$. Anal. calc. for $C_{19}H_{20}F_3N_5O_3S.1.4\ CF_3COOH$: C, 42.57; H, 3.51; N, 11.39. Found: C, 42.78; H, 3.58; N, 11.24.

Example 307

2-(2,2,2-Trifluoroethyl)-4-(2R-hydroxylpropylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting (R)-(-)-2-propanolamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 109.6 mg, 50%). M.p .=140-142 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d,

J=18.0 Hz, 2H), 7.56 (d, J=18.0 Hz, 2H), 7.49 (s, 1H), 6.42 (br, 1H), 4.79 (m, 2H), 3.80 (m, 1H), 3.12 (s, 3H), 2.68 (m, 2H), 1.02 (d, J=12.0 Hz, 3H). MS (DCI/NH_3) m/z 406 $(M+H)^+$, m/z 423 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{18}F_3N_3O_4S$: C, 47.41; H, 4.48; N, 10.37. Found: C, 47.56; H, 4.41; N, 10.25.

Example 308

2-(2,2,2-Trifluoroethyl)-4-(2-cyanoethylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 295 , substituting 2-cyanoethylamine in place of 3-methoxypropylamine to provide an off-white solid (yield: 27 mg, 12%). mp 172-174 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J=18.0 Hz, 2H), 7.63 (d, J=18.0 Hz, 2H), 7.51 (s, 1H), 6.08 (br t, 1H), 4.87 (q, J=18.0 Hz, 2H), 3.17 (dt, J=13.2, 13.2 Hz, 2H), 3.13 (s, 3H), 2.39 (t, J=13.2 Hz, 2H). MS (DCI/NH_3) m/z 418 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{15}F_3N_4O_3S$: C, 48.00; H, 3.78; N, 13.99. Found: C, 48.28; H, 3.77; N, 13.80.

Example 309

2-(2,2,2-Trifluoroethyl)-4-(4-cyanoanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A suspension of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (300 mg, 0.820 mmol), prepared according to the method of Example 193E, 4-aminobenzonitrile (290 mg, 2.46 mmol), and silver oxide (760 mg, 3.28 mmol) in pyridine (1.5 mL) was stirred at 80 °C for 24 hours. The reaction was cooled to room temperature, adsorbed onto silica gel (2 g) and solvent removed under reduced pressure. The adsorbed silica gel was layered over an Extract-Clean Cartridge® (Alltech, packing: 10 g silica gel) and the cartridge eluted with a hexanes/acetone step gradient consisting of 60 mL of each of the following mixtures: hexanes, 8:1 hexanes/acetone, 4:1, 2:1, and 1:1. Fractions containing desired product were combined, concentrated, and further purified using HPLC (Technikrom Kromasil 60-5sil column, 20 mm x 25 cm). The column was

eluted with a linear gradient consisting of 30% ethyl acetate/hexanes to 100% ethyl acetate at 10 mL/min over 50 minutes. Fractions containing product were combined and concentrated under reduced pressure to provide the product as a tan solid (yield: 149.9 mg, 41%). mp>230 °C. ^{1}H NMR (300 MHz, DMSO) δ 9.49 (s, 1H), 8.00 (s, 1H), 7.69 (d, J=17.4 Hz, 2H), 7.43 (d, J=16.8 Hz, 2H), 7.32 (d, J=18.0 Hz, 2H), 6.78 (d, J=18.0 Hz, 2H), 5.06 (q, J=18.0 Hz, 2H), 3.13 (s, 3H), 2.68 (m, 2H), 1.02 (d, J=12.0 Hz, 3H). MS (DCI/NH_3) m/z 466 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{15}F_3N_4O_4S$: C, 53.57; H, 3.37; N, 12.49. Found: C, 53.47; H, 3.49; N, 12.35.

Example 310

2-(2,2,2-Trifluoroethyl)-4-[3-methoxy-5-(trifluoromethyl)anilino]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting 3-methoxy-5-(trifluoromethyl)aniline in place of 4-aminobenzonitrile to provide a brown solid (yield: 226.5 mg, 80%). mp 206-208 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.77 (s, 1H), 7.71 (d, J=18.0 Hz, 2H), 7.28 (d, J=17.4 Hz, 2H), 6.61 (br s, 1H), 6.46 (br s, 1H), 6.31 (br s, 1H), 4.90 (q, J=17.4 Hz, 2H), 3 72 (s, 3H), 2.94 (s, 3H). MS (DCI/NH_3) m/z 539 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{17}F_6N_3O_4S$: C, 48.37; H, 3.29; N, 8.06. Found: C, 48.60; H, 3.33; N, 7.94.

Example 311

2-(2,2,2-Trifluoroethyl)-4-anilino-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting aniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 90 mg, 53%). mp 154-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.72 (s, 1H), 7.62 (d, J=18.0 Hz, 2H), 7.19 (d, J=18.0 Hz, 2H), 7.96-7.82 (m, 3H), 6.61 (d, J=14.4 Hz, 2H), 4.90 (q, J=18.0 Hz, 2H), 2.94 (s, 3H). MS (DCI/NH_3) m/z 424 $(M+H)^+$, m/z 441 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{16}F_3N_3O_3S$: C, 53.90; H, 3.81; N, 9.92. Found: C, 53.87; H, 3.73; N, 9.89.

Example 312

2-(2,2,2-Trifluoroethyl)-4-(2,5-dimethoxyphenylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting 2,5-dimethoxyaniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 140 mg, 53%). mp 95-96 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.72 (s, 1H), 7.63 (d, J=18.0 Hz, 2H), 7.18 (d, J=18.0 Hz, 2H), 6.54 (d, J=18.0 Hz, 1H), 6.38 (dd, J=6.0, 18.0 Hz, 1H), 4.89 (q, J=18.0 Hz, 2H), 3.73 (s, 3H), 3.47 (s, 3H), 2.96 (s, 3H). MS (DCI/NH_3) m/z 484 $(M+H)^+$, m/z 501 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{20}F_3N_3O_5S$: C, 52.17; H, 4.17; N, 8.69. Found: C, 52.47; H, 4.17; N, 8.43.

Example 313

2-(2,2,2-Trifluoroethyl)-4-(3-fluoroanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting 3-fluoroaniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 151.3 mg, 42%). mp 156-158 °C. ^{1}H NMR (300 MHz, DMSO) δ 9.18 (s, 1H), 7.91 (s, 1H), 7.62 (d, J=17.4 Hz, 2H), 7.36 (d, J=17.4 Hz, 2H), 6.88 (dd, J=15.0, 15.0 Hz, 1H), 6.56 (m, 1H), 6.49 (m, 2H), 5.04 (q, J=18.0 Hz, 2H), 3.08 (s, 3H). MS (DCI/NH_3) m/z 442 $(M+H)^+$, m/z 459 $(M+NH_4)^+$, m/z 476 $(M+2NH_4-H)^+$. Anal. calc. for $C_{19}H_{15}F_4N_3O_3S.0.5\ CH_3COCH_3$: C, 52.33; H, 3.85; N, 8.93. Found: C, 52.51; H, 3.58; N, 8.81.

Example 314

2-(2,2,2-Trifluoroethyl)-4-(2,4-difluoroanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting 2,4-difluoroaniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 63.1 mg, 17%). mp 170-175 °C. ^{1}H NMR (300 MHz, DMSO) δ 9.00 (s, 1H), 7.80 (s, 1H), 7.57 (d, J=17.4 Hz, 2H), 7.26 (d, J=17.4 Hz, 2H), 7.05 (m, 1H), 6.75 (m, 2H), 5.05 (q, J=18.0 Hz,

2H), 3.09 (s, 3H). MS (DCI/NH_3) m/z 460 $(M+H)^+$, m/z 477 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{14}F_5N_3O_3S$: C, 49.68; H, 3.07; N, 9.15; found: C, 50.00; H, 2.95; N, 9.10.

Example 315

2-(2,2,2-Trifluoroethyl)-4-(2,3,5-trifluoroanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting 2,3,5-trifluoroaniline in place of 4-aminobenzonitrile to provide a pale purple solid (yield: 85.3 mg, 22%). mp 190-194 °C. ^1H NMR (300 MHz, DMSO) δ 9.27 (s, 1H), 7.90 (s, 1H), 7.70 (d, J=17.4 Hz, 2H), 7.39 (d, J=17.4 Hz, 2H), 7.03 (m, 1H), 6.76 (m, 1H), 5.06 (q, J=18.0 Hz, 2H), 3.14 (s, 3H). MS (DCI/NH_3) m/z 495 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{13}F_6N_3O_3S$. C, 47.80; H, 2.74; N, 8.80. Found: C, 47.51; H, 2.55; N, 8.63.

Example 316

2-(2,2,2-Trifluoroethyl)-4-(4-fluoroanilino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The product was prepared according to the method of Example 309, substituting 4-fluoroaniline in place of 4-aminobenzonitrile to provide a tan solid (yield: 15.8 mg, 4%). mp 158-160 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.69 (s, 1H), 7.65 (d, J=18.0 Hz, 2H), 7.18 (d, J=18.0 Hz, 2H), 6.63 (d, J=3.6 Hz, 2H), 6.61 (s, 2H), 4.89 (q, J=17.4 Hz, 2H), 2.96 (s, 3H). MS (DCI/NH_3) m/z 459 $(M+NH_4)^+$. Anal. calc. for $C_{19}H_{15}F_4N_3O_3S.1.25\ H_2O$: C, 49.19; H, 3.80; N, 9.05. Found: C, 59.57; H, 3.53; N, 8.70.

Example 317

2-Benzyl-4-(3-thienyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone prepared in Example 78 (150 mg, 0.4 mmol), thiophene-3-boronic acid (66.5 mg, 0.52 mmol), CsF (145.8 mg, 0.96 mmol), and tetrakis-(triphenylphosphine)-palladium(0) (13.9 mg, 0.012 mmol) in DME (25 mL) were stirred at reflux for 6 hours TLC (1CH_2Cl_2:1 hexanes:1.5

ethyl acetate) indicated that all starting materials were consumed. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified using a silica gel column (0.5:2.5:0.5 CH_2Cl_2/hexanes/ethyl acetate). A yellow powder was obtained (yield: 50 mg, 31%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 3H), 5.41 (s, 2H), 6.72 (dd, J=1.5 Hz, 9 Hz, 1H), 7.13 (dd, J=3 Hz, 3 Hz, 1H), 7.3-7.45 (m, 5H), 7.5-7.6 (m, 3H), 7.78 (s, 1H), 7.92 (d, 9 Hz, 2H). MS (DCI/NH_3) m/z 423 $(M+H)^+$. Anal. calc. for $C_{22}H_{18}N_2O_3S_2$. 0.5 H_2O: C, 6.23; H, 4.43; N, 6.49. Found C, 61.29; H, 4.40; N, 6.16.

Example 318

2-Benzyl-4-(2-benzofuranyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317 , substituting 2-benzofuranboronic acid for 3-thiopheneboronic acid (yield: 46 mg, 25%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.13 (s, 3H), 5.5 (s, 2 H,), 6.85-6.92 (m, 1H), 7.15-7.25 (m, 3H), 7.3-7.42 (m, 3H), 7.45-7.7 (m, 5H), 7.79 (s, 1H) 8.0 (d, J=9 Hz, 2H), 8.08 (s, 1H). MS (DCI/NH_3), m/z 457 $(M+H)^+$. Anal. calc. for $C_{26}H_{20}N_2O_4S.H_2O$: C, 65.80; H, 4.67; N, 5.90. Found C, 65.44; H, 4.42; N, 6.14.

Example 319

2-Benzyl-4-(1-oxo-1,3-dihydro-2-benzofuran-5-yl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 221, substituting 2-benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 78, in place of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 112 mg, 44%). mp > 250 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 3.20 (s, 3H), 5.34 (s, 2H), 5.36 (s, 2H), 7.30-7.44 (m, 6H), 7.48 (d, J=8 Hz, 2H), 7.57 (s, 1H), 7.73 (d, J=8 Hz, 1H), 7.85 (d, J=8 Hz, 2H), 8.17 (s,

1H). MS (DCI/NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$ Anal. calc. for $C_{26}H_{20}N_2O_5S$: C, 65.46; H, 4.33; N, 5.87. Found: C, 65.56; H, 4.48; N, 5.75.

Example 320

2-Benzyl-4-(5-chloro-2-thienyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317, substituting 5-chloro-2-thiopheneboronic acid in place of 3-thiopheneboronic acid (yield: 21 mg, 17%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.15 (s, 3H), 5.45 (s, 2H), 6.51 (d, J=4.5 Hz, 1H), 6.7 (d, J=4.5 Hz, 1H), 7.3-7.4 (m, 3H), 7.5=7.6 (m, 4H), 7.6 (s, 1H), 8.05 (d, J=9 Hz, 2H). MS (DCI/NH_3), m/z 457 $(M+H)^+$. Anal. calc. for $C_{18}H_{15}ClN_2O_3S$: C, 57.68; H, 4.03; N, 7.47. Found C, 57.61; H, 3.84; N, 7.14.

Example 321

2-Benzyl-4-(3-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317 , substituting 3-nitrobenzeneboronic acid in place of 3-thiopheneboronic acid (yield: 20 mg, 11%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.0 (s, 3H), 5.93 (s, 2H), 7.6-7.8 (m, 9H), 7.8 (t, J=4.5 Hz, 3H), 8.04 (s, 1H), 8.15 (m, 1H). MS (DCI/NH_3), m/z 462 $(M+H)^+$. Anal. calc. for $C_{24}H_{19}N_3O_5S$. 0.75 H_2O: C, 60.68; H, 4.35; N, 8.84 Found C, 60.99; H, 3.97; N, 8.35

Example 322

2-Benzyl-4-(4-vinylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317 , substituting 4-vinylbenzeneboronic acid in place of 3-thiopheneboronic acid (yield: 40 mg, 23%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 5.28 (d, J=12 Hz, 1H), 5.41 (s, 2H), 5.74 (d, J=18 Hz, 1H) 6.65 (dd , J=12 Hz, 18 Hz, 1H), 7.1-7.6 (m, 11H) 7.83 (d, J=3 Hz, 2H), 7.85 (s, 1H). MS (DCI/NH_3), m/z 443 $(M+H)^+$. Anal. calc. for $C_{26}H_{22}N_2O_3S$. C, 70.57; H, 5.01; N, 6.33. Found C, 70.34; H, 4.67; N, 5.97.

Example 323

2-Benzyl-4-(4-trifluormethylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317, substituting 4-(trifluoromethyl)benzeneboronic acid in place of 3-thiopheneboronic acid (yield: 101 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s. 3H), 5.42 (s, 2H), 7.3-7.5 (m, 8H), 7.55-7.6 m, 3H), 7.85 (s, 2H), 7.9 (s, 1H). MS (DCI/NH_3) m/z 485 $(M+H)^+$. Anal. calc. for $C_{25}H_{19}F_3N_2O_3S.0.25\ H_2O$: C, 61.40; H, 4.01; N, 5.72. Found C, 61.26; H, 4.01; N, 5.35.

Example 324

2-Benzyl-4-(2-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 317 , substituting 2-methoxybenzeneboronic acid in place of 3-thiopheneboronic acid (yield: 75 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 3H), 3.5 (s, 3H), 5.40 (dd, J=12 Hz, 18 Hz, 2H), 6.76 (d, J=9 Hz, 1H), 6.85-6.95 (m, 1H), 7.09 (dd, J=1.5 Hz, 9 Hz, 1H), 7.26-7.41 (m, 6H), 7.55 (dd, J=1.5 Hz, 9 Hz, 2H), 7.82 (d, J=9 Hz, 3H). MS (DCI/NH_3) m/z 447 $(M+H)^+$. Anal. calc. for $C_{25}H_{22}N_2O_4S.0.5\ H_2O$: C, 65.91; H, 5.08; N, 6.14. Found C, 65.86; H, 5.08; N, 5.58.

Example 325

2-Benzyl-4-(3,4-dimethylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-Benzyl-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (150 mg, 0.4 mmol) prepared in Example 78 was dissolved in anhydrous DME (10 mL) and heated to reflux with 3,4-dimethylbenzeneboronic acid in presence of CsF (146 mg, 0.96 mmol) and tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol) for 6 hours. After cooling to room temperature the reaction mixture was diluted with water and extracted with ethyl acetate (100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The compound was purified on a silica gel column, eluting with 30% ethyl acetate in pentanes, providing the desired compound (yield: 100 mg, 56%). ^{1}H NMR

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(300 MHz, $CDCl_3$) δ 2.15, 2.20 (2s, 3H), 2.25, 2.30 (2s, 3H), 3.05, 3.08 (2s, 3H), 5.35, 5.40 (2s, 2H), 6.60-7.1 (m, 3H), 7.30-7.40 (m, 4H), 7.42-7.60 (m, 2H), 7.70-8, 02 (m, 4H). MS (DCI/NH_3) m/z 445 $(M+H)^+$. Anal. calc. for $C_{26}H_{24}N_2O_3S.H_2O$: C, 67.51; H, 5.66; N, 6.05. Found: C, 67.45;H, 5.56; N, 5.85.

Example 326

2-Benzyl-4-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 325 , substituting 3-fluoro-4-methoxybenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 35 mg, 19%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.85 (s, 3H), 5.3, 5.4 (2s, 2H), 6.75-7.03 (m, 3H), 7.3-7.40 (m, 5H), 7.4-7.55 (dd, J=1.5 Hz; 7.5 Hz, 2H), 7.8-7.95 (m, 3H). MS (DCI/NH_3) m/z 465 $(M+H)^+$. Anal. calc. for $C_{25}H_{21}N_2O_4S.0.25\ H_2O$: C, 64.02; H, 4.62; N, 5.97. Found: C, 63.93; H, 4.54; N, 5.43

Example 327

2-Benzyl-4-(2-methoxypyrid-3-yl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 325 , substituting 2-methoxy-3-pyridylboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 35 mg, 19%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.58 (s, 3H), 5.4 (dd, J=15 Hz, 18 Hz; 2H), 6.88 (m, 1H), 7.28-7.40 (m, 5H), 7.5-7.6 (dd, J=1.5 Hz; 7.5 Hz, 3H), 7.82 (s, 1H), 7.85 (d, J=18 Hz, 2H), 8.15 (br s, 1H). MS (DCI/NH_3) m/z 448 $(M+H)^+$. Anal. calc. for $C_{24}H_{21}N_3O_4S$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.17; H, 5.11; N, 9.04

Example 328

2-Benzyl-4-(3-ethoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 325 , substituting 3-ethoxybenzeneboronic acid in place of 3,4-dimethylbenzeneboronic acid (yield: 115 mg, 67%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J=7.5 Hz, 3H), 3.05 (s, 3H),

3.89 (q, J=7.5 Hz, 2H). 5.14 (s, 2H), 6.65 (d, J=9 Hz, 1H). 6.72 (t, J=1.5 Hz, 1H), 6.8 (dd, J=1.5 Hz, 9 Hz, 1H), 7.15 (t, J=9 Hz, 1H), 7.3-7.4 (m, 5H), 7.5-7.6 (m, 2H), 7.85 (d, J=9 Hz, 3H). MS (DCI/NH_3) m/z 461 $(M+H)^+$. Anal. calc. for $C_{26}H_{24}N_2O_4S.0.5H_2O$: C, 66.50; H, 5.36; N, 5.96. Found: C, 66.39; H, 5.02; N, 5.77

Example 329

2-Benzyl-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-(2H)-pyridazinone

Example 329A

2-Benzyl-4,5-dibromo-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 194A, substituting benzyl hydrazine hydrochloride in place of 4-fluorophenyl hydrazine hydrochloride (yield: 7.86 g, 60%). ^1H NMR (300 MHz, DMSO d_6) δ 5.27 (s, 2H), 7.26-7.41 (m, 5H), 8.19 (s, 1H). MS (DCI/NH_3) m/z 345 $(M+H)^+$. 362 $(M+H)^+$.

Example 329B

2-Benzyl-5-bromo-4-methoxy-3(2H)-pyridazinone

The title compound was prepared according to the method described in Example 194B, substituting 2-benzyl-4,5-dibromo-3(2H)-pyridazinone for 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (yield: 2.877 g; 85%). ^1H NMR (300 MHz, DMSO-d_6) δ 4.14 (s, 3H), 5.23 (s, 2H), 7.26-7.38 (m, 5H), 8.11 (s, 1H). MS (DCl-NH_3) m/z 295 $(M+H)^+$, 312 $(M+NH_4)^+$.

Example 329C

2-Benzyl-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method described in Example 6, substituting 2-benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone for 2-benzyl-4-methoxy-5-bromo-3(2H)-pyridazinone (yield. 3.705 g). ^1H NMR (300 MHz, DMSO-d_6) δ 2.52 (s,

3H), 3.99 (s, 3H), 5.28 (s, 2H), 7.26-7.41 (m, 7H), 7.55 (m, 2H), 8.02 (s, 1H). MS (DCI-NH_3) m/z 339 $(M+H)^+$, 356 $(M+NH_4)^+$.

Example 329D

2-Benzyl-4-(4-fluorobenzyl-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228, substituting 4-fluorobenzyl magnesium chloride in place of cyclohexylmagnesium chloride and 2-benzyl-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone was substituted in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone.

Example 329E

2-Benzyl-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-(2H)-pyridazinone

The sulfide compound, Example 329D, was oxidized to the methyl sulfonyl compound according to the method of Example 10. mp 186-189 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.27 (s, 3H), 3.83 (s, 2H), 5.31 (s, 2H), 6.94-7.05 (m, 4H), 7.27-7.40 (m, 5H), 7.67 (m, 2H), 7.94 (s, 1H), 8.03 (m, 2H). MS (DCI/NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{21}FN_2O_3S$: C, 66.95; H, 4.72; N, 6.25. Found: C, 66.68; H, 4.75; N, 6.14.

Example 330

2-(tert-Butyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 330A

2-(tert-Butyl)-4,5-dichloro-3(2H)-pyridazinone

A solution of mucochloric acid (33.8 g, 200 mmol) and tert.-butylhydrazine hydrochloride (24.9 g, 200 mmol) in methanol (400 mL) was stirred at reflux overnight. Methanol was removed in vacuo and the residue was partitioned between ether and water. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated in

vacuo and the residue was purified by column chromatography (silica gel, 100% hexanes). Product-containing fractions were combined and the title compound was crystallized from ether/hexanes (yield: 10.0 g, 22.6%). mp 63-64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 9H), 7.73 (s, 1H). MS (DCI/NH_3) m/z 221 $(M+H)^+$, 238 $(M+NH_4)^-$.

Example 330B

2-(tert-Butyl)-4-(3-methylbutoxy)-5-chloro-3(2H)-pyridazinone

A stirred, room temperature solution of 3-methyl-1-butanol (0.5 mL, 4.52 mmol) in tetrahydrofuran (10 mL) was treated with a 60% oil suspension of sodium hydride (0.24 g, 5.88 mmol). After 5 minutes, hydrogen gas evolution had subsided, so the dichloro-intermediate from Example 330A (1.0 g, 4.52 mmol) was added and the reaction mixture was stirred at room temperature for 20 hours. The reaction was quenched with 10% aqueous citric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 100% hexanes). The title compound was obtained as a pale yellow oil (yield: 0.7 g, 56.7%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J=6 Hz, 6H), 1.63 (s, 9H), 1.64 (q, J=6 Hz, 2H), 1.85 (nonet, J=6 Hz, 1H), 4.49 (t, J=6 Hz, 2H), 7.64 (s, 1H). MS (DCI/NH_3) m/z 273 $(M+H)^+$, 290 $(M+NH_4)^-$.

Example 330C

2-(tert-Butyl)-4-(3-methylbutoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

A solution of the intermediate from Example 330B (700 mg, 2.57 mmol), 4-(methylthio)benzeneboronic acid (560 mg, 3.34 mmol), cesium carbonate (2.17 g, 6.67 mmol), and tetrakis(triphenylphosphine)palladium(0) (210 mg, 0.18 mmol) in dimethoxyethane (40 mL) was heated at reflux for 5 hours. The heat source was then removed and the reaction mixture was stirred at room temperature for 64 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuo to provide a brown oil. This oil was purified by column chromatography twice (silica gel, 97:3 hexanes/ethyl acetate, then 96:4 hexanes/ethyl acetate) to provide a semi-solid product

(yield: 270 mg, 29.2%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J=6 Hz, 6H), 1.49 (q, J=6 Hz, 2H), 1.63 (nonet, J=6 Hz, 1H), 1.69 (s, 9H), 2.52 (s, 3H), 7.32 (d, J=9 Hz, 2H), 7.50 (d, J=9 Hz, 2H), 7.73 (s, 1H). MS (DCI) m/z 361 $(M+H)^+$.

Example 330D

2-(tert-Butyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 10, substituting 2-(tert.-butyl)-4-(3-methylbutoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone for 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 188 mg, 63.9%). mp 138-139°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, J=6 Hz, 2H), 1.48 (q, J=6 Hz, 2H), 1.48-1.68 (m, 1H), 1.69 (s, 9H), 3.10 (s, 3H), 4.38 (t, J=6 Hz, 2H), 7.71 (s, 1H), 7.74 (d, J=9 Hz, 2H), 8.03 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 393 $(M+H)^+$. Anal. calc. for $C_{20}H_{28}N_2O_4S$: C, 61.20; H, 7.19; N, 7.14. Found: C, 61.13; H, 7.23; N, 6.89.

Example 331

2-(3-Chlorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 10, substituting 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (Example 207C) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 3.31 g, 96%). mp 112-114 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.31 (m, 3H), 4.10 (m, 3H), 7.52-7.65 (m, 3H), 7.75 (m, 1H), 7.90 (m, 2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 391 $(M+H)^+$, 408 $(M+NH_4)^+$. Anal. calc. for: $C_{18}H_{15}ClN_2O_4S.0.25\ H_2O$: C, 54.68; H, 3.95; N, 7.08. Found: C, 54.59; H, 3.65; N, 6.98.

Example 332

2-(3-Chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A suspension of 2-(3-chlorophenyl)-4-(methoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (6.26 g, 16 mmol) in 5% NaOH (54 mL) dioxane (39.4 mL) was

heated at reflux and stirred for 1.5 hours. As the reaction proceeds, the solution becomes orange and homogeneous. The mixture was cooled and poured into 1N HCl, with constant stirring. The resulting white solid was filtered and rinsed with H_2O and left to dry overnight. The mostly dry product was taken up in CH_2Cl_2 and azeotroped with toluene to remove any remaining H_2O, to provide the desired product as a white solid (yield: 6.79 g, >100%). ^1H NMR (300 MHz, DMSO d_6) δ 2.27 (s, 3H), 7.51-7.62 (m, 2H), 7.68 (m, 1H), 7.79 (m, 1H), 8.03 (m, 4H), 8.24 (s, 1H). MS (DCI/NH_3) m/z 377 $(M+H)^+$, 396 $(M+NH_4)^+$.

Example 333

2-(3-Chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a 0 °C solution of 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 332, (6.79 g, 16 mmol) in pyridine (160 mL) was added p-toluenesulfonyl chloride (3.06 g, 16 mmol). The solution was left to warm slowly to room temperature with stirring under nitrogen. After 2.5 hours, the mixture was poured into H_2O with constant stirring. The resulting off-white solid was filtered, rinsed with H_2O and dried to provide the desired product (yield: 6.26 g, 79%). mp 198-200 °C. ^1H NMR (300 MHz, DMSO d_6) δ 2.35 (s, 3H), 3.28 (s, 3H), 7.20 (m, 2H), 7.52-7.64 (M, 5H), 7.70 (m, 3H), 7.89 (m, 2H), 8.32 (s, 1H). MS APCI+ 531 $(M+H)^+$, 548 $(M+H_2O)^+$. APCI-493 $(M+35)^-$. Anal. calc. for $C_{24}H_{19}ClN_2O_6S_2$: C, 54.29, H, 3.61; N, 5.28. Found: C, 54.55; H, 3.46; N, 5.57.

Example 334

2-(3-Chlorophenyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 332, in $POCl_3$ was heated to reflux for 3 hours while stirring under nitrogen. The mixture was cooled to room temperature and poured into ice with constant swirling. The resulting white solid was extracted with ethyl acetate. The combined organics were washed with H_2O, dried over $MgSO_4$, and concentrated to a solid.

The crude product was purified using flash chromatography (SiO_2, eluting with 1:1 ethyl acetate/hexanes) to provide the desired product (yield: 0.151 g, 29%). mp 203-204 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.29-3.36 (3H, obstructed by H_2O), 7.60 (m, 3H), 7.76 (m, 1H), 7.92 (m, 2H), 8.14 (m, 2H), 8.25 (s, 1H). MS (DCI/NH_3) m/z 395 $(M+H)^+$, 412 $(M+NH_4)^+$. Anal. calc. for $C_{17}H_{12}Cl_2N_2O_3S$: C, 51.66; H, 3.06; N, 7.09. Found: C, 51.67; H, 3.03; N, 6.93.

Example 335

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred suspension of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 333, (0.175 g, 0.33 mmol) in THF (3.3 mL) was added isobutanol (0.03 mL, 0.33 mmol), and NaH (0.0132 g, 0.33 mmol). The resulting solution was stirred under nitrogen for 1 hour. The reaction was poured into H_2O and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude solid was purified using flash chromatography (SiO_2, 2:1 hexanes:ethyl acetate) to provide the desired product (yield: 0.1088 g 76%). mp 166-169 °C. ^1H NMR (300 MHz, DMSO d_6) δ 0.78 (d, J=6 Hz, 6H), 1.84 (m, 1H), 3.29 (s, 3H), 4.20 (d, J=6 Hz, 2H), 7.51-7.63 (m, 3H), 7.76 (m, 1H), 7.92 (m, 2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 433 $(M+H)^+$, 450 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}ClN_2O_4S$: C, 57.07; H, 5.01; N, 6.33. Found: C, 57.06; H, 4.78; N, 6.13.

Example 336

2-(3-Chlorophenyl)-4-(t-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting t-butanol in place of isobutanol (yield: 0.093 g, 66%). mp 232-235 °C. ^1H NMR (300 MHz, DMSO d_6) δ 1.18 (s, 9H), 3.30 (s, 3H), 7.52-7.64 (m, 3H), 7.74 (m, 1H), 7.92 (m, 2H), 8.08 (m, 2H), 8.20 (s, 1H). MS (DCI/NH_3) m/z 433 $(M+H)^+$, 450

$(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}ClN_2O_4S$: C, 58.26. H. 4.89: N, 6.47. Found: C. 58.21: H, 4.88; N, 6.28.

Example 337

2-(3-Chlorophenyl)-4-(cyclohexyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting cyclohexanol in place of isobutanol (yield: 0.139 g. 92%). semi-solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09-1.50 (m, 6H), 1.57 (m. 2H). 1.88 (m, 2H), 3.13 (s, 3H), 5.19 (m, 1H), 7.38-7.48 (m. 2H), 7.59 (m, 1H), 7.70 (m, 1H). 7.83 (m. 2H), 7.92 (s, 1H). 8.07 (m. 2H). MS APCI+ 459 $(M+H)^+$, 476 $(M+H_2O)^+$. APCI-458 (M)-. 493 $(M+35)^-$. Anal. calc. for $C_{23}H_{23}ClN_2O_4S.0.25\ H_2O$: C. 59.60; H. 5.11: N. 6.04. Found: C. 59.48; H. 4.86; N, 5.88.

Example 338

2-(3-Chlorophenyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting neopentyl alcohol in place of isobutanol (yield: 0.109 g, 74%). mp 151-153 °C. ^1H NMR (300 MHz. DMSO d_6) δ 0.78 (s. 9H). 3.29 (s. 3H), 4.10 (s. 2H), 7.52-7.64 (m, 3H). 7.76 (m, 1H). 7.92 (m, 2H), 8.07 (m, 2H), 8.20 (s, 1H). MS (DCI/NH_3) m/z 447 $(M+H)^+$, 464 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}ClN_2O_4S$: C. 59.12; H, 5.19; N, 6.27. Found C, 59.40; H, 5.31; N, 5.99.

Example 339

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-methyl-1-butanol in place of isobutanol (yield: 0.229 g, 80.5%). mp 134-135 °C. ^1H NMR (300 MHz, DMSO d_6) δ 0.79 (d, J=6 Hz. 6H). 1.42-1.64 (m. 3H), 3.30 (s. 3H). 4 43 (t, J=6 Hz, 2H). 7.52-7.65 (m. 3H). 7.76 (m. 1H). 7 90 (m, 2H). 8.07 (m. 2H).

8.21 (s, 1H). MS (DCI/NH_3) m/z 447 $(M+H)^+$, 464 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}ClN_2O_4S$: c, 59.12; H, 5.19; N, 6.27. Found: C, 58.91; H, 5.12; N, 6.01.

Example 340

2-(3-Chlorophenyl)-4-(3-octyn-1-yloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-octyn-1-ol in place of isobutanol (yield: 0.128 g, 77%). Oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.25-1.44 (m, 4H), 2.05 (m, 2H), 2.52 (m, 2H), 4.68 (t, J=6 Hz, 2H), 7.43 (m, 2H), 7.59 (m, 1H), 7.70 (m, 1H), 7.86 (m, 2H), 7.92 (s, 1H). MS (DCI/NH_3) m/z 485 $(M+H)^+$. Anal. calc. for $C_{25}H_{25}ClN_2O_4S$: C, 61.94; H, 5.20; N, 5.78. Found: C, 61.82; H, 4.99; N, 5.57.

Example 341

2-(3-Chlorophenyl)-4-[2-(dimethylamino)ethoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting N,N-(dimethyl)ethanolamine in place of isobutanol (yield: 0.111 g, 75%). mp 110-113 °C. ^1H NMR (300 MHz, DMSO d_6) δ 2.29 (bs, 6H), 2.68 (bs, 2H), 4.68 (t, J=5 Hz, 2H), 7.38-7.48 (m, 2H), 7.57 (m, 1H), 7.68 (m, 1H), 7.89 (m, 2H), 8.07 (m, 2H). MS (DCI/NH_3) m/z 448 $(M+H)^+$. Anal. calc. for $C_{21}H_{22}ClN_3O_4S.0.50\ H_2O$: C, 55.19; H, 5.07; N, 9.19. Found: C, 55.24, H, 4.97; N, 9.07.

Example 342

2-(3-Chlorophenyl)-4-[2-methyl-1-(1-methylethyl)propoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2,4-dimethyl-3-pentanol in place of isobutanol (yield: 0.075 g, 48%). Semi-solid; ^1H NMR (300 MHz, DMSO d_6) δ 0.79 (m, 12H), 1.78-1.92 (m, J=6 Hz, 2H), 3.29 (s,

3H), 5.40 (t, J=6 Hz, 1H), 7.57 (m, 3H), 7.72 (m, 1H), 7.91 (m, 2H), 8.07 (m, 2H), 8.17 (m, 1H). MS (DCI/NH_3) m/z 475 $(M+H)^+$, 492 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{27}ClN_2O_4S$ (0.75 H_2O): C, 59.00; H, 5.88; N, 5.78. Found: C, 58.83; H, 5.74; N, 5.52.

Example 343

2-(3-Chlorophenyl)-4-(phenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting phenol in place of isobutanol (yield: 0.053 g, 35%). mp 205-207 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.28 (s, 3H), 7.08 (m, 3H), 7.31 (m 2H), 7.50-7.64 (m, 3H), 7.73 (m, 1H), 7.90 (m, 2H), 8.05 (m, 2H), 8.40 (s, 1H). MS (DCI/NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}ClN_2O_4S$: C, 60.99; H, 3.78; N, 6.19. Found: C, 60.79; H, 3.65; N, 5.87.

Example 344

2-(3-Chlorophenyl)-4-[3-(dimethylamino)phenoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-(dimethylamino)phenol in place of isobutanol (yield: 0.057 g, 60%). mp 191-193; ^1H NMR (300 MHz, DMSO d_6) δ 2.85 (s, 6H), 3.27 (s, 3H), 6.36 (m, 3H), 7.05 (m, 1H), 7.51-7.63 (m, 3H), 7.72 (m, 1H), 7.90 (m, 2H), 8.05 (m, 2H), 8.39 (s, 1H). MS APCI+ 495 $(M+H)^+$, APCI-, 495 (M)-, 590 $(M+35)^-$. Anal. calc. for $C_{25}H_{22}ClN_3O_4S$: C, 60.54; H, 4.47; N, 8.47. Found: C, 60.04; H, 4.49; N, 8.26.

Example 345

2-(3-Chlorophenyl)-4-(4-methoxyphenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 4-methoxyphenol in place of isobutanol (yield: 0.080 g, 69%). mp 182-184 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.27 (s, 3H), 3.70 (s, 3H), 6.84 (m, 2H), 7.00 (m,

2H), 7.56 (m, 3H), 7.72 (m, 1H), 7.90 (m, 2H), 8.04 (m, 2H), 8.38 (s, 1H). MS (DCI/NH_3) m/z 483 $(M+H)^+$, 500 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_5S$: C, 59.64; H, 3.97; N, 5.80. Found: C, 59.86; H, 3.94; N, 5.62.

Example 346

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 150 mg, 61%). mp 116-117 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.78 (d, 6H), 1.84, (m, 1H), 3.3 (s, 3H), 4.2 (d, 2H), 7.54 (m, 1H), 7.6 (m, 1H), 7.82 (m, 1H), 7.91 (d, 2H), 8.07 (d, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 435 $(M+H)^+$, 452 $(M+NH_4)^+$. Anal. calc. for $C_{21}F_2H_{20}N_2O_4S$: C, 58.06; H, 4.64. N, 6.45.

Example 347

2-(3,4-Difluorophenyl)-4-(3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 3-methyl-1-butanol in place of isobutanol (yield: 63 mg, 23%). mp 121-123 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 0.78 (d, 6H), 1.48, (m, 3H), 3.3 (s, 3H), 4.43 (t, 2H), 7.54 (m, 1H), 7.6 (m, 1H), 7.82 (m, 1H), 7.91 (d, J=9 Hz, 2H), 8.07 (d, J=9 Hz, 2H), 8.2 (s, 1H). MS (DCI/NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$ Anal. calc. for $C_{22}H_{22}F_2N_2O_4S$: C, 58.92; H, 4.94; N, 6.25. Found, C, 59.22; H, 4.97; N, 6.07.

Example 348

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-fluorophenol in place of isobutanol mp 168-170 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.39 (s, 3H), 7.15 (d, 4H), 7.51 (m, 1H), 7.6 (m, 1H) 7.75 (m, 3H), 7.97 (t, 1H); 8.4 (s, 1H). MS (DCI/NH_3) m/z 491 $(M+H)^+$, 508 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{14}F_4N_2O_4S$: C, 56.33; H, 2.88; N, 5.71. Found, C, 56.07; H, 2.94; N, 5.33.

Example 349

2-(3,4-Difluorophenyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting neopentyl alcohol in place of isobutanol (yield: 1.18 g, 94%). mp 126-128 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78 (s, 9H), 3.3 (s, 3H), 4.1 (s, 2H), 7.51 (m, 1H), 7.6 (m, 1H), 7.82 (m, 1H), 7.91 (d, J=9 Hz, 2H), 8.07 (d, J=9 Hz, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_4S$: C, 58.92; H, 4.94; N, 6.25. Found: C, 59.03; H, 5.03; N, 6.18.

Example 350

2-(3,4-Difluorophenyl)-4-[2-(isopropoxy)ethoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 2-(isopropoxy)ethanol in place of isobutanol (yield: 432 mg, 72%). mp 105-107 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (d, 6H), 3.3 (s, 3H), 3.43 (m, 1H), 3.54 (m, 2H), 4.63 (m, 2H), 7.54 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 8.01 (m, 4H), 8.2 (s, 1H). MS (DCI/NH_3) m/z 465 $(M+H)^+$, 482 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_5S$: C, 56.89; H, 4.77; N, 6.03. Found, C, 57.03; H, 4.65; N, 5.83.

Example 351

2-(3,4-Difluorophenyl)-4-(3-methylpentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 3-methylpentyl-1-ol in place of isobutanol (yield: 400 mg, 80%). mp 100-102 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (m, 6H), 1.05 (m, 1H), 1.28 (m, 3H) 1.6 (m, 1H), 3.3 (s, 3H), 4.45 (m, 2H), 7.5 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 7.9 (d, J=9 Hz, 2H) 8.05 (d, J=9 Hz, 2H), 8.2 (s, 1H). MS (DCI/NH_3) m/z 463 $(M+H)^+$, 480 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{24}F_2N_2O_4S$: C, 59.73; H, 5.23; N, 6.06. Found, C, 59.78, H, 5.31; N, 6.00.

Example 352

2-(3,4-Difluorophenyl)-4-(4-methyl-3-penten-1-yloxy)-5-[4-(methylsulfonyl)phenyl]-5-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 4-methyl-3-pentene-1-ol in place of isobutanol (yield: 405 mg, 67.8%). mp 88-90 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.5 (d, 6H), 2.27 (m, 2H) 3.3 (s, 3H), 4.43 (t, 2H), 4.95 (m, 1H), 7.5 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 7.9 (d, 2H), 8.06 (d, 2H), 8.2 (s, 1H). MS (DCI/NH_3) m/z 461 $(M+H)^+$, 478 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{22}F_2N_2O_4S$: C, 59.99; H, 4.82; N, 6.08. Found, C, 59.88; H, 4.76; N, 5.84.

Example 353

2-(3,4-Difluorophenyl)-4-[3-(methoxy)butoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 346 substituting 3-methoxybutyl-1-ol in place of isobutanol (yield: 350 mg, 68%) . mp 99-101 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (d, 3H), 1.7 (m, 2H), 3.05 (s, 3H), 3.2 (m, 1H) 3.3 (s, 3H), 4.45 (m, 2H), 7.54 (m, 1H), 7.6 (m, 1H), 7.8 (m, 1H), 7.9 (d, J=9 Hz, 2H) 8.01 (d, J=9 Hz, 2H), 8.2 (s, 1H). MS (DCI/NH_3) m/z 465 $(M+H)^+$, 482 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}F_2N_2O_5S$: C, 56.89; H, 4.77; N, 6.03. Found, C, 56.60; H, 4.83; N, 5.96.

Example 354

2-(3-Chlorophenyl)-4-(N-methylbenzylamino)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone:

To a rapidly stirred 0 °C mixture of N-methylbenzylamine (67.5 mg, 0.56 mmol) and tetrahydrofuran (3.7 mL) was slowly added dropwise an n-BuLi solution (0.235 mL, 0.59 mmol, 2.5 M in hexanes). The reaction mixture was stirred for 10 minutes at 0 °C and 1 hour at 23 °C. The solution was cooled to -78 °C, and a tetrahydrofuran (10-15 mL) solution of the 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (200 mg, 0.56 mmol) slowly added along the interior wall of the reaction vessel This reaction mixture was stirred overnight, slowly warming to 23 °C as the cooling bath evaporated. The reaction was quenched with water and diluted with a large excess of ethyl acetate. The layers were separated, and the ethyl acetate layer washed with additional water and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes 1:9) to provide 2-(3-chlorophenyl)-4-(N-methyl benzylamino)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 145 mg, 58%).

The title compound was prepared according to the method of Example 10, substituting 2-(3-chlorophenyl)-4-(N-methylbenzylamino)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 143 mg, 95%). mp 60-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.09 (s, 3H), 4.63 (s, 2H), 7.19 (d, J=8.7 Hz, 2H), 7.24-7.29 (m, 2H), 7.32-7.48 (m, 5H), 7.60 (ddd, J=7.2, 1.8, 1.8 Hz, 1H), 7.67 (s, 1H), 7.70 (dd, J=1.8, 1.8 Hz, 1H), 7.91 (d, J=8.7 Hz, 2H). MS (APCI+) m/z 480 $(M+H)^+$.

Example 355

2-(4-Fluorophenyl)-4-(1-piperidinyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a slightly heterogeneous solution of piperidine (99.7 mg, 1.17 mmol) and toluene (8 mL) cooled to -78 °C was slowly added dropwise an n-BuLi solution (0.235

mL, 0.59 mmol, 2.5 M in hexanes). After stirring at -78 °C for 10 minutes, the cooling bath was removed and the mixture stirred an additional 1 hour at 23 °C. The 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (400 mg, 1.17 mmol) was dissolved in portions in toluene (3 x 6-7 mL aliquots) with a heat gun and cooled to 0 °C prior to transfer via syringe to the lithium amide solution (cooled to -78 °C). The addition was made slowly along the interior wall of the reaction vessel. This reaction mixture was stirred overnight, slowly warming to 23 °C as the cooling bath evaporated. The reaction was quenched with water and diluted with a large excess of ethyl acetate. The layers were separated, and the ethyl acetate layer washed with additional water and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed (flash silica gel, ethyl acetate/hexanes 1:2) to provide 440 mg (95%) of 2-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-4-piperidino-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 10, substituting 2-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-4-piperidino-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (yield: 165 mg, 98%). mp 80-100 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (br s, 6H), 2.59 (br s, 4H), 3.14 (s, 3H), 7.17 (dd, J=8.7, 8.7 Hz, 2H), 7.51 (d, J=8.7 Hz, 2H), 7.55-7.62 (m, 2H), 7.68 (s, 1H), 8.06 (d, J=8.7 Hz, 2H). MS (APCI+) m/z 428 $(M+H)^+$. Powdered out in CH_2Cl_2/C_6H_{14}. Anal. calc. for $C_{22}H_{22}FN_3O_3S.0.25C_6H_{14}$: C, 62.85; H, 5.72; N, 9.35. Found: C, 62.46; H, 5.77; N, 9.13.

Example 356

2-(4-Fluorophenyl)-4-(1-pyrrolidinyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 355 , substituting pyrrolidine for piperidine (yield: 107 mg, 82%). mp 192-195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71-1.80 (m, 4H), 3.13 (s, 3H), 3.40-3.49 (m, 4H), 7.16 (dd, J=8.7, 8.7 Hz, 2H), 7.47-7.60 (m, 5H), 7.99 (d, J=8.7 Hz, 2H). MS (APCI+) m/z 414 $(M+H)^+$. Anal. calc. for $C_{21}H_{20}FN_3O_3S$: C, 61.00; H, 4.87; N, 10.16. Found: C, 60.95; H, 4.94; N, 10.07.

Example 357

2-(3-Chlorophenyl)-4-(4-methylphenylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred suspension of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 333, (0.0802 g, 0.15 mmol) in EtOH (1.5 mL) was added thiocresol (0.019 g, 0.15 mmol) and K_2CO_3 (0.0203 g, 0.15 mmol). The suspension was heated to 50 °C with stirring for 2.5 hours. The mixture was poured into H_2O with constant stirring. The resulting precipitate was filtered, rinsed with H_2O and dried to provide the desired product (yield: 0.060 g, 83%). mp 178-178 °C. ^1H NMR (300 MHz, DMSO d_6) δ 2.19 (s, 3H), 3.23 (s, 3H), 6.95 (m, 2H), 7.08 (m, 2H), 7.52-7.66 (m, 3H), 7.72 (m, 1H), 7.88 (m, 2H), 8.08 (s, 1H). MS (DCI/NH_3) m/z 483 $(M+H)^+$, 500 $(M+NH_4)^+$. Anal. calc. for: $C_{24}H_{19}ClN_2O_3S_2.0.75\ H_2O$: C, 58.05; H, 4.16; N, 5.64. Found: C, 57.99; H, 3.69; N, 5.76.

Example 358

2-(3-Chlorophenyl)-4-(2-pyridylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 357, substituting 2-mercaptopyridine in place of thiocresol (yield: 0.061 g, 39%). mp 110-114 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.28 (s, 3H), 7.16 (m, 1H), 7.37 (m, 1H), 7.51-7.71 (m, 5H), 7.81 (m, 2H), 8.03 (m, 2H), 8.27 (s, 1H), 8.34 (m, 1H). MS (DCI/NH_3) m/z 470 $(M+H)^+$. Anal. calc. for $C_{22}H_{16}ClN_1O_3S_2.0.50\ H_2O$: C, 55.16; H, 3.57; N, 8.77. Found: C, 54.88; H, 3.19; N, 8.59.

Example 359

2-(3-Chlorophenyl)-4-(phenylmethylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred suspension of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 333, (0.175 g, 0.33

mmol) in THF (3.3 mL) was added benzyl mercaptan (0.04 mL, 0.33 mmol) and TEA (0.046 mL, 0.33 mmol). The resulting solution was stirred at room temperature under nitrogen for 1 hour. The mixture was poured into H_2O and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The resulting crude product was purified using flash chromatography (SiO_2, 2:1 hexanes:ethyl acetate) to provide the desired product (yield: 0.136 g 85%). mp 142-145 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.31 (s, 3H), 4.36 (s, 2H), 7.17 (m, 2H), 7.21-7.33 (m, 3H), 7.51 (m, 2H), 7.57-7.64 (m, 3H), 7.74 (m, 1H), 8.01 (m, 2H). MS (DCI/NH_3) m/z 483 $(M+H)^+$, 500 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_3S_2$: C, 59.68; H, 3.96; N, 5.80. Found: C, 59.40; H, 4.11; N, 5.71.

Example 360

2-(3-Chlorophenyl)-4-(2-furylmethylthio)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 359, substituting furfuryl mercaptan in place of benzyl mercaptan (yield: 0.162 g, 100%). mp 140-149 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.31 (s, 3H), 4.46 (s, 2H), 6.20 (m, 1H), 6.37 (m, 1H), 7.50-7.67 (m, 6H), 7.77 (m, 1H), 8.03 (m, 2H), 8.08 (s, 1H). MS (DCI/NH_3) m/z 473 $(M+H)^+$, 490 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{17}ClN_2O_4S_2$: C, 55.87; H, 3.62; N, 5.92. Found: C, 55.84; H, 3.61; N, 5.82.

Example 361

2-(3-Chlorophenyl)-4-[2-(methylpropyl)thio]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 359, substituting 2-methyl-1-propanethiol in place of benzyl mercaptan (yield: 0.134 g, 91%). Oil. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.61 (d, J=6 Hz, 6H), 1.54-1 69 (m, 1H), 2.91 (d, J=6 Hz, 2H), 3.33 (s, 3H), 7.52-7.64 (m, 3H), 7.74 (m, 1H), 7.79 (m, 2H), 8.04 (m, 3H).

MS (DCI/NH_3) m/z 449 $(M+H)^+$. 466 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}ClN_2O_3S_2$ (0.50 H_2O): C, 55.07; H, 4.84; N, 6.11. Found: C, 54.70; H, 4.64; N, 5.85.

Example 362

2-(3-Chlorophenyl)-4-(cyclopentyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a -78 °C solution of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, prepared in Example 333, (0.175 g, 0.33 mmol) in THF (3.3 mL) was added cyclopentyl magnesium chloride (0.17 mL, 1.0 M in diethyl ether). The resulting solution was stirred under nitrogen less than 1hour with warming to room temperature. The reaction was poured into water and extracted with ethyl acetate. The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The resulting crude product was purified using flash chromatography (SiO_2, 2:1 ethyl acetate:hexanes) to provide the desired product (yield: 0.1328 g, 94%). mp 155-157 °C. ^1H NMR (300 MHz, DMSO d_6) δ 1.50 (m, 2H), 1.66 (m, 2H), 1.79 (m, 2H), 2.09 (m, 2H), 2.90 (m, J=8 Hz, 1H), 3.26-3.37 (3H, obstructed by H_2O), 7.49-7.63 (m, 3H), 7.71 (m, 3H), 7.97 (s, 1H), 8.10 (m, 2H). MS (DCI/NH_3) m/z 429 $(M+H)^+$, 446 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}ClN_2O_3S$: C, 61.60; H, 4.93; N, 6.53. Found: C, 61.48; H, 4.81; N, 6.22.

Example 363

2-(3-Chlorophenyl)-4-(2-methylpropyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound, an oil, was prepared according to the method of Example 362, substituting isobutyl magnesium chloride in place of cyclopentylmagnesium chloride, (yield: 0.132 g, 96%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J=6 Hz, 6H), 2.08 (m, 1H), 2.54 (d, J=7 Hz, 2H), 7.36-7.46 (m, 2H), 7.56 (m, 2H), 7.62 (m, 1H), 7.73 (m, 2H), 8.11 (m, 2H). MS (DCI/NH_3) m/z 417 $(M+H)^+$, 434 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}ClN_2O_3S.0.50\ H_2O$: C, 59.21; H, 5.20; N, 6.57. Found: C, 59.27; H, 5.40; N, 6.12.

Example 364

2-(3-Chlorophenyl)-4-(cyclopentylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound, an oil, was prepared according to the method of Example 362, substituting cyclopentylmethyl magnesium bromide in place of cyclopentyl magnesium chloride (yield: 0.0579 g, 38%). ^{1}H NMR (300 MHz, DMSO d_6) δ 0.66 (m, 2H), 1.03 (m, 3H), 1.50 (m, 6H), 1.61 (m, 1H), 2.46 (m, 1H), 3.27-3.42 (3H, obstructed by H_2O), 7.50-7.66 (m, 3H), 7.75 (m, 3H), 7.99 (s, 1H), 8.10 (m, 2H). MS (DCI/NH_3) m/z 457 $(M+H)^+$, 474 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{25}ClN_2O_3S$: C, 63.08; H, 5.51; N, 6.13 Found: C, 63.08; H, 5.47; N, 6.04.

Example 365

2-(3-Chlorophenyl)-4-(2-cyclopentylethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting cyclopentylethyl magnesium bromide in place of cyclopentyl magnesium chloride (yield: 0.165 g, 94%). ^{1}H NMR (300 MHz, DMSO d_6) δ 0.76 (m, 3H), 0.99-1.21 (m, 5H), 1.31-1.62 (m, 8H), 2.42-2.56 (1H, obstructed by DMSO), 3.25-3.34 (2H, obstructed by H_2O), 7.48-7.65 (m, 3H), 7.48-7.65 (m, 3H), 7.76 (m, 3H), 8.01 (s, 1H), 8.10 (m, 2H). MS (DCI/NH_3) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{27}ClN_2O_3S$. C, 63.75; H, 5.78, N, 5.95. Found: C, 63.48; H, 5.70; N, 5.67.

Example 366

2-(3-Chlorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting 3-methylbutyl magnesium bromide in place of cyclopentylmagnesium chloride (yield: 0.0221 g, 16%). mp 60-65 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.75 (d, J=7 Hz, 6H), 1.32-1.52 (m, 3H), 3.31 (s, 3H), 7.50-7.65 (m, 3H), 7.77 (m, 3H), 8.03 (s, 1H), 8.11 (m, 2H). MS (DCI/NH_3) m/z 431 $(M+H)^+$, 448 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}ClN_2O_3S.0.25\ H_2O$: C, 60.68; H, 5.43; H, 6.43. Found C, 60.29; H, 5.60; N, 6.17.

Example 367

2-(3-Chlorophenyl)-4-benzyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting benzyl magnesium chloride in place of cyclopentylmagnesium chloride. mp 174-177 °C (yield: 25.9 g, 57%). ^{1}H NMR (300 MHz, DMSO d_6) δ 3.30 (s, 3H), 3.91 (bs, 2H), 7.02 (m, 2H), 7.12-7.25 (m, 3H), 7.51-7.64 (m, 3H), 7.72 (m, 3H), 8.07 (m, 2H), 8.12 (s, 1H). MS (DCI/NH_3) m/z 451 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_3S$: C, 63.92; H, 4.25; N, 6.21. Found: C, 63.69; H, 4.28; N, 6.02.

Example 368

2-(3-Chlorophenyl)-4-cyclohexyl-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362 substituting cyclohexylmagnesium chloride in place of cyclopentylmagnesium chloride (yield: 0.099 g, 68%). mp 85-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01-1.30 (m, 3H), 1.48-1.69 (m, 3H), 1.75 (m, 2H), 2.28 (m, 2H), 2.57 (m, 1H), 3.16 (s, 3H), 7.35-7.46 (m, 2H), 7.50-7.62 (m, 3H), 7.68 (m, 2H), 8.11 (m, 2H). MS (DCI/NH_3) m/z 443 $(M+H)^+$, 460 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}ClN_2O_3S$ (1.25 H_2O): C, 59.34; H, 5.52; N, 6.01. Found: C, 59.02; H, 5.24; N, 5.65.

Example 369

2-(3-Chlorophenyl)-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 using the product from Example 207C and substituting 4-fluorobenzyl magnesium chloride in place of cyclohexyl magnesium chloride (yield: 0.1895 g, 41%). mp 183-185 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.25-3.36 (3H, obstructed by H_2O), 3.89 (bs, 2H), 6.97-7.09 (m, 4H), 7.50-7.64 (m, 3H), 7.71 (m, 3H), 8.06 (m, 2H), 8.11 (s, 1H). MS (DCI/NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{18}ClFN_2O_3S$: C, 61.47; H, 3.87; N, 5.97. Found: C, 61.23; H, 3.84; N, 5.77.

Example 370

2-(3-Chlorophenyl)-4-(4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362 substituting p-tolylmagnesium bromide in place of cyclopentylmagnesium chloride (yield: 65 mg, 40.9%). mp 222-224 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.28 (s, 3H), 3.25 (s, 3H), 7.12 (t, 4H), 7.6 (m, 5H), 7.79 (t, 1H) 7.9 (d, J=9 Hz, 2H), 8.22 (s, 1H). MS (DCI/NH_3) m/z 451 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_3S.0.25\ H_2O$: C, 63.92; H, 4.25; N, 6.21. Found: C, 62.99; H, 4.28; N, 5.85.

Example 371

2-(3,4-Difluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(3,4-Difluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 362, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 3-fluoro-4-methylphenylmagnesium bromide in place of cyclopentylmagnesium chloride to provide the methyl sulfide compound.

The methyl sulfide was oxidized according to the method of Example 10 to provide the title compound (yield: 265 mg, 85.4%). mp 204-206 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (br s, 3H), 3.08 (s, 3H), 6.83 (dd, J=9 Hz, 1.5 Hz, 1H), 6.96 (dd, J=9 Hz, 1.5 Hz, 1H), 7.08 (t, J=9 Hz, 1H), 7.23-7.33 (m, 1H), 7.41 (d, J=9 Hz, 2H), 7.49-7.56 (m, 1H), 7.61-7.69 (m, 1H), 7.93 (d, J=9 Hz, 2H), 7.99 (s, 1H). MS (DCI/NH_3) m/z 471 $(M+H)^+$, 488 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{17}F_3N_2O_3S$: C, 61.28, H, 3.62; N, 5.96. Found: C, 61.07; H, 3.95; N, 5.56.

Example 372

2-(3-Chlorophenyl)-4-(phenethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , starting with 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting phenethyl magnesium chloride in place of cyclohexylmagnesium chloride then oxidizing by the method of Example 10 (yield: 0.100 g. 39%). mp 142-145 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 2.80 (m, 4H), 3.30 (s, 3H), 7.01 (m, 2H), 7.21 (m, 3H), 7.51-7.60 (m, 4H), 7.63 (m. 1H), 7.78 (m, 1H), 8.03 (m. 3H). MS (DCI/NH_3) m/z 465 $(M+H)^+$, 482 $(M+NH_4)^+$. Anal. calc. for $C_{25}H_{21}ClN_2O_3S$ C. 64.58; H, 4.55; N. 6.02. Found: C. 64.24; H, 4.50; N, 5.90.

Example 373

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 373A

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-bromo-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 194B, starting with 2-(3-chlorophenyl)-4,5-dibromo-3(2H)-pyridazinone (Example 207A) in place of 2-(4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone and substituting 2-methyl-1-propanol in place of methanol.

Example 373B

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 6, starting with 2-(3-chlorophenyl)-4-(2-methylpropoxy)-5-bromo-3(2H)-pyridazinone in place of 2-benzyl-4-bromo-5-methoxy-3(2H)-pyridazinone and substituting 3-fluoro-4-(methylthio)benzeneboronic acid (Example 72D) in place of 4-fluorobenzeneboronic acid.

Example 373C

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 373B was oxidized according to the method of Example 10 to provide the title compound (yield: 0.73 g, 100%). mp 180-183 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.82 (d, J=6 Hz, 2H), 3.30-3.39 (3H, obstructed by H_2O) 4.25 (d, J=6 Hz, 2H), 7.57 (m, 3H), 7.75 (m, 1H), 7.85 (m, 1H), 8.00 (m, 1H), 8.23 (s, 1H). MS (DCI/NH_3) m/z 451 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{20}ClFN_2O_4S$: C, 55.94; H, 4.47; N, 6.21. Found: C, 55.73; H, 4.58; N, 6.01.

Example 374

2-(3-Chlorophenyl)-4-(benzyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a stirred solution of 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 332) (0.100 g, 0.28 mmol) in DMF (2.8 mL) was added benzyl chloride (0.32 mL, 0.28 mmol). The resulting solution was stirred with heating to 60 °C overnight. The solvent was removed in vacuo and the resulting residue partitioned between ethyl acetate and 10% citric acid. After extracting with ethyl acetate, the combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified using flash chromatography (SiO_2, 1:1 ethyl acetate:hexanes) to provide the desired product (yield: 0.096 g, 76%). mp 110-113 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.39 (s, 3H), 5.48 (s, 2H), 7.29 (m, 4H), 7.59-7.71 (m, 3H), 7.76 (m, 3H), 8.00 (m, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 467 $(M+H)^+$, 484 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{19}ClN_2O_4S$: C, 61.73; H, 4.10; N, 6.00. Found: C, 62.00; H, 4.18; N, 5.93.

Example 375

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

2-(4-Fluorophenyl)-4-methoxy-5-bromo-3(2H)-pyridazinone (Example 194B) was converted into 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-

pyridazinone according to the method of Example 194C followed by the oxidation method in Example 10. The methoxy compound was converted to the 2-(4-fluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, by treatment with NaOH according to the procedure of Example 332. The hydroxy compound was treated with p-toluenesulfonyl chloride according to the procedure of Example 333, to furnish 2-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone.

The title compound was prepared according to the method of Example 335, , starting with 2-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone substituting 3-methyl-1-butanol in place of isobutanol (yield: 0.3932 g, 94%). mp 117-120 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.79 (d, J=6 Hz, 6H), 1.41-1.59 (m, 3H), 3.30 (s, 3H), 4.42 (d, J=5 Hz, 2H), 7.36 (m, 2H), 7.65 (m, 2H), 7.90 (m, 2H), 8.06 (m, 2H), 8.18 (s, 1H). MS (DCI/NH_3) m/z 431 $(M+H)^+$, 448 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}FN_2O_4S$: C, 61.38; H, 5.39; N, 6.51. Found: C, 61.42: H, 5.30; N, 6.40.

Example 376

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone (prepared as an intermediate in Example 375) in place of 2-(3-chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-4-tosyloxy-3(2H)-pyridazinone (yield: 0.486 g, 100%). mp 121-128 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.78 (d, J=7 Hz, 6H), 1.84 (m, 1H), 3.30 (s, 3H), 4.20 (d, J=6 Hz, 2H), 7.37 (m, 2H), 7.66 (m, 2H), 7.92 (m, 2H), 8.07 (m, 2H), 8.19 (s, 1H). MS (DCI/NH_3) m/z 417 $(M+H)^+$, 434 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}FN_2O_4S.0.50\ H_2O$: C, 59.28; H, 5.21; N, 6.58. Found: C, 59.49; H, 4.97; N, 6.34.

Example 377

2-(4-Fluorophenyl)-4-(4-fluorobenzyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 62, starting with 4-(4-fluorophenylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and reacting with 1-iodo-4-fluorobenzene (yield: 0.0881 g, 78%). mp 175-177 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.27-3.36 (3H, obstructed by H_2O), 3.88 (bs, 2H), 6.98-7.09 (m, 4H), 7.34 (m, 2H), 7.65 (m, 2H), 7.71 (m, 2H), 8.06 (m, 3H). MS (DCI/NH_3) m/z 453 $(M+H)^+$, 470 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{18}F_2N_2O_3S$: C, 63.71; H, 4.01; N, 6.19. Found: C, 63.61; H, 4.26; N, 6.03.

Example 378

2-(4-Fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , substituting 3-methylbutyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 0.325 g, 69%). mp 151-154 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.75 (d, J=7 Hz, 6H), 1.32-1.51 (m, 3H), 3.31 (s, 3H), 7.37 (m, 2H), 7.66 (m, 2H), 7.77 (m, 2H), 8.00 (s, 1H), 8.10 (m, 2H). MS (DCI/NH_3) m/z 415 $(M+H)^+$, 432 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{23}FN_2O_3S.0.50\ H_2O$: C, 62.39; H, 5.71; N, 6.61. Found: C, 62.04; H, 5.78; N, 6.46.

Example 379

2-(Tetrahydro-2H-pyrano-2-yl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To the solution of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone prepared according to Example 11 (172 mg, 0.5 mmol) and p-toluenesulfonic acid hydrate (19 mg, 0.1 mmol) in dioxane (10 mL) was added 2,3-dihydropyran (2 mL). The mixture was stirred at room temperature for 6 hours. The mixture was then poured into a solution of saturated $NaHCO_3$ and extracted with ethyl acetate. The ethyl acetate was concentrated in vacuo and the residue was chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide the title compound (yield: 25 mg, 11%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.54 (m, 2H), 1.74 (m, 2H), 2.00 (m, 1H), 2.17 (m, 1H), 3.23 (s, 3H), 3.62 (m,

1H), 4.00 (m, 1H), 5.98 (m, 1H), 7.13 (7, J=9 Hz, 2H), 7.23 (m, 2H), 7.47 (d, J=9 Hz, 2H), 7.86 (d, J=9 Hz, 2H), 8.12 (s, 1H). MS (DCI/NH_3) m/z 429 $(M+H)^+$.

Example 380

2-(3-(4-Fluorophenyl)phenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 4, starting with 2-(3-bromophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 166) in place of 2-benzyl-4-bromo-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting cesium fluoride for sodium carbonate (yield: 0.62g, 62%). mp 222-225 °C. ^1H NMR (300 MHz, DMSO d_6) δ 3.24 (s, 3H), 7.16 (m, 2H), 7.36 (m, 3H), 7.53 (m, 2H), 7.64 (m, 2H), 7.73-7.81 (m, 3H), 7.93 (m, 3H), 8.27 (s, 1H). MS (DCI/NH_3) m/z 515 $(M+H)^+$, 532 $(M+NH_4)^+$. Anal. calc. for $C_{29}H_{20}F_2N_2O_3S.0.25\ H_2O$: C, 67.10; H, 3.98; N, 5.35. Found: C, 66.93; H, 3.99; N, 5.17.

Example 381

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone was prepared according to the method of Example 261, substituting 2-(2,2,2-trifluoroethyl)-4-chloro-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone in place of 2-(2,2,2-trifluoroethyl)-4-chloro-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

The methyl sulfide was oxidized with one equivalent of meta-chloroperoxybenzoic acid to give the methyl sulfoxide. The sulfoxide was converted to the title compound according to the method of Example 68 (yield: 196 mg, 28%). mp 144-145 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 9H), 4.23 (s, 2H), 4.82 (q, J=8 Hz, 2H), 5.10 (s, 2H), 7.46 (s, 1H), 7.48 (br s, 1H), 7.79 (s, 1H), 8.03 (t, J=8 Hz, 1H). MS (DCI/NH_3) m/z 438 $(M+H)^+$.

Anal. calc. for $C_{17}H_{19}F_4N_3O_3S$: C, 46.68; H, 4.38; N, 9.61. Found: C, 46.76; H, 4.30; N, 9.52.

Example 382

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 68 substituting 2-(2,2,2-trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone in place of 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 260 mg, 26%). mp 163-164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J=6.6 Hz, 6H), 1.91 (septet, J=6.6 Hz, 1H), 4.34 (d, J=6.6 Hz, 2H), 5.11 (br s, 2H), 7.43-7.52 (m, 2H), 7.80 (s, 1H), 8.02 (t, J=8 Hz, 1H). MS (DCI/NH_3) m/z 424 $(M+H)^+$, m/z 441 $(M+NH_4)^+$. Anal. calc. for $C_{16}H_{17}F_4N_3O_4S$: C, 45.39; H, 4.05; N, 9.92. Found: C, 59.89; H, 3.83; N, 8.61.

Example 383

2-Benzyl-4-(4-fluorobenzyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-benzyl-4-(4-fluorophenylmethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.5723 g 34%). mp 120-123 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.83 (bs, 2H), 5.30 (bs, 2H), 6.95-7.06 (m, 4H), 7.28-7.40 (m, 5H), 7.48 (m, 2H), 7.60 (m, 2H), 7.91 (m, 2H), 7.95 (s, 1H). MS (DCI/NH_3) m/z 450 $(M+H)^+$, 467 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{20}FN_3O_3S$: C, 64.13; H, 4.48, N, 9.35. Found: C, 63.76; H, 4.71; N, 9.02.

Example 384

2-Benzyl-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (130 mg, 0.3 mmol) and di-t-butylazodicarboxylate (DBAD) (69 mg, 0.3 mmol) in THF (30 mL) at -78 °C was added dropwise a 1 N solution of lithium 1,1,1,3,3,3-hexamethyldisilazide (0.9 mL, 0.9 mmol) in THF

After addition, the reaction was stirred an additional 45 minutes at -78 °C (or until the TLC indicated a disappearance of starting material). The reaction was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate. The acetate extract was dried over $MgSO_4$ and concentrated in vacuo to obtain 220 mg of crude adduct.

The above adduct was dissolved in THF (30 ML) and was treated at room temperature with 1 N NaOH (3 mL) for 5 hours. Sodium acetate (NaOAc.3 H_2O, 1.38 g, 10 mmol) was added followed by addition of hydroxylamine-O-sulfonic acid (1.13 g, 10 mmol) and H_2O (30 mL). The resulting mixture was stirred at room temperature for 18 hours and then extracted with ethyl acetate. The extract was washed with water, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (silica gel, 1:1 hexanes-ethyl acetate) to provide the desired product (yield: 70 mg, 54%). mp 185-189 °C. ^1H NMR (DMSO-d_6, 300 MHz) δ 5.33 (s, 2H), 7.11 (m, 2H), 7.22 (m, 2H), 7.40 (m, 7H), 7.83 (d, J=9 Hz, 2H), 8.10 (s, 1H). MS (DCI/NH_3) m/z 436 $(M+H)^+$. Anal. calc. for $C_{23}H_{18}FN_3O_3S.0.75\ H_2O$: C, 61.65; H, 4.26; N, 9.04. Found: C, 61.67; H, 4.61; N, 8.66.

Example 385

2-(4-Fluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 108 was converted to the title sulfonamide according to the method of Example 384 , (yield: 65 mg, 28.8%). mp 227-229 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 7.08-7.17 (m, 4H), 7.36 (t, J=3 Hz, 2H), 7.47 (br s, 2H), 7.61-7.69 (m, 2H), 7.83 (d, J=9 Hz, 2H), 7.93 (d, J=9 Hz, 2H), 8.40 (s, 1H). MS (DCI/NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{15}F_2N_3O_4S$: C, 58.02; H, 3.30; N, 9.24. Found: C, 57.84; H, 3.34; N, 9.01.

Example 386

2-(3,4-Difluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 371 was converted to the title sulfonamide according to the method of Example 384 (yield: 45 mg, 28%). mp 198-200 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.87 (dd, J=9 Hz, 3 Hz, 1H), 7.13 (dt, J=9 Hz, 3 Hz, 1H), 7.19 (t, J=7 Hz, 1H), 7.46 (d, J=9 Hz, 2H), 7.47 (br s, 2H), 7.52-7.69 (m, 2H), 7.79 (d, J=9 Hz, 2H), 7.82-7.89 (m, 1H), 8.25 (s, 1H). MS (DCI/NH_3) m/z 472 $(M+H)^+$, 489 $(M+NH_4)^+$.

Example 387

2-(4-Fluorophenyl)-4-(3-fluoro-4-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 250 was converted to the title sulfonamide according to the method of Example 384 (yield: 185 mg, 46%). mp 187-188 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.22 (br s, 3H), 6.87 (dd, J=9 Hz, 3 Hz, 1H), 7.16 (q, J=9 Hz, 2H), 7.38 (t, J=9 Hz, 2H), 7.46 (br s, 2H), 7.47 (d, J=9 Hz, 2H), 7.67-7.73 (m, 2H), 7.77 (d, J=9 Hz, 2H), 8.22 (s, 1H). MS (DCI/NH_3) m/z 454 $(M+H)^+$, 471 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}F_2N_3O_3S.0.25\ H_2O$: C, 60.36; H, 3.87; N, 9.19 Found: C, 60.30; H, 4.26; N, 8.83.

Example 388

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 109 was converted to the title sulfonamide according to the method of Example 384 (yield: 110 mg, 45.7%). mp 224-226 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (br s, 2H), 6.89-7.03 (m, 4H), 7.19-7.30 (m, 1H), 7.45-7.52 (m, 1H), 7.56-7.66 (m, 1H), 7.79 (d, J=9 Hz, 2H), 8.04 (d, J=9 Hz, 1H), 8.08 (s, 1H). MS (DCI/NH_3) m/z 474 $(M+H)^+$, 491 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{14}F_3N_3O_4S.0.25\ H_2O$: C, 55.32; H, 2.93; N, 8.80. Found: C, 55.26; H, 3.11; N, 8.58

Example 389

2-(3-Chloro-4-fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product from Example 247 was converted to the title sulfonamide according to the method of Example 384 (yield: 230 mg, 38%) mp 243-245 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (br s, 3H), 6.94-7.09 (m, 2H), 7.25 (dd, J=9 Hz, 3 Hz, 1H), 7.41-7.48 (m, 4H), 7.60 (t, J=9 Hz, 1H), 7.68-7.75 (m, 1H), 7.77 (d, J=9 Hz, 2H), 7.95 (dd, J=6 Hz, 3 Hz, 1H), 8.25 (s, 1H). MS (DCI/NH_3) m/z 469 $(M+H)^+$, 486 $(M+NH_4)^+$ Anal. calc. for $C_{23}H_{16}ClF_2N_3O_3S$: C, 56.67; H, 3.29; N, 8.63 Found: C, 56.81, H, 3.35; N, 8.95.

Example 390

2-(4-Fluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The methyl sulfone product of Example 245 was converted to the title sulfonamide according to the method of Example 384 (yield: 78 mg, 28.3%). mp 202-204 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 4.86 (s, 2H), 6.83-6.91 (m, 2H), 7.14-7.25 (m, 3H), 7.36 (d, J=9 Hz, 2H), 7.65-7.72 (m, 2H), 7.91 (d, J=9 Hz, 2H), 8.0 (s, 1H). MS (DCI/NH_3) m/z 454 $(M+H)^+$, 471 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{17}F_2N_3O_3S.0.25\ H_2O$: C, 60.36; H, 3.77; N, 9.19. Found: C, 60.24; H, 3.93; N, 9.25.

Example 391

2-(3-Chlorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2h)-pyridazinone

The methyl sulfone product of Example 244 was converted to the title sulfonamide according to the method of Example 384 (yield: 125 mg, 39%). mp 187-188 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 4.71 (s, 2H), 6.85-6.92 (m, 2H), 7.21 (d, J=9 Hz, 1H), 7.32-7.47 (m, 2H), 7.37 (d, J=9 Hz, 2H), 7.64 (dt, J=7 Hz, 3 Hz, 1H), 7.77 (br s, 1H), 7.91 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 470 $(M+H)^+$, 487 $(M+NH_4)^+$. Anal.

calc. for $C_{23}H_{17}ClFN_3O_3S.0.25\ H_2O$: C, 58 32; H, 3.65; N, 8.88. Found: C, 58.27; H, 3.91: N, 8.62.

Example 392

2-(3-Chlorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chlorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 366) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.0756 g, 16%). mp 167-170 °C. ^1H NMR (300 MHz, DMSO d_6) δ 0.78 (d, J=6 Hz, 6H), 1.47 (5H, obstructed by hexanes). 7.51-7.65 (m, 4H), 7.68 (m, 2H), 7.75 (m, 1H), 7.98 (m, 2H), 8.03 (s, 1H), 8.60 (bs, 1H). MS (DCI/NH_3) m/z 432 $(M+H)^+$, 449 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{22}ClN_3O_3S$ (0.25 H_2O): C, 57.79; H, 5.19; N, 9.62. Found: C, 57.78; H, 5.02; N, 9.40.

Example 393

2-(3-Chlorophenyl)-4-(phenethyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chlorophenyl)-4-(phenethyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 372) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.075 g. 17%). semi-solid: ^1H NMR (300 MHz, DMSO d_6) δ 2.80 (m, 4H), 3.29-3.42 (3H, obstructed by H_2O), 6.96 (m, 2H), 7.14-7.28 (m, 3H), 7.46-7.68 (m, 7H), 7.78 (m, 1H), 7.92 (m, 2H), 8.01 (s, 1H). MS (DCI/NH_3) m/z 466 $(M+H)^+$, 483 $(M+NH_4)^+$. Anal. calc. for $C_{24}H_{20}ClN_3O_3S.0.25\ H_2O$: C, 61.27; H, 4.39; N, 8.93. Found: 61.18; H, 4.68; N, 8.58.

Example 394

2-(3-Chlorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chlorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-

pyridazinone (Example 339) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.575 g, 18%). mp 137-139 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.81 (d, J=7 Hz, 6H), 1.49 (m, 2H), 1.57 (m, 1H), 4.42 (t, J=7 Hz, 2H), 7.44-7.65 (m, 5H), 7.76 (m, 1H), 7.84 (m, 2H), 7.94 (m, 2H), 8.20 (s, 1H). MS (DCI/NH_3) m/z 448 $(M+H)^+$, 465 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{22}ClN_3O_4S$: C, 56.31; H, 4.95; N, 9.38. Found C, 56.02; H, 4.82; N, 9.31.

Example 395

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chlorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 335) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.0458 g, 25%). mp 80-85 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.80 (d, J=6 Hz, 6H), 1.74-1.92 (m, 3H), 4.20 (d, J=6 Hz, 2H), 7.49-7.64 (m, 5H), 7.76 (m, 1H), 7.85 (m, 2H), 7.95 (m, 2H), 8.21 (m, 1H). MS (DCI/NH_3) m/z 434 $(M+H)^+$, 451 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{20}ClN_3O_4S$: C, 55.36; H, 4.65; N, 9.68. Found: C, 55.12; H, 4.58; N, 9.42.

Example 396

2-(4-Fluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 378) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (0.090 g 21%). mp 180-183 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.78 (d, J=6 Hz, 6H), 1.49 (m, 5H), 7.36 (m, 2H), 7.53 (m, 2H), 7.62-7.73 (m, 4H), 7.98 (m, 3H). MS (DCI/NH_3) m/z 416 $(M+H)^+$, 433 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{22}FN_3O_3S$: C, 60.71; H, 5.34; N, 10.11. Found: C, 60.37, H, 5 36, N, 9.84.

Example 397

2-(4-Fluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(4-fluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 376) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.024 g, 6%). mp 132-136 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0 79 (d, J=6 Hz, 6H), 1.83 (m, 1H), 4.19 (d, J=6 Hz, 2H), 7.36 (m, 2H), 7.50 (m, 2H), 7.66 (m, 2H), 7.84 (m, 2H), 7.95 (m, 2H), 8.18 (s, 1H). MS (DCI/NH_3) m/z 418 $(M+H)^+$, 435 $(M+NH_4)^+$ Anal. calc. for $C_{20}H_{20}FN_3O_4S$: C, 57.54; H, 4.83; N, 10.07. Found C, 57.26; H, 5.00; N, 9.78.

Example 398

2-(4-Fluorophenyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(4-fluorophenyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 375) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.051 g, 18%). Yellow oil. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.80 (d, J=5 Hz, 6H), 1.47 (m, 3H), 4.42 (t, J=6 Hz, 2H), 7.37 (m, 2H), 7.50 (m, 1H), 7.65 (m, 2H), 7.83 (m, 2H), 7.93 (m, 2H), 8.18 (s, 1H), 8.60 (bs, 1H). MS (DCI/NH_3) m/z 432 $(M+H)^+$, 449 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{22}FN_3O_4S$: C, 58.46; H, 5.14; N, 9.74. Found: C, 58.16; H, 5.21; N, 9.57.

Example 399

2-(t-Butyl)-4-(3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

2-(t-Butyl)-4-(3-methyl-1-butoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 330C was oxidized with one equivalent of meta-chloroperoxybenzoic acid to the corresponding methyl sulfoxide. The sulfoxide was converted to the title sulfonamide by the method of Example 68 (yield: 1.25 g, 54%). mp 153-155°C. ^{1}H

NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J=6 Hz, 2H), 1.48 (q, J=6 Hz, 2H), 1.49-1.69 (m, 1H), 1.70 (s, 9H), 4.37 (t, J=6 Hz, 2H), 4.32 (s, 2H), 7.70 (d, J=9 Hz, 2H), 7.72 (s, 1H), 8.01 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 394 $(M+H)^+$. Anal. calc. for $C_{19}H_{27}N_3O_4S$: C, 57.99; H, 6.91; N, 10.67. Found: C, 58.11; H, 6.71; N, 10.58.

Example 400

2-(3,4-Difluorophenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to Example 384 substituting 2-(3,4-difluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 182) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 950 mg, 54%). mp 177-181 °C ^1H NMR (300 MHz, DMSO-d_6) δ 7.15 (t, 2H), 7.29 (m, 2H), 7.43 (s, 1H), 7.45 (bs, 2H), 7.59 (m, 2H), 7.76 (d, J=9 Hz, 2H), 7.85 (m, 1H), 8.27 (s, 1H). MS (DCI/NH_3) m/z 458 $(M+H)^+$, 475 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{14}F_3N_3O_3S$: C, 57.77; H, 3.08; N, 9.19. Found: C, 57.22; H, 3.28; N, 8.99.

Example 401

2-(3-Chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384, substituting 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 380 mg, 47%). mp 208-210 °C. ^1H NMR (300 MHz, DMSO-d_6) δ 7.15 (t, 2H), 7.27 (m, 2H), 7.43 (s, 1H), 7.45 (bs, 2H) 7.51 (d, J=9 Hz, 4H), 7.6 (t, 1H), 7.7 (m, 1H), 7.75 (d, J=9 Hz, 2H), 7.94 (dd, 1H), 8.25 (s, 1H). MS (DCI/NH_3) m/z 474 $(M+H)^+$, 491 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{14}F_2Cl_2N_3O_3S.0.5\ H_2O$: C, 55.76; H, 2.98; N, 8.87. Found: C, 56.05, H, 3.42; N, 8.65.

Example 402

2-(3,4-Difluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of procedure Example 384, substituting 2-(3,4-difluorophenyl)-4-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 105 mg, 27%). mp 243-245 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.2 (s, 3H), 7.01 (m, 2H), 7.25 (m, 1H), 7.45 (s, 1H), 7.47 (bs, 2H), 7.6 (m, 2H), 7.77 (d, J=9 Hz, 2H), 7.85 (m, 1H), 8.26 (s, 2H). MS (DCI/NH_3) m/z 472 $(M+H)^+$, 489 $(M+NH_4)^+$ Anal. calc. for $C_{24}H_{17}F_3N_2O_3S.0.5\ H_2O$: C, 58.59; H, 3.42; N, 8.91. Found: C, 57; H, 4.23; N, 8.89.

Example 403

2-(3,4-Difluorophenyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 , substituting 2-(3,4-difluorophenyl)-4-(2-methylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 35 mg, 42%). mp 169-171 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78 (d, 6H), 1.84, (m, 1H), 4.2 (d, 2H), 7.54 (m, 3H), 7.6 (m, 1H), 7.82 (m, 3H), 7.91 (d, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 436 $(M+H)^+$, 453 $(M+NH_4)^+$. Anal. calc. for $C_{20}H_{19}F_2N_3O_4S.0.25\ H_2O$: C, 55.17; H, 4.40; N, 9.65. Found: C, 54.19; H, 4.25; N, 9.35

Example 404

2-(3,4-Difluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 , substituting 2-(3,4-difluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-

3(2H)-pyridazinone (yield: 58 mg, 52%). mp 171-173 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 3.3 (s, 3H), 7.51 (m, 1H), 7.65 (m, 1H), 7.75 (d, J=9 Hz, 2H), 7.81 (m, 1H) 8.05 (s, 1H), 8.12 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 434 $(M+H)^+$, 451 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}F_2N_3O_3S.0.25\ H_2O$: C, 58.19; H, 4.88; N, 9.69. Found: C, 57.69; H, 5.01; N, 9.18.

Example 405

2-(3-Chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 , substituting 2-(3-chloro-4-fluorophenyl)-4-(3-methylbutyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 102 mg, 61.8%). mp 154-156 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.4, (m, 3H), 2.48 (m, 2H), 7.54 (s, 2H), 7.6 (m, 1H), 7.69 (m, 2H), 7.93 (dd, 1H), 8.05 (m, 2H). MS (DCI/NH_3) m/z 450 $(M+H)^+$, 468 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{22}FN_2O_3SCl.0.25\ H_2O$: C, 58.86; H, 4.94; N, 6.24. Found: C, 59.23; H, 5.12; N, 6.00.

Example 406

2-(3,4-Difluorophenyl)-4-(2,2-dimethylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 substituting 2-(3,4-difluorophenyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 310 mg, 38%). mp 173-175 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.8 (s, 9H), 3.3 (s, 3H), 4.1 (s, 2H), 7.51 (m, 3H), 7.6 (m, 1H), 7.85 (m, 3H), 7.95 (d, J=9 Hz, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 450 $(M+H)^+$, 467 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}F_2N_3O_4S$: C, 56.12; H, 4.71, N, 9 35. Found, C, 55.83; H, 4.73; N, 9.08.

Example 407

2-(3,4-Difluorophenyl)-4-(4-fluorophenoxy)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 substituting 2-(3,4-difluorophenyl)-4-(4-fluorophenoxy)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 125 mg, 31%). mp 224-226 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (d, 4H), 7.51 (m, 1H), 7.6 (m, 2H) 7.75 (m, 4H), 7.9 (t, 1H); 8.4 (s, 1H). MS (DCI/NH_3) m/z 492 $(M+H)^+$, 509 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{13}F_4N_3O_4S$: C, 53.77; H, 2.67; N, 8.55. Found,; C, 53.33; H, 2.84; N, 8.22

Example 408

2-(3,3-Difluoro-2-propenyl)]-4-(4-fluorophenyl)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The intermediate, 2-benzyl-4-(4-fluorophenyl)-5-[3-fluoro-4-(methylthio)phenyl]-3(2H)-pyridazinone prepared according to the method of Example 72 . was oxidized with one equivalent of meta-chloroperoxybenzoic acid to provide the methyl sulfoxide which was converted to the sulfonamide according to the method of Example 68 . The sulfonamide material was N-debenzylated according to the method of Example 11 and N-alkylated according to the method of Example 20 , substituting 1,3-dibromo-1,1-difluoropropane in place of 4-fluorobenzyl bromide and employing 4 equivalents of potassium carbonate to provide the title compound (yield: 120 mg, 27%). mp 180-183 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (dt, J=15 Hz, 7.5 Hz, 2H). 4.75 (d, J=7.5 Hz, 2H), 5.06 (s, 2H). 7.02 (m, 2H), 7.19 (dd, J=9 Hz, 6 Hz, 2H). 7.81 (s, 1H), 7.87 (t, J=7.5 Hz, 2H). MS (DCI/NH_3) m/z 440 $(M+H)^+$. Anal. calc. for $C_{19}H_{11}F_4N_3O_3S$: C, 51.93; H, 2.98; N, 9.56. Found: C, 51.71; H, 3.15; N, 9.28.

Example 409

2-(3,4-Difluorophenyl)-4-[2-(2-propoxy)ethoxy]-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 , substituting 2-(3,4-difluorophenyl)-4-[2-(2-propoxy)ethoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 110 mg, 34%). mp 54-56 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.0 (d, 6H), 3.43 (m, 1H), 3.54 (m, 2H), 4.63 (m, 2H), 7.5 (m, 3H), 7.6 (m, 1H), 7.8 (m, 1H), 7.95 (m, 4H), 8.2 (s, 1H). MS (DCI/NH_3) m/z 466 $(M+H)^+$, 483 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}F_2N_3O_5S$: C, 54.19; H, 4.55; N, 9.03. Found, C, 54.29; H, 4.67; N, 8.95.

Example 410

2-(3,4-Difluorophenyl)-4-(4-methyl-3-pentenyloxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 substituting 2-(3,4-difluorophenyl)-4-(4-methyl-3-pentenyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone. mp 70-73 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.5 (d, 6H), 2.27 (m, 2H) 4.43 (t, 2H), 4.5 (m, 1H), 7.5 (m, 2H), 7.6 (m, 1H), 7.8 (m, 2H), 7.92 (d, J=2 H, 2H), 8.2 (s, 1H). MS (DCI/NH_3) m/z 462 $(M+H)^+$, 479 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}F_2N_3O_4S$: C, 57.26; H, 4.59; N, 9.11. Found, : C, 56.96; H, 4.70; N, 9.01.

Example 411

2-(3-Chlorophenyl)-4-(3-fluorophenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335. , substituting 3-fluorophenol in place of isobutanol (yield: 0.034 g, 22%). mp 178-180 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 3.27 (s, 3H), 6.88-7.00 (m, 2H), 7.10 (m, 1H), 7.36 (m, 1H), 7.59 (m, 3H), 7.74 (m, 1H), 7.90 (m, 2H), 8.06 (m, 2H), 8.43 (s, 1H). MS (DCI/NH_3)

m/z 488 $(M+H)^+$. Anal. calc. for $C_{23}H_{16}ClFN_2O_4S.0.25\ H_2O$: C, 58.10; H, 3.49; N, 5.89. Found C, 58.04; H, 3.59; N, 5.80.

Example 412

2-(3-Chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 384 , substituting 2-(3-chlorophenyl)-4-(2-methylpropoxy)-5-[3-fluoro-4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 0.019 g, 10%). mp 157-159 °C. ^1H NMR (300 MHz, DMSO d_6) δ 0 81 (d, J=6 Hz, 6H), 1.86 (m, 1H), 4.24 (d, J=6 Hz, 2H), 7.75 (m, 3H), 7.66 (m, 1H), 7.73 (m, 2H), 7.83 (m, 2H), 7.91 (m, 1H), 8.23 (s, 1H). Anal. calc. for $C_{21}H_{19}ClFN_3O_4S$: C, 53.16; H, 4.24; N, 9.30. Found: C, 53.02; H, 4.43; N, 9.10.

Example 413

2-(3-Chlorophenyl)-4-(4-methylpentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 4-methyl-1-pentanol in place of isobutanol (yield: 0.137 g, 90%). mp 139-140 °C. ^1H NMR (300 MHz, DMSO d_6) δ 0.74 (d, J=6 Hz, 6H), 1.03 (m, 2H), 1.39 (m, 1H), 1.54 (m, 2H), 3.29 (s, 3H), 4.40 (t, J=5 Hz, 2H), 7.51-7.60 (m, 3H), 7.75 (m, 1H), 7.90 (m, 2H), 8.07 (m, 2H), 8.20 (s, 1H). MS (DCI/NH_3) m/z 461 $(M+H)^+$, 478 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{25}ClN_2O_4S$: C, 59.95; H, 5.97; N, 6.08. Found: C, 59.62; H, 5.63; N, 5.86.

Example 414

2-(4-Fluorophenyl)-4-(4-methylpentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, starting with 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in

place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-methyl-1-pentanol in place of isobutanol (yield: 0.128 g, 85%). mp 123-125 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.74 (d, J=6 Hz, 6H), 1.03 (m, 2H), 1.39 (m, 1H), 1.54 (m, 2H), 3.28 (s, 3H), 4.39 (t, J=6 Hz, 2H), 7.37 (m, 2H), 7.66 (m, 2H), 7.91 (m, 2H), 8.07 (m, 2H), 8.18 (s, 1H). MS (DCI/NH_3) m/z 445 $(M+H)^+$. Anal. calc. for $C_{23}H_{25}FN_2O_4S$: C, 62.14; H, 5.67, N, 6.30. Found: C, 62.28; H, 5.59; N, 6.25.

Example 415

2-(4-Fluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 332, substituting 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone for 2-(3-chlorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 2.022 g, 97%). ^{1}H NMR (300 MHz, DMSO d_6) δ 3.28 (s, 3H), 7.38 (m, 2H), 7.70 (m, 2H), 8.03 (m, 4H), 8.22 (s, 1H). MS (APCI-+Q1MS) 361 $(M+H)^+$, (-Q1MS) 359 $(M-H)^-$.

Example 416

2-(4-Fluorophenyl)-4-cyclopropylmethoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting cyclopropylmethanol in place of isobutanol (yield: 0.117 g, 83%). mp 166-167 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.22 (m, 2H), 0.46 (m, 2H), 1.10 (m, 1H), 3.31 (s, 3H), 4.30 (d, J=7 Hz, 2H), 7.36 (m, 2H), 7.66 (m, 2H), 7.96 (m, 2H), 8.07 (m, 2H), 8.20 (s, 1H). MS (DCI/NH_3) m/z 415 $(M+H)^+$, 432 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{25}ClN_2O_4S$: C, 60.86; H, 4.62; N, 6.76. Found C, 60.76; H, 4.72; N, 6.61.

Example 417

2-(4-Fluorophenyl)-4-(2-cyclopropyl-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 2-cyclopropane ethanol in place of isobutanol (yield: 0.1472 g, 100%). mp 111-117 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ -0.01 (m, 2H), 0.31 (m, 2H), 0.60 (m, 1H), 1.49 (q, J=6 Hz, 2H), 3.29 (s, 3H), 4.48 (t, J=6 Hz, 2H), 7.37 (m, 2H), 7.65 (m, 2H), 7.91 (m, 2H), 8.06 (m, 2H), 8.17 (s, 1H). MS (DCI/NH_3) m/z 429 $(M+H)^+$, 446 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}FN_2O_4S$. C, 61.67, H, 4.94; N, 6.54. Found: C, 61.59; H, 5.02; N, 6.45.

Example 418

2-(3-Chlorophenyl)-4-cyclopropanemethoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting cyclopropane methanol in place of isobutanol (yield: 0.0917 g, 64%). mp 158-161 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.22 (m, 2H), 0.46 (m, 2H), 1.13 (m, 1H), 3.31 (s, 3H), 4.31 (d, J=7 Hz, 2H), 7.57 (m, 3H), 7.75 (m, 1H), 7.96 (m, 2H), 8.08 (m, 2H), 8.23 (s, 1H). MS (DCI/NH_3) m/z 431 $(M+H)^+$, 448 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{19}ClN_2O_4S.0.25\ H_2O$: C, 57.92; H, 4.51; N, 6.43. Found: C, 57.86; H, 4.35; N, 6.27.

Example 419

2-(3-Chlorophenyl)-4-(2-cyclopropane-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-cyclopropane ethanol in place of isobutanol (yield: 0.114 g, 78%). mp 124-128 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 0.00 (m, 2H), 0 32 (m, 2H), 0.61 (m, 1H), 1.49 (q, J=6 Hz, 2H), 3.30 (s, 3H), 4.50 (t, J=6 Hz, 2H), 7.58 (m, 3H), 7.76 (m, 1H), 7.91 (m,

2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}ClN_2O_4S$: C, 59.39; H, 4.76; N, 6.30. Found: C, 58.92; H, 4.94; N, 6.15.

Example 420

2-(4-Fluorophenyl)-4-(4-methylpentyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-methylpentane-1-magnesium bromide for cyclopentyl magnesium chloride (yield: 0.165 g, 99%). mp 112-115 °C. ^1H NMR (300 MHz, DMSO d_6) δ 0.75 (d, J=7 Hz, 6H), 1.07 (q, J=7 Hz, 2H), 1.32-1.53 (m, 3H), 2.45 (t, 2H), 3.31 (s, 3H), 7.37 (m, 2H), 7.66 (m, 2H), 7.76 (m, 2H), 8.00 (s, 1H), 8.10 (m, 2H). MS (DCI/NH_3) m/z 429 $(M+H)^+$. 446 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{25}FN_2O_3S$: C, 64.47; H, 5.88; N, 6.54. Found: C, 64.44; H, 5.90; N, 6.49.

Example 421

2-(3-Chlorophenyl)-4-(4-methylpentyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 362, substituting 4-methylpentane-1-magnesium bromide in place of cyclopentyl magnesium chloride (yield: 165 mg, 98%). oil. ^1H NMR (300 MHz, DMSO d_6) δ 0.76 (d, J=6 Hz, 6H), 1.07 (m, 2H), 1.33-1.55 (m, 3H), 2.45 (m, 2H), 3.32 (s, 3H), 7.51-7.65 (m, 4H), 7.76 (m, 2H), 8.03 (s, 1H), 8.11 (m, 2H). MS (DCI/NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{25}ClN_2O_3S$: C, 62.06; H, 5.66; N, 6.30. Found: C, 61.86; H, 5.64; N, 6.18.

Example 422

2-(4-Fluorophenyl)-4-(3-methyl-2-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 3-methyl-2-buten-1-ol in place of isobutanol (yield: 0.1284 g, 88%). mp 128-132 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.58 (s, 3H), 1.67 (s, 3H), 3.30 (s, 3H), 4.95 (d, J=7 Hz, 2H), 5.31 (m, 1H), 7.38 (m, 2H), 7.65 (m, 2H), 7.89 (m, 2H), 8.06 (m, 2H), 8.18 (s, 1H). MS (DCI/NH_3) m/z 429 $(M+H)^+$, 446 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}FN_2O_4S$: C, 61.67; H, 4.94; N, 6.54. Found. C, 61.41; H, 4.95; N, 6.47.

Example 423

2-(3-Chlorophenyl)-4-(3-methyl-2-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-methyl-2-buten-1-ol in place of isobutanol (yield: 0.119 g, 81%). mp 113-115 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.58 (s, 3H), 1.67 (s, 3H), 3.31 (s, 3H), 4.96 (m, 2H), 5.32 (m, 1H), 7.58 (m, 3H), 7.75 (m, 1H), 7.89 (m, 2H), 8.07 (m, 2H), 8.21 (s, 1H). MS (APCI+Q1MS) 445 $(M+H)^+$, (APCI-Q1MS) 479 $(M+35)^-$. Anal. calc. for $C_{22}H_{21}ClN_2O_4S$: C, 59.39; H, 4.76; N, 6.30. Found: C, 59.14; H, 4.66; N, 6.16.

Example 424

2-(4-Fluorophenyl)-4-(4-methyl-3-pentenyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-methyl-3-penten-1-ol in place of isobutanol (yield: 0.1165 g, 77%). mp 111-114 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.46 (s, 3H), 1.56 (s, 3H), 2.26 (m, 2H), 3.30 (s, 1H), 4.43 (t, J=7 Hz, 2H), 4.96 (m, 1H), 7.37 (m, 2H), 7.65 (m, 2H), 7.91 (m, 2H), 8.06 (m, 2H), 8.18 (s, 1H). MS (DCI/NH_3) m/z 443 $(M+H)^+$, 460

$(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}FN_2O_4S$. C. 62.43; H. 5.24: N, 6.33. Found: C. 62.32; H, 5.30; N, 6.25.

Example 425

2-(4-Fluorophenyl)-4-(3-methyl-3-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3-chlorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 3-methyl-3-butene-1-ol in place of isobutanol (yield: 0.1327 g, 91%). mp 109-111 °C. ^{1}H NMR (300 MHz. DMSO d_6) δ 1.61 (s, 3H), 2.32 (t, J=7 Hz, 2H), 3.30 (s, 3H), 4.56 (t, J=7 Hz. 2H), 4.63 (bs, 1H). 4.68 (bs, 1H), 7.37 (m, 2H), 7.66 (m, 2H), 7.90 (m, 2H). 8.05 (m, 2H). 8.19 (s, 1H). MS (DCI/NH_3) m/z 429 $(M+H)^+$, 446 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}FN_2O_4S$: C, 61.67; H. 4.94; N, 6.54. Found: C, 61.50; H, 5.00; N, 6.45.

Example 426

2-(3-Chlorophenyl)-4-(4-methyl-3-pentenyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 4-methyl-3-pentene-1-ol in place of isobutanol (yield: 0.1149 g, 76%). mp 110-111 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.47 (s, 3H). 1.55 (s, 3H), 2.27 (m, 2H), 3.30 (s, 3H), 4.44 (t. J=6 Hz, 2H), 4.96 (m, 1H), 7.52-7.64 (m. 3H), 7.75 (m, 1H), 7.91 (M, 2H). 8.06 (m, 2H). 8.21 (s. 1H). MS (DCI/NH_3) m/z 459 $(M+H)^+$, 476 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{23}ClN_2O_4S$: C. 60.19; H. 5.05; N, 6.10. Found: C. 60.06; H. 4 90; N, 5.96.

Example 427

2-(3-Chlorophenyl)-4-(3-methyl-3-butenoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 335, substituting 3-methyl-3-butene-1-ol in place of isobutanol (yield: 0.1159 g, 79%). mp 110-112 °C. ^{1}H NMR (300 MHz, DMSO d_6) δ 1.62 (s, 3H), 2.32 (t, J=7 Hz, 2H), 3.30 (s, 3H), 4.57 (t, J=6 Hz, 2H), 4.63 (bs, 1H), 4.68 (bs, 1H), 7.51-7.64 (m, 3H), 7.76 (m, 1H), 7.90 (m, 2H), 8.05 (m, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 445 $(M+H)^+$, 462 $(M+NH_4)^+$. Anal. calc. for $C_{22}H_{21}ClN_2O_4S$: C, 59.39; H, 4.76; N, 6.30. Found: C, 59.27; H, 4.68; N, 6.18.

Example 428

2-(4-Fluorophenyl)-4-(1,5-hexadienyl-3-oxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 1,5-hexadien-3-ol in place of 2-ethyl-1-hexanol (yield: 150 mg, 85%). mp 104-105 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.42 (m, 2H), 3.30 (s, 3H), 5.00 (m, 2H), 5.17 (m, 2H), 5.64 (m, 2H), 7.36 (t, J=9 Hz, 2H), 7.64 (m, 2H), 7.92 (d, J=9 Hz, 2H), 8.06 (d, J=9 Hz, 2H), 8.19 (s, 1H). MS (APCI+) m/z 441 $(M+H)^+$; (APCI-) m/z 475 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{21}FN_2O_4S$: C, 62.71; H, 4.80; N, 6.35. Found: C, 62.96; H, 4.93; N, 5.85.

Example 429

2-(4-Fluorophenyl)-4-(5-methyl-2-hexyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 5-methyl-2-hexanol in place of 2-ethyl-1-hexanol (yield: 150 mg, 82%). mp 102-103 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 (d, J=7 Hz, 6H), 1.04 (m, 2H), 1.14 (d, J=7 Hz, 3H), 1.40 (m, 3H), 3.29 (s, 3H), 5.12 (m, 1H), 7.36 (t, J=9 Hz, 2H), 7.66 (m, 2H), 7.92 (d, J=9 Hz, 2H), 8.07 (d, J=9 Hz, 2H), 8.19 (s, 1H). MS (APCI+) m/z 459 $(M+H)^+$; (APCI-) m/z 493 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{27}FN_2O_4S$: C, 62.86; H, 5.93; N, 6.10. Found: C, 62.83; H, 5.99; N, 6.07.

Example 430

2-(4-Fluorophenyl)-4-(2-ethyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-ethyl-1-butanol in place of 2-ethyl-1-hexanol (yield: 140 mg, 80%). mp 107-108 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 (t, J=7 Hz, 6H), 1.20 (quintet, J=7 Hz, 4H), 1.40 (m, 1H), 3.29 (s, 3H), 4.29 (d, J=7 Hz, 2H), 7.37 (t, J=9 Hz, 2H), 7.66 (m, 2H), 7.90 (d, J=9 Hz, 2H), 8.07 (d, J=9 Hz, 2H), 8.19 (s, 1H). MS (APCI+) m/z 445 $(M+H)^+$; (APCI-) m/z 479 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{25}FN_2O_4S$: C, 62.14; H, 5.66; N, 6.30. Found: C, 62.05; H, 5.86; N, 6.30.

Example 432

2-(4-Fluorophenyl)-4-(2-thioisopropyl-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-(isopropylthio)ethanol in place of 2-ethyl-1-hexanol (yield: 138 mg, 74%). mp 137-139 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13 (d, J=7 Hz, 6H), 2.77 (t, J=7 Hz, 2H), 2.88 (quintet, J=7 Hz, 1H), 3.29 (s, 3H), 4.58 (t, J=7 Hz, 2H), 7.37 (t, J=9 Hz, 2H), 7.66 (m, 2H), 7.92 (d, J=9 Hz, 2H), 8.06 (d, J=9 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 463 $(M+H)^+$. Anal. calc. for $C_{22}H_{23}FN_2O_4S_2$: C, 57.12; H, 5.01; N, 6.05. Found: C, 56.82; H, 4.91; N, 5.99.

Example 433

2-(4-Fluorophenyl)-4-(3-methylthio-1-hexyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 3-(methylthio)-1-hexanol in place of 2-ethyl-1-hexanol (yield: 155 mg, 79%). mp 90-92 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.78 (t, J=7 Hz, 3H), 1.30 (m, 4H), 1.76

(m, 2H), 2.82 (s, 3H), 2.38 (m, 1H), 3.29 (s, 3H), 4.55 (m, 2H), 7.37 (t, J=9 Hz, 2H), 7.66 (m, 2H), 7.92 (d, J=9 Hz, 2H), 8.06 (d, J=9 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 491 $(M+H)^+$; (APCI-) m/z 525 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{27}FN_2O_4S_2$: C, 58.75; H, 5.54; N, 5.70. Found: C, 58.66; H, 5.54; N, 5.66.

Example 434

2-(4-Fluorophenyl)-4-(2-methyl-4-pentenyl-1-oxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-methyl-4-penten-1-ol in place of 2-ethyl-1-hexanol (yield: 135 mg, 76%). mp 106-107 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76 (d, J=7 Hz, 3H), 1.78 (m, 2H), 2.00 (m, 1H), 3.29 (s, 3H), 4.25 (m, 2H), 4.90 (m, 2H), 5.67 (m, 1H), 7.37 (t, J=9 Hz, 2H), 7.66 (m, 2H), 7.92 (d, J=9 Hz, 2H), 8.06 (d, J=9 Hz, 2H), 8.18 (s, 1H). MS (APCI+) m/z 443 $(M+H)^+$; (APCI-) m/z 477 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{23}FN_2O_4S$. C, 62.42; H, 5.23; N, 6.33. Found: C, 62.13; H, 5.12; N, 6.22.

Example 435

2-(3,4-Difluorophenyl)-4-(3-trifluoromethyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyidazinone (189mg, 0.5 mmol), Ph_3P (262 mg, 1 mmol) and 3-trifluoromethyl-1-butanol (66 mg, 0.5 mmol) in THF (25 mL) was added dropwise a solution of DIAD (0.2 mL, 1 mmol) in THF (5 mL) and the resulting mixture was stirred at room temperature for 8 hours. The mixture was concentrated in vacuo and the residue was chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide the desired product, (yield: 180 mg 71%). mp 126-128 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (d, J=7 Hz, 3H), 1.55 (m, 1H), 1.97 (m, 1H), 2.30 (m, 1H), 3.29 (s, 3H), 4.46 (m, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J=9 Hz, 2H), 8.08 (d, J=9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 503

(M+H)$^+$; (APCI-) m/z 537 (M+Cl)$^-$. Anal. calc. for $C_{22}H_{19}F_5N_2O_4S$: C, 52.59; H, 3.81; N, 5.57. Found: C, 52.70; H, 3.73, N, 5.63.

Example 436

2-(3,4-Difluorophenyl)-4-ethoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting ethanol in place of 2-ethyl-1-hexanol (yield: 25 mg, 12%). mp 121-123 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.23 (t, J=7 Hz, 3H), 3.30 (s, 3H), 4.51 (q, J=7 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J=9 Hz, 2H), 8.08 (d, J=9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 407 (M+H)$^+$; (APCI-) m/z 441 (M+Cl)$^-$. Anal. calc. for $C_{19}H_{16}F_2N_2O_4S.0.25\ H_2O$: C, 55.53; H, 4.04; N, 6.81. Found. C, 55.58; H, 4.21; N, 6.61.

Example 437

2-(3,4-Difluorophenyl)-4-(4-methyl-1-pentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-methyl-1-pentanol in place of 2-ethyl-1-hexanol (yield: 120 mg, 52%). mp 98-99 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.73 (d, J=7 Hz, 6H), 1.02 (m, 2H), 1.29 (m, 1H), 1.54 (m, 2H), 3.30 (s, 3H), 4.40 (t, J=7 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J=9 Hz, 2H), 8.08 (d, J=9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 463 (M+H)$^+$, (APCI-) m/z 497 (M+Cl)$^-$. Anal. calc. for $C_{23}H_{24}F_2N_2O_4S$: C, 59.72; H, 5.23; N, 6.05. Found: C, 59.57; H, 5.28; N, 6.01.

Example 438

2-(3,4-Difluorophenyl)-4-(4-methyl-2-pentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-methyl-2-pentanol for 2-ethyl-1-hexanol (yield: 115 mg, 50%). mp 132-133 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80 (d, J=7 Hz, 3H), 0.87 (d, J=7 Hz, 3H), 1.10 (d, J=7 Hz, 3H), 1.26 (m, 1H), 1.50 (m, 1H), 1.63 (m, 1H), 3.30 (s, 3H), 5.31 (m, 1H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J=9 Hz, 2H), 8.08 (d, J=9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 463 $(M+H)^+$, (APCI-) m/z 497 $(M+Cl)^-$. Anal. calc. for $C_{23}H_{21}F_2N_2O_4S$: C, 59.72; H, 5.23; N, 6.05. Found: C, 59.44; H, 5.26; N, 5.99.

Example 439

2-(3,4-Difluorophenyl)-4-(2-cyclopentyl-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 2-cyclopentyl-1-ethanol in place of 2-ethyl-1-hexanol (yield: 115 mg, 60%). mp 100-101 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.00 (m, 2H), 1.38 (m, 2H), 1.57 (m, 7H), 3.30 (s, 3H), 4.42 (t, J=7 Hz, 2H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J=9 Hz, 2H), 8.08 (d, J=9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 475 $(M+H)^+$; (APCI-) m/z 509 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{24}F_2N_2O_4S.0.25\ H_2O$: C, 60.17; H, 5.15; N, 5.84. Found: C, 60.12; H, 5.14; N, 5.76.

Example 440

2-(3,4-Difluorophenyl)-4-(2-cyclopent-2-enyl-1-ethoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, starting with 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 2-cyclopent-2-enyl-1-ethanol in place of 2-ethyl-1-hexanol (yield: 95 mg, 48%). mp 126-127 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (m, 1H), 1.57 (sextet, J=7 Hz, 1H), 1.69 (sextet, J=7 Hz, 1H), 1.87 (m, 2H), 2.57 (m, 1H), 3.30 (s, 3H), 4.45 (m, 2H), 5.60 (m, 1H), 5.68 (m, 1H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.90 (d, J=9 Hz, 2H), 8.08 (d, J=9 Hz, 2H), 8.22 (s, 1H). MS (APCI+) m/z 473 $(M+H)^+$; (APCI-) m/z 507 $(M+Cl)^-$. Anal. calc. for $C_{24}H_{22}F_2N_2O_4S$: C, 61.00; H, 4.69; N, 5.92. Found: C, 60.76; H, 4.65; N, 5.80.

Example 441

2-(2-Hydroxy-2-phenylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of the product from Example 46, 2-phenacyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (700 mg, 1.5 mmol), and sodium borohydride (69 mg, 1.8 mmol) in ethanol (200 mL), was stirred at 40 °C for 2 hours. The reaction mixture was then concentrated in vacuo and the residue was partitioned between ethyl acetate and 2 N aqueous hydrochloric acid. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to provide a pale yellow solid which was crystallized from ethyl acetate/hexanes to provide the title compound as white crystals (yield: 540 mg, 78%). mp 205-207 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 3.75 (br s, 1H), 4.63-4.47 (m, 2H), 5.33 (dd, J=9 Hz, 3 Hz, 1H), 7.00 (t, J=9 Hz, 2H), 7.20 (dd, J=9 Hz, 3 Hz, 2H), 7.30-7.45 (m, 5H), 7.52 (d, J=9 Hz, 2H), 7.91 (s, 1H), 7.91 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 465 $(M+H)^+$. Anal. calc. for $C_{25}H_{21}FN_2O_4S$: C, 64.64; H, 4.55; N, 6.03. Found: C, 64.34; H, 4.66; N, 5.93.

Example 442

2-(2-Methoxy-2-phenylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of the product from Example 441 , 2-(2-hydroxy-2-phenylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (210 mg, 0.45 mmol), iodomethane (56 µL, 0.90 mmol), and an 80% oil dispersion of sodium hydride (18 mg, 0.59 mmol) in anhydrous DMF (16 mL) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate and 2 N aqueous hydrochloric acid. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to provide a yellow oil which was purified by column chromatography (silica gel, 70:30 hexanes/ethyl acetate). Fractions containing product were combined and concentrated in vacuo , and the residue was triturated with hexanes to provide the title compound (yield: 75 mg, 34.7%). mp 135-137 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 3.26 (s, 3H), 4.33-4.52 (m, 2H), 4.91 (dd, J=9 Hz, 3 Hz, 1H), 6.99 (t, J=9 Hz, 2H), 7.20 (dd, J=9 Hz, 3 Hz, 2H), 7.31-7.50 (m, 7H), 7.87 (s, 1H), 7.89 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 479 $(M+H)^+$. Anal. calc. for $C_{26}H_{23}FN_2O_4S$. C, 65.25; H, 4.84; N, 5.85. Found: C, 64.98; H, 4.83; N, 5.81.

Example 443

2-(2-Methoxyimino-2-phenylethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of the product from Example 46, 2-phenacyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (220 mg, 0.476 mmol), methoxylamine hydrochloride (318 mg, 3.8 mmol), and sodium acetate (518 mg, 3.8 mmol) in methanol (100 mL) was stirred at reflux for 48 hours. The reaction mixture was concentrated in vacuo , and the residue was partitioned between ethyl acetate and saturated aqueous ammonium chloride. The organic layer was washed with brine then dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to provide a brown oil which was purified by column chromatography (silica gel, 70:30 hexanes/ethyl acetate). Fractions containing product were combined and concentrated in vacuo . The residue was

crystallized from methanol/water to provide the title compound as a mixture of E and Z oximes (yield: 82 mg, 35%). mp 95-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (s, 3H), 4.07 (s, 3H), 5.57 (s, 2H), 6.94 (t, J=9 Hz, 2H), 7.07 (dd, J=9 Hz, 3 Hz, 2H), 7.24 (d, J=9 Hz, 2H), 7.31-7.37 (m, 3H), 7.60-7.67 (m, 2H), 7.74 (s, 1H), 7.83 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 492 $(M+H)^+$. Anal. calc. for $C_{26}H_{22}FN_3O_4S$: C, 63.53; H, 4.51; N, 8.54. Found: C, 63.40; H, 4.51; N, 8.31.

Example 444

2-(3,4-Difluorophenyl)-4-(4-methylpentyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 255, substituting 1-bromo-4-methylpentane in place of 3,4-difluorobenzyl bromide (yield: 145 mg, 58%). mp 111-113 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 6H), 1.09 (m, 2H), 1.4 (m, 3H), 2.48 (m, 2H), 3.4 (s, 3H), 7.61 (m, 2H), 7.75 (d, 2H), 7.81 (m, 1H), 8.02 (s, 1H), 8.1 (d, 2H). MS (DCI/NH_3) m/z 447 $(M+H)^+$, 464 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{24}F_2N_2O_3S$: C, 61.87; H, 5.42; N, 6.27. Found: C, 61.76; H, 5.55; N, 6.11.

Example 445

2-(3,4-Difluorophenyl)-4-(3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared as described in Example 384, substituting 2-(3,4-difluorophenyl)-4-(3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 347) in place of 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 248 mg, 42%). mp 149-151 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.8 (d, J=6 Hz, 6H), 1.48 (m, 2H), 1.54 (m, 1H), 4.4 (t, 2H), 7.51 (m, 3H), 7.6 (m, 1H), 7.85 (m, 3H), 7.95 (d, J=9 Hz, 2H), 8.21 (s, 1H). MS (DCI/NH_3) m/z 450 $(M+H)^+$, 467 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{21}F_2N_3O_4S$: C, 56.12; H, 4.71; N, 9.35. Found, C, 56.12; H, 4.67; N, 9.15.

Example 446

2-(2,2,2-Trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The intermediate, 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 90C was reacted with 2,2-dimethylpropanol to provide 2-(2,2,2-trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone according to the method of Example 90D.

The product was oxidized with one equivalent of meta-chloroperoxybenzoic acid to provide the methyl sulfoxide. The sulfoxide was converted to the title compound according to the method of Example 68 , substituting 2-(2,2,2-trifluoroethyl)-4-(2,2-dimethylpropoxy)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone for 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 125 mg, 53%). mp 123-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 9H), 4.18 (s, 2H), 4.82 (q, J=9 Hz, 2H), 4.84 (s, 2H), 7.70 (d, J=9 Hz, 2H), 7.81 (s, 1H), 8.04 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 420 $(M+H)^+$. Anal. calc. for $C_{17}H_{20}F_3N_3O_4S$: C, 48.68; H, 4.80; N, 10.01. Found: C, 48.76; H, 4.77; N, 9.94.

Example 447

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 83, substituting 3-methyl-1-butanol in place of isopropanol (yield: 65 mg, 85%). mp 111-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J=6 Hz, 6H), 1.51 (m, 2H), 1.63 (m, 1H), 3.11 (s, 3H), 4.54 (t, J=6 Hz, 2H), 4.83 (q, J=9 Hz, 2H), 7.73 (d, J=9 Hz, 2H), 7.82 (s, 1H), 8.05 (d, J=9 Hz, 2H); MS (DCI/NH_3) m/z 419 $(M+H)^+$. Anal. calc. for $C_{18}H_{21}F_3N_2O_4S$: C, 51.66; H, 5.05; N, 6.69. Found: C, 51.91; H, 5.06; N, 6.56.

Example 448

2-(2,2,2-Trifluoroethyl)-4-(3-methylbutoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The intermediate, 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 90C was reacted with 3-methyl-1-butanol to provide 2-(2,2,2-trifluoroethyl)-4-(3-methylbutoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone according to the method of Example 90D.

The product was oxidized with one equivalent of meta-chloroperoxybenzoic acid to provide the methyl sulfoxide. The sulfoxide was converted to the title compound according to the method of Example 68 , substituting 2-(2,2,2-trifluoroethyl)-4-(3-methylbutoxy)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone for 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 65 mg, 50%). mp 123-124 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J=6 Hz, 6H), 1.52 (q, J=6 Hz, 2H), 1.60 (h, J=7.5 Hz, 1H), 4.52 (t, J=6 Hz, 2H), 4.83 (q, J=9 Hz, 2H), 4.90 (s, 2H), 7.69 (d, J=9 Hz, 2H), 7.82 (s, 1H), 8.04 (d, J=9 Hz, 2H). MS (DCI/NH_3) m/z 420 $(M+H)^+$. Anal. calc. for $C_{17}H_{20}F_3N_3O_4S$: C, 48.68; H, 4.80; N, 10.01. Found: C, 48.86; H, 4.83; N, 9.92.

Example 449

2-(2,2,2-Trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The intermediate, 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone prepared in Example 90C was reacted with 2-methyl-1-propanol to provide 2-(2,2,2-trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone according to the method of Example 90D.

The product was oxidized with one equivalent of meta-chloroperoxybenzoic acid to provide the methyl sulfoxide. The sulfoxide was converted to the title compound according to the method of Example 68 , substituting 2-(2,2,2-trifluoroethyl)-4-(2-methylpropoxy)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone for 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone

(yield: 120 mg, 40%) mp 170-172 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, J=6 Hz, 6H), 1.9 (m, 1H), 4.3 (m, 2H), 4.82 (s, 2H), 4.88 (m, 2H), 7.70 (d, J=9 Hz, 2H), 7.79 (s, 1H), 8.03 (d, J=9 Hz, 2H); MS (DCI/NH_3) m/z 406 $(M+H)^+$. Anal. calc. for $C_{16}H_{18}F_3N_3O_4S$: C, 47.4; H, 4.47; N, 10.36. Found: C, 47.48; H, 4.36; N, 10.25.

Example 450

2-(2,3,3-Trifluoropropenyl)-4-(4-fluorophenyl)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The product of Example 4, 2-benzyl-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone, was N-debenzylated by the method of Example 11 to provide 4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone. The intermediate was mixed with one equivalent of 1-methylsufonyloxy-2,3,3-trifluoro-2-propene, (Example 88A) in ethyl acetate, followed by one equivalent of cesium carbonate. The reaction mixture was heated to 50 °C for 5 hours. Aqueous work-up, followed by chromatography provided 2-(2,3,3-trifluoropropenyl)-4-(4-fluorophenyl)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (650 mg, 63%). The product was oxidized with one equivalent of meta-chloroperoxybenzoic acid to provide the methyl sulfoxide which was converted to the title compound according to the method of Example 68 , substituting 2-(2,3,3-trifluoropropenyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone for 2-(2,2,2-trifluoroethyl)-4-(4-fluorophenyl)-5-[4-(methylsulfinyl)phenyl]-3(2H)-pyridazinone (yield: 65 mg, 35%). mp 190-193°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 2H), 5.10 (dt, J=21 Hz, J=3 Hz, 2H), 7.05 (m, 4H), 7.19 (dd, J=9 Hz, J=6 Hz, 2H), 7.84 (s, 1H), 7.87 (t, J=7 5 Hz, 1H). MS (ESI-NH_3) m/z 456 $(M-H)^-$. Anal. calc. for $C_{19}H_{12}F_5N_3O_3S$: C, 49.89; H, 2.64; N, 9.18. Found: C, 49.89; H, 2.73; N, 9.03.

Example 451

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 3-methyl-1,3-butanediol in place of 2-ethyl-1-hexanol (yield: 110 mg, 61%). mp 133-134 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (s, 6H), 1.72 (t, J = 7 Hz, 2H), 3.29 (s, 3H), 4.32 (s, 1H), 4.53 (t, J = 7 Hz, 2H), 7.37 (t, J = 9 Hz, 2H), 7.66 (m, 2H), 7.90 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.19 (s, 1H); MS (APCI+) m/z 447 $(M+H)^+$; (APCI-) m/z 481 $(M+Cl)^-$; Anal. calc. for $C_{22}H_{23}FN_2O_5S \cdot 0.25\ H_2O$: C, 58.59; H, 5.25; N, 6.21. Found: C, 58.42; H, 5.00; N, 6.02.

Example 452 2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-(3,4-difluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(4-fluorophenyl)-4-tosyloxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 2-methyl-1,2-propanediol in place of 2-ethyl-1-hexanol (yield: 55 mg, 31%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (s, 6H), 3.30 (s, 3H), 4.20 (s, 2H), 4.54 (s, 1H), 7.52 (m, 1H), 7.62 (m, 1H), 7.81 (m, 1H), 7.98 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), 8.21 (s, 1H); MS (APCI+) m/z 451 $(M+H)^+$; (APCI-) m/z 485 $(M+Cl)^-$; Anal. calc. for $C_{21}H_{20}F_2N_2O_5S$: C, 55.99; H, 4.47; N, 6.21. Found: C, 56.00; H, 4.48; N, 5.87.

Example 453

2-(3,4-Difluorophenyl)-4-methoxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was isolated from the reaction mixture in Example 233, as a product of oxidation of unreacted starting material (yield: 22 mg, 8%). mp 113-115 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3H), 4.1 (s, 3H), 7.53 (m, 1H), 7.63 (m, 1H), 7.8 (m, 1H), 8.15 (d, 2H), 8.2 (s, 2H). MS (DCI/NH_3) m/z 393 $(M+H)^+$, 410 $(M+NH_4)^+$. Anal. calc. for $C_{18}H_{14}F_2N_2O_4S$: C, 55 10; H, 3.60; N, 7.14.

Example 454

2-(2,3,4,5,6-Pentafluorobenzyl)-4-(4-fluorophenyl)-5-[4-(dimethylamino)methylaminosulfonylphenyl]-3(2H)-pyridazinone

The title compound was isolated from the reaction mixture in Example 125 , as a product resulting from a reaction with the solvent, N,N-dimethylformamide (yield: 53 mg, 16%). mp 194-196 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.17 (s, 3H), 5.49 (s, 2H), 6.97 (t, J=9 Hz, 2H), 7.18 (dd, J=9 Hz, 6 Hz, 2H), 7.20 (d, J=9 Hz, 2H), 7.81 (s, 1H), 7.82 (d, J=9 Hz, 2H), 8.14 (s, 1H). MS (DCI/NH_3) m/z 581 $(M+H)^+$. Anal. calc. for $C_{26}H_{18}F_6N_4O_3S$: C, 53.79; H, 3.12; N, 9.65. Found: C, 53.50; H, 3.24; N, 9.56.

Example 455

2-(2,4-Difluorobenzyl)-4-(4-fluorophenyl)-5-[4-(dimethylamino)methylaminosulfonylphenyl]-3(2H)-pyridazinone

The title compound was isolated from the reaction mixture in Example 124 , as a product resulting from a reaction with the solvent, N,N-dimethylformamide (yield: 55 mg, 18%). mp 193-195 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (s, 3H), 3.16 (s, 3H), 5.43 (s, 2H), 6.88 (m, 2H), 6.95 (t, J=9 Hz, 2H), 7.18 (dd, J=9 Hz, 6 Hz, 2H), 7.20 (d, J=9 Hz, 2H), 7.52 (m, 1H), 7.81 (d, J=9 Hz, 2H), 7.84 (s, 1H), 8.13 (s, 1H). MS (DCI/NH_3) m/z 527 $(M+H)^+$. Anal. calc. for $C_{26}H_{21}F_3N_4O_3S$: C, 59.30; H, 4.02; N, 10.64. Found: C, 59.08; H, 3.97; N, 10.48.

Example 456

(4-Fluorophenyl)-5-[4-(methylselenonyl)phenyl]-3(2H)-pyridazinone

Example 456A

4-Bromoselenoanisole

Freshly crushed magnesium turnings (6.1 g, 0.25 mol) were suspended with vigorous stirring in a solution of diethyl ether (360 mL) and 1,4-dibromobenzene (10 g, 0.04 mol). The solution was brought to reflux for 30 minutes, without initiation. Several crystals of iodine were added which initiated the reaction to a self-sustained reflux. The

reflux was maintained as the remainder of the 1,4-dibromobenzene (49 g, 0.21 mol) was slowly added. The reaction was refluxed for an additional 2 hours after addition of the 1,4-dibromobenzene was completed. When nearly all of the magnesium turnings had been consumed, the yellow/gray heterogeneous solution was cooled to 23 °C, and selenium (19 g, 0.24 mol) was added in small portions via spatula so as to maintain a gentle reflux. The selenium that became stuck to the sides of the flask was washed in with additional diethyl ether. After addition, the solution was stirred for 20 minutes at 23 °C and then was cooled to 0 °C. A diethyl ether (20 mL) solution of methyl iodide (35.5 g, 0.25 mol) was slowly added dropwise to the reaction mixture. Upon completion of addition, the cooling bath was removed, and the solution stirred for 3 hours at 23 °C. The reaction solution was slowly poured into ice water/1 M HCl , and then the biphasic solution filtered through a glass wool plug. The ethereal layer was separated and the aqueous phase extracted twice more with diethyl ether. The combined ethereal extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to provide a semi-viscous orange oil. On standing overnight at -20 °C, large yellow needles formed. The residual oil was drawn off via pipette to provide 17 g (27%) of crystalline product. (J. Org. Chem., 1983, 48, 4169) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.12 (d, J=8.7 Hz, 2H), 7.39 (d, J=8.7 Hz, 2H). MS (APCI+) m/z 248 (Se_{76} M+H)$^+$, m/z 250 (Se_{78} M+H)$^+$, m/z 252 (Se_{80} M+H)$^+$, and m/z 254 (Se_{82} M+H)$^+$.

Example 456B

2,4-Bis(4-fluorophenyl)-5-[4-(methylseleno)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 228 , substituting 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylseleno)phenyl]-3(2H)-pyridazinone (prepared according to the method of Example 194C, substituting 4-(methylseleno)benzeneboronic acid from Example 1 in place of 4-(methylthio)benzeneboronic acid) in place of 2-(4-fluorophenyl)-4-methoxy-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone and substituting 4-fluorophenyl magnesium bromide in place of cyclohexylmagnesium chloride (yield: 44 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.98 (dd, J=8.8, 8.8 Hz, 2H), 7.05 (d, J=8.7 Hz, 2H), 7.17

(dd, J=8.7, 8.7 Hz, 2H), 7.23-7.31 (m, 2H), 7.32 (d, J=8.7 Hz, 2H), 7.65-7.72 (m, 2H), 8.00 (s, 1H). MS (APCI+) m/z 455 $(M+H)^+$.

Example 456C

2,4-Bis(4-fluorophenyl)-5-[4-(methylselenonyl)phenyl]-3(2H)-pyridazinone

A stirred solution of the 2,4-bis(4-fluorophenyl)-4-(4-fluorophenyl)-5-[4-(methylseleno)phenyl]-3(2H)-pyridazinone (40 mg, 88.1 mmol) in methylene chloride (2 mL) was treated with 3-chloroperoxybenzoic acid (100 mg, 342 mmol, 57-86%) at 23 °C. After 2 hours, the reaction appeared to be only slightly more than 50% completed. Additional 3-chloroperoxybenzoic acid (80 mg, 274 mmol, 57-86%) was added. The reaction ran to completion over the next 16 hours of stirring at 23 °C. The solution was diluted with ethyl acetate and carefully shaken with a $NaHSO_3$ solution (two times) for several minutes to consume the excess 3-chloroperoxybenzoic acid. The ethyl acetate solution was subsequently washed with a saturated Na_2CO_3 solution (two times), water, and brine and dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed (flash silica gel, acetone/methylene chloride/hexanes 2:2:1) to provide the product (yield: 40 mg, 93%). (J. Chem. Soc., Chem. Commun., 1985, 569). mp 110-150 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (s, 3H), 6.91 (dd, J=8.7, 8.7 Hz, 2H), 7.14-7.27 (m, 4H), 7.48 (d, J=8.4 Hz, 2H), 7.65-7.73 (m, 2H), 7.97 (s, 1H), 8.00 (d, J=8.4 Hz, 2H). MS (APCI+) m/z 487 $(M+H)^+$ and m/z 504 $(M+NH_4)^+$. Anal. calc. for $C_{23}H_{16}F_2N_2O_3Se.0.5\ H_2O$. C, 55.88; H, 3.46; N, 5.66. Found: C, 55.60; H, 3.61; N, 5.29.

Example 457

2-(3,4-Difluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared as described in Example 62, starting with 4-(3,4-difluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 3,4-difluorobromobenzene in place of 1-bromo-4-fluorobenzene (yield: 185 mg, 46.5%). mp

182-185 °C. ^{1}H NMR (300 MHz. DMSO-d_6) δ 3.23 (s. 3 H), 6.98 (d, J=9 Hz. 1H), 7.18 (m, 2H). 7.32 (m. 1H). 7.52 (d, J=9 Hz, 2 H), 7.6 (m. 2H). 7.85 (m, 1 H), 7.9 (d. J=9 Hz, 2H). 8.3 (s, 1 H). MS (DCI/NH_3) m/z 457 $(M+H)^+$. 474 $(M+NH_4)^+$.

Example 458

2-(4-Fluorophenyl)-4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared as described in Example 62. substituting 4-(3-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 135 mg, 34%). mp 199-201 °C. ^{1}H NMR (300 MHz. DMSO-d_6) δ 3.24 (s, 3H). 6.98 (d, J=9 Hz. 1H). 7.18 (m, 2H), 7.32 (m, 1H). 7.39 (t. 1H), 7.54 (d. J=9 Hz. 2 H), 7.71 (m. 2H). 7.91(d, J=9 Hz, 2 H), 8.27 (s, 1 H). MS (DCI/NH_3) m/z 439 $(M+H)^+$, 456 $(M+NH_4)^+$.

Example 459

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

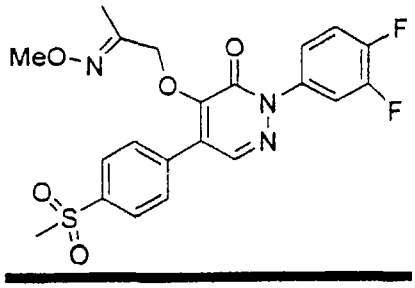
To a solution of 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (139 mg, 0 309 mmol) and di-t-butylazodicarboxylate (71.2 mg, 0.309 mmol) in THF (25 mL) at -78 °C was added dropwise a 1M solution of NaHMDS (0.93 mL. 0.928 mmol) in THF. After addition the reaction was stirred another 45 min at -78 °C (or until TLC indicated a disappearance of starting material) and then was treated with 1N NaOH (20 mL). The reaction mixture was stirred at room temperature for the next 18 h. Sodium acetate trihydrate (758 mg, 5.57 mmol) was added followed by addition of hydroxylamine-O-sulphonic acid (630 mg, 5.57 mmol) and H_2O (50 mL). The resulting mixture was stirred at ambient temperature for the next 18 hours and then extracted with EtOAc. The extract was washed with water. brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (silica gel, 1:1 hexanes-EtOAc) to provide the title compound (yield: 25 mg; 18%). mp 65-69°C; ^{1}H NMR (300 MHz. DMSO-d_6) δ 1.0 (s. 6H), 4.2 (s. 2H). 4.56

(s, 1H), 7.51 (m, 3H), 7.6 (m, 1H), 7.85 (m, 1H), 7.95 (s, 4H), 8.21 (s, 1H); MS (DCI/NH_3) m/z 451 $(M+H)^+$, 467 $(M+NH_4)^+$.

Example 460

2-(3,4-Difluorophenyl)-4-(2-oxo-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A solution of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (378 mg, 1 mmol), Ph_3P (524 mg, 2 mmol) and acetol (74 mg, 1 mmol) in THF (25 mL) at room temperature was treated dropwise with a solution of DIAD (0.4 mL, 2 mmol) in THF (5 mL). The mixture was stirred at room temperature for 6 hours and concentrated in vacuo. The residue was chromatographed (silica gel, 1:1 hexanes-ethyl acetate) to provide the desired product (yield: 205 mg, 48%). mp 169-170 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.08 (s, 3H), 3.30 (s, 3H), 5.30 (s, 2H), 7.48 (m, 1H), 7.62 (q, J = 10 Hz, 1H), 7.75 (m, 1H), 7.94 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), 8.21 (s, 1H); MS (APCI+) m/z 435 $(M+H)^+$, (APCI-) m/z 469 (M+Cl)-; Anal. calc. for $C_{20}H_{16}F_2N_2O_5S$ 0.75H_2O: C, 53.62; H, 3.93; N, 6.25. Found: C, 53.26; H, 3.61, N, 6.08.



Example 461

2-(3,4-Difluorophenyl)-4-[2-(methoxyimino)-1-propoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of 2-(3,4-difluorophenyl)-4-(2-oxo-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone from Example 460 (150 mg, 0.3 mmol) in H_2O (10 mL) and dioxane (20 mL) was treated with methoxyamine hydrochloride (84 mg, 1 mmol) and sodium acetate trihydrate (138 mg, 1 mmol). The mixture was stirred at room temperature for 6 hours. The reaction mixture was extracted with ethyl acetate and

purified by column chromatography (silica gel, 1:1 hexanes-ethyl acetate) to provide the title compound (yield: 20 mg, 15%). mp 143-145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.63 (s, 3H), 3.30 (s, 3H), 3.74 (s, 3H), 4.93 (s, 2H), 7.54 (m, 1H), 7.65 (q, J = 10 Hz, 1H), 7.82 (m, 1H), 7.92 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.24 (s, 1H); MS (APCI+) m/z 464 $(M+H)^+$; (APCI-) m/z 498 $(M+Cl)^-$. Anal. calc. for $C_{21}H_{19}F_2N_3OS$: C, 54.42; H, 4.13; N, 9.06. Found: C, 54.33; H, 3.93; N, 8.92.

Example 462

(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 462A

(R)-3-t-Butoxy-2-methyl-1-propanol

A solution of (S)-(+)-methyl 3-hydroxy-2-methylpropionate (1.18 g, 10 mmol) in t-butyl acetate (30 mL) was treated with 70% $HClO_4$ (0.1 mL) and the reaction mixture was left at room temperature in a tightly closed flask for 24 hours. The mixture was then poured into a saturated solution of $NaHCO_3$ and extracted with ethyl ether. The ether was removed in vacuo and the residue was dissolved in THF (50 mL). To the resulting solution was added $NaBH_4$ (925 mg, 25 mmol) and at 55 °C dropwise methanol (10 mL). The reaction was continued at 55 °C for 1 hours, then it was cooled to ambient temperature, acidified with 10% citric acid to pH 5 and extracted with ethyl acetate. The acetate extract was washed with water, brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (silica gel, 2:1 hexane-ethyl acetate) to provide (R)-3-t-butoxy-2-methyl-1-propanol (yield: 1 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 7 Hz, 3H), 1.20 (s, 9H), 2.03 (m, 1H), 3.30 (t, J = 12 Hz, 1H), 3.53 (dd, J = 4.5 Hz, 12 Hz, 1H), 3.70 (m, 2 H); MS (DCI/NH_3) m/z 164 $(M+NH_4)^+$.

Example 462B

(S)-2-(3,4-Difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-(4-methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a solution 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone (378 mg, 1 mmol), Ph_3P (524 mg, 2 mmol) and Example 462A (146 mg, 1 mmol) in THF (25 mL) at room temperature was added dropwise a solution of DIAD (0.4 mL, 2 mmol) in THF (5 mL). The mixture was then stirred at room temperature for 6 hours and concentrated in vacuo. The residue was passed through a silica gel pad (hexane-ethyl acetate as an eluent) to provide 550 mg of roughly purified (S)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, still contaminated with reduced DIAD. MS (APCI+) m/z 507 $(M+H)^+$, (APCI-) m/z 541 $(M+Cl)^-$.

Example 462C

(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A mixture of Example 462B (100 mg, ~0.2 mmol) in TFA (5 mL) was left at ambient temperature for 24 hours. The mixture was then concentrated in vacuo, the residue was neutralized with saturated solution of $NaHCO_3$ and extracted with ethyl acetate. Purification on a column (silica gel, 1:2 hexanes-EtOAc) gave a foamy product (yield: 51 mg, 56%). ^1H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, J = 7 Hz, 3H), 1.81 (sextet (J = 7 Hz, 1H), 3.21 (d, J = 6 Hz, 2H), 3.30 (s, 3H), 4.29 (dd, J = 6 Hz, 12 Hz, 1H), 4.40 (dd, J = 6 Hz, 12 Hz, 1H), 4.48 (br s, 1H), 7.52 (m, 1H), 7.61 (m, 1H), 7.80 (m, 1H), 7.91 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.20 (s, 1H); MS (APCI+) m/z 451 $(M+H)^+$; (APCI-) m/z 485 (M+Cl)-, Anal. calc. for $C_{21}H_{20}F_2N_2O_5S$: C, 55.99; H, 4.47; N, 6.21. Found: C, 55.65, H, 4.65; N, 5.92.

Example 463

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by the method described in Example 462, substituting (R)-(-)-methyl 3-hydroxy-2-methylpropionate in place of (S)-(+)-methyl 3-hydroxy-2-methylpropionate (yield: 65 mg, 61%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, J = 7 Hz, 3H), 1.81 (sextet, J = 7 Hz, 1H), 3.21 (t, J = 6 Hz, 2H), 3.30 (s, 3H), 4.29 (dd, J = 6 Hz and 12 Hz, 1H), 4.40 (dd, J = 6 Hz, 12 Hz, 1H), 4.49 (t, J = 6 Hz, 1H), 7.52 (m, 1H), 7.61 (m, 1H), 7.80 (m, 1H), 7.91 (d, J = 9 Hz, 2H), 8.07 (d, J = 9 Hz, 2H), 8.20 (s, 1H); MS (APCI+) m/z 451 $(M+H)^+$; (APCI-), m/z 485 (M+Cl)-. Anal. calc. for $C_{21}H_{20}F_2N_2O_5S$: C, 55.99; H, 4.47; N, 6.21. Found: C, 55.62; H, 4.52; N, 6.06.

Example 464

(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of (S)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 462B, 450 mg, ~0.9 mmol) and DBAD (207 mg, 0.9 mmol) in THF (25 mL) at -78 °C was added dropwise a1M solution of LiHMDS (3 mL, 3 mmol) and the resulting mixture was stirred at -78 °C for 2 hours. The mixture was warmed to room temperature and 1N NaOH (5 mL, 5 mmol) was added. After 12 hours at ambient temperature, sodium acetate trihydrate (2.76 g, 20 mmol) and water (10 mL) followed by hydroxylamine-O-sulfonic acid (2g, 15 mmol) were added and the mixture was stirred at room temperature for 5 hours. The product was extracted with ethyl acetate and purified by chromatography (silica gel, 1:2 hexanes-EtOAc) to afford crude intermediate (yield: 160 mg, 35%). MS (APCI+) m/z 508 $(M+H)^+$; (APCI-) m/z 542 (M+Cl)-.

TFA (5 mL) was added to the above intermediate and the resulting solution was left at room temperature for 24 hours. The TFA was removed in vacuo, then the residue was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ then filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 1:2 hexane-ethyl acetate) to provide the title compound (yield: 50 mg, 33%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76

(d, J = 7 Hz, 3H), 1.81 (sextet, J = 7 Hz, 1H), 3.22 (t, J = 6 Hz, 2H), 4.28 (dd, J = 6 Hz, 12 Hz, 1H), 4.40 (dd, J = 6 Hz, 12 Hz, 1H), 4.50 (t, J = 6 Hz, 1H), 7.51 (m, 3H), 7.61 (m, 1H), 7.80 (m, 1H), 7.84 (d, J = 9 Hz, 2H), 7.95 (d, J = 9 Hz, 2H), 8.20 (s, 1H); MS (APCI+) m/z 452 $(M+H)^+$; (APCI-) m/z 486 (M+Cl)-.

Example 465

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The desired material was prepared according to the procedure of Example 464 substituting (R)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of (S)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 30 mg, 20%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.76 (d, J = 7 Hz, 3H), 1.81 (sextet, J = 7 Hz, 1H), 3.22 (t, J = 6 Hz, 2H), 4.28 (dd, J = 6 Hz, 12 Hz, 1H), 4.40 (dd, J = 6 Hz and 12 Hz, 1H), 4.50 (t, J = 6 Hz, 1H), 7.51 (m, 3H), 7.61 (m, 1H), 7.80 (m, 1H), 7.84 (d, J = 9 Hz, 2H), 7.95 (d, J = 9 Hz, 2H), 8.20 (s, 1H); MS (APCI+) m/z 452 $(M+H)^+$, (APCI-) m/z 486 (M+Cl)-. Anal. calc. for $C_{20}H_{19}F_2N_3O_5S$: C, 53.21; H, 4.24; N, 9.30. Found: C, 53.45; H, 5.53; N, 9.50.

Example 466

2-(4-Fluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-methyl-1,4-butandiol in place of 2-ethyl-1-hexanol and separating the regioisomeric products by multiple preparative thin layer chromatography runs, eluting with 4:1 ethyl acetate/hexanes (yield: 65 mg, 19%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 8.1 Hz, 3H), 1.48-1.87 (m, 4H), 3.13 (s, 3H), 3.41 (dd, J = 6.3, 13.5 Hz, 1H), 3.46 (dd, J = 6.3, 13.5 Hz, 1H), 4.48-4.63 (m, 2H), 7.15-7.24 (m, 2H), 7.58-7.66 (m, 2H), 7.79

(d, J = 10.5 Hz, 2H), 7.91 (s, 1H), 8.07 (d, J = 10.5 Hz, 2H); MS (APCI+) m/z 447 $(M+H)^+$.

Example 467

2-(3,4-Difluorophenyl)-4-(3-oxo-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 460 substituting 4-hydroxy-2-butanone in place of acetol. (yield: 95.0 mg, 21%). mp 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.81 (t, J = 9 Hz, 2H), 3.13 (s, 3H), 4.75 (t, J = 9 Hz, 2H), 7.30 (m, 1H), 7.45 (m, 1H), 7.58 (m, 1H), 7.73 (d, J = 9 Hz, 2H), 7.89 (s, 1H), 8.05 (d, J = 9 Hz, 2H); MS (DCI/NH_3) m/z 449 $(M+H)^+$, 466 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{18}F_2N_2O_5S$: C, 56.25; H, 4.02; N, 6.25. Found: C, 55.97; H, 4.17; N, 6.11.

Example 468

2-(4-Fluorophenyl)-4-(3-oxo-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 460 starting with 2-(4-fluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone and substituting 4-hydroxy-2-butanone in place of acetol. (yield: 85.0 mg, 20%). mp 133-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.80 (t, J = 9 Hz, 2H), 3.13 (s, 3H), 4.76 (t, J = 9 Hz, 2H), 7.20 (t, J = 9 Hz, 2H), 7.55 (m, 2H), 7.75 (d, J = 9 Hz, 2H), 7.91 (s, 1H), 8.05 (d, J = 9 Hz, 2H). MS (DCI/NH_3) m/z 431 $(M+H)^+$, 448 $(M+NH_4)^+$. Anal. calc. for $C_{21}H_{19}FN_2O_5S$: C, 58.60; H, 4.42; N, 6.52. Found: C, 58.87; H, 4.55; N, 6.51.

Example 469

2-(4-Fluorophenyl)-4-(4-hydroxy-2-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 178, substituting 2-methyl-1,4-butandiol in place of 2-ethyl-1-hexanol and separating the regioisomeric products by multiple preparative thin layer chromatography runs, eluting with 4:1 ethyl acetate/hexanes (yield: 43 mg, 12%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 8.1 Hz, 3H), 1.33-1.46 (m, 1H), 1.50-1.67 (m, 2H), 1.93-2.04 (m, 1H), 3.13 (s, 3H), 3.54-3.72 (m, 2H), 4.29 (dd, J = 6.0, 9.3 Hz, 1H), 4.43 (dd, J = 6.0, 9.3 Hz, 1H), 7.15-7.24 (m, 2H), 7.58-7.66 (m, 2H), 7.79 (d, J = 10.5 Hz, 2H), 7.91 (s, 1H), 8.07 (d, J = 10.5 Hz, 2H); MS (APCI+) m/z 447 $(M+H)^+$.

Example 470

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 459, substituting 2-(4-fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 600 mg, 60%). mp 163-164°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (s, 6H), 1.73 (t, J = 6 Hz, 2H), 4.30 (s, 1H), 4.52 (t, J = 6 Hz, 2H), 7.37 (t, J = 9 Hz, 1H), 7.47 (s, 2H), 7.65 (dd, J = 9 Hz, J = 3 Hz, 2H), 8.83 (d, J = 9 Hz, 2H), 8.95 (d, J = 9 Hz, 2H), 8.18 (s, 1H); MS (DCI/NH_3) m/z 448 $(M+H)^+$. Anal. calcd. for $C_{21}H_{22}FN_3O_5S$: C, 56.36; H, 4.95; N, 9.39. Found: C, 55.96; H, 4.89; N, 9.09.

Example 471

2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 471A

3,4-Difluorophenylhydrazine

A stirred mixture of 3,4-difluoroaniline (12.9 g, 0.1 mol) in concentrated hydrochloric acid (60 mL) was chilled to -10°C with an ice/methanol bath. A solution of sodium nitrite (6.9 g, 0.1 mol) in water (30 mL) was added at a rate which maintained the temperature of the reaction mixture below 10°C. After stirring for 2 hours, the reaction mixture was cooled to 0°C and a solution of tin(II) chloride (56.88 g, 0.3 mol) in concentrated hydrochloric acid (50 mL) was added dropwise with vigorous stirring. Additional concentrated hydrochloric acid (150 mL) was added to the reaction mixture and stirring was continued for 2 hours. The reaction mixture was filtered to collect the precipitated hydrochloride salt of the title compound. This precipitate was dissolved in water (75 mL) and the resulting solution was basified with 50% aqueous sodium hydroxide and extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated in vacuo to provide the title intermediate as a brown oil (8.11 g, 57.4%).

Example 471B

2-(3,4-Difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone

The title intermediate was prepared by the method of Example 194A, substituting 3,4-difluorophenylhydrazine (Example 471A) for 4-fluorophenylhydrazine hydrochloride.

Example 471C

2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-bromo-3(2H)-pyridazinone

The dibromo-intermediate from Example 471B was reacted according to the procedure described in Example 194B, substituting 3-methyl-1,3-butanediol in place of methanol, to selectively react at the 4-position and provide the title intermediate.

Example 471D

2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The product from Example 471C (12.79 g, 32.86 mmol) was coupled to 4-(methylthio)phenylboronic acid (6.07 g, 36.15 mmol) with K_2CO_3 (10 g, 72.3 mmol) and $PdCl_2(PPh_3)_2$ (1.15 g, 1.64 mmol) in ethanol (200 mL) at 60-65 °C for 40-70 minutes to provide the title intermediate (yield: 9.16 g, 64.5%).

Example 471E

2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The sulfide from Example 471D was oxidized to the title compound by the method of Example 10 (yield: 7.46 g, 76%). m.p. 131-133°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (s, 6H), 1.73 (t, J = 6 Hz, 2H), 3.29 (s, 3H), 4.43 (s, 1H), 4.54 (t, J = 6 Hz, 2H), 7.52 (m, 1H), 7.62 (ddd, J = 9 Hz, J = 9 Hz, J = 1.5 Hz, 1H), 7.82 (ddd, J = 9 Hz, J = 9 Hz, J = 3Hz, 1H), 7.91 (d, J = 9 Hz, 1H), 8.08 (d, J = 9 Hz, 2H), 8.20 (s, 1H); MS (DCI-NH_3) m/e 465 $(M+H)^+$. Anal. calcd. for $C_{22}H_{22}F_2N_2O_5S$: C, 56.88; H, 4.77; N, 6.03. Found: C, 56.92; H, 4.88; N, 5.94.

Example 472

2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 459, substituting 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 300 mg, 50%). mp 181-181°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.04 (s, 6H), 1.72 (t, J = 6 Hz, 2H), 4.43 (s, 1H), 4.53 (t, J = 6 Hz, 2H), 7.49 (s, 2H), 7.53 (m, 1H), 7.63 (ddd, J = 9 Hz, J = 9 Hz, J = 1.5 Hz, 1H), 7.79 (ddd, J = 9 Hz, J = 9 Hz, J = 3 Hz, 1H), 7.83 (d, J = 9 Hz, 1H), 7.95 (d, J = 9 Hz, 2H), 8.19 (s, 1H); MS (DCI/NH_3) m/z 466 $(M+H)^+$. Anal. calcd. for $C_{21}H_{21}F_2N_2O_5S$. C, 54.12; H, 4.66; N, 8.81. Found: C, 54.19; H, 4.55; N, 9.03.

Example 473

2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 3-chloro-4-fluorophenylhydrazine in place of 3,4-difluorophenylhydrazine (yield: 200 mg, 89%). mp 108-110°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 6H), 1.89 (t, 2H, J = 6 Hz), 2.34 (s, 1H), 3.12 (s, 3H), 4.57 (t, J = 6 Hz, 2H), 7.25 (t, J = 9 Hz, 1H), 7.60 (m, 1H), 7.78 (d, J = 6 Hz, 1H), 7.79 (d, J = 9 Hz, 2H), 7.92 (s, 1H), 8.08 (d, J = 9 Hz, 2H); MS (DCI/NH_3) m/z 481 $(M+H)^+$; Anal. calcd. for $C_{22}H_{22}FClN_2O_5S$: C, 54.94; H, 4.61; N, 5.82. Found: C, 54.87; H, 4.65; N, 5.72.

Example 474

2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 459, substituting 2-(3-chloro-4-fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 473) in place of 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (yield: 160 mg, 45%). mp 59-62°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05 (s, 6H), 1.73 (t, 2H, J = 6 Hz), 4.32 (s, 1H), 4.54 (t, J = 6 Hz, 2H), 7.50 (s, 2H), 7.60 (t, J = 9 Hz, 1H), 7.66 (m, 1H), 7.73 (d, J = 9 Hz, 2H), 7.74 (d, J = 9 Hz, 2H), 7.75 (m, 1H), 8.22 (s, 1H); MS (DCI/NH_3) m/z 482 $(M+H)^+$. Anal. calcd. for $C_{21}H_{21}FClN_3O_5S$: C, 52.33; H, 4.39; N, 8.71. Found: C, 52.30; H, 5.03; N, 8.10.

Example 475

2-(3-Chlorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 3-chlorophenylhydrazine in place of 3,4-difluorophenylhydrazine (yield: 200 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.5 Hz, 2H), 7.91 (s, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.67 (m, 1H), 7.57 (m, 1H), 7.40 (t, J = 8.8 Hz, 1H), 7.36 (m, 1H), 4.54 (t, J = 6.3 Hz, 2H), 3.10 (s, 3H), 2.56 (s, 1H), 1.86 (t, J = 6.3 Hz, 2H), 1.20 (s, 6H), MS (DCI/NH_3) m/z 462(M+H)$^+$.

Example 476

2-(3-Chlorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 459, substituting 2-(3-chlorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 475) in place of 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 8.7 Hz, 2H), 7.91 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.68 (m, 1H), 7.57 (m, 1H), 7.41 (m, 1H), 7.38 (m, 1H), 5.65 (s, 2H), 4.51(t, J = 6.6 Hz, 2H), 2.70 (br s, 1H), 1.87 (t, J = 6.6 Hz, 2H), 1.20 (s, 6H); MS (DCI/NH_3) m/z 463 (M+H)$^+$.

Example 477

2-(4-Fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 4-fluorophenylhydrazine in place of 3,4-difluorophenylhydrazine and substituting 2-methyl-1,2-propanediol (prepared by the LAH reduction of methyl 2-hydroxyisobutyrate) in place of 3-methyl-1,3-butanediol. mp 152-154°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 2H, J = 18 Hz), 7.95 (s, 1H), 7.83 (d, 2H, J = 18 Hz), 7.63 (d, 1H, J = 18 Hz), 7.61 (d, 1H, J = 18 Hz), 4.18 (s, 2H), 3.13 (s, 3H), 1.19

(s, 6H). MS (DCI/NH_3) m/z 433 $(M+H)^+$, 450 $(M+NH_4)^+$. Analysis for $C_{21}H_{21}FN_2O_5S$, Calcd: C, 58.32; H, 4.89; N, 6.48. Found: C, 58.42. H, 5.05; N, 6.43.

Example 478

2-(4-Fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 459, substituting 2-(4-fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 477) in place of 2-(3,4-difluoro-phenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone. mp 155-158°C, ^1H NMR (300 MHz, DMSO-d_6) δ 8.17 (s, 1H), 7.92 (s, 4H), 7.67 (d, 1H, J = 18 Hz), 7.64 (d, 1H, J = 18 Hz), 7.49 (s, 2H), 7.38 (d, 1H, J = 18 Hz), 7.35 (d, 1H, J = 18 Hz), 4.54 (s, 1H), 4.19 (s, 2H), 1.00 (s, 6H), MS (ESI+): m/z 434 $(M+H)^+$, 456 $(M+Na)^+$, 889 $(2M+Na)^+$; Analysis for $C_{20}H_{20}FN_3O_5S$, Calcd: C, 55.42; H, 4.65; N, 9.69. Found: C, 55.64; H, 4.85; N, 9.53.

Example 479

2-(3-Chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 3-chloro-4-fluorophenylhydrazine in place of 3,4-difluorophenylhydrazine and substituting 2-methyl-1,2-propanediol (prepared by the LAH reduction of methyl 2-hydroxyisobutyrate) in place of 3-methyl-1,3-butanediol. mp 122-124 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 6H), 3.29 (s, 3H), 4.21 (s, 2H), 4.56 (s, 1H), 7.61 (dd, 1H, J = 7.17 Hz), 7.67 (ddd, 1H, J = 2.4.7 Hz), 7.93 (dd, 1H, J = 2,7 Hz), 7.98 (d, 2H, J = 8 Hz), 8.06 (d, 2H, J = 8 Hz), 8.22 (s, 1H); MS (DCI/NH_3) m/z 465$(M-H)^-$; Anal. Calcd for $C_{21}H_{20}ClFN_2O_5S$: C 54.02, H 4.32, N 6.00. Found: C 54.06, H4.57, N 5.95.

Example 480

2-(3-Chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 459, substituting 2-(3-chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 479) in place of 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone. mp 176-178 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 6H), 4.19 (s, 2H), 4.54 (s, 1H), 7.49 (s, 2H), 7.62 (t, 1H, J = 9 Hz), 7.66 (ddd, 1H, J = 2,5,9 Hz), 7.92 (s, 4.5H), 7.94 (d, 0.5H, J = 2 Hz), 8.20 (s, 1H); MS (DCI/NH_3) m/z 468 $(M+H)^+$; 1 Cl, 490 $(M+Na)^+$;1Cl; Anal. Calcd for $C_{20}H_{19}ClFN_2O_5S$: C 51.34, H 4.09, N 8.98. Found: C 51.33, H 4.23, N 8.76.

Example 481

2-(3-Chlorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 3-chlorophenylhydrazine in place of 3,4-difluorophenylhydrazine and substituting 2-methyl-1,2-propanediol (prepared by the LAH reduction of methyl 2-hydroxyisobutyrate) in place of 3-methyl-1,3-butanediol ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (m, 2H), 7.98 (s, 1H), 7.85 (m, 2H), 7.76 (m, 1H), 7.62 (m, 1H), 7.43 (m, 2H), 4.22 (s, 2H), 3.15 (s, 3H), 1.21 (s, 6H); MS (DCI/NH_3) m/z 449 $(M+H)^+$; Anal. Calcd for $C_{21}H_{21}ClN_2O_5S$: C 56.18, H 4.72, N 6.24. Found: C 56.08, H 4.67, N 6.23.

Example 482

2-(3-Chlorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 459, substituting 2-(3-chlorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 481) in place of 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone. ^{1}H NMR (400 MHz. DMSO-d_6) δ 8.19 (s, 1H), 7.93 (m, 4H), 7.75 (m, 1H), 7.61-7.48 (m, 5H), 4.53 (s, 2H), 4.20 (s, 3H), 1.00 (s, 6H); MS (ESI-) m/z 448 $(M-H)^-$; Anal. Calcd for $C_{20}H_{20}ClN_3O_5S$: C 53.39, H 4.48, N 9.34. Found: C 53.11, H 4.82, N 9.24.

Example 483

2-(2,2,2-Trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 2,2,2-trifluoroethylhydrazine in place of 3,4-difluorophenylhydrazine and substituting 2-methyl-1,2-propanediol (prepared by the LAH reduction of methyl 2-hydroxyisobutyrate) in place of 3-methyl-1,3-butanediol. ^{1}H NMR (300MHz. $CDCl_3$) δ 1.18 (s, 6H) , 2.62 (br s, 1H), 3.15 (s, 3H), 4.20 (s, 2H), 4.85 (q, J = 9 Hz, 2H), 7.78 (d, J = 9 Hz, 2H), 7.85 (s, 1H), 8.08 (d, J = 9 Hz, 2H); MS (DCI/NH_3) m/z 421 $(M+1)^+$; Analysis calculated for $C_{17}H_{19}F_3N_2O_5S$: C, 48.57; H, 4.56; N, 6.66. Found: C, 48.72; H, 4.78; N, 6.56.

Example 484

2-(2,2,2-Trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by the following sequence of reactions. Mucobromic acid and 2,2,2-trifluoroethylhydrazine hydrochloride were reacted to provide 2-(2,2,2-trifluoroethyl)-4,5-dibromo-3(2H)-pyridazinone following the procedure in Example 194A. The dibromo-intermediate was reacted according to the procedure described in Example 194B, substituting 2-methyl-1,2-propanediol in place of methanol.

to selectively react at the 4-position and provide 2-(2.2.2-trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-bromo-3(2H)-pyridazinone. This 5-bromo-compound was coupled to 4-[2-(tetrahydropyranyl)thio]phenylboronic acid (prepared from THP-protected 4-bromothiophenol and triisopropyl borate) with K_2CO_3 and $PdCl_2(PPh_3)_2$ in ethanol at 60-65 °C for 40-70 minutes to provide 2-(2,2,2-trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-[2-(tetrahydropyranyl)thio]phenyl]-3(2H)-pyridazinone. This intermediate THP-sulfide was then converted to the title compound by treatment with N-chloro-succinimide (3.5 equivalents) at 0 °C in THF/H_2O for 15 minutes to an hour followed by addition of excess ammonium hydroxide at 0 °C and stirring at ambient temperature for 3 hours. Aqueous work-up and column chromatographic purification (80.20 pentane/ethyl acetate) provided the title compound. ^{1}H NMR (300MHz, $CDCl_3$) δ 1.18 (s, 6H) , 2.65 (br s, 1H), 4.15 (s, 2H), 4.85 (q, J = 9 Hz, 2H), 4.9 (s, 2H), 7.75 (d, J = 9 Hz, 2H), 7.85 (s, 1H), 8.05 (d, J = 9 Hz, 2H); MS (DCI/NH_3) m/z 422 $(M+H)^+$; Analysis calculated for $C_{16}H_{18}F_3N_3O_5S$: C, 45.60; H. 4.30; N, 9.97. Found: C. 45.86; H, 4.63; N, 9.81.

Example 485

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 483, substituting neopentyl glycol in place of 2-methyl-1,2-propanediol.

Example 486

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 484, substituting neopentyl glycol in place of 2-methyl-1,2-propanediol.

Example 487

2-(4-Fluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 459, substituting 2-(4-fluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 466) for 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 488

2-(3,4-Difluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 471, substituting 2-methyl-1,4-butanediol for 3-methyl-1,3-butanediol, then separating the regioisomeric products by multiple preparative thin layer chromatography runs.

Example 489

2-(3-Chloro-4-fluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 471, substituting 3-chloro-4-fluorophenylhydrazine for 3,4-difluorophenylhydrazine and substituting 2-methyl-1,4-butanediol for 3-methyl-1,3-butanediol, then separating the regioisomeric products by multiple preparative thin layer chromatography runs.

Example 490

2-(3-Chlorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 471, substituting 3-chlorophenylhydrazine for 3,4-

difluorophenylhydrazine and substituting 2-methyl-1,4-butanediol for 3-methyl-1,3-butanediol, then separating the regioisomeric products by multiple preparative thin layer chromatography runs.

Example 491

2-(3,4-Difluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 459, substituting 2-(3,4-difluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 488) for 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 492

2-(3-Chloro-4-fluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 459, substituting 2-(3-chloro-4-fluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 489) for 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 493

2-(3-Chlorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 459, substituting 2-(3-chlorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 490) for 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 494

(S)-2-(4-Fluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 464, substituting (S)-2-(4-fluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone for (S)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 495

(R)-2-(4-Fluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 465, substituting (R)-2-(4-fluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone for (R)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 496

(S)-2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 462, substituting 2-(3-chloro-4-fluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone.

Example 497

(S)-2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound can be prepared according to the method of Example 464, substituting (S)-2-(3-chloro-4-fluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-

(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of (S)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 498

(R)-2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 463, substituting 2-(3-chloro-4-fluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone.

Example 499

(R)-2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 464, substituting (R)-2-(3-chloro-4-fluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of (S)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 500

(S)-2-(3-Chlorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 462, substituting 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone.

Example 501

(S)-2-(3-Chlorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 464, substituting (S)-2-(3-chlorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of (S)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 502

(R)-2-(3-Chlorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound can be prepared according to the method of Example 463, substituting 2-(3-chlorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 503

(R)-2-(3-Chlorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound can be prepared according to the method of Example 464, substituting (R)-2-(3-chlorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of (S)-2-(3,4-difluorophenyl)-4-(3-t-butoxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 504

(S)-2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 462, substituting 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-

pyridazinone in place of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone.

Example 505

(S)-2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 484, substituting (R)-3-t-butoxy-2-methyl-1-propanol (Example 462A) in place of 2-methyl-1,2-propanediol. After Suzuki coupling with 4-[2-(tetrahydropyranyl)thio]phenylboronic acid, the resulting intermediate is treated with NCS and NH_4OH as in Example 484. This sulfonamide product is then treated with TFA (as in Example 462C) to cleave the t-butyl ether and provide the title compound.

Example 506

(R)-2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 463, substituting 2-(2,2,2-trifluoroethyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-hydroxy-5-[4-(methylsulfonyl)phenyl-3(2H)-pyridazinone.

Example 507

(R)-2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 505, substituting (S)-3-t-butoxy-2-methyl-1-propanol in place of (R)-3-t-butoxy-2-methyl-1-propanol.

Example 508

2-(4-Fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 471, substituting 4-fluorophenylhydrazine in place of 3,4-difluorophenylhydrazine and substituting neopentyl glycol in place of 3-methyl-1,3-butanediol.

Example 509

2-(4-Fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 459, substituting 2-(4-fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone for 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 510

2-(3,4-Difluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting neopentyl glycol in place of 3-methyl-1,3-butanediol (yield: 300 mg, 71%). mp 161-162°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.72 (s, 6H), 3.05 (d, J = 6 Hz, 2H), 3.30 (s, 3H), 4.19 (s, 2H), 4.54 (t, J = 6 Hz, 1H), 7.52 (m, 1H), 7.62 (dd, J = 9 Hz, J = 9 Hz, 1H), 7.82 (ddd, J = 9 Hz, J = 9 Hz, J = 3 Hz, 1H), 7.92 (d, J = 9 Hz, 1H), 8.08 (d, J = 9 Hz, 2H), 8.21 (s, 1H); MS (DCI/NH_3) m/z 465 $(M+H)^+$; Anal. calcd. for $C_{22}H_{22}F_2N_2O_5S$: C, 56.88; H, 4.77; N, 6.03. Found: C, 56.84; H, 4 83; N, 5.99.

Example 511

2-(3,4-Difluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 459, substituting 2-(3,4-difluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone for 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 512

2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 471, substituting 3-chloro-4-fluorophenylhydrazine in place of 3,4-difluorophenylhydrazine and substituting neopentyl glycol in place of 3-methyl-1,3-butanediol.

Example 513

2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(amino-sulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 459, substituting 2-(3-chloro-4-fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone for 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 514

2-(3-Chlorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 471, substituting 3-chlorophenylhydrazine in place of 3,4-difluorophenylhydrazine and substituting neopentyl glycol in place of 3-methyl-1,3-butanediol.

Example 515

2-(3-Chlorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the method of Example 459, substituting 2-(3-chlorophenyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone for 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

Example 516

N-[[4-[2-(3,4-Difluorophenyl)-4-(2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide

A mixture of 2-(3,4-difluorophenyl)-4-(2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone (Example 403, 1 equivalent), acetic anhydride (3 equivalents), 4-(dimethylamino)pyridine (0.3 equivalents), and triethylamine (1.2 equivalents) is stirred at room temperature for 16 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine then dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to give the title compound.

Example 517

N-[[4-[2-(3,4-Difluorophenyl)-4-(2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]-sulfonyl]acetamide, sodium salt

To a suspension of N-[[4-[2-(3,4-Difluorophenyl)-4-(2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide (Example 516, 1 equivalent) in absolute ethanol is added a solution of sodium hydroxide (1 equivalent) in absolute ethanol. The mixture is stirred at room temperature for 10 minutes and concentrated in vacuo. The residue is dried at high vacuum to provide the title compound.

Example 518

N-[[4-[2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide

A mixture of 2-(4-fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone (Example 470, 1 equivalent), acetic anhydride (3 equivalents), 4-(dimethylamino)pyridine (0.3 equivalents), and triethylamine (1.2 equivalents) is stirred at room temperature for 16 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine then dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to give the title compound.

Example 519

N-[[4-[2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide, sodium salt

To a suspension of N-[[4-[2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide (Example 518, 1 equivalent) in absolute ethanol is added a solution of sodium hydroxide (1 equivalent) in absolute ethanol. The mixture is stirred at room temperature for 10 minutes and concentrated in vacuo. The residue is dried at high vacuum to provide the title compound.

Example 520

N-[[4-[2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide

A mixture of 2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone (Example 459, 1 equivalent), acetic anhydride (3 equivalents), 4-(dimethylamino)pyridine (0.3 equivalents), and triethylamine (1.2 equivalents) is stirred at room temperature for 16 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine then dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to give the title compound.

Example 521

N-[[4-[2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide, sodium salt

To a suspension of N-[[4-[2-(3,4-difluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide (Example 520, 1 equivalent) in absolute ethanol is added a solution of sodium hydroxide (1 equivalent) in absolute ethanol. The mixture is stirred at room temperature for 10 minutes and concentrated in vacuo. The residue is dried at high vacuum to provide the title compound.

Example 522

N-[[4-[2-(3-Chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide

A mixture of 2-(3-chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone (Example 480, 1 equivalent), acetic anhydride (3 equivalents), 4-(dimethylamino)pyridine (0.3 equivalents), and triethylamine (1.2 equivalents) is stirred at room temperature for 16 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine then dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to give the title compound.

Example 523

N-[[4-[2-(3-Chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide, sodium salt

To a suspension of N-[[4-[2-(3-chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide (Example 522, 1 equivalent) in absolute ethanol is added a solution of sodium hydroxide (1 equivalent) in absolute ethanol. The mixture is stirred at room temperature for 10 minutes and concentrated in vacuo. The residue is dried at high vacuum to provide the title compound.

Example 524

N-[[4-[2-(3-Chlorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide

A mixture of 2-(3-chlorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone (Example 482, 1 equivalent), acetic anhydride (3 equivalents), 4-(dimethylamino)pyridine (0.3 equivalents), and triethylamine (1.2 equivalents) is stirred at room temperature for 16 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine then dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to give the title compound.

Example 525

N-[[4-[2-(3-Chlorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide, sodium salt

To a suspension of N-[[4-[2-(3-chlorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide (Example 525, 1 equivalent) in absolute ethanol is added a solution of sodium hydroxide (1 equivalent) in absolute ethanol. The mixture is stirred at room temperature for 10 minutes and concentrated in vacuo. The residue is dried at high vacuum to provide the title compound.

Example 526

N-[[4-[2-(2,2,2-Trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide

A mixture of 2-(2,2,2-trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone (Example 484, 1 equivalent), acetic anhydride (3 equivalents), 4-(dimethylamino)pyridine (0.3 equivalents), and triethylamine (1.2 equivalents) is stirred at room temperature for 16 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine then

dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to give the title compound.

Example 527

N-[[4-[2-(2,2,2-Trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide, sodium salt

To a suspension of N-[[4-[2-(2,2,2-trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide (Example 526, 1 equivalent) in absolute ethanol is added a solution of sodium hydroxide (1 equivalent) in absolute ethanol. The mixture is stirred at room temperature for 10 minutes and concentrated in vacuo. The residue is dried at high vacuum to provide the title compound.

Example 528

N-[[4-[2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide

A mixture of 2-(2,2,2-trifluoroethyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone (Example 486, 1 equivalent), acetic anhydride (3 equivalents), 4-(dimethylamino)pyridine (0.3 equivalents), and triethylamine (1.2 equivalents) is stirred at room temperature for 16 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine then dried over $MgSO_4$ and filtered. The filtrate is concentrated in vacuo to give the title compound.

Example 529

N-[[4-[2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide, sodium salt

To a suspension of N-[[4-[2-(2,2,2-trifluoroethyl)-4-(3-hydroxy-2,2-dimethyl-1-propoxy)-2H-pyridazin-3-on-5-yl]phenyl]sulfonyl]acetamide (Example 528, 1 equivalent) in absolute ethanol is added a solution of sodium hydroxide (1 equivalent) in absolute

ethanol. The mixture is stirred at room temperature for 10 minutes and concentrated in vacuo. The residue is dried at high vacuum to provide the title compound.

Example 530

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 2,2,2-trifluoroethylhydrazine in place of 3,4-difluorophenylhydrazine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6H) , 1.88 (t, 2H, J = 9 Hz), 2.35 (br s, 1H), 3.15 (s, 3H), 4.55 (t, 2H, J = 7.5 Hz), 4.85 (q, 2H, J = 9 Hz), 7.75(d, 2H J = 9 Hz), 7.65 (s, 1H), 8.05 (d, 2H J = 9 Hz); MS (DCI/NH_3) m/z 435 $(M-H)^-$, Analysis calculated for $C_{18}H_{21}F_3N_2O_5S$: C, 49.77; H, 4.87; N, 6.45. Found: C, 49.71; H, 4.90; N, 6.45.

Example 531

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 484, substituting 3-methyl-1,3-butanediol in place of 2-methyl-1,2-propanediol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (t, 2H, J = 6 Hz) , 2.78 (s, 6H), 4.55 (t, 2H, J = 6 Hz), 4.85 (q, 2H, J = 9 Hz), 5.3 (s, 2H), 7.68 (d, 2H J = 9 Hz), 7.85 (s, 1H), 8.05 (d, 2H J = 9Hz), 8 45 (br s, 1H); MS (DCI/NH_3) m/z 436 $(M+H)^+$; Analysis calculated for $C_{17}H_{20}F_3N_3O_5S$: C, 46.89; H, 4.62; N, 9.65. Found: C, 47.18; H, 4.93; N, 9.86.

Example 532

2-(3,4-Dichlorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 3,4-dichlorophenylhydrazine in place of 3,4-

difluorophenylhydrazine. mp 118-120°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 6H), 1.92 (t, J = 6 Hz, 2H), 3.13 (s, 3H), 4.07 (t, J = 6 Hz, 2H), 7.58 (d, J = 9 Hz, 1H), 7.59 (dd, J = 9 Hz, J = 2 Hz, 1H), 7.80 (d, J = 9 Hz, 2H), 7.87 (d, J = 2 Hz, 1H), 7.84 (s, 1H), 8.19 (d, J = 9 Hz, 2H); MS (DCI/NH_3) m/z 497 $(M+H)^+$. Anal. calcd. for $C_{22}H_{22}Cl_2N_2O_5S$: C, 53.12; H, 4.45; N, 5.63. Found: C, 52.80; H, 4.53; N, 5.35.

Example 533

2-[(3-Trifluoromethyl)phenyl]-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 3-(trifluoromethyl)phenylhydrazine in place of 3,4-difluorophenylhydrazine and substituting 2-methyl-1,2-propanediol (prepared by the LAH reduction of methyl 2-hydroxyisobutyrate) in place of 3-methyl-1,3-butanediol (yield: 200 mg, 75%). mp 143-144°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 6H), 3.13 (s, 3H), 4.11 (s, 2H), 7.64 (m, 2H), 7.84 (d, J = 9 Hz, 2H), 7.90 (d, J = 9 Hz, 1H), 7.97 (d, J = 9 Hz, 1H), 7.98 (s, 1H), 8.13 (d, J = 9 Hz, 2H); MS (DCI/NH_3) m/z 483 $(M+H)^+$; Anal. calcd. for $C_{22}H_{21}F_3N_2O_5S\ 0.5C_4H_{10}O_2$: C, 54.75; H, 4.79; N, 5.32. found: C, 55.15; H, 4.77; N, 5.09.

Example 534

2-(3,4-Dichlorophenyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the sequence of reactions described in Example 471, substituting 3,4-dichlorophenylhydrazine in place of 3,4-difluorophenylhydrazine and substituting 2-methyl-1,2-propanediol (prepared by the LAH reduction of methyl 2-hydroxyisobutyrate) in place of 3-methyl-1,3-butanediol (yield: 1.7 g, 75%). mp 108-110°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.96 (s, 6H), 3.38 (s, 3H), 4.20 (s, 2H), 4.52 (s, 1H), 7.68 (dd, J = 9 Hz, J = 3 Hz, 1H), 7.83 (d, J = 9 Hz, 1H), 7.78 (d, J = 9 Hz, 2H), 7.79 (d, J = 3 Hz, 1H), 8.04 (d, J = 9 Hz, 2H), 8.22 (s, 1H); MS (DCI/NH_3) m/z

483 $(M+H)^+$; Anal. calcd. for $C_{21}H_{20}Cl_2N_2O_5S$: C, 52.18; H, 4.17; N, 5.79. Found: C, 52.41; H, 4.22; N, 5.53.

Example 535

(R,S)-2-(4-Fluorophenyl)-4-(3-hydroxy-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared by reacting the product from Example 468, 2-(4-fluorophenyl)-4-(3-oxo-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (20 mg, 0.05 mmol) in methanol (5 mL) at 0°C with sodium borohydride (4 mg, 0.1 mmol). The reaction mixture was allowed to warm to room temperature, then volatile components were removed under reduced pressure. The residue was treated with water and 10% aqueous citric acid solution was added to bring the pH to 7. The resulting precipitate was collected by filtration and dried to provide the title compound as an off-white solid (11 mg, 50.9%). mp 63-66°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, J = 6 Hz, 3H), 1.60-1.73 (m, 1H), 1.84-1.96 (m, 1H), 3.14(s, 3H), 4.01-4.14 (m, 1H), 4.20-4.28 (m, 1H), 4.64 (dt, J = 3 Hz, J = 9 Hz, 1H), 7.20 (t, J = 9 Hz, 2H), 7.43-7.55 (m, 2H), 7.81 (d, J = 9 Hz, 2H), 7.96 (s, 1H), 8.10 (d, J = 9 Hz, 2H); MS (DCI/NH_3) m/z 433 $(M+H)^+$.

Example 536

2-(3,4-Difluorophenyl)-4-(1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 536A

2-(3,4-Difluorophenyl)-4-(1-butoxy)-5-chloro-3(2H)-pyridazinone

To a stirred, room temperature solution of n-butanol (0.81 g, 10.93 mmol, 1.1 equiv.) in THF (20 mL) was slowly added 1.0 M sodium bis(trimethylsilyl)amide in THF (12 mL, 12 mmol, 1.2 equiv.). The reaction mixture was stirred for 0.5 hours, then it was transferred to a solution of 2-(3,4-difluorophenyl)-4,5-dichloro-3(2H)-pyridazinone (2.88 g, 10.4 mmol, 1.0 equiv.) in THF (80 mL) The resulting reaction mixture was stirred for 0.5 hours at room temperature to provide the title compound (2.5 g, 79.4%).

Example 536B

2-(3,4-Difluorophenyl)-4-(1-butoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

A slurry of palladium(II) acetate (9.0 mg, 0.04 mmol), triphenylphosphine (21.0 mg, 0.08 mmol) and isopropanol (1 mL) was stirred at room temperature for 10 minutes. To this mixture was added 2-(3,4-Difluorophenyl)-4-(1-butoxy)-5-chloro-3(2H)-pyridazinone (Example 536A, 0.63 g, 2 mmol), 4-(methylthio)benzeneboronic acid (0.403 mg, 2.4 mmol) and isopropanol (4 mL). A solution of K_3PO_4 (0.66 g, 3 mmol) in water (1 mL) was also added and the resulting reaction mixture was deoxygenated by bubbling nitrogen through it for 2 minutes. The reaction mixture was then stirred under a nitrogen atmosphere for 15 hours at 70 °C. The reaction mixture was then cooled to room temperature and water (15 mL) was added to provide a precipitate. The precipitate was collected by filtration and rinsed with water then hexane to give after drying the title compound (0.77 g, 95%).

Example 536C

2-(3,4-Difluorophenyl)-4-(1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

To a solution of 2-(3,4-difluorophenyl)-4-(1-butoxy)-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (Example 536B, 0.6 g, 1.5 mmol) in acetone (10 mL) at -20 °C was slowly added over 5 minutes a 32% solution of peracetic acid in acetic acid (3.75 mmol). The reaction mixture was allowed to warm to room temperature at which point water (30 mL) was added. Stirring was continued for 0.5 hours, then the precipitate was collected by filtration and washed with water to provide the title compound (0.61 g, 94%). mp 129-132°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6 Hz, 3H), 1.20-1.36 (m, 2H), 1.54-1.68 (m, 2H), 3.14 (s, 3H), 4.52 (t, J = 6 Hz, 2H), 7.25-7.34 (m, 1H), 7.44-7.50 (m, 1H), 7.55-7.62 (m, 2H), 7.77-7.82 (m, 2H), 7.92 (s, 1H), 8.05-8.10 (m, 2H); MS (DCI/NH_3) m/z 435 $(M+H)^+$; Anal. calcd. for $C_{21}H_{20}F_2N_2O_4S$: C, 58.06; H, 4.64; N, 6.44. Found: C, 57.82, H, 4.53; N, 6.31.

Example 537

2-(3-Chloro-4-fluorophenyl)-4-(2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 536 substituting 2-methyl-1-propanol in place of n-butanol and substituting 2-(3-chloro-4-fluorophenyl)-4,5-dibromo-3(2H)-pyridazinone for 2-(3,4-difluorophenyl)-4,5-dichloro-3(2H)-pyridazinone in Example 536A. The resulting intermediate was subjected to the conditions in Example 536B, substituting the catalyst $PdCl_2(PPh_3)_2$ in place of the palladium(II) acetate-triphenylphosphine slurry. The resulting intermediate was then oxidized by the method of Example 536C to provide the title compound (0.58 g, 92%). mp 116-120°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6 Hz, 6H), 1.85-1.94 (m, 1H), 3.14 (s, 3H), 4.32 (d, J = 6 Hz, 2H), 7.24-7.30 (m, 1H), 7.56-7.62 (m, 1H), 7.77-7.83 (m, 3H), 7.86 (m, 1H), 7.92 (s, 1H), 8.05-8.10 (m, 2H); MS (DCI/NH_3) m/z 451 $(M+H)^+$; Anal. calcd. for $C_{21}H_{20}ClFN_2O_4S$: C, 55.94; H, 4.47; N, 6.21. Found: C, 55.81; H, 4 38; N, 6.18.

Example 538

2-(3-Chloro-4-fluorophenyl)-4-(3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 536 substituting 3-methyl-1-butanol in place of n-butanol to provide the title compound (0.62 g, 92%). mp 148-152°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6 Hz, 6H), 1.50-1.70 (m, 3H), 3.14 (s, 3H), 4.54 (t, J = 6 Hz, 2H), 7.24-7.30 (m, 1H), 7.56-7.62 (m, 1H), 7.77-7.83 (m, 3H), 7.86 (m, 1H), 7.92 (s, 1H), 8.05-8.10 (m, 2H); MS (DCI/NH_3) m/z 465 $(M+H)^+$; Anal. calcd. for $C_{22}H_{22}ClFN_2O_4S$: C, 56.83, H, 4.77; N, 6.02. Found: C, 56.70; H, 4.77; N, 6.11.

Example 539

2-(3,4-Dichlorophenyl)-4-(2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 536 substituting 2-methyl-1-propanol in place of n-butanol and substituting 2-(3,4-dichlorophenyl)-4,5-dibromo-3(2H)-pyridazinone for 2-(3,4-difluorophenyl)-4,5-dichloro-3(2H)-pyridazinone to provide the title compound (0.63 g, 98%). mp 127-129°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6 Hz, 6H), 1.82-1.94 (m, 1H), 3.14 (s, 3H), 4.30 (d, J = 6 Hz, 2H), 7.56-7.62 (m, 2H), 7.77-7.82 (m, 2H), 7.86 (m, 1H), 7.92 (s, 1H), 8.06-8.10 (m, 2H); MS (DCI/NH_3) m/z 467 $(M+H)^+$; Anal. calcd. for $C_{21}H_{20}Cl_2N_2O_4S$: C, 53.97; H, 4.31; N, 5.99. Found: C, 53.82; H, 4.29; N, 5.89.

Example 540

2-(3,4-Dichlorophenyl)-4-(3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 536 substituting 3-methyl-1-butanol in place of n-butanol to provide the title compound (0.63 g, 98%). mp 130-134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6 Hz, 6H), 1.50-1.68 (m, 3H), 3.14 (s, 3H), 4.51 (t, J = 6 Hz, 2H), 7.56-7.62 (m, 2H), 7.77-7.82 (m, 2H), 7.86 (m, 1H), 7.92 (s, 1H), 8.06-8.10 (m, 2H); MS (DCI/NH_3) m/z 481 $(M+H)^+$; Anal. calcd. for $C_{22}H_{22}Cl_2N_2O_4S$: C, 54.89; H, 4.61; N, 5.82. Found: C, 54.72; H, 4.56; N, 5.73.

Example 541

2-(3,4-Difluorophenyl)-4-(4-hydroxy-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 536 substituting 1,4-butanediol in place of n-butanol and substituting 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone for 2-(3,4-difluorophenyl)-4,5-dichloro-3(2H)-pyridazinone to provide the title compound (0.61 g, 95%). mp 110-113°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.60 (m, 2H), 1.72-1.82 (m, 2H), 3.15 (s, 3H), 3.62 (t, J = 6 Hz, 2H), 4.52 (t, J = 6 Hz, 2H), 7.25-7.34 (m, 1H), 7.44-7.50 (m, 1H), 7.55-7.62 (m, 1H), 7.77-7.82

(m, 2H), 7.92 (s, 1H), 8.05-8.10 (m, 2H): MS (DCI/NH_3) m/z 468 $(M+H)^+$; Anal. calcd. for $C_{21}H_{20}F_3N_3O_5S$: C, 55.99; H, 4.48; N, 6.22. Found: C, 55.79; H, 4.41; N, 5.96.

Example 542

2-[3-(Trifluoromethyl)phenyl]-4-(2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 536 substituting 2-methylpropanol for n-butanol and substituting 2-[3-(trifluoromethyl)phenyl]-4,5-dibromo-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4,5-dichloro-3(2H)-pyridazinone to provide the title compound (0.58 g, 90%). mp 125-127 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6 Hz, 6H), 1.86-1.98 (m, 1H), 3.14 (s, 3H), 4.30 (d, J = 6 Hz, 2H), 7.60-7.70 (m, 2H), 7.79-7.84 (m, 2H), 7.94 (s, 1H), 7.88-7.98 (m, 2H), 8.06-8.12 (m, 2H); MS (DCI/NH_3) m/z 484 $(M+H)^+$; Anal. calcd. for $C_{22}H_{21}F_3N_2O_4S$: C, 56.65, H, 4.54, N, 6.00. Found: C, 56.49; H, 4.56, N, 5.81.

Example 543

2-[3-(Trifluoromethyl)phenyl]-4-(3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 536 substituting 3-methyl-1-butanol in place of n-butanol and substituting 2-[3-(trifluoromethyl)phenyl]-4,5-dibromo-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4,5-dichloro-3(2H)-pyridazinone to provide the title compound (0.53 g, 74%). mp 82-85 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J = 6 Hz, 6H), 1.52-1.64 (m, 3H), 3.14 (s, 3H), 4.52 (d, J = 6 Hz, 2H), 7.60-7.70 (m, 2H), 7.79-7.84 (m, 2H), 7.94 (s, 1H), 7.88-7.98 (m, 2H), 8.06-8.12 (m, 2H); MS (DCI/NH_3) m/z 498 $(M+H)^+$; Anal. calcd. for $C_{23}H_{23}F_3N_2O_4S$, C, 57.49; H, 4.82; N, 5.83. Found: C, 57.47; H, 4.94; N, 5.60.

Example 544

2-[3-(Trifluoromethyl)phenyl]-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 536 substituting 3-methyl-1,3-butanediol in place of n-butanol and substituting 2-[3-(trifluoromethyl)phenyl]-4,5-dibromo-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4,5-dichloro-3(2H)-pyridazinone to provide the title compound (1.2 g, 75%). mp 90-93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 6H), 1.90 (t, J = 6 Hz, 2H), 3.14 (s, 3H), 4.58 (t, J = 6 Hz, 2H), 7.60-7.70 (m, 2H), 7.79-7.84 (m, 2H), 7.94 (s, 1H), 7.88-7.98 (m, 2H), 8.06-8.12 (m, 2H); MS (DCI/NH_3) m/z 514 $(M+H)^+$; Anal. calcd. for $C_{23}H_{23}F_3N_2O_4S$: C, 55.64; H, 4.67; N, 5.64. Found: C, 56.01; H, 4.83; N, 5.06.

Example 545

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 545A

Ethyl (R)-3-(tert-butyldimethylsiloxy)butanoate

To a stirred, room temperature solution of ethyl (R)-3-hydroxybutanoate (5.00 g, 37.8 mmol) and tert-butyldimethylsilyl chloride (6.85 g, 45.5 mmol) in DMF (90 mL) was added imidazole (3.87 g, 56.9 mmol). This reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was partitioned between hexane (300 mL) and water (100 mL). The organic layer was washed with water (2 X 100 mL) then dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure to give the title compound.

Example 545B

(R)-3-(tert-Butyldimethylsiloxy)-1-butanol

The crude product from Example 545A (~37 mmol) was dissolved in dichloromethane (100 mL). To this stirred solution, chilled to -78°C, was added dropwise

a 1M solution of diisobutylaluminum hydride in dichloromethane (185 mL, 185 mmol). The reaction mixture was stirred at -78°C for two hours, then it was allowed to warm to -30°C and stirred an additional 0.5 hours. Methanol was then added carefully at -20°C to quench any remaining hydride. The reaction mixture was then diluted with methyl tert-butylether (200 mL) and washed with aqueous sodium tartrate solution (4 X 100 mL) and brine (2 X 100 mL). The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated under reduced pressure to give the crude title compound (6.3 g, 83%).

Example 545C

(R)-2-(3,4-Difluorophenyl)-4-[3-(tert-butyldimethylsiloxy)-1-butoxy]-5-bromo-3(2H)-pyridazinone

To a stirred, 0°C solution of the product from Example 545B (3.4 g, 10 mmol) in THF (20 mL) was added 1M sodium bis(trimethylsilyl)amide in THF (12 mL, 12 mmol). The reaction mixture was stirred at room temperature for 0.5 hours, then it was transferred to a stirred, -30°C solution of 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone (3.66 g, 10 mmol) in THF (100 mL). The reaction mixture was stirred at -30°C for 1 hour, then overnight while warming to room temperature. The reaction was quenched with saturated aqueous ammonium chloride solution (100 mL) and extracted with ethyl acetate (2 X 100 mL). The organic layer was washed with brine (2 X 20 mL), then dried ($MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, 90:10 hexane/ethyl acetate) to provide the title intermediate (2.5 g, 51%).

Example 545D

(R)-2-(3,4-Difluorophenyl)-4-[3-(tert-butyldimethylsiloxy)-1-butoxy]-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

Under a nitrogen atmosphere, a mixture of the product from Example 545C (0.98 g, 2 mmol), 4-(methylthio)benzeneboronic acid (0.4 g, 2.4 mmol), K_3PO_4 (1.2 g, 6 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol), isopropanol (9 mL), and water (1 mL) was stirred at 70°

C for 4 hours. The reaction mixture was then cooled to room temperature, water (30 mL) was added and stirring was continued for 2 hours. The crude black precipitate was collected by filtration then washed with water (10 mL) and hexane (10 mL). This title intermediate was used without further purification in the following oxidation/deprotection step.

Example 545E

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

A stirred solution of the product from step Example 545D(~2 mmol) in acetone (10 mL) was chilled to 0°C. To this was added 32% peracetic acid in acetic acid solution (1.42 mL, 6 mmol). The reaction mixture was stirred for 1 hour while warming to room temperature. At this point the oxidation was complete, but some of the product's hydroxy group was still silylated so 1M tetrabutylammonium fluoride in THF (4 mL, 4 mmol) was added and stirring was continued for 0.5 hours. The reaction mixture was then treated with 5% aqueous sodium thiosulfate solution (30 mL) for 2 hours. The precipitated product was collected by filtration, washed with water (10 mL) and hexane (10 mL). The solid was stirred in isopropanol (5 mL) for 6 hours then collected by filtration and dried to provide the title compound (0.78 g, 87%). mp 126-129 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J = 6 Hz, 3H), 1.62-1.74 (m, 1H), 1.84-1.94 (m, 1H), 3.16 (s, 3H), 3.30 (s br, 1H), 4.00-4.10 (m, 1H), 4.20-4.30 (m, 1H), 4.63 (td, J = 9.6 Hz, J = 4 Hz, 1H), 7.25-7.34 (m, 1H), 7.46-7.52 (m, 1H), 7.56-7.64 (m, 1H), 7.78-7.84 (m, 2H), 7.97 (s, 1H), 8.06-8.12 (m, 2H); MS (DCI/NH_3) m/z 468 $(M+NH_4)^+$.

Example 546

(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound was prepared according to the method of Example 545 substituting ethyl (S)-3-hydroxybutanoate in place of ethyl (R)-3-hydroxybutanoate (0.72

g, 80%). mp 128-130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, J = 6 Hz, 3H), 1.62-1.74 (m, 1H), 1.84-1.94 (m, 1H), 3.16 (s, 3H), 3.30 (s br, 1H), 4.00-4.10 (m, 1H), 4.20-4.30 (m, 1H), 4.63 (td, J = 9.6 Hz, J = 4 Hz, 1H), 7.25-7.34 (m, 1H), 7.46-7.52 (m, 1H), 7.56-7.64 (m, 1H), 7.78-7.84 (m, 2H), 7.97 (s, 1H), 8.06-8.12 (m, 2H); MS (DCI/NH_3) m/z 468 $(M+NH_4)^+$.

Example 547

(S)-2-(3,4-Difluorophenyl)-4-(2-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 547A

Methyl (S)-2-hydroxy-3-methylbutanoate

The title compound (CAS Registry # [17392-84-6]) is prepared by literature procedures (e.g Journal of Organic Chemistry, (1994) 59(7), 1933-1936).

Example 547B

Methyl (S)-2-(tert-butyldimethylsiloxy)-3-methylbutanoate

The title compound is prepared by the method of Example 545A, substituting methyl (S)-2-hydroxy-3-methylbutanoate (Example 547A) in place of ethyl (R)-3-hydroxybutanoate.

Example 547C

(S)-2-(tert-Butyldimethylsiloxy)-3-methyl-1-butanol

The title compound is prepared by the method of Example 545B, substituting methyl (S)-2-(tert-butoxydimethylsiloxy)-3-methylbutanoate (Example 547B) in place of ethyl (R)-3-(tert-butyldimethylsiloxy)butanoate (Example 545A).

Example 547D

(S)-2-(3,4-Difluorophenyl)-4-[2-(tert-butyldimethylsiloxy)-3-methyl-1-butoxy]-5-bromo-3(2H)-pyridazinone

The title compound is prepared by the method of Example 545C, substituting (S)-2-tert-butyldimethylsiloxy-3-methyl-1-butanol (Example 547C) in place of (R)-3-(tert-butyldimethylsiloxy)-1-butanol (Example 545B).

Example 547E

2-(3,4-Difluorophenyl)-4-[(S)-2-(tert-butyldimethylsiloxy)-3-methyl-1-butoxy]-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone

The title intermediate is prepared by the method of Example 545D, substituting (S)-2-(3,4-difluorophenyl)-4-[2-(tert-butyldimethylsiloxy)-3-methyl-1-butoxy]-5-bromo-3(2H)-pyridazinone (Example 547D) in place of (R)-2-(3,4-difluorophenyl)-4-[3-(tert-butyldimethylsiloxy)-1-butoxy]-5-bromo-3(2H)-pyridazinone (Example 545C).

Example 547F

(S)-2-(3,4-Difluorophenyl)-4-(2-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound is prepared by the method of Example 545E, substituting (S)-2-(3,4-difluorophenyl)-4-[2-(tert-butyldimethylsiloxy)-3-methyl-1-butoxy]-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (Example 547E) in place of (R)-2-(3,4-difluorophenyl)-4-[3-(tert-butyldimethylsiloxy)-1-butoxy]-5-[4-(methylthio)phenyl]-3(2H)-pyridazinone (Example 545D).

Examples 548-558

The following compounds may be prepared according to the sequence of reactions described in Example 547, substituting the appropriate 2-(X-phenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

Example Number	X
548	4-F
549	4-Cl

550	3-F
551	3-Cl
552	3-Br
553	3-CF_3
554	3-Cl-4-F
555	4-Cl-3-F
556	3,4-di-Cl
557	4-F-3-CF_3
558	3-Br-4-F

Example 559

(R)-2-(3,4-Difluorophenyl)-4-(2-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 547, substituting methyl (R)-2-hydroxy-3-methyl-butanoate [17392-84-6] prepared as described in (Tetrahedron, 1995, 51(38), 10513-10522) in place of methyl (S)-2-hydroxy-3-methylbutanoate.

Examples 560-570

The following compounds can be prepared according to the sequence of reactions described in Example 559, substituting the appropriate 2-(X-phenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

Example Number	X
560	4-F
561	4-Cl
562	3-F
563	3-Cl
564	3-Br

565	3-CF_3
566	3-Cl-4-F
567	4-Cl-3-F
568	3,4-di-Cl
569	4-F-3-CF_3
570	3-Br-4-F

Example 571

2-(3,4-Difluorophenyl)-4-[(S)-2,3-dihydroxy-3-methyl-1-butoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 547, substituting methyl (R)-2,3-dihydroxy-3-methylbutanoate [37504-90-8] (Australian Journal of Chemistry, (1986) 39(11), 1907-1909) in place of methyl (S)-2-hydroxy-3-methylbutanoate.

Examples 572-582

The following compounds may be prepared according to the sequence of reactions described in Example 571, substituting the appropriate 2-(X-phenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

Example Number	X
572	4-F
573	4-Cl
574	3-F
575	3-Cl
576	3-Br
577	3-CF_3
578	3-Cl-4-F
579	4-Cl-3-F

580	3,4-di-Cl
581	4-F-3-CF_3
582	3-Br-4-F

Example 583

2-(3,4-Difluorophenyl)-4-[(R)-2,3-dihydroxy-3-methyl-1-butoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 547, substituting methyl (S)-2,3-dihydroxy-3-methylbutanoate [75347-92-1] (Journal of Organic Chemistry, 1980, 45(25), 5218-5220) in place of methyl (S)-2-hydroxy-3-methylbutanoate.

Examples 584-594

The following compounds may be prepared according to the sequence of reactions described in Example 571, substituting the appropriate 2-(X-phenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

Example Number	X
584	4-F
585	4-Cl
586	3-F
587	3-Cl
588	3-Br
589	3-CF_3
590	3-Cl-4-F
591	4-Cl-3-F
592	3,4-di-Cl
593	4-F-3-CF_3
594	3-Br-4-F

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Example 595

2-(3,4-Difluorophenyl)-4-(4-hydroxy-4-methyl-1-pentyloxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 471, substituting 4-methyl-1,4-pentanediol [1462-10-8] (Journal of Organic Chemistry, (1972) 37, 3310-3322) in place of methyl 3-methyl-1,3-butanediol.

Example 596-606

The following compounds may be prepared according to the sequence of reactions described in Example 471, substituting 4-methyl-1,4-pentanediol [1462-10-8] (Journal of Organic Chemistry, (1972) 37, 3310-3322) in place of methyl 3-methyl-1,3-butanediol and substituting the appropriate 2-(X-phenyl)-4,5-dibromo-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

Example Number	X
596	4-F
597	4-Cl
598	3-F
599	3-Cl
600	3-Br
601	3-CF_3
602	3-Cl-4-F
603	4-Cl-3-F
604	3,4-di-Cl
605	4-F-3-CF_3
606	3-Br-4-F

.....

Example 607

2-(3,4-Difluorophenyl)-4-[3-(2-aminoacetyloxy)-3-methyl-1-butoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared by a carbodiimide-mediated coupling (method described in Angew. Chem., Int. Ed. Engl., (1979) 18(9), 686) of 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 471) with an N-protected-glycine (such as N-Fmoc-glycine); followed by an amino group deprotection step (such as treatment at room temperature with tetrabutylammonium fluoride in DMF).

Examples 608-618

The following compounds may be prepared by the method of Example 607, substituting the appropriate 2-(X-phenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 471).

Example Number	X
608	4-F
609	4-Cl
610	3-F
611	3-Cl
612	3-Br
613	3-CF_3
614	3-Cl-4-F
615	4-Cl-3-F
616	3,4-di-Cl
617	4-F-3-CF_3
618	3-Br-4-F

Example 619

2-(3,4-Difluorophenyl)-4-[3-{[(2R,3R)-3-carboxy-2,3-dihydroxypropanoyl]oxy}-3-methylbutoxy]-3-methyl-1-butoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared in a manner similar to that described in J. Chem. Soc., Chem Commun., (1993) 410-412, reacting 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 471) with an appropriately protected L-tartaric acid diester (such as below), followed by deprotection.

Example 619A

dibenzyl (2R,3R)-2,3-bis{[tert-butyl(diphenyl)silyl]oxy}butanedioate

The alcohol groups of (+)-dibenzyl-L-tartrate can be protected as the tert-butyldiphenylsilyl ethers by standard methods as described in (Greene, TW, Wuts, PGM; Protective Groups in Organic Synthesis; 3rd Edition; 1999; John Wiley & Sons, Inc.; NY, NY; 141-144) to provide the title intermediate.

Example 619B

(2R,3R)-2,3-bis{[tert-butyl(diphenyl)silyl]oxy}butanedioic acid

The dibenzyl ester of Example 619A can be cleaved by standard hydrogenolysis procedures as described in (Greene, TW, Wuts, PGM; Protective Groups in Organic Synthesis, 3rd Edition; 1999; John Wiley & Sons, Inc.; NY, NY; 415-419) to provide the title intermediate.

Example 619C

(3R,4R)-3,4-bis{[tert-butyl(diphenyl)silyl]oxy}dihydro-2,5-furandione

Example 619B may be reacted by standard methods as described in (Journal of Organic Chemistry, (1987) 52(3), 455-457) with trifluoroacetic anhydride to provide the title intermediate.

Example 619D

(2R,3R)-2,3-bis{[tert-butyl(diphenyl)silyl]oxy}-4-methoxy-4-oxobutanoic acid

Example 619C may be reacted with anhydrous methanol by standard methods as described in (Organic Syntheses. Collective Volume III. (1955) 169-171) to provide the title intermediate.

Example 619E

1-isopropenyl 4-methyl (2R,3R)-2,3-bis{[tert-butyl(diphenyl)silyl]oxy}butanedioate

Example 619D may be reacted with isopropenyl acetate in the presence of catalytic boron trifluoride etherate and mercury(II) acetate as described in (J. Chem. Soc., Chem Commun., (1993) 410-412) to provide the title intermediate.

Example 619F

2-(3,4-Difluorophenyl)-4-{3-[((2R,3R)-2,3-bis{[tert-butyl(diphenyl)silyl]oxy}-4-methoxy-4-oxobutanoyl)oxy]-3-methylbutoxy}-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 619E may be coupled to 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 471) in the presence of catalytic 4-toluene sulfonic acid by the method described in (J. Chem. Soc., Chem Commun., (1993) 410-412) to provide the title intermediate.

Example 619G

2-(3,4-Difluorophenyl)-4-[3-{[(2R,3R)-3-carboxy-2,3-dihydroxypropanoyl]oxy}-3-methylbutoxy]-3-methyl-1-butoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

Example 619F can be treated with aqueous sodium hydroxide in methanol as described in (J. Chem. Soc., Chem Commun., (1993) 410-412) to provide the title compound.

Example 620-630

The following compound may be prepared by the method of Example 619F, substituting the appropriate 2-(X-phenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-

(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 471), followed by treatment with aqueous sodium hydroxide in methanol as in Example 619G.

Example Number	X
620	4-F
621	4-Cl
622	3-F
623	3-Cl
624	3-Br
625	3-CF_3
626	3-Cl-4-F
627	4-Cl-3-F
628	3,4-di-Cl
629	4-F-3-CF_3
630	3-Br-4-F

Example 631

3-({2-(3,4-difluorophenyl)-5-[4-(methylsulfonyl)phenyl]-3-oxo-2,3-dihydro-4-pyridazinyl}oxy)-1,1-dimethylpropyl dihydrogen phosphate

The title compound may be prepared as described in (Kosolapoff, GM and Maier, L, Organic Phosphorus Compounds, (1973) Volume 6, John Wiley & Sons, NY,NY); such as reacting 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 471) with 2-cyanoethylphosphate (Fieser, LF and Fieser, M. Reagents for Organic Synthesis, 1967, Volume 1, 172-173, John Wiley & Sons, NY, NY) in the presence of DCC and pyridine. Mild alkaline hydrolysis of the cyanoethyl ester selectively provides the title compound.

Example 632-642

The following compounds may be prepared by the method of Example 631, substituting the appropriate 2-(X-phenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone in place of 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 471).

Example Number	X
632	4-F
633	4-Cl
634	3-F
635	3-Cl
636	3-Br
637	3-CF_3
638	3-Cl-4-F
639	4-Cl-3-F
640	3,4-di-Cl
641	4-F-3-CF_3
642	3-Br-4-F

Example 643

2-(tert-Butyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared according to the sequence of reactions described in Example 471, substituting 2-tert-butyl-4,5-dichloro-3(2H)-pyridazinone (Example 330A) in place of 2-(3,4-difluorophenyl)-4,5-dibromo-3(2H)-pyridazinone.

Example 644

2-(tert-Butyl)-4-[3-(2-aminoacetyloxy)-3-methyl-1-butoxy]-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone

The title compound may be prepared by the method of Example 607, substituting

2-(tert-butyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 643) in place of 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone (Example 471).

Example 645

2-(tert-Butyl)-4-[3-{[(2R,3R)-3-carboxy-2,3-dihydroxypropanoyl]oxy}-3-methylbutoxy]-3-methyl-1-butoxy]-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone

The title compound may be prepared by the method of Example 619, substituting 2-(tert-butyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (Example 643) in place of 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (Example 471).

Example 646

3-({2-(tert-Butyl)-5-[4-(methylsulfonyl)phenyl]-3-oxo-2,3-dihydro-4-pyridazinyl}oxy)-1,1-dimethylpropyl dihydrogen phosphate

The title compound may be prepared by the method of Example 631, substituting 2-(tert-butyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (Example 643) in place of 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)-phenyl]-3(2H)-pyridazinone (Example 471).

Prostaglandin Inhibition Determination

Compound Preparation and Administration

For oral administration, test compounds were suspended on the day of use in 100% polyethyleneglycol (PEG 400) with a motorized homogenizer equipped with a Teflon-coated pestle (TRI-R Instrument, Jamaica, NY).

To compare the mean responses of the treatment groups, analysis of variance was applied. Percent inhibition values were determined by comparing the individual treatment mean values to the mean of the control group. Linear regression was used to estimate IC_{50}'s/ED_{50}'s in appropriate assays.

EIA Determination of Prostaglandins

EIA reagents for prostaglandin determination were purchased from Perseptive Diagnostics, (Cambridge, MA). Prostaglandin E_2 (PGE_2) levels in lavage fluids were determined after the samples were dried under nitrogen and reconstituted with assay buffer. PGE_2 levels in enzyme assays or cell culture media were measured against standards prepared in the same milieu. The immunoassays were conducted as recommended by the manufacturer. The EIA was conducted in 96 well microtiter plates (Nunc Roskilde, Denmark) and optical density was measured using a microplate reader (Vmax, Molecular Devices Corp., Menlo Park, CA).

Recombinant Human PGHS-1 and PGHS-2 Enzyme Assays

Inhibition of prostaglandin biosynthesis in vitro was evaluated using recombinant human Cox-1 (r-hu Cox1) and Cox-2 (r-hu Cox-2) enzyme assays. Representative compounds dissolved in DMSO (3.3% v/v) were preincubated with microsomes from recombinant human PGHS-1 or PGHS-2 expressed in the baculovirus/Sf9 cell system (Gierse, J. K., Hauser,S. D., Creely, D. P., Koboldt, C., Rangwala, S., H., Isakson, P. C., and Seibert. K. Expression and selective inhibition of the constituitive and inducible forms of cyclooxygenase , Biochem J. 1995, 305: 479.), together with the cofactors phenol (2 mM) and hematin (1 μM) for 60 minutes prior to the addition of 10 μM arachidonic acid. The reaction was allowed to run for 2.5 minutes at room temperature prior to quenching with HCl and neutralization with NaOH. PGE_2 production in the presence and absence of the drug was determined by EIA analysis. The EIA was conducted in 96 well microtiter plates (Nunc Roskilde, Denmark) and optical density was measured using a microplate reader (Vmax, Molecular Devices Corp., Menlo Park, CA). EIA reagents for prostaglandin determination were purchased from Perseptive Diagnostics (Cambridge, MA). PGE_2 levels were measured against standards prepared in the same milieu. The immunoassays were conducted as recommended by the manufacturer.

The data illustrating the inhibition of prostaglandin biosynthesis in vitro by compounds of this invention is shown in Table 1. The compounds are designated by the Example Number. Column 2 shows Cox-1 percent inhibition at the particular micromolar

dose level and Column 3 shows Cox-2 percent inhibition at the particular nanomolar dose level. Values for Cox-1 and Cox-2 inhibition that are parenthetical indicate IC_{50}

Table 1

Example Number	RHUCX1 % Inh. at Dose (μM)	RHUCX2 % Inh. at Dose (μM)
10	2 @ 100	(0.014)
12	0 @ 100	97 @ 10 77 @ 1 9 @ 0.1
20	10 @ 100	86 @ 0.1 9 @ 0.01
21	19 @ 100	(0.92)
22	25 @ 100	91 @ 0.03 35 @ 0.01
23	0 @ 100	68 @ 0.1 27 @ 0.01
24	60 @ 100 0 @ 10	99 @ 1 61 @ 0.1 45 @ 0.01
25	1 @ 100	93 @ 1 66 @ 0.1
26	10 @ 100	91 @ 1 44 @ 0.1 44 @ 0.01
32	20 @ 100	96 @ 1 83 @ 0.1
34	16 @ 100	(0.92)

35	34 @ 100	(0.017)
36	21 @ 10	(0.57)
39	0 @ 100	(0.44)
40	76 @ 10 69 @ 1	97 @ 1 89 @ 0.1
41	13 @ 100	49 @ 1 17 @ 0.1
42	0 @ 100	99 @ 1 92 @ 0.1
43	8 @ 100	100 @ 1 96 @ 0.1
45	5 @ 100	85 @ 1 63 @ 0.1
48	0 @ 100	73 @ 1 2 @ 0.1
50	23 @ 100	99 @ 1 59 @ 0.1
52	32 @ 10	99 @ 1 83 @ 0.1
53	10 @ 100	99 @ 1 77 @ 0.1
54	0 @ 100	95 @ 1 58 @ 0.1
58	0 @ 100	(0.95)
60	7 @ 100	100 @ 1.000
62	6 @ 100	(0.624)
64	68 @ 1	34@ 1 36@ 0.1

65	13 @ 100	98 @ 1 65 @ 0.1
68	32 @ 100	(0.297)
69	2 @ 100	88 @ 1 29 @ 0.1 30 @ 0.01
72	0 @ 100	65 @ 1 18 @ 0.1
73	9 @ 100	(1.34)
74	11 @ 100	86 @ 1 75 @ 0.1
77	35 @ 100	82 @ 10 39 @ 1
80	41 @ 10 37 @ 1	(0.064)
81	6 @ 100	97 @ 1 44 @ 0.1
84	49 @ 10 9 @ 1	87 @ 0.3
88	0 @ 100	97 @ 1.000 35 @ 0.1
89	62 @ 30 40 @ 10	(0.35)
97	35 @ 100	(0.332)
100	62 @ 10 65 @ 1	100 @ 10 61 @ 0.1
105	85 @ 1	98 @ 1 52 @ 0.1

106	19 @ 200	(0.135)
107	88 @ 10 50 @ 1	86 @ 1 36 @ 0.1
108	0 @ 100	(0.279)
109	6 @ 100	(0.147)
110	5 @ 100	93 @ 1 50 @ 0.1
111	13 @ 100	(0.052)
112	5 @ 100	(0.136)
118	31 @ 100	72 @ 0.1 17 @ 0.01
119	(0.178)	(0.027)
120	15 @ 100	97 @ 1 45 @ 0.1
121	0 @ 100	(0.005)
122	1 @ 100	(0.285)
124	26 @ 100	(0.044)
127	50 @ 10 30 @ 1	74 @ 1 51 @ 0.1
128	14 @ 100	(0.477)
132	93 @ 1	88 @ 1 43 @ 0.1
133	23 @ 100	(0.358)
134	54 @ 100 35 @ 10	(0.053)
140	(3.06)	(0.022)
141	55 @ 100 62 @ 10	99 @ 1 95 @ 0.1

142	80 @ 10 53 @ 1	96 @ 1 45 @ 0.1 32 @ 0.01
143	62 @ 100 43 @ 10	(0.076)
144	(0.058)	88 @ 1 78 @ 0.1 65 @ 0.01
145	(0.238)	86 @ 0.1 56 @ 0.01
146	82 @ 10 53 @ 1	100 @ 1 73 @ 0.1
147	(0.067)	100 @ 1 64 @ 0.1 0 @ 0.03
149	45 @ 10 40 @ 1	(0.003)
150	56 @ 100 39 @ 10	100 @ 0.1
153	54 @ 100 35 @ 10	(0.062)
154	(0.126)	(0.018)
165	0 @ 100	(1.08)
166	3 @ 100	(0.199)
168	0 @ 100	85 @ 1 93 @ 0.1

171	0 @ 100	82 @ 10 74 @ 1 61 @ 0.1
178	6 @ 100	92 @ 1.000 34 @ 10
180	8 @ 100	78 @ 1 48 @ 0.1
182	(5.01)	(0.07)
183	25 @ 100	97 @ 1 51 @ 0.1
187	2 @ 100	(0.094)
188	18 @ 100	(0.526)
190	(1.88)	(0.134)
194	35 @ 100	90 @ 10 73 @ 1 72 @ 0.1
198	10 @ 100	68 @ 1 23 @ 0.1
207		97 @ 1 81 @ 0.1
209	0 @ 100	79 @ 1 55 @ 0.1 40 @ 0.01
213	0 @ 100	(0.812)
219	20 @ 100	90 @ 1 75 @ 0.1
220	51 @ 100 38 @ 1	96 @ 1 90 @ 0.1

226	0 @ 100	(1.09)
228	7 @ 100	(0.209)
230	4 @ 100	(0.215)
231	7 @ 100	90 @ 1 68 @ 0.1
232	23 @ 100	(0.024)
234	0 @ 100	(0.328)
235	22 @ 100	(0.21)
237	54 @ 10 44 @ 1	89 @ 0.1
240	14 @ 100	(0.297)
241	0 @ 100	(0.028)
245	9 @ 100	(1.38)
246	0 @ 100	(0.054)
247	72 @ 10 55 @ 1	99 @ 10 71 @ 1 51 @ 0.1
248	13 @ 100	(0.08)
249	6 @ 100	98 @ 1 68 @ 0.1 43 @ 0.01
252	0 @ 100	87 @ 0.1 26 @ 0.01
253	77 @ 100 29 @ 10	(0.272)
254	7 @ 100	84 @ 1 48 @ 0.1
256	0 @ 100	(0.134)

257	0 @ 100	(0.04)
260	8 @ 100	2 @ 10
261	0 @ 200	(0.161)
262	15 @ 100	(0.432)
263	1 @ 100	85 @ 10 76 @ 1 53 @ 0.1
265	8 @ 100	53 @ 10 48 @ 1 33 @ 0.1
272	0 @ 100	70 @ 1 55 @ 0.1
273	16 @ 100	54 @ 10 42 @ 1
278	36 @ 100	96 @ 1 91 @ 0.1
279	0 @ 100	60 @ 1 31 @ 0.1
281	7 @ 100	71 @ 1 52 @ 0.1 47 @ 0.01
283	0 @ 100	90 @ 10 71 @ 1 54 @ 0.1
287	0 @ 100	93 @ 10 79 @ 1 25 @ 0.1

314	7 @ 100	51 @ 10 4 @ 1
318	23 @ 100	97 @ 1 77 @ 0.1
321	4 @ 100	(0.192)
322	39 @ 100 54 @ 10	(0.058)
323	1 @ 100	(0.365)
325		(0.199)
330	15 @ 100	85 @ 1 72 @ 0.03 5 @ 0.01
335	5 @ 100	(0.001)
338	0 @ 100	100 @ 1 83 @ 0.1
339	2 @ 100	(0.088)
344	16 @ 100	(0.897)
345	0 @ 100	(0.242)
346	14 @ 100	94 @ 1 76 @ 0.1 48 @ 0.01
347	11 @ 100	(0.075)
349	0 @ 100	(0.086)
351	3 @ 100	91 @ 1 63 @ 0.1 42 @ 0.01
352	0 @ 100	(0.154)
353	6 @ 100	(0.826)

354	0 @ 100	45 @ 10 45 @ 1 36 @ 0.1
355	0 @ 100	79 @ 10 66 @ 1 46 @ 0.1
358	30 @ 100	(2.45)
361	3 @ 100	(0.011)
362	1 @ 100	84 @ 10 49 @ 1
364	0 @ 100	86 @ 1 0 @ 0.1
366	0 @ 100	(0.03)
367	0 @ 100	(0.077)
368	13 @ 100	96 @ 1 65 @ 0.1
369	0 @ 100	70 @ 1 48 @ 0.1
370	8 @ 100	(0.048)
371	8 @ 100	(0.166)
372	0 @ 100	94 @ 10 88 @ 1 59 @ 0.1
374	2 @ 100	(0.02)
375	46 @ 100 31 @ 10	(0.18)
376	12 @ 100	(0.027)
381	0 @ 100	(0.188)

384	82 @ 100 49 @ 10	99 @ 1 78 @ 0.1
386	58 @ 100 47 @ 1	83 @ 1 63 @ 0.1 58 @ 0.01
387	57 @ 10 60 @ 1	76 @ 1 65 @ 0.1 56 @ 0.01
388	74 @ 10 36 @ 1	(0.049)
390	88 @ 10 45 @ 1	99 @ 10 72 @ 1 60 @ 0.1
392	56 @ 100 35 @ 10	82 @ 0.1 65 @ 0.01
393	15 @ 100	85 @ 1 58 @ 0.1
394	86 @ 100 38 @ 10	94 @ 1 64 @ 0.1 20 @ 0.01
395	91 @ 100 35 @ 10	93 @ 1 77 @ 0.1 34 @ 0.01
396	22 @ 100	(0.059)
397	25 @ 100	93 @ 1 58 @ 0.1 39 @ 0.01
398	26 @ 100	(0.202)

400	27 @ 100	(0.142)
401	(0.753)	96 @ 1 62 @ 0.1 48 @ 0.01
402	89 @ 1	(0.221)
403	(150.76)	92 @ 1 64 @ 0 1 36 @ 0.01
404	77 @ 100 47 @ 10	92 @ 0.1 57 @ 0.01
405	90 @ 100 61 @ 10	(0.198)
406	23 @ 100	100 @ 1 64 @ 0.1 18 @ 0.01
407	32 @ 100	(0.17)
408	0 @ 100	(0.279)
410	48 @ 100 1 @ 10	67 @ 0.035 47 @ 0.017
411	96 @ 10 81 @ 1	(0.009)
412	31 @ 100	(0.002)
413	0 @ 100	(0.11)
414	0 @ 100	87 @ 1 76 @ 0.1
418	33 @ 100	85 @ 1 52 @ 0.1 53 @ 0.025

419	12 @ 100	(0.1)
420	29 @ 100	(0.323)
421	(0.269)	92 @ 1 81 @ 0.1 38 @ 0.01
422	53 @ 100 82 @ 10 76 @ 1	52 @ 1 37 @ 0.1
423	0 @ 100	87 @ 1 68 @ 0.1 36 @ 0.01
424	7 @ 100	75 @ 1 58 @ 0.1 33 @ 0.01
425	12 @ 100	69 @ 0.1 31 @ 0.01
426	1 @ 100	(0.057)
434	0 @ 100	(0.081)
437	16 @ 100	(0.124)
438	0 @ 100	(0.127)
440	20 @ 100	84 @ 1 59 @ 0.1 22 @ 0.01
442	55 @ 100	90 @ 0.1 56 @ 0.01
443	35 @ 100	86 @ 0.1 74 @ 0.01

444	0 @ 100	83 @ 1 62 @ 0.1 14 @ 10
445	(56.62)	(0.069)
446	0 @ 200	(0.373)
447	0 @ 100	90 @ 1 57 @ 0.1 35 @ 0.01
449	5 @ 200	(0.129)
450	29 @ 100	87 @ 1 40 @ 0.1 22 @ 0.01
451	10 @ 100	(0.470)
452	14 @ 100	15 @ 1
467	4@100	(1.96)
475	0@100	(0.71)
471	(3.68)	(0.49)
478	33 @100	(0.81)
528	(3.4)	(0.72)

IL-1β Induced PGE_2 Production in WISH Cells

Human amnionic WISH cells were grown to 80% confluence in 48 well plates. Following removal of the growth medium and two washings with Gey's Balanced Salt Solutn, 5 ng IL-1β/ml (UBI, Lake Placid, NY) was added to the cells with or without test compound in DMSO (0.01% v/v) in Neuman-Tytell Serumless Medium (GIBCO, Grand Island, NY). Following an 18 hour incubation to allow for the maximal induction of PGHS-2, the conditioned medium was removed and assayed for PGE_2 content by EIA analysis as described above.

Monocyte U937 (ATCC, Rockville, MD) cells were grown in a similar fashion to the WISH cells. After incubation, the conditioned medium was removed and assayed for Cox-1 content by EIA analysis as described above.

The data illustrating the inhibition of prostaglandin biosynthesis in vitro by compounds of this invention is shown in Table 2. U937 values indicate Cox-1 percent inhibition at the particular micromolar dose level while partenthetical values indicate IC_{50} values. WISH cell values indicate percent inhibition at the particular micromolar dose level while parenthetical values indicate IC_{50} values.

Human Whole Platelet Cyclooxygenase-1 Assay (HWCX)

Blood from normal healthy volunteers is collected into tubes containing ACD (acid citrate dextrose) as the anticoagulant. This blood is centrifuged at 175 x g to prepare platelet rich plasma. The platelet rich plasma is then centrifuged at 100 x g to pellet the white blood cells, leaving the platelets in the supernatant. The supernatant is layered on a cushion of 0.7 mL of 10% bovine serum albumin in Tyrodes solution (Gibco; Grand Island, NY) and then centrifuged at 1000 x g. The resulting supernatant from this centrifugation is then removed and 11 mL of Tyrodes solution is added to the remaining pellet of platelets. The platelets are then aliquoted at 120 µl into a 96 well plate. Experimental compounds are added and allowed to pre-incubate for 10 minutes. At the end of this pre-incubation period, the calcium ionophore A23187 is added to a final concentration of 8.8 µM and the incubation is continued for ten minutes. The reaction is stopped by adding cold 6 mM EDTA, the incubation mixture is centrifuged at 220 x g, and the supernatants are then analyzed for thromboxane using a commercial kit from Cayman Chemical (Ann Arbor, MI).

Table 2

Example Numbers	U937 % Inhib. at Dose (µM)	HWPX % Inhib. at Dose (µM)	Wish % Inhib. at Dose (µM)
10		(4.1)	(0.014)

20	33 @ 1		(0.001)
24	(0.19)		(0.007)
43		86 @ 10 9 @ 1	(0.008)
53		78 @ 10 8 @ 1	90 @ 0.1 44 @ 0.01
65			(0.02)
69		(1.14)	(0.02)
72		(25)	(0.072)
75		84 @ 10 0 @ 3	(0.001)
77		(8.8)	(0.126)
85			(0.47)
86			52 @ 1 47 @ 0.01
89	(3.8)	(2.1)	(0.05)
100		(0.13)	(0.02)
102			(0.05)
105		62 @ 1	(0.018)
106		(17.5)	(0.03)
108		(8)	(0.097)
109		(2.693)	(0.018)
119		(0.076)	(0.001)
120		74 @ 3 58 @ 1	(0.025)
121			(0.041)
123		90 @ 1 29 @ .1	(0.001)

126			(0.05)
129			(0.04)
132			100 @ 0.1 36 @ 0.01
140		(0.773)	(0.01)
141		56 @ 0.3	(0.004)
142		(7.53)	(0.088)
143			(0.007)
145		72 @ 1 30 @ .3	(0.009)
146		84 @ 10 46 @ 3	(0.044)
147		84 @ 0.3	(0.029)
148		51 @ 0.3	(0.042)
149		89 @ 10 34 @ 3	(0.03)
152			(0.029)
153		(2.95)	(0.046)
154		81 @ .3 48 @ .1	100 @ 0.1 69 @ 0.01
160		(7.2)	(0.03)
162			(0.034)
165		(1.9)	(0.030)
166		(9.4)	(0.02)
168		47 @ 1	(0.009)
171			90 @ 1 56 @ 0.1
187		(12.6)	(0.015)

189		31 @ 100	(0.041)
190		(9.96)	(0.03)
191			(0.06)
194		(28.09)	(0.069)
198			(0.184)
203			77 @ 1 23 @ 0.1
207			(0.068)
228		(19.6)	(0.086)
241			(0.0474)
243			(0.03)
244		(3.67)	(0.019)
245			(0.046)
246			(0.02)
247		(7.76)	(0.02)
248		82 @ 30 17 @ 10	(0.005)
252			(0.044)
256		(4.7)	(0.028)
261		(34)	(0.099)
271			52 @ 1 15 @ 0.1
278			(0.07)
279			(0.391)
287			(0.16)
317			(0.027)
320		29 @ 3	78 @ .1 15 @ .01

321			50 @ 0.01
322			(0.026)
323			57 @ 0.01
324			(0.047)
325		(2.3)	(0.04)
326			(0.05)
330		(16.7)	(0.005)
335			(0.023)
338		(14.93)	(0.004)
339		(0.393)	(0.026)
343		(0.191)	(0.016)
344			(0.1)
345			(0.03)
349		34 @ 100	(0.041)
352		(5.5)	(6.048)
358			69 @ 1 0 @ 0.1
366		(1.615)	(0.002)
367		50 @ 1 8 @ .3	(0.018)
368		(13.7)	64 @ 0.03 33 @ 0.01
370		(8.4)	(0.02)
375		(2.04)	(0.089)
381		31 @ 30 91 @ 100	(0.075)
385		(2.18)	(0.023)
388		0 @ .3	(0.032)

392		(1.95)	(0.02)
394			(0.019)
396		(12.7)	(0.02)
397		(13.8)	(0.04)
399			82 @ 0.1 39 @ 0.03
400		(0.3)	(0.026)
401		(0.32)	(0.017)
403		(0.902)	(0.018)
404		(0.337)	96 @ 0.1 58 @ 0.01
406		(1.61)	(0.026)
408			(0.029)
410			(0.053)
414			54 @ 1 46 @ 0.1
418		(14.25)	(0.25)
430		34 @ 10 89 @ 100	(0.054)
442			(0.42)
445		100 @ 100 22 @ 1 0	(0.025)
446		(24.4)	(0.02)
449		(40)	(0.089)
450			(0.05)
451		(22.4)	(0.15)
452			56 @ 1 1 @ 0.1

475		50 @ 100	(0.44)
467			(0.135)
471		(0.32)	(0.04)
478		(0.5)	(0.108)
528		(3.5)	(0.054)

Carrageenan Induced Paw Edema (CPE) in Rats

Hindpaw edema was induced in male rats as described by Winter et al., Proc. Soc. Exp. Biol. Med., 1962, 111, 544. Briefly, male Sprague-Dawley rats weighing between 170 and 190 g were administered test compounds orally 1 hour prior to the subplantar injection of 0.1 ml of 1% sodium carrageenan (lambda carrageenan, Sigma Chemical Co., St Louis, MO) into the right hindpaw. Right paw volumes (ml) were measured immediately following injection of carrageenan for baseline volume measurements using a Buxco plethysmograph (Buxco Electronics, Inc., Troy, NY). Three hours after the injection of carrageenan, right paws were remeasured and paw edema calculated for each rat by subtracting the zero time reading from the 3 hour reading. Data are reported as mean percent inhibition +/- SEM. Statistical significance of results was analyzed by Dunnetts multiple comparison test where $p < 0.05$ was considered statistically significant.

Rat Carrageenan Pleural Inflammation (CIP) Model

Pleural inflammation was induced in male adrenalectomized Sprague-Dawley rats following the method of Vinegar et al., Fed. Proc. 1976, 35, 2447-2456. Animals were orally dosed with experimental compounds, 30 minutes prior to the intrapleural injection of 2% lambda carrageenan (Sigma Chemical Co., St. Louis MO). Four hours later the animals were euthanized and the pleural cavities lavaged with ice cold saline. The lavage fluid was then added to two volumes of ice cold methanol (final methanol concentration 66%) to lyse cells and precipitate protein. Eicosanoids were determined by EIA as described above.

The data illustrating the inhibition of prostaglandin biosynthesis in vivo by the compounds of this invention is shown in Table 3. Values reported are percent inhibition at 10 milligrams per kilogram body weight.

Carrageenan induced air pouch prostaglandin biosynthesis model (CAP)

Air pouches are formed in the backs of male Sprague Dawley rats by injecting 20 mL of sterile air on day 0. Three days later the pouch was reinflated with an additional 10 mL of sterile air. On day 7, 1 mL of saline containing 0.2 % lambda carrageenan (Sigma Chemical Co.) is injected into the pouch to induce the inflammatory reaction that is characterized by the release of prostaglandins. Test compounds are dosed at 0.1 to 10 mg/kg 30 minutes prior to carrageenan. Four hours after the carrageenan injection the pouch is lavaged and levels of prostaglandins are determined by enzyme immuno-assay using commercially available kits. Percent inhibitions are calculated by comparing the response in animals which have received vehicle to those which received compound. Values for Cox-2 inhibition that are parenthetical indicate ED_{50} values.

The data illustrating the inhibition of prostaglandin biosynthesis in vivo by the compounds of this invention is shown in Table 3. Values reported are percent inhibition at 10 milligrams per kilogram body weight for CIP and CPE tests and at 3 milligrams per kilogram body weight for CAP testing.

Table 3

Example Numbers	CIP % Inhib. @ 10 mpk	CPE % Inhib. @ 10 mpk	CAP % Inhib. @ 3 mpk
10	44		
12	42	25	
34	36	31	
54	31	30	
58	42	14	67
62	57	21	

66	59	7	0
67	40 @ 3mpk		
68	64	40.3	
69	61	45.5 ED_{30} = 5.4	87
72			
73		46	29
74	46.5	18	34
77	51	21	
80	60	28.5	91
89	68.3 ED_{50} = 3.4	45.5	94
106			47
109		13	71
112		21	42.5
119	82	27	76
120	5	11	
121	19	8	
123			23
143			59
153			51
160	56	35	
166	40		59
168	0	6	
180	34.5		
182	59	27	98
185	59	20	53
187	51	28	30

190	60	28	71
205			54
226		21	40.5
243			7
245			47
246			48
248			49
256			47
257			60
261		28	79
330			4.5
335			45
339		43	90.5 ED_{50} = 0.58
346			49.5
347		27	66.5
349			63
351/64			0
352			89 ED_{50} = 5.0
353/63			0
361			65
366			63 ED_{50} = 1.5
367			48
375		47	77.5 ED_{50} = 0.57
376		17	77.5

378			59
384/33	51	15	51
385			65
388		28	80
390			60
391			61
392			60
394			70
395			71
396		23	85
397			70
400	65	41	82.5
403		43	68.5 ED_{50} = 0.35
405			53
406		23	66.5
407			61
419			48
427			78
445		15	73
446		44	92 ED_{50} = 0.5
449		23	76 ED_{50} = 1.8
450			86
451		ED_{30}=0.82	80.5 ED_{50} = 0.7
452			71

459			45
464			70
475		33	ED_{50}=1.4
467		ED_{30}=1.7	ED_{50}=0.4
471		41	ED_{50}=0.9
478		26	75
528		40	ED_{50}=1.4

Human whole blood assays

Cyclooxygenase-1

Heparin anticoagulatd blood was incubated with drugs dissolved in DMSO. The samples are incubated at 37 degrees Celsius for 4.5 hours after which calcium ionophore at a final concentration of 30 μM was added and the mixture allowed to incubate for 30 minutes. The reaction was stopped with the addition of EGTA and cold methanol (50% final concentration). After 18 hours at -70 degrees Celsius, the plates were centrifuged and supernatants analyzed for TXB_2.

Cyclooxygenase-2

Heparin anticoagulated blood was incubated with drugs dissolved in DMSO. The samples are incubated at 37 degrees Celsius for 15 minutes. E. coli lipopolysaccaride (LPS) 5 μg/ml was then added and the samples incubated for 5 hours. The reaction was stopped with the addition of EGTA and cold methanol (50% final concentration). After 18 hours at -70 degrees Celsius, the plates were centrifuged and supernatants analyzed for TXB_2.

Example 451- Human whole blood Cox-1 IC_{50} = 29.12 micromolar

Example 451-Human whole blood Cox-2 IC_{50} = 0 47 micromolar

Example 471- Human whole blood Cox-1 = 55.5% at 30 micromolar

Example 471- Human whole blood Cox-2 = 85% at 0.03 micromolar

The 4-hydroxyalkoxy-3(2H)-pyridazinone Cox-2 inhibition and in vivo activity has been found to be suprisingly good. In addition, when compared to the 4-alkoxy-3(2H)-pyridazinones, the hydroxyalkoxy compounds typically possess a superior oral pharmacokinetic profile, such as better plasma half-life, plasma concentration maxima, and area under the curve. For example, Example 375 shows a 14 day plasma micromolar concentration (based on 10mg/kg dosage) of 0.0 while Example 451 shows a 3.43 micromolar level. In addition, the half life of Rat IV (3mg/kg) for Example 375 was 2.9 while Example 451 showed 5.2. The AUC value (micromolar/hour) for Example 375 was 1.8 while Example 451 was 69.

It is anticipated that the 4-hydroxyalkoxy compounds are preferred to parent alkoxy compounds with regard to once-a-day dosing to achieve predictable exposure levels across a wide range of doses while producing an antiinflammatory effect.

Pharmaceutical Compositions

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers. The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's

solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the procedures and judgements well known to one skilled in the art. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray.

The compounds of the present invention may be potentially useful in the treatment of several illness or disease states such as inflammatory diseases, dysmennorhea, asthma, premature labor, adhesions and in particular pelvic adhesions, osteoporosis, and ankylosing spondolitis. Current Drugs Ltd, ID Patent Fast Alert, AG16, May 9, 1997.

The compounds of the present invention may also be potentially useful in the treatment of cancers, and in particular, colon cancer. Proc. Natl. Acad. Sci . 94, pp. 3336-3340, 1997.

The compounds of the present invention may be useful by providing a pharmaceutical composition for inhibiting prostaglandin biosynthesis comprising a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, ester, or prodrug thereof, and a pharmaceutically acceptable carrier.

In addition, the compounds of the present invention may be useful by providing a method for inhibiting prostaglandin biosynthesis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In addition, the compounds of the present invention may be useful by providing a method for treating pain, fever, inflamation, rheumatoid arthritis, osteoarthritis, adhesions, and cancer comprising administering to a mammal in need of such teratment a therapeutically effective amount of a compound of formula I.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the

active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (such as, for example, cottonseed, groundnut, corn, germ, olive, castor, sesame oils, and the like), glycerol, tetrahydrofurfuryl alcohol, poly-ethyl-ene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, such as, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, such as, for example, a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, isotonic sodium chloride solution, and the like. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectable preparations.

The injectable formulations can be sterilized by any method known in the art, such as, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or

suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsulated matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and thus melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is usually mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as, for example, sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as, for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid. b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as, for example, glycerol, d) disintegrating agents such as, for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as, for example, paraffin, f) absorption accelerators such as, for example, quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as, for example, kaolin and bentonite clay, and) lubricants such as, for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients such as, for example. lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using excipients such as. for example, lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets. dragees. capsules. pills. and granules can be prepared with coatings and shells such as enteric coatings. release controlling coatings and other coatings well known in the pharmaceutical formulation art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as, for example. sucrose. lactose or starch. Such dosage forms may also comprise, as is normal practice. additional substances other than inert diluents. e.g., tableting lubricants and other tableting aids such as. for example, magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only. or preferentially, in a certain part of the intestinal tract. optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments. pastes, creams. lotions. gels. powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments. pastes. creams and gels may contain. in addition to an active compound of this invention. excipients such as. for example. animal and vegetable fats. oils, waxes. paraffins, starch. tragacanth. cellulose derivatives. polyethylene glycols, silicones. bentonites. silicic acid, talc and zinc oxide. or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as, for example, lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in a suitable medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, a patient, such as a human or mammal, is treated by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to provide the relief desired, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

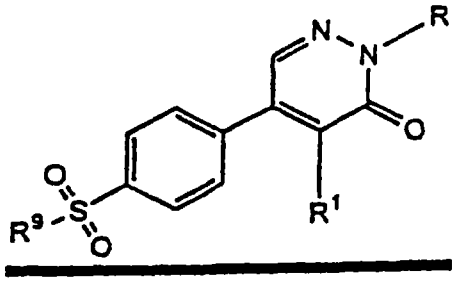
The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, from 0.001 to about 1000 mg/kg body weight daily or more preferably from about 0.1 to about 100 mg/kg body weight for oral administration or 0.01 to about 10 mg/kg for parenteral

administration daily Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The reagents required for the synthesis of the compounds of the invention are readily available from a number of commercial sources such as Aldrich Chemical Co. (Milwaukee, WI, USA); Sigma Chemical Co. (St. Louis, MO, USA); and Fluka Chemical Corp. (Ronkonkoma, NY, USA); Alfa Aesar (Ward Hill, MA 01835-9953); Eastman Chemical Company (Rochester, New York 14652-3512); Lancaster Synthesis Inc. (Windham, NH 03087-9977), Spectrum Chemical Manufacturing Corp. (Janssen Chemical) (New Brunswick, NJ 08901); Pfaltz and Bauer (Waterbury, CT. 06708). Compounds which are not commercially available can be prepared by employing known methods from the chemical literature.

1. A compound of formula VI



VI,

or a pharmaceutically acceptable salt thereof, wherein

R is selected from the group consisting of: a) alkyl, b) aryl, wherein the aryl is optionally substituted phenyl wherein said substituents are selected from alkyl, halogen, and haloalkyl, c) arylalkyl, wherein the aryl of the arylalkyl is optionally substituted phenyl wherein said substituents are selected from alkyl, halogen, and haloalkyl, d) haloalkyl, and e) haloalkenyl;

R^1 is hydroxyalkoxy, and

R^9 is selected from the group consisting of alkyl, alkylcarbonylamino, and amino.

2. A compound according to claim 1 wherein

R is aryl wherein aryl is optionally substituted phenyl wherein said substituents are selected from alkyl, halogen, and haloalkyl; and

R^9 is selected from the group of consisting of alkyl and amino.

3. A compound according to claim 1 wherein

R is aryl wherein aryl is optionally substituted phenyl wherein said substituents are selected from alkyl, halogen, and haloalkyl ; and

R^9 is methyl.

4. A compound according to claim 1 wherein

R is phenyl optionally substituted with substituents independently selected from the group consisting of halogen and haloalkyl; and

R^9 is selected from the group consisting of alkyl and amino.

5. A compound according to claim 1 wherein

R is phenyl optionally substituted with 1 or 2 substituents independently selected from the group of consisting chlorine and fluorine; and

R^9 is selected from the group consisting of alkyl and amino.

6. A compound according to claim 4 selected from the group consisting of

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl- 1 -propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(2-hydroxy-2-methyl- 1 -propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl- 1 -propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3,4-Difluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chloro-4-fluorophenyl)-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(4-hydroxy-3-methyl-l-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-hydroxy-3-methyl-l-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chloro-4-fluorophenyl)-4-(4-hydroxy-3-methyl-l-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(4-hydroxy-3-methyl-l-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(4-hydroxy-3-methyl-l-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chloro-4-fluorophenyl)-4-(4-hydroxy-3-methyl-1-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(4-hydroxy-3-methyl-l-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(4-Fluorophenyl)-4-(3-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(4-Fluorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5- [4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(3-Chlorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(3-Chlorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3-Chlorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(3-Chlorophenyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(4-Fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Difluorophenyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(aminosulfonyl)-phenyl]-3(2H)-pyridazinone;

2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chloro-4-fluorophenyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3-Chlorophenyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Dichlorophenyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-[(3-Trifluoromethyl)phenyl]-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(3,4-Dichlorophenyl)-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-[3-(Trifluoromethyl)phenyl]-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

7. A compound according to claim 1 wherein

R is haloalkyl

8. A compound according to claim 7 selected from the group consisting of 2-(2,2,2-Trifluoroethyl)-4-(2-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(2-hydroxy-2-methyl-1-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2,2-dimethyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(S)-2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone;

(R)-2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-2-methyl-l-propoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone;

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-methylsulfonyl)phenyl]-3(2H)-pyridazinone; and

2-(2,2,2-Trifluoroethyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(aminosulfonyl)phenyl]-3(2H)-pyridazinone.

9. 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-l-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone or a pharmaceutically acceptable salt thereof.

10. 2-(4-Fluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfony)phenyl]-3(2H)-pyridazinone or a pharmaceutically acceptable salt thereof.