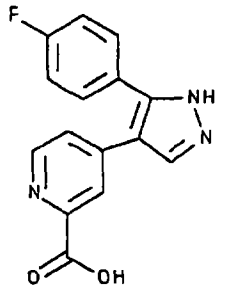
**Example A-226**



4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylic acid

To a solution of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylate prepared as set forth in Example A-224 (0.90 g, 0.003 mol) in 10 mL of ethanol was added a solution of sodium hydroxide (0.24 g, 0.006 mol) in 5 mL of water. The reaction mixture was heated at reflux for 10 hours. After the removal of solvent, the residue was dissolved in water and acidified with citric acid solution to pH 5. Then the aqueous phase was extracted with ethyl acetate and the organic phase was dried over magnesium sulfate and concentrated. The crude was purified by treating with ether to give 0.62 g of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinecarboxylic acid as a white solid (73% yield), mp: 245°C(dec). Anal Calc'd for $C_{15}H_{10}FN_3O$ + 0.2 $H_2O$: C, 62.80; H, 3.65; N, 14.65. Found: C, 62.77; H, 3.42; N, 14,58.

Additional compounds of the present invention which were prepared according to one or more of above reaction schemes (particularly Schemes IX through XVIII) are disclosed in Table 3. The specific synthesis scheme or schemes as well as the mass spectroscopy and elemental analysis results for each compound also are disclosed in Table 3.

*G00001*

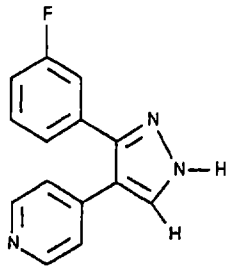
TABLE 3

| Example | General | MS | Microanalysis | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Procedure | M+1 | C calc | C found | H calc | H found | N calc | N found | *water added* | *EtOAc added* |
| A-227 | IX | 240 | 69 | 69 | 4.3 | 4.6 | 17.2 | 16.8 | 0.25 | |
| A-228 | IX | 266 | 65.69 | 65.69 | 4.41 | 4.33 | 15.32 | 14.98 | | |
| A-229 | XI | 254 | 70.6 | 70.6 | 4.8 | 4.5 | 16.5 | 16.3 | 0.1 | |
| A-230 | IX | 256 | 65.76 | 65.48 | 3.94 | 3.78 | 16.43 | 16.52 | | |
| A-231 | XI | 280 | 64.18 | 63.95 | 4.39 | 4.31 | 13.86 | 13.90 | | |
| A-232 | XI | 271 | 66.79 | 66.79 | 4.48 | 4.24 | 15.58 | 15.32 | | |
| A-233 | XI | 284 | 66.9 | 66.8 | 5 | 5 | 14.6 | 14.9 | 0.2 | |
| A-234 | XI | 270 | 65.9 | 65.6 | 4.6 | 4.6 | 15.4 | 15.4 | 0.2 | |
| A-235 | XI | 264 | 77 | 76.7 | 6.5 | 6.5 | 15.8 | 15.7 | 0.1 | |
| A-236 | IX | 221 | 75.38 | 75.44 | 5.06 | 5.1 | 18.84 | 19 | 0.1 | |
| A-237 | IX | 290 | 61.52 | 61.67 | 3.58 | 3.51 | 14.35 | 14.32 | | |
| A-238 | XI | 304 | 63.36 | 63.28 | 3.99 | 3.91 | 13.85 | 13.83 | | |
| A-239 | IX | 258 | 65.37 | 65.39 | 3.53 | 3.52 | 16.33 | 16.31 | | |
| A-240 | IX | 274 | 61.44 | 61.14 | 3.31 | 3.01 | 15.35 | 14.95 | | |
| A-241 | IX | 300 | 56.02 | 55.99 | 3.36 | 3.26 | 14.00 | 14.01 | | |
| A-242 | XI | 272 | 66.42 | 66.41 | 4.09 | 4.04 | 15.49 | 15.32 | | |
| A-243 | XI | 314 | 57.34 | 57.22 | 3.85 | 3.68 | 13.37 | 13.27 | | |
| A-244 | IX | 342 | 76.39 | 76.16 | 4.81 | 4.51 | 12.31 | 12.05 | 0.25 | |
| A-245 | XII | 341 | 64.89 | 64.65 | 6.36 | 6.17 | 15.93 | 15.82 | 0.6 | |
| A-246 | XII | 391 | 66.08 | 66.18 | 5.04 | 5.56 | 14.01 | 12.26 | 0.5 | |
| A-247 | XII | 362 | 64.46 | 64.16 | 4.65 | 4.34 | 18.79 | 18.65 | 0.6 | |
| A-249 | XII | 258 | 64.91 | 64.84 | 3.58 | 3.63 | 16.22 | 15.98 | 0.1 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| A-250 | IX | 348 | 48.44 | 48.07 | 2.9 | 2.82 | 12.1 | 12.01 | | |
| A-251 | XI | 362 | 49.88 | 49.89 | 3.35 | 3.51 | 11.63 | 11.54 | | |
| A-252 | XI | 304 | 63.36 | 63.34 | 3.99 | 3.96 | 13.85 | 13.81 | | |
| A-253 | XII | 377 | 68.24 | 68.17 | 5 | 4.71 | 14.47 | 14.34 | 0.6 | |
| A-254 | XII | 363 | 66.31 | 66.12 | 4.77 | 4.31 | 14.73 | 14.6 | 1 | |
| A-215 | XIV | 265 | 67.3 | 67.4 | 3.5 | 3.4 | 20.9 | 20.7 | 0.2 | |
| A-255 | XII | 298 | 64.63 | 64.64 | 5.42 | 5.41 | 23.55 | 23.32 | | |
| A-256 | XI | 272 | 66.42 | 66.58 | 4.09 | 4.26 | 15.49 | 14.78 | | |
| A-257 | IX | 276 | 60.11 | 60.4 | 3.06 | 3.18 | 15.02 | 14.73 | 0.25 | |
| A-258 | IX | 254 | | | | | | | | |
| A-259 | XI | 268 | 71.89 | 71.63 | 5.28 | 5.24 | 15.72 | 15.84 | | |
| A-260 | X | 290 | 62.28 | 62.41 | 3.48 | 3.48 | 14.53 | 14.51 | | |
| A-261 | X, XV | 311 | 69.26 | 69.2 | 6.2 | 6.25 | 17.95 | 17.89 | 0.1 | |
| A-262 | XI | 376 | 72.71 | 72.5 | 5.17 | 4.98 | 11.06 | 10.99 | 0.25 | |
| A-263 | XII | 428 | 70.81 | 70.59 | 6.28 | 6.45 | 15.88 | 15.08 | 0.75 | |
| A-264 | XII | 326 | 63.79 | 63.76 | 6.39 | 6.09 | 20.66 | 20.45 | 0.75 | |
| A-265 | IX | 400 | 66.18 | 66.77 | 4.1 | 4.23 | 16.78 | 15.83 | 1 | |
| A-266 | XII | 368 | 62.32 | 62.38 | 6.28 | 6.5 | 18.17 | 17.56 | 1 | |
| A-267 | XI | 302 | 62.66 | 62.85 | 4.47 | 4.34 | 13.7 | 13.53 | 0.4 | |
| A-268 | XII | 349 | 62.9 | 63.2 | 5.2 | 4.8 | 22.7 | 22.5 | 0.75 | 0.1 |
| A-269 | XI, XV | 371 | 61.85 | 61.84 | 5.71 | 5.24 | 14.42 | 14.17 | 1 | |
| A-270 | XI, XV | 404 | 70.66 | 70.7 | 4.82 | 4.61 | 10.3 | 10.15 | 0.25 | |
| A-271 | XI, XV | 329 | 65.8 | 65.3 | 5.5 | 5.6 | 17.1 | 16.8 | | |
| A-272 | XI | 406 | 69.95 | 70.13 | 5.35 | 5.28 | 10.14 | 9.89 | 0.5 | |
| A-273 | XI | 354 | 66.9 | 67.2 | 6.9 | 6.6 | 19.1 | 18.7 | 0.2 | 0.1 |
| A-274 | XI, XII, XV | 434 | 63.6 | 63.1 | 6.3 | 5.8 | 14.4 | 14 | 2 | 0.2 |

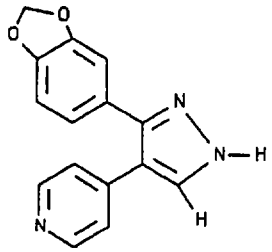
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| A-275 | XI, XV | 433 | 70.44 | 70.74 | 6.18 | 6.3 | 12.64 | 12.05 | 0.6 | |
| A-276 | XI, XII, XV | 476 | 65.9 | 66.2 | 6.1 | 6.1 | 13.3 | 13.6 | 0.5 | 0.5 |
| A-277 | XII | 338 | 61.11 | 63.02 | 6.48 | 6.39 | 18.75 | 16.61 | | |
| A-278 | XI, XV | 357 | 64.2 | 63.8 | 6.5 | 6 | 15 | 14.8 | 1 | |
| A-279 | XI, XII, XV | 462 | 67.4 | 67.1 | 6.7 | 6.2 | 13.6 | 13.7 | 0.6 | 0.5 |
| A-280 | XII | 299 | 61.27 | 61.47 | 5.37 | 5.11 | 17.86 | 17.21 | 0.9 | |
| A-281 | XII | 313 | 64.63 | 64.94 | 5.55 | 5.63 | 17.73 | 17.48 | 0.2 | |
| A-282 | XII | 313 | 64.63 | 64.81 | 5.55 | 5.43 | 17.73 | 17.38 | 0.3 | |
| A-283 | XI, XII | 407 | 67.2 | 67 | 5 | 5.2 | 13.6 | 13.2 | 0.25 | |
| A-284 | XI, XV | 339 | 70 | 70.3 | 6.9 | 6.9 | 16.3 | 16.2 | 0.25 | |
| A-285 | XI, XII, XV | 476 | 68.2 | 68.5 | 5.7 | 6.2 | 14.7 | 13.6 | | |
| A-286 | XVII | 382 | 59.77 | 59.69 | 6.81 | 6.56 | 16.6 | 16.65 | 2.25 | |
| A-287 | XVII | 340 | 56.07 | 56.26 | 7.31 | 7.1 | 17.21 | 17.27 | 3.75 | |
| A-288 | XVII | 293 | 69.42 | 69.4 | 4.52 | 4.6 | 19.05 | 19.09 | 0.1 | |
| A-289 | XI, XII | 407 | 68 | 67.5 | 5 | 4.5 | 13.8 | 13.5 | | |
| A-290 | XI, XII | 407 | 64 | 64.5 | 5.3 | 4.9 | 13 | 12.4 | 1.4 | |
| A-291 | IX | 290 | 74.7 | 74.9 | 4.2 | 4.2 | 14.5 | 14.5 | | |
| A-292 | XVII | 326 | 61.22 | 61.46 | 4.77 | 4.53 | 16.8 | 16.97 | 0.4 | |
| A-293 | XVII | 313 | 55.75 | 55.98 | 4.85 | 4.02 | 16.25 | 16.37 | 1.8 | |
| A-294 | XI | 278 | 73.6 | 73.2 | 4.4 | 4.2 | 15.2 | 15 | | |
| A-295 | XI | 278 | 67.9 | 67.7 | 4.9 | 4.3 | 14 | 13.7 | 1.3 | |
| A-296 | IX | | 70.3 | 70.4 | 4.5 | 4.7 | 25.2 | 25.4 | | |
| A-297 | IX | | 57.9 | 57.7 | 3.1 | 2.9 | 14.5 | 14.5 | | |
| | | | | | | | | | | |

**Example A-227**



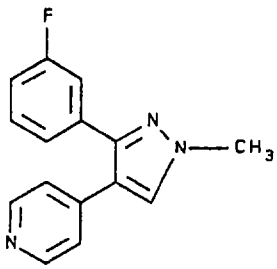
4-[3-(3-fluorophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-228**



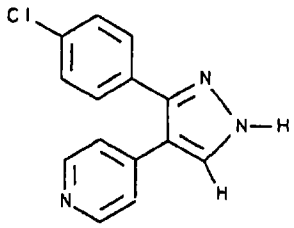
4-[3-(1,3-benzodioxol-5-yl)-1H-pyrazol-4-yl]pyridine

**Example A-229**



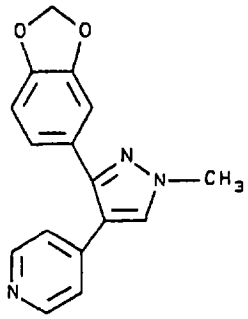
4-[3-(3-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-230**



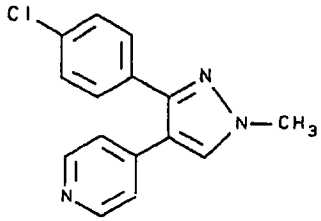
4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-231**



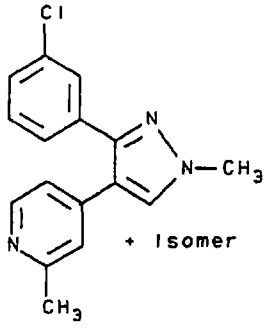
4-[3-(1,3-benzodioxol-5-y)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-232**



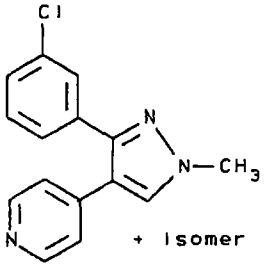
4-[3-(4-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-233**



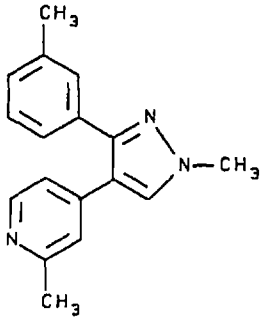

4-[3-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-methylpyridine and 4-[5-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-methylpyridine

**Example A-234**




4-[3-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine
and
4-[5-(3-chlorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

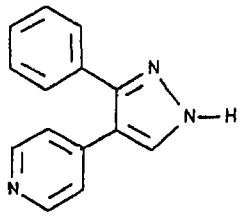
**Example A-235**




2-methyl-4-[1-methyl-3 (or 5)-(3-methylphenyl)-1H-pyrazol-4 -yl]pyridine

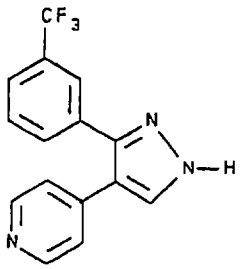
16 MAY 2003

**Example A-236**



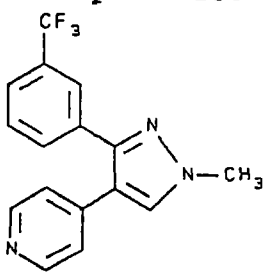
4-(3-phenyl-1H-pyrazol-4-yl)pyridine

**Example A-237**



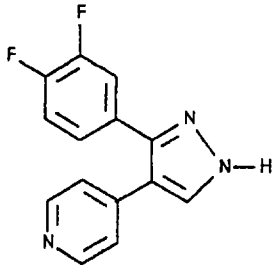
4-[3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl]pyridine

**Example A-238**



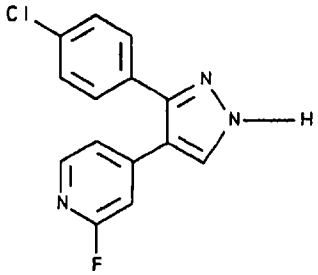
4-[1-methyl-3-[3-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl]pyridine

**Example A-239**



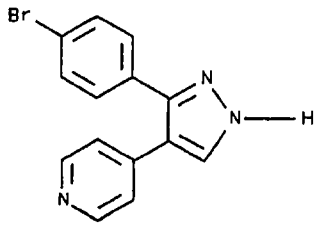
4-[3-(3,4-difluorophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-240**



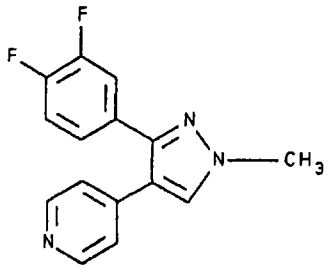
4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-fluoropyridine

**Example A-241**



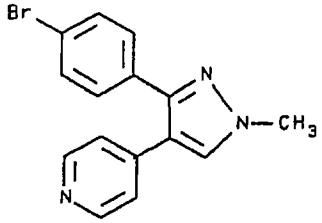
4-[3-(4-bromophenyl)-1H-pyrazol-4yl]pyridine

**Example A-242**



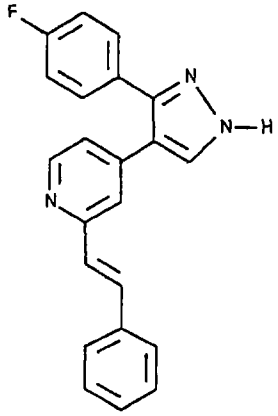
4-[3-(3,4-difluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-243**



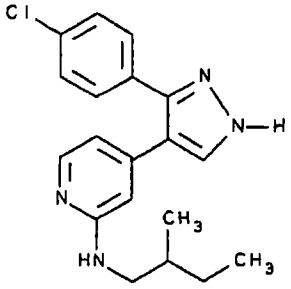

4-[3-(4-bromophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-244**




(E)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-(2-phenyleth enyl)pyridine

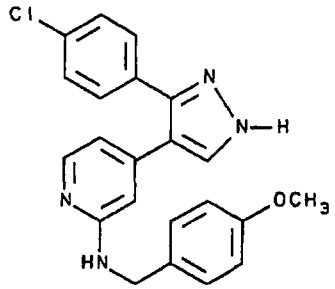
**Example A-245**




S

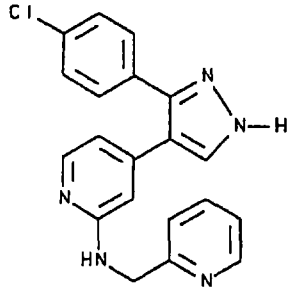
(S)-4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-N-(2-methylbut yl)- 2-pyridinamine

**Example A-246**



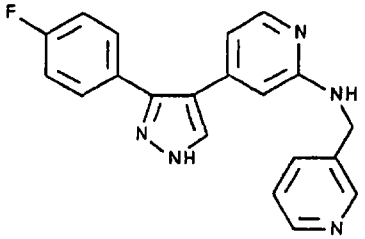
4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxy-phenyl)methyl]- 2-pyridinamine

**Example A-247**



N-[4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-2-pyridinemethanamine

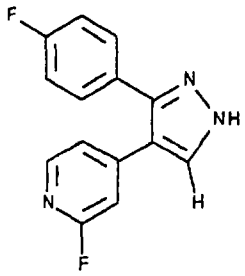
**Example A-248**



N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-2-pyridinemethanamine

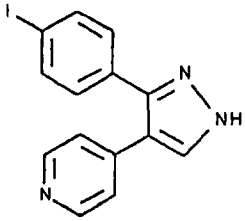
Anal Calc'd: C, 41.12; H, 3.58; N, 9.22. Found: C, 41.74; H, 5.05; N, 11.11.

**Example A-249**



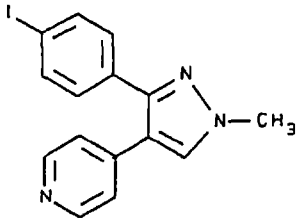
2-fluoro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-250**



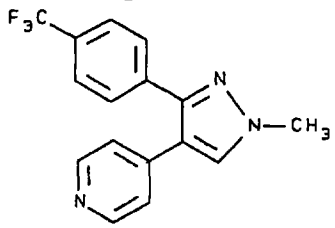
4-[3-(4-iodophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-251**



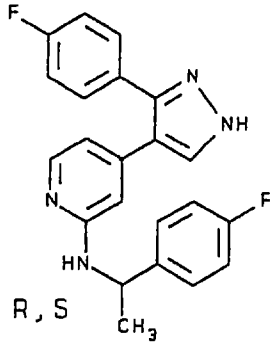
4-[3-(4-iodophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-252**



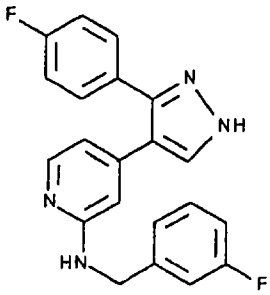
4-[1-methyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazol-4-yl ]pyridine

**Example A-253**



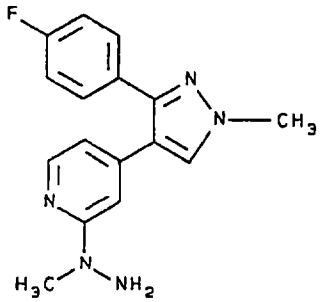
N-[1-(4-fluorophenyl)ethyl]-4-[3-(4-fluorophenyl)-1H-pyra zol-4-yl]- 2-pyridinamine

**Example A-254**



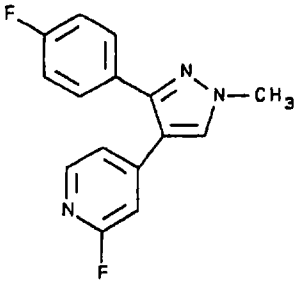
N-[(3-fluorophenyl)methyl]-4-[3-(4-fluorophenyl)-1H-pyraz ol-4-yl]- 2-pyridinamine

**Example A-255**



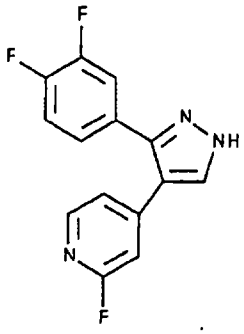
4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-(1-methylhydrazino)pyridine

**Example A-256**



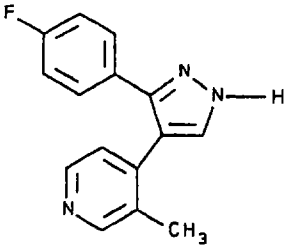
2-fluoro-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-257**



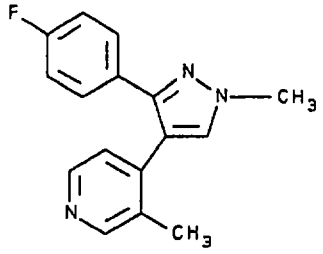
4-[3-(3,4-difluorophenyl)-1H-pyrazol-4-yl]-2-fluoropyridine

**Example A-258**



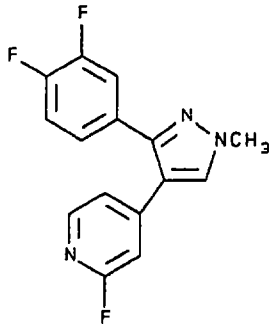
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-3-methylpyridine

**Example A-259**



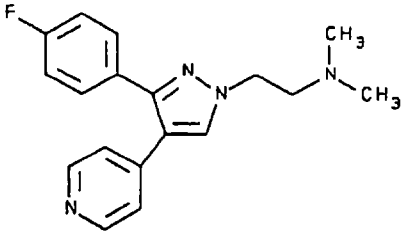
4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-3-methylpyridine

**Example A-260**



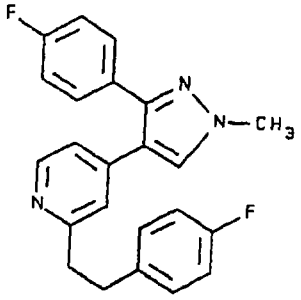
4-[3-(3,4-difluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-fluoropyridine

**Example A-261**



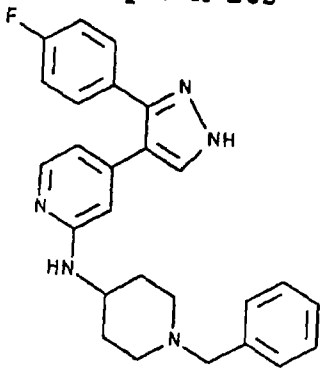
3-(4-fluorophenyl)-N,N-dimethyl-4-(4-pyridinyl)-1H-pyrazole-1-ethanamine

**Example A-262**



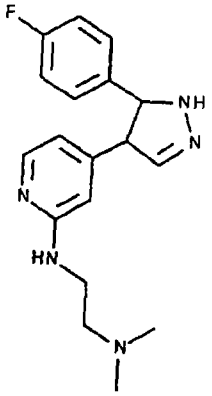
2-[2-(4-fluorophenyl)ethyl]-4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]pyridine

**Example A-263**



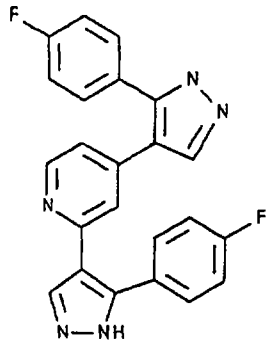
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[1-(phenylmethyl)-4-piperidinyl]-2-pyridinamine

**Example A-264**



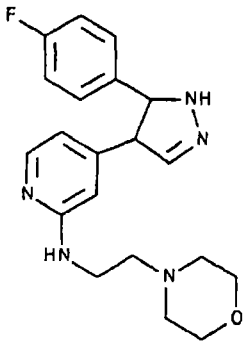
N'-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-N,N-dimethyl-1,2-ethanediamine

**Example A-265**



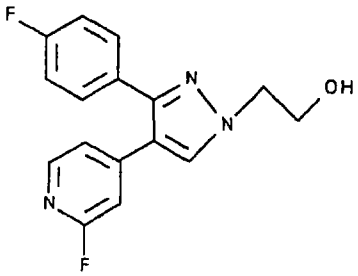
2,4-bis[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyridine

**Example A-266**



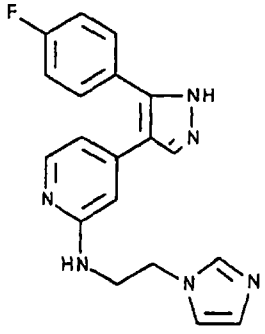
N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-4-morpholineethanamine

**Example A-267**



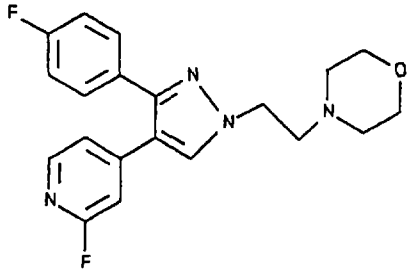
3-(4-fluorophenyl)-4-(2-fluoro-4-pyridinyl)-1H-pyrazole-1-ethanol

**Example A-268**



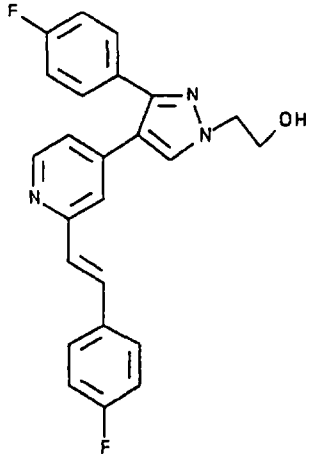
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[2-(1H-imidazol-1-yl)ethyl]-2-pyridinamine

**Example A-269**



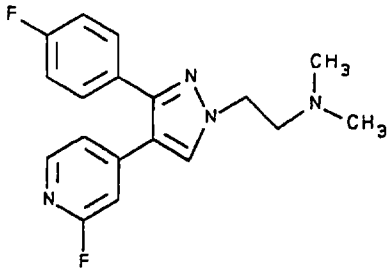
4-[2-[3-(4-fluorophenyl)-4-(2-fluoro-4-pyridinyl)-1H-pyrazol-1-yl]ethyl]morpholine

**Example A-270**



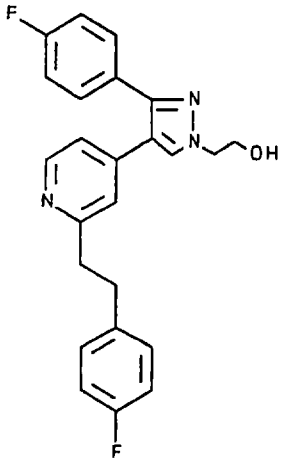
(E)-3-(4-fluorophenyl)-4-[2-[2-(4-fluorophenyl)ethenyl]-4-pyridinyl]-1H-pyrazole-1-ethanol

**Example A-271**



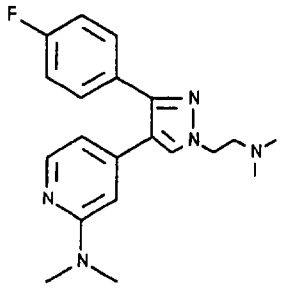
3-(4-fluorophenyl)-4-(2-fluoro-4-pyridinyl)-N,N-dimethyl-1H-pyrazole-1-ethanamine

**Example A-272**



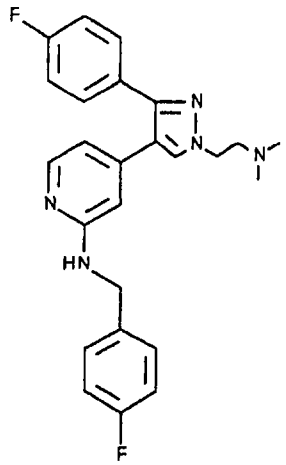
3-(4-fluorophenyl)-4-[2-[2-(4-fluorophenyl)ethyl]-4-pyridinyl]-1H-pyrazole-1-ethanol

**Example A-273**



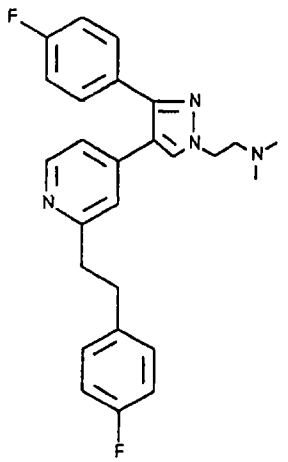
4-[1-[2-(dimethylamino)ethyl]-3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyridinamine

**Example A-274**



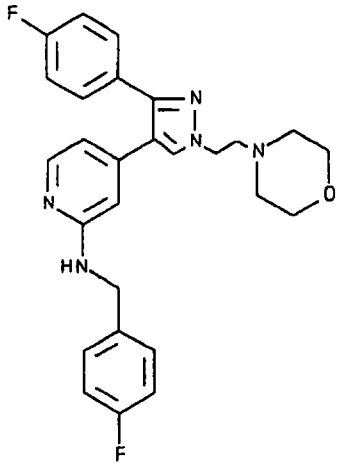
4-[1-[2-(dimethylamino)ethyl]-3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-fluorophenyl)methyl]-2-pyridinamine

**Example A-275**



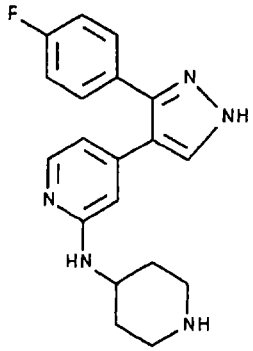
3-(4-fluorophenyl)-4-[2-[2-(4-fluorophenyl)ethyl]-4-pyridinyl]-N,N-dimethyl-1H-pyrazole-1-ethanamine

**Example A-276**



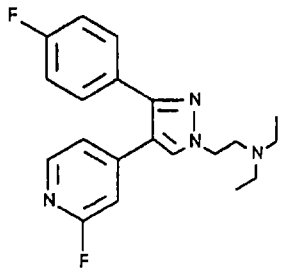
N-[(4-fluorophenyl)methyl]-4-[3(or 5)-(4-fluorophenyl)-1-[[2-(4-morpholinyl)ethyl]-1H-pyrazol-4-yl]-2-pyridinamine

**Example A-277**



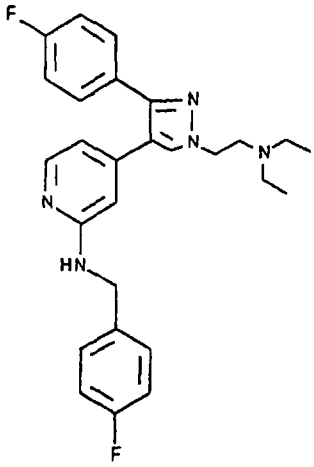
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-4-piperadinyl-2-pyridinamine

**Example A-278**



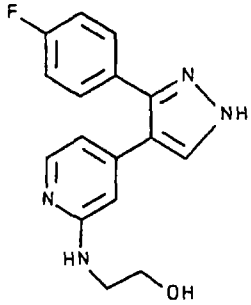
N,N-diethyl-3-(4-fluorophenyl)-4-(2-fluoro-4-pyridinyl)-1H-pyrazole-1-ethanamine

**Example A-279**



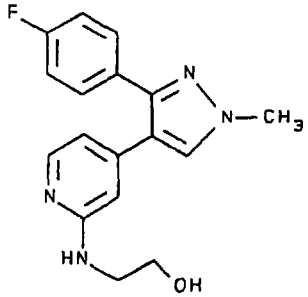
4-[1-[2-(diethylamino)ethyl]-3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-fluorophenyl)methyl]-2-pyridinamine

**Example A-280**



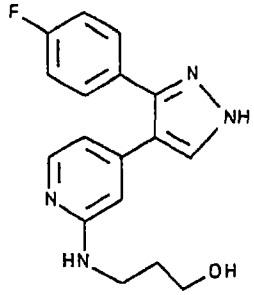
2-[[4-[3-(4-(fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethanol

**Example A-281**



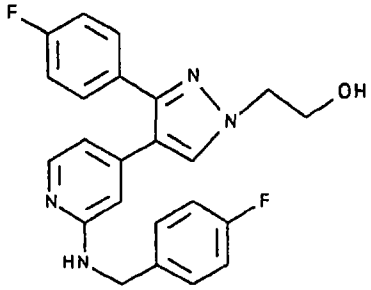
2-[[4-[3-(4-fluorophenyl)-1-methyl-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethanol

**Example A-282**



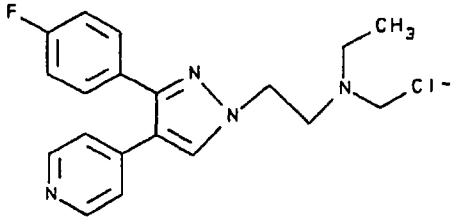
3-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1-propanol

**Example A-283**



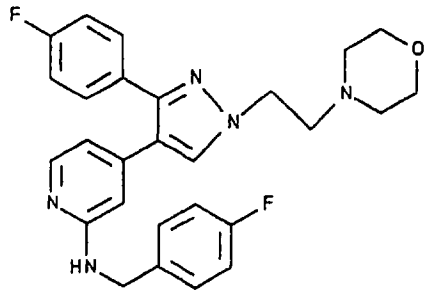
3 (or 5)-(4-fluorophenyl)-4-[2-[[(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol

**Example A-284**



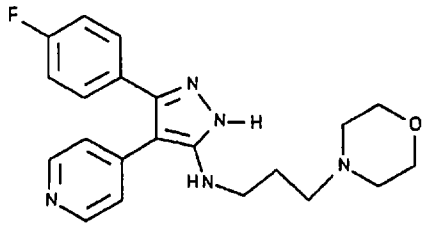
N,N-diethyl-3-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanamine

**Example A-285**



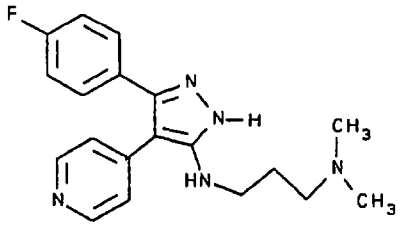
N-[(4-fluorophenyl)methyl]-4-[3-(4-fluorophenyl)-1-[2-(4-morpholinyl)ethyl]-1H-pyrazol-4-yl]-2-pyridinamine

**Example A-286**



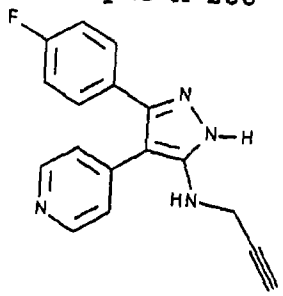
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-morpholinepropanamine

**Example A-287**



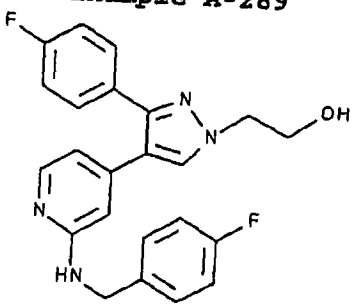
N'-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-dimethyl-1,3-propanediamine

**Example A-288**



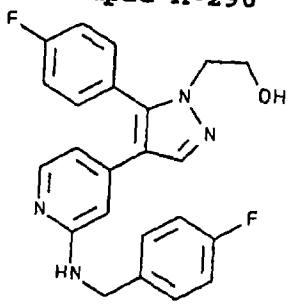
5-(4-fluorophenyl)-N-2-propynyl-4-(4-pyridinyl)-1H-pyrazol-3-amine

**Example A-289**



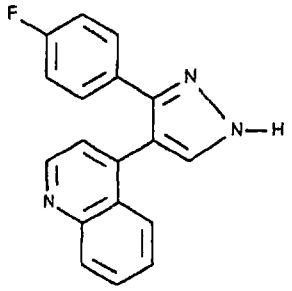
3-(4-fluorophenyl)-4-[2-[[(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol

**Example A-290**



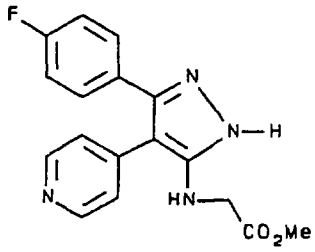
5-(4-fluorophenyl)-4-[2-[[(4-fluorophenyl)methyl]amino]-4-pyridinyl]-1H-pyrazole-1-ethanol

**Example A-291**



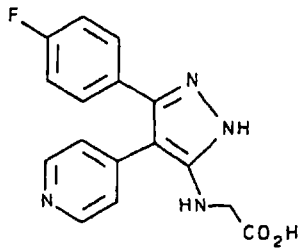
4-[3-[(4-fluorophenyl)-1H-pyrazol-4-yl]quinoline

**Example A-292**



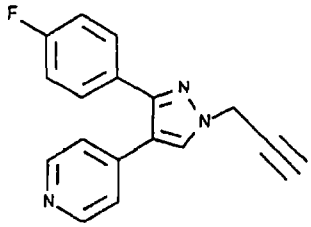
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]glycine methyl ester

**Example A-293**



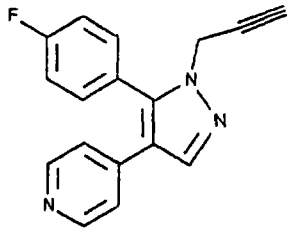
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]glycine

**Example A-294**



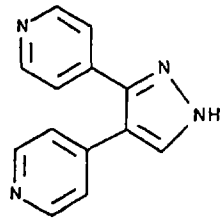
4-[3-(4-fluorophenyl)-1-(2-propynyl)-1H-pyrazol-4-yl]pyridine

**Example A-295**



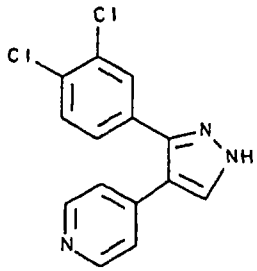
4-[5-(4-fluorophenyl)-1-(2-propynyl)-1H-pyrazol-4-yl]pyridine

**Example A-296**



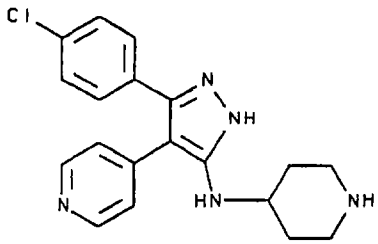
4,4'-(1H-pyrazole-3,4-diyl)bis[pyridine]

**Example A-297**



4-[3-(3,4-dichlorophenyl)-1H-pyrazol-4-yl]pyridine

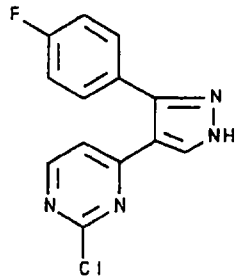
**Example A-298**



N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinamine

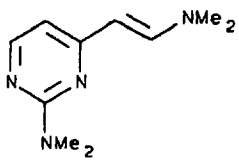
The pyrimidine-substituted compounds of Examples A-299 through A-312 were synthesized in accordance with the chemistry described in Schemes I-XVIII by selection of the corresponding starting reagents:

**Example A-299**



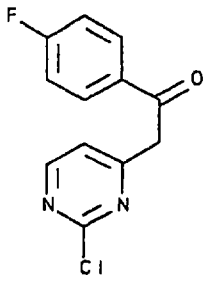

2-Chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine

Step 1:




A mixture of 2,6-dichloro-4-methylpyrimidine (5.0 g, 0.031 mol), triethylamine (6.23 g, 0.062 mol) and catalytic amount of 5% Pd/C in 100 mL of THF was hydrogenated on a Parr apparatus under 40 psi at room temperature. After 0.5 hour, the catalyst was filtered and the filtrate was concentrated. The crude was purified by chromatography on silica gel (ethyl acetate/hexane, 3:7) to give 2.36 g of product as a pale yellow crystal (50% yield); mp: 47-49 °C.

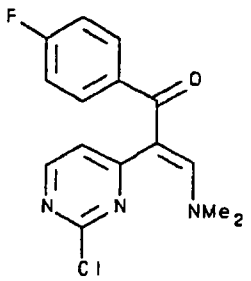
Step 2: Preparation of 2-(2-chloro-4-pyrimidinyl)-1-(4-fluorophenyl)ethanone




2-(2-chloro-4-pyrimidinyl)-1-(4-fluorophenyl)ethanone

To a solution of lithium diisopropylamide (generated from BuLi (0.045 mol) and diisopropylamine (0.048 mol) in THF) at -78 °C was added a solution of the compound prepared in step 1 (5.5 g, 0.037 mol) in THF slowly over 30 minutes. After 1 hour, a solution of ethyl 4-fluorobenzoate (7.62 g, 0,045 mol) in THF was added and the reaction mixture was stirred overnight and allowed to warm up to room temperature. Water was added and the aqueous phase was extracted with ethyl acetate. Organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product purified by chromatography on silica gel (ethyl acetate/hexane, 3:7) to give 4.78 g of a yellow solid (51% yield), mp: 112-113 °C.

Step 3: Preparation of (E)-2-(2-chloro-4-pyrimidinyl)-3-(dimethylamino)-1-(4-fluorophenyl)-2-propen-1-one



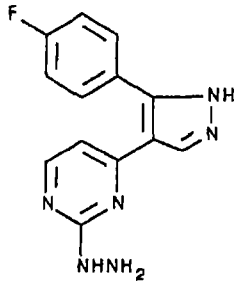
(E)-2-(2-chloro-4-pyrimidinyl)-3-(dimethylamino)-1-(4-fluorophenyl)-2-propen-1-one

A mixture of the compound prepared in step 2 (4.7 g, 0.017 mol) in 100 mL of dimethylformamide dimethyl acetal was stirred at room temperature overnight. Excess dimethylformamide dimethyl acetal was removed under vacuum to give 4.5 g of crude product as a thick brown oil, which was used without further purification.

Step 4: Preparation of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine

A solution of the compound prepared in step 3 (4.4 g) and hydrazine hydrate (0.82 g, 0.014 mol) was stirred at room temperature for 6 hours. The yellow precipitate was collected by filtration and air-dried to give 1.85 g of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine as a yellow solid, mp: 204-205 °C; Anal. Calc'd for $C_{13}H_8ClFN_4$: C, 56.84; H, 2.94; N, 20.40; Cl, 12.91. Found: C, 56.43; H, 2.76; N, 20.02; Cl, 12.97.

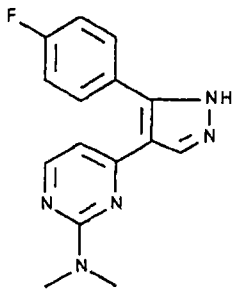
**Example A-300**



4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2(1H)-pyrimidinone hydrazone

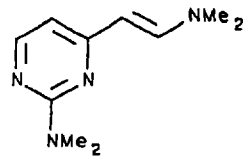
A solution of the compound prepared in step 3 of Example A-299 (1.5 g) and hydrazine hydrate (5mL) in ethanol was heated at reflux overnight. After the reaction mixture was cooled, the solvent was removed. The residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product was purified by recrystallization from ethyl acetate and hexane to give 0.5 g of product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2(1H)-pyrimidinone hydrazone, as a pale yellow solid (38% yield), mp: 149-150 °C; Anal. Calc'd for $C_{13}H_{11}FN_6$: C, 57.77; H, 4.10; N, 31.10. Found: C, 57.70; H, 4.31; N, 30.73.

**Example A-301**



4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyrimidinamine

Step 1: Preparation of



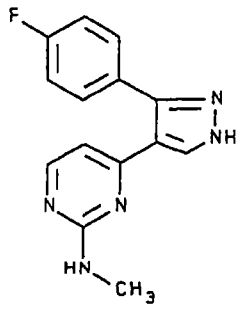
A solution of the compound prepared in step 2 of Example A-299 (3.0 g, 0.02 mol) and *tert*-butylbis(dimethylamino)methane (10.45 g, 0.06 mol) in 40 mL of DMF was stirred at 110 °C overnight. After the solvent was removed under vacuum, water was added and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by recrystallization from ethyl acetate and hexane to give 1.23 g of a yellow solid product (32% yield), mp: 76-77 °C; Anal. Calc'd for $C_{10}H_{16}N_4$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.19; H, 8.58; N, 29.02.

Step 2: Preparation of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyrimidinamine

To a solution of the compound prepared in step 1 of the present Example (1.2 g, 0.0064 mol) and triethylamine (0.65 g, 0.0064 mol) in 10 mL of toluene was added 4-fluorobenzoyl chloride dropwise. The mixture was heated at reflux for 10 hours and the solvent was removed. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude (1.6 g) was then dissolved in 50 mL of ethanol. The solution was treated with hydrazine hydrate (0.36 g, 0.006 mol) and the mixture was heated at reflux for 2 hours. After ethanol was removed, the residue was partitioned between water and ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and filtered. The filtrate was

concentrated and the crude was purified by chromatography on silica gel (ethyl acetate/hexane, 1:1) to give 0.6 g of product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N,N-dimethyl-2-pyrimidinamine, as a yellow solid (33% yield), mp: 155-156 °C; Anal. Calc'd for $C_{15}H_{14}FN_5$: C, 63.59; H, 4.98; N, 24.72. Found: C, 63.32; H, 4.92; N, 24.31.

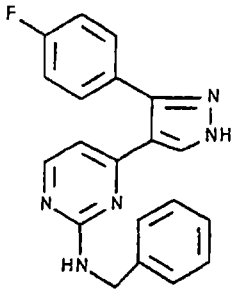
**Example A-302**



4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-methyl-2-pyrimidinamine

A suspension of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine prepared in accordance with Example A-299 (0.3 g, 0.0011 mol) in 10 mL of methylamine (40% water solution) was heated in a sealed tube at 100 °C overnight. The mixture was then cooled to room temperature and the precipitate was filtered, air-dried to give 0.2 g of product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-methyl-2-pyrimidinamine, as a white solid (68% yield), mp: 217-218 °C; Anal Calc'd for $C_{14}H_{12}FN_5$: C, 62.45; H, 4.49; N, 26.01. Found: C, 62.58; H, 4.36; N, 25.90.

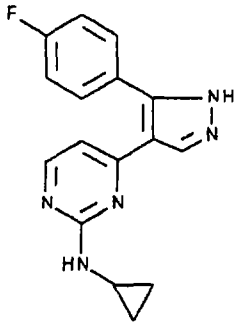
**Example A-303**



4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-2-pyrimidinamine

This compound was synthesize by refluxing 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine prepared in accordance with Example A-299 in benzylamine overnight. The product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-2-pyrimidinamine, was obtained as a white solid in 95% yield; mp: 216-217 °C; Anal. Calc'd for $C_{20}H_{16}FN_5$: C, 69.55; H, 4.67; N, 20.28. Found: C, 69.73; H, 4.69; N, 19.90.

**Example A-304**

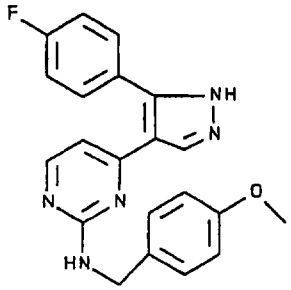


N-cyclopropyl-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine

This compound was synthesized by stirring 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine prepared in accordance with Example A-299 with excess cyclopropylamine in methanol at 50 °C for 12 hours. The

product, N-cyclopropyl-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine, was obtained as a white solid in 26% yield, mp: 203-204 °C; Anal. Calc'd for $C_{16}H_{14}FN_5$: C, 65.07; H, 4.78; N, 23.71. Found: C, 64.42; H, 4.82; N, 23.58.

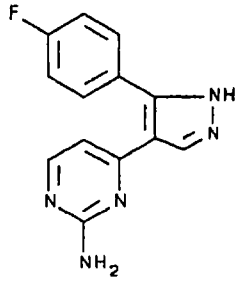
**Example A-305**



4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)methyl]-2-pyrimidinamine

This compound was synthesized by refluxing 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine prepared in accordance with Example A-299 in 4-methoxybenzylamine overnight. The product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)methyl]-2-pyrimidinamine, was obtained as a off-white solid in 80% yield, mp: 183-185 °C; Anal. Calc'd for $C_{21}H_{18}FN_5O$: C, 67.19; H, 4.83, N, 18.66. Found: C, 67.01; H, 5.11; N, 18.93.

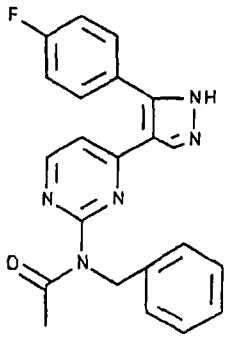
**Example A-306**



4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine

A solution of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[(4-methoxyphenyl)methyl]-2-pyrimidinamine prepared in accordance with Example A-305 (0.35 g, 0.00093 mol) in 15 mL of trifluoroacetic acid was heated at reflux for 16 hours. Solvent was removed and the residue was partitioned between ethyl acetate and 1 N ammonia hydroxide. Organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and purified by chromatography on silica gel (ethyl acetate) to give 0.14 g of product, 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine, as a pale yellow solid (59% yield), mp: 273-274 °C; Anal. Calc'd for $C_{13}H_{10}FN_5 \cdot 0.25\ H_2O$: C, 60.11; H, 4.07; N, 26.96. Found: C, 60.15; H, 3.82; N, 26.38.

**Example A-307**

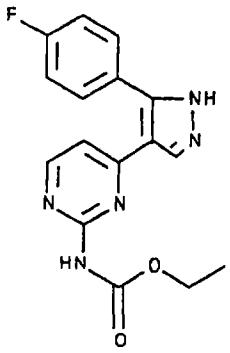



N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-N-(phenylmethyl)acetamide

To a mixture of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(phenylmethyl)-2-pyrimidinamine prepared in accordance with Example A-303 (0.15 g, 0.00043 mol), DMAP (0.027 g, 0.00022 mol) and acetic anhydride (0.066 g, 0.00066 mol) in 10 mL of THF was added triethylamine

(0.053 g, 0.00052 mol). The solution was stirred at room temperature overnight. After the removal of solvent, the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated $NaHCO_3$, washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product was triturated with ether to give 0.1 g of product, N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-N-(phenylmethyl)acetamide, as a white solid (60% yield), mp: 176-178 °C; Anal. Calc'd for $C_{22}H_{18}FN_5$: C, 68.21; H, 4.68; N, 18.08. Found: C, 67.67; H, 4.85; N, 17.79.

**Example A-308**

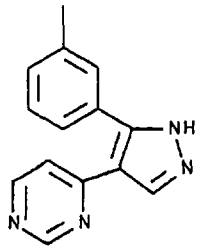



Ethyl [4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]carbamate

To a suspension of 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine prepared in accordance with Example A-306 (0.26 g, 0.001 mol) in 5 mL of pyridine was added ethyl chloroformate dropwise. After the addition, the clear solution was stirred at room temperature for 6 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude was trituated with ether to give 0.15 g of product, ethyl [4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-

pyrimidinyl]carbamate, as a white solid (46% yield), mp: 163-165 °C; Anal. Calc'd for $C_{16}H_{14}FN_5O_2$: C, 58.71; H, 4.31; N, 21.04. Found: C, 59.22; H, 4.51; N, 21.66.

**Example A-309**

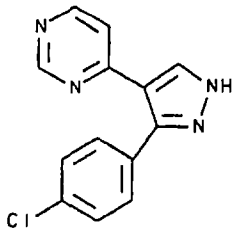


4-[3-(3-methylphenyl)-1H-pyrazol-4-yl]pyrimidine

This compound was prepared by the same procedure as described for Example A-208 except that 1-methyl-3-(4'-pyrimidinylacetyl) benzene (prepared as set forth in Step 1 of Example A-19 from 4-methyl-pyrimidine and methyl 3-methylbenzoate) was used in place of 4-fluorobenzoyl-4-pyridinyl methane.

Anal. Calc'd for $C_{14}H_{12}N_4$ (236.27): C, 71.17; H, 5.12; N, 23.71. Found C, 70.67; H, 5.26; N, 23.53. m.p. (DSC): 151.67 °C.

**Example A-310**



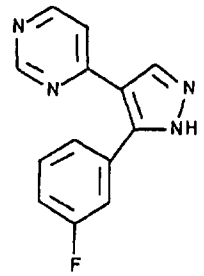
4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]pyrimidine

This compound was prepared according to the chemistry described in Schemes VI and IX by selection of the corresponding pyrimidine starting material in place

of the pyridine starting material.

Anal. Calc'd for $C_{13}H_9N_4Cl \bullet 0.25MH_2O$: C, 59.78; H, 3.67; N, 21.45. Found: C, 59.89; H, 3.32; N, 21.56. m.p. (DSC): 218.17 °C.

**Example A-311**

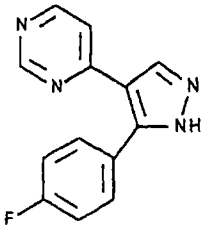


4-[3-(3-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine

This compound was prepared according to the chemistry described in Schemes VI and IX by selection of the corresponding pyrimidine starting material in place of the pyridine starting material.

Anal. Calc'd for $C_{13}H_9N_4F$ (240.24): C, 64.99; H, 3.78; N, 23.22. Found: C, 64.78; H, 3.75; N, 23.31. m.p. (DSC): 168.58 °C.

**Example A-312**



4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine

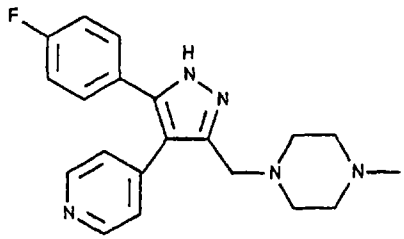
This compound was prepared according to the chemistry described in Schemes VI and IX by selection of

the corresponding pyrimidine starting material in place of the pyridine starting material.

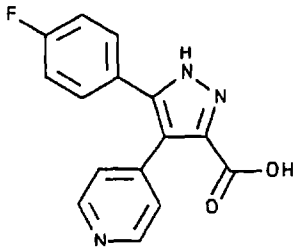
Anal. Calc'd for $C_{13}H_9N_4F$ (240.24): C, 64.99; H, 3.78; N, 23.32. Found: C, 64.94; H, 3.56; N, 23.44. m.p. (DSC): 191.47 °C.

**Example A-313**

The compound 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine was prepared in accordance with general synthetic Scheme VII:



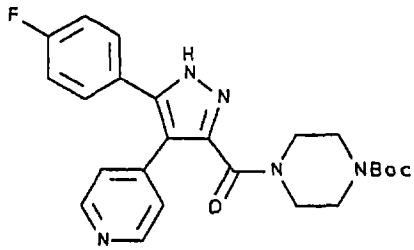
Step 1: Preparation of 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate



A mixture of 4-[3-(4-fluorophenyl)-5-methyl-1H-pyrazol-4-yl)pyridine (5.8 g, 24.0909 mmol; prepared as set forth in Example A-4) and potassium permanganate (7.6916 g, 48.1818 mmol) in water (7.5 mL) and *tert*-butanol (10 mL) was heated to reflux at 95 to 100 °C for 6 hours (or until all the potassium permanganate was consumed) and stirred at room temperature overnight. The mixture was diluted with water (150 mL) and filtered to remove manganese dioxide. The aqueous filtrate (pH >10) was extracted with ethyl acetate to remove unreacted starting material. The aqueous layer was acidified with 1N HCl to a pH of about 6.5. A white precipitate was formed. This precipitate was collected by filtration, dried in air, and then dried in a vacuum oven overnight at 50 °C to give 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate (2.7677 g, 40.6 %). The remaining product (0.21 g, 3.1%) was isolated from the

mother liquid by reverse phase chromotograhpy. The total isolated yield of 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate was 43.7 %. Anal. Calc'd for $C_{15}H_{10}N_3FO_2 \cdot H_2O$: C, 59.80; H, 4.01; N, 13.95; Found: C, 59.48; H, 3.26; N, 13.65. MS ($MH^+$): 284 (base peak).

Step 2: Preparation of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate




In a solution of 5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazole-3-carboxylic acid, monohydrate (0.9905 g, 3.5 mmol) from step 1 and 1-hydroxybenzotriazole hydrate (0.4824 g, 3.57 mmol) in dimethylformamide (20 mL) at 0 °C under $N_2$, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6983 g, 3.57 mmol) was added. The solution was stirred at 0 °C under $N_2$ for 1 hour, then was added 1-tert.-butoxycarbonylpiperazine (0.6585 g, 3.5 mmol) followed by N-methyl morpholine (0.40 mL, 3.6 mmol). The reaction was stirred from 0 °C to room temperature overnight. The reaction mixture was diluted with ethyl acetate and saturated $NaHCO_3$ solution, extracted. The organic layer was washed with water and brine, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and crude product was obtained (1.7595 g). The desired product 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate (1.2375 g, 78.4 %) was isolated by chromatography (silica gel, 10:90

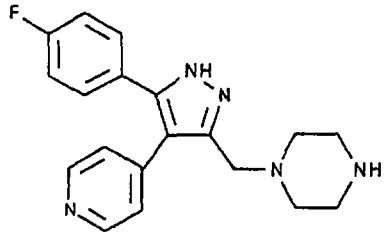
isopropyl alcohol/toluene). Anal. Calc'd for $C_{24}H_{26}N_5FO_3$: C, 63.85; H, 5.80; N, 15.51; Found: C, 63.75; H, 5.71; N, 15.16. MS ($MH^+$): 452(base peak).

Step 3: Preparation of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine

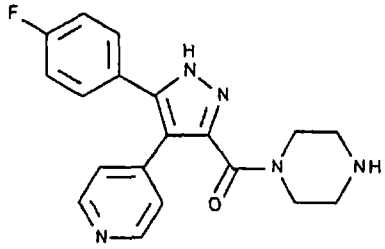
To a suspension of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate (0.451 g, 1.0 mL) in dry tetrahydrofuran (8 mL), 1.0N $LiAlH_4$ in tetrahydrofuran (2.5 mL, 2.5 mmol) was added dropwise at such a rate as to maintain reflux over 15 minutes. Upon the addition, the suspension became a clear light yellow solution, which was kept boiling for an additional 1.5 hours. Excess $LiAlH_4$ was decomposed by cautious addition of a solution of KOH (0.5611 g, 10.0mmol) in water (3.5 mL). Upon hydrolysis, a white salt precipitated. After the addition was completed, the mixture was heated to reflux for 1 hour. The hot solution was filtered by suction through a buchner funnel. Any remaining product was extracted from the precipitate by refluxing with tetrahydrofuran (10mL) for 1 hour, followed again by suction filtration. The combined filtrates were concentrated under reduced pressure to give a crude residue, which was then diluted with ethyl acetate and washed with water and brine. The organic layer was dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and a crude product was obtained. The desired product 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine (0.1509 g, 50.1 %) was obtained by chromatography (silica gel, 70:30:1 methanol/ethyl acetate/$NH_4OH$). Anal. Calc'd for $C_{20}H_{22}N_5F \cdot 0.6H_2O$: C, 66.32; H, 6.46; N, 19.33; Found: C, 66.31; H, 5.96; N, 18.83. MS ($MH^+$): 352 (base peak).

**Example A-314**

The compound 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-piperazine was prepared in accordance with general synthetic Scheme VII:



Step 1: Preparation of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine, monhydrate



A solution of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate (0.6349 g; 1.4077 mmol; prepared as set forth in step 2 of Example A-313) in methylene chloride (3.5 mL) and TFA (1.1 mL, 14.077 mmol) was stirred at room temperature under $N_2$ for 2 hours. The solvents were removed under reduced pressure,. and TFA was chased by methylene chloride and methanol. The resulting colorless oily residue was triturated with methanol. The resulting solid was collected by filtration and dried in a vacuum oven overnight to give the desired product 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine, monohydrate (0.7860 g, 96.4%). Anal. Calc'd for $C_{19}H_{18}N_5OF \cdot 2TFA \cdot H_2O$: C, 46.24; H, 3.71; N, 11.72; Found: C, 45.87; H, 3.43; N, 11.45. MS ($MH^+$): 352

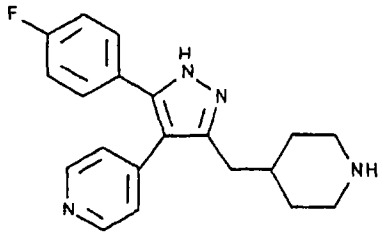
(base peak).

Step 2: Preparation of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-piperazine

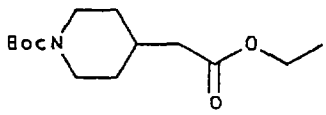
By following the method of Example A-313, step 3 and substituting of 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine, monohydrate (prepared in step 1 of this Example) for 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate, the title product 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-piperazine was obtained. Anal. Calc'd for $C_{19}H_{20}N_5F.0.75H_2O$: C, 65.03, H, 6.18, N,19.96. Found: C, 65.47, H, 5.83, N,19.35. MS ($MH^+$): 338 (base peak).

**Example A-315**

The compound 4-[3-(4-fluorophenyl)-5-(4-piperidinylmethyl)-1H-pyrazol-4-yl]pyridine was prepared in accordance with general synthetic Scheme XX:

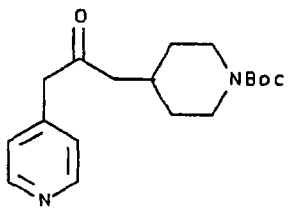



Step 1: Preparation of ethyl 1-[(1,1-dimethylethoxy)carbonyl]-4-piperidineacetate



Ethyl 4-pyridyl acetate was converted to 2-(4-piperidinyl) ethyl acetate hydrochloride by hydrogenation (60 psi $H_2$) catalyzed by 5% Pt/C at 40 °C in ethanol and HCl solution. To a solution of 2-(4-piperidinyl)ethyl acetate hydrochloride (21.79g, 0.105mol) in tetrahydrofuran (500 mL) at 0 °C, triethylamine (32.06 mL, 0.230 mL) was added followed by di-tert-butyldicarbonate (23.21g, 0.105mol). The reaction mixture was stirred under $N_2$ from 0 °C to room temperature overnight. After removing tetrahydrofuran, the reaction mixture was diluted with ethanol, washed with saturated $NaHCO_3$, 10 % citric acid, water and brine, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The resulting oily product was dried under vacuum to give ethyl 1-[(1,1-dimethylethoxy)carbonyl]-4-piperidineacetate (27.37 g, 95.9 %). The structure of this product was confirmed by NMR.

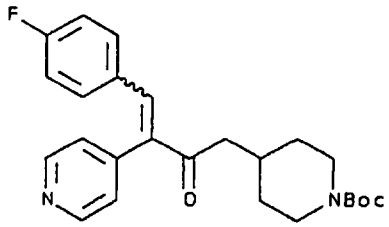
Step 2: Preparation of 1,1-dimethylethyl 4-[2-oxo-3-(4-pyridinyl)propyl]-1-piperidinecarboxylate




To a solution of diisopropylamide (6.15 mL, 43.91 mmol) in dry tetrahydrofuran (40 mL) at 0 °C was added 2.5 M butyl lithium solution in hexane (16.22 mL, 40.53 mmol) dropwise over 10 minutes. After the addition, the lithium diisopropylamide solution was stirred at 0 °C for 20 minutes, then cooled to -78 °C. 4-Picoline (3.98 mL, 40.53 mmol) was added to the above lithium diisopropylamide solution under $N_2$ dropwise over 10 minutes. The resulting solution was stirred at -78 °C under $N_2$ for 1.5 hours, then transfered into a suspension

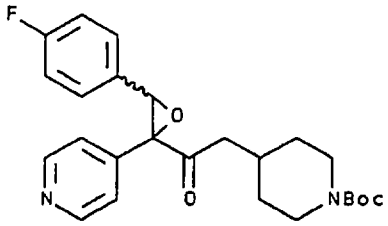
of anhydrous cerium chloride (10.0 g, 40.53 mmol) in tetrahydrofuran (40 mL) at -78 °C under $N_2$. The mixture was stirred at -78 °C under $N_2$ for 2 hours, then a solution of ethyl 1-[(1,1-dimethylethoxy)carbonyl]-4-piperidineacetate (from step 1 of this Example) (10.98 g, 40.53 mmol) in tetrahydrofuran (40 mL) was added slowly for 1 hour. The mixture was stirred under $N_2$ from -78 °C to room temperature overnight. The reaction was quenched with water, diluted with ethyl acetate, and washed with a pH 7 buffer. The organic layer was washed with water and brine. After filtration, the solvent was removed under reduced pressure to give a crude product mixture. The desired product 1,1-dimethylethyl 4-[2-oxo-3-(4-pyridinyl)propyl]-1-piperidinecarboxylate (3.19 g, 25%) was isolated by chromatography (silica gel, 50:50 - 75:25- 100:0 ethyl acetate/hexane).

Step 3: Preparation of 1,1-dimethylethyl 4-[4-(4-fluorophenyl)-2-oxo-3-(4-pyridinyl)-3-butenyl]-1-piperidinecarboxylate



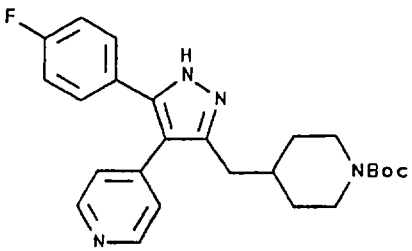

1,1-Dimethylethyl 4-[4-(4-fluorophenyl)-2-oxo-3-(4-pyridinyl)-3-butenyl]-1-piperidinecarboxylate was prepared by the same method as described for step 1 of Example A-1 by replacing 4-pyridylacetone and 3-fluoro-p-anisaldehyde with the ketone of step 2 of the present Example and 4-fluorobenzaldehyde, respectively.

Step 4: Preparation of 1,1-dimethylethyl 4-[2-[3-(4-fluorophenyl)-2-(4-pyridinyl)oxiranyl]-2-oxoethyl]-1-piperidinecarboxylate




1,1-Dimethylethyl 4-[2-[3-(4-fluorophenyl)-2-(4-pyridinyl)oxiranyl]-2-oxoethyl]-1-piperidinecarboxylate was prepared by the same method as described for step 3 of Example A-2 by replacing 4-phenyl-3-(4-pyridyl)-3-butene-2-one with the $\alpha,\beta$ unsaturated ketone of step 3 of the present Example.

Step 5: Preparation of 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-1-piperidinecarboxylate



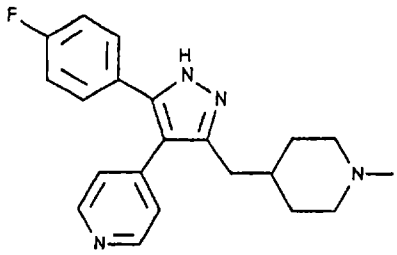

To a solution of 1,1-dimethylethyl 4-[2-[3-(4-fluorophenyl)-2-(4-pyridinyl)oxiranyl]-2-oxoethyl]-1-piperidinecarboxylate prepared in step 4 of this Example (3.45 g, 7.8409 mmol) in ethanol (15 mL), anhydrous hydrazine (0.50 mL, 15.6818 mmol) was added. The reaction was heated to reflux overnight. The reaction solution was cooled to room temperature and ethanol was removed under reduced pressure. The resulting residue was taken into ethyl acetate, washed with water and brine, and dried over $MgSO_4$. After filtration the solvent

was removed under reduced pressure. The crude residue was purified by chromatography (silica gel, 2:1 - 1:1 - 1:2 hexane/ethyl acetate) to give 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4,5-dihydro-4-hydroxy-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-1-piperidinecarboxylate (1.9187 g, 53.9%). This intermediate (1.8611 g, 4.0993 mmol) was dissolved in dry methylene chloride (40 mL) and treated with Martin sulfurane dehydrating reagent (4.13 g, 6.1490 mmol). The reaction solution was stirred at room temperature under $N_2$ overnight, then diluted with ethyl acetate, washed with 1N sodium hydroxide solution, water and brine, dried over $MgSO_4$. After filtration the solvents were removed. The resulting crude pruduct mixture was purified by flash chromatoghaphy (silica gel, 2:1 - 1:1 - 1:2 Hexane/ethyl acetate) to give 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-1-piperidinecarboxylate (0.6964 g, 39 %).

Step 6: Preparation of 4-[3-(4-fluorophenyl)-5-(4-piperidinylmethyl)-1H-pyrazol-4-yl]pyridine

4-[3-(4-Fluorophenyl)-5-(4-piperidinylmethyl)-1H-pyrazol-4-yl]pyridine was prepared using the same method as described for Example A-314, step 1 by replacing 1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]piperazine, monohydrate with the pyrazole of step 5 of the present Example. Anal. Calc'd for $C_{20}H_{21}N_4F \cdot 2TFA \cdot 1.25H_2O$: C, 49.11; H, 4.38; N, 9.54; Found: C, 48.74; H, 4.02; N, 9.57. MS ($MH^+$): 337 (base peak).

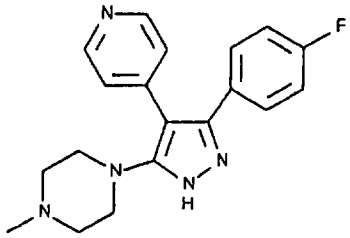
**Example A-316**



4-[3-(4-fluorophenyl)-5-[(1-methyl-4-piperidinyl)methyl]-1H-pyrazol-4-yl]pyridine was prepared by the same method as described for step 3 of Example A-313 by replacing 1,1-dimethylethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]carbonyl]-1-piperazinecarboxylate with the pyrazole of step 5 of the present Example. Anal. Calc'd for $C_{21}H_{23}N_4F \cdot 0.2\ H_2O$: C, 71.24; H, 6.66; N, 15.82; Found: C, 71.04; H, 6.54; N, 15.56. MS ($MH^+$): 351 (base peak).

**Example A-317**

The compound 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate was prepared in accordance with general synthetic Scheme II:

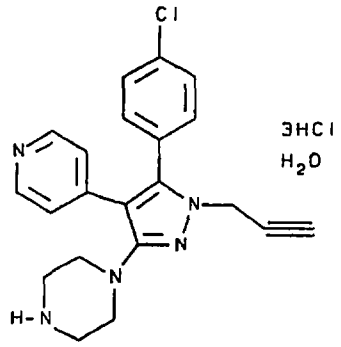


2-(4-Pyridyl)-1-(4-fluorophenyl)ethanone hydrochloride (5.9g, 0.023 moles) was dissolved in a methylene chloride/methanol solution (70/15) at room temperature and N-chlorosuccinimide (3.25g, 0.024 moles) was added as a solid. The mixture was stirred at room temperature for 2.5 hours. N-methylpiperazinylthiosemicarbazide (4.1g, 0.023 moles) was added as a solid and the mixture was stirred for 3

days at room temperature. The mixture was diluted with 100 mL of methylene chloride and washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and solvent removed using a rotary evaporator. The residue was treated with ethyl acetate with stirring while cooling in an ice bath. The solid formed was filtered and recrystallized from ethyl acetate with a small amount of methanol to give 1.7g (22%) of 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate. Anal. Calc'd. for $C_{19}H_{20}FN_5 \cdot 2H_2O$: C, 61.11; H, 6.48; N, 18.75. Found: C, 60.59; H, 6.41; N, 18.44. M.p. (DSC) 262-264 °C; MH+ = 338.

**Example A-318**

The compound 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1-(2-propynyl)-1H-pyrazol-3-yl]piperazine, trihydrochloride monohydrate was prepared in accordance with general synthetic Scheme VII:



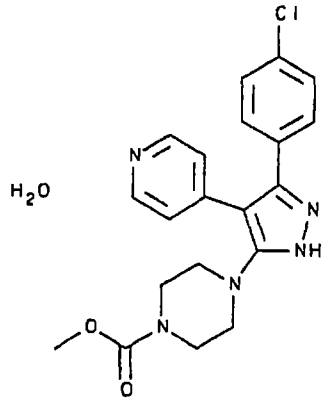

To a mixture of sodium hydride (30 mg, 1.5 mmol) in dimethylformamide (25 mL) stirred under a nitrogen atmosphere at room temperature was added 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-N-tert.-butoxycarbonylpiperazinyl)pyrazole (500 mg, 1.1 mmol; prepared as set forth in Example A-169). After stirring for 1 hour, propargyl bromide (225 mg, 1.5 mmol, 80% solution in toluene) was added. After stirring for an

additional 2 hour at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using 70% ethyl acetate/hexane as the eluent to give 110 mg of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-N-tert.-butoxycarbonyl-piperazinyl)pyrazole (24%), m. p. 204-205 °C. Anal. Calc'd. for $C_{26}H_{28}ClN_5O_2$: C, 65.33; H, 5.90; N, 14.65. Found: C, 65.12; H, 5.81; N, 14.70.

A solution of HCl in methanol (5 mL) was generated by addition of acetyl chloride (200 mg) to methanol while cooling (5 °C). 3-(4-Chlorophenyl)-4-(4-pyridyl)-5-(4-N-tert.-butoxycarbonylpiperazinyl)pyrazole (100 mg, 0.2 mmol) prepared above was added and the reaction stirred in the cold for one hour. The reaction mixture was concentrated in vacuo and the residue azeotroped with toluene to give 100 mg of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1-(2-propynyl)-1H-pyrazol-3-yl]piperazine, trihydrochloride monohydrate (90%), m.p.=231-233 °C (dec.). Anal. Calc'd. for $C_{21}H_{20}N_5Cl \cdot 3HCl \cdot H_2O$: C, 49.92; H, 4.99; N, 13.86. Found: C, 49.71; H, 4.89; N, 13.61.

**Example A-319**

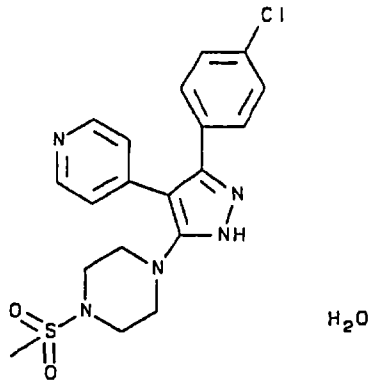
The compound methyl 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate, monohydrate was prepared in accordance with general synthetic Scheme II:



Methyl chloroformate (55 mg) was added to a solution of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-piperazinyl) pyrazole (200 mg, 0.54 mmol; prepared as set forth in Example A-169) and 4-dimethylaminopyridine (5 mg) in pyridine (10 mL). The mixture was stirred at room temperature for 3 hours. Additional methyl chloroformate (30 mg) was added and stirring was continued for 24 hours. The solvent was removed in vacuo. The residue was treated with water and extracted with ethyl acetate. After drying the organic layer ($MgSO_4$), the solvent was blown down to a volume of 10 mL and refrigerated. The resultant crystalline solid was filtered and air dried to give 103 mg (48%) of methyl 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate, monohydrate, mp 264-265 °C. Anal. Calc'd. for $C_{20}H_{20}ClN_5O_2 \cdot H_2O$: C, 57.76; H, 5.33; N, 16.84. Found: C, 57.98; H, 4.89; N, 16.44.

**Example A-320**

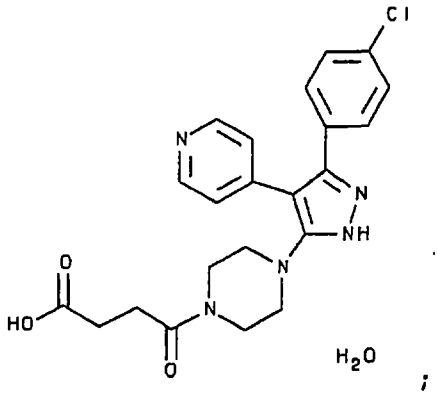
The compound 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(methylsulfonyl)piperazine, monohydrate was prepared in accordance with general synthetic Scheme II:



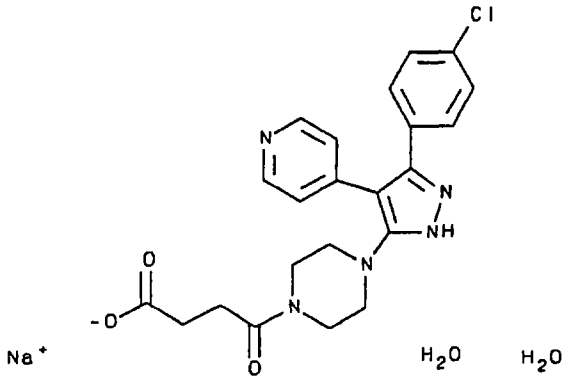
A solution of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-piperazinyl)pyrazole (200 mg; 0.54 mmol; prepared as set forth in Example A-169), methanesulfonyl chloride (75 mg) and 4-dimethylaminopyridine (5 mg) in pyridine was stirred at room temperature for 3 hours. The solvent was removed in vacuo and the residue was treated with water. The resultant crystalline solid was filtered, air dried and recrystallized from methanol and water to give 118 mg (37%) of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(methylsulfonyl)piperazine, monohydrate, m.p. 245-248 °C. Anal. Calc'd. for $C_{19}H_{20}ClN_5SO_2 \cdot H_2O$: C, 52.35; H, 5.09; N, 16.07. Found: C, 52.18; H, 5.31; N, 16.00.

**Example A-321**

The compounds 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, dihydrate, and 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, monosodium salt dihydrate, were prepared in accordance with general synthetic Scheme II:



and



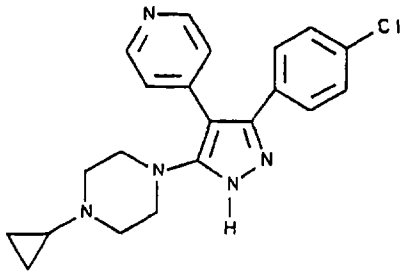
A solution of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-piperzinyl)pyrazole (200 mg; 0.54 mmol; prepared as set forth in Example A-169), succinic anhydride (60 mg, 0.55 mmol) and 4-dimethylaminopyridine (5 mg) was stirred at room temperature for 24 hours. The solvent was removed in vacuo and the residue treated with methanol and water (1:1). The resultant crystalline solid was filtered and air dried to give 170 mg (58%) of 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, dihydrate, m. p. 281-283 °C (dec.). Anal. Calc'd. for $C_{22}H_{22}ClN_5O_3 \cdot 2H_2O$: C, 55.52; H, 5.51; N, 14.72. Found: C, 55.11; H, 5.20; N, 14.44.

A slurry of 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, dihydrate (150 mg, 0.31 mmol) from above in methanol (10 mL) was treated with a solution of sodium hydroxide (12

mg, 0.31 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 15 minutes until dissolution was completed. The solvent was removed in vacuo. The residue was treated with tetrahydrofuran and filtered and air dried to give 150 mg (97%) of 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-γ-oxo-1-piperazinebutanoic acid, monosodium salt dihydrate as a solid. Anal. Calc'd. for $C_{22}H_{21}ClN_5O_3Na \cdot 2H_2O$: C, 53.07; H, 5.06; N, 14.07. Found: C, 52.81; H, 5.11; N, 13.90.

**Example A-322**

The compound 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl)-4-cyclopropylpiperazine was prepared in accordance with general synthetic Scheme II:

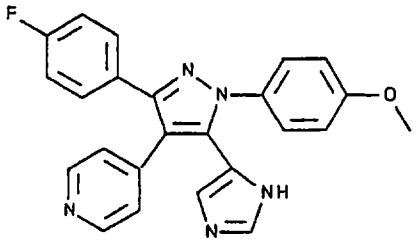



To a solution of 3-(4-chlorophenyl)-4-(4-pyridyl)-5-(4-piperazinyl)pyrazole (1.95g; 5.8 mmoles; prepared as set forth in Example A-169) and acetic acid (3.6 g, 60 mmol) containing 5A molecular sieves (6 g) was added [(1-ethoxycyclopropyl)oxy]trimethylsilane (6 g, 35 mmol). After stirring for 5 minutes, sodium cyanoborohydride (1.7 g, 26 mmol) was added and the mixture was refluxed under a nitrogen atmosphere for 6 hours. The reaction mixture was filtered hot and the filtrate concentrated in vacuo. Water (50 mL) was added and the solution made basic with 2N sodium hydroxide. The resultant gel was extracted with dichloroethane and the combined organic extracts dried ($MgSO_4$). Evaporation again yielded a gel which was treated with hot methanol. Upon cooling, the product crystallized to give 1.4 g (63%) of 1-[5-(4-

chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl)-4-cyclopropylpiperazine, m. p. 264-265 °C. Anal. Calc'd. for $C_{21}H_{22}ClN_5 \cdot 1.5\ H_2O$: C, 61.99; H, 6.19; N, 17.21. Found: C, 62.05; H, 5.81; N, 16.81.

**Example A-323**

The compound 4-[3-(4-fluorophenyl)-5-(1H-imidazol-4-yl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]pyridine was prepared in accordance with general synthetic Scheme V:



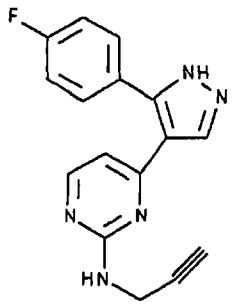

To a suspension of sodium hydride (1.0 g, 0.025 mol) in 50 mL of dimethylformamide was added methyl 4-imidazolecarboxylate (2.95 g, 0.023 mol) portionwise at room temperature. The mixture was stirred at room temperature for 0.5 hour. Then 2-(trimethylsilyl)ethoxymethyl chloride (4.17 g, 0.025 mol) was added dropwise over 5 minutes. The reaction mixture was stirred for 4 hours and quenched by cautiously adding water. The aqueous phase was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude was purified by chromatography on silica gel using ethyl acetate/hexane (8:2) as the eluent to give 4.0 g of the major regioisomer as a clear oil.

To a solution of 4-fluorobenzoyl-4'-pyridyl methane (8.6 g, 0.04 mol, prepared as set forth in Step 1 of Example A-208) in 150 mL of ethanol was added p-methoxyphenylhydrazine hydrochloride (7.34 g, 0.042 mol), followed by triethylamine (4.05 g, 0.04 mol). The reaction mixture was refluxed for 16 hours. After the

removal of solvent, 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 and the crude residue was purified by recrystallization from ethyl acetate and hexane to give 8.45 g of the product hydrazone as a yellow solid. To a solution of sodium hexamethyldisilazide (9 mL of 1.0 M tetrahydrofuran solution, 0.009 mol) was added a solution of this hydrazone (1.35 g, 0.004 mol) in 10 mL of dry tetrahydrofuran at 0 °C. After stirring for 30 minutes at this temperature, a solution of the regioisomer prepared above (1.1 g, 0.0042 mol) in 5 mL of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred for 3 hours at room temperature. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude product was purified by chromatography on silica gel using ethyl acetate as the eluent to give 0.74 g of the desired product as an orange solid (34%). Deprotection of the above solid by using tetrabutylammonium fluoride afforded 0.37 g of 4-[3-(4-fluorophenyl)-5-(1H-imidazol-4-yl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl]pyridine as a yellow solid (75%), mp: 124-126 °C. Anal. Calc'd. for $C_{24}H_{18}FN_5O \cdot 0.5\ H_2O$: C, 68.56; H, 4.55; N, 16.66. Found: C, 68.44; H, 4.39; N, 16.00.

**Example A-324**

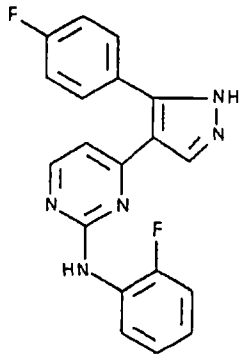
The compound 4-[3-(4-fluorophenyl)-1H-pyazol-4-yl]-N-2-propynyl-2-pyrimidinamine was prepared in accordance with general synthetic Scheme XII:



A mixture of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine (0.28 g; 0.001 mol; prepared as set forth in Example A-299) and 10 mL propargylamine was heated at reflux for 16 hour. Excess amine was removed in vacuo and 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 and the residue purified by chromatography on silica gel using ethyl acetate/hexane (1:1) as the eluent to give 0.21 g of 4-[3-(4-fluorophenyl)-1H-pyazol-4-yl]-N-2-propynyl-2-pyrimidinamine as a pale yellow solid (68% yield), mp: 186-187 °C. Anal. Calc'd. for $C_{16}H_{12}FN_5$: C, 65.52; H, 4.12; N, 23.88. Found: C, 64.99; H, 4.15; N, 23.91.

**Example A-325**

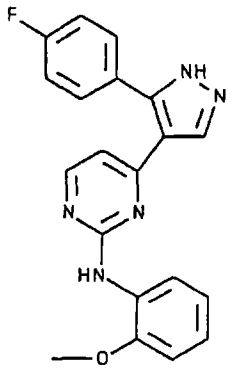
The compound N-(2-fluorophenyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine was prepared in accordance with general synthetic Scheme XII:



A mixture of 2-chloro-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]pyrimidine (0.37 g; 0.0013 mol; prepared as set forth in Example A-299), 7 mL of 2-fluoroaniline and 2 drops of methanol was heated at 180 °C in a sealed tube for 16 hours. Excess amine was removed by vacuum distillation and the residue was treated with ethyl acetate to give 0.35 g of N-(2-fluorophenyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine as a yellow solid (77%), mp: 239-240 °C. Anal. Calc'd. for $C_{19}H_{13}F_2N_5$: C, 65.33; H, 3.75; N, 20.05. Found: C, 64.95; H, 3.80; N, 19.77.

**Example A-326**

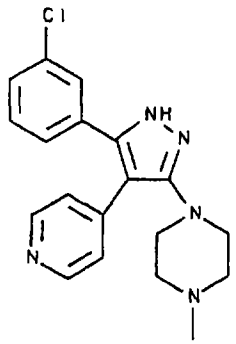
The compound 4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(2-methoxyphenyl)-2-pyrimidinamine was prepared in accordance with general synthetic Scheme XII:




4-[3-(4-Fluorophenyl)-1H-pyrazol-4-yl]-N-(2-methoxyphenyl)-2-pyrimidinamine was synthesized in 41% yield using the same method described for the preparation of N-(2-fluorophenyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinamine in Example A-325 using 2-methoxyaniline in place of 2-fluoroaniline; mp: 265 °C (dec.). Anal. Calc'd. for $C_{20}H_{16}FN_5O$: C, 66.47; H, 4.46; N, 19.38. Found: C, 66.70; H, 4.53; N, 19.20.

**Example A-327**

The compound 1-[5-(3-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine was prepared in accordance with general synthetic Scheme II:



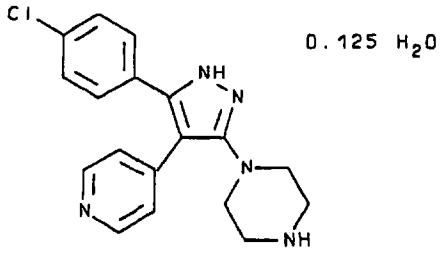

1-[5-(3-Chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine was synthesized in 12% yield as a pale yellow solid using the same method described for the preparation of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine in Example A-170 using 2-(4-pyridyl)-1-(3-chlorophenyl)ethanone in place of 2-(4-pyridyl)-1-(4-chlorophenyl)ethanone; mp: 229-231 °C. Anal. Calc'd. for $C_{19}H_{20}ClN_5 \cdot 0.4\ H_2O$: C, 63.21; H, 5.81; N, 19.40. Found: C, 62.85; H, 5.57; N, 19.77.

Additional aminopyrazole compounds that were synthesized in accordance with the chemistry described in Scheme II by selection of the corresponding starting reagents include the compounds disclosed in Table 3-1 below.

TABLE 3-1

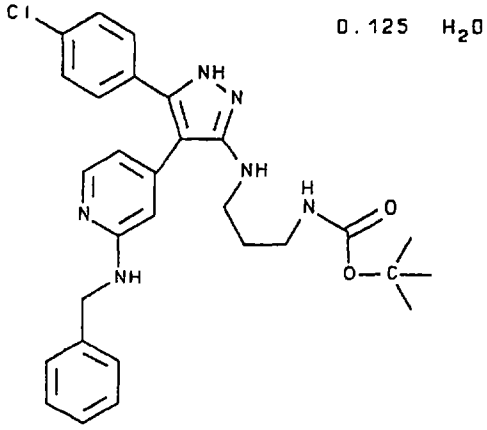
| EXAMPLE | FORMULA | MW | Theoretical C | Theoretical H | Theoretical N | Found C | Found H | Found N | DSC (mp) |
|---|---|---|---|---|---|---|---|---|---|
| A-328 | $C_{18}H_{18}ClN_5 \cdot 1/8H_2O$ | 342.08 | 63.20 | 5.30 | 20.47 | 63.04 | 5.36 | 20.33 | 199°C |
| A-329 | $C_{23}H_{33}ClN_6O_2$ | 533.08 | 65.34 | 6.24 | 15.77 | 64.98 | 6.11 | 15.58 | (168-171°C) |
| A-330 | $C_{23}H_{25}ClN_5O_2$ | 457.94 | 60.33 | 5.50 | 15.29 | 59.97 | 5.52 | 15.17 | (253-255°C) |
| A-331 | $C_{22}H_{24}ClN_5O_2$ | 425.92 | 62.04 | 5.68 | 16.44 | 61.64 | 5.94 | 16.29 | (273-275°C) |
| A-332 | $C_{19}H_{23}Cl_4N_5 \cdot H_2O$ | 481.26 | 47.42 | 4.82 | 14.35 | 47.66 | 5.11 | 13.74 | (217-219°C) |
| A-333 | $C_{21}H_{20}ClN_5 \cdot 2.5H_2O$ | 422.92 | 59.64 | 4.77 | 16.56 | 59.67 | 4.88 | 15.96 | (247°C) (d) |
| A-334 | $C_{20}H_{22}ClN_5 \cdot 1/4H_2O$ | 372.39 | 64.51 | 5.96 | 18.81 | 64.79 | 5.97 | 18.95 | 242°C |
| A-335 | $C_{24}H_{22}ClN_5 \cdot 3/4H_2O$ | 429.44 | 67.13 | 5.16 | 16.31 | 67.04 | 5.31 | 16.32 | 230°C |
| A-336 | $C_{25}H_{24}ClN_5O \cdot 1/4H_2O$ | 450.46 | 66.66 | 5.37 | 15.55 | 66.64 | 5.11 | 15.69 | (270-271°C) |
| A-337 | $C_{22}H_{24}FN_5O_2 \cdot H_2O$ | 427.48 | 61.81 | 5.66 | 16.38 | 61.88 | 5.96 | 16.41 | 249°C |
| A-338 | $C_{20}H_{22}FN_5 \cdot 1/2H_2O$ | 360.44 | 66.65 | 6.15 | 19.43 | 66.74 | 6.59 | 19.37 | 241°C |
| A-339 | $C_{19}H_{20}FN_5 \cdot 3HCl \cdot 1/2H_2O$ | 455.79 | 50.07 | 5.09 | 15.30 | 49.87 | 5.47 | 15.30 | (237-239°C) |

**Example A-328**



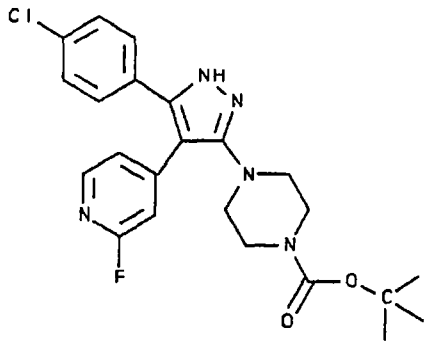

1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine

**Example A-329**



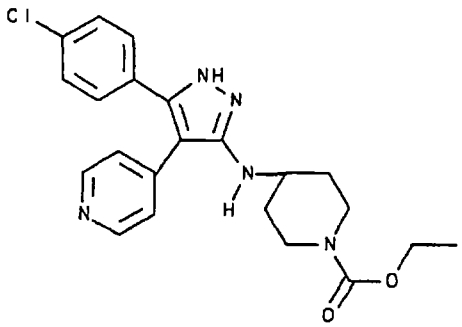

1,1-dimethylethyl [3-[[5-(4-chlorophenyl)-4-(2-[(phenylmethyl)amino]-4-pyridinyl-1H-pyrazol-3-yl]amino]propyl]carbamate

**Example A-330**



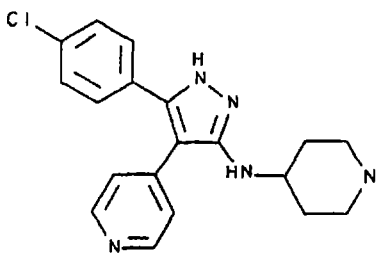
1,1-dimethylethyl 4-[5-(4-chlorophenyl)-4-(2-fluoro-4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate

**Example A-331**



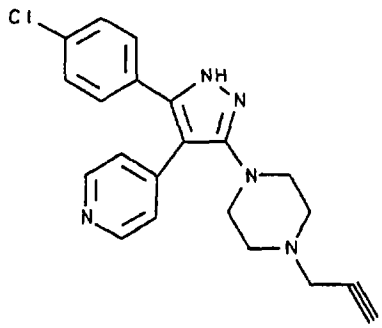
ethyl 4-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]amino]-1-piperidinecarboxylate

**Example A-332**



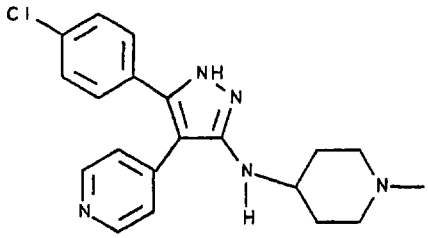
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-3H-pyrazol-3-yl]-4-piperidineamine, trihydrochloride, monohydrate

**Example A-333**



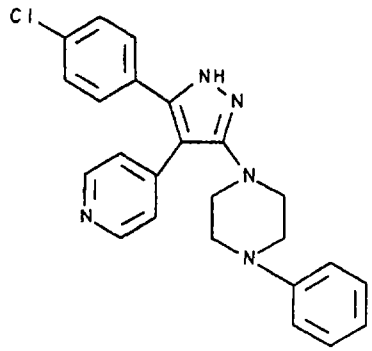
The compound 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(2-propynyl)piperazine was prepared in accordance with general synthetic Scheme II. To a suspension of of 1-[5-(4-Chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine (92 mg, 0.27 mmole) in 2 mL of dimethylformamide was added 75 mg (0.54 mmole) of anhydrous potassium carbonate and then 60 microliters of 80% propargyl bromide solution in toluene (containing 64 mg, 0.54 mmole). The resulting mixture was stirred for 30 minutes and then partitioned betwen ethyl acetate and water. The aqueous layer was further extracted with ethyl acetate, and the combined organic extracts filtered through silica gel using 10% methanol-ethyl acetate as eluent to give, after evaporation of the appropriate fractions, 34 mg of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(2-propynyl)piperazine as a pale yellowish solid, m.p. 247 °C (decomp.). Anal. Calc'd. for $C_{21}H_{20}ClN_5 \cdot 2.5H_2O$ (MW 422.92): C, 59.64, H, 4.77, N, 16.56. Found: C, 59.67, H, 4.88, N, 15.96.

**Example A-334**



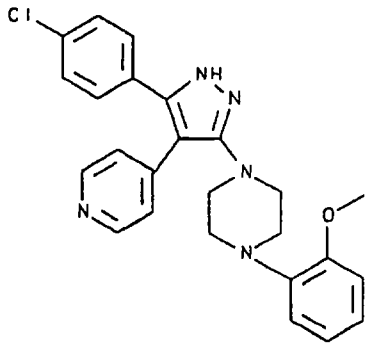
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-4-piperidinamine

**Example A-335**



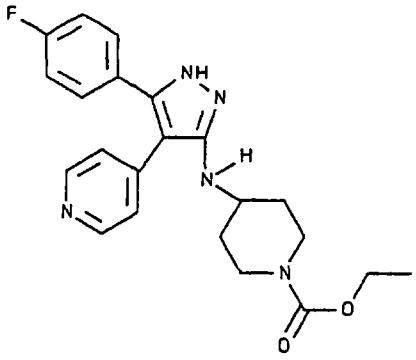
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-phenylpiperazine

**Example A-336**



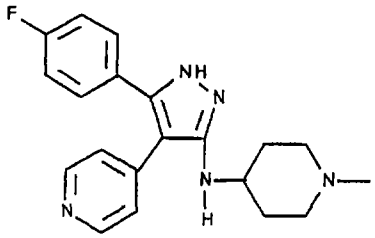
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-(2-methoxyphenyl)piperazine

**Example A-337**



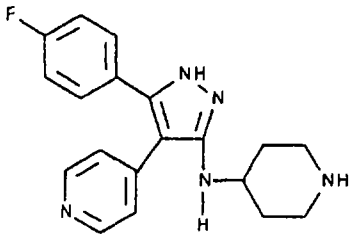
Ethyl 4-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]amino]-1-piperidinecarboxylate, monohydrate

**Example A-338**



N-[5-(4-fluorophenyl)-4-(pyridinyl)-1H-pyrazol-3-yl]-1-methyl-4-piperidinamine

**Example A-339**



N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinamine, trihydrochloride

**Example A-340**

The compound of Example A-170 was also synthesized in the following manner. 1-[5-(4-Chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine (12.2g, 36 mmol, prepared as set forth in Example A-169), 88% formic acid (20 mL), and formaldehyde (37% formalin solution; 44g, 540 mmol) were combined and stirred at 60 °C for 16 hours under a nitrogen atmosphere. Excess solvent was removed on the rotary evaporator and the residue was dissolved in water (150 mL). The pH was adjusted to 8-9 by addition of solid sodium bicarbonate. The resulting precipitate was filtered and air dried. It was then treated with hot methanol (400 mL), filtered and blown down to a volume of 75 mL, cooled and filtered. After drying in a vacuum oven at 80 °C overnight, there was obtained 8.75g (68%) of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, m. p. 262-264 °C. Anal. Calc'd. for $C_{19}H_{20}N_5Cl$: C, 64.49; H, 5.70; N, 19.79. Found: C, 64.04; H, 5.68; N, 19.63.

The compounds of Examples A-341 through A-345 were synthesized, for example, in accordance with the chemistry described in Scheme XXI by selection of the corresponding starting reagents.

**Example A-341**

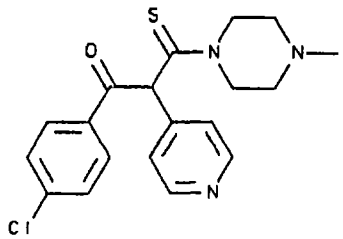
The compound of Example A-170 was also synthesized in the following manner:

Step 1: Preparation of 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone

To a solution of 2-(4-pyridyl)-1-(4-chlorophenyl)ethanone (70.0 g, 0.3 mol) prepared in a similar manner as the compound of Step 1 of Example A-19, dibromomethane (200 mL) and carbon disulfide (25.9 g, 0.34 mol) in acetone (800 mL) was added potassium

carbonate (83.0 g, 0.6 mol). The reaction mixture was stirred at room temperature for 24 hours. An additional two equivalents of potassium carbonate and one equivalent of carbon disulfide was added and the stirring was continued for another 24 hours. Solvent was removed and the residue was partitioned between dichloromethane and water. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the crude was stirred with 1000 mL of a mixture of ethyl acetate and ether (1:9) to give 78.4 g of pure product, 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone, as a yellow solid (82%), mp: 177-179 °C. Anal. Calc'd. for $C_{15}H_{10}ClNOS_2$: C, 56.33; H, 3.15; N, 4.38. Found: C, 55.80; H, 2.84; N, 4.59.

Step 2: Preparation of 1-[3-(4-chlorophenyl)-3-oxo-2-(4-pyridinyl)-1-thiopropyl]-4-methylpiperazine

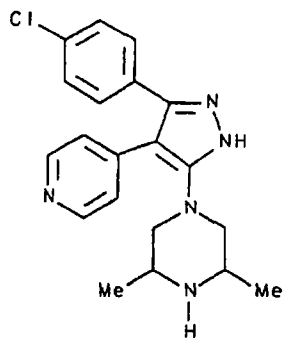


A mixture of 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone (78.3 g, 0.24 mol) and 1-methylpiperazine (75.0 g, 0.73 mol) in 800 mL of toluene was heated at reflux for 2 hours. Solvent and excess 1-methylpiperazine was removed under vacuum and the residue was triturated with a mixture was ethyl acetate and ether (1:3) to give 53.0 g of product, 1-[3-(4-chlorophenyl)-3-oxo-2-(4-pyridinyl)-1-thiopropyl]-4-methylpiperazine, as yellow crystals (60%), mp: 149-151 °C. Anal. Calc'd. for $C_{19}H_{20}ClN_3OS$: C, 61.03; H, 5.39; N, 11.24. Found: C, 60.74; H, 5.35; N, 11.14.

Step 3: Preparation of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine

To a suspension of 1-[3-(4-chlorophenyl)-3-oxo-2-(4-pyridinyl)-1-thiopropyl]-4-methylpiperazine (52.0 g, 0.14 mol) in 500 mL of dry tetrahydrofuran was added anhydrous hydrazine (8.9 g, 0.28 mol) dropwise. The reaction mixture was stirred at room temperature for 16 hours. The pale yellow precipitate was filtered and recrystallized from hot methanol to give 30.2 g of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine as a white powder (60%), mp: 267-268 °C. Anal. Calc'd. for $C_{19}H_{20}ClN_5$: C, 64.49; H, 5.70; N, 19.79. Found: C, 64.89; H, 5.55; N, 19.99.

**Example A-342**

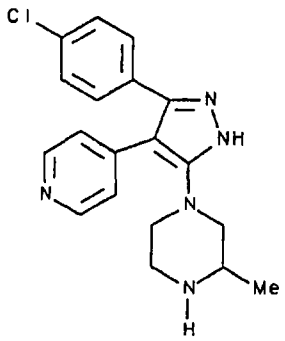



1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3,5-dimethylpiperazine

A mixture of 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone (3.2 g, 0.01 mol; prepared as set forth in Step 1 of Example A-341) and 2,6-dimethylpiperazine (3.43 g, 0.03 mol) in 35 mL of toluene was heated at reflux for 12 hours. Toluene and excess 2,6-dimethylpiperazine were then removed under vacuum and the crude thiamide produced was used without purification. A solution of the crude thiamide and

anhydrous hydrazine (0.65 g, 0.02 mol) in 40 mL of dry tetrahydrofuran was stirred at room temperature overnight. After the removal of tetrahydrofuran, the residue was stirred with a mixture of ethyl acetate and ammonium hydroxide for one hour. The precipitate was filtered and air dried to give 1.6 g of 1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3,5-dimethylpiperazine as a white solid (43% overall yield), mp: 236-238°C. Anal. Calc'd. for $C_{20}H_{22}ClN_5 \cdot 0.25H_2O$: C, 64.51; H, 6.09; N, 18.81; Cl, 9.52. Found: C, 64.28; H, 5.85; N, 18.70; Cl, 9.67.

**Example A-343**




1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-methylpiperazine

1-[5-(4-Chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-methylpiperazine was prepared according to the same procedure set forth above in Example A-342 except that 2-methylpiperazine was used in place of 2,6-dimethylpiperazine (4% overall yield), mp: 235-237°C. Anal. Calc'd. for $C_{19}H_{20}ClN_5 \cdot 0.75H_2O$: C, 62.12; H, 5.90; N, 19.06. Found: C, 62.23; H, 5.53; N, 18.80.

**Example A-344**

The compound of Example A-317 was also synthesized in the following manner:

Step 1: Preparation of 1-(4-pyridyl)-1-(methylenedithioketene)-2-(4-fluorophenyl)-ethanone

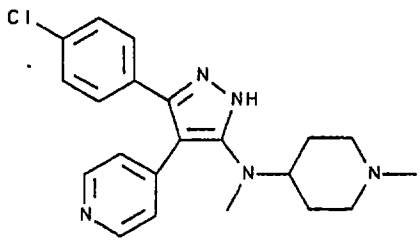
To a solution of 4-fluorobenzoyl-4'-pyridyl methane (70.0 g, 0.3 mol, prepared as set forth in Step 1 of Example A-208) and dibromomethane (125 mL) was added solid anhydrous potassium carbonate (55.0 g, 0.4 mol) portionwise over five minutes. Carbon disulfide (17 g, 0.22 mol) was added dropwise over 15 minutes at room temperature. After stirring for 16 hours under a nitrogen atmosphere, the reaction was incomplete. Additional carbon disulfide (15 g) was added and the reaction mixture was stirred for an additional 24 hours. The reaction mixture was filtered and the potassium carbonate was washed on the filter with methylene chloride. The filtered solid was dissolved in water and extracted with methylene chloride. The extract was combined with the filtrate and dried over magnesium sulfate. The drying agent was filtered and the filtrate concentrated in vacuo. The residue was treated with ethyl acetate/ether (1:1), filtered and air dried to give 1-(4-pyridyl)-1-(methylenedithioketene)-2-(4-fluorophenyl)-ethanone (26 g, 86%) as a solid, m.p. 182-183 °C; Anal. Calc'd. for $C_{15}H_{10}FNOS_2$: C, 59.39; H, 3.32; N, 4.62. Found: C, 59.18; H, 3.41; N, 4.49.

Step 2: Preparation of 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate

A mixture of the 1-(4-pyridyl)-1-(methylenedithioketene)-2-(4-fluorophenyl)-ethanone (3 g, 0.01 mol) prepared in Step 1 and 1-methylpiperazine (3 g, 0.03 mol) in 30 mL of toluene was refluxed under a nitrogen atmosphere for three hours. The mixture was cooled and solvent was removed under vacuum. The residue was dissolved in dry tetrahydrofuran (30 mL) and

anyhydrous hydrazine (640 mg, 0.02 mol) was added. The reaction mixture was stirred at room temperature for 16 hours and the resulting precipitate was filtered. The precipitate was warmed in methanol and a few drops of concentrated ammonium hydroxide were added. The mixture was filtered hot and the filtrate blown down to half the volume. As the filtrate cooled, a product crystallized and was filtered to give 1.5 g (42%) of 1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine, dihydrate, mp: 238-240 °C; Anal. Calc'd. for $C_{19}H_{20}FN_5 \cdot 2H_2O$: C, 61.11; H, 65.48; N, 18.75. Found: C, 60.79; H, 6.21; N, 18.98.

**Example A-345**




N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-N,1-dimethyl-4-piperidinamine, dihydrate

Step 1: Preparation of 1-methyl-4-methylaminopiperidine

A mixture of 1-methyl-4-piperidone (20 g, 0.18 mol) in methanol:tetrahydrofuran (100 mL, 1:1) and methyl amine (2 M in tetrahydrofuran, 3 mole excess) was placed in a Parr shaker with 5% Pd/C and hydrogenated for two hours at 60 psi and 70°C. The catalyst was filtered and the filtrate concentrated on the rotary evaporator. The crude material was distilled at 44-45°C at 0.3 mm Hg to give 20 g (87%) of 1-methyl-4-methylaminopiperidine. Anal. Calc'd for $C_7H_{16}N_2$: C, 65.57; H, 12.58; N, 21.85. Found: C, 65.49; H, 12.44; N: 21,49.

Step 2: Preparation of N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-N,1-dimethyl-4-piperidinamine, dihydrate

A solution of 1-(4-chlorophenyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridinyl)ethanone (3.2 g, 0.01 mol; prepared as set forth in Step 1 of Example A-341) and 1-methyl-4-methylaminopiperidine (3.8 g, 0.03 mol) in 30 mL of toluene refluxed for six hours under nitrogen. The mixture was cooled and solvent was removed under vacuum. The residue was dissolved in dry tetrahydrofuran (30 mL) and anyhydrous hydrazine (650 mg, 0.02 mol) was added. The reaction mixture was stirred at room temperature under nitrogen for 16 hours. The resulting precipitate was filtered and warmed in methanol and a few drops of concentrated ammonium hydroxide. The mixture was filtered hot and the filtrate blown down to half the volume. As the filtrate cooled, a product separated and was filtered to give 395 of pure N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-N,1-dimethyl-4-piperidinamine, dihydrate, m.p. 260-261°C. Anal. Calc'd for $C_{21}H_{24}ClN_5 \cdot 2H_2O$: C, 60.35; H, 6.75; N, 16.76. Found: C, 59.89; H, 6.56; N: 16.40.

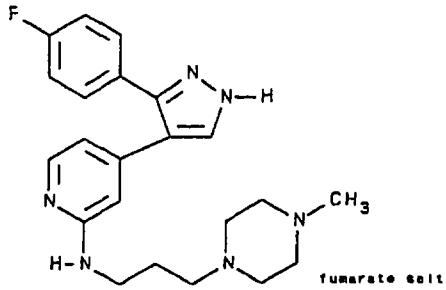
Additional compounds of the present invention that were prepared according to one or more of above reaction schemes (particularly Schemes IX through XVIII) are disclosed in Table 3-2. The specific synthesis scheme or schemes as well as the mass spectroscopy and elemental analysis results for each compound also are disclosed in Table 3-2.

TABLE 3-2

| Example | General | MS | Microanalysis | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | M+ | C Found | C Found | H Calc | H Found | N Calc | N Found | Water Added | EtOAc Added | $CHCl_3$ Added | Toluene Added | HCl Added |
| A-346 | XII | | | | | | | | | | | | |
| A-347 | XII | 329 | 59.33 | 59.59 | 5.65 | 5.47 | 15.55 | 15.41 | 0.8 | 0.2 | | | |
| A-348 | XII | 439 | 68.46 | 66.59 | 8.04 | 8.48 | 19.16 | 16.17 | | | | | |
| A-349 | XII | 397 | 61.85 | 61.99 | 7.79 | 7.52 | 17.45 | 17.39 | 1.3 | 0.7 | | | |
| A-350 | XII | 449 | 66.29 | 66.75 | 7.60 | 7.68 | 17.84 | 17.00 | 1.25 | | | | |
| A-351 | XII | 352 | 68.36 | 57.51 | 6.31 | 7.31 | 19.93 | 17.17 | | | | | |
| A-352 | XII | 366 | 69.02 | 66.27 | 6.62 | 6.59 | 19.16 | 18.22 | | | | | |
| A-353 | XII | 430 | 69.26 | 71.50 | 7.40 | 6.91 | 18.36 | 14.87 | | | | | |
| A-354 | XII | 355 | 70.48 | 70.12 | 6.80 | 7.15 | 13.99 | 13.91 | | | | 0.5 | |
| A-355 | XII | 341 | 66.73 | 67.09 | 6.29 | 6.77 | 16.04 | 15.78 | | 0.1 | | | |
| A-356 | XVII | 410 | 63.42 | 63.61 | 6.00 | 6.06 | 16.81 | 16.63 | 0.4 | | | | |
| A-357 | XVII | 392 | 54.37 | 53.93 | 5.91 | 6.32 | 13.78 | 14.68 | 0.4 | | | | |
| A-358 | XII | 394 | 70.20 | 68.50 | 7.17 | 7.68 | 17.80 | 16.58 | | | | | |
| A-359 | XVII | 396 | 69.21 | 69.33 | 7.68 | 8.01 | 17.55 | 17.61 | 0.2 | | | | |
| A-360 | XVII | 366 | 50.81 | 50.74 | 5.97 | 5.80 | 14.11 | 14.00 | 1.2 | | | | 3 |
| A-361 | XII | 389 | 71.12 | 68.67 | 5.45 | 5.64 | 14.42 | 12.90 | | | | | |
| A-362 | XII | 375 | 70.57 | 68.54 | 5.12 | 5.39 | 14.96 | 13.90 | | | | | |
| A-363 | XII | 389 | 71.12 | 68.86 | 5.45 | 5.58 | 14.42 | 13.09 | | | | | |
| A-364 | XVII | 368 | 68.31 | 68.39 | 7.15 | 7.49 | 18.97 | 18.93 | 0.1 | | | | |
| A-365 | XVII | 338 | 48.72 | 48.57 | 5.47 | 5.45 | 14.95 | 14.79 | 1.2 | | | | 3 |
| A-366 | XII | 397 | 56.34 | 56.21 | 7.31 | 7.03 | 17.92 | 17.89 | 2 | | | | 1 |

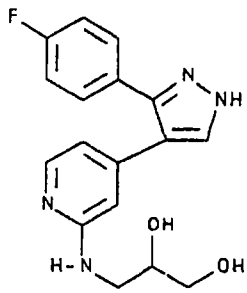
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A-367 | XVII | 321 | 70.25 | 69.83 | 5.43 | 5.62 | 17.25 | 17.82 | 0.25 | | | | |
| A-368 | XII | 313 | 64.66 | 64.28 | 5.73 | 5.62 | 16.76 | 16.93 | | 0.25 | | | |
| A-369 | XII | 412 | 66.76 | 66.60 | 7.36 | 7.61 | 16.93 | 16.74 | 0.1 | | | | |
| A-370 | XII | 313 | 64.66 | 64.36 | 5.73 | 5.59 | 16.76 | 16.82 | | 0.25 | | | |
| A-371 | XVII | | 63.78 | 63.63 | 6.37 | 6.09 | 17.71 | 17.24 | 1 | | | | |
| A-372 | XII | | 68.63 | 68.80 | 7.26 | 7.53 | 17.40 | 17.14 | 0.5 | | | | |
| A-373 | XVII | 389 | 58.10 | 57.99 | 5.00 | 4.88 | 17.83 | 17.48 | 0.25 | | | | |
| A-374 | XII | 354 | 67.97 | 67.23 | 6.84 | 6.81 | 19.81 | 19.38 | | | | | |
| A-375 | XII | 366 | 68.18 | 68.06 | 6.67 | 6.80 | 18.93 | 18.56 | 0.25 | | | | |
| A-376 | XII | 375 | 70.57 | 68.19 | 5.12 | 6.06 | 14.96 | 13.13 | | | | | |
| A-377 | XII | 396 | 64.14 | 64.44 | 6.99 | 6.78 | 16.02 | 16.02 | | | 0.35 | | |
| A-378 | XVII | 337 | 66.42 | 66.44 | 5.22 | 4.91 | 16.31 | 16.27 | 0.4 | | | | |
| A-379 | XVII | 339 | 62.76 | 62.80 | 6.04 | 5.43 | 15.41 | 15.17 | 1.4 | | | | |
| A-380 | XVII | 381 | 63.31 | 63.40 | 5.19 | 5.82 | 14.06 | 13.84 | 1 | | | | 1 |
| A-381 | XVII | 307 | 70.57 | 69.69 | 4.94 | 5.00 | 18.29 | 17.68 | | | | | |
| A-382 | XVII | | | | | | | | | | | | |
| A-383 | XVII | | | | | | | | | | | | |
| A-384 | 320 | 55.48 | 53.44 | 5.64 | 5.00 | 17.03 | 21.60 | | | | | | |
| A-385 | XI | 280 | 52.65 | 52.51 | 5.98 | 5.17 | 10.83 | 11.12 | | | | | 1 |
| A-386 | XII | 351 | 64.96 | 64.77 | 5.82 | 5.34 | 14.85 | 15.03 | 1 | 0.1 | | | |
| A-387 | XII | 353 | 65.29 | 65.62 | 6.32 | 6.14 | 14.64 | 14.47 | 0.7 | 0.2 | | | |
| A-388 | | 394 | 54.93 | 55.34 | 6.21 | 6.79 | 13.93 | 14.01 | | | | | 3 |

**Example A-346**



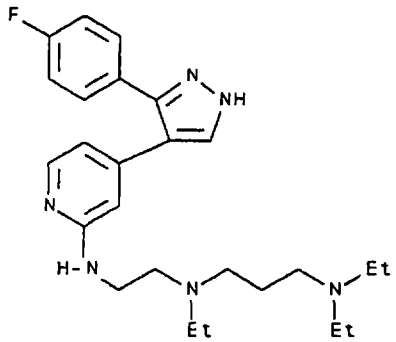

N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-4-methyl-1-piperazinepropanamine(2E)-2-butenedioate (1:1)

**Example A-347**



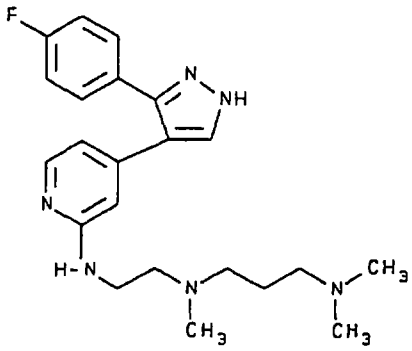

3-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1,2-propanediol;

**Example A-348**



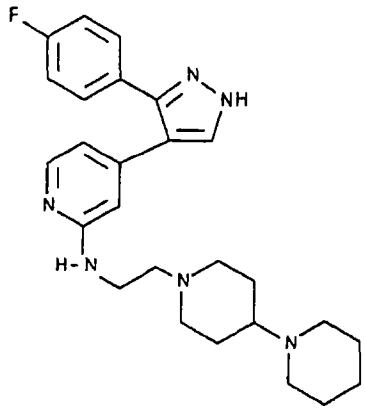
N,N,N''-triethyl-N'-[2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethyl]-1,3-propanediamine;

**Example A-349**



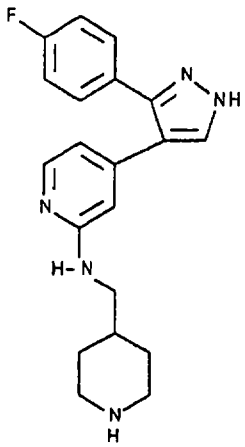
N-[2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]ethyl]-N,N',N'-trimethyl-1,3-propanediamine;

**Example A-350**



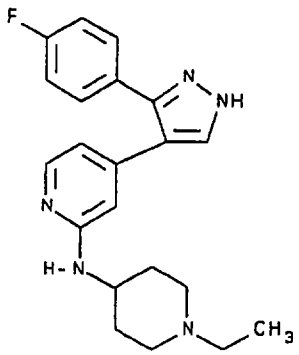
N-(2-[1,4'-bipiperidin]-1'-ylethyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine;

**Example A-351**



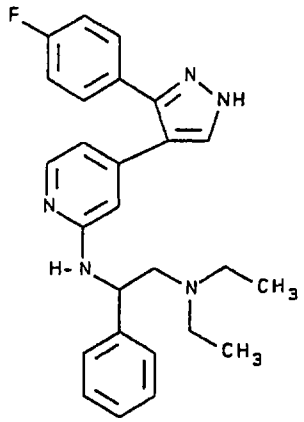
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-(4-piperidinylmethyl)-2-pyridinamine;

**Example A-352**



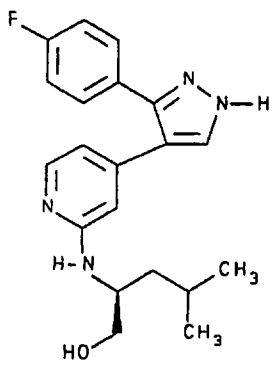
N-(1-ethyl-4-piperidinyl)-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine;

**Example A-353**



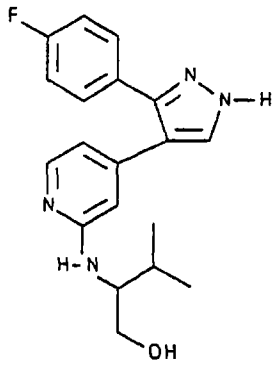
N2,N2-diethyl-N1-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-1-phenyl-1,2-ethanediamine;

**Example A-354**



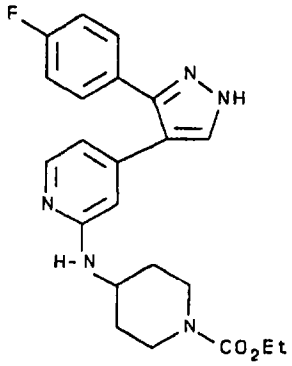
(2S)-2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-4-methyl-1-pentanol;

**Example A-355**



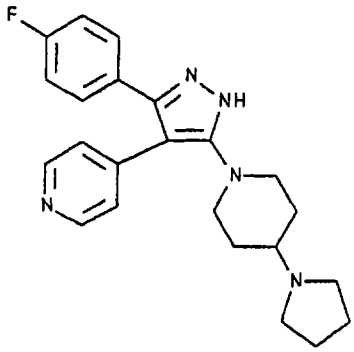
2-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-3-methyl-1-butanol;

**Example A-356**



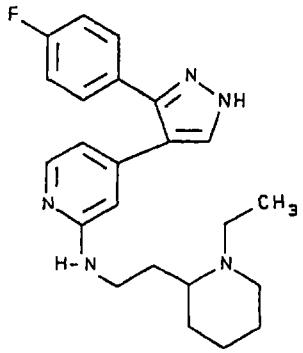
ethyl 4-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-1-piperidinecarboxylate;

**Example A-357**



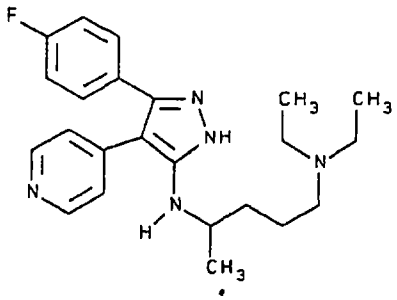
4-[3-(4-fluorophenyl)-5-(4-(1-pyrrolidinyl)-1-piperidinyl]-1H-pyrazol-4-yl]pyridine, trihydrochloride;

**Example A-358**



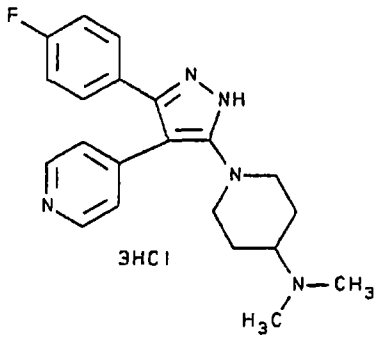
N-[2-(1-ethyl-2-piperidinyl)ethyl]-4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinamine;

**Example A-359**



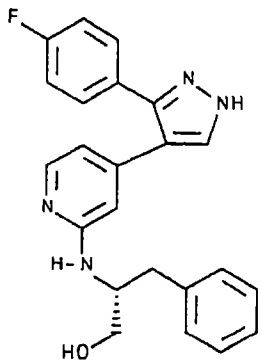
N1,N1,-diethyl-N4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,4-pentanediamine;

**Example A-360**



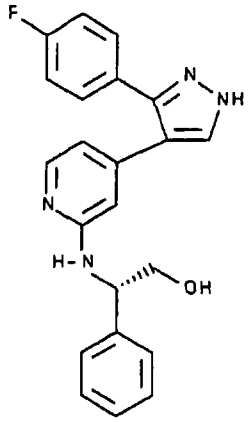

1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-dimethyl-4-piperidinamine, trihydrochloride;

**Example A-361**



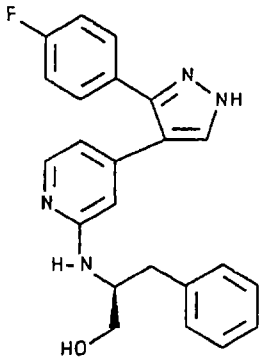

(βR)-β-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene propanol;

**Example A-362**



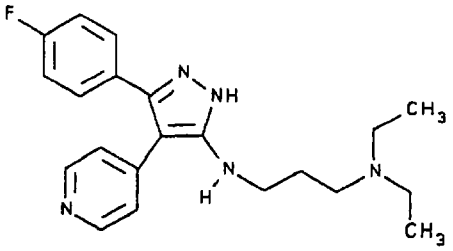
(βS)-β-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene ethanol;

**Example A-363**



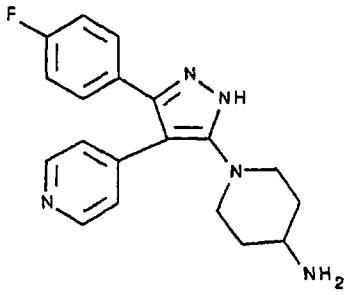
(βS)-β-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene propanol;

**Example A-364**



N,N-diethyl-N'-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,3-propanediamine;

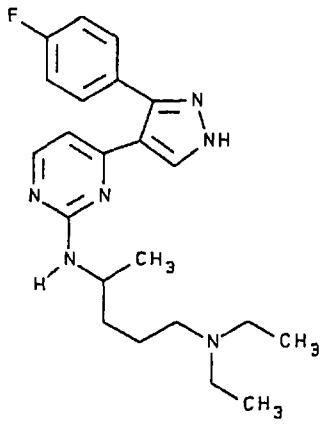
**Example A-365**




3HCl

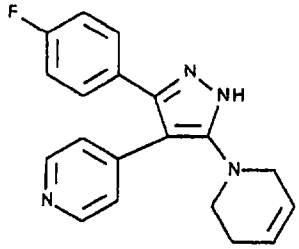
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinamine, trihydrochloride;

**Example A-366**



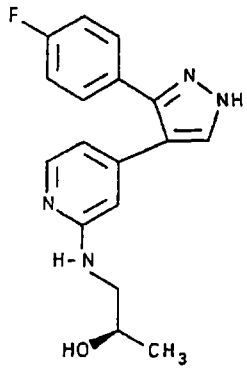

N1,N1-diethyl-N4-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-1,4-pentanediamine;

**Example A-367**



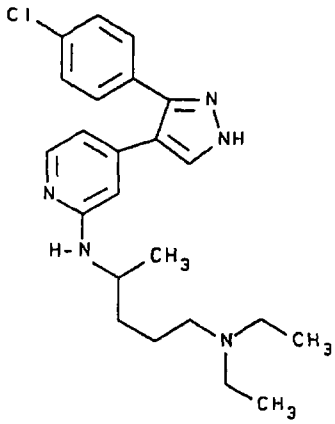
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,2,3,6-hexahydropyridine;

**Example A-368**



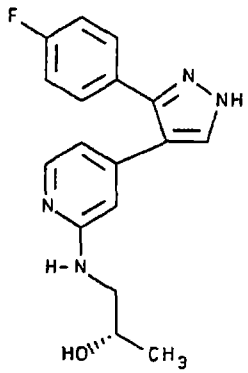
(2R)-1-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-2-propanol;

**Example A-369**



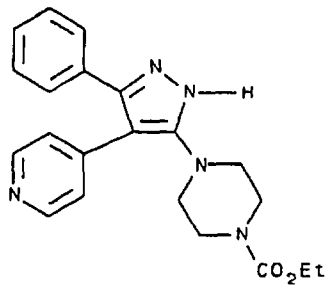
N4-[4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-N1,N1-diethyl-1,4-pentanediamine;

**Example A-370**



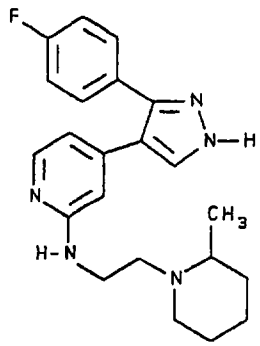

(2S)-1-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]-2-propanol;

**Example A-371**



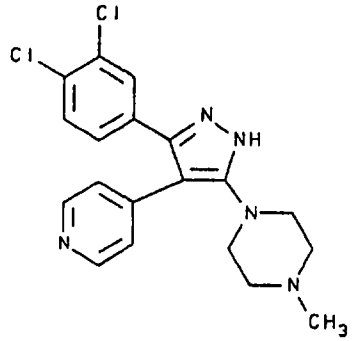

ethyl 4-[5-phenyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazinecarboxylate;

**Example A-372**



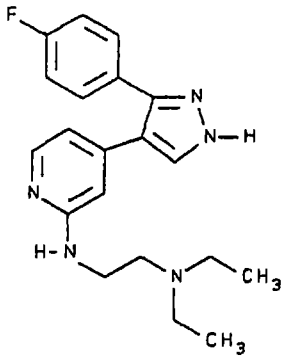
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[3-(2-methyl-1-piperidinyl)propyl]-2-pyridinamine;

**Example A-373**



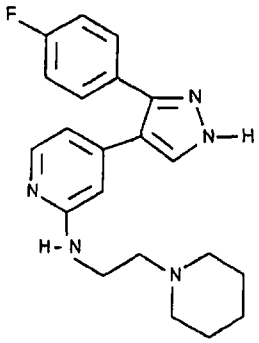
1-[5-(3,4-dichlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine;

**Example A-374**



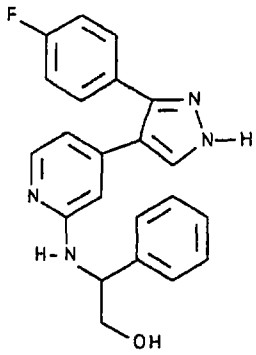
N,N-diethyl-N'-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-1,2-ethanediamine;

**Example A-375**



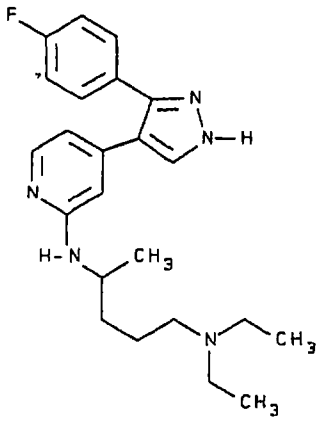
4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-N-[2-(1-piperidinyl)ethyl]-2-pyridinamine;

**Example A-376**



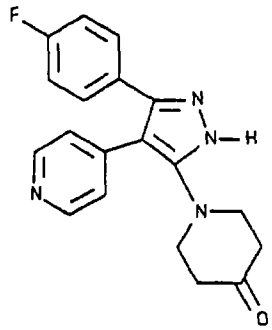
(βR)-β-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]benzene ethanol;

**Example A-377**



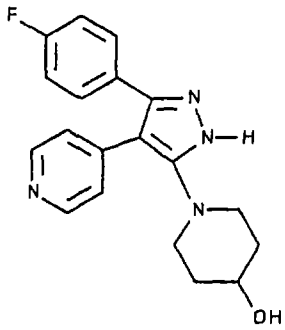
N1,N1-diethyl-N4-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]-1,4-pentanediamine;

**Example A-378**



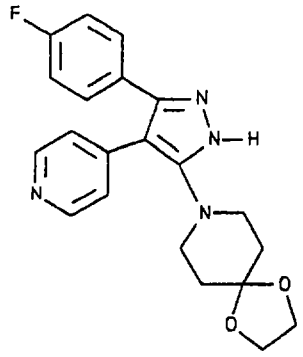
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinone;

**Example A-379**



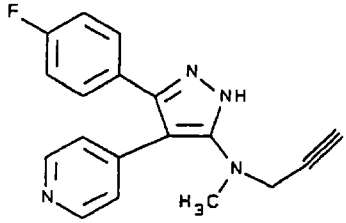
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinol;

**Example A-380**



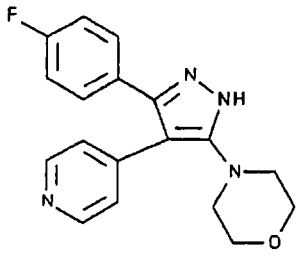
8-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,4-dioxa-8-azaspiro[4.5]decane;

**Example A-381**



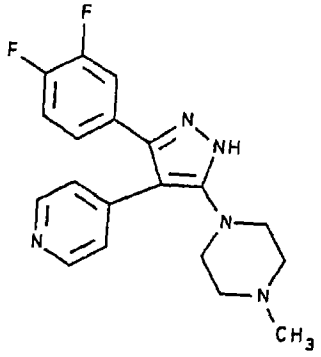
5-(4-fluorophenyl)-N-methyl-N-2-propynyl-4-(4-pyridinyl)-1H-pyrazol-3-amine;

**Example A-382**



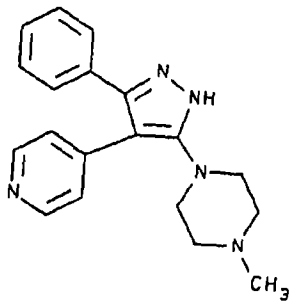
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]morpholine;

**Example A-383**



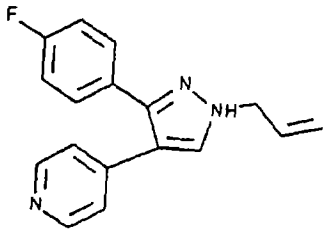
1-[5-(3,4-difluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine;

**Example A-384**



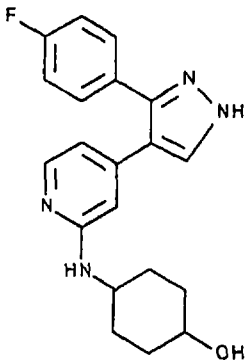
1-methyl-4-[5-phenyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine;

**Example A-385**



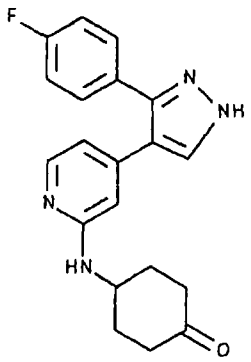
4-[3-(4-fluorophenyl)-1-(2-propenyl)-1H-pyrazol-4-yl]pyridine, monohydrochloride;

**Example A-386**



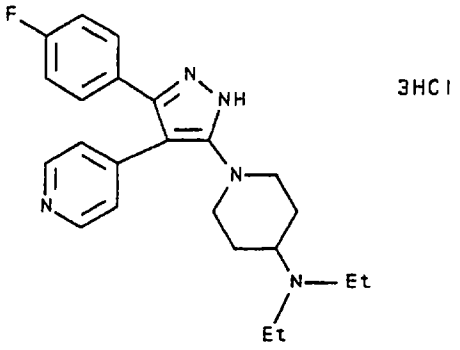
trans-4-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]cyclohexanol;

**Example A-387**



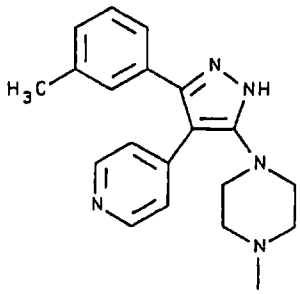
4-[[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyridinyl]amino]cyclohexanone;

**Example A-388**



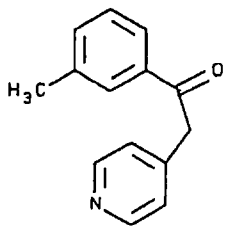

1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-diethyl-4-piperidinamine, trihydrochloride;

**Example A-389**




1-[5-(3-tolyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl-4-methylpiperazine:

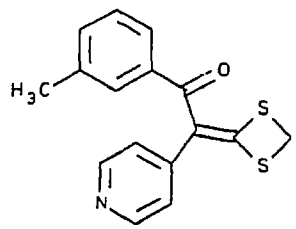
Step 1. Preparation of 1-tolyl-2-(4-pyridyl)ethanone




Methyl 3-methylbenzoate (6.0 g, 40 mmol), tetrahydrofuran (50 mL), and 4-picoline (4.1 g, 44 mmol) were stirred at -78 °C under an atmosphere of nitrogen.

Sodium (bis)trimethylsilylamide 1.0 M in tetrahydrofuran (88 mL, 88 mmol) was added dropwise. The mixture was allowed to warm to room temperature, stirred for 16 hours and then was poured into saturated aqueous sodium bicarbonate solution. The mixture was then extracted with ethyl acetate (3 X 50 mL). The combined organics were washed with brine (2 X 50 mL), dried over magnesium sulfate, and concentrated. The product was recrystallized from ethyl acetate/hexane to yield a light yellow solid (5.7 g, 67%), mp 118.0-119.0 °C; $^1$H NMR (acetone-d6/300 MHz) 8.50 (m, 2H), 7.90 (m, 2H), 7.44 (m, 2H), 7.29 (m, 2H), 4.45 (s, 2H), 2.41 (s, 3H); ESHRMS *m/z* 212.1067 (M+H, $C_{14}H_{13}NO$ requires 212.1075); Anal. Calc'd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.54; H, 6.30; N, 6.56.

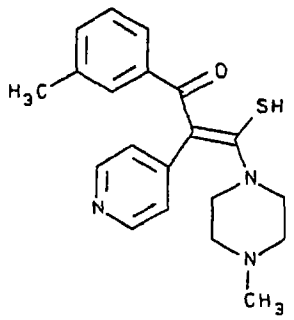
Step 2. Preparation of 1-(3-tolyl)-2-(1,3-dithietan-2-ylidene)-2-(4-pyridyl)ethanone




1-tolyl-2-(4-pyridyl)ethanone (4.22 g, 20 mmol), acetone (100 mL), potassium carbonate (8.3 g, 60 mmol), carbon disulfide 4.56 g, 60 mmol), and dibromomethane (10.43 g, 60 mmol) were stirred at room temperature for 16 hours. Water (100 mL) was added and the mixture was extracted with ethyl acetate (3 X 50 mL). The combined organic extracts were washed with brine (2 X 50 mL), dried over magnesium sulfate and concentrated. This crude material was purified by either flash column chromatography eluting with ethyl acetate:hexane or crystallization from ethyl acetate/hexane to yield a

yellow solid (4.8 g, 80%), mp 178.6-179.2 °C; $^1$H NMR (acetone-d6/300 MHz) 8.47 (m, 2H), 7.08 (m, 6H), 4.37 (s, 2H), 2.21 (s, 3H); ESHRMS *m/z* 300.0521 (M+H, $C_{16}H_{13}NOS_2$ requires 300.0517); Anal. Calc'd for $C_{16}H_{13}NOS_2$: C, 64.18; H, 4.38; N, 4.68. Found: C, 64.08; H, 4.25; N, 4.62.

Step 3. Preparation of 1-[3-(3-tolyl)-3-oxo-2-(4-pyridinyl)-1-thiopropyl]-4-methylpiperazine



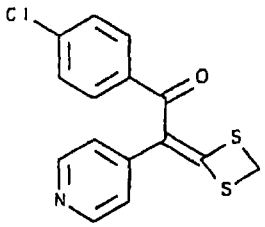

The dithietane compound from step 2 above (3.0 g, 10 mmol), N-methylpiperazine (5.0 g, 50 mmol), and toluene (50 mL) were refluxed using a Dean-Stark apparatus for one to three hours. The reaction was allowed to cool to room temperature and was concentrated to dryness under high vacuum. This thick, oily material was crystallized from ethyl acetate / hexane (2.9 g, 82%), mp 124.8-125.8 °C; $^1$H NMR (acetone-d6/300 MHz) 8.57 (m, 2H), 7.75 (m, 2H), 7.54 (m, 2H), 7.37 (m, 2H) 6.54 (s, 1H), 4.27 (m, 2H), 4.19 (m, 1H), 3.83 (m, 1H), 2.47-2.28 (m, 6H), 2.22 (s, 3H), 2.17 (m, 1H); ESHRMS *m/z* 354.1669 (M+H, $C_{20}H_{23}N_3OS$ requires 354.1640); Anal. Calc'd for $C_{20}H_{23}N_3OS$: C, 67.96; H, 6.56; N, 11.89. Found: C, 67.79; H, 6.66; N, 11.88.

Step 4. Preparation of 1-[5-(3-tolyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl-4-methylpiperazine.

The thioamide compound from step 3 above (1.06 g, 3 mmol), tetrahydrofuran (50 mL), and hydrazine (15 mL, 15 mmol, 1.0 M) in tetrahydrofuran were stirred at room temperature for 16 hours. A white solid was collected by filtration. Purification when necessary was by trituration or recrystallization (0.98 g, 97%), mp 261.9-262.0 °C; $^1$H NMR (DMSO-d6/300 MHz) 12.6 (brs, 1H), 8.42 (m, 2H), 7.2 (m, 4H), 7.12 (s, 1H), 7.0 (m, 1H), 2.86 (m, 4H), 2.34 (m, 4H) 2.25 (s, 3H), 2.16 (s, 3H); ESHRMS *m/z* 334.2049 (M+H, $C_{20}H_{23}N_5$ requires 334.2032); Anal. Calc'd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00. Found: C, 71.83; H, 7.06; N, 20.83.

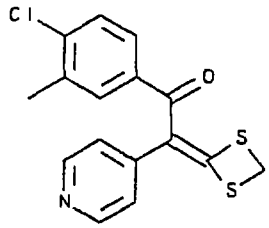
Additional dithietanes and pyrazoles that were synthesized by selection of the corresponding starting reagents in accordance with the chemistry described in Scheme XXI and further illustrated in Example 389 above include compounds A-390 through A-426 disclosed below.

**Example A-390**




mp 185.3-185.4 °C; $^1$H NMR (acetone-d6/300 MHz) 8.49 (m, 2H), 7.31 (m, 4H), 7.09 (m, 2H), 4.39 (s, 2H); ESHRMS *m/z* 319.9981 (M+H, $C_{15}H_{10}ClNOS_2$ requires 319.9971); Anal. Calc'd for $C_{15}H_{10}ClNOS_2$: C, 56.33; H, 3.15; N, 4.38. Found: C, 56.47; H, 3.13; N, 4.44.

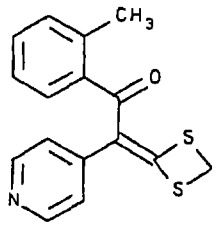
**Example A-391**



1-(4-chloro-3-methylphenyl)-2-1,3-dithietan-2-ylidene-2-pyridin-4-yl-ethanone

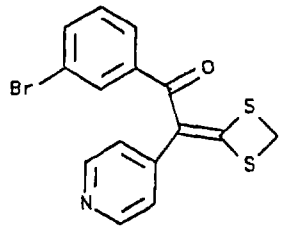
mp 164.0-165.0 °C; $^1$H NMR (acetone-d6/300 MHz) 8.49 (m, 2H), 7.25 (m, 2H), 7.0 (m, 3H), 4.38 (s, 2H), 2.24 (s, 3H); ESHRMS *m/z* 334.0130 (M+H, $C_{16}H_{12}ClNOS_2$ requires 334.0127); Anal. Calc'd for $C_{16}H_{12}ClNOS_2$: C, 57.56; H, 3.62; N, 4.20. Found: C, 57.68; H, 3.67; N, 4.17.

**Example A-392**



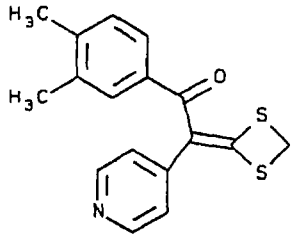
mp 126.5-126.6 °C; $^1$H NMR (acetone-d6/300 MHz) 8.40 (m, 2H), 7.17 (m, 2H), 7.0 (m, 4H), 4.39 (s, 2H), 2.85 (s, 3H); ESHRMS *m/z* 300.0483 (M+H, $C_{16}H_{13}NOS_2$ requires 300.0517); Anal. Calc'd for $C_{16}H_{13}NOS_2$: C, 64.18; H, 4.38; N, 4.68. Found: C, 64.05; H, 4.27; N, 4.59.

**Example A-393**



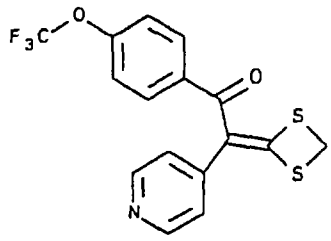

mp 159.6-159.7 °C; $^1$H NMR (acetone-d6/300 MHz) 8.52 (m, 2H), 7.6 (m, 1H), 7.50 (s, 1H), 7.21 (m, 2H), 7.13 (m, 2H), 4.40 (s, 2H); ESHRMS *m/z* 363.9503 (M+H, $C_{15}H_{10}BrNOS_2$ requires 363.9465); Anal. Calc'd for $C_{15}H_{10}BrNOS_2$: C, 49.46; H, 2.77; N, 3.84. Found: C, 49.51; H, 2.68; N, 3.74.

**Example A-394**



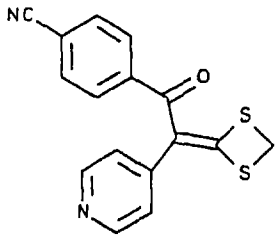

mp 198.8-198.9 °C; $^1$H NMR (acetone-d6/300 MHz) 8.45 (m, 2H), 7.05 (m, 3H), 6.95 (m, 1H), 6.82 (m, 1H), 4.29 (s, 2H), 2.14 (s, 3H), 2.08 (s, 3H); ESHRMS *m/z* 314.0691 (M+H, $C_{17}H_{15}NOS_2$ requires 314.0673).

**Example A-395**



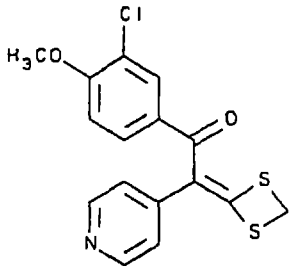
mp 182.6-183.0 °C. $^1$H NMR (acetone-d6/300 MHz) 8.50 (m, 2H), 7.42 (d, 2H, *J* = *8.5 Hz*), 7.23 (d, 2H, *J* = *8.5 Hz*), 7.10 (m, 2H), 4.40 (s, 2H). ESHRMS *m/z* 370.0173 (M+H, $C_{16}H_{10}F_3NO_2S_2$ requires 370.0183).

**Example A-396**



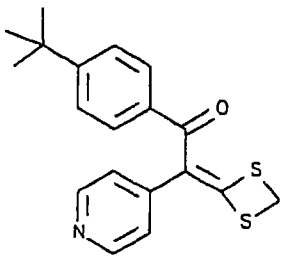
mp 193.3-193.4 °C. $^1$H NMR (acetone-d6/300 MHz) 8.49 (m, 2H), 7.69 (d, 2H, *J* = *8.2 Hz*), 7.46 (d, 2H, *J* = *8.2 Hz*), 7.01 (m, 2H), 4.43 (s, 2H). ESHRMS *m/z* 311.0327 (M+H, $C_{16}H_{10}N_{20}S_2$ requires 311.0313).

**Example A-397**



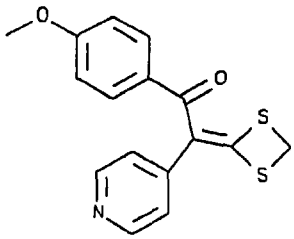
mp 191.5-192.5 °C; $^1$H NMR ($CDCl_3$/ 300 MHz) 8.55 (dd, 2H, $J$ = 4.6, 1.6 Hz), 7.4 (m, 1H), 7.09-7.03 (m, 3H), 6.67 (d, 1H, $J$ = 8.7 Hz), 4.17 (s, 2H), 3.86 (s, 3H); ESHRMS $m/z$ 350.0090 (M+H, $C_{16}H_{12}ClNO_2S_2$ requires 350.0076); Anal. Calc'd. for $C_{16}H_{12}ClNO_2S_2$: C, 54.93; H, 3.60; N, 4.00; Cl, 10.13; S, 18.33. Found: C, 54.74; H, 3.60; N, 3.89; Cl, 10.45; S, 18.32.

**Example A-398**



mp 172.1-173.1 °C; $^1$H NMR ($CDCl_3$ / 300 MHz) 8.51 (dd, 2H, $J$ = 4.4, 1.6 Hz), 7.23-7.21 (m, 4H), 7.04 (dd, 2H, $J$ = 4.6, 1.6 Hz), 4.17 (s, 2H), 1.25 (s, 9H); ESHRMS $m/z$ 342.1004 (M+H, $C_{19}H_{19}NOS_2$ requires 342.0986); Anal. Calc'd for $C_{19}H_{19}NOS_2$: C, 66.83; H, 5.61; N, 4.10; S, 18.78. Found: C, 66.97; H, 5.89; N, 4.02; S, 18.64.

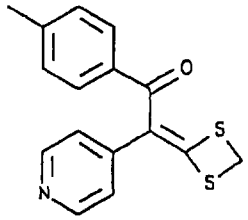
**Example A-399**



mp 203.0-204.1 °C; $^1$H NMR ($CDCl_3$ / 300 MHz) 8.52 (dd, 2H, $J$ = 4.4, 1.6 Hz), 7.29 (d, 1H, $J$ = 6.8 Hz), 7.28 (d, 1H, $J$ = 7.0 Hz), 7.05 (dd, 2H, $J$ = 4.4, 1.6 Hz), 6.70 (d, 1H, $J$ = 6.8 Hz), 6.69 (d, 1H, $J$ = 6.8 Hz), 4.17 (s, 2H), 3.79 (s, 3H); ESHRMS $m/z$ 316.0475 (M+H, $C_{16}H_{13}NO_2S_2$

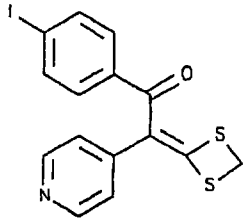
requires 316.0466); Anal. Calc'd. for $C_{16}H_{13}NO_2S_2$: C, 60.93; H, 4.15; N, 4.44; S, 20.33. Found: C, 60.46; H, 4.17; N, 4.37; S, 19.84.

**Example A-400**



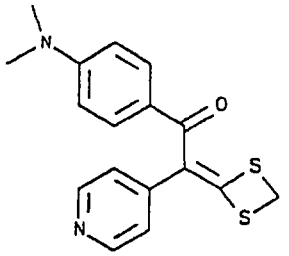
mp 209.1-215.1 °C; $^1$H NMR ($CDCl_3$ / 300 MHz) 8.50 (dd, 2H, $J$ = 4.4, 1.6 Hz), 7.20 (d, 2H, $J$ = 8.0 Hz), 7.03-6.99 (m, 4H), 4.18 (s, 2H), 2.30 (s, 3H); ESHRMS $m/z$ 300.0517 (M+H, $C_{16}H_{13}NOS_2$ requires 300.0517); Anal. Calc'd. for $C_{16}H_{13}NOS_2$: C64.18; H, 4.38; N, 4.69; S, 21.42. Found: C, 64.02; H, 4.62; N, 4.54; S, 21.24.

**Example A-401**



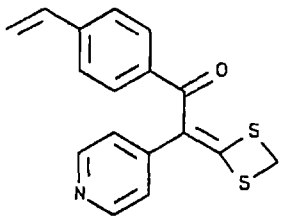
mp 257.6-257.7 °C; $^1$H NMR ($CDCl_3$ / 300 MHz) 8.51 (dd, 2H, $J$ = 4.4, 1.6 Hz), 7.57 (d, 2H, $J$ = 8.5 Hz), 7.27-6.99 (m, 4H), 4.18 (s, 2H); ESHRMS $m/z$ 411.9348 (M+H, $C_{15}H_{10}NIOS_2$ requires 411.9327); Anal. Calc'd. for $C_{15}H_{10}NIOS_2$: C, 43.81; H, 2.45; N, 3.41. Found: C, 43.71; H, 2.27; N, 3.41.

**Example A-402**



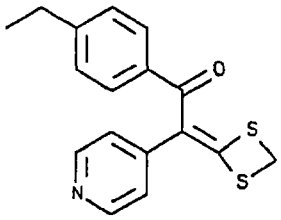
mp 197.3-202.2 °C; $^1$H NMR ($CDCl_3$ / 300 MHz) 8.53(dd, 2H, $J$ = 4.4, 1.6 Hz), 7.26 (d, 2H, $J$ = 9.3 Hz), 7.09 (dd, 2H, $J$ = 4.4, 1.6 Hz), 6.43 (d, 2H, $J$ = 9.3 Hz), 4.14 (s, 2H), 2.97 (s, 6H); ESHRMS $m/z$ 329.0789 (M+H, $C_{17}H_{16}N_2OS_2$ requires 329.0782); Anal. Calc'd. for $C_{17}H_{16}N_2OS_2$: C, 62.17; H, 4.91; N, 8.53; S, 19.53. Found: C, 61.93; H, 5.12; N, 8.46; S,19.26.

**Example A-403**



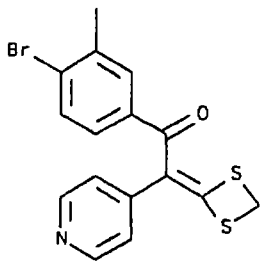
mp 176.6-176.7 °C; $^1$H NMR ($CDCl_3$ / 300 MHz) 8.51 (dd, 2H, $J$ = 4.4, 1.6 Hz), 7.29-7.22 (m, 4H), 7.03(dd, 2H, $J$ = 4.4, 1.6 Hz), 6.64 (dd, 1H, $J$ = 17.5, 10.9 Hz), 5.76 (d, 1H, $J$ = 17.7 Hz), 5.31 (d, 1H, J = 10.9 Hz), 4.19 (s, 2H); ESHRMS 312.0513 (M+H, $C_{17}H_{13}NOS_2$ requires 312.0517); Anal. Calc'd. for $C_{17}H_{13}NOS_2$: C, 65.56; H, 4.21; N, 4.50. Found: C, 65.75; H, 4.11; N, 4.46.

**Example A-404**



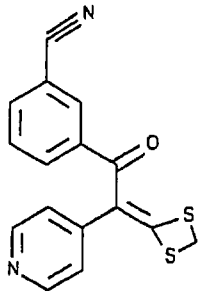
mp 174.8-175.0 °C; $^1$H NMR ($CDCl_3$ / 300 MHz) 8.50 (dd, 2H, $J$ = 4.4, 1.6 Hz), 7.23-7.20 (m, 4H), 7.03 (dd, 2H, $J$ = 4.6, 1.6 Hz), 4.17 (s, 2H), 2.59 (q, 2H, $J$ = 7.6 Hz), 1.17 (t, 3H, $J$ = 7.7 Hz); ESHRMS $m/z$ 314.0677 (M+H, $C_{17}H_{15}NOS_2$ requires 314.0673); Anal. Calc'd. for $C_{17}H_{15}NOS_2$: C, 65.14; H, 4.82; N, 4.47. Found: C, 64.90; H, 4.62; N, 4.45.

**Example A-405**



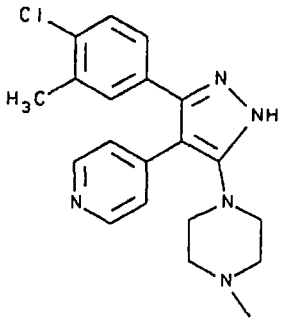
mp 167.1-167.5 °C; $^1$H NMR ($CDCl_3$ / 300 MHz) 8.52 (dd, 1H, $J$ = 4.4, 1.6 Hz), 7.33 (d, 1H, $J$= 8.3 Hz), 7.02-7.00 (m, 3H), 6.87-6.83 (m, 1H), 4.19 (s, 2H), 2.28 (s, 3H); ESHRMS $m/z$ 379.9577 (M+H, $C_{16}H_{12}BrNOS_2$ requires 379.9622); Anal. Calc'd. for $C_{16}H_{12}BrNOS_2$: C, 50.80; H, 3.20; N, 3.70. Found: C, 50.69; H, 3.19; N, 3.71.

**Example A-406**



mp 168.6-168.7 °C; $^1$H NMR ($CDCl_3$/300 MHz) 8.54 (dd, 2H, $J$ = 4.6, 1.8 Hz), 7.68-7.62 (m 2H), 7.43-7.39 (m, 1H), 7.33-7.28 (m, 1H), 6.99 (dd, 2H, $J$ = 4.4, 1.6 Hz), 4.22 (s, 2H); ESHRMS $m/z$ 311.0330 (M+H, $C_{16}H_{10}N_2OS_2$ requires 311.0313); Anal. Calc'd. for $C_{16}H_{10}N_2OS_2$: C, 61.91; H, 3.25; N, 9.02. Found: C, 61.45; H, 3.18; N, 8.91.

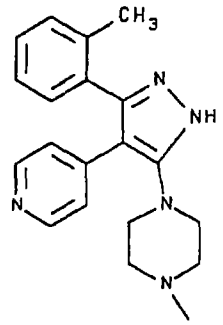
**Example A-407**



1-[5-(3-methyl-4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 236.7-239.3 °C; $^1$H NMR (DMSO-d6/300 MHz) 12.6 (brs, 1H), 8.45 (m, 2H), 7.41 (m, 1H), 7.26 (m, 3H), 7.0 (m, 1H), 2.86 (m, 4H), 2.35 (m, 4H), 2.27 (s, 3H), 2.16 (s, 3H); ESHRMS $m/z$ 368.4653 (M+H, $C_{20}H_{22}ClN_5$ requires 368.1642).

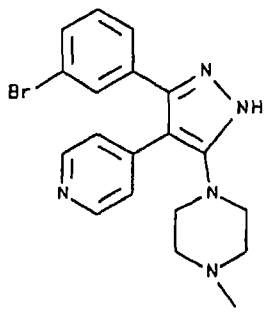
**Example A-408**



1-[5-(2-tolyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 244.0-244.2 °C; $^1$H NMR (acetone-d6/300 MHz) 11.6 (brs, 1H), 8.35 (m, 2H), 7.35 (m, 2H), 7.25 (m, 4H), 3.05 (m, 4H), 2.47 (m, 4H), 2.25 (s, 3H), 2.00 (s, 3H); ESHRMS *m/z* 334.2018 (M+H, $C_{20}H_{23}N_5$ requires 334.2032); Anal. Calc'd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00. Found: C, 72.03; H, 7.00; N, 20.85.

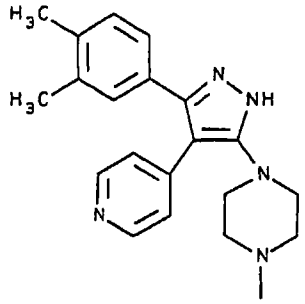
**Example A-409**



1-[5-(3-bromophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 222.5-223.4 °C; $^1$H NMR (acetone-d6/300 MHz) 11.8 (brs, 1H), 8.51 (m, 2H), 7.55 (m, 2H), 7.34 (m, 4H), 3.0 (m, 4H), 2.41 (m, 4H), 2.22 (s, 3H); ESHRMS *m/z* 398.0982 (M+H, $C_{19}H_{20}BrN_5$ requires 398.0980).

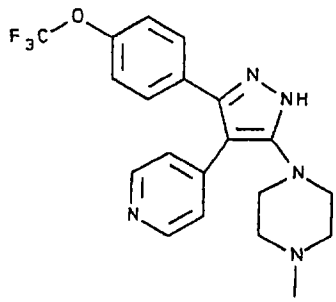
**Example A-410**



1-[5-(3,4-dimethylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 270.9-272.7 °C; $^1$H NMR (DMSO-d6/300 MHz) 12.5 (brs, 1H), 8.41 (m, 2H), 7.24 (m, 2H), 7.26 (m, 3H), 7.10 (m, 2H), 6.92 (m, 1H), 2.86 (m, 4H), 2.38 (m, 4H), 2.21 (s, 3H), 2.19 (s, 3H), 2.16 (s, 3H); ESHRMS *m/z* 348.2183 (M+H, $C_{21}H_{25}N_5$ requires 348.2188).

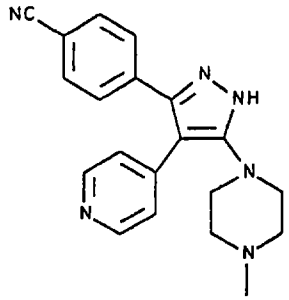
**Example A-411**



1-[5-(4-trifluoromethoxyphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 221.0-221.2 °C; $^1$H NMR (DMSO-d6/300 MHz) 12.7 (brs, 1H), 8.45 (m, 2H), 7.38 (s, 4H), 7.24 (m, 2H), 2.86 (m, 4H), 2.34 (m, 4H), 2.16 (s, 3H); ESHRMS *m/z* 404.1698 (M+H, $C_{20}H_{20}F_3N_5O$ requires 404.1698).

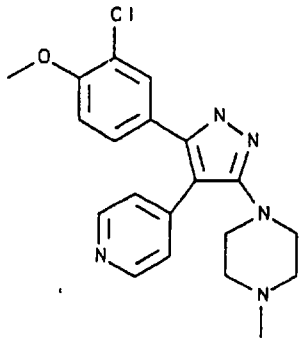
**Example A-412**



1-[5-(4-cyanophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp > 300 °C; $^1$H NMR (DMSO-d6/300 MHz) 12.8 (brs, 1H), 8.47 (m, 2H), 7.83 (m, 2H), 7.42 (m, 2H), 2.88 (m, 4H), 2.39 (m, 4H), 2.20 (s, 3H); ESHRMS *m/z* 345.1848 (M+H, $C_{20}H_{20}N_6$ requires 345.1828).

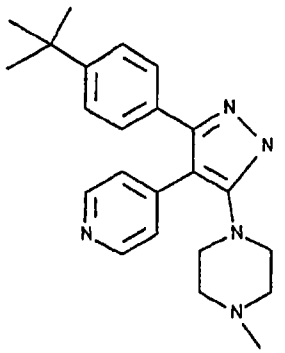
**Example A-413**



1-[5-(3-chloro-4-methoxyphenyl)-4-(4-pyridinyl-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 272.7-276.4 °C; $^1$H NMR (DMSO-d6/300 MHz) 8.44 (dd, 2H, *J* = 4.6, 1.6 Hz), 7.32-7.13 (m, 5H), 3.84 (s, 3H), 2.90-2.85 (m, 4H), 2.38-2.35 (m, 4H), 2.16 (s, 3H); ESHRMS *m/z* 384.1580 (M+H $C_{20}H_{22}ClN_5O$ requires 384.1591).

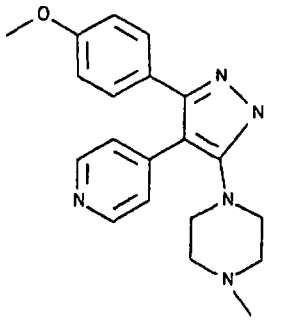
**Example A-414**



1-[5-(4-tert-butylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 243.6-244.3 °C; $^1$H NMR (DMSO-d6/300 MHz) 8.44 (dd, 2H, *J* = 4.6, 1.6, Hz), 7.40 (d, 2H, *J* = 8.3 Hz), 7.28-7.18 (m, 4H), 2.90-2.85 (m, 4=H), 2.38-2.34 (m, 4H), 2.16 (s,3H), 1.26 (s, 9H); ESHRMS *m/z* 376.2491 (M+H, $C_{23}H_{29}N_5$ requires 376.2501).

**Example A-415**

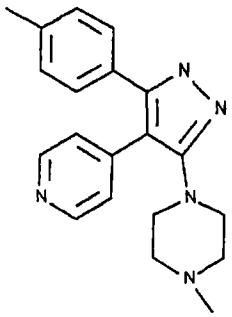


1-[4-(4-methoxyphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 259.0-260.2 °C; $^1$H NMR (DMSO-d6/300 MHz) 8.53 (dd, 2H, *J* = 4.4, 1.6 Hz), 7.24 (dd, 2H, *J* = 4.4, 1.6 Hz), 7.18 (d, 2H, *J* = 8.9 Hz), 6.94 (d, 2H, *J* = 8.9 Hz),

3.75 (s, 3H), 2.90-2.85 (m, 4H), 2.39-2.35 (m, 4H), 2.16 (s, 3H); ESHRMS *m/z* 350.1991 (M+H, $C_{20}H_{23}N_5O$ requires 350.1981); Anal. Calc'd. for $C_{20}H_{23}N_5O$ + 3.93%H2O: C, 66.04; H, 6.81; N, 19.25. Found: C, 66.01; H, 6.62; N, 19.32.

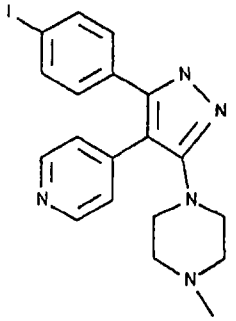
**Example A-416**



1-[5-(4-methylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 243.0-246.8 °C; $^1$H NMR (DMSO-d6/300 MHz) 8.41 (dd, 2H, *J* = 4.6, 1.6 Hz), 7.24 (m, 6H), 2.91-2.86 (m, 4H), 2.40-2.35 (m, 4H), 2.29 (s, 3H), 2.16 (s, 3H); ESHRMS *m/z* 334.2041 (M+H, $C_{20}H_{23}N_5$ requires 334.2032); Anal. Calc'd for $C_{20}H_{23}N_5$ + 4.09%H2O: C, 69.10; H, 7.13; N, 20.14. Found: C, 69.10; H, 7.08; N, 20.13.

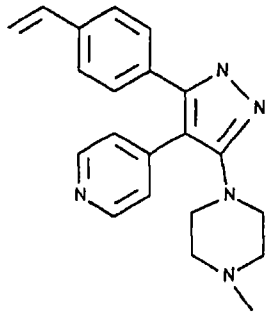
**Example A-417**



1-[5-(4-iodophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 265.2-265.8 °C; $^1$H NMR ($CD_3OD$/300 MHz) 8.41 (dd, 2H, $J$ = 4.6, 1.6 Hz), 7.76-7.74 (m, 2H), 7.41-7.39 (m, 2H), 7.08-7.05 (m, 2H), 3.08-3.04 (m, 4H), 2.61-2.58 (m, 4H), 2.35 (s, 3H); ESHRMS $m/z$ 446.0847 (M+H, $C_{19}H_{20}IN_5$ requires 446.0842); Anal. Calc'd. for $C_{19}H_{20}IN_5$ + 12.09%$H_2O$: C, 44.60; H, 5.39; N, 13.69. Found: C, 44.50; H, 4.56; N, 13.66.

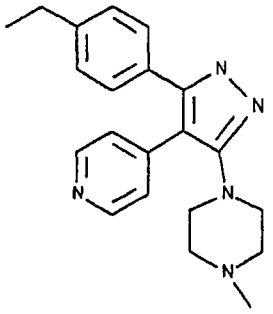
**Example A-418**



1-[5-(4-ethenylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp >300 °C; $^1$H NMR ($CD_3OD$/300 MHz) 8.49 (dd, 2H, $J$ = 4.6, 1.6 Hz), 7.47-7.44 (m, 4H), 7.26 (d, 2H, $J$ = 8.4 Hz), 6.75 (dd, $J$ = 17.7, 11.1 Hz), 5.83 (d, 1H, $J$ = 17.5 Hz), 5.28 (d, 1H, $J$ = 11.1 Hz), 3.07-3.03 (m, 4H), 2.58-2.53(m, 4H), 2.31 (s, 3H); ESHRMS $m/z$ 346.2034 (M+H, $C_{21}H_{23}N_5$ requires 346.2032); Anal. Calc'd. for $C_{21}H_{23}N_5$ + 2.83%$H_2O$: C, 70.95; H, 6.84; N, 19.70. Found: C, 70.97; H, 6.49; N, 19.54.

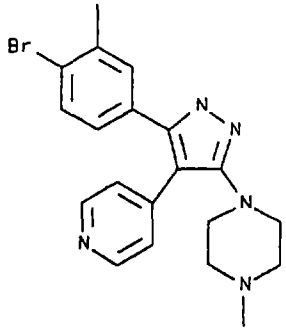
**Example A-419**



1-[5-(4-ethylphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 221.6-222.6 °C; $^1$H NMR ($CD_3OD$/300 MHz) 8.38 (dd, 2H, $J$ = 4.6, 1.6 Hz), 7.44-7.40 (m, 2H), 7.26-7.19 (m, 4H), 3.06-3.02 (m, 4H), 2.66 (q, 2H, $J$ = 7.5 Hz), 2.59-2.54 (m, 4H), 2.32 (s, 3H), 1.23 (t, 3H, $J$ = 7.5 Hz); ESHRMS $m/z$ 348.2188 (M+H, $C_{21}H_{25}N_5$ requires 348.2188); Anal. Calc'd for $C_{21}H_{25}N_5$ + 2.59%$H_2O$: C, 70.71; H, 7.35; N, 19.63. Found: C, 70.76; H, 7.40; N, 19.46.

**Example A-420**

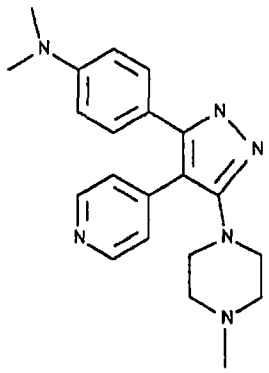


1-[5-(4-bromo-3-methylphenyl)-4-(4-pyrdinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 294.7 °C decomp.; $^1$H NMR ($CD_3OD$/300 MHz) 8.41 (dd, 2H, $J$ = 4.6, 1.6 Hz), 7.55 (d, 1H, $J$ = 8.2 Hz), 7.45-7.42 (m, 2H), 7.27-7.25 (m, 1H), 7.00-6.97 (m 2H),

3.08-3.03 (m, 4H), 2.59-2.54 (m, 4H), 2.35 (s, 3H), 2.31 (s, 3H); ESHRMS *m/z* 412.1124 (M+H, $C_{20}H_{22}BrN_5$ requires 412.1137).

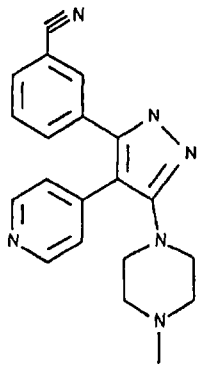
**Example A-421**



1-[5-(4-dimethylaminophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp >300 °C (decomposed); $^1$H NMR ($CD_3OD$ / 300 MHz) 8.37 (d, 2H, *J* = 4.6 Hz), 7.44 (d, 2H, *J* = 4.8 Hz), 7.12, (d, 2H, *J* = 8.9 Hz), 6.73 (d, 2H, *J* = 8.7 Hz), 3.04-3.02 (m, 4H), 2.96 (s, 6H), 2.54-2.49 (m, 4H), 2.31 (s, 3H); ESHRMS *m/z* 363.2266 (M+H, $C_{21}H_{26}N_6$ requires 363.22972).

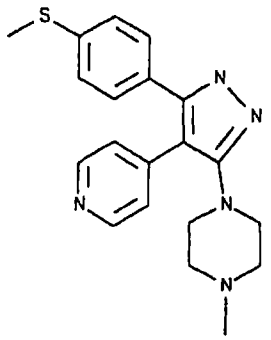
**Example A-422**



1-[5-(3-cyanophenyl)-4-(4-pyrdinyl)-1H-pyrazol-3-yl]4-methylpiperazine.

mp 223.4-224.3 °C; $^1$H NMR ($CD_3OD$ / 300 MHz) 8.44 (dd, 2H, *J*= 4.6, 1.4 Hz), 7.75-7.69 (m, 2H), 7.56-7.54 (m, 2H), 7.40-7.38 (m, 2H), 3.05-3.03 (m, 4H), 2.54-2.49 (m, 4H), 2.53 (s, 3H); ESHRMS *m/z* 345.1840 (M+H, $C_{20}H_{20}N_6$ requires 345.1828).

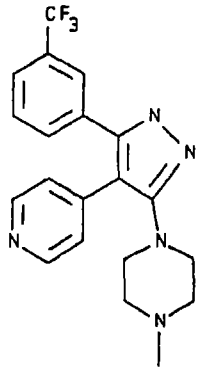
**Example A-423**



1-[5-(4-thiomethoxyphenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 275.6-281.9 °C; $^1$H NMR ($CD_3OD$ / 300 MHz) 8.44-8.40 (m, 2H), 7.46-7.41 (m, 2H), 7.28-7.23 (m, 4H), 3.04-3.00 (m, 4H), 2.59-2.53 (M, 4H), 2.48 (s, 3H), 2.31 (s, 3H); ESHRMS *m/z* 366.1777 (M+H, $C_{20}H_{23}N_5S$ requires 366.1752).

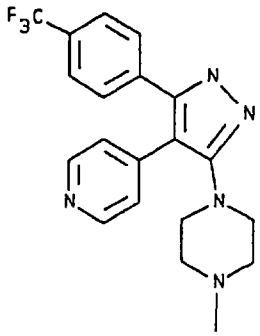
**Example A-424**



1-[5-(3-trifluoromethylphenyl)-4-(4-pyridinyl-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 212.6-213.7 °C; $^1$H NMR ($CD_3OD$ / 300 MHz) 8.43 (d, 2H, $J$ = 4.8 Hz), 7.69-7.56 (m, 4H), 7.41 (s, 2H), 3.07-3.04 (m, 4H), 2.56-2.53 (m, 4H), 2.32 (s, 3H); ESHRMS $m/z$ 388.1764 (M+H, $C_{20}H_{20}F_3N_5$ requires 388.1749).

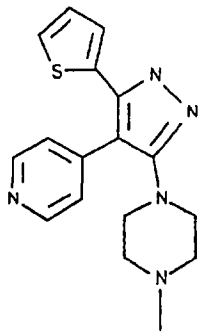
**Example A-425**



1-[5-(4-trifluoromethylphenyl)-4-(4-pyridinyl-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 240.5 °C (decomposed); $^1$H NMR ($CD_3OD$ / 300 MHz) 8.43 (dd, 2H, $J$ = 4.6, 1.6 Hz), 7.70-7.67 (m, 2H), 7.51-7.48 (m, 2H), 7.42-7.38 (m 2H), 3.09-3.04 (m, 4H), 2.59-2.53 (m, 4H), 2.31 (s, 3H); ESHRMS $m/z$ 388.1768 (M+H, $C_{20}H_{20}F_3N_5$ requires 388.1749).

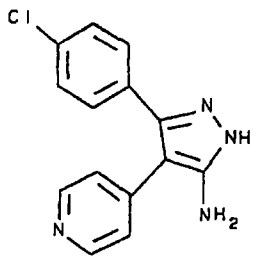
**Example A-426**



1-[5-(2-thienyl)-4-(4-pyridinyl-1H-pyrazol-3-yl]-4-methylpiperazine.

mp 199.7 °C (decomposed); $^1$H NMR ($CD_3OD$ / 300 MHz) 8.44 (d, 2H, $J$ = 5.8 Hz), 7.47 (d, 2H, $J$ = 5.6 Hz), 7.13 - 7.07 (m, 3H), 3.04-3.00 (m, 4H), 2.53-2.49 (m, 4H), 2.30 (s, 3H); ESHRMS $m/z$ 326.1454 (M+H, $C_{17}H_{19}N_5S$ requires 326.1439).

**Example A-427**




Step 1: Preparation of 3-dimethylamino-1-(4-chlorophenyl)-2-(pyridin-4-yl)-2-propene-1-one

A solution of 4-chlorophenyl-2-(pyridin-4-yl)ethan-1-one (20.0 g, 86.4 mmol) and N,N-dimethylformamide dimethylacetal (57.6 mL, 0.43 mole) was heated at 100 °C for 3 ½ hours. The reaction mixture was concentrated in vacuo, and the residue crystallized from methyl butyl ether to give 3-dimethylamino-1-(4-chlorophenyl)-2-(pyridin-4-yl)-2-propen-1-one (22.80 g, 93%). $^1$H NMR ($CDCl_3$/300 MHz) $\delta$ 8.52 (d, 2H), 7.38 (d, 2H), 7.29 (d, 2H), 7.08 (d, 2H), 2.83 (s, 6H).

Step 2: Preparation of 5-(4-chlorophenyl)-4-(pyridin-4-yl)isoxazole

A solution of 3-dimethylamino-1-(4-chlorophenyl)-2-(pyridin-4-yl)-2-propen-1-one (22.80 g, 79.7 mmol), hydroxylamine hydrochloride (18.01 g, 0.26 mole), and 150

mL ethanol was heated to reflux for 30 minutes. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in 1N hydrochloric acid and then treated with an aqueous saturated solution of sodium bicarbonate. The precipitates were collected by filtration, washed with water and ethanol, and dried to yield 5-(4-chlorophenyl)-4-(pyridin-4-yl)isoxazole (20.50 g, 93%). m.p. 120.8-120.9 °C. $^1$H NMR ($CDCl_3/CD_3OD$/300 MHz) δ 8.53 (d, 2H), 8.46(s, 1H), 7.51(d, 2H), 7.41-7.34 (m, 4H). ESLRMS *m/z* 257 (M+H). ESHRMS *m/z* 257.0457 (M+H, $C_{14}H_9N_2OCl$ requires 257.0482).

Step 3: Preparation of 3-(4-chlorophenyl)-3-oxo-2-(pyridin-4-yl)propanenitrile:

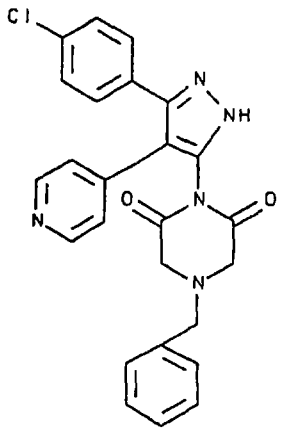
A solution of 5-(4-chlorophenyl)-4-(pyridin-4-yl)isoxazole (20.5 g, 79.9 mmol) and 150 mL of a 1N sodium hydroxide solution was stirred at 60 °C for 1 hour. The reaction mixture was cooled to room temperature and adjusted to pH 6 with concentrated hydrochloric acid. The precipitates were filtered, washed with water and ethanol, and dried to give 3-(4-chlorophenyl)-3-oxo-2-(pyridin-4-yl)propanenitrile (20.0 g, quantitative yield). m.p. 225.4-234.9 °C. $^1$H NMR ($CDCl_3/CD_3OD$/300 MHz) δ 8.12 (brs, 2H), 7.73-7.59 (m, 5H), 7.30 (d, 3H). ESLRMS m/z 257 (M+H). ESHRMS m/z 257.0481 (M+H, $C_{14}H_9N_{20}Cl$ requires 257.0482).

Step 4: 5-amino-3-(4-chlorophenyl)-4-(pyridin-4-yl)-pyrazole

A solution of 3-(4-chlorophenyl)-3-oxo-2-(pyridin-4-yl)propanenitrile (3.50 g, 13.6 mmol) in 40 mL acetonitrile and phosphorous trichloride (14.2 ml, 163 mmol) was stirred at 100 °C for 5 hours. The reaction

mixture was concentrated in vacuo, and the residue taken up in toluene and concentrated again. The residue was then taken up in ethanol (150 mL) and treated with anhydrous hydrazine (1.71 mL, 54.4 mmol). The reaction mixture was heated to reflux for 3 hours, cooled, and concentrated in vacuo. The residue was triturated with a mixture of ethanol and dichloromethane (1:4), and filtered. The solid was washed with the ethanol/dichloromethane mixture, and dried to give 5-amino-3-(4-chlorophenyl)-4-(pyridin-4-yl)-pyrazole (2.0 g, 54%): m.p. >300 °C. $^1$H NMR (DMSO/300 MHz) δ 8.40 (d, 2H), 7.40 (d, 2H), 7.29 (d, 2H), 7.11 (d, 2H), 5.05 (s, 2H). ESLRMS *m/z* 271 (M+H). ESHRMS *m/z* 271.0752 (M+H, $C_{14}H_{11}N_4Cl$ requires 271.0750).

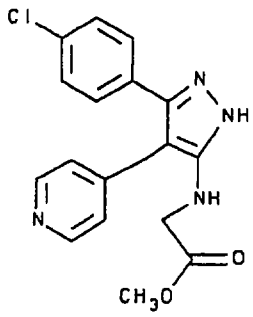
**Example A-428**




A solution of 1,1'-carbonyldiimidazole (1.19 g, 7.38 mmol) and N-benzyliminodiacetic acid (0.824 g, 3.69 mmol) in dimethylformamide was heated at 75 °C for 30 minutes. To this mixture the 5-amino-3-(4-chlorophenyl)-4-(pyridin-4-yl)-pyrazole (1.0 g, 3.69 mmol) was added, and heating was continued at 75 °C overnight. The white solid was filtered, was washed with diethyl ether, methylene chloride, 5% methanol/methylene chloride, and ethanol, and was dried to give the desired imide as an

off-white solid (0.9 g, 53%): m.p. >300 °C. $^1$H NMR (DMSO/300 MHz) $\delta$ 8.53 (m, 2H), 7.5(d, 2H), 7.44- 7.16 (m, 7H), 6.98(m, 2H), 3.64 (m, 4H), 3.48 (m, 2H). ESLRMS *m/z* 458 (M+H). ESHRMS *m/z* 458.1380 (M+H, $C_{25}H_{20}N_5O_2Cl$ requires 458.1384).

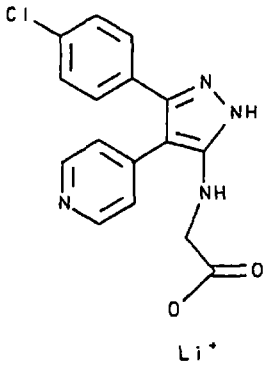
**Example A-429**




Methyl 2-{[3-94-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]amino}acetate

A solution of 5-amino-3-(4-chlorophenyl)-4-(pyridin-4-yl)-pyrazole (1.0 g, 3.7 mmol) in dimethylformamide (30 mL) was heated to 95 °C and methyl bromo acetate (0.34 mL, 3.7 mmol) was added dropwise. The resulting solution was stirred at 95 °C for 4 hours, cooled, and concentrated *in vacuo* to an orange viscous oil (1.79 g). A portion of this product mixture (1.20 g) was crystallized from ethanol and diethyl ether to give methyl 2-{[3-4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]amino}acetate as a bright yellow solid (805 mg): m.p. 195.4-196.8 °C. $^1$H NMR ($CD_3OD$/300 MHz) $\delta$ 8.49 (d,2H), 7.68 (d, 2H), 7.44 (m, 4H), 5.37 (s, 2H), 3.84 (s, 3H). ESLRMS *m/z* 343 (M+H). ESHRMS *m/z* 343.0975 (M+H, $C_{17}H_{16}N_4O_2Cl$ requires 343.0962).

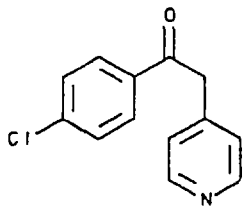
**Example A-430**



Lithium 2-{[3-4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]amino}acetate

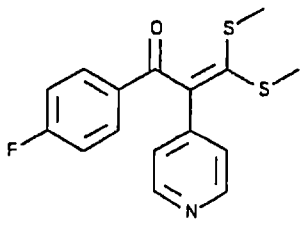
To a solution of methyl 2-{[3-4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]amino}acetate (500 mg, 1.5 mmol) in 15 mL of methanol and 5 mL of water was added lithium hydroxide (189 mg, 4.5 mmol). The reaction mixture was stirred at room temperature for 5 hours. The solvent was removed *in vacuo*, and the residue taken up in ethanol. The precipitate was filtered and washed with methanol, and the filtrate was concentrated to give lithium 2-{[3-4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-5-yl]amino}acetate as a yellow/orange solid (479 mg, 95%). mp >300 °C. $^1$H NMR ($CD_3OD$/300 MHz) δ 8.06 (d, 2H), 7.43 (d, 2H), 7.37 (m, 4H), 3.34 (s, 2H). ESLRMS m/z 329 (M+H), 335 (M+Li), 351 (M+Na). ESHRMS m/z 329.0772 (M+H, $C_{16}H_{14}N_4O_2Cl$ requires 329.0805).

**Example A-431**



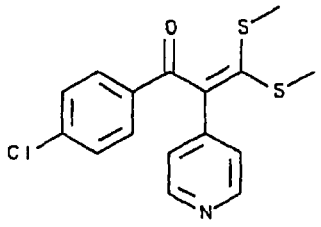
The above 4-chlorophenylketone was prepared according to the procedure used in Step 1 of Example C-1, infra, substituting methyl 4-chlorobenzoate for ethyl 4-fluorobenzoate. Yield; (74 %), yellow solid, mp = 95.5-97.3 °C; 1H-NMR (DMSO-d6/300 MHz) 8.57 (br d, 2H), 7.92 (d, 2H), 7.46 (d, 2H), 7.20 (d, 2H), 4.28 (s, 2H); ESLRMS *m/z* 232 (M+H).

**Example A-432**



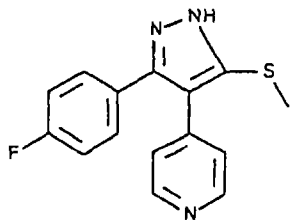

To the ketone (1.0gm, 4.7 mmol) from Step 1 of Example C-1, infra, in anhydrous tetrahydrofuran (10 mL) was added 1M potassium t-butoxide in tetrahydrofuran (10 mL, 10 mmol). The reaction mixture was stirred for 15 minutes at room temperature, then carbon disulfide (0.31 mL, 5.1 mmol) was added. After several minutes, methyl iodide (0.64 mL, 10.3 mmol) was added and the reaction allowed to stir for 4 hours. The reaction mixture was diluted with saturated sodium bicarbonate solution (25 mL) and extracted twice with ethyl acetate (35 mL). The combined ethyl acetate layers were washed with water (25 mL) and brine (25mL). The organic solution was dried ($MgSO_4$), filtered and concentrated to an orange oil. The oil solidified on standing. Yield 1.4 gm (94%), mp 80.2-82.1 °C; $^1$H-NMR ($CDCl_3$/300 MHz) 8.59 (d, 2H), 7.96 (m, 2H), 7.38 (m, 2H), 7.14 (m, 2H), 2.33 (s, 3H), 2.23 (s, 3H); Anal. Calc'd for $C_{16}H_{14}FNOS_2$: C, 60.16; H, 4.42; N, 4.39; S, 20.08. Found: C, 59.89; H, 4.09; N, 4.31; S, 20.14.

**Example A-433**



The above compound was prepared in a manner analogous to Example A-432 starting with the product of Example A-431. Crude yield: 100 %; mp 87.6-88.2 °C; $^1$H-NMR ($CDCl_3$/300 MHz) 8.60 (d, 2H), 7.87 (d, 2H), 7.44 (d, 2H), 7.37 (m, 2H), 2.33 (s, 3H), 2.22 (s, 3H); ESHRMS *m/z* 336.0297 (M+H, $C_{16}H_{15}ClNOS_2$ requires 336.0283); Anal. Calc'd for $C_{16}H_{14}ClNOS_2$: C, 57.22; H, 4.20; N, 4.17. Found: C, 57.44; H, 3.97; N, 4.04.

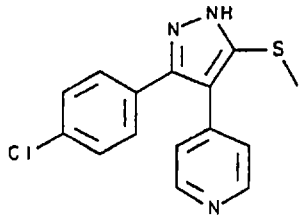
**Example A-434**



To the compound of Example A-432 (1.4 gm, 4.4 mmol) in ethanol (15 mL) was added 1M hydrazine in acetic acid (5 mL, 5 mmol). The reaction was stirred at room temperature for 18 hours. No reaction had occurred, so additional hydrazine hydrate (1.08 mL, 22 mmol) was added and the reaction heated to reflux for 6 hours. The product began to precipitate from the reaction mixture. The reaction was cooled to room temperature and water was added to precipitate the product. The solid was collected by suction filtration and air dried. Yield: 675 mg (53%). The product was recrystallized from ethanol: 494 mg; mp 249.9-249.9 °C; $^1$H-NMR (DMSO-d6/300

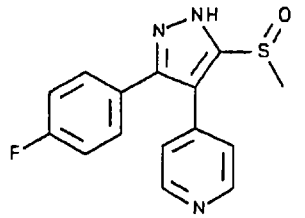
MHz) 13.51 (br s, 1H), 8.50 (d, 2H), 7.34 (m, 2H), 7.23 (m, 2H), 7.16 (m, 2H), 2.43 (s, 3H); ESHRMS *m/z* 286.0807 (M+H, $C_{15}H_{13}FN_3S$ requires 286.0814); Anal. Calc'd for $C_{15}H_{12}FN_3S$: C, 63.14; H, 4.24; N, 14.73. Found: C, 63.01; H, 4.43; N, 14.81.

**Example A-435**



The above compound was made in an analogous manner to Example A-434 starting with the compound of Example A-433. Yield: 750 mg (33%); mp 250.2-250.2 °C; $^1$H NMR (DMSO-d6/300 MHz) 13.57 (br s, 1H), 8.51 (m, 2H), 7.45 (br s, 2H), 7.32 (m, 2H), 7.17 (m, 2H), 2.43 (s, 3H); ESHRMS *m/z* 302.0537 (M+H, $C_{15}H_{13}ClN_3S$ requires 302.0518); Anal. Calc'd for $C_{15}H_{12}ClN_3S$: C, 59.70; H, 4.01; N, 13.92. Found: C, 59.56; H, 3.96; N, 13.96.

**Example A-436**

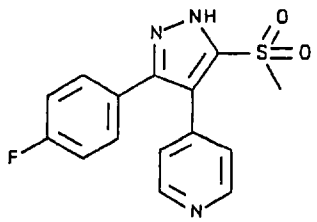


3-(4-fluorophenyl)-4-(methylsulfinyl)-4-pyridin-4-yl-1H-pyrazole

To the compound of Example A-434 (150 mg, 0.52 mmol) in ethanol (15 mL) was added ammonium persulfate (450 mg, 1.97 mmol). The reaction mixture was stirred at ambient

temperature. After several hours an additional amount of ammonium persulfate (450 mg) was added. The reaction mixture was monitored by TLC (silica) using 5% methanol in dichloromethane as the eluting solvent. When the stating material had been consumed, the reaction mixture was quenched with saturated sodium bicarbonate (25 mL) and extracted with ethyl acetate (2 x 25 mL). The ethyl acetate layers were combined, washed with brine (25 mL) and dried ($MgSO_4$). Filtration and concentration produced a white solid. The solid was triturated with diethyl ether, collected by suction filtration, and air dried. Yield 150 mg (96%), mp 262.9-262.9 °C; $^1H$ NMR (DMSO-d6/300 MHz) 14.22 (br s, 1H), 8.56 (d, 2H), 7.42-7.23 (br m, 6H), 2.94 (s, 3H); Anal. Calc'd for $C_{15}H_{12}FN_3OS \cdot 0.25 H_2O$: C, 58.91; H, 4.12; N, 13.74; Found: C, 58.88; H, 4.17; N, 13.39.

**Example A-437**

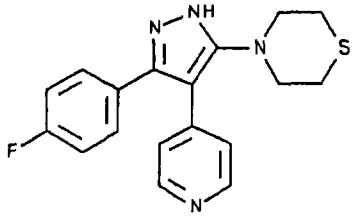



3-(4-fluorophenyl)-5-(methylsulfonyl)-4-pyridin-4-yl-1H-pyrazole

To the compound of Example A-434 (285 mg, 1 mmol) in ethanol (10 mL) was added potassium peroxymonosulfate (2.45 gm, 4 mmol) and water (5 mL). The reaction mixture was stirred at ambient temperature. After 6 hours the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The ethyl acetate layers were combined, washed with brine (25 mL) and dried ($MgSO_4$). The ethyl acetate did not efficiently extract the product from the aqueous phase, so the

aqueous layer was saturated with sodium chloride and extracted with acetonitrile (50 mL). The acetonitrile solution was dried ($MgSO_4$), filtered, and combined with the filtered ethyl acetate solution. The solvents were evaporated and the resulting solid was triturated with a small amount of acetonitrile, collected by suction filtration, and air dried. Yield: 203 mg (64 %); mp 297.1->300 °C; $^1H$ NMR (DMSO-d6/300 MHz) 14.37 (br s, 1H), 8.54 (m, 2H), 7.29 (m, 6H), 3.26 (s, 3H); Anal. Calc'd for $C_{15}H_{12}FN_3O_2S$: C, 56.77; H, 3.81; N, 13.24. Found: C, 56.52; H, 4.03; N, 13.11.

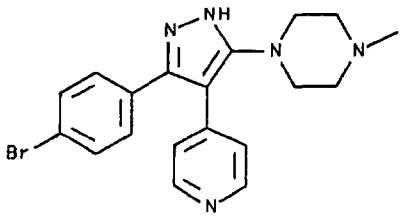
**Example A-438**



To the compound of Example A-432 (638 mg, 2 mmol) in toluene (6 mL) was added thiomorpholine (502 uL, 5 mmol). The reaction mixture was heated to between 80 and 110 °C. After about three hours the bis-thiomorpholine substituted product began to precipitate from the reaction mixture. When the dithioketene acetal had been completely consumed, the reaction mixture was cooled to room temperature and the insoluble bis-thiomorpholine compound removed by filtration. To the toluene solution was added hydrazine hydrate (1 mL) and sufficient ethanol to create a homogeneous solution. The reaction mixture was then stirred at room temperature for 72 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and extracted twice with water (25 mL) and once with brine (25 mL). The organic solution was dried ($MgSO_4$), filtered and concentrated to a reddish solid. The solid was triturated with acetonitrile, collected by suction

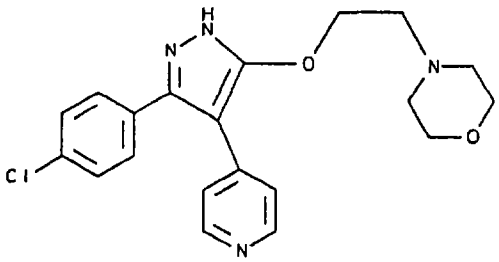
filtration, and dried in-vacuo. The solid was then suspended in acetonitrile and heated to reflux. Ethyl acetate was then added until the solid almost completely dissolved. A small amount of ethanol was then added and the homogeneous yellow solution concentrated until a solid began to form. Allow to cool to room temperature. Collected a white solid by suction filtration. Yield: 63 mg, (7%); $^1$H NMR (DMSO-d6/300 MHz) 12.65 (br s, 1H), 8.45 (d, 2H), 7.27 (m, 6H), 3.14 (m, 4H), 2.63 (m, 4H). ESLRMS *m/z* 341 (M+H); ESHRMS *m/z* 341.1241 (M+H, $C_{18}H_{18}FN_4S$ requires 341.1236).

**Example A-439**



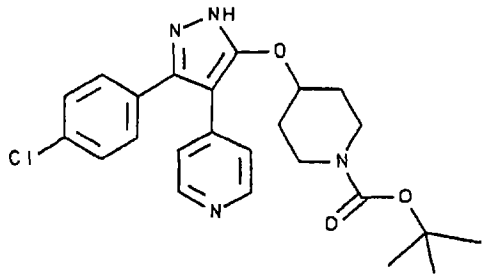
The above compound was prepared in a similar manner to Example A-438 starting with the appropriate dithioketene acetal and N-methylpiperazine. A white solid was obtained, mp 270.2-270.7 °C; $^1$H NMR (DMSO-d6/300 MHz) 12.7 (br s, 1H), 8.47 (m, 2H), 7.57 (m, 2H), 7.21 (m, 2H), 2.85 (m, 4H), 2.34 (m, 4H) 2.15 (s, 3H); ESHRMS 398.0993 (M+H, $C_{19}H_{21}BrN_5$ requires 398.0980).

**Example A-440**



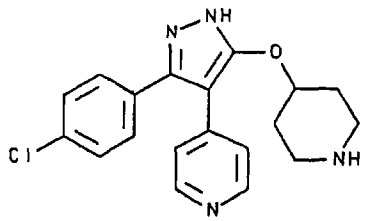
To N-(2-hydroxyethyl)morpholine (363 uL, 3 mmol) in anhydrous tetrahydrofuran (7 mL), under nitrogen, was added 1M sodium hexamethyldisilamide (3 ml, 3 mmol) in tetrahydrofuran at ambient temperature. The reaction mixture was stirred for 15 minutes, then the dithietane prepared as set forth in Step 1 of Example A-341 (636mg, 2 mmol) was added as a solid. The reaction mixture gradually became dark orange. After about 18 hours at ambient temperature, the reaction was quenched with saturated sodium bicarbonate solution (30 mL) and extracted twice with ethyl acetate (30 mL). The organic solutions were combined and washed with saturated NaCl solution (20 mL), then dried ($MgSO_4$), filtered, and concentrated to an orange oil. The oil was taken up in methanol (10 mL) and reconcentrated to remove any remaining ethyl acetate. The oil was then taken up in methanol (5 mL) and anhydrous hydrazine (69 uL) was added. The reaction mixture was allowed to stir at ambient temperature 18 hours, then quenched with saturated sodium bicarbonate solution (30 mL) and extracted twice with ethyl acetate (30 mL). The organic solutions were combined and washed with water (20 mL) and saturated NaCl solution (20 mL), then dried ($MgSO_4$), filtered, and concentrated to an orange semi-solid. The solid was triturated with acetonitrile (5 mL), collected by suction filtration, washed with acetonitrile and dried in-vacuo. Yield: off-white solid, 114 mg (14.8%); mp 198.9-199.9 °C; $^1$H-NMR (DMSO-d6/300 MHz) 12.61 (br s, 1H), 8.41 (d, 2H), 7.52 (d, 2H), 7.38 (d, 2H), 7.21 (d, 2H), 4.33 (t, 2H), 3.54 (m, 4H), 2.70 (t, 2H), 2.44 (m 4H); ESHRMS *m/z* 385.1444 (M+H, $C_{20}H_{22}ClN_4O_2$ requires 385.1431).

**Example A-441**



The above compound was prepared in an analogous manner to that of Example A-440, starting with 4-hydroxy-N-t-boc piperidine. Recrystallized from acetone/methanol. Yield: white solid 263 mg (29%); mp 230.1-231.8 °C; 1H-NMR (DMSO-d6/300 MHz) 12.61 (br s, 1H), 8.42 (d, 2H), 7.52 (d, 2H), 7.38 (d, 2H), 7.20 (d, 2H), 4.88 (m, 1H), 3.52 (m, 2H), 3.30 (m, 2H), 1.93 (m, 2H), 1.65 (m, 2H), 1.39 (s, 9H); Anal. Calc'd for $C_{24}H_{27}ClN_4O_3$: C,63.36; H, 5.98; N, 12.31; Found: C, 63.34; H, 5.97; N, 12.22.

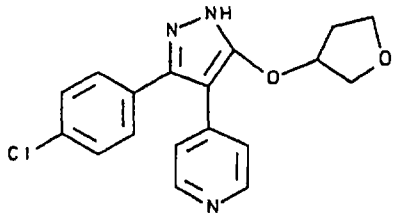
**Example A-442**



Example A-441 (130 mg, 0.28 mmol) was treated with concentrated HCl (0.5 mL) in ethanol (5 mL) for two hours. The solvent was removed in-vacuo and the resulting residue dissolved in ethanol and reconcentrated twice. The resulting solid was triturated with acetonitrile to afford a white solid. Yield: 119 mg (91%) tri-hydrochloride salt; mp 220.6-222.1 °C; $^1$H-NMR (DMSO-d6/300 MHz) 13.25 (br s, 1H), 9.10 (br s, 2H), 8.67 (d, 2H), 7.75 (d, 2H), 7.60 (d, 2H), 7.50 (d, 2H), 5.04

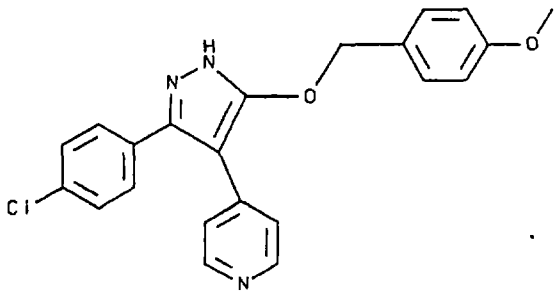
(m, 1H), 3.17 (br d, 4H), 2.21 (m, 2H), 2.03 (m, 2H); Anal. Calc'd for $C_{19}H_{19}ClN_4O \cdot 3\ HCl$: C, 49.16; H, 4.78; N, 12.07. Found: C, 49.24; H, 4.72; N, 12.02.

**Example A-443**



The above compound was prepared in a manner analogous to Example A-440 starting with (+/-)3-hydroxytetrahydrofuran. Recrystallized from ethanol. Yield: white crystalline solid, 57 mg (8%); mp >300 °C; $^1$H-NMR (DMSO-d6/300 MHz) 12.65 (br s, 1H), 8.42 (d, 2H), 7.52 (d, 2H), 7.38 (d, 2H), 7.18 (d, 2H), 5.28 (m, 1H), 3.86 (m, 2H), 3.82 (m, 1H), 3.75 (m, 1H), 2.26-2.01 (br m, 2H); Anal. Calc'd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.12; H, 4.51; N, 12.31.

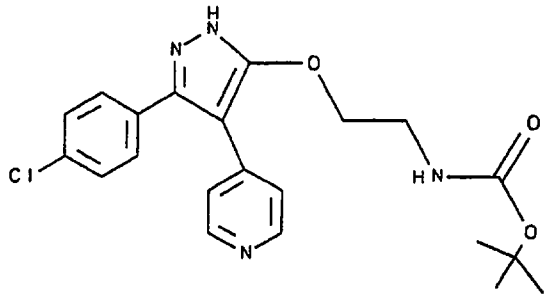
**Example A-444**



The above compound was prepared in a manner analogous to Example A-440 starting with p-methoxybenzyl alcohol. Yield: off-white solid, 252 mg (21%); mp =229.1-229.2 °C; $^1$H-NMR (acetone-d6/300 MHz) 11.62 (br s, 1H), 8.40 (br s, 2H), 7.76 (s, 2H), 7.39 (m, 4H), 7.30 (br s, 2H), 6.87 (d, 2H), 5.27 (s, 2H), 3.77 (s, 3H); Anal.

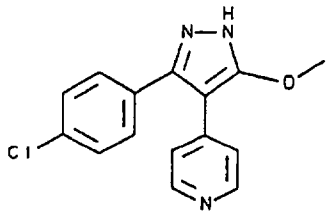
Calc'd for $C_{22}H_{18}ClN_3O_2 \cdot 0.25\ H_2O$: C, 66.67; H, 4.70; N, 10.60. Found: C, 66.79 ; H, 4.95 ; N, 10.54.

**Example A-445**



The above compound was prepared in a manner analogous to Example A-440 starting with N-tert-butoxycarbonyl-ethanolamine. Recrystallized from ethyl acetate/methanol. Yield: white solid, 75 mg (4 %); mp >300 °C; $^1$H-NMR (DMSO-d6/300 MHz) 12.60 (br s, 1H), 8.38 (d, 2H), 7.53 (d, 2H), 7.38 (d, 2H), 7.22 (d, 2H), 7.02 (t, 1H), 4.20 (t, 2H), 3.34 (m, 2H), 1.36 (s, 9H); ESHRMS *m/z* 415.1551 (M+H, $C_{21}H_{24}ClN_4O_3$ requires 415.1537)

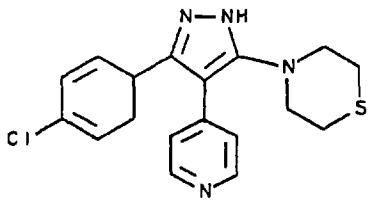
**Example A-446**



The above compound was prepared in a manner analogous to Example A-440 starting with methanol. Yield: off-white solid, 119 mg (14 %); mp = 265.3-265.3 °C; $^1$H-NMR (DMSO-d6/300 MHz) 12.61 (br s, 1H), 8.41 (d, 2H), 7.52 (d, 2H), 7.38 (d, 2H), 7.17 (d, 2H), 3.90 (s, 3H); ESHRMS *m/z* 286.0766 (M+H, $C_{15}H_{13}ClN_3O$ requires 286.0747); Anal. Calc'd for $C_{15}H_{12}ClN_3O \cdot 0.25$ H2O: C, 62.08; H, 4.34; N, 14.48. Found: C, 62.24; H, 4.11; N,

14.16.

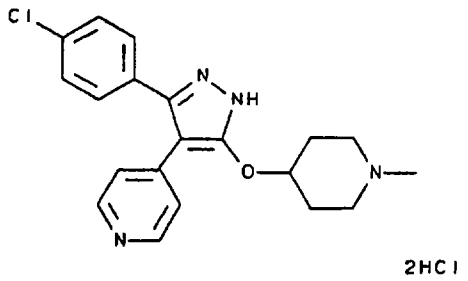
**Example A-447**



To the dithietane of Step 1 of Example A-341 (638 mg, 2 mmol) in toluene (15 mL) was added thiomorpholine (800 uL, 8 uL). The reaction mixture was heated to reflux for 6 hours, then cooled to room temperature and diluted with toluene (20 mL). The reaction mixture was then extracted twice with water (20 mL) and brine (20 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated to an oil. Hexane was added to the residue and heated to reflux, then decanted. The oil became semi-solid. The semi-solid was dissolved in tetrahydrofuran (10 mL) and potassium t-butoxide 1M in tetrahydrofuran (2 mL, 2 mmol) was added. This was followed by iodomethane (125 uL, 2 mmol). The reaction was stirred at room temperature for 1 hour, then quenched with water (20 mL). The reaction mixture was extracted with ethyl acetate (2 x 30 mL). The organic layers were pooled, washed with brine (20 mL) and dried ($MgSO_4$). Filtration and concentration produced an oil which was chased once with toluene to remove any ethyl acetate. The residue was dissolved in ethanol (10 mL) and hydrazine hydrate (97 uL, 2 mmol) was added. The reaction mixture was stirred at room temperature for 4 hours then partitioned between ethyl acetate and saturated sodium bicarbonate solution (30 mL each). The layers were separated and the aqueous layer extracted again with ethyl acetate (30 mL). The combined organic

layers were washed with brine (20 mL) and dried ($MgSO_4$). Filtration and concentration produced an orange residue which was triturated with acetonitrile to generate a tan solid. Yield: 295 mg (43%); mp >300 °C; $^1H$ NMR (DMSO-d6/300 MHz) 12.70 (br s, 1H), 8.47 (d, 2H), 7.46 (d, 2H), 7.26 (m, 4H), 3.13 (m, 4H), 2.62 (m, 4H); ESHRMS *m/z* 357.0942 (M+H, $C_{18}H_{18}ClN_4S$ requires 357.0941); Anal. Calc'd for $C_{18}H_{17}ClN_4S$: C, 60.58; H, 4.80; N, 15.70. Found: C, 60.32; H, 4.96; N, 15.60.

**Example A-448**

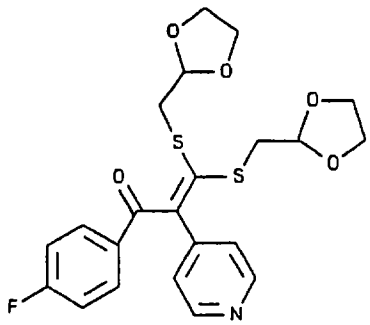



3-(4-chlorophenyl)-5-[(1-methylpiperidin-4-yl)-oxy]-4-pyridin-4-yl-1H-pyrazole

The compound of Example A-441 (455 mg, 1.5 mmol) was combined with 98% formic acid (6 mL) and heated to 100 °C. After three hours, 37% formaldehyde (1.22 mL, 15 mmol) was added and the reaction was heated for an additional five hours at 100 °C. The reaction mixture was allowed to cool to room temperature and filtered. The solution was diluted with water (15 mL) and extracted once with ethyl acetate (30 mL). The aqueous solution was then basified with 2.5 N sodium hydroxide to pH 8. The cloudy mixture was then extracted twice with 1:1 tetrahydrofuran:ethyl acetate (30 mL). The organic layers were pooled and washed once with brine (25 mL), dried ($MgSO_4$), filtered and concentrated to an oil which solidified on standing. The solid was triturated with

acetonitrile and collected by suction filtration. The solid was suspended in ethanol:water 2:1 (15 mL) and 1 mL of concentrated HCl was added. The solution was allowed to stir at room temperature for one hour, then filtered and concentrated. The residue was combined with ethanol (10 mL) and reconcentrated twice. The resulting solid was triturated with acetonitrile (10 mL) containing a small amount of ethanol (0.5 mL) to remove some colored impurities. The solid was collected by suction filtration, washed with acetonitrile and dried in-vacuo. Yield: 490 mg (88 %); mp 255.9-256.8 °C; $^1$H NMR ($D_2O$/DMSO-d6/NaOD/300 MHz) 7.93 (d, 2H), 7.09 (s, 4H), 7.00 (d, 2H), 4.42 (m, 1H), 2.26 (br m, 2H,) 2.12 (br m, 2H), 1.92 (s, 3H), 1.68 (br m, 2 H), 1.57 (br m , 2H); ESLRMS *m/z* 369 (M+H).

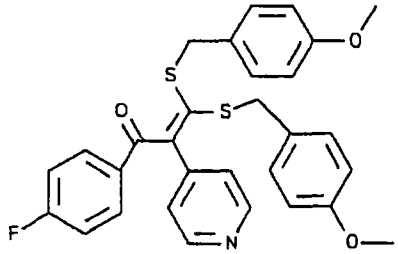
**Example A-449**



To the compound of Example C-1, infra, (4'-fluoro-1-(4-pyridyl)acetophenone, 14.0 g, 0.065 mol) in anhydrous tetrahydrofuran (200 mL) was added dropwise potassium t-butoxide (1M in tetrahydrofuran, 150 mL). The mixture was stirred 30 minutes. Carbon disulfide (4.2 mL, 0.07 mol) in tetrahydrofuran (25 mL) was added dropwise and stirred 15 minutes. 2-Bromomethyl-1,3-dioxolane (25.0 g, 0.15 mol) in tetrahydrofuran (25 mL) was added dropwise and contents were refluxed 10 hours. The mixture was allowed to cool and partitioned between ethyl acetate and

water. The ethyl acetate layer was dried over $MgSO_4$ and concentrated *in vacuo* leaving a red oil (29.3 g). Chromatography on silica gel eluting with 25% ethyl acetate/hexanes gave the desired compound as a red oil, (5.5 g, 18% yield). $^1H$ NMR ($CDCl^3$) 8.62-8.52 (m, 2H); 8.07-7.95 (m, 2H); 7.48-7.40 (m, 2H); 7.20-7.05 (m, 2H); 5.15-5.05 (m, 1H); 4.98-4.90 (m, 1H); 4.00-3.77 (m, 8H); 3.08 (d, $J$ = 6 Hz, 2H); 3.03 (d, $J$ = 6 Hz, 2H); ESHRMS m/z 464.0966 (M+H, $C_{22}H_{23}FNO_5S_2$ requires 464.1001); Anal. Calc'd for: $C_{22}H_{22}FNO_5S_2$ (0.1 $H_2O$): C, 56.79; H, 4.81; N, 3.01. Found: C, 56.45; H, 4.71; N, 3.02.

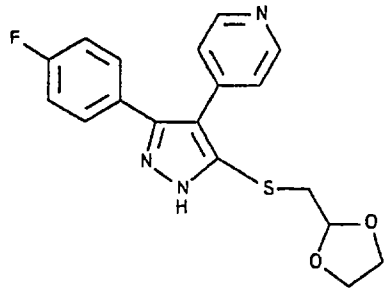
**Example A-450**




To the compound of Example C-1, infra, (4'-fluoro-1-(4-pyridyl)acetophenone, 7.0 g, 0.0325 mol) in anhydrous tetrahydrofuran (200 mL) was added dropwise potassium t-butoxide (1M in tetrahydrofuran, 75 mL). The mixture was stirred 30 minutes. Carbon disulfide (2.1 mL, 0.035 mol) in tetrahydrofuran (25 mL)was added dropwise and stirred 15 minutes. 4-Methoxybenzyl chloride (10.2 mL, 0.075 mol) in tetrahydrofuran (10 mL) was added dropwise and contents were stirred overnight. The contents were partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$ and concentrated in vacuo leaving a red oil (19.1 g). Chromatography on silica gel eluting with 25% ethyl acetate/hexanes gave the desired as a white solid (11.8 g, 68% yield). Recrystallization from ethyl acetate/hexanes gave the desired as colorless crystals: mp 118.5 - 120.6 °C; $^1H$

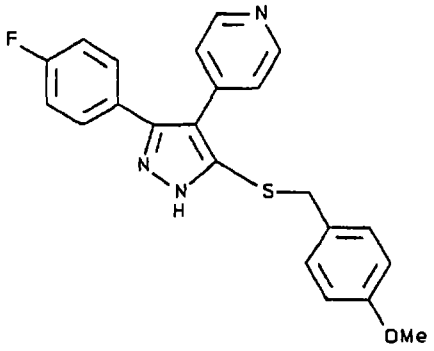
NMR ($CDCl_3$) 8.43 (d, $J$ = 7 Hz, 2H); 7.62-7.52 (m, 2H); 7.20-6.72 (m, 12H); 3.98 (d, J = 6 Hz, 4H); 3.83 (s, 3H); 3.81 (s, 3H); ESHRMS m/z 532.1408 (M+H, $C_{30}H_{27}FNO_3S_2$ requires 532.1416); Anal. Calc'd for: $C_{30}H_{26}FNO_3S_2$ (0.5 $H_{20}$): C, 66.65; H, 5.03; N, 2.59. Found: C, 66.34; H, 4.96; N, 2.55.

**Example A-451**



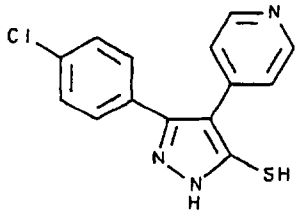

The compound of Example A-449 (4.0 g, 9.2 mmol) and hydrazine monohydrate (2.2 mL, 46 mmol) were refluxed in ethanol (100 mL) for three hours. The mixture was allowed to cool and stand overnight. A yellow precipitate was filtered to give the desired product as a yellow solid, (1.34 g, 41% yield); mp 202.1-205.4°C; $^1H$ NMR (DMSO-*d6*) 13.5 (br s, 1H); 8.55-8.45 (m, 2H); 7.40-7.12 (m, 6H); 5.01 (s, 1H); 3.92-3.70 (m, 4H); 3.13 (s, 2H); ESHRMS m/z 358.1025 (M+H, $C_{18}H_{17}FN_3O_2S$ requires 358.1025); Anal. Calc'd for: $C_{18}H_{16}FN_3O_2S$: C, 60.49; H, 4.51; N, 11.76. Found: C, 60.26; H, 4.55 N, 11.87.

**Example A-452**



The above compound was prepared similarly to the compound of Example A-451 starting with the compound prepared in Example A-450. The desired product was obtained as a white solid (2.15 g, 49% yield); mp 214.7-215.8 °C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.70 (d, 2H); 7.60 (d, 2H); 7.42-7.38 (m, 2H); 7.30-7.20 (m, 2H); 6.70 (d, 2H); 4.10 (s, 2H); 3.68 (s, 3H); ESHRMS m/z 392.1225 (M+H, $C_{22}H_{19}FN_3OS$ requires 392.1232); Anal. Calc'd for: $C_{22}H_{18}FN_3OS$: C, 67.50; H, 4.63; N, 10.73. Found: C, 67.46; H, 4.67 N, 10.77.

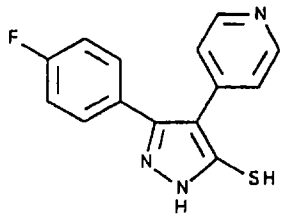
**Example A-453**



The compound prepared in step 1 of Example A-341 (50 g, 0.156 mol) and anhydrous hydrazine (25 mL, 0.8 mol) were refluxed in ethanol (500 mL) for five hours. The mixture was allowed to cool and the precipitate filtered to afford the desired product as a yellow-orange solid (21.8 g). The filtrate was diluted with water (200 mL) and a second crop was obtained as a yellow-orange solid

(18.0 g). The pH of the filtrate was adjusted to pH 8 with 3N HCl and the precipitated solid filtered to give more desired as a yellow-orange solid (2.0 g). The product was obtained in 93% yield. mp 266.3-268.9°C; $^1$H NMR (DMSO-*d6*) 13.80 (br, 1H); 12.20 (br s, 1H); 8.32 (s, 4H); 7.50-7.30 (m, 4H); ESHRMS m/z 288.0358 (M+H, $C_{14}H_{11}ClN_3S$ requires 288.0362); Anal. Calc'd for: $C_{14}H_{10}ClN_3S$ (0.4 $H_2O$): C, 57.01; H, 3.69; N, 14.25. Found: C, 56.95; H, 3.50 N, 14.14.

**Example A-454**



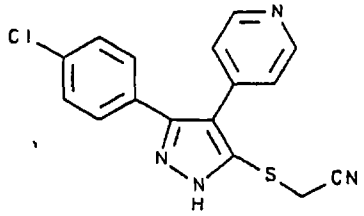

The above compound was prepared similarly to the compound of Example A-453. mp 261.3-263.9°C; $^1$H NMR (DMSO-*d6*) 11.55 (br s, 1H); 8.25-8.13 (m, 2H); 7.61-7.50 (m, 2H); 7.36-7.20 (m, 2H); 7.19-7.05 (m, 2H); ESHRMS m/z 272.0691 (M+H, $C_{14}H_{11}FN_3S$ requires 272.0657); Anal. Calc'd for: $C_{14}H_{10}FN_3S$ (0.25 $H_2O$): C, 60.97; H, 3.84; N, 15.24. Found: C, 61.05; H, 3.64 N, 15.12.

**Example A-455**

To the compound prepared in Example A-453 (100 mg, 0.35 mmol) in methanol (2 mL) was added 0.5 M sodium methoxide (0.7 mL, 0.35 mmol). The mixture was stirred for 15 minutes and filtered to remove some small particles. The filtrate was concentrated in vacuo, dissolved in water and concentrated in vacuo leaving the desired product as a white solid. $^1$H NMR (DMSO-*d6*) 11.60 (br s, 1H); 8.20 (d, 2H); 7.60-7.50 (m, 2H); 7.40-7.20 (m, 4H); Anal. Calc'd for: $C_{14}H_9ClN_3NaS$ (2.5 H20): C,

47.40; H, 3.98; N, 11.84. Found: C, 47.39; H, 3.33; N, 11.50.

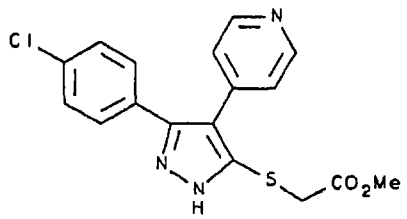
**Example A-456**



[3-(4-chlorophenyl)-4-pyridin-4-yl-1H-pyrazole-5-yl]thio]-acetonitrile

To the compound prepared in Example A-453 (584 mg, 2.0 mmol) and bromoacetonitrile (140 ul, 2.0 mmol) in dimethylformamide (5 mL) was added anhydrous potassium carbonate (276 mg, 2.0 mmol). The contents were stirred overnight, then partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$ and concentrated in vacuo leaving a tan solid. The solid was triturated with methanol and filtered to give the desired as a off-white solid (369 mg, 56% yield). mp 230.0-230.5°C; $^1H$ NMR (DMSO-*d*6) 13.90 (br s, 1H); 8.58 (d, 2H); 7.60-7.13 (m, 6H); 4.10 (s, 2H); ESHRMS m/z 327.0482 (M+H, $C_{16}H_{12}ClN_4S$ requires 327.0471); Anal. Calc'd for: $C_{16}H_{11}C_{11}N_4S$ (0.3 $H_2O$): C, 57.85, H, 3.52; N, 16.87. Found C, 57.88; H, 3.31; N, 16.77.

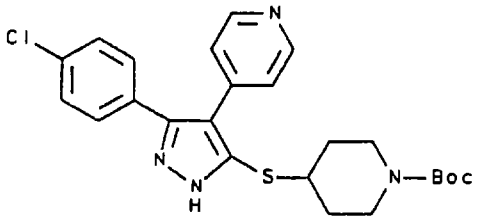
**Example A-457**



The above compound was prepared similarly to the

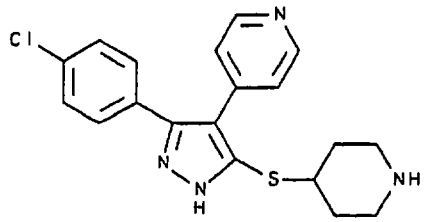
compound of Example A-456 except that when the contents were partitioned between ethyl acetate and water, an insoluble solid was filltered to give the desired product as a white solid (2.16 g). A second crop (1.68 g) of desired product gave a total yield of 61%. mp 192.8-195.2°C; $^1$H NMR (DMSO-*d6* + approximately 10%TFA) 9.80 (d, 2H); 7.80 (d, 2H); 7.52-7.34 (m, 4H); 3.92 (s, 2H); 3.57 (s, 3H); ESHRMS m/z 360.05735 (M+H, $C_{17}H_{14}ClN1_3O_2S$ requires 360.05732); Anal. Calc'd for: $C_{17}H_{14}ClN_3O_2S$ (0.25 $H_2O$): C, 56.05, H, 4.01; N, 11.53. Found C, 56.10; H, 3.72; N, 11.51.

**Example A-458**




The compound prepared in Example A-453 (1.2 g, 4.2 mmol), potassium carbonate (630 mg, 4.6 mmol), N-tert-butoxycarbonyl-4-bromo piperidine (1.2 g, 4.5 mmol) were heated in dimethylformamide (15 mL) at 105 °C for three hours. Contents were allowed to cool and partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was triturated with ethyl acetate and filtered to give the desired as a white solid (1.2 g, 61% yield). mp 220.9-221.0°C; $^1$H NMR (DMSO-*d6*) 13.70 (br, 1H); 8.60-8.50 (m, 2H); 7.58-7.10 (m, 6H); 3.80-3.60 (m, 2H); 3.40-3.20 (m, 1H); 3.00-2.63 (m, 2H); 2.00-1.53 (m, 2H); 1.50-1.05 (m, 2H); 1.40 (s, 9H); ESHRMS m/z 471.1605 (M+H, $C_{24}H_{28}ClN_4OS$ requires 471.1622); Anal. Calc'd for: $C_{24}H_{27}ClN_4OS$ (0.5 $H_20$): C, 60.05; H, 5.88; N, 11.67. Found: C, 60.04; H, 5.57; N, 11.31.

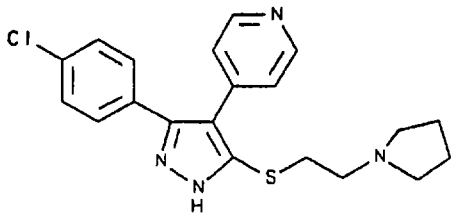
**Example A-459**



3-(4-chlorophenyl)-5-[(piperidin-4-yl)-thio]-4-pyridin-4-yl-1H-pyrazole

The compound prepared in Example A-458 (5.0 g, 11 mmol), and TFA (30 mL) were mixed in methylene chloride (50 mL) and stirred overnight. The mixture was concentrated in vacuo leaving a pale yellow oil which was dissolved in water. The pH was adjusted with 2.5 N sodium hydroxide to pH 9, precipitating a white solid which was filtered to give the desired product as a white solid (3.7 g, 93% yield). mp 211.1-211.2°C; $^1$H NMR (DMSO-*d*6) 13.80 (br, 1H); 8.55 (d, 2H); 8.40 (br, 1H); 7.50-7.15 (m, 6H); 3.50-3.00 (m, 3H); 3.00-2.80 (m, 2H); 2.05-1.80 (m, 2H); 1.65-1.42 (m, 2H); ESHRMS m/z 371.1103 (M+H, $C_{19}H_{20}ClN_4S$ requires 371.1097); Anal. Calc'd for: $C_{19}H_{19}ClN_4S$ ($H_2O$): C, 58.68; H, 5.44; N, 14.41. Found: C, 58.86; H, 5.28; N, 14.25.

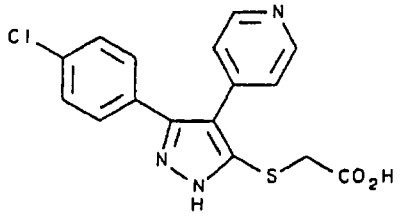
**Example A-460**



To 1-(2-chloroethyl)pyrrolidine hydrochloride (306 mg, 1.8 mmol) in methanol (10 mL) was added 0.5 M sodium methoxide (7.0 mL, 3.6 mmol). The mixture was stirred 10

minutes and the compound of Example A-453 (500 mg, 1.8 mmol) added. The contents were refluxed one hour, allowed to cool and partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$ and concentrated in vacuo leaving a light amber solid. The solid was recrystallized from methanol (15 mL) to give the desired product as a white solid (213 mg, 33% yield). mp 189.9-190.1°C; $^1H$ NMR (DMSO-*d6*) 13.65 (br, 1H); 8.52 (d, 2H); 7.42 (d, 2H); 7.38-7.10 (m, 4H); 3.10-2.93 (m, 2H); 2.63-2.51 (m, 2H); 2.38 (br s, 4H); 1.70-1.52 (m, 4H); ESHRMS m/z 385.1262 (M+H, $C_{20}H_{22}ClN_4S$ requires 385.1254); Anal. Calc'd for: $C_{20}H_{21}ClN_4S$: C, 62.41, H, 5.50; N, 14.56. Found C, 62.22; H, 5.62; N, 14.48.

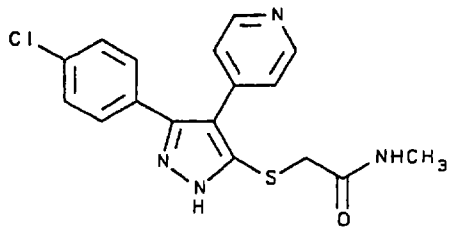
**Example A-461**




Method A: The compound prepared in Example A-457 (1.3 g, 3.6 mmol) in methanol (10 mL), 2.5N sodium hydroxide (4 mL) and water (10 mL) were stirred overnight. The mixture was concentrated in vacuo to remove the methanol and the aqueous solution left was made acidic to pH 6 with 3N HCl, precipitating a solid. The solid was extracted into ethyl acetate, dried over $MgSO_4$ and concentrated in vacuo leaving light tan crystals (205 mg). Brine was added to the aqueous layer precipitating more solid. The solid did not extract into ethyl acetate, but was filtered to give more desired product as a light tan powder (529 mg). Total yield was 61% yield. $^1H$ NMR (DMSO-*d6* + 10%TFA) 8.80 (d, 2H); 7.83 (d, 2H); 7.55-7.35 (m, 4H); 3.87 (s, 2H).

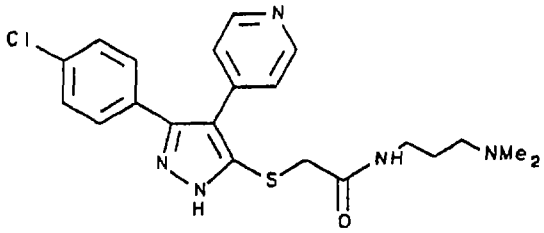
Method B: The compound prepared in Example A-457 (3.8 g, 11 mmol) and 3N HCl (30 mL) were reluxed for three hours. The mixture was allowed to cool and concentrated in vacuo. The residue was mixed with $CH_3CN$ (50 mL). Upon standing overnight, pale yellow crystals grew and were filtered to give the desired product as the HCl salt (2.9 g, 69% yield). $^1H$ NMR (DMSO-*d6*) 8.79 (d, 2H); 7.75 (d, 2H); 7.51-7.38 (m, 4H); 3.88 (s, 2H); ESHRMS m/z 346.0435 (M+H, $C_{17}H_{16}ClN_4OS$ requires 346.0417); Anal. Calc'd for: $C_{16}H_{12}ClN_3O_2S$ (HCl, 0.5 $H_2O$): C, 49.12; H, 3.61; N, 10.74. Found: C, 49.36; H, 3.48; N, 10.72.

**Example A-462**



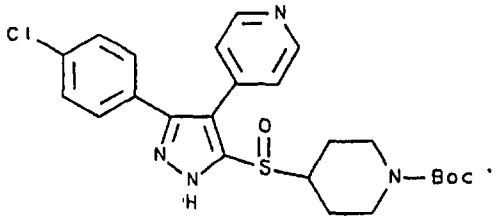

The compound prepared in Example A-457 (400 mg, 11 mmol) and a 2M solution of methyl amine in tetrahydrofuran (25 mL) were refluxed for three hours. The mixture was stirred overnight at room temperature before filtering to give the desired as a light amber solid (335 mg, 85 % yield). mp 284.0-288.4°C; $^1H$ NMR (DMSO-*d6*) 13.58 (br, 1H); 8.60-8.45 (m, 2H); 7.98 (br s, 1H); 7.55-7.12 (m, 6H); 3.60 (s, 2H); 2.46 (s, 3H); ESHRMS m/z 359.0733 (M+H, $C_{17}H_{16}ClN_{14}OS$ requires 359.0745); Anal. Calc'd for: $C_{17}H_{15}ClN_4OS$: C, 56.90; H, 4.21; N, 15.61. Found: C, 56.74; H, 4.11; N, 15.17.

**Example A-463**



The compound prepared in Example A-457 (415 mg, 12 mmol) and N, N-dimethylaminopropylamine were refluxed in methanol (25 mL) for three hours. The mixture was stirred overnight at room temperature before concentrating in vacuo leaving a solid. The solid was triturated with ethyl acetate and filtered to give the desired as a white solid (256 mg, 50 % yield). mp 168.8-169.5°C; $^1$H NMR (DMSO-*d*6) 13.80 (br, 1H); 8.55-8.50 (m 2H); 8.02 (t, 1H); 7.50-7.40 (m, 6H); 3.61 (s, 2H); 3.30-2.98 (m, 2H); 2.14-2.10 (m, 2H); 2.04 (s, 6H); 1.50-1.40 (m, 2H); ESHRMS m/z 430.1472 (M+H, $C_{21}H_{25}ClN_{12_5}OS$ requires 430.1468); Anal. Calc'd for: $C_{21}H_{24}ClN_5OS$ (0.5 $H_2O$): C, 57.46; H, 5.74; N, 15.95. Found: C, 57.71; H, 5.56; N, 16.12.

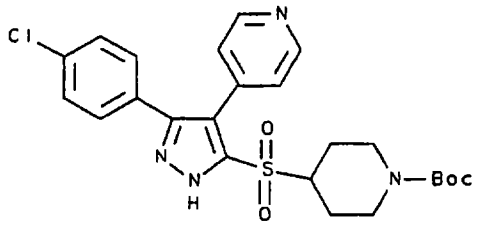
**Example A-464**



To the compound prepared in Example A-458 (1.0 g, 2.1 mmol) in methylene chloride (25 mL) was added *meta*-chloroperbenzoic acid (425 mg, 2.1 mmol). The mixture was stirred 15 minutes and chromatographed on silica gel (20 g) eluting with ethyl acetate. The desired product precipitated out of the ethyl acetate elutant upon

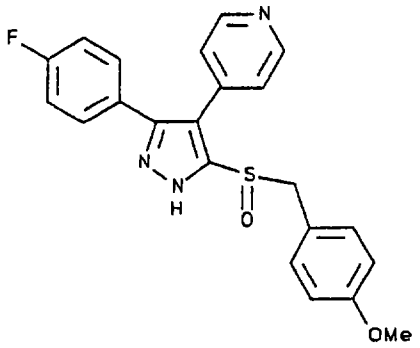
standing and was filtered to give the desired product as a white solid (958 mg, 93% yield). mp 215.8-215.9°C; $^1$H NMR (DMSO-*d6*) 14.34 (br s, 1H); 8.57-8.54 (m, 2H); 7.51-7.25 (m, 6H); 4.00-3.82 (m, 2H); 3.60-3.40 (m, 1H); 2.85-2.70 (m, 2H); 2.10-1.95 (m, 1H); 1.56-1.10 (m, 3H); 1.36 (s, 9H); ESHRMS m/z 487.1580 (M+H, $C_{17}H_{16}ClN_4OS$ requires 487.1571); Anal. Calc'd for: $C_{24}H_{27}ClN_{12}4O_3S$: C, 59.19; H, 5.59; N, 11.50. Found: C, 59.00; H, 5.76; N, 11.46.

**Example A-465**



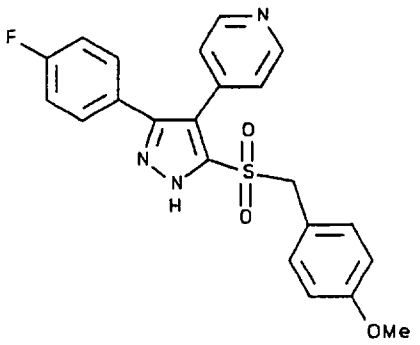

To the compound prepared in Example A-458 (320 mg, 0.68 mmol) in ethanol (5 mL) was added an aqueous solution of potassium peroxymonosulfate (420 mg, 0.68 mmol). The mixture was stirred two hours and extracted into ethyl acetate which was dried over $MgSO_4$ and concentrated in vacuo leaving a white solid. The solid was triturated with methanol and filtered to give the desired as a white solid (90 mg, 26% yield). mp 228.0-230.8°C; $^1$H NMR (DMSO-*d6*) 8.61 (d, 2H); 7.48 (d, 2H); 7.31-7.20 (m, 4H); 4.05-3.90 (m, 2H); 3.54-3.35 (m, 1H); 2.85-2.60 (m, 2H); 1.92-1.80 (m, 2H); 1.48-1.25 (m, 2H); 1.32 (s, 9H); ESHRMS m/z 503.1541 (M+H, $C_{24}H_{27}ClN_4O_4S$ requires 503.1520); Anal. Calc'd for: $C_{24}H_{27}ClN_4O_4S$ ($H_2O$): C, 56.30; H, 5.51; N, 10.94. Found: C, 56.41; H, 5.78; N, 10.54.

**Example A-466**




The above compound was prepared similarly to the compound of Example A-464. After chromatography the solid obtained was recrystallized from $CH_3CN$ to give the desired product as white crystals (64 mg, 33% yield). mp 189.5-189.5°C; $^1H$ NMR (DMSO-*d6*) 14.28 (br s, 1H); 8.50 (d, 2H); 7.40-7.20 (m, 4H); 7.20-7.05 (m, 4H); 6.85 (d, 2H); 4.41 (s, 2H); 3.70 (s, 3H); ESHRMS m/z 408.1168 (M+H, $C_{22}H_{19}FN_3O_2S$ requires 408.1182); Anal. Calc'd for: $C_{22}H_{18}FN_3O_2S$: C, 64.85; H, 4.45; N, 10.31. Found: C, 64.44; H, 4.34; N, 10.70.

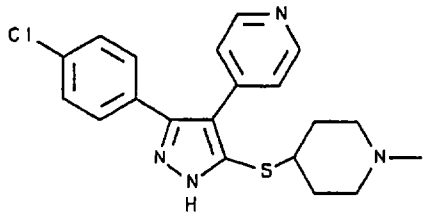
**Example A-467**




To the compound prepared in Example A-466 (1.2 g, 2.5 mmol) in methylene chloride (50 mL) was added *meta*-chloroperbenzoic acid (1.0 g, 5.0 mmol). The mixture was stirred 1.5 hours and filtered a white solid (620 mg)

which was inorganic salts. The filtrate was chromatographed on silica gel (20 g) eluting with ethyl acetate to give the desired product as a white solid (98 mg, 9% yield). mp 241.9-242.0°C; $^1$H NMR (DMSO-*d6*) 8.48-8.40 (m, 2H); 7.33-6.80 (m, 10H); 4.55 (s, 2H); 3.72 (s, 3H); ESHRMS m/z 424.1143 (M+H, $C_{24}H_{27}ClN_4O_4S$ requires 424.1131); Anal. Calc'd for: $C_{22}H_{18}FN_3O_3S$: C, 62.40; H, 4.28; N, 9.92. Found: C, 62.14; H, 4.42; N, 9.68.

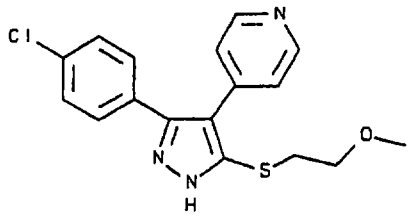
**Example A-468**




3-(4-chlorophenyl)-5-[(1-methylpiperidin-4-yl)-thio]-4-pyridin-4-yl-1H-pyrazole

The compound prepared in Example A-458 (5.0 g, 0.01 mol) and formic acid (96%, 7 mL) were heated at 100 °C for one hour. The mixture was allowed to cool to about 50 °C and formaldehyde (37%, 13 mL) was added. The contents were heated at 80 °C for two hours. The contents were allowed to cool, diluted with water (200 mL) and made basic to pH 11 with 2.5N sodium hydroxide, precipitating a white solid. The solid was filtered and recrystallized from methanol to give the desired as a white solid (174 mg. 33% yield). mp 227.7-227.7°C; $^1$H NMR (DMSO-*d6*) 13.70 (br s, 1H); 8.56-8.48 (m, 2H); 7.50-7.15 (m, 6H); 3.10-2.92 (m, 1H); 2.63-2.50 (m, 2H); 2.05 (s, 3H); 1.95-1.65 (m, 4H); 1.50-1.30 (m, 2H); ESHRMS m/z 385.1233 (M+H, $C_{20}H_{22}ClN_4S$ requires 385.1254); Anal. Calc'd for: $C_{20}H_{21}ClN_4S$: C, 62.41; H, 5.50; N, 14.56. Found: C, 62.40; H, 5.80; N, 14.61.

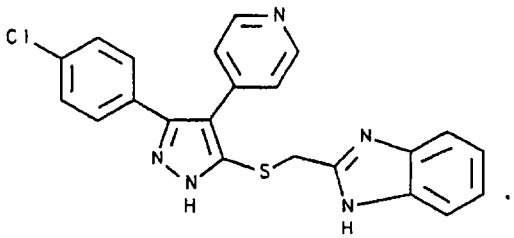
**Example A-469**



3-(4-chlorophenyl)-5-[(2-methoxyethyl)-thio]-4-pyridin-4-yl-1H-pyrazole

The above compound was prepared similarly to the compound of Example A-456 using bromoethyl methyl ether except contents were heated at 70 °C for one hour before partitioning between ethyl acetate and water. The crude product was recrystallized from methanol/ethyl acetate to give the desired product as a white solid (210 mg, 35% yield). mp 189.2-190.2°C; $^1$H NMR (DMSO-*d*6) 8.60-8.45 (m, 2H); 7.60-7.10 (m, 6H); 3.60-2.85 (m, 7H); ESHRMS m/z 346.0799) M+H, $C_{17}H_{17}ClN_3OS$ requires 346.0781); Anal. Calc'd for: $C_{17}H_{16}ClN_3OS$ ($H_2O$): C, 58.73; H, 4.70; N, 12.09. Found: C, 58.67; H, 4.86; N, 12.03.

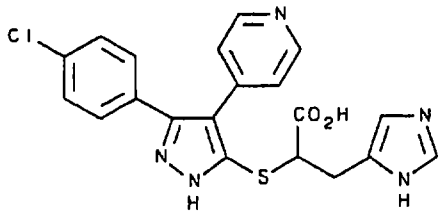
**Example A-470**



The above compound was prepared similarly to the compound of Example A-456 using 2-chloromethylbenzimidazole except contents were heated at 70 °C for one hour before partitioning between ethyl acetate and water. An insoluble solid was filtered from the two layers and triturated with methanol to give the

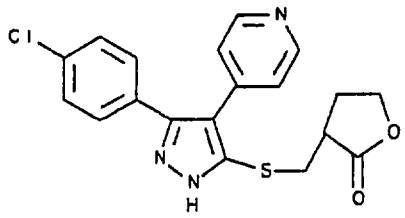
desired product as a light amber solid (292 mg, 40% yield). mp 257.7-257.7°C; $^1$H NMR (DMSO-*d6*) 13.75 (br s, 1H); 12.30 (br s, 1H); 8.55-8.30 (m, 2H); 7.65-6.90 (m, 10H); 4.40 (br s, 2H); ESHRMS m/z 418.0895 (M+H, $C_{22}H_{17}ClN_5S$ requires 418.0893); Anal. Calc'd for: $C_{22}H_{16}ClN_5S$ (0.75 $H_2O$): C, 61.25; H, 4.09; N, 16.23. Found: C, 61.27; H, 3.90; N, 15.92.

**Example A-471**



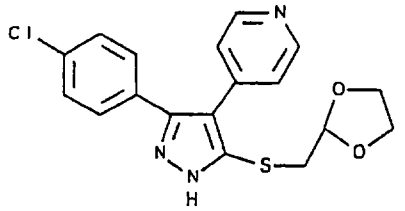
The above compound was prepared similarly to the compound of Example A-456 using DL-*alpha*-bromo-*beta*-(5-imidazolyl)propionic acid except the mixture was heated at 70 °C for one hour. The mixture contained an insoluble solid which was diluted with water and the pH was adjusted with 3N HCl to pH 7. The mixture was filtered and triturated with methanol to give the desired product as a white solid (1.5 g, 81% yield). mp 163.0-165.5°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.92 (d, 1H); 8.83-8.75 (m, 2H); 7.80 (d, 2H); 7.55-7.30 (m, 5H); 4.20-4.05 (m, 1H); 3.25-3.00 (m, 2H). ESHRMS m/z 426.0799 (M+H, $C_{20}H_{17}ClN_5O_2S$ requires 426.0791); Anal. Calc'd for: $C_{20}H_{16}ClN_5O_2S$ (1.8 $H_2O$): C, 52.41 H, 4.31; N, 15.28. Found: C, 52.68; H, 4.58; N, 15.37.

**Example A-472**



To the compound prepared in Example A-453 (264 mg, 0.9 mmol) and *alpha*-methylenebutyrolactone (0.08 mL, 0.9 mmol) in ethanol was added a drop of triethylamine. The mixture was stirred overnight. The resulting solid was filtered and triturated with methanol to give the desired product as a pale yellow solid (181 mg, 51% yield). mp 224.2-225.9°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.80 (d, 2H); 7.80 (d, 2H); 7.53-7.33 (m, 4H); 4.30-4.05 (m, 2H); 3.50-3.40 (m, 1H); 3.15-2.90 (m, 2H); 2.32-2.20 (m, 1H) 2.10-1.90 (m, 1H); ESHRMS m/z 386.0760 (M+H, $C_{19}H_{17}ClN_3O_2S$ requires 386.0730); Anal. Calc'd for: $C_{19}H_{16}ClN_3O_2S$: C, 59.14 H, 4.18; N, 10.89. Found: C, 58.97; H, 4.21; N, 10.96.

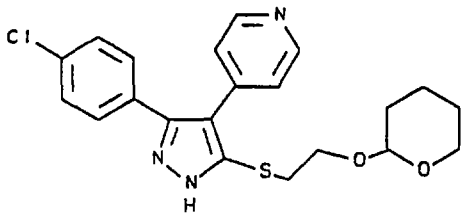
**Example A-473**



The above compound was prepared similarly to the compound of Example A-456 using 2-bromomethyl-1,3-dioxolane except the mixture was heated at 80°C for two hours. The mixture was diluted with water and filtered to give a white solid (502 mg). The solid was recrystallized from ethanol to give the desired product as off-white crystals (280 mg, 43% yield). mp 197.0-

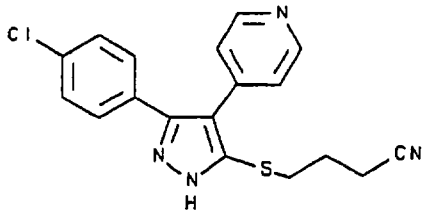
198.2°C; $^1$H NMR (DMSO-*d6*) 13.60 (br s, 1H); 8.60-8.45 (m, 2H); 7.60-7.10 (m, 6H); 5.15-4.85 (m, 1H); 3.95-3.62 (m, 4H); 3.40-2.95 (m, 2H); ESHRMS m/z 374.0741 (M+H, $C_{18}H_{17}ClN_3O_2S$ requires 374.0730); Anal. Calc'd for: $C_{18}H_{16}ClN_3O_2S$: C, 57.83 H, 4.31; N, 11.24. Found: C, 57.69; H, 4.41; N, 11.15.

**Example A-474**



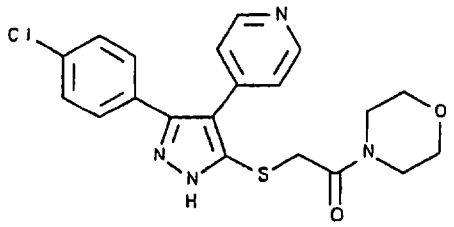
The above compound was prepared similarly to the compound of Example A-456 using 2-(2-bromoethoxy)tetrahydro-2H-pyran except that the mixture was heated at 80 °C for four hours. The mixture was allowed to cool and partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$ and concentrated in vacuo leaving a solid (737 mg). The solid was recrystallized from ethanol to give the desired product as pale yellow crystals (281 mg, 39% yield). mp 163.2-163.5°C; $^1$H NMR (DMSO-*d6*) 13.80-13.70 (m, 1H), 8.60-8.42 (br s, 1H); 7.60-7.10 (m, 6H); 4.60-4.30 (m, 1H); 3.90-2.90 (m, 6H); 1.70-1.20 (m, 6H); ESHRMS m/z 416.1200 (M+H, $C_{21}H_{23}ClN_3O_2S$ requires 416.1198); Anal. Calc'd for: $C_{21}H_{22}ClN_3O_2S$: C, 60.64 H, 5.33; N, 10.10. Found: C, 60.49; H, 5.71; N, 9.96.

**Example A-475**



The above compound was prepared similarly to the compound of Example A-456 using 4-bromobutyronitrile except the mixture was heated at 55 °C for one hour. The mixture was diluted with water (75 mL) and filtered to give a white solid (567 mg). The solid was recrystallized from methanol to give the desired product as white crystals (333 mg, 54% yield). mp 216.7-216.9°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.80-8.75 (m, 2H); 7.83-7.75 (m, 2H); 7.50-7.35 (m, 4H); 3.10-3.00 (m, 2H); 2.60-2.45 (m, 2H); 1.95-1.80 (m, 2H); ESHRMS m/z 355.0818 (M+H, $C_{18}H_{16}ClN_4S$ requires 355.0784); Anal. Calc'd for: $C_{18}H_{15}ClN_4S$ (0.5 $H_2O$): C, 59.42 H, 4.43; N, 15.40. Found: C, 59.64; H, 4.11; N, 15.44.

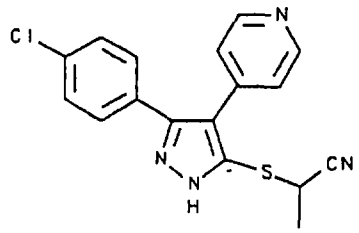
**Example A-476**



The compound prepared in Example A-461 (416 mg, 1.1 mmol), morpholine (4 mL), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (481 mg, 1.5 mmol) and dimethylformamide (10 mL) were stirred overnight. The mixture was diluted with water (75 mL) and the resulting solid was filtered (363 mg). The solid was recrystallized from ethanol to give the desired product

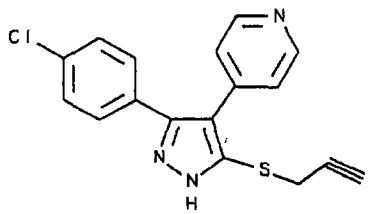
as a white solid (219 mg, 48% yield). mp 215.4-215.5°C; $^1$H NMR (DMSO-*d6*) 13.70-13.60 (m, 1H); 8.60-8.50 (m, 2H); 7.50-7.10 (m, 6H); 3.93-3.80 (m, 2H); 3.60-3.20 (m, 8H); ESHRMS m/z 415.0995 (M+H, $C_{20}H_{20}ClN_4O_2S$ requires 415.1001); Anal. Calc'd for: $C_{20}H_{19}ClN_4O_2S$: C, 57.90 H, 4.62; N, 13.50. Found: C, 57.87; H, 4.86; N, 13.53.

**Example A-477**



The above compound was prepared similarly to the compound of Example A-456 using 2-bromopropionitrile except the mixture was heated at 70 °C for one hour. The mixture was diluted with water (75 mL) and filtered to give an off-white solid (662 mg). The solid was recrystallized from methanol to give the desired product as a white solid (220 mg, 37% yield). mp 211.1-212.8°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.87-8.80 (m, 2H); 7.90-7.80 (m, 2H); 7.55-7.45 (m, 6H); 4.42 (q, 1H); 1.50 (d, 3H); ESHRMS m/z 341.0628 (M+H, $C_{18}H_{16}ClN_4S$ requires 341.0628); Anal. Calc'd for: $C_{17}H_{13}ClN_4S$: C, 59.91 H, 3.84; N, 16.44. Found: C, 59.64; H, 4.01; N, 16.18.

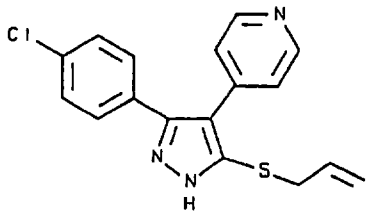
**Example A-478**



The above compound was prepared similarly to the

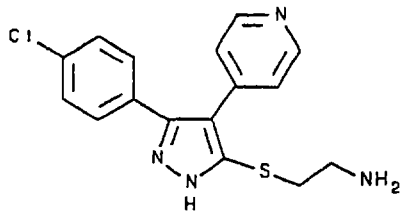
compound of Example A-456 using propargyl bromide. The mixture was diluted with water (75 mL) and filtered to give a pale yellow solid (577 mg). The solid was triturated with methanol to give the desired product as a white solid (388 mg, 68% yield). mp 212.7-213.2°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.80 (d, *J* = 6.8 Hz, 2H); 7.82 (d, *J* = 6.8 Hz, 2H); 7.50-7.35 (m, 4H); 3.81 (d, *J* = 2.6 Hz, 2H); 3.05 (t, *J* = 2.6 Hz, 1H); ESHRMS m/z 326.0533 (M+H, $C_{17}H_{13}ClN_3S$ requires 326.0519); Anal. Calc'd for: $C_{17}H_{12}ClN_3S$ (0.2 $H_2O$): C, 61.98 H, 3.79; N, 12.76. Found: C, 61.89; H, 3.45; N, 12.67.

**Example A-479**



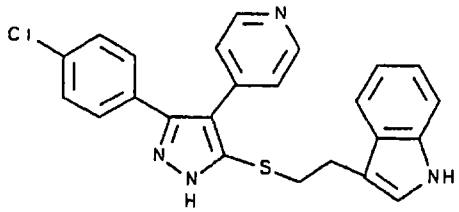

The above compound was prepared similarly to the compound of Example A-456 using allyl bromide. The mixture was diluted with water (75 mL) and filtered to give a pale yellow solid (509 mg). The solid was recrystallized from methanol to give the desired product as a pale yellow solid (187 mg, 33% yield). mp 207.3-208.1°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.80 (d, 2H); 7.80 (d, 2H); 7.50-7.30 (m, 4H); 5.90-5.70 (m, 1H); 5.10-4.95 (m, 2H); 3.62 (d, 2H); ESHRMS m/z 328.0693 (M+H, $C_{17}H_{15}ClN_3S$ requires 328.0675); Anal. Calc'd for: $C_{17}H_{14}ClN_3S$ (0.1 $H_2O$): C, 61.94 H, 4.34; N, 12.75. Found: C, 61.83; H, 4.21; N, 12.76.

**Example A-480**



The above compound was prepared similarly to the compound of Example A-456 using 2-bromoethylamine except two equivalents of potassium carbonate were used. The mixture was diluted with water (75 mL) and filtered to give a pale yellow solid (509 mg). The solid was recrystallized from methanol to give the desired product as a pale yellow solid (262 mg, 45% yield). mp 186.8-187.8°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.85-8.75 (m, 2H); 8.90 (br s, 2H); 8.85-8.75 (m, 2H); 7.55-7.35 (m, 4H); 3.30-3.00 (m, 4H); ESHRMS m/z 331.0779 (M+H, $C_{16}H_{16}ClN_4S$ requires 331.0784); Anal. Calc'd for: $C_{16}H_{15}ClN_4S$ (0.5 $H_2O$): C, 56.55; H, 4.75; N, 16.49. Found: C, 56.28; H, 4.38; N, 16.20.

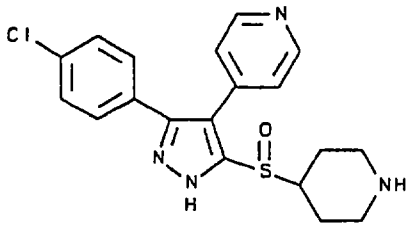
**Example A-481**



The above compound was prepared similarly to the compound of Example A-456 using 3-(2-bromoethyl)indole. The mixture was diluted with water (75 mL) and filtered to give a pale yellow solid (752 mg). The solid was triturated with methanol to give the desired product as a white solid (682 mg, 91% yield). mp 211.9-213.2°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 10.80 (s, 1H); 8.72 (d,

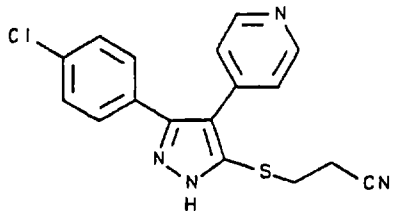
2H); 7.71 (d, 2H); 7.55-7.35 (m, 5H); 7.29 (d, 1H); 7.12-6.88 (m, 3H); 3.40-3.30 (m, 2H); 3.05-2.95 (m, 2H); ESHRMS m/z 431.1095 (M+H, $C_{24}H_{20}ClN_4S$ requires 431.1097); Anal. Calc'd for: $C_{24}H_{19}ClN_4S$ (0.15 $H_2O$): C, 66.47 H, 4.49; N, 12.92. Found: C, 66.44; H, 4.51; N, 12.84.

**Example A-482**



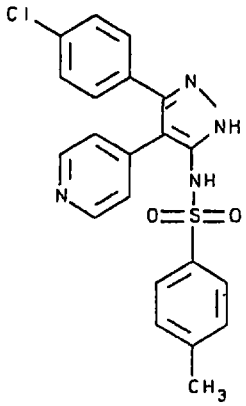
The compound of Example A-464 (464 mg, 0.95 mmol) and TFA (8 mL) were mixed in methylene chloride (10 mL) and stirred overnight. The mixture was concentrated in vacuo and the residue was partitioned between ether and water. The aqueous layer was made basic to pH 10 with 2.5N sodium hydroxide and extracted with ethyl acetate (2 x 100 mL). Upon standing overnight, a solid precipitated from the aqueous layer and was filtered to give the desired product as a white solid (183 mg, 50% yield). mp 189.1-190.8°C; $^1$H NMR (DMSO-*d6* + approx. 10%TFA) 8.85 (d, 2H); 8.80-8.60 (m 1H); 8.45-8.25 (m, 1H); 7.90 (d, 2H); 7.55-7.30 (m, 4H); 3.65-3.20 (m 3H); 3.10-2.80 (m 2H); 2.20-2.00 (m, 1H); 1.90-1.50 (m, 3H); ESHRMS m/z 387.1032 (M+H, $C_{19}H_{20}ClN_4OS$ requires 387.1046); Anal. Calc'd for: $C_{19}H_{20}ClN_4OS$ (2 $H_2O$): C, 53.96 H, 5.48; N, 13.25. Found: C, 53.75; H, 4.99; N, 13.21.

**Example A-483**



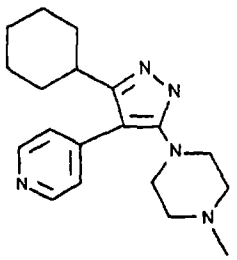
The above compound was prepared similarly to the compound of Example A-456 using 3-bromopropionitrile. The mixture was diluted with water (75 mL) and extracted into ethyl acetate, which was dried over $MgSO_4$ and concentrated in vacuo leaving an orange waxy solid (523 mg). The solid was dissolved in $CH_3CN$ and filtered through a pad of silica gel and eluted with ethyl acetate to give a white solid. The solid was triturated with ethyl acetate and filtered to give the desired product as a white solid (76 mg, 13% yield). mp 205.7-206.5°C; $^1H$ NMR (DMSO-*d6* + approx. 10%TFA) 8.80 (d, 2H); 7.80 (d, 2H); 7.55-7.35 (m, 4H); 3.30-3.20 (m, 2H); 2.90-2.80 (m, 2H); ESHRMS m/z 341.0639 (M+H, $C_{19}H_{20}ClN_4OS$ requires 341.0628); Anal. Calc'd for: $C_{17}H_{13}ClN_4S$ (0.25 $H_2O$): C, 59.13 H, 3.94; N, 16.22. Found: C, 59.03; H, 3.93; N, 15.90.

**Example A-484**



A solution of 5-amino-3-(4-chlorophenyl)-4-(pyridin-4-yl)-pyrazole (200 mg, 0.74 mmol) and toluene sulfonyl chloride (564 mg, 2.94 mmol, prepared as set forth in Example A-427) in pyridine (5 mL) was stirred at 100 °C for two days. The mixture was concentrated *in vacuo* to a brown residue. The residue was chromatographed on a silica gel column eluting with 10% methanol/dichloromethane. The fractions containing the desired product were combined and concentrated to a yellow solid which was washed with diethyl ether and filtered to afford 78 mg (25%) of the desired sulfonamide as a white solid. m.p.284.3-284.4 °C. $^1$H NMR (DMSO/300 MHz) $\delta$ 13.33 (brs, 0.8H), 9.94 (brs, 0.75H), 8.48 (brs, 1.75H), 8.22 (brs, 0.3H), 7.63 (d, 1.7H), 7.47 (d, 1.85H), 7.24 (m, 6.45H), 7.02 (brs, 0.25H), 6.81 (brs, 0.20H). ESLRMS m/z 425 (M+H). ESHRMS m/z 425.0848 (M+H, $C_{21}H_{18}N_4ClS$ requires 425.0839).

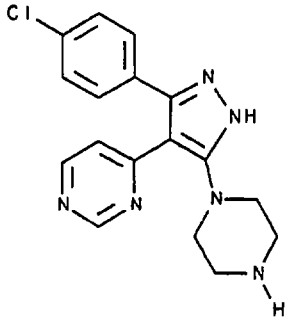
**Example A-485**



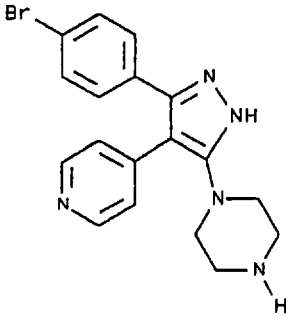
1-[cyclohexyl-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-methylpiperazine.

mp >300 °C (decomposed). $^1$H NMR ($CD_3OD$ / 300 MHz) 8.50 (d, 2H, $J$ = 6.0 Hz), 7.51 (d, 2H, $J$ = 5.8 Hz), 2.99-2.93, (m, 4H), 2.52-2.48 (m, 4H), 3.04-3.02 (m, 4H), 2.96 (s, 3H), 2.54-2.49 (m, 1H), 2.31-2.26 (m, 4H), 1.84-1.33 (m, 10H). FABLRMS *m/z* 326 (M+H).

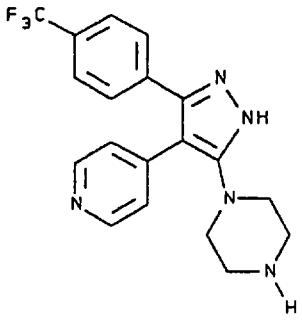
Additional compounds of the present invention which could be prepared using one or more of the reaction schemes set forth in this application include, but are not limited to, the following:



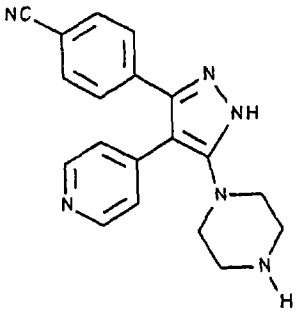
4-[3-(4-chlorophenyl)-5-(1-piperazinyl)-1H-pyrazol-4-yl]pyrimidine ;



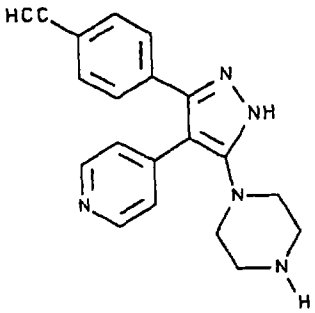
1-[5-(4-bromophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]piperazine ;



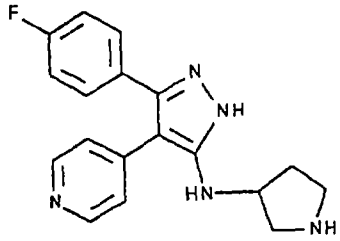
1-[4-(4-pyridinyl)-5-[4-(trifluoromethyl)phenyl]-1H-pyrazol-3-yl]piperazine ;



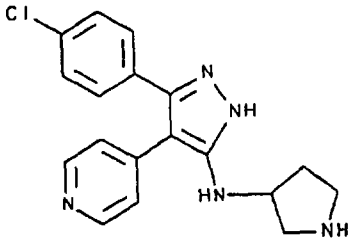
4-[5-(1-piperazinyl-4-(4-pyridinyl)
-1H-pyrazol-3-yl]benzonitrile ;



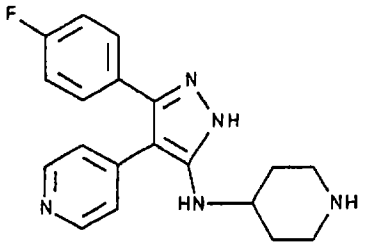
1-[5-(4-ethynylphenyl)-4-(4-pyridinyl)
-1H-pyrazol-3-yl]piperazine ;



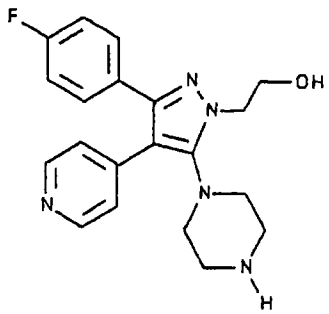
5-(4-fluorophenyl)-4-
(4-pyridinyl)-N-3-pyrrolidinyl-
1H-pyrazol-3-amine ;



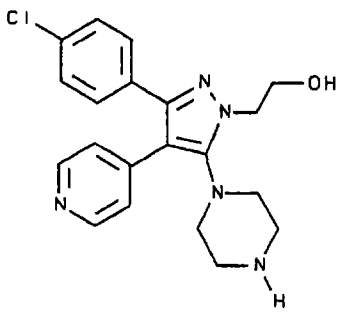
5-(4-chlorophenyl)-4-
(4-pyridinyl)-N-3-pyrrolidinyl-
1H-pyrazol-3-amine ;



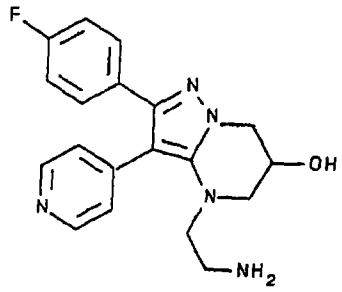
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinamine ;



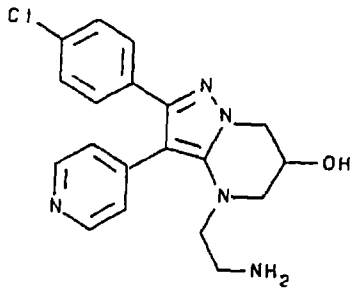
3-(4-fluorophenyl)-5-(1-piperazinyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol ;



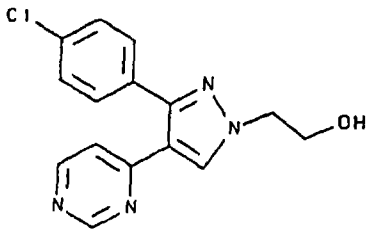
3-(4-chlorophenyl)-5-(1-piperazinyl)-4-(4-pyridinyl)-1H-pyrazole-1-ethanol ;



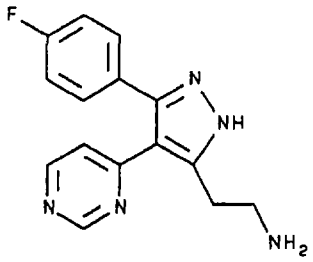
4-[2-aminoethyl]-2-(4-fluoro phenyl)-4,5,6,7-tetrahydro-3-(4-pyridinyl)pyrazolo [1,5-a]pyrimidin-6-ol ;



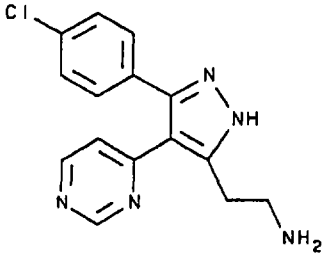
4-[2-aminoethyl]-2-(4-chloro phenyl)-4,5,6,7-tetrahydro-3-(4-pyridinyl)pyrazolo [1,5-a]pyrimidin-6-ol ;



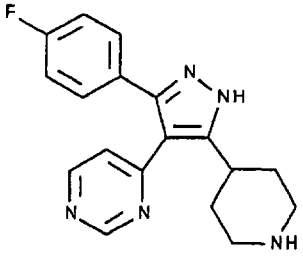
3-(4-chlorophenyl)-4-(4-pyrimidinyl)-1H-pyrazole-1-ethanol ;



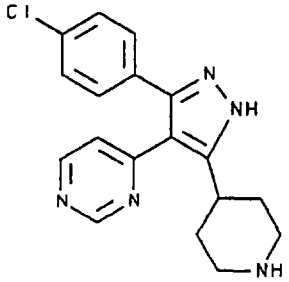
5-(4-fluorophenyl)-4-(4-pyrimidinyl)-1H-pyrazole-3-ethanamine ;



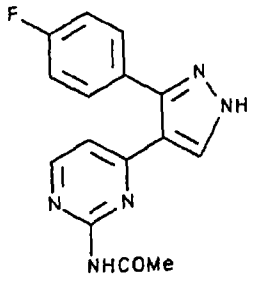
5-(4-chlorophenyl)-4-(4-pyrimidinyl)-1H-pyrazole-3-ethanamine ;



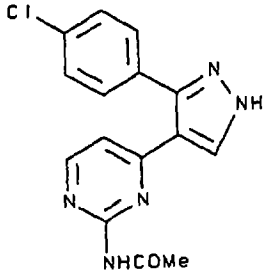
4-[3-(4-fluorophenyl)-5-(4-piperidinyl)-1H-pyrazol-4-yl]pyrimidine ;



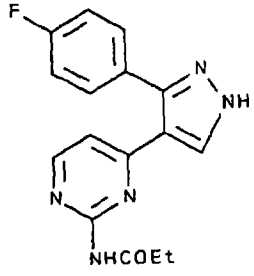
4-[3-(4-chlorophenyl)-5-(4-piperidinyl)-1H-pyrazol-4-yl]pyrimidine ;



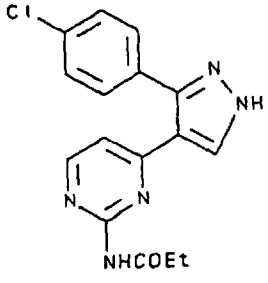
N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]acetamide ;



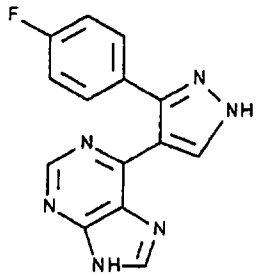
N-[4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]acetamide ;



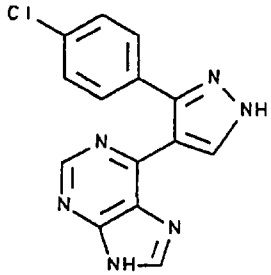
N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinylpropanamide ;



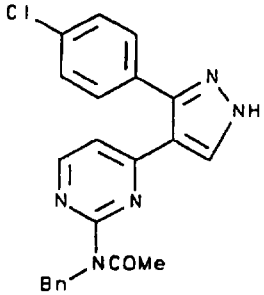
N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]propanamide ;



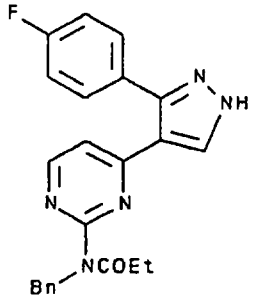
6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-1H-purine;



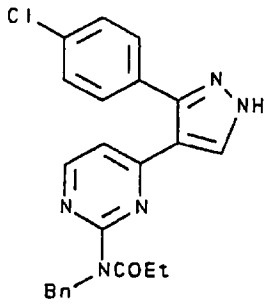
6-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-1H-purine;



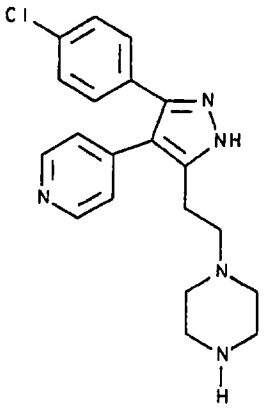
N-[4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-
2-pyrimidinyl]-N-(phenylmethyl)acetamide;



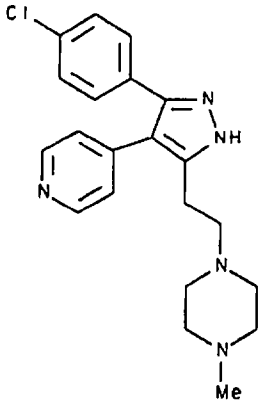
N-[4-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-
2-pyrimidinyl]-N-(phenylmethyl)propanamide;



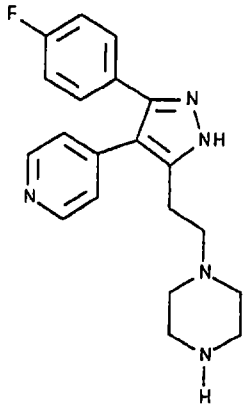
N-[4-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-2-pyrimidinyl]-N-(phenylmethyl)propanamide;



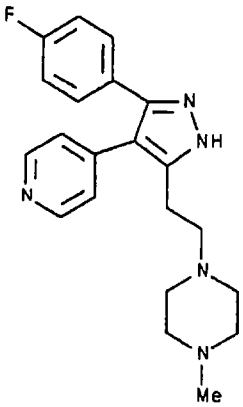
1-[2-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]ethyl]piperazine;



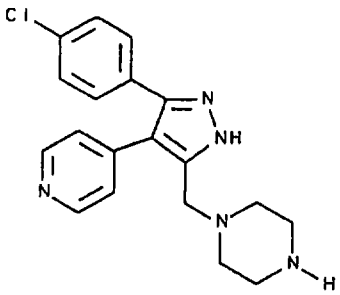
1-[2-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]ethyl]-4-methylpiperazine;



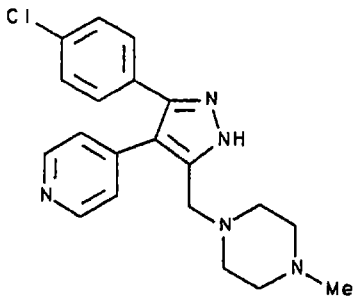
1-[2-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]ethyl]piperazine;



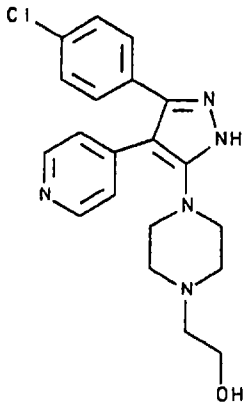
1-[2-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]ethyl]-4-methylpiperazine;



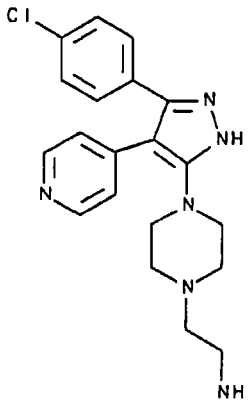
1-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methylpiperazine;



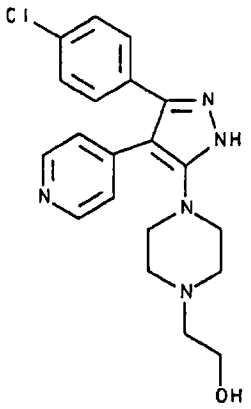
1-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-methylpiperazine;



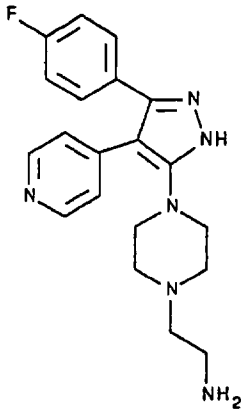
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazineethanol;



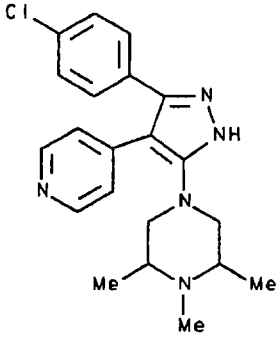
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazineethanamine;



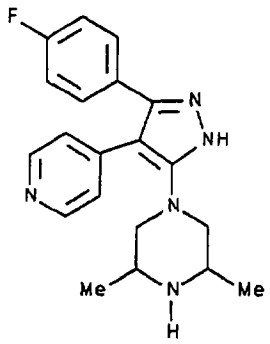
4-[5-[4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazineethanol;



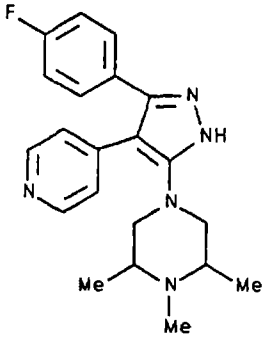
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-piperazineethanamine;



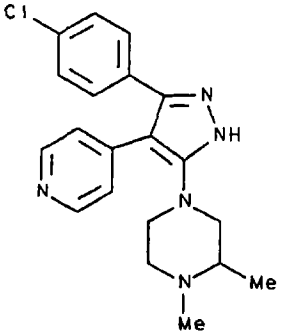
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,2,6-trimethylpiperazine;



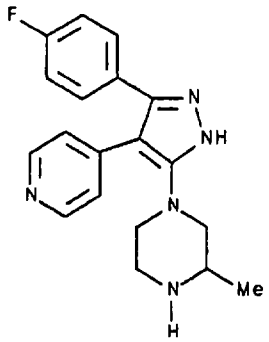
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3,5-dimethylpiperazine;



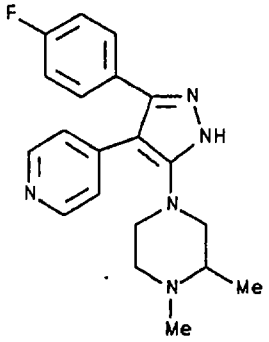
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,2,6-trimethylpiperazine;



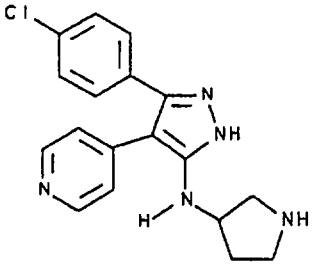
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,2-dimethylpiperazine;



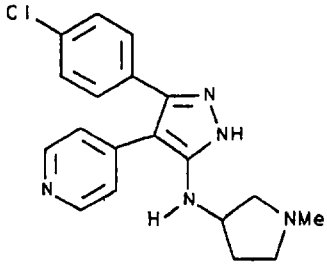
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-methylpiperazine;



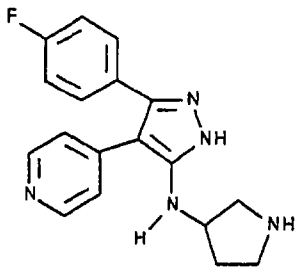
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1,2-dimethylpiperazine;



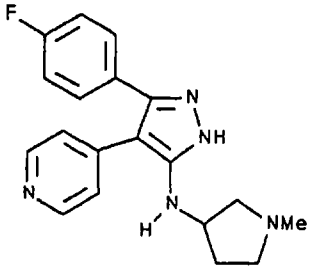
5-(4-chlorophenyl)-4-(4-pyridinyl)-N-3-pyrrolidinyl-1H-pyrazol-3-amine;



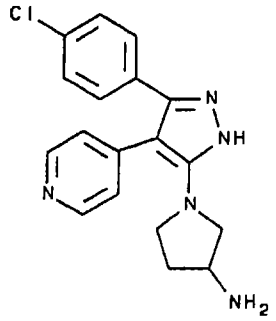
5-(4-chlorophenyl)-N-(1-methyl-3-pyrrolidinyl)-4-(4-pyridinyl)-1H-pyrazol-3-amine;



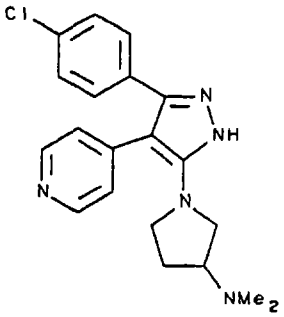
5-(4-fluorophenyl)-4-(4-pyridinyl)-N-3-pyrrolidinyl-1H-pyrazol-3-amine;



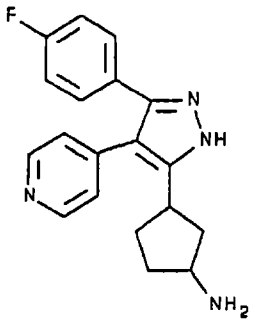
5-(4-fluorophenyl)-N-(1-methyl-3-pyrrolidinyl)-4-(4-pyridinyl)-1H-pyrazol-3-amine;



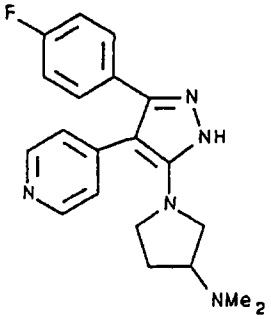
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-pyrrolidinamine;



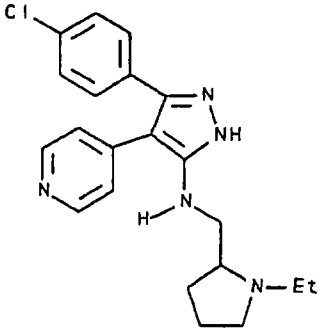
1-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-dimethyl-3-pyrrolidinamine;



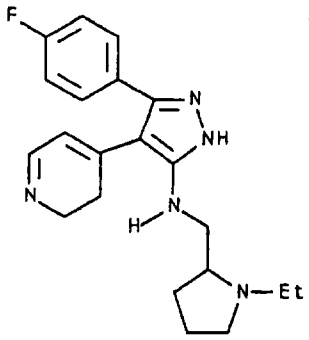
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-pyrrolidinamine;



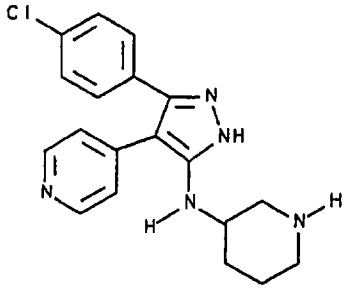
1-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-N,N-dimethyl-3-pyrrolidinamine;



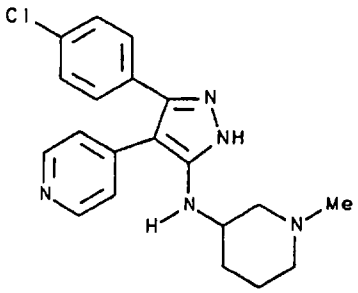
5-(4-chlorophenyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-(4-pyridinyl)-1H-pyrazol-3-amine;



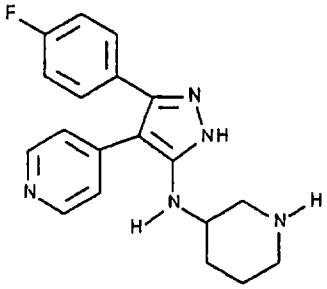
5-(4-fluorophenyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-(4-pyridinyl)-1H-pyrazol-3-amine;



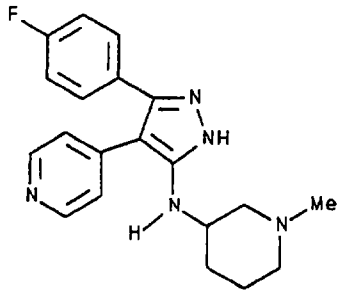
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-piperidinamine;



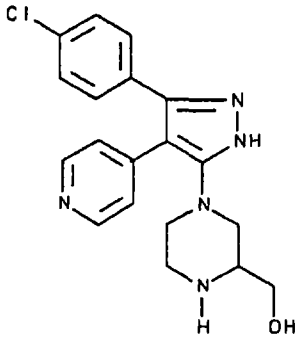
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-3-piperidinamine;



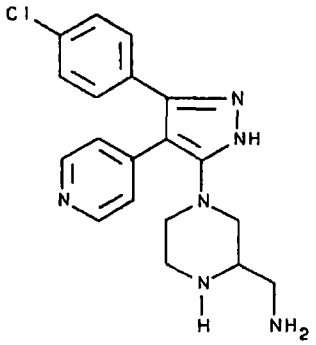
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-3-piperidinamine;



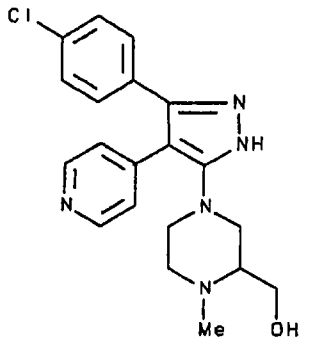
N-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-3-piperidinamine;



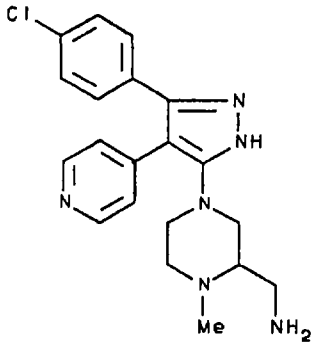
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinemethanol;



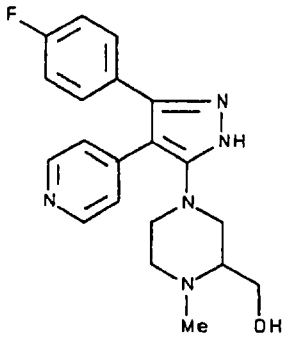
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinemethanamine;



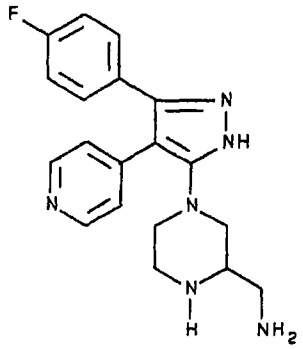
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinemethanol;



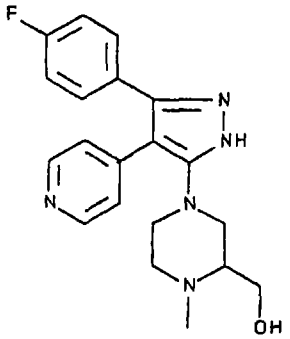
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinemethanamine;



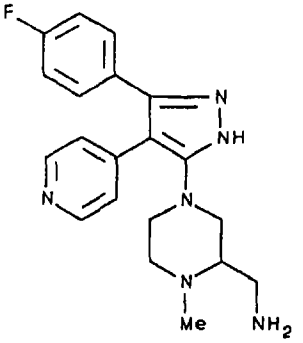
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinemethanol;



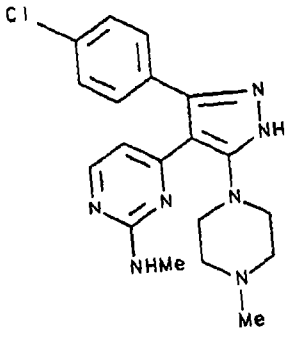
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinemethanamine;



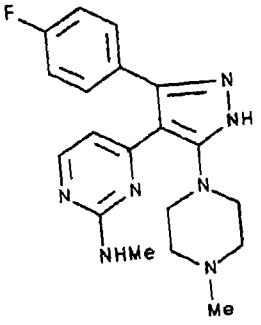
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinemethanol;



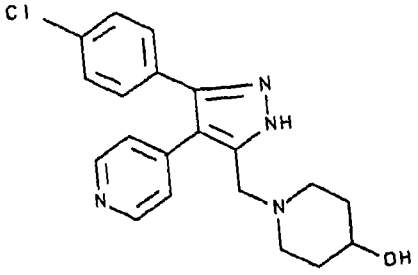
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinemethanamine;



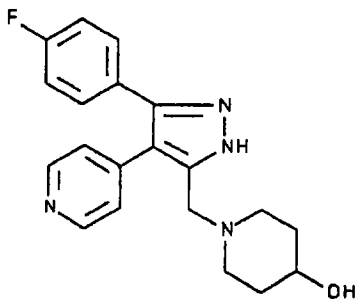
4-[3-(4-chlorophenyl)-5-(4-methyl-1-piperazinyl)-1H-pyrazol-4-yl]-N-methyl-2-pyrimidinamine;



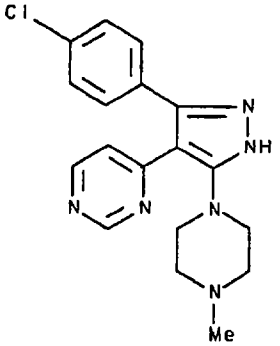
4-[3-(4-fluorophenyl)-5-(4-methyl-1-piperazinyl)-1H-pyrazol-4-yl]-N-methyl-2-pyrimidinamine;



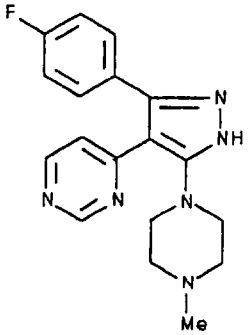
1-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl]-4-piperidinol;



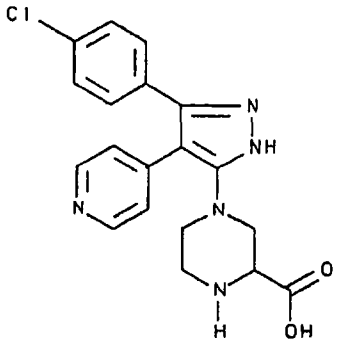
1-[[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]methyl-4-piperidinol;



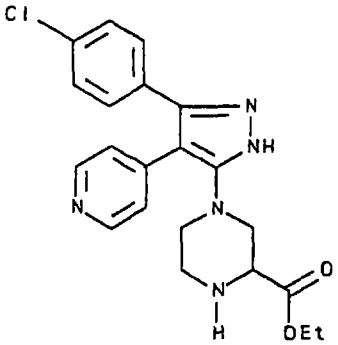
4-[3-(4-chlorophenyl)-5-(4-methyl-1-piperazinyl)-1H-pyrazol-4-yl]pyrimidine;



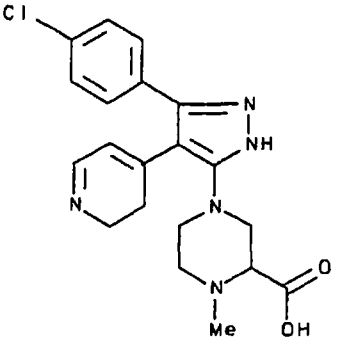
4-[3-(4-fluorophenyl)-5-(4-methyl-1-piperazinyl)-1H-pyrazol-4-yl]pyrimidine;



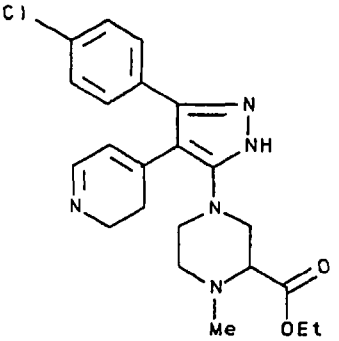
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinecarboxylic acid;



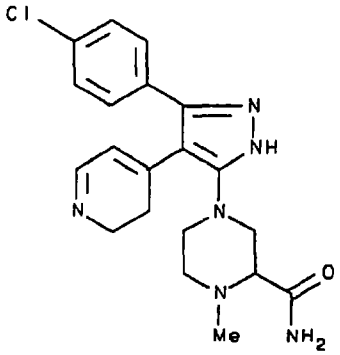
ethyl 4-[5[-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinecarboxylate;



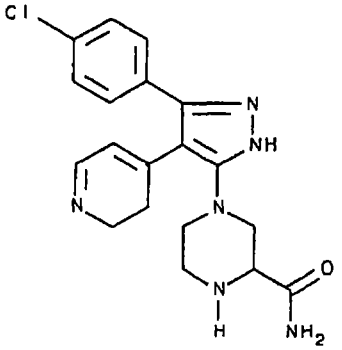
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinecarboxylic acid;



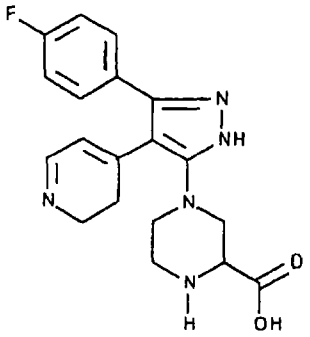
ethyl 4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinecarboxylate;



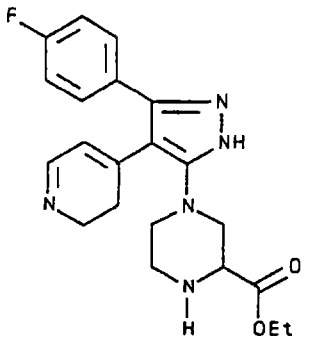
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinecarboxamide;



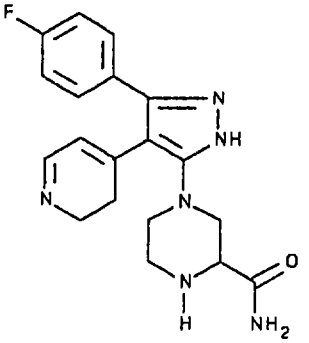
4-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinecarboxamide;



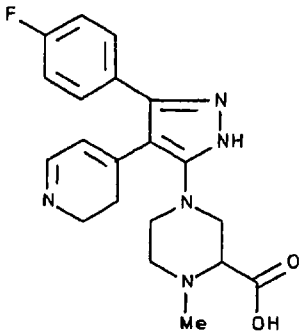
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinecarboxylic acid;



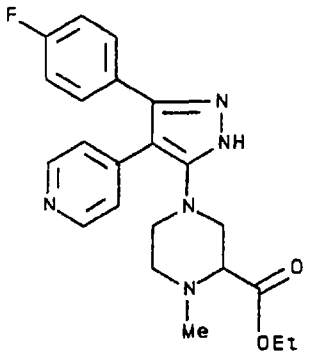
ethyl 4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinecarboxylate;



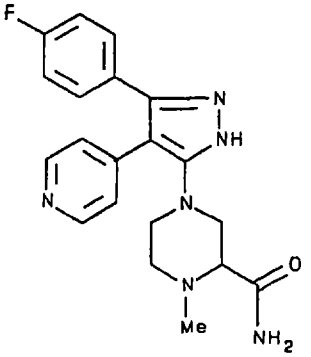
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-2-piperazinecarboxamide;



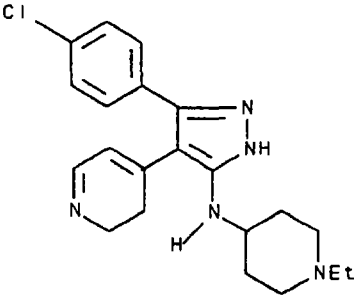
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinecarboxylic acid;



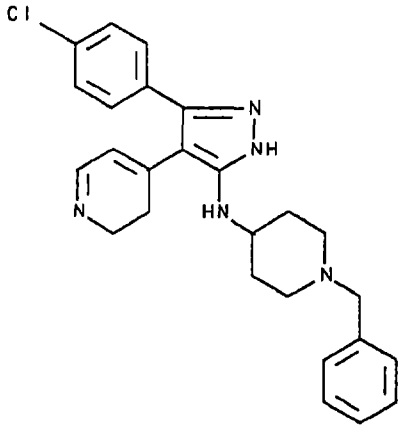
ethyl 4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinecarboxylate;



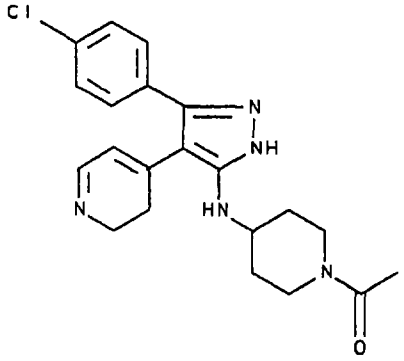
4-[5-(4-fluorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-methyl-2-piperazinecarboxamide;



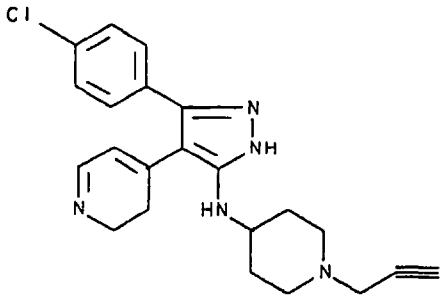
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-ethyl-4-piperidinamine;



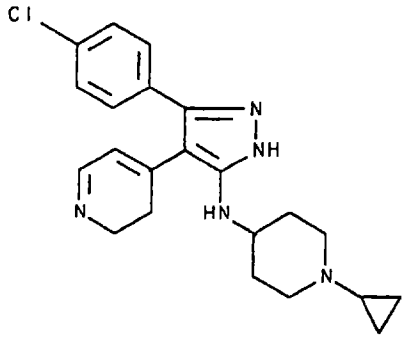
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-(phenylmethyl)-4-piperidinamine;



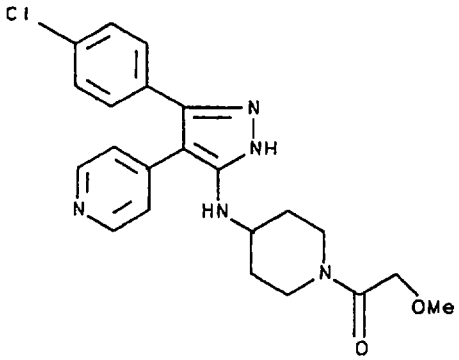
1-acetyl-N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-4-piperidinamine;



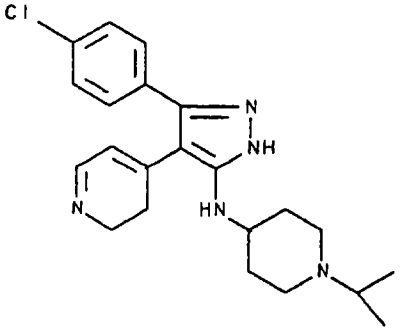
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-(2-propynyl)-4-piperidinamine;



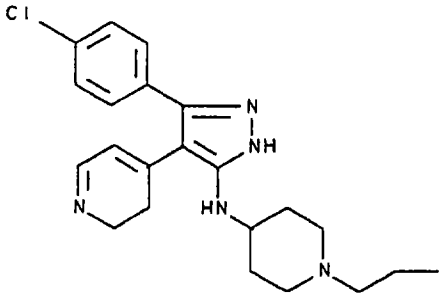
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-cyclopropyl-4-piperidinamine;



N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-(methoxyacetyl)-4-piperidinamine;

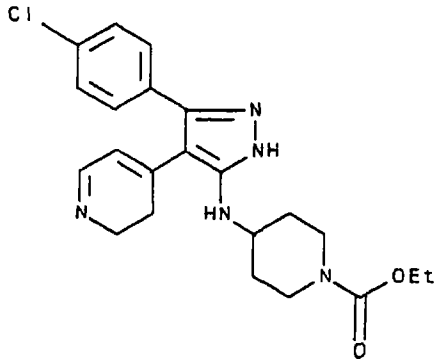


N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-(methylethyl)-4-piperidinamine;

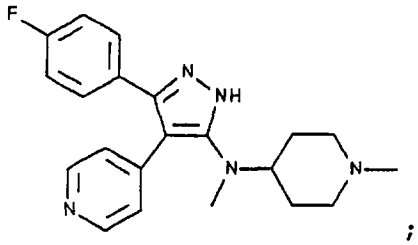


481

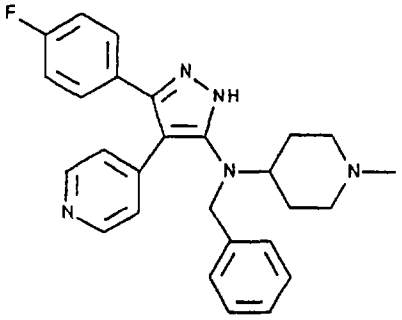
N-[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]-1-propyl-4-piperidinamine;



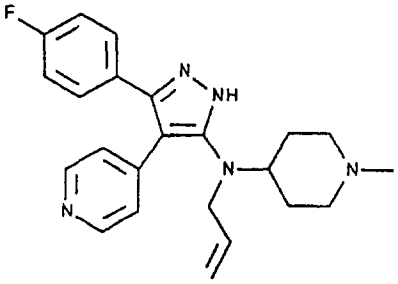
ethyl 4-[[5-(4-chlorophenyl)-4-(4-pyridinyl)-1H-pyrazol-3-yl]amino]-1-piperidinecarboxylate;



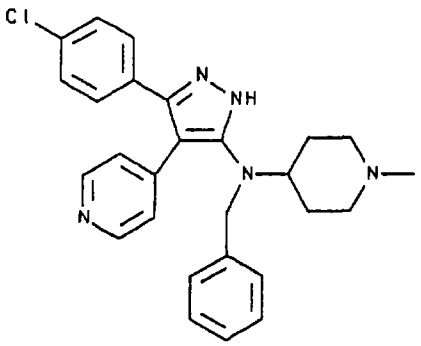
;



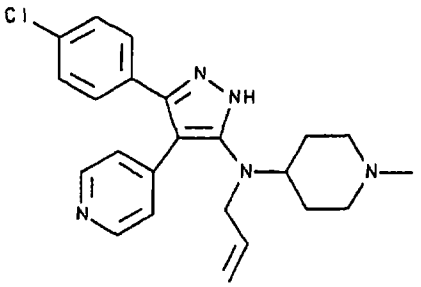
;



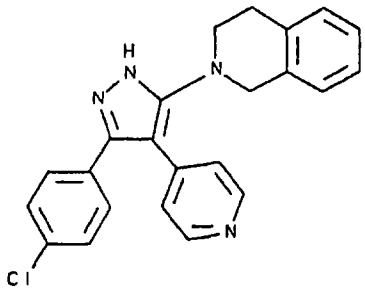
;



;



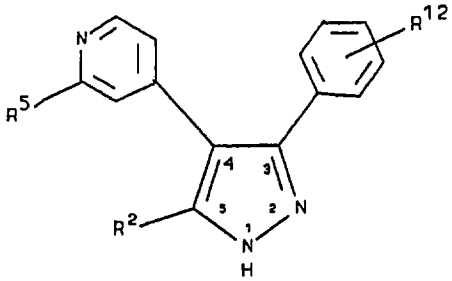
; and



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Additional compounds of specific interest include the compounds of Tables 3-3, 3-4, 3-5 and 3-6:

TABLE 3-3



| $R^2$ | $R^5$ | $R^{12}$ |
|---|---|---|
| 4-piperidinyl | methyl | m- or p-fluoro |
| 4-piperidinyl | ethyl | m- or p-fluoro |
| 4-piperidinyl | amino | m- or p-fluoro |
| 4-piperidinyl | methylamino | m- or p-fluoro |
| 4-piperidinyl | dimethylamino | m- or p-fluoro |
| 4-piperidinyl | ethylamino | m- or p-fluoro |
| 4-piperidinyl | diethylamino | m- or p-fluoro |
| 4-piperidinyl | propylamino | m- or p-fluoro |
| 4-piperidinyl | dipropylamino | m- or p-fluoro |
| 4-piperidinyl | hydroxyethylamino | m- or p-fluoro |
| 4-piperidinyl | 1-hydroxy-1,1-dimethylethyl | m- or p-fluoro |
| 4-piperidinyl | methoxyethylamino | m- or p-fluoro |
| 4-piperidinyl | methyl | m- or p-chloro |
| 4-piperidinyl | ethyl | m- or p-chloro |
| 4-piperidinyl | amino | m- or p-chloro |
| 4-piperidinyl | methylamino | m- or p-chloro |
| 4-piperidinyl | dimethylamino | m- or p-chloro |
| 4-piperidinyl | ethylamino | m- or p-chloro |
| 4-piperidinyl | diethylamino | m- or p-chloro |
| 4-piperidinyl | propylamino | m- or p-chloro |
| 4-piperidinyl | dipropylamino | m- or p-chloro |
| 4-piperidinyl | hydroxyethylamino | m- or p-chloro |
| 4-piperidinyl | 1-hydroxy-1,1-dimethylethyl | m- or p-chloro |
| 4-piperidinyl | methoxyethylamino | m- or p-chloro |
| 4-piperidinyl | methyl | m- or p-methyl |
| 4-piperidinyl | ethyl | m- or p-methyl |
| 4-piperidinyl | amino | m- or p-methyl |
| 4-piperidinyl | methylamino | m- or p-methyl |
| 4-piperidinyl | dimethylamino | m- or p-methyl |

| | | |
|---|---|---|
| 4-piperidinyl | ethylamino | m- or p-methyl |
| 4-piperidinyl | diethylamino | m- or p-methyl |
| 4-piperidinyl | propylamino | m- or p-methyl |
| 4-piperidinyl | dipropylamino | m- or p-methyl |
| 4-piperidinyl | hydroxyethylamino | m- or p-methyl |
| 4-piperidinyl | 1-hydroxy-1,1-dimethylethyl | m- or p-methyl |
| 4-piperidinyl | methoxyethylamino | m- or p-methyl |
| 4-piperazinyl | methyl | m- or p-fluoro |
| 4-piperazinyl | ethyl | m- or p-fluoro |
| 4-piperazinyl | amino | m- or p-fluoro |
| 4-piperazinyl | methylamino | m- or p-fluoro |
| 4-piperazinyl | dimethylamino | m- or p-fluoro |
| 4-piperazinyl | ethylamino | m- or p-fluoro |
| 4-piperazinyl | diethylamino | m- or p-fluoro |
| 4-piperazinyl | propylamino | m- or p-fluoro |
| 4-piperazinyl | dipropylamino | m- or p-fluoro |
| 4-piperazinyl | hydroxyethylamino | m- or p-fluoro |
| 4-piperazinyl | 1-hydroxy-1,1-dimethylethyl | m- or p-fluoro |
| 4-piperazinyl | methoxyethylamino | m- or p-fluoro |
| 4-piperazinyl | methyl | m- or p-chloro |
| 4-piperazinyl | ethyl | m- or p-chloro |
| 4-piperazinyl | amino | m- or p-chloro |
| 4-piperazinyl | methylamino | m- or p-chloro |
| 4-piperazinyl | dimethylamino | m- or p-chloro |
| 4-piperazinyl | ethylamino | m- or p-chloro |
| 4-piperazinyl | diethylamino | m- or p-chloro |
| 4-piperazinyl | propylamino | m- or p-chloro |
| 4-piperazinyl | dipropylamino | m- or p-chloro |
| 4-piperazinyl | hydroxyethylamino | m- or p-chloro |
| 4-piperazinyl | 1-hydroxy-1,1-dimethylethyl | m- or p-chloro |
| 4-piperazinyl | methoxyethylamino | m- or p-chloro |
| 4-piperazinyl | methyl | m- or p-methyl |
| 4-piperazinyl | ethyl | m- or p-methyl |
| 4-piperazinyl | amino | m- or p-methyl |
| 4-piperazinyl | methylamino | m- or p-methyl |
| 4-piperazinyl | dimethylamino | m- or p-methyl |
| 4-piperazinyl | ethylamino | m- or p-methyl |
| 4-piperazinyl | diethylamino | m- or p-methyl |
| 4-piperazinyl | propylamino | m- or p-methyl |
| 4-piperazinyl | dipropylamino | m- or p-methyl |

| | | |
|---|---|---|
| 4-piperazinyl | hydroxyethylamino | m- or p-methyl |
| 4-piperazinyl | 1-hydroxy-1,1-dimethylethyl | m- or p-methyl |
| 4-piperazinyl | methoxyethylamino | m- or p-methyl |
| aminocyclohexyl | methyl | m- or p-fluoro |
| aminocyclohexyl | ethyl | m- or p-fluoro |
| aminocyclohexyl | amino | m- or p-fluoro |
| aminocyclohexyl | methylamino | m- or p-fluoro |
| aminocyclohexyl | dimethylamino | m- or p-fluoro |
| aminocyclohexyl | ethylamino | m- or p-fluoro |
| aminocyclohexyl | diethylamino | m- or p-fluoro |
| aminocyclohexyl | propylamino | m- or p-fluoro |
| aminocyclohexyl | dipropylamino | m- or p-fluoro |
| aminocyclohexyl | hydroxyethylamino | m- or p-fluoro |
| aminocyclohexyl | 1-hydroxy-1,1-dimethylethyl | m- or p-fluoro |
| aminocyclohexyl | methoxyethylamino | m- or p-fluoro |
| aminocyclohexyl | methyl | m- or p-chloro |
| aminocyclohexyl | ethyl | m- or p-chloro |
| aminocyclohexyl | amino | m- or p-chloro |
| aminocyclohexyl | methylamino | m- or p-chloro |
| aminocyclohexyl | dimethylamino | m- or p-chloro |
| aminocyclohexyl | ethylamino | m- or p-chloro |
| aminocyclohexyl | diethylamino | m- or p-chloro |
| aminocyclohexyl | propylamino | m- or p-chloro |
| aminocyclohexyl | dipropylamino | m- or p-chloro |
| aminocyclohexyl | hydroxyethylamino | m- or p-chloro |
| aminocyclohexyl | 1-hydroxy-1,1-dimethylethyl | m- or p-chloro |
| aminocyclohexyl | methoxyethylamino | m- or p-chloro |
| aminocyclohexyl | methyl | m- or p-methyl |
| aminocyclohexyl | ethyl | m- or p-methyl |
| aminocyclohexyl | amino | m- or p-methyl |
| aminocyclohexyl | methylamino | m- or p-methyl |
| aminocyclohexyl | dimethylamino | m- or p-methyl |
| aminocyclohexyl | ethylamino | m- or p-methyl |
| aminocyclohexyl | diethylamino | m- or p-methyl |
| aminocyclohexyl | propylamino | m- or p-methyl |
| aminocyclohexyl | dipropylamino | m- or p-methyl |
| aminocyclohexyl | hydroxyethylamino | m- or p-methyl |
| aminocyclohexyl | 1-hydroxy-1,1-dimethylethyl | m- or p-methyl |
| aminocyclohexyl | methoxyethylamino | m- or p-methyl |

Still other compounds of specific interest include those compounds of Table 3-3 modified as follows:

(1) The 4-piperidinyl moiety is replaced with a 1-, 2- or 3-piperidinyl moiety; and/or

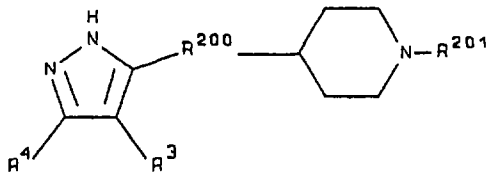
(2) The 4-piperidinyl, 3-piperidinyl, 2-piperidinyl or piperazinyl ring is substituted at a nitrogen ring atom with methyl, ethyl, isopropyl, cyclopropyl, propargyl, benzyl, hydroxyethyl, methoxyethyl, or methoxyacetyl; and/or

(3) The 1-piperidinyl ring is substituted at a carbon ring atom with methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, cyclopropylamino, propargylamino, benzylamino, hydroxyethylamino, methoxyethylamino, or methoxyacetylamino; and/or

(4) The amino group of the aminocyclohexyl is replaced with methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, methoxyethylamino, or methoxyacetylamino; and/or

(5) A linking group selected from the group consisting of methylene, -S-, -O-, and -NH- separates the piperidinyl, piperazinyl or cyclohexyl moiety from the pyrazole nucleus.

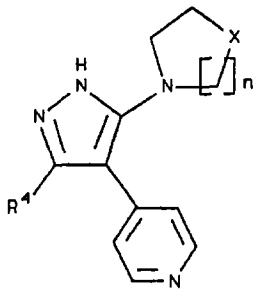
TABLE 3-4




| $R^4$ | $R^3$ | $R^{200}$ | $R^{201}$ |
|---|---|---|---|
| 4-pyridyl | 4-methylphenyl | H | O |
| 4-pyridyl | 4-methylphenyl | $CH_3$ | O |
| 4-pyrimidyl | 4-methylphenyl | H | O |
| 4-pyrimidyl | 4-methylphenyl | $CH_3$ | O |
| 4-pyridyl | 4-methylphenyl | H | S |
| 4-pyridyl | 4-methylphenyl | $CH_3$ | S |

| | | | | |
|---|---|---|---|---|
| | 4-pyrimidyl | 4-methylphenyl | H | S |
| | 4-pyrimidyl | 4-methylphenyl | $CH_3$ | S |
| | 4-pyridyl | 3-methylphenyl | H | O |
| | 4-pyridyl | 3-methylphenyl | $CH_3$ | O |
| | 4-pyrimidyl | 3-methylphenyl | H | O |
| | 4-pyrimidyl | 3-methylphenyl | $CH_3$ | O |
| | 4-pyridyl | 3-methylphenyl | H | S |
| | 4-pyridyl | 3-methylphenyl | $CH_3$ | S |
| | 4-pyrimidyl | 3-methylphenyl | H | S |
| | 4-pyrimidyl | 3-methylphenyl | $CH_3$ | S |

TABLE 3-5

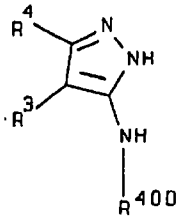


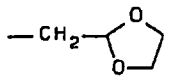
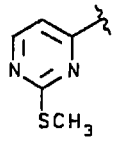
| $R^4$ | n | X |
|---|---|---|
| 4-chlorophenyl | 1 | S |
| 4-chlorophenyl | 2 | SO |
| 4-chlorophenyl | 2 | $SO_2$ |
| 4-chlorophenyl | 2 | $CH_2$ |
| 4-chlorophenyl | 2 | $CHCH_3$ |
| 4-chlorophenyl | 2 | CHOH |
| 4-chlorophenyl | 1 | $CH_2$ |
| 4-chlorobenzyl | 2 | $NCH_3$ |
| 2-chlorophenyl | 2 | $NCH_3$ |
| 3,4-methylenedioxyphenyl | 2 | $NCH_3$ |
| cyclohexyl | 2 | $NCH_3$ |
| 2-thienyl | 2 | $NCH_3$ |
| 5-chloro-2-thienyl | 2 | $NCH_3$ |
| 4-propynylphenyl | 2 | $NCH_3$ |
| 4-methylsulfoxylphenyl | 2 | $NCH_3$ |
| 4-methylsulfonylphenyl | 2 | $NCH_3$ |
| 2-(1-methyl-5-chloro)indolyl | 2 | $NCH_3$ |

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TABLE 3-6



| $R^4$ | $R^3$ | $R^{400}$ |
|---|---|---|
| p-Cl phenyl | 4-pyridyl | $-SO_2CH_3$ |
| p-Cl phenyl | 4-pyridyl | $-CH_2CN$ |
| p-Cl phenyl | 4-pyridyl |  |
| p-Cl phenyl |  | H |

## BIOLOGICAL EVALUATION

**p38 Kinase Assay**

Cloning of human p38a:

The coding region of the human p38a cDNA was obtained by PCR-amplification from RNA isolated from the human monocyte cell line THP.1. First strand cDNA was synthesized from total RNA as follows: 2 μg of RNA was annealed to 100 ng of random hexamer primers in a 10 μl reaction by heating to 70 °C for 10 minutes followed by 2 minutes on ice. cDNA was then synthesized by adding 1 μl of RNAsin (Promega, Madison WI), 2 μl of 50 mM dNTP's, 4 μl of 5X buffer, 2 μl of 100 mM DTT and 1 μl (200 U) of Superscript II ™ AMV reverse transcriptase. Random primer, dNTP's and Superscript ™ reagents were all purchased from Life-Technologies, Gaithersburg, MA. The reaction was incubated at 42 °C for 1 hour. Amplification of p38 cDNA was performed by aliquoting 5 μl of the reverse transcriptase reaction into a 100 μl

PCR reaction containing the following: 80 µl $dH_2O$, 2 µl 50 mM dNTP's, 1 µl each of forward and reverse primers (50 pmol/µl), 10 µl of 10X buffer and 1 µl Expand ™ polymerase (Boehringer Mannheim). The PCR primers incorporated Bam HI sites onto the 5' and 3' end of the amplified fragment, and were purchased from Genosys. The sequences of the forward and reverse primers were 5'-GATCGAGGATTCATGTCTCAGGAGAGGCCCA-3' and 5'GATCGAGGATTCTCAGGACTCCATCTCTTC-3' respectively. The PCR amplification was carried out in a DNA Thermal Cycler (Perkin Elmer) by repeating 30 cycles of 94 °C for 1 minute, 60 °C for 1 minute and 68 °C for 2 minutes. After amplification, excess primers and unincorporated dNTP's were removed from the amplified fragment with a Wizard ™ PCR prep (Promega) and digested with Bam HI (New England Biolabs). The Bam HI digested fragment was ligated into BamHI digested pGEX 2T plasmid DNA (PharmaciaBiotech) using T-4 DNA ligase (New England Biolabs) as described by T. Maniatis, *Molecular Cloning: A Laboratory Manual, 2nd ed.* (1989). The ligation reaction was transformed into chemically competent *E. coli* DH10B cells purchased from Life-Technologies following the manufacturer's instructions. Plasmid DNA was isolated from the resulting bacterial colonies using a Promega Wizard™ miniprep kit. Plasmids containing the appropriate Bam HI fragment were sequenced in a DNA Thermal Cycler (Perkin Elmer) with Prism™ (Applied Biosystems Inc.). cDNA clones were identified that coded for both human p38a isoforms (Lee et al. Nature 372, 739). One of the clones which contained the cDNA for p38a-2 (CSBP-2) inserted in the cloning site of pGEX 2T, 3' of the GST coding region was designated pMON 35802. The sequence obtained for this clone is an exact match of the cDNA clone reported by Lee et al. This expression plasmid allows for the production of a GST-p38a fusion protein.

Expression of human p38a:

GST/p38a fusion protein was expressed from the plasmid pMON 35802 in *E. coli*, stain DH10B (Life Technologies, Gibco-BRL). Overnight cultures were grown in Luria Broth (LB) containing 100 mg/ml ampicillin. The next day, 500 ml of fresh LB was inoculated with 10 ml of overnight culture, and grown in a 2 liter flask at 37 °C with constant shaking until the culture reached an absorbance of 0.8 at 600 nm. Expression of the fusion protein was induced by addition of isopropyl b-D-thiogalactosidse (IPTG) to a final concentration of 0.05 mM. The cultures were shaken for three hours at room temperature, and the cells were harvested by centrifugation. The cell pellets were stored frozen until protein purification.

Purification of p38 Kinase-α:

All chemicals were from Sigma Chemical Co. unless noted. Twenty grams of *E. coli* cell pellet collected from five 1 L shake flask fermentations was resuspended in a volume of PBS (140 mM NaCl, 2.7 mM KCl, 10 mM $Na_2HPO_4$, 1.8 mM $KH_2PO_4$, pH 7.3) up to 200 ml. The cell suspension was adjusted to 5 mM DTT with 2 M DTT and then split equally into five 50 ml Falcon conical tubes. The cells were sonnicated (Ultrasonics model W375) with a 1 cm probe for 3 X 1 minutes (pulsed) on ice. Lysed cell material was removed by centrifugation (12,000 x g, 15 minutes) and the clarified supernatant applied to glutathione-sepharose resin (Pharmacia).

Glutathione-Sepharose Affinity Chromatography:

Twelve ml of a 50% glutathione sepharose-PBS suspension was added to 200 ml clarified supernatant and incubated batchwise for 30 minutes at room temperature. The resin was collected by centrifugation (600 x g, 5 min) and washed with 2 x 150 ml PBS/1% Triton X-100,

followed by 4 x 40 ml PBS. To cleave the p38 kinase from the GST-p38 fusion protein, the glutathione-sepharose resin was resuspended in 6 ml PBS containing 250 units thrombin protease (Pharmacia, specific activity > 7500 units/mg) and mixed gently for 4 hours at room temperature. The glutathione-sepharose resin was removed by centrifugation (600 x g, 5 min) and washed 2 x 6 ml with PBS. The PBS wash fractions and digest supernatant containing p38 kinase protein were pooled and adjusted to 0.3 mM PMSF.

Mono Q Anion Exchange Chromatography:

The thrombin-cleaved p38 kinase was further purified by FPLC-anion exchange chromatography. Thrombin-cleaved sample was diluted 2-fold with Buffer A (25 mM HEPES, pH 7.5, 25 mM beta-glycerophosphate, 2 mM DTT, 5% glycerol) and injected onto a Mono Q HR 10/10 (Pharmacia) anion exchange column equilibrated with Buffer A. The column was eluted with a 160 ml 0.1 M-0.6 M NaCl/Buffer A gradient (2 ml/minute flowrate). The p38 kinase peak eluting at 200 mM NaCl was collected and concentrated to 3-4 ml with a Filtron 10 concentrator (Filtron Corp.).

Sephacryl S100 Gel Filtration Chromatography:

The concentrated Mono Q- p38 kinase purified sample was purified by gel filtration chromatography (Pharmacia HiPrep 26/60 Sephacryl S100 column equilibrated with Buffer B (50 mM HEPES, pH 7.5, 50 mM NaCl, 2 mM DTT, 5% glycerol)). Protein was eluted from the column with Buffer B at a 0.5 ml/minute flowrate and protein was detected by absorbance at 280 nm. Fractions containing p38 kinase (detected by SDS-polyacrylamide gel electrophoresis) were pooled and frozen at -80 °C. Typical purified protein yields from 5 L *E. coli* shake flasks fermentations were 35 mg p38 kinase.

**In Vitro Assay**

The ability of compounds to inhibit human p38 kinase alpha was evaluated using two in vitro assay methods. In the first method, activated human p38 kinase alpha phosphorylates a biotinylated substrate, PHAS-I (phosphorylated heat and acid stable protein-insulin inducible), in the presence of gamma $^{32}$P-ATP ($^{32}$P-ATP). PHAS-I was biotinylated prior to the assay and provides a means of capturing the substrate which is phosphorylated during the assay. p38 Kinase was activated by MKK6. Compounds were tested in 10 fold serial dilutions over the range of 100 μM to 0.001 μM using 1% DMSO. Each concentration of inhibitor was tested in triplicate.

All reactions were carried out in 96 well polypropylene plates. Each reaction well contained 25 mM HEPES pH 7.5, 10 mM magnesium acetate and 50 μM unlabeled ATP. Activation of p38 was required to achieve sufficient signal in the assay. Biotinylated PHAS-I was used at 1-2 μg per 50 μl reaction volume, with a final concentration of 1.5 μM. Activated human p38 kinase alpha was used at 1 μg per 50 μl reaction volume representing a final concentration of 0.3 μM. Gamma $^{32}$P-ATP was used to follow the phosphorylation of PHAS-I. $^{32}$P-ATP has a specific activity of 3000 Ci/mmol and was used at 1.2 μCi per 50 μl reaction volume. The reaction proceeded either for one hour or overnight at 30 °C.

Following incubation, 20 μl of reaction mixture was transferred to a high capacity streptavidin coated filter plate (SAM-streptavidin-matrix, Promega) prewetted with phosphate buffered saline. The transferred reaction mix was allowed to contact the streptavidin membrane of the Promega plate for 1-2 minutes. Following capture of biotinylated PHAS-I with $^{32}$P incorporated, each well was washed to remove unincorporated $^{32}$P-ATP three times with 2M NaCl, three washes of 2M NaCl with 1% phosphoric, three washes of distilled water and finally a single wash

of 95% ethanol. Filter plates were air dried and 20 µl of scintillant was added. The plates were sealed and counted. Results are shown in Table 4.

A second assay format was also employed that is based on p38 kinase alpha induced phosphorylation of EGFRP (epidermal growth factor receptor peptide, a 21 mer) in the presence of $^{33}$P-ATP. Compounds were tested in 10 fold serial dilutions over the range of 100µM to 0.001µM in 10% DMSO. Each concentration of inhibitor was tested in triplicate. Compounds were evaluated in 50µl reaction volumes in the presence of 25 mM Hepes pH 7.5, 10 mM magnesium acetate, 4% glycerol, 0.4% bovine serum albumin, 0.4mM DTT, 50µM unlabeled ATP, 25 µg EGFRP (200µM), and 0.05 uCi gamma $^{33}$P-ATP. Reactions were initiated by addition of 0.09 µg of activated, purified human GST-p38 kinase alpha. Activation was carried out using GST-MKK6 (5:1,p38:MKK6) for one hour at 30 °C in the presence of 50µM ATP. Following incubation for 60 minutes at room temperature, the reaction was stopped by addition of 150µl of AG 1X8 resin in 900 mM sodium formate buffer, pH 3.0 (1 volume resin to 2 volumes buffer). The mixture was mixed three times with pipetting and the resin was allowed to settle. A total of 50µl of clarified solution head volume was transferred from the reaction wells to Microlite-2 plates. 150µl of Microscint 40 was then added to each well of the Microlite plate, and the plate was sealed, mixed, and counted.

TABLE 4

| Example | p38 kinase IC50 (µM) |
|---|---|
| 1 | 4.6 |
| 2 | 1.5 |
| 8 | <0.1 |
| 16 | 3.8 |
| 23 | 1.5 |
| 25 | 2.6 |
| 26 | 0.7 |

| | |
|---|---|
| 28 | 0.3 |
| 33 | 2.5 |
| 34 | 8.0 |
| 36 | 12.1 |
| 38 | 0.8 |
| 39 | 1.1 |
| 40 | 1.3 |
| 42 | 0.3 |
| 43 | <0.1 |
| 44 | <0.1 |
| 45 | <0.1 |
| 46 | <0.1 |
| 47 | 3.2 |
| 48 | 1.8 |
| 50 | 2.3 |
| 51 | <0.1 |
| 52 | 0.1 |
| 53 | 0.9 |
| 54 | 0.7 |
| 55 | 6.4 |
| 143 | <0.1 |

**TNF Cell Assays**

Method of Isolation of Human Peripheral Blood Mononuclear Cells:

Human whole blood was collected in Vacutainer tubes containing EDTA as an anticoagulant. A blood sample (7 ml) was carefully layered over 5 ml PMN Cell Isolation Medium (Robbins Scientific) in a 15 ml round bottom centrifuge tube. The sample was centrifuged at 450-500 x g for 30-35 minutes in a swing out rotor at room temperature. After centrifugation, the top band of cells were removed and washed 3 times with PBS w/o calcium or magnesium. The cells were centrifuged at 400 x g for 10 minutes at room temperature. The cells were resuspended in Macrophage Serum Free Medium (Gibco BRL) at a concentration of 2 million cells/ml.

LPS Stimulation of Human PBMs:

PBM cells (0.1 ml, 2 million/ ml) were co-incubated with 0.1 ml compound (10-0.41 $\mu$M, final concentration) for 1 hour in flat bottom 96 well microtiter plates.

Compounds were dissolved in DMSO initially and diluted in TCM for a final concentration of 0.1% DMSO. LPS (Calbiochem, 20 ng/ml, final concentration) was then added at a volume of 0.010 ml. Cultures were incubated overnight at 37 °C. Supernatants were then removed and tested by ELISA for TNF-a and IL1-b. Viability was analyzed using MTS. After 0.1 ml supernatant was collected, 0.020 ml MTS was added to remaining 0.1 ml cells. The cells were incubated at 37 °C for 2-4 hours, then the O.D. was measured at 490-650 nM.

Maintenance and Differentiation of the U937 Human Histiocytic Lymphoma Cell Line:

U937 cells (ATCC) were propagated in RPMI 1640 containing 10% fetal bovine serum, 100 IU/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine (Gibco). Fifty million cells in 100 ml media were induced to terminal monocytic differentiation by 24 hour incubation with 20 ng/ml phorbol 12-myristate 13-acetate (Sigma). The cells were washed by centrifugation (200 x g for 5 min) and resuspended in 100 ml fresh medium. After 24-48 hours, the cells were harvested, centrifuged, and resuspended in culture medium at 2 million cells/ml.

LPS Stimulation of TNF production by U937 Cells:

U937 cells (0.1 ml, 2 million/ml) were incubated with 0.1 ml compound (0.004-50 μM, final concentration) for 1 hour in 96 well microtiter plates. Compounds were prepared as 10 mM stock solutions in DMSO and diluted in culture medium to yield a final DMSO concentration of 0.1% in the cell assay. LPS (E coli, 100 ng/ml final concentration) was then added at a volume of 0.02 ml. After 4 hour incubation at 37°C, the amount of TNF-α released in the culture medium was quantitated by ELISA. Inhibitory potency is expressed as IC50 (μM).
Results of these TNF Cell Assays are shown in Table 5.

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TNF Inhibition: Human Whole Blood Assay

Human peripheral blood is obtained in heparinized tubes. A 190 μL aliquot of blood is placed in each well of a 96 well u-bottom plate. A compound or control vehicle (phosphate buffered saline with dimethylsulfoxide and ethanol) is added to the blood in 10 μL aliquots for serial dilutions providing final concentrations of 25, 5, 1 and 0.25 μM. The final dimethylsulfoxide and ethanol concentrations are 0.1% and 1.5%, respectively. After one hour of incubation at 37 °C, 10 mL of lipopolysaccharide (Salmonella typhosa, Sigma) in phosphate buffered saline is added resulting in a final concentration of 10 mg/mL. After four to five hours of incubation at 37 °C, the supernatants are harvested and assayed at 1:10 or 1:20 dilutions for human TNF using ELISA.

TABLE 5

| Example | Human PBM Assay IC50 (μM) | U937 Cell Assay IC50 ((μM) |
|---|---|---|
| 1 | 0.5 | |
| 2 | 1.6 | 0.578 |
| 4 | 0.1 | 0.222 |
| 5 | | 0.274 |
| 7 | 0.2 | 0.201 |
| 8 | <0.1 | |
| 9 | 0.4 | |
| 10 | 0.7 | 1.687 |
| 12 | 8.5 | |
| 13 | 4.8 | |
| 14 | 1.2 | |
| 17 | 1.1 | |
| 19 | 0.3 | 0.484 |
| 20 | | 1.089 |
| 21 | | 0.077 |
| 22 | 3.2 | |
| 24 | 8.2 | |
| 26 | <0.1 | 0.029 |
| 27 | 2.7 | |
| 28 | 0.1 | |
| 29 | 2.2 | |
| 30 | 2.6 | |
| 31 | 0.8 | 1.053 |
| 32 | | 2.696 |
| 33 | 0.4 | |
| 34 | 0.5 | |
| 35 | 0.7 | |
| 36 | 1.4 | |
| 37 | 1.5 | 0.099 |
| 38 | 0.2 | 0.208 |
| 39 | 0.7 | 0.244 |
| 40 | 0.4 | |
| 41 | 1.0 | |
| 42 | 0.7 | |
| 43 | <0.1 | 0.243 |
| 44 | 0.4 | 0.477 |
| 45 | <0.1 | 0.04 |
| 46 | | 0.329 |
| 47 | | 2.359 |
| 48 | 2.2 | 0.522 |
| 49 | 6.8 | |
| 50 | 0.9 | |
| 51 | | 0.074 |
| 54 | 0.2 | 0.13 |
| 55 | <0.1 | 0.228 |
| 143 | | 0.301 |

**Rat Assay**

The efficacy of the novel compounds in blocking the production of TNF also was evaluated using a model based on rats challenged with LPS. Male Harlen Lewis rats [Sprague Dawley Co.] were used in this model. Each rat weighed approximately 300 g and was fasted overnight prior to testing. Compound administration was typically by oral gavage (although intraperitoneal, subcutaneous and intravenous administration were also used in a few instances) 1 to 24 hours prior to the LPS challenge. Rats were administered 30 μg/kg LPS [salmonella typhosa, Sigma Co.] intravenously via the tail vein. Blood was collected via heart puncture 1 hour after the LPS challenge. Serum samples were stored at -20 °C until quantitative analysis of TNF-α by Enzyme Linked-Immuno-Sorbent Assay ("ELISA") [Biosource]. Additional details of the assay are set forth in Perretti, M., et al., Br. J. Pharmacol. (1993), 110, 868-874, which is incorporated by reference in this application.

**Mouse Assay**

Mouse Model Of LPS-Induced TNF Alpha Production:

TNF alpha was induced in 10-12 week old BALB/c female mice by tail vein injection with 100 ng lipopolysaccharide (from S. Typhosa) in 0.2 ml saline. One hour later mice were bled from the retroorbital sinus and TNF concentrations in serum from clotted blood were quantified by ELISA. Typically, peak levels of serum TNF ranged from 2-6 ng/ml one hour after LPS injection.

The compounds tested were administered to fasted mice by oral gavage as a suspension in 0.2 ml of 0.5% methylcellulose and 0.025% Tween 20 in water at 1 hour or 6 hours prior to LPS injection. The 1 hour protocol allowed evaluation of compound potency at Cmax plasma levels whereas the 6 hour protocol allowed estimation of

compound duration of action. Efficacy was determined at each time point as percent inhibition of serum TNF levels relative to LPS injected mice that received vehicle only.

Additional results obtained using the above-described assays are set forth in Table 6 below. p38 assay and U937 cell assay results are expressed as $IC_{50}$ ($\mu$m). Mouse-LPS assay results are expressed as percent inhibition.

TABLE 6

| Example | p38[1] | p38[2] | U937 | mLPS 8h | mLPS 6h dose | mLPS 1h, 30mpk |
|---|---|---|---|---|---|---|
| | | | | | | |
| A-212 | 0.49 | 0.74 | 0.0967 | 20 | 10 | 93 |
| A-208 | 0.104 | 0.049 | 0.1896 | 98 | 30 | 97 |
| A-227 | | 0.06 | | | | 96 |
| A-228 | 0.76 | 0.339 | 0.4173 | 32 | 30 | 92 |
| A-229 | | 1.4 | 0.4622 | 76 | | 91 |
| A-230 | 0.42 | 0.178 | | | | 96 |
| A-231 | | 0.174 | 0.3225 | 86 | 30 | 94 |
| A-232 | | 0.048 | | | | 96 |
| A-233 | | 0.044 | | | | 53 |
| A-234 | | 0.103 | | | | |
| A-235 | | 0.104 | | | | 56 |
| A-236 | | 0.237 | | | | 94 |
| A-237 | | 0.093 | 0.087 | | | 60 |
| A-238 | | 0.177 | 0.4016 | | | |
| A-239 | | 0.034 | | 51 | 30 | 87 |
| A-240 | | 0.961 | | 78 | 30 | 85 |
| A-241 | | 0.338 | | 79 | 30 | 87 |
| A-242 | | 0.047 | | 95 | 30 | 87 |
| A-243 | | 0.729 | | | | 82 |
| A-244 | | 0.099 | | | | |
| A-245 | | <.001 | 0.0337 | | | 65 |
| A-246 | 0.403 | 0.592 | 0.4952 | | | |
| A-247 | | <0.01 | 0.166 | | | |
| A-249 | | 0.432 | | 73 | 30 | 86 |
| A-250 | | 2.873 | | | | |
| A-251 | | 0.637 | | 32 | | 87 |
| A-252 | | 0.774 | 1.197 | 48 | 30 | 75 |
| A-253 | | <.001 | 0.0044 | | | 61 |
| A-254 | | 0.081 | 0.1411 | | | |
| A-215 | | 2.34 | 0.2976 | 38 | 30 | 80 |
| A-256 | | 0.813 | 0.4562 | | | |
| A-257 | 1.081 | <.01 | 0.5167 | | | |
| A-213 | | 0.22 | | | | 57 |
| A-258 | | 0.48 | 1.2083 | | | 68 |
| A-259 | | 0.17 | 0.7574 | | | 62 |
| A-210 | 0.16 | | 0.1983 | 85 | 30 | 93 |
| A-260 | | 0.23 | 1.2821 | 47 | 30 | 79 |
| A-214 | | 0.06 | 1.4006 | | | 70 |
| A-261 | | 0.008 | 0.2542 | 48 | 30 | 92 |
| A-216 | | 0.018 | 1.8287 | 27 | 30 | 91 |
| A-262 | | <0.1 | 0.3267 | | | 45 |
| A-263 | <0.01 | <0.1 | 0.5434 | | | 49 |

| Example | p38[1] | p38[2] | U937 | mLPS 8h | mLPS 6h dose | mLPS 1h, 30mpk |
|---|---|---|---|---|---|---|
| A-264 | | | 0.2594 | | | 61 |
| A-265 | | <0.1 | 0.6016 | | | 32 |
| A-266 | | | 0.5393 | | | 0 |
| A-267 | | 0.43 | 2.6681 | | | 80 |
| A-268 | | <0.01 | 0.0074 | | | 11 |
| A-217 | 0.697 | | 0.3486 | | | 9 |
| A-269 | | | >10 uM | | | 51 |
| A-270 | | 0.015 | 0.3466 | | | 53 |
| A-271 | | 0.216 | 4.2144 | | | 68 |
| A-272 | 0.073 | | 0.583 | | | -8 |
| A-273 | 6.98 | | >10 | | | 43 |
| A-274 | <0.1 | | 0.92 | 21 | 30 | |
| A-275 | 10.142 | | >10 | | | |
| A-276 | 0.176 | | 0.45 | -24 | 30 | |
| A-277 | 0.026 | | | 33 | 30 | |
| A-278 | 0.285 | | 2.3 | 62 | 30 | |
| A-279 | 0.005 | | 0.7 | 64 | 30 | |
| A-280 | 0.134 | | | 15 | 30 | |
| A-281 | 0.053 | | | 22 | 30 | |
| A-218 | 0.044 | | | 18 | 30 | |
| A-282 | 0.045 | | 0.0973 | 30 | 30 | |
| A-283 | <0.1 | | 0.7998 | -20 | 30 | |
| A-284 | 0.98 | | 0.5088 | -1 | | |
| A-285 | <0.1 | | 0.1795 | 11 | 30 | |
| A-286 | 0.057 | | 0.09 | 29 | 30 | |
| A-287 | 0.041 | | 0.27 | -24 | 30 | |
| A-288 | 0.017 | | 0.3 | 40 | 30 | |
| A-289 | <0.1 | | 0.14 | 44 | 30 | |
| A-290 | | | 6.0191 | 4 | 30 | |
| A-291 | 0.388 | | 1.1309 | 36 | 30 | |
| A-292 | 1.15 | | >10 | | | |
| A-293 | 0.73 | | | | | |
| A-294 | 0.015 | | 0.5 | 61 | 30 | |
| A-295 | 7.66 | | >10 | 94 | 30 | |
| A-296 | 26 | | | | | |
| A-297 | 0.52 | | 0.17 | 89 | 30 | |

[1] p38α in vitro assay results based on PHAS-I assay procedure

[2] p38α in vitro assay results based on EGFRP assay procedure

Induction And Assessment Of Collagen-Induced Arthritis In Mice:

Arthritis was induced in mice according to the procedure set forth in J.M. Stuart, Collagen Autoimmune Arthritis, Annual Rev. Immunol. 2:199 (1984), which is incorporated herein by reference. Specifically, arthritis was induced in 8-12 week old DBA/1 male mice by injection of 50 μg of chick type II collagen (CII) (provided by Dr. Marie Griffiths, Univ. of Utah, Salt Lake City, UT) in complete Freund's adjuvant (Sigma) on day 0 at the base of the tail. Injection volume was 100 μl. Animals were boosted on day 21 with 50 μg of CII in incomplete Freund's adjuvant (100 μl volume). Animals were evaluated several times each week for signs of arthritis. Any animal with paw redness or swelling was counted as arthritic. Scoring of arthritic paws was conducted in accordance with the procedure set forth in Wooley et al., Genetic Control of Type II Collagen Induced Arthritis in Mice: Factors Influencing Disease Suspectibility and Evidence for Multiple MHC Associated Gene Control., Trans. Proc., 15:180 (1983). Scoring of severity was carried out using a score of 1-3 for each paw (maximal score of 12/mouse). Animals displaying any redness or swelling of digits or the paw were scored as 1. Gross swelling of the whole paw or deformity was scored as 2. Ankylosis of joints was scored as 3. Animals were evaluated for 8 weeks. 8-10 animals per group were used.

Preparation And Administration Of Compounds:

The compounds tested on mice having collagen-induced arthritis were prepared as a suspension in 0.5% methylcelluose (Sigma, St. Louis, MO), 0.025% Tween 20 (Sigma). The compound suspensions were administered by oral gavage in a volume of 0.1 ml b.i.d. Administration began on day 20 post collagen injection and continued

daily until final evaluation on day 56. Scoring of arthritic paws was conducted as set forth above. Assay results are set forth in Table 7.

TABLE 7

| Compound | % Inhibition of Arthritis |
|---|---|
| A-210 | 58.5 @ 15 mpk |
| A-172 | 49.3 @ 100 mpk |
| A-189 | 51.6 @ 30 mpk |
| A-208 | 97.5 @ 60 mpk |
| A-208 | 75.0 @ 60 mpk |

Additional results for selected compounds obtained using the above-described assays are set forth in Tables 8, 9 and 10 below:

TABLE 8

| Example | Rat LPS Assay % Inhibition (Dose in mg/kg) | TNF Inhibition-Human Whole Blood Assay ($\mu$M) | p38$\alpha$ Kinase Assay $IC_{50}$ in $\mu$M (% DMSO) |
|---|---|---|---|
| A-313, Step 1 | | | 1.34 (1) |
| A-313, Step 3 | 96.0 (20.0) | 0.12 | 0.036 (1)<br>0.37 (10) |
| A-314, Step 1 | | | 0.85 (1)<br>0.37 (10) |
| A-314, Step 2 | 0 (1.0)<br>53.0 (5.0)<br>85.0 (20.0) | 0.47 | 0.032 (10) |
| A-315 | | 1.75 | 0.049 (10) |
| A-317 | 58.0 (3.0)<br>10.0 (3.0)<br>69.0 (10.0) | 0.45 | 0.07 (10)<br>0.11 (10) |
| A-318 | 54.0 (3.0) | 0.167 | 0.29 (1)<br>0.58 (10)<br>0.37 (10)<br>0.6 (10) |
| A-319 | 62.0 (3.0) | >25.0 | 6.06 (1)<br>0.13 (10) |

| | | | |
|---|---|---|---|
| A-320 | 1.0 (3.0) | | 0.27 (1)<br>0.05 (10)<br>0.15 (10) |
| A-321 (dihydrate) | | >25.0 | 0.77 (1) |
| A-321 (monosodium salt dihydrate) | 14.0 (3.0) | | |
| A-322 | 51.5 (3.0) | 4.2 | 0.15 (10)<br>0.25 (10) |
| A-323 | 40.0 (30.0)<br>54.0 (30.0) | | 0.39 (10) |
| A-324 | 44.0 (3.0) | | 0.08 (10) |
| A-325 | 25.0 (3.0)<br>11.0 (30.0) | 0.057 | 0.021 (1)<br><0.1 (10) |
| A-326 | 0 (10.0) | >25.0 | 0.97 (10) |
| A-327 | 83.0 (20.0) | 0.18 | 0.15 (10) |
| A-328 | | | 0.012 (1) |
| A-331 | 13.0 (20.0) | | >100 (1)<br>0.64 (10) |
| A-332 | 33.0 (1.0)<br>26.0 (3.0)<br>25.0 (5.0)<br>-85.0 (10.0) | 0.45 | 0.04 (1)<br>0.04 (10)<br>0.015 (10)<br><0.1 (10) |
| A-333 | 69.0 (5.0) | 0.585 | 0.052 (10) |
| A-334 | 95.0 (20.0)<br>57.0 (5.0)<br>36.0 (1.0) | 0.22 | 0.07 (10) |
| A-335 | | >25.0 | 89.9 (10) |
| A-336 | | | 1.16 (10) |
| A-337 | | >25.0 | 1.35 (10) |
| A-338 | | 0.059 | 0.018 (10) |
| A-339 | | 0.056 | 0.052 (10) |
| A-342 | 98.0 (20.0) | 0.31 | 0.012 (10) |
| A-343 | 96.0 (20.0) | | 0.016 (10) |

TABLE 9

| Example | Rat LPS Assay % Inhibition (Dose in mg/kg) | TNF Inhibition-Human Whole Blood Assay ($\mu$M) | p38$\alpha$ Kinase Assay $IC_{50}$ in $\mu$M (10% DMSO) |
|---|---|---|---|
| A-350 | 65 (20) | | |
| A-351 | 0 (20) | 0.49 | 0.27 |
| A-352 | 36 (20) | 9.8 | 0.13 |
| A-353 | 49 (20) | 5.3 | 0.037 |
| A-354 | 0 (20) | 25 | 0.22 |
| A-355 | 0 (20) | 0.095 | 0.05 |
| A-356 | 73 (20) | 5.3 | <0.01 |
| A-357 | 74 (20) | 0.25 | 0.12 |
| A-358 | 71 (20) | 4 | 0.23 |
| A-359 | 70 (20) | 1 | 0.3 |
| A-360 | 95 (20)<br>14 (5)<br>0 (1) | 0.5 | 0.06 |
| A-361 | 9 (20) | 1 | |
| A-362 | 0 (20) | 5.5 | 0.69 |
| A-363 | 6 (20) | 25 | 1.5 |
| A-364 | 79 (20) | 0.255 | 0.49 |
| A-365 | 95 (20)<br>50 (5)<br>12 (1) | 0.057 | 0.032 |
| A-366 | 92 (20)<br>DR: 6 (1)<br>45 (5)<br>97 (20) | 0.29 | 0.041<br>0.06<br>0.04 |
| A-368 | 88 (20)<br>DR: 28 (1)<br>41 (5)<br>97 (20) | 0.66 | 0.042 |
| A-369 | 94 (20)<br>52 (5) | 0.84 | 0.019<br>0.011<br>0.0027 |
| A-370 | 90 (20)<br>46 (5) | 1.92 | 0.16 |

| | | | |
|---|---|---|---|
| A-371 | 52 (20) | 25 | 7.9 |
| A-372 | 56 (20) | 21 | 0.53 |
| A-374 | 88 (20)<br>0 (5)<br>3 (1) | 0.31 | 0.38 |
| A-375 | 43 (20) | 28% | 2.3 |
| A-376 | 24 (20) | 1 | 0.032 |
| A-377 | 84 (20)<br>DR: 32 (1)<br>67 (5)<br>96 (20) | 0.67 | 0.004<br>0.0019 |
| A-378 | 73 (10) | 49% | 6.2 |
| A-379 | 61 (10) | 44% | 0.19 |
| A-380 | 85 (30)<br>62 (10)<br>33 (3) | 32% | 0.85 |
| A-385 | | | 0.18<br>1.25 |
| A-386 | 91 (20) | 0.16 | 0.016 |
| A-387 | 83 (20) | 0.11 | 0.005 |
| A-388 | 97 (20)<br>67 (5) | 0.34 | 0.21 |

TABLE 10

| Example | Rat LPS Assay % Inhibition (Dose in mg/kg @ 4.0 hours) | TNF Inhibition-Human Whole Blood Assay ($\mu$M) | p38$\alpha$ Kinase Assay $IC_{50}$ ($\mu$M) (10% DMSO; @ 1.0 hour) |
|---|---|---|---|
| | | | |
| A-389, Step 4 | 55.0 (5.0)<br>94.0 (20.0) | | 0.16 |
| A-389, Step 1 | | | 1.72 |
| A-390 | | >25.0 | 15.1 |
| A-391 | 53.0 (20.0) | >25.0 | 4.83 |

| | | | |
|---|---|---|---|
| A-392 | | | 29.7 |
| A-393 | | | 2.32 |
| A-394 | | | 9.11 |
| A-395 | | | >100 |
| A-397 | | | 30.0 |
| A-398 | | >25.0 | 45.6 |
| A-399 | | | 22.9 |
| A-400 | | >25.0 | 4.77 |
| A-401 | | | 21.2 |
| A-402 | | | 28.9 |
| A-403 | | >25.0 | 4.89 |
| A-404 | | >25.0 | 4.13 |
| A-405 | | >25.0 | 4.85 |
| A-406 | | >25.0 | 7.24 |
| A-407 | 21.0 (5.0)<br>82.0 (20.0) | 3.86 | 0.18 |
| A-408 | 20.0 (5.0)<br>49.0 (20.0) | 11.7 | 5.59 |
| A-409 | 41.0 (5.0)<br>89.0 (20.0) | 5.27 | 0.21 |
| A-410 | 11.0 (5.0)<br>0 (20.0) | | 0.21 |
| A-411 | 40.0 (5.0)<br>0 (20.0) | | 3.37 |
| A-412 | 0 (5.0)<br>0 (20.0) | | 2.15 |
| A-413 | 45.0 (5.0)<br>85.0 (20.0) | 6.51 | 0.91 |
| A-414 | 3.0 (5.0)<br>14.0 (20.0) | 11.2 | 9.51 |
| A-415 | 17.0 (5.0)<br>84.0 (84.0) | | 0.51 |
| A-416 | | 5.07 | 0.041 |
| A-417 | 40.0 (5.0)<br>70.0 (20.0) | 12.0 | 0.19 |
| A-418 | | | 0.12 |

| | | | |
|---|---|---|---|
| A-419 | 24.0 (5.0)<br>58.0 (10.0) | | 1.31 |
| A-420 | 47.0 (5.0)<br>91.0 (20.0) | | 0.32 |
| A-427 | 56.0 (5.0)<br>77.0 (20.0) | 24.1 | 0.19 |
| A-428 | | 0.68 | 0.4 |
| A-429 | | | 56.3 |
| A-430 | | | >100 |
| A-434 | | | 5.84 |
| A-435 | 10.0 (1.0)<br>0 (5.0)<br>14.0 (20.0) | >25.0 | 0.35 |
| A-436 | | 4.61 | 2.81 |
| A-437 | | >25.0 | 7.76 |
| A-438 | 49.0 (20.0) | >25.0 | 0.56 |
| A-439 | 58.0 (5.0)<br>93.0 (20.0) | 5.63 | 0.15 |
| A-440 | | | |
| A-441 | 14.0 (5.0)<br>62.0 (20.0) | >25.0 | 1.21 |
| A-442 | 51.0 (1.0)<br>56.0 (5.0)<br>92.0 (20.0) | 0.16 | 0.022 |
| A-443 | | 4.89 | 0.47 |
| A-444 | | | 6.99 |
| A-445 | | >25.0 | 1.08 |
| A-446 | | 3.38 | 0.9 |
| A-447 | | >25.0 | 0.77 |
| A-448 | 73.0 (5.0)<br>97.0 (20.0) | 0.12 | 0.084 |
| A-449 | | | 59.0 |
| A-450 | | | >100 |
| A-451 | | 15.0 | 0.078 |
| A-452 | | 0.24 | 2.87 |
| A-454 | | | 8.41 |

| | | | |
|---|---|---|---|
| A-453 | | | 10.2 |
| A-455 | | | 12.9 |
| A-456 | 36.0 (1.0)<br>48.0 (5.0)<br>53.0 (20.0) | 0.98 | 0.12 |
| A-457 | | >25.0 | 0.4 |
| A-458 | | >25.0 | 8.7 |
| A-459 | 0 (1.0)<br>54.0 (5.0)<br>80.0 (20.0) | 0.26 | 0.027 |
| A-459 (salt) | | 0.28 | 0.1 |
| A-460 | | 8.91 | 1.84 |
| A-461 | | | 30.6 |
| A-462 | | >25.0 | 1.66 |
| A-463 | | >25.0 | 1.66 |
| A-464 | | | >100 |
| A-465 | | | >100 |
| A-466 | | | 20.1 |
| A-467 | | | 21.4 |
| A-468 | 46.0 (1.0)<br>50.0 (5.0)<br>94.0 (20.0) | | 0.3 |
| A-469 | 51.0 (5.0)<br>68.0 (20.0) | 7.17 | 0.095 |
| A-470 | | | 10.4 |
| A-471 | | | 4.92 |
| A-472 | | >25.0 | 0.39 |
| A-473 | 58.0 (20.0) | 0.56 | 0.17 |
| A-474 | 59.0 (20.0) | 1.47 | 0.11 |
| A-475 | | 5.11 | 0.28 |
| A-476 | 35.0 (20.0) | 0.97 | 1.01 |
| A-477 | | | 0.34 |
| A-478 | | 0.49 | 0.18 |
| A-479 | | 2.97 | 0.072 |
| A-480 | | 0.16 | 0.11 |

| | | | |
|---|---|---|---|
| A-481 | | >25.0 | 0.2 |
| A-482 | 15.0 (20.0) | 0.69 | 1.62 |
| A-483 | | 0.51 | 0.3 |

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this invention in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly (IV), intraperitoneally, subcutaneously, intramuscularly (IM) or topically. For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, hard or soft capsule, lozenges, dispensable powders, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection (IV, IM, subcutaneous or jet) as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. The pH of the composition may be adjusted, if necessary, with suitable acid, base, or buffer. Suitable bulking, dispersing, wetting or suspending agents, including mannitol and PEG 400, may also be included in the composition. A suitable parenteral composition can also include a compound formulated as a sterile solid substance, including lyophilized powder, in injection vials. Aqueous solution can be added to dissolve the

compound prior to injection. The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the inflammation or inflammation related disorder, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 1000 mg, preferably in the range of about 7.0 to 350 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 0.5 to 30 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day. In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day. For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active

ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch. The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others. The choice of suitable oils or fats for the formulation

is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used. Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The anti-inflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w. For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os*, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active

compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

All patent documents listed herein are incorporated by reference.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

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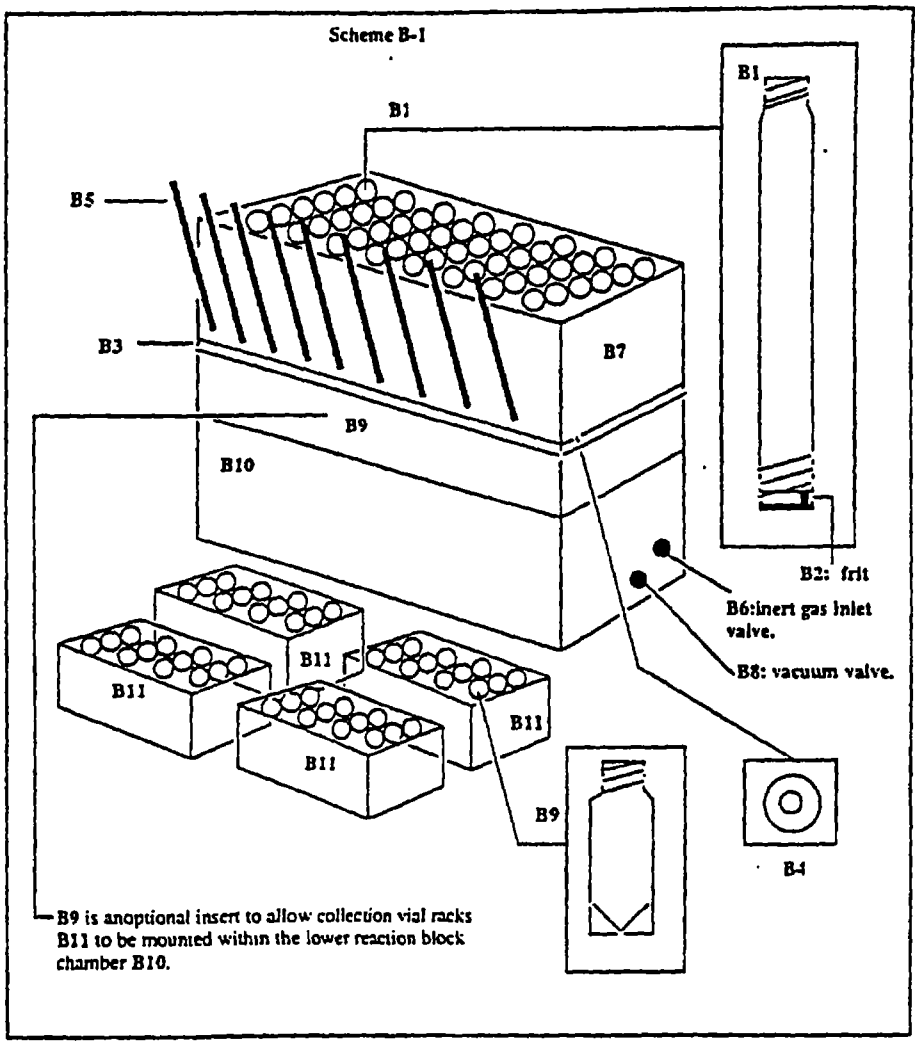
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**Description of parallel array synthesis methodology utilized to prepare compounds of Examples B-i, B-ii, and B-iii.**

Scheme B-1 describes the parallel array reaction blocks that were utilized to prepare compounds of Examples B-0001 through B-1574, and by analogy could also be used to prepare compounds of Examples B-1575 through B-2269. Parallel reactions were performed in multi-chamber reaction blocks. A typical reaction block is capable of performing 48 parallel reactions, wherein a unique compound is optionally prepared in each reaction vessel **B1**. Each reaction vessel **B1** is made of either polypropylene or pyrex glass and contains a frit **B2** toward the base of the vessel. Each reaction vessel is connected to the reaction block valve assembly plate **B3** via leur-lock attachment or through a threaded connection. Each vessel valve **B4** is either opened or closed by controlling the leur-lock position or by the opening or closing of levers **B5** within a valve assembly plate row. Optionally, solutions can be either drained or maintained above the vessel frits by leaving the valves in the opened position and controlling the back pressure beneath the valve assembly plate by control of inert gas flow through the inert gas inlet valve **B6**. The parallel reactions that are performed in these reaction blocks are allowed to progress by incubation in a jacketed, temperature controlled shaking station. Temperature control of the reaction chambers is effected by passing a heat-transfer liquid through jacketed aluminum plates that make contact with the reaction block

mantle B7. Mixing is effected at the shaking station by either vertical orbital shaking of the up-right reaction block or by lateral shaking of the reaction block tilted on its side.

Functionalized resins are optionally added to each reaction vessel B1 during the course of reaction or at the conclusion of the reaction. These functionalized resins enable the rapid purification of each reaction vessel product. Vacuum filtration of the reaction block apparatus by opening of the vacuum valve B8 allows purified products to be separated from resin-sequestered non-product species. Valve B8 is located on the bottom reaction block chamber B10 which houses the quadrant collection vial racks B11. The desired products are obtained as filtrates in unique collection vials B9. Removal of solvent from these collection vials affords desired products.

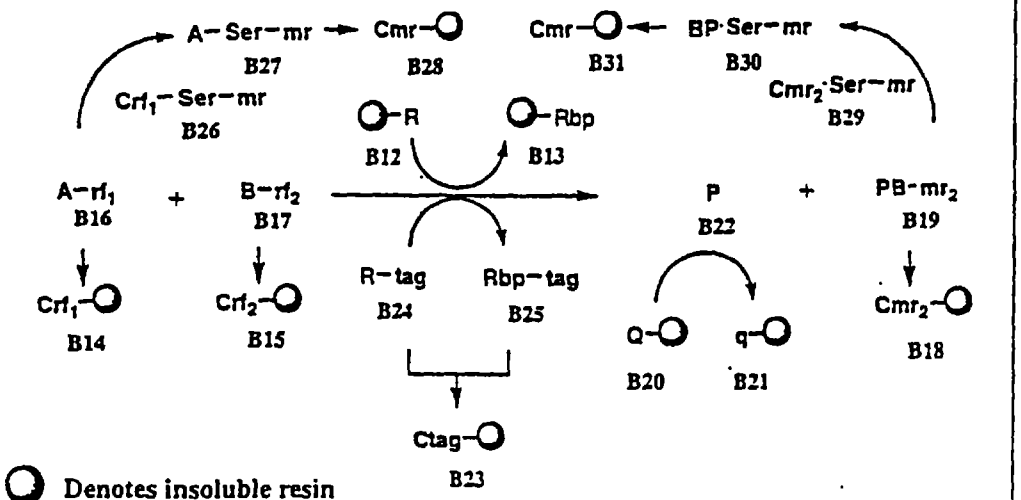



Scheme B-2 illustrates the various utilizations of functionalized resins to purify reaction vessel products **B22** prior to filtration from the fritted vessels **B1** into collection vials **B9**. Said functionalized resins perform as 1) resin-bound reagents **B12**, which give rise to resin-bound reagent byproducts **B13**; 2) sequestrants **B14** or **B15** of excess solution-phase reactants **B16** or **B17**, respectively. Solution-phase reactants **B16** and **B17** contain inherent reactive functionality $-rf_1$ and $-rf_2$

which enable their chemoselective sequestration by the complementary reactive functionality -$Crf_1$ and -$Crf_2$ attached to resins **B14** and **B15**; 3) sequestrants **B18** of solution-phase byproducts **B19**. Byproduct **B19** contains molecular recognition functionality -$mr_2$ which enables its chemoselective sequestration by the complementary functionality -$Cmr_2$ attached to resin **B18**; 4) reaction-quenching resins **B20** which give rise to quenched resins **B21**. Resin **B20** contains functionality -Q which mediates reaction quenching (for instance, proton transfer) of product **B22** to form a desired isolable form of product **B22**. Upon performing reaction quench, the resin **B20** is converted to resin **B21** wherein -q represents the spent functionality on resin **B21** ; 5) sequestrants **B23** of chemically-tagged reagents **B24** and their corresponding reagent byproducts **B25**. The soluble reagent **B24** contains a bifunctional chemical group, -tag, which is inert to the reaction conditions but is used to enable the post-reaction sequestration of **B24** by the complementary functionality -Ctag attached to resin **B23**. Additionally, the soluble reagent byproduct **B25**, formed during the course of reaction, contains the same chemical function -tag that also enables its sequestration by resin **B23**. Additionally, some reactants **B16**, particularly sterically-hindered reactants and/or electron deficient nucleophiles, contain poorly sequestrable functionality (rf1 in this case is a poorly sequestable functionality). These poorly sequestable reactants **B16** can be transformed *in situ* to more robustly sequestrable species **B27** through their reaction with sequestration-enabling-reagents **B26**. **B26** contain highly reactive, complementary functionality $Crf_1$ which reacts with **B16** to form **B27** *in situ*. The

bifunctional molecular recognition functionality, mr, contained within **B26** is also present on the *in situ* derivatized **B27**. Both **B26** and **B27** are sequestered by the complementary molecular recognition functionality attached to resin **B28**. By analogy, some reactions contain poorly sequestable byproducts **B19**, wherein the molecular recognition functionality $mr_2$ in this case is not able to mediate the direct sequestration of **B19** by the complementary functionality attached to resin **B18**. Similar use of the bifunctional sequestration-enabling-reagent **B29** transforms **B19** into the more readily sequestrable species **B30**. The imparted molecular recognition functionality, mr, present in **B30** is readily sequestered by the complementary functionality, Cmr, attached to resin **B31**. In some reactions, multiple sequestration resins are utilized simultaneously to perform reaction purifications. Even resins containing incompatible (mutually reactive) functional groups can be used simultaneously because these resins scavenge complementary functionalized solution phase reactants, reagents, or byproducts from solution phase faster than resin cross-neutralization. Similarly, resins containing mutually reactive or neutralizing reaction-quenching functionality are able to quench solution phase reactants, products, or byproducts faster than resin cross-neutralization.

Scheme B-2




Scheme B3 describes the modular robotics laboratory environment that was utilized to prepare compounds of Examples B0001 through Bxxxx. Chemicals that are utilized in the robotics laboratory are weighed and then dissolved or suspended into solvents at Station #1 (Automated Chemistry Prep Station). Thus, solutions or suspensions of known molarity are prepared for use at the other robotics workstations. Station #1 also optionally bar-code labels each chemical solution so that its identity can be read by bar-code scanning at this and other robotics workstations.

Reactions are initiated at the modular Stations #2 and #2 DUP. Station #2DUP is defined as a duplicate of Station #2 and is used to increase capacity within the robotics laboratory. A reaction block is mounted at Station #2 or #2 DUP. Also, racks containing reactants, reagents, solvents, and resin slurries are also mounted at Station #2 or #2 DUP. Under the control of a chemical

informatics mapping file, reactions are initiated by the transfer of reactant solutions, reagent solutions, solvents, and/or resin slurries into each mounted reaction block vessel. The transfer of known volumes of solutions, suspensions, or solvents is mediated by syringes which control a one-up septum piercing/argon purging cannula, a wide-bore resin slurry-despensing cannula, or by a six-up cannula which can simultaneously deliver volumes to a row of six reaction vessels. The reaction block and/or chemical solution racks may be optionally cooled below room temperature during the chemical solution transfer operations. After the transfer of chemical solutions and solvents has been performed by Station#2 or #2DUP, incubation of the reaction block may occur while the reaction block is mounted at the robot station. Preferably, however, the reaction block is removed after all volume transfers are complete and the reaction block is brought to ambient temperature. The reaction block is transferred off-line to either a vertical- or lateral shaking Incubator Station #5.

The Automated weighing/archival Station #3 performs the functions of weighing empty collection vials (to obtain tare weights of collection vials) and also performs the functions of weighing collection vials containing filtered, purified products (to obtain gross weights of collection vials). After product-containing collection vials have been weighed (gross weight determinations) at workstation #3, the collection vial products are optionally redissolved into an organic solvent at workstation #3. Transfer of solvents is accomplished with syringes which control a mounted one-up septum-piercing/argon purging cannula. Each product-containing

collection vial is prepared as a solution of known molarity as directed and recorded by the chemical informatics system. These product solutions may be subsequently mounted at Station #2 or #2DUP for subsequent reaction steps or taken to Station #7 or #7DUP for analytical processing.

Rapid solvent evaporation of product-containing collection vials is accomplished by mounting the collection racks at Savant Automated Solvent Evaporation Stations #4, #4 DUP, or #4 TRIP, wherein #4DUP and #4TRIP are defined as a duplicate and a triplicate of Station #4 to increase the capacity for solvent removal within the robotics laboratory. Commercially available solvent removal stations were purchased from the Savant Company (model # SC210A speedvac unit equipped with model # RVT4104 vapor trap and model # VN100 vapornet cryopump).

Stations #7 and #7DUP perform analytical processing functions. Station #7DUP is defined as a duplicate of Station #7 to increase capacity within the robotics laboratory. Product-containing collection racks are mounted at either of these stations. Each product-containing collection vial is then prepared as a solution of known molarity as directed and recorded by the chemical informatics mapping file. Optionally, this dissolution function is performed by prior processing of the collection vial rack at Station #3 as described above. Station#7 or #7DUP, under the control of the chemical informatics mapping file, transfers aliquots of each product vial into unique and identifable microtiter plate wells that are utilized to perform analytical determinations.

One such microtiter plate is prepared at Station #7 or #7DUP for subsequent utilization at the Automated HPLC/Mass Spectrometer Station #8 or #8DUP. Station #8DUP is a duplicate of Station #8 to increase the analytical capacity of the robotics laboratory. Stations #8 and #8DUP are commercially available benchtop LC/Mass spec units purchased from Hewlett Packard (model HP1100 HPLC connected to HP1100 MSD (G1946A) mass spectrometer; this unit is also equipped with a model# G1322A solvent degasser, model # G1312A binary pump, a model # G1316A column heater, and a model # G1315A diode array detector. The HP unit has been interfaced with a commercially available autosampler rack (Gilson Company # 215 autosampler). Station #8 or #8DUP is utilized for the determination of product purity and identity by performing high performance liquid chromatography (HPLC) and companion atmospheric pressure chemi-ionization (APCI) or electrospray mass spectrometry for molecular weight determination.

Another microtiter plate is prepared at Station #7 or #7DUP for subsequent utilization at a commercially available flow-probe Varian NMR spectrometer Station #10 (Varian Instruments flow probe NMR, 300 MHz, interfaced with a commercially available Gilson 215 autosampler). Proton, $^{13}$-Carbon, and/or $^{19}$-Fluorine NMR spectra are determined at this Station #10.

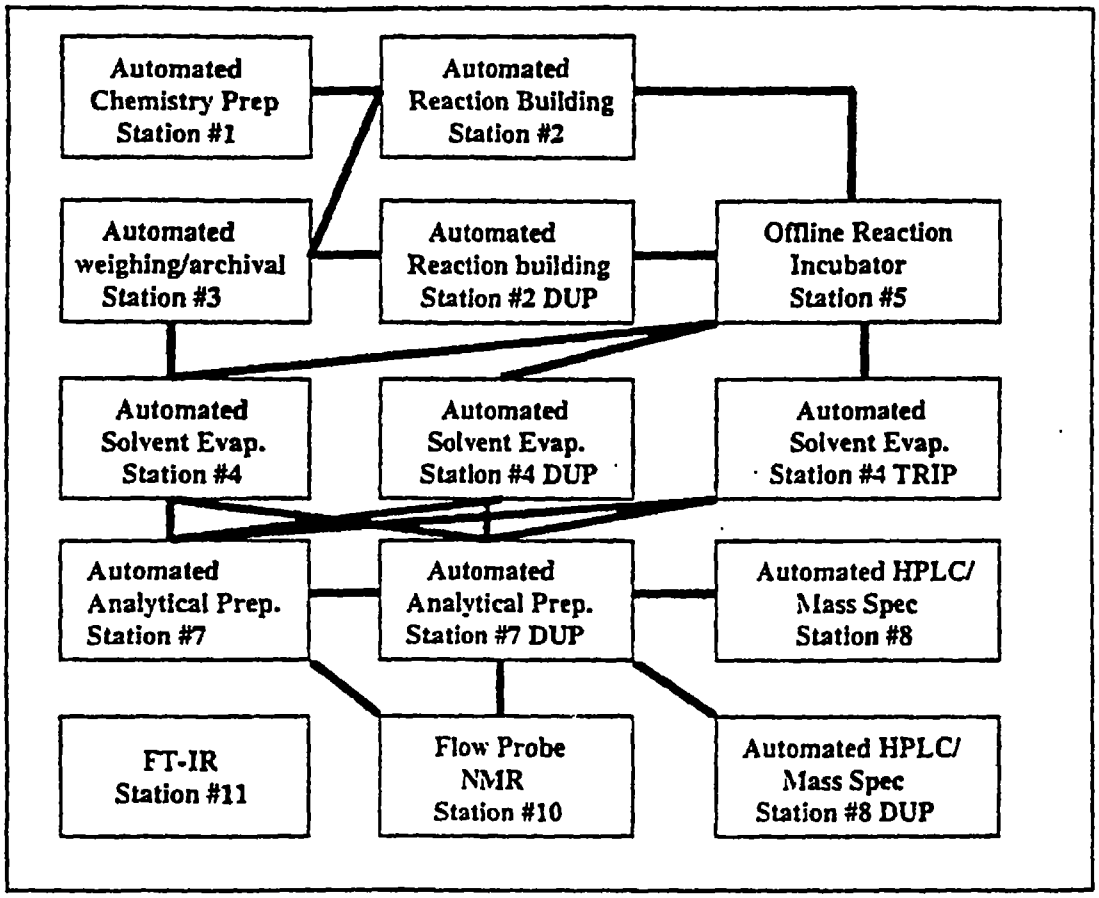
Other microtiter plates are optionally mounted at Station #7 or #7DUP for the purpose of preparing product-containing plates for biological assays. Aliquots of product-containing collection vials are transferred to these biological assay microtiter plates under the control of the chemical informatics mapping file. Identity and amount of each transferred product is

recorded by the chemical informatics system for retrieval by biologists who perform the biological assaying of products.

The Fourier Transfrom · InfraRed (FT-IR) Spectrometer Station #11 is utilized to analyze resins for the identity of organic functional groups chemically attached to these resins. The resins, as mentioned above, contain chemical functionality utilized as reagents, chemoselective sequestrants, or reaction quenching media for the workup and purification of the crude product mixtures contained within reaction block vessels. The robotics laboratory utilizes a commercially available FT-IR spectrometer purchased from Nicolet Instruments (model # MagnaIR 560 interfaced with an InspectIR microscope for resin mounting and positioning).

Scheme B-3

The lines interconnecting the modular Stations denote the transfer of chemical racks, reaction blocks, and/or collection vial racks from one modular Station to another.




The ChemLib IT system is a composite of software running on the client's desktop and software running on a remote server.

The ChemLib IT system is a client/server software application developed to support and document the data handling flow in the robotics laboratory described above. This IT system integrates the chemist with the robotics synthesis laboratory and manages the data generated by this processes.

The software running on the server warehouses all the electronic data for the robotics chemistry unit. This

server, a Silicon Graphics IRIX station v6.2, runs the database software, Oracle 7 v7.3.3.5.0, that warehouses the data. Connection from the client's desktop to the server is provided by Oracle's TCP/IP Adapter v2.2.2.1.0 and SQL*Net v2.2.2.1.0A. SQL*Net is Oracle's network interface that allows applications running on the client's desktop to access data in Oracles' database. The client's desktop is Microsoft Windows 95. The ChemLib IT system client software is composed of Omnis7 v3.5 and Microsoft Visual C++ v5.0. This composition on the client side is what is herein referred to as ChemLib. ChemLib communicates with the server for its data via Oracle's PL/SQL v2.3.3.4.0. These PL/SQL calls within ChemLib creates a network socket connection to Oracle's SQL*Net driver and the TCP/IP Adapter thereby allowing access to the data on the server.

A "library" is defined as a composite number of wells, where each well defines a single compound. ChemLib defines a library in a module called the *Electronic Spreadsheet*. The *Electronic Spreadsheet* is then a composite of n-number of wells containing the components that are required to synthesize the compound that exist in each these well(s).

The chemist begins by populating the *Electronic Spreadsheet* with those components required for the compound synthesis. The identity and the availability of these components are defined in the *Building Block Catalog* module of ChemLib. The *Building Block Catalog* is a catalog of a listing of all reagents, solvents, peripherals available in the robotics laboratory. Upon selecting the components for each compound we also

declare the quantity of each component to be utilized. The quantity of each component can be identified by its molarity and volumetric amounts (ul) or by it's solid state form (mg). Therefore a well in the *Electronic Spreadsheet* defines a compound that is identified by its components and the quantity of each of these components.

The assembly or the synthesis of these components for each compound in the Electronic Spreadsheet is defined in the *WS Sequence* module of ChemLib. The *Define WS Sequence* module identifies the synthesis steps to be performed at the robotics workstations and any activities to be performed manually or off-line from the robotics workstation. With this module we identify which components from the *Electronic Spreadsheet* and the activity that should be performed with this component in the robotics laboratory. In the *Define WS Sequence* module the chemist chooses from a list of activities to be performed in the robotics laboratory and assembles them in the order in which they are to occur. The ChemLib system takes these set of activities identified, and with the component data in the *Electronic Spreadsheet* assembles and reformats these instructions into terminology for the robotics workstation use. This robotics terminology is stored in a 'sequence' file on a common server that is accessible by the robotics workstation.

The robotics workstation performs the synthesis in a reaction block apparatus as described. Each well in the *Electronic Spreadsheet* is tracked and mapped to a unique location in the reaction block apparatus on the robotics workstation. The compound or product synthesized at the

robotics workstation in the reaction block is then captured into collection vials.

The collection vials are first tarred then grossed on the robotics workstation after collecting their products from the reaction block. These weights (tare and gross) are recorded into the ChemLib system with the *Tare/Gross Session* module. The *Tare/Gross Session* module then calculates the product or compound yields and its final mass.

Preparation of the compound for analytical analysis and screening is defined by the *Analytical WS Setup* module in ChemLib. The *Analytical WS Setup* module identifies the dilution factor for each well in the *Electronic Spreadsheet*, based on the compound's product yield and the desired molar concentration. This identifies the quantity, in uL, to be transferred at the robotics workstation, to a specific location on the MTP (microtiter plate) to be sent for analysis and/or biological assaying. The mass spectrometric and HPLC results for each well are recorded and scored into the ChemLib system.

The *Dilute/Archive WS* module further identifies each compound by mapping the compound's well from the *Electronic Spreadsheet* to a specific MX block location for long term storage and archival as part of the registration process.

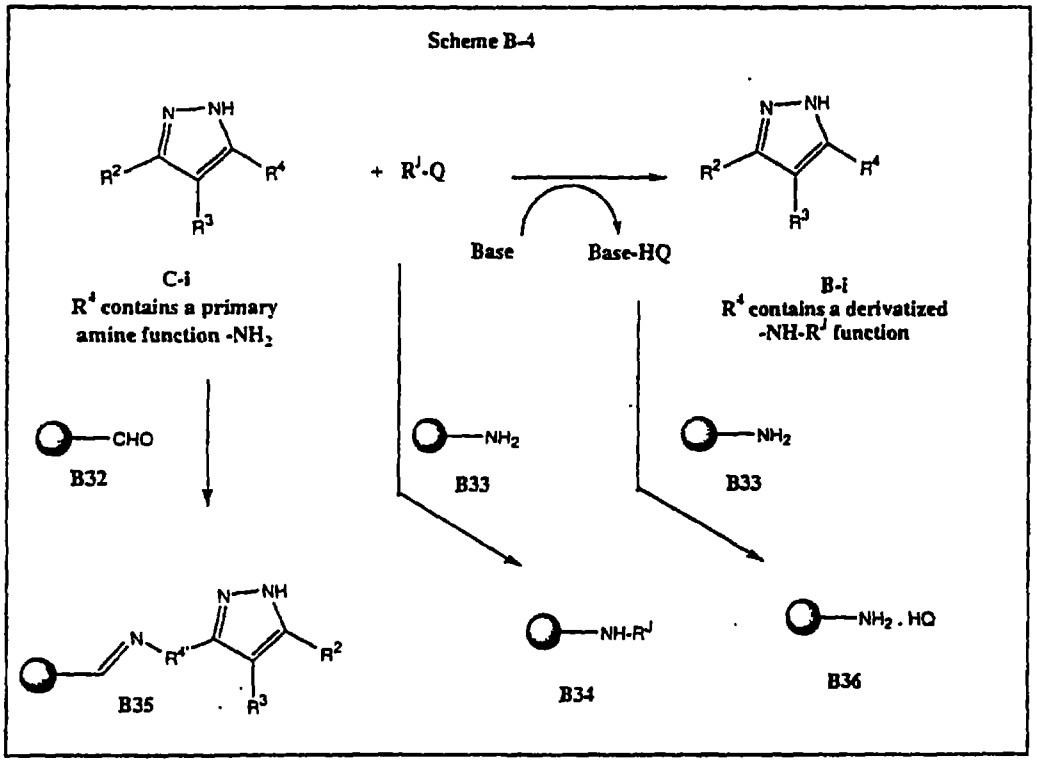
All communications between ChemLib and the robotics workstations are by ASCII files. These files are placed on a server by the ChemLib system that is accessible by

the robotics workstations. Reports generated by the robotics workstations are also placed on the server where the ChemLib system can read these files to record the data generated. Each robotics workstation consists of robotics hardware by Bohdan Automation, Inc. Mundelein, Illinois, and a PC currently running Microsoft Windows for Workgroup v3.11 and Ethernet software. The robotics workstation PC is logged into the network for one-way communication that allows the workstation to access the server for file access only.

**General Scheme B4**

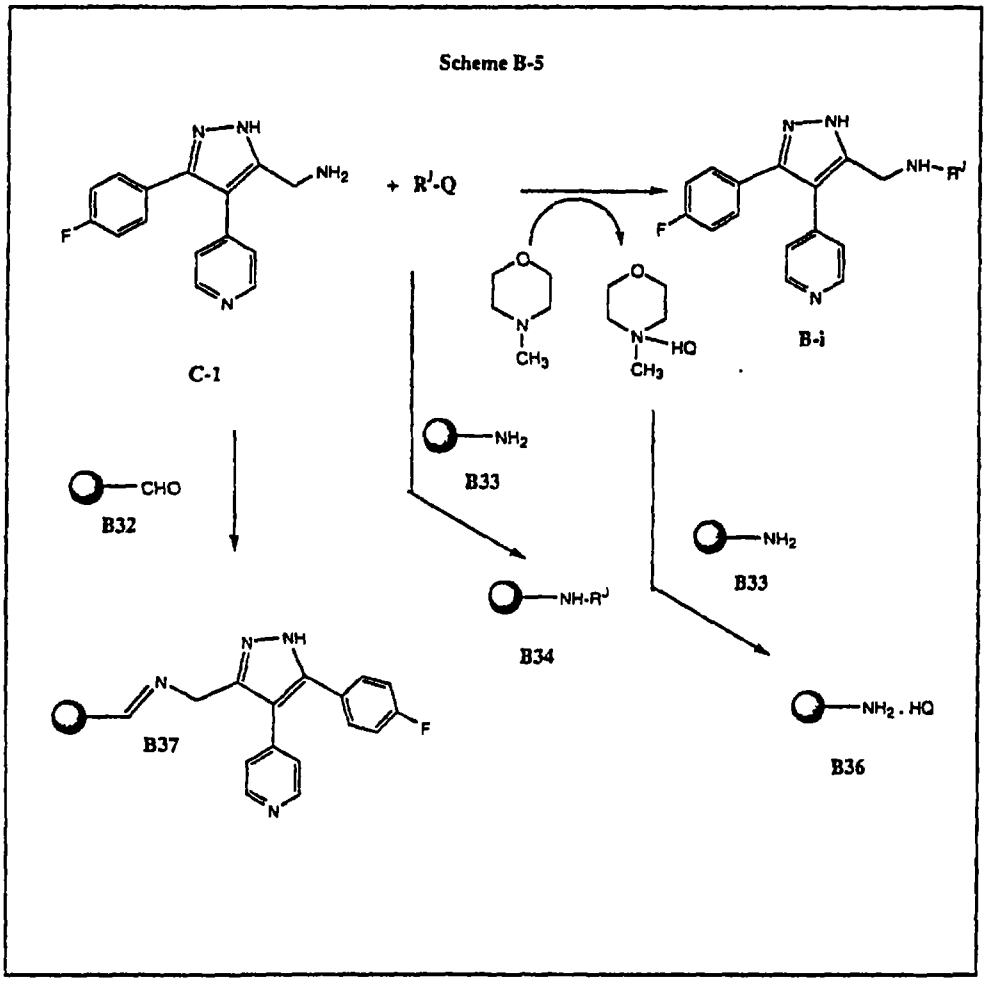
Scaffold **C-i** with a primary amine functionality contained within the $R^i$ substituent is reacted in spatially addressed, parallel array reaction block vessels with excess of electrophiles $R^J$-Q wherein Q is chloro, bromo, or an acid activating group including but not limited to N-hydroxysuccinimide. $R^J$-Q includes acid chlorides, alkyl chloroformates, sulfonyl chlorides, activated esters of carboxylic acids, activated carbamates, and isocyanates. Reaction of scaffold **C-i** with $R^J$-Q is effected in the presence of a tertiary amine base at room temperature in a mixture of a polar aprotic solvent and/or a halogenated solvent. As illustrated in Scheme B-4 the products of the general formulae **B-i** are isolated in purified form by addition of a carbonyl-functionalized resin **B32** which covalently sequesters any unreacted primary amine scaffold **C-i** as resin-bound adduct **B35**, and also by the addition of a primary amine-functionalized resin **B33** which covalently sequesters any remaining electrophile $R^J$-Q from each reaction mixture as

resin-bound adduct **B34**. Resin **B33** also sequesters the HQ byproduct from the reaction mixture by proton transfer from solution-phase **Base-HQ**. Incubation at room temperature, filtration, rinsing of the resin cake, and concentration of the filtrates affords purified products **B-i** filtered away from resin-bound adducts **B32**, **B33**, **B34**, **B35**, and **B36**.



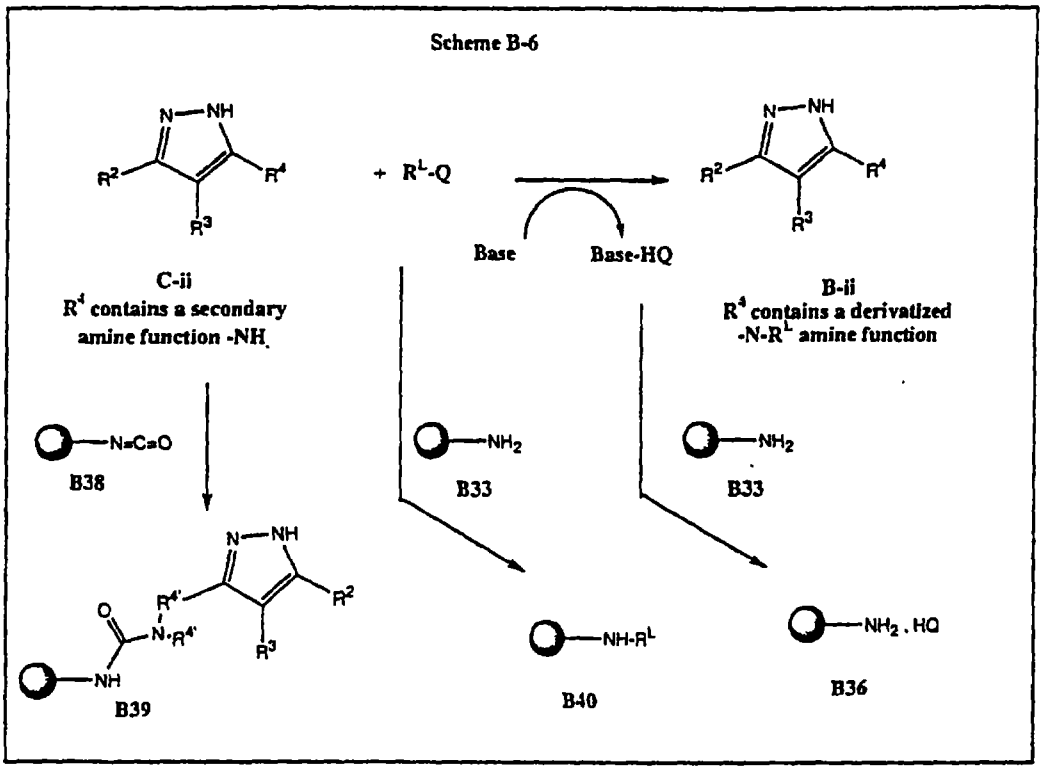

Scheme B-5 specifically illustrates the derivatization of the primary amine-containing scaffold **C1** to afford the desired products **B-i** in a parallel array synthesis format. In a parallel array synthesis reaction block, individual reaction products are prepared in each of multiple reaction block vessels in a spatially

addressed format. A solution of the desired primary amine-containing scaffold **C1** (limiting amount,) in dimethylformamide (DMF) is added to the reaction vessels followed by a 4.0 fold stoichiometric excess solution of N-methylmorpholine in DMF. To each reaction vessel is then added the electrophiles: either a 2.0 fold stoichiometric excess when $R^J$-Q is an acid chloride or alkyl chloroformate, or a 1.5 fold stoichiometric excess when $R^J$-Q is a sulfonyl chloride, or a 1.25 fold stoichiometric excess when $R^J$-Q is an isocyanate. Excess electrophiles and N-methylmorpholine were used to effect more rapid and/or more complete conversion of scaffold C1 to products B-0001-B-0048 compared to reactions that do not utilize stoichiometric excesses of electrophiles and N-methylmorpholine. The reaction mixtures are incubated at ambient temperature for 2-3 h. Each reaction vessel is then charged with a large excess (15-20 fold stoichiometric excess) of the amine-functionalized resin **B33** and the aldehyde-functionalized resin **B32**. The resin-charged reaction block is shaken vertically for 14-20 h on an orbital shaker at ambient temperature to allow optimum agitation of the resin-containing vessel mixtures. The excess electrophiles $R^J$-Q and any unreacted scaffold amine **C1** are removed from the reaction medium as insoluble adducts **B34** and **B37** respectively. In addition the N-methylmorpholine hydrochloride salt formed during the course of the reaction is also neutralized to its free base form by proton transfer reaction to the amine-functionalized resin **B33**. Simple filtration of the insoluble resin- adducts **B32**, **B33**, **B34**, **B36**, and **B37**, rinsing of the resin cake with dichloroethane, and evaporation of the filtrates affords the desired products **B-i** in purified form.



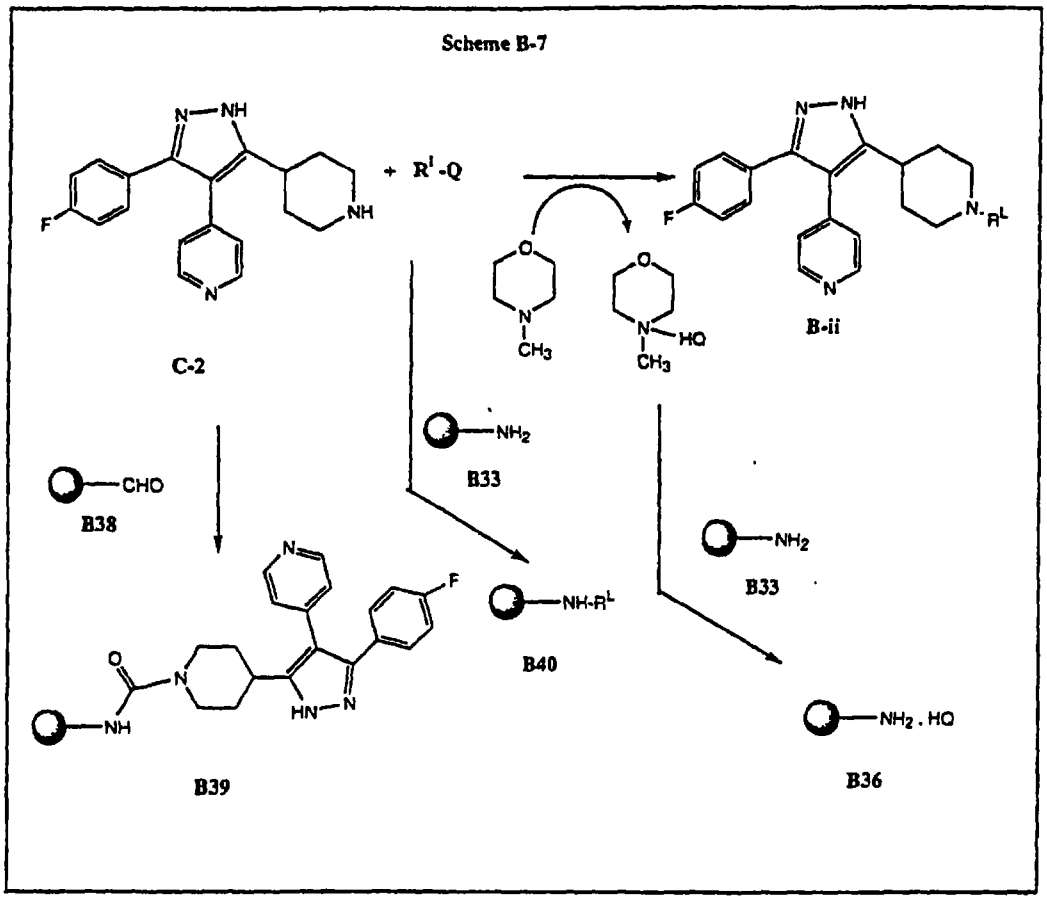

Scheme B-6 illustrates a general synthetic method involving the parallel array reaction of a scaffold **C-ii** containing a secondary amine functionality within the definition of the $R^4$ substituent. Each reaction vessel is charged with the secondary amine-containing scaffold **C-ii**, followed by the introduction of a stoichiometric excess of an optionally unique electrophile $R^L$-Q into each vessel, wherein Q is chloro, bromo, or an acid activating group including but not limited to N-hydroxysuccinimide. $R^L$-Q includes acid chlorides, alkyl chloroformates,

sulfonyl chlorides, activated esters of carboxylic acids, activated carbamates, and isocyanates. Reaction of scaffold **C-ii** with $R^L$-Q is effected in the presence of tertiary amine base at room temperature or elevated temperature in a mixture of a polar aprotics solvent and/or a halogenated solvent. After solution-phase reactions have progressed to afford crude product mixtures in each vessel, the products **B-ii** are isolated in purified form by the addition of the isocyanate-functionalized resin **B38** which covalently sequesters remaining secondary amine scaffold **C-ii** as resin-bound adduct **B39**, and also by the addition of the primary amine-functionalized resin **B33** which covalently sequesters remaining electrophile $R^L$-Q from each reaction vessel as resin-bound adducts **B40**. Resin **B33** also sequesters the HQ byproduct in each vessel as **B36**, formed by proton transfer from solution-phase Base-HQ. Incubation with these resins, either simultaneously or sequentially, followed by filtration, rinsing, and concentration of the filtrates affords purified products **B-ii** filtered away from resin-adducts **B33**, **B36**, **B38**, **B39**, and **B40**.



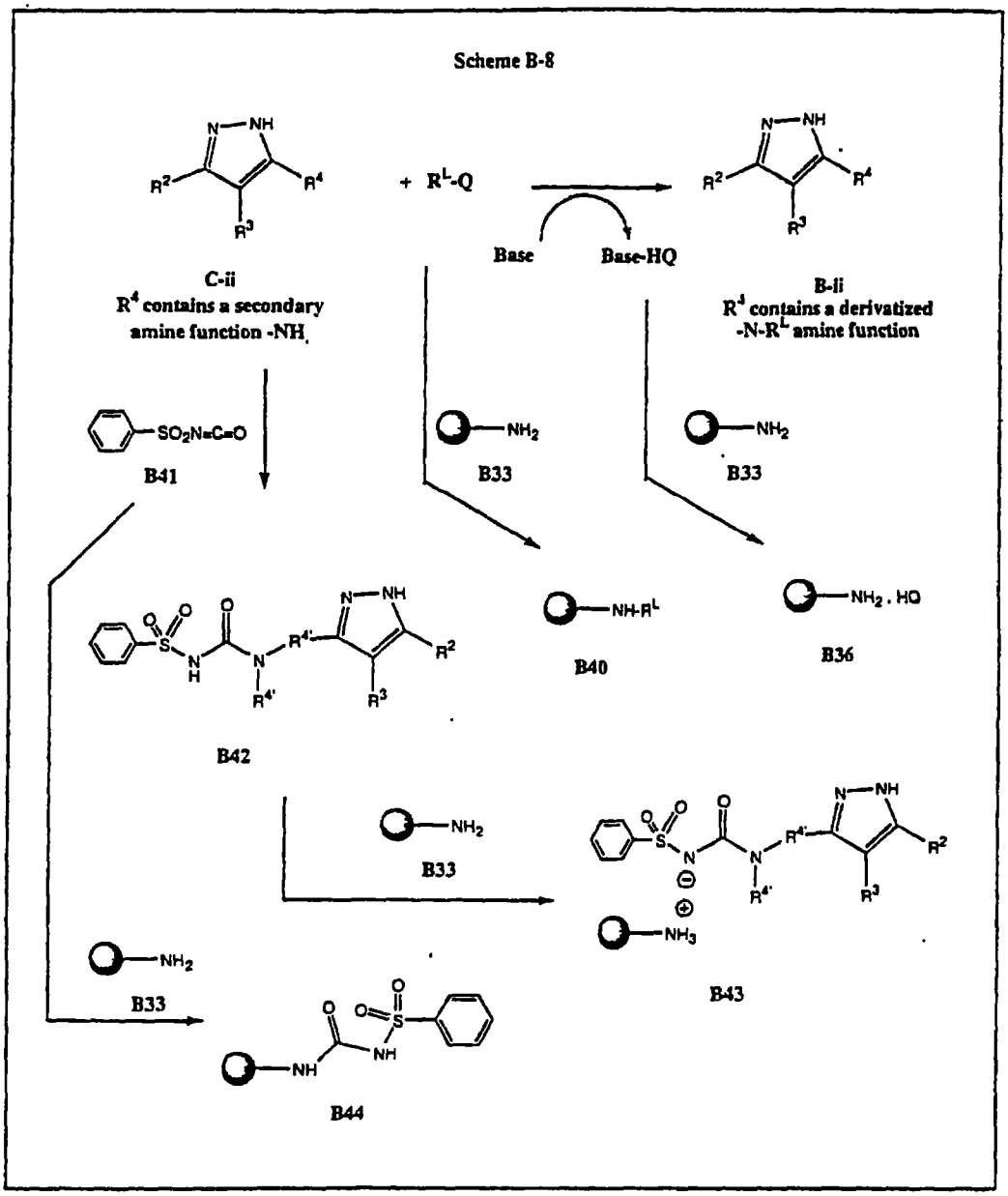

Scheme B-7 illustrates the conversion of the secondary-amine containing scaffold **C-2** to the desired products **B-ii**. In a parallel array synthesis reaction block, individual reaction products are prepared in each of 48 multiple reaction block vessels. A solution of the scaffold **C-2** (limiting amount) in dimethylformamide (DMF) is added to the reaction vessels followed by a 4.0-fold stoichiometric excess solution of N-methylmorpholine in DMF. To each reaction vessel is then added an electrophile $R^L$-Q as a dichloroethane (DCE) solution: either a 2.0 fold stoichiometric excess is used when $R^L$-Q is an acid chloride or alkyl chloroformate, or a 1.5 fold stoichiometric excess when $R^L$-Q is a sulfonyl chloride, or a 1.25 fold stoichiometric excess when $R^L$-Q is an isocyanate. The reaction mixtures are incubated at

ambient temperature for 2-6 h. Each reaction vessel is then charged with a large excess (15-20 fold stoichiometric excess) of the amine-functionalized resin **B33** and the isocyanate-functionalized resin **B32**. The resin-charged reaction block is shaken vertically for 14-20 h on an orbital shaker at ambient temperature to allow optimum agitation of the resin-containing vessel mixtures. The excess electrophiles $R^L$-Q and unreacted scaffold amine **C-2** are removed from the reaction medium as insoluble adducts **B40** and **B39**, respectively. Resin **B33** also sequesters the HQ byproduct in each vessel as **B36**, formed by proton transfer from solution-phase Base-HQ. Incubation with these resins, followed by filtration and rinsing with solvent mixtures of DMF and/or DCE, affords purified product solutions in collection vials filtered away from resin-adducts **B33**, **B36**, **B38**, **B39**, and **B40**. Concentration of filtrates affords purified products **B-ii**.



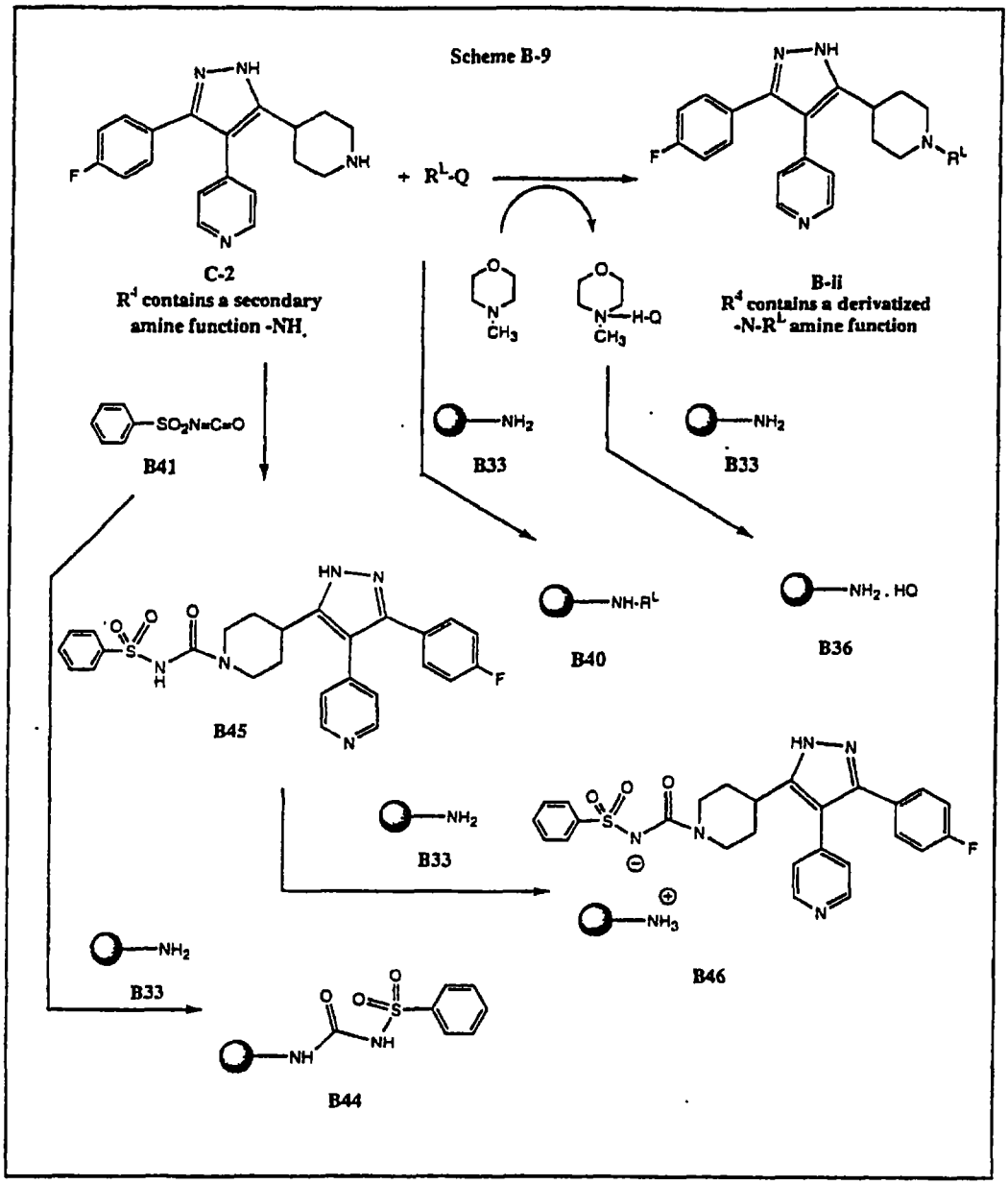

Scheme B-8 illustrates another general synthetic method involving the parallel array reaction of a scaffold C-ii containing a secondary amine functionality within the definition of the $R^4$ substituent. Each reaction vessel is charged with the secondary amine-containing scaffold C-ii, followed by the introduction of a stoichiometric excess of an optionally unique electrophile $R^L$-Q into each vessel. Reaction of scaffold C-ii with $R^L$-Q is effected in the presence of tertiary amine base at room temperature or elevated temperature in a mixture of a polar aprotic solvent and/or a halogenated solvent.

Excess electrophiles and N-methylmorpholine are used to effect more rapid and/or more complete conversion of scaffold **C-ii** to products **B-ii** compared to reactions that do not utilize stoichiometric excesses of electrophiles and N-methylmorpholine. The reaction mixtures are incubated at ambient temperature for 2-8 h. Each reaction vessel is then charged with the sequestration-enabling reagent phenylsulfonylisocyanate **B41**. This reagent **B41** reacts with remaining secondary amine scaffold **C-ii**, converting **C-ii** to the *in situ*-derivatized compound **B42**. Subsequent incubation of these vessel mixtures with a large excess (15-20 fold stoichiometric excess) of the amine-functionalized resin **B33** sequesters the solution-phase species $R^L$-Q, HQ, **B41**, and **B42** as the resin-bound adducts **B40**, **B36**, **B44**, and **B43**, respectively. The resin-charged reaction block is shaken vertically for 14-20 h on an orbital shaker at ambient temperature to allow optimum agitation of the resin-containing vessel mixtures. Filtration of the insoluble resin- adducts **B33**, **B36**, **B40**, **B43** and **B44** and subsequent rinsing of the vessel resin-bed with DMF and/or DCE affords filtrates containing the purified products **B-ii**. Concentration of the filtrates affords the purified products **B-ii**.




Scheme B-9 illustrates the method of Scheme B-8 using scaffold C-2. A solution of the scaffold C-2 (limiting

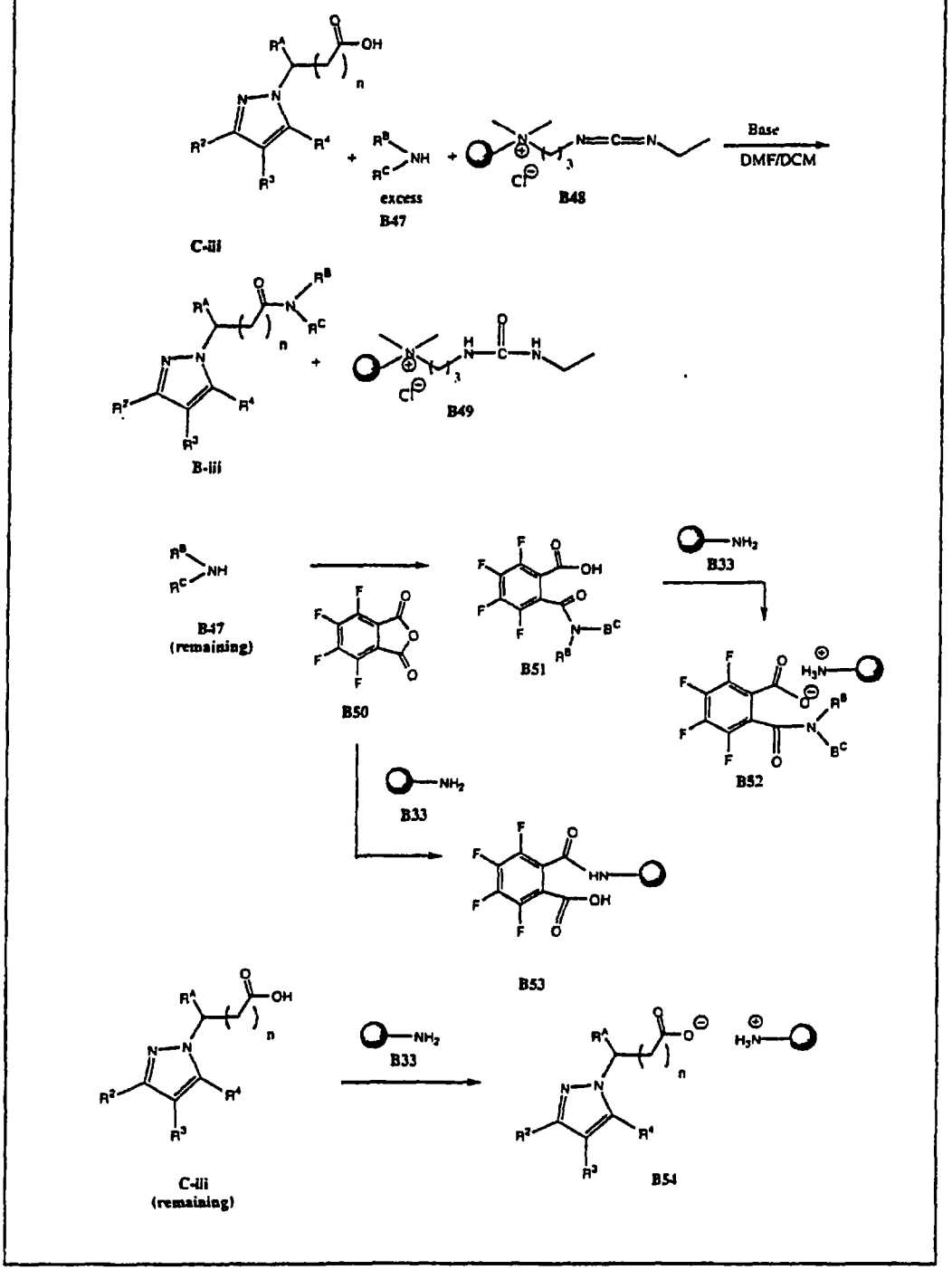
amount) in dimethylformamide (DMF) is added to the reaction vessels followed by a 4.0-fold stoichiometric excess solution of N-methylmorpholine in DMF. To each reaction vessel is then added an electrophile $R^L$-Q as a dichloroethane (DCE) solution: either a 2.0 fold stoichiometric excess is used when $R^L$-Q is an acid chloride or alkyl chloroformate, or a 1.5 fold stoichiometric excess when $R^L$-Q is a sulfonyl chloride, or a 1.25 fold stoichiometric excess when $R^L$-Q is an isocyanate. The reaction mixtures are incubated at ambient temperature for 2-6 h. After solution-phase reactions have progressed to afford crude product mixtures, each reaction vessel is then charged with a dichloroethane solution of the sequestration-enabling reagent phenylsulfonylisocyanate **B41**. This reagent **B41** reacts with remaining secondary amine scaffold **C-2**, converting **C-2** to the *in situ*-derivatized compound **B45**. Subsequent incubation of these vessel mixtures with a large excess (15-20 fold stoichiometric excess) of the amine-functionalized resin **B33** sequesters the solution-phase species $R^L$-Q, HQ, **B41**, and **B45** as the resin-bound adducts **B40**, **B36**, **B44**, and **B46**, respectively. The resin-charged reaction block is shaken vertically for 20 h on an orbital shaker at ambient temperature to allow optimum agitation of the resin-containing vessel mixtures. Filtration of the insoluble resin- adducts **B33**, **B36**, **B40**, **B44**, and **B46** and subsequent rinsing of the vessel resin-bed with DCE affords filtrates containing the purified products **B-ii**. Concentration of the filtrates affords the purified products **B-ii**.




Another general method for the parallel array reaction block synthesis is illustrated in Scheme B-10 for the derivatization of the carboxylic acid-containing scaffold

**C-iii**. Scaffold **C-iii** with a free carboxylic acid functionality is reacted in spatially addressed, parallel array reaction block vessels with excesses of optionally different primary or secondary amines **B47** in the presence of the polymer-bound carbodiimide reagent **B48** and a tertiary amine base in a mixture of a polar aprotic solvent and/or a halogenated solvent. After filtration of each crude vessel product misture away from resins **B48** and **B49**, each reaction mixture is purified by treatment with the sequestration-enabling-reagent **B50** (*tetra*-fluorophthalic anhydride). The reagent **B50** reacts with remaining excess amine **B47** to afford the *in situ*-derivatized intermediates **B51** which contain carboxylic acid molecular recognition functionality. Subsequent incubation of each reaction mixture with a 15-20-fold stoichiometric excess of the primay amine-functonalized resin **B33** sequesters **B51**, **B50**, and any remaining acid scaffold **C-iii** as resin-bound adducts **B52**, **B53**, and **B54**, respectively. Filtration of soluton-phase products **B-iii** away from these resin-bound adducts and rinsing of the resin beds with a polar aprotic solvent and/or halogenated solvent affords filtrates containing purified products **B-iii**. Concentration of the filtrates affords purified **B-iii**.

Scheme B-10

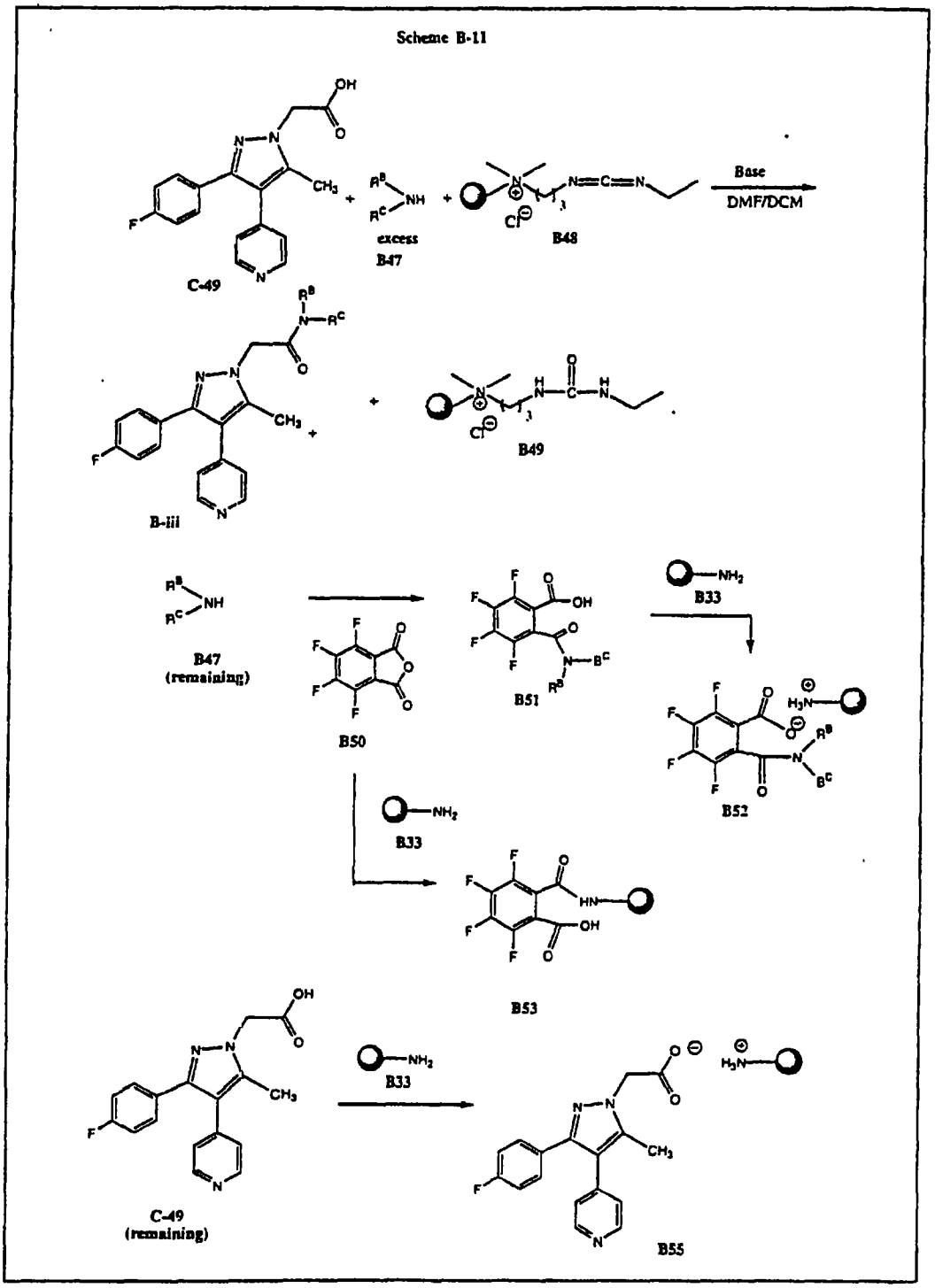

Base
DMF/DCM
excess
B47
B48
C-iii
B49
B-iii
B47
(remaining)
B50
B51
B33
B52
B33
B53
B33
B54
C-iii
(remaining)

Scheme B-11 illustrates the conversion of the acid containing scaffold **C-49** to the desired amide products **B-iii** in a parallel synthesis format. A limiting amount of the scaffold **C-49** is added as a solution in dimethylformamide to each reaction vessel containing the polymer bound carbodiimide reagent **B48** (5 fold stoichiometric excess). A solution of pyridine (4 fold stoichiometric excess) in dichloromethane is added to this slurry, followed by addition of an excess amount of a dimethylformamide solution of a unique amine **B47** (1.5 fold stoichiometric excess) to each vessel. The parallel reaction block is then agitated vertically on an orbital shaker for 16-18 h at ambient temperature and filtered to separate the solution phase product mixture away from resin-bound reagent **B48** and resin-bound reagent byproduct **B49**. The resulting solutions (filtrates) containing a mixture of the desired amide products **B-iii**, excess amines **B47** and any unreacted acid containing scaffold **C-49**, are treated with tetrafluorophthalic anhydride **B50**. **B50** converts the excess amines **B47** in each filtrate vessel to its respective sequestrable half acid form **B51**. After two h incubation time, an excess of the amine-functionalized resin **B33** and dichloromethane solvent are added to each reaction vessel. The amine-containing resin **B33** converts **B51**, any remaining **B50**, and any remaining **C-49** to their resin-bound adducts **B52**, **B53**, and **B55**, respectively. The resin-charged reaction block is shaken vertically for 16 h on an orbital shaker at ambient temperature to allow optimum agitation of the resin-containing vessel mixtures. Filtration of the insoluble resin- adducts **B33**, **B52**, **B53**, and **B55** and subsequent rinsing of the vessel resin-bed with

dimethylformamide affords filtrates containing the purified products **B-iii**. Concentration of the filtrates affords the purified products **B-iii**.

5

Scheme B-11


C-49
excess
B47
B48
Base
DMF/DCM
B-iii
B49
B47
(remaining)
B50
B51
B33
B52
B33
B53
C-49
(remaining)
B33
B55

Although Schemes B-1 through B-11 describe the use of parallel array chemical library technology to prepare compounds of general formulae **B-i**, **B-ii**, and **B-iii**, it is noted that one with ordinary skill in the art of classical synthetic organic chemistry would be able to prepare **B-i**, **B-ii**, and **B-iii** by conventional means (one compound prepared at a time in conventional glassware and purified by conventional means such as chromatography and/or crystallization).

A general synthesis of pyridylpyrazole scaffolds **C-i**, **C-ii**, and **C-iii** is depicted in Scheme C-1.

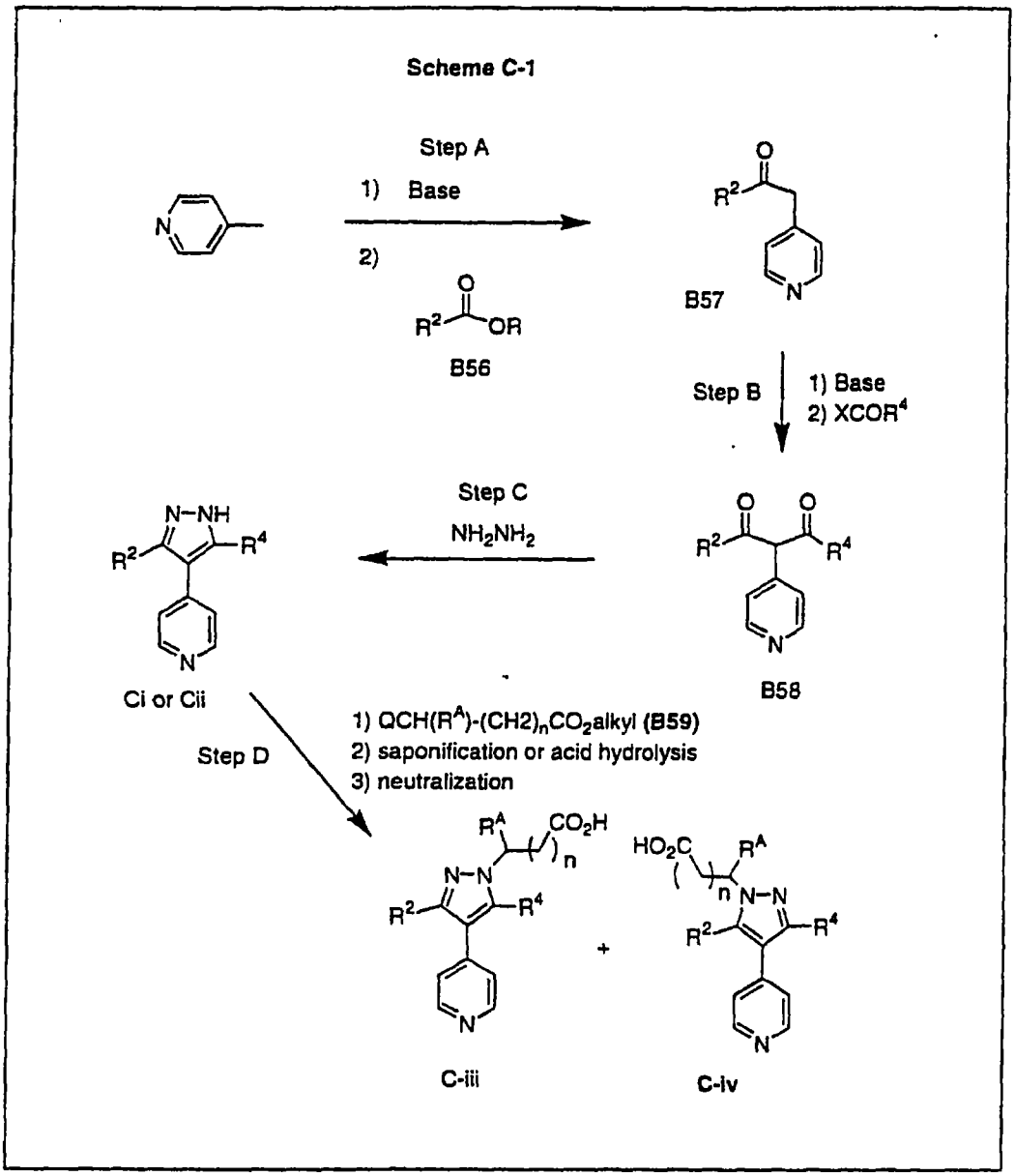
Step A: Picoline is treated with a base chosen from but not limited to n-butyllithium (n-BuLi), lithium di-*iso*-propylamide (LDA), lithium hexamethyldisilazide (LiHMDS), potassium *t*-butoxide (*t*BuOK), or sodium hydride (NaH) in an organic solvent such as tetrahydrofuran (THF), diethyl ether, *t*-butyl methyl ether, *t*-BuOH or dioxane from -78 °C to 50 °C for a period of time from 10 minutes to 3 hours. The metallated picoline solution is then added to a solution of ester **B56**. The reaction is allowed to stir from 30 minutes to 48 hours during which time the temperature may range from -20 °C to 120 °C. The mixture is then poured into water and extracted with an organic solvent. After drying and removal of solvent the pyridyl monoketone **B57** is isolated as a crude solid which can be purified by crystallization and/or chromatography.

Step B: A solution of the pyridyl monoketone **B57** in ether, THF, tBuOH, or dioxane is added to a base chosen from but not limited to n-BuLi, LDA, LiHMDS, tBuOK, or NaH contained in hexane, THF, diethyl ether, t-butyl methyl ether, or t-BuOH from -78 °C to 50 °C for a period of time from ranging from 10 minutes to 3 hours. An appropriately substituted activated ester or acid halide derived from $R^4$-$CO_2H$ is then added as a solution in THF, ether, or dioxane to the monoketone anion of **B57** while the temperature is maintained between -50 °C and 50 °C. The resulting mixture is allowed to stir at the specified temperature for a period of time from 5 minutes to three hours. The resulting pyridyl diketone intermediate **B58** is utilized without purification in Step C.

Step C: The solution containing the pyridyl diketone **B58** is quenched with water and the pH is adjusted to between 4 and 8 utilizing an inorganic or organic acid chosen from HOAc, $H_2SO_4$, HCl, or $HNO_3$. The temperature during this step is maintained between -20 °C and room temperature. Hydrazine or hydrazine hydrate was then added to the mixture while maintaining the temperature between -20 °C and 40 °C for a period of 30 minutes to three hours. The mixture is then poured into water and extracted with an organic solvent. The pyridyl pyrazole **C-i** or **C-ii** is obtained as a crude solid which is purified by chromatography or crystallization.

Step: D In some cases the pyridyl pyrazole **C-i** or **C-ii** is alkylated with Q-C($R^A$)-$(CH2)_nCO_2$alkyl wherein Q is halogen. **C-i** or **C-ii** is treated with a base chosen from NaH, NaOEt, KOtBu, or $NEt_3$ in an organic solvent such as THF, methylene chloride, dioxane, or DMF at temperatures

between -20 °C and 150 °C and reaction times between 30 minutes and 12 hours. The resulting alkylated pyridyl pyrazole ester is then hydrolyzed to the acid by treament with NaOH or LiOH in aqueous/alcohol solvent mixtures or in THF/water solvent mixtures. Alternatively, the ester function is removed by treatment with an organic or inorganic acid if the alkyl residue is t-butyl. Acidification, followed by extraction with an organic solvent affords **C-iii** which may be purified by chromatography or crystallography. In some cases, regioisomeric alkylated products **C-iv** are also formed. The desired **C-iii** can be separated away from **C-iv** by chromatographic purification or by fractional crystallization.




A synthesis of pyridylpyrazole scaffold C-1 is depicted in Scheme C-2.

Step A:

Picoline is added to a solution of LiHMDS in THF at room temperature over a time period ranging from 30 minutes to 1 hour. The resulting solution is stirred for an additional 30 minutes to 1 hour at room temperature. This solution is then added to neat ethyl p-fluorobenzoate **B60** at room temperature over 1-2 h. The mixture is then allowed to stir at room temperature for 16-24 h. Equal portions of water and ethyl acetate are then added to the reaction and the mixture is partitioned in an extraction funnel. The organic layer is dried, filtered, and evaporated to give an oily solid. Hexanes are then added and the solid is filtered and washed with cold hexanes leaving the pyridyl monoketone **B61** for use in Step B.

Step B:

The pyridyl monoketone **B61** is added as a solution in THF to a flask maintained at room temperature which contains *t*-BuOK in a THF/ *t*-BuOH cosolvent. A yellow precipitate forms and stirring at room temperature is continued for 1-3 h. After this time, N-Cbz-protected glycine N-hydroxysuccinimide **B62** is added dropwise at room temperature as a solution in THF over 1-3 h. This solution, containing crude diketone **B63**, is used directly in Step C.

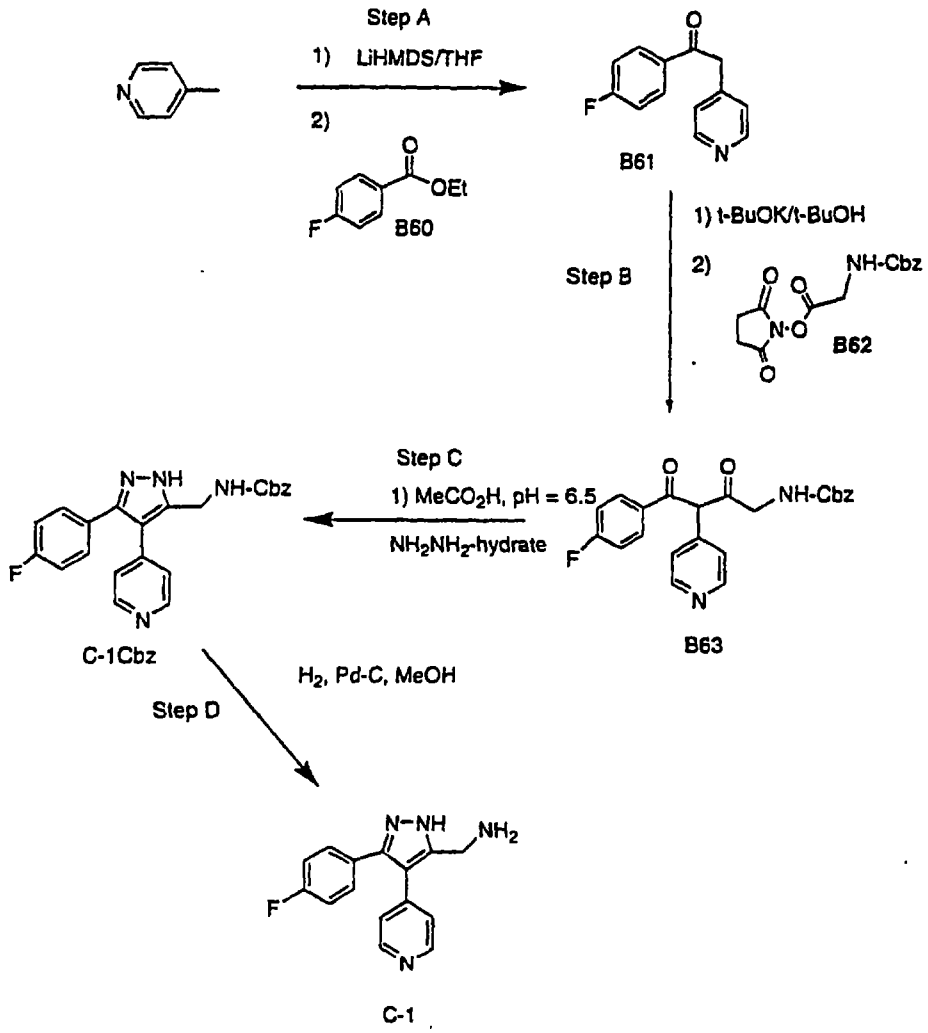
Step C:. The solution from step C is treated with water and the pH is adjusted to between 6 and 7 with acetic acid. Hydrazine hydrate is then added dropwise to the mixture as a solution in water over 30 minutes to 1h at room temperature. Water and ethyl acetate are then added to the flask and the mixture is then partitioned in a separatory funnel. The organic layer is dried, filtered, and evaported to give a crude oil which is purified by

silica gel chromatography, giving rise to purified **C-1Cbz**.

Step: D

The Cbz protecting group contained in compound **C-1Cbz** is cleaved using hydrogen gas under pressure and Pd-C in methanol solvent. The resulting amine **C-1** is obtained by filtration and concentration.

Scheme C-2


Step A
1) LiHMDS/THF
2)
B60
B61
Step B
1) t-BuOK/t-BuOH
2)
B62
Step C
1) MeCO2H, pH = 6.5
NH2NH2-hydrate
B63
C-1Cbz
H2, Pd-C, MeOH
Step D
C-1

A number of pyridyl pyrazole scaffolds of type **C-v** are prepared as shown in Scheme C-3.

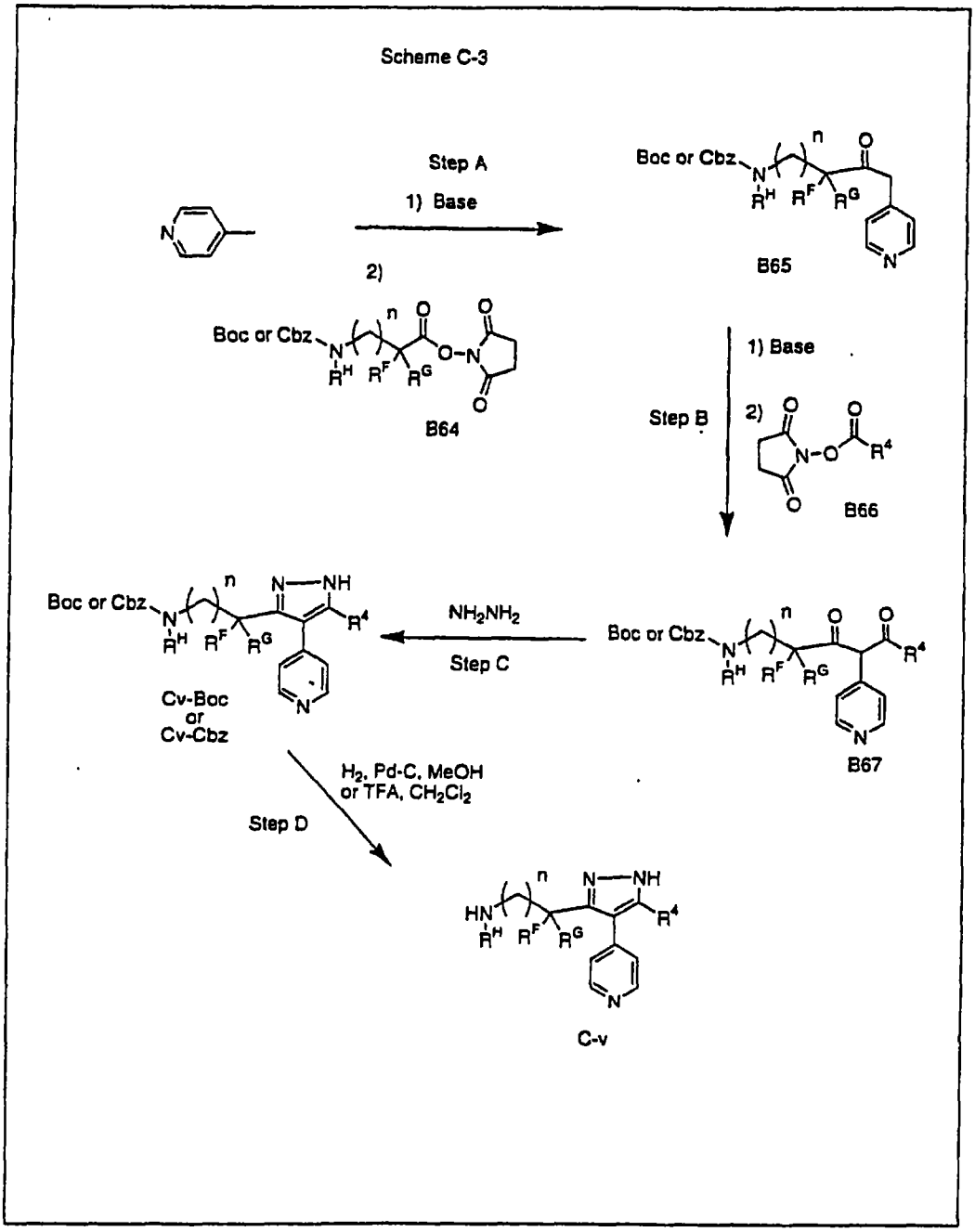
Step A: Picoline is treated with a base chosen from but not limited to *n*-BuLi, LDA, LiHMDS, *t*BuOK, or NaH in an organic solvent such as THF, ether, *t*-BuOH or dioxane from -78 °C to 50 °C for a period of time from 10 minutes to 3 hours. The metallated picoline solution is then added to a solution of an appropriately activated ester analog of a carboxylic acid $CbzNR^H-(CH_2)_nCR^F(R^G)-CO_2H$ or $BocNR^H-(CH_2)_nCR^F(R^G)-CO_2H$, preferably but not limited to the N-hydroxysuccinimide **B64**. The reaction is allowed to stir from 30 minutes to 48 hours during which time the temperature may range from -20 °C to 120 °C. The mixture is then poured into water and extracted with an organic solvent. After drying and removal of solvent the pyridyl monoketone **B65** is isolated as a crude solid which can be purified by crystallization and/or chromatography.

Step B: A solution of the pyridyl monoketone **B65** in ether, THF, tBuOH, or dioxane is added to a base chosen from but not limited to *n*-BuLi, LDA, LiHMDS, *t*BuOK, or NaH contained in hexane, THF, ether, dioxane, or *t*BuOH from -78 °C to 50 °C for a period of time from 10 minutes to 3 hours. The anion sometimes precipitates as a yellow solid. An appropriately substituted activated ester such as the N-hydroxysuccinimide **B66** is then added as a solution in THF, ether, or dioxane to the monoketone anion while the temperature is maintained between -50 °C and 50 °C. The resulting mixture is allowed to stir at the specified temperature for a period of time from ranging from 5 minutes to 3 hours. The resulting pyridyl diketone intermediate **B67** is utilized without further purification in Step C.

Step C: The solution containing the pyridyl diketone **B67** is quenched with water and the pH is adjusted to between 4 and 8 utilizing an inorganic or organic acid chosen from HOAc, $H_2SO_4$, HCl, or $HNO_3$. The temperature during this step is maintained between -20 °C and room temperature. Hydrazine or hydrazine hydrate is then added to the mixture while maintaining the temperature between -20 °C and 40 °C for a period of 30 minutes to three hours. The mixture is then poured into water and extracted with an organic solvent. The pyridyl pyrazole **C-vBoc** or **C-vCbz** is obtained as a crude solid which is purified by chromatography or crystallization.

Step: D

The carbamate protecting groups from **C-vBoc** or **C-vCbz** are removed to afford the scaffolds **C-v** containing either a free primary amine ($R^H$ is hydrogen) or a free secondary amine ($R^H$ not equal to hydrogen). The Boc protecting carbamate groups are cleaved utilizing 1:1 trifluoroacetic acid (TFA)/methylene chloride at room temperature for several hours. The CBZ carbamate protecting groups are cleaved using hydrogen gas under pressure and Pd-C in an alcoholic solvent. The resulting amines **C-v** are then optionally crystallized or purified by chromatography.


Scheme C-3
Step A
1) Base
2)
Boc or Cbz
B64
B65
Step B
1) Base
2)
B66
Boc or Cbz
Cv-Boc
or
Cv-Cbz
NH2NH2
Step C
B67
H2, Pd-C, MeOH
or TFA, CH2Cl2
Step D
C-v

5

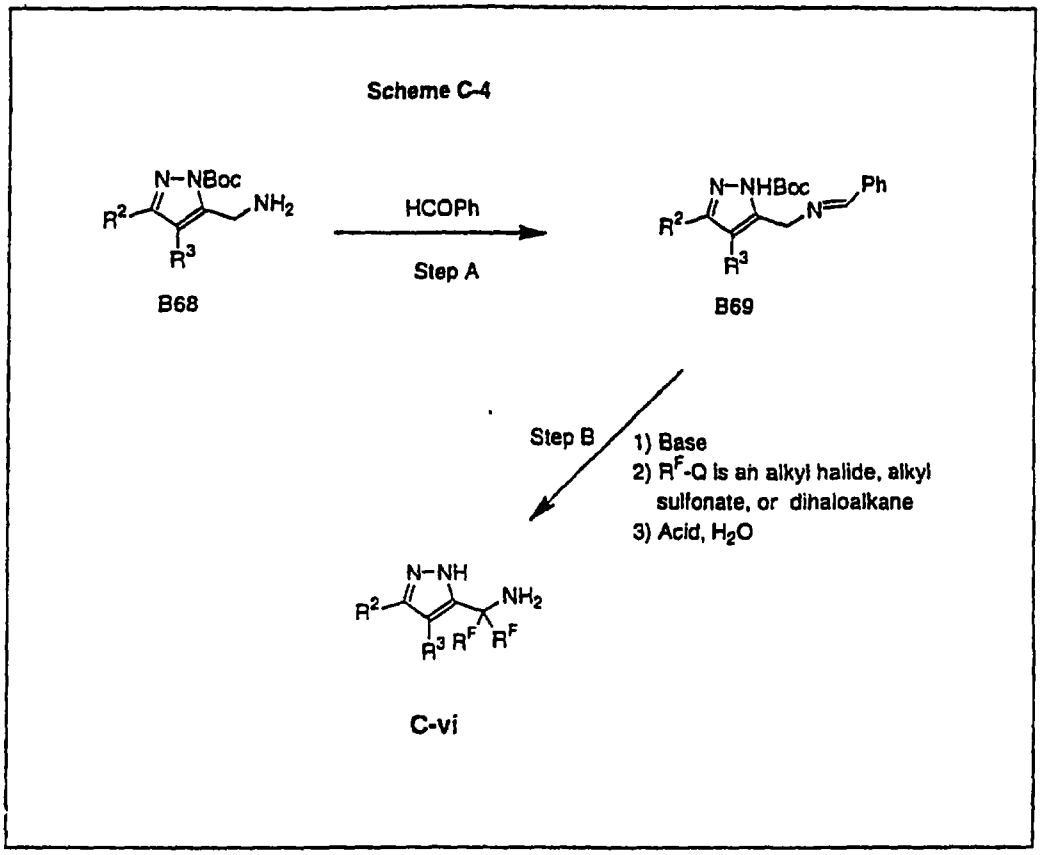
The synthesis of scaffolds **C-vi** is accomplished as shown in Scheme C-4.

Step A:

A Boc protected pyridylpyrazole **B68** is treated with benzaldehyde in methylene chloride at room temperature in the presence of a drying agent for a period of time ranging from 1-24 h. Solvent is then evaporated and the resulting imine **B69** is used in step B without further purification.

Step B:

The pyridylpyrazole imine **B69** is dissolved in THF and stirred under nitrogen at temperatures ranging from -78 to -20 °C. A base such as LDA, *n*-BuLi, or LiHMDS is added dropwise to the mixture which is then stirred for an additional 10 minutes to 3 h. Two-five equivalents of an alklyating agent $R^F$-Q are then added to the mixture and stirring is continued for several hours. The mixture is then quenched with acid and allowed to warm to room temperature and stirred several hours until cleavage of the Boc and the imine functions is complete. The pH is adjusted to 12 and then the mixture is extracted with an organic solvent, which is dried and evaporated. The crude pyridylpyrazole is then crystallized and/or chromatographed to give **C-vi**.

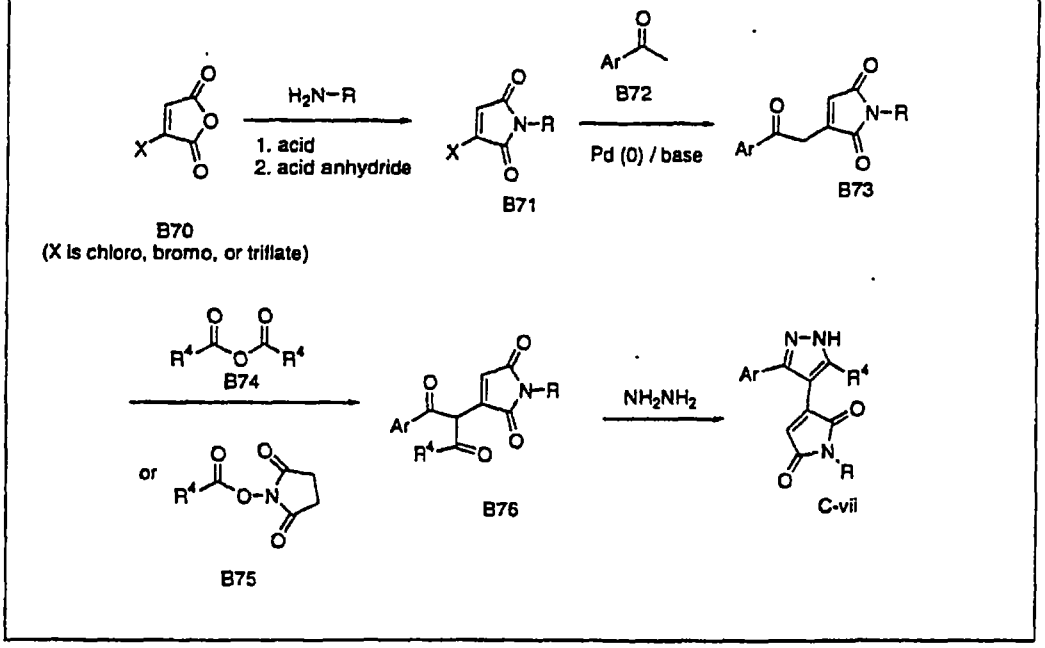



The synthesis of maleimide-containing scaffolds **C-vii** is accomplished as shown in Scheme C-5.

The maleimide pyrazole scaffolds **C-vii** are synthesized as depicted in scheme C-5. Condensation reaction of a primary amine $H_2N$-R with a maleic anhydride **B70** that is substituted at position 3 with either a bromo, chloro, or triflate group generates compound **B71**. The formed maleimide derivative **B71** then reacts with an acetophenone derivative **B72** in the presence of a Pd(0)

catalyst and base to afford compound **B73**. The methylene position of **B73** is then acylated with an acid anhydride **B74** or an activated acid ester **B75**, forming the di-ketone derivative **B76** . The di-ketone **B76** condenses with hydrazine to afford the desired maleimide pyrazole scaffold **C-vii**.

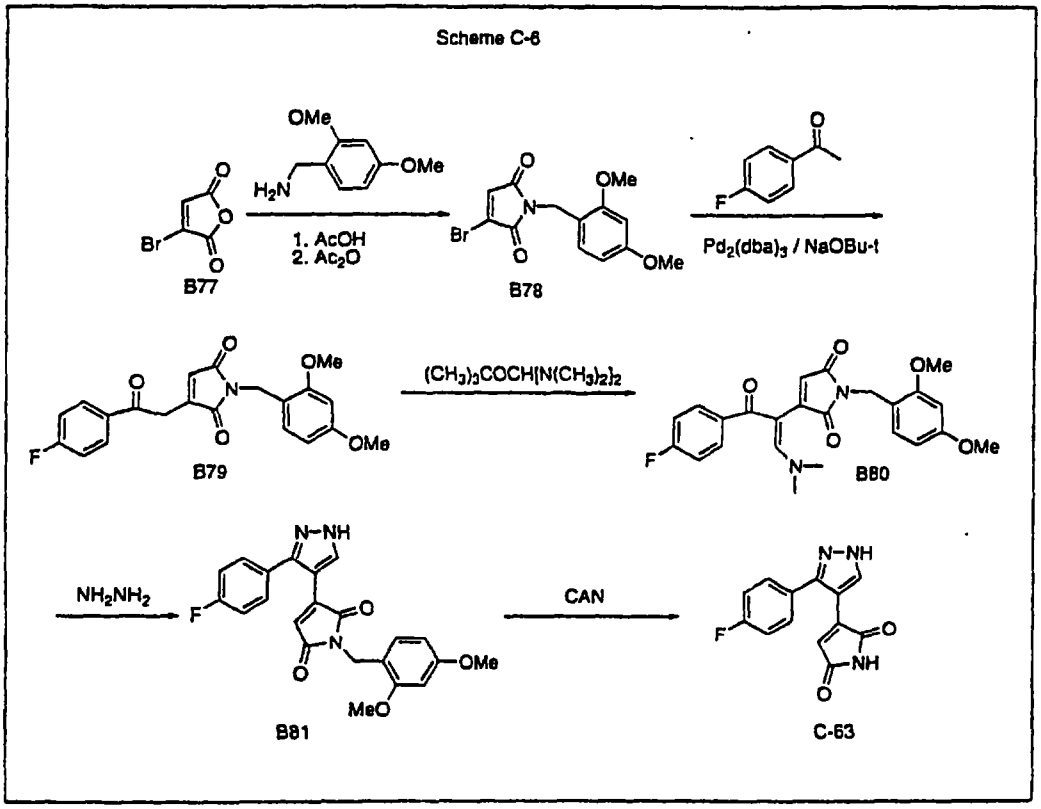
**Scheme C-5**




Scheme C-6 illustrates the synthesis of the maleimide pyrazole scaffold **C-63** wherein $R^4$ is hydrogen. The synthesis starts with the condensation reaction of bromomaleic anhydride **B77** with 2, 4-dimethoxybenzylamine in acetic acid and acetic anhydride, giving rise to intermediate **B78**. The maleimide **B78** is then treated with 4'-fluoroacetophenone in the presence of catalytic amount

$Pd_2(dba)_3$ and sodium t-butoxide to form the fluoroacetophenone substituted maleimide **B79**. The **B79** is treated with *tert*-butoxybis(dimethylamino)methane to yield the a-ketoenamine **B80**. The a-ketoenamine **B80** is condensed with hydrazine to form the maleimide pyrazole skeleton **B81**. The 2, 4-dimethoxybenzyl group protecting group is optionally removed with ceric ammonium nitrate (CAN) to give compound **C-63**.

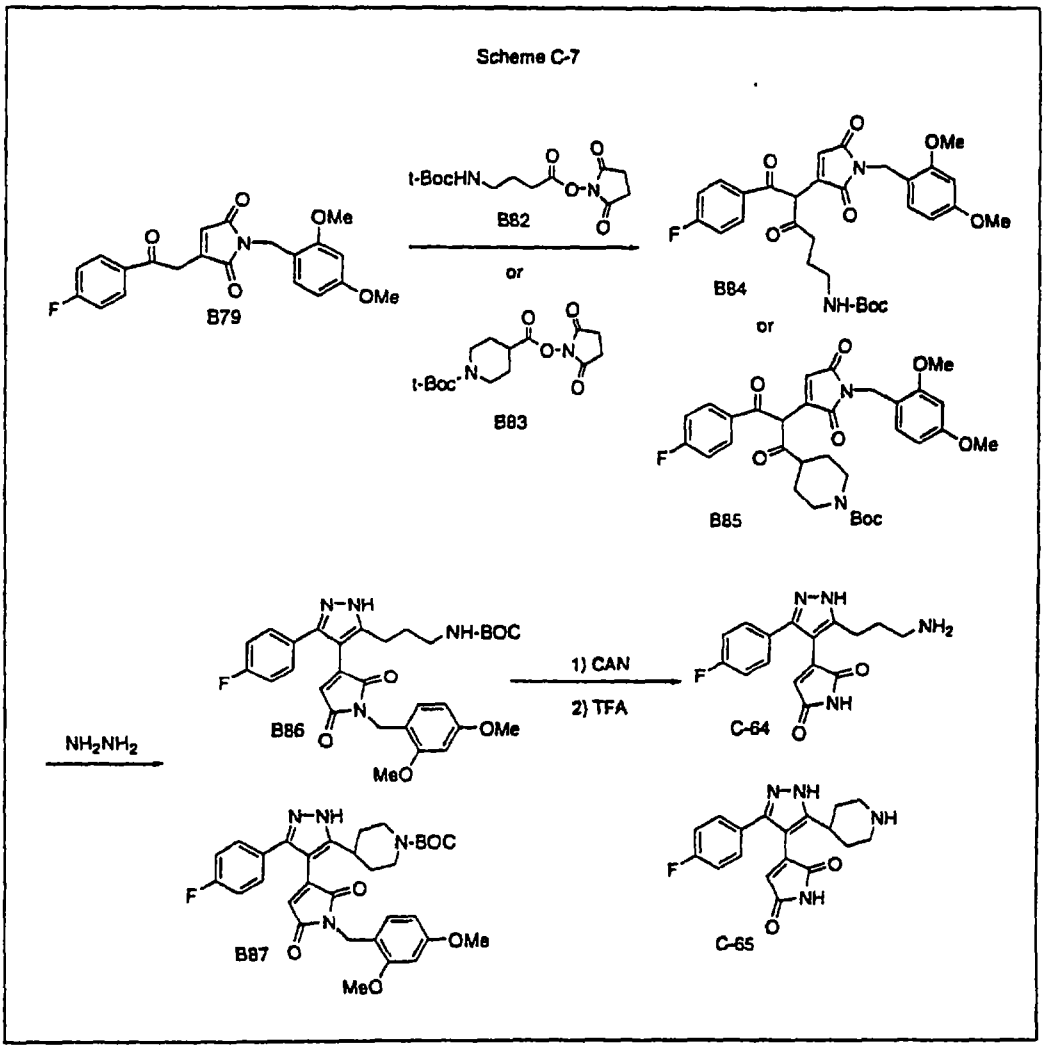
Scheme C-6



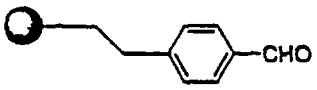

Scheme C-7 illustrates the synthesis of maleimide-containing scaffolds **C-64** and **C-65**. These scaffolds **C-49** and **C-50** are synthesized according to the general methods

illustrated in Scheme C-5 and exemplified with the utilization of N-hydroxysuccinimides **B82** and **B83** to afford the maleimide-containing pyrazoles **B86** and **B87**, respectively. Optional removal of the 2,4-dimethoxylbenzyl groups with CAN and subsequent removal of the Boc-protecting groups with trifluoroacetic acid (TFA) affords the scaffolds **C-64** and **C-65**.

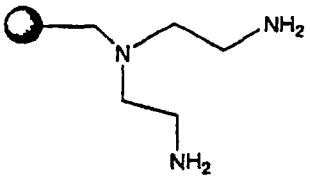
Scheme C-7



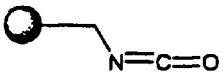
The various functionalized resins and sequestration-enabling-reagents utilized to prepare and purify parallel reaction mixtures are more fully described below, including their commercial source or literature reference to their preparation.

B32 

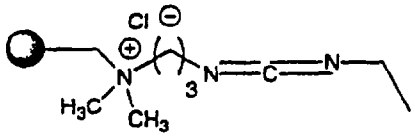
4-benzyloxybenzaldehyde functionalized polystyrene. Novabiochem cat. #01-64-0182

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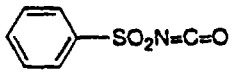
Prepared as reported in D. L. Flynn *et al*, *J. American Chemical Society* (1997) 119, 4874-4881.

B38 

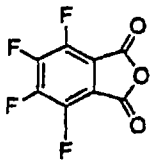
Methylisocyanate functionalized polystyrene. Novabiochem cat. # 01-64-0169

B48 

Polymer bound EDC, prepared as reported by M. C. Desai *et al*, *Tetrahedron Letters* (1993) 34, 7685.

B41 

Benzenesulfonylisocyanate, purchased from Aldrich Chemical Company. Cat# 23,229-7

B50 

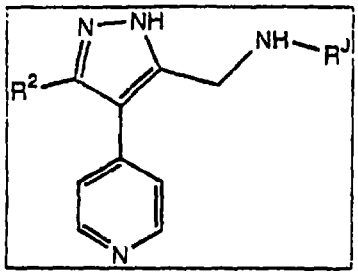
Tetra-fluorophthalic anhydride, purchased from Aldrich Chemical Company. Cat # 33,901-6

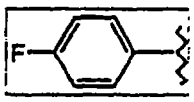
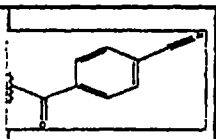
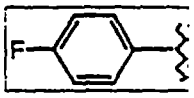
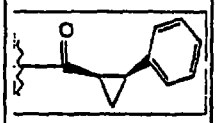
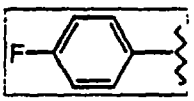
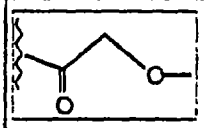
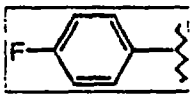
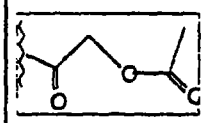
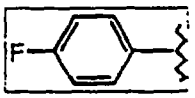
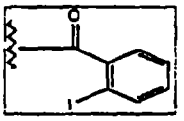
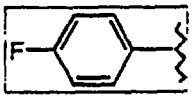
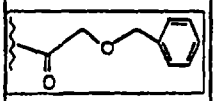
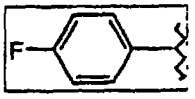
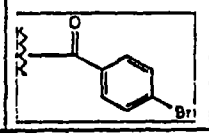
**Experimental procedure for the parallel synthesis of a series of amides, carbamates, ureas and sulfonamides B-0001 through B-0048 from scaffold C-1.**

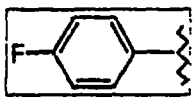
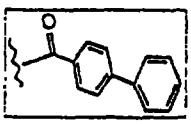
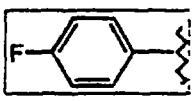
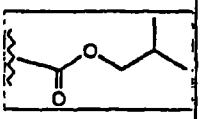
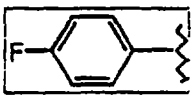
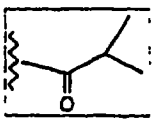
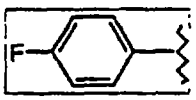
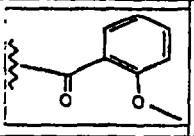
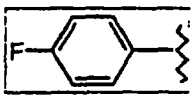
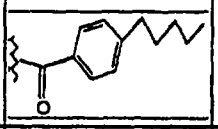
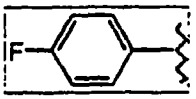
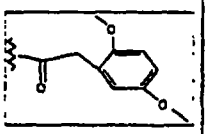
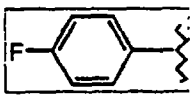
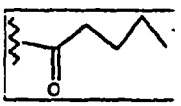
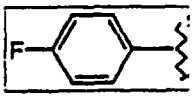
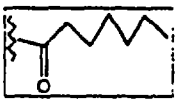
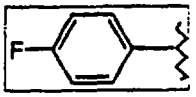
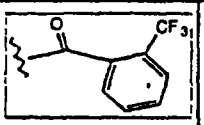
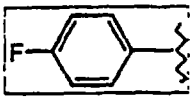
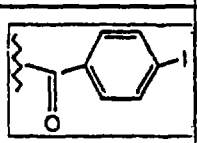
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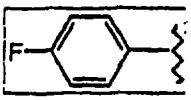
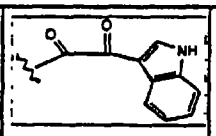
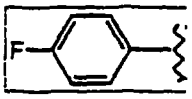
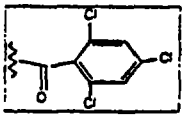
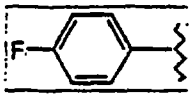
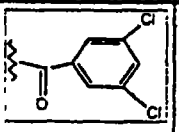
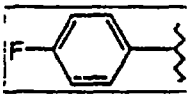
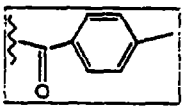
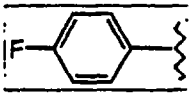
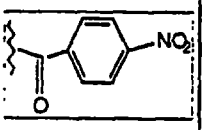
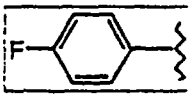
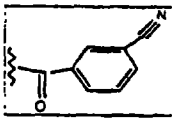
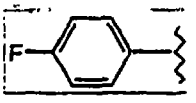
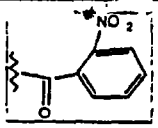
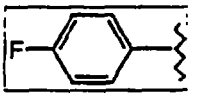
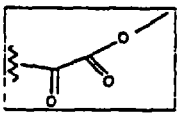
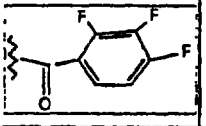
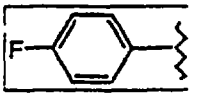
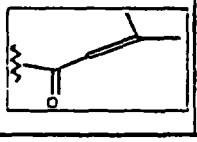
To each reaction vessel (polypropylene syringe tubes fitted with a porous frit, closed at the bottom) of a parallel reaction apparatus was added 200 uL of dimethylformamide. A stock solution of the scaffold amine **C-1** in dimethylformamide (0.1 M, 500 uL) was added to each reaction vessel followed by the addition of a stock solution of N-methylmorpholine in dimethylformamide (1.0 M., 200 uL). A stock solution of each of the electrophiles was then added to the appropriate reaction vessels: a) 500 uL of a 0.2 M solution of the acid chlorides in dichloroethane or b) 500 uL of a 0.2 M solution of the chloroformates in dichloroethane or c) 313 uL of a 0.2 M solution of the isocyanates in dichloroethane or d) 375 uL of a 0.2 M solution of the sulfonyl chlorides in dichloroethane. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop orbital shaker) at 200 RPM at ambient

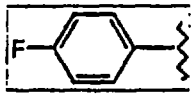
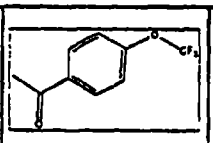
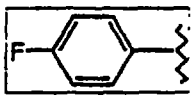
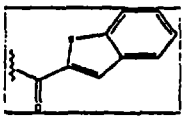
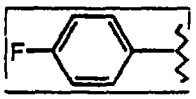
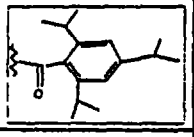
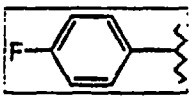
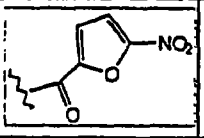
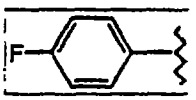
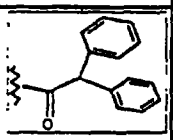
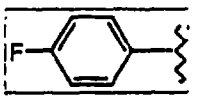
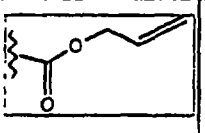
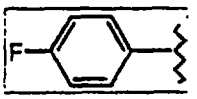
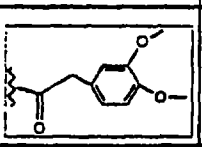
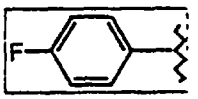
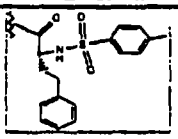
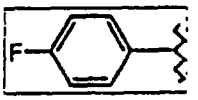
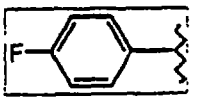
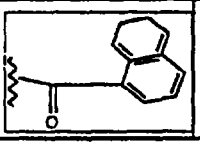
temperature (23-30 °C) for a period of 2-3 h, under a gentle flow of nitrogen. At this time each reaction vessel was treated with approximately 250 mg of polyamine resin **B33** (4.0 meq N/g resin) and approximately 100 mg of polyaldehyde resin **B32** (2.9 mmol/g resin). Each reaction vessel was diluted with 1 mL dimethylformamide and 1 mL dichloroethane and the orbital shaking was continued at 200 RPM for a period of 14-20 h at ambient temperature. Each reaction vessel was then opened and the desired solution phase products separated from the insoluble quenched byproducts by filtration and collected in individual conical vials. Each vessel was rinsed twice with dichloroethane (1 mL) and the rinsings were also collected. The solutions obtained were then evaporated to dryness in a Savant apparatus (an ultracentrifuge equipped with high vacuum, scalable temperature settings and a solvent trap to condense the volatile solvent vapors). The resulting amide, carbamate, urea and sulfonamide products were then weighed and characterized. The yields and analytical data for the products obtained using this method are shown below.

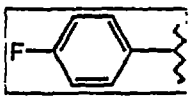
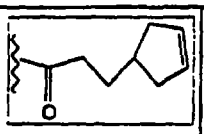
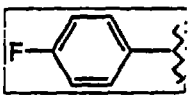
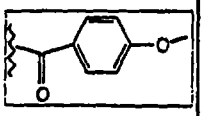
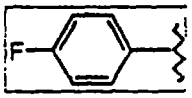
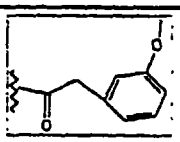
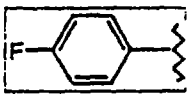
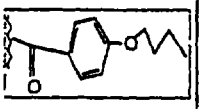
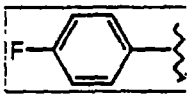
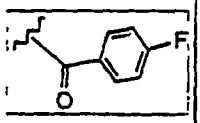
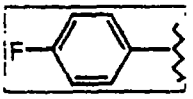
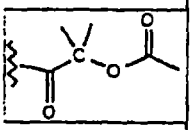
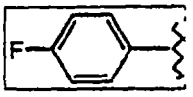
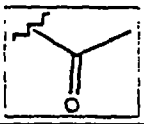
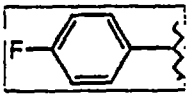
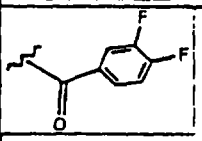
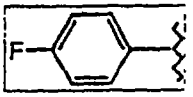
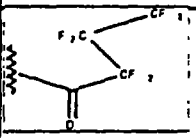
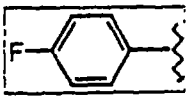
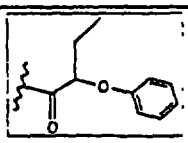


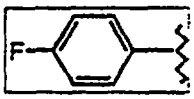
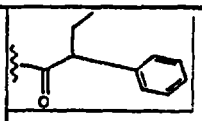
| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0001 |  |  | 85 | 397 | 398 |
| B-0002 |  |  | 94 | 412 | 413 |
| B-0003 |  |  | 91 | 340 | 341 |
| B-0004 |  |  | 79 | 368 | 369 |
| B-0005 |  |  | 92 | 498 | 499 |
| B-0006 |  |  | 92 | 416 | 417 |
| B-0007 |  |  | 86 | 450 | 451 |

| Example# | $R^2$ | $R^3$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0008 |  |  | 86 | 448 | 449 |
| B-0009 |  |  | 83 | 368 | 369 |
| B-0010 |  |  | 86 | 338 | 339 |
| B-0011 |  |  | 92 | 402 | 403 |
| B-0012 |  |  | 74 | 442 | 443 |
| B-0013 |  |  | 91 | 446 | 447 |
| B-0014 |  |  | 84 | 352 | 353 |
| B-0015 |  |  | 94 | 380 | 381 |
| B-0016 |  |  | 89 | 440 | 441 |
| B-0017 |  |  | 83 | 498 | 499 |

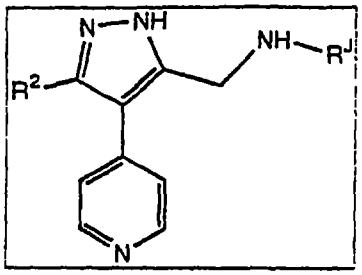
| Example# | $R^2$ | $R^3$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0018 |  |  | 24 | 439 | 440 |
| B-0019 |  |  | 89 | 474 | 475 |
| B-0020 |  |  | 90 | 440 | 441 |
| B-0021 |  |  | 85 | 386 | 387 |
| B-0022 |  |  | 35 | 417 | 418 |
| B-0023 |  |  | 94 | 397 | 398 |
| B-0024 |  |  | 87 | 417 | 418 |
| B-0025 |  |  | 5 | 354 | - |
| B-0026 |  |  | 87 | 426 | 427 |
| B-0027 |  |  | 89 | 350 | 351 |

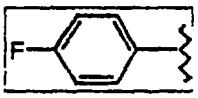
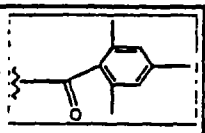
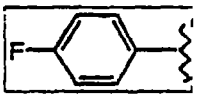
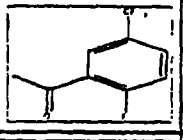
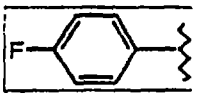
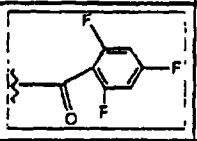
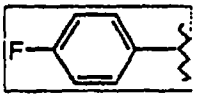
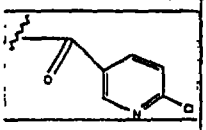
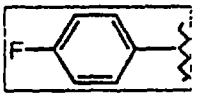
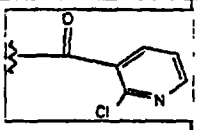
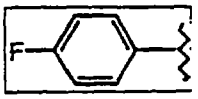
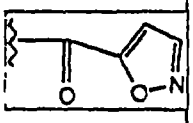
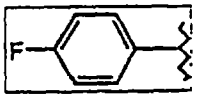
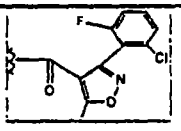
| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0028 |  |  | 92 | 456 | 457 |
| B-0029 |  |  | 89 | 428 | 429 |
| B-0030 |  |  | 37 | 498 | 499 |
| B-0031 |  |  | 18 | 407 | 408 |
| B-0032 |  |  | 86 | 462 | 463 |
| B-0033 |  |  | 3 | 352 | - |
| B-0034 |  |  | 92 | 446 | 447 |
| B-0035 |  |  | 28 | 569 | 570 |
| B-0036 |  |  | 93 | 416 | 417 |
| B-0037 |  |  | 91 | 422 | 423 |

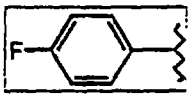
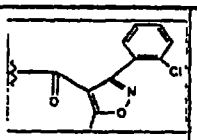
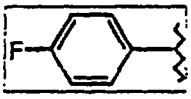
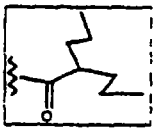
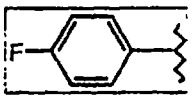
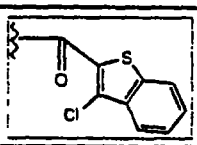
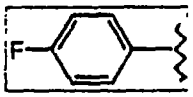
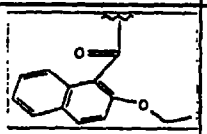
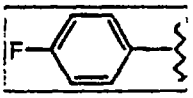
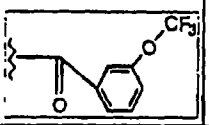
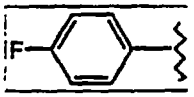
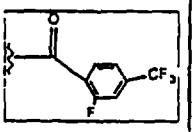
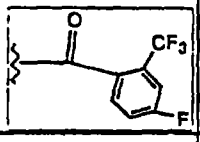
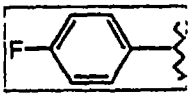
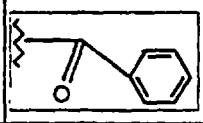
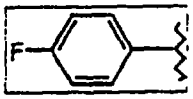
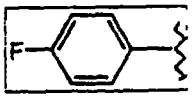
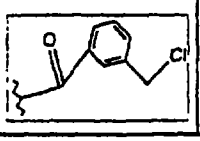
| Example# | $R^2$ | $R^4$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0038 |  |  | 84 | 390 | 393 |
| B-0039 |  |  | 87 | 402 | 403 |
| B-0040 |  |  | 92 | 416 | 417 |
| B-0041 |  |  | 75 | 444 | 445 |
| B-0042 |  |  | 54 | 390 | 391 |
| B-0043 |  |  | 80 | 396 | 397 |
| B-0044 |  |  | 81 | 310 | 311 |
| B-0045 |  |  | 91 | 408 | 409 |
| B-0046 |  |  | 25 | 464 | 465 |
| B-0047 |  |  | 88 | 430 | 431 |

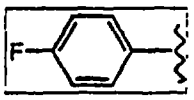
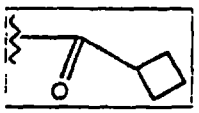
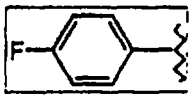
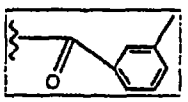
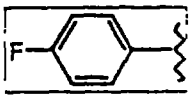
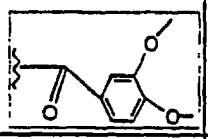
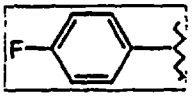
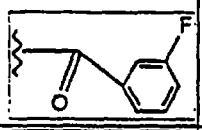
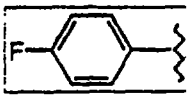
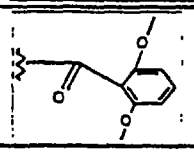
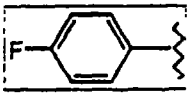
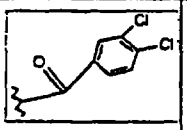
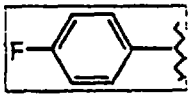
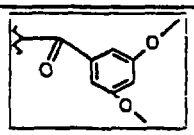
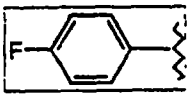
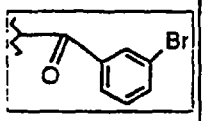
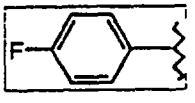
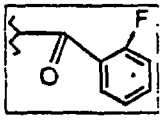
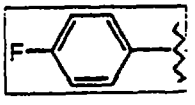
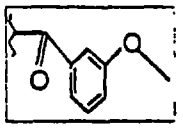
| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0048 |  |  | 95 | 414 | 415 |

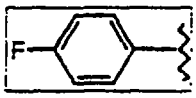
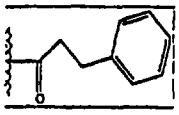
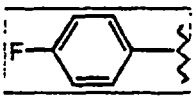
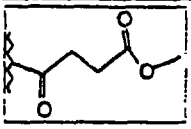
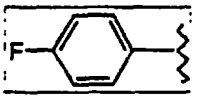
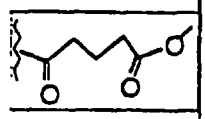
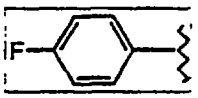
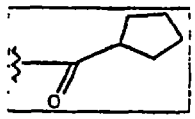
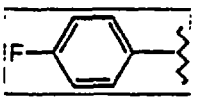
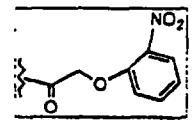
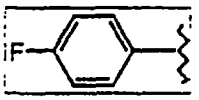
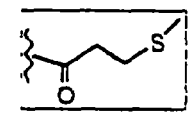
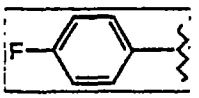
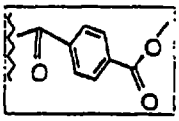
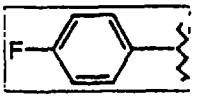
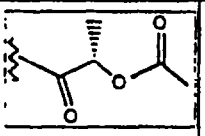
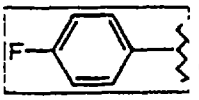
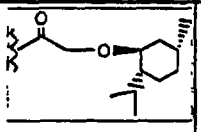
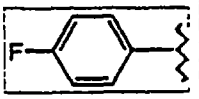
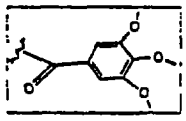
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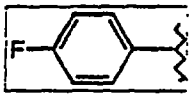
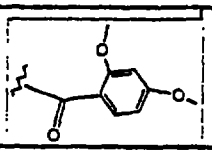
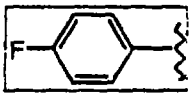
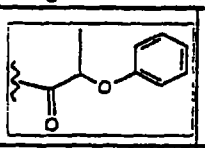
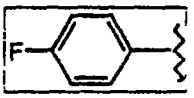
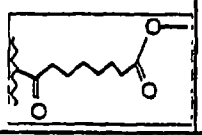
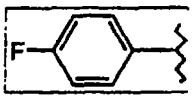
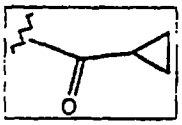
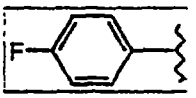
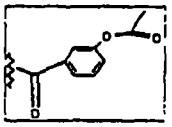
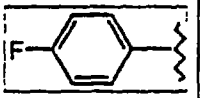
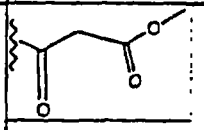
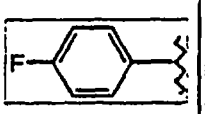
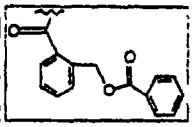
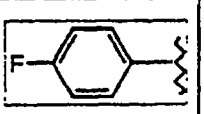
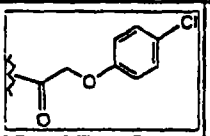
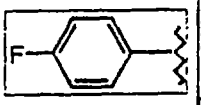
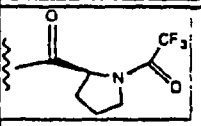
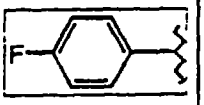
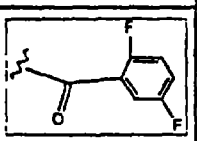


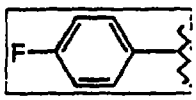
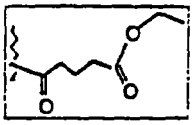
| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0049 |  |  | 85 | 414 | 415 |
| B-0050 |  |  | 9 | 458 | 459 |
| B-0051 |  |  | 91 | 426 | 427 |
| B-0052 |  |  | 79 | 407 | 408 |
| B-0053 |  |  | 92 | 407 | 408 |
| B-0054 |  |  | 92 | 363 | 364 |
| B-0055 |  |  | 86 | 505 | 506 |

| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0056 |  |  | 86 | 487 | 488 |
| B-0057 |  |  | 83 | 394 | 395 |
| B-0058 |  |  | 86 | 462 | 463 |
| B-0059 |  |  | 92 | 466 | 467 |
| B-0060 |  |  | 74 | 456 | 457 |
| B-0061 |  |  | 35 | 458 | 459 |
| B-0062 |  |  | 94 | 458 | 459 |
| B-0063 |  |  | 87 | 372 | 373 |
| B-0064 |  |  | 5 | 394 | 395 |
| B-0065 |  |  | 87 | 420 | 395 |

| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0066 |  |  | 89 | 350 | 351 |
| B-0067 |  |  | 92 | 386 | 387 |
| B-0068 |  |  | 89 | 432 | 433 |
| B-0069 |  |  | 37 | 390 | 391 |
| B-0070 |  |  | 18 | 432 | 433 |
| B-0071 |  |  | 86 | 440 | 441 |
| B-0072 |  |  | 3 | 432 | 433 |
| B-0073 |  |  | 92 | 450 | 451 |
| B-0074 |  |  | 28 | 390 | 391 |
| B-0075 |  |  | 93 | 402 | 403 |

| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0076 |  |  | 91 | 400 | 401 |
| B-0077 |  |  | 84 | 382 | 383 |
| B-0078 |  |  | 87 | 396 | 397 |
| B-0079 |  |  | 92 | 364 | 365 |
| B-0080 |  |  | 75 | 447 | 448 |
| B-0081 |  |  | 54 | 370 | 371 |
| B-0082 |  |  | 80 | 430 | 431 |
| B-0083 |  |  | 81 | 382 | 383 |
| B-0084 |  |  | 91 | 464 | 465 |
| B-0085 |  |  | 25 | 462 | 463 |

| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0086 |  |  | 88 | 432 | 433 |
| B-0087 |  |  | 95 | 416 | 417 |
| B-0088 |  |  | | 438 | 439 |
| B-0089 |  |  | | 336 | 337 |
| B-0090 |  |  | | 444 | 445 |
| B-0091 |  |  | | 368 | 369 |
| B-0092 |  |  | | 506 | 507 |
| B-0093 |  |  | | 436 | 437 |
| B-0094 |  |  | | 461 | 462 |
| B-0095 |  |  | | 408 | 409 |

| Example# | $R^2$ | $R^J$ | %Yield | Calcd. Mass Spec | Observed Mass Spec (M+H) |
|---|---|---|---|---|---|
| B-0096 |  |  | | 410 | 411 |