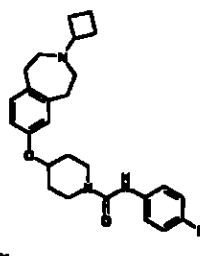
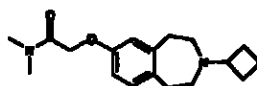


42
43**Example 67****4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylic acid (4-fluoro-phenyl)-amide (E67)**

5

Example 67 was prepared from 3-cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) and 4-fluorophenyl-isocyanate using the method described for Example 66 (E66); MS (ES+) m/e 438 [M+H]⁺.

10

Example 68**2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N,N-dimethyl-acetamide (E68)**

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Sodium hydride (60% disp. in mineral oil, 60 mg, 1.5 mmol) was added to a stirred solution of 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) (200 mg, 0.9 mmol) in dimethyl sulfoxide (10 ml). After 0.5 hours, 2-chloro-N,N-dimethyl acetamide (0.3 ml, 2.4 mmol) was added and the reaction mixture was heated to 120 °C for 8 hours. The reaction was allowed to cool, the crude mixture was applied to a SCX cartridge ion exchange (Varian bond-elute, 10 g) and washed with methanol and then a mixture of .880 ammonia:methanol (1:9). The combined basic fractions were reduced in vacuo to afford the title compound (E68). MS (ES+) m/e 303 [M+H]⁺.

20

Examples 69-71

Examples 69-71 (E69-E71) were prepared using the method described for Example 68 (E68) from 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) and the appropriate chloride indicated in the table.

25

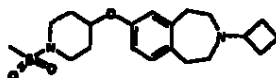
Example	Chloride	LC/MS (M+H ⁺)
2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-phenyl-acetamide (E69)	2-Chloro-N-phenyl-acetamide	351
2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-1-pyrrolidin-1-yl-ethanone (E70)	2-Chloro-1-pyrrolidin-1-yl-ethanone	329

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2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-1-morpholin-4-yl-ethanone (E71)	2-Chloro-1-morpholinyl-4-yl-ethanone	345
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Example 72

3-Cyclobutyl-7-(1-methanesulfonyl-piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E72)



- 5 3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6) (150 mg, 0.5 mmol) was stirred in dichloromethane (5 ml) with diethylaminomethyl polystyrene (3.2 mmol/g, 625 mg, 2 mmol). Methane sulfonyl chloride (43 μ L, 0.55 mmol) was added and the mixture stirred at room temperature for 18 hours. The resin was filtered, washed with
10 dichloromethane and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography eluting with a mixture of .880 ammonia:ethanol: dichloromethane (1:9:90) to afford the title product (E72); MS (ES+) m/e 379 [M+H]⁺.

Examples 73-78

- 15 Examples 73-78 (E73-E78) were prepared using an analogous method to that described for Example 72 (E72) from the appropriate amine and sulfonyl chloride indicated in the table:

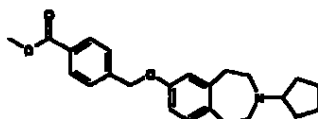
Example	Amine	Sulfonyl Chloride	LC/MS (M+H ⁺)
4-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-sulfonyl]-benzonitrile (E73)	3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)	4-Cyano-benzenesulfonyl chloride	466
3-Cyclobutyl-7-[1-(3,5-dimethyl-isoxazole-4-sulfonyl)-piperidin-4-yloxy]-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E74)	3-Cyclobutyl-7-(piperidin-4-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E6)	3,5-Dimethyl-isoxazole-4-sulfonyl chloride	460
4-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-piperidine-1-sulfonyl]-benzonitrile (E75)	3-Cyclobutyl-7-(piperidin-4-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E7)	4-Cyano-benzenesulfonyl chloride	480
4-[(R)-2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-pyrrolidine-1-	3-Cyclobutyl-7-[(R)-1-pyrrolidin-2-ylmethoxy]-2,3,4,5-	4-Cyano-benzenesulfonyl chloride	466

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3-Cyclobutyl-7-(pyridin-3-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E83)	3-Bromomethyl-pyridine	309
3-Cyclobutyl-7-(pyridin-4-ylmethoxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E84)	4-Bromomethyl-pyridine	309
2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzonitrile (E85)	2-Bromomethyl-benzonitrile	333
4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzonitrile (E86)	4-Bromomethyl-benzonitrile	333
6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-1-methyl-1H-quinolin-2-one (E87)	6-Bromomethyl-1-methyl-1H-quinolin-2-one	389

Example 88

4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzoic acid methyl ester (E88)



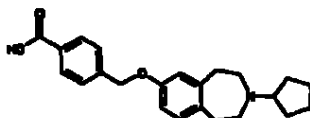
5

4-(2,3,4,5-Tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzoic acid methyl ester (D4) (2.83 g, 9.1 mmol) and cyclopentanone (1.6 ml, 18.2 mmol) were dissolved in dichloromethane (30 ml) and acetic acid (0.5 ml). Sodium triacetoxy borohydride (3.85 g, 18.2 mmol) was added and the solution was stirred at room temperature for 4 hours. The reaction mixture was washed with a saturated solution of sodium carbonate, the organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography eluting with a mixture of 0.880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (E88); MS (ES+) *m/e* 380 [M+H]⁺.

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Example 89

4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzoic acid (E89)



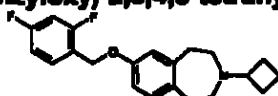
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4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzoic acid methyl ester (E88) (3.1 g, 8.1 mmol) was dissolved in a mixture of methanol (80 ml), 2N sodium hydroxide (12 ml) and water (30 ml). The resulting mixture was stirred at 60 °C for 4 hours and then cooled to room temperature. The mixture was concentrated *in vacuo* to remove the organic solvents and then acidified to pH 6 (2N hydrochloric acid). The resulting precipitates were filtered, washed with water and dried under vacuum to afford the title compound (E89); MS (ES+) *m/e* 386 [M+H]⁺.

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sulfonyl]-benzonitrile (E76)	tetrahydro-1 <i>H</i> -benzo[d]azepine (E8)		
4-[(<i>R</i>)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxy)-pyrrolidine-1-sulfonyl]-benzonitrile (E77)	3-Cyclobutyl-7-[(<i>R</i>)-pyrrolidin-3-yloxy]-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E9)	4-Cyano-benzenesulfonyl chloride	452
4-[(<i>S</i>)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxy)-pyrrolidine-1-sulfonyl]-benzonitrile (E78)	3-Cyclobutyl-7-[(<i>S</i>)-pyrrolidin-3-yloxy]-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E10)	4-Cyano-benzenesulfonyl chloride	452

Example 79**3-Cyclobutyl-7-(2,4-difluoro-benzyloxy)-2,3,4,5-tetrahydro-1*H*-benzo[d]azepine (E79)**

- 5 Potassium carbonate (778 mg, 5.6 mmol) was added to a stirred solution of 3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-ol (E3) (868 mg, 4.0 mmol), 2,4-difluorobenzyl bromide (0.25 ml, 2.1 mmol) and potassium iodide (25 mg) in butanone (9 ml). The reaction mixture was stirred at reflux for 18 hours, cooled, filtered and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate and washed with water and
- 10 brine. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the resulting residue by column chromatography eluting with a mixture of .880 ammonia: ethanol: dichloromethane (0.25:2.25:97.5 then 1:9:10) afforded the title compound (E79); MS (ES+) *m/e* 344 [M+H]⁺.

15 Examples 80-87

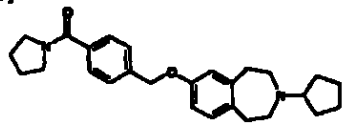
Examples 80-87 (E80-E87) were prepared from 3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[d]azepin-7-ol (E3) and the appropriate halide indicated in the table using the general method described for Example 80 (E80):

Example	Halide	LC/MS (M+H ⁺)
3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepin-7-yloxymethyl)-benzonitrile (E80)	3-Bromomethyl-benzonitrile	333
3-Cyclobutyl-7-(3-methoxy-benzyloxy)-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E81)	1-Bromomethyl-3-methoxybenzene	338
3-Cyclobutyl-7-(pyridin-2-ylmethoxy)-2,3,4,5-tetrahydro-1 <i>H</i> -benzo[d]azepine (E82)	2-Bromomethyl-pyridine	309

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Example 90

1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-phenyl]-1-pyrrolidin-yl-methanone (E90)



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15
4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzoic acid (E89) (0.201 mg, 0.55 mmol)), 1,3-diisopropylcarbodiimide (44 μ l, 0.6 mmol) and 1-hydroxybenzotriazole hydrate (82 mg, 0.6 mmol) were dissolved in a mixture of dichloromethane (2 ml) and dimethyl formamide (1 ml). After stirring at room temperature for 0.5 hours, pyrrolidine (41 μ l, 0.5 mmol) was added and the resulting mixture was allowed to stir for 16 hours. The crude reaction was applied to a SCX ion exchange cartridge (Varian bond-elute, 5 g) and washed with methanol and then a mixture of .880 ammonia:methanol (1:9). The combined basic fractions were concentrated *in vacuo*, and the resulting residue was purified by column chromatography eluting with a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (E90); MS (ES+) m/e 419 [M+H]⁺.

Examples 91-93

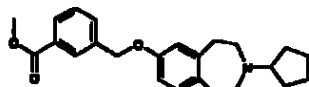
20
Examples 91-93 (E91-E93) were prepared using an analogous method to that described for Example 90 (E90) from 4-(3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzoic acid (E89) and the appropriate amine indicated in the table:

Example	Amine	LC/MS (M+H ⁺)
1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-phenyl]-1-morpholin-4-yl-methanone (E91)	Morpholine	435
1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-phenyl]-1-(4-pyridin-4-yl-piperazin-1-yl)-methanone (E92)	1-Pyridin-4-yl-piperazine	511
1-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-phenyl]-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone (E93)	1-(4-Fluoro-phenyl)-piperazine	528

Example 94

25
3-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxymethyl)-benzoic acid methyl ester (E94)

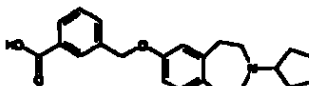
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Example 94 (E94) was prepared in an analogous manner to Example 88 (E88) from 7-hydroxy-1,2,4,5-tetrahydro-benzo[d]azepine-3-carboxylic acid tert-butyl ester (WO 02/40471) and 3-bromomethyl-benzoic acid methyl ester using the methods highlighted in Description 3 (D3), Description 4 (D4) and Example 88 (E88); MS (ES⁺), m/e 380 [M+H]⁺.

Example 95

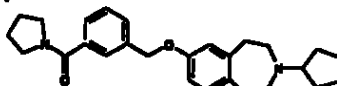
3-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-benzoic acid (E95)



Example 95 (E95) was prepared from 3-(3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-benzoic acid methyl ester Example 94 (E94) using the procedure outlined for Example 89 (E89); MS (ES⁺), m/e 366 [M+H]⁺.

Example 96

1-[3-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-phenyl]-1-pyrrolidin-yl-methanone (E96)



Example 96 (E96) was prepared from pyrrolidine and 3-(3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-benzoic acid (E95) using the procedure outlined for Example 90 (E90); MS (ES⁺), m/e 419 [M+H]⁺.

Examples 97-99

Examples 97-99 (E97-E99) were prepared from 3-(3-cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-benzoic acid (E95) and the appropriate amine indicated in the table using an analogous method to that described for Example 96 (E96).

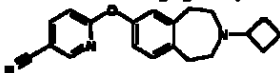
Example	Amine	LC/MS (M+H ⁺)
1-[3-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-phenyl]-1-morpholin-4-yl-methanone (E97)	Morpholine	435
1-[3-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-phenyl]-1-(4-pyridin-4-yl-piperazin-1-yl)-methanone (E98)	1-Pyridin-4-yl-piperazine	511
1-[3-(3-Cyclopentyl-2,3,4,5-tetrahydro-1H-	1-(4-Fluoro-	528

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benzo[d]azepin-7-yloxymethyl)-phenyl]-1-[4-(4-fluoro-phenyl)-piperazin-1-yl]-methanone (E99)	phenyl)-piperazine	
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Example 100

6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-nicotinonitrile (E100)



- 5 Sodium hydride (60% disp. in mineral oil, 60 mg, 1.5 mmol) was added to a stirred solution of 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) (200 mg, 0.9 mmol) in dimethyl sulfoxide (10 ml). After 0.5 hours, 6-chloronicotinyl nitrile (250 mg, 1.8 mmol) was added and the reaction mixture was heated to 120 °C for 6 hours. The reaction was allowed to cool and the crude mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 10 g) and washed with methanol and then a mixture of .880 ammonia:methanol (1:9). The combined basic fractions were reduced *in vacuo* to afford the title compound (E100); MS (ES+) *m/e* 320 [M+H]⁺.
- 10

Examples 101-120

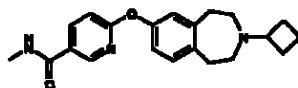
- 15 Examples 101-120 (E101-E120) were prepared using an analogous method to that described for Example 100 (E100) from 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) and the appropriate aromatic chloride indicated in the table:

Example	Chloride	LC/MS (M+H ⁺)
3-Cyclobutyl-7-(pyridin-2-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E101)	2-Chloro-pyridine	295
1-[6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-3-yl]-1-morpholin-4-yl-methanone (E102)	1-(6-Chloro-pyridin-3-yl)-1-morpholin-4-yl-methanone (D5)	408
1-[6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-3-yl]-1-pyrrolidin-1-yl-methanone (E103)	1-(6-Chloro-pyridin-3-yl)-1-pyrrolidin-1-yl-methanone (D6)	392
6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-nicotinamide (E104)	6-Chloro-nicotinamide (D7)	338
6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N,N-dimethyl-nicotinamide (E105)	6-Chloro-N,N-dimethyl-nicotinamide (D8)	366
6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-ethyl-N-methyl-nicotinamide (E106)	6-Chloro-N-ethyl-N-methyl-nicotinamide (D9)	380

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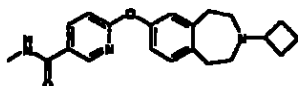
6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-cyclopentyl-nicotinamide (E107)	6-Chloro-N-cyclopentyl-nicotinamide (D11)	408
1-[6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-3-yl]-1-piperidin-1-yl-methanone (E108)	1-(6-Chloro-pyridin-3-yl)-1-piperidin-1-yl-methanone (D12)	408
1-[2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-4-yl]-1-piperidin-1-yl-methanone (E109)	1-(2-Chloro-pyridin-4-yl)-1-piperidin-1-yl-methanone (D13)	408
1-[2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-4-yl]-1-pyrrolidin-1-yl-methanone (E110)	1-(2-Chloro-pyridin-4-yl)-1-pyrrolidin-1-yl-methanone (D14)	392
1-[2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-4-yl]-1-morpholin-4-yl-methanone (E111)	1-(2-Chloro-pyridin-4-yl)-1-morpholin-4-yl-methanone (D15)	408
1-[6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-2-yl]-1-piperidin-1-yl-methanone (E112)	1-(6-Chloro-pyridin-2-yl)-1-piperidin-1-yl-methanone (D16)	408
1-[6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-2-yl]-1-(1,1-dioxothiomorpholin-4-yl)-methanone (E113)	1-(6-Chloro-pyridin-2-yl)-1-(1,1-dioxothiomorpholin-4-yl)-methanone (D17)	488
1-[6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-2-yl]-1-pyrrolidin-1-yl-methanone (E114)	1-(6-Chloro-pyridin-2-yl)-1-pyrrolidin-1-yl-methanone (D18)	392
1-[6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-2-yl]-1-morpholin-4-yl-methanone (E115)	1-(6-Chloro-pyridin-2-yl)-1-morpholin-4-yl-methanone (D19)	408
1-[2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-3-yl]-1-morpholin-4-yl-methanone (E116)	1-(2-Chloro-pyridin-3-yl)-1-morpholin-4-yl-methanone (D20)	408
1-[2-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyridin-3-yl]-1-piperidin-1-yl-methanone (E117)	1-(2-Chloro-pyridin-3-yl)-1-piperidin-1-yl-methanone (D21)	408
3-Cyclobutyl-7-(pyrazin-2-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E118)	2-Chloro-pyrazine	298
3-Cyclobutyl-7-(pyrimidin-2-yloxy)-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E119)	2-Chloro-pyrimidine	298
7-(5-Bromo-pyrimidin-2-yloxy)-3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E120)	5-Bromo-2-chloro-pyrimidine	375

Example 121

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51**6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-methyl-nicotinamide (E121)**

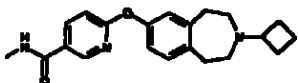
5 Sodium hydride (60% disp. in mineral oil, 60 mg, 1.5 mmol) was added to a stirred solution of 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) (200 mg, 0.9 mmol) in dimethyl sulfoxide (10 ml). After 0.5 hours, 6-chloro-N-methyl-nicotinamide (D10) (400 mg, 2.5 mmol) was added and the reaction mixture was heated to 120 °C for 6 hours. The reaction was allowed to cool and the crude mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 10 g) and washed with methanol and then a mixture of .880 ammonia:methanol (1:9). The combined basic fractions were reduced *in vacuo* to afford the title compound (E121). ¹H NMR (DMSO-*d*₆) δ 8.56 (1H, dd, J = 2.4, 0.4Hz), 8.48 (1H, br m), 8.20 (1H, dd, J = 8.4, 2.4 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.03 (1H, dd, J = 8.4, 0.4 Hz), 6.91 (1H, d, J = 2.4Hz), 6.86 (1H, dd, J = 8.0, 2.4Hz), 2.87 - 2.77 (8H, m), 2.36 (4H, m), 2.00 (2H, m), 1.78 (2H, m), 1.58 (2H, m); MS (ES+) *m/e* 352 [M+H]⁺.

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Example 121 (Alternative Procedure 1)**6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-methyl-nicotinamide (E121)**

20 Sodium hydride (0.331g, 8.28 mmol, 60% disp. in mineral oil) was added to a stirred solution of 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) (1.5g, 6.9 mmol) in dimethyl sulfoxide (15 ml). After 0.5 hours, 6-chloro-N-methyl-nicotinamide (D10) (2.34g, 13.8 mmol) was added and the reaction mixture was heated to 100 °C for 18 hours. The reaction was allowed to cool to room temperature and then partitioned between ethyl acetate and water. The ethyl acetate layer was separated and the water layer washed with further volumes of ethyl acetate. The combined organic layers were then washed with water, brine, dried (Na₂SO₄) and then filtered. The mixture was concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with a mixture of .880 ammonia:ethanol:dichloromethane (0.5:4.5:95 then 1:9:90) to afford the title compound (E121) which then was recrystallised from toluene. ¹H NMR (DMSO-*d*₆) δ 8.56 (1H, dd, J = 2.4, 0.4Hz), 8.48 (1H, br m), 8.20 (1H, dd, J = 8.4, 2.4 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.03 (1H, dd, J = 8.4, 0.4 Hz), 6.91 (1H, d, J = 2.4Hz), 6.86 (1H, dd, J = 8.0, 2.4Hz), 2.87 - 2.77 (8H, m), 2.36 (4H, m), 2.00 (2H, m), 1.78 (2H, m), 1.58 (2H, m); MS (ES+) *m/e* 352 [M+H]⁺.

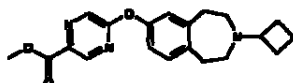
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Example 121 (Alternative Procedure 2)**6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-N-methyl-nicotinamide (E121)**

A mixture of *N*-methyl-6-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yloxy)-3-pyridinecarboxamide (D40) (1.04 g, 3.5 mmol) in dichloromethane (12 ml) containing acetic acid (240 μ L) at 0°C was treated dropwise with cyclobutanone (400 μ L, 5.3 mmol) and then stirred at room temperature for 1 hour. The mixture was then cooled to 0°C and treated portionwise with sodium triacetoxyborohydride (1.11 g, 5.3 mmol) and stirred at room temperature for 16 hours. The solution was carefully basified with 2*N* sodium hydroxide, stirred for 30 minutes and then extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulphate and concentrated *in vacuo*. The crude material was purified by column chromatography eluting with dichloromethane then a mixture of .880 ammonia: methanol: dichloromethane (1:9:90) to afford the title compound (E121); MS (ES+) *m/e* 352 [M+H]⁺.

Example 122

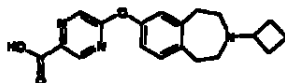
5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-pyrazine-2-carboxylic acid methyl ester (E122)



Sodium hydride (60% disp. in mineral oil, 332 mg, 8.3 mmol) was added to a stirred solution of 3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-ol (E3) (1.64 g, 7.5 mmol) in dimethyl formamide (4 ml). After 0.5 hours, a solution of 5-chloro-pyrazine-2-carboxylic acid methyl ester (1.95 g, 11.3 mmol) in dimethyl formamide (8 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with dichloromethane and the organic layer was washed with water, brine and dried over magnesium sulfate. The organic layer was filtered, concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (E122). MS (ES+) *m/e* 354 [M+H]⁺.

Example 123a

5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-pyrazine-2-carboxylic acid (E123a)



5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepin-7-yloxy)-pyrazine-2-carboxylic acid methyl ester (E122) (880 mg, 2.5 mmol) was dissolved in a mixture of ethanol (15 ml) and 2*N* sodium hydroxide (4 ml). The resulting mixture was stirred at room temperature for 0.5 hours and then concentrated *in vacuo* to remove the organic solvents. The reaction mixture was then acidified to pH 5 (2*N* hydrochloric acid) and the resulting precipitates were filtered, washed with water and dried under vacuum to afford the title compound (E123a); MS (ES+) *m/e* 340 [M+H]⁺.