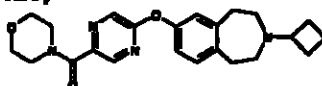


52
53**Example 123****1-[5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazin-2-yl]-1-morpholin-4-yl-methanone (E123)**

5

Step 1: 5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazine-2-carbonyl chloride

Thionyl chloride (5 ml) was added slowly to 5-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazine-2-carboxylic acid (E123a) (485 mg). The resulting reaction mixture was stirred at room temperature for 1 hour and then heated at reflux for a further 1 hour. The reaction mixture was cooled, diluted with toluene and concentrated *in vacuo* to afford the title compound which was used without further characterisation.

Step 2: 1-[5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazin-2-yl]-1-morpholin-4-yl-methanone

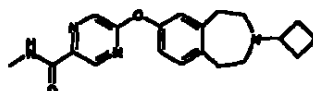
Morpholine (0.17 ml, 2.0 mmol) was added to a stirred solution of the product of step 1 (394 mg, 1 mmol) and diethylaminomethyl polystyrene (1.88 g, 3.2 mmol/g, 8 mmol) in dichloromethane (10 ml). The resulting mixture was allowed to stir at room temperature for 24 hours and the filtered. The filtrate was concentrated *in vacuo* and the resulting crude residue was purified column chromatography eluting with a mixture of .880 ammonia:ethanol:dichloromethane (1:9:90) to afford the title compound (E123). MS (ES+) *m/e* 409 [M+H]⁺.

Examples 124 and 126-127

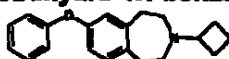
Examples 124 and 126-127 (E124 and E126-E127) were prepared from the product of Example 123, step 1 and the appropriate amine indicated in the table using an analogous method to that described for Example 123, step 2:

Example	Amine	LC/MS (M+H ⁺)
5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazine-2-carboxylic acid ethylmethyl amide (E124)	N-Ethylmethyl amine	381
1-[5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazin-2-yl]-1-piperidin-4-yl-methanone (E126)	Piperidine	407
1-[5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazin-2-yl]-1-pyrrolidin-4-yl-methanone (E127)	Pyrrolidine	393

Example 125

83
54**5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-pyrazine-2-carboxylic acid methyl amide (E125)**

- The product of Example 123, step 1 (1.59 mmol) in dry dichloromethane (10ml) was treated with methylamine (5ml, 10mmol, 2M solution in THF) and stirred at room temperature for 18 hours. The mixture was reduced *in vacuo* and the resulting crude material 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 basic fractions were then reduced and the crude product purified by column chromatography eluting with a mixture of .880 ammonia:ethanol:dichloromethane (0.2:1.8:98 and then 0.4:3.6:96) to afford the title compound (E125). ¹H NMR (CDCl₃) δ 8.91 (1H, d, 1.3 Hz), 8.26 (1H, d, 1.3 Hz), 7.61 (1H, br quartet, 4.8 Hz), 7.15 (1H, m), 6.92 (2H, m), 3.03 (3H, d, 5.1 Hz), 2.93 (4H, m), 2.79 (1H, m), 2.47 (4H, m), 2.08 (2H, m), 1.91 (2H, m), 1.70-1.62 (2H, m).

Example 128**3-Cyclobutyl-7-phenoxy-2,3,4,5-tetrahydro-1H-benzo[d]azepine (E128)**

- Sodium hydride (80% disp. in mineral oil, 96 mg, 2.4 mmol) was added to a stirred solution of 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) (435 mg, 2.0 mmol) and copper (I) bromide (402 mg, 2.8 mmol) in pyridine (10 ml) at 0 °C. After stirring for 0.5 hour at room temperature, iodobenzene (0.45 ml, 4.0 mmol) was added and the reaction mixture was heated to reflux for 24 hours. The reaction was allowed to cool, filtered and the filtrate then concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* and the resulting residue purified by column chromatography eluting with a mixture of .880 ammonia:ethanol:dichloromethane (0.25:2.25:97.5 to 1:9:90) to afford the title compound (E128); MS (ES⁺) m/e 294 [M+H]⁺.

Examples 129-138

- Examples 129-138 (E129-E138) were prepared from 3-cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-ol (E3) and the appropriate aromatic halide indicated in the table using an analogous method to that described for Example 128 (E128):

Example	Aromatic halide	LC/MS (M+H ⁺)
1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-phenyl]-1-morpholin-4-yl-methanone (E129)	1-(4-iodo-phenyl)-1-morpholin-4-yl-methanone (D22)	407