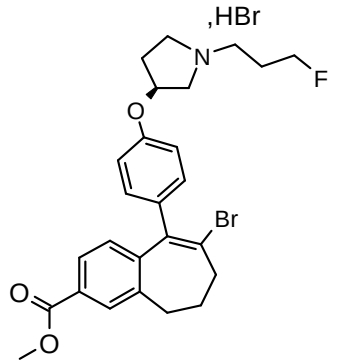
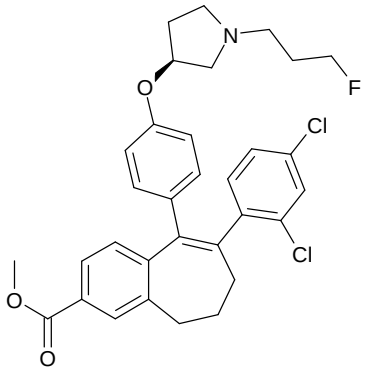


To a solution of methyl 9-(4-{[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxy}phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate (**G**) (13.93 g, 32.89 mmol), in DCM (150 ml) was added under argon pyridinium tribromide (15.78 g, 44.41 mmol). The reaction mixture was stirred for 1 hour at room temperature. Water (200 ml) was added, organic phase was then dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with a gradient of DCM/MeOH from 100/0 to 95/05 to give 16.4 g (85%) of methyl 8-bromo-9-(4-{[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxy}phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate hydrobromide (**H**) as a yellow meringue.
LC/MS (m/z, MH^+): 502

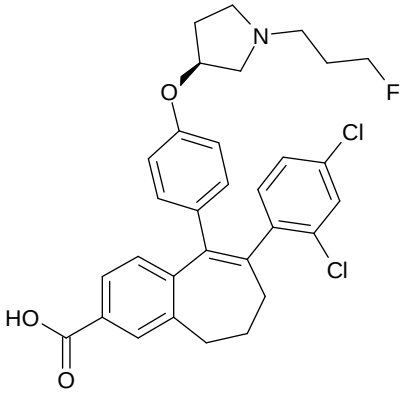
Intermediate (I). 6-(2,4-dichloro-phenyl)-5-{4-[1-(3-fluoro-propyl)-pyrrolidin-3-yloxy]-phenyl}-8,9-dihydro-7H-benzocycloheptene-2-carboxylic acid methyl ester.



To a solution of methyl 8-bromo-9-(4-{[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxy}phenyl)-6,7-dihydro-5H-benzo[7]annulene-3-carboxylate hydrobromide (**H**) (150 mg, 298.56 µmol), in dioxane (12 ml) and water (2 ml), was added 2,4-dichlorophenyl-boronic acid (62.67 mg, 328.41 µmol), Cs_2CO_3 (204.48 mg, 626.97 µmol), and $Pd(dppf)Cl_2$ (14.63 mg, 17.91 µmol). The reaction mixture was heated at 90°C for 3 hours, and partitioned between AcOEt and water. The phases were separated and the organic phase washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column

chromatography eluting with a mixture of DCM, acetonitrile and MeOH (96/2/2; V/V/V) to give 80 mg (47%) of 6-(2,4-dichloro-phenyl)-5-{4-[1-(3-fluoro-propyl)-pyrrolidin-3-yloxy]-phenyl}-8,9-dihydro-7H-benzocycloheptene-2-carboxylic acid methyl ester (**I**).
LC/MS (m/z, MH^+): 568

Compound (1). 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid



To a solution of 6-(2,4-dichloro-phenyl)-5-{4-[1-(3-fluoro-propyl)-pyrrolidin-3-yloxy]-phenyl}-8,9-dihydro-7H-benzocycloheptene-2-carboxylic acid methyl ester (**I**) (80 mg, 140.72 µmol) in MeOH (5 ml) was added a solution of NaOH (562.88 µl, 5 M) and the reaction mixture was heated at 60°C for 5 hours and the solvent removed under reduced pressure. The residue was taken up in water (10 ml) and aqueous HCl (5 M) added to pH 7. The slurry was extracted with DCM, dried over $MgSO_4$ and concentrated under reduced pressure. The solid was purified by column chromatography eluting with a mixture of DCM, acetonitrile and MeOH (90/5/5; V/V/V) to give 60 mg (77%) of 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid.
^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 1.68 (m, 1 H); 1,79 (dm, J=25.3 Hz, 2 H); 2.07 to 2.23 (m, 5 H); 2.38 (m, 1 H); 2.46 (t, J=7.2 Hz, 2 H); 2.52 (m, 1 H); 2.62 (m, 1 H); 2.55 to 2.89 (m, 3 H); 4.47 (td, J=6.2 and 47.6 Hz, 2 H); 4.72 (m, 1 H); 6.63 (d, J=8.9 Hz, 2 H); 6.71 (m, 3 H); 7.18 (d, J=8.4 Hz, 1 H); 8.26 (dd, J=2.0 and 8.4 Hz, 1 H); 7.58 (d, J=2,0 Hz, 1 H); 7.63 (d, J=8.4 Hz, 1 H); 7.79 (s, 1 H); 12.3 (m, 1 H)
LC/MS (m/z, MH+): 554

2 - <u>Evaluation of the efficacy of 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl) pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid combined with palbociclib against a subcutaneous breast cancer cell line xenograft in female nude mice</u>

CLAIMS

1. A combination comprising 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, or a pharmaceutically acceptable salt thereof, and palbociclib.

2. The combination according to claim 1, showing therapeutic synergy.

3. The combination according to claim 1 or claim 2, for use in the treatment of cancer.

4. The combination according to claim 3, wherein the cancer is breast cancer.

5. A pharmaceutical composition comprising 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, or a pharmaceutically acceptable salt thereof, and palbociclib, and at least one pharmaceutically acceptable excipient.

6. The pharmaceutical composition according to claim 5, wherein 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid, or a pharmaceutically acceptable salt thereof, and palbociclib are administered simultaneously, separately, or spaced out over a period of time.

7. The pharmaceutical composition according to claim 5 or claim 6, for use in the treatment of cancer.

8. The pharmaceutical composition according to claim 7, wherein the cancer is breast cancer.

9. Compound 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid or a pharmaceutically acceptable salt thereof for use in the treatment of cancer by co-administration with palbociclib.

10. Palbociclib for use in the treatment of cancer by co-administration with compound 6-(2,4-dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8,9-dihydro-7H-benzo[7]annulene-2-carboxylic acid or a pharmaceutically acceptable salt thereof.