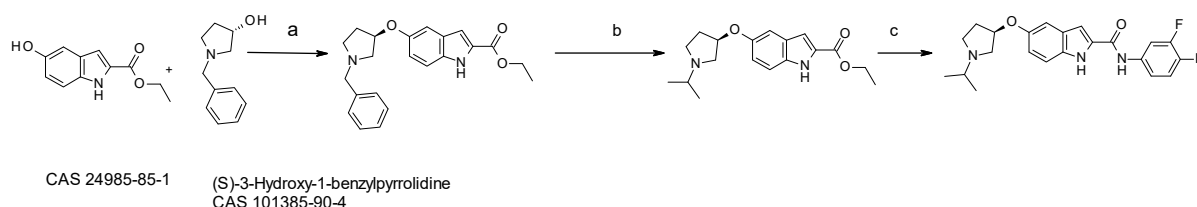


Supplementary Material 14: Supplementary Information

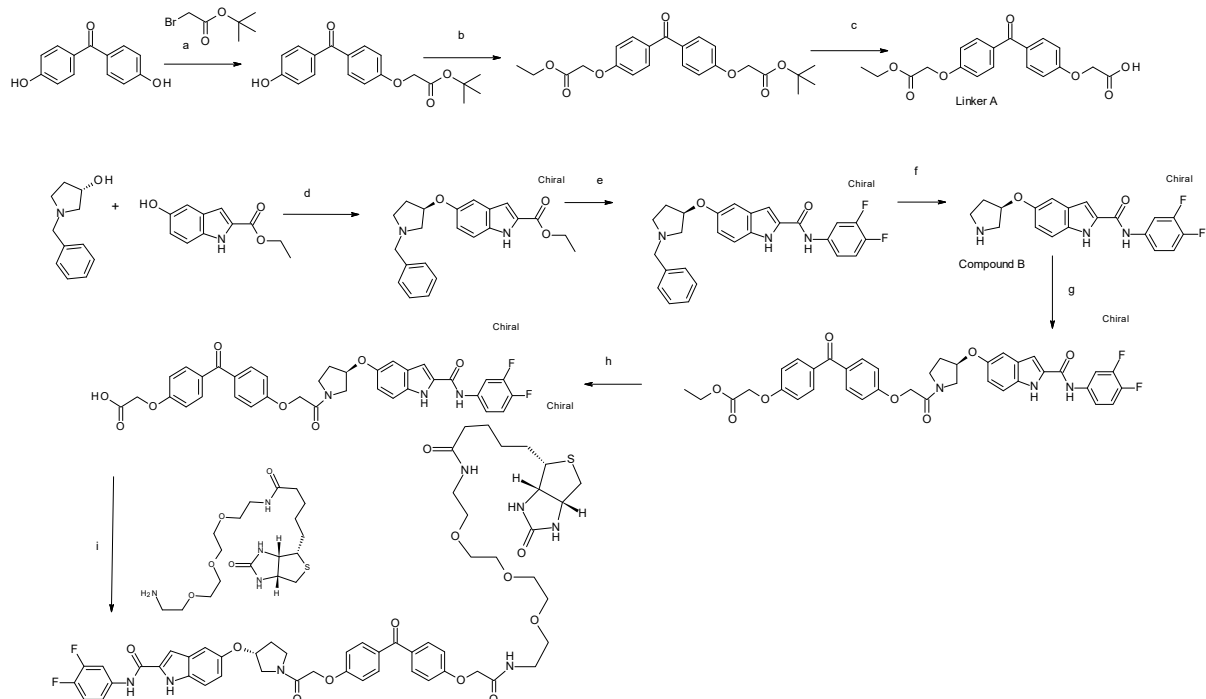
Indole-type GSMs – Indole-type GSMs such as 5-(1-Acetyl-piperidin-3-yl)-1*H*-indole-2-carboxylic acid (3,5-difluoro-phenyl)-amide (RO5254601) and 5-((*R*)-1-Isopropyl-piperidin-3-yl)-1*H*-indole-2-carboxylic acid (3-fluoro-phenyl)-amide (RO5218165) were prepared as described in the Roche patent WO2014/060386. In more detail, preparation of RO5254601 (example 46) is on page 58 in the patent, while preparation of the racemic precursor of RO5218165 (example 52) is mentioned on page 63. Chiral separation of the enantiomer, precursor of RO5218165, was performed using a chiral column and the data for the *R* enantiomer or RO5218165 (example 112) is on page 97 (Table 8) on the mentioned patent. 5-((*R*)-1-Isopropyl-pyrrolidin-3-yloxy)-1*H*-indole-2-carboxylic acid (3,4-difluoro-phenyl)-amide (RO5218863) and its photocrosslinkable derivative N-(3,4-difluorophenyl)-5-((*R*)-1-(2-(4-(4-(2,16-dioxo-20-((3*a*S,4*S*,6*a*R)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)-6,9,12-trioxa-3,15-diazaicosyloxy)benzoyl)phenoxy)acetyl)pyrrolidin-3-yloxy)-1*H*-indole-2-carboxamide RO6874585 were synthesised as described on the schemes below.

Preparation of 5-((*R*)-1-Isopropyl-pyrrolidin-3-yloxy)-1*H*-indole-2-carboxylic acid (3,4-difluoro-phenyl)-amide (RO5218863)



a) Ph_3P (1.5 eq), DIAD (1.5 eq), THF, 56%; b) i) H_2/Pd (10%) (1 eq) in EtOH/AcOH; ii) Iodo-Propane (1.5 eq), K_2CO_3 (2 eq) in DMF, 50°C, 48%; c) Me_3Al (2M in heptane) (4 eq), difluoroaniline (3 eq), dioxane reflux, overnight, 65%.

Preparation of N-(3,4-difluorophenyl)-5-((R)-1-(2-(4-(4-(2,16-dioxo-20-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)-6,9,12-trioxa-3,15-diazaicosyloxy)benzoyl)phenoxy)acetyl)pyrrolidin-3-yloxy)-1*H*-indole-2-carboxamide (RO6874585)



a) Bis (4-hydroxyphenyl)methanone (1 eq), tert-butyl 2-bromoacetate, NaH (1.1 eq), 2h, 0°C, 37%; b) ethyl 2-bromoacetate (1.0 eq), K₂CO₃ (2 eq), CH₃CN/NMP (30/1) (crude 100%); c) formic acid (20 eq), CH₂Cl₂, NMP (30/1), room temperature (r.t) overnight, 82%; d) ethyl 5-hydroxy-1*H*-indole-2-carboxylate (1 eq), (*S*)-1-benzylpyrrolidin-3-ol (1.3 eq), Ph₃P (1.5 eq), DIAD (1.5 eq), THF, 56%; e) Me₃Al (4 eq), difluoroaniline (3.2 eq), dioxane reflux, overnight, 69%; f) H₂, Pd/C10% (1 eq), HCl (0.01 eq) in THF, 25% at r.t overnight, 100%; g) 2-(4-(4-(2-ethoxy-2-oxoethoxy)benzoyl)phenoxy)acetic acid (1 eq), indole (1.2 eq), TBTU (1 eq), Hunig's base (5 eq), overnight, DMF, 53%; h) LiOH (1 eq), THF/H₂O/MeOH (5/2/1), 79%; i) (R)-2-(4-(4-(2-(3-(2-(3,4-difluorophenyl)carbamoyl)-1*H*-indol-5-yloxy)pyrrolidin-1-yl)-2-oxoethoxy) benzoyl)phenoxy) acetic acid (1 eq), N-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethyl-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide (CAS359860-27-8) (1 eq)), N-Methylmorpholine (3 eq), HBTU (1.5 eq), DMF, overnight, 80%.