Supporting Information for:

Synthetic Routes to the Neuropeptide Y Y1 receptor antagonist 1229U91 and related analogues for SAR studies and cell-based imaging.
Simon J Mountford¹, Mengjie Liu¹, Lei Zhang², Marleen Groenen³, Herbert Herzog², Nicholas Holliday³, Philip E Thompson*¹

¹Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences, 381 Royal Parade Parkville, VIC 3052, Australia
²Neuroscience Research Program, Garvan Institute of Medical Research, St. Vincent’s Hospital, Darlinghurst, NSW 2010, Australia
³Institute of Cell Signalling, School of Biomedical Sciences, University of Nottingham, Queen’s Medical Centre, Nottingham, UK
Table of Contents

Scheme S1. General strategy for synthesis of 1229U91. PG1 and PG2 refer to protecting groups

Figure S1. HPLC trace of crude products from (a) synthesis of 1229U91 using TMP as base, and (b) synthesis of V and VI.

Figure S2. HPLC trace of crude products in synthesis of 10 according to Figure 5. (a) Coupling with TMP. (b) Coupling with DIEA.

Figure S3. Synthesis of III according to Scheme 2. HPLC trace of intermediates in (a) 16 (b) 17 (PhSiH (c) Pd(PPh3)4 in CHCl3/AcOH/NMM (d) 18 (e) III

Figure S4. LC-MS analysis [RP-HPLC with UV detection at 214 nM and ESI-MS (m/z range 200-2000)] of 1229U91 linear intermediates I – 9.

Figure S5. LC-MS analysis [RP-HPLC with UV detection at 214 nM and ESI-MS (m/z range 200-2000)] of 1229U91 analogues I - X.

Figure S6. Dose-response curves for 1229U91 and analogues in competition binding assays. (see also Table 2)

Figure S7. Studies of 1229U91, III and VIII in Y1-transfected HEK293 cells. (A) Dose-response curves in competition binding assays v. PYY. (B) Antagonist activity versus NPY-induced arrestin recruitment
Scheme S1  General strategy for synthesis of 1229U91. PG1 and PG2 refer to protecting groups
Figure S1  HPLC trace of crude products from (a) synthesis of 1229U91 using TMP as base, and (b) synthesis of V and VI.
Figure S2  HPLC trace of crude products in synthesis of 10 according to Figure 5. (a) Coupling with TMP. (b) Coupling with DIEA.
Figure S3 according to Scheme 2. HPLC trace of intermediates in synthesis of III (a) 16 (b) 17 using Pd(PPh₃)₄ in CHCl₃/AcOH/NMM (c) 17 using Pd(PPh₃)₄ & PhSiH (d) 18 (e) III
Figure S4. LC-MS analysis [RP-HPLC with UV detection at 214 nM and ESI-MS (m/z range 200-2000)] of 1229U91 linear intermediates 1 – 9. (a) 1; (b) 2; (c) 3[crude]; (d) 4; (e) 5.
Figure S4. LC-MS analysis [RP-HPLC with UV detection at 214 nM and ESI-MS (m/z range 200-2000)] of 1229U91 linear intermediates 1 – 9. (f) 6; (g) 7; (h) 8; (i) 9.
Figure S5 LC-MS analysis [RP-HPLC with UV detection at 214 nM and ESI-MS (m/z range 200-2000)] of 1229U91 analogues I - X. (a) 1229U91; (b) I; (c) II; (d) III; (e) IV.
Figure S5 cont. LC-MS analysis [RP-HPLC with UV detection at 214 nM and ESI-MS (m/z range 200-2000)] of 1229U91 analogues I - X. (f) V; (g) VI; (h) VII; (i) VIII; (j) IX.
Figure S6 Dose-response curves for 1229U91 and analogues in competition binding assays.
Figure S7 Studies of 1229U91, III and VIII in Y1-transfected HEK293 cells. (A) Dose-response curves in competition binding assays v. PYY. (B) Antagonist activity versus NPY-induced arrestin recruitment.