Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information for:

Synthetic Routes to the Neuropeptide Y Y1 receptor antagonist 1229U91 and related analogues for SAR studies and cell-based imaging.

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

a

b

VI

V

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

a

b

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

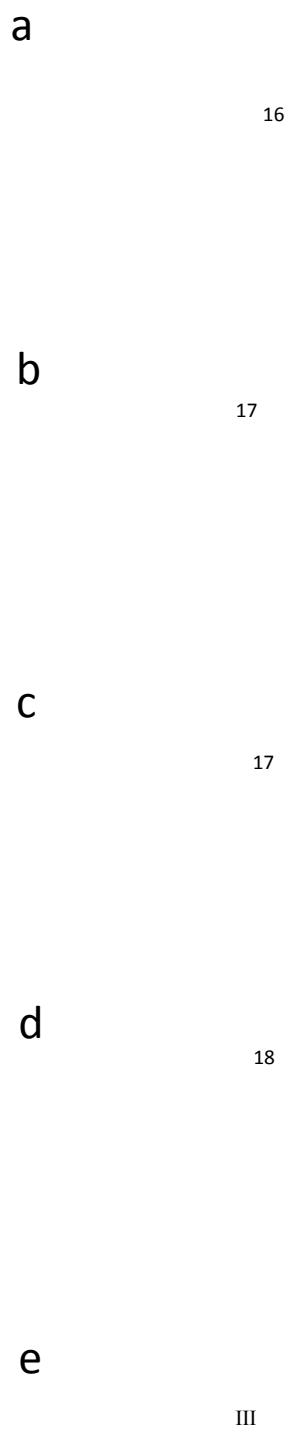

Figure S3 according to Scheme 2. HPLC trace of intermediates in synthesis of III (a) 16 (b) 17 using $Pd(PPh_3)_4$ in $CHCl_3$/AcOH/NMM (c) 17 using $Pd(PPh_3)_4$ & PhSiH (d) 18 (e) III

a

b

C*

d

e

Figure S4 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**.

f

g

h

i

Figure S5 cont. 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**.

a

b

c

d

e

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**.

f

g

h

i

j

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**.

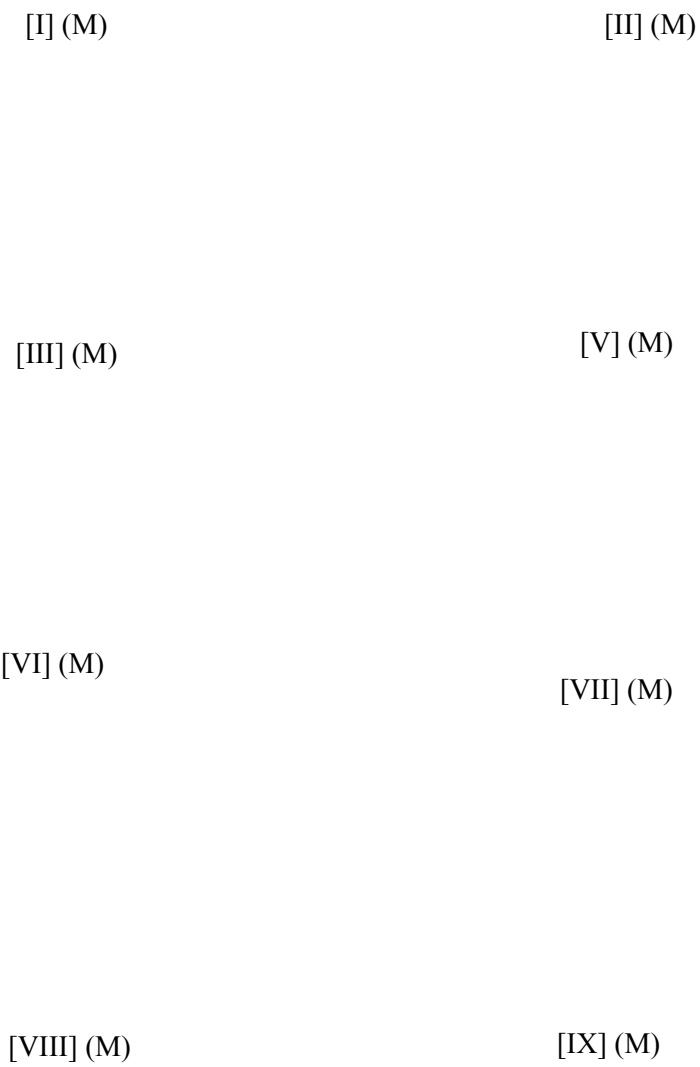

Figure S6 Dose-response curves for 1229U91 and analogues in competition binding assays.

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.