Table S1. Biological assays used to evaluate the β-catenin activity.

Entry	Compd	Assay
1	FH535	TOPFLASH luciferase activity
2	GW9662	TOPFLASH luciferase activity
3–6	FH535 analogs	Luciferase-based TOPFlash assay
7	MSAB	TOP-Luc activity assay
8–9	MSAB analog	TOPFlash assay
10	LF3	AlphaScreen
11	LF3 analog	AlphaScreen
12–14	iCRTs	Coimmunoprecipitation (coIP)
15	ZINC02092166	Wnt-responsive luciferase reporter assay
16,17	ZINC analogs	Wnt-responsive luciferase reporter assay
18	PNU-74654	ITC, NMR, Luciferase reporter system for Tcf-4 transactivation
19	UU-T01	AlphaScreen, fluorescence polarization (FP)
20, 21	UU-T02/03	Fluorescence polarization (FP)
22	HI-B1	β-catenin/TCF4 luciferase activity
23–26	PKF	Tcf4 fragment (residues 8–54) fused to glutathione-S-transferase (GST), anti-GST antibody, and alkaline phosphatase (AP)-conjugated secondary antibody
27	Henryn	Purified recombinant proteins β-catenin and TCF4 (0.5μg) were incubated with Henryin
28	BC21	FP-based assay developed for that purpose (unpublished data)
29,30	StAx-35, StAx-35R	Pull down assay. Competitive binding to Immobilized GST-tagged CBD of TCF4(1–52).
31	Carnosic acid	His-HD2 to glutathione S-transferase (GST)-ARD (immobilized on glutathione-coated microplates),
32	Pyrrolidinio	Alpha screen, ITC
33	hsBCL9CT-24	LEF/TCF reporter assay robust ALPHA competition assays were developed to determine the potency of inhibitors in disrupting the b-cat/BCL9 interaction.

Table S2. Summary of the activitiies of compounds **1–33.**

Comp	Label	Assay
1	FH535	Low micromolar LC_{50} values as Inhibitors of colon, lung and liver carcinomas expressing high or active Wnt/b-catenin, antagonist of PPAR◎ and PPAR.
2	GW9662	Specific PPAR◎ antagonistic, unable to antagonize PPAR◎ and to inhibit the Wnt/◎-catenin pathway.
3	FH535 analog	Superior to FH535 in the [^{3}H]-thymidine incorporation assay, weak activity in the TOPFlash assay.
6	FH535 analog	Weak activity in the [3H]-thymidine incorporation assay, comparable to FH535 in the TOPFlash assay.
7	MSAB	Decreased cell viability of Wnt-dependent HCT116, HT115 and H23 cells; inhibited tumor growth in xenograft mice model after 2 weeks treatment at 10–20 mg/kg.
8–9	MSAB analogs	Inhibition of Wnt reporter with an IC_{50} value of 7.0 μM, reducion the c-Myc levels, inhibition of HCT116 with IC_{50} of 20.2 μM.
10	LF3	IC_{50} of 1.65 and 1.82 ◎M in the AlphaScreen and ELISA assays.
11	LF3 analog	Showed inhibitory activity as potent as that of LF3 in the AlphaScreen and ELISA assays.
12–14	iCRTs	Selective disruption β-catenin/Tcf4 interactions; efficacy comparable with 5-FU in human CRC
15	ZINC02092166	Inhibition the TOPFlash luciferase activity in pcDNA3.1-β-catenin transfected HEK293 and SW480 cells (IC_{50} of 0.86 and 0.71 μM); SW480, HCT116, and HT29 cell growth inhibition with low micromolar IC_{50} values.
16,17	ZINC analog	Similar to that of ZINC02092166 In the AlphaScreen and FP assays.
16,17	ZINC analog	IC_{50} of 26 ◎M in the TOPFlash and FOPFlash luciferase reporter assay; i SW480 and HCY116 cancer cell growth inhibition with IC_{50} of 2.0 and 31 M.
18	PNU-74654	Kd of 450 nM in direct binding ITC experiments; specific inhibition for Tcf-4 transactivation in the cellular luciferase reporter system.
19	UU-T01	Ki of 3.14 ◎M as disruptor of ◎-catenin/Tcf interactions. ITC, Kd of 0.531 ◎M to WT -catenin, AlphaScreen Ki of 7.60 ◎M
20	UU-T02	Ki value of 1.32 μM against the WT ◎-catenin; complete disruption of the β-catenin/Tcf PPI.
21	UU-T03	IC_{50} of 28.7 mM in SW480 cells and IC_{50} of 37.6 ◎M in Wnt-activated HEK293 cells in the Wnt-responsive luciferase reporter assay.
22	HI-B1	β-catenin/Tcf4 interction inhibition in vitro in DLD-1 and Caco-2 cell lines; Reduction of growth of a PDX colon cancer with a high expression level of β-catenin.
23–25	PKF	Inhibition of Tcf4/◎-catenin association IC_{50} values of 2, 4, 0.8 and 0.64 mM, respectively.
26	PKF	In MM blocked expression of Wnt target genes and induced cytotoxicity, In xenograft models of hMM, inhibited tumor growth and prolonged survival.
27	Henryn	Reduced the expression of Cyclin D1 and c-Myc, and induced G1/S phase arrest in HCT116 cells by impairing the association of β-catenin/Tcf4.
28	BC21	Inhibitor of the β-catenin/Tcf4 driven luciferase activity. Decreased the HCT116 cell viability; at 5 ◎M inhibited >80% colony forming activities

29,30	StAx-35, StAx-35R	Both fStAx-35 and -35R suppressed luciferase activity. Proliferation of DLD1 and SW480 cells was blocked by aStAx-35R.
31	Carnosic acid	inhibited the binding of β-catenin to BCL9 in vitro, and β-catenin-dependent transcription in CRC cell
32	Pyrrolidinio	Selectively disruption β-catenin/BCL9 in cells overexpressing the Wnt signaling with IC_{50} values in the low micromolar range
33	hsBCL9CT-24	Kd value of 4.21 nM In the HTRF binding assay. Kd value of 4.73 nM in disrupting the ◎-catenin/BCL9 interaction.