Figure S1. Six compounds increased Treg cells percentage in T cell differentiation marked by Foxp3.

Naive CD4+ T cells sorted from B6 Foxp3-GFP mice were cultured with or without compounds [the concentration is 100 nM (compounds 1-23) or 1 μM (compounds 24-34)] in the absence or presence of TGF-β (5 ng/mL) for 3 days. The increased percentage of Foxp3 was analyzed by flow cytometry. One typical staining of three independent ex-periments was shown. SSC=side-scatter.
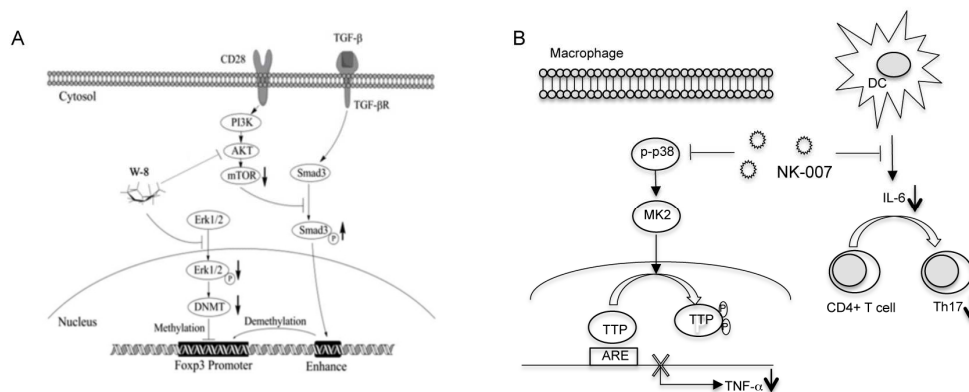

Figure S2. Anti-inflammatory mechanisms of compounds 31 (W-8) and 18 (NK-007) were summarized.

The anti-inflammatory mechanisms of 31 (W-8) and 18 (NK-007) demonstrated in our recently works were summarized to facilitated understanding in these DCB-3503 derivatives.

Experimental Procedures.

Mice. Male C57BL/6 or BALB/c mice (body weight 18-22 g) were purchased from Vital River laboratory Animal Technology Co.. All mice were fed with standard food and received humane care in accordance with the animal care provision. Ethics Statement: All experimental procedures and treatments using animals (mice) were

approved by the Institutional Animal Care and Use Committee at College of Life Sciences of Nankai University, permit number (2012-1179). All surgeries were performed under sodium pentobarbital anesthesia.

Materials. Anti-mouse CD3 mAb (clone 145-2C11), anti-mouse CD28 mAb (clone PV1) were from Sungene (Tianjin, P.R. China). Recombinant mouse (rm) IL-2 and TGF-□ were purchased from R&D Systems (Minneapolis, MN). LPS (Escherichia coli serotype 0111:B4), MTT were obtained from Sigma (St. Louis, MO). Mouse TNF-α ELISA kit was purchased from Biolegend (San Diego, CA).

Cell Culture. Murine splenocytes or CD4$^+$ T cells were maintained in RPMI 1640 (HyClone, Logan, UT) containing 10% FBS, 100 units/mL penicillin and streptomycin (Gibco, Renfrewshire, UK); Raw 264.7 murine macrophages (ATCC, Rockville, MD, USA) were grown in DMEM (HyClone, Logan, UT) containing 10% FBS, 100 units/mL penicillin, and 100 μg/mL streptomycin at 37°C in a 5% CO_2 humidified atmosphere.

Chemistry. Reagents were purchased from commercial sources and used as received. All anhydrous solvent were dried and purified by standard techniques just before use. Reaction progress was monitored by thin-layer chromatography on silica gel GF-254 with detection by UV. Melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and the

thermometer was uncorrected. ^{1}H NMR spectra were obtained by using Bruker AC-P

400 spectrometers. Chemical shift values (δ) were given in ppm and were downfield

from internal tetramethylsilane. ^{13}C NMR spectra were recorded by using Bruker AV

400 (100 MHz) with $CDCl_3$ or DMSO-d_6 as a solvent. Chemical shifts (δ) were

reported in parts per million using the solvent peak. High-resolution mass spectra were

obtained with an FT-ICR MS spectrometer (Ionspec, 7.0 T).

Synthetic Procedure for 2,3,6,7-Tetramethoxyphenanthrene-9-carbaldehyde (36).

The mixture of alcohol **35**[20] (5 g, 15.23 mmol), silica (10 g) and

pyridiniumchlorochromate (PCC, 9.85 g, 45.69 mmol) in CH_2Cl_2 (150 mL) was stirred

at room temperature for 10 h, and then filtered. The filtrate was concentrated by rotary

evaporation and purified by flash column chromatography to give compound **36** (4.02 g,

80%) as a yellow powder: mp 227–228 °C (lit.[21] 210–214 °C); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 10.27 (s, 1H), 8.98 (s, 1H), 8.07 (s, 1H), 7.80 (s, 1H), 7.78 (s, 1H), 7.35 (s,

1H), 4.17 (s, 3H), 4.14 (s, 3H), 4.11 (s, 3H), 4.07 (s, 3H).

Synthetic   Procedure   for   Methyl

6-(((2,3,6,7-tetramethoxyphenanthren-9-yl)methyl)amino)hexanoate   (32). The

mixture of aldehyde **36** (1.2 g, 3.68 mmol), Et_3N (0.42 g, 4.12 mmol), AcOH (5 d) and

methyl 6-aminohexanoate hydrochloride (0.74 g, 4.05 mmol) in CH_2Cl_2 (40 mL) was

refluxed for 6 h. The solution was cooled to room temperature and concentrated *in*

vacuo. The result solid was dissolved in MeOH (30 mL), followed addition of AcOH (5

d) and $NaBH_3CN$ (0.47 g, 7.40 mmol). The solution was stirred at room temperature for 3 h, and concentrated *in vacuo*. To the result mixture was added CH_2Cl_2 (30 mL), H_2O (20 mL) and saturated $NaHCO_3$ solution (10 mL), and the two layers were separated. The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography to give compound **32** (1.14 g, 68%) as a yellow powder: mp: 104–106 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.67 (s, 1H), 7.58 (s, 1H), 7.42 (s, 1H), 7.18 (s, 1H), 4.16 (s, 2H), 4.08 (s, 3H), 4.07 (s, 3H), 4.06 (s, 3H), 4.02 (s, 3H), 3.64 (s, 3H), 2.79 (t, J = 8.0 Hz, 2H), 2.28 (t, J = 8.0 Hz, 2H), 1.71–1.65 (m, 2H), 1.64–1.57 (m, 2H), 1.40–1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 149.3, 149.0, 148.9, 148.8, 130.1, 126.0, 125.1, 125.0, 124.8, 124.3, 108.3, 104.7, 103.4, 102.8, 56.1, 56.0, 56.0, 55.9, 51.7, 51.5, 49.2, 33.9, 29.2, 26.8, 24.7; ESI-HRMS (m/z): calcd. for $C_{26}H_{33}NO_6Na$ $[M+Na]^+$ 478.2200; found 478.2208.

Foxp3-GFP$^+$ cells detection assay

Naïve CD4$^+$ T cells isolated from spleen of C57BL/6 Foxp3-GFP transgenic mice were treated with anti-CD3 and anti-CD28 in the presence of IL-2 (20 ng/mL) and TGF-☐ (5 ng/mL) to induce expression of Foxp3. All these 34 compounds were added to the culture with concentration of 100 nM for 3 days, and cells were then used for GFP detection by flow cytometry (FACS calibur (BD)) upon gating on CD4$^+$ T cells. Promoting ratio was calculated as the following formula: (GFP$^+$ cell percentage of compound treated - GFP$^+$ cell percentage of vehicle control) / GFP$^+$ cell percentage of vehicle control × 100%.

TNF-α□ detection assay

Splenocytes were isolated from BALB/c mice and suspended in 1640 with 10% FBS. Cells were added to 96-microwell plates coated with different compounds for 2 h prior to LPS (100 ng/mL) stimulation. Supernatants were collected at 4 or 24 h post culture and frozen at -20°C until analysis. Raw 264.7 cells were grown in DMEM supplemented with 10% FBS and these compounds were added 2 hours prior to LPS stimulation. Supernatants were collected at 6 hours after LPS treatment and stored at -20°C until analysis. TNF-α□level in the supernatants was measured by ELISA. Inhibition percentage was calculated as the following formula: (TNF-α level of vehicle control - TNF-α level of compound treated) / TNF-α level of vehicle control × 100%.

Cell Survival assay

Cell survival rate was evaluated by a microculture tetrazolium assay using MTT. Briefly, cells were added to 96-microwell flat-bottom plates with different compounds or DMSO control for 2 h prior to LPS stimulation. After 48 h, 50uL of MTT stock solution (2 mg/mL in PBS) was added to 150uL cell cultures for 4 h incubation at 37°C. Plates were then centrifuged and culture medium was removed. Precipitated formazan was dissolved in 150uL DMSO. Results were read within 15 min in a spectrometer at 570 nm, and the means of triplicates were calculated. Cell survival rate is expressed as cell viability percentage of control samples and was calculated as the following formula: (cell numbers of compound treated / cell numbers of vehicle control)× 100%. The

inhibitory concentration (IC50) was calculated using Graphpad Prism.

Statistic

All offline data were measured by investigators blinded to treatment. Results were presented as Mean ± SD. Significant statistical difference was defined at $P<0.05$. The SPSS 13.0 software package was used for statistical analysis. An independent 2-sample Student's t-test was used to compare all experimental measurements. Throughout the text, figures, and legends, the following terminology is used to show statistical significance: *$P<0.05$, ** $P<0.01$, *** $P<0.001$.