**Supplementary Table 1.** The sequences of oligonucleotide primers.

| Genes                        | Sequence                                      |
|------------------------------|-----------------------------------------------|
| rat actin forward            | CGAGTACAACCTTCTTGCAG                          |
| rat actin reverse            | GAGTCCTTCTGAACCATACC                         |
| tubulin (rat, mouse) forward | TAGCAGAGATCAACATGACC                         |
| tubulin (rat, mouse) reverse | GGCAGCAAGCATTGATTTA                          |
| PGC-1α (rat, mouse) forward  | ACTGAGCTACCTTGGGAGATG                        |
| PGC-1α (rat, mouse) reverse  | TAAGAATTTCCTGTTGGGAC                        |
| Cytochrome-C (rat, mouse) forward | GGAGGCAAGCATAAGACCT                        |
| Cytochrome-C (rat, mouse) reverse | TCCATCACGGATATTCTCCTCC                      |
| G6Pase (rat, mouse) forward  | ACACCGACTACTACAGGAC                         |
| G6Pase (rat, mouse) reverse  | CCTGAAGAGAGGCAAGGAT                         |
| PEPCK (rat, mouse) forward   | CATATGCTGATCTGGGACCA                         |
| PEPCK (rat, mouse) reverse   | CAAACTTCACAGGCAATGTG                        |
| ERRα (rat, mouse) forward    | ATCTGCTGTGTTGGACACT                         |
| ERRα (rat, mouse) reverse    | AGAAGCCTGGGATGCTCTTTG                      |
| mouse cox5b forward          | GCTGCACTGTTGAAAGGAC                         |
| mouse cox5b reverse          | CAGCGTAGGTGCTCCACAG                         |
| rat cox5b forward            | GGAGATCATGATGAGAC                          |
| rat cox5b reverse            | CTCTTCAGATGAGCCCAC                         |
| mouse glut4 forward          | GTGAUGAGACACTTGTCCTG                        |
| mouse glut4 reverse          | CCAGCAGGTGATGTGAATG                        |
| rat glut4 forward            | CTCATGGCCTAGCATAATG                        |
| rat glut4 reverse            | GGCGATTTTCTCCCACATAC                      |
| mouse AOX forward            | GCTGCACTGTTGAAAGGAC                         |
| mouse AOX reverse            | AATGAACTCTTGGTCTCAGG                       |
| rat AOX forward              | CCAATCAAGCAATGTCTCGG                      |
| rat AOX reverse              | CGCTGTAATGTCAGCTAG                         |
| mouse NRF1 forward           | TGGAGGAGACAGGACTGGA                       |
| mouse NRF2 reverse           | CAGCCAGATGGGAGAATG                        |
| rat NRF1 forward             | GTATGCTAAGTGCTGAA                          |
| rat NRF2 reverse             | GGTTTGGAGGATGATG                         |
| mouse UCP-3 forward          | TGCCCTCTACGACTCTGTAAGGAC                   |
| mouse UCP-3 reverse          | CTCTCTCTCTCTTTGGGAT                       |
| mouse ATPase-F1α forward     | TCCATGCTCTCTTTACACT                        |
| mouse ATPase-F1α reverse     | CCAAGTGTAAGAGAGAC                        |
| mouse CPT-1 forward          | ATAGCACGCTATGTCGTCTCC                     |
| mouse CPT-1 reverse          | TGCCATCATGCTGCTTC                         |
| mouse MCAD forward           | AGCTGCTAGTGAGGGAGAC                      |
| mouse MCAD reverse           | TCGCGATTCTGCGAGCA                        |
| mouse LCAD forward           | TCACCAACAGCTGAGCTGCA                      |
| mouse LCAD reverse           | CCAAAAAAGAGGTCAATGACCCATG                  |
| mouse 16S RNA mtDNA forward  | CCGCAAGGGAAGAGAGGAGCAAG                    |
| mouse 16S RNA mtDNA reverse  | TGGTTGTTTGGGAGTTT                        |
| mouse hexokinase 2 gene, intron 9 forward | GGCAAGCTCTCTGATTTTAGT                  |
| mouse hexokinase 2 gene, intron 9 reverse | GGGAAACACAAAAGACCTTTCTCGG             |
Supplementary Table 2. Body weight of SD rats gavaged with ZLN005 for 14 days. D: day.

| Sex     | Time(day) | vehicle (g) | 75 mg/kg (g) |
|---------|-----------|-------------|--------------|
| Female  | D1        | 201.00±7.75 | 203.50±8.35  |
| (n=4)   | D7        | 222.25±12.69| 219.75±10.78 |
|         | D14       | 234.50±18.59| 231.75±16.38 |
|         | △D7       | 21.25±8.81  | 16.25±2.99   |
|         | △D14      | 33.50±14.06 | 28.25±8.73   |
| Male    | D1        | 257.00±12.11| 256.00±9.83  |
| (n=4)   | D7        | 300.75±17.65| 292.25±15.26 |
|         | D14       | 323.25±19.03| 318.75±25.91 |
|         | △D7       | 43.75±8.06  | 36.25±8.18   |
|         | △D14      | 66.25±8.54  | 62.75±18.82  |
**Supplementary Table 3.** Blood routine examination of SD rats gavaged with ZLN005 for 14 days.

| Sex   | Variable     | Vehicle      | 75 mg/kg     |
|-------|--------------|--------------|--------------|
| Female (n=4) | WBC(10^9/L) | 4.860±0.87   | 4.46±0.72    |
|        | RBC(10^12/L) | 6.91±0.31    | 6.68±0.19    |
|        | HGB (g/L)    | 12.93±0.46   | 12.55±0.31   |
|        | HCT(%)       | 38.18±1.53   | 37.25±0.93   |
|        | MCV(μL)      | 55.25±1.32   | 55.83±1.79   |
|        | MCH(pg)      | 18.75±0.31   | 18.83±0.48   |
|        | MCHC (g/L)   | 33.90±0.37   | 33.68±0.29   |
|        | RDW(μL)      | 11.70±0.51   | 13.53±1.13** |
|        | PLT(10^3/μL) | 1188.50±73.84| 1246.75±84.65|
|        | MPV (μL)     | 8.10±0.14    | 8.00±0.29    |
|        | %NEUT        | 16.15±8.80   | 14.90±6.22   |
|        | %LYM         | 79.35±9.47   | 81.38±7.22   |
|        | %MONO        | 1.68±0.29    | 1.75±0.75    |
|        | %EOS         | 1.78±0.68    | 1.05±0.17    |
|        | %BASO        | 0.18±0.10    | 0.18±0.13    |
|        | %LUC         | 0.85±0.21    | 0.78±0.13    |
|        | PT(sec)      | 8.43±0.12    | 8.50±0.14    |
| Male (n=4) | WBC(10^9/L) | 5.28±1.58    | 6.44±1.62    |
|        | RBC(10^12/L) | 7.68±0.26    | 7.28±0.29    |
|        | HGB (g/L)    | 14.48±0.39   | 13.88±0.51   |
|        | HCT(%)       | 43.10±1.10   | 41.68±1.64   |
|        | MCV(μL)      | 56.13±0.50   | 57.28±1.33   |
|        | MCH(pg)      | 18.85±0.17   | 19.03±0.48   |
|        | MCHC (g/L)   | 33.60±0.22   | 33.28±0.21   |
|        | RDW(μL)      | 11.75±0.65   | 12.35±0.58   |
|        | PLT(10^3/μL) | 1253.00±87.48| 1269.50±69.81|
|        | MPV (μL)     | 7.78±0.15    | 7.58±0.17    |
|        | %NEUT        | 15.18±4.99   | 21.65±6.46   |
|        | %LYM         | 81.45±4.85   | 74.48±7.53   |
|        | %MONO        | 1.65±0.26    | 2.00±0.87    |
|        | %EOS         | 0.90±0.22    | 0.78±0.22    |
|        | %BASO        | 0.15±0.10    | 0.20±0.08    |
|        | %LUC         | 0.70±0.34    | 0.88±0.49    |
|        | PT(sec)      | 8.90±0.29    | 8.95±0.13    |

*, p < 0.05, **, p < 0.01 compared with vehicle group. WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean cell haemoglobin; MCHC: mean cell haemoglobin concentration; RDW: blood cell distribution width; HDW: hemoglobin distribution width; PLT: platelets; MPV: mean platelet volume; NEUT: neutrophilic granulocyte; LYM: lymphocyte; MONO: monocyte; EOS: eosinophilic granulocyte; BASO: basophile granulocyte; LUC: large unstained cells; PT: prothrombin time.
### Supplementary Table 4. Plasma metabolites of SD rats gavaged with ZLN005 for 14 days.

| Sex       | Variable | Vehicle | 75 mg/kg |
|-----------|----------|---------|----------|
|           | ALT (U/L) | 39.50±5.00 | 43.25±5.56 |
| Female    | AST (U/L) | 98.50±14.11 | 118.00±4.24* |
| (n=4)     | ALP (U/L) | 112.25±13.72 | 119.50±34.22 |
|           | BUN (mmol/L) | 7.04±1.50 | 7.69±1.00 |
|           | CREA (µmol/L) | 27.75±1.26 | 25.50±1.29* |
|           | GLU (mmol/L) | 7.14±0.24 | 7.15±0.32 |
|           | TBIL (µmol/L) | 2.08±0.60 | 2.09±0.50 |
|           | CHOL (mmol/L) | 1.64±0.30 | 2.12±0.19 |
|           | TP (g/L) | 54.50±1.73 | 55.00±2.83 |
|           | ALB (g/L) | 41.50±3.11 | 41.50±1.00 |
|           | CK (U/L) | 523.00±84.19 | 781.25±81.06** |
|           | TG (mmol/L) | 0.31±0.06 | 0.31±0.06 |
|           | GGT (U/L) | 0.94±0.15 | 1.12±0.11 |
|           | DBIL (µmol/L) | 1.31±0.33 | 1.38±0.34 |
|           | A/G | 3.26±0.67 | 3.11±0.36 |
|           | GLO (g/L) | 13.00±1.83 | 13.50±1.91 |
|           | Na (mmol/L) | 137.18±1.32 | 137.08±0.88 |
|           | K (mmol/L) | 4.65±0.31 | 4.88±0.08 |
|           | Cl (mmol/L) | 108.05±1.70 | 107.28±1.41 |
| Male      | ALT (U/L) | 41.50±4.93 | 59.75±23.08 |
| (n=4)     | AST (U/L) | 93.75±12.69 | 107.00±24.23 |
|           | ALP (U/L) | 213.50±57.67 | 250.25±19.72 |
|           | BUN (mmol/L) | 6.43±0.46 | 6.42±0.77 |
|           | CREA (µmol/L) | 23.25±0.96 | 23.75±1.26 |
|           | GLU (mmol/L) | 7.52±0.25 | 7.32±0.56 |
|           | TBIL (µmol/L) | 1.27±0.52 | 1.61±0.56 |
|           | CHOL (mmol/L) | 0.91±0.27 | 1.40±0.18 |
|           | TP (g/L) | 56.25±1.26 | 53.50±1.91 |
|           | ALB (g/L) | 41.25±0.50 | 40.25±1.50 |
|           | CK (U/L) | 465.00±176.92 | 299.50±73.76 |
|           | TG (mmol/L) | 0.31±0.08 | 0.33±0.07 |
|           | GGT (U/L) | 0.69±0.17 | 0.60±0.10 |
|           | DBIL (µmol/L) | 0.99±0.43 | 1.15±0.51 |
|           | A/G | 2.76±0.13 | 3.05±0.24 |
|           | GLO (g/L) | 15.00±0.82 | 13.25±0.96* |
|           | Na (mmol/L) | 140.00±0.70 | 139.65±0.99 |
|           | K (mmol/L) | 4.40±0.15 | 4.42±0.19 |
|           | Cl (mmol/L) | 107.63±1.70 | 106.60±2.81 |

*, p < 0.05, **, p < 0.01 compared with vehicle group. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; BUN: blood urea nitrogen; CREA: creatinine; GLU: glucose; TBIL: total bilirubin; CHOL: total cholesterol; TP: total protein; ALB: albumin; CK: creatine phosphokinase; TG: triglycerides; GGT: gamma-glutamyl transpeptidase; DBIL: direct bilirubin; A/G: albumin-globulin ratio; GLO: globulin.
Supplementary Figure 1. Identification of ZLN027 and ZLN005 by HTS in HEK293 cells. A: Compound structure of ZLN027. B: Effect of ZLN027 and ZLN005 in HEK293 PGC-1α-luc stable cells. FSK (5 μM) and DEX (100 nM) as positive control. Luciferin signal was normalized by cell survival of the cells. C: Effect of ZLN027 and ZLN005 in luciferase enzyme, black circles, = ZLN005, white squares, = ZLN027. D-E: 24 h SRB results of ZLN027 and ZLN005 on HEK293 PGC-1α-luc stable cells and L6 myotubes.*, p < 0.05, **, p < 0.01 compared with DMSO.
Supplementary Figure 2. ZLN005 has no effect on AMPK pathway in primary hepatocytes. A: Effect of ZLN005 on the AMPK, CREB and p38 phosphorylation by western blots for 24 h. B: Effect of ZLN005 on the AMPK and ACC phosphorylation by western blots for 3 h. C: Effect of ZLN005 and CCCP on the rat liver tissue mitochondria respiration. D: Effect of ZLN005 and CCCP on ADP/ATP ratio AMPK in rat primary hepatocytes for 3 h.

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Supplementary Figure 3. AMPK and ACC phosphorylation from the abdominal muscle (A) and liver tissue (B) of lean mice. The ratio of the phosphorylation level to the protein level of AMPK and ACC was determined.