

**CSIR-CDRI Synthetic molecule  
S007-867 as  
Anti-platelet agent**

**Efficacy in experimental models**

Compound showed dose dependent (10 µM/Kg, 30 µM/Kg and 100 µM/Kg) protection in various models of thrombosis in mice and rats.

In a Golden Syrian Hamster hyperlipidemic model, thrombogenic potential as measured by the enhanced platelet adhesion, augmented platelet aggregation, endothelial dysfunction & reduction in thrombin time, were reverted in the animals treated with S007-867. Mice treated with the compound exhibited less prolongation in bleeding time as compared to Aspirin and Clopidogrel.

*In vitro* studies demonstrated that collagen induced human platelet aggregation was significantly reduced in the presence of this compound, while no appreciable effect was seen on ADP, thrombin, PMA or A23187 induced aggregation even at more than twenty fold increase in its concentration. Human, rat, & mouse platelet adhesion under static conditions were also significantly reduced on collagen coated surface. It also reduced collagen induced tyrosine phosphorylation of signalling proteins and prevented increase in the intracellular calcium.

**Advantages over existing products**

Less bleeding at efficacy dose in comparison to Aspirin and Clopidogrel, and new mechanism of action.

**Mechanism of action**

Collagen antagonist.

**ADME profile**

The preclinical pharmacokinetic evaluations of compound S007-867 in male NZ rabbits by oral route at 20 mg/kg body weight provided plasma levels beyond 24 hr post dose which may have a very good pharmacodynamic correlation with one single dosing of the molecule.

**Pharmacological activity**

Inhibitor of platelet aggregation and adhesion.

**Safety evaluation**

Safety Pharmacological studies have been completed. It is found to be safe upto 50 times effective dose in single dose oral toxicity studies in rat and mice. Single dose toxicity study in rat by intramuscular route is in progress.

**Patent status** - PCT application filed

**CSIR-CDRI Synthetic molecule  
S002-333 as  
Anti-platelet agent**

**Efficacy in experimental models**

Compound exhibited dose dependent protection against collagen and adrenaline induced thrombosis in mice with nominal increase in the bleeding time as compared to aspirin and Clopidogrel. In Golden Syrian Hamster dyslipidemic model, enhanced platelet adhesion on collagen exposed surface, augmented platelet aggregation and endothelial dysfunction were reverted in the animals treated with this compound.

Collagen induced aggregation of human platelet rich plasma was significantly reduced while no effect was seen on ADP, thrombin, PMA, or A23187 induced aggregation.

**Advantages over existing products**

Less bleeding at efficacy dose in comparison to Aspirin and Clopidogrel & new mechanism of action

**Possible mechanism of action**

It seems to act as collagen GP VI antagonist, as it significantly inhibited convulxin (GP VI agonist) induced platelet aggregation, as well as attenuated the increase in collagen induced tyrosine phosphorylation of various signalling proteins along with prevention of increase in intracellular calcium.

**ADME profile**

A single dose of 20 mg/kg body weight in male NZ rabbits by oral route provided plasma levels beyond 24 hr post dose which may have a very good pharmacodynamic correlation with one single dosing of the molecule.

**Safety pharmacology & regulatory toxicology**

It is found to be safe upto 50 times of effective dose in single dose oral toxicity in rat.

**Patent status** - PCT application filed

**CSIR-CDRI Standardized fraction of  
Plant 4655 (K09) as  
Anti-dyslipidemic agent**

**Efficacy in experimental models**

The lipid lowering activity of K09 is very promising as a potential candidate for its development as antidyslipidemic agent. The structural feature in K09 is very distantly related to Simvastatin/Lovastatin but it showed better activity than clinically used standard drug Lovastatin in terms of efficacy at a dose of 25 mg/kg in hamsters.

It is isolated from leaves in quantitative yields (0.28%) from a commonly available tree in India.

**Regulatory studies** to be initiated.

**Patent status**-PCT application filed

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**LEAD MOLECULES  
FROM  
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**CSIR-CDRI Synthetic molecule 99-373 as Anti-resorptive agent**

**Efficacy in experimental models**

Antiresorbing activity *in vitro*, antiresorbing activity *in vivo* in rat, long term antiresorbing activity *in vivo* in rat, estrogenic agonist activity, estrogenic antagonist activity, relative binding affinity for rat uterine estrogen receptor, anticancer breast activity in pre-menopausal rat model, anticancer breast activity in post menopausal rat model, lipid lowering activity, thrombogenic activity, *in vitro* cytotoxicity and micro CT.

**Advantages over existing products**

Compound has no/negligible estrogenic profile (Uterotrophic side effect) on genital tract tissue. Compound has low thrombogenic activity in comparison to known drug (Raloxifene)

**Possible mechanism of action**

Antiresorptive agent possible target RANK

**Pharmacokinetics, metabolism and toxicokinetics studies** completed in rats & rabbits.

**Safety Evaluation**

Regulatory pharmacological Studies, single dose and repeated dose studies and regulatory toxicity studies such as 10 day DRF study in rats by oral route, 28 day study in rats by oral route, 28 day study in rhesus monkey by oral route, genotoxicity studies, Salmonella reverse mutation study, micronucleus assay in mouse by oral route, chromosomal aberration in mouse by oral route and male fertility studies in rats have been completed.

**Chemical process** - Single step synthesis.

**Current status**

Phase-I Clinical trial is to be initiated.

**Patent status** - PCT application filed

**CSIR-CDRI Synthetic molecule S007-1500 as Oral rapid fracture healing agent**

**Efficacy in experimental models**

S007-1500 stimulates osteoblast differentiation and mineralization  $10^{-12}$ M. S007-1500 does not affect osteoclast function. It induced osteoblast differentiation (measured by ALP activity) is abolished by an anti-estrogen, ICI-182780 suggesting its estrogen receptor (ER) mediated mode of action. It enhances BMP2 secretion and stimulates mRNA levels of type I collagen and BMP-2. In growing female rats, S007-1500 treatment at 1.0 - and 10.0 mg.kg<sup>-1</sup>.day<sup>-1</sup> doses orally for one month promotes all aspects of peak bone mass (PBM). In osteopenic rats [(made by 3 months of ovariectomized (Ovx)] oral treatment of S007-1500 (10.0 mg.kg<sup>-1</sup>.day<sup>-1</sup> dose) for the next 3 months promoted bone formation rate that is comparable to that of injectable parathyroid hormone (PTH), the only osteogenic therapy available. S007-1500 is devoid of estrogen-agonistic or antagonistic actions in uterus.

S007-1500 stimulated callus formation and stimulated fracture healing at only 1.0 mg.kg<sup>-1</sup>.day<sup>-1</sup> dose in adult female rats compared to vehicle treated rats when evaluated in rapid fracture healing model. New bone formation at the fracture site is increased by ~40% in rats treated with S007-1500 compared to vehicle treated controls.

**Advantages over existing products**

Intraosseous application of rh-BMP-2 (Infuse<sup>®</sup>) for spine surgery and open tibial fracture.

**Possible mechanism of action**

Activates osteoblastic ER to stimulate BMP-2 secretion.

**ADME profile & pharmacological Activity**

To be carried out.

**Chemical process** - Five step synthesis

**Patent status** - PCT application filed

**CSIR-CDRI Pure compound from plant 914/K058 as Osteogenic agent**

**Efficacy in experimental models**

914/K058 stimulates all aspects of osteoblast function, i.e. proliferation, survival, differentiation and mineralization. 914/K058 does not affect osteoclast function.

914/K058 acts as aryl hydrocarbon receptor (AHR) modulator. In osteoblasts,  $10^{-7}$ M 914/K058 stimulates mRNA levels of AHR and cyp1-a1a (a downstream gene of AHR). However, the extent of stimulation by 914/K058 was much less than the known AHR agonist, trichloro-dihydroxydioxane (TCDD).

Presence of AHR inhibitor, DMF attenuated K058-stimulated proliferation of osteoblasts. It has been reported that AHR is required for osteoblast functions and mice lacking AHR gene has bone loss phenotype. In growing female rats, 914/K058 treatment at 1.0- and 5.0 mg/kg doses for 3 months dose-dependently promotes all aspects of peak bone mass (PBM). In ovariectomized (Ovx) rats, treatment of 914/K058 (5.0 mg/kg) prevented bone loss and promoted bone formation. Furthermore, 914/K058 treatment to dexamethasone-treated rats prevented steroid-induced bone loss. 914/K058 is devoid of estrogen-agonistic or antagonistic actions in uterus. Together, these data indicate a robust osteogenic action of 914/K058 in three different animal models. This is the only pure osteogenic compound that is orally active in both primary and secondary osteoporosis.

**Possible mechanism of action** - Acts as AHR modulator in osteoblasts.

**ADME profile, safety evaluation and pharmacological activity** - in progress.

**Yield** - 2.6% of 13% of the crude extract

**Patent status** - PCT application filed

**CSIR-CDRI Standardized fraction of plant A-4744/F004 as Osteogenic agent**

**Efficacy in experimental models**

Following an ethno-medicinal practise, a standardized fraction (A-4744/F004 having 4.5% yield) obtained from a renewable source of a widely available terrestrial plant was found to have osteoprotective and bone anabolic effects in a WHO approved model for postmenopausal osteopenia [(adult *Sprague Dawley* rats with bilateral ovariectomy (OVx)]. OVx rats treated with vehicle for 12 weeks presented with reduced bone mineral density, loss of microarchitectural integrity in the trabecular bones and increased levels of bone turnover markers (serum osteocalcin and urinary collagen breakdown products).

The fraction administered daily by oral route at 50 and 100 mg.kg<sup>-1</sup>.day<sup>-1</sup> doses for 12 weeks to OVx rats resulted in prevention of bone loss evident from comparable levels of bone mineral density (BMD), trabecular microarchitecture (3D- $\mu$ CT) and bone turnover markers with that of sham operated (ovary intact; estrogen sufficient), suggesting an anti-catabolic action of A-4744/F004 in skeleton. 17 $\beta$ -Estradiol (17 $\beta$ -EST) at 2.5  $\mu$ g.kg<sup>-1</sup>.day<sup>-1</sup> was used as reference standard. Furthermore, treatment of OVx rats with (A-4744/F004) increased indices of new bone formation compared with OVx + vehicle group, suggesting a bone anabolic action of A-4744/F004 and is devoid of estrogen agonistic effect in uterus, suggesting that it is safe in terms of undesirable uterine effects.

It is concluded that A-4744/F004 and its active constituents was effective in prevention of OVx-induced bone loss. Hence, a nutraceutical use of the phytopreparation, A-4744/F004 for optimum bone health in postmenopausal women is suggested.

**Patent status** - PCT application filed