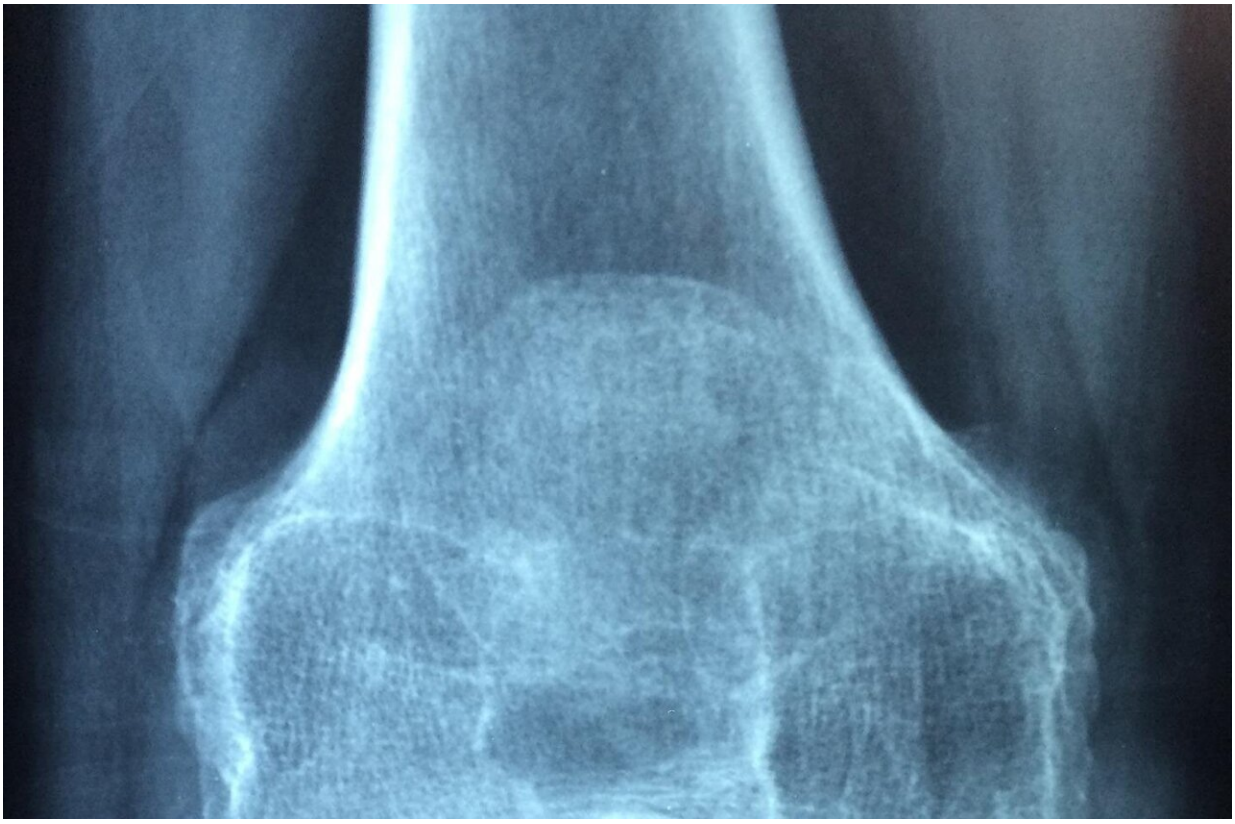
New oral compound may help prevent and treat osteoporosis

December 7 2022, by Noah Brown



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Parathyroid hormone can stimulate bone formation, and analogs of the hormone are often prescribed to patients with osteoporosis; however, these medications are only effective when administered by daily

injection.

A team led by investigators at Massachusetts General Hospital (MGH) recently identified a promising compound that influences components of the parathyroid hormone signaling pathway and that, when given orally to mice, increases bone mass. The group's discovery, which is published in *PNAS*, might lead to a new, more convenient drug for preventing and treating osteoporosis.

"Currently there are no orally available medications for osteoporosis that stimulate bone formation. We sought to develop such medications based upon our detailed understanding of the pathways that normally govern bone production," says senior author Marc Wein, MD, Ph.D., an endocrinologist at MGH and an Assistant Professor of Medicine at Harvard Medical School.

The pathway that involves parathyroid hormone inhibits salt-inducible kinase isoforms 2 and 3 (SIK2 and SIK3), which are enzymes with roles in the regulation of bone growth and remodeling.

Wein and his colleagues generated a novel structural model of these enzymes and then used advanced methods including structure-based drug design and iterative medicinal chemistry to identify a compound that potently inhibits SIK2 and SIK3. This compound, termed SK-124, had parathyroid hormone–like effects when given to cells and, most importantly, when fed to mice. In mice, oral treatment once a day for three weeks increased blood levels of calcium and vitamin D and also boosted bone formation and bone mass without evidence of short-term toxicity.

"Based on these findings, we propose that small molecules like SK-124 might represent 'next generation' oral bone building therapies for osteoporosis," says Wein. "We are currently collaborating with a

pharmaceutical company—Radius Health, Inc.—to further optimize and develop this compound into a treatment for patients."

Additional MGH co-authors include Tadatoshi Sato, Christian D. Castro Andrade, Sung-Hee Yoon, Yingshe Zhao, Daniel J. Brooks, Marie B. Demay, and Mary L. Bouxsein.

More information: Tadatoshi Sato et al, Structure-based design of selective, orally available salt-inducible kinase inhibitors that stimulate bone formation in mice, *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2214396119