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A series of novel indazole derivatives of Sirt 1 activator as osteogenic regulators

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ABSTRACT

A series of indazole derivatives were identified as Sirt 1 activators though high-throughput screening. Optimization of each substituent on the indazole ring led to the identification of compound **13.** Compound **13** appeared to give the best Sirt 1 activity of the compounds tested and also showed osteogenesis activity in a cell assay. Sirt 1 activators are therefore potential candidates for the treatment of osteoporosis.

Osteoporosis is a disorder characterized by reduced bone strength, diminished bone density, and altered macrogeometry and microscopic architecture. Adult bone mass is determined by the integral measurement of the bone mass level achieved at the peak minus the rate and duration of subsequent bone loss.[1] Bone loss with age and following menopause in women are universal, but rates vary among individuals. Both peak bone mass and subsequent bone loss can be modified by environmental factors, such as nutrition, physical activity, and concomitant diseases and medications.[2] Medications that affect bone loss include both antiresorptive and anabolic drugs.[3] Antiresorptive medications – estrogens, selective estrogen receptor modulators (raloxifene), bisphosphonates (alendronate, risedronate, and ibandronate), and calcitonins – work by reducing the rates of bone remodeling. On the other hand, for instance, Teriparatide (parathyroid hormone, brand name: Teribone®) is an anabolic agent currently approved for treating osteoporosis in Japan. Teriparatide stimulates new bone formation, repairing architectural defects and improving bone density.[4] Although there are a wide variety of antiresorptive agents, new anabolic agents have yet to be identified.

Silent information regulator two homologue 1 (Sirt 1) is a member of the sirtuin family and possesses nicotinamide adenine dinucleotide dependent deacetylase activity.[5] Sirt 1 regulates a variety of cellular processes such as energy metabolism, cell-cycle progression, muscle differentiation, fat mobilization, and aging, through the deacetylation of its substrates, including histones H1, H3, and H4, p53, p300, FOXOs 1, 3a, and 4, p65, HIVTat, peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, P300/CBP-associated factor, MyoD, peroxisome proliferation activated receptor γ, Ku70, and others.[6] Sirt 1 has attracted considerable attention as a target for new therapies for a broad range of age-related diseases[7], especially osteoporosis. Tseng et al. described that the activation of Sirt 1 by resveratrol dose-dependently increased alkaline phosphatase (ALP) activity and calcium deposition in human bone marrow-derived mesenchymal stem cells (hBMSC).[8] Furthermore, Su et al. reported that resveratrol increases osteogenic responses and prevents ovariectomy-induced bone loss.[9] These data indicated that Sirt 1 activators may be anabolic agents for osteoporosis. Resveratrol is the most potent natural Sirt 1 activator identified to date.[10–12] However, it has a low bioavailability and is rapidly metabolized, and its direct effect on Sirt 1 is controversial.[13–15] It is therefore important to obtain new potent Sirt 1 activators and check their initial bone-anabolic activities using in vitro assays with our alternative Sirt 1 activators to determine if Sirt 1 activators are efficacious in the treatment of osteoporosis.

To date, several small-molecule Sirt 1 activators have been reported by several groups.[16] To identify a novel class of Sirt 1 activators, we used high through-put screening (HTS) to design a novel

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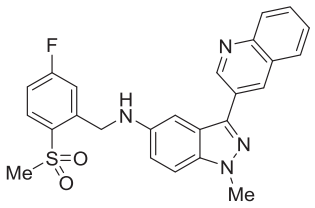
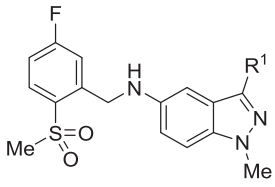


Fig. 1. HTS hit compound.

activator. Screening our in-house compound library resulted in the identification of **1**, an indazole compound bearing an 3-quinolyl group exhibiting potent Sirt 1 activating activity (Fig. 1). We then focused on investigating the structure–activity relationship (SAR) of **1** to optimize the compound.

Table 1 shows the results of SAR studies of the 3-position of the indazole ring. Replacement of the 3-quinolyl group with a naphthalene ring (**2**) or benzothiophene (**3**) resulted in moderate Sirt

Table 1
Modification of the 8-quinolyl group.



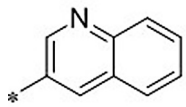
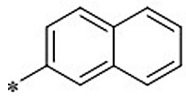
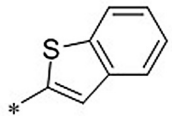
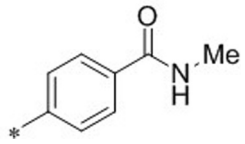
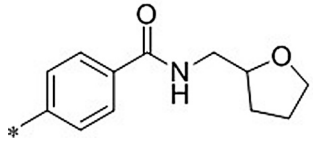
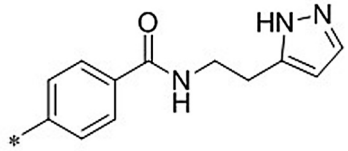
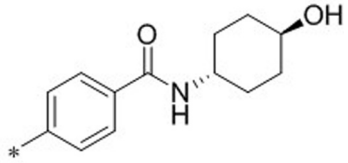
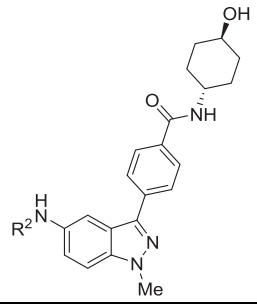
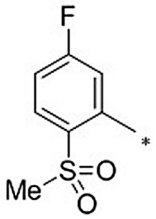
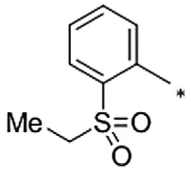
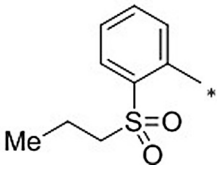
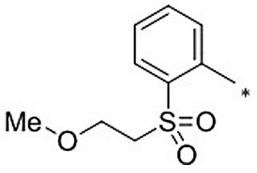
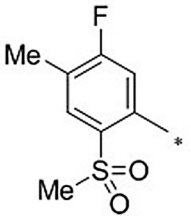
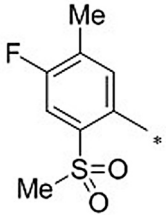
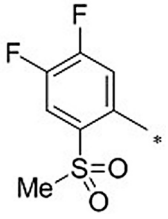
Cpd.	Structure (R^1)	EC_{150}(μM)	clogP
1		1.49	3.63
2		2.88	4.85
3		1.52	4.93
4		2.92	2.42
5		1.46	3.06
6		1.36	2.38
7		0.95	2.36

Table 2
Modification of the methylsulfonylbenzyl group.



Cpd.	Structure	EC_{150} (μM)
7		0.95
8		2.40
9		4.54
10		7.23
11		0.40
12		>20
13		0.40