Study of 1,4-dihydropyridine structural scaffold: discovery of novel sirtuin activators and inhibitors.


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NAD(+)—dependent sirtuin deacetylases have emerged as potential therapeutic targets for treatment of human illnesses such as cancer, metabolic, cardiovascular, and neurodegenerative diseases. The benefits of sirtuin modulation by small molecules have been demonstrated for these diseases. In contrast to the discovery of inhibitors of SIRT1, -2, and -3, only activators for SIRT1 are known. Here, we rationalized the potential of the previously unexplored dihydropyridine scaffold in developing sirtuin ligands, thus we prepared a series of 1,4-dihydropyridine-based derivatives 1-3. Assessment of their SIRT1-3 deacetylase activities revealed the importance of the substituent at the N1 position of the dihydropyridine structure on sirtuin activity. Placement of cyclopropyl, phenyl, or phenylethyl groups at N1 conferred nonselective SIRT1 and SIRT2 inhibition activity, while a benzyl group at N1 conferred potent SIRT1, -2, and -3 activation. Senescence assays performed on hMSC and mitochondrial function studies conducted with murine C2C12 myoblasts confirmed the compounds' novel and unique SIRT-activating properties.

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