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Pyrazoline containing malonyl CoA decarboxylase inhibitors: Design, synthesis and in vitro evaluation

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Introduction: Cardiovascular disease is one of the leading causes of death in the modern world. Impaired cardiac efficiency is an important contributor to the severity of cardiovascular disease. Impaired cardiac efficiency is caused by an inadequate supply of oxygen to the heart. Malonyl-CoA decarboxylase (MCD) decarboxylates malonyl-CoA to acetyl-CoA. Therefore, the inhibition of MCD increases the level of malonyl-CoA, which further reduces fatty acid oxidation and increases glucose oxidation in the mitochondria. A shift in the mitochondrial metabolism from fatty acid to glucose oxidation increases Adenosine tri phosphate production. Thus, the heart may receive more energy even if the oxygen supply is less. In addition, increased glucose oxidation reduces pyruvate in cellular fluids, improving the pH balance of heart cells. Recently, researchers have synthesized MCD inhibitors based on this novel approach of increasing energy supply to the heart.

In the present work series of small molecules (5a–5m, 6a–6j) were schematically designed and synthesized using simple chemical procedures. Their structures were confirmed based upon findings from infrared, 1H nuclear magnetic resonance (NMR), 13C NMR, and mass spectra. The derivatives were evaluated for their in vitro malonyl CoA decarboxylase inhibition activity by using fluorimetric assay. Pyrazol-1-yl-1, 3-thaizol-4(5H)-one derivative (5a–5m) showed better activity than pyrazol-1- yl-1-ethanone derivatives (6a–6j). Compounds 5e, 5j, and 6f showed an excellent in vitro malonyl CoA decarboxylase inhibition activity with IC50 value 0.10, 0.27, and 0.26 μM, respectively. These most active compounds 5e, 5j, and 6f were docked into malonyl-CoA decarboxylase (HsMCD, PDB ID: 2YGW) to study ligand–protein interaction.

Biography

C S Ramaa is a Professor and Head of Department of Pharmaceutical Chemistry at Bharati Vidyapeeth's College of Pharmacy, Navi Mumbai. She received her PhD in Pharmaceutical Chemistry from University Department of Chemical Technology. She has been working at Bharati Vidyapeeth's College of Pharmacy, Navi Mumbai. She has received several grants from renowned funding agencies like Department of Science and Technology, Basic Research in Nuclear Sciences, Lady Tata Memorial Trust and University of Mumbai. She has published more than 35 research and review articles in international and national esteemed journals. She has also presented more than 30 presentations at national and international conferences. She has been awarded as Best Research Guide for national level PharmInnova Award.

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