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Inotropic and chronotropic effects of ٦-hydroxy-٤-methylquinolin-٢(١H)-one derivatives in isolated rat atria

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View references (٢٤)

Abstract

Background: Selective phosphodiesterase (PDE٣) inhibitors improve cardiac contractility and may use in congestive heart failure. However, their proarrhythmic potential is the most important side effect. Methods: In this research, we evaluated the potential cardiotonic activity of six new synthesized selective PDE٣ inhibitors (٦-hydroxy-٤-methylquinolin-٢(١H)-one derivatives) using the spontaneously beating atria model. In each experiment, atrium of reserpine-treated rat was isolated and the contractile and chronotropic effects of a synthesized compound were assessed. The ٣-isobutyl-١-methylxanthine, a non-selective PDE inhibitor, was used for comparison. Results: The results showed that, among new compounds, the best pharmacological profile was obtained with the compound ٦-[٤-(٤-methylpiperazine-١-yl)-٤-oxobutoxy]-٤-methylquinolin- ٢(١H)-one, C٦, which displayed selectivity for increasing the force of contraction (١٦٨ ± ٥٪ change over the control) rather than the frequency rate (١٣٨ ± ٥٪ change over the control) at ٣٠٠ μM. However, C٦ at concentrations of ١٠ and ١٠٠ μM produced left and upward shift in the positive inotropic concentrationresponse curve of isoprenaline. The -log EC ٥٠ of isoprenaline was ٨,٨٤٣ ± ٠,١٧١ in the absence, ٩,٤٤٨ ± ٠,١٣٨ and ٩,٤٥٦ ± ٠,١٠٧ in the presence of ١٠, ١٠٠ μM of C٦, respectively (P<٠,٠٠١, n = ٦). Also, amrinone, a selective PDE٣ inhibitor, shifted the isoprenaline concentration-response curve to the left and upward. The concentration of ١٠ and ١٠٠ μM amrinone decreased -log EC ٥٠ of isoprenaline to ٩,٥٢٧ ± ٠,٢٨٧ and ٩,٤٢٣ ± ٠,٢٤٣, respectively (P<٠,٠٠١, n = ٦). Moreover, the positive chronotropic effect of isoprenaline was not affected by amrinone or C٦. Conclusion: This study provides functional evidence for the positive inotropic effect of C٦. Considering the augmentation of isoprenaline positive inotropic concentration-response with C٦ and amrinone, we conclude that C٦ produces its effect via potentiation of cAMP-dependent signaling system and possibly by inhibition of PDE٣ activity.

Reaxys Database Information

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Author keywords

٤-methylquinolinone derivatives; Inotropic activity; Isoprenaline; Phosphodiesterase inhibitor; Rat atria

Indexed Keywords

EMTREE drug terms: ٤ (١،٢ dihydro ٤ methyl ٢ oxoquinolin ٦ yloxy) n cyclohexyl n methylbutanamide; ٤ (١،٢ dihydro ٤ methyl ٢ oxoquinolin ٦ yloxy) n methyl n phenylbutanamide; ٦ [٤ (٤ methyliperazine ١ yl) ٤ oxobutoxyl] ٤ methylquinolin ٢(١h) one; ٦ hydroxy ٤ methylquinolin ٢(١h) one; ٦ hydroxyquinolin ٢(١h) one; amrinone; cyclic AMP; ethyl ٤ (١،٢ dihydro ٤ methyl ٢ oxoquinolin ٦ yloxy)butanoate; isobutylmethylxanthine; isoprenaline; phosphodiesterase III inhibitor; phosphodiesterase inhibitor; reserpine

EMTREE medical terms: animal tissue; article; chronotropism; concentration (parameters); controlled study; drug activity; drug effect; drug selectivity; enzyme inhibition; heart atrium; heart muscle contractile force; heart muscle contractility; heart rate; inotropism; male; nonhuman; rat

MeSH: Amrinone; Animals; Atrial Function; Cardiotonic Agents; Cyclic Nucleotide Phosphodiesterases, Type ٣; Dose-Response Relationship, Drug; Heart Rate; Isoproterenol; Male; Phosphodiesterase Inhibitors; Quinolines; Rats;