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Design of Novel Thiazole Bearing Pyrazole Derivatives and Their Dual Activities as ACE Inhibitors and Calcium Channel Blockers in Cardiovascular Disease

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SUMMARY. In an attempt to develop drugs for cardio-vascular disease, present manuscript deal with the development of dual acting agents targeting angiotensin converting enzyme (ACE) and calcium channel to treat hypertension. These molecules were developed via efficient multi-step synthetic route in excellent yield. In ACE inhibitors assay, these compounds showed considerable percentage of inhibition (32-94 %) with IC_{50} = 1.2 and 1.5 μM for most promising compound **6e** and **6o**, respectively. In molecular docking study with ACE, compound 6e revealed similar fashion of molecular interaction with catalytic residues His353, Ala 354, Tyr 523, Tyr 520, and Glu 152, comparable with standard lisinopril. Additionally, in rat aortic strip model, these molecules significantly induce vasorelaxation via inhibiting Ca^{2+} channel in dose dependent manner.

RESUMEN. En un intento de desarrollar medicamentos para enfermedades cardiovasculares, el presente trabajo está relacionado con el desarrollo de fármacos de acción dual dirigidos a la acción de la enzima convertidora de angiotensina (ACE) y a los canales de calcio, para el tratamiento de la hipertensión. Estas moléculas se desarrollaron a través de múltiples pasos de síntesis con un excelente rendimiento. En el ensayo con la ACE, estos compuestos mostraron una considerable porcentaje de inhibición (32-94%) con IC_{50} = 1,2 y 1,5 μM en el caso de los compuestos más prometedores **6e** y **6o**, respectivamente. En el estudio de acoplamiento molecular con ACE, 6e reveló similar interacción molecular con los residuos catalíticos His353, Ala 354, Tyr 523, Tyr 520 y Glu 152, comparable con el estándar lisinopril. Además, en el modelo de tira aórtica de rata estas moléculas inducen significativamente vasorrelajación través de la inhibición del canal de Ca^{2+} en forma dependiente de la dosis.

KEY WORDS: angiotensin converting enzyme inhibitors, hypertension, synthesis, thiazole, vasorelaxation.

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