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Synthesis of Novel Pyrimidine Derivatives as Bioisosters of Nifedipine and *In Vitro* Evaluation of their Antihypertensive Activity

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SUMMARY. 3,4-dihydropyrimidin-2(1H) compounds have been attracted researchers to synthesize them via Beginilli reaction and evaluate their antihypertensive activities as bioisosters of nifedipine. The aim was to evaluate the antihypertensive activities of new synthetic pyrimidine compounds compare with nifedipine. The new compounds were prepared from one pot reaction of thiourea (**1**), ethyl acetoacetate (**2**) and/or p-nitrobenzaldehyde, p-tolualdehyde (**3**), respectively, in acid medium (HCl) yielding pyrimidine **4a-c** which in turn were hydrolyzed to carboxylic acid derivatives **5a-c** which were chlorinated by SOCl2 to give acyl chlorides **6a-c**; finally the latter were reacted with some selected aromatic amines namely, aniline, p-anisidine and p-nitroanilin producing amides **7a-c**, **8a-c**, and **9a-c**, respectively. A total of 95 adult rats were divided into 7 groups and given the new compounds and one group received nifedipine. Rats were anaesthetized and the blood pressure was measured though the carotid artery by using of mercury manometer. Results showed that compound **7a** has a better antihypertensive activity with insignificant difference compared to nifedipine, while **8a-c** and **9a-c** have significant difference as compared with nifedipine that indicated when aniline was used as an aromatic amine provides the highest calcium blocking activity. In conclusion, the best antihypertensive active compounds were amides **7a-c**, **8a-c** and **9a-c**. Better results were obtained especially when the benzene ring of amide is unsubstituted.

RESUMEN. Los compuestos de 3,4-dihidropirimidin-2 (1H) han atraído a investigadores para sintetizarlos mediante la reacción de Beginilli y evaluar sus actividades antihipertensivas como bioisósteres de nifedipina. El objetivo era evaluar las actividades antihipertensivas de los nuevos compuestos pirimidínicos sintéticos en comparación con la nifedipina. Los nuevos compuestos se prepararon a partir de una reacción en un recipiente de tiourea (**1**), acetoacetato de etilo (**2**) y/o p-nitrobenzaldehído, p-tolualdehído (**3**), respectivamente, en medio ácido (HCl), produciendo pirimidina **4a-c** que a su vez fueron hidrolizados a derivados de ácido carboxílico **5a-c** que fueron clorados por SOCl2 para dar cloruros de acilo **6a-c**, finalmente estos últimos se hicieron reaccionar con algunas aminas aromáticas seleccionadas, a saber, amidas productoras de anilina, p-anisidina y p-nitroanilina **7a-c**, **8a-c**, y **9a-c**, respectivamente. Un total de 95 ratas adultas se dividieron en 7 grupos y se les administraron los nuevos compuestos y un grupo recibió nifedipina. Se anestesiaron ratas y se midió la presión sanguínea a través de la arteria carótida usando un manómetro de mercurio. Los resultados mostraron que el compuesto 7a tiene una mejor actividad antihipertensiva con una diferencia insignificante en comparación con la nifedipina, mientras que 8a-c y 9a-c tienen una diferencia significativa en comparación con la nifedipina que indica que cuando se usa anilina como una amina aromática se proporciona la mayor actividad de bloqueo del calcio. En conclusión, los mejores compuestos activos antihipertensivos fueron las amidas **7a-c**, **8a-c** y **9a-c**. Se obtuvieron mejores resultados especialmente cuando el anillo de benceno de la amida no está sustituido.

KEY WORDS: antihypertensive activity, bioisosters, blood pressure, calcium channel blocker, nifedipine.

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