Synthesis and Preliminary Pharmacological Screening of 4-Aryl Substituted-3,4-Dihydropyrimidin-2 (1h) One/ Thione Derivatives as Calcium Channal Blockers

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ABSTRACT

A new series of 4-aryl substituted-3,4-dihydropyrimidin-2 (1h) one/thione derivatives (Ar-A) were prepared by using Hantzsch synthesis method for synthesis of dihydropyrimidines. Hydrochloric acid was used as a proton abstractor. The structures of the synthesized compounds were confirmed by IR, NMR, Mass & CHN analysis these compounds were screened for Calcium channel blocker activity by standard methods. Most of these compounds have shown promising Calcium channel blocker activity.

Key words: 3, 4-dihydropyrimidin-2 (1h) one, 3, 4-dihydropyrimidin-2 (1h) thione, Calcium channel blockers, Elementary analysis.

INTRODUCTION

The different chemical categories of LCC targeting drugs exist: 1,4-dihydropyrimidines (DHPs) such as (nifedipine), phenylalkylamines (PAAs such as verapamil) and benzothiazepines (BTZs such as diltiazem). They are extensively used in the treatment of cardiovascular disorders, including hypertension, arrhythmias, angina, and central and peripheral vascular disorders. While verapamil and diltiazem are the only therapeutically available members of their respective families, DHPs are well represented by several second and third generation agents. The binding domains of these drugs were extensively probed by radiolabeled ligands in particulate and purified Ca+2 channel preparations, these studies clearly revealed that the different chemical classes of Ca+2 channel antagonists do not interact with the same binding site on a, subunit. DHPs bind to a single site at which agonists increase Ca+2 channel activity and antagonists reduce it. Therefore, DHP antagonists are believed to block the pore indirectly by stabilizing a channel closed state with a single Ca+2 ion bound in a blocking position in the pore. In fact, site directed mutagenesis experiments confirmed that the binding of Ca+2 to the selectivity filter stabilizes the DHP receptor in its high affinity closed state. It was thought worthwhile to synthesize some derivatives of 3,4-dihydropyrimidin and evaluate them for calcium channel blocking activity.

MATERIALS AND METHODS

Experimental:
Melting points were determined in open capillary method and are uncorrected. The 1-H NMR spectra were recorded on sophisticated multinuclear FT-NMR Spectrometer model Avance-II (Bruker) using dimethylsulfoxide-d6 as solvent and tetramethylsilane as internal standard. IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method.

Spectral And Physicochemical Data Of Synthesized Compounds

<table>
<thead>
<tr>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.p. °C</th>
<th>IR ν/cm-1</th>
<th>1H NMR δ ppm (%)</th>
<th>Mass Spectra (M+H) FAB-MS (M/Z, 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (6-methyl-1-(4-(4-nitrophenyl-5-(ethoxycarbonyl)-3,4-dihydropyrimidin-2(1H)-one).</td>
<td></td>
<td>215-217°C</td>
<td>R_f-0.61</td>
<td>Ethyl acetate: n hexane : 80:20</td>
<td>3240 (-NH str), 3120 (Ar-H str), 2985 (C-H str), 1728 (C=O str), 1643 (NHCO) 1595, 1348, 1319 (C-N str), 1199 (-NO2 str), 1290 (-C-N str), 7.44 (d, 1H), 7.17 (t, 1H), 4.05 (q, 2H), 2.23 (S, 3H), 8.13 (S, 1H), 8.90 (S, 1H), 7.24-7.54 (m, 4H)</td>
</tr>
</tbody>
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Pharmacological Screening:
Barium Chloride Stimulated Rat Ileum Method
The substances to be tested were investigated using the single dose technique. Barium chloride contractions were induced after addition of the test substances at the 10-4M concentration and 5 min exposure time. Only one compound was tested in each preparation. Because of solubility problems, the compounds were dissolved in dimethylsulfoxide (DMSO) and the control responses were taken after the addition of 0.1 ml DMSO. Results were expressed as the percentage of the maximum relaxation of the contractions of the compounds. The responses of the compounds were compared to those of nicardipine. The data were expressed as means ± SD. Student’s t test was used for statistical analysis. P values <0.05 were considered to be statistically significant.

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A: 6-Methyl-4-(4-ethoxyphenyl)-5-(methoxycarbonyl)-3,4-dihydro pyrimidin-2(1H)-one.

m.p. 180-182°C, Rf 0.79 (ethyl acetate:n-hexane; 80:20); IR (KBr) Cm-1: 3336 (-NH str), 3113 (Ar-H str), 1240 (C-N str); 1230 (-C-N str); 1700 (C=O str), 1651 (CONH str); 1586 (-NH str), 1226 (C-N str).  

FAB-MS (M/Z, 100%): 260; Elemental Analysis: found C 62.04%, H 6.22%, N 9.63%; for C21H21NO2: calc. C 62.06%, H 6.25%, N 9.65%.

A: 6-Methyl-4-(4-Flurophenyl)5-(methoxycarbonyl)-3,4-dihydro pyrimidin-2(1H)-one.

m.p. 178-180°C, Rf 0.79 (ethyl acetate: n-hexane; 80:20); IR (KBr) Cm-1: 3327(NH str), 3105 (Ar-H str), 1251 (C-N str), 1230 (C-N str); 1730 (C=O str), 1654 (CONH str), 1586 (-NH str), 1226 (C-N str).  

FAB-MS (M/Z, 100%): 264; Elemental Analysis: found C 59.06%, H 4.92%, N 10.58%; for C21H19FNO2: calc. C 59.09%, H 4.96%, N 10.60%.

RESULT AND DISCUSSION

The synthesized compounds were screened for Calcium channel blocker activity using Barium chloride stimulated rat ileum method. Nicardipine was used as a standard drug. Compound A1, A2, A3, A4, A5, and A6 have shown promising calcium channel blocker activity.

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