Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 43 (2008) 486–500
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

# Synthesis and antihypertensive effects of new methylthiomorpholinphenol derivatives

A. Ma. Velázquez [a], L. Martínez [a], V. Abrego [a], M.A. Balboa [b], L.A. Torres [a], B. Camacho [a], S. Díaz-Barriga [a], A. Romero [a], R. López-Castañares [c], E. Angeles [a,*]

[a] *División de Ciencias Químico Biológicas, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México, 54740 Cuautitlán Izcalli, Estado de México, Mexico*
[b] *Facultad de C. Químicas, UNACH, Mexico*
[c] *Facultad de Química, Universidad Autónoma del Estado de México, Toluca, Estado de México, Mexico*

Received 17 March 2006; received in revised form 25 March 2007; accepted 4 April 2007
Available online 25 April 2007

**Abstract**

We present in this work the synthesis and cardiovascular effects of new methylthiomorpholine compounds and they were compared with cardiovascular drugs such as captopril, losartan and omapatrilat.


*Keywords:* Cardiovascular effects; Thiomorpholin; Methylthiomorpholinphenols

## 1. Introduction

In the last twenty years, cardiovascular diseases have become the world's leading cause of death [1]. In this setting, well-formulated health promotion programs may play an important role, as they are thought to reduce chronic disease-related morbidity and mortality, as well as health care costs [2]. It is known that such health programs may be effectively delivered at the workplace, in addition to improve absenteeism and work safety [3–6]. Under most real-world conditions, it is difficult and costly for worksite health promotion programs to follow strictly controlled research designs over an extended period of time, impeding the evaluation and determination of the most effective programmatic structure to achieve health improvements. On the other hand, it is estimated that about one million patients are hospitalized for acute coronary events each year in the United States, and it is well known that low socioeconomic status is associated with increased risk of cardiovascular disease in both men and women, and in different ethnic groups [7–9]. Risk factors for cardiovascular disease are prevalent in men and women [10]. In young adults, education level is inversely associated with 5-year weight gain [11] and 10-year incidence of high blood pressure [12], while financial hardship is associated with 10-year incidence of hypertension [13].

The dihydropyridine calcium channel blocker compounds such as nifedipine and isradipine were originally developed for the treatment of hypertension [14,15], and today there are many compounds used as antihypertensives [16]. In 1979, a research group in the People's Republic of China noted, while examining the antimalarial properties of derivatives of febrifugine, that one compound in clinical trials, changrolin, Fig. 1, was effective as an arrhythmic agent. In 1983, Stout and his research group of the American Hospital Supply Corporation, McGaw Park, Illinois, studied the structure of changrolin for its dissimilarity with currently marketed antiarrhythmics [17–20]; there are also other recent studies about the biological structure–activity relationships [21,22]. And so, we take the phenol and methylpyrrolidine rings as a structural

* Corresponding author. Tel./fax: +52 55 56232066.
*E-mail address:* angeles@servidor.unam.mx (E. Angeles).

0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.04.003

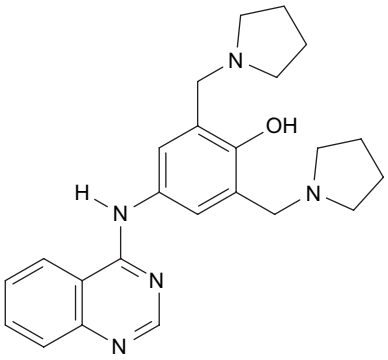


Fig. 1. Changrolin.

requirement to show cardiovascular effects and we change the pyrrolidine rings to methylthiomorpholin rings. In our experience, methylmorpholinphenol and methylpiperidinylphenol derivatives show cardiovascular effects [23] and, in the literature, there is only one report about the cardiovascular effects of methylmorpholinphenols [24], and only two reports about the biological activity of thiomorpholinphenols, which have been reported with antimycobacterial activity [25] and against *Candida* [26]. We now report, as part of the Drug Design in Medicinal Chemistry Program of the UNAM, new methylthiomorpholinphenol compounds with cardiovascular effects, considering that the development of new antihypertensive drugs is justified as there is a need to search for medicines that promote a decrease in blood pressure, such as monotherapy, to achieve a good protection for most hypertensive patients and a reduction in adverse reactions.

## 2. Experimental

### 2.1. Chemistry

#### 2.1.1. General methodology of synthesis

Methylthiomorpholinphenol compounds were prepared from phenol derivatives (1 eq.), thiomorpholine (2.1 eq.) and formaldehyde (37%) (2 eq.). They were mixed in a round flask fitted with a condenser. The mixture was irradiated with infrared light using a medicinal infrared lamp (250 W) under solvent-free conditions [27]. The reaction was monitored with TLC using a gradient solvent system (*n*-hexane/ethylacetate) until the reaction was complete. The products were purified by recrystallization and by using silica gel column chromatography using gradient solvents (*n*-hexane/ethylacetate). The temperature of the reaction mixture is in the range of 120 °C–180 °C. Summary of reaction is described in Table 1.

#### 2.1.2. Spectroscopy

*2.1.2.1. 4-Chloro-2-(thiomorpholin-4-ylmethyl)phenol – compound **2** (LQM301).* IR ($CHCl_3$ film) $cm^{-1}$ 3502 (O–H), 3010 ($C_{sp^2}$–H Ar), 2985 ($C_{sp^3}$–H). $^1H$ NMR ($CDCl_3$) $\delta$: 10.56 (1H, s, OH), 7.11 (1H, dd, $J = 8.7$ Hz, 2.7 Hz), 6.94 (1H, d, $J = 2.7$ Hz), 6.74 (1H, d, $J = 8.7$ Hz), 3.65 (2H, s, Ar-$CH_2$), 2.81 (4H, m, –S–$CH_2$–), 2.71 (4H, m, –N–$CH_2$–). $^{13}C$ NMR ($CDCl_3$) $\delta$: 156 (C), 128.56 (CH), 128.31 (CH), 123.61 (C), 122.11 (C), 117.37 (CH), 61.63 (Ar-$CH_2$), 54.27 (–S–$CH_2$–), 27.73 (–N–$CH_2$–). FAB-MS *m/z* (rel%) (M + 1) 244 (100%), 215, 180, 154.

*2.1.2.2. 4-tert-Butyl-2-(thiomorpholin-4-ylmethyl)phenol – compound **3** (LQM302).* IR ($CHCl_3$ film) $cm^{-1}$ 3456 (O–H), 3197 ($C_{sp^2}$–H Ar), 2886 ($C_{sp^3}$–H). $^1H$ NMR ($CDCl_3$) $\delta$: 10.33 (1H, s, OH), 7.18 (1H, dd, $J = 8.4$ Hz, 2.7 Hz), 6.94 (1H, d, $J = 2.7$ Hz), 6.74 (1H, d, $J = 8.4$ Hz), 3.70 (2H, s, Ar-$CH_2$), 2.82 (4H, m, –S–$CH_2$–), 2.71 (4H, m, –N–$CH_2$–), 1.27 (9H, $CH_3$). $^{13}C$ NMR ($CDCl_3$) $\delta$: 155 (C), 141.8 (C), 125.60 (CH), 125.49 (CH), 119.77 (C), 115.47 (CH), 62.51 (Ar-$CH_2$), 54.36 (–N–$CH_2$–), 33.84 (C), 31.48 (CH3), 27.79 (–S–$CH_2$–). FAB-MS *m/z* (M + 1) 266 (80%), 265 (100%), 163 (45%).

*2.1.2.3. 4-tert-Butyl-2,6-bis(thiomorpholin-4-ylmethyl)phenol – compound **4** (LQM303).* IR ($CHCl_3$ film) $cm^{-1}$ 3403 (O–H), 3089 ($C_{sp^2}$–H Ar), 2986 ($C_{sp^3}$–H). $^1H$ NMR ($CDCl_3$) $\delta$: 10.69 (1H, s, OH), 7.09 (2H, s,), 3.71 (4H, s, Ar-$CH_2$), 2.86 (8H, m, –S–$CH_2$–), 2.76 (8H, m, –N–$CH_2$–), 1.27 (9H, $CH_3$). $^{13}C$ NMR ($CDCl_3$) $\delta$: 153.6 (C), 141.14 (C), 125.79 (CH), 121.22 (C), 58.81 (Ar-$CH_2$), 54.42 (–N–$CH_2$–), 33.78 (C), 31.47 ($CH_3$), 27.74 (–S–$CH_2$–). FAB-MS *m/z* (M + 1) 381 (35%), 278 (100%), 175 (50%).

*2.1.2.4. 4,6-Bis(thiomorpholin-4-ylmethyl)1,2,3-benzenetriol – compound **5** (LQM304).* IR ($CHCl_3$ film) $cm^{-1}$ 3429 (O–H), 3065 ($C_{sp^2}$–H Ar), 2872 ($C_{sp^3}$–H). $^1H$ NMR ($CDCl_3$) $\delta$: 8.401 (3H, s, OH), 6.20 (1H, s), 3.61 (4H, s, Ar-$CH_2$), 2.81 (8H, m, –S–$CH_2$–), 2.72 (8H, m, –N–$CH_2$–). $^{13}C$ NMR ($CDCl_3$) $\delta$: 144.8 (C), 132.51 (C), 118.42 (CH), 111.74 (C), 61.63 (Ar-$CH_2$), 54.22 (–N–$CH_2$–), 27.81 (–S–$CH_2$–). FAB-MS *m/z* (M + 1) 357 (10%), 254 (100%), 102 (91%).

*2.1.2.5. 4-[1-(4-Hydroxy-3-(thiomorpholin-4-ylmethyl)phenyl)-1-methylethyl]-2-(thiomorpholin-4-ylmethyl)phenol – compound **6** (LQM305).* IR ($CHCl_3$ film) $cm^{-1}$ 3473 (O–H), 3034 ($C_{sp^2}$–H Ar), 2895 ($C_{sp^3}$–H). $^1H$ NMR ($CDCl_3$) $\delta$:10.42 (2H, s, OH), 7.0 (1H, dd, $J = 2.4$ Hz, 8.4 Hz), 6.79 (1H, d, $J = 2.4$ Hz), 6.70 (1H, d, $J = 8.4$ Hz), 3.64 (4H, s, Ar-$CH_2$), 2.80 (8H, m, –S–$CH_2$–), 2.74 (8H, m, –N–$CH_2$–), 1.57 (3H, s, $CH_3$). $^{13}C$ NMR ($CDCl_3$) $\delta$: 155.09 (C), 141.70 (C), 127.06 (CH), 126.85 (CH), 119.78 (C), 115.30 (CH), 62.48 (Ar-$CH_2$), 54.35 (–N–$CH_2$–), 41.38 (C), 31.07 ($CH_3$), 27.83 (–S–$CH_2$–). FAB-MS *m/z* (M + 1) 459 (40%), 238 (100%), 237 (32%).

## 3. Biological activity

### 3.1. Materials and methods

We compared methylthiomorpholinphenol derivatives with captopril (angiotensin-converting enzyme, ACE), losartan ($AT_1$ receptor antagonist) and omapatrilat (neutral