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A Novel Antiarrhythmic Compound 4–tertbutyl–2–(thiomorpholin–4–ylmethyl)phenol, Crystal Structure

E.Angeles[1*], Ana M.Velazquez S[1]., M.Jesus Rosales H[2]., Marco A.Leyva R[2]., T[1]., Luis A.Torres C[1]., Luisa Martinez A[3]., J.G.Alfonso Ramos A[5].,

[1]Laboratorio de Química Medicinal, Departamento de Ciencias Químicas, Facultad de Estudios Superiores Cuautitlán (UNAM)

[2]Departamento de Química (CINVESTAV)

[3]Laboratorio de Farmacología del Miocardio, FESC-(UNAM)

[4]Lab.Termofluidos, FESC-(UNAM)

E-mail : angeles@servidor.unam.mx

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ABSTRACT

In this article, we present the crystallographic Ray X of a new antihypertensive compound, obtained from a Mannich reaction.

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KEYWORDS

Thiomorpholine;
Mannich reaction;
Antihypertensive.

INTRODUCTION

In 1983, Stout and his research group of the American Hospital Supply Corporation, McGaw Park, Illinois[1,2] studied changrolin structure by its dissimilarity with currently marketed antiarrhythmics. They found that the changrolin molecule can be conceptually divided into the following three regions: (1) the heteroatom region, it is consisting of the quinazoline moiety, (2) the aromatic region with the bis(pyrrolidin-yl-methyl) phenol and (3) the linkage between the first two regions.

They found that the antiarrhytmic activity of the compounds to be lowest en those products that differed from changrolin at the phenolic region. Thus, compounds which lacked pyrrolidinylmethyl groups, were inactive. Also, this activity generally was maintained in analogues that differed from changrolin at the heteroaromatic region of the molecule.

Thus, while the bis(pyrrolidinylmethyl) - phenol pattern of changrolin appears to be optimal in this series, a wide latitude exists for the heteroaryl substituent for maintaining good ant arrhythmic activity.

In 1985, the Stout researcher's group worked en the modifications to de linkage region of changrolin. Their goal was to optimize the spectrum of activity of changrolin through changes in each or the three regions of the prototype. It is shown in the figure 1.

Thus, while the bis(pyrrolidinylmethyl)phenol pattern of changrolin appears to be optimal in this series, a wide latitude exists for the heteroaryl substituent for maintaining good ant arrhythmic activity.

In the news investigations, morpholin and thiomorpholin phenol derivates have showed hypotensor activity in a model of anesthetic rat. This compounds have studied from changrolin.

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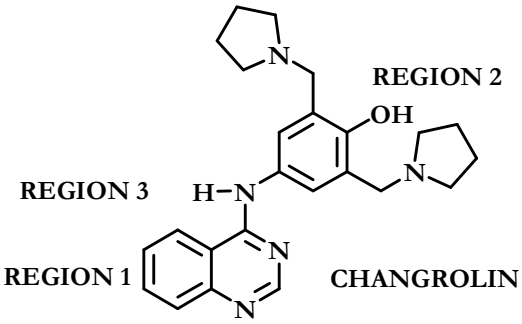

Figure 1 : Changrolin regions

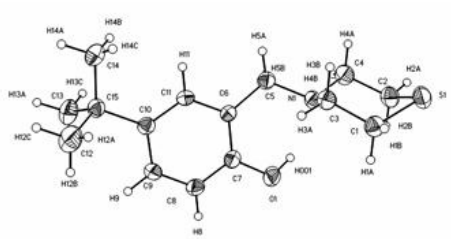

Figure 2 : A view of the structure of 4–tertbutyl–2–(thiomorpholin–4–ylmethyl)phenol

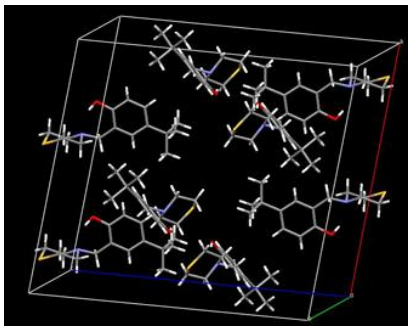

Figure 3 : A unit cell plot for 4–tertbutyl–2–(thiomorpholin–4–ylmethyl)phenol

Twenty four structural derivatives of the antiarrhythmic drug changrolin were synthesized and tested for hypotensor activity. It was found that while the bis(pyrrolidin-ylmehyl) phenol pattern of changrolin appeared to be optimal for ant arrhythmic activity (region 2)[3], the bis(mopholinylmethyl) phenol is important for hypotensor activity. The proof series was characterized by mass spectrometry, IR, ^{1}HNMR, ^{13}CNMR spectroscopy and X-ray crystallography. And the hypotensor activity was proof in a anesthetic rat, used BPA(Blood Pressure Analyzer) plus the program DMSI_2001. We report here the crystal structure of 4-tert-butyl-2-(thiomorpholin-4-ylmethyl)phenol which was obtained as a typical Mannich synthesis reaction[4,5].

EXPERIMENTAL

4-tertbutyl-2-(thiomorpholin-4-ylmethyl)phenol was prepared from 4-tertbutylphenol(1.0g., 6.6 mmol) and thiomorpholine(0.72g., 7.0 mmol) and 5 ml of formaldehyde(37%), they were mixed in a round flask fitted with a condenser. The mixture was irradiated with infrared light for 0.15 hr using a medicinal infrared lamp(250 Watts) and the reaction was monitored by tlc. The mixture was chromatographed on silica gel using a solvent gradient hexane/ethyl acetate. afforded one crystalline product, yield 70%. Colorless plates for X-Ray diffraction were obtained by recrystalization from a η-hexane/ethyl acetate solution of the compound, m.p.85-87^{0}C. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 634633.

RESULTS

The Crystal data of 4–tertbutyl–2–(thiomor pholin–4–ylmethyl)phenol, $C_{15}H_{23}NOS$ has the follow properties:

$C_{15}H_{23}N_1O_1S_1$, Monoclinic, C2/c, a=20.961 (4) A°, b=6.233(12) A°, c=23.980(5) A°, α=90°, β=06.27(3)°, γ=90°, 3008(6)A°3, Z=8, $R_{gt}(F)$= 0.0501, $wR_{ref}(F2)$=0.1269, T=293.15K.

The structure determination reveals one substituted 4–tertbutyl phenol with thiomorpholin linked via a methylene. There is a torsion angle of –38.00^{0} in N1/C5/C6/C7. The most notable feature of the crystal packing is the formation of a centro symmetric (H-O-C-C-C-N) six-member ring mediated by hydrogen bonds. The parameters associated with this ring are d(N1–H001)=1.9439 A°, with an angle of 102.27° at C7/O1/H001 and 90.98° for C5/N1/H001. Further a torsion angle between O1/H001/N1/C5 of -9.44°.

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SUPLEMNTARY INFORMATION

A cif file is available

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