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Research Article

Synthesis and characterization of thiosalicylamide derivatives as antihypertensive agents.

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Abstract

The foremost objective of present study is synthesis of Novel Thiosalicylamide derivatives as calcium channel blockers. The significance of Thiosalicylamide however cannot be ruled out owing to its better known advantage on the basis of SAR. Benzothiazipine derivative (diltiazem) and the thiosalicylamide derivatives as calcium channel blocker besides being very effective for lowering of blood pressure with the help of blocking of calcium channels. Among the various chemical classes of calcium channel blocker reported in the literature few significant once include derivatives of Thiosalicylamide. A series of compounds were synthesized taking 2-(benzylthio) benzoyl chloride as lead molecule and substitution were done in this molecule to obtain different derivatives. Synthesized compounds were obtained in satisfactory yield and were characterized by TLC, FT-IR, H^1 NMR spectral data. On the basis of above study it is suggested that substituted compounds is having significant calcium channel antagonistic action.

Key words: Benzodiazepine, thiosalicylamide, calcium channel blocker, Synthesis**.**

Introduction :

It is a discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties, and their quantitative structure-activity relationships (QSAR). Pharmaceutical chemistry isfocused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products. Compounds used as medicines are overwhelmingly organic compounds including small organic molecules and biopolymers. However, inorganic compounds and metal-containing compounds have been found to be useful as drugs. For example, the cis-platin series of platinum-containing complexes have found use as anti-cancer agents.[1]

Hypertension is defined as condition in which systolic and or diastolic blood pressure exceed above 140/90mm Hg, an agent that lowers blood pressure is called the antihypertensive agent.

The most desired action is slow reduction of blood pressure with prolonged effect further increased doses should cause a more prolonged effect rather than a more pronounced fall in blood pressure finally the drug should be active after oral administration because they would be used for extended periods.[2]

Voltage-gated calcium channels are integral membrane proteins that allow calcium ions to flow into the cell cytoplasm from the extracellular milieu, in response to membrane depolarization. This class of ion channel is found in virtually all types of excitable cells, ranging from neurons and glial cells to muscle cells. The functional inventory of calcium channels is equally broad, spanning from triggering of muscle contraction over control of neurotransmitter release to electrical excitation (calcium action potentials). The diversity of calcium channel function is reflected in their molecular heterogeneity: Several genes, encoding biophysically and pharmacologically distinct types of calcium channels, have been cloned and characterized functionally. These different types of calcium channels play specialized roles in cellular function; for instance, L-type calcium channels mediate muscle contraction and N- and P/Q-type calcium channels control neurotransmitter release.[3]

The foremost objective of present study is synthesis of Novel Thiosalicylamide derivatives as calcium channel blockers. The significance of Thiosalicylamide however cannot be ruled out owing to its better known advantage on the basis of SAR.

Materials and Methods[6-13]

Method of Preparation

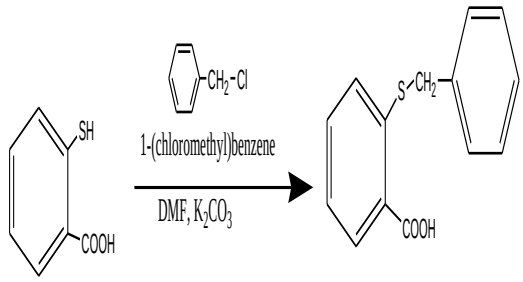
The present work comprises synthesis of the thiosalicylamide derivatives. The steps involved in the synthesis:

1. 2(benzyl thio) benzoic acid
2. 2(benzyl thio) benzoyl chloride (lead molecule)
3. (a) N1- (S- (4- Methoxybenzyl) thiosalicyloyl)- N4- Hydroxy phenyl piperazin (b) N1-(S-(Methoxybenzyl) thiosalicyloyl)- N4- fluoro phenyl piperazine

STEP 1 –

CHEMISTRY –

Synthesis

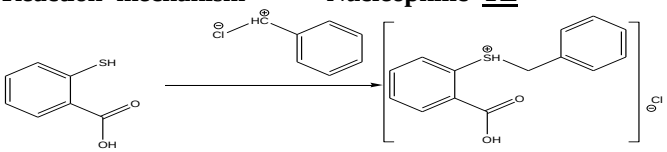


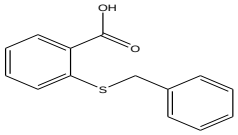
2-mercaptobenzoic acid 2-(benzylthio)benzoic acid

Procedure

To a solution of 1.542 gm of Thiosalicylic acid and 4.14 gm of K_2CO_3 in 20 ml of dimethyl formamide (DMF) , 1.56 gm of benzyl chloride was slowly added with stirring. The mixture was refluxed at 152^0 C for 22 hours , and then cooled to room temperature . Addition of water (20 ml) and adjusting the pH to 3.0 with 3.0 M HCl resulted in the formation of white precipitate. The precipitate was collected by filtration and washed with acetone and recrystalisation with methanol to give intermediate (2 benzylthio-benzoic acid) as a white powder.

Reaction mechanism[4,5,6] – Nucleophilic TL

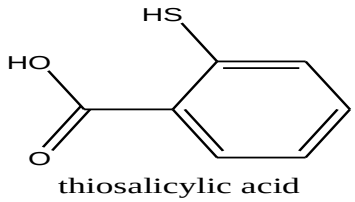




displacement

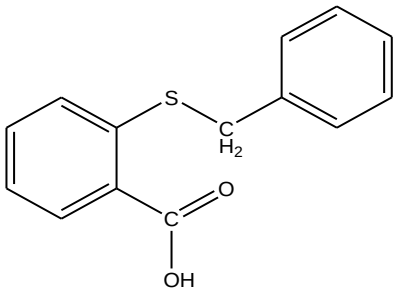
TLC –
Solvent system - ethanol: chloroform : n-Haxane (8:1:1)
R_f value of Thiosalicylic acid = 0.80
R_f value of 2 benzyl thio benzoic acid = 0.72
Melting Point -
1. Melting Point range of thiosalicylic acid = 158^0C – 165^0C (162^0C – 164^0C)
2. Melting Point range of 2 benzyl thio benzoic acid = 194^0C – 198^0C (195^0-200^0C)

FTIR interpretation
Thiosalicylic acid (starting material)



IR(KBr)cm^{-1}

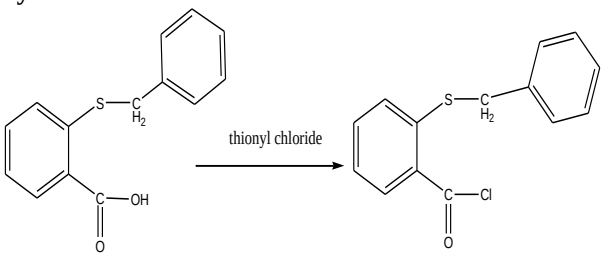
2 (benzyl thio) benzoic acid (Intermediate)



^{1}HNMR Interpretation
2 (benzyl thio) benzoic acid

Step 2
2 (benzyl thio) benzoyl chloride (lead molecule)

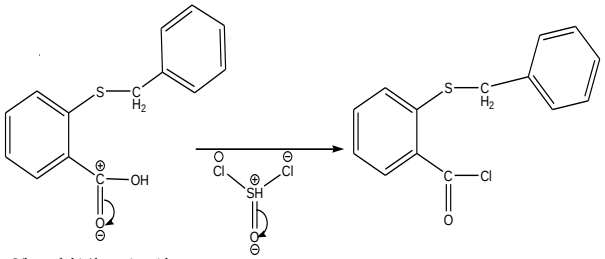
Synthesis



2(benzyl thio)benzoic acid 2-(benzyl thio)benzoyl chloride

Reaction mechanism

Chlorination



2(benzyl thio)benzoic acid 2-(benzyl thio)benzoyl chloride

Procedure

2 (benzyl thio) benzoyl chloride were obtained by refluxing 100^{0}C a mixture of 0.822 mg (3.0 mmol) of 2 (benzyl thio) benzoic acid and 10 ml thionyl chloride for 6 hours. Removal of excess thionyl chloride by evaporation at 80^{0}C left as 2 (benzyl thio) benzoyl chloride of pale yellow semisolid , which was used in subsequent steps without further purification (70%)

TLC –

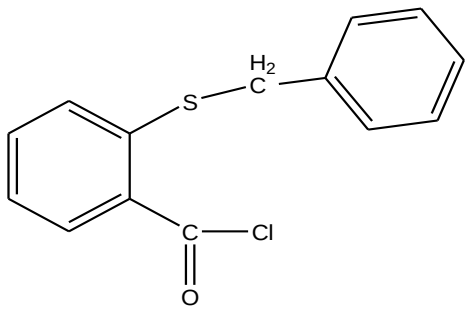
Solvent system - ethanol: chloroform : n-Haxane (8:1:1)

R_f value of 2- (benzyl thio)Benzoyl chloride = 0.79

R_f value of 2 -(benzyl thio) benzoic acid = 0.97

FTIR Interpretation

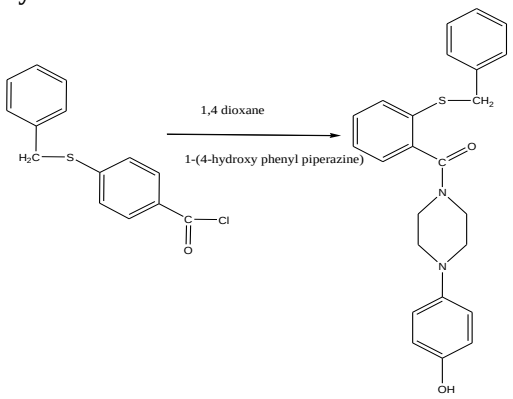
2 (benzyl thio) benzoyl chloride in KBr (cm^{-1})



STEP-3 (a)

N1-(S-(4-Methoxybenzyl) thiosalicyloyl)-N4-hydroxy phenylpiperazine

Synthesis::



Procedure:

A suspension of intermediate in warm benzene (30 mL) was slowly added to a 20 mL solution of 4.0 g (0.04 mol) 1-(4- hydroxyl phenylpiperazine) in 20 mL benzene. The mixture was stirred overnight at room temperature. After the addition of 40 mL water the aqueous layer was extracted twice with 15 mL methyl chloride. The combined methylene chloride extracts and the benzene layer Washed with 10% NaOH were dried over anhydrous magnesium sulphate . Removal of the solvents under reduced pressure left an oily product that gave a solid upon crystallization from hot petroleum ether (10 mL). Collection of the separated solid by suction filtration followed by washing with cold petroleum ether gave 3.4 g (75%) of compound N1-(S-(4-Methoxybenzyl) thiosalicyloyl)-N4-hydroxy phenylpiperazine [8-15].

TLC-

Solvent system- Ethanol: chloroform: n-Hexane

8 : 1 : 1

R_f value of 2 (benzyl thio) benzoyl chloride = 0.79

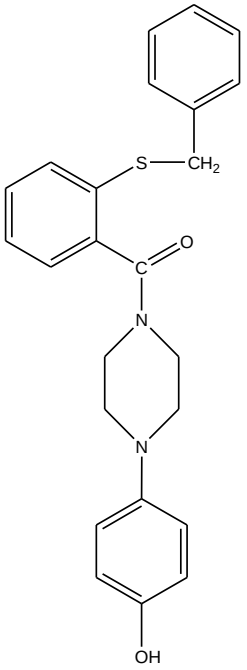
R_f value of N1-(S-(4-Methoxybenzyl) thiosalicyloyl)-N4-phenylpiperazine = 0.60

Melting point :

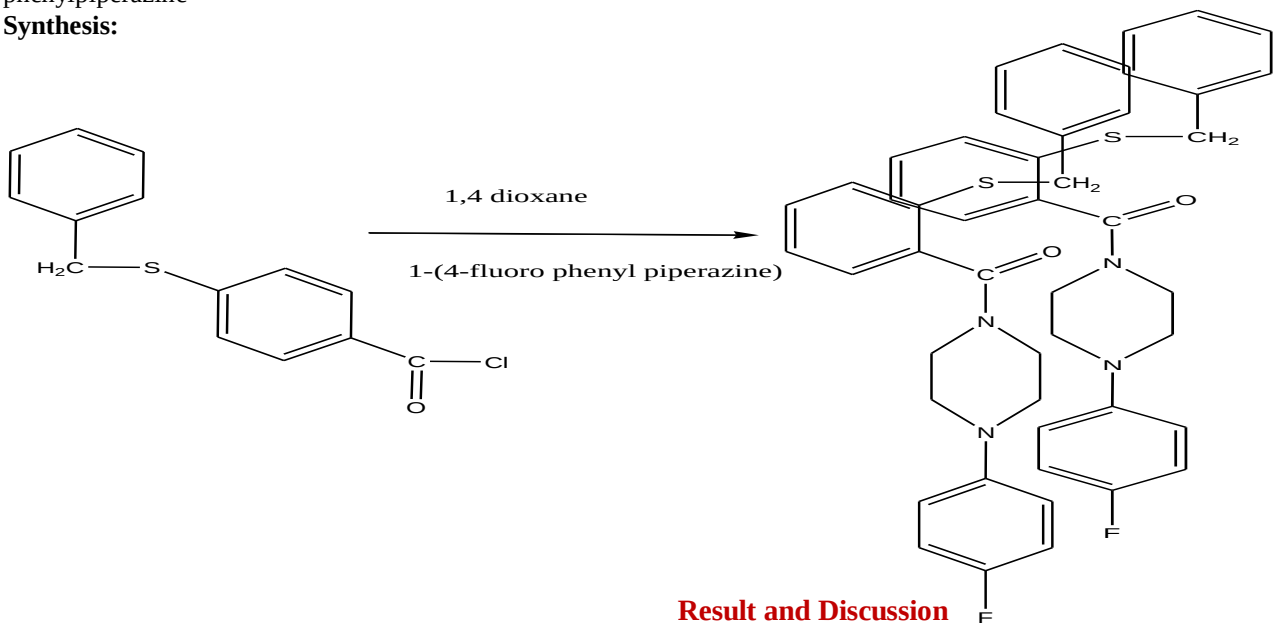
Melting point range for 2(benzyl thio) benzoyl chloride = 140-146^{0}C

Melting point range for N1-(S-(4-Methoxybenzyl) thiosalicyloyl)-N4 hydroxy-phenylpiperazine = 100 -150^0 C

FTIR Interpretation:



Step 3 (b)
N1-(S-(4-Methoxybenzyl) thiosalicyloyl)-N4- fluoro phenylpiperazine
Synthesis:



Procedure:
A suspension of intermediate in warm benzene (30 mL) was slowly added to a 20 mL solution of 4.0 g (0.04 mol) 1 –(4-fluoro phenylpiperazine) in 20 mL benzene. The mixture was stirred overnight at room temperature. After the addition of 40 mL water the aqueous layer was extracted twice with 15 ml methyl chloride . The combined methylene chloride extracts and the benzene layer Washed with 10% NaOH were dried over anhydrous MgSO 4 . Removal of the solvents under reduced pressure left an oily product that gave a solid upon crystallization from hot petroleum ether (10 mL). Collection of the separated solid by suction filtration followed by washing with cold petroleum ether gave 3.4 g (68%) of compound N1-(S-(4-Methoxybenzyl) thiosalicyloyl)-N4- fluoro phenylpiperazine.
TLC-
Solvent system- Ethanol: chloroform: n-Hexane
8 : 1 : 1

R_f value of 2 (benzyl thio) benzoyl chloride = 0.79
R_f value of N1-(S-(4-Methoxybenzyl) thiosalicyloyl)-N4-phenylpiperazine = 0.70

Melting point :
Melting point range for 2(benzyl thio) benzoyl chloride = 140-146^{0}C
Melting point range for N1-(S-(4-Methoxybenzyl) thiosalicyloyl)-N4- fluoro phenylpiperazine = 25-29^0 C
FTIR Interpretation :

Result and Discussion

Literature survey conducted on the current research work showed that the Thiosalicylamide possess calcium channel blocking activity. The activity of the thiosalicylamide can be enhanced by the attachment of different substitution in the lead molecule which possess

calcium channel blocking activity. In the current research work few thiosalicylamide derivatives have been synthesized and characterized by thin layer chromatography, melting point, IR and proton NMR, Mass spectroscopy.

Benzothiazines derivatives (diltiazem) and Thiosalicylamide derivatives as calcium channel blocker being very effective for lowering of blood pressure with the help of blocking calcium channels. Among the various chemical classes of calcium channel blocker reported in the literature few significant one include derivative of thiosalicylamide. The foremost objective of present study was synthesis of novel Thiosalicylamide derivatives as calcium channel blocker. The significance of Thiosalicylamide however cannot be ruled out owing to its better known advantages on the basis of SAR.

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Reference

1 James S.; "A development of a database analysis that provides putative metabolic enzyme reactions for Ligand-based drug design". *Computational Biology and Chemistry*, **2009**, 149–159.

the Essentials of Medical Pharmacology", 5th edition, Jaypee brothers medical publishers Pvt. Ltd., New Delhi, 2003, 503-504.

2 Kulkarni, S.K. *Hand Book of Experimental Pharmacology*. 3rd ed.; Vallabh Prakashan, 1999, pp 13.

3 1. American Heart Association. 2002 Heart and Stroke Statistical Update. Dallas, Tex: American Heart Association; 2001. [Context Link]

4 Cutler JA, MacMahon SW, Furberg CD. Controlled clinical trials of drug treatment for hypertension: a review. Hypertension. 1989;13:I36–I44. [Medline Link] [BIOSIS Previews Link] [Context Link]

5 Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as firstline agents: a systematic review and meta-analysis. JAMA. 1997;277:739–745. [Fulltext Link] [Medline Link] [BIOSIS Previews Link] [Context Link]

6 The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med. 1997;157:2413–2446. [Fulltext Link] [Medline Link] [BIOSIS Previews Link] [Context Link]

7 US Renal Data System, *USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States.* Bethesda, Md National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases2003;

8 National Kidney Foundation, K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39S1- S246 PubMed

9 Rahman MSmith MC Chronic renal insufficiency: a diagnostic and therapeutic approach. *Arch Intern Med* 1998;1581743- 1752 PubMed Link to Article

10 Mailloux LU Hypertension in chronic renal failure and ESRD: prevalence, pathophysiology, and outcomes. *Semin Nephrol* 2001;21146- 156 PubMed Link to Article

11 Black DM, Brand RJ, Greenlick M,Hughes G, Smith J, for the SHEP Pilot Research Group.Compliance to treatment for hypertension in elderly patients: the SHEP pilot study.J Gerontol1987;42:552–7.

12 Mark J Cziraky PharmD, Assistant Professor of Clinical Pharmacy, Philadelphia College of Pharmacy and Science, Philadelphia, PA; and Consultant, Department of Health Outcomes and Clinical Research, HealthCare Center at Christiana, 200 Hygeia Dr, Newark, DE 19713, FAX 302/421-215

13 Kohlhardt, M. *Basic Res. Cardiol.* **76**, 589−601 (1981). | PubMed | ISI | ChemPort |.

14 Reuter, H. *Nature* **301**, 569−574 (1983). | PubMed | ISI | ChemPort |.