International Journal of Pharmaceutical Chemistry
ISSN: 2249-734X (Online)
Journal DOI: 10.7439/ijpc
CODEN: IJPCH3 (American Chemical Society)
Research Article

Synthesis, Characterization and Pharmacological Evaluation of Thiosalicylamide Derivative as a Class of Calcium Channel Blocker

Anirudh Joshi[1*], D. N. Shrivastava[1] and Chain Singh Base[2]

[1]*B. R. Nahata College of Pharmacy, Mandsaur (M.P.) India*
[2]*Jodhpur National University, Jodhpur Rajasthan, India*

Abstract
Objective: Hypertension is one of the major causes of the cardiovascular diseases and in the later stages, it also damages the brain, kidneys, eyes and coronary arteries. It is also life threatening as it causes heart strokes and attacks. The calcium channels regulate blood pressure by muscle contraction triggered by neurotransmitter release to electrical excitation.
Method: Calcium channel blocker drugs reduce intracellular calcium transfer to limit ATP release to reduce muscle cell contractility. They act, especially on the nodal tissues in the heart and arterial smooth muscle cells in which only slow calcium channel blockers opens without triggering of fast sodium ion channels. Pharmacophore approach is employed to generate novel thiosalicylamide derivatives having calcium channel blocking activity for treatment of hypertension.
Result: These novel thiosalicylamide derived lead molecules are synthesized and tested for their in-vivo pharmacological activity by using isolated guinea-pig ileum muscles.
Keywords: Thisalicylamide, Hypertension, Calcium Channel Blocker, Pharmacological evaluation, Guinea pig ileum.

1. Introduction

In today's era of globalization, characterized by hurry, worry, and curry, the incidences of cardiovascular diseases are on the rise. Hypertension is a condition where the blood pressure is constantly higher than normal. This poses a serious health risk because it forces the heart to work extra hard. Constantly higher blood pressure can damage the coronary arteries, the brain, the kidneys, and the eyes. Hypertension is a major cause of strokes and heart attacks.[4]

High blood pressure is a potential risk factor for cardiovascular diseases, independent of the presence or absence of other risk factors, for example, smoking, diabetes, and/or hypercholesterolemia. The other factors such as genetics, age, sex, race, diet, and environmental factors (e.g., stress and physical activity), also play important role in elevation of the blood pressure.

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).

Arterial blood pressure is controlled with a narrow range to provide a sufficient perfusion of the tissues without causing damage to the vascular system, specially the arterial intimae. The arterial blood pressure is directly proportional to the product of cardiac output and peripheral vascular resistance. In normal and abnormal hypertensive individual both the cardiac output and peripheral resistance are regulated mainly by two overlapping controlled mechanisms. In controlling of blood pressure Benzothiazepine and thiosalicylamide analogous play important role by the blocking calcium channel present in blood vessels. The baroreflexes are mediated by the

* Correspondence Info
Anirudh Joshi
B. R. Nahata College of Pharmacy,
Mandsaur (M.P.) India
E mail: anijosh.joshi@gmail.com

sympathetic nervous system and the rennin angiotensin- aldosteron system. Most of the antihypertensive drugs lower the blood pressure by reducing cardiac output, or decreasing peripheral resistance.

Thiosalicylamide is a similar to Benzothiazepine compound which contain sulphur in form of thiol as well as amide group which are responsible for biological and pharmacological activity. On the basis of Pharmacophore study Benzothiazepine as calcium channel blocker the ring system is not important in terms of any biological activity only The Changing the ring shape and size generated derivatives that not only help in their right placement with the receptor. Thiosalicylamide as the calcium channel blocking activity but also resulted in several compounds that were more active than diltiazem [16].

A receptor-binding model identifying the benzene ring as a lipophilicity group that facilitates transport into the channel, and the absolute stereochemistry for the selective binding. Thiosalicylamide nucleus is similar to the Benzothiazepine nucleuses which are used as calcium channel blockers [36]. In these synthesis series, Benzothiazepine nucleus containing nitrogen atom which is replace by bioisosterism of nitrogen (-s-c-) [16].

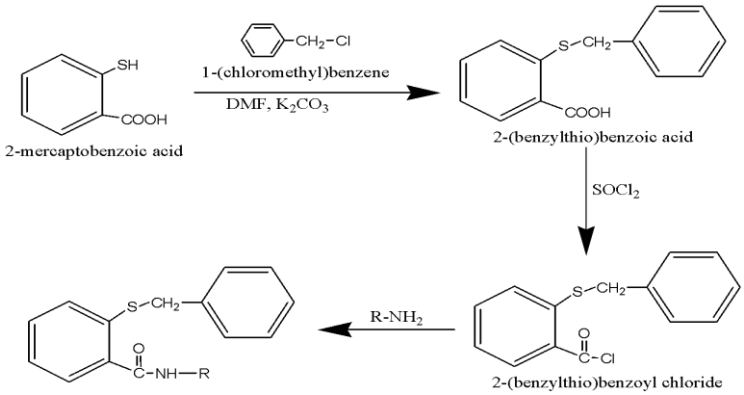
Pharmacophore is defined as the functional group or element in the drug molecule which is essential for the pharmacological action. In case of Benzothiazepine as calcium channel blocker the ring system is not important in terms of any biological activity. The ring bears the Pharmacophore and only help in their right placement with the receptor. Changing the heterocyclic ring size generated derivatives that not only retained the calcium channel blocking activity but also resulted in several compounds that were more active than Diltiazem. It has been proved by extensive studies that the ring system is not important in terms of any biological activity, but it bears the Pharmacophore and only help in their right placement with the receptor. In Diltiazem two essential Pharmacophore holds responsibility for binding with calcium channels: the aryl ether (to act as hydrogen bond acceptor), and the basic nitrogen (for ionic bonding with a negative charge on the channel). The current series of compounds were designed to lack the ring system, and accordingly the stereo-chemical factors were eliminated [37].

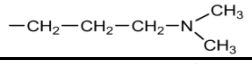
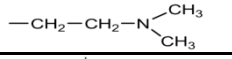
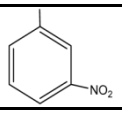
In spite of lacking the stereochemistry, the spatial conformational relationships of the remaining Pharmacophore are expected to be maintained for the fully extended methoxy-phenethylamines [16].

2. Experimental

Melting point reported is uncorrected, and determined by digital melting point apparatus model VMP-DS, Veego. FT-IR spectra were obtained with KBr on FT-IR 8400 S (Shimadzu, Japan), spectrophotometer.^{1}HNMR spectra were obtained on Brucker Avance II 400 NMR using Tetramethylsilane (TMS) as internal standard (chemical shift in δ, ppm).The purity of all chemicals and compound was tested by performing thin layer chromatography run on silica gel plates. Iodine vapors were used for visualization of chromatographic run on silica plates. All the solvent were distilled before use according to purification of organic solvent procedures.

2.1 Synthetic Scheme



S. No.	R Substitution
I.	
II.	
III.	

Method of Preparation

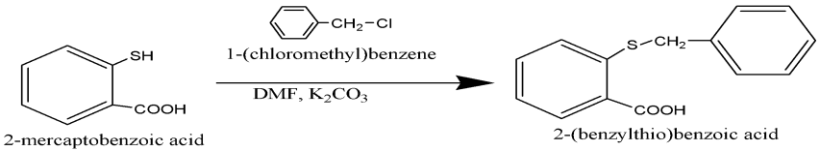
The present work comprises synthesis of the Thiosalicylamide derivatives. The steps involved in the synthesis:

1. 2(benzyl thio) benzoic acid.
2. 2(benzyl thio) benzoyl chloride.(lead molecule).
3. (i) 2(benzyl thio)-N-(3-(dimethyl amino) propyl) benzamide.
   (ii) 2(benzyl thio)-N-(3-(dimethyl amino) ethyl) benzamide.
   (iii) 2(benzyl thio)-N-(3-nitro phenyl) benzamide.

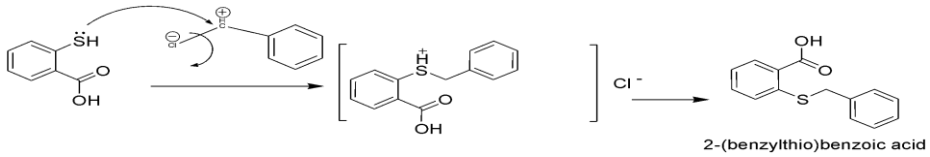
Chemistry

Step 1: Preparation of 2(benzylthio)benzoic acid (Intermediate-1)from 2-mercaptobenzoic acid (starting material)

Synthesis



Reaction mechanism [31,32]: Nucleophilic displacement



Procedure

To a solution of 1.542 g of Thiosalicylic acid (1) and 4.14 g of K_2CO_3 in 20mL of dimethyl formamide (DMF), 1.56 g of benzyl chloride was slowly added with stirring. The mixture was refluxed at 152 ^{0}C for 22 h, 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 0.780 mg of intermediate (2 (benzyl thio) benzoic acid) as a white powder (0.49%, melting point 195-200 ^{0}C).

TLC

Solvent system-

Ethanol: chloroform: n-Hexane (8:1:1),

R_f value of Thiosalicylic acid = 0.89, R_f value of 2(benzyl thio) benzoic acid= 0.95.

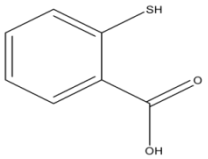
Melting point

Melting point range of Thiosalicylic acid = 154 – 159 ^{0}C

Melting point range of 2(benzyl thio) benzoic acid = 185 – 190 ^{0}C

FTIR Interpretation [33, 34]

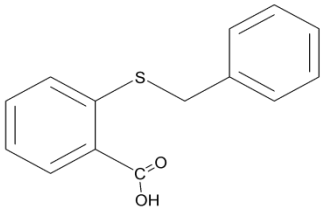
(i) Thiosalicylic acid (starting material)



IR(KBr) cm^{-1}

S. No.	Reported Value	Observed Value	Comment
1.	3050-3010 cm^{-1} (Pavia 51)	3055.03 cm^{-1}	C-H Stretch of aromatic ring
2.	1600-1585cm^{-1}and 1500-1400cm^{-1} (Silverstein 86)	1560 cm^{-1} and 1471 cm^{-1}	C=C Stretch of aromatic ring
3.	3200-2400 cm^{-1} (Pavia 70)	3200-2500cm^{-1}	O-H Stretch of acid (broad peak)
4.	1730-1700 cm^{-1} (Pavia 69)	1677cm^{-1} (decreased due to conjugation)	C=O Stretch of acid
5.	Near 2550cm^{-1} (Pavia 87)	2522.72 cm^{-1}	S-H Stretch of thiol group

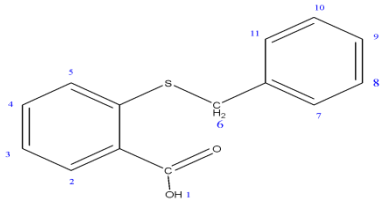
(ii) 2(benzylthio) benzoic acid (Intermediate)



S. No.	Reported Value	Observed Value	Comment
1.	3050-3010 cm^{-1} (Pavia 51)	3031.68 cm^{-1}	C-H Stretch of aromatic ring
2.	1600-1585cm^{-1} and 1500-1400 cm^{-1} (Silverstein 86)	1564.16 cm^{-1} and 1460 cm^{-1}	C=C Stretch of aromatic ring
3.	3050-3010 cm^{-1} (Pavia 51)	3031.68 cm^{-1}	C-H Stretch of alkane
4.	1300-1000 cm^{-1}(Pavia 52)	1261.36 cm^{-1}	C-H bending of alkane
5.	1730-1710cm^{-1} (Pavia 69)	1676.03cm^{-1} (due to conjugation)	C=O Stretch of acid
6.	3200-2400cm^{-1}(Pavia 70)	3200-5200 cm^{-1}	O-H Stretch of acid(broad peak)
7.	700-600 cm^{-1} (Silverstein 106)	698 cm^{-1}	C-S Stretch of thio methyl group

^{1}H-NMR Interpretation (DMSO) [33, 34]

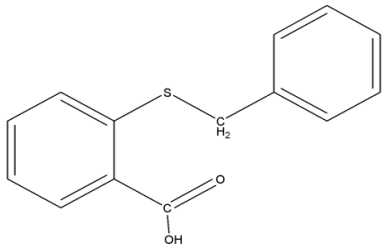
2(benzylthio) benzoic acid



S. No.	Values	Comment
1	δ 4.33, s,2H	Ar aliphatic proton methyl to thiol group (6)
2.	δ 7.29,t, and,td,2H,J_m= 9.8 Hz, J_m=9.0Hz	Ar proton meta to methyl group (8,9,10)
3.	δ 7.40,dt,2H,J_o=9.1Hz,J=2.6 Hz,	Ar proton ortho to methyl group (3,7,11)
4.	δ 7.65,dd, 2H,J_o=2.2 Hz,	Ar proton ortho to thiol group (5)
5.	δ 7.73,dt,2H,Jm=9.1 Hz, J_o=2.6 Hz,	Ar proton to acid group(4)
6.	δ 7.81, dd,2H,J_o= 2.2 Hz ,	Ar proton ortho to acid group (2)
7.	δ 12.33, s,1H,	Due to acid proton attach to Ar ring(1)

MASS Interpretation: [33, 34]

2(benzylthio) benzoic acid (Intermediate)



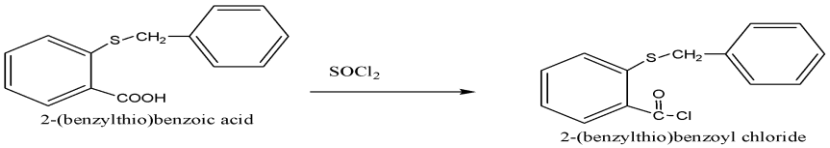
Mass: MS (ESI) m/z 244.15 (M^+), m/z 245.06 (M+1), m/z 153.01,m/z 107, m/z 91.09 .

Elemental Analysis:

Element	% Calculated	% Found	Difference
C	68.83	68.43	0.40
H	4.95	4.51	0.44
O	13.10	13.04	0.06

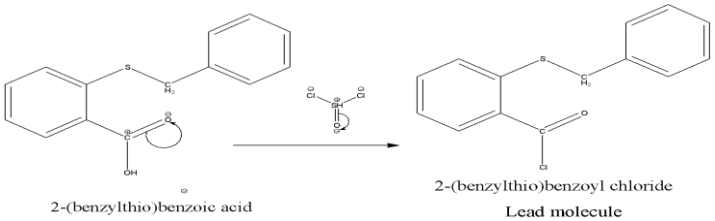
Step 2: Preparation of 2 (benzylthio) benzoyl chlorides (Intermediate-2) from 2(benzylthio)-benzoic acid (Intermediate-1)

Synthesis



Reaction Mechanism [31, 32]

Chlorination



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 solid, which was used in subsequent steps without further purification (70%).

TLC– Solvent system- ethanol: chloroform: n-Hexane (8.2:1:0.8), R_f value of 2(benzylthio) benzoic acid= 0.97, R_f value of 2(benzyl thio) benzoyl chloride = 0.89.

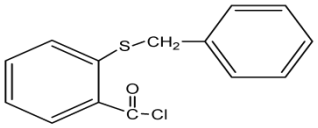
Melting Point:

Melting point range for 2 (benzyl thio) benzoic acid = 185– 190 ^{0}C

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

FTIR Interpretation [33, 34]

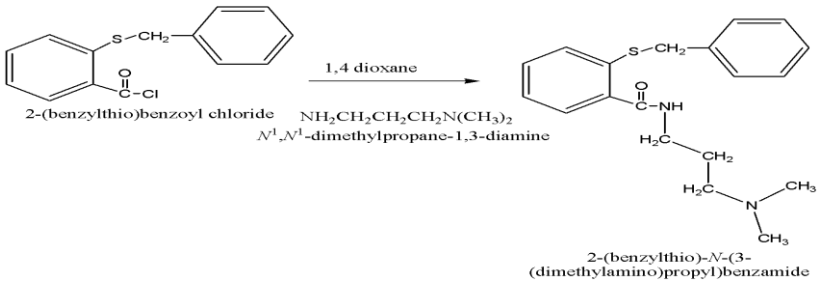
2 (benzyl thio) benzoyl chloride in KBr (cm^{-1})



S. No.	Reported Value	Observed Value	Comment
1.	3050-3010 cm^{-1}(Pavia 51)	3031.68 cm^{-1}	C-H Stretch of aromatic ring
2.	1600-1585 cm^{-1} and 1500-1400 cm^{-1} (Silverstein 86)	1564.16 cm^{-1} and 1460 cm^{-1}	C=C Stretch of aromatic ring
3.	3050-3010 cm^{-1}(Pavia 51)	3031.68 cm^{-1}	C-H Stretch of alkane
4.	1300-1000 cm^{-1}(Pavia 52)	1261.36 cm^{-1}	C-H bending of alkane
5.	1780-1775cm^{-1}(Pavia 78)	1760 cm^{-1} (due to conjugation)	C=O Stretch for acid chloride
6.	730-550cm^{-1}(Pavia78)	655cm^{-1}	C-Cl Stretch of acid chloride
7.	700-600 cm^{-1}(Silverstein 106)	700.11 cm^{-1}	C-S Stretch of thio methyl group

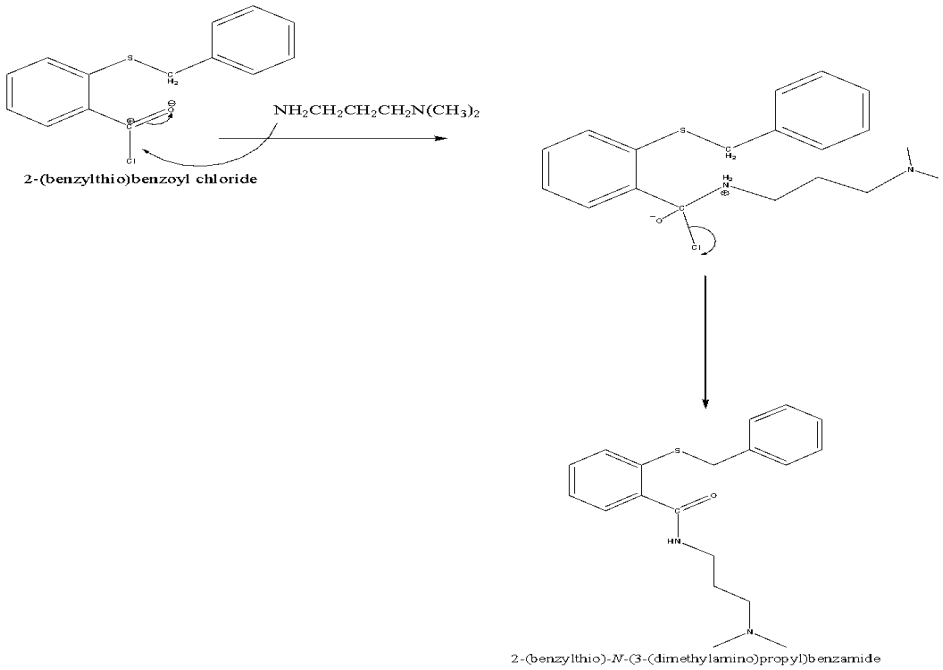
Step-3 (i): Preparation of 2(benzylthio)-N-(3-(dimethylamino)propyl) benzamide (Lead Molecule-1) from 2(benzylthio)benzoyl chloride (Intermediate-2)

Synthesis



Reaction Mechanism [31, 32]

Amidation



Procedure

2(benzylthio)-N-(3-(dimethylamino)propyl)benzamide was prepared by slowly adding a suspension of the acid chloride 3 (878 mg, 3.0 mmol) in 10 mL 1,4 Dioxane to a solution of 528 mg (6 mmol) of N,N-dimethylpropanediamine in 10 mL1,4 Dioxane. The mixture was stirred overnight at room temperature. Water (20 mL) was added and the aqueous layer separated. The 1,4 Dioxane layer was further washed with 10% NaOH solution (10 mL) and the combined aqueous layers were extracted with two portions of dichloromethane(10 mL each) to recover any trapped product. Filtration of the drying material followed by solvent removal left 2(benzylthio)-N-(3-(dimethylamino) propyl) benzamide as an oily residue. Refluxing with petroleum ether at 70^{o}C for 4 hr and cold 0 ^{o}C for overnight and gave white crystalline material. Filtration of the separated crystals and characterized.

TLC-

Solvent system – Ethanol: chloroform: n-Hexane

8 : 1 : 1

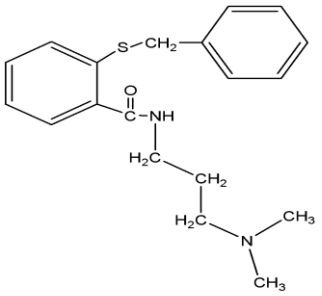
R_f value of 2(benzylthio)benzoyl chloride = 0.85.

R_f value of 2(benzylthio) -N-(3 dimethylamino)propylbenzamide =0.33.

Melting point:

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

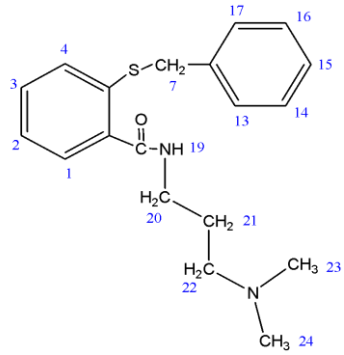
Melting point range for 2(benzylthio)-N-(3 dimethylamino)propylbenzamide = 64-70 ^{0}C



FTIR Interpretation [33, 34]

S. No.	Reported Value	Observed Value	Comment
1.	3050-3010 cm^{-1}(Pavia 51)	3058.89 cm^{-1}	C-H Stretch of aromatic ring
2.	1600-1585 cm^{-1} and 1500-1400 cm^{-1} (Silverstein 86)	1583.45 cm^{-1} and 1463.87 cm^{-1}	C=C Stretch of aromatic ring
3.	3050-3010 cm^{-1} (Pavia 51)	2977.89 cm^{-1}	C-H Stretch of alkane
4.	3000-2800 cm^{-1}(Pavia 40)	2943.17 cm^{-1}	C-H Stretch of chain of alkane
5.	1680-1630cm^{-1}(Pavia 77)	1635.52 cm^{-1}	C=O Stretch of amide
6.	3350-3180 cm^{-1}(Pavia 77)	3382.91 cm^{-1} and 3170.76 cm^{-1}	N-H Stretch of primary amide group
7.	1640-1550 cm^{-1}(Pavia 77)	1583 cm^{-1}	N-H banding of amide group
8.	700-600 cm^{-1}	711 cm^{-1}	C-S Stretch of thiol
9.	3400-3300 cm-^{1} (Silverstein 102)	3382cm^{-1}	N-H Stretch of primary amine

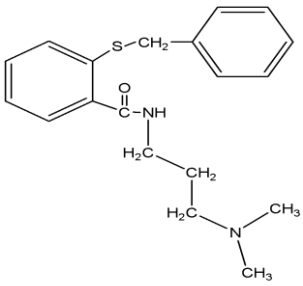
^{1}H NMR Interpretation [33, 34]



2-(benzylthio)-*N*-(3-(dimethylamino)propyl)benzamide

S. No.	Values	Comment
1	δ1.76, q, 2H,*J*=1.8Hz	Aliphatic proton to amide group (21)
2.	δ 2.14, s, 6H	Aliphatic proton to amide group (23,24)
3.	δ 2.37, t,2H,*J* =7.5 Hz	Aliphatic proton to amide group (22)
4.	δ 3.41, t, 2H,*J*=7.4Hz	Aliphatic proton to amide group(20)
5.	δ 4.33, s,2H	Due to methyl hydrogen(7)
6.	δ 6.92, td, 2H,J_m= 9.3, *J*=1.4 Hz ,	Ar proton meta to amide group (2)
7.	δ 7.18, td, 2H,J_m=9.1, J_m=1.9 Hz	Ar proton to methyl group(14,16)
8.	δ 7.24, tt,2H, *J*= 9.8 Hz	Ar proton to methyl group (15)
9.	δ 7.40, dt,2H, *J*= 9.1, *J*=2.6 Hz	Ar proton to methyl group(13,17)
10.	δ 7.65, dd, 2H, *J*= 9.1, *J*=2.1Hz,	Ar proton to amide group (4)
11.	δ 7.73, td,2H, *J*= 9.3, *J*=2.6Hz	Ar proton to amide group (3)
12.	δ 7.80, dd,2H,J_o=9.2, *J*=2.02Hz	Ar proton to amide group (1)

MASS Interpretation [33, 34]:



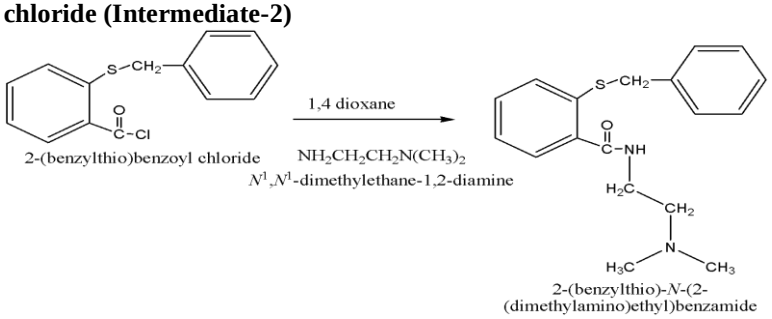
2-(benzylthio)-*N*-(3-(dimethylamino)propyl)benzamide

Mass: MS (ESI) m/z 328.03 (M^{+}), m/z 329.09 (M+1), m/z 237,m/z 207,m/z 149, m/z 91.24 .

Elemental analysis:

Element	% Calculated	% Found	Difference
C	69.47	68.98	0.49
H	7.36	6.88	0.48
N	8.53	8.01	0.52
O	4.87	4.40	0.47

Step 3(ii): Preparation of 2(benzylthio)-N-(3-(dimethylamino)ethyl) benzamide (Lead Molecule-2) from 2(benzylthio)benzoyl chloride (Intermediate-2)



Procedure

2(benzylthio)-N-(3-(dimethylamino)ethyl)benzamide was prepared by slowly adding a suspension of the acid chloride 3 (878 mg, 3.0 mmol) in 10 mL 1,4 Dioxane to a solution of 528 mg (6 mmol) of N,N-dimethylpropanediamine in 10 mL1,4 Dioxane. The mixture was stirred overnight at room temperature. Water (20 mL) was added and the aqueous layer separated. The 1,4 Dioxane layer was further washed with 10% NaOH solution (10 mL) and the combined aqueous layers were extracted with two portions of dichloromethane (10 mL each) to recover any trapped product. Filtration of the drying material followed by solvent removal left 2(benzylthio)-N-(3-(dimethylamino) ethyl) benzamide as an oily residue. Refluxing with petroleum ether at 70 ^{0}C for 4 hr and cold 0 ^{0}C for overnight and gave white crystalline material. Filtration of the separated crystals and characterized (0.46 gm., 55%).

TLC- Solvent system – Ethanol: chloroform: n-Hexane

8.3 : 1 : 0.7

R_f value of 2(benzyl thio) benzoyl chloride =0.89.

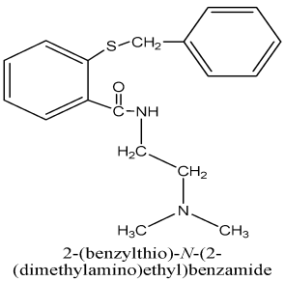
R_f value of 2(benzyl thio)-N-(2- (dimethyl amino) ethyl) benzamide =0.68.

Melting Point:

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

Melting point range for 2(benzyl thio)-N-(2- (dimethyl amino) ethyl) benzamide= 78-81^{0}C

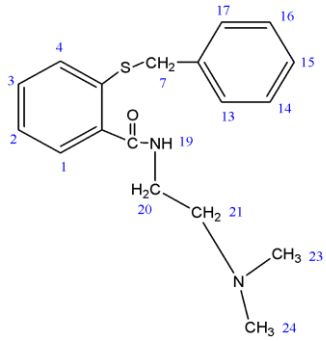
FTIR Interpretation



In KBr (cm^{-1})

S. No.	Reported Value	Observed Value	Comment
1.	3050-2950 cm^{-1}(Pavia 51)	2943.73cm^{-1}	C-H Stretch of aromatic ring
2.	1600-1585 cm^{-1} and 1500-1400cm^{-1} (Silverstein 86)	1542cm^{-1} and 1496 cm^{-1}	C=C Stretch of aromatic ring
3.	3050-2850 cm^{-1}(Pavia 51)	2819cm^{-1}	C-H Stretch of alkane
4.	3000-2800 cm^{-1}(Pavia 40)	2900 cm^{-1}	C-H Stretch of chain of alkane
5.	1680-1630cm^{-1}(Pavia 77)	1635 cm^{-1}	C=O Stretch of amide
6.	3350-3180 cm^{-1}(Pavia 77)	3345 cm^{-1}	N-H Stretch of primary amide group
7.	1640-1550 cm^{-1}(Pavia 77)	1635cm^{-1}	N-H banding of amide group
8.	700-600 cm^{-1}	675cm^{-1}	C-S Stretch of thiol
9.	3400-3300 cm-^{1}(Silverstein 102)	3345cm^{-1}	N-H Stretch of primary amine
10	1350-1000 cm^{-1}(Pavia 81)	1163 cm^{-1}	C-N Stretch of primary amide group

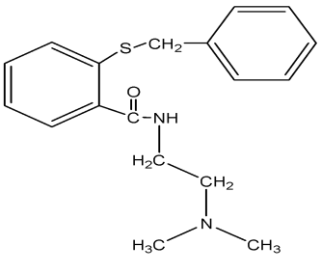
^{1}HNMR Interpretation ($CDCl_3$) [33, 34]



2-(benzylthio)-*N*-(2-(dimethylamino)ethyl)benzamide

S. No.	Values	Comment
1	δ2.19, s, 6H	Aliphatic proton to amide group (23,24)
2.	δ 2.37, t, 2H,*J*= 2.2 Hz	Aliphatic proton to amide group (21)
3.	δ 3.22, t,2H,*J*= 7.4Hz	Aliphatic proton to amide group (20)
4.	δ 4.30, s, 2H	Due to methyl hydrogen(7)
5.	δ 6.88, td,2H,*J*= 9.3Hz, J= 2.6Hz	Ar proton meta to amide group (2)
6.	δ 7.16, td, 2H, *J*= 1.92 Hz ,	Ar proton meta to amide group (14,16)
7.	δ 7.20, tt, 2H, J_m=7.8 Hz,	Ar proton to methyl group(15)
8.	δ 7.42,dt,2H, *J*= 2.6 Hz,	Ar proton to methyl group (13,17)
9.	δ 7.649, dd,2H, *J*= 9.0, *J*= 2.0 Hz	Ar proton to amide group(4)
10.	δ 7.72, td, 2H, *J*= 8.2, *J*=2.1 Hz	Ar proton to amide group (3)
11.	δ 7.81, dd,2H, *Jo*=2.6Hz	Ar proton to amide group (1)

MASS Interpretation [33, 34]:



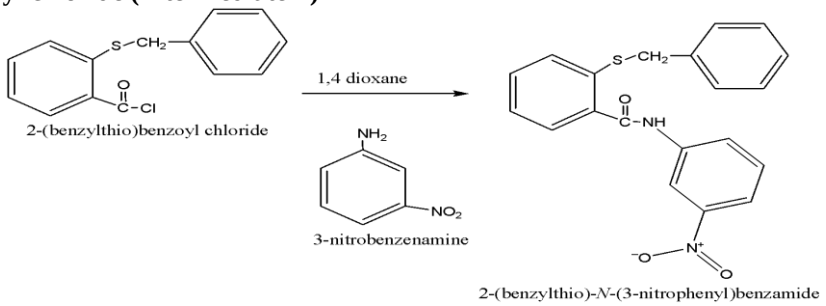
2-(benzylthio)-*N*-(2-(dimethylamino)ethyl)benzamide

Mass: MS (ESI) m/z 314.12 (M^+), m/z 315.01(M+1), m/z 223,m/z 193, m/z , m/z 91.06.

Elemental Analysis:

Element	% Calculated	% Found	Difference
C	68.75	68.57	0.18
H	7.05	6.52	0.53
N	8.91	8.69	0.22
O	5.09	4.90	0.19

Step-3(iii): Preparation of 2(benzylthio)-N-(3-nitrophenyl)benzamide (Lead Molecule-2) from 2(benzylthio)benzoyl chloride (Intermediate-2)



2-(benzylthio)benzoyl chloride

3-nitrobenzenamine

2-(benzylthio)-*N*-(3-nitrophenyl)benzamide

Procedure

2-(benzylthio)-N-(3-nitrophenyl) benzamide was prepared by slowly adding a suspension of the acid chloride 3 (878 mg, 3.0 mmol) in 10 mL 1,4 Dioxane to a solution of 528 mg (6 mmol) of N,N-dimethylpropanediamine in 10 mL1,4 Dioxane. The mixture was stirred overnight at room temperature. Water (20 mL) was added and the aqueous layer separated. The 1,4 Dioxane layer was further washed with 10% NaOH solution (10 mL) and the combined aqueous layers were extracted with two portions of dichloromethane (10 mL each) to recover any trapped product. Filtration of the drying material followed by solvent removal left 2(benzylthio)-N-(3-nitrophenyl) benzamide as an oily residue. Refluxing with petroleum ether at 70 ^{0}C for 4 hr and cold 0 ^{0}C for overnight and gave white crystalline material. Filtration of the separated crystals and characterized. (0.53 gm, 53%)

TLC-

Solvent system – Ethanol: chloroform: n-Hexane

8.2 : 0.8 : 1

R_f value of 2(benzyl thio) benzoyl chloride =0.82

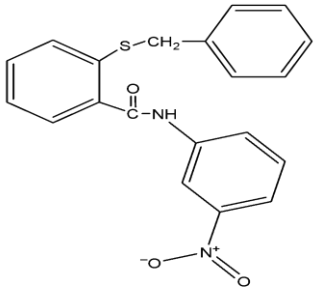
R_f value of 2(benzyl thio) -N-(3 dimethyl amino) propyl benzamide =0.62

Melting Point:

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

Melting point range for 2(benzyl thio)-N-3 (nitro phenyl) benzamide= 85-89^{0}C

FTIR Interpretation

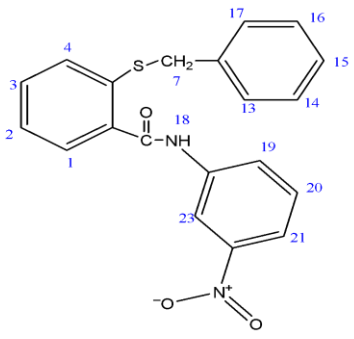


2-(benzylthio)-*N*-(3-nitrophenyl)benzamide

In KBr(cm^{-1})

S. No.	Reported Value	Observed Value	Comment
1.	3050-2950cm^{-1} (Pavia 51)	2977.89cm^{-1}	C-H Stretch of aromatic ring
2.	1600-1585cm^{-1}and 1500-1400cm^{-1} (Silverstein 86)	1583cm^{-1} and 1463cm^{-1}	C=C Stretch of aromatic ring
3.	1680-1630cm^{-1} (Pavia 77)	1635.52cm^{-1}	C=O Stretch of amide group
4.	3350-3180 cm^{-1} (Pavia 77)	3323cm^{-1}	N-H Stretch of primary amide group
5.	1640-1550 cm^{-1} (Pavia 77)	1635cm^{-1}	N-H banding of amide group
6.	700-600 cm^{-1} (Pavia 87)	675 cm^{-1}	C-S Stretch of thiol group
7.	1550-1490cm-^{1}and 1355-1315 cm^{-1} (Pavia 85)	1533cm^{-1} and 1334cm^{-1}	NO_2Stretch of nitro group

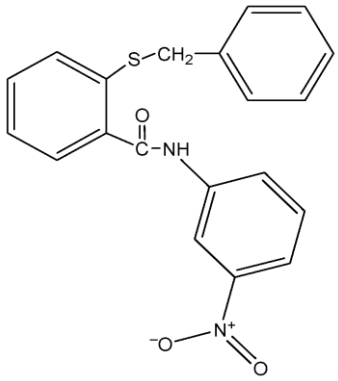
^{1}H-NMR Interpretation ($CDCl_3$) [33,34]



2-(benzylthio)-*N*-(3-nitrophenyl)benzamide

MASS Interpretation [33, 34]:

S. No.	Values	Comment
1	δ4.35,s,2H.	Due to methyl hydrogen (7)
2.	δ 6.93,td,2H,J_m=2.6 Hz.	Ar meta proton to amide group (2)
3.	δ 7.17,dt,2H,J_m=2.08 Hz.	Ar proton to amide group (14,16)
4.	δ 7.24, tt, 2H.	Ar proton to methyl hydrogen(15)
5.	δ 7.41, td,2H, J=2.9 Hz.	Ar proton ortho to methyl group (13,17)
6.	δ 7.66,dd,2H,J=3 Hz, Jo= 7.0 Hz.	Ar proton meta to amide group (4,20)
7.	δ 7.72, td,2H,Jm=1.5 Hz.	Ar proton to amidegroup(3)
8.	δ 7.79,dd,2H, J=2.2 Hz.	Ar proton ortho to amide group (1)
9.	δ 7.93, dt, 2H, J=8.1 Hz.	Ar proton ortho to nitro group (21)
9.	δ 8.04, dt,2H, J_o=2.1 Hz.	Ar proton ortho to amide group(19)
10.	δ8.77, t, 2H, J=7.8 Hz.	Ar proton ortho to nitro group (23)



2-(benzylthio)-*N*-(3-nitrophenyl)benzamide

Mass: MS (ESI) m/z 364.10 (M^+), m/z 365.02 (M+1), m/z 273.80, m/z 227.03, m/z 149.50, m/z 91.03.

Elemental Analysis:

Element	% Calculated	% Found	Difference
C	65.92	65.23	0.69
H	4.43	3.98	0.45
N	7.69	7.20	0.49
O	13.17	13.01	0.16

2.2 Pharmacological Evaluation

2.2.1 *Isolated tissue experiments*

The spasmogenic and spasmolytic activities of the synthesized lead molecules were studied by using isolated guinea-pig ileum preparations as described previously (Gilani et al., 2000). Respective segments of 2 cm length were suspended separately in 10 ml tissue baths containing Tyrode's solution, bubbled with a mixture of 95% oxygen and 5% carbon dioxide (carbogen) and maintained at 37°C. Composition of Tyrode's solutionwas: KCl 2.68, NaCl 136.9, MgCl2 1.05, NaHCO3 11.90, NaH2PO4 0.42, CaCl2 1.8 and glucose 5.55 mM. Intestinal responses were recorded isotonically using Harvard transducers and oscillograph. Each tissue was allowed to equilibrate for at least 30 min before the addition of any drug. Under these experimental conditions, guinea-pig ileum behaves as a quiescent smooth muscle preparation and is considered suitable for spasmogenic activity (Gilani and Aftab, 1992), allowing to test the relaxant (spasmolytic) activity directly without the use of an agonist. The contractile effect of the test materials was assessed as the percent of the maximum effect produced by the control drug, Nifedipine (10_M), and the inhibitory effect was measured as the percent change in spontaneous contractions of guinea-pig ileum obtained immediately before the addition of test substances.

2.2.1 *Guinea-pig trachea*

Trachea was dissected out and then cleaned free of the surrounding fatty tissues. The tracheal tube was cut into rings, 2–3mm wide, each containing about two cartilages. Each ring was opened by a longitudinal cut on the ventral side opposite to the smooth muscle layer, forming a tracheal strip with a central part of smooth muscle sandwiched between cartilaginous portions on the edges. The preparation was then mounted in a 20ml tissue bath containing Kreb's solution maintained at 37°C and aerated with carbogen gas. A tension of 1 g was applied to each

of the tracheal strip and was kept constant throughout the experiment. The tissue was equilibrated for 1 hour after which contractile responses to submaximal concentrations of carbachol (1 _M) were recorded until constant responses were obtained with a dose interval of 45 min, thus allowing to study the effects of test substances.

2.2.2 *Determination of calcium antagonist activity*

To assess whether the spasmolytic activity of the test substances was through calcium channel blockade, K+ was used to depolarize the preparations as described by Farre et al. (1991). K+ (50 mM) was added to the tissue bath, which produced a sustained contraction. Test materials were then added to the tissue bath in a cumulative fashion to obtain concentration-dependent inhibitory responses (Van Rossum, 1963). The relaxation of intestinal as well as aortic preparations, precontracted with K+ (50 mM) was expressed as percent of the control response mediated by K+.

To confirm the calcium antagonist activity of test substances, the tissue was allowed to stabilize in normal Tyrode's solution, which was then replaced with Ca2+-free Tyrode's solution containing EDTA (0.1 mM) for 30 min in order to remove calcium from the tissues. This solutionwas further replaced with K+-rich and Ca2+-free Tyrode's solution, having the following composition: KCl 50, NaCl 91.04, MgCl2 1.05, NaHCO3 11.90, NaH2PO4 0.42, glucose 5.55 and EDTA 0.1 mM. Following an incubation period of 30 min, control dose–response curves of Ca2+ were constructed. When the control DRCs of Ca2+ were found super-imposable (usually after two cycles), the tissue was pretreated with the plant extract for 60 min to test the possible calcium channel blocking effect. The DRCs of Ca2+ were reconstructed in the presence of different concentrations of the test material.Nifedipinewas used as a positive control.

3. Result and Discussion

In the current research work some Thiosalicylamide derivatives have been synthesized and characterized by thin layer chromatography, melting point, IR and ^{1}H NMR, MASS spectroscopy and calcium channel blocking activity data.

Table 5: Physicochemical data

S. No.	Name of compound	Melting point	% of yield	Mol. weight	Mol. formula
S.M.	Thiosalicylic acid	154-159^{o}C		154	$C_7H_6O_2S$

Chemical Characterization

I. By TLC

Solvent system – Ethanol: chloroform: n-hexane (8:1:1)

TLC Result – by R_f value

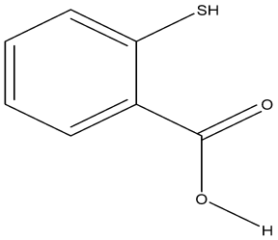
1. Thiosalicylic acid R_f value = 0.89

II. By melting point

1 Melting point of Thiosalicylic acid = 154 – 159^{o}C

III. By IR Interpretation

Thiosalicylic acid[33, 34](Starting material)



S. No	Functional group	Standard peaks	Observed peaks
1	S-H Stretch	Near 2550cm^{-1}	2522 cm^{-1}
2	O-H Stretch	3400-2400cm^{-1}	3200-2500 cm^{-1}
3	C=O Stretch	1730-1690cm^{-1}	1677 cm^{-1}

Melting point reported is uncorrected, and determined by digital melting point apparatus model VMP-DS, Veego. FT-IR spectra were obtained with KBr on FT-IR 8400 S (Shimadzu, Japan) spectrophotometer.^{1}HNMR spectra were obtained on Brucker Avance II 400 NMR using Tetramethylsilane (TMS) as internal standard

(chemical shift in δ, ppm).The purity of all chemicals and compound was tested by performing thin layer chromatography run on silica gel plates. Iodine vapors were used for visualization of chromatographic run on silica plates. All the solvent were distilled before use according to purification of organic solvent procedures.

Table 5: Physicochemical data

S. No.	Name of compound	Melting point	% of yield	Mol. weight	Mol. formula
S.M.	Thiosalicylic acid	154-159^{o}C		154	$C_7H_6O_2S$
1	2(benzylthio)benzoic acid	185– 190^{0}C	49%	244	$C_{14}H_{11}O_2S$

2(benzylthio)benzoicacid

For synthesizing compound 2(benzyl thio) benzoic acidwas condensed with Thiosalicylic acid and benzyl chloride by refluxing in DMF and potassium carbonate to afford 2(benzyl thio) benzoic acid.

Characterization

I. By TLC

Solvent system – Ethanol: chloroform: n-hexane (8:1:1)

TLC Result – by R_f value

2. Thiosalicylic acid R_f value = 0.89
3. 2 (benzyl thio) benzoic acid R_f value = 0.95

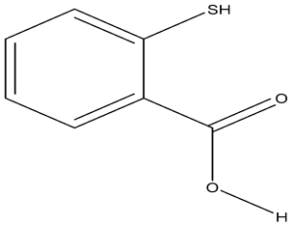
II. By melting point

2 Melting point of Thiosalicylic acid = 154 – 159^{o}C

3 Melting point of 2(benzyl thio)benzoic acid = 185 – 190^{0}C

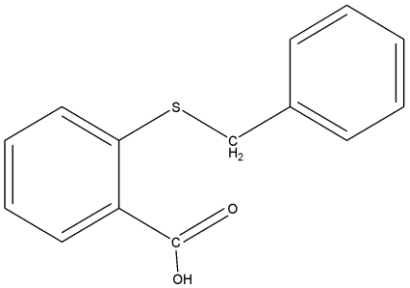
III. By IR Interpretation

Thiosalicylic acid[33, 34](Starting material)



S.No	Functional group	Standard peaks	Observed peaks
1	S-H Stretch	Near 2550cm^{-1}	2522 cm^{-1}
2	O-H Stretch	3400-2400cm^{-1}	3200-2500 cm^{-1}
3	C=O Stretch	1730-1690cm^{-1}	1677 cm^{-1}

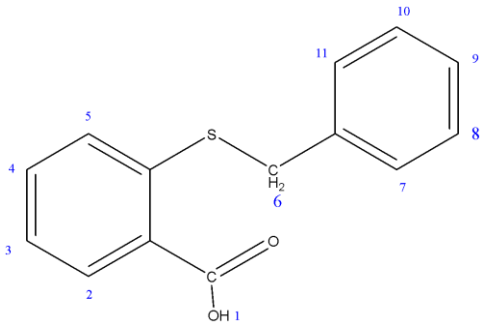
2(benzylthio)benzoic acid[33, 34](First intermediate)



S. No	Functional group	Standard peaks	Observed peaks
1	O-H Stretch	3400-2400cm-1	3200-2500cm^{-1}
2	C=O Stretch	1730-1700cm-1	1676 cm^{-1}
3	C-S Stretch	700-600cm-1	655 cm^{-1}

IV. By ^{1}H-NMR Interpretation (DNSO)

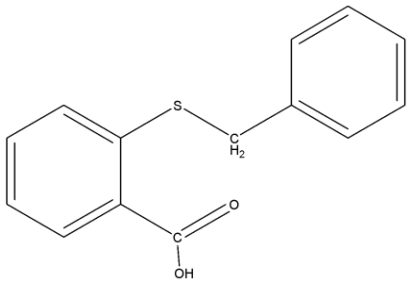
2 (benzylthio) benzoic acid



S. No.	Values	Comment
1	δ 4.33, s,2H	Ar aliphatic proton methyl to thiol group (6)
2.	δ 7.29,t, and,td,2H,J_m= 9.8 Hz, J_m=9.0Hz	Ar proton meta to methyl group (8,9,10)
3.	δ 7.40,dt,2H,J_o=9.1Hz,J=2.6 Hz,	Ar proton ortho to methyl group (3,7,11)
4.	δ 7.65,dd, 2H,J_o=2.2 Hz,	Ar proton ortho to thiol group (5)
5.	δ 7.73,dt,2H,Jm=9.1 Hz, J_o=2.6 Hz,	Ar proton to acid group(4)
6.	δ 7.81, dd,2H,J_o= 2.2 Hz ,	Ar proton ortho to acid group (2)
7.	δ 12.33, s,1H,	Due to acid proton attach to Ar ring(1)

V. By MASS Interpretation [33, 34]

1. 2 (benzyl thio) benzoic acid (Intermediate)



Mass: MS (ESI) m/z 244.15 (M^+), m/z 245.06 (M+1), m/z 153.01, m/z 107, m/z 91.09.

2. 2(benzylthio)benzoyl chloride (Lead molecule)

For synthesizing compound 2(benzylthio)benzoylchloride refluxing of 2(benzylthio)benzoic acid was done in thionyl chloride.

Characterization

I. By TLC

Solvent system- Ethanol: Chloroform: n-Hexane (8.2:1:0.8),

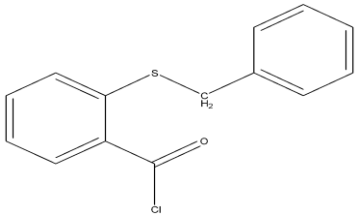
R_f value of 2(benzylthio) benzoic acid= 0.97.

$R_f$value of 2(benzyl thio) benzoyl chloride = 0.89.

II. By melting point

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

III. By IR Interpretation [33.34]



2(benzyl thio)benzoyl chloride(Lead molecule)

In KBr(cm^{-1})

S. No	Functional group	Standard peaks	Observed peaks
1	C=O Stretch (COCl)	1800-1700cm-1	1760cm^{-1}
2	C-Cl Stretch	750-550cm-1	655cm^{-1}
3	C-S Stretch	700-600cm-1	711cm^{-1}

3(i). 2(benzylthio)-N-(3-(dimethyl amino) propyl) benzamide

For synthesizing compound, 2(benzyl thio)-N-(3-(dimethyl amino) propyl) benzamide, amidation of 2(benzyl thio) benzoyl chloride was done in 1, 4 Dioxane.

Characterization

I. By TLC

Solvent system – Ethanol: chloroform: n-Hexane (8:1:1)

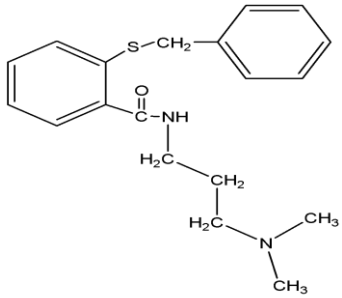
R_f value of 2(benzyl thio) benzoyl chloride = 0.85.

R_f value of 2(benzyl thio) -N-(3 dimethyl amino) benzamide = 0.33.

II. By melting point

Melting point of 2(benzyl thio)-N-(3-(dimethyl amino) = 64 – 70 ^{0}C

III. By IR Interpretation[33.34]

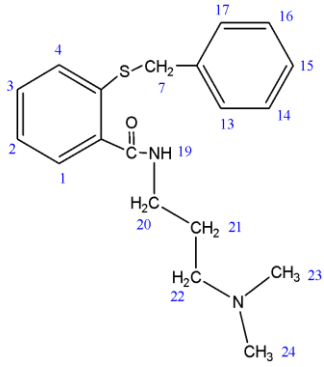


2-(benzylthio)-*N*-(3-(dimethylamino)propyl)benzamide

In KBr (cm^{-1})

S.NO	Functional group	Standard peaks	Observed peaks
1	N-H Stretch	3300 cm^{-1}	3323 cm^{-1}
2	C=O Stretch	1680-1630 cm^{-1}	1635 cm^{-1}
3	N-H Stretch	1640-1550 cm^{-1}	1533 cm^{-1}
4	C-S Stretch	700-500 cm^{-1}	711cm^{-1}

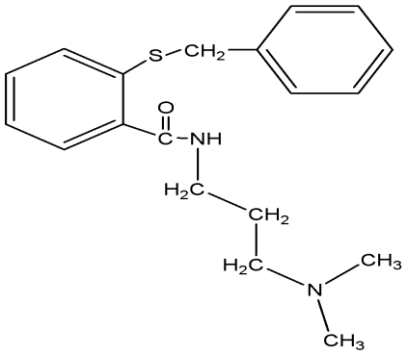
IV. By ^{1}H NMR Interpretation[33.34]



2-(benzylthio)-*N*-(3-(dimethylamino)propyl)benzamide

S. No.	Values	Comment
1	δ1.76, q, 2H,*J*=1.8Hz	Aliphatic proton to amide group (21)
2.	δ 2.14, s, 6H	Aliphatic proton to amide group (23,24)
3.	δ 2.37, t,2H,*J* =7.5 Hz	Aliphatic proton to amide group (22)
4.	δ 3.41, t, 2H,*J*=7.4Hz	Aliphatic proton to amide group(20)
5.	δ 4.33, s,2H	Due to methyl hydrogen(7)
6.	δ 6.92, td, 2H,J_m= 9.3, *J*=1.4 Hz ,	Ar proton meta to amide group (2)
7.	δ 7.18, td, 2H,J_m=9.1, J_m=1.9 Hz	Ar proton to methyl group(14,16)
8.	δ 7.24, tt,2H, *J*= 9.8 Hz	Ar proton to methyl group (15)
9.	δ 7.40, dt,2H, *J*= 9.1, *J*=2.6 Hz	Ar proton to methyl group(13,17)
10.	δ 7.65, dd, 2H, *J*= 9.1, *J*=2.1Hz,	Ar proton to amide group (4)
11.	δ 7.73, td,2H, *J*= 9.3, *J*=2.6Hz	Ar proton to amide group (3)
12.	δ 7.80, dd,2H,J_o=9.2, *J*=2.02Hz	Ar proton to amide group (1)

V. By MASS Interpretation[33.34]:



2-(benzylthio)-*N*-(3-(dimethylamino)propyl)benzamide

Mass: MS (ESI) m/z 328.03 (M^+), m/z 329.09 (M+1), m/z 237,m/z 207,m/z 149, m/z 91.24 .

3(ii). 2(benzyl thio)-N-(2-(dimethyl amino) ethyl) benzamide

For synthesizing compound, 2(benzyl thio)-N-(2-(dimethyl amino) ethyl) benzamide, amidation of 2(benzyl thio) benzoyl chloride was done in 1, 4 Dioxane.

Characterization

I. By TLC

Solvent system – Ethanol: chloroform: n-Hexane

8.3 : 1 : 0.7

R_f value of 2(benzyl thio) benzoyl chloride =0.89.

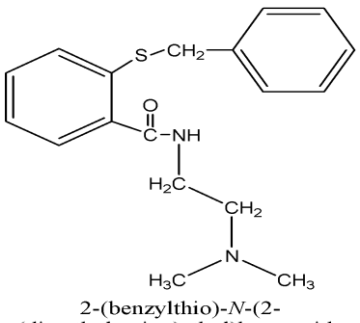
R_f value of 2(benzyl thio) -N-(3 dimethyl amino) propyl benzamide =0.68.

II. By Melting Point:

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

Melting point for 2(benzyl thio)-N-(3 dimethyl amino) propyl benzamide= 78-81^{0}C

III. FTIR Interpretation

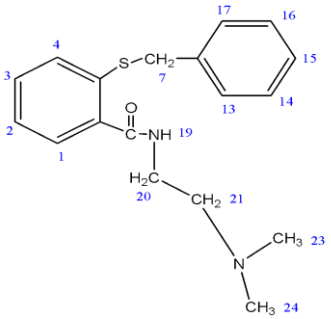


2-(benzylthio)-*N*-(2-(dimethylamino)ethyl)benzamide

In KBr (cm^{-1})

S. No.	Functional group	Standard peak	Observed peak
1.	C-H Stretch of alkane	3050-2850 cm^{-1}(Pavia 51)	2819cm^{-1}
2.	C-H Stretch of chain of alkane	3000-2800 cm^{-1}(Pavia 40)	2900 cm^{-1}
3.	C=O Stretch of amide	1680-1630cm^{-1}(Pavia 77)	1635 cm^{-1}
4.	N-H Stretch of primary amide group	3350-3180 cm^{-1}(Pavia 77)	3345 cm^{-1}
5.	C-S Stretch of thiol	700-600 cm^{-1}	675cm^{-1}
6.	N-H Stretch of primary amine	3400-3300 cm^{-1} (Silverstein 102)	3345cm^{-1}
7.	C-N Stretch of primary amide group	1350-1000 cm^{-1}(Pavia 81)	1163 cm^{-1}

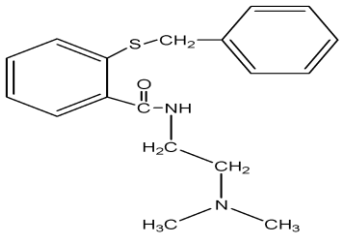
V. By ^{1}HNMR Interpretation ($CDCl_3$) [33,34]



2-(benzylthio)-*N*-(2-(dimethylamino)ethyl)benzamide

S. No.	Values	Comment
1	δ 2.19, s, 6H	Aliphatic proton to amide group (23,24)
2.	δ 2.37, t, 2H, *J*= 2.2 Hz	Aliphatic proton to amide group (21)
3.	δ 3.22, t, 2H, *J*= 7.4Hz	Aliphatic proton to amide group (20)
4.	δ 4.30, s, 2H	Due to methyl hydrogen(7)
5.	δ 6.88, td, 2H, *J*= 9.3Hz, J= 2.6Hz	Ar proton meta to amide group (2)
6.	δ 7.16, td, 2H, *J*= 1.92 Hz ,	Ar proton meta to amide group (14,16)
7.	δ 7.20, tt, 2H, J_m=7.8 Hz,	Ar proton to methyl group(15)
8.	δ 7.42, dt, 2H, *J*= 2.6 Hz,	Ar proton to methyl group (13,17)
9.	δ 7.649, dd, 2H, *J*= 9.0, *J*= 2.0 Hz	Ar proton to amide group(4)
10.	δ 7.72 , td, 2H, *J*= 8.2, *J*=2.1 Hz	Ar proton to amide group (3)
11.	δ 7.81, dd, 2H, *Jo*=2.6Hz	Ar proton to amide group (1)

IV. By MASS Interpretation[33,34]:



2-(benzylthio)-*N*-(2-(dimethylamino)ethyl)benzamide

Mass: MS (ESI) m/z 314.12 (M^+), m/z 315.01(M+1), m/z 223,m/z 193, m/z, m/z 91.06.

3(iii).2(benzylthio)-N-(2-(dimethylamino)ethyl)benzamide

For synthesizing compound, 2(benzyl thio)-N-(3-nitro phenyl) benzamide, amidation of 2(benzyl thio) benzoyl chloride was done in 1,4 Dioxane.

Characterization

I. By TLC

Solvent system – Ethanol: chloroform: n-Hexane

8.2 : 0.8 : 1

R_f value of 2(benzyl thio) benzoyl chloride =0.82

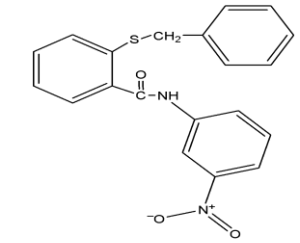
R_f value of 2(benzyl thio) -N-(3 dimethyl amino) propyl benzamide =0.62

II. By Melting Point:

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

Melting point for 2(benzylthio)-N-(3dimethyamino) propylbenzamide= 85-89^{0}C.

III. By FTIR Interpretation

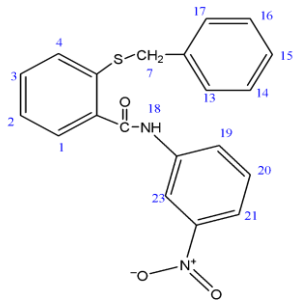


2-(benzylthio)-*N*-(3-nitrophenyl)benzamide

In KBr (cm^{-1})

S.No.	Functional group	Standard peak	Observed peak
1.	C=O Stretch of amide group	1680-1630cm^{-1}(Pavia 77)	1635.52cm^{-1}
2.	N-H Stretch of primary amide group	3350-3180 cm^{-1}(Pavia 77)	3323cm^{-1}
3.	N-H banding of amide group	1640-1550 cm^{-1} (Pavia 77)	1635cm^{-1}
4.	C-S Stretch of thiol group	700-600 cm^{-1}(Pavia 87)	675 cm^{-1}
5.	NO_2Stretch of nitro group	1550-1490cm-^{1}and 1355-1315 cm^{-1}(Pavia 85)	1533cm^{-1}and 1334cm^{-1}

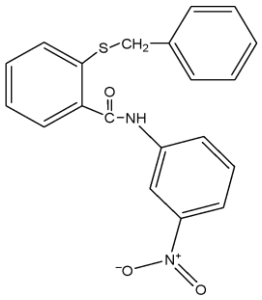
IV. By ^{1}HNMR Interpretation($CDCl_3$)[33, 34]



2-(benzylthio)-*N*-(3-nitrophenyl)benzamide

S. No.	Values	Comment
1	δ4.35,s,2H.	Due to methyl hydrogen (7)
2.	δ 6.93,td,2H,J_m=2.6 Hz.	Ar meta proton to amide group (2)
3.	δ 7.17,dt,2H,J_m=2.08 Hz.	Ar proton to amide group (14,16)
4.	δ 7.24, tt, 2H.	Ar proton to methyl hydrogen(15)
5.	δ 7.41, td,2H, J=2.9 Hz.	Ar proton ortho to methyl group (13,17)
6.	δ 7.66,dd,2H,J=3 Hz, Jo= 7.0 Hz.	Ar proton meta to amide group (4,20)
7.	δ 7.72, td,2H,Jm=1.5 Hz.	Ar proton to amidegroup(3)
8.	δ 7.79,dd,2H, J=2.2 Hz.	Ar proton ortho to amide group (1)
9.	δ 7.93, dt, 2H, J=8.1 Hz.	Ar proton ortho to nitro group (21)
9.	δ 8.04, dt,2H, J_o=2.1 Hz.	Ar proton ortho to amide group(19)
10.	δ8.77, t, 2H, J=7.8 Hz.	Ar proton ortho to nitro group (23)

V. By MASS Interpretation[33, 34]:



2-(benzylthio)-*N*-(3-nitrophenyl)benzamide

Mass: MS (ESI) m/z 364.10 (M^+), m/z 365.02 (M+1), m/z 273.80, m/z 227.03, m/z 149.50, m/z 91.03.

Pharmacological Evaluation:

The pharmacological approach for evaluation of calcium channel blocking activity of compounds (3(i)) on guinea-pig ileum by concentration response curve.

Table 6(i): Effect of Compound 3(i) in the Concentration Response Curve.

Dose	Concentration (Mm)	Mean± S.E.M. (Compound 3(i))
KCl	80	2.700 ± 0.0577
I	60	2.067 ± 0.0666***
II	80	1.433± 0.0881**
III	100	0.700 ± 0.0577*
Nifedipine	10	0.100 ± 0.000***

Table 6(ii): Effect of Compounds3(ii) in the Concentration Response Curves.

Dose	Concentration (mM)	Mean± S.E.M. (Compound 3(ii))
KCl	80	2.633 ± 0.0333
I	60	1.900± 0.0577***
II	80	1.500 ± 0.0577**
III	100	0.733 ± 0.0333*
Nifedipine	10	1.333 ± 0.0333***

Table 6(iii): Effect of Compounds3(iii) in the Concentration Response Curves.

Dose	Concentration (MM)	Mean± S.E.M. (Compound 3(iii))
KCl	80	2.600± 0.0577
I	60	1.900 ± 0.0577***
II	80	1.433 ± 0.0333**
III	100	0.733 ± 0.0333*
Nifedipine	10	0.133 ± 0.0333***

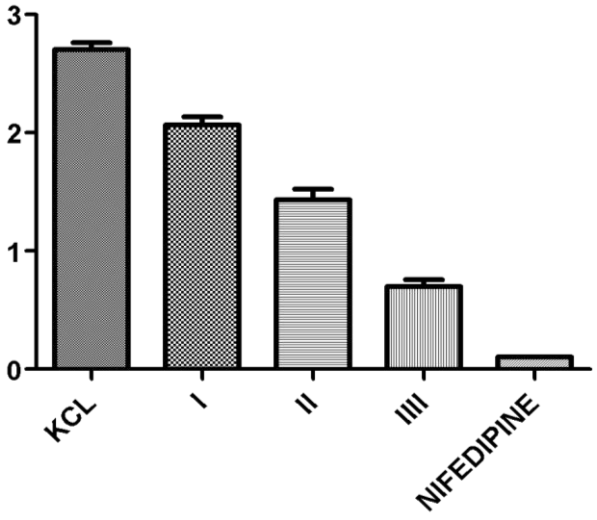


Figure 3(i): Bar diagram showing the effect of compound 3(i) on various concentration (60, 80, 100 mM) and reference drug (Nifedipine 10mM).

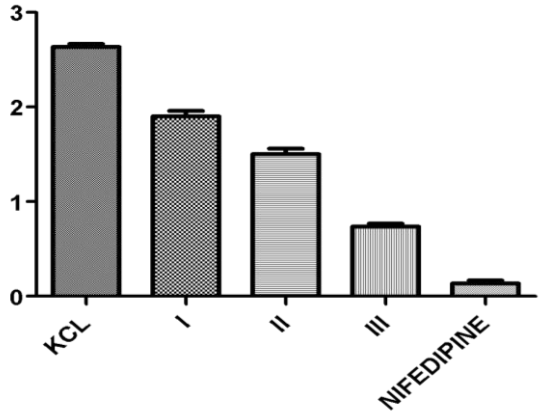


Figure 3(ii): Bar diagram showing the effect of compound 3(ii) on various concentration (60, 80, 100 mM) and reference drug (Nifedipine 10mM).

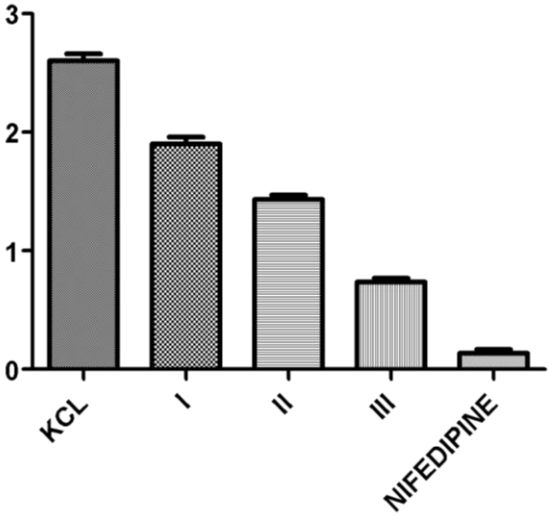


Figure 3(iii): Bar diagram showing the effect of compound 3(iii) on various concentration (60, 80, 100 mM) and reference drug (Nifedipine 10mM).

Present study of calcium channel blocking activity of 2(benzyl thio)-N-(3 dimethyl amino)benzamide "compound 3(i)" was carried on guinea-pig ileum. The guinea-pig ileum shows spontaneous contraction when KCl solution was adding to tissue bath at concentration of 80 mM, after this different derivative were tested for their antagonistic activity with reference to all derivative,on increasing the concentration of test compounds significant antagonistic activity was seen. In all derivatives the 100 mM concentration of test compound shows highest antagonistic activity that is highest muscle relaxation as compare to KCl induce muscle contraction.

4. Conclusion

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

Benzothiazine derivative (diltaizem) and Thiosalicylamide derivative 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. The foremost objective of present study was synthesis of Novel Thiosalicylamide derivative as calcium channel blocker. The significance of Thiosalicylamide however cannot be ruled out owing to its better known advantage on the basis of SAR.

A series of compounds were synthesized taking 2-(benzylthio)benzoyl chloride as lead molecule and substitutions were done in this molecule to obtain different derivatives. Synthesized compounds were obtained in satisfactory yield and were characterized by TLC, FT-IR, ^{1}HNMR, Mass and Elemental analysis. In pharmacological evaluation, synthesize compounds 3(i), 3(ii), 3(iii) gave *in-vitro*Calcium channel antagonist activity. On the basis of above study it is suggest that substituted 2(benzyl thio)-N-(3-dimethyl amino) benzamide is having significant calcium channel antagonistic action.

Reference

[1] James S. A development of a database analysis that provides putative metabolic enzyme reactions for Ligand-based drug design. *Comp Bio and Chem* 2009; 149–159.

[2] Larsen PK. Text book of Drug Design and Discovery, published by British Library Cataloguing Publication; first Indian reprint 2004: 1-33.

[3] Tripathi KD. Antihypertensive drugs in the Essentials of Medical Pharmacology. Jaypee brothers medical publishers Pvt. Ltd., New Delhi, 2003;5: 503-504.

[4] Kishor SJ. Recent advances in selective a1-adrenoreceptor antagonists as antihypertensive agents. *Bioorg and Med chem* 2008;16: 4759-4800.

[5] Williams and Wilkins. Illustrated Reviews: Pharmacology. 2006;2: pp 213-214.

[6] www.google.com / www.neurosearch.com on 23/03/2010.

[7] Rang HP, Dale MM, Ritter JM, Flower RJ. The Heart. Pharmacology. *Elsevier publisher*. 2007;6: 54-58.

[8] Striggow F. Verapamil and diltaizem inhibit receptor-operated calcium channels and intracellular calcium oscillations in rat hepatocytes. Federation of European, *Biochemical science*, 1993;318: 341-344.

[9] Snutch TP. Chronic and Neuropathic Pain: The N-type Calcium Channel Comes of Age.*J Amer Sci Exp Neurotherap* 2005;2(4): 662-670.

[10] www.wikipedia.org/T-type_calcium_channel on 23/03/2010

[11] www.online-medicaldictionary.org/L+Calcium+Channel on 15/03/2010.

[12] www.google.com / www.neurosearch.com on 23/03/2010.

[13] Rang HP, Dale MM, Ritter JM, Flower RJ. The Heart. Pharmacology Elsevier 2007;6: 54-58.

[14] Remington. Calcium channel blocker. The science and practice of pharmacy.2000;20: 1290.

[15] Barar FSK. Antianginal drug Essential of pharmacotherapeutics 2000;3: 271.

[16] Mehanna AS, Kim JY Kim JT. United States Patent 2003;6: 541,479 B1.

[17] Lee JY. Growth inhibition of human cancer cells in vitro by T-type Calcium channel blockers. *J bioorg and med chem* 2006;16: 5014-5017.

[18] Mehanna A, Kim JY. Design, Synthesis, and Biological testing of thiosalicylamide as a novel class of calcium channel blocker. *J bioorg and med chem* 2005;13: 4323-4331.

[19] Pergament E. Calcium channel blockers and pregnancy. Illinois Teratogen Information Service 1996;5.

[20] www.wikipedia.org/Calcium_Channel_Blocker on 24/03/2010.

[21] Parks R. Calcium channel blockers for coronary artery disease, Heath home 2008.

[22] www.en.worldlifeexpectancy.com/sort.php on 24/03/2010

[23] Silverberg MA. Toxicity and Calcium Channel Blocker. *Medicine Specialties* 2009.

[24] www.yourtotalhealth.ivillage.com/calcium-channel-blockers on 24/03/2010.

[25] Horowitz BZ. Toxicity, Calcium Channel Blocker.*Medicine Specialties* 2008.

[26] Tripathi KD. Antihypertensive Drugs Essentials of Medical Pharmacology. 2003;5: 504-506.

[27] www.texasheart.org/HIC/Topics/Meds/calciumchannelblockermedicinalchemistry.com. on 24/03/2010.

[28] www.srspharma.com/calcium-channel-blockers.htm. on 25/03/2010.

[29] Klabunde RE. Calcium channel blocker cardiovascular pharmacology concepts. 2008.

[30] Craig RC, Stitzel RE. Calcium Channel Blocker. Modern Pharmacology with Clinical Application, 2008; 5: 218-224.

[31] Bahl BS and Bahl A. Text Book of Advanced Organic Chemistry. Published by S. Chand & Company 2004; 19: 202-204.

[32] March J. Advanced Organic Chemistry and Reaction, Mechanism and Structure. *A Wiley – Interscience Publication* 2005; 4: 590-596: 639.

[33] Pavia, D.L.; Lampman, G. M.; Kriz, G.S.; Vyvyan, J. R. ; "Spectroscopy", Published by *Cengage Learning Publisher* first edition reprint, 2008, 60, 87.
[34] Silverstein RM and Webster FX. Spectrometric Identification of Organic Compounds. Published by library of congress cataloging publication, reprint 1998; 76: 149.
[35] Fujita M, Ito S, Ota A. Synthesis of calcium channel antagonistic activity of Benzothiazine. C.R.L. Santen Pharmaceutical Co., Ltd., *J Med Chem* 1989.
[36] Yamamoto K, Fujita M, Tabashi, K. Synthesis and SAR of Benzothiazepine derivatives as novel calcium antagonists. Santen Pharmaceutical Co. Ltd., J Med Chem 1987.
[37] Gualtieri F, Teodori E, Bellucci C. SAR studies in the field of calcium channel antagonist effect of Verapamil like compounds. Santen Pharmaceutical Co. Ltd., J Med Chem 1985.
[38] Fossheim R, Svarteng K, Mosted A.Crystal Structure and Pharmacological Activity of Calcium Channel Antagonist Verapamil like compound. Norway and School of Pharmacy USA, *J Med Chem* 1981.
[39] Luis MM, Aguilar A. Effect of Gnaphalium conoideum HBK on Guinea pig airway smooth muscle: role of L-type Calcium Channels. *J Bio and Biomed Sci* 2004.
[40] Pavia DL, Lampman GM, Kriz GS, Vyvyan JR. Infrared Spectroscopy. Spectroscopy. Cengage Learning India 2007: pp 26-92.
[41] Godfraind T, Miller R, Wibo M. Calcium Antagonism and Calcium entry Blockade. *Pharmacol Rev* 1986;38: 321–416.
[42] Gilani AH, Bashir S, Janbaz KH, Shah AJ. Presence of Cholinergic and Calciun Channel Blocking Activities Explains the traditional use of *Hibiscus Rosasinensis* in Constipation and Diarrhoea. *J of Ethnopharmaco* 2005; 102: 289-294.
[43] Kulkarni SK. Hand Book of Experimental Pharmacology. 1999; 3: Vallabh Prakashan, pp 13.