CHAPTER - IV

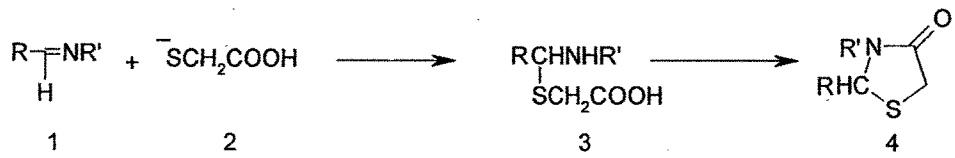
SYNTHESIS OF 4-THIAZOLIDINONES USING (R) & (S)-2-AMINO-1-BUTANOLS

4.1 INTRODUCTION

Thiazolidinones are the derivatives of thiazolidine which belongs to an important group of heterocyclic compounds. The application of thiazolidinones as toxic agents into cells of pathogenic microorganisms has evoked considerable attention during the past 20 years.[1-3] 4-Thiazolidinones are well known for their hypnotic[4] and anticonvulsant[5, 6] properties. The presence of the N-C-S linkage in the heterocycles has been reported to have antitubercular[7] antifungal[8] and antianalgesic[9] activity. 4-Thiazolidinones have also been shown to have an anti-HIV[10] activity.

4.1.1 Methods Of Preparation Of 4-Thiazolidinones

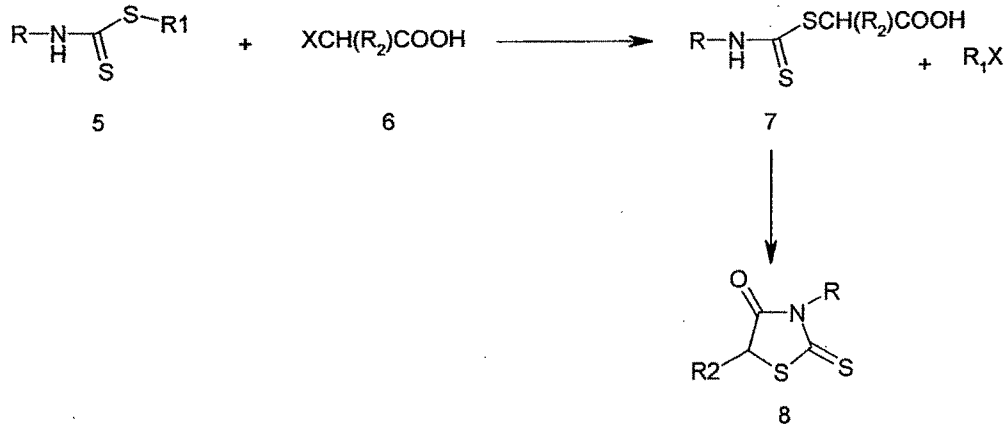
4-Thiazolidinones are conventionally synthesized by reaction of Schiff bases, usually formed from an aromatic or heterocyclic aldehyde with α-mercaptoalkanoic acids in a an inert solvent such as dry ether,[11] dry benzene[12] or Skellysolve E[13,14] for anils derived from aliphatic amines. The use of a water separator has been found to be advantageous and the course of the reaction can be followed by the volume of water collected. The reaction proceeds by the attack of the mercaptoacetic acid upon the C=N group with the SCH_2COOH adding to the carbon atom, followed by the capture of a proton by nitrogen, and subsequent cyclization (**Scheme IV.1**).



1 2 3 4

Scheme IV.1

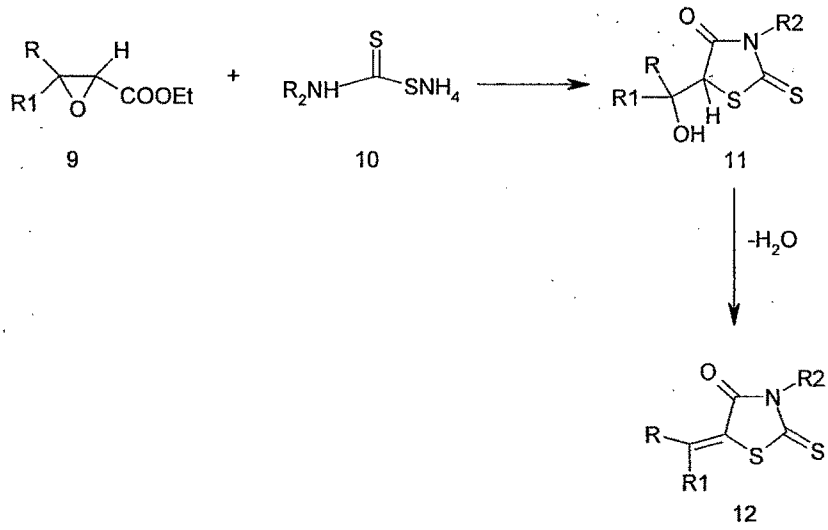
Dithiocarbamates(5), formed by reaction of primary amine with carbon disulphide in the presence of a base, reacts with α-haloalkanoic acids(6) in the presence of sodium bicarbonate gives substituted 2-thiono-4-thiazolidinones(8) (**Scheme IV.2**).[15, 16]



R= -CH_3, -NH_2; R2= Ph, H; X=Halogen

Scheme IV.2

Ammonium ditiocarbamates (10) condense with glycidic esters (9) to give 2-thiono-3-substituted-5-(hydroxyalkyl)-4-thiazolidinones (11) which are readily dehydrated in refluxing acetic acid to 2-thiono-3-substituted-5-alkylidene-4-thiazolidinones (12) **(Scheme IV.3)**.[17]

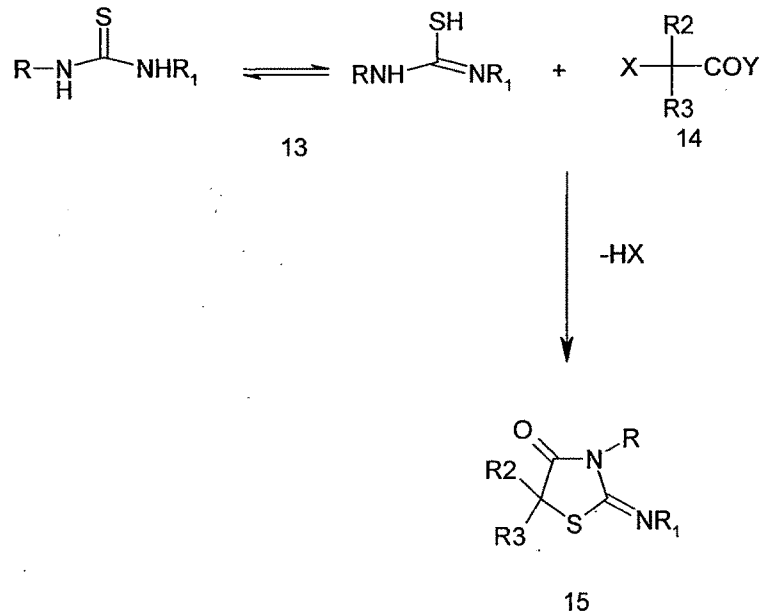


R=-CH_3, C_2H_5 or Ph, R_1= CH_3 or C_2H_5, R_2= Ph

Scheme IV.3

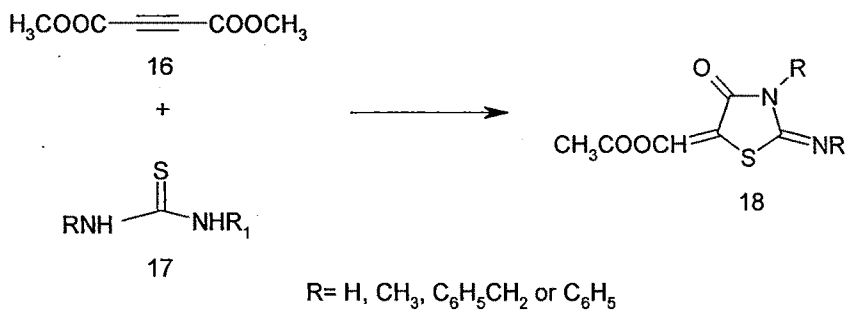
Substituted 2-imino-4-thiazolidinones (15) are obtained in good yields by the reaction of symmetrical and unsymmetrical thioureas (13) with various substituted and unsubstituted

α-haloalkanoic acids (14), their esters, acid chlorides, amides, or carbamates (**Scheme IV.4**).[18, 19]



Scheme IV.4

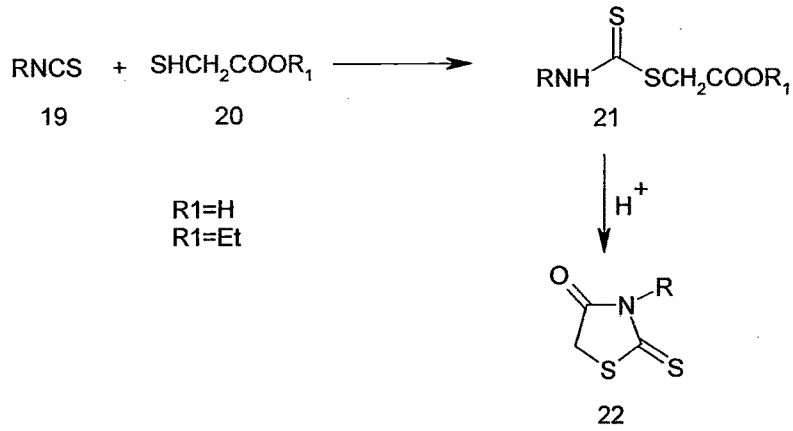
Dimethyl acetylenedicarboxylate (DMAD) (16) reacts readily with substituted and unsubstituted thioureas, dithiocarbamates, thiocarbamates, thiosemicarbazides and thiosemicarbazones to give 4-thiazolidinones (18) (**Scheme IV.5**).[20, 21]



Scheme IV.5

Various 3-substituted-2-thiono-4-thiazolidinones (22) can be conveniently prepared by the reaction of substituted isothiocyanates (19) with α-mercaptoactetic acid or its ester

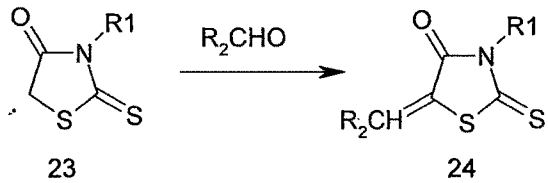
(20) followed by acid cyclization of the resulting (thiocarbamoyl)mercaptoacetic acids and acetates (**Scheme IV.6**).[22]

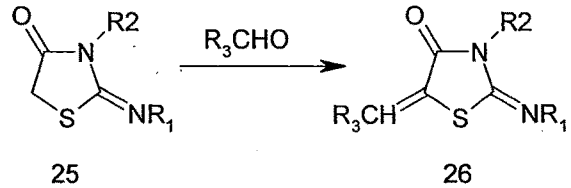


Scheme IV.6

4.1.2 Reactions of 4-Thiazolidinones

The aldol condensation reaction of the methylene group at the position 5 of 4-thiazolidinones possesses nucleophilic activity. The product of the reaction contains α, β-unsaturated carbonyl group. 2-thiono-4-thiazolidinones (23) and 2-imino-4-thiazolidinones (25) have been reported to undergo aldol condensation reaction with a variety of aliphatic, aromatic, and heterocyclic aldehydes in presence of anhydrous sodium acetate in benzene or acetic acid (**Scheme IV.7**).[23, 24, 25]

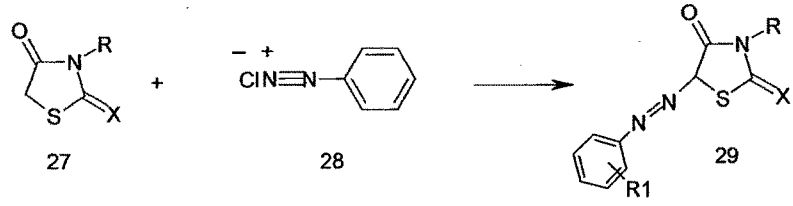




R_1, R_2, R_3 = Alkyl, aryl or heterocyclic

Scheme IV.7

Diazonium salts (28) undergo coupling reaction with a variety of substituted 4-thiazolidinones at the 5-methylene group in the presence of aqueous ammonium hydroxide to give 5-arylazo-4-thiazolidinones (29) **(Scheme IV.8)**.[26, 27, 28]



27 28 29

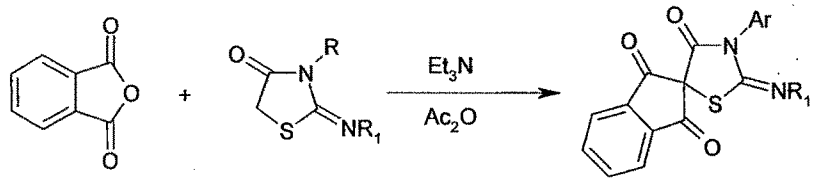
R= Alkyl, or aryl

R_1= Alkyl, alkoxy, halo or heterocyclic

X=S or O

Scheme IV.8

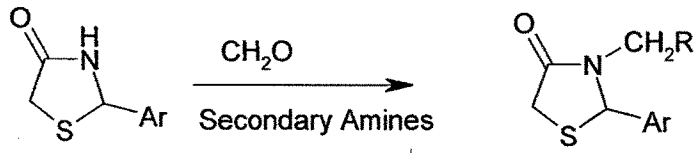
Phthalic anhydride (30) undergoes condensation at the 5 position of various 2-substituted imino-4-thiazolidinones (31) in acetic anhydride and triethylamine to give 2-substituted imino-5-phthalyl-4-thiazolidinones (32) **(Scheme IV.9)**.[29]



30 31 32

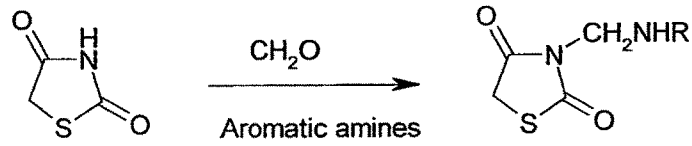
Scheme IV.9

Kononenko *et al.*[30] have reported aminomethylation reactions of 2-aryl-4-thiazolidinones (33) and 2, 4-thiazolidinediones (35) with formaldehyde and amines by heating in alcohol **(Scheme IV.10)**.



33 34

R= Piperidino or morpholino

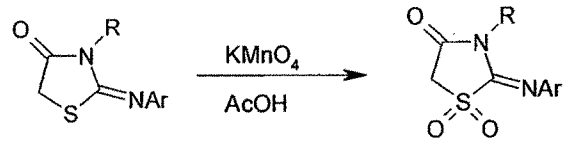


35 36

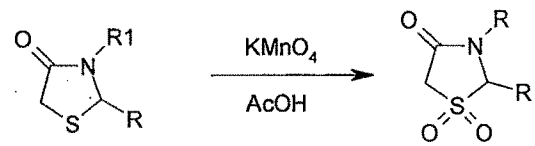
R = Aryl

Scheme IV.10

2-(Arylimino)-3-substituted-4-thiazolidinones (37) and 2, 3-disubstituted-4-thiazolidinones (39) are oxidized to the corresponding 1, 1-dioxides on treatment with $KMnO_4$ in glacial acetic acid at 0°C (**Scheme IV.11**).[31]



37 R= Alkyl or aryl 38



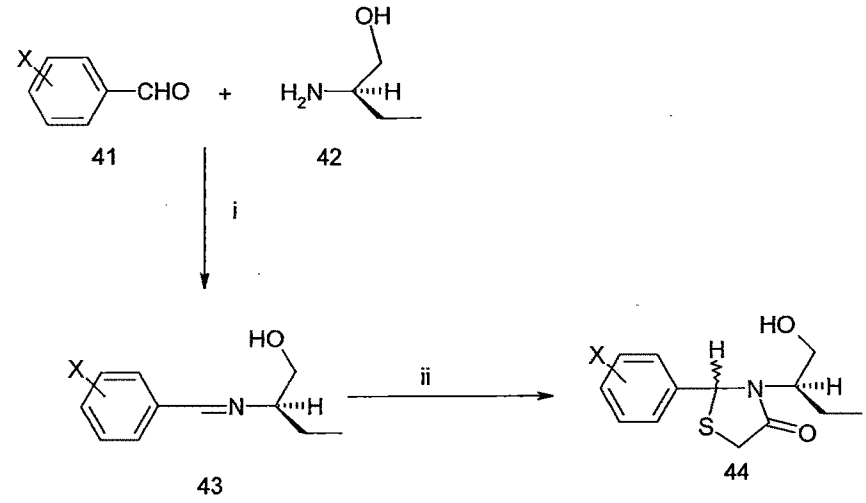
39 40

R=R1=Aryl

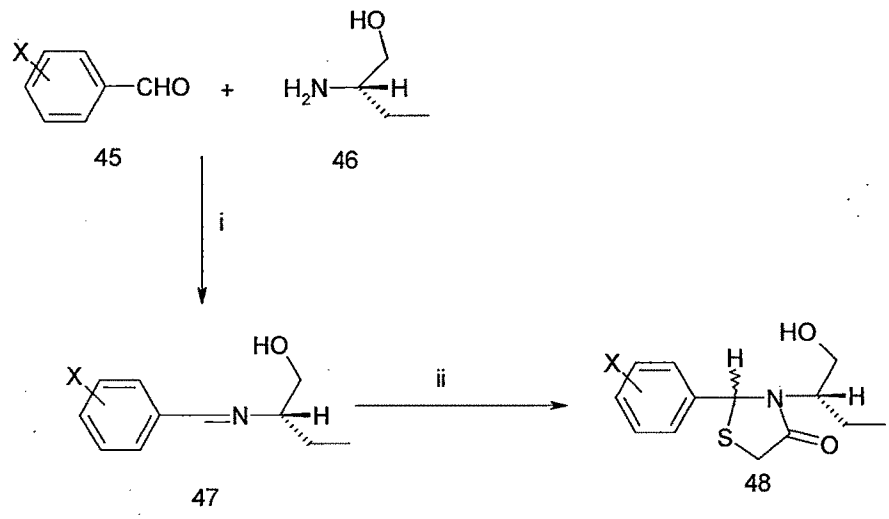
Scheme IV.11

4.2 RESULTS AND DISCUSSION

(*R*) and (*S*)-2-Amino-1-butanols (42) or (46) are reacted with substituted and unsubstituted aromatic aldehydes to give the corresponding Schiff bases by a known methodology. The Schiff bases were isolated as good, crystalline solids. The Schiff bases were reacted with thioglycollic acid in benzene and water was continuously removed from the reaction mixture using a dean and stark apparatus to furnish the 4-thiazolidinone derivatives44a-44e and 48a-48e as thick liquids after column purification over silica gel (**Scheme IV.12**).



X= -H (44a), -Cl (44b), $-NO_2$ (44c), $-OCH_3$ (44d), $-OCH_3$ $-OCH_3$ (44e)



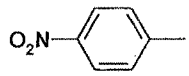
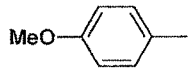
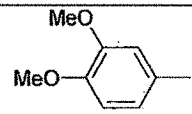
X= -H, -Cl, NO_2, $-OCH_3$, OCH_3 OCH_3

X= -H (48a), -Cl (48b), $-NO_2$ (48c), $-OCH_3$ (48d), $-OCH_3$ $-OCH_3$ (48e)

Scheme IV.12: Reagents and conditions i. Toluene, reflux, azeotropic distillation. ii. Thioglycollic acid, benzene, azeotropic distillation, 4-5 hours.

The reaction of thioglycollic acid with optically pure Schiff bases lead to the formation of two diastereomeric thiazolidinones. The two diastereomers could not be separated by column chromatography. The presence of the two diastereomers could be easily detected

by proton NMR. All the thiazolidinones show characteristic pmr spectra. Two triplets are observed in the region of δ0.8-0.9 for six protons of the two methyl groups of the diastereomers. Two multiplets for the four protons of two methylene groups are observed in the region δ1.5-2.0. A broad singlet for –OH group is observed in the region δ2.0-3.0. A multiplet in the region of δ3.0-4.0 for five protons shows the presence of the –CH group, two non equivalent protons of $-CH_2-O$ group and a singlet for $S-CH_2$ group. A doublet is observed for the S-CH group in the region of δ5.0-6.0 indicating the presence of two nonequivalent protons of the two diastereomers. The aromatic region shows the required multiplet in the region δ7.5-8.3. In the case of 44e the mixture of diastereomers was again purified over silica gel to obtain one of the diastereomers in excess. 44e was obtained as a solid and was further crystallized in petroleum ether-ethyl acetate. A singlet for the $-CH_3$ group was observed at δ0.9 and another singlet for the S-CH group was observed at δ5.5.All the thiazolidinones showed a typical band at 1640-1660cm^{-1} in the infrared spectra which is the characteristic band for the carbonyl of the thiazolidinone(**Figure IV.9**). The ratio of the two diastereomers is calculated by finding out the ratio of the integration values of the two methyl peaks. The ratios of the diastereomers found from the proton NMR is given in the table V.1

Compound No.	Aromatic Group	Configuration of the 2-Amino 1-butanol side chain	Ratio of diastereomers
48c		S	53:47(**Fig. IV.6**)
48b		S	60:40(**Fig. IV.5**)
48d		S	90:10(**Fig. IV.7**)
48e		S	40:60(**Fig. IV.8**)

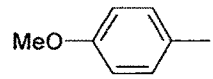
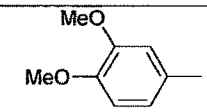
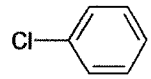
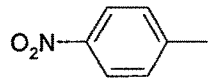
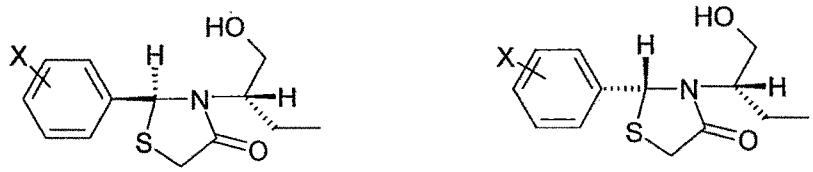
44d		R	74:26**(Fig. IV.3)**
44e		R	100**(Fig. IV.4)**
44a		R	60:40**(Fig. IV.2)**
44c		R	50:50 **(Fig. IV.1)**

Table IV.1: Diasteromeric ratios of thiazolidinone derivatives

The probable structures of the two diastereomers can be given as follows (**Figure IV.1**):

44



48

X = -H, -Cl, $-NO_2$, $-OCH_3$, $-OCH_3$ $-OCH_3$

Figure IV.1

The probable mechanism of the reaction which can explain the formation of the diastereomers can be given as follows (**Scheme IV.3**)

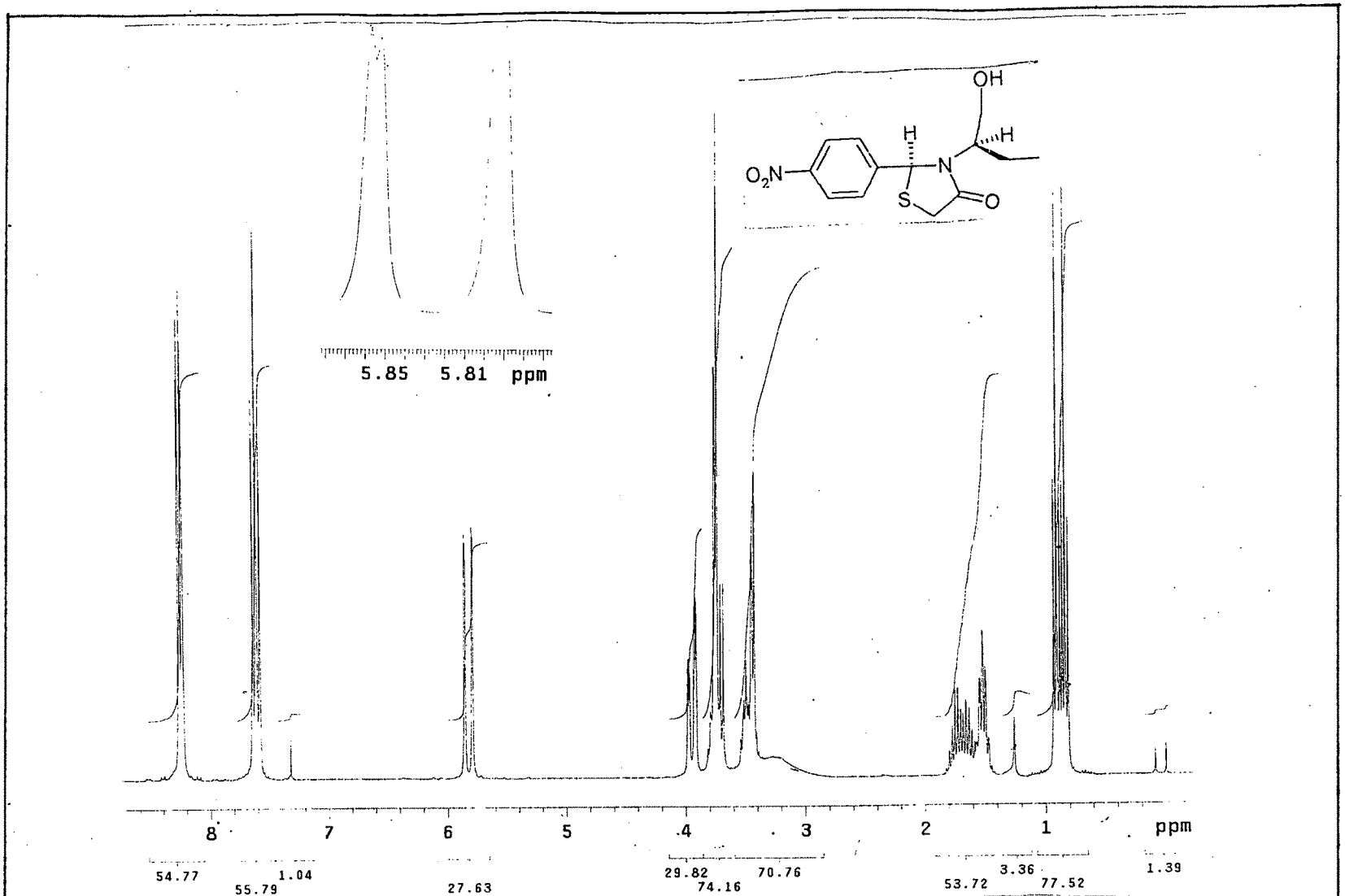
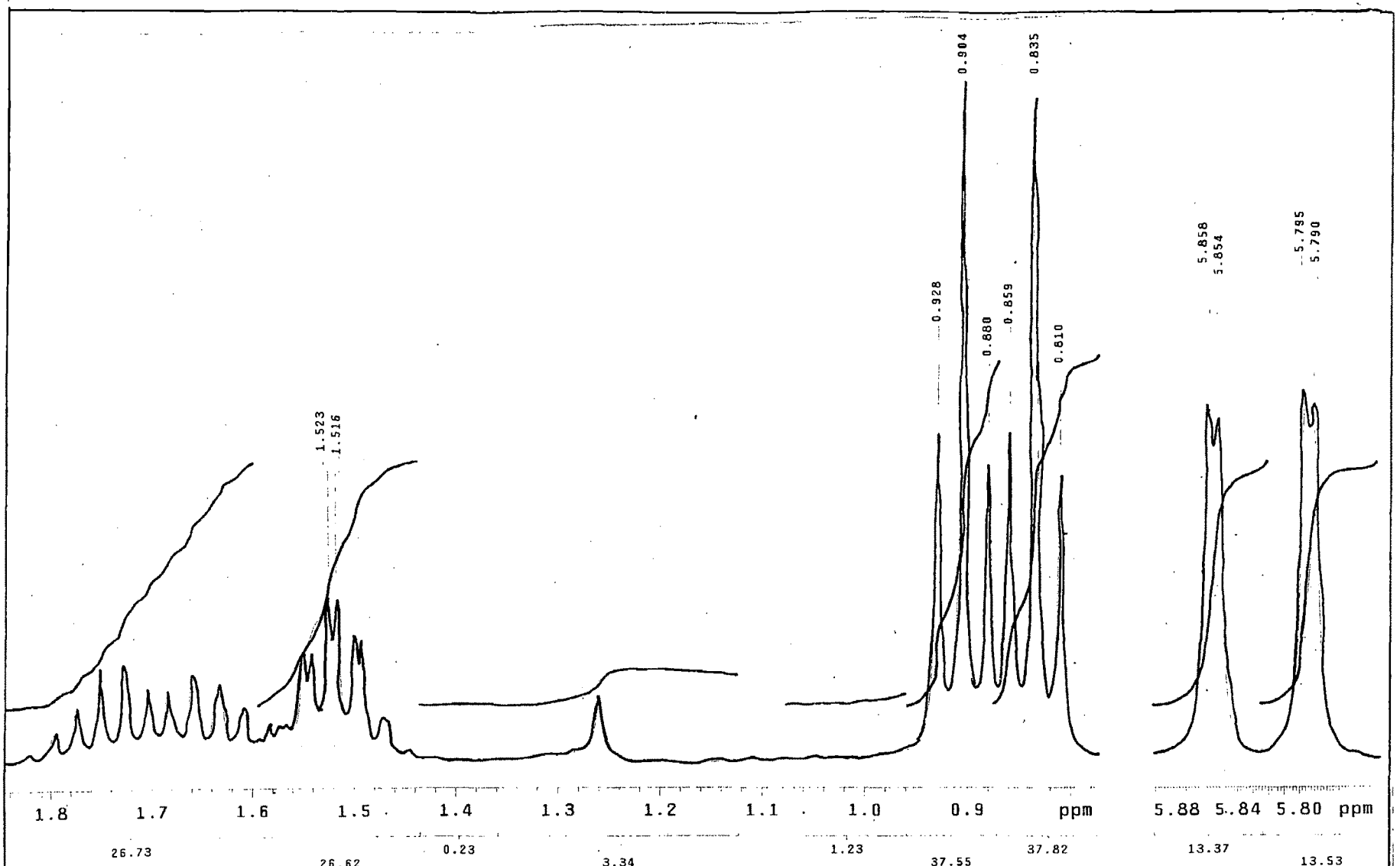


Figure IV.1 1H NMR($CDCl_3$) spectrumof 2-(4-Nitrophenyl)-3-((R)-1-hydroxymethyl propyl)-thiazolidin-4-one 44c



Expansion of Figure IV.1

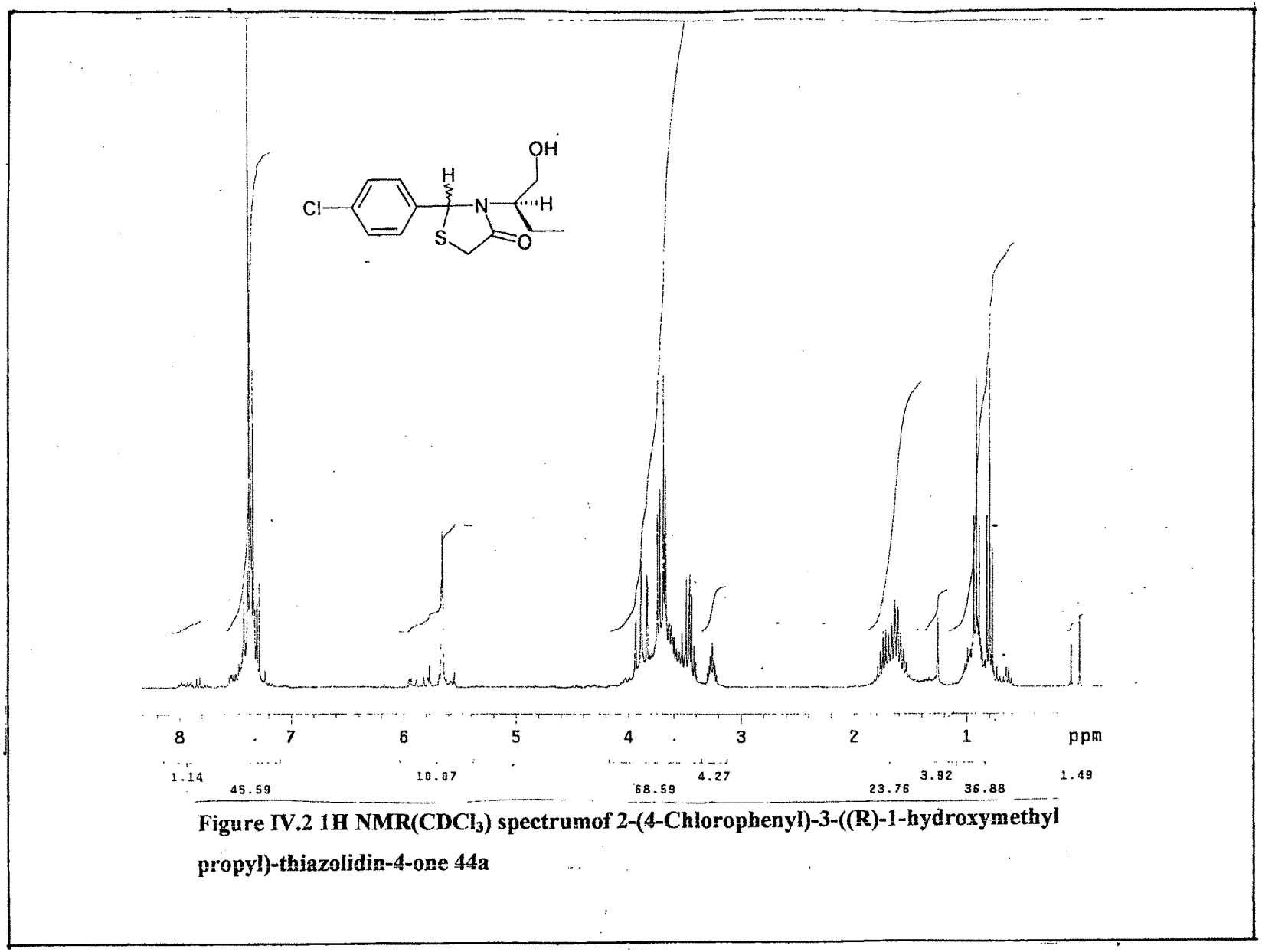
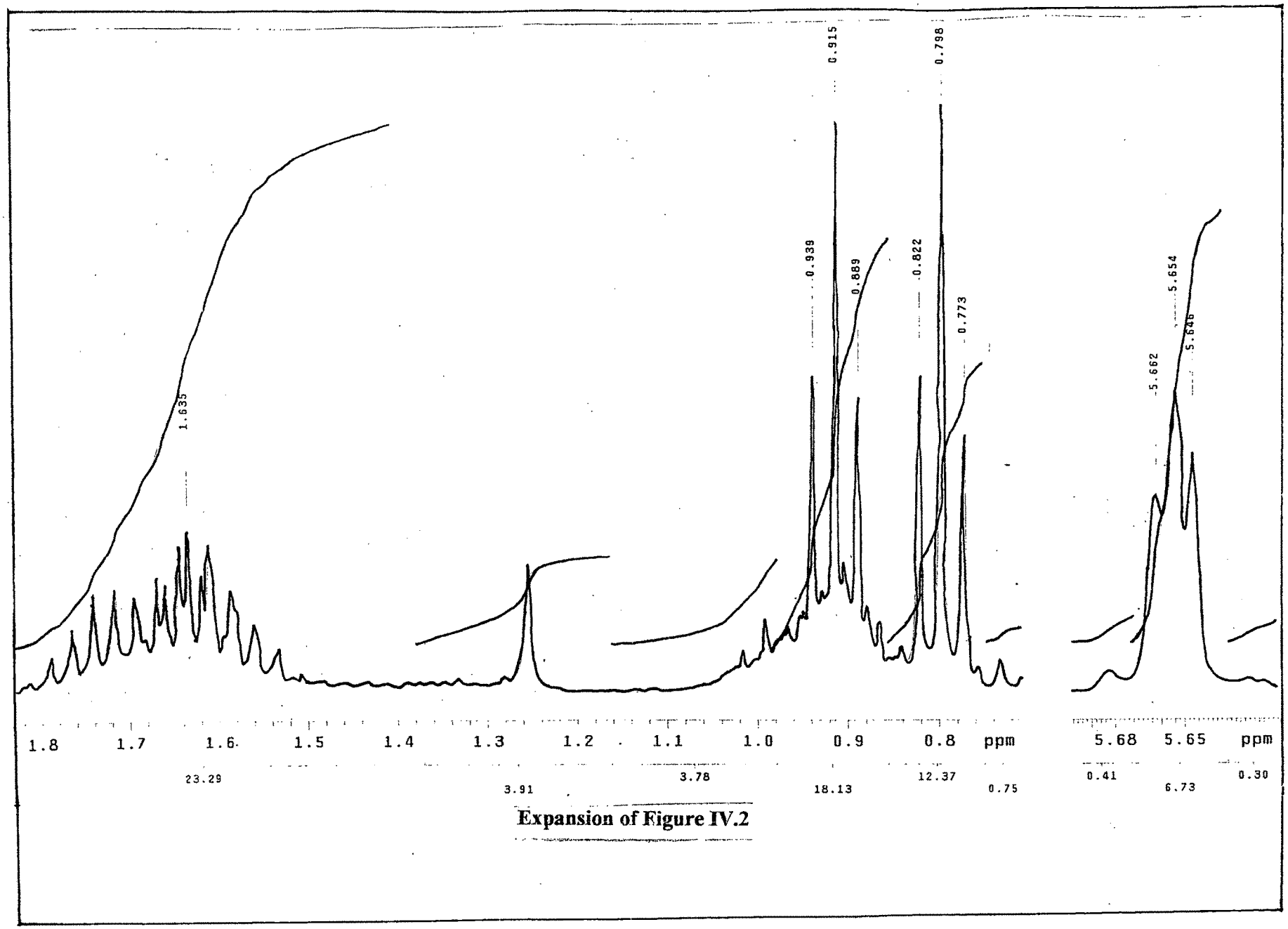


Figure IV.2 1H NMR($CDCl_3$) spectrumof 2-(4-Chlorophenyl)-3-((R)-1-hydroxymethyl propyl)-thiazolidin-4-one 44a



Expansion of Figure IV.2

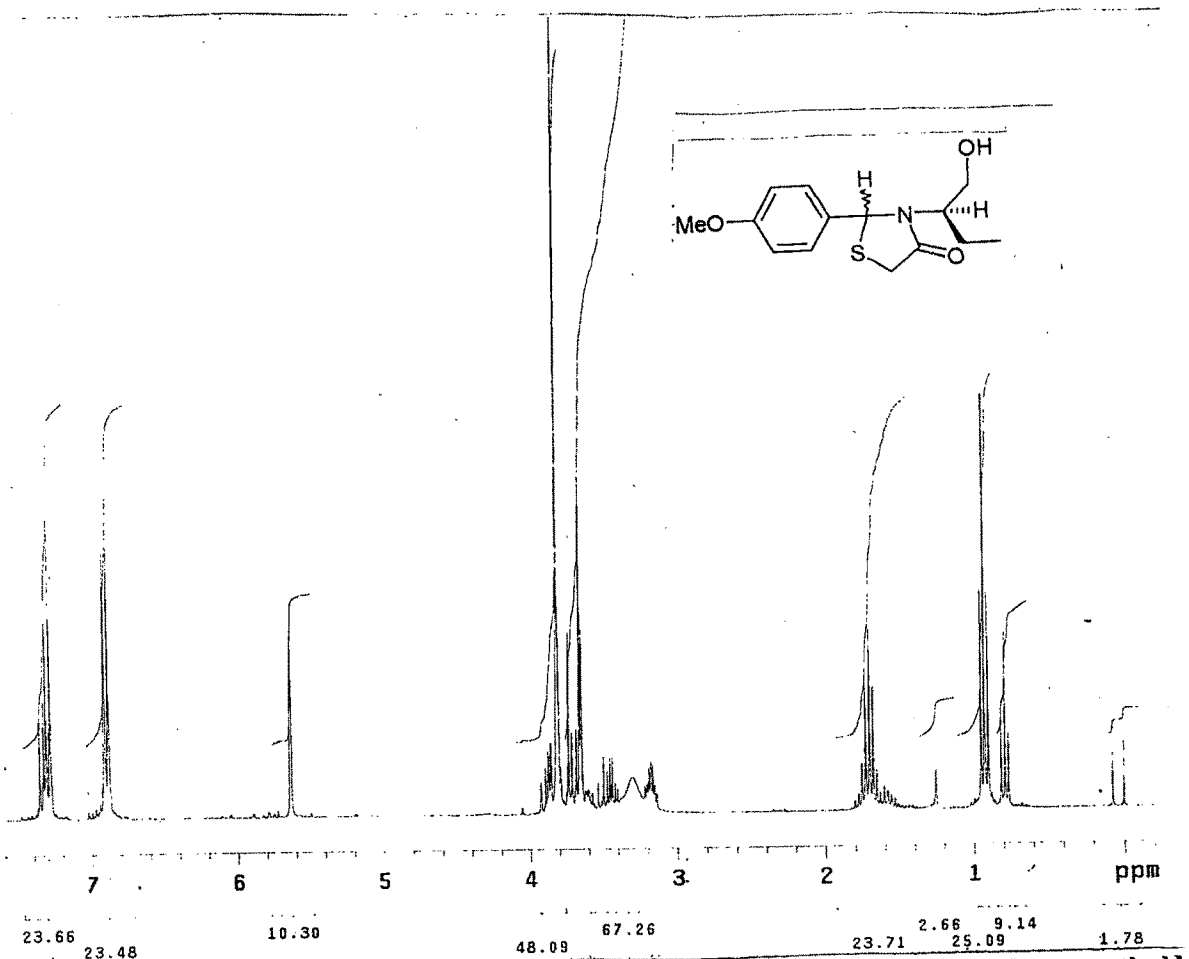
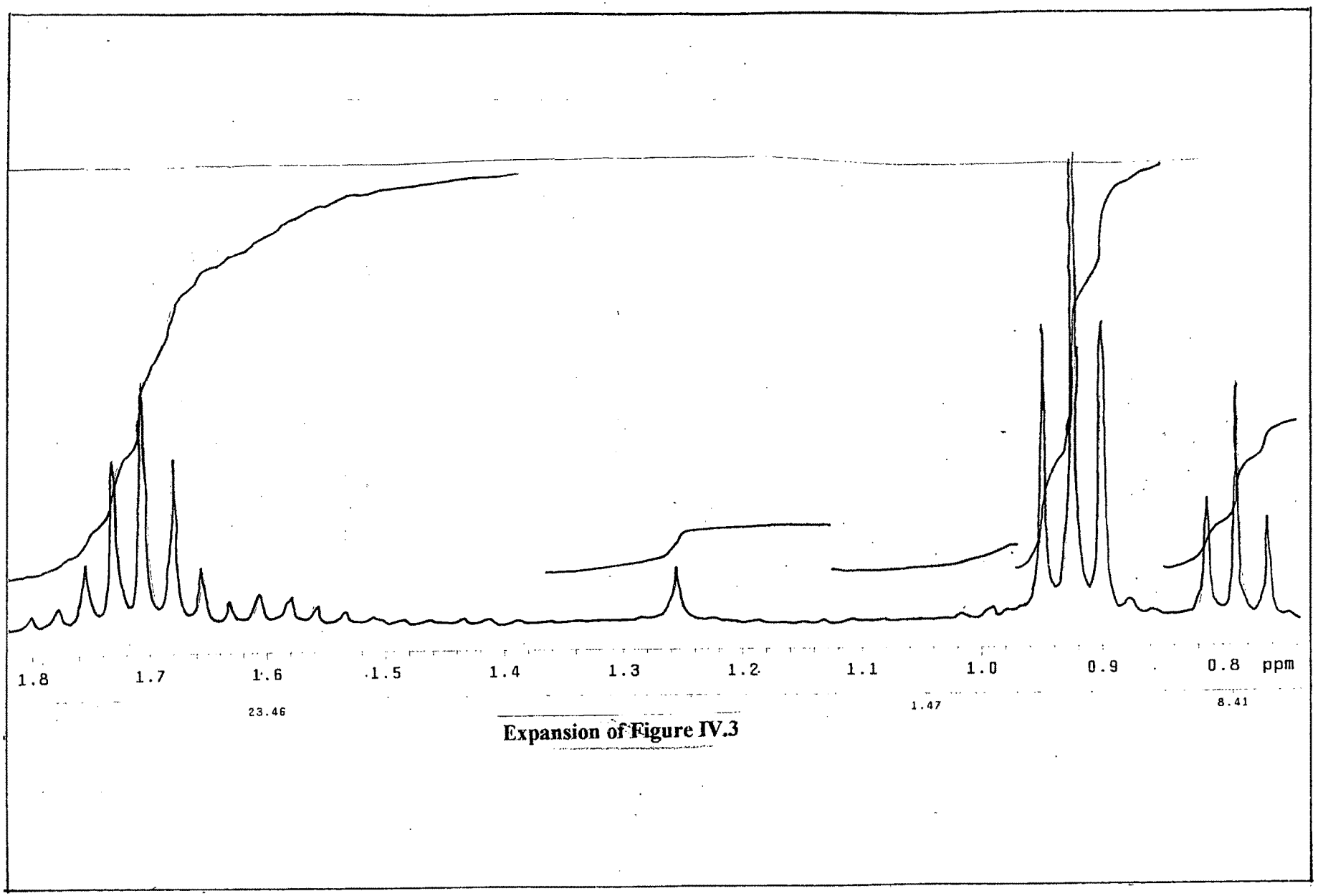


Figure IV.3 1H NMR($CDCl_3$) spectrum of 2-(4-Methoxyphenyl)-3-((R)-1-hydroxymethyl propyl)-thiazolidin-4-one 44d



Expansion of Figure IV.3

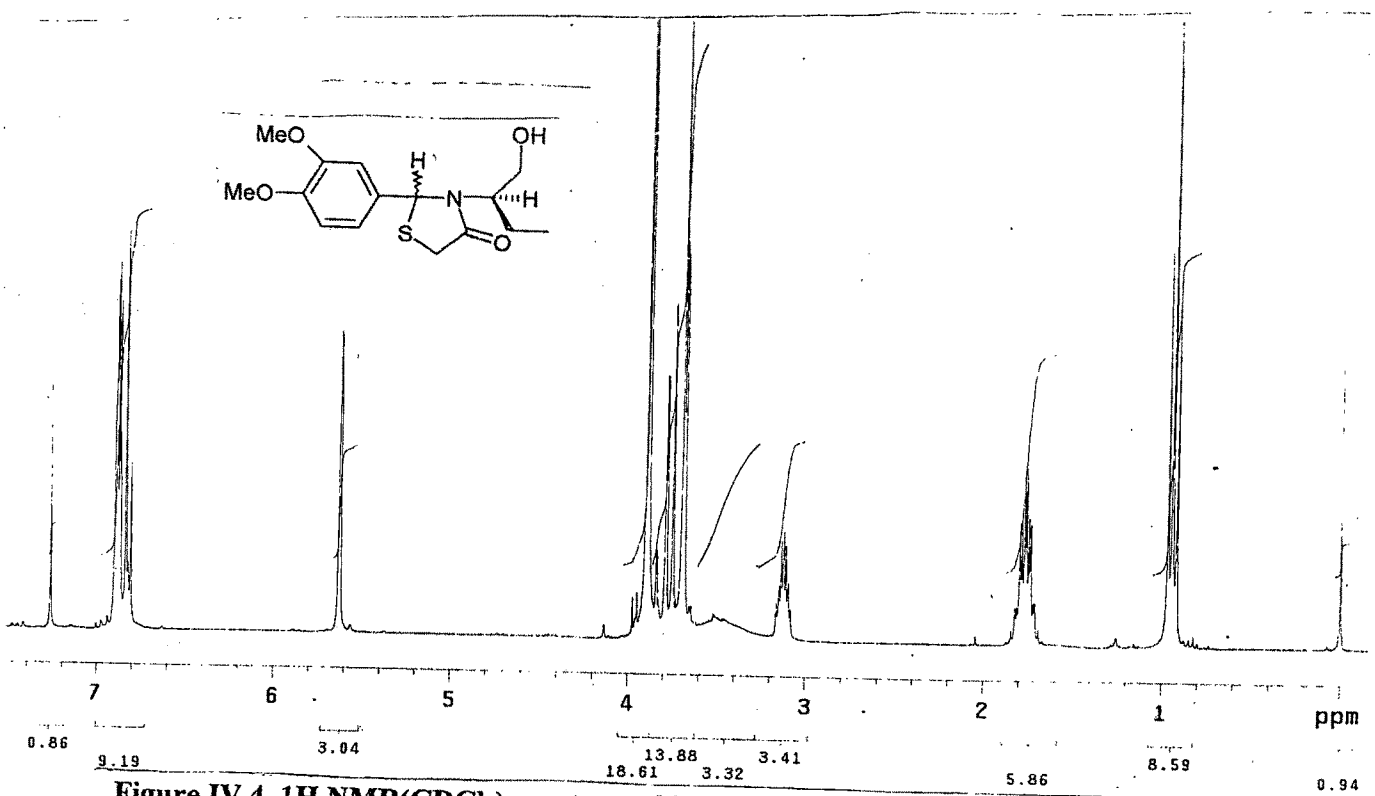
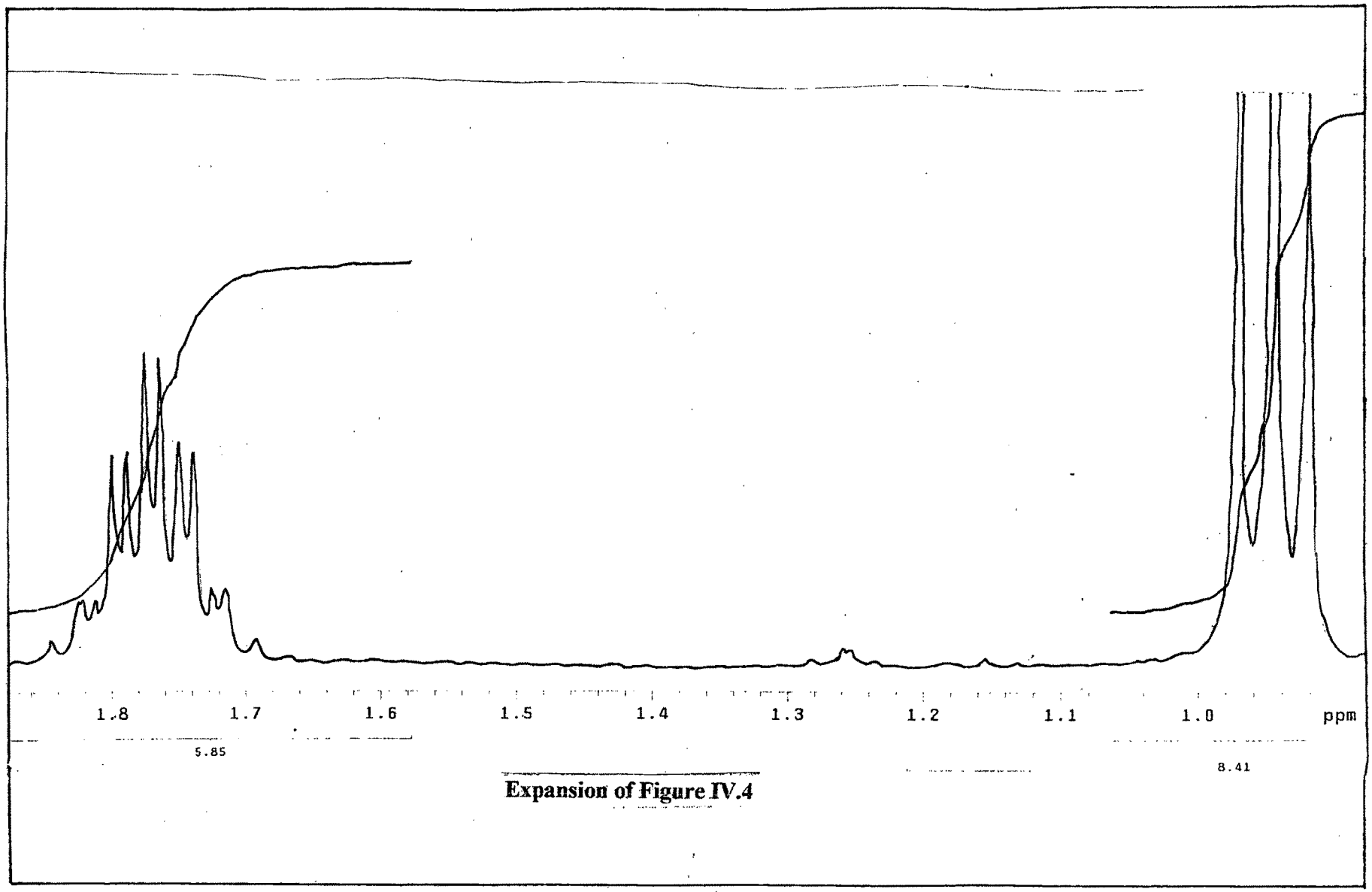


Figure IV.4 1H NMR($CDCl_3$) spectrumof 2-(3, 4-Dimethoxyphenyl)-3-((R)-1-hydroxy methylpropyl)-thiazolidin-4-one 44e



Expansion of Figure IV.4

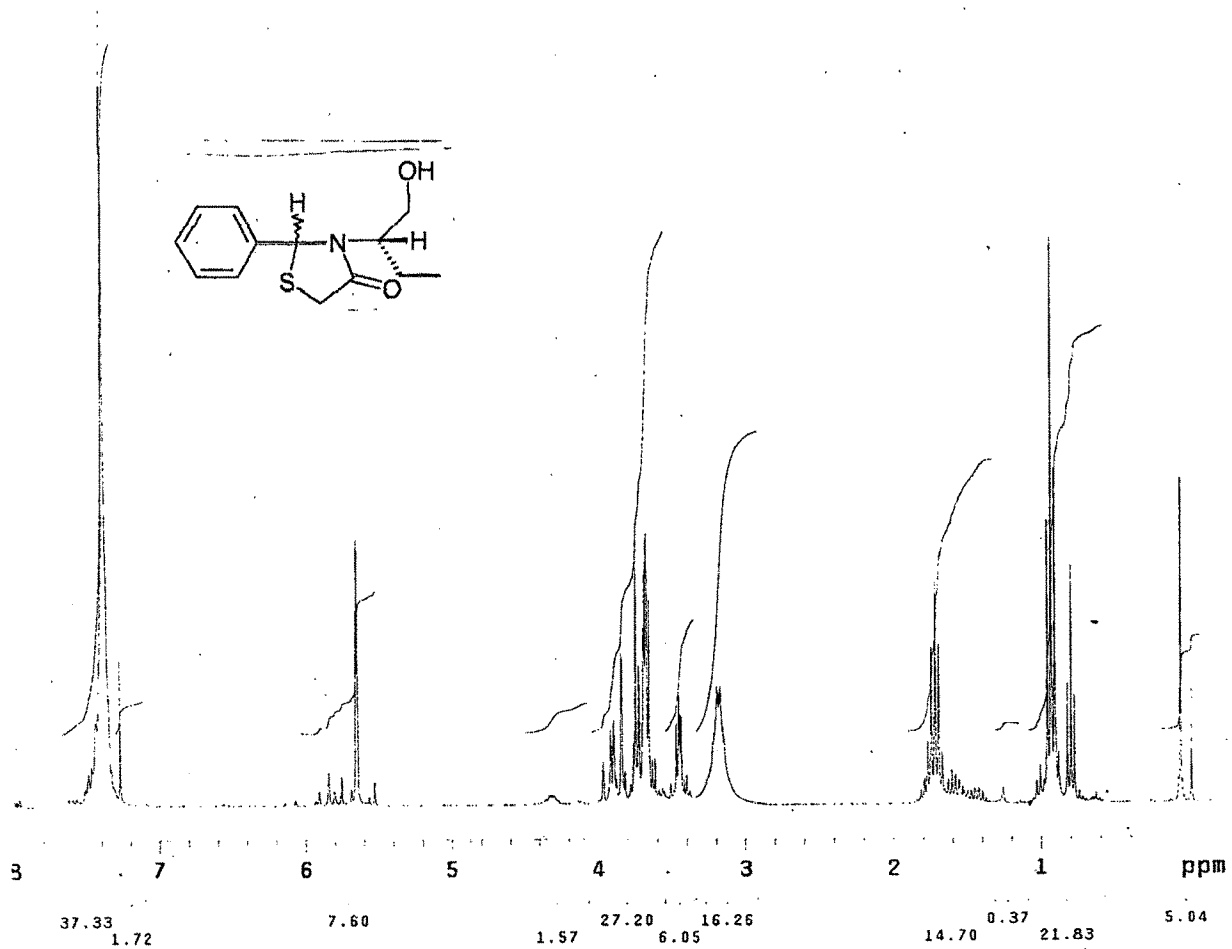
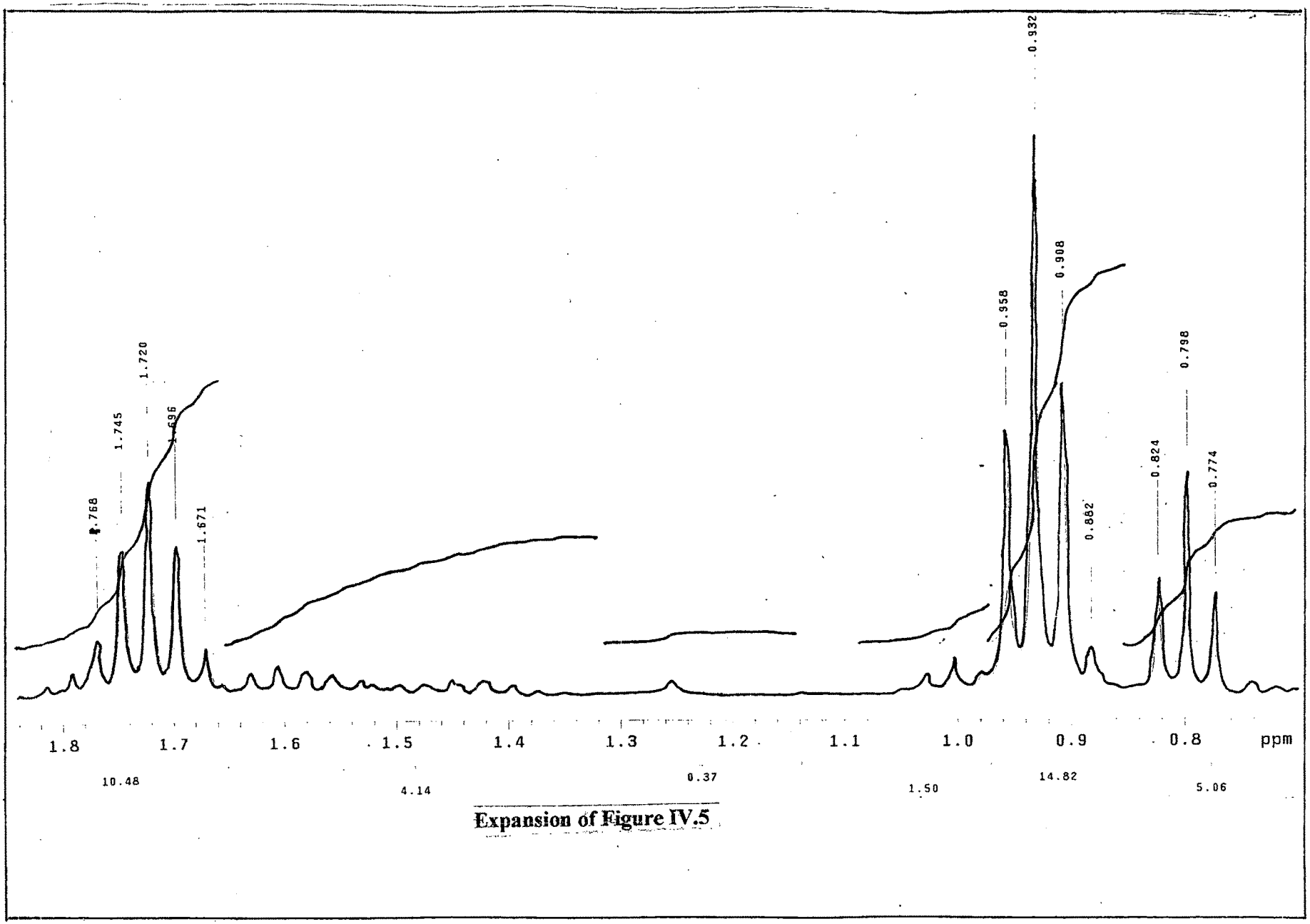


Figure IV.5 1H NMR($CDCl_3$) spectrum of 2-Phenyl-3-((S)-1-hydroxymethyl propyl)-thiazolidin-4-one 48b



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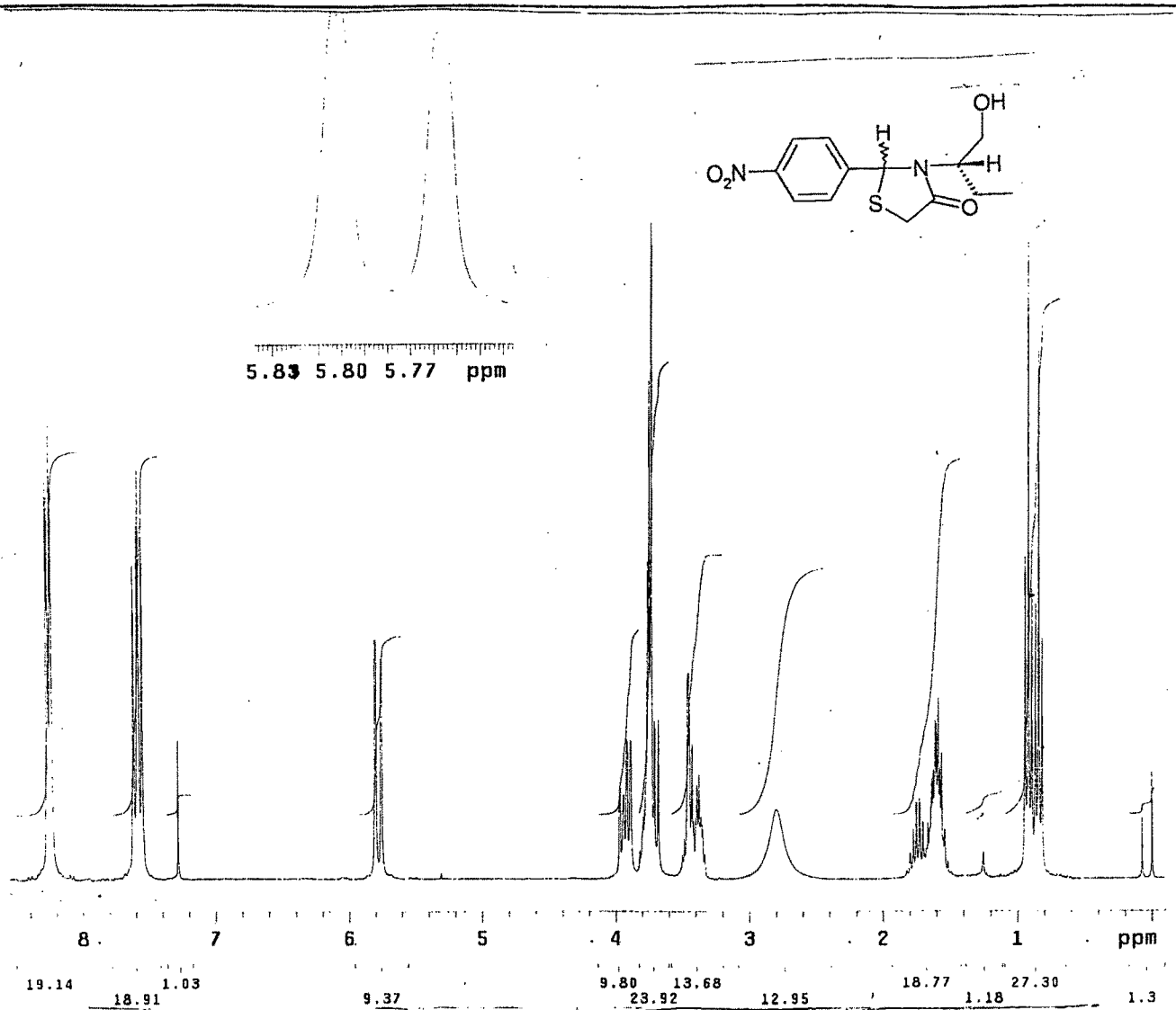
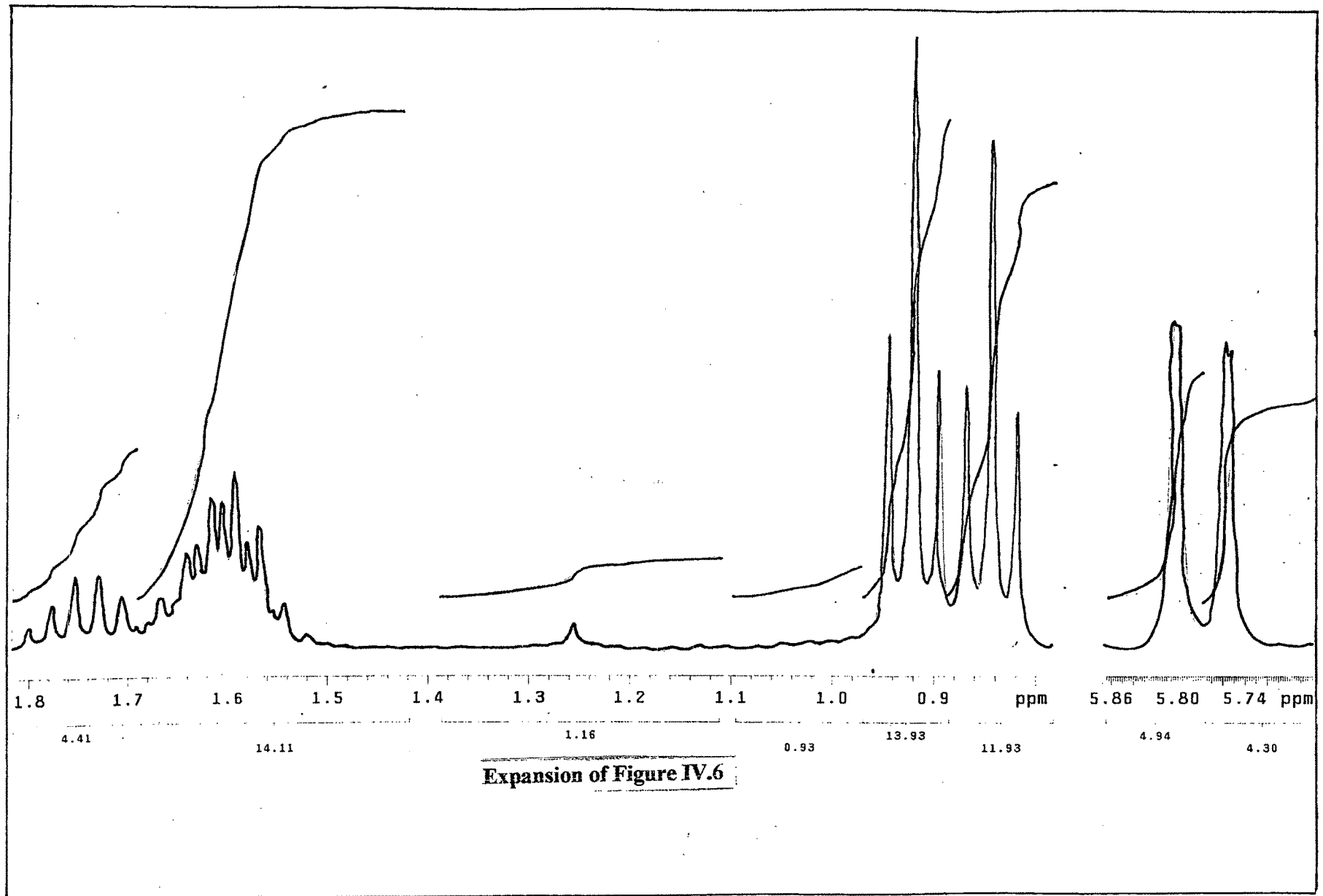


Figure IV.6 1H NMR($CDCl_3$) spectrum of 2-(4-Nitrophenyl)-3-((S)-1-hydroxymethyl propyl)-thiazolidin-4-one 48c



Expansion of Figure IV.6

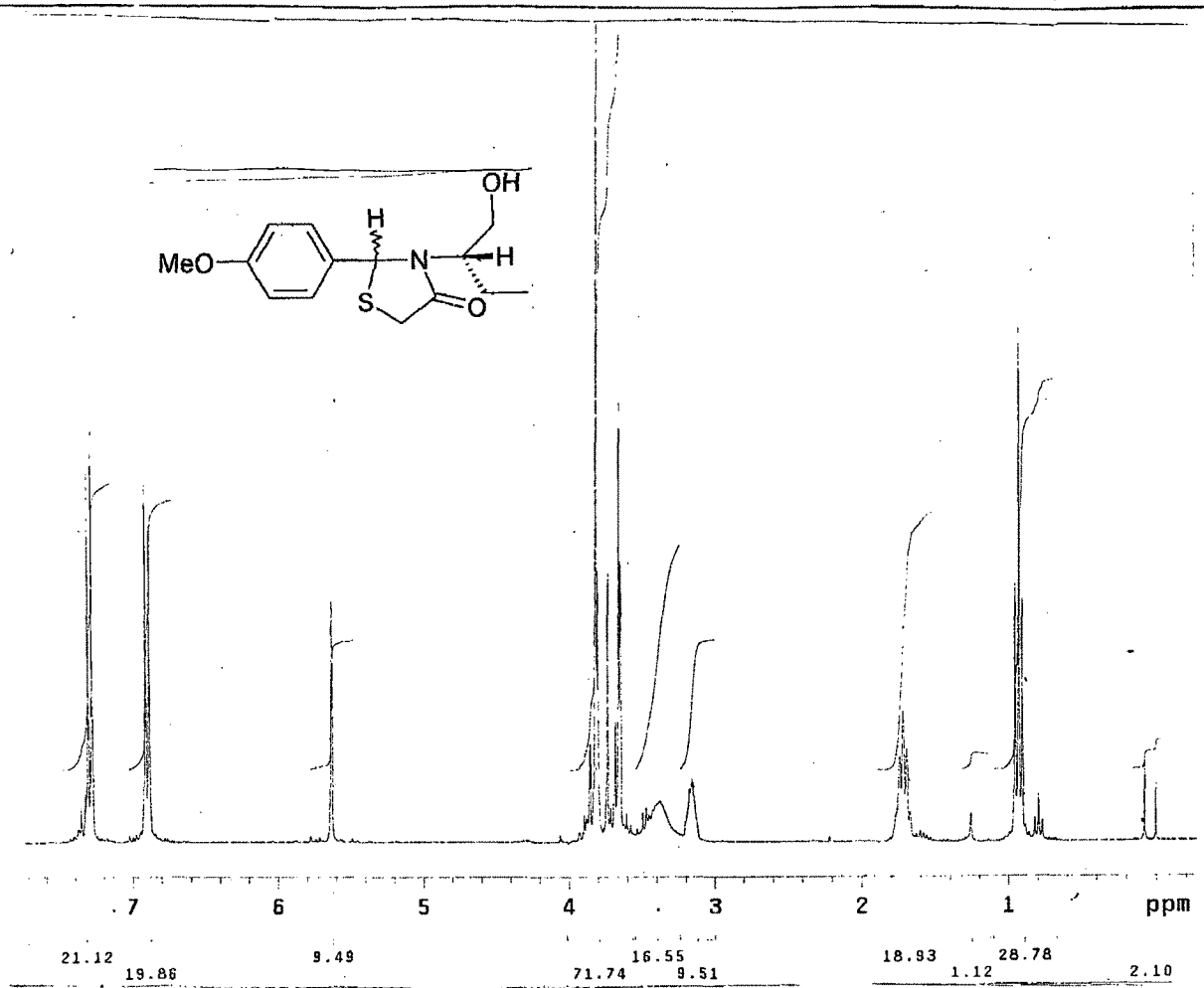
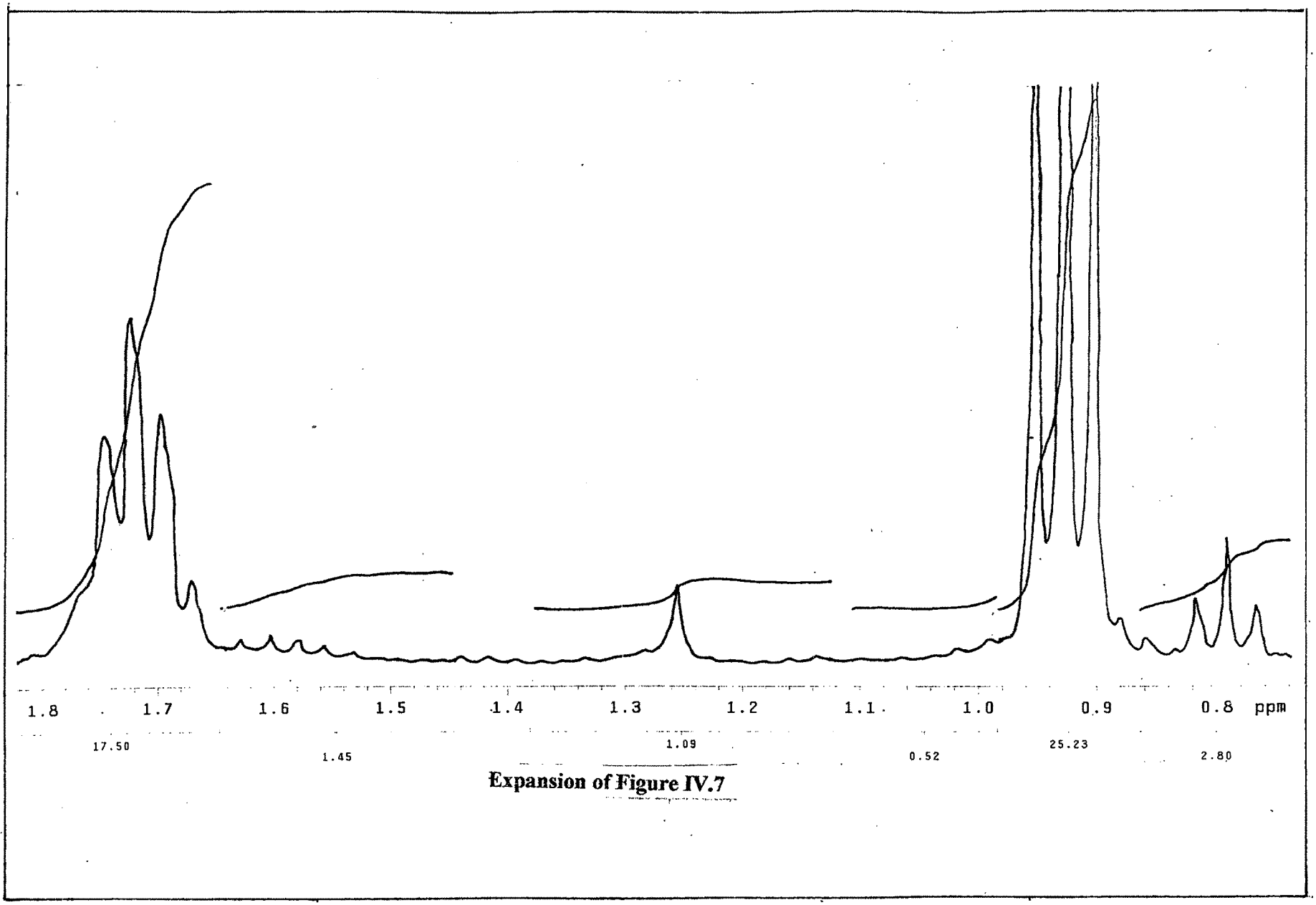


Figure IV.7 1H NMR($CDCl_3$) spectrum of 2-(4-Methoxyphenyl)-3-((S)-1-hydroxymethyl propyl)-thiazolidin-4-one 48d



Expansion of Figure IV.7

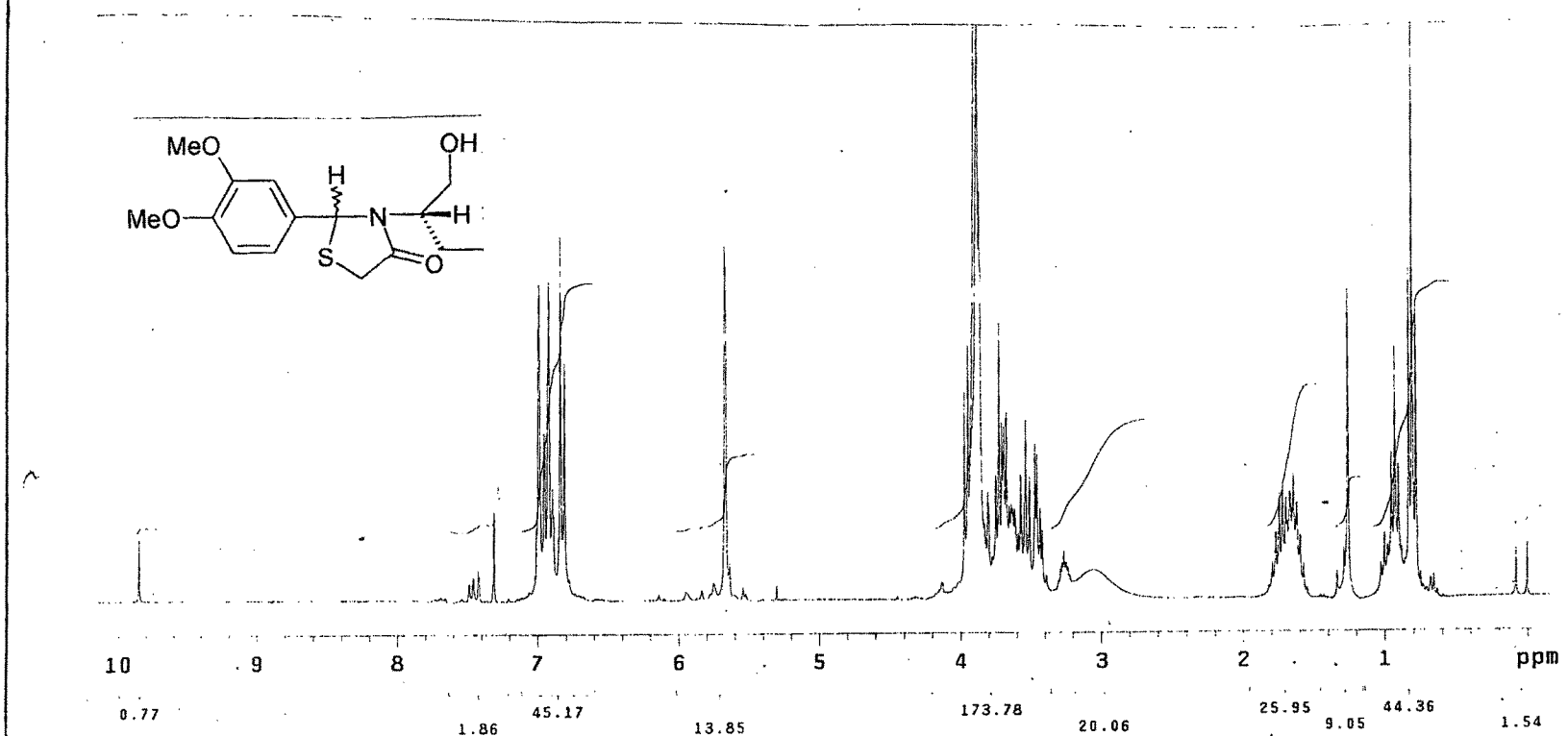


Figure IV.8 1H NMR($CDCl_3$) spectrum of 2-(3, 4-Dimethoxyphenyl)-3-((S)-1-hydroxy methylpropyl)-thiazolidin-4-one 48e

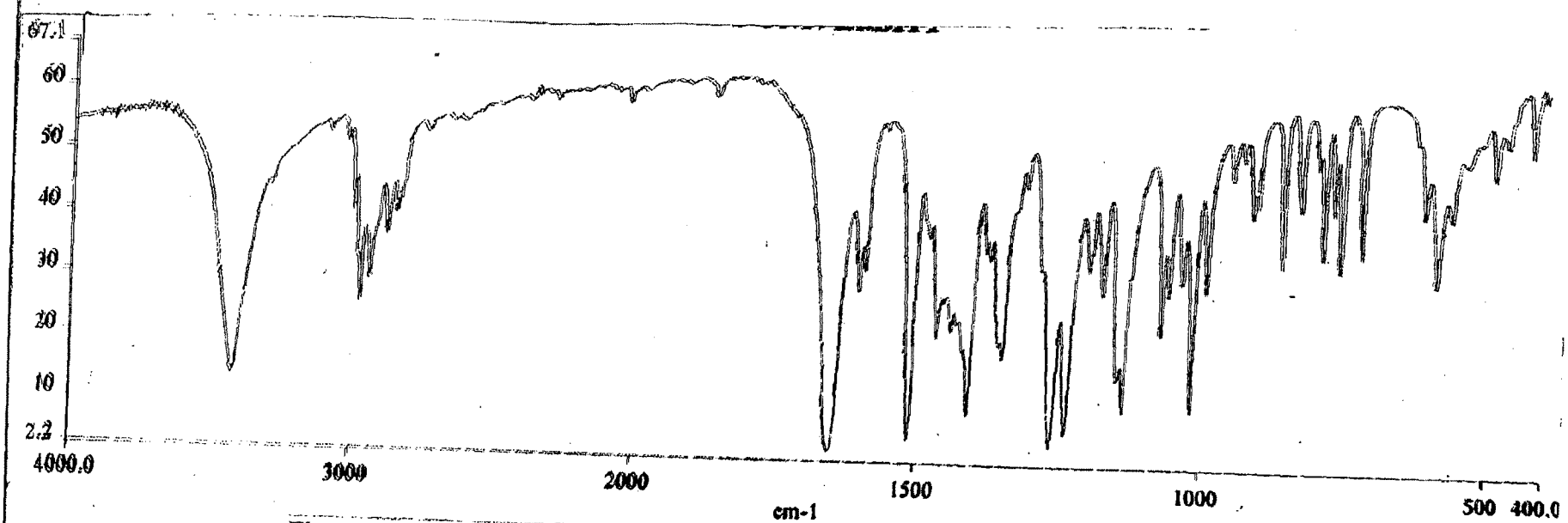
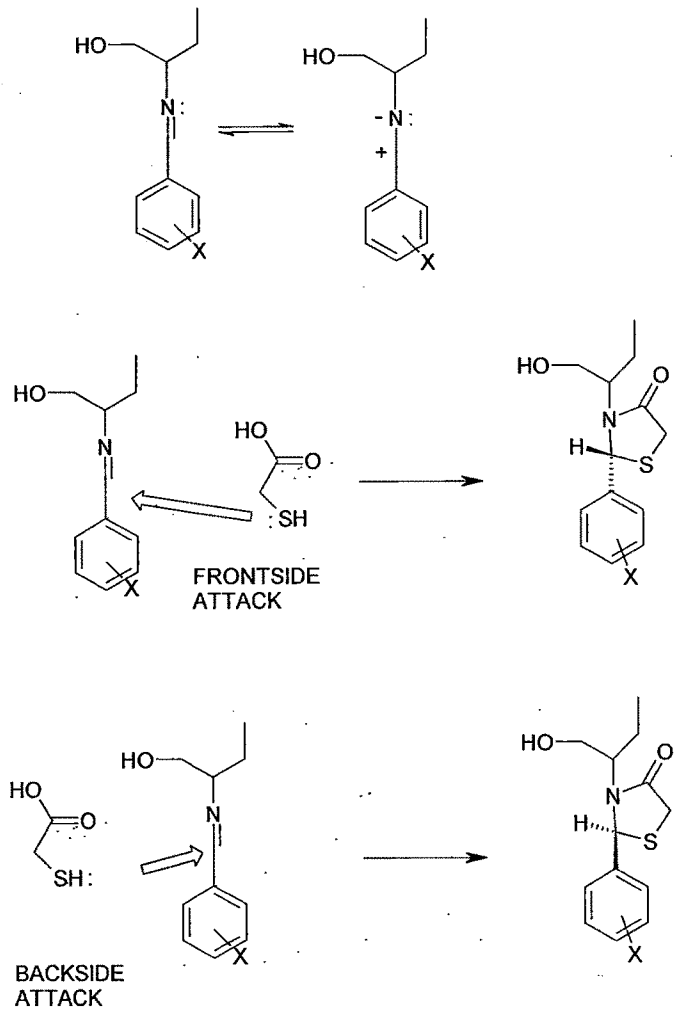


Figure IV.9 IR(KBr) spectrum of 2-(3, 4-Dimethoxyphenyl)-3-((R)-1-hydroxymethyl propyl)-thiazolidin-4-one 44e



Scheme IV.13

As shown in the scheme, the reaction may involve attack of the electron pair on the sulphur of thioglycollic acid on the electropositive carbon of the imine. Depending on the backside or front side attack of the thiol on the carbon two possible diastereomers may be formed. From the table of the ratios of the diastereomers it can be easily seen that when the aromatic aldehyde has electron withdrawing groups like the nitro group and the chloro group the diastereomers are formed in almost equal amounts i.e. the diastereoselectivity of the reaction is less and when the aromatic aldehyde has electron releasing groups then one of the diastereomers is formed in greater amount i.e. the

diastereoselectivity of the reaction is more. This may be related to the fact that in case of the electron releasing groups the transition state leading to the formation of one of the diastereomers may be stabilized to a greater extent.

4.3 EXPERIMENTAL

Reagent chemicals were purchased from Lancaster synthesis ltd and Aldrich chemical co. ltd. and were purified when necessary before use. Solvents were distilled and dried before use. Benzene and toluene were distilled and stored over sodium wire. Column chromatography was carried out using silica gel (60-120 mesh). Thin layer chromatography (TLC) was carried out using silica gel (75μ). Yields are quoted for isolated, purified and dried products. Infrared spectra for the solids were recorded in the range 4000-600cm^{-1} using Perkin-Elmer FT-IR16PC spectrometer using the KBr pellet technique in case of solids and neat in case of liquids. Proton NMR was recorded using Bruker 300 MHz spectrometer. Elemental analysis was carried out on a Perkin-Elmer C, H, and N elemental analyzer.

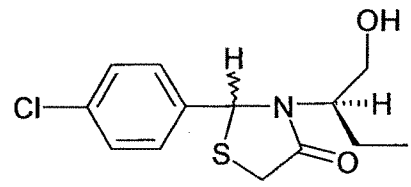
4.3.1 Chiral imines from (*R*) & (*S*)-2-amino-1-butanol

To a solution of aromatic aldehyde (20mmole) in toluene was added, a solution of (R) or (S)-2-amino-1-butanol (20mmole) in toluene at 10°C. The reaction mixture was brought to room temperature and azeotropically distilled for 2 hours. The water collected in the Dean-Stark apparatus was removed from time to time. To remove the traces of water, the reaction mixture was refluxed for an additional one hour, with a bypassed dropping funnel with 4A° molecular sieves placed in between the flask and the reflux condensed. The completion of the reaction is monitored by TLC. After completion of the reaction the toluene was removed on an oil bath under reduced pressure. The solid obtained was recrystallized from petroleum ether (60-80°C)-ethyl acetate mixture to furnish the imines.

4.3.2 Synthesis of 4-thiazolidinones

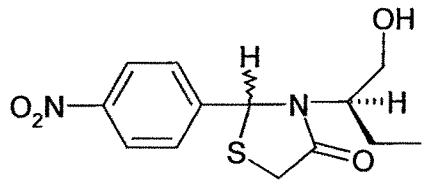
To a solution of the imine (2.36mmoles) in dry benzene was added thioglycollic acid (2.832mmoles) drop wise at room temperature. The reaction mixture was refluxed and water in the reaction mixture was removed azeotropically using a Dean-stark apparatus. The reaction is continued for 3 hours. To remove traces of water, the reaction mixture was refluxed for an additional one hour. The completion of the reaction was monitored by TLC. After completion of the reaction, benzene was removed on a rotary evaporator under reduced pressure. The residue obtained was treated with a 10% solution of sodium bicarbonate and was stirred for one hour. The residue was then extracted using three fractions of 50mL benzene. The benzene layer was dried over anhydrous sodium sulphate and was distilled off under reduced pressure. The residue was taken up for column chromatography over silica gel (60-120mesh) using petroleum ether-ethyl acetate as the eluent and the products 44a-44e and 48a-48e were isolated as viscous liquids.

2-(4-Chlorophenyl)-3-((R)-1-hydroxymethylpropyl)-thiazolidin-4-one 44b



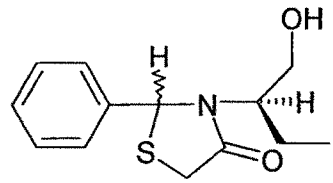
State	Liquid
Molecular formula	$C_{13}H_{16}NO_2S$
Yield	70%
CHN	C-62.02(62.3), H-5.88(6.4),
found (calculated)	N-5.2(5.6)
ν_{max} (KBR)/ cm^{-1}	1645
δ_H (200MHz, $CDCl_3$)	0.8-0.9(6H,t,2x-CH_3),1.5-1.7(4H,m,-2xCH_2), 2.5(2H,s,-2xOH),3.5-4.0(5H,m,-CH,CH_2-O,S-CH_2),5.7(1H,d,S-CH), 7.5-8.3(4H,m,Ar-H).

2-(4-Nitrophenyl)-3-((R)-1-hydroxymethylpropyl)-thiazolidin-4-one 44c



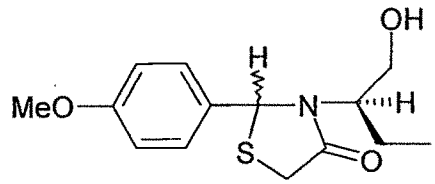
State	Liquid
Molecular formula	$C_{13}H_{16}N_2O_4S$
Yield	75%
CHN found (calculated)	C-52.39(52.7), H-5.49(5.40), N-9.25(9.459)
ν_{max} (KBR)/ cm^{-1}	1651
δ_H (200MHz, $CDCl_3$)	0.8-0.9(6H,t,2x-CH_3), , 1.5-1.8(4H,m,-2xCH_2), 2.8(2H,s,-2xOH),3.5-4.0(5H,m,-CH,CH_2-O,S-CH_2),5.7(1H,d,S-CH), 7.5-8.3(4H,m,Ar-H).

2-Phenyl-3-((R)-1-hydroxymethylpropyl)-thiazolidin-4-one 44a



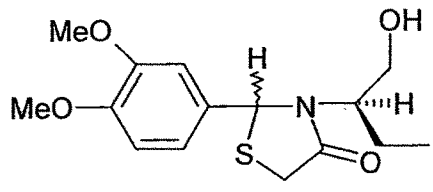
State	Liquid
Molecular formula	$C_{13}H_{17}NO_2S$
Yield	65%
CHN	C-61.49(62.15), H-6.72(6.77),
found (calculated)	N-6.0(5.57)
ν_{max} (KBR)/ cm^{-1}	1650
δ_H (200MHz, $CDCl_3$)	0.8-0.9(6H,t,2x-CH_3), 1.5-1.7(4H,m,-2xCH_2), 2.5(2H,s,2x-OH), 3.0-4.0(5H,m,-CH,CH_2-O,S-CH_2), 5.65(2H,d,2xS-CH),7.5-8.3(5H,m,Ar-H)

2-(4-Methoxyphenyl)-3-((R)-1-hydroxymethylpropyl)-thiazolidin-4-one 44d



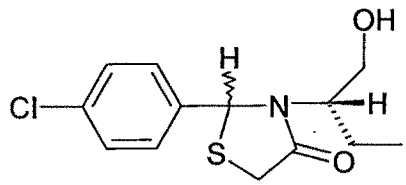
State	Liquid
Molecular formula	$C_{14}H_{19}NO_3S$
Yield	80%
CHN	C-61.20(62.45), H-6.81(7.06),
found (calculated)	N-5.51(5.20)
ν_{max} (KBR)/ cm^{-1}	1640
δ_H (200MHz, $CDCl_3$)	0.8-0.9(6H,t,2x-CH_3), 1.72(4H,m,-2xCH_2), 2.8(2H,s,2x-OH), 3.0-4.0(8H,m,OCH_3,-CH,CH_2-O,S-CH_2), 5.7(2H,d,2xS-CH),6.95-7.4(4H,m,Ar-H)

2-(3, 4-Dimethoxyphenyl)-3-((R)-1-hydroxymethylpropyl)-thiazolidin-4-one 44e



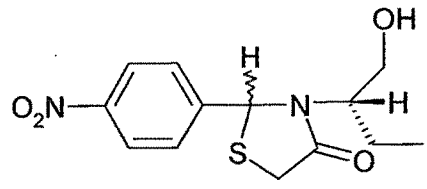
State	Liquid
Molecular formula	$C_{15}H_{21}NO_4S$
Yield	85%
CHN	C-58.51(57.87), H-7.13(6.75),
found (calculated)	N-3.85(4.50)
ν_{max} (KBR)/ cm^{-1}	1650
δ_H (200MHz, $CDCl_3$)	0.8-0.9(6H,t,2x-CH_3), 1.70(4H,m,-2xCH_2), 2.8(2H, s,2x-OH), 3.0-4.0(11H,m,2XOCH_3,-CH,CH_2-O,S-CH_2), 5.7(2H,d,2xS-CH),6.95-7.4(3H,m,Ar-H)

2-(4-Chlorophenyl)-3-((S)-1-hydroxymethylpropyl)-thiazolidin-4-one 48b



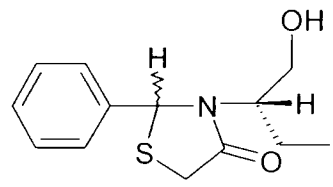
State	Liquid
Molecular formula	$C_{13}H_{16}NO_2S$
Yield	65%
CHN	C-62.4(62.3), H-6.15(6.4),
found (calculated)	N-5.3(5.6)
ν_{max} (KBR)/ cm^{-1}	1645
δ_H (200MHz, $CDCl_3$)	0.8-0.9(6H,t,2x-CH_3),1.5-1.7(4H,m,-2xCH_2), 2.5(2H,s,-2xOH),3.5-4.0(5H,m,-CH,CH_2-O,S-CH_2),5.7(1H,d,S-CH), 7.5-8.3(4H,m,Ar-H).

2-(4-Nitrophenyl)-3-((S)-1-hydroxymethylpropyl)-thiazolidin-4-one 48c



State	Liquid
Molecular formula	$C_{13}H_{16}N_2O_4S$
Yield	75%
CHN	C-51.4(52.7), H-5.34(5.40),
found (calculated)	N-9.04(9.459)
ν_{max} (KBR)/ cm^{-1}	1651
δ_H (200MHz, $CDCl_3$)	0.8-0.9(6H,t,2x-CH_3),1.5-1.8(4H,m,-2xCH_2), 2.8(2H,s,-2xOH),3.5-4.0(5H,m,-CH,CH_2-O,S-CH_2), 5.7(1H, d, S-CH), 7.5-8.3(4H, m, Ar-H).

2-Phenyl-3-((S)-1-hydroxymethylpropyl)-thiazolidin-4-one 48a



State	Liquid
Molecular formula	$C_{13}H_{17}NO_2S$
Yield	70%
CHN	C-61.49(62.15), H-6.72(6.77),
found (calculated)	N-6.0(5.57)
ν_{max} (KBR)/ cm^{-1}	1651
δ_H (200MHz, $CDCl_3$)	0.8-0.9(6H,t,2x-CH_3), 1.5-1.7(4H,m,-2xCH_2), 2.5(2H,s,2x-OH), 3.0-4.0(5H,m,-CH,CH_2-O,S-CH_2), 5.65(2H,d,2xS-CH),7.5-8.3(5H,m,Ar-H)

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