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SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF NOVEL THIAZOLOQUINAZOLINE AS NEW CLASS OF H_1-ANTIHISTAMINIC AGENT

T.Panneer Selvam*[1], P. Vijayaraj Kumar[2], C.R. Prakash[1]

*[1] Department of Pharmaceutical Chemistry, D.C.R.M. Pharmacy College, Inkollu-523167 Andhrapradesh, India.

[2] Bharat Institute of Technology (Pharmacy), Hyderabad, Andhrapradesh, 501510, India.

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Abstract:

A series of novel 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline were synthesized the reaction with appropriate aromatic aldehydes and *p* –nitro aniline in the presence of anhydrous sodium acetate The starting material 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl) thiazolo (2, 3-*b*) quinazolin-3(2*H*)-one **3** by a new innovative route with improved yield. When tested for their *in vivo* H-antihistaminic activity on conscious guinea pigs, all the test compounds significantly protected the animals from histamine induced bronchospasm. The compound **5b** emerged as the most active compound of the series and it is more potent (73.93% protection) when compared to the reference standard, chlorpheniramine maleate (71% protection), it showed negligible sedation (10%) when compared to chlorpheniramine maleate (30%). Therefore compound **5b** will serve as prototype molecule for further development as a new class of H_1-antihistamines.

Key words: Thiazolo quinazoline; Benzylidine thiazolo quinazoline; Nitrophenyl amino thiazolo quinazoline; H_1-Antihistaminic.

INTRODUCTION

A large number of synthetic antihistaminic drugs for oral use have been developed over the last thirty years. Also, synthetic compounds and natural products have been investigated for anti-histaminic activity in both pharmacological and clinical terms. Nowadays, the antihistaminic drugs, particularly antagonists of the H1-receptors, are used to avoid the health problems related to widespread allergic affections, a high incidence pathology on the population. The first generation antihistamines penetrate the blood brain barrier and also possess anticholinergic properties; this has led to the development of a second generation of H_1-antagonists such as terfenadine, cetirizine and astemizole [1]. A common feature of first generation compounds includes two aryl or hetero aryl rings linked to an aliphatic tertiary amine *via* the side chain [2] (*e.g*. diphenhydramine and pheniramine). The second generation compounds (terfenadine and cetirizine) also contain many of the structural features of first generation compounds. The real breakthrough of non-sedative antihistamines came in the early eighties of the twentieth century when the discovery of modern antihistamines, was found to exhibit potent antihistaminic activity without sedative effect [3]. Condensed heterocycles containing new generation of H_1-antihistamines (*e.g*. loratadine, azelastine and flazelastine) that does not possess the above mentioned pharmacophore for H_1-antihistamines gave way for the discovery of many novel antihistamines temelastine [4] and mangostin [5]. Quinazolines and condensed quinazolines show excellent antihistaminic activity [6, 7]. In this continuation we demonstrated that [8, 9] the quinazoline derivatives as potent antihistamines with least sedation. The present work is an extension of our ongoing efforts towards for the development and identification of new molecules therefore; we aimed to synthesize a series of 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidine)-3-(4-nitrophenyl amino) thiazolo

quinazoline containing aromatic aldehydes substitution at position 2. The title compounds **5a -5f** were synthesized by the reaction of **3** with appropriate aromatic aldehydes and *p* –nitro aniline in the presence of anhydrous sodium acetate and DMF as presented in Scheme. Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds; the purity of these compounds was ascertained by microanalysis. The synthesized products were tested for their *in vivo* H_1-antihistaminic activity on conscious guinea pigs. As sedation is one of the major side effects associated with antihistamines, the test thiazolo quinazolines were also evaluated for their sedative potentials, by measuring the reduction in locomotor activity using actophotometer.

Results and Discussion

Chemistry

The synthesized series of heterocycles, **4** and **5a-5f** by the reaction of **3** with appropriate aromatic aldehydes and *p* –nitro aniline in the presence of anhydrous sodium acetate and DMF as presented in Scheme 1. The IR, ^{1}H-NMR, mass spectroscopy and elemental analysis for the new compound is in accordance with the assigned structures. The IR spectra of compounds **4** showed stretching bands of keto group at 1715-1740 cm^{-1}. In **5a-5f**, stretching and bending NH bands of thiazolo quinazoline moiety appear at 3300-3400 cm^{-1}, 1300-1350 cm^{-1} respectively. The recorded IR spectra of representative compounds **5a-5f** showed missing of keto group bands. This clearly envisages that the keto group of **4** is converted in to secondary NH. The proton magnetic resonance spectra of thiazolo quinazoline and their corresponding derivatives have been recorded in $CDCl_3$. In this **5a-5f** NH signal of 3-(4-nitro phenyl) amino thiazolo quinazoline moiety appear at 7.19-7.67 (s) ppm respectively. The position and presence of NH signal in the ^{1}H-NMR spectra of final compounds conforms the secondary NH proton in thiazolo quinazoline moiety. This clearly envisages that

thiazole-3-one moiety involve in 3-(4-nitro phenyl) amino formation. All these observed facts clearly demonstrate that 3rd position of keto group in thiazole ring is converted in to secondary amino group as indicated in **scheme** and conforms the proposed structure (**5a -5f**).

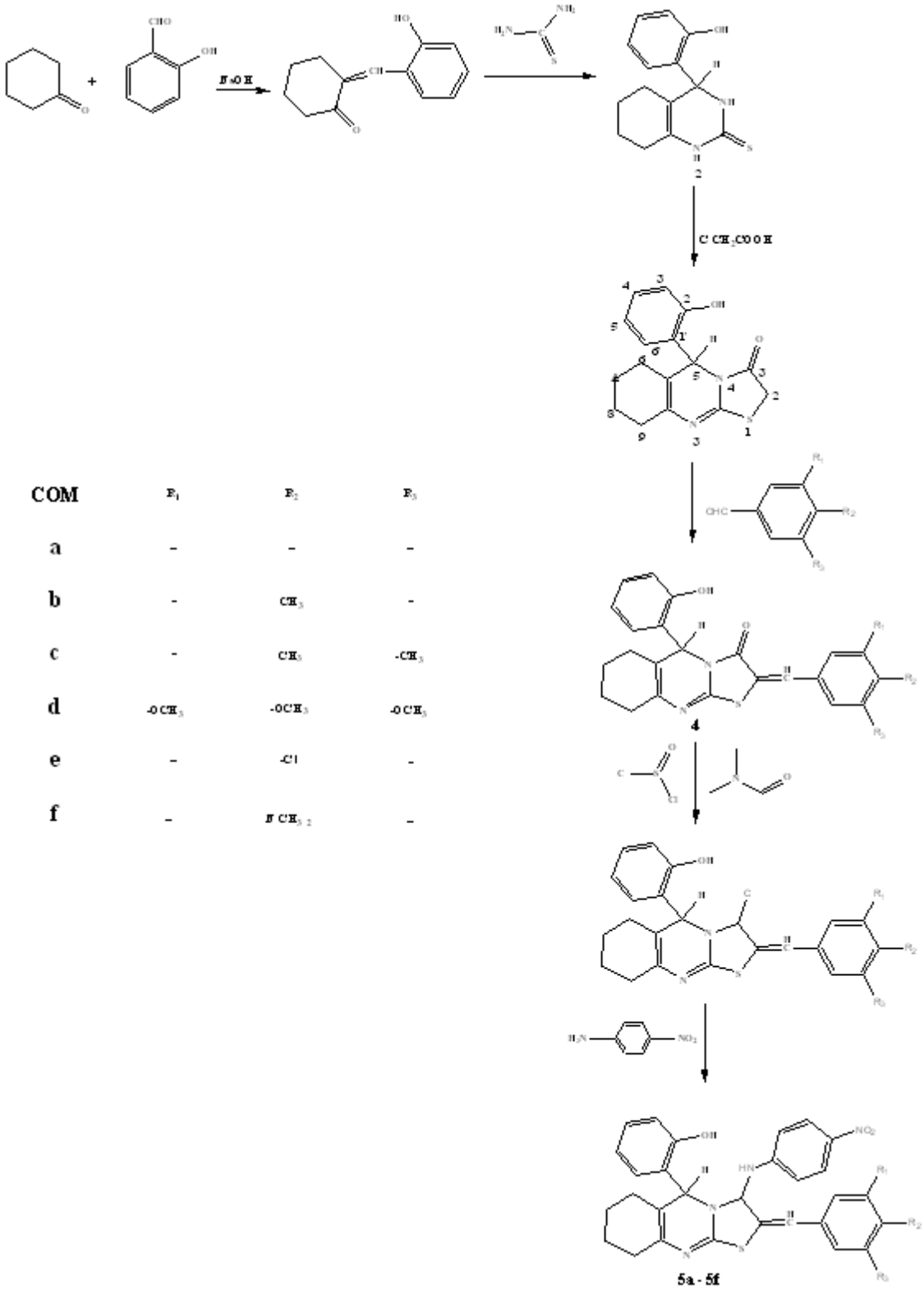
The compounds containing the 2, 3- substituted thiazolo quinazoline ring system (**5a -5f**) were evaluated for heir *in vivo* antihistaminic activity. Histamine causes bronchospasm and the guinea pigs are the most susceptible animals for histamine, hence protection against histamine-induced bronchospasm on conscious guinea pigs method was adopted to determine the antihistaminic potential of the test compounds. The advantage of this method is it is a non-invasive method and the animals are recovered after the experiment. All the test compounds were found to exhibit good antihistaminic activity (Table 1). Percentage protection data showed that all compounds of the series show significant protection in the range of 69-73 %. Biological studies indicated that different substituents over the second position of thiazolo quinazoline ring exerted varied biological activity. The presence of methyl group (compound **5b**) showed better activity over the unsubstituted compound (compound **5a**), with increased lipophilicity (*i.e.*, dimethyl compound **5c**) activity retained, further increase in lipophilicity (*i.e.*, methoxy compound **5d**) leads to decrease in activity. Replacement of the methyl group by chloro (compound **5e**) showed further decrease in activity. Replacement of methyl group by dimethyl amino (compound **5f**) showed increase in activity over the chloro substituent. As the test compounds could not be converted to a water-soluble form, *in vitro* evaluation for antihistaminic activity could not be performed. The results of sedative-hypnotic activity indicate that all the test compounds were found to exhibit only negligible sedation (10-13%), whereas the reference standard chlorpheniramine maleate showed 30% sedation. In the present study, synthesis of new series of 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted

benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline have been described. The key intermediate compound of 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl) thiazolo (2, 3-*b*) quinazolin-3(2*H*)-one **3** has been synthesized by new innovative route with improved the yield. The title compounds have exhibited promising antihistaminic activity against histamine induced bronchospasm on conscious guinea pigs *in vivo* model. Among the series, 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methyl benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline **5b** was found to be the most active compound (73.93%), which is more potent than the reference standard chlorpheniramine maleate (71%). Interestingly compound **5b** also showed negligible sedation (10%) compared to chlorpheniramine maleate (30%) and could therefore serve as a lead molecule for further modification to obtain a clinically useful novel class of non-sedative antihistamines.

Experimental
Chemistry

The synthetic strategy leading to the key intermediate and the target compounds are illustrated in **Scheme**.

SCHEME



COM	R_1	R_2	R_3
a	-	-	-
b	-	CH_3	-
c	-	CH_3	$-CH_3$
d	$-OCH_3$	$-OCH_3$	$-OCH_3$
e	-	-Cl	-
f	-	$NCH_{3\,2}$	-

6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl) thiazolo (2, 3-*b*) quinazolin-3(2*H*)-one **3** prepared by the equimolar quantities of each (0.039 mol) of cyclohexanone and salicylaldehyde (0.039 mol) were taken in a beaker, to this sodium hydroxide solution was added to make the solution alkaline, this was shaken and kept aside. The solid thus obtained, was filtered, washed with water and recrystallized from absolute ethanol. A mixture of 2-hydroxy benzylidine cyclohexanone ring **1** (0.039 mol) thiourea (0.03 mol) and potassium hydroxide (2.5g) in ethanol (100 mL) was heated under reflux for 3h. The reaction mixture was concentrated to half of its volume, dilute with water, then acidified with dilute acetic acid and kept overnight. The solid thus obtained, was filtered, washed with water and recrystallized from ethanol to give 4-hydroxy phenyl 3, 4, 5, 6, 7, 8-hexahydro quinazolin-2-thione **2**. The chloroacetic acid (0.096 mol) was melted on a water bath and thione (0.009 mol) added to it portion wise to maintain its homogeneity. The homogeneous mixture was further heated on a water bath for 30 min and kept overnight. The solid thus obtained was washed with water until neutralized and crystallized from ethanol to give 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl) thiazolo (2, 3-*b*) quinazolin-3(2*H*)-one **3** [20]. A mixture of **3** (0.002 mol)**,** substituted benzaldehyde (0.002 mol) and anhydrous sodium acetate (0.2g 0.002 mol) in glacial acetic acid (10 mL) was heated under reflux for 4h. The reaction mixture was kept overnight and the solid, thus separated, was filtered, washed with water and recrystallized from ethanol to furnish of 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidine) thiazolo (2,3-b) quinazolin-3(2H)-one **4**. Equimolar quantities (0.004 mol) of compound **4** treated with thionyl chloride and DMF to get chloro derivative and then coupled with *p*-nitro anilines in DMF at 80^0C and quenched in ice-water to get the product were separated by filtration, vaccum dried and recrystallized from warm ethanol to yields 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some

substituted benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (**5a-5f**) **Scheme**. The spectral data IR, ^{1}H NMR, mass spectroscopy and elemental analyses were used to ascertain the structures of all the compounds.

The melting points were taken in open capillary tube and are uncorrected. IR spectra were recorded with KBr pellets (ABB Bomem FT-IR spectrometer MB 104 ABB Limited, Bangaluru, India). Proton (^{1}H) NMR spectra (Bruker 400 NMR spectrometer Mumbai, India) were recorded with TMS as internal references. Mass spectral data were recorded with a quadrupol mass spectrometer (Shimadzu GC MS QP 5000, Chennai, India), and microanalyses were performed using a *vario EL* V300 *elemental* analyzer (*Elemental* Analysensysteme *GmbH* Chennai, India). The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates (E.Merck) using ethyl acetate: benzene (1:3) and visualized in UV chamber. IR, ^{1}H-NMR, mass spectral datas and elemental analysis were consistent with the assigned structures.

^{1}H NMR spectra were recorded for all the target compounds. The ^{1}H NMR spectra were recorded for the representative key intermediate **3**.

6,7,8,9 tetra hydro-5H-5-(2-hydroxy phenyl) thiazoloquinazolin-3-one.

Yield: 71%; m.p.153-155 °C; IR (KBr, cm^{-1}): 3402 (phenolic OH), 3046 (Ar-CH), 1719 (C=O), 1462 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 6.61-6.89 (m,4H Ar-H), 5.71 (s, 1H; -CH) 9.91 (s, 1H; Ar-OH), 3.76 (s, 2H; -CH_2) 1.6-2.42 (m, 8H; CH_2, CH_2, CH_2, CH_2).EI-MS m/z (M+): 300 (Calcd for $C_{16}H_{16}N_2O_2S$; 300.38). Anal. Calcd for $C_{16}H_{16}N_2O_2S$; C, 63.98; H, 5.37; N, 9.32; Found: C, 63.92; H, 5.28; N, 9.30.

Figure 1 - 6,7,8,9 tetra hydro-5H-5-(2-hydroxy phenyl) thiazoloquinazolin-3-one (**3**)(IR)

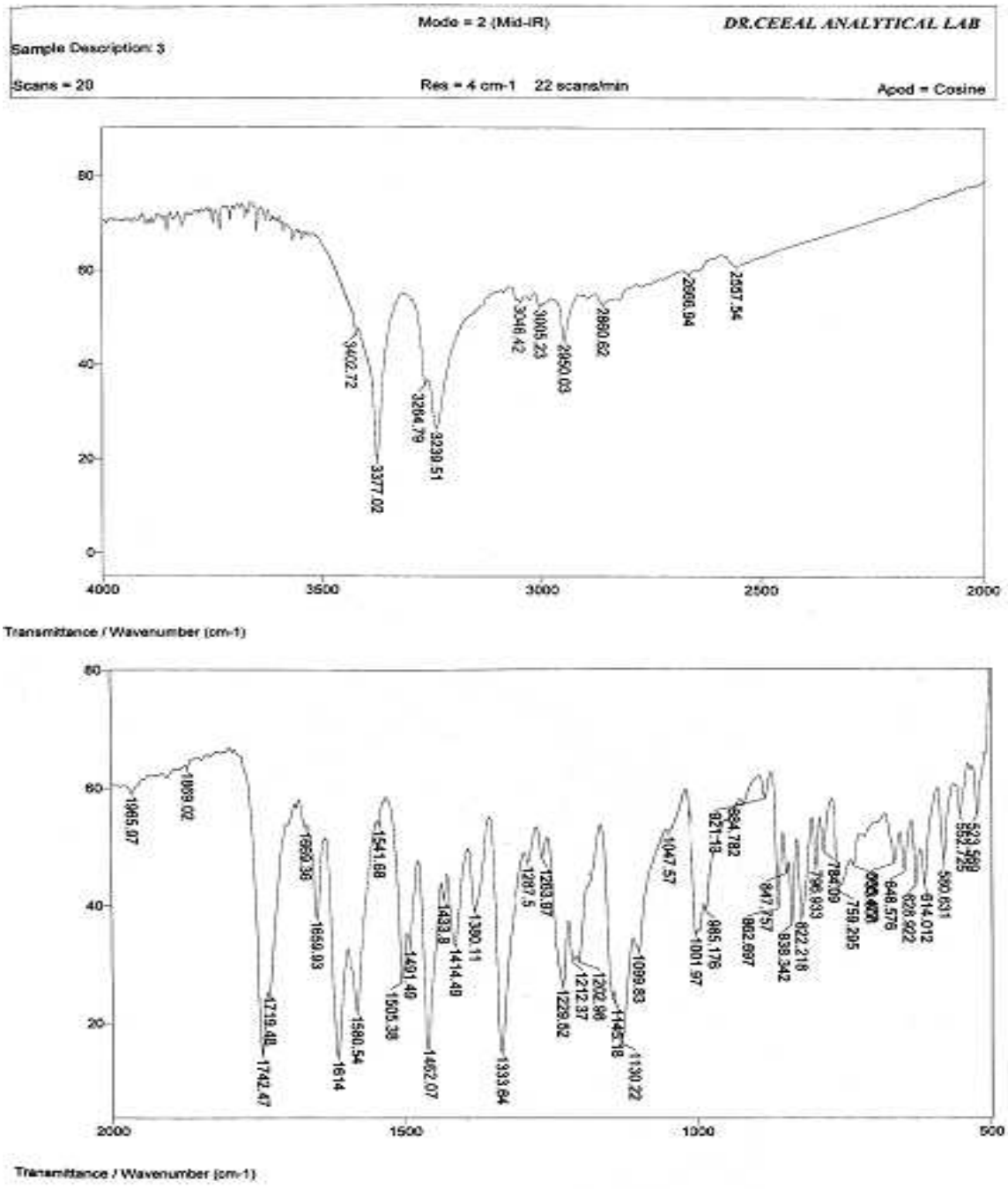


Figure 2 - 6,7,8,9 tetra hydro-5H-5-(2-hydroxy phenyl) thiazoloquinazolin-3-one (**3**)(^{1}H-NMR)

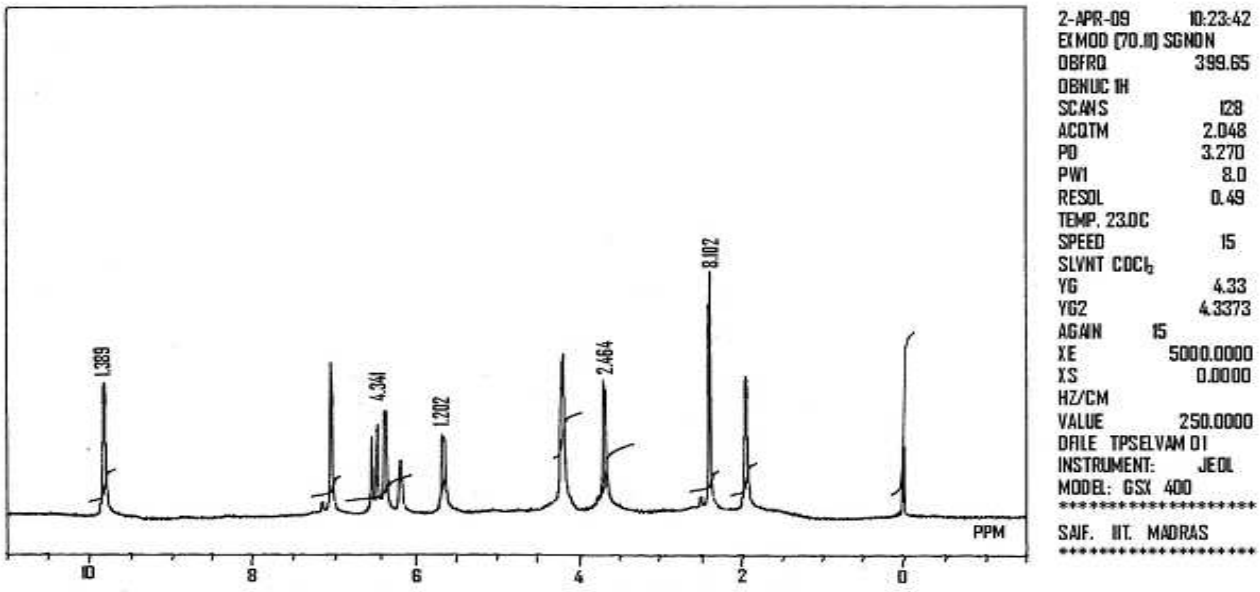
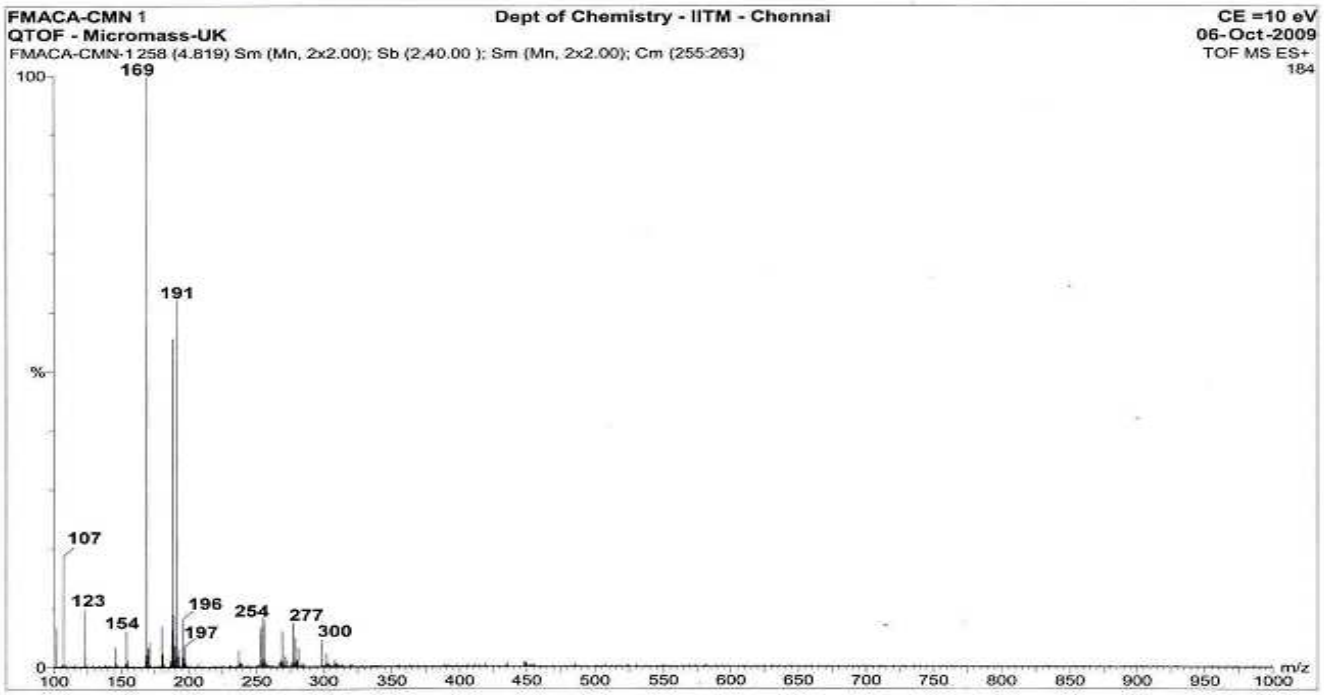


Figure 3 - The 6,7,8,9 tetra hydro-5H-5-(2-hydroxy phenyl) thiazoloquinazolin-3-one **(3)**(MASS)



6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-benzylidine thiazolo (2, 3-b) quinazolin-3(2H)-one (4) Yellow solid; Yield: 82%; mp. 153-155 °C; IR : 3450 (O-H), 3051 (Ar-CH), 1724 (C=O), 1472 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 6.92-7.56 (m, 9H, Ar-H), 6.63 (s, 1H, =CH), 5.81 (s, 1H, H-5), 9.74 (s, 1H, Ar-OH), 1.58-2.67 (m, 8H, 4 × CH_2); EI-MS (m/z): 377 (M+); (Calcd for $C_{23}H_{20}N_2O_2S$; 377.48). Anal. Calcd for $C_{23}H_{20}N_2O_2S$, C, 71.11; H, 5.19; N, 7.21; Found: C, 71.19; H, 5.26; N, 7.14

Figure 4:6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-benzylidine thiazolo (2, 3-b) quinazolin-3(2H)-one **(4)** (IR)

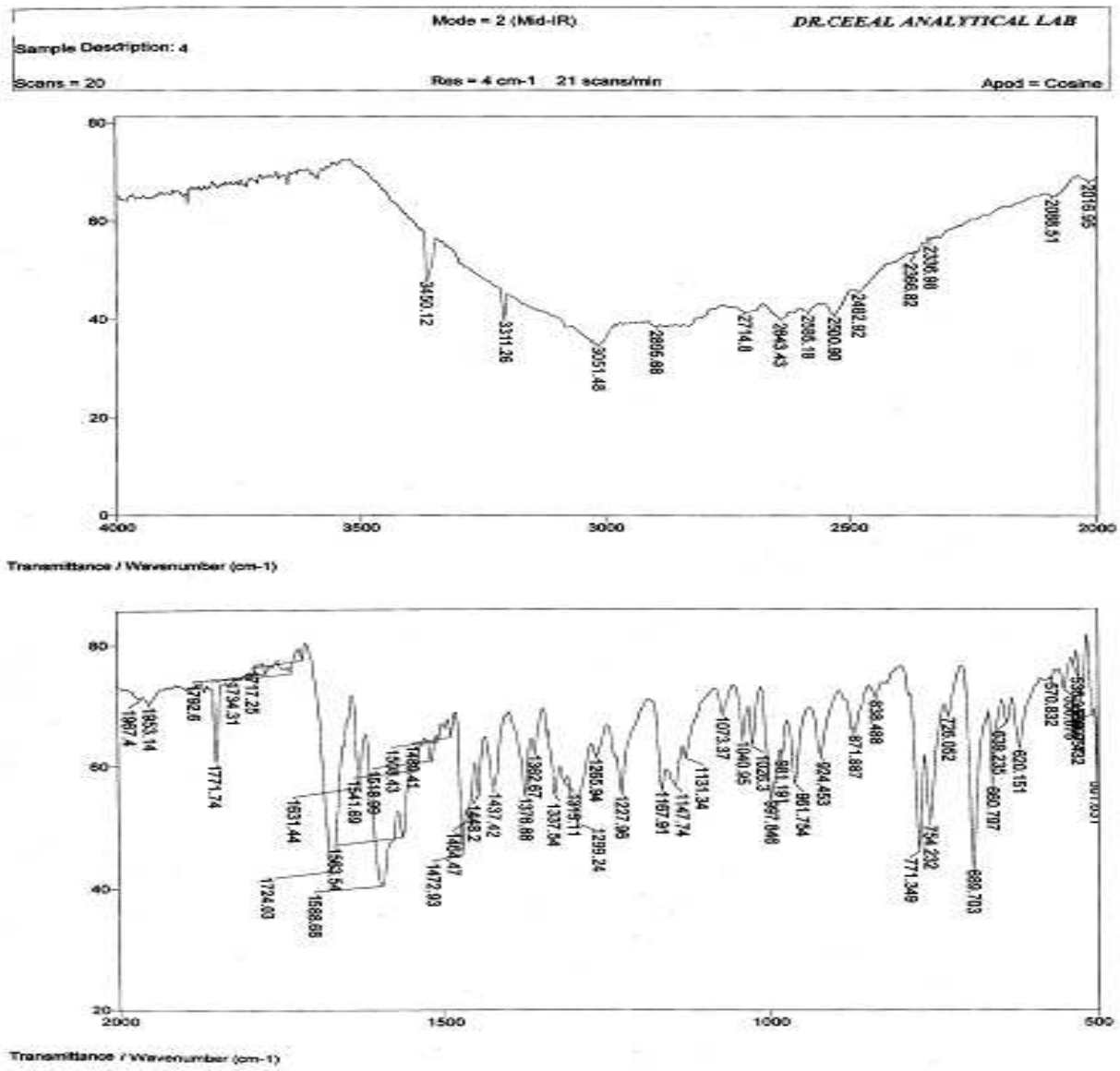


Figure 5- 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-benzylidine thiazolo (2, 3-b) quinazolin-3(2H)-one **(4)** (^{1}H NMR)

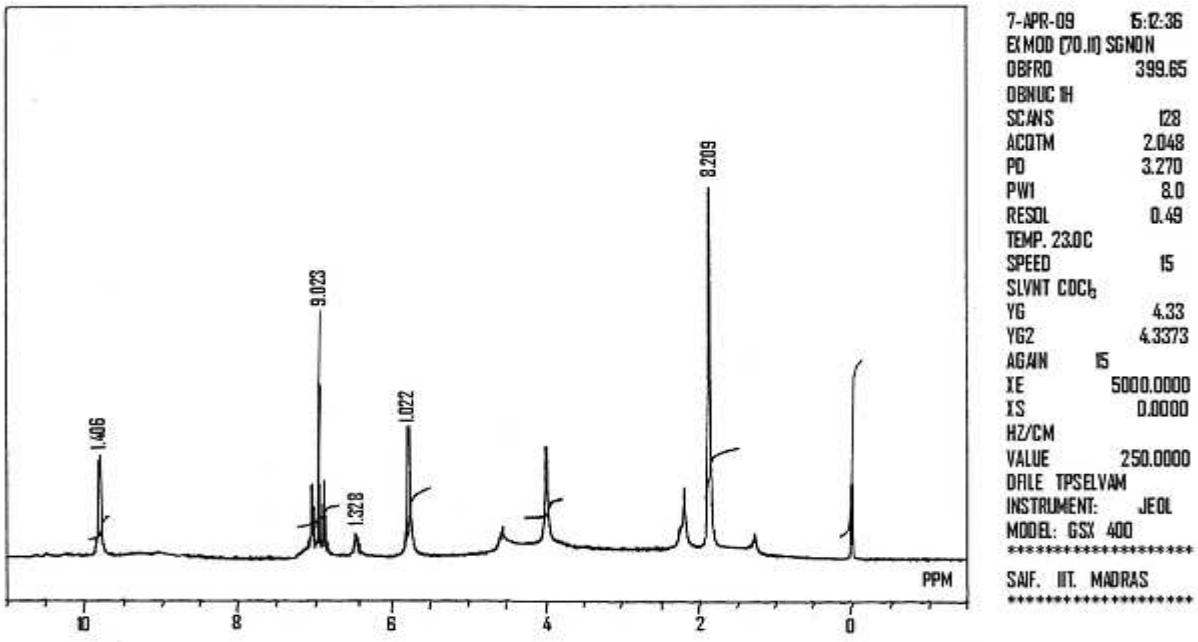
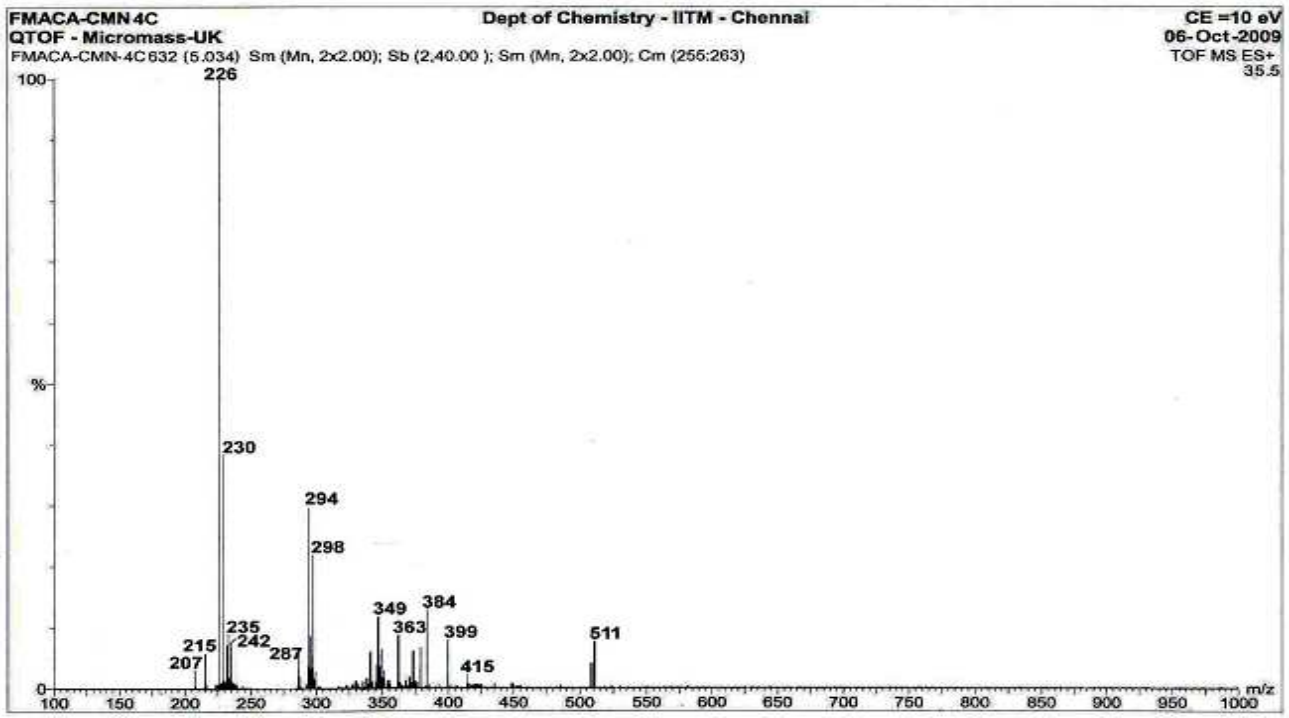


Figure 6– 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-benzylidine thiazolo (2, 3-b) quinazolin-3(2H)-one **(4)**



6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-benzylidine-3-(4-nitrophenyl amino) thiazolo quinazoline ***(5a)***

Pale solid; Yield: 78%; mp. 157-159 °C IR : 3461 (O-H), 3029 (Ar-CH), 1492 (C=C), 1316 (N-H bending), 3391 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.74-7.13 (m, 13H, Ar-H), 6.32 (s, 1H, =CH),5.59 (s, 1H, H-5), 9.81 (s, 1H, Ar-OH), 4.42 (s, 1H, thiazole), 7.26 (s, 1H, N-H), 1.46-2.42 (m, 8H, 4 × CH_2); EI-MS (m/z): 510 (M+); (Calcd for $C_{29}H_{26}N_4O_3S$; 510.61). Anal. Calcd for $C_{29}H_{26}N_4O_3S$; C, 68.21; H, 5.13; N, 10.97; Found: C, 68.26; H, 5.19; N, 10.82.

6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methyl benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline ***(5b)***

Cream solid; Yield: 76%; mp. 193-192 °C IR : 3438 (O-H), 3024 (Ar-CH), 1412 (C=C), 1322 (N-H bending), 3310 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.69-7.24 (m, 12H, Ar-H), 6.28 (s, 1H, =CH), 5.72 (s, 1H, H-5), 9.82 (s, 1H, Ar-OH), 4.45 (s, 1H, thiazole), 2.28 (s, 3H, –CH_3), 7.69 (s, 1H, N-H), 1.36-2.41 (m, 8H, 4 × CH_2); EI-MS (m/z): 524 (M+); (Calcd for $C_{30}H_{28}N_4O_3S$; 524.19). Anal. Calcd for $C_{30}H_{28}N_4O_3S$; C, 68.68; H, 5.38; N, 10.68; Found: C, 68.65; H, 5.36; N, 10.70.

6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3',4'-dimethyl benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline ***(5c)***

Yellow solid; Yield: 77%; mp. 181-183 °C IR : 3429 (O-H), 3027 (Ar-CH), 1413 (C=C), 1334 (N-H bending), 3313 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.79-7.24 (m, 12H, Ar-H), 6.26 (s, 1H, =CH), 5.74 (s, 1H, H-5), 9.93 (s, 1H, Ar-OH), 4.39 (s, 1H, thiazole), 2.34 (s, 6H, –CH_3), 7.42 (s, 1H, N-H), 1.36-2.41 (m, 8H, 4 × CH_2); EI-MS (m/z): 538 (M+); (Calcd for $C_{31}H_{31}N_4O_3S$; 538.2). Anal. Calcd for $C_{31}H_{31}N_4O_3S$; C, 69.12; H, 5.61; N, 10.40; Found: C, 69.14; H, 5.63; N, 10.43.

6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3', 4', 5'-tri methoxy benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline ***(5d)***

Cream solid; Yield: 71%; mp. 187-189 °C IR : 3429 (O-H), 3027 (Ar-CH), 1413 (C=C), 1334 (N-H bending), 3311 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.72-7.21 (m, 10H, Ar-H), 6.27 (s, 1H, =CH), 5.72 (s, 1H, H-5), 9.91 (s, 1H, Ar-OH), 4.32 (s, 1H, thiazole), 3.32 (s, 9H,–OCH_3), 7.67 (s, 1H, N-H), 1.34-2.46 (m, 8H, 4 × CH_2); EI-MS (m/z): 600 (M+); (Calcd for $C_{32}H_{32}N_4O_6S$; 600.68). Anal. Calcd for $C_{32}H_{32}N_4O_6S$; C, 63.98; H, 5.37; N, 9.33; Found: C, 63.81; H, 5.39; N, 9.37.

6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-chlorobenzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline ***(5e)***

Pale solid; Yield: 72%; mp. 164-166 °C IR : 3445 (O-H), 3025 (Ar-CH), 1523 (C=C), 1315 (N-H bending), 3320 (N-H stretching), 829 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.71-7.35 (m, 12H, Ar-H), 6.23 (s, 1H, =CH), 5.84 (s, 1H, H-5), 9.96 (s, 1H, Ar-OH), 4.42 (s, 1H, thiazole), 7.16 (s,1H, N-H), 1.24-2.32 (m, 8H, 4 × CH_2); EI-MS (m/z): 545 (M+); (Calcd for $C_{29}H_{25}ClN_4O_3S$; 545.05). Anal. Calcd for $C_{29}H_{25}ClN_4O_3S$; C, 63.90; H, 4.62; N, 10.28; Found: C, 63.84; H, 4.67; N, 10.30.

6.1.10. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-dimethyl amino benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline ***(5f)***

Yellow solid; Yield: 81%; mp. 187-189 °C IR : 3439 (O-H), 3026 (Ar-CH), 1417 (C=C), 1336 (N-H bending), 3376 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.72-7.23 (m, 12H, Ar-H), 6.46 (s, 1H, =CH), 5.74 (s, 1H, H-5), 9.86 (s, 1H, Ar-OH), 4.46 (s, 1H, thiazole), 2.28 (s, 6H, –CH_3), 7.89 (s, 1H, N-H), 1.39-2.43 (m, 8H, 4 × CH_2); EI-MS (m/z, %): 553 (M+); (Calcd for $C_{31}H_{31}N_5O_3S$; 553.21). Anal. Calcd for $C_{31}H_{31}N_5O_3S$; C, 67.25; H, 5.64; N, 12.65; Found: C, 67.23; H, 5.63; N, 12.67.

Figure 7- 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3', 4', 5'-tri methoxy benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (**5f**)

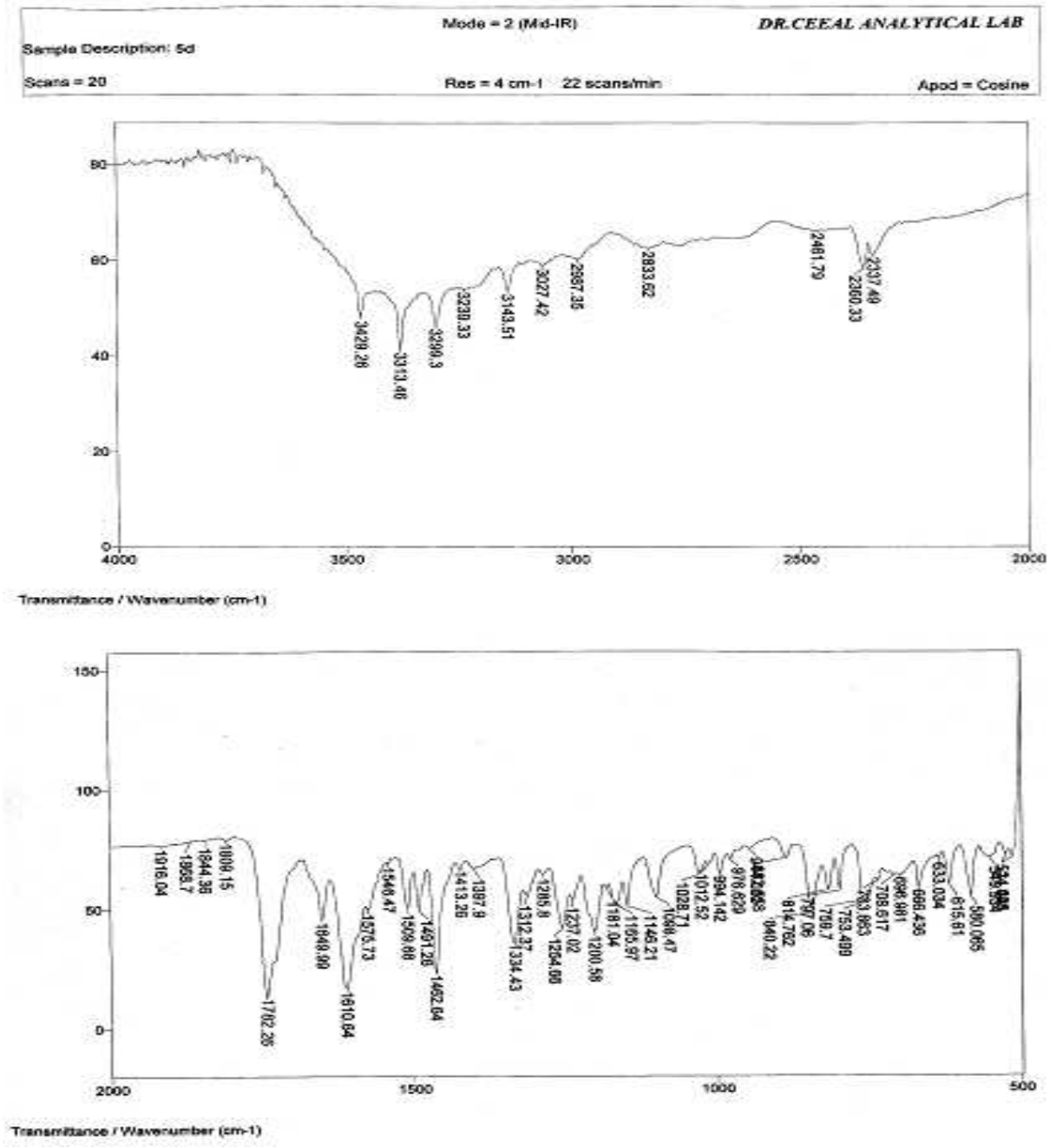


Figure 8- 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3', 4', 5'-tri methoxy benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (**5f**)

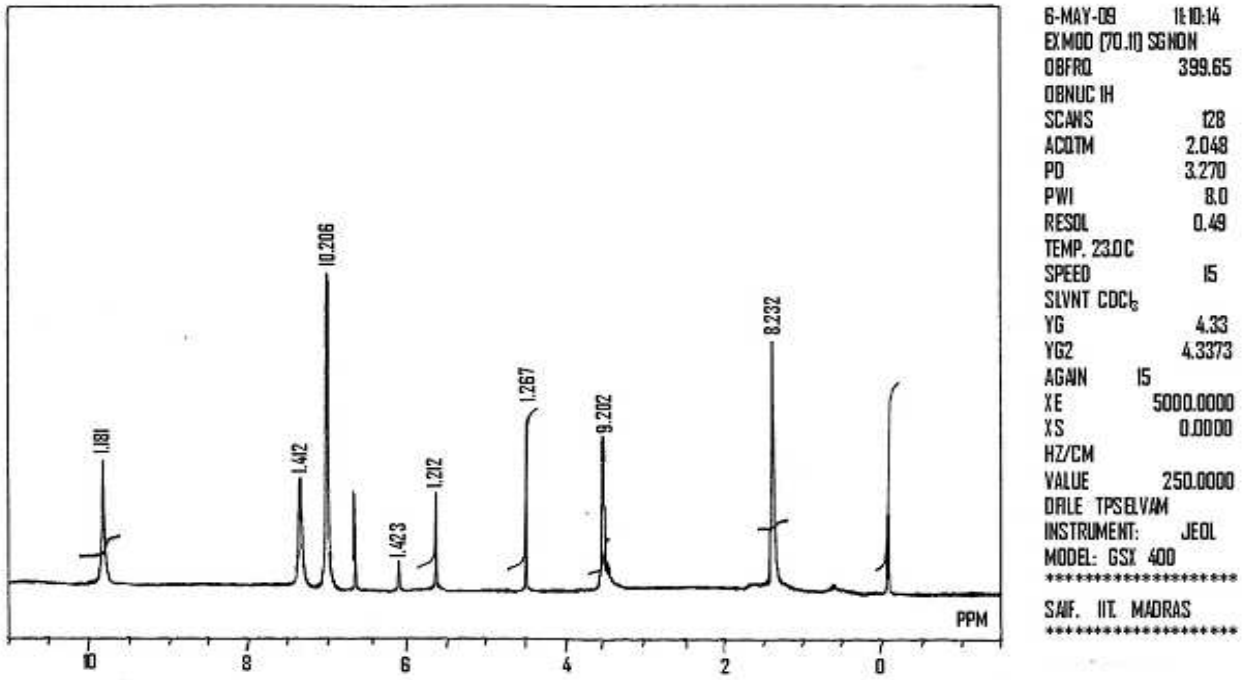
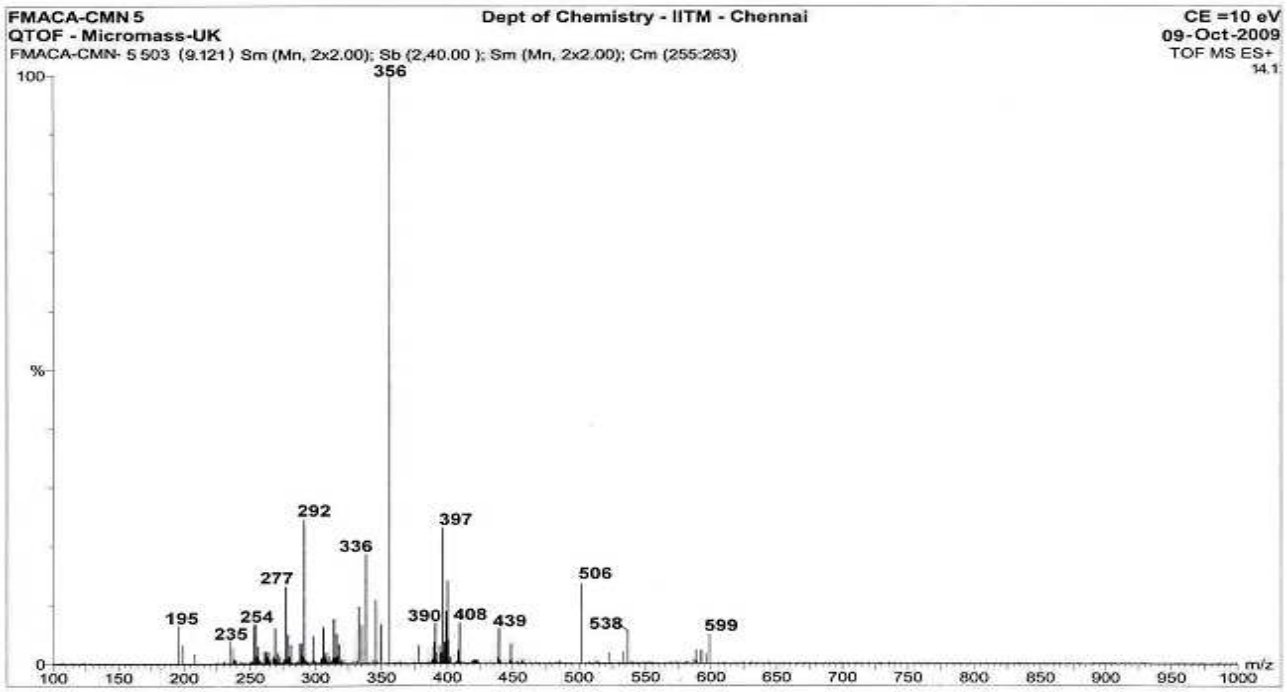


Figure 9- 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3', 4', 5'-tri methoxy benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline **(5f)**



Pharmacology

The synthesized compounds were evaluated for antihistaminic and sedative-hypnotic activities. The animals were maintained in colony cages at 25±2°C, relative humidity of 45-55%, under a 12 h light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for a week before use. The Institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals.

Antihistaminic activity

A modification of the technique of Van Arman [14] was adopted to determine the antihistaminic potential of the synthesized compounds. Male Dunkin Hartley Guinea pigs (250-300 g) were fasted for 12 h. Six animals were taken in each group. The test compounds, was administered orally at a dose of 10 mg/kg in 1% CMC and challenged with histamine aerosol (0.2% aqueous solution of histamine acid chloride 3 mL) in a vaponephrin pocket nebulizer sprayed into a closed transparent cage. The respiratory status reflecting the increasing degree of bronchoconstriction was recorded. The time for onset of convulsions (preconvulsion) was recorded. Animals remaining stable for more than 6 min were considered protected against histamine-induced bronchospasm. An intraperitoneal injection of chlorpheniramine maleate (Avil; Hoechst, Mumbai, India) at a dose of 25 mg/kg was given for the recovery of the test animals. The mean preconvulsion time of animals, treated with the test compounds was compared to control and is expressed in terms of percentage protection.

Percent protection = [1- (T1 / T2)] × 100

T_2 -preconvulsive time of test compound; T_1 - preconvulsive time of control.

The activity of the test compounds was compared with the standard antihistamine chlorpheniramine maleate.

Sedative-hypnotic activity

It was determined by measuring the reduction in locomotor activity using actophotometer [15, 16]. Swiss albino mice were chosen as test animals in a group of 6. Basal activity score was taken and then compounds (**5a-5f**) and standard chlorpheniramine maleate were administered orally at the dose of 5 mg/kg in 1% CMC. Scores were recorded at 1, 2 and 3 h after the drug administration. Student-t-test was performed to ascertain the significance of the exhibited activity. The percent reduction in locomotor activity was calculated by the following formula and shown in Table.

% Reduction in motor activity = [(A-B)/A] × 100
Where A-basal score, B-score after drug treatment.

Antihistaminic and sedative-hypnotic activity of compounds **5a-5f.**

Compound Code	Time of onset of convulsion (in sec)	% Protection	Percent CNS Depression		
			1 h	2 h	3 h
5a	398 ± 6.11*	70.85 ± 1.53*	9 ± 1.36 *	13 ± 1.42**	6 ± 1.41*
5b	445 ± 7.32*	73.93 ± 1.69*	8 ± 1.31*	14 ± 1.71**	8 ± 1.73*
5c	416 ± 9.65*	72.11 ± 1.32*	12 ± 1.62**	14 ± 1.46**	9 ±1.57*
5d	393 ± 6.39*	70.48 ± 1.81*	13 ± 1.73**	16 ± 1.41**	10 ± 1.82*
5e	381 ± 7.31*	69.55 ± 1.46*	7 ± 1.41*	11 ± 1.62 *	5 ± 1.64^{Ns}
5f	389 ± 4.74*	70.17 ± 1.71*	9 ± 1.84*	12 ± 1.33**	7 ± 1.72*
Chlorpheniramine	400 ± 29.50*	71.00 ± 1.36*	37 ± 1.82***	32.0 ± 1.73***	22 ± 1.98***

Each value represents the mean ± SEM (n=6). Significance levels *p<0.5, **p<0.1 and ***p<0.05; ^{NS} indicate not significant.

Statistical analysis

Statistical analysis of the biological activity of the test compounds on various animals was performed by two-tailed student‘t’ test (manually). In all cases significance level of the means of individual groups were performed and compared with control. A significance level of $p < 0.5$ denoted significance in all cases.

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For Corresponding Author

T.Panneer Selvam*

Department of Pharmaceutical Chemistry,

D.C.R.M. Pharmacy College, Inkollu-523167 Andhrapradesh, India.