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Research Article

SYNTHESIS OF NEW RING SYSTEM 6,7,8,9 TETRA HYDRO-5H-5-(2'-HYDROXY PHENYL)-2-(4'-SOME SUBSTITUTED BENZYLIDINE)-3-(4-NITROPHENYL AMINO) THIAZOLO QUINAZOLINE

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

[1]Department of Pharmaceutical Chemistry, D.C.R.M. Pharmacy College, Inkollu-523 167, Andhrapradesh, India.
*[2] Department of Pharmaceutics, Bharat Institute of Technology, Hyderabad-501 510, Andhra Pradesh, India.
Email: *tpsphc@gmail.com*

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Abstract

A convenient synthesis of the 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline ring system is reported. Our synthetic approach consisted of the annelation of a 4-hydroxy phenyl 3, 4, 5, 6, 7, 8-hexahydro quinazolin-2-thione moiety using chloroacetic acid as building blocks. The procedure needs the formation of the thiazolo quinazoline derivatives by substituted benzaldehyde and *p*-nitro aniline.

Key words: Quinazolin-2-thione, Thiazolo quinazoline; Benzylidine thiazolo quinazoline; Nitrophenyl amino thiazolo quinazoline.

Introduction

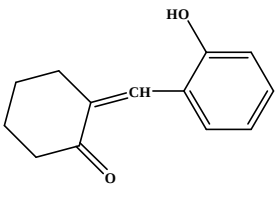
The quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances with pronounced biological activities [1]. Several quinazolines and condensed quinazolines derivatives have associated with a broad range of physiological activities, exhibiting anti-oxidant, analgesic, anti-inflammatory and anti-convulsant [2-6]. On the other hand, some thiazole derivatives also have various biological properties like anti-oxidant [7-10], anti-

inflammatory [11], anti-microbial [12], anthelmintic [13] and immunorestoration [14]. Based on prior observations we synthesized a series of compounds a wide range of five-membered ring containing nitrogen atoms based on fused quinazolines exhibit anti-arthritic [15], anti-histaminic [16], phosphodiesterase IV inhibitor [17]. While structures **2** and **3** are well documented, only a few papers described the synthesis and the reactivity of heterocycles in which the quinazoline ring is fused with thiazole as 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl) thiazolo (2, 3-*b*) quinazolin-3(2*H*)-one **3**. Thus far, one major synthetic strategy have been reported to access the core ring system **3** and these approaches are limited in that the 2nd and 3rd position of thiazole ring was always undergoes substitution.

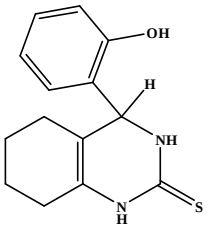
Results and Discussion

Chemistry

As indicated in Scheme, the novel 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline ring system was synthesized in six steps. In that first step 2-hydroxy benzylidine cyclohexanone ring **1** was prepared with cyclohexanone and salicylaldehyde in the presence of base. The 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl) thiazolo (2, 3-*b*) quinazolin-3(2*H*)-one **3** was prepared by 4-hydroxy phenyl 3, 4, 5, 6, 7, 8-hexahydro quinazolin-2-thione **2**. The key intermediate **3** treated with different aromatic aldehydes and *p*-nitro aniline leads to produce the target compounds **4a-4j** and **5a-5j**.



1



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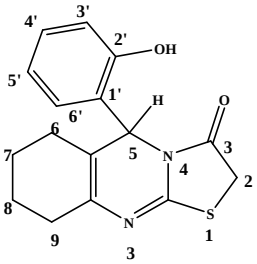
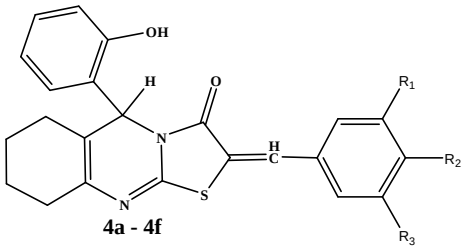
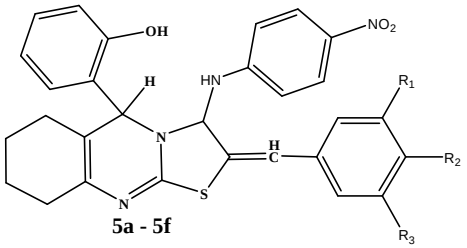


3



4a - 4f



5a - 5f

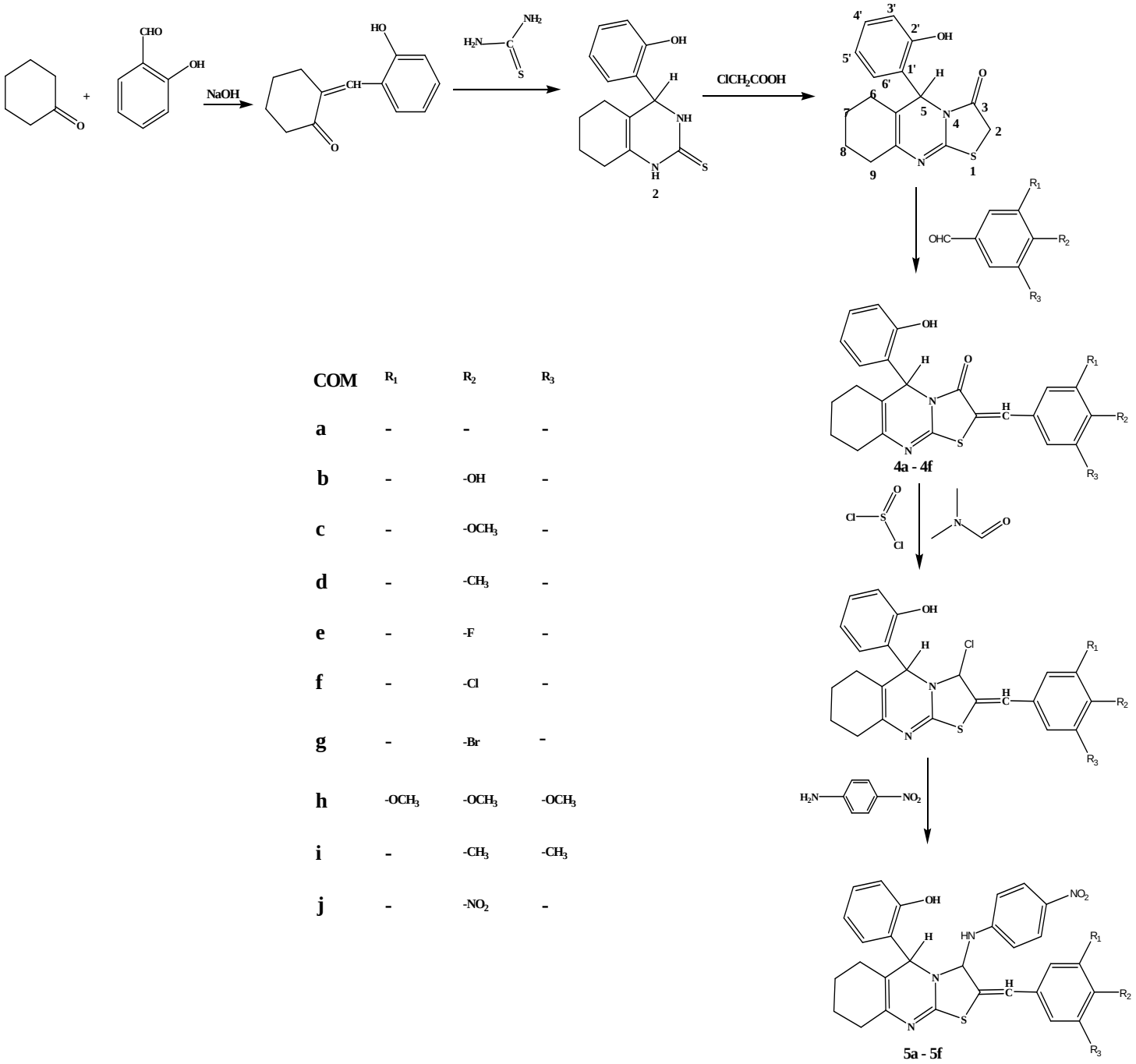
The synthesized series of heterocycles, **4a-4j** and **5a-5j** by the reaction of **3** with appropriate aromatic aldehydes and *p* –nitro aniline in the presence of anhydrous sodium acetate and DMF as presented in Scheme. The IR, ^{1}H-NMR, mass spectroscopy and elemental analysis for the new compound is in accordance with the assigned structures. The IR spectra of compounds **4a-4j** showed stretching bands of keto group at 1715-1740 cm^{-1}. In **5a-5j**, 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-5j** showed missing of keto group bands. This clearly envisages that the keto group of **4a-4j** is converted into secondary NH. The proton magnetic resonance spectra of thiazolo quinazoline and their corresponding derivatives have been recorded in $CDCl_3$. In this **5a-5j** NH signal of 3-(4-nitro phenyl) amino thiazolo quinazoline moiety appear at 7.26 (s), 7.23 (s), 7.29 (s), 7.69 (s), 7.34 (s), 7.16 (s), 7.79 (s), 7.67 (s), 7.42 (s), 7.19 (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 the 3rd position of keto group in thiazole ring is converted into secondary amino group as indicated in scheme-1 and conforms the proposed structures (**5a -5j**).

Experimental

Chemistry

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

Synthesis of 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-some substituted benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline



COM	R_1	R_2	R_3
a	-	-	-
b	-	-OH	-
c	-	$-OCH_3$	-
d	-	$-CH_3$	-
e	-	-F	-
f	-	-Cl	-
g	-	-Br	-
h	$-OCH_3$	$-OCH_3$	$-OCH_3$
i	-	$-CH_3$	$-CH_3$
j	-	$-NO_2$	-

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** [18]. 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 (**4a-4j)**. Equimolar quantities (0.004 mol) of compound **4a-4j** 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-5j**) **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**. The 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)

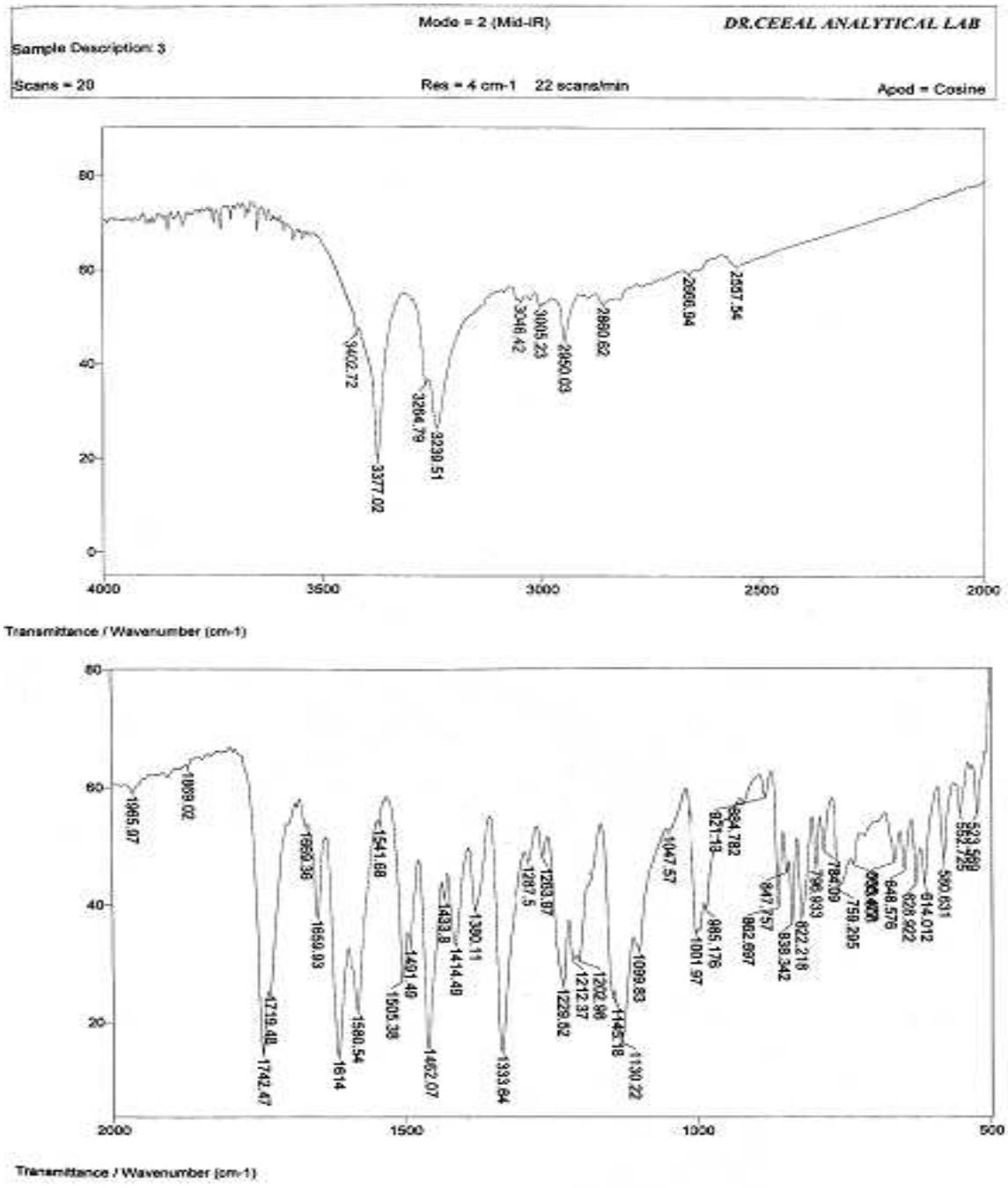


Figure 2 - 6,7,8,9 tetra hydro-5H-5-(2-hydroxy phenyl) thiazoloquinazolin-3-one (**3**)(^{1}H-NMR)

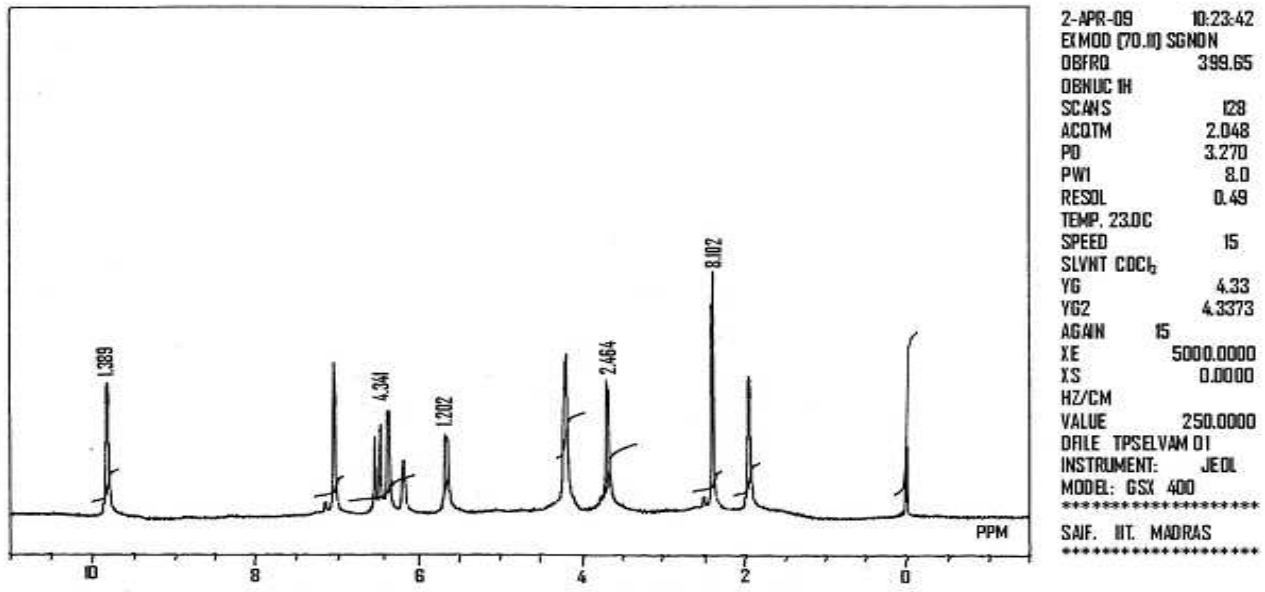
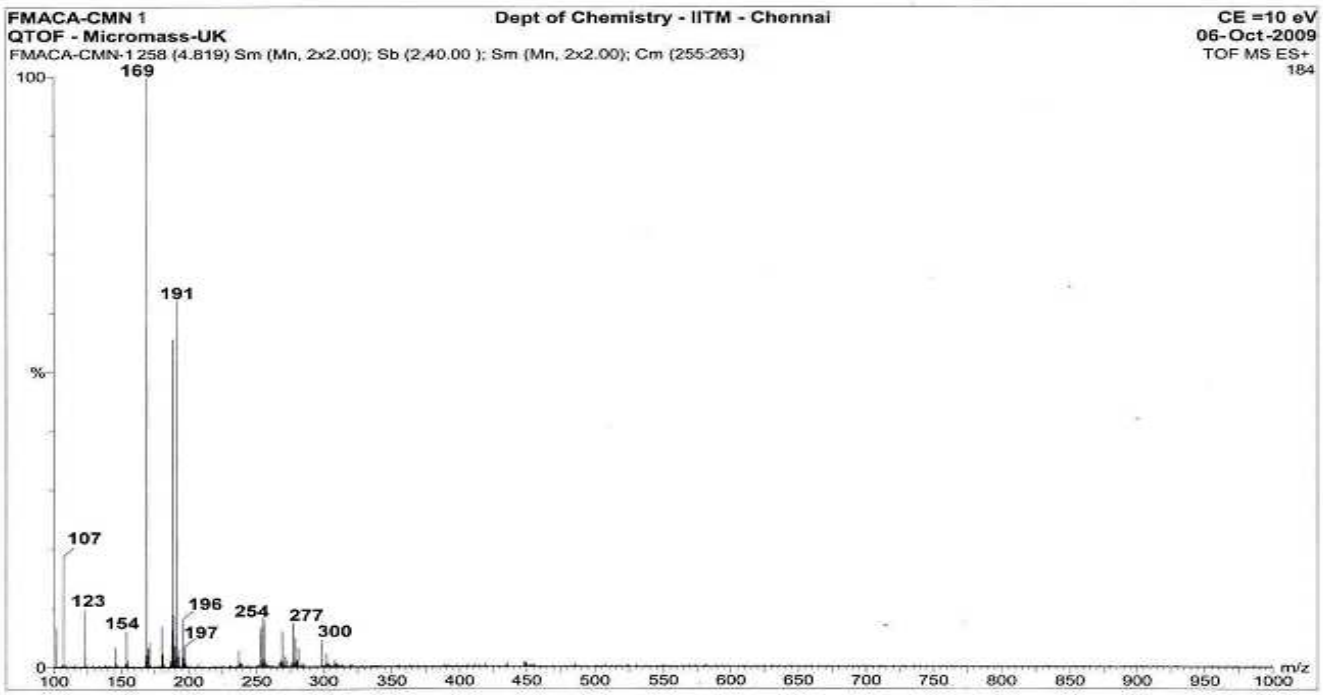


Figure 3 - The 6,7,8,9 tetra hydro-5H-5-(2-hydroxy phenyl) thiazoloquinazolin-3-one **(3)**(MASS)



6.1.1. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-benzylidine thiazolo (2, 3-b) quinazolin-3(2H)-one (4a)

Yellow solid; Yield: 82%; mp.159-161°C; IR: 3474 (O-H), 3093 (Ar-CH), 1725 (C=O), 1461 (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)

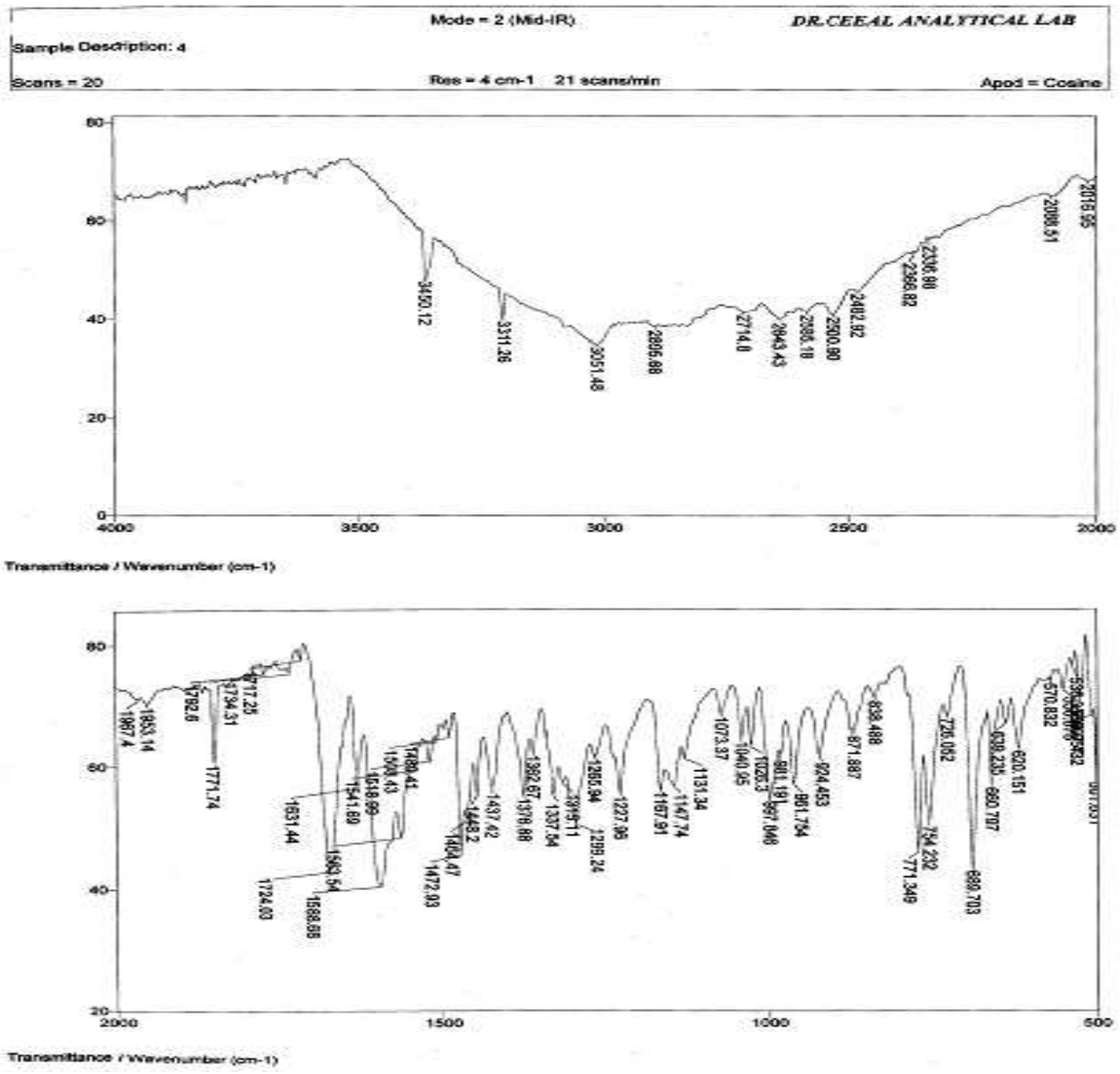


Figure 5- 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-benzylidine thiazolo (2, 3-b) quinazolin-3(2H)-one **(4)** (^{1}H NMR)

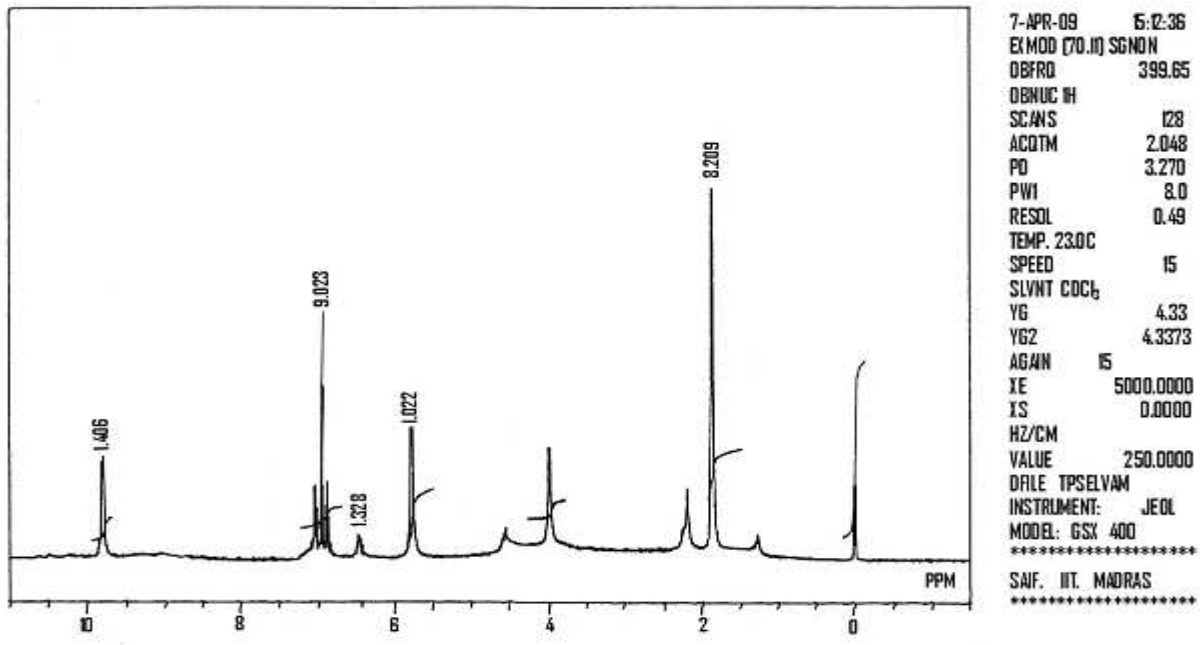
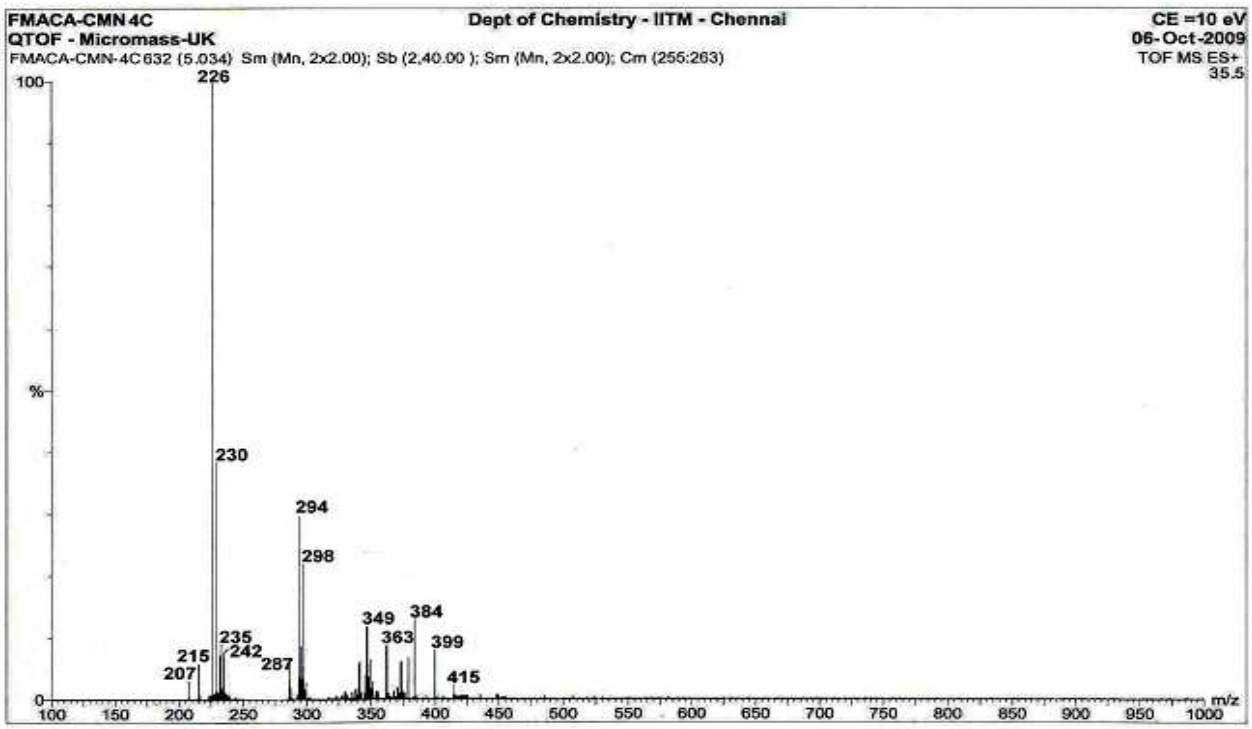


Figure 6– 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-benzylidine thiazolo (2, 3-b) quinazolin-3(2H)-one **(4a)**



6.1.2. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-hydroxy benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4b)

Cream solid; Yield: 79%; mp.176-178°C; IR: 3442 (O-H), 3041 (Ar-CH), 1723 (C=O), 1431 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.81-7.71 (m, 8H, Ar-H), 6.73 (s, 1H, =CH), 5.71 (s, 1H, H-5), 9.76 (s, 2H, Ar-OH), 1.61-2.35 (m, 8H, 4 × CH_2); EI-MS (m/z): 404 (M+); (Calcd for $C_{23}H_{20}N_2O_3S$; 404.48). Anal. Calcd for $C_{23}H_{20}N_2O_3S$; C, 68.30; H, 4.98; N, 6.93; Found: C, 68.37; H, 4.87; N, 6.99.

6.1.3. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methoxy benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4c)

Pale yellow solid; Yield: 78%; mp.183-185°C; IR: 3476 (O-H), 3096 (Ar-CH), 1728 (C=O), 1468 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 6.96-7.54 (m, 8H, Ar-H), 6.67 (s, 1H, =CH), 5.83 (s, 1H, H-5), 9.84 (s, 1H, Ar-OH), 3.75 (s, 3H –OCH_3), 1.58-2.62 (m, 8H, 4 × CH_2); EI-MS (m/z): 418 (M+); (Calcd for $C_{24}H_{22}N_2O_3S$; 418.51). Anal. Calcd for $C_{24}H_{22}N_2O_3S$, C, 68.88; H, 5.30; N, 6.69; Found: C, 68.90; H, 5.33; N, 6.72.

6.1.4. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methyl benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4d)

Cream solid; Yield: 76%; mp.186-188°C; IR: 3448 (O-H), 3049 (Ar-CH), 1721 (C=O), 1434 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.86-7.74 (m, 8H, Ar-H), 6.72 (s, 1H, =CH), 5.76 (s, 1H, H-5), 9.76 (s, 1H, Ar-OH), 2.20 (s, 3H –CH_3), 1.62-2.32 (m, 8H, 4 × CH_2); EI-MS (m/z): 402 (M+); (Calcd for $C_{24}H_{22}N_2O_2S$; 402.14). Anal. Calcd for $C_{24}H_{22}N_2O_2S$; C, 71.00; H, 5.51; N, 6.96; Found: C, 69.87; H, 5.32; N, 6.74.

6.1.5. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-fluoro benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4e)

Pale yellow solid; Yield: 69%; mp.153-155°C; IR: 3437 (O-H), 3026 (Ar-CH), 1729 (C=O), 1522 (C=C), 826 (C-F) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.63-7.32 (m, 8H, Ar-H), 6.38 (s, 1H, =CH), 5.87 (s, 1H, H-5), 9.94 (s, 1H, Ar-OH), 1.34-2.33 (m, 8H, 4 × CH_2); EI-MS (m/z): 406 (M+); (Calcd for $C_{23}H_{19}FN_2O_2S$; 406.12). Anal. Calcd for $C_{23}H_{19}FN_2O_2S$; C, 67.96; H, 4.71; N, 6.89; Found: C, 67.97; H, 4.73; N, 6.87.

6.1.6. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-chloro benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4f)

Yellow solid; Yield: 65%; mp.157-159°C; IR: 3431 (O-H), 3021 (Ar-CH), 1722 (C=O), 1527 (C=C), 816 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.61-7.32 (m, 8H, Ar-H), 6.32 (s, 1H, =CH), 5.89 (s, 1H, H-5), 9.97 (s, 1H, Ar-OH), 1.32-2.37 (m, 8H, 4 × CH_2); EI-MS (m/z): 424 (M+2); (Calcd for $C_{23}H_{19}ClN_2O_2S$; 422.93). Anal. Calcd for $C_{23}H_{19}ClN_2O_2S$; C, 65.32; H, 4.53; N, 6.62; Found: C, 65.44; H, 4.41; N, 6.67.

6.1.7. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-bromo benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4g)

yellow solid; Yield: 75%; mp.162-164°C; IR: 3447 (O-H), 3025 (Ar-CH), 1716 (C=O), 1523 (C=C), 823 (C-Br) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.73-7.29 (m, 8H, Ar-H), 6.48 (s, 1H, =CH), 5.73 (s, 1H, H-5), 9.89 (s, 1H, Ar-OH), 1.26-2.32 (m, 8H, 4 × CH_2); EI-MS (m/z): 468 (M+2); (Calcd for $C_{23}H_{19}BrN_2O_2S$; 466.04). Anal. Calcd for $C_{23}H_{19}BrN_2O_2S$; C, 59.11; H, 4.10; N, 5.99; Found: C, 59.14; H, 4.13; N, 5.97.

6.1.8. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3',4',5'-tri methoxy benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4h)

Pale solid; Yield: 81%; mp.185-187°C; IR: 3452 (O-H), 3059 (Ar-CH), 1727 (C=O), 1439 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.82-7.75 (m, 6H, Ar-H), 6.71 (s, 1H, =CH), 5.73 (s, 1H, H-5), 9.84 (s, 1H, Ar-OH), 2.23 (s, 9H $–OCH_3$), 1.64-2.38 (m, 8H, 4 × CH_2); EI-MS (m/z): 478 (M+); (Calcd for $C_{26}H_{26}N_2O_5S$; 478.56). Anal. Calcd for $C_{26}H_{26}N_2O_5S$; C, 65.25; H, 5.48; N, 5.85; Found: C, 65.29; H, 5.32; N, 5.89.

6.1.9. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3',4'-dimethyl benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4i)

Cream solid; Yield: 79%; mp.181-183 °C; IR: 3450 (O-H), 3051 (Ar-CH), 1724 (C=O), 1437 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.89-7.76 (m, 7H, Ar-H), 6.74 (s, 1H, =CH), 5.78 (s, 1H, H-5), 9.84 (s, 1H, Ar-OH), 2.23 (s, 6H $–CH_3$), 1.62-2.32 (m, 8H, 4 × CH_2); EI-MS (m/z): 416 (M+); (Calcd for $C_{25}H_{24}N_2O_2S$; 416.16). Anal. Calcd for $C_{25}H_{24}N_2O_2S$; C, 72.09; H, 5.81; N, 6.73; Found: C, 72.12; H, 5.79; N, 6.75.

6.1.10. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-nitro benzylidine) thiazolo (2, 3-b) quinazolin-3(2H)-one (4j)

Yellow solid; Yield: 79%; mp.184-186°C; IR: 3441 (O-H), 3042 (Ar-CH), 1723 (C=O), 1435 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.82-7.71 (m, 8H, Ar-H), 6.77 (s, 1H, =CH), 5.72 (s, 1H, H-5), 9.71 (s, 1H, Ar-OH), 1.64-2.36 (m, 8H, 4 × CH_2); EI-MS (m/z): 433 (M+); (Calcd for $C_{23}H_{19}N_3O_4S$; 433.48). Anal. Calcd for $C_{23}H_{19}N_3O_4S$; C, 63.73; H, 4.42; N, 9.69; Found: C, 63.81; H, 4.54; N, 9.52.

6.1.11. 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.

6.1.12. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-hydroxybenzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5b)

Pale yellow solid; Yield: 72%; mp.151-153°C; IR: 3467 (O-H), 3021 (Ar-CH), 1497 (C=C), 1312 (N-H bending), 3391 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.74-7.29 (m, 12H, Ar-H), 6.36 (s, 1H, =CH),5.62 (s, 1H, H-5), 9.87 (s, 2H, Ar-OH), 4.46 (s, 1H, thiazole), 7.23 (s, 1H, N-H), 1.46-2.42 (m, 8H, 4 × CH_2); EI-MS (m/z): 526 (M+); (Calcd for $C_{29}H_{26}N_4O_4S$; 526.61). Anal. Calcd for $C_{29}H_{26}N_4O_4S$; C, 66.14; H, 4.98; N, 10.64; Found: C, 66.22; H, 4.88; N, 10.69.

6.1.13. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methoxy benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5c)

Pale yellow solid; Yield: 76%; mp.156-158°C; IR: 3464 (O-H), 3027 (Ar-CH), 1494 (C=C), 1306 (N-H bending), 3396 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.72-7.23 (m, 12H, Ar-H), 6.36 (s, 1H, =CH),5.62 (s, 1H, H-5), 9.87 (s, 1H, Ar-OH), 4.46 (s, 1H, thiazole), 3.78 (s, 3H –OCH_3), 7.29 (s, 1H, N-H), 1.46-2.42 (m, 8H, 4 × CH_2); EI-MS (m/z): 540 (M+); (Calcd for $C_{30}H_{28}N_4O_4S$; 540.18). Anal. Calcd for $C_{30}H_{28}N_4O_4S$; C, 66.65; H, 5.22; N, 10.36; Found: C, 66.67; H, 5.25; N, 10.38.

6.1.14. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-methyl benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5d)

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.

6.1.15. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-fluoro benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5e)

Cream solid; Yield: 89%; mp.184-186°C; IR: 3449 (O-H), 3026 (Ar-CH), 1524 (C=C), 1316 (N-H bending), 3319 (N-H stretching), 821 (C-F) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.74-7.32 (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), 7.34 (s,1H, N-H), 1.24-2.32 (m, 8H, 4 × CH_2); EI-MS (m/z): 528 (M+); (Calcd for $C_{29}H_{25}FN_4O_3S$; 528.16). Anal. Calcd for $C_{29}H_{25}FN_4O_3S$; C, 65.89; H, 4.77; N, 10.60; Found: C, 65.91; H, 4.79; N, 10.62.

6.1.16. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-chlorobenzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5f)

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): 547 (M+2); (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.

6.1.17. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-bromo benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5g)

Pale yellow solid; Yield: 82%; mp.183-185°C; IR: 3447 (O-H), 3021 (Ar-CH), 1519 (C=C), 1327 (N-H bending), 3319 (N-H stretching), 818 (C-Br) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.81-7.36 (m, 12H, Ar-H), 6.49 (s, 1H, =CH), 5.84 (s, 1H, H-5), 9.81 (s, 1H, Ar-OH), 4.46 (s, 1H, thiazole), 7.79 (s, 1H, N-H), 1.29-2.34 (m, 8H, 4 × CH_2); EI-MS (m/z): 590 (M+2); (Calcd for $C_{29}H_{25}BrN_4O_3S$; 588.08). Anal. Calcd for $C_{29}H_{25}BrN_4O_3S$; C, 59.09; H, 4.27; N, 9.50; Found: C, 59.11; H, 4.29; N, 9.57.

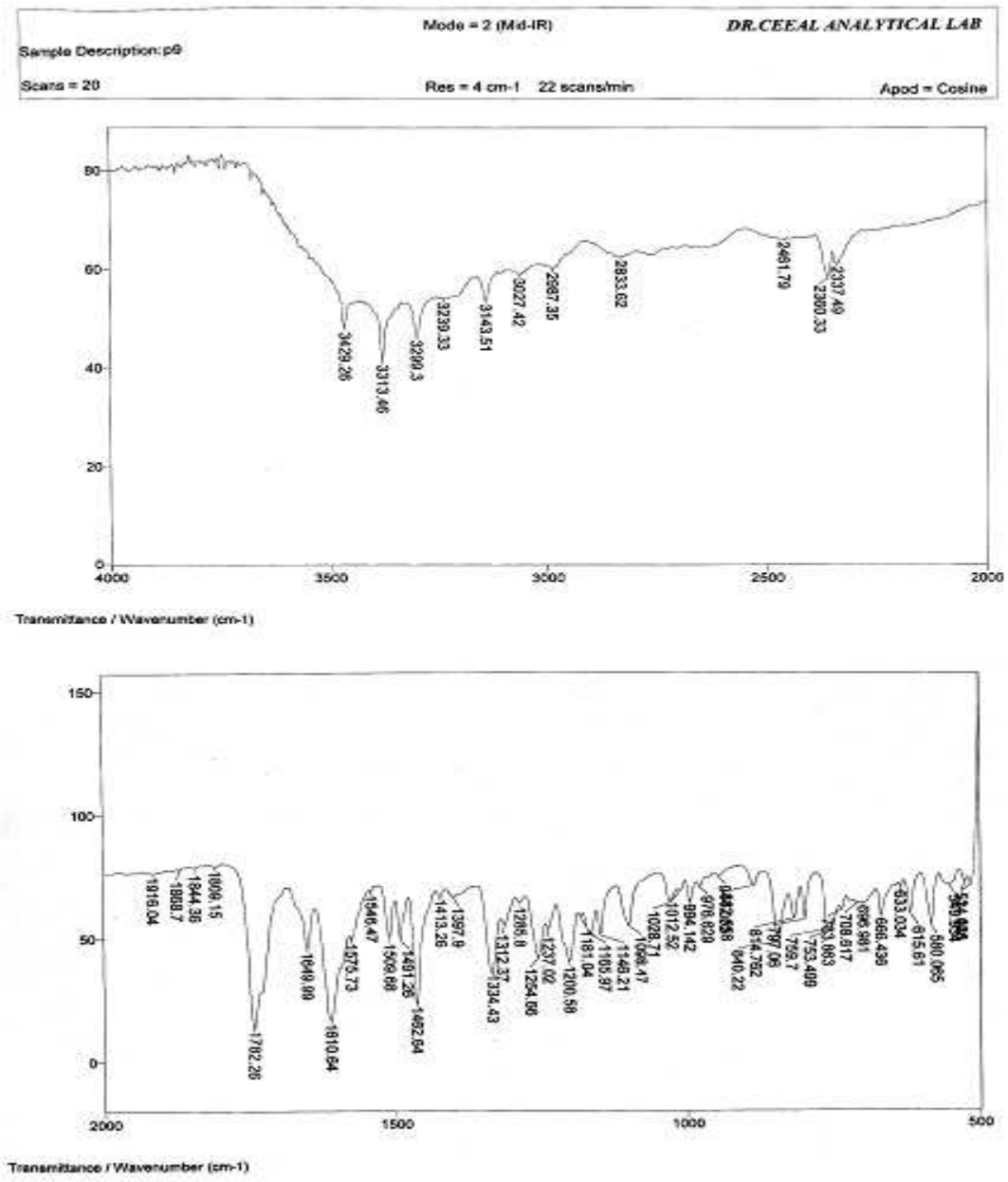
6.1.18. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3', 4', 5'-tri methoxy benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5h)

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.

6.1.19. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(3',4'-dimethyl benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5i)

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.

Figure7- tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-dimethyl benzylidine)-3-(4- nitrophenyl amino) thiazolo quinazoline **(5i)**



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

Figure 8- tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-dimethyl benzylidine)-3-(4- nitrophenyl amino) thiazolo quinazoline **(5i)**

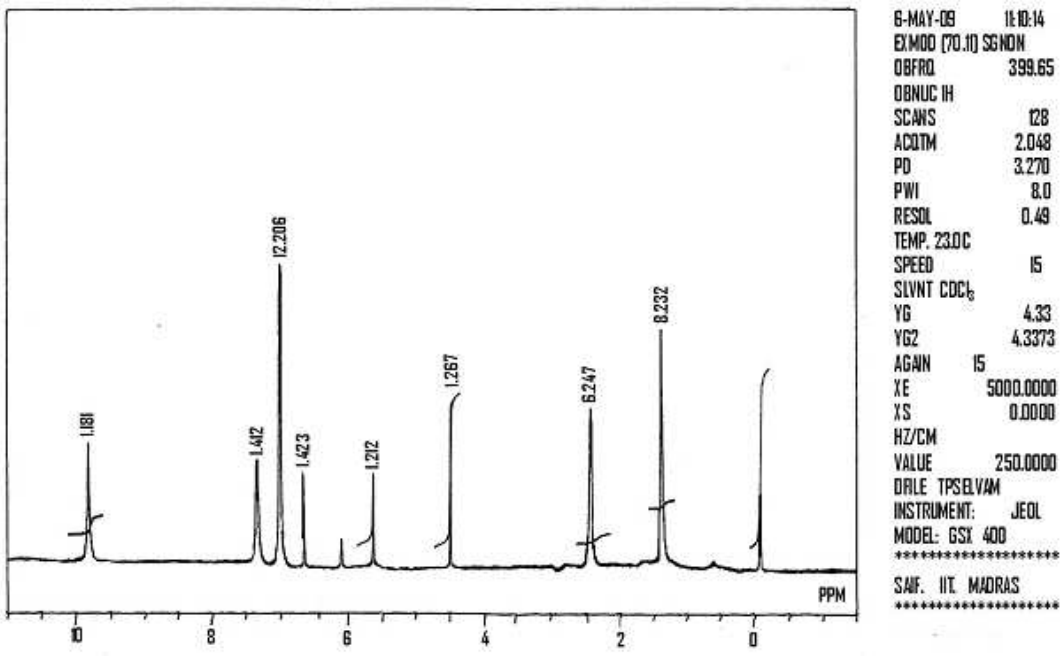
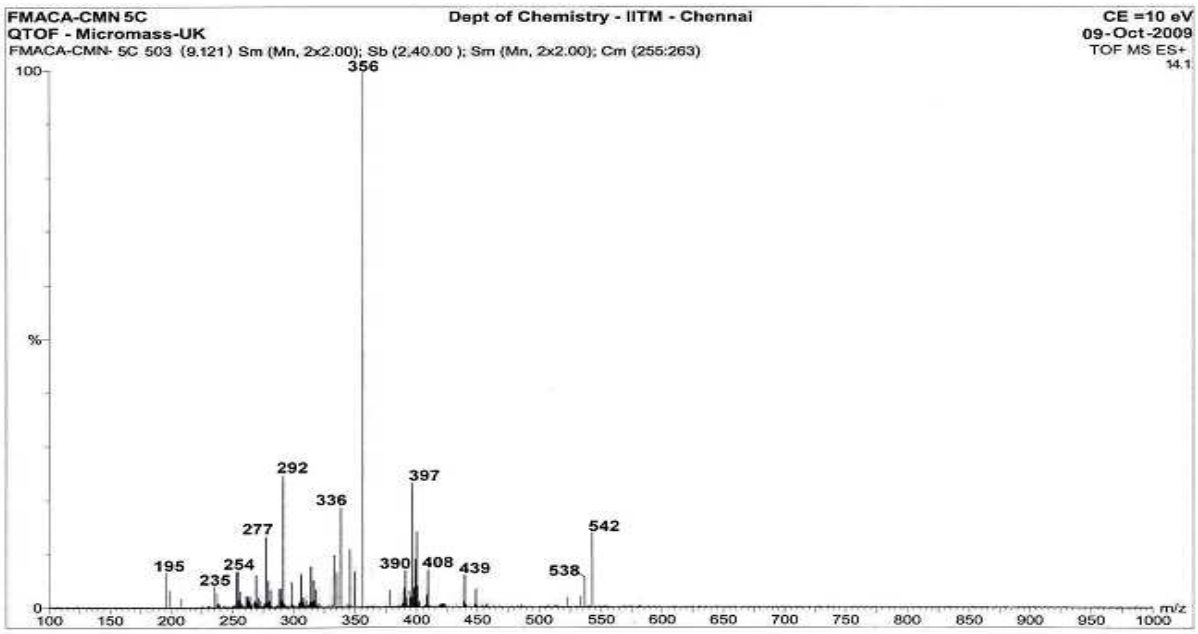


Figure 9- tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-dimethyl benzylidine)-3-(4- nitrophenyl amino) thiazolo quinazoline **(5i)**



6.1.20. 6,7,8,9 tetra hydro-5H-5-(2'-hydroxy phenyl)-2-(4'-nitro benzylidine)-3-(4-nitrophenyl amino) thiazolo quinazoline (5j)

Pale yellow solid; Yield: 71%; mp.152-154°C; IR: 3461 (O-H), 3021 (Ar-CH), 1493 (C=C), 1309 (N-H bending), 3392 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.73-7.21 (m, 12H, Ar-H), 6.33 (s, 1H, =CH), 5.67 (s, 1H, H-5), 9.81 (s, 1H, Ar-OH), 4.46 (s, 1H, thiazole), 7.19 (s, 1H, N-H), 1.46-2.42 (m, 8H, 4 × CH_2); EI-MS (m/z): 555 (M+); (Calcd for $C_{29}H_{25}N_5O_5S$; 555.6). Anal. Calcd for $C_{29}H_{25}N_5O_5S$; C, 62.69; H, 4.54; N, 12.60; Found: C, 62.62; H, 4.51; N, 12.67.

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References

1. (a) S. Johne, W. Herz, H. Grisebach, G. W. Kirby, Ch. Tamm, In Progress in the Chemistry of Organic Natural Products. 1984, 159–229. (b) S. Johne, In the Alkaloids, Chemistry and Pharmacology; Brossi, A. Ed, Academic, New York, 1986, Vol. 29, pp 99–140. (c) T. Besson, E. Chosson, Comb. Chem. High. T. Scr. 2007, 10, 903-917.
2. D. Michael, K. Birgit, Bioorg. Med.Chem. 2008, 16, 4252–4261.
3. K. U. Natalia, A. D. Vladimir, Tetrahedron Letters. 2007, 48, 4445–4447.
4. A. B. A. El-Gazzar, M. M. Youssef, Eur.J. Med.Chemistry. 2009, 44, 609-624.
5. V. Alagarsamy, R. Revathi, S. Vijayakumar, K. V. Ramseshu, Pharmazie. 2003, 58, 4-8.
6. V. Alagarsamy, A. Thangathirupathy, S. C. Mandal, S. Rajasekaran, S. Vijayakumar, R. Revathi, Indian J Pharm Sci. 2006, 68, 108-11.

7. S. Feng, L. Chunmei, X. Ming, Bioorganic & Medicinal Chemistry Letters. 2009, 19, 5565–5568.
8. Q. M. Charles, N. Liming, J. Kimberly, J. Med. Chem. 2007, 50, 1304-1315.
9. A. G. Athina, A. L. Alexey, J. Med. Chem. 2008, 51, 1601–1609.
10. C. S. Hong, L. Silvi, J. Med. Chem. 2007, 50, 6303–6306.
11. A. Tajana, F. Portioli, D. Nardi, M. Magistretti, J. Boll. Chim. Farm. 1979, 118, 397.
12. J. S. Shukla, J. Indian Chem. Soc. 66 (1989) 209.
13. M. Malesic, A. Krbovcic, A. Golobio, L. Golic, B. Stanovnik, J. Heterocyclic Chem. 1997, 34, 43.
14. L. A. McDonald, M. P. Foster, D. R. Phillips, C. N. Ireland, J. Org. Chem. 1992, 57, 4616.
15. T. Takahashi, T. Imaoka, N. Mori, M. Kaneko, K. Tanida, Y. Torii, International Patent PCT/JP1999/006792.
16. (a) V. Alagarsamya, R. Giridharb, M. R. Yadav, Bioorg.Med. Chem. Lett. 2005, 15, 1877-1880. (b) V. Alagarsamya, R. Giridharb, M. R. Yadav, Biol. Pharm. Bull. 2005, 28, 1531-1534. (c) V. Alagarsamy, V. Solomon, M. Murugan, Bioorg. Med. Chem. 2007, 15, 4009-4015.
17. B. Gaudilliere, R. Lavalette, C. Andrianjara, International Patent PCT/ R1999/2792938.

***Corresponding Author:**

T. Panneer Selvam[*],
Department of Pharmaceutical Chemistry,
D.C.R.M. Pharmacy College, Inkollu-523 167.
Andhrapradesh, India