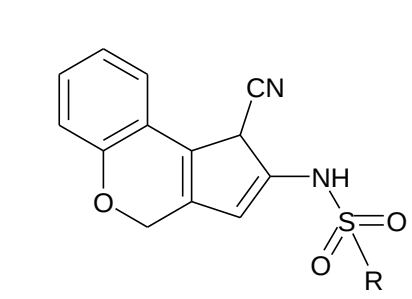
International Research Journal of Natural and Applied Sciences
Volume-2, Issue-1 (January 2015) ISSN: (2349-4077)

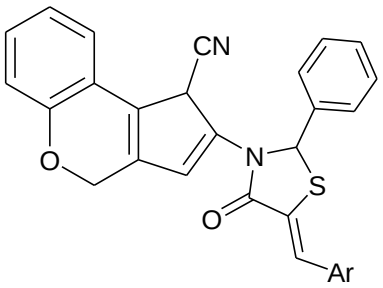
SYNTHESIS AND CHARACTERIZATION OF NOVEL CHROMEN BASED THIAZOLIDINE DERIVATIVES AS MEDICINALLY POTENTIAL AGENTS

Kokila Parmar[a] Arun Suthar[a]

[a]Department of Chemistry, Hemchandracharya North Gujarat University, Patan, 384 265, Gujarat, India.



3



6

3a: R= —CH_3 3d: R= —C_6H-CH_3

3b: R= —C_2H_5 3e: R= —C_6H-F

3c: R= —C_6H_5

6a: Ar= —C_6H 6e: Ar= —C_6H-F

6b: Ar= —C_6H-CH_3 6f: Ar= —C_6H_4N

6c: Ar= —C_6H-Br

ABSCTRACT

Chromen based thiazolidin derivatives is worldwide used in pharmaceuticals industries. A novel series of chromen containing thiazolidin derivatives are described, The method of chemical synthesis of these derivatives to gives excellent isolated yield and The structures of the synthesized compounds were elucidated by UV, IR and 1H NMR spectroscopic techniques, and elemental analysis. The antibacterial and antifungal screens of the synthesized compounds were performed. All compounds were tested for antibacterial activity against S. Aureus, S. Pyogenes, E.Ccoli, P. Aeruginosa, S. Typhi and V.Parahaemolyticus.

Keywords. 1,4-dihydro-cyclopenta[c]Chromen,antibacterial and antifungal activity, MIC

Introduction

Numerous Chromen derivatives have entire been various biological properties, mainaly as antiviral, anti bacterial, anti fungal, anti inflammatory agents. The 1, 4-dihydro-cyclopenta[c] Chromen ring system is of considerable interest due to several biological effects including antibacterial[1] and antifungal activity[2-3]. A survey of the literature provides information that Chromen containing methylenedioxy group (–O–CH2–O–) widely occur in natural plant pigments.[4] The Chromen are an group of natural products founds in fruits, vegetables, nuts, seeds and flowers as well as in teas and wines, and are an important constituent of human diet. They have been demonstrated to possess many biological and Pharmacological activities such as antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, antimutagenic and antiallergic activities and inhibitory activities on several enzymes.[5,6] Our previous articles[7–10] have reported the antibacterial and antifugal effects of the Chromen ring system.

Chromen is a derivative of benzopyran with a substituted keto group on the pyran ring. It is an isomer of coumarin.[11-13] Derivatives of chromen are collectively known as chromen. Most, though not all, chromen are also phenylpropanoids.Chromones constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents.

Chromen is a chemical compound found in many plants, notably in high concentration in the tonka bean (Dipteryx odorata), vanilla grass (Anthoxanthum odoratum), woodruff (Galium odoratum), and sweet grass (Hierochloe odorata).[14-15] The name comes from a French word, coumarou, for the tonka bean. It has a sweet scent, readily recognized as the scent of newly-mown hay, and has been used in perfumes since 1882.[16]

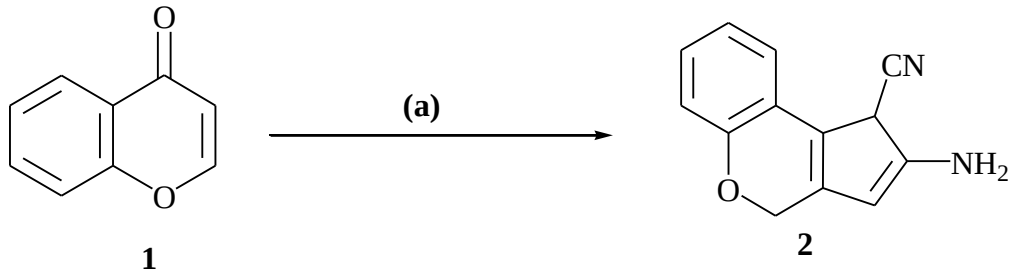
Some of the biological activities attributed to Chromen derivatives include cytotoxic (anticancer), neuroprotective, HIV-inhibitory, antimicrobial, antifungal and antioxidant activity. Due to their abundance in plants and their low mammalian toxicity, chromen derivatives are present in large amounts in the diet of humans.

Results and Discussion

Chemistry:

The General procedure synthetic routs of compound 2 outlined in Scheme 1.

Chromen-4-one **1** was react with Malononitrile and Morpholine in presence of sulfur to obtained 2-Amino-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile **2.**



1 **2**

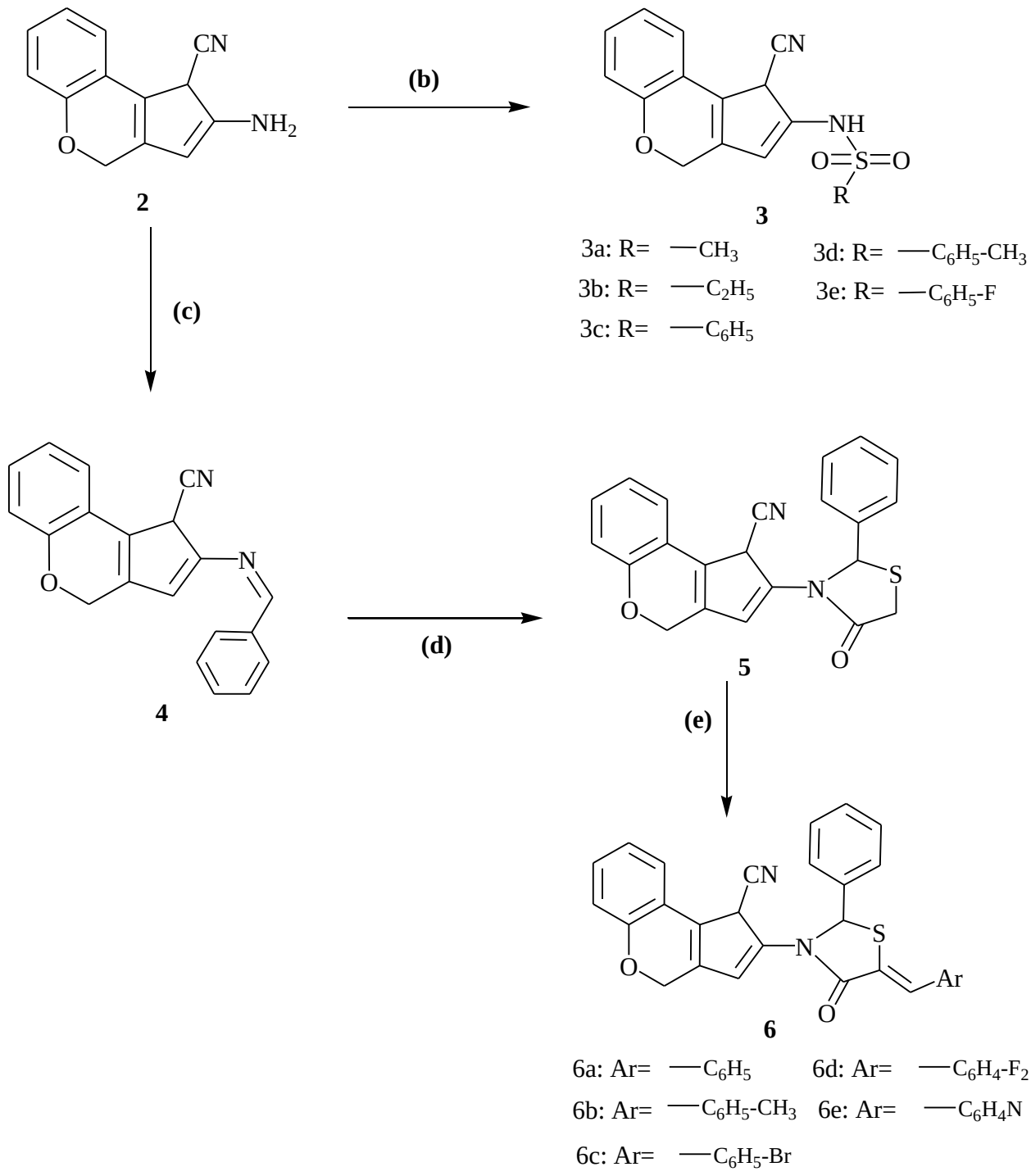
Scheme-I

Scheme-I. Reagent and condition**: (a)** Malononitrile, Morpholine, sulfur, ethanol, 65^0C yield 80%.

The synthetic routs of compound 3a-e and 6a-e are outlined in Scheme 2.

2-Amino-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile **2** is react with various aromatic and aliphatic sulfonyl chloride to obtained compounds **3a-e**.

2-Amino-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile **2** is react with benzaldehyde in presence of acetic acid in ethanol solvent to obtained 2-(Benzylidene-amino)-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile **4** (Schiff base) and further react with merapto acetic acid in presence of potassium tert-butoxide used as a base to cyclize to obtained 2-(4-Oxo-2-phenyl-thiazolidin-3-yl)-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile compound **5** further react with various aromatic aldehyde undergo Knowelgel Condensation to obtained compound **6a-e.**



2

3

3a: R= —CH_3 3d: R= —C_6H_5-CH_3

3b: R= —C_2H_5 3e: R= —C_6H_5-F

3c: R= —C_6H_5

4

5

6

6a: Ar= —C_6H_5 6d: Ar= —C_6H_4-F_2

6b: Ar= —C_6H_5-CH_3 6e: Ar= —C_6H_4N

6c: Ar= —C_6H_5-Br

Scheme-II

Scheme-I. Reagent and condition**: (b)** R-SO_2Cl (R=Different aromatic and aliphatic sulfonyl chloride), TEA THF, rt 4-7 hr., yield 68-79%. **(c)** benzaldehyde, glacial acetic acid, ethanol,8 hrs,reflux, yield 75%.; **(d) (i)** merapto acetic acid, Toluene,reflux,8h,yield 68%. **(e)** Potassium tert-butoxide, Aromatic Aldehyde,Toluene,rt,1-5 hrs ,yield 69-73%.

Table 1

Physical characterization data of compounds **9a-e** and **10a-e**

Compound	Physical state	Time hours	Mp ^{0}C	Yield %	Molecular Formula/M.W
3a	White crystal	7	194-196	65	$C_{14}H_{12}N_3O_2S$ 288
3b	Off-white crystal	6	171-173	66	$C_{15}H_1N_2O_3S$ 302
3c	Off-White crystal	5	145-147	68	$C_{19}H_{14}N_2O_3S$ 350
3d	Off-White crystal	7	185-187	75	$C_{20}H_{16}N_2O_3S$ 364
3e	Off-White crystal	6	269-271	67	$C_{20}H_{16}N_2O_3S$ 368
6a	White crystal	2	115-118	65	$C_{29}H_{20}N_2O_2S$ 460
6b	Off-White crystal	4	121-123	71	$C_{30}H_{22}N_2O_2S$ 474
6c	Off-White crystal	5	163-165	61	$C_{29}H_{19}N_2O_2SBr$ 539
6d	white crystal	5	105-107	65	$C_{29}H_{18}N_2O_2S_2$ F_2 333
6e	White crystal	5	86-88	73	$C_{28}H_{19}N_3O_2S$ 298

The structures of all compounds 3a-e and 6a-e were determined using IR, 1H-NMR and EI-MS spectral data together with elemental analysis. IR spectra of compounds **6a-e** showed absorption bands around 1637 - 1705 cm-1 regions resulting from SO_2 function of sulfonamide, while compound 3a-e showed one additional absorption bands around 3419.62 cm-1 regions resulting from N-H function of –SO_2NH. ^{1}H NMR spectra of compound 3a-e showed singlet proton at chemical shift around 2.07-2.08 ppm for –$NHSO_2$- proton. The EI-MS spectra of **3a-e** and **6a-e** showed molecular ion peak (M+, 90%).

Biological Activities. The newly synthesized derivatives were evaluated for their *in vitro* antibacterial activity against E. Coli, P. Aeruginosa, S. Aureus, S. Pyogenes, S. typhi and V. parahaemolyticus by micro broth dilution methods [18]. The standard strains used for screening of antibacterial and antifungal activities were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India. The MIC values are given in Table 1. The standard drug used for antibacterial activity was ciprofloxacin. Mueller Hinton Broth was used as nutrient medium for bacteria and sabouraud dextrose broth for fungal to grow. Inoculums size for test strain was adjusted to 108 CFU/ mL by comparing the turbidity. The serial dilutions were prepared in primary and secondary screening. The target compounds and standard drugs were dissolved in DMSO-water (1:1 v/v) at a concentration of 2.0 mg/mL. In primary screening, 500 µg/mL, 250 µg/mL and 125 µg/mL concentrations of the synthesized drugs were taken. Data were not taken for the initial solution because of the high DMSO concentration (10%). The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. In secondary screening, the drugs found active in primary screening were similarly diluted to obtain 100 µg/mL, 50 µg/ mL, 25 µg/mL, 12.5 µg/mL and 6.25 µg/mL concentrations. The inoculated wells were incubated overnight at 37°C in a humid atmosphere. The highest dilution showing at least 99% inhibition zone is taken as MIC.

Table 2

Antimicrobial activity data of newly synthesized compounds **3a-e** and **6a-e**

Compounds	Antibacterial MIC in µg/ml					
	E.coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*S. typhi* TCC98	*V.parahaemolyticus* MTCC 82
3a	62.5	100	62.5	100	200	250
3b	125	250	50	250	500	1000
3c	50	200	50	250	200	500
3d	200	250	125	200	250	500
3e	100	500	62.5	200	250	500
6a	1000	500	500	1000	250	125

6b	50	125	50	125	1000	1000
6c	100	500	125	500	500	1000
6d	125	100	500	125	200	500
6e	500	125	50	250	500	500
Ciprofloxacin	25	25	50	50	-	-

The investigation of antibacterial screening revealed that all the newly synthesized compounds showed moderate to excellent inhibition. Compound **3a** shows good activity against *E. coli* and *S. Aureus* while moderate activity against *P. Aeruginosa* and *S. pyogenes*. Compounds **3b** exhibit very good activity against all tested microorganism except *S. Aureus*. while compound **3c** shows very good activity against *E.coli* and *S. Aureus* only. Compound **3d** is moderate activity against *S. Aureus.* and **3e** good activity against all tested microorganism except *S. Aureus*. Exhibit excellent activity against *P. aeruginosa* and *S. typhi* respectively only. Compound **6a** shows excellent activity against *V.parahaemolyticus*, while compound **6b** exhibits excellent activity against *E.coli* and *S. aureus*. Compound **6d** exhibits excellent activity against *S. aureus* only, while compounds **6e** show very good activity against all tested microorganism except *S. Aureus*.

Conclusions

Present study reports synthesis of novel 2-(5-Benzylidene-4-oxo-2-phenyl-thiazolidin-3-yl)-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile and successively different aromatic and aliphatic. The antibacterial screening of newly synthesize compounds was carried out against six different organism, and some of compounds exhibits moderate to excellent activity. Many known drugs posses cyclopenta[c]chromene nucleus as active core and it well known to shows the potential pharmacological activities. The presence of diphenyl ether moiety is also instrumental in contributing to the net biological activity of a system.

Experimental Section

Melting points were determine with Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer PE-1600 FTIR spectrometer in KBr

disc. 1H NMR spectra were recorded on a Varian spectrometer using TMS as an internal standard. EI-MS spectra were measured on a Waters mass spectrometer. Progress of the reaction was checked by thin layer chromatography (TLC) on silica gel coated aluminum sheets (silica gel 60 F254) using a mixture of ethyl acetate and hexane (5:5 v/v). All of the solvents and materials were reagent grade and purified as required.

General Synthesis of 2-Amino-1, 4-dihydro-cyclopenta[c]chromene-1-carbonitrile (2).

A mixture of Chromen-4-one (A) (0.1 mol),Malanonitrile (0.12 mol),Morpholine (0.15) and sulfur (0.15) in Ethanol (100 ml) was stirred at 10^0C for 2 h. Reaction mixture was cooled at rt. Water was added to reaction mixture and stirred at RT for 20 min. Solid was separated by filtration washed with water and suck dried. Solid was recrystalized from rectified spirit to give compound **(2)** in yield 80 %.Ana Obs.: C-74.30%, H-4.82%, N-13.29 %; Calc. for $C_{13}H_{10}N_2O$ C-74.27%, H-4.79%, N-13.25%. mp 113 -116^{o}C. IR υ (cm-1): 3436.22 (NH_2), 1272.32 (C-O), 2232.45(-CN). ^{1}H-NMR (400 MHz, DMSO-*d*6) δ 4.50-4.52 (s, 2H, -OCH_2), 5.59-5.61 (s, 1H, =CH), 3.65-3.71(s, 1H, -CH),6.77-6.72 (t, 2H, ArH ,J=8.5 Hz), 7.01-7.03 (s,1H, ArH) 7.10-7.15 (s, 1H, ArH), 2.06-2.10 (s, 1H, SO_2NH),. Mass spectrum (ES) *m*/*z* 211.33 (M+1).

Synthesis of compound 3b-e

N-(1-Cyano-1,4-dihydro-cyclopenta[c]chromen-2-yl)-methanesulfonamide (3a): A mixture of 2-Amino-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile **(2)** (0.023 mol), Triethyl amine (0.077 mol), N,N-dimethyl amino pyridine (0.0023 mol) and methan sulfonyl chloride (0.028 mol) in THF 50 ml was stirred at rt for 7 h. Water was added to reaction mixture and extracted with ethyl acetate. Ethyl acetate layer was washed with water, dried on sodium sulfate and evaporated completely giving solid product. Solid was re-crystallized from ethanol giving compound **(3a)** in 65%, yield. Obtained as white crystals, mp 194-196^{0}C Ana Obs.: C-58.33%, H-4.22%, N-9.74%, S-11.10%.; Calc. for $C_{14}H_{14}N_4O_2S_2$: C-58.32%, H-4.20%, N-9.72%, S-11.12%. IR υ (cm-1): 3419.62 (SO_2NH), 1288.08 (C-O), 2235.68(-CN). 1H-NMR (400 MHz, DMSO-d6) δ 4.52-4.54 (s, 2H, -OCH2), 5.64-5.66 (s, 1H, =CH), 3.67-3.79 (s, 1H, -CH), 6.75-6.79 (t, 2H, ArH ,J=8.5 Hz), 7.04-7.06 (t,1H, ArH J=8.5 Hz) 7.11-7.13 (d, 1H, ArH J=6.5 Hz), 2.07-2.08 (s, 1H, SO_2NH),. Mass spectrum (ES) m/z 289.21 (M+1).

Synthesis of compound 3b-e as per above process using various aromatic and aliphatic sulfonyl chloride.

Ethanesulfonic acid (1-cyano-1,4-dihydro-cyclopenta[c]chromen-2-yl)-amide (3b): Obtained as off-white crystals, 66 % yield. mp 171-173^{o}C. Anal. Calcd. for $C_{15}H_{14}N_2O_3S_2$: C, 59.59; H, 4.67; N, 9.27; S 10.61;. Found: C, 59.61; H, 4.68; N, 9.29, S 10.63. IR υ (cm-1): 3419.62 (SO2NH), 1288.08 (C-O) 2235.68 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 1.45-1.49 (t, 3H, -CH_3 J=8.5 Hz), 3.42-3.44 (q, 2H, -CH_2), 3.76-3.82 (s, 1H, -CH) 4.55-4.57 (s, 2H, -OCH_2), 5.66-5.68 (s, 1H, =CH), , 6.82-6.90 (t, 2H, ArH ,J=8.5 Hz), 7.06-7.08 (t,1H, ArH J=8.5 Hz) 7.15-7.15 (s, 1H, ArH J=6.5 Hz), 2.05-2.08 (s, 1H, SO_2NH).Mass spectrum (ES): m/z 303.28 (M+1).

N-(1-Cyano-1, 4-dihydro-cyclopenta[c]chromen-2-yl)-benzenesulfonamide (3c): Obtained as off-white crystals, 6 % yield. mp 145-147^{o}C. Anal. Calcd. for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 7.99; S 9.15;. Found: C, 65.15; H, 4.05; N, 8.01, S 9.13. IR υ (cm-1): 3420.21 (SO_2NH), 1287.58 (C-O) 2236.33 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 3.80-3.82 (s, 1H, -CH) 4.61-4.63 (s, 2H, -OCH_2), 5.32-5.36 (s, 1H, =CH), , 6.78-6.81 (t, 2H, ArH ,J=8.5 Hz), 7.10-7.11 (t,1H, ArH J=8.5 Hz) 7.18-7.20 (d, 1H, ArH J=6.5 Hz), 7.29-7.31 (t, 1H, ArH J=5.5 Hz), 7.58-7.61 (t,2H, ArH J=8.5 Hz) 7.89-7.91 (t,2H, ArH J=7.2 Hz) 2.11-2.13 (s, 1H, SO_2NH).Mass spectrum (ES): m/z 351.44 (M+1).

N-(1-Cyano-1,4-dihydro-cyclopenta[c]chromen-2-yl)-4-methyl-benzenesulfonamide (3d): Obtained as off-white crystals, 75 % yield. mp 185-187^{o}C. Anal. Calcd. for $C_{20}H_{16}N_2O_3S$: C, 65.92; H, 4.43; N, 7.69; S 8.80;. Found: C, 65.95; H, 4.44; N, 7.70, S 8.81. IR υ (cm-1): 3421.11 (SO_2NH), 1285.66 (C-O),2233.32 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 2.25-2.28 (s, 3H, -CH_3), 3.74-3.75 (s, 1H, -CH) 4.66-4.68 (s, 2H, -OCH_2), 5.33-5.34 (s, 1H, =CH), , 6.78-6.80 (t, 2H, ArH ,J=8.5 Hz), 7.12-7.14 (t,1H, ArH J=8.5 Hz) 7.22-7.24 (s, 1H, ArH J=6.5Hz), 7.33-7.35 (t, 1H, ArH J=8.5 Hz), 7.55-7.57 (t,2H, ArH J=8.5 Hz) 7.88-7.90 (t,2H, ArH J=7.2 Hz) 2.07-2.09 (s, 1H, SO_2NH).Mass spectrum (ES): m/z 365.40 (M+1).

N-(1-Cyano-1,4-dihydro-cyclopenta[c]chromen-2-yl)-4-fluoro-benzenesulfonamide (3e) : Obtained as white crystals, 67 % yield. mp 269-271^{o}C. Anal. Calcd. For $C_{20}H_{16}N_2O_3S$: C, 61.95; H, 3.56; N, 7.60; S 8.70;. Found: C, 61.93; H, 3.58; N, 7.59, S 8.68. IR υ (cm-1): 3411.25 (SO_2NH), 1278.62 (C-O), 2235.89(-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 3.77-3.79 (s, 1H, -

CH) 4.66-4.65 (s, 2H, -OCH_2), 5.33-5.36 (s, 1H, =CH), , 6.75-6.80 (t, 2H, ArH ,J=8.5 Hz), 7.07-7.09 (t,1H, ArH J=8.5 Hz) 7.15-7.17 (d, 1H, ArH J=6.5 Hz), 7.31-7.35 (t,2H, ArH J=8.5 Hz) 7.91-7.93 (t,2H, ArH J=7.2 Hz) 2.02-2.06 (s, 1H, SO_2NH).Mass spectrum (ES): m/z 369.22 (M+1).

Synthesis of compound 6b-e

Synthesis of 2-(Benzylidene-amino)-1, 4-dihydro-cyclopenta [c]chromene-1-carbonitrile (4). A mixture of 2-Amino-1, 4-dihydro-cyclopenta[c] chromene-1-carbonitrile (A) (0.011 mol), add 50 ml ethanol, add benzaldehyde (0.011 mol) and rinse with 10 ml ethanol. Add 1 ml of glacial acetic acid. The solution was reflux for 8 hours after completion of reaction cool to 25-30^0 C and filter the solid and wash with ethanol giving product. Solid was re-crystalized from ethanol diving compound **(4)** in 66% yield Obtained as a white crystals. mp 83-85^{0}C Ana Obs.: C-80.55%, H-4.75%, N-9.41%; Calc. for $C_{20}H_{14}N_2O_2$: C-80.52%, H-4.73%, N-9.39%. IR υ (cm-1): 1152.53 (C-O), 2256.9 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 3.79-3.81 (s, 1H, -CH) 4.57-4.59 (s, 2H, -OCH_2), 5.94-5.96 (s, 1H, =CH), , 6.75-6.77 (t, 2H, ArH ,J=8.5 Hz), 7.08-7.10 (t,1H, ArH J=8.5 Hz) 7.29-7.31 (d, 1H, ArH J=6.5 Hz), 7.47-7.49 (m,3H, ArH) 7.65-7.67 (d,2H, ArH J=7.2 Hz) 8.19-8.22 (s, 1H, -N=CH-).Mass spectrum (ES): m/z 299.30 (M+1).

Synthesis of 2-(4-Oxo-2-phenyl-thiazolidin-3-yl)-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile (5) : A mixture 2-(Benzylidene-amino)-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile **(4)** (0.016 mol), Mercapto-acetic acid (i) (0.40 mmol), in Toluene (100 ml) was stirred at 111 ^{0}C. for 8 h. Solvent was removed completely and water was added to residue, stirred for 25 min. Solid product was separated by filtration and washed with water and suck dry to give compound (XI) in 72 % yield. Compound was re-crystallized from 95 % ethanol giving pure compound (XI) in 68 % yield Obtained as a off-white crystals. mp 119-121^{0}C Ana Obs.: C-70.97%, H-4.35%, N-7.55%, S-8.59%,; Calc. for $C_{22}H_{16}N_2O_2S$: C- 70.95%, H- 4.33%, N-7.52,S-8.61%. IR υ (cm-1): 1150.21 (C-O), 2255.23 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 3.23-3.25 (s, 2H, S-CH_2-),3.88-3.90 (s, 1H, -CH),4.44-4.47 (s, 2H, -OCH_2), 5.72-5.75 (s, 1H, =CH), 5.88-5.90 (s, 1H, -CH-S), 6.70-6.72 (t, 2H, ArH ,J=8.5 Hz), 7.03-7.04 (d,1H, ArH J=6.5

Hz), 7.06-7.08 (m, 3H, ArH), 7.10-7.11 (t, 2H, ArH J=8.5 Hz),7.13-7.15 (d, 1H, ArH J=8.5 Hz)Mass spectrum (ES): m/z 373.35 (M+1).

Synthesis of 2-(5-Benzylidene-4-oxo-2-phenyl-thiazolidin-3-yl)-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile (6a): A mixture of 2-(4-Oxo-2-phenyl-thiazolidin-3-yl)-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile (IV) (0.0053 mol), Benzaldehyde (0.0059 mol), and dry toluene 30 volume.Then ,potassium tert-butoxide (0.0059 mol),was added dropwise.stirr reaction mass at RT for 2 hour and monitor by TLC after completion of reaction the solvent was removed under vacuume and crude material purify by ethyl acetate to give desire product**(6a)** with 65% yield. Obtained as white crystals. mp 115-118^{0}C Ana Obs.: C-75.65%, H-4.40%, N-6.10%, S-6.98%.; Calc. for $C_{29}H_{20}N_2O_2S$: C-75.63%, H-4.38%, N-6.08% S-6.96%. IR υ (cm-1): 1152.53 (C-O), 1775.43 (-C=O) 2218.61 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 3.85-3.87 (s, 1H, -CH),4.54-4.56 (s, 2H, -OCH_2), 5.78-5.80 (s, 1H, =CH), 5.86-5.88 (s, 1H, -CH-S), 6.09-6.11 (s, 1H, -N=CH-),6.72-6.74 (t, 2H, ArH ,J=8.5 Hz), 7.03-7.10 (m,4H, ArH), 7.12-7.18 (m, 3H, ArH), 7.28-7.33 (m,3H, ArH),7.45-7.47 (d,2H, ArH J=7.2 Hz).Mass spectrum (ES): m/z 461.73 (M+1).

Synthesis of compound 6b-e as per above process using various aromatic aldehyde

Synthesis of 2-[5-(4-Methyl-benzylidene)-4-oxo-2-phenyl-thiazolidin-3-yl]-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile (6b): Obtained as off-white crystals, 71 % yield. mp 121-123^{0}C Ana Obs.: C-75.92%, H-4.66%, N-5.92%, S-6.77%.; Calc. for $C_{30}H_{22}N_2O_2S$: C-75.93%, H-4.67%, N-5.90% S-6.76%. IR υ (cm-1): 1161.22 (C-O), 1770.22 (-C=O) 2221.51 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 2.30-2.32(s, 3H, Ar-CH_3), 3.88-3.89 (s, 1H, -CH),4.50-4.52 (s, 2H, -OCH_2), 5.77-5.78 (s, 1H, =CH), 5.80-5.82 (s, 1H, -CH-S), 6.13-6.14 (s, 1H, -N=CH-),6.70-6.72 (t, 2H, ArH ,J=8.5 Hz), 7.12-7.15 (m,4H, ArH), 7.18-7.20 (m, 3H, ArH), 7.25-7.27 (d,2H, ArH J=8.5 Hz),7.47-7.49 (d,2H, ArH J=7.2 Hz).Mass spectrum (ES): m/z 475.50 (M+1).

Synthesis of 2-[5-(4-Bromo-benzylidene)-4-oxo-2-phenyl-thiazolidin-3-yl]-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile (6c): Obtained as off-white crystals, 61 % yield. mp 163-165^{0}C Ana Obs.: C-64.58%, H-3.53%, N-5.21%, S-5.93%.; Calc. for $C_{29}H_{19}Br\ N_2O_2S$: C-64.57%, H-3.55%, N-5.19% S-5.94%. IR υ (cm-1): 1166.11 (C-O), 1774.24 (-C=O) 2218.27 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 3.81-3.83 (s, 1H, -CH),4.48-4.50 (s, 2H, -OCH_2), 5.66-

5.68 (s, 1H, =CH), 5.82-5.84 (s, 1H, -CH-S), 7.13-7.14 (s, 1H, -N=CH-),6.77-6.79 (t, 2H, ArH ,J=8.5 Hz), 7.07-7.09 (m,4H, ArH), 7.11-7.13 (m, 3H, ArH), 7.29-7.31 (d,2H, ArH J=8.5 Hz),7.38-7.41 (d,2H, ArH J=7.2 Hz).Mass spectrum (ES): m/z 540.24 (M+1).

Synthesis of 2-[5-(3,5-Difluoro-benzylidene)-4-oxo-2-phenyl-thiazolidin-3-yl]-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile (6d): Obtained as white crystals, 75 % yield. mp 105-107^{0}C Ana Obs.: C-70.12%, H-3.63%, N-5.66%, S-6.48%.; Calc. for $C_{29}H_{18}F_2N_2O_2S$: C-70.15%, H-3.65%, N-5.64% S-6.46%. IR υ (cm-1): 1173.33 (C-O), 1770.54 (-C=O) 2227.78 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 3.77-3.79(s, 1H, -CH),4.60-4.62 (s, 2H, -OCH_2), 5.52-5.54 (s, 1H, =CH), 5.85-5.87 (s, 1H, -CH-S), 7.07-7.09 (s, 1H, -N=CH-),6.88-6.89 (t, 2H, ArH ,J=8.5 Hz), 6.99-7.01 (s,1H, ArH), 7.03 -7.05 (s,2H, ArH),7.09-7.11 (m,2H, ArH), 7.16-7.18 (m, 3H, ArH), ,7.38-7.41 (d,2H, ArH J=7.2 Hz).Mass spectrum (ES): m/z 497.22 (M+1).

Synthesis of 2-(4-Oxo-2-phenyl-5-pyridin-4-ylmethylene-thiazolidin-3-yl)-1,4-dihydro-cyclopenta[c]chromene-1-carbonitrile (6e): Obtained as white crystals, 75 % yield. mp 98-100^{0}C Ana Obs.: C-72.85%, H-4.13%, N-9.09%, S-6.98%.; Calc. for $C_{28}H_{19}N_3O_2S$: C-72.87%, H-4.15%, N-9.10% S-6.95%. IR υ (cm-1): 1166.54 (C-O), 1778.55 (-C=O) 2227.85 (-CN). ^{1}H-NMR (400 MHz, DMSO-d6) δ 3.79-3.81(s, 1H, -CH),4.59-4.61 (s, 2H, -OCH_2), 5.55-5.56 (s, 1H, =CH), 5.88-5.89 (s, 1H, -CH-S), 7.09-7.11 (s, 1H, -N=CH-),6.75-6.76 (t, 2H, ArH ,J=8.5 Hz), 7.05-7.07. (d,2H, ArH,J=8.5 Hz), 7.10 -7.12 (m,3H, ArH),7.15-7.17 (m,2H, ArH), 7.45-7.47 (d, 2H, ArH,J=8.5 Hz), 8.11-8.13 (d,2H, ArH J=8.2 Hz).Mass spectrum (ES): m/z 462.12 (M+1).

Acknowledgements

We gratefully acknowledge the most willing help and co-operation shown by CDRI Lucknow, India. for spectroscopic analysis and, Microcare Laboratory & Tuberculosis Research Centre, Surat, Gujarat, India for biological activity acquisition coordinating facility

References

1. Rhajaouri M,Oumzil H, Faid M, Lyagoubi M, Elyachioui M and Benjouad A 2001 *Science Lett.* 3.
2. Miroslawa K-B and Marian W 2003 *Z. Naturforsch* C58, 65.

3. Weidenbörner M and Jha H CC 2003 *Int. Symp. on Natural phenols in Plant Resistance*, Int. Soc. Horticultural Sci. Acta Horticulture, p 381.
4. Tanaka T, Iinuma M, Yuki K, Fujii Y and Mizuno M 1992 *Phytochemistry* 31,993.
5. Vender Berghe D A R, Haemers A and Vlieunek A J 1993 In *Bioactive natural products; Detection and structural determination* (eds) S M Colegate and K J Molyneux (London: CRC Press) ch 17, pp 405– 440
6. Bors W, Heller W, Michel C and Saran M 1990 In *Methods in enzymology* (eds) L Packer and A N Glazer (New York: Academic Press) vol 186, pp 343–355.
7. Alam S, Sarkar Z and Islam A 2004 *J. Chem. Sci.* 116, 29.
8. Alam S, Miah M A J and Islam A 2004 *J. Biol. Sci.* 4,527.
9. Alam S 2004 *Acta Chim. Slov*. 2004, 51 (in press).
10. Alam S, Miah M A J and Islam A 2004 *ACGC Chem. Res. Commun.* 17 (in press).
11. Doshi A G, Soni P A and Ghiya B J 1986 *Indian J. Chem*. 258,759.
12. Hoshino Y, Ohinata T and Taken N 1986 *Bull. Chem. Soc.* (*Jpn*) 59, 2351.
13. Mahal H S, Raj H S and Venkataraman K 1935 *J. Chem. Soc.* 1965.
14. Arima H, Ashida H and Danno G-I 2002 *Biosci. Bio technol Biochem*. 66,1014.
15. Jeongmok K, Maurice R M and Cheng I W 1995 *J. Agric. Food Chem*. 43, 2834.
16. Nishina C, Enoki N, Tawata S, Mori A, Kobayashi K and Fukushima M 1987 *Agric. Biol. Chem*. 51,139.