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Synthesis and biological evaluation of some new 3-cyano-2-amino substituted chromene derivatives

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ABSTRACT

Chromenes are the one of the important class of heterocyclic compounds which poses wide range of pharmaceutical and biological importance. Different functional groups at different positions in the core structure of chromene deliberately yields novel derivatives which play a prominent role in in the field of medicinal chemistry. In this work one pot synthesis of a few new series of 2-amino-3-cyano-4H-chromene derivatives were designed, synthesized , characterized and biological activity like anti-bacterial and anti-fungal studies were screened, where most of the compounds have shown good growth inhibition activity.

Key words: HMTA(hexa methylene tetra amine), MIC(minimum Inhibition concentration), chromene

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INTRODUCTION

Chromenes comes under benzopyran family is a fuzed form benzene and pyran ring . This hetero cyclic compound extended in various natural compound and other synthetic compounds. In recent times there are several drug moieties are in use bearing chromene entity in the treatment of various diseases like hypertension, asthma etc.
Due to oxygen atom presence in the structure, chromenes aquires broad pharmaceutical significance in heterocyclic compounds. Basically chromenes are the unsaturated form chromans. Shown in figure-1. 2*H*-chromene and 4*H*-chromene [1] are the two main core structures which are present in most of the naturally existing and synthetic compounds. Chromene are classified into various categories like substituted chromenes and fused chromenes.
Among fused chromenes- Dihydropyrano[3,2-c]chromene[2], Seselin[3], Tephrosin [4], Calanone [5,6], Acronycine [7], Conrauinone A[8], Erysenegalensein C [9] and Cromakalim [10] are the most important compounds.

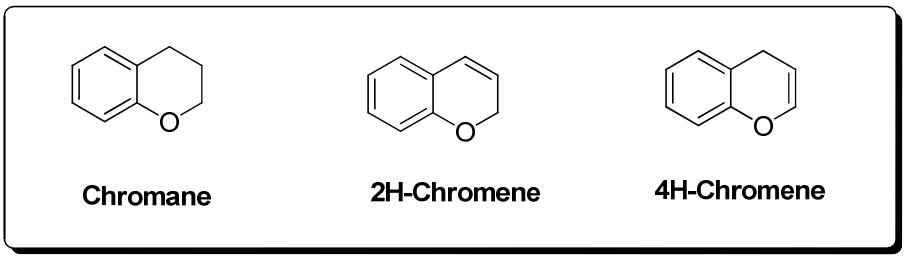


Figure-1: Three different forms of benzo Pyran molecules

Chromene found in various types of natural alkaloids, anthocyanins , polyphenols , tocopherols, and flavonoids [11]

Vitamin-E is an example of naturally occurring chromene which has anti oxidant property. Among other naturally occurring chromenes - 7-hydroxy-6-methoxy-4*H*-chromene[12] and Uvafzlelin[13] are the initially discovered compounds.

Chromenes and its derivatives are considered as the good class of heterocylic compounds which exhibit many pharmacological properties including antimicrobial[14] , antiviral [15],mutagenicity[16], antiproliferative[17] ,sex pheromone[18], antitumor [19], cancer therapy [20] and Central nervous system activity[21].

2-amino-4*H*-chromenes are considered as privileged medicinal scaffold serving for generation of small-molecule ligands with highly potent molecules which exhibit anti-anaphylactic activities[22] .

Among chromenes family 3-cyano chromene derivatives have tremendous biological importance. Various chemical methods were adopted to synthesize 2-amino -3-cyano chromene. By keeping the 2-amino -3-cyano chromene moiety intact , it has been well observed that many derivatives were synthesized by substituting various functional groups at different position of chromene ring .

During the last decade, such compounds have shown interesting pharmacological properties including, antimicrobial[23] ,antiviral [24,25], mutagenicity [26],anti-proliferative [27] ,antitumour [28] ,cancer therapy [29,30] and central nervous system activities[31] . 2-Aminochromenes were also used as biodegradable agrochemicals and components of many natural products[32].

The most general route of synthesis of chromenes is condensation of phenol, aldehyde, and malononitrile in the presence of an organic base, such as piperdine[33].

The most common methodology for the chemical synthesis 2-amino-chromene derivatives has been reported. But so far the synthesis of the 2-substituted amino chromene derivatives has not been reported.

After thorough screening of literature on the 2- amino-3-cyano chromene , we have come across several chemical paths of preparation of the above compounds. In most of the cases malano nitrile is treated as key starting material [34]. Concisely most of the methodology , an aldehyde, alcohol and malanonitrile is treated in slight basic medium to get the desired 2- amino-3-cyano chromene derivatives[35]. In some cases 2- imino-3-cyano chromene is reduced to get 2- amino-3-cyano chromene derivatives[36]. Several chemical were adopted to synthesize the chromene derivatives. Different approaches like Ionic liquids, microwave irradiation , nano particles , green chemistry , solid state catalysts and of course the traditional chemical reagents have continuously been used , implemented and developed for these type of molecules.

V.A. Osyanin et al [37] reported the synthesis 2- amino-3-cyano chromene derivatives under water-acetonitrile reflux system with good yield.

Nirav K Shah, et al [38] ,prepared the 2- amino-3-cyano chromene derivatives with sodium acetate and ethanol combination under microwave irradiation conditions in less than five minutes with good output.

Majid M. Heravi and co workers[39] has prepared one pot synthesis of 2-amino-3-cyano chromene derivatives by condensing an aldehyde, malaonitrile and a naphthol in presence of acetonitrile and methane sulfonic acid medium with good outputs.

Jin et al. was synthesed 4*H*-benzo[*h*]chromenes in aqueous medium under ultrasonic irradiation by reacting aromatic aldehydes , malononitrile and naphthols in one pot using cetyltrimethylammonium bromide (CTABr) as catalyst [40] *Elison M.N et al*[41] prepared new series of 2- amino-3-cyano chromene derivatives under neat reaction conditions by heating mixture of salicylaldehyde , an active methylene group and a nitro alkane with excess mole equivalents of potassium fluoride or sodium acetate.

Perumal et al[42-46] initially prepared 2-amino-3-cyano chromene-4-phosphonic acid diethyl ester by using Indium chloride as Lewis acid catalyst. Based on this principal many other catalyst like DEA, EDDA, potassium phosphate , various scaffolds of phosphonate chromenes were prepared.

Magara et al [47] reported the preparation of 2-amino-4H-chromene derivatives by reaction of substituted phenols , aldehydes and active methylene group in presence of silica gel supported polyamine heterogeneous catalyst under aq.ethanol reflux conditions.

Nano particle approach was implemented by *Safari J el al* [48] for the preparation of 2-amino-3-cyano chromene derivatives , nano-Magnesium oxide on silica gel has efficiently worked for one pot condensation between resorcinol, aldehyde and malano nitrile.

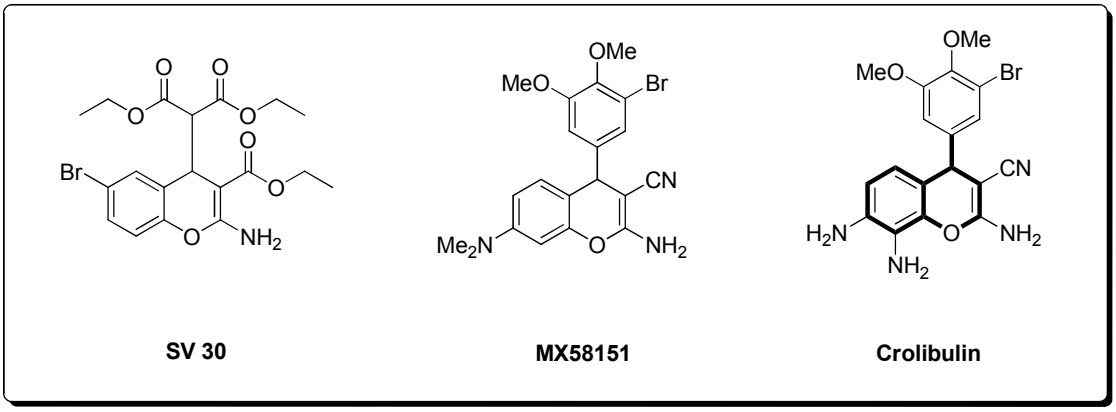


Figure 2 : Three derivatives of 4H-Chromene moieties which has exhibited different biological activities

The above chromene related compounds like " SV 30" [49] , MX5815 and Crolibulin [50] which were used for anti cancer and tubulin inhibitor and micro tubulin inhibitors respectively inspired us to design few simple new series of molecules.

Here we are reporting a new approach for the synthesis of 2-substituted amino chromene derivatives by the condensation of o-salycilaldehyde and N-subsituted cyano acetamide derivatives in presence of organic base like piperidine or tri ethyl amine(TEA).

MATERIALS AND METHODS

All the chemicals were purchased from SD fine Chem, India. Melting points were determined on a Creative digital Melting point apparatus and are uncorrected. Thin layer chromatography for completion of reaction and column purification was performed on silicagel coated plates from Macherey-Nagel-Germany , which were visualized by UV light and ninhydrin spray. FT-IR spectra were recorded on Bucker Alpha-T.^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on a Varian 400 MHz spectrometer using DMSO-d^{6} and $CDCl_3$ as solvent. Mass spectra was recorded on an Agilent triple quadrapole mass spectrometer equipped with a turbo ion spray interface at 360 ^{o}C. Elemental analyses were performed using EA 1112 Thermo Finnigan instrument. Anti bacterial and anti fungal

activity screening was conducted in Sigma Analytical Tool Pvt Ltd-Hyderabad keeping ciproflaxin and Flucanozole as standard anti bacterial and anti fungal drugs as standards

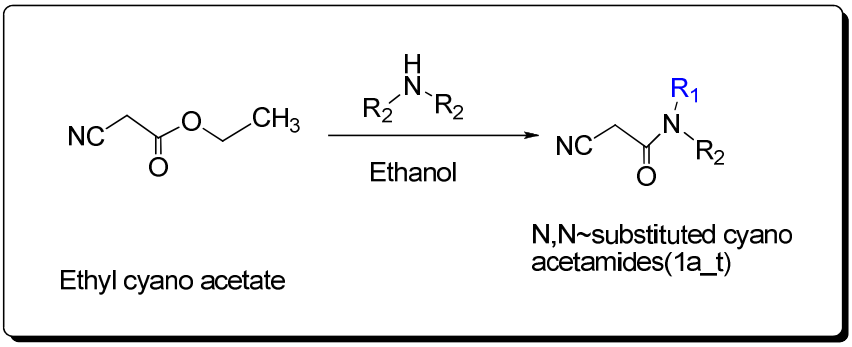
2.1.Chemical synthesis :

General procedure for procedure for the preparation of N-substituted-2-amino-3-cyano-4H chromene derivatives:

This procedure consists of two stages , preparation of N-substituted cyano acetamide derivatives and preparation of N-substituted-2-amino-3-cyano-4H chromene derivatives**.** The schematic path was shown below.

2.1.1. Preparation Of N-Substituted Cyano Acetamide Derivatives(1a-t) [51] In a 100 mL reaction flask equipped with reflux condenser, thermometer, stirrer and addition funnel ,ethyl cyano acetate(1.0 eq) is mixed with 1.2 eq of different amines like aliphatic, aromatic , alicyclic and hetero cyclic amines in ethanol medium under reflux for 1.0 hr. The reaction mass was cooled to room temperature. The isolated solid was separated by filtration. These compounds were directly used in the next step.

Scheme-1:



2.1.2. N-substituted-2-amino-3-cyano-4H chromene derivatives(2a-t)

Salicylaldehyde(20 g, 0.1639 mol) is stirred with 1.2 eq. of cyano acetamide derivatives in presence of mild organic base piperidine(catalytic amount) in ethanol(10 vol) medium under reflux condition. After one hour the reaction mass was cooled to room temperature , the isolated compound was filtered and washed with cold ethanol. All the reactions were yielded good out put and quality. Yield varied from 75-85 %. All these compounds were characterized by NMR, Mass, IR and elemental analysis. The acetamide derivatives which were used in the preparation of final desired compounds were shown in table-1

Scheme-2 :

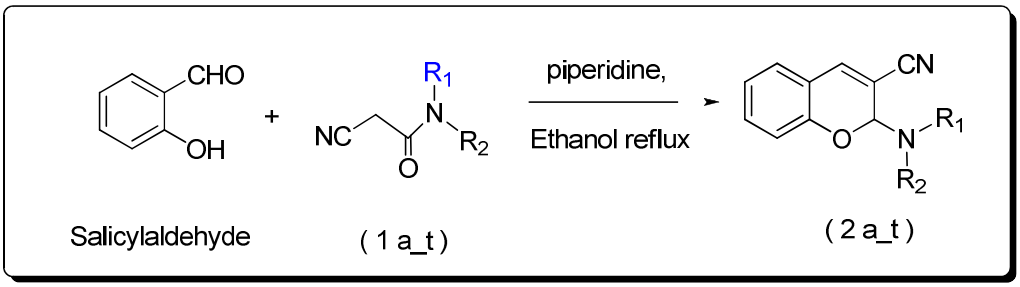
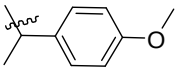
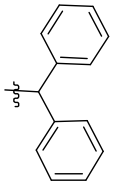
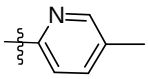
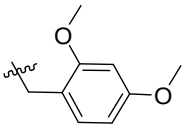
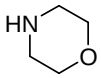
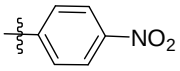
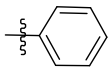
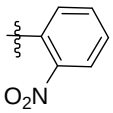
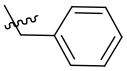
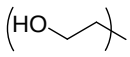
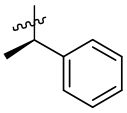
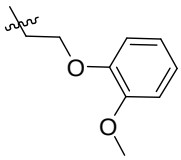


Table-1

Compound	R_1	R_2	Compound	R_1	R_2
2a	$-CH_3$	-H	**2l**		-H
2b	$-CH_3$	$-CH_3$	**2m**		-H
2c	$-C_2H_5$	-H			
2d	$-C_2H_5$	$-C_2H_5$	**2n**		-H
2e		-H			
2f		-H	**2o**		-H
2g					
2h			**2p**		-H
2l		-H	**2q**		-H
2j		-H	**2r**		-H
2k		-H	**2s**		-H
2t		-H			

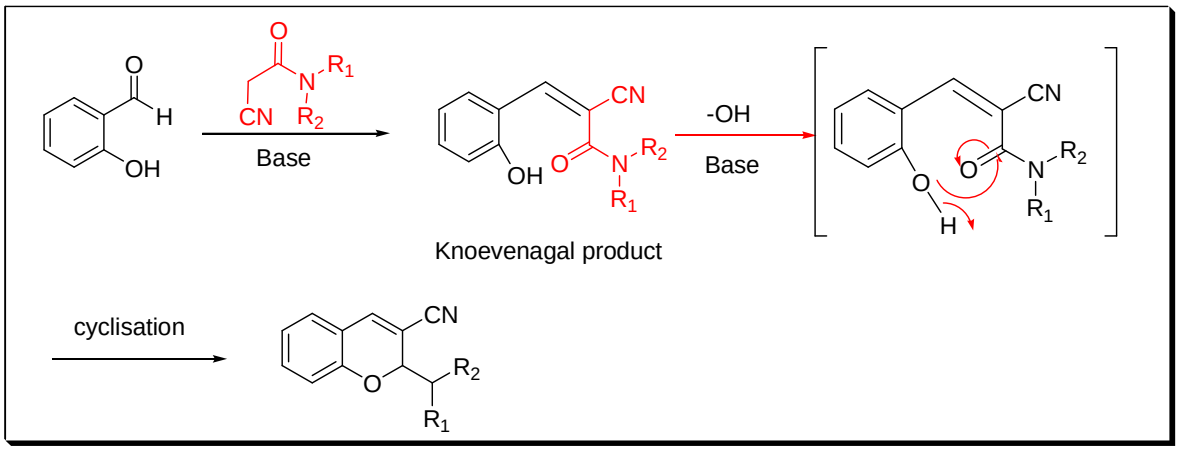
Anti Microbial Activity[52-57] :
The nutrient agar broth was prepared by general method, was inoculated aseptically with 0.5 mL of 24 h old sub-culture of *S. aureus* ATCC 2353, *P. vulgaris*, and E. coli ATCC1225 in separate conical flasks at 40–50 °C and swirled well by gentle shaking. 20 mL of this contents of the flask were poured and evenly spread in petridish (90 mm in diameter) and left to set for 2 h. All the compounds were subjected to anti bacterial activity by means of agar-well diffusion assay according Baran et al. Mueller-Hinton Broth and agar supplemented with 5% defribinated blood have been selected for testing aerobic and facultative anaerobic bacteria such as streptococci. The inoculums were prepared from broth culture that has been incubated for 4-5 h, when growth was considered in the logarithmic phase. The micro susceptibility test were standardized at pH 7.4, agar-broth were incubated in an ambient air incubator at 37°C. Ciproflaxacin (an antibiotic drug) was taken as standard antibacterial drug. These were sub cultured on saboured dextrose agar slant and incubated at 2°C for 10-12 days and the zones of inhibition of the bacterial growth were measured in millimeter.

Antifungal Activity
Aspergillus niger was extracted from soil, tested at **Sigma Analytical Testing Tools Pvt Limited. Hyderabad.** The sterile discs with 6 mm diameter were further sterilized and charged with compound as per requirement. After drying the discs were stored at 4^{o}C. Solutions (20µM/ml) of the synthesized compounds were applied to the prepared discs and incubated for 18 hr at 37°C. Subsequent measurements of the zone of activity were carried out.

RESULTS AND DISCUSSION

Chemistry
Ethyl cyano acetate(1.0 eq) was condensed with different amines (1.1 eq) in ethanol under reflux to get various N-substituted cyano acetamides (**1a-t**). All the reactions were given good yield and proceeded to next step with out purification.

The next reaction involving heating salicylaldehyde with different cyano acetaamides (**1a- t**) in presence of mild base piperidine in Ethanol yielded 70-90 % of various desired compounds(**2a-t**).Here the by incorporating the Knoevenagal[58,59] reaction conditions like mild base an adduct with E-Z isomer was formed which then undergo cyclisation to give a pyrene ring which is attached to benzene ring.



Strategic possible mechanism of the reaction
The chemical structures of these final compounds were established using spectroscopic methods including IR, ^{1}H-, ^{13}C-NMR, and HR-MS. Elemental analyses established the composition which was further confirmed by high resolution ESI(+) MS spectral analysis. The percent abundance coincides with the respective molecular ion peaks. Since the IR spectra of all the compounds were quite similar therefore discussion is confined to the important vibrations only. The carbonyl stretching frequency of chromene moiety varies from 1644-1729 cm^{-1}. A band in the range of 1546-1594 cm^{-1} was assigned to the stretching frequency of C=C bond. The IR spectrum showed a characteristic band in the range of 2220-2257cm^{-1} that supports the presence in the molecule of CN group. The IR

spectra of these amides showed the -C-O absorption peaks around 1110–1200 cm^{-1}. The IR spectra showed -N-C stretching band at the range of 3200–3342 cm^{-1}.

The weak deshielded signals suggest that -NH protons are most probably involved in hydrogen bond formation. In addition, a pair of cis coupled doublets of –C=C- unsaturated protons at were observed at 6.0–6.8 and 7.5–7.8 ppm and assigned for H-3 and H-4 protons in ^{1}H-NMR which is characteristic for chromene moieties. A pair of ortho coupled doublets for aromatic moiety of chromene was also resolved well in case of compounds where aliphatic moieties were substituted on N. Also deshielded peaks at around 8.9 ppm were attributed to N-H group of side chain. The rest of the resonances for compounds were assigned to the protons of aliphatic and aromatic ring system on 'N' in acetamide side chain. The compounds were also confirmed by studying the proton decoupled ^{13}C-NMR which show peaks around 116 ppm, assigned to -CN group moiety.

Antifungal Activity [46-50]

The antifungal activity of all synthesized 8- N-substituted-3-cyano chromene derivatives (2a-t) against specific fungi *viz. Candida albicans* and *Aspergillus niger* was evaluated using fluconazole as control fungicide. The complete antifungal analysis was done under strict aseptic conditions. The zones of inhibition were calculated with antibiotic zone scale in mm and each test was performed in triplicates and the MICs reported the result of at least repetitions. Each test was performed in triplicate and the MICs (Minimum inhibitory concentration) reported represent the result of at least two repetitions.

Table 2: Antifungal activity of chromene derivatives (Zone of inhibition in mm) against different fungal stains

Fungi	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	2m	2n	2o	2p	2q	2r	2s	2t	Flucanozol
Aspergillus niger	10	10	8	5	6	10	16	12	13	14	10	8	6	15	13	15	10	9	6	10	12
Candida Albicans	12	8	11	8	8	12	14	12	13	15	6	10	8	14	10	13	11	12	8	9	10

All twenty molecules 2a-t showed good anti fungal activity on multi-resistant organism against fluconazole, an antifungal drug. The results are tabulated in table 2 and pictorial view is shown in **fig.3.**

There is a wide inhibition zone around compounds 2g,2l,2n and 2p were observed against fluconazole after 5 days of incubation at 28^{0}C (Fig.).

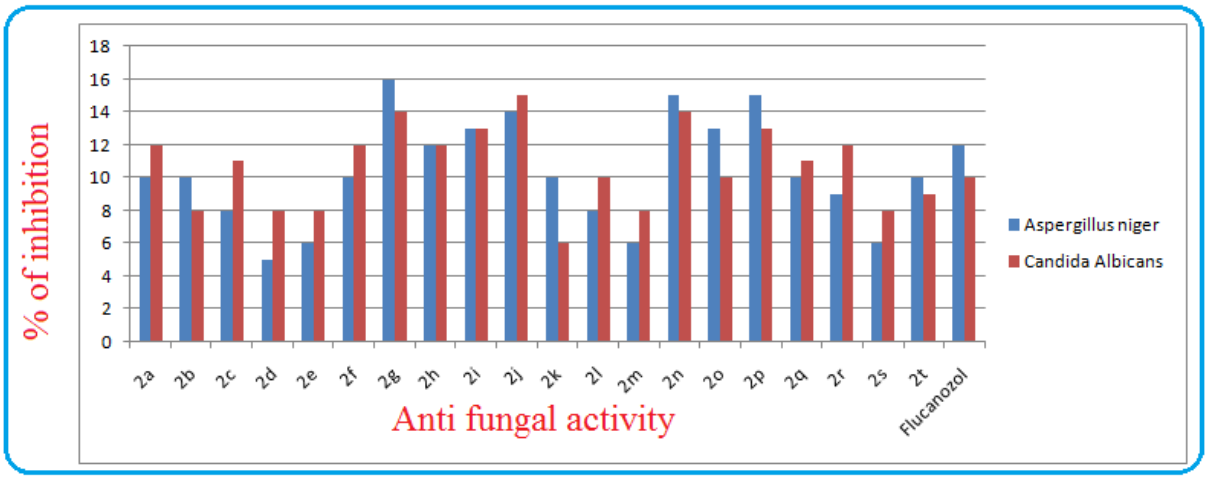


Fig.3 : Anti fungal activity of synthesized compounds 2a-t in diagrammatic view

The most encouraging results were obtained in case of compound (2i), (2l) having MIC value 4µM/ml against *Aspergillus niger* and 4-5µM/ml against *Candida albicans*, while Fluconazole, the best marketed antifungal drug shows MIC of 12-14µM/ml, 2 times more effective than fluconazole at the similar concentrations. The results shown in the Table 3 inferred that all synthesized molecules 2a-2t showed almost double or equal activity against *Aspergillus niger* and *Candida albicans*.

Antimicrobial Activity

All synthesized N-substituted-3-cyano chromene derivatives were assayed for their antifungal and antibacterial activities, as described below using different bacterial and fungal strains. The results are tabulated in Tables 2, 3, 4 and 5.

Susceptibility test *in vitro* was done on multi-resistant bacteria for example *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginos* specially causing secondary infections in human being. The antibacterial activity of synthetic chromene derivatives (2a-2t) was carried out using known micro dilution broth susceptibility test method. The disc containing 20 µM/ml of ciproflaxin was purchased and same amount of synthesized molecules were loaded on separate discs. Each test was performed in triplicate and the MICs reported represent the result of at least two repetitions. Twelve chromene derivatives (2a-2t) showed good positive results on multi-resistant organisms. The results are summarized in Table 4 and figure 4. The lowest concentration of synthesized molecules in µM/ml that prevented *in vitro* growth of microorganism has been represented as correlated with zone of inhibition

Table 4 and MIC (Minimum inhibitory concentration) in figure 4.

Bacteria	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	2m	2n	2o	2p	2q	2r	2s	2t	Ciproflaxin
Escherichia coli	8	6	14	5	6	10	8	6	14	14	10	8	6	14	8	6	14	9	8	6	11
Staphylococcus aureus	10	6	16	8	8	12	10	6	16	15	6	10	6	16	10	6	16	12	10	6	12
Pseudomonas aeruginosa	10	8	14	12	9	9	10	8	14	11	8	10	8	14	10	8	14	10	10	8	10

Table 4: Antibacterial activity of chromene derivatives (Zone of inhibition in mm) against different bacterial strains.

The result of zone of inhibition is encouraging from the results shown in the table 4. The result of zone of inhibition of ciproflaxin was 10 mm , while synthesized molecules 2c , 2i, 2j, 2n and 2q showed 10-16 mm inhibition against tested bacteria strains *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa.* Photographs showing the zone of inhibition in different bacterial strains by synthesized molecules are shown in Fig. 4.

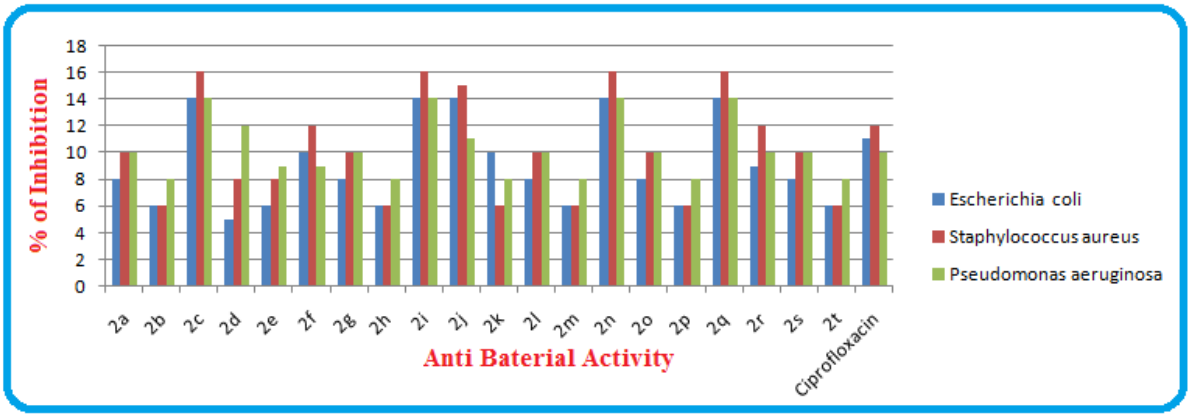


Fig.4: Anti bacterial activity of synthesized compounds 2a-t in diagrammatic view

Spectral Analysis of the synthesized compounds:

2-(methylamino)-2H-chromene-3-carbonitrile (2a)

IR (KBr, cm^{-1}) : 3287(-NH), 2221 (-C≡N), 1557 (-C=C), 1255(-C-N), 1174(-C-O).; **^{1}H NMR ($CDCl_3$):** δ 2.1(s,H,-NH),3.5(s,3H,-CH_3),5.45(s,H,C-2),7.04 (d,H, C-7), 7.19(m,H,C-8),7.65(d,2H,C-4,C-5). ; **^{13}C NMR ($CDCl_3$):** δ 160(C,C-10), 141.8 (C,C-4), 129(2C,C-5,C-7),121.8 (C,C-6), 117(C,-CN), 115(2C,C-4,C-8), 108(C,C-3),83(C,C-2),2(C,-CH_3); MS: m/z 187.25 (M^++1). ; Anal.Calcd for $C_{11}H_{10}N_2O$: C 70.98; H 5.41; N 15.04; O 8.59 ,Found; C 71.08; H 5.50; N 15.12; O 8.45.

2-(dimethylamino)-2H-chromene-3-carbonitrile (2b)

IR (KBr, cm^{-1}) : 2252 (-CN), 1545 (-C=C), 1261(-C-N), 1098(-C-O).; **^{1}H NMR ($CDCl_3$):** δ 3.1(s,6H,-2xCH_3),5.35(s,H,C-2),7.04(d,H,C-6,C-8),7.24(m,H,C-7),7.65(d,2H,C-4,C-5). ; **^{13}C NMR ($CDCl_3$):** δ 158(C,C-10),

142 (C,C-4), 12(2C,C-5,C-7),122 (C,C-6), 119(C,-CN), 113(2C,C-4,C-8), 110(C,C-3),91(C,C-2),40(2C,-2xCH_3).; MS: m/z 201.25 (M^++1). ; Anal.Calcd for $C_{12}H_{12}N_2O$: C 71.98; H 6.04; N 13.99; O 7.99,Found; C 72.10; H 6.10; N 13.87; O 7.89.

2-(ethylamino)-2H-chromene-3-carbonitrile (2c)
IR (KBr, cm^{-1}) : 3275(-NH), 2255 (-CN), 1547 (-C=C), 1265(-C-N), 1109(-C-O). **^{1}H NMR ($CDCl_3$):** δ 1.2(t,3H,-CH_3),1.87(s,H,-NH),3.21(q,2H,-CH_2),5.65(s,H,C-2),7.10 (dd,2H, C-6, C-8),7.25(m,H,C-7),7.55(d,2H,C-4,C-5).
^{13}C NMR ($CDCl_3$): δ 160(C,C-10), 143.3 (C,C-4), 129(2C,C-5,C-7), 121 (C,C-6), 117(C,-CN), 114(2C,C-4,C-8), 109(C,C-3),83(C,C-2),37(C,- CH_2),15(C,- CH_3) MS: m/z 201.32 (M^++1). Anal.Calcd for $C_{12}H_{12}N_2O$: C 71.98; H 6.04; N 13.99; O 7.99 ,Found; C 72.00; H 6.07; N 13.89; O 8.04.

2-(diethylamino)-2H-chromene-3-carbonitrile (2d)
IR (KBr, cm^{-1}) : 2229 (-CN), 1560 (-C=C), 1259(-C-N), 1154(-C-O). **^{1}H NMR ($CDCl_3$):** δ 1.2(t,3H,-CH_3),1.87(s,H,-NH),3.21(q,2H,-CH_2),5.65(s,H,C-2),7.10 (dd,2H, C-6, C-8),7.25(m,H,C-7),7.55(d,2H,C-4,C-5).
^{13}C NMR ($CDCl_3$): δ 160(C,C-10), 143.3 (C,C-4), 129(2C,C-5,C-7), 121 (C,C-6), 117(C,-CN), 114(2C,C-4,C-8), 109(C,C-3),83(C,C-2),37(C,- CH_2),15(C,- CH_3) MS: m/z 229.32 (M^++1). Anal.Calcd for $C_{14}H_{16}N_2O$: C 73.66; H 7.66; N 12.27; O 7.01,Found; C 73.87; H 7.49; N 12.2; O 7.08.

2-(cyclopropylamino)-2H-chromene-3-carbonitrile (2e)
IR (KBr, cm^{-1}) : 3300(-NH), 2239 (-CN), 1545 (-C=C), 1250(-C-N), 1145(-C-O). **^{1}H NMR ($CDCl_3$):** δ 0.4-0.5(m,4H,2xCH_2),1.54(m,H,-N-CH),2.0(s,H,-NH),5.52(s,H,C-2),7.10 (dd,2H, C-6, C-8),7.25(m,H,C-7),7.75(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$):** δ 162(C,C-10), 142 (C,C-4), 132(2C,C-5,C-7), 120 (C,C-6), 117(C,-CN), 114(2C,C-4,C-8), 109(C,C-3),80(C,C-2), 25(C,-CH, cyclopropyl),10(2C,cyclopropyl). MS: m/z 213.2 (M^++1). Anal.Calcd for $C_{13}H_{12}N_2O$: C 73.56; H 5.70; N 13.20; O 7.54,Found; C 73.45; H 5.67; N 13.25; O 7.65.

2-(cyclohexylamino)-2H-chromene-3-carbonitrile (2f)
IR (KBr, cm^{-1}) : 3300(-NH), 2229 (-CN), 1551 (-C=C), 1245(-C-N), 1165(-C-O). **^{1}H NMR ($CDCl_3$):** δ 1.0-1.7(m,10H,-CH_2,cyclohexyl),2.12(s,H,-NH),2.87(m, H,-CH, cyclohexyl),5.45(s,H,C-2),7.10 (dd,2H, C-6, C-8), 7.26(m,H,C-7),7.55(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$):** δ 159(C,C-10), 145 (C,C-4), 129(2C,C-5,C-7), 121 (C,C-6), 117(C,-CN), 114(2C,C-4,C-8), 109(C,C-3),83(C,C-2),55(C,-CH, cyclohexyl),35(2C,-CH_2, cyclohexyl),26(3C, CH_2, cyclohexyl). MS: m/z 255.35 (M^++1). Anal.Calcd for $C_{16}H_{18}N_2O$: C 75.56; H 7.13; N 11.01; O 6.29,Found; C 75.66; H 7.20; N 11.23; O 6.31.

2-(pyrrolidin-1-yl)-2H-chromene-3-carbonitrile (2g)
IR (KBr, cm^{-1}) 2219 (-CN), 1571 (-C=C), 1265(-C-N), 1170(-C-O). **^{1}H NMR ($CDCl_3$):** δ 1.7(m,4H,-CH_2,cyclopentyl) , 2.2(m,4H, cyclopentyl), 5.55(s,H,C-2),7.08 (dd,2H, C-6, C-8), 7.25(m,H,C-7),7.62(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$):** δ 161(C,C-10), 142 (C,C-4), 12(2C,C-5,C-7), 122 (C,C-6), 118(C,-CN), 115(2C,C-4,C-8), 110(C,C-3),85(C,C-2),52(2C,-N-CH_2),25(2C,-CH_2, cyclopentyl),26(3C, CH_2, cyclohexyl). MS: m/z 227.51 (M^++1). Anal.Calcd for $C_{14}H_{14}N_2O$: C 74.31; H 6.24; N 12.38; O 7.07,Found; C 74.29; H 6.33; N 12.2; O 7.10.

2-morpholino-2H-chromene-3-carbonitrile (2h)
IR (KBr, cm^{-1}) : 2222 (-CN), 1570 (-C=C), 1263(-C-N), 1159(-C-O). **^{1}H NMR ($CDCl_3$):** δ 2.7(t,4H,-N-CH_2,morpholine) , 3.71(t,4H, ,-O-CH_2,morpholine), 5.55(s,H,C-2),7.10 (dd,2H, C-6, C-8), 7.22(m,H,C-7),7.75(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$):** δ 158(C,C-10), 141 (C,C-4), 129(2C,C-5,C-7), 123 (C,C-6), 117(C,-CN), 114(2C,C-4,C-8), 108(C,C-3),84(C,C-2),70(2C,-O-CH_2 , morpholine),50(2C,-N-CH_2, morpholine) MS: m/z 243.2 (M^++1). Anal.Calcd for $C_{14}H_{14}N_2O$: C 69.41; H 5.82; N 11.56; O 13.21,Found; C 70.01; H 5.42; N 11.66; O 13.22.

2-(phenylamino)-2H-chromene-3-carbonitrile (2i)
IR (KBr, cm^{-1}) : 3300(-NH), 2229 (-CN), 1574 (-C=C), 1255(-C-N), 1098(-C-O). **^{1}H NMR ($CDCl_3$):** δ 4.5(s,H,-NH),5.45(s,H,C-2),6.7-7.1 (m,5H, C-6, C-8,C′-2,C′-6,C′-4), 7.2-7.4(m,3H,C-7,C-′3,C′-5),7.60(d,2H,C-4,C-5).
^{13}C NMR ($CDCl_3$): δ 160(C,C-10),150(C,C′-1), 142 (C,C-4), 129(4C,C-5,C-7, C-′3,C′-5), 121.6 (2C,C-6, C-′4), 117(C,-CN), 113(4C,C-4,C-8, C-′2,C′-6), 109(C,C-3),86(C,C-2). MS: m/z 249.20 (M^++1). Anal.Calcd for $C_{16}H_{12}N_2O$: C 77.40; H 4.87; N 11.28; O 6.44,Found; C 77.39; H 4.67; N 11.2; O 6.50.

2-(benzylamino)-2H-chromene-3-carbonitrile (2j)
IR (KBr, cm^{-1}) : 3300(-NH), 2219 (-CN), 1549 (-C=C), 1249(-C-N), 1159(-C-O). **^{1}H NMR ($CDCl_3$):** δ 2.12(s,H,-NH), 4.25(q, H,-N-CH),5.32(s,H,C-2),7.11 (m,2H, C-6,C-8),7.2-7.4(m,4H, C-7,C′-2,C′-4,C′-6), 7.5(m,2H,C-′3,C′-5),7.75(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$) :** δ 158(C,C-10),145(C,C′-1),141 (C,C-4),138(C,C′-1),12(4C,C-5,C-7, C-′3,C′-5), 127(2C, C-′2,C′-6),121 (C,C-6), 116(C,-CN), 112(2C,C-9,C-8,), 108(C,C-3),88(C,C-2),50(C,-N-CH_2). MS: m/z 263.35 (M^++1). Anal.Calcd for $C_{17}H_{14}N_2O$: C 77.84; H 5.38; N 10.68; O 6.10,Found; C 78.00; H 5.40; N 10.71; O 6.08.

2-((R)-1-phenylethylamino)-2H-chromene-3-carbonitrile (2k).
IR (KBr, cm^{-1}) : 3294(-NH), 2232 (-CN), 1570 (-C=C), 1245(-C-N), 1182(-C-O). **^{1}H NMR ($CDCl_3$):** δ 1.41(d,3H,-CH_3),2.09(s, H,-NH),4.21(q, H,-N-CH),5.45(s,H,C-2),6.99 (m,2H, C-6,C-8),7.2(m,C,C-7),7.4(m,3H, C-7,C′-2,C′-4,C′-6), 7.65(m,2H,C-′3,C′-5),7.81(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$) :** δ 160(C,C-10), 140 (C,C-4),137(C,C′-1),131(4C,C-5,C-7, C-′3,C′-5), 126(2C, C-′2,C′-6),122 (C,C-6), 118(C,-CN), 113(2C,C-9,C-8,), 110(C,C-3),82(C,C-2),51(C,-N-CH_2),20(C,-CH_3). MS: m/z 277.41 (M^++1). Anal.Calcd for $C_{18}H_{16}N_2O$: C 78.24; H 5.84; N 10.14; O 5.79 ,Found; C 78.09; H 5.96; N 10.21; O 5.80.

2-((R)-1-(4-methoxyphenyl)ethylamino)-2H-chromene-3-carbonitrile (2l)
IR (KBr, cm^{-1}) : 3300(-NH), 2218 (-CN), 1549 (-C=C), 1274(-C-N), 1100(-C-O). **^{1}H NMR ($CDCl_3$):** δ 1.2(d,3H,-CH_3),2.12(s, H,-NH),3.65(s,3H, -OCH_3),4.12(q, H,-N-CH),5.59(s,H,C-2),7.08 (m,4H, C-6,C-8, C-′3,C′-5),7.27(m,3H,C-7, C′-2,C′-6), 7.55(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$) :** δ 163(C,C′-4),158(C,C-10), 142 (C,C-4),137(C,C′-1),129(4C,C-5,C-7, C′-2,C′-6), 123(C,C-6), 117(C,-CN),114(4C,C-9,C-8,C′-3,C′-5), 108(C,C-3),91(C,C-2),62(C, -OCH_3)55(C,-N-CH),23(C,-CH_3). MS: m/z 27.51 (M^++1). Anal.Calcd for $C_{19}H_{18}N_2O_2$: C 74.49; H 5.92; N 9.14; O 10.44 ,Found; C 74.52; H 6.00; N 9.14; O 10.50.

2-(benzhydrylamino)-2H-chromene-3-carbonitrile (2m)
IR (KBr, cm^{-1}) : 3300(-NH), 2222 (-CN), 1561 (-C=C), 1239(-C-N), 1120(-C-O). **^{1}H NMR ($CDCl_3$):** δ 2.05(s, H,-NH),5.79(s , H,-N-CH),5.39(s,H,C-2),7.05 (m,2H, C-6,C-8), 7.18(m,C,C-7),7.32(m,2H, C′-4,C″-4),7.42(m,2H,C-4,C-5), 7.51-7.84(m,8H,C-′3,C′-2, C-′5,C′-6, C″-3,C″-2, C″-5,C″-6). **^{13}C NMR ($CDCl_3$) :** δ 158(C,C-10), 148(2C, C′-1, C″-1),142 (C,C-4),137(C,C′-1),12(8C,C-5,C-7, C′-2,C-′3,C′-5 C″-2,C″-3,C″-5), 125(2C, C′-4,C″-4,),121 (C,C-6), 119(C,-CN), 114(2C,C-9,C-8,), 108(C,C-3),81(C,C-2),54(C,-N-CH_2). MS: m/z 339.2 (M^++1). Anal.Calcd for $C_{23}H_{18}N_2O$: C 81.63; H 5.36; N 8.28; O 4.73,Found; C 81.69; H 5.2; N 8.29; O 4.72.

2-(5-methylpyridin-2-ylamino) 2H- chromene-3-carbonitrile (2n)
IR (KBr, cm^{-1}) : 3274(-NH), 2231 (-CN), 1600 (-C=C), 1238(-C-N), 1154(-C-O). **^{1}H NMR ($CDCl_3$):** δ 2.12(s,3H,-CH_3),4.1(s,H,-NH),5.45(s,H,C-2),6.47-7.1 (m,3H, C-6, C-8,C′-3), 7.27(t,H,C-7),7.4(d,H,C′-4),7.51(d,2H,C-4,C-5),7.88(s,H,C′-6). **^{13}C NMR ($CDCl_3$):** δ 159(C,C-10),154(C, C′-1), 148(C,C′-6),139 (C,C-4), 133(C,C′-3),129 (2C,C-5, C-7), 118(C,-CN), 114(2C,C-8, C-9), 108(2C,C-3,C′-2),84(C,C-2),20(C,-CH_3) MS: m/z 264.15 (M^++1). Anal.Calcd for $C_{16}H_{13}N_3O$: C 72.99; H 4.98; N 15.96; O 6.08,Found; C 73.00; H 5.00; N 15.85; O 6.05.

2-(2,4-dimethoxybenzylamino)-2H-chromene-3-carbonitrile (2o)
IR (KBr, cm^{-1}) : 3310(-NH), 2229 (-CN), 1589 (-C=C), 1281(-C-N), 1129(-C-O). **^{1}H NMR ($CDCl_3$):** δ 2.21(s,H,-NH), 4.00(s, 6H,2x-OCH_3),3.75(s,2H,-CH_2),5.00(s,H,C-2),6.55 (m,2H, C′-3,C′-5),7.1(m,3H, C-6,C-8,C′-6), 7.3(t, H,C-7),7.75(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$) :** δ 158(3C,C-10,C′-2,C′4), 140 (C,C-4),12(3C,C′-2,C-5,C-7), 120 (C,C-6), 117(C,-CN), 114(3C,C-9,C-8,C′-1), 107(C,C′-5),100(C,C′-3),85(C,C-2),55(2C,2x-CH_3),44(C,-N-CH_2) MS: m/z 323.40 (M^++1). Anal.Calcd for $C_{19}H_{18}N_2O_3$: C 70.79; H 5.63; N 8.69; O 14.89,Found; C 70.54; H 5.72; N 8.74; O 14.79.

2-(4-nitrophenylamino)-2H-chromene-3-carbonitrile (2p)
IR (KBr, cm^{-1}) : 3198(-NH), 2198 (-CN), 1489 (-C=C), 1198(-C-N), 1200(-C-O). **^{1}H NMR ($CDCl_3$):** δ 4.15(s,H,-NH),5.34(s,H,C-2),7.0(m,4H, C-6, C-8,C′-2,C′-6), 7.32(t,H,C-7),7.74(d,2H,C-4,C-5),8.10(d,2H,C′-3,C′-5). **^{13}C NMR ($CDCl_3$):** δ 158(C,C-10),151(C,C′-1), 140 (C,C-4), 129(4C,C-5,C-7, C-′3,C′-5), 120 (C,C-6), 116(C,-CN), 112(4C,C-9,C-8, C-′2,C′-6), 108(C,C-3),85(C,C-2). MS: m/z 294.31 (M^++1). Anal.Calcd for $C_{16}H_{11}N_3O_3$: C 65.53; H 3.78; N 14.33; O 16.37, Found; C 65.55; H 3.80; N 14.35; O 16.32.

2-(2-nitrophenylamino)-2H-chromene-3-carbonitrile (2q)
IR (KBr, cm^{-1}) : 3225(-NH), 2229 (-CN), 1555 (-C=C), 1300(-C-N), 1189(-C-O). **^{1}H NMR ($CDCl_3$):** δ 3.95(s,H,-NH),5.52(s,H,C-2),7.0(m,2H,C-6,C-8)7.2(d,H,C-7),7.4(m,2H,C′-4,C′-6), 7.6(m,3H,C-4,C-5, C′-5),8.00(d,H,C′-3). **^{13}C NMR ($CDCl_3$):** δ 160(C,C-10),148(C,C′-1), 138 (C,C-4),135(C,C′-5),132(C,C′-2), 129(2C,C-5,C-7),123 (C,C-6), 118(2C,-CN,C′-4), 114(3C,C-9,C-8,C′-6), 109(C,C-3),82(C,C-2). MS: m/z 294.25 (M^++1). Anal.Calcd for $C_{16}H_{11}N_3O_3$: C 65.53; H 3.78; N 14.33; O 16.37,Found; C 65.65; H 3.38; N 14.32; O 16.40.

2-(2-hydroxyethylamino)-2H-chromene-3-carbonitrile (2r)
IR (KBr, cm^{-1}) : 3447(-OH),3251(-NH), 2230 (-CN), 1587 (-C=C), 1300(-C-N), 1179(-C-O). **^{1}H NMR ($CDCl_3$):** δ 2.05(s,H,-NH), 3.0(t,2H,-OCH_2), 3.2(t,2H,-N-CH_2), 4.0(s,H,-OH),5.45(s,H,C-2),7.00 (dd,2H, C-6, C-8),7.15(t,H,C-7),7.60(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$):** δ 157.5(C,C-10), 142 (C,C-4), 131(2C,C-5,C-7), 123 (C,C-6), 120(C,-CN), 115(2C,C-4,C-8), 110(C,C-3),84(C,C-2),62(C,-O-CH_2),44(C,-N-CH_2). MS: m/z 217.25 (M^++1).
Anal.Calcd for $C_{12}H_{12}N_2O_2$: C 66.65; H 5.59; N 12.96; O 14.80,Found; C 66.55; H 5.55; N 12.99; O 14.90.

2-(2-(2-methoxyphenoxy)ethylamino)-2H-chromene-3-carbonitrile (2s)
IR (KBr, cm^{-1}) : 3302(-NH), 2219 (-CN), 1547 (-C=C), 1285(-C-N), 1200(-C-O). **^{1}H NMR ($CDCl_3$):** δ 1.95(s,H,-NH),3.08(t,2H,-NCH_2), 4.00(t,2H,-OCH_2),3.75(s,2H,-CH_2),5.45(s,H,C-2),6.8-7.0 (m,6H, C-6,C-8,C′-3, C′-4,C′-5, C′-6),7.23(t, H,C-7), 7.59(d,2H,C-4,C-5). **^{13}C NMR ($CDCl_3$):** δ 160(C,C-10), 151(2C,C′-1,C′-2),143 (C,C-4),12(2C,C-5,C-7),124(2C, C′-4, C′-5),120 (2C,C-6, C′-6), 116(C,-CN), 112(3C,C-9,C-8,C′-3), 108(C,C-3),84(C,C-2),72(C,-OCH_2),52(C,-CH_3),43(C,-N-CH_2) MS: m/z 323.41 (M^++1). Anal.Calcd for $C_{19}H_{18}N_2O_3$: C 70.79; H 5.63; N 8.69; O 14.89 ,Found; C 70.85; H 5.71; N 8.95; O 14.75.

2-**((2,5-dihydrothiazol-2-yl)methylamino)-2H-chromene-3-carbonitrile(2t)**
IR (KBr, cm^{-1}) : 3298(-NH), 2221 (-CN), 1549 (-C=C), 1259(-C-N), 1190(-C-O), 750 (C-S); **^{1}H NMR ($CDCl_3$):** δ 2.15(s,H,-NH),2.56(d,2H,-S-CH_2-),3.02(t,H,-S-CH-),3.18(d,2H,-NCH_2), 5.55(s,H,C-2), 6.80 (m,2H, C-6,C-8,),7.12(t, H,C-7), 7.25(d,H,C-5),7.65(d,H,C-4),7.71(d,H, C′-3) **^{13}C NMR ($CDCl_3$) :** δ 161(C, C′-3), 158(C,C-10), 140 (C,C-4),129(2C,C-5,C-7),121(C,C-6),119(C,-CN),115(2C,C-9,C-8,),110(C,C-3),83(C,C-2),72(C,-S-CH),51(C,-N-CH_2),47(C,-N-CH_2). MS: m/z 272.34 (M^++1). Anal.Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49; O, 5.90; S, 11.82 ,Found; C, 61.97; H, 4.83; N, 15.49; O, 5.90; S, 11.82

CONCLUSION

A simple and efficient method for the synthesis of biologically active N-substituted-3-cyano chromene derivatives from Salicylaldehyde with different N-substituted-cyano acetamides in presence of mild organic base . The remarkable feature of the method of preparation is that the process is economically cheap i.e. enhanced rate of reaction and negligible byproducts, cleaner reaction profiles which makes it a useful and attractive process, especially for commercial synthesis. The generality and simple experimental and product isolation procedures certainly play an important role in the development of a greener and much efficient commercial synthesis of chromene derivatives having commercially importance.

All synthesized chromene derivatives exerted excellent inhibitory activity against *Aspergillus niger* and *Candida albicans*. Most of the synthesized compounds are more active against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* than standard reference. Some of the compounds were found equipotent to Ciprofloxacin..

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