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Design, Synthesis and Antimicrobial Evaluation of Polyhydroxy 4H-Chromene Derivatives

Surjeet[1], Sarita Prajapati[2], Shivani[3], Abhinay Gupta[3], Sanjna Keshari[3], Ritu singh[3], Triloki Prasad[1,3*], Sachin Kumar Yadav[4], Manoj Kumar[3], Surjeet Singh[4]

[1]Research Scholar, National Institute of Pharmaceutical Education & Research, Raebareli, (U.P.) India.
[2]Associate professor, Accurate college of Pharmacy, Greater Noida, (UP), India.
[3]Assistant Professor, Kalka Institute for research and Advanced studies, partapur by-pass, Meerut (U.P.) India.
[4]Assistant professor, Sunder deep pharmacy college, NH-24, Delhi-Hapur Road, Dasna, Ghaziabad, Uttar Pradesh 201015.
Email: trilokiprasad2018@gmail.com

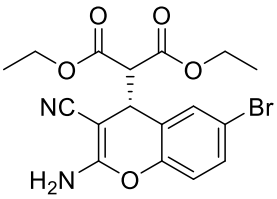
Towards achievement of new polyhydro 4H-chromene subsidiaries, the halfway mixtures for example cyanoacrylate subsidiary were combined by utilizing benzaldehyde and ethyl cyano-acetate in presence of a base as the key stage. The created methodology might demonstrate advantageous to deliver a few new frameworks. Critically, the last objective particles bear different halogen containing aromatics at fourth position can enjoy benefits to show great primary movement connections. Recently planned particles have been incorporated through a therapeutic science course, and their portrayal was finished by utilizing NMR and HR-MS strategies. Natural assessment of the blended mixtures has been finished on Gram-negative and Gram-positive microscopic organisms.

Keywords: 4-chromene, Anti-microbial agents, anti-viral, lactone, Anticancer drug.

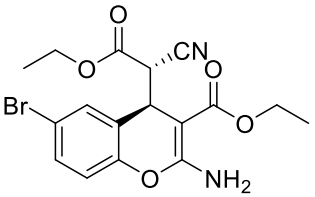
1. Introduction

Medicinal Importance of 4H-Chromene Derivatives

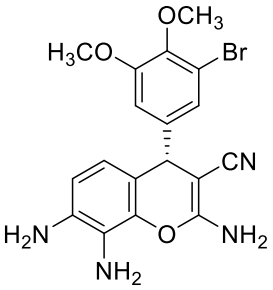
Chromene derivatives are an important class of heterocyclic compounds which are widely found in variety of natural products. They have also been recognized as one of the ‘privileged medicinal scaffolds’ due to their unique pharmacological and biological activities. Among various chromene derivatives, 4H-chromene derivatives are especially important due to their several biological and pharmacological.



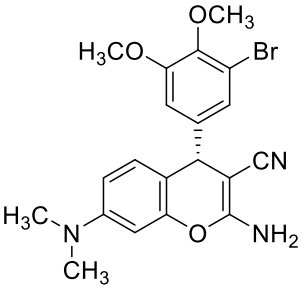
1: Anticancer
and Bcl-2 inhibitor



2 :HA 14-1
Bcl-2 inhibitor



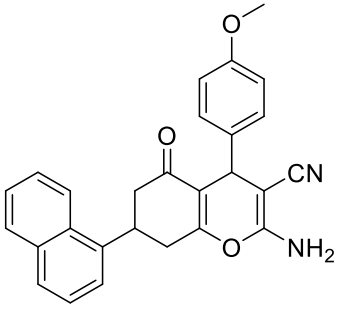
3: EPC2407
Anticancer activity



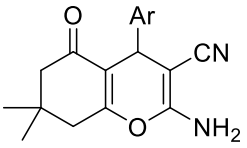
4: MX58151
anticancer activity

Figure 1. Bioactive chromene derivatives

Among the chromene family members, the 4H-chromene (or 4H-benzo[b]pyrans) and their derivatives have attracted strong interest in medicinal and pharmaceutical chemist due to their useful biological and pharmacological properties, such as anticoagulant, diuretic, anticancer, and antianaphylactin characteristics.[1] Furthermore, poly-substituted 4H-chromenes also constitute structural units of a series of natural products.[2]



5: Inhibitor
of EAAT1



6 Antibacterial
and anticancer activity

Antimicrobial Activity

A series of 2-amino-4H-pyrans and 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromenes has been described under solvent-free conditions in one pot using magnesium oxide as a catalyst to yield products in good to excellent yields.. All the synthesized compounds have been screened for in vitro antibacterial activity, selected compounds showed complete inhibition of bacterial growth at 128 μg/mL or less. These results indicates that 4H-chromene derivatives can be modified to have a better antibacterial agent.[3]

Figure 3. Amino-pyron Derivatives show potential anti-bacterial agent.

Antiviral Activity

A series of dihydropyrancarboxamides Related to Zanamivir have been synthesized and evaluated as inhibitors of influenza virus sialidases. These molecules have shown promising activities as antiviral agents.[4] The unprecedented Friedländer reaction of densely functionalized 2-amino-3-cyano-4H-pyrans with cyclohexanone has afforded in one step 5-amino-4-aryl-3-ethoxycarbonyl-2-methyl-6,7,8,9-tetrahydro-4H-chromene derivatives and evealuated as antiviral agents.[5]

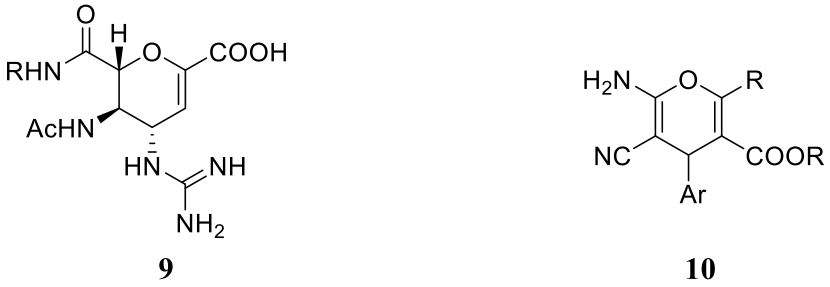


Figure 4. 4H-chromene derivative as antiviral agents

Mutagenicity Activity

A series of 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one (DDMP) were synthesized by Millard reaction and evaluated for their DNA strand-breaking activity and mutagenicity. Some of the selected derivatives were found highly active in causing mutagenicity.[6]

Figure 5. Dihydropyran derivative as mutagenic agents

Sex Pheromone Activity

2,3-Dihydro-2-ethyl-6-methyl-4//-pyran4-one (1) is a sex pheromone which isolated in 1984 by Kubo et al from hairpencils of the male moth Hepialus californicus Bvd. Shortly after, the isomer 2,3-dihydro-6-ethyl-2-methyl-4//-pyran-4-one was reported as the major component in a pheromone blend of another line of the primitive Hepialidae family, the Hepialus hecta species, The syntheses of racemic and optically pure molecules were reported along with as analogue of sex pheromone. [7]

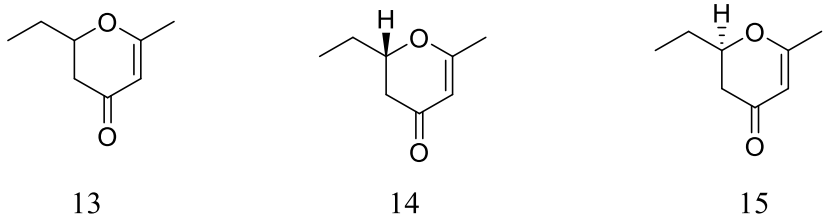


Figure 6. Dihydropyran derivative as sex pheromone analog

Anticancer Activity

The Bcl-2 and related proteins are key regulators of apoptosis or programmed cell death implicated in human disease including cancer. It has recently showed that cell-permeable Bcl-2 binding peptides could induce apoptosis of human myeloid leukemia in vitro and suppress its growth in severe combined immunodeficient mice. The 4H-chromene based molecule HA14-1 ha been demonstrated to act as nonpeptidic ligand of a Bcl-2 surface pocket. The In vitro binding studies have demonstrated that the interaction of HA14-1 with this Bcl-2 surface pocket that is essential for Bcl-2 biological function. [8,9]

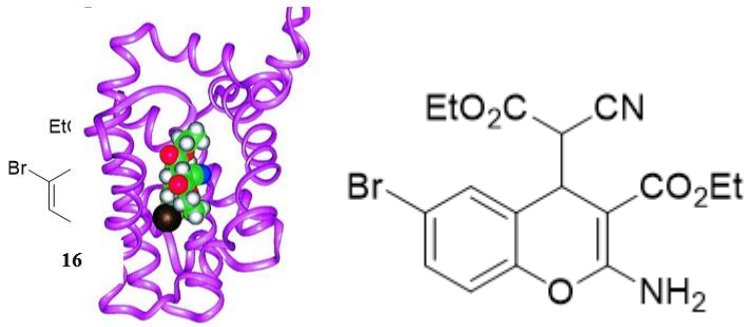
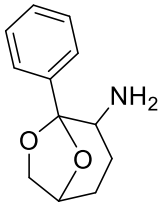


Figure 7 Anticancer Activity.

CNS Activity

The amino nitriles derivatives have been prepared from (1S,5R)-6,8-dioxabicyclo[3,2,1]octan-4-one and reacted with phenylmagnesium bromide to afford the diastereomeric 4-amino-4-phenyl derivatives 7a,b and 8a,b, respectively. The diastereomeric piperidine derivatives have found to show interesting CNS-activity.[10]



17

Figure 8 The diastereomeric piperidine derivatives have found to show interesting CNS-activity.[10]

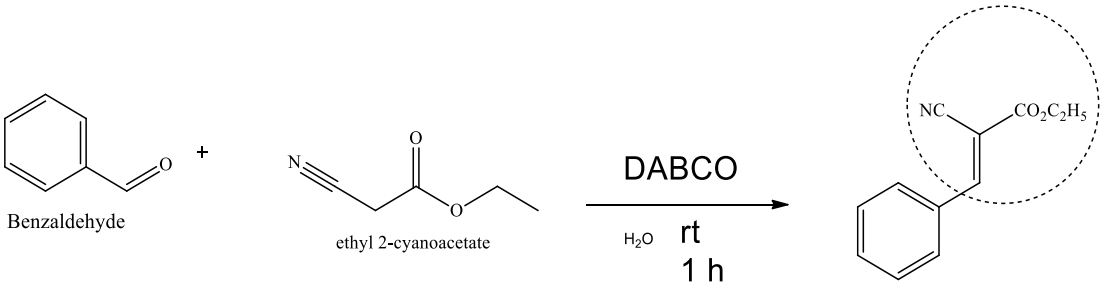
2. Results and Discussion

Based upon literature study, we have done retrosynthetic analysis of designed prototype as depicted, to accomplish target moiety we started to synthesize scheme 12 (Cyanoacrylate synthesis) as the key step followed by synthesis of scheme 13 (Synthesis of Polyhydroquinoline), scheme 14 (synthesis of chromene derivatives) and scheme 4 (Synthesis of pyrole).

In these schemes (1, 2 and 3). we explored the use of cyanoacrylate derivatives as the key step to synthesize various bio-active pharmaceutically important ring moieties.

Synthesis of Cyanoacrylate

The synthesis of starting precursor cyanoacrylate derivative was planned to synthesize by condensation of benzaldehyde and ethyl cyanoacetate in presence of a base. Accordingly, the reaction of benzaldehyde (1 eq.) and ethylcyanoacetate (1.2 eq.) was attempted using DABCO as a catalyst and water as reaction media (Scheme 1). The reaction was continued at room temperature for 1 hours after the TLC indicated the disappearance of starting precursor and a white fluffy solid was obtained. The solid was filtered off and was found pure by TLC. The structural characterization with the help of 1H NMR and Mass spectral analysis confirmed the structure of product as acrylate derivative.



Scheme 1. Two component synthesis of cyanoacrylate

The structure of isolated product was confirmed by spectral analysis using NMR and massspectroscopy. In ^{1}H NMR, the singlet appeared at δ 8.33 ppm for single proton was assigned as olefinic proton. The peak of triplet at δ 1.33 and quartet at 4.36 indicated the presence of $–CH_3$ and $–CH_2$ respectively confirming presence of ester group.

Although, the product was obtained but in order to find optimal reaction conditions, the reaction was performed using different solvents and bases. The effect of solvent on the reaction is shown in Table 1. As evident from the table 1, most of the organic solvents provided product with lower yield and higher reaction time at room temperature. The elevation of reaction temperature with organic solvents didn't provide significant enhancement of yield of product.

Table 1. Optimization of reaction solvent

S. No.	Solvent	Time (h)	Base	Yield*
1	Water	1	DABCO	75-90%
2	Acetonitrile	3	DABCO	60%
3	Toluene	2	DABCO	40%
4	DCE	3	DABCO	40%
5	Ethanol	3	DABCO	-
6	Methanol	3	DABCO	-

*Isolated yield

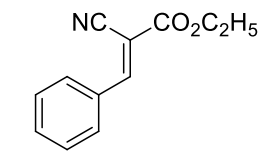
The effect of base was evaluated next for the reaction. As shown in Table 2, the DABCO was found most suitable base for this particular reaction using water as a reaction media as the yield was found maximum.

Table 2. Optimization of Base

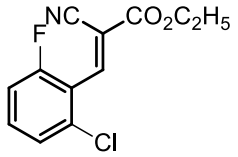
S. No.	Base	Time (h)	Yield
1	DABCO	1	80
2	DBU	2	70
3	NaOH	2	-
4	Piperidine	3	30
5	Pyridine	3	30
6	K_2CO_3	2	-

*Isolated yield

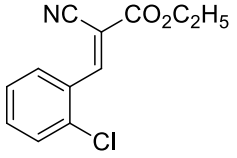
After optimal reaction conditions in hand, a series of cyanoacrylate derivatives were prepared. The protocol was found wide applicable to a broad range of substrate as various substituted benzaldehydes provided good to excellent yields of products. The reaction time and yield of synthesized derivatives are given in figure 1.In order to diversifying the reaction scope, substituted benzaldehyde and different benzaldehyde were used to synthesized various type of acrylate. We found very good yield (70-90%) with various type of benzaldehyde. Cyanoacrylate has been synthesized shown below with their respective yield.



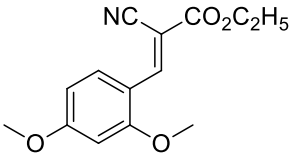
IA, 85% (1h)



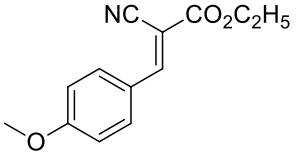
I B, 80% (2h)



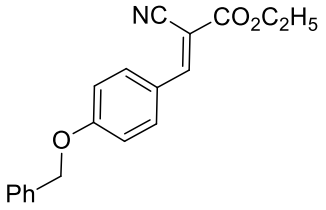
I C, 70% (2h)



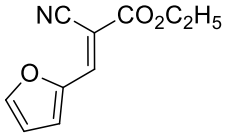
I D, 75% (2h)



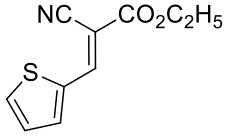
I E, 80% (1.5h)



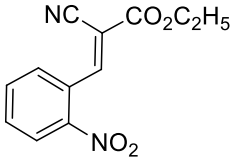
I F, 77% (2h)



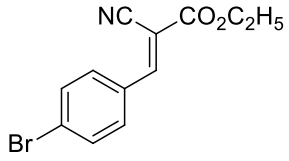
I G, 90% (1h)



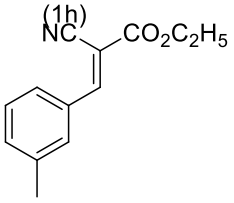
I H, 90% (1h)



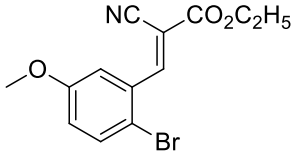
I I, 70% (1h)



I J, 75% (1h)



I K, 80% (1h)

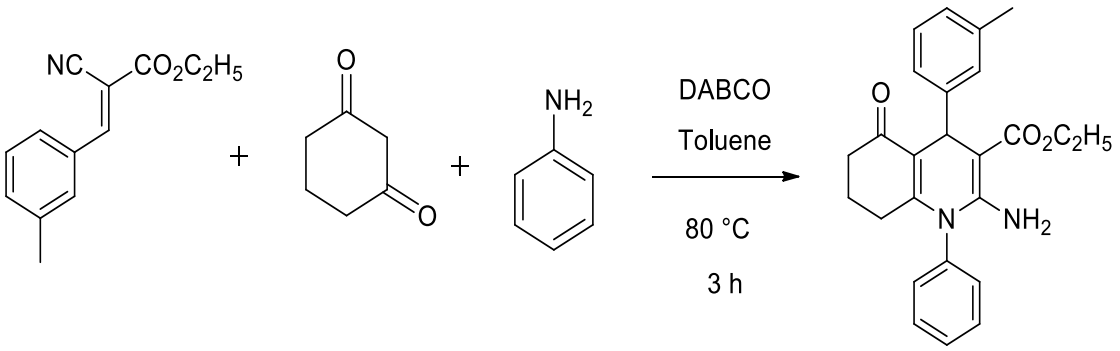


I L, 75% (2h)

Figure: 9 Synthesized cyanoacrylate derivatives with reaction time and yield

Synthesis of Polyhydroquinoline Derivative

The three component reaction of cyanoacrylate (73K) (1 eq.), 1,3-cyclohexanedione (74) (1 eq.) and aniline (75) (1 eq.) was attempted in toluene as a solvent and DABCO as a base. (Scheme 13).The reaction was continued for 3 hours at 80 °C and after TLC indicated the product formation along with two other minor spot. The solvent was evaporated and crude reaction mixture was purified by column chromatography using 6:4 hexane : ethyl acetate as eluent. The structure of isolated product was confirmed by spectral analysis using NMR and mass spectroscopy.



Scheme 3. Synthesis of Polyhydroquinoline.

In ^{1}H NMR, the singlet appeared at δ 6.66 ppm for -$NH_2$and other characteristic peak of –CH_2 appeared between δ 3.00 ppm to δ 1.50 ppm. The mass spectra confirmed the molecular mass of product. Although the expected product was obtained during the reaction but yield of product was found low. Therefore optimization of reaction condition was required. In order to find optimal reaction conditions, the reaction was performed using different solvents. The effect of solvent on the reaction is shown in Table 3. As evident from the table, most of the organic solvents provided product with lower yield and higher reaction time at 80 °C. The elevation of reaction temperature with organic solvents didn't provide significant enhancement of product yield.

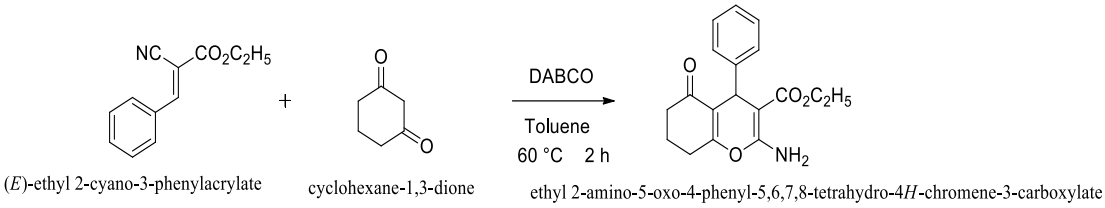
Table 3. Solvent Impact in compounds yields

S. No.	Solvent	Time (h)	Base	Yield*
1	Toluene	3	DABCO	80%
2	Acetonitrile	2	DABCO	-
3	DCE	3	DABCO	40%
4	Ethanol	3	DABCO	-
5	THF	3	DABCO	70%

Unexpected formation of polyfunctionalized 4H-chromene derivatives

During the course of optimization of reaction, we also attempted two component reaction of cyanoacrylate with 1,3 cyclohexanedione in toluene as a solvent and DABCO as a base. Accordingly, the reaction of cyanoacrylate (1 eq.) and dione (1 eq.) was attempted using DABCO as a catalyst and toluene as reaction media (Scheme 4) which provided a single

product. after 2h of reaction at 60 °C. The reaction mixture was purified by column chromatography using 6:4 hexane : ethyl acetate as an eluent. After structural characterization with 1H NMR and Mass spectral analysis, the structure of isolated product was confirmed as 4H-chromene derivatives.

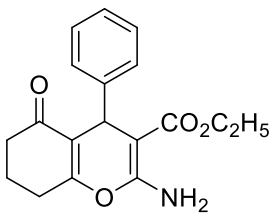


Scheme 4 Synthesis of polyfunctionalized 4H-chromene

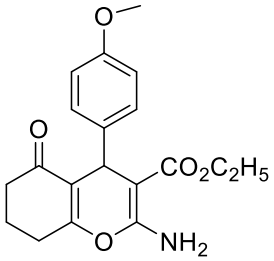
Isolated product structure elucidated by characteristic peak in ^{1}H NMR at δ 7.52 ppm of NH_2 and at δ 4.53 ppm of alicyclic proton. Even when three component reaction was attempted, it provided the 4H-chromene derivative as major product.

Since the chromene derivatives have also been demonstrated with wide range of pharmaceutical activities, we decided to adopt the protocol to make a series of 4H-chromene derivatives. While going through literature, we found that the two component reaction leading to 4H-chromene derivatives have not been widely explored. The most common method for synthesis of chromene derivatives are three component reaction of cyclohexane dione, aromatic aldehyde and ethyl acyanoacetate. However, three component reaction suffers with several limitation like longer reaction hours, formation of several side products etc.

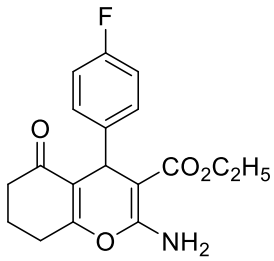
The two component protocol for synthesis of 4H-chromene derivative is found better protocol as it provide better yield of products with shorter reaction time. This protocol was found wide applicable to a broad range of substrate as various acrylate and substituted 1,3 cyclohexanedione provided good to excellent yields of products. The reaction time and yield of synthesized derivatives are are shown below. In order to diversifying the reaction scope, substituted acrylateand different dione were used to synthesized various type of chromene. We found very good yield (60-80%) with various type of benzaldehyde. Chromene has been synthesized shown in figure 3with their respective yield.



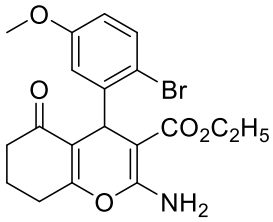
77, 70%



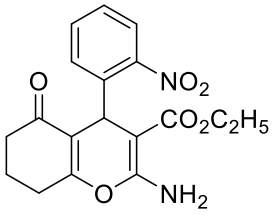
77 (a), 60%



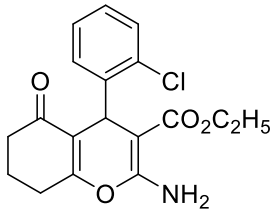
77(b) 80%



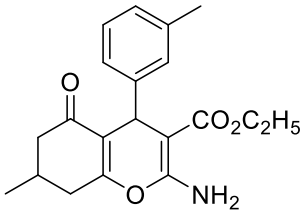
77(c),66%



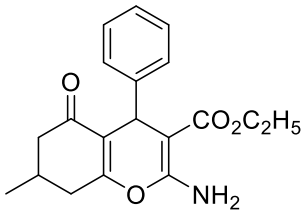
77(d), 58%



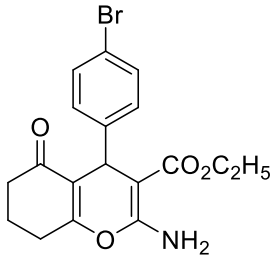
77(e),75%



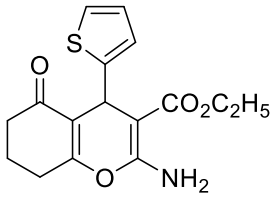
77(f), 70%



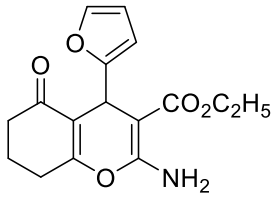
77(g),72%



77(h),74%



77(i), 76%



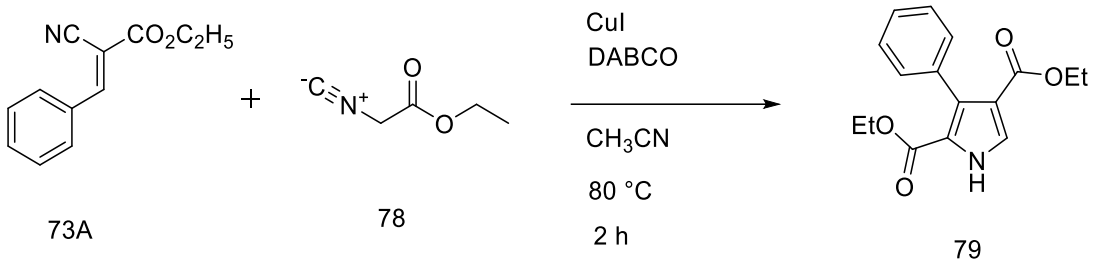
77(j), 80%

Figure:10 Synthesized chromene derivatives with their yield

Pyrrole introduction

The synthesis of trisubstituted pyrrole derivative was planned by reaction of cyanoacrylate and ethyl isocyanoacetate using CuI and DABCO as catalyst and CH_3CN as solvent. The reaction provided a polar product on TLC which was purified by column chromatography. The

structure of product was confirmed by spectral analysis using mass and NMR. The structure of product was confirmed by spectral analysis with mass and NMR. The singlet at δ 9.71 ppm for one protons assigned for the protons of –NH. The singlet at proton



Scheme4. Synthesis of tri-substituted pyrrole

3. General remarks

Commercially available Benzaldehyde, Dimedone, Aniline, Ethyl isocyanoacetate, Copper Iodide and Ethyl cyanoacetate from Sigma Aldrich, Spectrochem, TCI chemicals were used. The progress of reactions was monitored by thin layer chromatography (TLC). 1D and 2D NMR spectra were recorded in MeOH-d_4/DMSO-d_6 at 300/400 MHz for ^{1}H and 75/100 MHz for ^{13}C. Chemical shifts were reported in δ (ppm) relative to DMSO-d_6 as internal standards. Integrals are in accordance with assignments, coupling constants are given in Hz. The HRMS was recorded on a JOEL-AccuTOF JMS-T100LC Mass spectrometer having a DART source. Yields refer to quantities obtained after column chromatography.

General experimental procedure

Synthesis of ethyl 3-(2-chloro-6-fluorophenyl)-2-cyanoacrylate (3)

A mixture of benzaldehyde (1) (1.0 g, 9.4 mmol) and ethyl cyanoacetate (2) (1.30g, 11.28 mmol) was stirred in 10 mL of water at room temperature for 1-2 hours. After the TLC indicated the consumption of benzaldehyde (1), the reaction mixture was filtered off. The residue organic layer was dried under high vacuum to provide acrylate (3) (0.9 g, 90%) as white solid.

1. Synthesis of Polyhydroquinoline Derivative

A mixture of ethyl 2-amino-5-oxo-1-phenyl-4-(m-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3 carboxylate (7) (500 mg, 2.32 mmol), 1,3-cyclohexanedione (6) (260 mg, 2.32 mmol) and aniline (216 mg, 2.32 mmol) were stirred at 80 °C for 3 hours. After TLC indicated the consumption of acrylate (6) the reaction mixture was extracted with ethyl acetate several times. The combined organic layer was dried over sodium sulphate and evaporated to give crude reaction mixture. The crude reaction mixture was purified for using silica gel column chromatography by using EA: hexane (4:6) as an eluent to provide desired product 7 as white solid in 72% yield.

2. Synthesis of polyfunctionalized 4H-chromene derivatives

A mixture of ethyl 2-cyano-3-phenylacrylate (500 mg, 2.48 mmol),and 1,3-

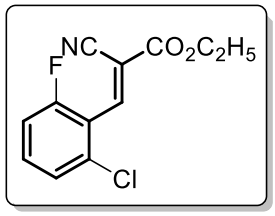
cyclohexanedione(278.08 mg, 2.48 mmol), was stirred at 60 °C for 2 hours. . After TLC indicated the consumption of acrylate (8) the reaction mixture was extracted with ethyl acetate several times. The combined organic layer was dried over sodium sulphate and evaporated to give crude reaction mixture. The crude reaction mixture was purified for using silica gel column chromatography by using EA: hexane (3:7) as an eluent to provide desired product 10 as solid in 70% yield.

3. Synthesis of trisubstituted pyrrole

A mixture of ethyl 2-cyano-3-phenylacrylate (300 mg, 1.49 mmol),and ethyl isocyanoacetate (200.29 mg,1.77mmol) using CuI and DABCO as catalyst and CH_3CN as solvent at 80 °C for 2 hours. TLC indicated consumption of acrylate and a more polar product which was purified by column chromatography using ethyl acetate and hexane (2:8) as an eluent to provide desired product 13 as solid in 70% yield.

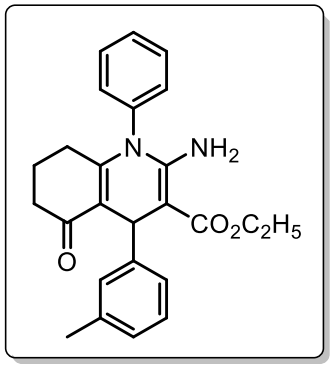
Characterization Data of Compounds

1. Ethyl 3-(2-chloro-6-fluorophenyl)-2-cyanoacrylate (73b)

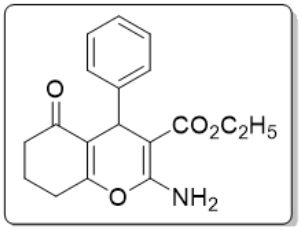


M.p.120-125 ºC; 90% as white solid; ^{1}H NMR (300 MHz, DMSO) δ 8.34 (s, 1H), 7.65 (td, J = 8.1, 6.0 Hz, 1H), 7.56 – 7.44 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 160.80, 160.26, 157.43, 147.46, 133.97, 133.84, 133.76, 126.03, 125.98, 119.81, 119.58, 115.58, 115.29, 113.61, 112.23, 112.20, 62.92, 13.8313.83; HRMS (ESI) m/z for $C_{12}H_9ClFNO_2$ [M + H] +, calcd., 254.038410, found, 254.0376.

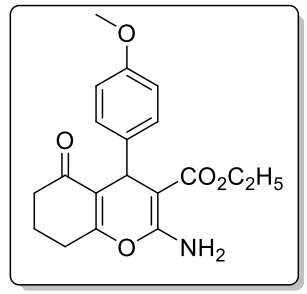
2. Ethyl 2-amino-5-oxo-1-phenyl-4-(m-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3 carboxylate (76) M.p.460-470 ºC; ^{1}H NMR (300 MHz, DMSO) δ 7.63 – 7.56 (m, 3H), 7.41 (d, J = 6.4 Hz, 2H), 7.11 (t, J = 5.3 Hz, 3H), 6.91 (d, J = 7.0 Hz, 1H), 6.67 (s, 2H), 4.96 (s, 1H), 3.99 (q, J = 7.1 Hz, 2H), 2.28 (s, 3H), 2.19 (dd, J = 10.5, 4.8 Hz, 2H), 1.83 (dd, J = 12.1, 5.3 Hz, 2H), 1.69 – 1.20 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 195.01, 168.80, 152.48, 151.78, 148.20, 136.45, 136.24, 130.15, 129.92, 129.61, 127.99, 127.80, 126.11, 124.17, 115.16, 79.29, 58.32, 36.12, 33.17, 27.67, 21.22, 20.60, 14.41; HRMS (ESI) m/z for $C_{25}H_{26}N_2O_3$ [M + H] +, calcd., 403.202168, found, 403.2031.



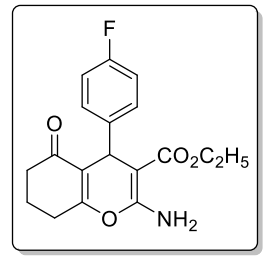
3. Ethyl 2-amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (77) M.p.340-345 ºC; ^{1}H NMR (300 MHz, DMSO) δ 7.52 (s, 2H), 7.23 – 7.06 (m, 5H), 4.53 (s, 1H), 3.95 (q, J = 7.0 Hz, 2H), 2.61 (t, J = 6.6 Hz, 2H), 2.35 – 2.18 (m, 2H), 2.01 – 1.78 (m, 2H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 195.98, 167.96, 163.95, 159.16, 146.54, 127.69, 127.63, 125.73, 116.78, 77.84, 58.71, 36.29, 33.14, 26.28, 19.86, 14.18; HRMS (ESI) m/z for $C_{18}H_{19}NO_4$ [M + H] +, calcd., 313.1 314, found, 314.1400.



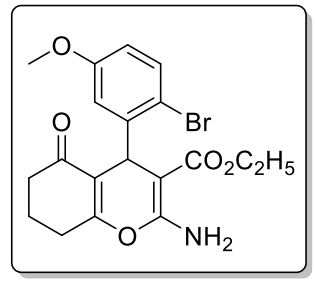
4. Ethyl 2-amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (77a) ^{1}H NMR (300 MHz, DMSO) δ 7.48 (s, 2H), 7.05 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 4.48 (s, 1H), 3.95 (qd, J = 7.0, 2.0 Hz, 2H), 3.68 (s, 3H), 2.60 (t, J = 5.5 Hz, 2H), 2.32 – 2.20 (m, 2H), 1.94 (dd, J = 15.8, 7.8 Hz, 2H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 196.01, 168.02, 163.68, 159.09, 157.32, 138.68, 128.52, 117.01, 113.10, 78.08, 58.70, 54.87, 36.32, 32.21, 26.27, 19.88, 14.22; HRMS (ESI) m/z for $C_{19}H_{21}NO_5$ [M + H] +, calcd., 343.1420, found, 344.1506.



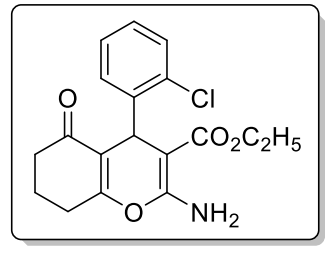
5. Ethyl 2-amino-4-(4-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3 carboxylate(77b) ^{1}H NMR (300 MHz, DMSO) δ 7.54 (s, 2H), 7.16 (dd, J = 7.7, 4.5 Hz, 2H), 7.01 (t, J = 8.9 Hz, 2H), 4.52 (s, 1H), 3.95 (q, J = 7.1 Hz, 2H), 2.61 (t, J = 5.7 Hz, 2H), 2.27 (dd, J = 14.9, 9.4 Hz, 2H), 2.00 – 1.81 (m, 2H), 1.07 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 196.06, 167.89, 164.00, 159.12, 142.71, 129.45, 129.34, 116.55, 114.49, 114.21, 77.61, 58.76, 36.28, 32.61, 26.30, 19.85, 14.20; HRMS (ESI) m/z for $C_{18}H_{18}FNO_4$ [M + H] +, calcd., 331.1220, found, 332.1307



6. Ethyl 2-amino-4-(2-bromo-5-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate(77c) ^{1}H NMR (300 MHz, DMSO) δ 7.62 (s, 2H), 7.31 (dd, J = 8.3, 0.6 Hz, 1H), 6.67 (dd, J = 11.6, 3.2 Hz, 2H), 4.75 (s, 1H), 3.97 – 3.88 (m, 2H), 3.69 (s, 3H), 2.59 (t, J = 6.0 Hz, 2H), 2.29 – 2.14 (m, 2H), 1.97 – 1.77 (m, 2H), 1.04 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 195.66, 168.12, 163.99, 159.11, 158.07, 145.56, 133.10, 118.19, 113.75, 112.78, 76.59, 58.65, 55.13, 36.44, 34.58, 26.40, 19.83, 14.29; HRMS (ESI) m/z for $C_{19}H_{20}BrNO_5$ [M + 2H] +, calcd., 422.0603, found, 424.0597.



7. Ethyl 2-amino-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (77e) ^{1}H NMR (300 MHz, DMSO) δ 7.66 (s, 2H), 7.19 – 7.09 (m, 2H), 7.07 – 6.99 (m, 1H), 5.07 (s, 1H), 3.94 – 3.85 (m, 2H), 2.55 (t, J = 5.5 Hz, 2H), 2.29 – 2.20 (m, 2H), 1.94 (dd, J = 12.4, 6.3 Hz, 2H), 0.99 (t, J = 7.1 Hz, 3H); 13C NMR (75 MHz, DMSO) δ 195.85, 168.05, 164.83, 159.71, 58.63, 36.41, 26.22, 19.94, 13.80.



4. Conclusion:

In summary, Towards accomplishment of new polyhydro 4H-chromene derivatives, the intermediate compounds i.e. cyanoacrylate derivative were synthesized by using benzaldehyde and ethyl cyan acetate in presence of a base as the key step. The developed strategy may prove beneficial to produce several new scaffolds. Importantly, the final target molecules bear different halogen containing aromatics at 4th position can have advantages to show good structural activity relationships. The structural modification of different position in chromene nucleus can alter different therapeutic activities. The synthesized compound could be further

used to accomplish the designed prototype for biological evaluation. The chromene ring is an important pharmacophore in modern drug discovery. Earlier it has proved that substituted chromene which interact easily with the receptors and possess different pharmacological activities with lower toxicity. The synthesized deisgn molecule may show more potent biological activity.

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