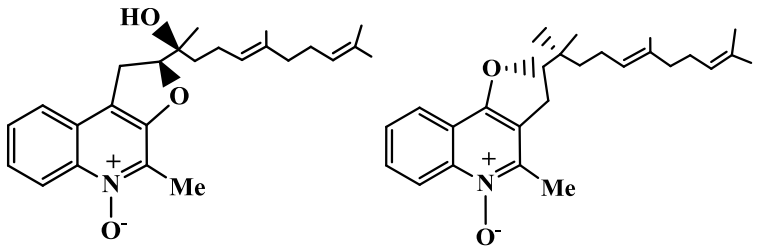
Objective and scope

Heterocyclic compounds possess anti-microbial [1-5], anticancer[6-8], antitubercular[9], anti-inflammatory, analgesic[10] and antimalarial [11] activities.

Due to the wide spread, pharmacological importance of heterocyclic compounds, the thirst to explore or to design newer heterocycles with enhanced properties of their mimic compounds are always need of the hour.

Apart from their pharmacological values, quinoline compounds also possess fluorescence and quenching behaviour[12], which might make quinoline fused compounds as good chemo sensors[13-15], bio sensors and OLED materials.

Evidently all the natural products are good examples of nature's preference for heterocycles such as the angular fused furo quinoline aurachin A (**1)** and aurachin H (**2**) are isolated from *Stigmatella aurantiaca*[16] and *Stigmatella erecta*[17]strain respectively.



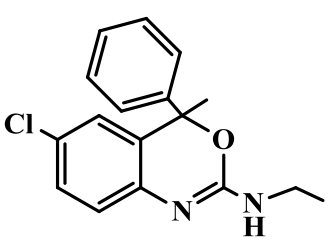
aurachin A **aurachin H**

1 **2**

Etifoxine (**3)** exhibits neuroprotective, neuroregenerative[18] and anticonvulsant activities[19].

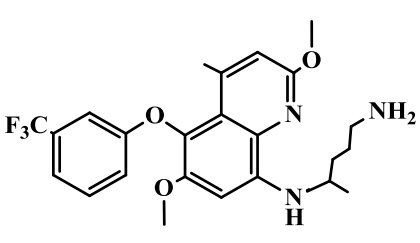
Tafenoquine (**4)**, Praziquantel (**5**), Drataverine (**6)**, Clioquinol (**7)** and Imiquimod (**8)** are the major drugs containing quinoline moiety are available in the market. Among which Tafenoquine (**4)**, Praziquantel (**5)** and Drataverine (**6)** behaves as an antimalarial drug [20-22], antischistosomal [23]and antimigraine drugs[24]respectively.

Clioquinol (**7)** is used for the treatment of neurological disorder and inflammation[25]. Imiquimod (**8)** an imidazo fused quinoline is an effective drug for lentigo maligma[26], cervical cancer[27], Bowen's disease[28] and tumor[29].



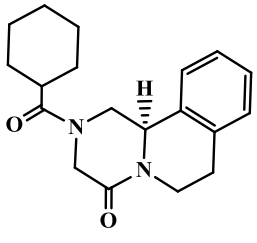
Etifoxine

3



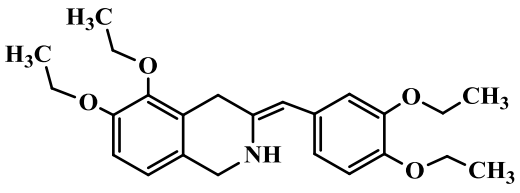
Tafenoquine

4



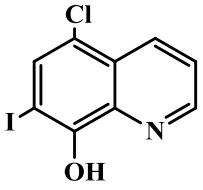
Praziquantel

5



Drataverine

6



Clioquinol

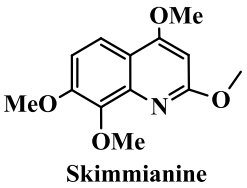
7

Imiquimod

8

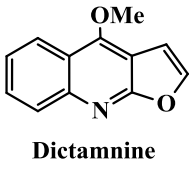
Alkaloids viz γ-fagarine, Platydesminium, Evoxime, Kokusaginine isolated from various sources contains furo quinoline skeleton[30] are evaluated for their anti-proliferative and anticancer activities[31].

The linear fused furo quinolines Skimmanine (**9)** Dictamnine (**10)** Dubinidine (**11),** (+)-balfourodine (**12),** Choisyine (**13)** and (+)-Isoplatydesmine (**14)** are found in natural products[32], among these alkaloids **9**, **10** and **11** are used as anti-inflammatory, antibacterial, antihypertensive, antipyretic and anticonvulsant activities[33,34].



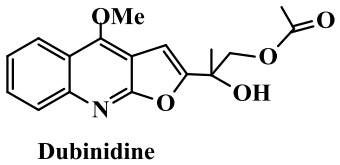
Skimmianine

9



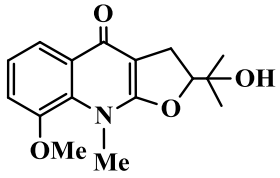
Dictamnine

10



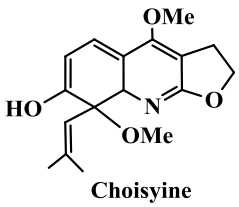
Dubinidine

11



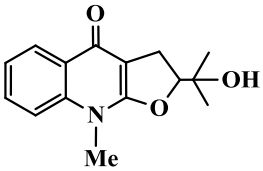
(+)- balfourodine

12



Choisyine

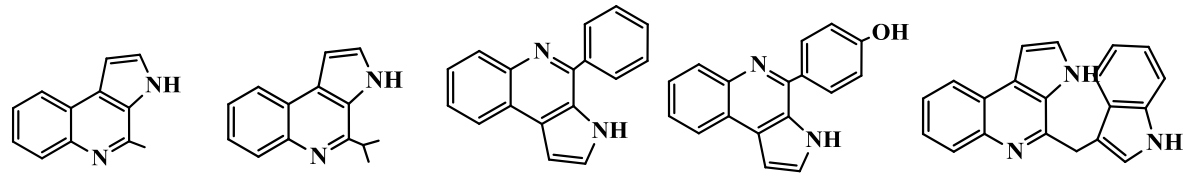
13



(+)- Isoplatydesmine

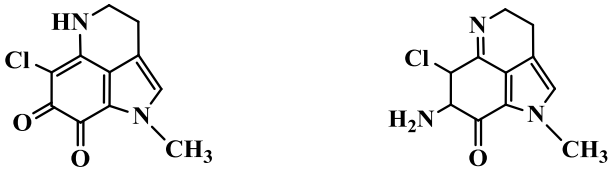
14

Pyrrolo[2,3-*b*] and [3,2-*c*] quinolines are known as good synthons for many biologically important substituted quinolines and few of their natural counter parts are Marinoquinoline[35,36] derivatives (A-E) (**15-19**) respectively.



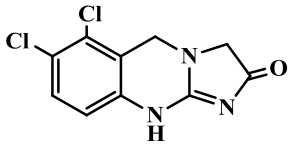
Marinoquinoline A **15** **Marinoquinoline B** **16** **Marinoquinoline C** **17** **Marinoquinoline D** **18** **Marinoquinoline E** **19**

Batzelline C (**20)** and isobatzellineC (**21)** which was isolated from the marine sponge *Batzella sp*[37,38] revealed effective inhibition against HIV-1 and cancer cell topoisomerase II[39].



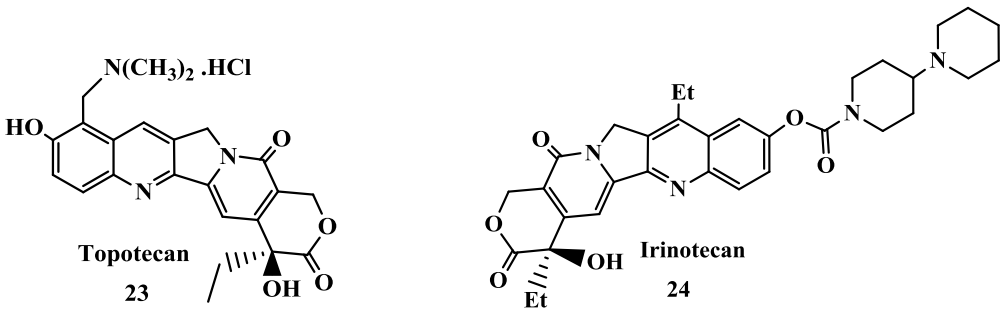
Batzelline C **20** **Isobatzelline C** **21**

Anagrelide (**22)** drug involved in the treatment of Cardiovascular adverse events[40]and used in chronic stress, inflammation[41-43].



Anagrelide **22**

Topotecan (**23)** and Irinotecan (**24)** have similar backbone structure to pyrrolo[3,4-b]quinoline scaffold which is noted as anticancer alkaloid[44].



Topotecan **23** **Irinotecan** **24**

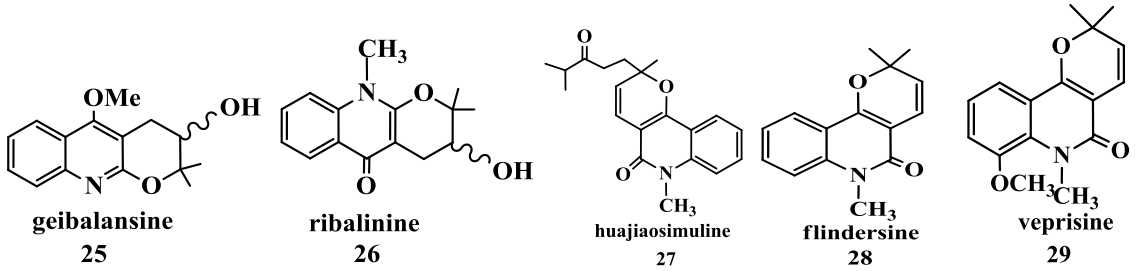
Naturally occurring [2,3-*b*] and [3,2-*c*] pyrrolo quinoline moieties are found to possess the substituted pyrrolo [2,3-*b*] and [3,2-*c*] fused quinoline moieties in their structure. Fused pyrrolo quinoline are found to be active against bacteria, fungi[45] and cancer cell of human breast cancer cell T47D, and also acts as potential chemotherapeutic agent[46] and Caspase-3 Inhibitors[47].

Thieno quinolines[48,49] are good Mer inhibitors[50] also they possess antiproliferative, antitumor activity.

Benzothieno[3,2-*b*] and[2,3-*c*] quinolines were studied for their interaction with salmon sperm DNA on 1HQ7 & 1DXA[51] by docking studies and spectroscopic methods.

Thieno[3,2-*c*]quinolines behaves as an electron accepting material which helps to organize polymer solar cell[52].

Pyrano quinoline and their derivatives possess essential role in the field of medicinal chemistry due to their special place as building blocks in natural products such as Geibalansine (**25)**, Ribalinine (**26)**[53], Huajiaosimuline (**27)**, Flindersine (**28)**, Veprisine (**29)**[54].



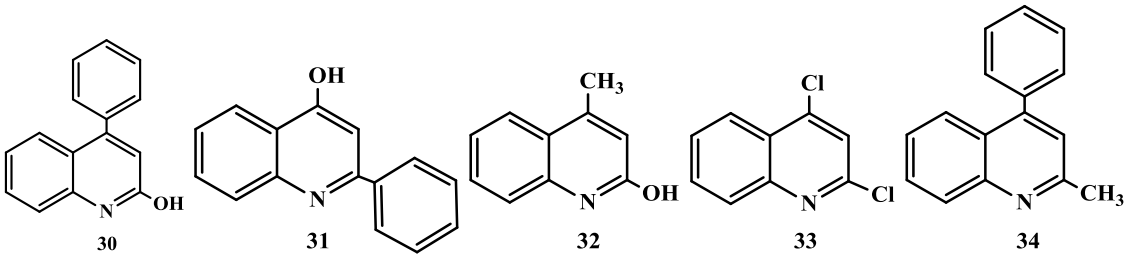
Among them, Geibalansine, Ribalinine are linear fused pyrano quinolines whereas Flindersine, Huajiaosimuline and Veprisine are angular fused pyrano quinolines.

Pyrano quinolines display a broad range of biological activities such as anticoagulant[55], coronary constructing[56], antitumor[57], anticancer[58]and antimicrobial activities[59, 60].

The above said, biological and pharmacological importance of quinoline fused linear and angular heterocycles containing oxygen, nitrogen and sulphur atoms viz furo, pyrrolo, thieno and pyrano quinolines intended as to focus our interest towards the synthesis of novel linear and angularly fused quinoline heterocycles namely 4-phenylfuro[2,3-*b*]quinolin-2 (3*H*)-one **35,** 4-phenylfuro[3,2-*c*]quinolin-2 (3*H*)-one (**36)**,

3-hydroxy-4-phenylfuro[2,3-*b*]quinoline(**37),** 3-hydroxy-4-phenylfuro[3,2-*c*]quinoline(**38**), 3-hydroxy-4-methyl-pyrrolo[2,3-*b*]quinoline(**39**), 3-hydroxy-4-phenyl-pyrrolo[2,3-*b*] quinolone(**40),** 3-hydroxy-4-phenyl-pyrrolo[3,2-*c*]quinoline(**41**), 4-methylthieno[2,3-*b*] quinoline-3 (2*H*)-one(**42**), 4-phenyl thieno[2,3-*b*]quinoline-3 (2*H*)-one(**43**), 4-phenylthieno [3,2-*c*]quinoline-3 (2*H*)-one(**44**), 4-hydroxy thieno[3,2-*c*]quinoline-3 (2*H*)-one (**45**), 5-hydroxypyrano[4,3-*c*]quinoline-1,3 (4*H*)-dione(**46**), 5-phenylpyrano[3,4-*b*] quinoline-1,3 (4*H*)-dione(**47**).

Precursors being the prior moiety to design the expected synthesis, we thought of synthesising the various precursors for our studies mainly 2-hydroxy-4-phenyl quinoline(**30),** 4-hydroxy-2-phenyl quinoline(**31)**, 2-hydroxy-4-methyl quinoline(**32),** 2,4-dichloro quinoline(**33**), 2-methyl-4-phneyl quinoline(**34**).

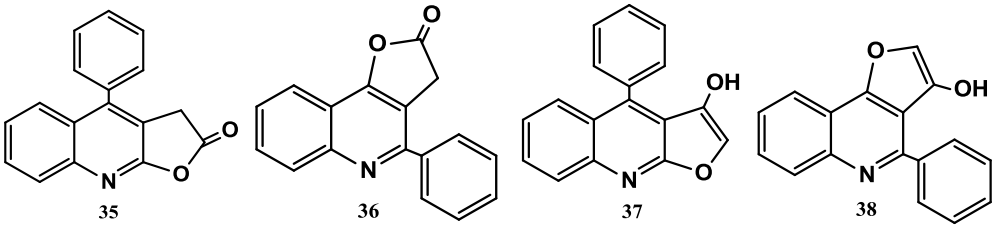


Chapter I deals with the synthesis of linear and angular furo quinolines from 2-hydroxy-4-phenylquinoline(**30**) and 4-hydroxy-2-phenyl quinoline(**31**) respectively. The second part of the synthesis describes linear and angular 3-hydroxy furo quinolines.

The precursors being 2-hydroxy-4-phenyl quinoline(**30)** and 4-hydroxy-2-phenylquinoline(**31)** for the synthesis of linear and angular furo quinolines are obtained from the cyclisation of benzoyl acetanilide(**117**) with H_2SO_4 and PPA respectively to achieve 2-hydroxy-4-phenyl quinoline(**30)** and 4-hydroxy-2-phenylquinoline(**31)**.

The synthesis of 4-phenylfuro[2,3-*b*]quinolin-2(3*H*)-one(**35)** was obtained from the potential precursor 2-hydroxy-4-phenyl quinoline(**30)**.

Accordingly, oxidative cyclisation of 2-hydroxy-4-phenyl quinoline(**30)** with chloro acetyl chloride in one pot results in the formation of furo quinolin-2-ones(**35)**.



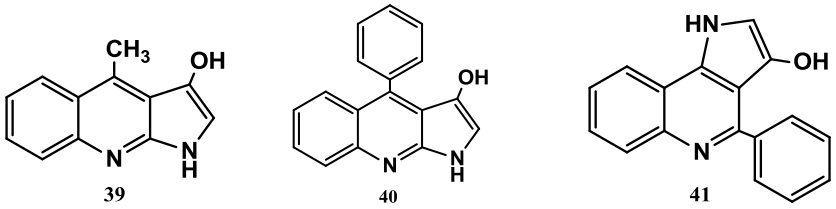
Similarly, 4-phenylfuro[3,2-*c*]quinolin-2(3*H*)-one(**36)** was obtained from the precursor 4-hydroxy-2-phenylquinoline(**31)**.

Followed by the synthesis of furo quinoline-2-ones, we have embraced the synthesis of linear and angular furo quinolin-3-ols.

3-hydroxy-4-phenylfuro[2,3-*b*]quinoline(**37)** and 3-hydroxy-4-phenylfuro[3,2-*c*] quinoline(**38)** was obtained by the cyclisation of 4-phenyl-quinolin-2-oxo carboxy ester and 2-phenyl-quinolin-4-oxo carboxy ester with Dowtherm A.

After achieving, the furo quinolines, we made an attempt to synthesise Pyrrolo quinolines.

Chapter II describes the synthesis of linear and angular 3-hydroxy-pyrrolo quinolines.



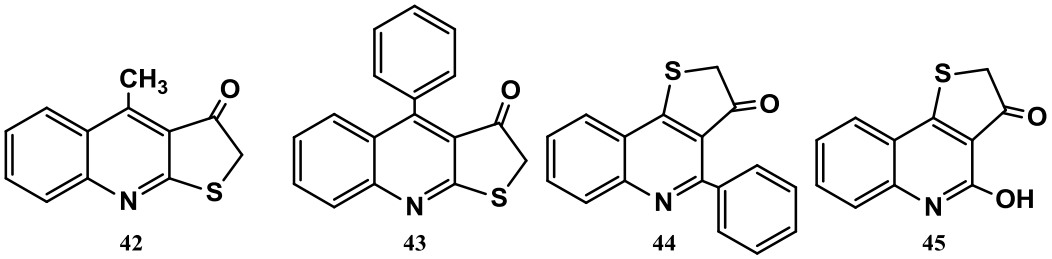
The linear 3-hydroxy-4-methyl-pyrrolo[2,3-*b*]quinoline(**39)**, 3-hydroxy-4-phenyl-pyrrolo[2,3-*b*]quinoline(**40)** are synthesised from the potential precursors 2-hydroxy-4-methyl quinoline(**32)** and 2-hydroxy-4-phenylquinoline(**30)** respectively via their intermediates 4-methyl-quinolin-2-amino carboxy ethyl ester and 4-phenyl-quinolin-2-amino carboxy ethyl ester.

Further we stepped towards the synthesis of angular pyrrolo quinoline viz 3-hydroxy-4-phenyl-pyrrolo[3,2-*c*]quinoline(**41)** which was obtained by the cyclisation of 2-phenylquinolin-4-amino carboxy ester.

From the above said biological importance of thieno quinolines, we felt that it was worthwhile to develop some newer strategies for the synthesis of linear and angular fused thieno quinline-3-ones **42**, **43, 44** and **45** from the starting compounds **32**, **30**, **31**, **33** respectively.

Hence, **Chapter III** envisages the synthetic strategy of novel linear and angular thieno quinolin-3-ones.

4-methylthieno[2,3-*b*]quinolin-3(2*H*)-one(**42)**, 4-phenylthieno[2,3-*b*]quinolin-3(2*H*)-one(**43)** was achieved by the reaction of potential precursors 2-hydoxy-4-methylquinoline(**32)** and 2-hydoxy-4-phenylquinoline(**30)** with thioglycolic acid via their chloro compounds respectively.



The linear and angular 4-phenylthieno[2,3-*b*]quinolin-3(2*H*)-one(**43**), 4-phenyl thieno[3,2-*c*]quinolin-3(2*H*)-one(**44)** was synthesised from 4-phenylquinolin-2-thioacetic acid and 2-phenylquinolin-4-thioacetic acid as an intermediate which inturn cyclised with PPA.

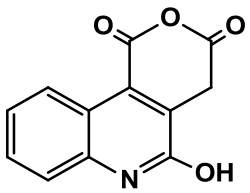
4-chloro-2-hydroxyquinoline was obtained by the selective hydrolysis of the potential precursor, 2,4-dichloroquinoline(**33)**. The dehydrohalogenation of 2-hydroxyquinolin-4-thio acetyl chloride issued 4-hydroxythieno[3,2-*c*]quinolin-3(2*H*)-one(**45)**.

Being achieved various five membered heterocycles viz furo, Pyrrolo, thieno quinolines we extend our synthetic routes towards six membered fused quinolines.

The synthesis of various substituted linear and angular pyrano quinolines from 2-hydroxy-4-methylquinoline(**32)**, 2-methyl-4-phenylquinoline(**34**) via their intermediates 2-hydroxyquinolin-4-carboxy chloride(**273**) and 4-phenylquinolin-2-carboxy chloride(**275**).

Chapter IV includes the synthesis of various substituted novel angular pyrano quinolin-1,3-diones. The synthesis of [4,3-*c*]pyrano quinolines were developed from the

potential precursor 2-hydroxy-4-methyl quinoline(**32)**. The precursor, methyl substituted quinoline **32** is first converted into corresponding quinoline-4-carboxy chloride derivatives through quinoline-4-carboxylic acid.



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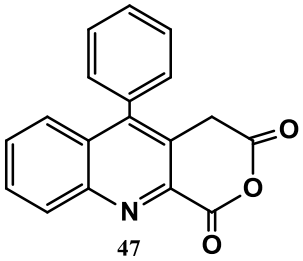

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The angular and linear pyrano quinoline 5-hydroxypyrano[4,3-*c*]quinolin-1,3(4*H*)-dione(**46)** and 5-phenylpyrano[3,4-*b*]quinolin-1,3(4*H*)-dione(**47)** are acquired from the cycloaddition of 4-hydroxyquinolin-4-carboxy chloride and 4-phenylquinolin-2-carboxy chloride.

The structure of all the intermediates and the hitherto novel linear and angular furo, pyrrolo, thieno, pyrano quinolines and their derivatives synthesised are confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral and analytical data.

As we have synthesised the pharmacologically important heterocycles, we are interested to know the biological and photophysical ability of our compounds. So that, the synthesised compounds might be an active probe as a drug, biomarker, biosensor, chemosensor and organic light emitting diodes in mere future.

Accordingly, **the chapter V** prescribes the *invitro*(antimicrobial, anti-oxidant) and *insilico* (DFT, molecular docking, molecular dynamic simulation) studies followed by the study on photophysical properties such as nonlinear optical activity, fluorescence and life time fluorescence thereby concluding the structure activity relationship of the synthesised compounds.

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