EXECUTIVE SUMMARY OF THE FINAL REPORT OF WORK DONE ON THE PROJECT (MRP)

Title of the Project : SYNTHETIC AND BIOLOGICAL STUDIES OF NAPHTHYRIDINE ALKALOID ANALOGUES AND FUSED NAPHTHYRIDINES.

Funding Agency : UNIVERSITY GRANTS COMMISSION, NEW DELHI

Name of Principal Investigator : Dr. S.P. Rajendran,
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Period of execution : 2007 to 2010

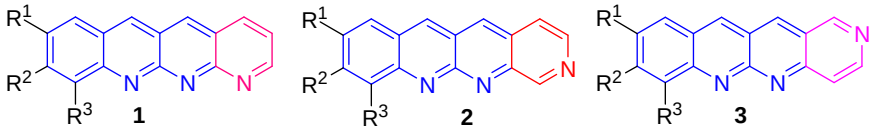
Objectives Achieved

- **We synthesized angular fused napthyridine 6-chloro dibenzo[c,f] [2,7] napthyridine from 3-substituted 4-hydroxyl quinolines as the base which was synthesized from cyclizing ethyl β anilino-α-carbethoxy acrylates.**
- **We carried out reactions of 2-oxo-quinolin-3-carboxylic acid chloride with various aminopyridines (2,3,4- amino pyridine) that yielded 3-(pyridyl) aminocarbonyl quinolin-2-(1H)ones. The formed 3-(pyridyl) aminocarbonyl quinolin-2-(1H)ones were cyclised to the targeted benzopyrido fused napthyridines by PPA.**
- **We achieved new hetero fused benzo napthyridine (benzo furo fused napthyridines)**
- **Then, we achieved linear benzo hetero fused napthyridines by the use of 2-chloro-3-formyl quinoline with 2-amino, 3-amino and 4-amino pyridines.**

- **We constructed 5-substituted linear benzo pyrido [1,8] napthyridines from the ideal precursor 2-iodo-quinolin-3-carboxylic acid which in turn was prepared from 2-chloro-3-formyl quinoline**
- **Then we synthesized the angular benzo hetero fused napthyridines, 1-hydroxy -5-methoxy benzo[f][2,7] napthyridine by using the same precursor 2-chloro-3-formyl quinoline in two ways**
- **Next, we constructed another angular fused benzo[2,6] naphthyridines from 2-hydroxy-4-formyl quinoline, which inturn was prepared from 4-methyl-2-hydroxy quinoline.**

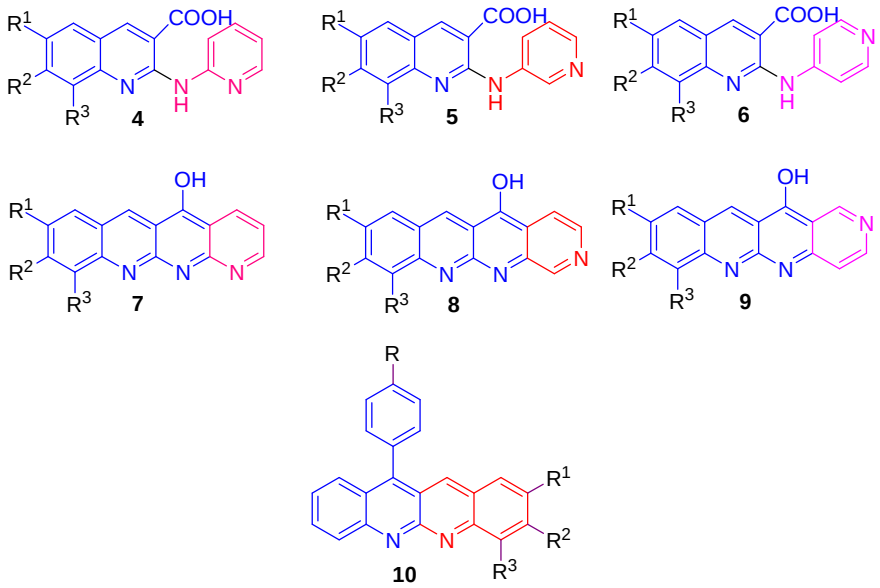
Selected schemes that are followed during the project and the compounds synthesized, biological activities done are mentioned below,

The one pot synthesis of various linear benzo pyrido fused naphthyridines (**1-3**) from substituted chloroquinoline aldehydes with various aminopyridines which include 2-amino, 3-amino, 4-amino pyridines.



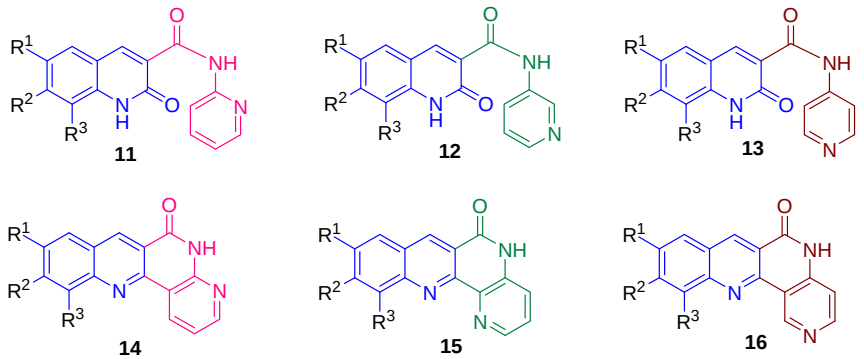
a) R^1 = H, R^2 = H, R^3 = H ; b) R^1 = CH_3, R^2 = H, R^3 = H ; c) R^1 = H, R^2 = CH_3, R^3 = H ; d) R^1 = H, R^2 = H, R^3 = CH_3 ; e) R^1 = OCH_3, R^2 = H, R^3 = H ; f) R^1 = H, R^2 = OCH_3, R^3 = H ; g) R^1 = H, R^2 =H, R^3 = OCH_3 ; h) R^1 = CH_3, R^2 = H, R^3 = CH_3;

Moreover, the synthesis of substituted linear benzo pyrido fused naphthyridines (**7-10**) and their derivatives through the intermediate 2-(*N*-aminopyrido)quinolin-3-carboxylic acids (**4-6**) using the same precursors.



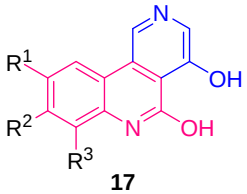
a) R^1 = H, R^2 = H, R^3 = H ; b) R^1 = CH_3, R^2 = H, R^3 = H ; c) R^1 = H, R^2 = CH_3, R^3 = H ; d) R^1 = H, R^2 = H, R^3 = CH_3 ; e) R^1 = OCH_3, R^2 = H, R^3 = H ; f) R^1 = H, R^2 = OCH_3, R^3 = H ; g) R^1 = H, R^2 =H, R^3 = OCH_3 ; h) R^1 = CH_3, R^2 = H, R^3 = CH_3;

The synthesis of angular benzo pyrido fused naphthyridines (**14-16**) using the precursor 2-chloro-3-formyl quinolines through the intermediates 3-(pyridyl)aminocarboxy quinolin-2[1*H*]ones (**11-13**).



a) R^1 = H, R^2 = H, R^3 = H ; b) R^1 = CH_3, R^2 = H, R^3 = H ; c) R^1 = H, R^2 = CH_3, R^3 = H ; d) R^1 = H, R^2 = H, R^3 = CH_3 ; e) R^1 = CH_3, R^2 = H, R^3 = CH_3; f) R^1 = OCH_3, R^2 = H, R^3 = H ; g) R^1 = H, R^2 = OCH_3, R^3 = H ; h) R^1 = H, R^2 = H, R^3 = OCH_3 ;

The synthesis of 4, 5-dichloro substituted benzo fused naphthyridines (**18**) from 4, 5-dihydroxy substituted benzo fused naphthyridines (**17**), which were synthesized from 2-hydroxy-4-formyl quinolines. We designed convenient synthesis of 4- aldehydes.



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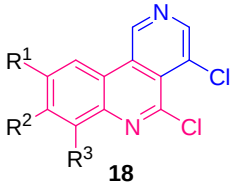

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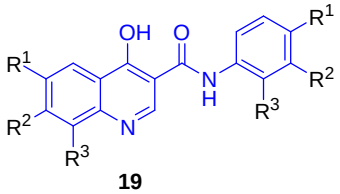
a) R^1 = H, R^2 = H, R^3 = H ; b) R^1 = CH_3, R^2 = H, R^3 = H ; c) R^1 = H, R^2 = CH_3, R^3 = H ; d) R^1 = H, R^2 = H, R^3 = CH_3 ; e) R^1 = CH_3, R^2 = H, R^3 = CH_3 ; f) R^1 = OCH_3, R^2 = H, R^3 = H ;g) R^1 = H, R^2 = OCH_3, R^3 = H ; h) R^1 = H, R^2 = H, R^3 = OCH_3 .

Synthesis of 6-hydroxy substituted dibenzo fused naphthyridines (**20**) by using *β*-anilino-*α*-(carbanilido) acrylates which were prepared by multicomponent method through the intermediate 3-carbanilido-4-hydroxy quinoline (**19**). Then, the 6-hydroxy substituted dibenzo fused naphthyridines (**20**) were converted to 6-chloro substituted dibenzo fused naphthyridines (**21**).



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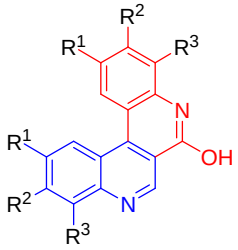

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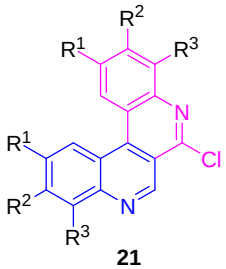

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a) R^1 = H, R^2 = H, R^3 = H ; b) R^1 = H, R^2 = H, R^3 = CH_3 ; c) R^1 = CH_3, R^2 = H, R^3 = H ; d) R^1 =CH_3, R^2 = H, R^3 = CH_3 ; e) R^1 =H, R^2 = H, R^3 = OCH_3; f) R^1 = OCH_3, R^2 = H, R^3 = H ;

2-amino-3-formyl quinolines were synthesized and they have been condensed with homophthalic acid to give benzopyrono fused naphthyridines

DNA binding, cleavage and anti cancer activities of the linear and angular fused naphthyridines. The *in vitro* cytotoxicity activities against the cancer cell line HeLa of linear and angular fused naphthyridine derivatives were compared

The anti bacterial and cytotoxic studies of typical samples have also been included.

Selected compounds viz., 6-hydroxy dibenzo[*c,f*][2,7]naphthyridines, 6-hydroxy 2,11- dimethyl dibenzo[*c,f*][2,7]naphthyridines, 6-hydroxy-2,4,9,11-tetramethyl dibenzo[*c,f*][2,7]naphthyridines, 3-(2,4-dimethyl carbanilido)-4-hydroxy-6,8-dimethyl quinoline, 3-carbanilido-4-hydroxy quinoline were screened for their *in vitro* growth inhibitory activity against pathogenic bacteria *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. It was found that the parent and methylated angular naphthyridines were generally active on increasing their concentrations.

The cytotoxicity of the compounds 6-chloro-4, 9-dimethyl dibenzo[*c,f*][2,7]naphthyridine , 6-chloro-2, 11-dimethyl dibenzo[*c,f*][2,7]naphthyridine , 6-chloro-4,9-dimethoxy dibenzo[*c, f*][2,7] naphthyridine compounds showed moderate toxicity against the cancer cell line HeLa.

In our next investigation, it was found that 10-substituted benzo[*b*]pyrido[2,3-*h*] [1,6] naphthyridine showed comparably high toxic against human cell line than all other derivatives.

Cytotoxic activities of the newly synthesised linear benzo pyrido[1,8]naphthyridines were studied.

Anti-proliferative analysis of the selected newly synthesised 9-Methyl derivatives of 1-hydroxy-5-methoxy/5-Chloro benzo[*f*] [2,7]napthyridine derivatives viz. 5-Chloro and 5-Methoxy derivatives were carried out in onion (Allium cepa) root tip cells and the effect of mutagens on eukaryotic nuclei can be assessed cytologically by observing the inhibition of cell growth or division. It was found that 5-Methoxy derivatives showed decreased mitotic index in low concentrations (40 and 50 µg/mL)*.

Summary of the findings

The project work was undertaken with a view to exploit newer and convenient synthetic methods of linear and angular benzo fused napthyridines. In addition, we also made an attempt towards the cytotoxic activities of newly synthesized linear and angular fused naphthyridines.

Angular benzo fused napthyridines wee synthesized from 3-pyridylaminocarbonyl quinolin-2(1H) ones by the treatment of insitu prepared 2-oxo-quinolin-3-carbonyl chlorides with various aminopyridines.

Linear benzo fused napthyridines wee synthesized from various substituted 2-chloro-3-formyl quinolines with various aminopyridines in DMF under nitrogen atmosphere in a single step in quantitative yield.

As per the objective of the project, we tried to prepare alkaloid analogues perlolidine and calycanine from the versatile precursors 2-chloro-3-formyl quinoline and 2-chloro-4-formyl quinoline. But in these parts we couldn't achieve dechlorination product after various methods.

List of publications

1) A.Murugesh and S.P.Rajendran,' Synthesis and biological evaluation of dibenzo angular fused napthyridines', *Biologically active Molecules*,96,364(2012)

2) A.Murugesh, A.Magesh Selvakumar and S.P.Rajendran,' Synthesis and cell line activity of angular benzo furo fused napthyridines, *International journal of applied biology and pharmaceutical technology*, 5,2 (2014)

3) A.Murugesh, M.Sangeetha and S.P.Rajendran,'Synthesis and antibacterial activity of pyrimido[5,4-c] quinolin-2,5-dione and their derivatives, *Der Chemica Sinica*,6,7 (2014)

4) A.Murugesh, K.Sampath Kumar and S.P.Rajendran,' A facile synthesis of 5-(4'-methoxy phenyl) dibenzo [b,g][1,8] napthyridines', *J.Het.Chem*,53,924 (2016)