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Review Article

Dihydropyridine: A Novel Pharmacophore

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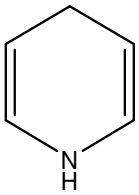
Dihydropyridine, a reduced form of pyridine with nitrogen element on first carbon, has been considered as a magic moiety (wonder nucleus) which posses almost all types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. Present article is sincere attempt to review chemistry, synthesis and applications of dihydropyridine.

Key words: *Dihydropyridine, pyridine, synthesis, pharmacological activity.*

Introduction

Dihydropyridine are the derivatives of pyridine which belong to an important group of heterocyclic compounds containing nitrogen in a six member ring.



A lot of research work on dihydropyridine has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. Numbers of methods for synthesis by using various agents are available in the references.

Chemistry of 1, 4-dihydropyridines: [1]

- Reduced form of pyridine
- Six member containing nitrogen
- Molecular formula : $C_5 H_7 N$
- Molecular Weight : 81
- Weaker base (pK_a 5.2)

Synthesis of Dihydropyridines: [2]

1. From 1, 5-dicarbonyl compounds and ammonia:

Ammonia reacts with 1, 5-dicarbonyl compounds to give 1, 4-dihdropyridines which are easily dehydrogenated to pyridines.

2. From an aldehyde, two equivalents of a 1, 3-dicarbonyl compound, and ammonia:

Symmetrical 1,4-dihydropyridines, which can be easily dehydrogenated, are produced from the interaction of ammonia, an aldehyde, and two equivalents of a 1, 3-dicarbonyl compound which must have a central methylene.

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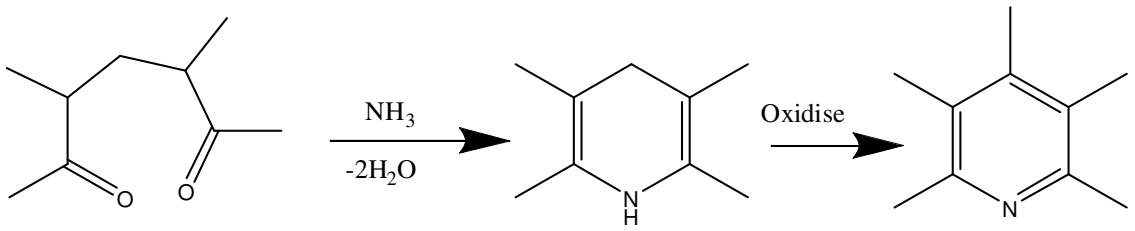

Fig. 1: From 1, 5-dicarbonyl compounds and ammonia

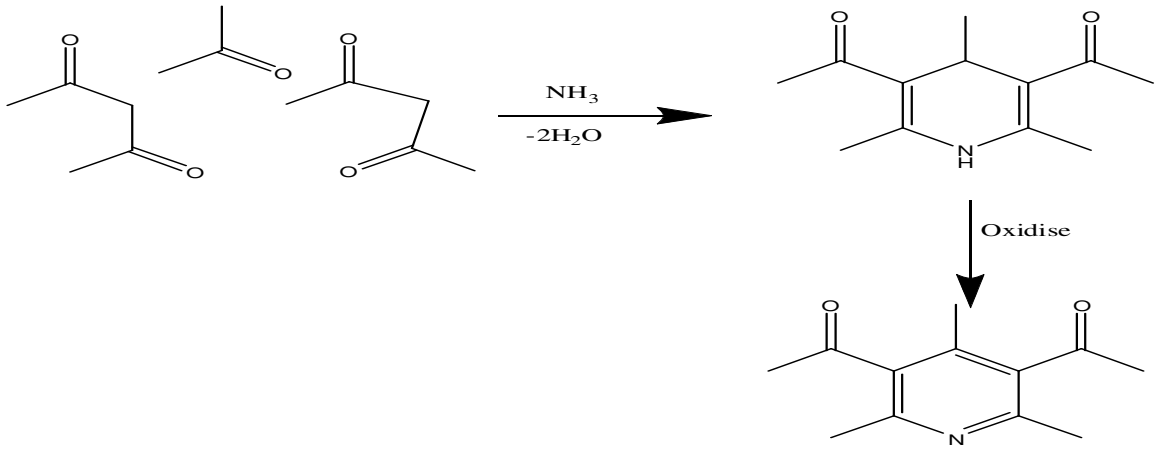

Fig.2 From an aldehyde, two equivalents of a 1, 3-dicarbonyl compound and ammonia

The Hantzsch synthesis:

The product from the classical Hantzsch synthesis is necessarily a symmetrically substituted 1, 4-dihydropyridine since two mol equivalents of the one dicarbonyl component are utilized, the aldehyde carbonyl carbon becoming the pyridine C-4. The sequence of intermediate steps would be aldol condensation followed by Michael addition generating, *in situ*, a 1, 5-dicarbonyl compound.[3, 4]

A number of improved methods have been reported in the literature for this condensation which involve the use of microwave, ionic liquids, reflux at high temperature, TMSI, I_2, $Yb(OTf)_3$, CAN, silica gel/$NaHSO_4$ and $Sc(OTf)_3$.[5]

3. **From 1, 3-dicarbonyl compounds and 3-amino-enones or nitriles:** [6]

Pyridines are formed from interaction between a 1, 3-dicarbonyl compound and 3-amino-enone and 3-aminoacrylate.

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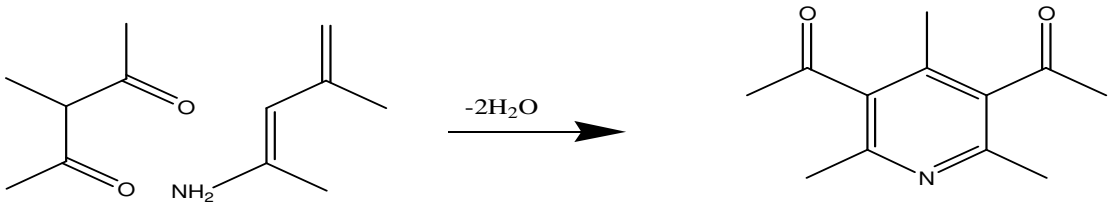
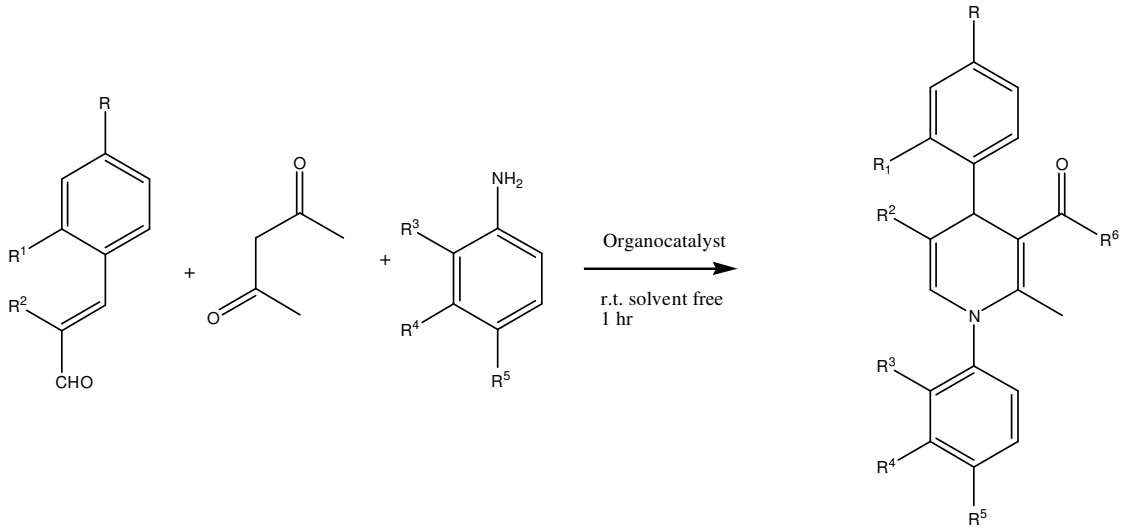
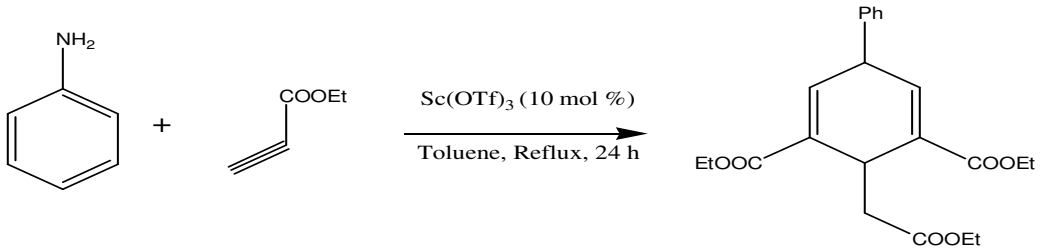


Fig. 3: From 1, 3-dicarbonyl compounds and 3-amino-enones or nitriles

4. Menendez et al. synthesized 5, 6-unsubstituted dihydro pyridines but even using inert/anhydrous conditions the products were isolated in moderate yields (61-74%). Similar multi-component reactions for the synthesis of substituted piperidines, dihydropyridones and tetrahydropyrans were also recently reported.[7]



4. A report on expeditious and useful method for the synthesis of N-substituted 1, 4-dihydropyridines in the presence of a catalytic amount of Sc (OTf) $_3$.[8]



Synthesis by Microwave: [9, 10, 11]

1. High speed microwave assisted chemistry has attracted a considerable amount of attention in recent years and has been applied successfully in various fields of synthetic organic chemistry including

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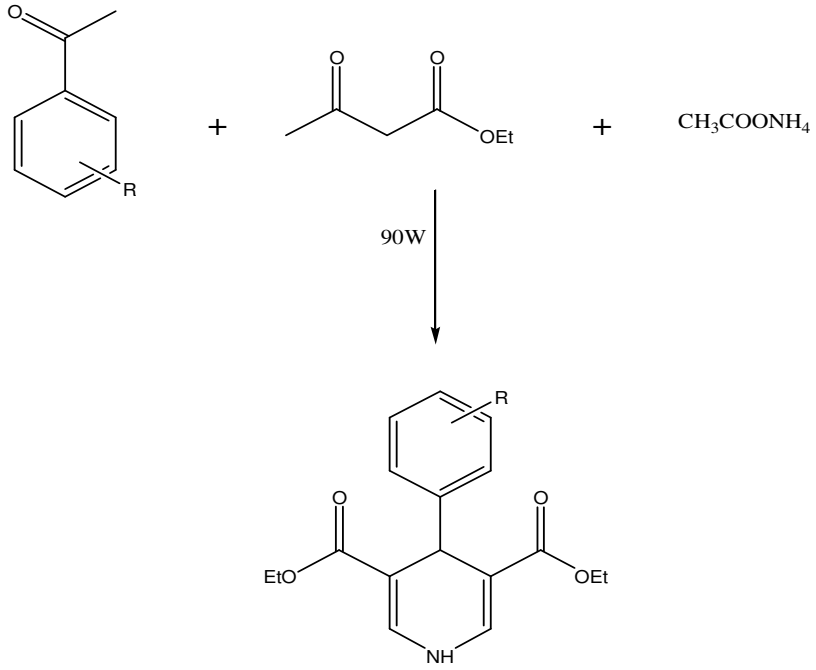
cycloaddition reactions, heterocyclic synthesis, the rapid preparation of radio labeled materials, transition metal catalyzed processes, solvent free reactions and phase transfer catalysis. In 1882 Hantzsch reported the first synthesized of 1, 4 DHP. The classical method for the synthesis of 1, 4 dihydropyridine is a one pot condensation of an aldehyde with ethyl acetoacetate, and ammonia either in acetic acid or refluxing in alcohol.



R = 3-Br C_6H_4, 3-NO_2 C_6H_4, 2-OMe C_6H_4, 3-Pyridil, 2-Furyl, 2-Thienyl,
Facile one pot synthesis of 1, 4 dihydropyridine

Biological Profile:

1, 4-Dihydropyridines are of considerable interest and are well-known compounds because of their pharmaceutical properties. In the human body, compounds are generally oxidized to their corresponding pyridine derivatives, which become biologically inactive. Chiral 1, 4-dihydropyridines have been employed as synthetic intermediates.[12]

A number of dihydropyridine calcium antagonists have been introduced as potential drugs for the treatment of angina pectoris, hypertension and other cardiovascular diseases like congestive heart failure.[13] Cerebrocrast (dihydropyridine derivative) has been introduced as a Neuroprotective agent. A number of dihydropyridine derivatives have been found as vasodilators,

antihypertensive, bronchodilators, antiatherosclerotic, hepatoprotective, antitumour, antimutagenic, geroprotective, antidiabetic, antiinflammatory and antiplatelet aggregation agents.[14]

The Dihydropyridine-pyridium redox reactions have primary role in metabolism with NAD and NADP coenzymes. The easily prepared Hantzsch esters (1, 4-dihydropyridine-3, 5-dicarboxylates) used as antioxidants in a variety of applications.[15]

Some other biological activities of 1, 4-Dihydropyridine derivatives also reported such as HIV protease inhibition, MDR reversal, radioprotection, These examples clearly indicate the remarkable potential of novel dihydropyridine derivatives as a source of valuable drug candidate. Due to the potential importance of 1, 4-dihydropyridyl compounds from a pharmaceutical, industrial and synthetic point of view, various methods for their preparation has been reported.[7]

Some of the representative compounds of this class possess antioxidant, acaricidal, insecticidal, bactericidal and herbicidal activities. DHP finds applications in stereo specific hydrogen transfer reactions. Krechi and Smrckova have reported stereo-specific reduction of phenylglyoxylic and pyruvic acid using DHP to biomimetic models of lactase dehydrogenase. Recently, dihydropyridines are used as organocatalysts for asymmetric reactions such as hydrogenation of quinolines in the synthesis of alkaloids, asymmetric reductive amination of aldehydes, and hydrogenation of α, β unsaturated aldehydes and ketones.[4]

Reactions:

1. Aromatization of 1,4-dihydropyridines

The oxidation (aromatization) of 1, 4-DHPs into the corresponding pyridines is one of the main metabolic pathways of these drugs. This process is catalyzed by the cytochrome P450 (CYP) 3A4 isoform. To develop a useful synthetic approach to polysubstituted pyridines, the oxidative aromatization of 1, 4-DHP derivatives has received considerable attention from synthetic chemists. Numerous oxidants were studied in the aromatization of 1, 4-DHPs such as nitric acid nitrous acid in situ formed by action of acids to $NaNO_2$, nitrogen oxides, metallic nitrates, chromium(VI) oxidants, CrO_2, manganese and iron (III) salts, mercury(II) and Tl (III) salts,SnCl4, $Pb(OAc)_4$, $K_2S_2O_8$, S_8, O_2, I_2.[16,17]

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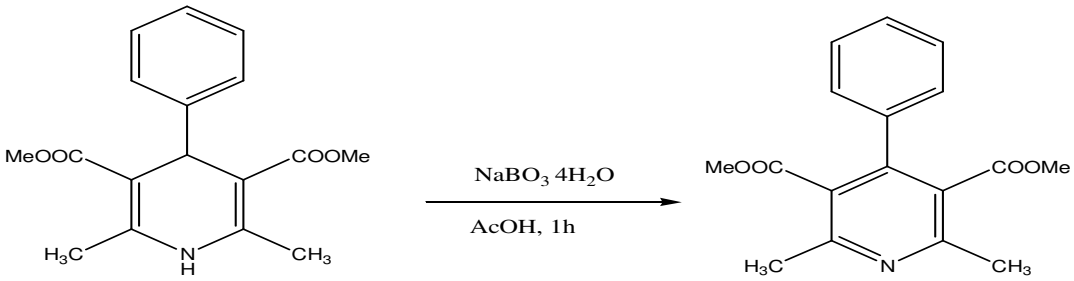
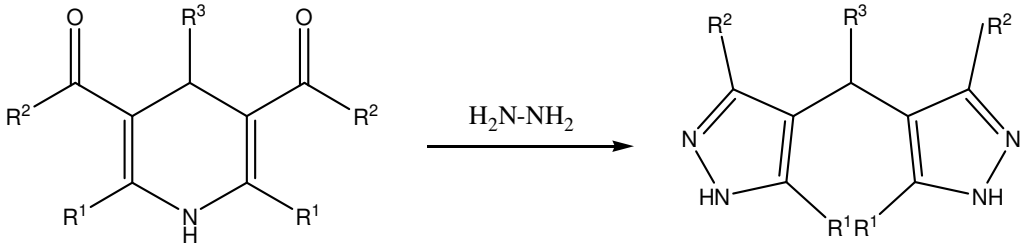


Aromatization suffer from drawbacks such as low yields, long reaction times, occurrence of several side products, use of stoichimetric amount of reagents, use of strong oxidants, high temperature Therefore, exploring the new catalytic system preferably in an environmentally benign method to overcome these drawbacks is a challenging task to the organic chemists.[5]

2. **Reaction with Hydrazines:**[18]

The reaction of 3, 5-acyl derivatives of 1, 4-dihydropyridine with hydrazine hydrate proceeds more readily and pure bispyrazolylmethanes are formed in high yield.



R^1 = H, Me
R^2 = Me, Ph
R^3 = H, 3-Py, 2-$C_6H_4OCHF_2$, 3, 4, 5-$(MeO)_3C_6H_2$

SAR: [18]

The majority of the known derivatives of 1, 4-dihydropyridine has electron-withdrawing substituents, which usually contain a carbonyl group, in positions 3 and 5. Conjugation of the carbonyl substituent with the NH group of the 1, 4-dihydropyridine ring reduces the tendency of these compounds towards oxidation, and simultaneously reduces the carbonyl reactivity and imparts weakly acidic properties to the ring NH group.

Pharmacological uses of 1, 4-dihydropyridine:

Antifungal activity:

1. **Sharma GL** *et al.* synthesized the ten 4-aryl-1, 4-dihydropyridine and three 4-aryl-1, 2, 3, 4-tetrahydropyrimidin-2-one

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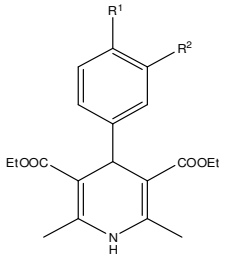
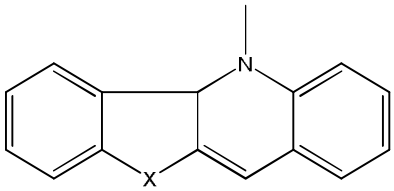
derivatives and examined for their activity against pathogenic strains of *Aspergillus fumigatus* and *Candida albicans* by disc diffusion, micro broth dilution and percent spore germination inhibition. The two of the compounds of dihydropyridine series exhibited significant activity against *A. fumigatus*. The most active diethyl dihydropyridine derivative exhibited a MIC value of 2.92 µg/disc in disc diffusion and 15.62 µg/ ml in micro broth dilution assays.[14]



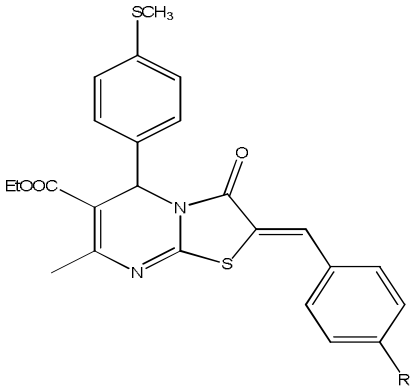
R_1 = Br, OMe, OH

R_2 = Cl, OH, OMe

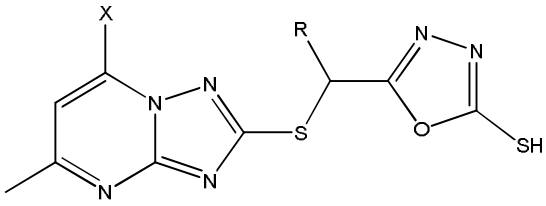
2. Kumari N. S. *et al.* synthesized a series



of new 2-(arylidene/5-arylfurfurylidene)-5-(4-methylthiophenyl) -5 H – thiazolo [2 ,3 – b] pyrimidin-3(1H)-ones 2 and 3 have been synthesized by a three component (MCR) reaction involving 4-(4-methylthiophenyl)-5-carbethoxy-6-methyl-3,4-dihydropyridine-2(1H)-thione, mono-chloroacetic acid and arylaldehydes / arylfurfuraldehydes, respectively. The newly synthesized compounds were screened for their antibacterial and antifungal activities and exhibited moderate to excellent growth inhibition of bacteria and fungi.[19]



R = 4-SCH_3, 4-OCH_3, 4-Cl, 4-F, 4-OH, 2, 4-Cl_2, 4-OH 3-OCH_3, 4-F-3-OPh



3. Ablordeppey S. Y *et al.* synthesized and evaluated the isosteres of cryptolepine for their anti-infective activities. Both the carbon and oxygen isosteres were less potent than cryptolepine. The evaluation of the activities of 5b compared with standard

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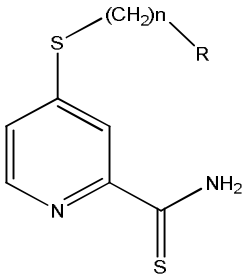
antifungal /anti-protozoal agents suggests that the benzothienoquinoline scaffold could serve as a lead for optimization.[20]

X = NH, S

4. Klimesova V. *et al.* synthesized a set of pyridine derivatives bearing a substituted alkylthio chain or a piperidyl ring in position 2 or 4 were synthesized, and their antimycobacterial and antifungal activities were evaluated. The most active compound was 2-cyanomethylthio pyridine -4-carbonitrile with MIC against *Mycobacterium kansasii* in the range of 8–4 µmol/l. The antifungal activities of the compounds were relatively low.[21]



n = 2, 3, 1

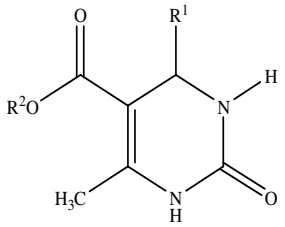
R = -CN, -CSNH$_2$, -C (=NH) NH$_2$

4. Yang G.F, *et al.* designed and synthesized, a series of new 1, 2, 4-triazolo [1, 5] pyrimidine derivatives bearing 1, 3, 4-oxadiazole moieties in order to search novel agrochemicals with higher antifungal activity. By determining the EC_{50} values of all the newly synthesized compounds 2-((5-(sec-butylthio)-1,3,4-oxadiazol-2-yl)- methyl thio)- 5-dimethyl-1,2,4-triazolo-[1,5-a] pyrimidine, was found to display the highest antifungal activity (EC_{50} = 6.57 µg /ml).[22]

X = H, CH_3,

R = H, CH_3

6. Singh OM, *et al.* efficiently catalyses the synthesis of dihydropyrimidinones (80–96% yields) by the Biginelli reaction in presence of Copper (II) chloride in the absence of any solvent. Six compounds were selected and examined their antifungal activities against the radial growth of three fungal species viz., Trichoderma hammatum, Trichoderma koningii and Aspergillus niger.[23]



R^1 = C_6H_5, 2-HO C_6H_4, 4-Cl C_6H_4

R^2 = C_2H_5, C_2H_5, C_2H_5

Anticonvulsant activity:

1. **Pattan S.R**. *et al* .synthesized a new series of 1, 4-dihydropyridine and their derivatives and the structures of the compounds has been confirmed by IR and NMR. The title compounds are evaluated for anticonvulsant activity by maximal electroshock method.[24]

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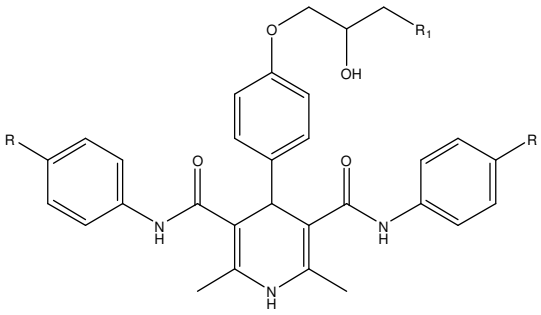
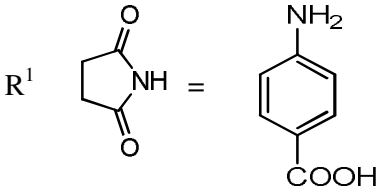
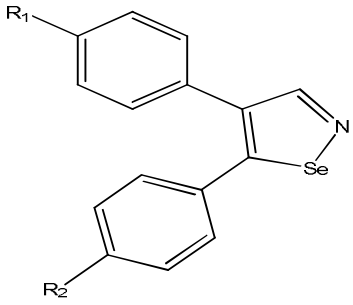


R = *p*-NO_2, *m*- NO_2, *m*-Cl, p-Cl



Anti-inflammatory activity:

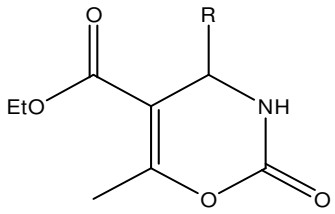
1. Dannhardt G. *et al.* investigate 4, 5-diaryl isoselenazoles as multiple target non-steroidal anti-inflammatory drugs (MTNSAIDs) which can intervene into the inflammatory process via different mechanisms of action creating a new class of compounds used in Parkinson's disease, Alzheimer's disease and rheumatoid arthritis.[25]



R_1 = CH_3, Cl, OCH_3, F,
R_2 = OCH_3, Cl, CH_3, SO_2CH_3

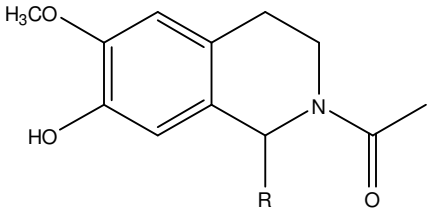
Anticancer activity:

1. **Sudalai A**. *et al.* afford a new multicomponent reaction comprising aldehyde, β-ketoester and methyl carbamate in acetonitrile effectively catalyzed by $Cu(OTf)_2$ to form substituted 3,4-dihydro[1,3] oxazin-2-ones in 60-82% yields. These compounds have been found to show inhibition activity against HL-60 cancer cell.[26]



R = Ph, 4-Cl-C_6H_4, 4-O_2N- C_6H_4, 4-NC- C_6H_4, 4-F_3C- C_6H_4,

2. **Hwang O**. *et al.* designed, synthesized and evaluated the seventeen tetrahydroisoquinoline derivatives for inhibition of NO production in lipopolysaccharide-stimulated BV-2 microglia cells by blocking BH4-dependent dimerization of newly synthesized NOS monomers.[27]



R = Me, Ph

3.Akberali P.M. *et al*. synthesized 2-(5-Arylfurfurylidene/5-nitrofurfurylidene)-5-aryl-7-(2, 4-dichloro-5-fluorophenyl)-5*H*-thiazolo[2,3-*b*]-pyrimidin-2(1*H*)-ones by a

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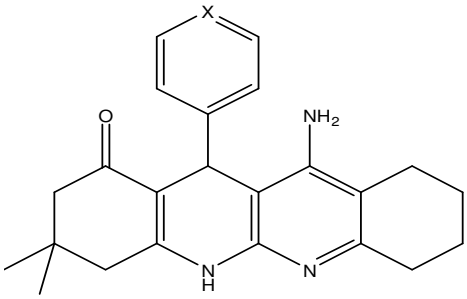
novel three component reaction of 4,6-diarylpyrimidino-2(1*H*)-thiones ,monochloroacetic acid, arylfurfuraldehydes and 5-nitro-2-furfuraldenediacetate, respectively. These compounds exhibited in vitro antitumour activity with moderate to excellent growth inhibition against a panel of 60 cell lines of leukemia.[28]

Selective ACHEIs :

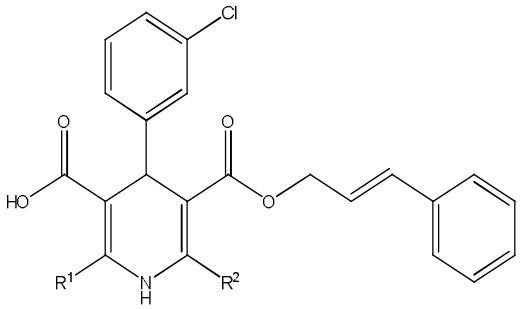
1.Villarroya M. *et al.* describe the synthesis and biological evaluation of tacri pyrimedones, a series of new tacrine-1,4-dihydropyridine hybrids bearing the general structure of 11-amino-12-aryl-3,3-dimethyl-3,4,5,7,8,9,10,12-octahydrodibenzo naphthyridine -1(2H)-one. These multifunctional compounds are moderately potent and selective AChEIs, therapeutic application for the treatment of Alzheimer's disease.[29]



X = C-H, C-F, C-Me, C-OMe, N, H, F, Me, OMe,

Calcium channel blocker:

1. Yamamoto T. *et al.* performed the structure–activity relationship (SAR) study on the 2-, 5-, and 6-position of 1, 4-dihydropyridine-3-carboxylate derivative APJ 2708 which is a derivative of Cilnidipine and has L/N-type calcium channel dual inhibitory activities, in order to find an injectable and selective N-type calcium channel blocker.[30]

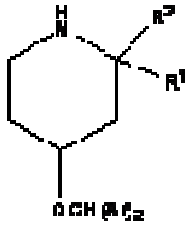


R^1 = CH_2CH_2CN, H, CH_2CH_2CN

R^2 = CHO, CN, CN

Antimycobacterial activity:

Weis R. *et al.* prepared 2-substituted derivatives of diphenylpyraline and their 1-phenyl and 1-phenethyl analogues from dihydropyridine-2(1H)-thiones. Their activity against Mycobacterium tuberculosis $H_{37}R_v$ as well as their cytotoxicity against human cells (HEK-293) has been determined via in vitro assays. [31]



R^1 = Me, iPr, Ph, H, Me, iPr

R^2 = iPr, Me, H, Ph

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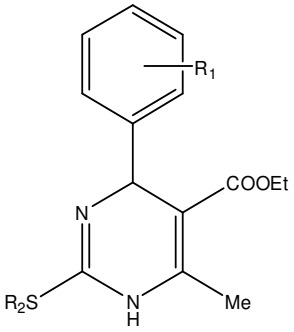
Neuroprotective agent:

1, 4-dihydropyridines (DHPs) are compounds that selectively block L-type Ca^{2+} channels, we considered the synthesis and the pharmacological study of new multipotent hybrid compounds, based on an AChEI and a DHP, such as tacrine and nimodipine Besides inhibition of AChE and blockade of voltage dependent calcium channels (VDCC), we were also interested in compounds targeted to prevent oxidative stress.[32]

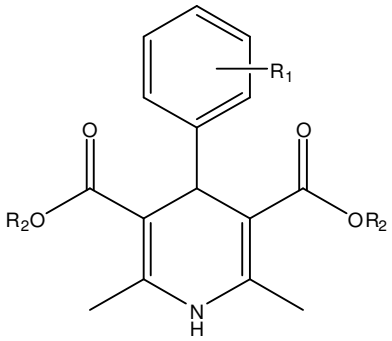
1. Gupta S.P. *et al.* a quantitative structure-activity relationship (QSAR) study has been made on four different series of dihydropyrimidine analogs that mimic the most widely studied class of calcium channel blockers (CCBs)-the 1, 4-dihydropyridine (DHP) class. The important characteristics indicated by the present study for dihydropyrimidine analogs are conformation of the molecule, the relative orientation of the aryl ring.[33]



R_1 = 3-NO_2, 2-NO_2, 2-CF_3, 2, 3-Cl_2,

R_2 = Me, $CH_2CH{=}CH_2$, $CH_2(CH_2)_3CH_3$, $CH_2C_6H_5$, $CH_2CH_2N(Me)_2$

2. Perumal T. P. *et al.* synthesized a variety of polyhydroquinolones under eco-benign conditions. The reaction proceeds

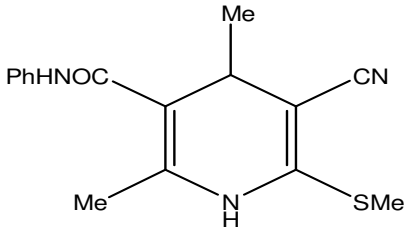


R_1 = 3-NO_2, 2-NO_2, 4-Cl, 2-Cl, 4-Me, 4-OMe

R_2 = Me, Et

smoothly without any catalyst at room temperature in short reaction time. The yields and purity are excellent.[34]

3. Krivokolysko S.G. *et al.* obtained substituted 2-alkylthio-3-cyano-4, 6-dimethyl-5-phenylcarbamoyl-l, 4-dihydropyridines by successive reaction of acetaldehyde with cyanothioacetamide



acetoacetanilide, α-chloracetamide or phenacyl bromide in the presence of piperidine.[35]

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