Introduction:

Heterocyclic compounds are cyclic compounds which contain one or more hetero atom in addition to carbon, such as nitrogen, oxygen or sulphur. According to the size of ring it can be classified into three,four,five, and six membered rings,these rings may be monocyclic or fused rings. Other classification depends upon the saturation state of the heterocyclic compounds (Geissman, 1976)

Heterocyclic compounds which contain nitrogen are very important compound. These nitrogenous hetero aromatic compounds further subdivided into systems deficient in π – electrons, and systems with an excess of π-electrons (Finar, 1975).

1.1- π-Deficient nitrogen-heterocyclic compounds:

Almost all π-Deficient heterocyclic compounds contain nitrogen, and almost all are six-membered rings. The nitrogen atoms in the six- membered hetero aromatic ring attract electrons from the π-double layer,the stability of this type of substances is due to the π-electrons but they are less stable than benzene.In practicalexperience,the replacement of one-CH= by-N=diminishes stability only slightly,but the effect is quite.Marked when two such replacements are made, particularly if they occur in positions that are separated by one carbon atom. Three such degree of instability unless substituents are introduced that can restore electrons to depleted π-orbital *(*Osborn *etal., 1956*).

1.2-dihydropyridine:

1.2.1-Introduction:

1.4-Dihydropyridines (DHPs) are class of nitrogen containing hetero cycles having a 6-membered ring. 1.4-DHPs, which are the most potent calcium antagonists or calcium channel blockers, have received much attention due to their wide range of pharmaceutical and biological properties such as inhibition of human cytochrome p450 enzyme (*Kato et al., 2000*), angiotensine-coverting enzyme inhibition, and

blood pressure control on chronic, nondiabeticnephropathies (Ruggenenti *et al*., 1998). 1.4-DHP compound play important roles in medicinal chemistry, for example nifedipine, amlodipine, felodipine, and nicordipine, which are the bestselling drug used in the treatment of cardiovascular diseases (Ortiz *et al*., 2003).

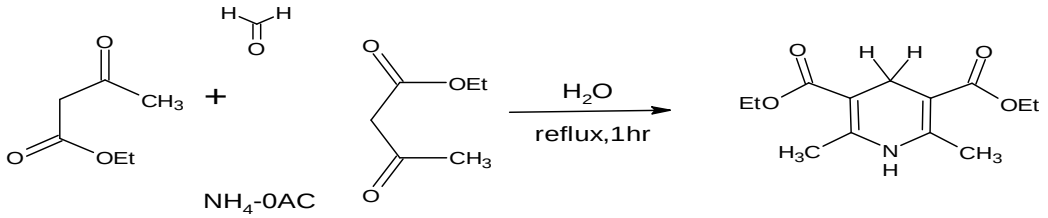
1,4-Dihydropyridine(DHP) (Stout*et al.*,1982) scaffold represents the heterocyclic unit of remarkable pharmacological efficiency. They are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, such as,nifedipine and nitrendipine are used for the treatment of hypertension and angina pectoris, nisoldipine is apotent vasodilator and nimodipine exhibits selectivity for cerebral vasculature (Boecker*etal.*, 1986). A number ofDHPs derivatives are employed as potential drug candidates for the treatment of congestive heart failure (Divot*et al*.,1995). Moreover DHPs also act as NADH mimics for the reduction of carbonyl compounds and their derivatives (Rueping*et al.*, 2006). In human body the main metabolic rout of dihydropyridine drugs involve their oxidation to pyridines catalyzed by cytochrome-450 in liver (Guengerich*et al*.,1986). Additionally, the synthesis of heteroaromatics by oxidative dehydrogenation is of fundamental importance in organic chemistry. These ubiquitous features always encourage synthetic chemist to explore improved protocols for the synthesis as well as the oxidation of 1,4-DHPs.

1.3-Hantzsch Dihydropyridine (Pyridine) Synthesis

The Hantzsch pyridine synthesis or Hantzschdihydropyridine synthesis is a multi-component organic reaction between an aldehyde such as formaldehyde, 2 equivalents of a β-keto ester such as ethyl acetoacetate and a nitrogen donor such as ammonium acetate or ammonia (Hantzsch,1881).The initial reaction product is a dihydropyridine which can be oxidized in a subsequent step to a pyridine. The driving force for this second reaction step is aromatization. This reaction was reported in 1881 by Arthur Rudolf Hantzsch.

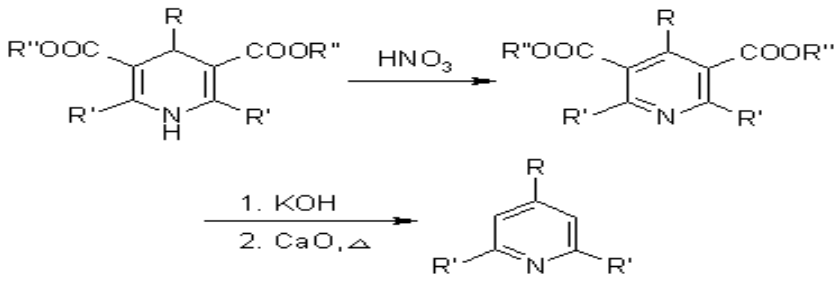
A 1,4-dihydropyridine dicarboxylate is also called a 1,4-DHP compound or a Hantzsch compound. These compounds are an important class of calcium channel blockers and as such commercialized in for instance nifedipine, amlodipine or nimodipine.

The reaction has been demonstrated to proceed in water as reaction solvent and with direct aromatization by ferric chloride or potassium permanganate in a one-pot synthesis(Wang*etal.*,2005).



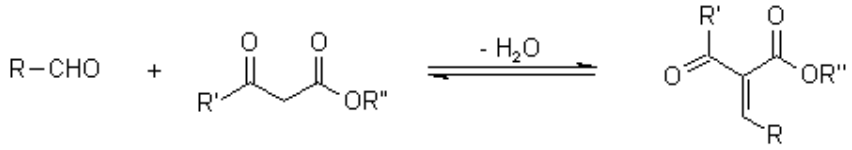
Scheme (1.1):Hantzsch 1,4-DHPs

This reaction allows the preparation of dihydropyridine derivatives by condensation of an aldehyde with two equivalents of a β-ketoester in the presence of ammonia. Subsequent oxidation (or dehydrogenation) gives pyridine-3,5-dicarboxylates, which may also be decarboxylated to yield the corresponding pyridines.

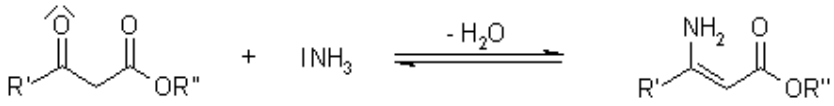


1.4. MechanismoftheHantzschDihydropyridine Synthesis:

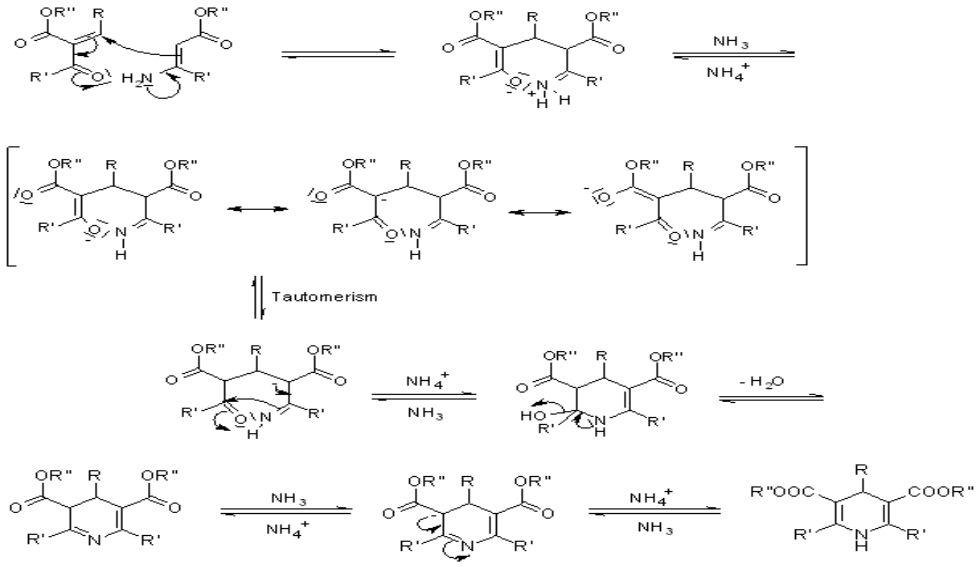
The reaction can be visualized as proceeding through a Knoevenagel Condensation product as a key intermediate:



A second key intermediate is an ester enamine, which is produced by condensation of the second equivalent of the β-ketoester with ammonia:



Further condensation between these two fragments gives the dihydropyridine derivative:



Scheme (1.2):Reaction mechanism of Hantzsch dihydropyridine synthesis

1.5. Biological Activity of 1,4-dihydropyridine:

In recent years, notable attention has been focused on the synthesis of 1,4-dihydropyridyl compounds due to their significant biological activities (Shan ., et al 2004). 1,4-Dihydropyridines (1,4-DHPs), as analogues of NADH coenzymes and other related derivatives, are widely used as calcium channel blockers for the treatment of cardiovascular disorder including hypertension, angina and cardiac arrhythmias (Emmet 1990). Today, commercial representatives such as nifedipine (1), amlodipine (2), felodipine (3) and nicardipine (4) are some of the best selling drugs that are used in the treatment of hypertension (figure 3).

1,4-Dihydropyridines are calcium antagonists (Visentin*et al.,* 2004), antitubercular agents (Eharkar*et al.,* 2002) and neuropeptide Y Y1 receptor antagonists (Poindexter et al., 2004). They possess neuroprotective (Klusa 1995), platelet antiaggregation (Bretzel *et al.,* 1993) and antidiabetic activities(Ogawa*et al.,* 2003).These cases clearly demonstrate the remarkable potential of New 1,4-DHPs derivatives as a source of valuable drug candidates.

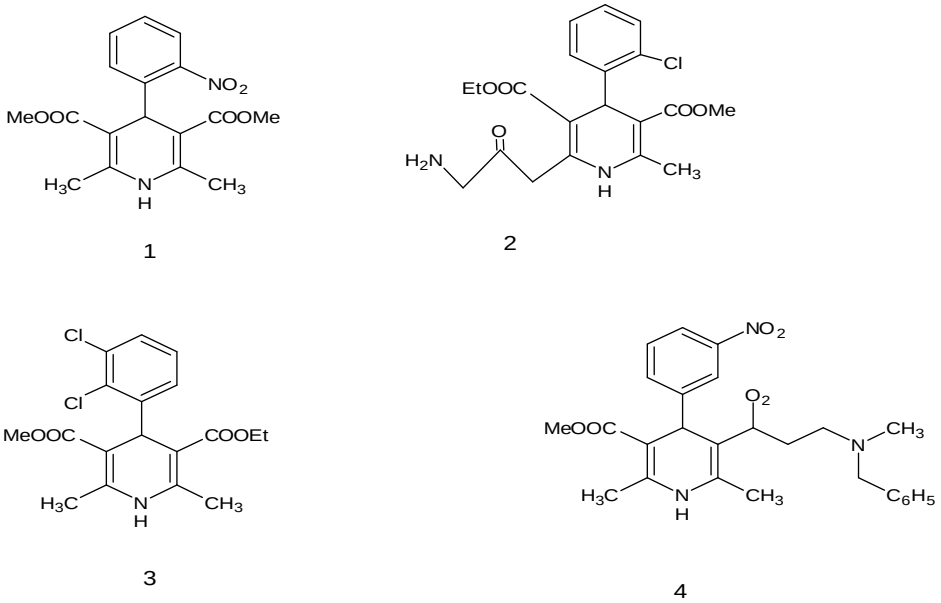


Figure (1.1) S0me commercial 1,4-DHPs

1.6-Molecular Modeling and Computational Chemistry:

1.6.1-The definition:

Molecular modeling is anything that requires the use of a computer to paint, describe or evaluate any aspect of the properties of the structure of a molecule" (Pensak, 1989). Methods used in the molecular modeling arena regard automatic structure generation, analysis of three-dimensional (3D) databases, construction of protein models by techniques based on sequence homology, diversity analysis, docking of ligands or continuum methods. Thus, today molecular modeling is regarded as a field concerned with the use of all sort of different strategies to model and to deduce information of a system at the atomic level. On the other hand, this discipline includes all methodologies used in computational chemistry, like computation of the energy of a molecular system, energy minimization, Monte Carlo methods or molecular dynamics. In other words, it is possible to conclude that computational chemistry is the nucleus of molecular modeling. Identification of bio molecular moieties involved in the interaction with a specific receptor permits to understand the molecular mechanism responsible of it specific biological activity. In turn, this knowledge is aimed at designing new active molecules that can be successfully used as drugs. Due to the fact that simulation accuracy is limited to the precision of the constructed models, when it is possible, computational simulations have to be compared with experimental results to confirm model accuracy and to modify them if necessary, in order to obtain better representations of the system (Barrel*et al*., 2006).

1.6.2. The major computational requirements are:

- Molecular energies and structures
- Geometry optimization from an empirical input.
- Energies and structures of transition states.
- Bond energies.

- Reaction energies and all thermodynamic properties.
- Molecular orbitals.
- Multipolar moments.
- Atomic charges and electrostatic potential.
- Vibrational frequencies.
- IR and Raman spectra.
- NMR spectra.
- CD spectra.
- Magnetic properties.
- Polarizabilities and hyperpolarizabilities.
- Reaction pathway.
- Properties such as the ionization potential electron affinity proton affinity.-
- Modeling excited states.
- Modeling surface properties and so on meeting these challenges could eliminate time-consuming and costly experimentations.
- Software tools for computational chemistry are often based on empirical information.

To use these tools effectively, need to understand the method of implementation of this technique and the nature of the database used in the parameterization of the method. With this knowledge, can redesign the tools for specific investigations and define the limits of confidence in results (Ramachandran*et al.*, 2008).

1.6.3. Quantitatives Structure-Activity Relationships (QSARs):

Many types of model are possible, with mathematical and statistical models being particularly common. Such models are often referred to as Quantitative Structure-Activity Relationships (QSARs) or Quantitative Structure-Property Relationships (QSPRs). (Tropsha*et al.,* 2003). Hansch was the first one to use QSARs to explain the biological activity of series of structurally related molecules (Fujita *et al.*,

1964) (Hansch*et al.,* 1968). Hansch pioneered the use of descriptors related to a molecule's electronic characteristics and to its hydrophobicity. This led him to propose that biological activity could be related to the molecular structure via equations of the following form:

Log (1/C) =k1 log P + K2σ + K3

C=the concentration of compound required to produce a standard response a given time.water.

σ = the appropriate Hammett substitution parameter.

K1, K2, k3=constants derived from regression analysis

This formalism expresses both sides of the equation in terms of free energy.

Hansch's rationale for suggesting the parabolic dependence on log P was that the drug's hydrophobicity should not be so low that the drug did not partition into the cell membrane nor so high that once in the membrane it simply remained there.

An early example of such a non-linear relationship between a biological response and the partition coefficient is the following equation derived for the narcotic effect of thirteen barbiturates on mice (Hansch*et al.,* 1968):

$$\boldsymbol{log\left(\frac{1}{C}\right) = -0.44\,(logP)2 + 1.58\,(logP) + 1.93}$$

The electronic characteristics of a molecule are also important in determining its activity against the target; the Hammett parameters provided a concise and convenient way to quantify these. Hammett and others had shown that for related compounds reaction rates (e.g. for the hydrolysis of benzoate esters) and positions of equilibrium (e.g. the ionization constants of substituted benzoic acids) could be quantified (Leach and Gillette, 2007) using equation of the following form:

$$\boldsymbol{Log\left(\frac{k}{ko}\right) = \rho\sigma}$$

$$Log\left(\frac{K}{Ko}\right) = \rho\sigma$$

K=these equation express the rate or equilibrium

K=constant for a particular substituent relative to that for a reference compound (indicated using the subscript 0 and typically that for which the substituent is hydrogen).

The substituent parameter σ is determined by the nature of the substituent and whether it is Meta or Para to the carboxylic acid or ester group on the aromatic ring.

The so-called 3D-QSAR models, however, are more representative of these new QSAR methods, and the Comparative Molecular Field Analysis (COMFA) method is probably one of the most popular of these.

In the COMFA method, the molecular descriptors are taken as steric and electric field calculated at a large number of points surrounding each molecule (Carteret*et al.*, 1989).

The main problem with 3D-QSAR methods such as COMFA is the alignment of the molecules in the test set (Sullivan *et al.*, 2000).

- It must be assumed that each of the molecules binds to the enzyme at the same site.
- It is not always clear that all the molecules bind to the active site in the same overall orientation.
- If the molecule has several conformation available, one has to guess or estimate which conformation actually binds to the enzyme.

1.7. Aim and objective:

The main objective of the presentresearch is to synthesis some 1,4-dihydropyridine derivatives and characterize the compounds by using IR spectroscopy.

Using ACD/lab program to designed and examined, in order to select specific compound to synthesize them, and predict and calculation of molecular properties.

2.1. Materials

2.1.1. Solvents:

Acetone Assay (GC) 99% LOBA Chemie India, Methanol Assay 97% and Chloroform Assay 99.5% Alpha chemikaIndia, Di ethyl ether Assay 98% Alpha chemika India and Ethanol Assay 99.8% mombai-400005.India.

2.1.2. Chemicals:

Benzaldehyde Assay (GC) 98.5-100.5% Alpha chemika India, Acetaldehyde Lab Assay (20-30)%, Formaldehyde Assay (37-40%) Alpha chemistry India, Ethyl aceto acetate Assay >98% Alpha Chemika India, p-amino benzoic acid Assay 99% LOBA Chemie, Sulphanilamide Assay 99% Lab Chemiepvt. Ltd. India, Benzaldehyde Alpha chemika India, p-nitro aniline Alpha chemika India, Calcium chloride laboratory Reagentand Aniline Assay 99% Alpha chemika India.

2.2. Thin layer chromatography (TLC):

TLC was carried out using silica gel Fertigfolien (Merck Germany) coated sheets ALUGRAM SIL G/UV254.

2.3. Instruments:

2.3.1. Infrared Spectrophotometer (IR):

Infra-red spectroscopy was recorded on FTIR-8400s instrument (Shamazu, Japan) using KBr disc.

2.4. ACD lab program:

ACD lab free ware 2015 downloaded fromwww.acd labs.com.

2.5. Equipment:

- Melting point apparatus, BIBBY STERILNLTD, UK.
- Water bath

- ## 2.6. Glassware:

All glass ware werePyrex type.

2.7. General method of ACD/lab program:

There were two modes to ACD/chemo sketch, namely structure and draw, structure mode was used to draw chemical molecules, while draw mode used to create and edit graphical objects. Upon startup, the draw normal mode and carbon automatically selected. By clicking and dragging the cursor in the windows, c-c bonds were created. Clicking on carbon atom produced a braced structure. The change was made by selecting heteroatom from the element list in the lift lobar and clicking on an atom in the structure to replace it. Radicals were made by selecting it from table which including carbon ring, carbon-based side chain and functional groups. A reaction requires were drawing by using the reaction arrow and reaction plus icons. Bond lengths and bond angle standardized by clicking on clean structure. The calculated properties were inserted into the chemo sketch window as text field; on the tools menu, point to calculate and choose the desired property. By selecting a structure and clicking on generating name for structure, the IUPC name was generated as text field underneath the structure see (tables No 3-1)

2.8. Synthetic methods:

2.8.1. Preparation of diethyl 1,4-dihydro-2,6-dimethylpyridine N-substitute-3,5-dicarboxylate derivatives (I,II,III)

Ina400ml beaker5.2g (5.1ml, 0.04mol) of ethyl acetoacetate was cooled to (0^0C), 1.5ml (0.02mol) of 40 per cent aqueous formaldehyde was added, followed by 3 drops of diethylamide as catalyst. The mixture was kept at (0^0C) for 6 hours, and then kept at room temperature for 40 hours. The lower organic layer was separated; the aqueous layer was extracted with ether. The combined organic fraction was dried using an hydrous calcium chloride, the ether was removed and transfered the

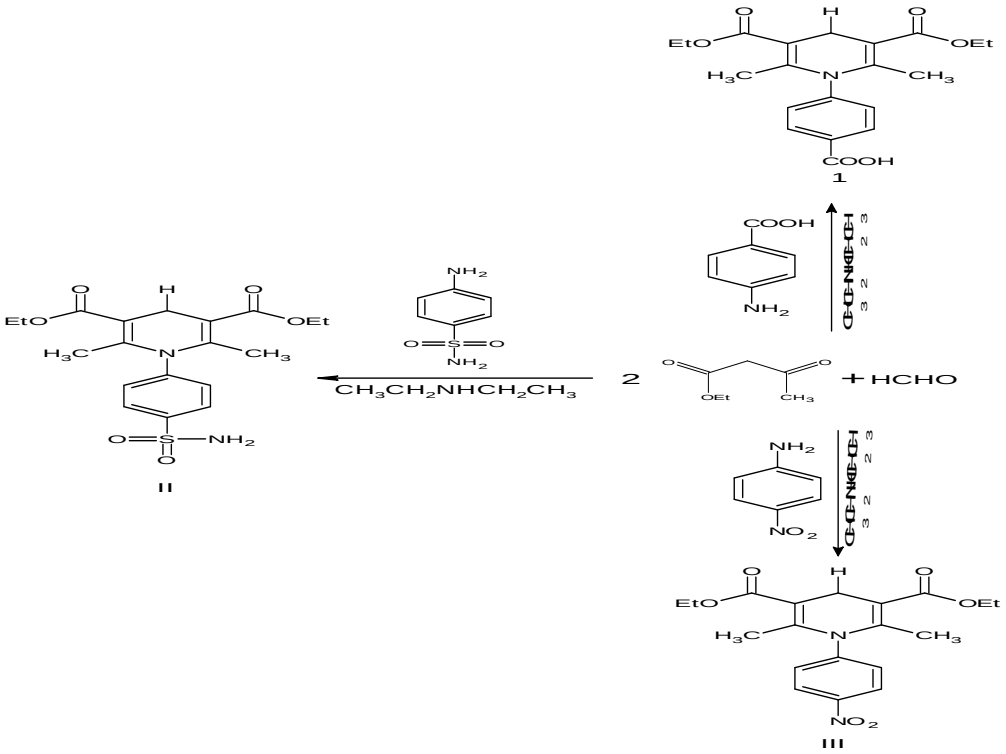
residue together with an equal volume of ethanol, the beaker was cooled in an ice bath, ((0.5941g of p-amino benzoic acid)(0.5344g of Sulphanilamide)(0.5933g of p-nitro aniline)) wereadded to the mixture, the beaker was kept at room temperature for 40 hours. The resulting yellow solution was filtered to remove a small quantity of most colorless material, the filtrate was heating in boiling water bath until most of the ethanol has been removed, the residue was cooled and crystalized of 20ml crystified sprit. For the reaction conditions see table (2:2)

2.8.2. Preparation of diethyl1,4-dihydro-2,4,6-trimethylpyridineN-substituted3,5-dicarboxylat derivatives (IV,V):

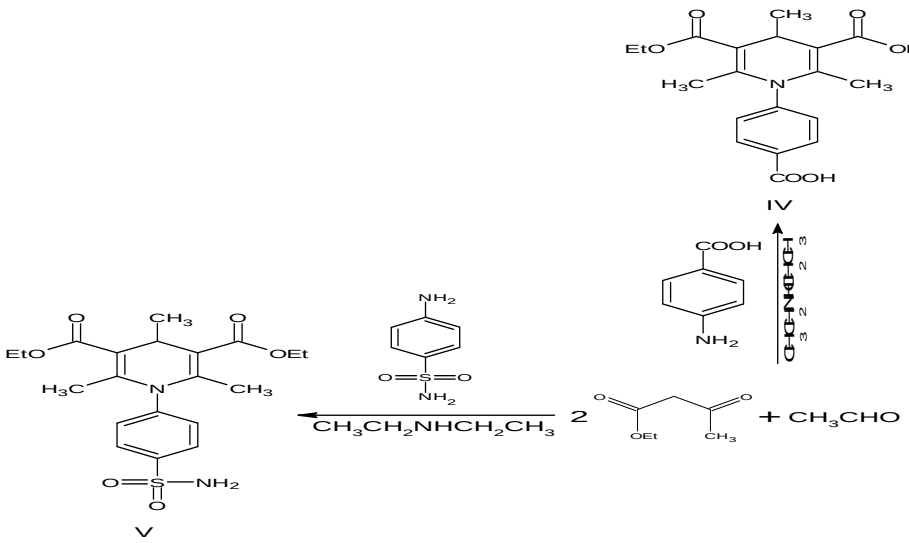
In a400ml beaker 5.2g (5.1ml, 0.04mole) of ethyl acetoacetate was cooled to (0^0C),1.5ml (0.02mol) of acetaldehyde was added,followed by 3 drops of diethylamide as catalyst. The mixture was kept at (0^0C) for 6 hours, and then kept at room temperature for 40 hours. The lower organic layer was separated; the aqueous layer was extracted with ether. The combined organic fraction was dried using an hydrous calcium chloride, the ether was removed and transfered the residue together with an equal volume of ethanol, the beaker was cooled in an ice bath, ((0.5941g of p-amino benzoic acid)(0.5344g of Sulphanilamide)) were added to the mixture, the beaker was kept at room temperature for 40 hours. The resulting yellow solution was filtered to remove a small quantity of most colorless material, the filtrate was heating in boiling water bath until most of the ethanol has been removed, the residue was cooled and crystalized of 20ml crystified sprit. For the reaction conditions see table (2:2)

2.8.3. Preparationof diethyl1,4-dihydro-2,6-dimethyl 4-phenylpyridinesubstituted3,5-dicarboxylate derivatives (VI,VII,VIII,IX):

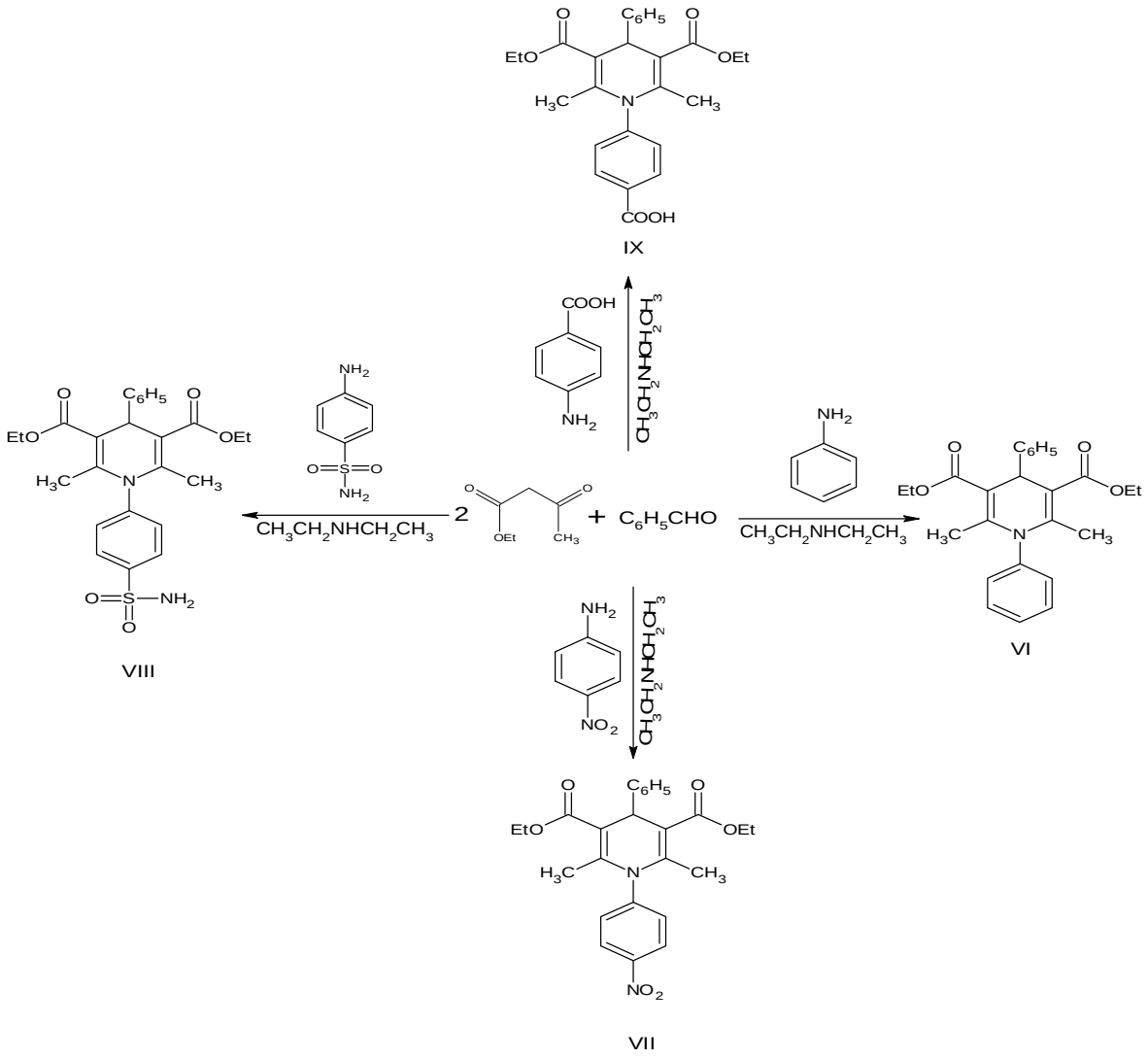
In a400ml beaker 5.2g (5.1ml, 0.04mole) of ethyl acetoacetate was cooled to (0^0C), 1.5ml (0.02mol) of Benzaldehydewas added,followed by 3 drops of diethylamide as catalyst. The mixture was kept at (0^0C) for 6 hours, and then kept at room temperature for 40 hours. The lower organic layer was separated; the aqueous layer was extracted with ether. The combined organic fraction was dried using an hydrous calcium chloride, the ether was removed and transfered the residue together with an equal volume of ethanol, the beaker was cooled in an ice bath, ((1.2ml, 0.013mole of aniline)(0.5941g of p-amino benzoic acid)(0.5344g of Sulphanilamide)(0.5933g of p-nitro aniline)) were added to the mixture, the beaker was kept at room temperature for 4o hours. The resulting yellow solution was filtered to remove a small quantity of most colorless material, the filtrate was heating in boiling water bath until most of the ethanol has been removed, the residue was cooled and crystalized of 20ml crystified sprit. For the reaction conditions see table (2:2)



Scheme (2.1) preparation of diethyl 1,4-dihydro-2,6-dimethylpyridineN-substitute3,5-dicarboxylare derivative (I,II,III)

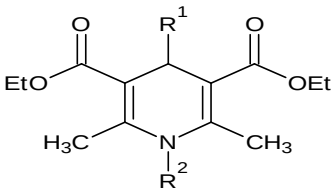


Scheme (2.2)preparation of diethyl1,4-dihydro2,4,6- trimethyl-1-Phenylsubstitutederivatives (IV,V)



Scheme (2.3)preparation of diethyl2,6-dimethyl4-phenyl1-phenylsubstitute derivatives(VI,VII,VIII,IX)

Table(2.1): Chemical name of the prepared compounds:



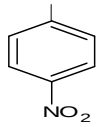
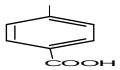
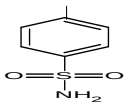
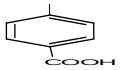
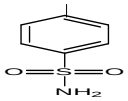
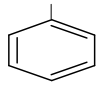
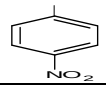
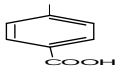
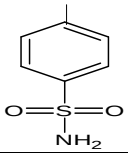
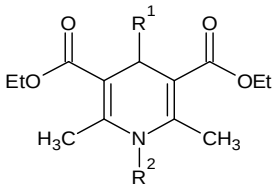
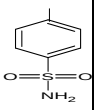
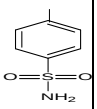
Compound No.	R1	R^2	Chemical name.
I	H		diethyl 2,6-dimethyl-1-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate
II	H		4-[3,5-bis(ethoxycarbonyl)-2,6-dimethylpyridin-1(4*H*)-yl]benzoic acid
III	H		4-[3,5-bis(ethoxycarbonyl)-2,6-dimethylpyridin-1-(4H)-yl]sulphanilamide
IV	CH_3		4-[3,5-bis(ethoxycarbonyl)-2,4,6-trimethylpyridin-1-(4H)-yl]benzoic acid
V	CH_3		1-(benzene sulphonamide)[3,5-bis(ethoxycarbonyl) 2,4,6-trimethyl]1,4-dihydropyridine
VI	C_6H_5-		Diethyl2,6-dimethyl1,4-diphenyl1,4-dihydropyridine3,5-dicarboxylate
VII	C_6H_5-		Diethyl2,6-dimethyl1-(4-nitro),4-diphenyl1,4-dihydropyridine3,5-dicarboxylate
VIII	C_6H_5-		4-[3,5-bis(ethoxycarbonyl)-2,4-dimethylpyridine-1-(4H)-yl)]benzoic acid
IX	C_6H_5-		Diethyl2,6-dimethyl-1-(phenylsulphonyl)-4-(phenyl)-1,4-dihydropyridine3,5-dicarboxylate

Table (2.2) Reaction condition of prepared compound:



Comp No.	**R**^{1}	**R**^{2}	**R**eacti on Tim	**R**ec. Solvent	Yiel d(g)	Yield (%)	Color	M.wt	M. p
I	H		4days	Rectified spirit	0.98	75.8	yello w	374.38 778	141-142
II	H		4days	Rectified spirit	1.33	82.60	yello w	373.39 972	181-183
III	H		4days	Rectified spirit	1.19	94.44	yello w	408.46 866	167-169
IV	CH_3		4days	Rectified spirit	1.2	80	yello w	387.42 63	120-122
V	CH_3		4days	Rectified spirit	o.96	73.84	yello w	422.49 524	133-135
VI	C_6H_5 -		4days	Rectified spirit	o.71	13.36	Brow n yello w	405.48 618	123-125
VII	C_6H_5 -		4days	Rectified spirit	0.97	26.50	yello w	450.48 374	143-145

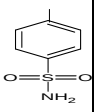
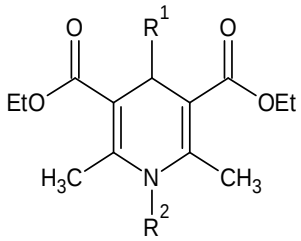
VIII	C_6H_5 -		4days	Rectified spirit	1.78	91.46	Brown pal	449.495668	143-145
IX	C_6H_5 -		4days	Rectified spirit	1.39	92.54	yellow	484.56462	243-245

Table (2.3) Infrared spectral data of the compound:



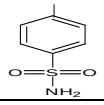
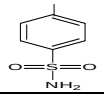
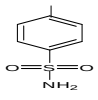
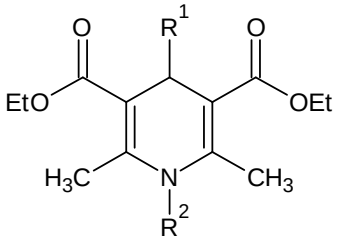
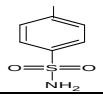
No. Comp	R^1	R^2	C=O St.vib	C-$N_{st.vib}$	C-$C_{st.vib}$.	Other
I	H		1720	1309	3243	-
II	H		1671,1601	1287,1170	1428	2976C-H $_{st.vib}$
III	H		1720,1627	1309,1149	1436	1094S=O $_{st,vib}$,3477$NH_{st,vib}$
IV	CH_3		1720,1627	1309	1436	3381$NH_{st,vib}$
V	CH_3		1632	1310	1501	2980C-$H_{st.vib}$ 1094S=$O_{st.vib}$
VI	C_6H_5-		1736	1184,1246	1457	2980C-$H_{st.vib}$,
VII	C_6H_5-		1710,1633	1106,1186	1473	2980C-$H_{st.vib}$,1301$NO_{2st,vib}$
VIII	C_6H_5-		1634	1311	1502	3381OH
IX	C_6H_5-		1661	1292	1434, 1509, 1593	2915C-$H_{st.vib}$,1169S=$O_{st.vib}$, 3367$NH_{st.vib}$

Table (2.4) Thin layer chromatography data of the compound prepared:



Comp No.	R^1	R^2	Solvent system Chloroform:methanol	Rf
I	H		9.5:0.5	0.9
II	H		9.7:0.3	0.47
III	H		9.7:0.3	0.62
IV	CH_3		9.7:0.3	0.84
V	CH_3		9:1	0.46
VI	C_6H_5-		9.5:0.5	0.71
VII	C_6H_5-		9.7:0.3	0.82
VIII	C_6H_5-		9.7:0.3	0.47
IX	C_6H_5-		9.5:0.5	0.43

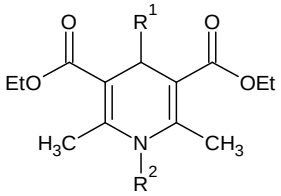
3. Discussion

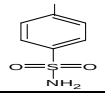
3.1. ACD/lab program:

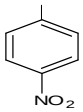
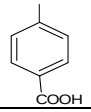
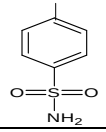
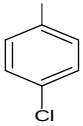
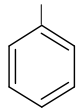
In the present work several 1,4-dihydropyridines derivative were designed and examined, in order to select specific compound to synthesize. 25 compounds of the 1,4-dihydropyridine derivative were designed from different amine and aldehyde, and ethylacetoacetate (table No.3-1) using (ACD/lab); which is free software that was used to draw chemical structure, calculation of molecular properties (molecular formula, molecular weight, molar volume, molar refractivity, surface tension, density and polarizability) Log p (table no.3-1).

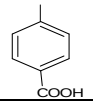
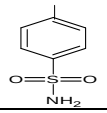
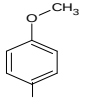
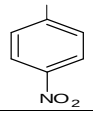
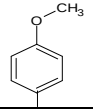
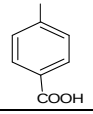
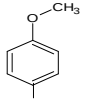
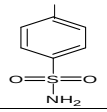
The selection of the target derivative was depend upon Log p, molar volume and polarizability. 1,4-dihydropyridine derivatives with low Log p value, high molar volume and large polarizability were selected for synthesis.

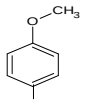
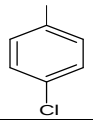
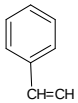
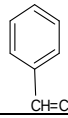
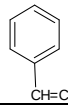
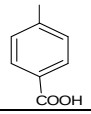
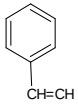
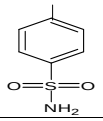
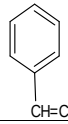
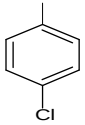
Table (3.1): ACD/lab data:



No	R1	R2	Log p	M.R ±0.3cm^3	M.V ±3cm^3	D±0.06 g/cm^3	S.T±3 dyne/cm	polarizability±0.5$10^{-24}$cm3	M.F
1	H		2.78+/_0.4	90.84	288.4	1.141	41.6	36.01	$C_{19}H_{23}NO_4$
2	H		2.35+/_0.58	97.38	300.3	1.246	47.8	38.60	$C_{19}H_{22}N_2O_6$
3	H		2.46+/_0.81	97.77	301.0	1.240	48.2	38.76	$C_{20}H_{23}NO_6$
4	H		0.89+/_0.8	103.84	317.4	1.286	49.1	41.16	$C_{19}H_{24}N_2O_6S$

5	H		3.38+/_0.41	95.73	300.4	1.211	43.1	37.95	$C_{19}H_{22}ClNO_4$
6	CH_3		3.28+/_0.40	95.55	308.4	1.113	38.9	37.87	$C_{20}H_{25}NO_4$
7	CH_3		2.85+/_0.59	102.09	320.3	1.212	44.47	40.47	$C_{20}H_{24}N_2O_6$
8	CH_3		2.95	102.48	321.0	1.206	44.9	40.62	$C_{21}H_{25}NO_6$
9	CH_3		1.380.81	108.45	337.4	1.252	45.9	42.99	$C_{20}H_2O_6S$
10	CH_3		3.87+/_0.41	100.44	320.4	1.179	40.4	39.82	$C_{20}H_{24}ClNO_4$
11			4.74+/_0.41	115.28	352.6	1.149	43.2	45.70	$C_{25}H_{27}NO_4$

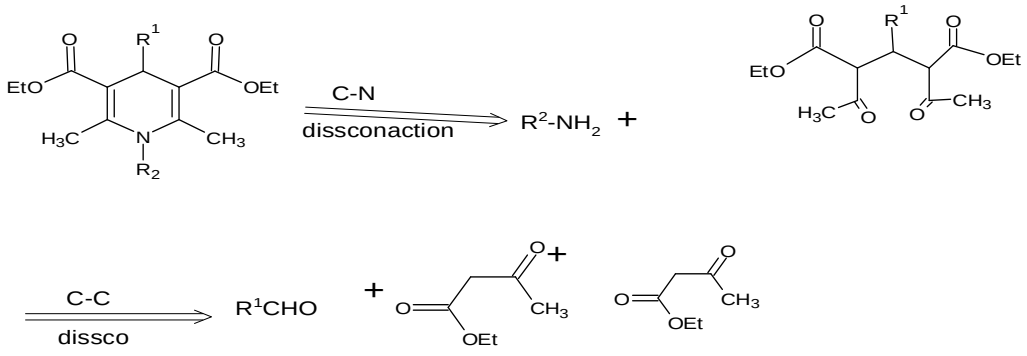
12			4.31+/_0.60	121.83	364.5	1.235	48.4	48.29	$C_{25}H_{26}N_2O_6$
13			4.42+/_0.82	122.4	365.1	1.230	48.7	45.45	$C_{26}H_{27}NO_6$
14			2.85+/_0.82	128.53	381.6	1.269	49.4	50.95	$C_{25}H_{28}N_2O_6S$
15			5.34+/_0.43	120.18	364.6	1.206	44.64	47.64	$C_{25}H_{26}ClNO_4$
16			4.66+/_0.42	121.96	376.6	1.156	42.7	48.35	$C_{26}H_{29}NO_5$
17			4.23+/_0.61	128.51	288.5	1.236	47.5	50.94	$C_{26}H_{28}N_2O_7$
18			4.34+/_0.83	128.89	389.1	1.232	47.8	51.05	$C_{27}H_{29}NO_7$
19			2.77+/_0.83	134.90	405.6	1.268	48.5	53.47	$C_{26}H_{30}N_2O_7S$

20			5.26+/_0.44	126.86	388.6	1.209	43.8	50.29	$C_{26}H_{28}ClNO_5$
21			5.15+/_0.42	128.09	366.5	1.177	49.4	50.78	$C_{27}H_{29}NO_4$
22			4.72+/_0.61	134.63	378.4	1.259	54.7	53.37	$C_{27}H_{28}N_2O_6$
23			4.82+/_0.83	135.02	379.1	1.254	55.0	53.52	$C_{28}H_{29}NO_6$
24			3.25+/_0.83	137.70	395.5	1.290	55.5	54.59	$C_{27}H_{30}N_2O_6S$
25			5.74+/_0.44	132.98	378.5	1.230	50.5	52.72	$C_{27}H_{28}ClNO_4$

3.2 Retro synthetic analysis (RSA):

Retro synthetic analysis (RSA), aid in the establishment of good synthetic scheme in (RSA), key step are developed by examine important structural element in the final product and figuring out how specific reaction could lead to the product. The procedure is performed so that a complex final molecule is reduced to simpler intermediates. The advantage of such an approach is that is greatly simplifies planning the synthesis of a complex product and readily leads to a convergent synthesis (Golan *et al.*,(2008).

In performing (RSA), it may also be useful to disconnect a bond showing the fragment not as real compounds but only as an electrophile and nucleophile (synthons). This may help bring to mind other reaction that can be used to reassemble the fragment (Hornback, 2005).

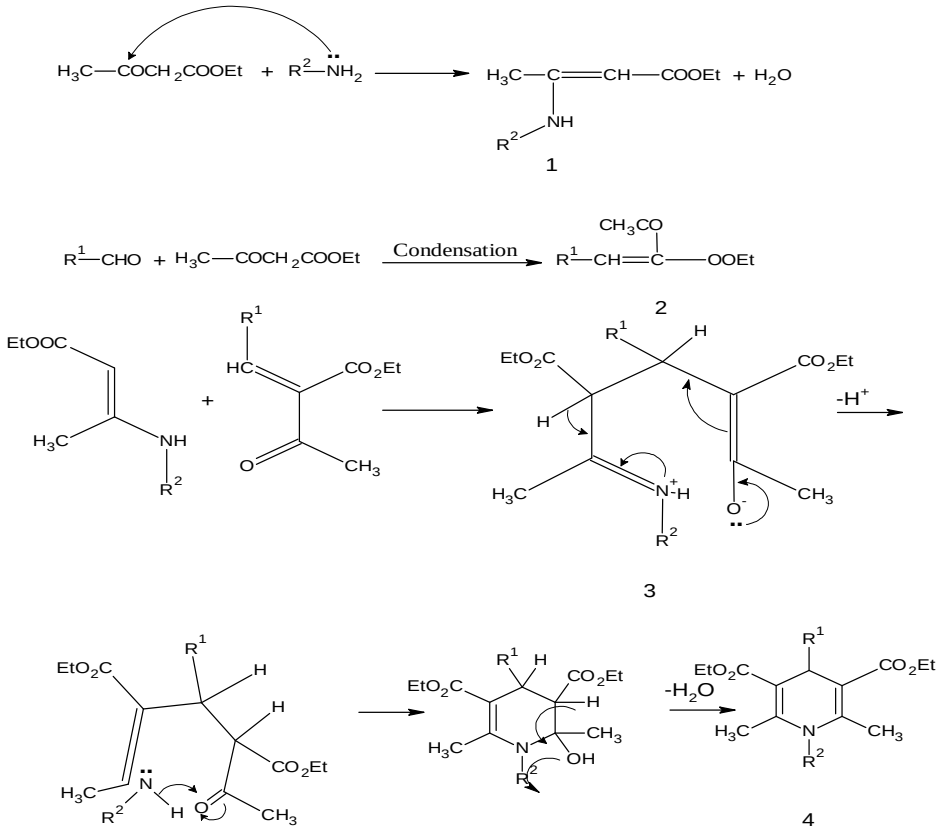


Scheme (3.1): Retro synthetic analysis of 1,4-dihydropyridine derivative.

3.3. Reaction mechanism of 1,4-dihydropyridine derivatives:

The reaction is believed to involve michaeal type addition of B-amino,α-β-unsaturated carbonyl compound (1) formed from β-keto ester and amine to alkylidine-1,3-dicarbonyl compound (2) formed from β-keto ester and aldehyde.

The condensation of (1) and (2) gives the intermediate (3) which cylises to dihydropyridine (4).



Scheme (3.2): Reaction mechanism of 2,4-dihydropyridine derivatives (i-xiii)

3.4. R_f-values:

Thin layer chromatography is a method for analyzing the purity of the compound and monitors the progress of reaction.

chloroform and methanol were used as solvent system andRf-values were recorded in table (2.4).

3.5. IR spectral data of the compound:

Infra-red (IR) radiation refers broadly to that part of the electromagnetic spectrum between the visible and the micro wave region of greatest practical use to the organic chemist, the limited portion between 4000-400Cm^{-1}. The spectra of the prepared compounds were recorded with FT-IR-8400s KBr disk. The prepared compounds No. I,II,III,IV in this work, reveals absorption band of carbonyl group (C=O)st.vib at 1671,and 1720 cm^{-1} respectively. C-O stretching appeared at 1170, 1149 cm^{-1}respectively. Compounds combining the NO_2 group (ii, vi, xi) showed absorptionat 1301$cm^{-1}$and 1550st-vib. The sulfonamidederivatives (iv, viii, xiii) showed absorption at 1169 and 1550st-vib. The N-H band at 3318, 3464 cm^{-1} due to Nst.vib. The C-Nst.vib for the prepared compounds appeared at ~1287cm^{-1}, for C-H st.vib of all prepared compound appeared at~2915cm^{-1}. The C-H bending appeared at~1301cm^{-1}.

3.6. Conclusions and Recommendations:

The following points can be concluded and or recommended from this study:

- Use (ACD/lab) in organic synthesis design as it provides vital information which saves time and effort.

- From the synthetic point of view the retro synthetic analysis adopted in this work proved to be correct and good in accordance with the proposed mechanism.

- ^{1}HNMR, GC-MS, UV, HPLC and X-ray analyses are highly recommended.

References:

- Barril, X. and soliva, R., (2006). Molecular modeling. Molecular Biosystems, 2(12), 660-681.

- Bretzel, R. G. Bollen, C. C. E. Maeser and K. F. Federlin, 1993 "Nephroprotective effects of nitrendipine in hypertensive type I and type II diabetic patients" ,*Am. J. Kidney DIS.*,*21*,53-64.

- Boecker, R. H. Guengerich, F. P.1986, A one-pot multi –component synthesis of dihydropyridine derivatives via Hantzsch condensation using Amberlite IRA 900 as a heterogeneous catalyst under solvent-free conditions *J. Med. Chem.*,29, 1596-1603.

- Cramer, R.D., Patterson, D.E. and Bunce, J.D., (1988). Comparative molecular field analysis;110(18):5959-67doi:10.1021/Ja00226a005.

- Emmet (Ed.), J. C. 1990 "Comprehensive Medicinal Chemistry", Vol. 3, pergammon press, Oxford, Ch. 14. 1.

- Eharkar, P. S. B. Desai, H. Gaveria, B. Varu, R. Loriya, Y. Naliapara, A. Shah and V. M. Kulkarni, "Three-dimensional quantitative structure-activity relationship of 1,4-dihydropyridines as antitubercular agents", J. Med. Chem., 2002, 45, 4858-4867.

- Finar, 1. L. (1975); organic chemistry, volume 2 "Stereo chemistry and, the chemistry of the natural product" longmanHous, Burnt mill Harlow Essexa. UK, 5thed, Chapter 16, pages; 626-631.

- Fujita, T., Iwasa, J. and Hansch, C., (1964). A new substituent constant, π, derived from partition coefficients. Journal of the American Chemical ssSociety, 86(23), 5175-5180.

- Geissman, T. A. (1976); principle of organic chemistry, John willey and son, 4th edition, chapter35, page 797-798.

- Gigante, A. and Tagarro, I., (2012). Non-Steroidal Anti-Inflammatory Drugs and Gastroprotection with proton Pump Inhibitors. Clinical*druginvestigation*, 32(4), 221-233.

- Golan, D.E., Jashjion,A.H., Armstrong, E.J. and Armstrong,A.W.(2008), Principles of pharmacology: the patho-physiogic basics of drug therapy, second edition, 860.

-Guengerich, F. P. Martin, M.V. Beaune, P. H. Kremers, P. Wolff, T. Waxman, D. J. 1986 Biol. J. Chem., 261, 5051-5060.

- Hansch, C., Steward, A.R., Anderson, S.M. and Bentley, D.L., (1968). Parabolic dependence of drug action upon lipophilic character as revealed by a study of hypnotics. *Journal of medicinal chemistry, 11(1)*, 1-11.18.

-Hornback, J.M. (2005), organic chemistry, second edition, chapter 23 the synthesis of organic compounds, Cengage learning, 1024.

- Klusa, V. 1995 “Cerebrocrast, neuroprotectant cognition enhancer”, Drugs Future, 20, 135-138.

- Leach, A. R. and Gillet, V.J., (2007). Computational Models. *An Introduction to chemoinformatics,* 75-97.

- Matowe, D. Vo, W. C. M. Ramesh, N. Iqbal, M.W. Wolowyk, S.E. Howlett, E.E. Knaus, J. Med. Chem., 19995, 38,2851-2859.

- Ogawa, A. K. C. A. Willoughby, R. Bergeron, K. P. Ellsworth, W. M. Gesssler, R. W. Myer, J. Yao, G. Harris and K. T. Chapman, (2003). “Glucose-lowering in a db/db mouse model by dihydropyridinediacid glycogen phosphorylase inhibitors”, *Bioorg. Med. Chem. Lett*., 13, 3405-3408.

- Osborn, D. G; Schofield, B. A. and short, M. B. (1956); Chemistry of π-deficient hetero cyclic compounds; J. Chem. SOC; 12:4191.

- Pensak, D. A., 1989. Molecular modeling: scientific and technological boundaries. Pure and Applied Chemistry, 61(3), pp.601-603.

- Poindexter, G. S. M. A. Bruce, J. G. Breitenbucher, M. A. Higgins, S. Y. Sit, J. L. Romine, S. W. Martin, S. A. Ward, R. T. McGovern, W. Clarke, J. Russsel and I. Antal-Zimanyi, (2004). "Di hydropyridine neuropeptide Y Y1 receptor antagonists 2: Bioisosteric urea replacements", Bioorg. Med. Chem., 12, 507-521.

- Ramachandran, K.I., Deepa, G. and Namboori, K., (2008). Computational chemistry and molecular modeling: principles and applications. Springer Science& Business Media.

- Shan, R. C. Velazquez and E. E. Knaus., (2004). "Syntheses, calcium channel agonist-antagonist modulation activities, and nitric oxide release studies of nitrooxyalkyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2,1,3-benzoxadiazol-4-yl) pyridine-5-carboxylate racemates, enantiomers, anddiastereomers",*J. Med. Chem., 47, 254-261*.

- Sullivan, J.J., Jones, A.D. and Tanji, K.K., (2000). QSAR treatment of electronic substituent effects using frontier orbital theory and topological parameters. *Journal of* chemical *information and computer sciences*, 40(5), 1113-1127.

- Tropsha, A., Gramatica, P. and Gombar, V.K., (2003). The importance of being earnest: validation is the absolute essential for successful application and interpretation of QSPR models.QSAR& C*ombinatorial Science*, 22(1), 69-77.

- Stout, D. M. A.I. Meyers., (1982).Aone-pot multi-component synthesis of dihydropyridine derivatives via Hantzsch condensation using Amberlite IRA 900 as a heterogenous catalyst under solvent-free conditions*Chem. Rev., 82, 223-243*.

- Rueping, M. A. P. Antonchich, T. Theissmann., (2006). Angew. Chem., Int. Ed. 45, 3683-3686, and references cited therein.

- Visentin, S. B. Rolando, A. D. Stilo, R. Frutterro, M. Novara, E. Carbone, C. Roussel, N. Vanthuyne and A. Gasco., (2004). "New 1,4-dihydropyridines endowed with NO-donor and calcium channel agonist properties", J. Med. Chem., 47, 2688-2693.

-Hantzsch, A. (1881). "CondensationprodukteausAldehydammoniak und KetonartigenVerbindungen". ChemischeBerichte 14 (2): 1637–8. doi:10.1002/cber.18810140214.

- Xia, J. J.; Wang, G. W. (2005). "One-Pot Synthesis and Aromatization of 1,4-Dihydropyridines in Refluxing Water". Synthesis (14): 2379–83. doi:10.1055/s-2005-870022.