SYNTHESIS OF MEDICINAL DRUGS FROM NITROGEN BASED HETEROCYCLE

M.Sc. Dissertation Report

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“Synthesis of Medicinal Drugs from Nitrogen Based Heterocycle”

A Dissertation Report

Submitted in partial fulfilment

Of

The degree of M.Sc. (Organic chemistry)

By

Mr. RANEET R. GAWADE

To the

School of Chemical Sciences

Goa University

Taleigao Plateau

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DECLARATION

I hereby declare that the matter presented in this dissertation certified “Synthesis of medicinal drugs from nitrogen based heterocycle” is the result of investigation carried out by me, under the supervision of Assistant Professor Dr. Sandesh Bugde and for the award of a degree.

RANEET R. GAWADE

20P0490031

CERTIFICATE

This is to certify that the dissertation entitled “Synthesis of Medicinal Drugs from Nitrogen Based Heterocycle”, is bonified work carried out by Mr. RANEET R. GAWADE under my supervision, in partial fulfilment of the requirements for the award of the degree of Master of Science in Chemistry at the school of science, Goa University.

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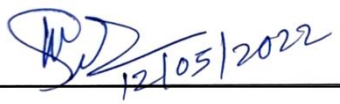

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ACKNOWLEDGEMENT

So finally the dissertation report is completed and it's a time to thank all, who were there in this journey. Firstly, I would like to thanks my project guide Dr. Sandesh Bugde, Assistant Professor, School of chemical sciences, Goa University, for giving me an opportunity to work under his guidance, for his patience and invaluable help during the course of work. I am also very much grateful to our respected dean Prof. Vidhyadatta Vernekar, School of chemical sciences, Goa University for his support and for providing me an opportunity to work in school of chemical sciences. Finally I would like to thank my friends and colleagues for sharing their ideas, and my family for their support.

Content

INTRODUCTION

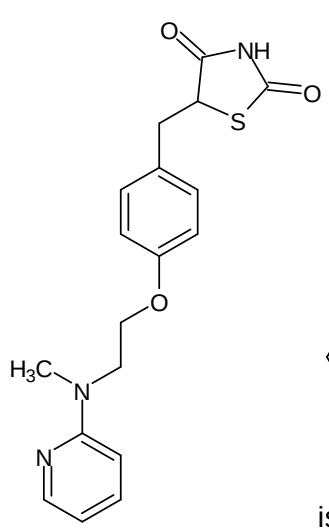
Heterocyclic compounds are of very much interest in our daily life, they have a Wide range of application. Heterocyclic compounds are predominantly used as pharmaceuticals[2], as agrochemicals and as veterinary products. They also find applications as Sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, Dye stuff.[3] they are used as vehicles in the synthesis of other organic Compounds. Some of the natural products e.g. antibiotics such as penicillin's, Cephalosporin; alkaloids such as vinblastine, morphine, reserpine etc. have Heterocyclic moiety.[1]

The presence of the Heteroatoms gives heterocyclic compounds physical and chemical properties that are often quite distinct from those of their all-carbon-ring analogs.[1]

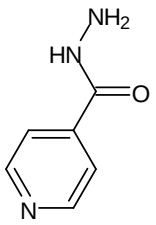
The Most common heterocycles are those having five- or Six-membered rings and containing heteroatoms of Nitrogen (N), oxygen (O), or sulfur (S). The best known Of the simple heterocyclic compounds are pyridine,Pyrrole, furan, and thiophene.[1]

Development in the heterocycle chemistry have created Several opportunities for new technique. Firstly, the opportunities emerge for the stereo-, regio- and chemo-selective production of new heterocycles to enhance the flexibility of the substitution patterns and the substituents. Secondly, opportunities emerge for regio-, chemo-, and stereo-selective functionalization of the already developed heterocycles to facilitate the flexibility of the substitution patterns and the substituent's. Thirdly, opportunities can emerge for the reaction conditions optimization for the functionalization and the manufacture of the heterocycles to facilitate the enhancement of tolerance of the different functional groups of aiding the late-stage modification of the multifaceted intermediates.[2] The development in heterocycle chemistry also streamline the synthesis processes by eliminating the steps or merging the steps into the one-pot procedures. Fourthly, the heterocycle chemical processes also aid in the removal of the toxic and costly reagents, vigorous reaction conditions, and the tedious product separations [2].

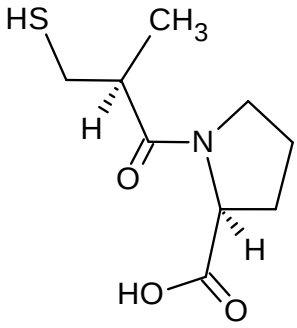
Nitrogen containing heterocycle have drawn considerable attention of researchers in past few decades.[3] N-based heterocycles are absolutely neccseeary diet components such as thiamin (vitamin B1), riboflavin (vitamin B2), pyridoxol (vitamin B6), nicotinamide (vitamin B3) which treats deficiencies, diseases and carry out vital processes of the body[1]. Nitrogen containing heterocyclic compounds are not only present as the backbone in biologically active natural products used as traditional medications or approved prescribed drugs, but also some of their synthetic derivatives in different sizes, nowadays are prescribed and are available in market. The most famous are diazepam, rosiglitazone, isoniazid, chlorpromazine, metronidazole, barbituric acid, captopril, chloroquine, azidothymidine and anti-pyrine. Furthermore, most of the vitamins, nucleic acid, enzymes, co-enzymes, hormones, and alkaloids contain N-based heterocycles as scaffolds.[3]



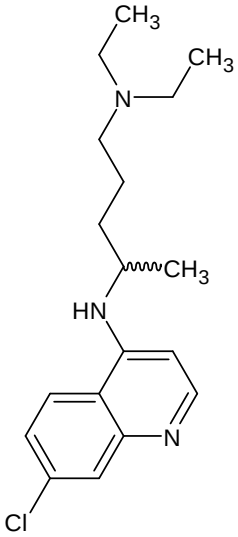
Rosiglitazone



isoniazide



captopril



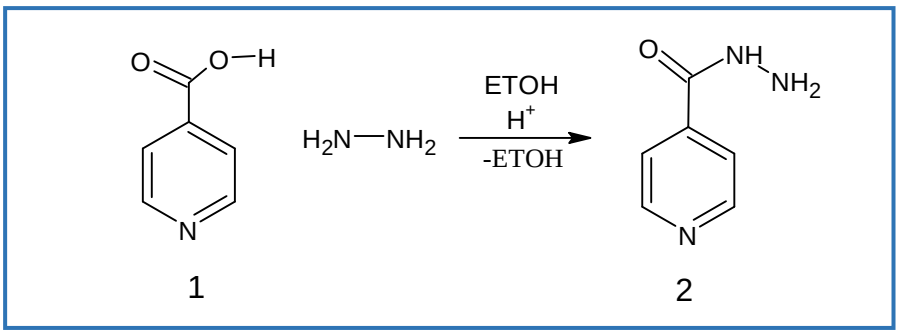
chloroquine

An FDA database has revealed that about 60% of small molecule drugs contain N-based heterocycles, showing the structural significance of N-based heterocycles in drug design and drug discovery. The prevalence of N-heterocyles in biologically active compounds can be due to their stability and operational efficiency in human body and due to the fact that the nitrogen atoms are readily bonded with DNA through hydrogen bonding. Anti-cancer activities of N-based heterocycle agents are largely due to their tendency of interaction with DNA via hydrogen bonding. Furthermore they show segment resemblance with histidine imidazole molecule, N-based-heterocycles can be linked with protein molecules more easily than some other heterocyclic scaffolds, thus, these types of N-heterocyclics are the most promising drugs for being designed and screened as anti-cancer drugs.[4]

Literature review

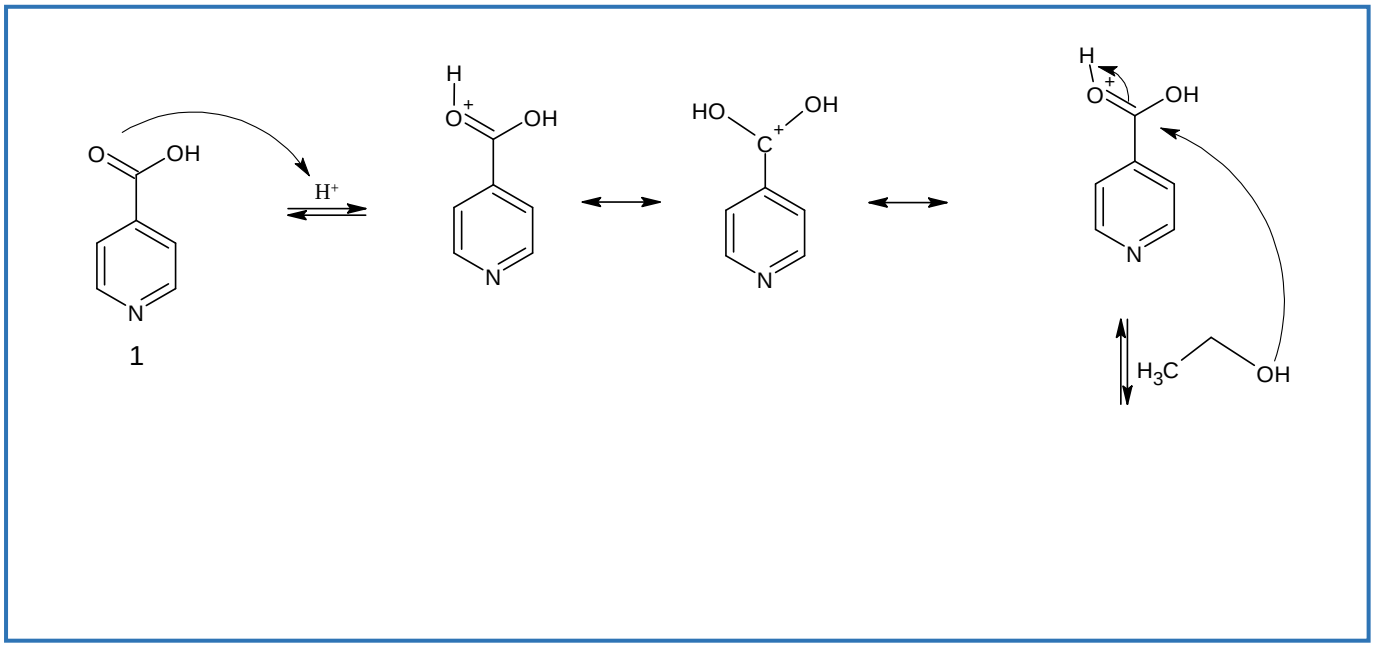
Synthesis of isoniazid (1) from isonicotinic acid.

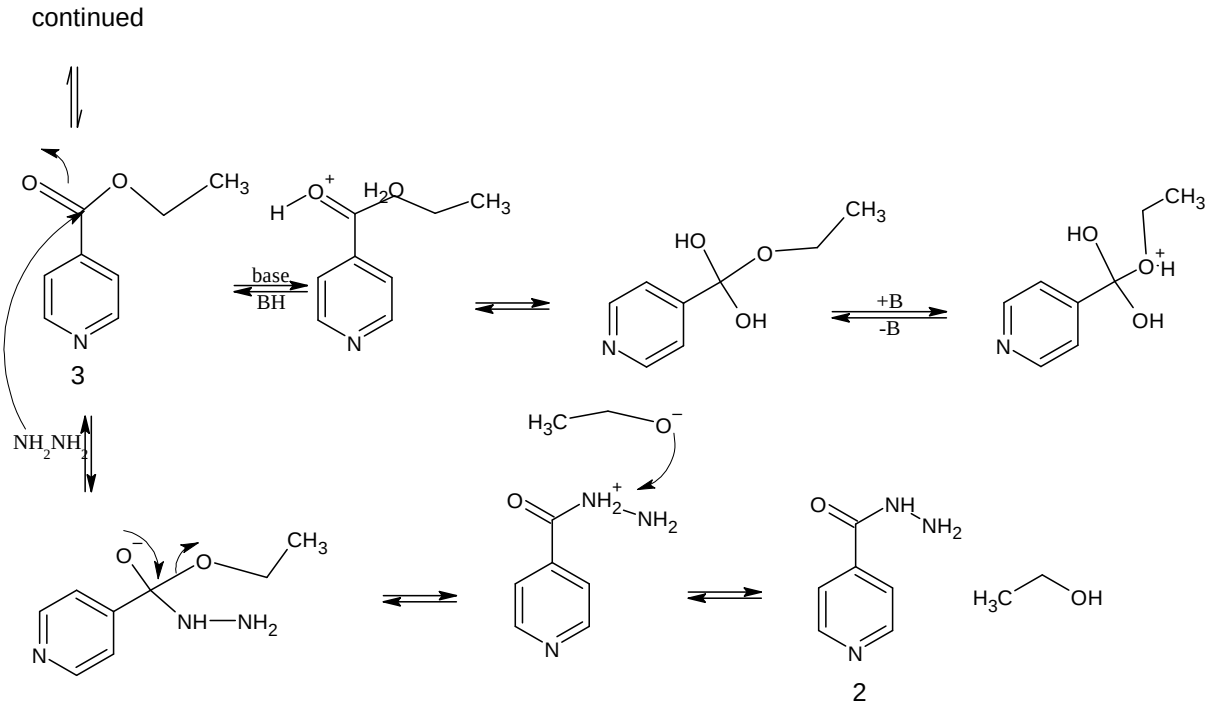
Isoniazid (2) is a white, superfine cristalline and scentless powder which dissolves moderately in water. . Meyer and Malley were the first to synthesize Isoniazid (2) in the year 1912. Isoniazid (2) is the most important antibiotic to fight tuberculosis and it's popular because of its bioavailability. It operates against the human causative organism (Mycobakterium tuberculosis) and the cattle germ (Mycobakterium bovis).[5]



Isoniazid (2) can be synthesized in a two-step from isonicotinic acid (1) as shown in scheme 1. In the beginning of the reaction the carbonylgroup of isonicotinic acid (1) is protonated by acid, as a result carbon gets more electrophillic. Thus Ethanol starts a nucleophile attack at this carbon. The proton is transferred to the hydroxide group of nicotinic acid and water molecule is eliminated. The catalyst is degenerated and isonicotinic-acidethylester (3) is built as an intermediate. Hydrazine attacks the carbon of the intermediate (3) and ethanol is eliminated, the yielding Isoniazid (2).[5, 6]

Reaction mechanism of synthesis of Isoniazid (2).





scheme 1: synthesis of isoniazide

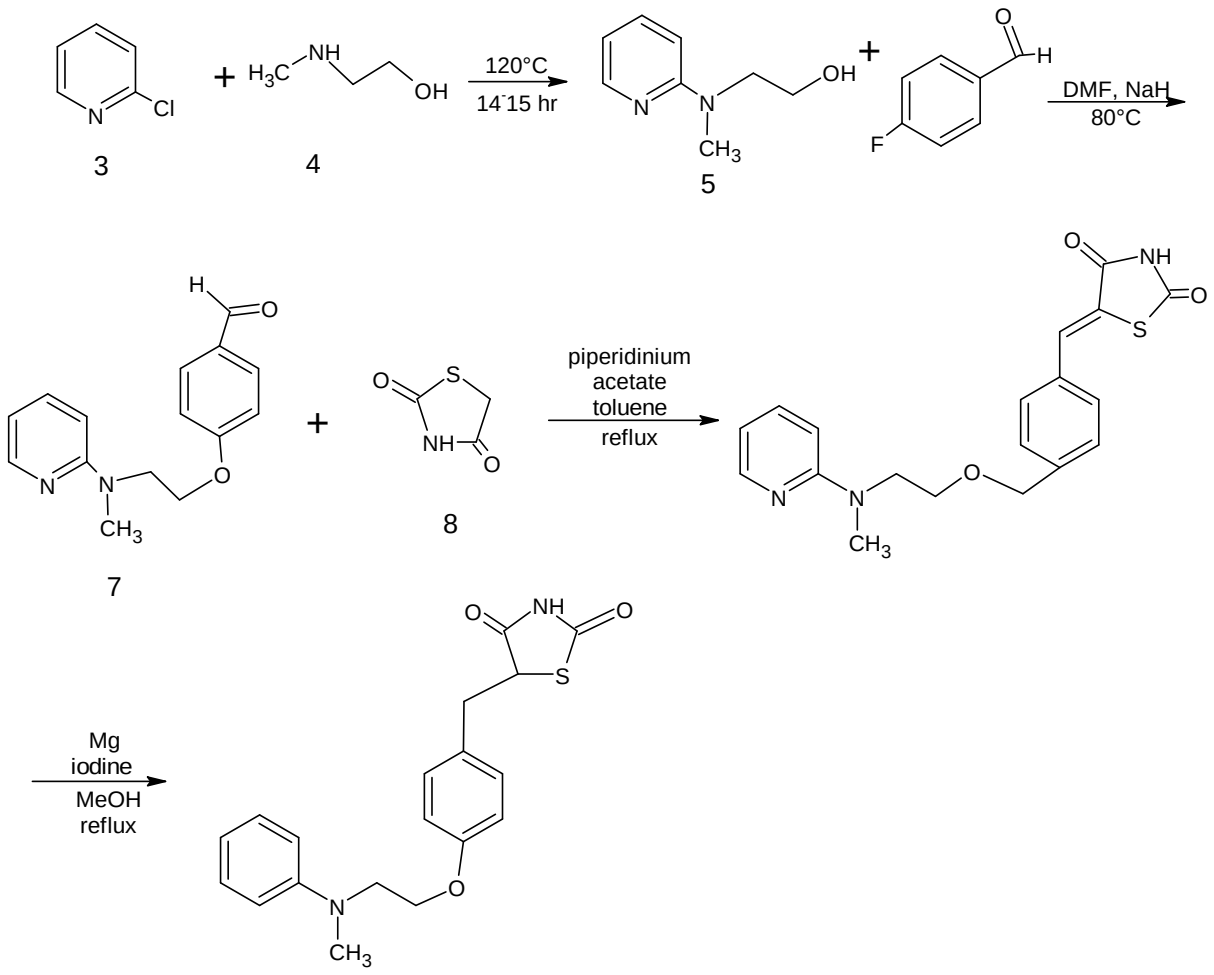
Isoniazid can also be synthesized from microwave assisted enzyme catalysis via lipase-catalyzed hydrazinolysis. [6]

Synthesis of Rosiglitazone (10) from 2-chloropyridine.

Rosiglitazone (10) is the important species containing a pyridine moiety. It is a members of the thiazolidinedione drug class,which are well-known as antihyperglycemic drugs used for the treatment of diabetes mellitus type II.. These pharmaceutical agents act as binders to the peroxisome proliferator-activated receptors that upon activation migrate to the DNA to regulate the transcription of specific genes which control the metabolism of carbohydrates and fatty acids. Rosiglitazone (10) is available in market under name Avandia by GlaxoSmithKline, is one of the most potent drugs in this class.[4, 8, 9]

Rosiglitazone (10) is synthesis as shown in Schemes 2. Here the pyridine unit is introduced via SNAr reaction between N-methylethanolamine (4) and 2-chloropyridine (3) which in turn is readily synthesized by chlorination of 2-pyridone with phosphorous oxychloride. The resulting primary alcohol (5) is subjected to a second SNAr reaction with 4-fluorobenzaldehyde (6). A Knoevenagel condensation reaction between aldehyde functionality compound (7) and thiazolidinedione (8) in the presence of a catalytic amount of piperidinium acetate leads to the exclusive formation of the desired Z-isomer product (9). The newly formed double bond was efficiently reduced by using magnesium in methanol thus

preventing catalyst poisoning issues pertaining to the thiazolidinedione (8) moiety as experienced while using other reducing agents.[4, 8, 9]

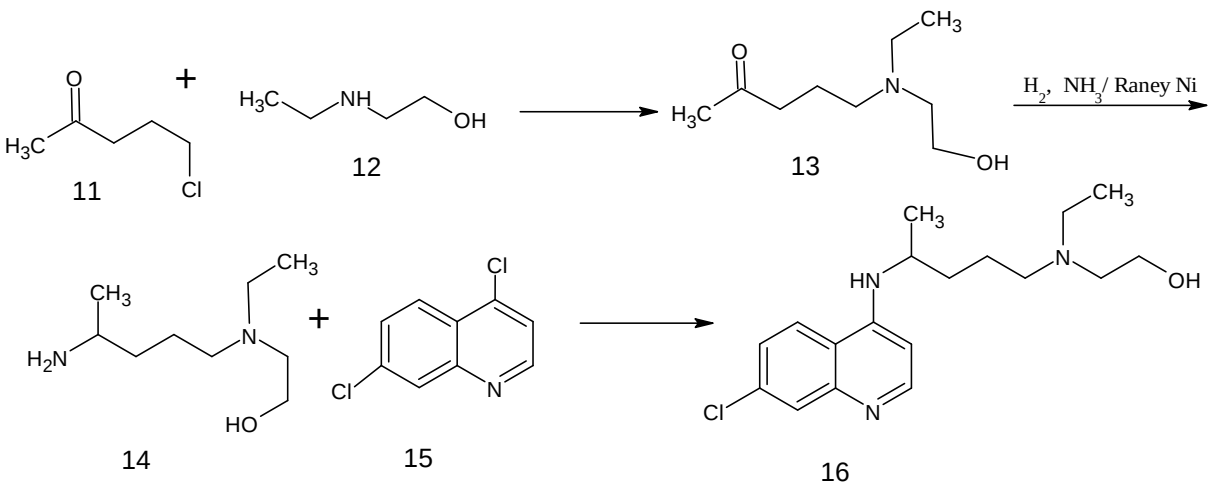


scheme 2 : synthesis of Rosilitazone

Synthesis of hydroxychloroquine (16) from 4, 7-dichlroquinoline

Hydroxychloroquine (16) (HCQ), is available in the market under the trade name, Plaquenil, It is an antimalarial drug developed for both treatment and prevention of the disease in response to the widespread malaria resistance to chloroquine. Hydroxychloroquine (16) is also an effective nonsteroidal drug with anti-inflammatory activity for the treatment of rheumatoid arthritis in patients with cardiovascular disease, lupus, and porphyria cutanea tarda. It is also being used as an experimental medication for possible treatment for notorious coronavirus disease 2019 which was very recently broken out. [11, 10, 4]

Hydroxychloroquine (16), is 7-chloro-4-[4-[ethyl(2-hydroxyethyl)amino]-1-methylbutylamino] quinoline which was synthesized in three steps, starting from commercially available 1-chloro-4-pentanone, as describe in Scheme 3. Reaction of 1-chloro-4-pentanone (11) with 2-ethylaminoethanol (12) yield the aminoketone (13) which was then subjected to reductive amination to yield 4-[ethyl(2- hydroxyethyl)amino]-1-methyl-butylamine (14). Reaction of the this with 4, 7-dichlroquinoline (15) gave the desired Hydroxychloroquine (16) [10, 4]



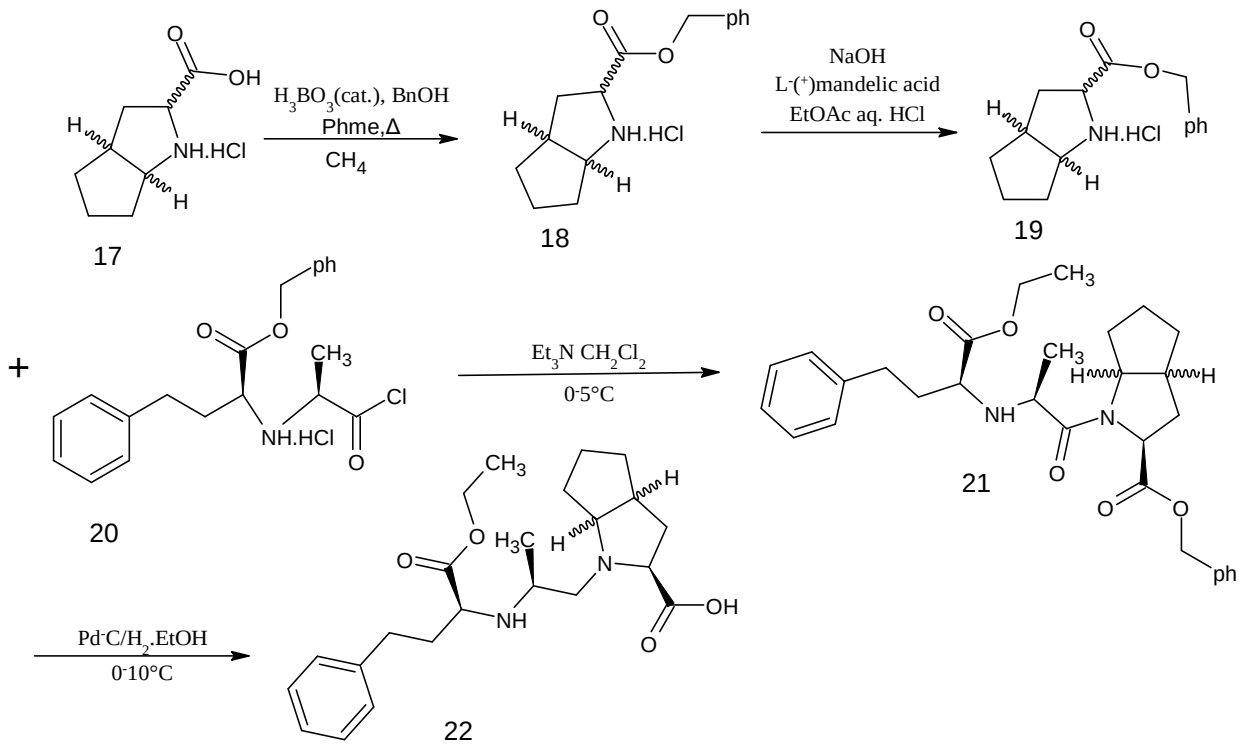
scheme 3: synthesis of hydroxychloroquine

Synthesis of Ramipril (22) from 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid hydrochloride

Ramipril (22) is available in pharmacies under the brand name, Altace® as capsules. Ramipril (22) is a 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid derivative, it belongs to a class of angiotensin converting enzyme (ACE) inhibitors which are used for treating high blood pressure and congestive heart failure and also for preventing kidney failure due to high blood pressure and diabetes.[12].

Highly enantioselective and cost-effective synthesis of Ramipril (22) was reported using an environmentally benign process as discuss in scheme 4. It start with esterification of racemic 2-aza-bicyclo-[3.3.0]-octane-3-carboxylic acid hydrochloride(17) with benzyl alcohol in refluxing toluene in the presence of boric acid, as a catalyst, followed by a fully-bodied resolution using cheap and recyclable L-(+)-mandelic acid as vital steps to give the ester, the (S,S,S)-2-aza-bicyclo-[3.3.0]- octane-3-carboxylic acid benzyl ester (19) in 83%. This was then coupled with benzyl N-(2S-carbethoxy-3-phenyl propyl)-S-alanine acid chloride (20) in the presence of Et_3N in CH_2Cl_2 to give ramipril benzyl ester (21) in 94% yield. In the last

step, ramipril benzyl ester (21) was hydrogenated over Pd/C in EtOH to produce, the desired target, optically pure ramipril (22) in 95% chemical yields.[12, 4]

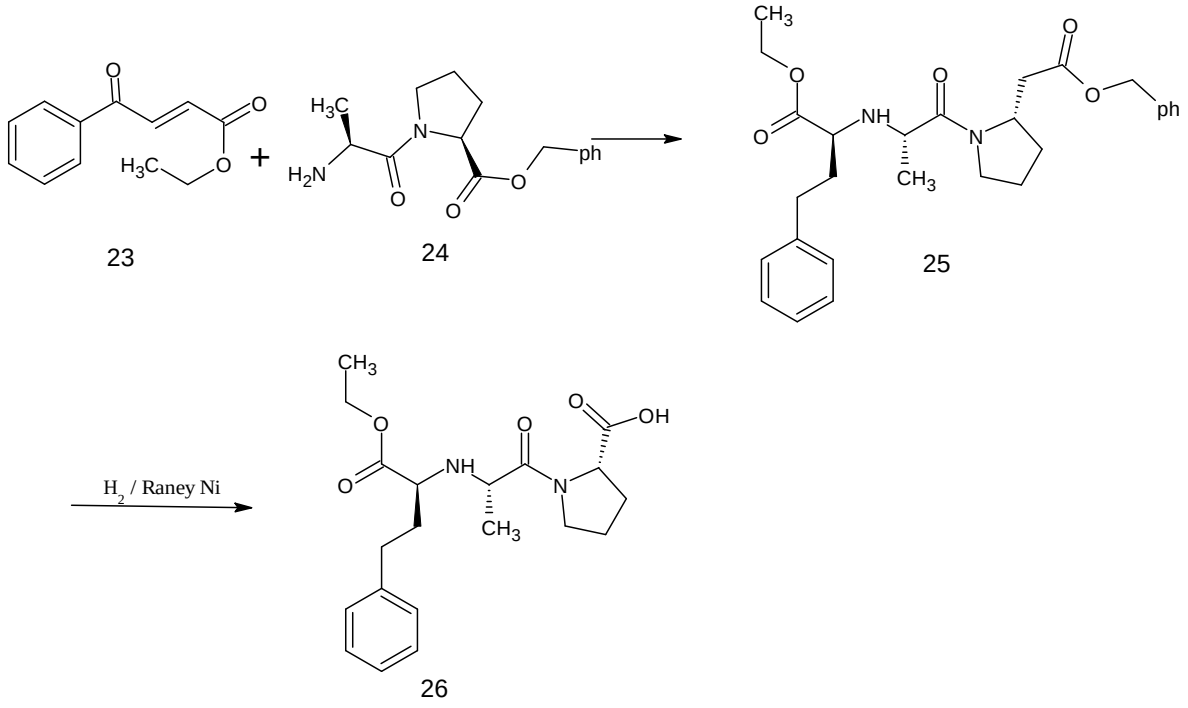


scheme 4: synthesis of ramipril

Synthesis of Enalapril (26) from benzyl ester of L-alanyl-L-proline

Enalapril (26), is available in market under the brand name Vasotec, it is a drug, employed for the treatment of high blood pressure, and kidney disease caused by diabetes and heart failure, in which it is frequently used with a diuretic, such as furosemide. These drugs block action of the angiotensin-converting enzyme, which results in less production of angiotensin II and inhibits its vasoconstricting action on arterial and venous blood vessels. [13, 4]

Synthesis of Enalapril (26) is shown in scheme 5. Enalapril (26) ((S)-1-[N- [1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline), was prepared by treating the benzyl ester of L-alanyl-L-proline (24) with the ethyl ester of 3-benzoylacrylic acid (23), giving the product (25), which on further hydrogenation in the presence of a RANEY® as catalyst eliminates the protective benzyl moiety, producing the desired product Enalapril (26) .[13,4]

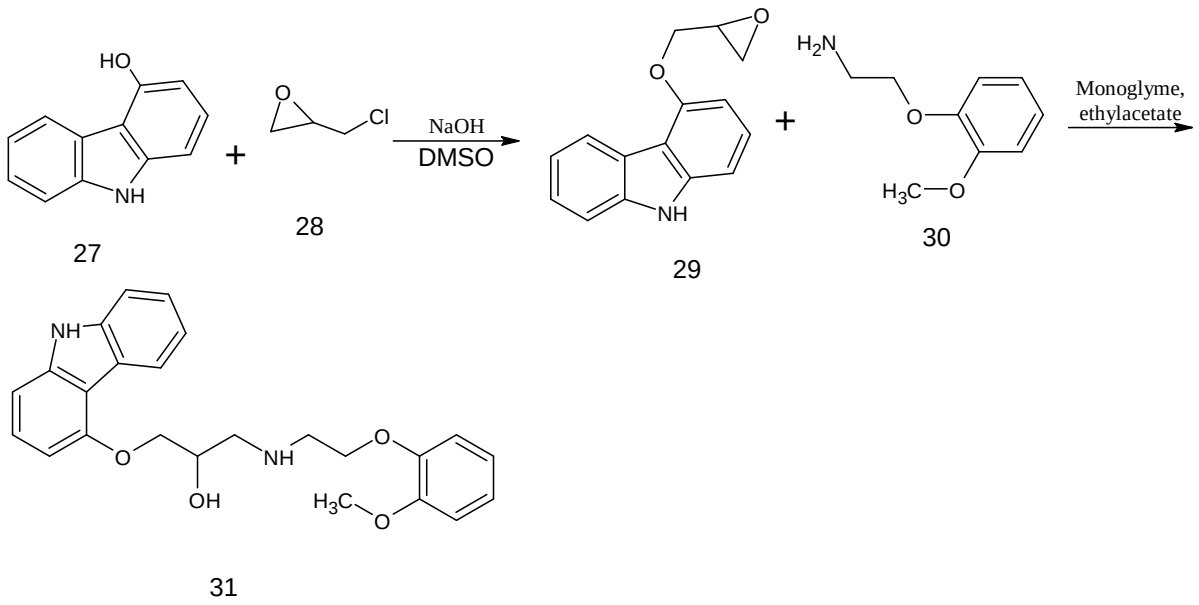


scheme 5: synthesis of enalapril

Synthesis of carvedilol (31) from 4-hydroxycarbazole

Carvedilol (31) is multiple-action drug and is sold in market under brand name of Coreg. It is a β1-, β2-, and α1-adrenoreceptor blocker with antioxidant and antiproliferative effects, it is prescribe for the treatment of hypertension, stable angina pectoris, and congestive heart failure. Carvedilol (31) significantly reduces mortality in patients with mild to severe congestive heart failure.[4, 15]

Carvedilol (31) is 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol and it can be produced via a two-step synthesis as shown in scheme 6. First step involves reaction between 4-hydroxycarbazole (27) and epichlorohydrin (28) in the presence of NaOH to produce 4- (2,3-epoxypropoxy)carbazole (29), which after isolation, when treated with 2-(2-methoxyphe-noxy)ethanamine (30) give the desired target molecule, Carvedilol (31) .[16,4]

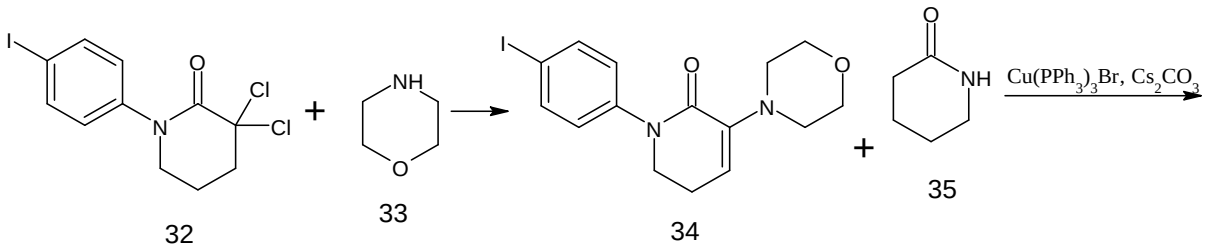


scheme 6: synthesis of carvedilol

Synthesis of apixaban (39) from lactam

Apixaban (39), is available in the market under the brand name eliquis . Apixaban (39), is a highly potent, selective, and orally bio available inhibitor of blood coagulation factor Xa. It was developed for the prevention and treatment of thromboembolic diseases by Bristol-Myers Squibb. It has also exhibited promising in treatment of severe coronary syndrome (ACS), cerebrova scular ischemia, and cancer.[17,4]

Several routes for the preparation of apixaban (39) have been reported. In this review apixaban (39) synthesis is discuss as shown in scheme 7. Here N-Phenylvalerolactam (36) was synthesized through an Ullmann reaction with iodide derivative (34) In presence of $Cu(PPh_3)_3Br$ as a catalyst. This was further reacted with hydrazone (37) (which was prepared in two step via diazotization of 4-methoxyaniline followed by the Japp–Klingemann reaction with ethyl 2-chloroacetoacetate) in an addition elimination fashion to give pyrazolecarboxylate (38). Finally aminolysis of pyrazolecarboxylate (38) in presence of formamide and sodium methoxide leads to target molecule, Apixaban (39). [17,4]



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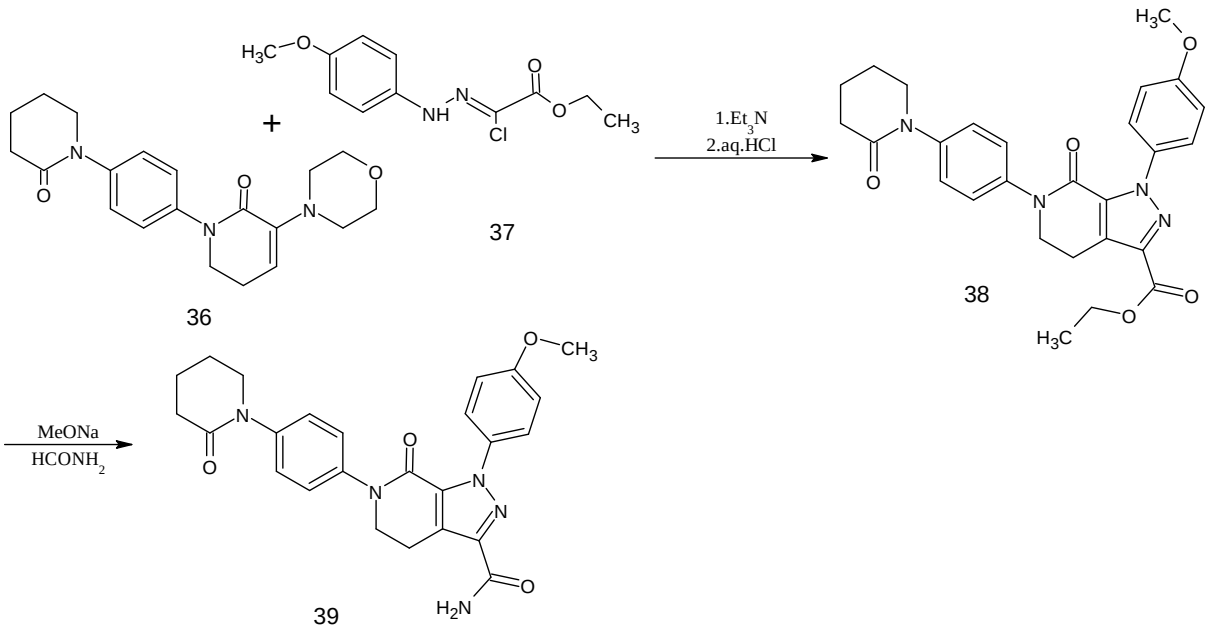


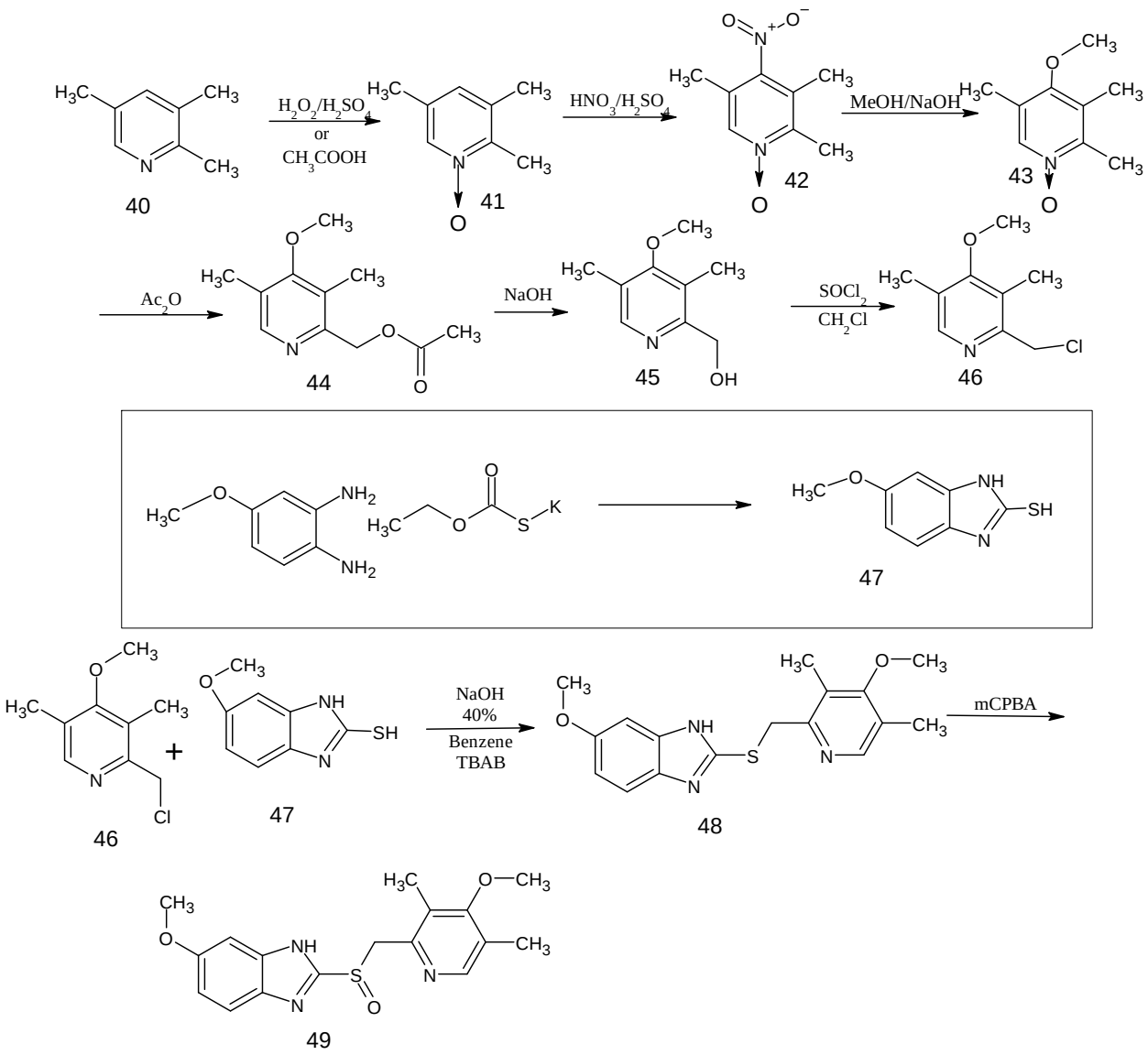
scheme 7: synthesis of apixaban

Synthesis of omeprazole (49) from 2,3,5-Trimethyl pyridine

Omeprazole (49) 5-methoxy-2-(4-methoxy-3,5-dimethyl-2- pyridinyl)methylsulfinyl)-1H-benzimidazole is marketed under the brand name Prilosec and is a known inhibitor of gastric acid Secretion. It is use where the inhibition of gastric acid secretion is beneficial, for the treatment and prevention of gastrointestinal inflammatory diseases, Such as gastritis, gastric ulcer and duodenal ulcers. It is a proton pump inhibitor which inhibits secretion of gastric acid by irreversibly blocking the enzyme system of hydrogen/potassium adenosine triphosphatase (Hþ/Kþ-ATPase) .Omeprazole (49) may be given by mouth as the base or magnesium salt or intravenously as the sodium salt. Omeprazole (49) is also used for the prophylaxis of acid aspiration during general anaesthesia.[18, 19, 4]

Omeprazole (49) is synthesis from nitrogen based heterocycle, as discuss in the scheme 8. Here,2,3,5-Trimethyl pyridine (40) was oxidized by using hydrogen peroxide in acetic acid to give the N-oxide (41). Further, it was nitrated using a mixture of sulfuric acid and nitric acid to give the 4-nitro derivative (42). The nitro group in (42) was replaced by hydroxymethylation to yield product (43). The Treatment of this compound with acetic acid anhydride reduces the ring and forms an ester derivative (44). The corresponding alcohol (45) was formed by the treatment with base, followed by replacement of the hydroxyl group with a chloride using thionyl chloride to give 2-chloromethyl-4-methoxy-2,3,5-trimethyl pyridine (46). The benzimidazole derivative (47) replaces the chloride of (46) giving 5-methoxy-2-

[((4-mrthoxy-3,5-dimethyl-2-pyridinyl)methyl)thio]-1H-benzimidzole (48). Oxidation of thioether group in (48) by hydrogen peroxide gives the final product, Omeprazole (49).[19, 4]

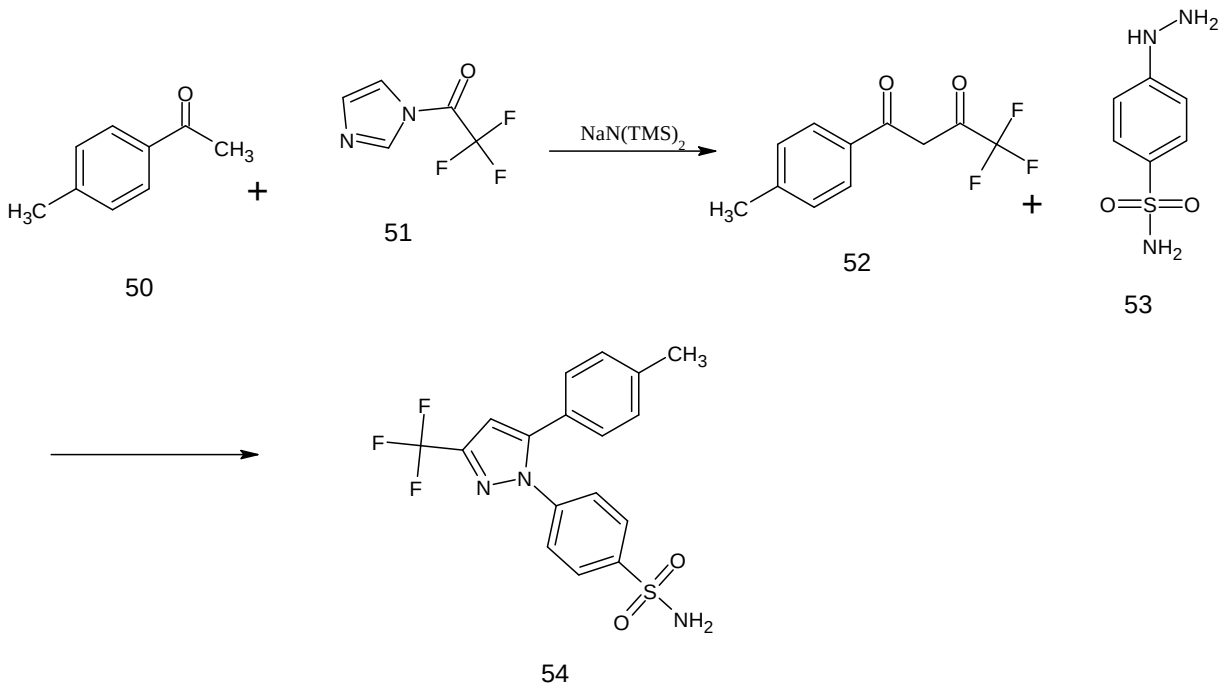


scheme 8: synthesis of omeprazole

Synthesis of celecoxib (54) from N-(trifluoroacetyl)imidazole

Celecoxib (54) is a 1,5- diarylpyrazole moiety integrates a sulfonamide or methylsulfonate pharmacophore at para position of N-aryl segment. It is a selective COX-II inhibitor developed and commercialized by Pfizer under the name Celebrex® in the treatment of rheumatoid arthritis, osteoarthritis, and painful menstruation related symptoms. The para substituted sulfonamide or methylsulfonate pharmacophore is known to interact effectively with the COX-II secondary pocket through slow tight binding kinetics, which is absent in COX-I .[21, 20, 4]

Celecoxib (54) was synthesized by a reaction of 4- sulfamoylaphenylhydrazine (53) with 4,4,4-trifluoro-1-(p-tolyl)butane1,3-dione (52) obtained via interaction of 4-methyl-acetophenone (50) with N-(trifluoroacetyl)imidazole (51) in the presence of sodium bis(trimethylsilyl) amide, as shown in scheme 9.[21, 20]

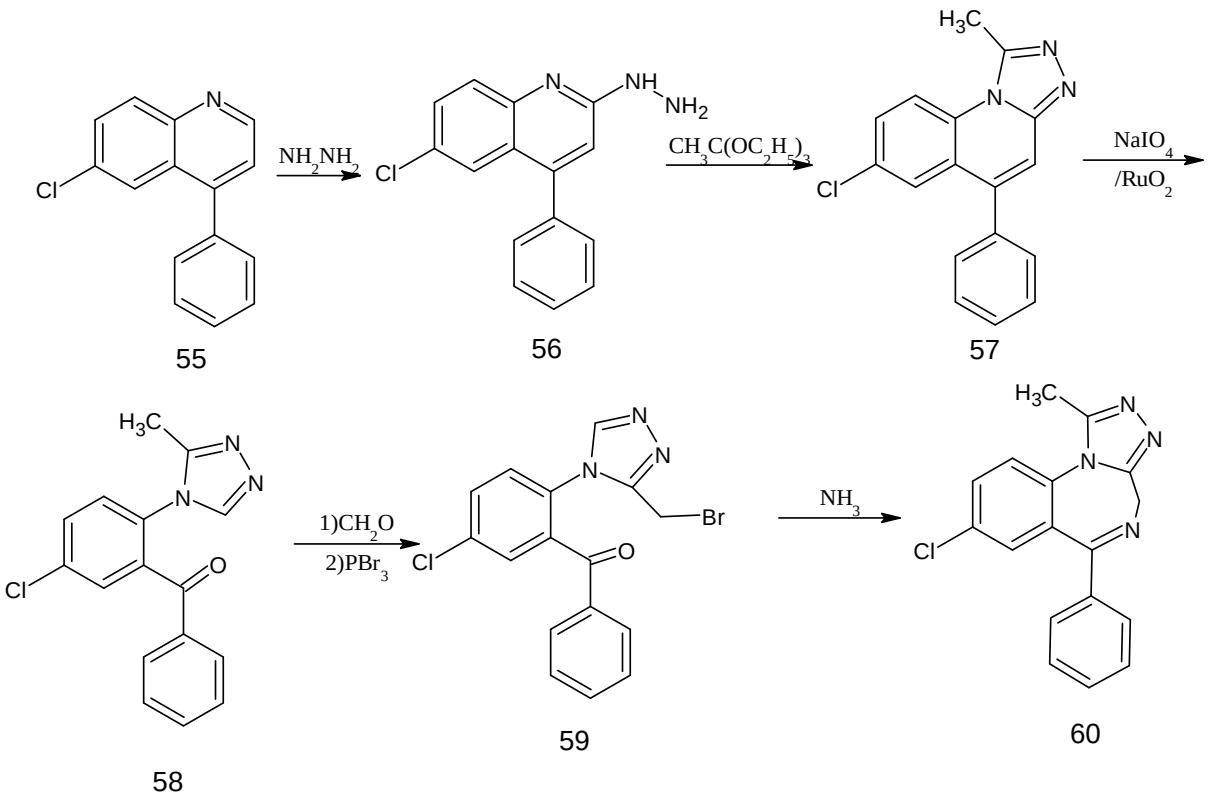


Scheme 9: synthesis of celecoxib

Synthesis of alprazolam (60) from of 2,6-dichloro-4-phenylquinoline.

Alprazolam (60) belongs to the class of Benzodiazepines. It is effective in treatment of panic disorders, agoraphobia, and controlling of anxiety disorders. Alprazolam (60) is also helpful for treatment of depression. It is short-lasting sedative taken orally in conditions of nervousness, panic disorders, anxiety which also treats depressive syndrome. Alprazolam (60) , sold under the brand name.[23,4]

Alprazolam (60), is actually 8- chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine. It can be synthesis from of 2,6-dichloro-4-phenylquinoline as shown in scheme 10. Here, 6-chloro-2-hydrazino-4-phenylquinoline (56) is treated with hydrazine and on heating this mixture with triethyl orthoacetate in xylene produces corresponding triazole (57) via the heterocyclization. When this is subjected to oxidative cleavage using sodium periodate and ruthenium dioxide in an acetone/water as solvent it gives 2-[4-(30 -methyl-1,2,4- triazolo)]-5-chlorobenzophenone (58). Further, Treatment of (58) with formaldehyde followed by substitution of the hydroxyl group by PBr_3 gives 2-[4-(30 -methyl-50 –bromomethyl-1,2,4-triazolo)]-5-chlorobenzophenone (59). Replacement of bromine group in (59) with an amino group using ammonia gives alprazolam (60).[22,23,4]

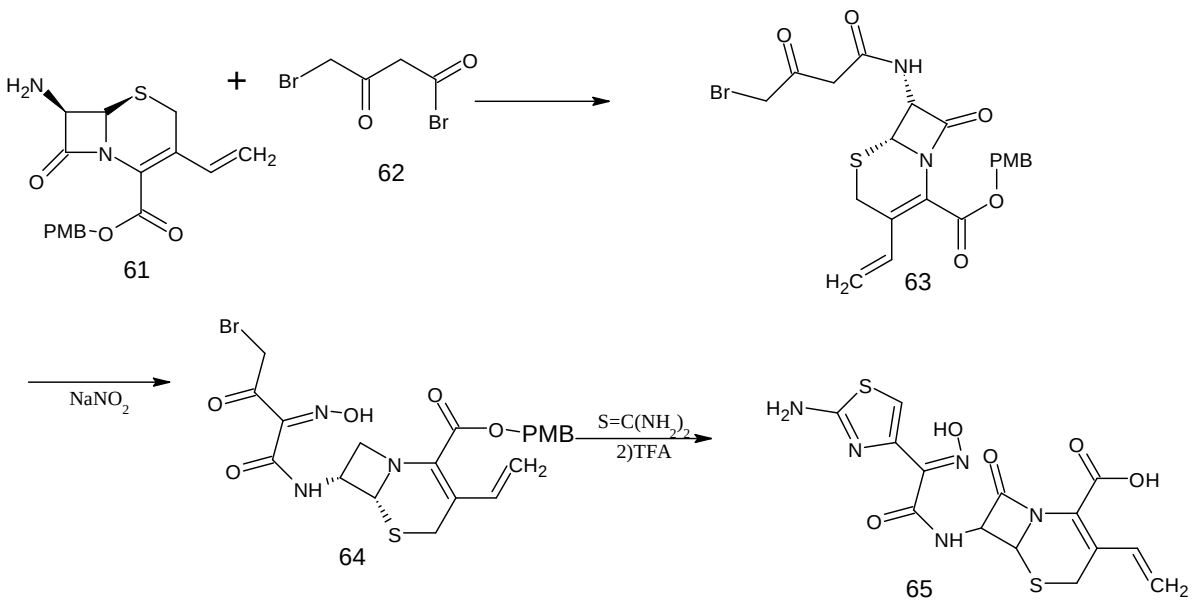


scheme 10: synthesis of alprazolam

Synthesis of cefdinir (65)

Cefdinir (65), 7-β-[(Z)-2-(2-amino-4-thiazolyl)-2-hydroxyiminoacetamido]-3vinylcephem-4-carboxylic acid, is a third-generation, semisynthetic cephalosporin antibiotic characterized by having a broad spectrum of antibacterial activity against staphylococci and streptococci. It made available in market under the brand name Omnicef. It is used for oral administration and has a broader antibacterial spectrum over gram-positive and gram-negative bacteria.[24, 4]

It can be synthesis from primary amine (61), as discuss in scheme 11. Here, the primary amine (61) is treated with 4-bromo-3-oxobutanoyl bromide (62) which gives the formation of amide (63). Active methlylene group in amide (63) is nitrosated by using sodium nitrite. This then undergo tautomarization to produce an oxime (64). Reaction of this oxime with thiourea result in the formation of cefdinir (65).[24, 4]

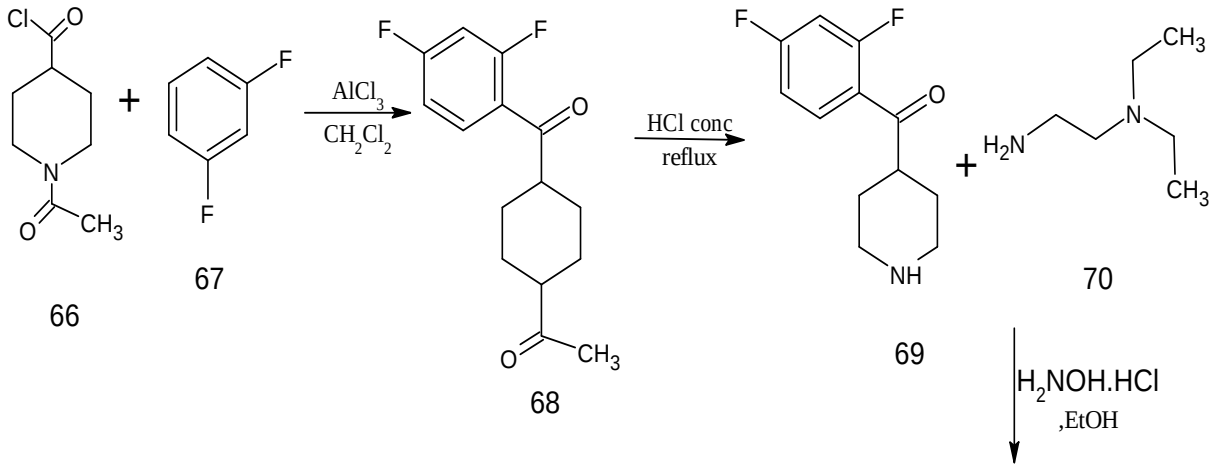


scheme 11: synthesis of cefdinir

Synthesis of risperidone (74) from 1-acetyl-4-piperidinecarbonyl chloride .

Risperidone (74) is the second-generation antipsychotic drug that was specifically designed as a combined D2 and serotonin 5-HT(2A) receptor antagonist. Initially it was approved for use in schizophrenia, mania of bipolar disorder, irritability and aggression of autism. it is also effectively used in other instances of psychosis, including schizoaffective disorder, depression with psychotic features, and psychosis secondary to general medical conditions. [25,26]

Risperidone (74) was synthesized using 1-acetyl-4-piperidinecarbonyl chloride (66) as shown in scheme 12. Here 1-acetyl-4-piperidinecarbonyl chloride (66) was used to acylate 1,3-difluorobenzene (67) in dichloromethane using aluminum chloride as Lewis acid. This reaction gave 1-(4-(2,4-difluorobenzoyl)piperidin-1-yl)ethan-1-one (68). The protecting acetyl group in (68) was removed by hydrolysis using 6 N hydrochloric acid, which gave (2,4-difluorophenyl)(piperidin-4-yl) methanone (69). The obtained product was converted into oxime (71) using hydroxylamine hydrochloride in ethanol in the presence of N,N-diethylenethanamine (70). Synthesized oxime (71) was cyclized to 6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole (72) by refluxing it with 50% potassium hydroxide solution in water. In the final step the obtained product (72) was alkylated using 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (73) by heating the reaction mix. at 85-90˚C in dimethylformamide in the presence of sodium carbonate and potassium iodide, thus yielding the desired product, risperidone (74) .[25,26]



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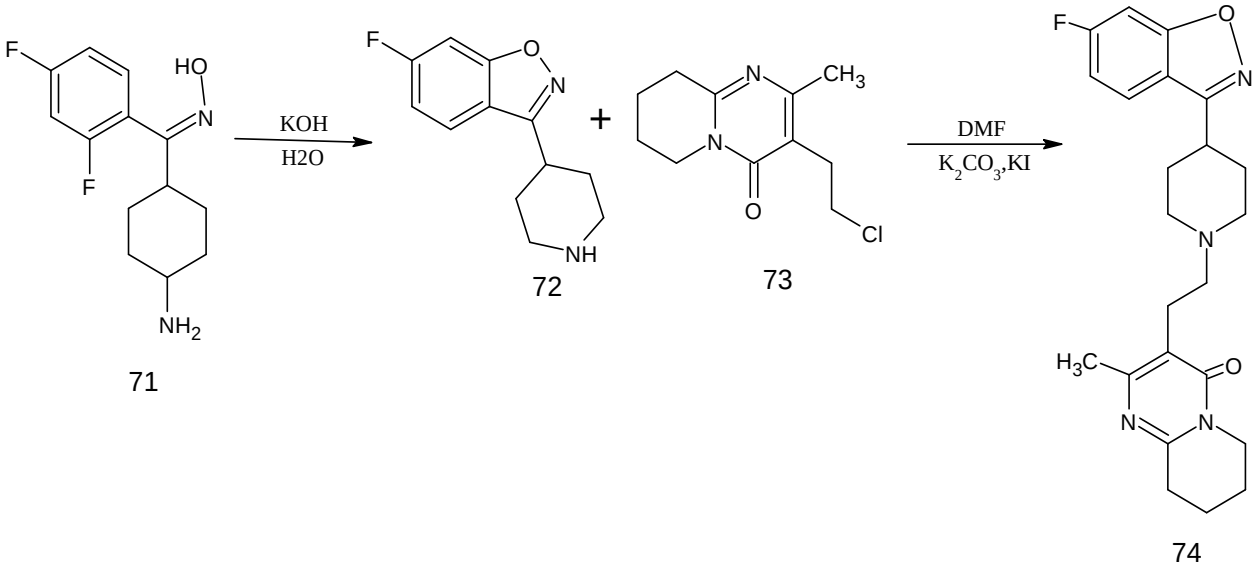
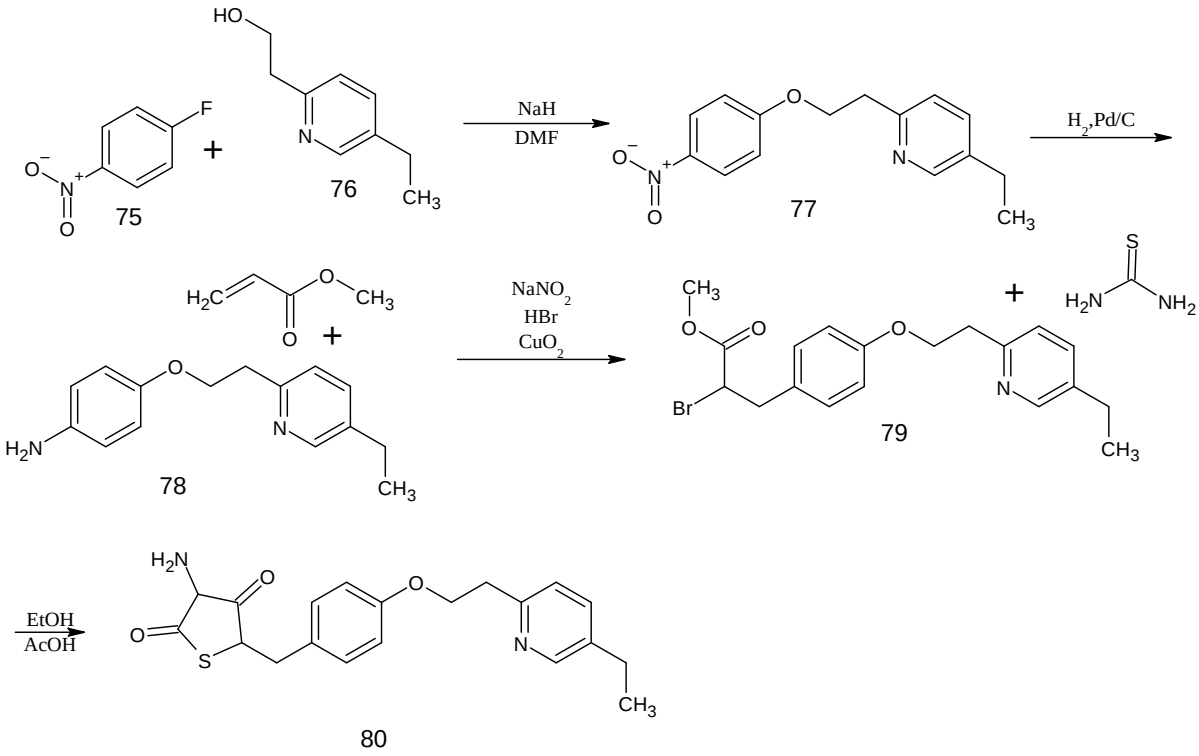


scheme 12: synthesis of risperidone

Synthesis of pioglitazone (80) form 2-(5-ethyl-2- pyridyl)ethanol .

Pioglitazone (80) is a medication prescribed for the treatment of type 2 diabetes. It is an orally administered insulin sensitising thiazolidinedione agent that has been developed for the treatment of type 2diabetes mellitus.[27,28]

Pioglitazone (80) was synthesized via a five step reaction pathway as shown in scheme 13, starting from commercially available 1-fluoro-4- nitrobenzene (75). Reaction of 1-fluoro-4-nitrobenzene (75) with 2-(5-ethyl-2- pyridyl)ethanol (76) yields pyridylethoxybenzene (77) which on reducing with Pd on charcoal as catalyst provide the anticipated aromatic amine (78). Later, aromatic amine (78) on diazotization in a mixture of acetone/methanol followed the workup with HBr, and coupling with methylacrylate in the presence of Cu_2O (the Meerwein arylation) gives the methyl 2-bromo-propanoate derivative (79). When this was subjected to cyclocondensation with thiourea, gave an imino compound as intermediate which upon hydrolysis provided the desired target product, pioglitazone (80) .[4,27]

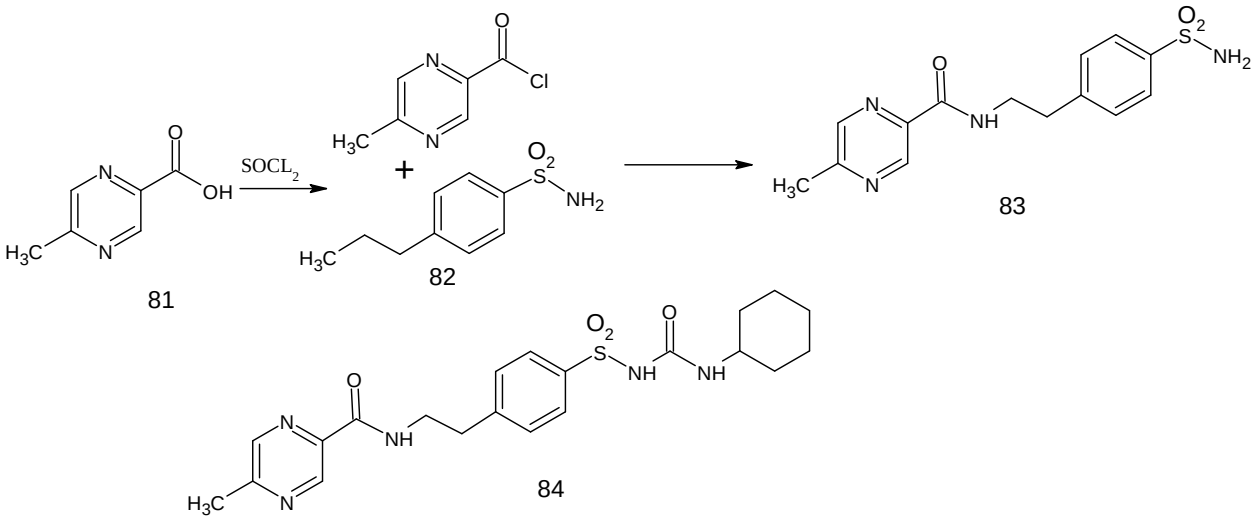


scheme 13: synthesis of pioglitazone

Synthesis of glipizide (84) from 6-methylpyrazincarboxylic acid.

Glipizide (84), 1-cyclohexyl-3-[[p-[2-(5-methylpyrazincarboxamido)ethyl]phenyl]sulfonyl]urea , is an anti-diabetic medication prescribed for the treatment of type 2 diabetes . It was introduced in market under the brand name Glucotrol.

Synthesis of glipizide (84) is discuss in Scheme 14, here 6-methylpyrazincarboxylic acid (81) is treated with $SOCl_2$, leading to the formation of respective chloride that is further reacted with 4-(2-aminoethyl)benzenesulfonamide (82), giving an amide (83). The resulting sulfonamide (83) upon reaction with cyclohexylisocyanate via conventional procedure resulted in formation of the desired glipizide (84).[29,4]

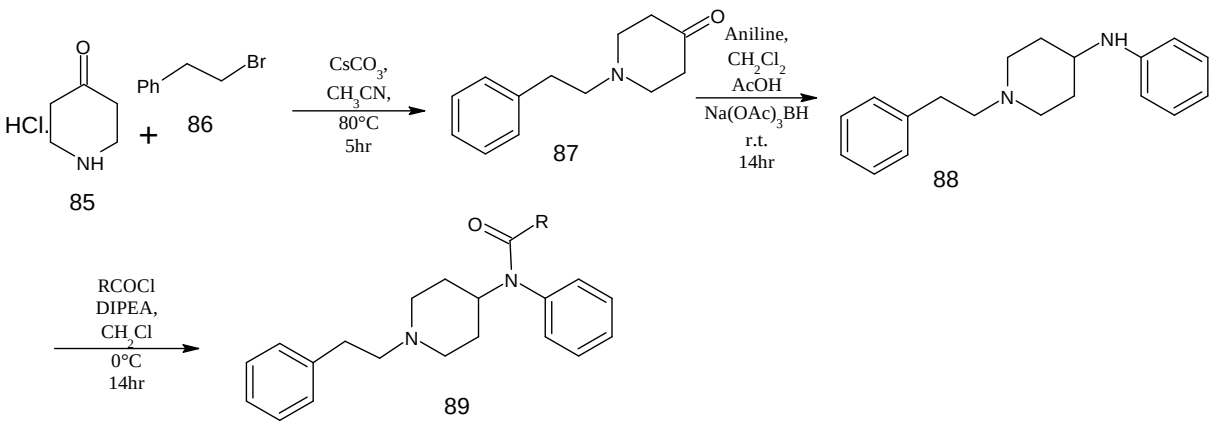


scheme 14: synthesis of glipizide

Synthesis of fentanyl (89) from 4-piperidone monohydrate hydrochloride.

Fentanyl (89) is a well known analgesic with higher efficacy compared to morphine. Its infusion produced μ opioid receptor downregulation and tolerance. It used as a pain killer and sometimes combined with other medicine for anesthesia. Fentanyl was initially synthesized by Paul Janssen in 1968. It is available in the market under brand name Sublimaze.[30]

Fentanyl (89) was synthesis as shown in scheme 15. Here, 4-piperidone monohydrate hydrochloride (85) was treated with 2-(bromoethyl)-benzene (86) giving alkylated piperidone (87). When (87) was further subjected to reductive amination with aniline in the presence of sodium triacetoxyborohydride in HOAc gives the 4-piperidineamine (88). Finally when (88) was acylated by propionyl chloride using Hunig's base it produce fentanyl (89).[30,4]



scheme 15: synthesis of fentanyl and acetythiofentanyl

Conclusion

Nitrogen based heterocyclic compound is an inseparable part of our daily life, They are part of necessary diet components like thiamin , riboflavin , pyridoxol etc. With the progress of research and development in these areas, they have contributed to numerous applications in the chemical sciences. They are largely used in pharmaceuticals industries for the synthesis of medicinal drugs like isoniazide rosiglitazone rampril etc, which are used to treat and prevent several diseases like diabetes, tuberculosis, blood pressure etc. They are also used in agrochemicals industries, in the manufacturing of fertilizers and pesticides, and in veterinary products. They have also found application in Sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dye stuff and is used as vehicles in the synthesis of other organic Compounds. Many nitrogen heterocycles shows anticancer activities thus making them a strong contender in the development of anticancer drugs. About 60% small molecule drug contain N- based heterocycle, it is due to their stability and operational efficiency in human body which is mainly due to their ability to interact with DNA via hydrogen bonding.

References

1. IMPORTANCE OF HETEROCYCLIC CHEMISTRY: A REVIEW

Pragi Arora*1, Varun Arora 1, H.S. Lamba 2 and Deepak Wadhwa 3 R.K.S.D. College of Pharmacy 1, Kaithal, Haryana, India H.R. Institute of Pharmacy 2, Ghaziabad, Uttar Pradesh, India Department of Chemistry, Kurukshetra University 3, Kurukshetra, Haryana, India

2. A mini review: recent developments of heterocyclic chemistry in some drug discovery scaffolds synthesis Ritu Sapra*, Dhara Patel, Dhananjay Meshram

3. Piperazine and morpholine: Synthetic preview and pharmaceutical applications Mohammed Al-Ghorbani, Bushra Begum A, Zabiulla, Mamatha S. V. And Shaukath Ara Khanum

4. Prescribed drugs containing nitrogen heterocycles: an overview Majid M. Heravi * and Vahideh Zadsirjan

5. Isoniazid: Von Michael Appold, Dominik Ohlig. Maria Öppling, Denise dos Santos

6. Synergism of microwave irradiation and enzyme catalysis in synthesis of isoniazid Ganapati D Yadav∗ and Ashwini D Sajgure

7. Enzymatic synthesis of isoniazid in non-aqueous medium Ganapati D. Yadav∗, Sachin S. Joshi, Piyush S. Lathi

8. An alternative synthetic route for an antidiabetic drug, rosiglitazone Dhanaji V. Jawale, Umesh R. Pratap, Ramrao A. Mane ⇑

9. Microwave-assisted synthesis of the antihyperglycemic drug rosiglitazone Santosh L. Gaonkar, Hiroki Shimizu *

10. 7-CHLORC) 4.5- (N-ETHYL-N - 2 - YEROXY ETHYLAMNO)- 2 - PENTYLAMNOQUENO LINE, ATS ACED ADDITION SALES, AND IVETHOD OF PREPARATION Alexander R. Stairey, Albany, N. Y., assigner to Stering Derg Inc., New York, N. Y., a corpo ration of Delaware

11. High-yielding continuous-flow synthesis of antimalarial drug hydroxychloroquine Eric Yu‡, Hari P. R. Mangunuru‡, Nakul S. Telang, Caleb J. Kong, Jenson Verghese, Stanley E. Gilliland III, Saeed Ahmad, Raymond N. Dominey and B. Frank Gupton*

12. Expeditious Synthesis of Ramipril: An Angiotensin Converting Enzyme (ACE) Inhibitor Golla China Malakondaiah,1,2 V. M. Gurav,1 Lekkala Amarnath Reddy,2 Karrothu Srihari Babu,2 Bolugoddu Vijaya Bhaskar,2 Padi Pratap Reddy,2 Apurba Bhattacharya,2 and Ramasamy Vijaya Anand2

13. Synthesis of Essential Drugs: Thanh Binh Le

14. Patchett, E. Harris, E.N. Tristram, M.J. Wyvratt, M.T. Wu, D. Taub, T.J. Ikeler, J. Ten Bracke, Nature, 288, 280 (1980).

15. Carvedilol: Kevin Beattie, Geeta Phadke, Jasmina Novakovic Apotex Inc., Toronto, Ontario, Canada

16. SYNTHESIS AND CHARACTERIZATION OF POTENTIAL IMPURITIES OF CARVEDILOL, AN ANTIHYPERTENSIVE DRUG

Somisetti Narender Rao,1 Devarasetty Sitaramaiah,1 Kema Srimannarayana,1 Challa Nageswar Rao,1 Peddi Srinivasa Rao,1 and K. Sudhakar Babu2

17. ALTERNATE SYNTHESIS OF APIXABAN (BMS-562247), AN INHIBITOR OF BLOOD COAGULATION FACTOR XA

Jian'an Jiang and Yafei Ji School of Pharmacy, East China University of Science and Technology, Shanghai, China

18. SYNTHETIC PROCEDURE FOR 5 METHOXY-2-(4-METHOXY-3,5-DIMETHYL 2-PYRIDINYL)-METHYLTHIO-IH BENZMIDAZOLE HYDROCHLORIDE AND ITS CONVERSION TO OMEPRAZOLE

Inventors: Shiva P. Singh, Gujarat; Siddiqui Mohammed Jaweed Mukarram, Maharashtra; Dilip Ganesh Kulkami, Maharashtra; Manish Purohit, Mahatashtra, all of (IN)

19. Omeprazole Abdullah A. Al-Badr

20. Synthesis of Celecoxib and Structural Analogs- A Review

Sureshbabu Dadiboyena1,* and Ashton T. Hamme II2

21. Synthesis of Best-Seller Drugs. http://dx.doi.org/10.1016/B978-0-12-411492-0.00003-1

22.7-CHLORO-1METHYL-5-PHENYL-STRAZOLO 4,3-a(UNOLINES Jackson B. Hester, Jr., Galesburg, Mich., assignor to The 5 R Upjohn Company, Kalamazoo, Mich.

23. Benzo- and Thienobenzo- Diazepines: Multi -target Drugs for CNS Disorders

F.J.B. Mendonça Júnior1, L. Scotti2*, H. Ishiki3, S.P.S. Botelho3, M.S. Da Silva2 and M.T. Scotti4

24. Improved Synthesis of Cefdinir and Its Polymorphic Form, an Antibacterial Active Pharmaceutical Ingredient

Korrapati V. V. Prasada Rao, Ramesh Dandala, Meenakshisunderam S. Sivakumaran, and Ananta Rani Research and Development Department, Aurobindo Pharma Ltd., Hyderabad, India

25. An Efficient Synthesis of Risperidone via Stille Reaction: Antipsychotic, 5-HT2, and Dopamine-Dz-Antagonist

Dong-myung Kim 1'2, Min-Seok Kang 1, Jeong Sook Kim 1, and Jin-Hyun Jeong ~,2 1PDT Bio Co. Ltd. and 2College of Pharmacy, Kyung Hee University, Seoul 130-701, Korea

26.Chapter 7

Piperidine-Based Nonfused Biheterocycles With CN and CC Coupling

27. Pioglitazone

Peter S. Gillies and Christopher J. Dunn Adis International Limited, Auckland, New Zealand

28. Pioglitazone A Review of its Use in Type 2 Diabetes Mellitus John Waugh, Gillian M. Keating, Greg L. Plosker, Stephanie Easthope and Dean M. Robinson

29. 26 –

Insulin and Synthetic Hypoglycemic Agents

30. Total synthesis of fentanyl young-ger kyung-ho cho and dong-yoon shin,college of pharmacy, seoul national university,san 56-1 shinrim-dong,kwanak-gu,seoul151-742,korea