Conventional inorganic salts as an alternate instead of precious metals in pharmaceutical moieties: A review

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***Abstract*—The pharmaceutical industry spends billions of dollars to find new drug molecules. With the pharmaceutical boom and the rise of bacterial resistance, the development of antibacterial medications has intensified. Drug development places significant emphasis on pharmacokinetic characteristics and antibacterial potency. Traditional synthetic methods often involve toxic reagents and environmentally taxing processes. On other way the sustainable, eco-friendly, robust and environment friendly reactions are the new trend in pharmaceutic moieties with developed path ways. The precious metals may replace by the conventional metal salts with less hazardous solvents give rise to the sustainable path way in new era. Here are some molecules that may synthesized with traditional way and with the conventional metal salts. The developed methods always give more sustainable and environment friendly way for the synthesis of pharmaceutical moieties.**

***Index Terms*—Conventional salt, eco-friendly, sustainable, synthesis, Pharmaceutical.**

I. INTRODUCTION

In the past, drugs were produced from plants, insects, fungi, etc. Examples of drugs that are extracted from plants are morphine from opium poppy, nicotine from tobacco plants, cannabinoids from cannabis, etc(1). Currently, the pharmaceutical industry spends billions of dollars to find new drug molecules. because amines and their derivatives are key intermediates to prepare fine chemical products like dyes, chemical fibers, pesticides, rubber additives, etc(2). The catalytic hydrogenation of nitro compounds by precious metals like Pd, Pt, and Rh is

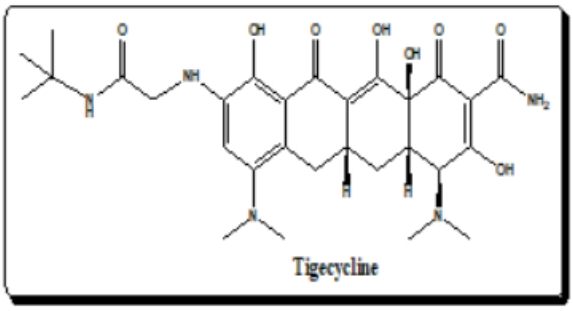
widely used for the production of amines. Catalytic approaches are becoming more and more popular in the synthesis and production of fine chemicals for a number of reasons, like it has a wide range of precursors, selectivity, catalytic stability, and many reactions that give results that can be carried out with common laboratory equipment, and mainly it can synthesize selective functional groups, etc(3). But it has some drawbacks, like it is very costly, poisonous, and hard to recover, which makes them unfriendly to the environment. Rethinking about environmental reasons, we must find a new reduction method. Some of the conventional inorganic salts that reduce drug molecules, like $FeCl_3$ or $FeSO_4$, $NaBH_4$, $ZnCl_2$, and $SnCl_2$, reduce nitro groups. Some of the conventional inorganic salts are widely used, like $NaBH_4$, because compared to other reducing agents, sodium borohydride is mild, homogenous, inexpensive, and environmentally friendly. $LiAlH_4$ has strong reductive power, selective reduction, and cost-effectiveness (4).

Tigecycline

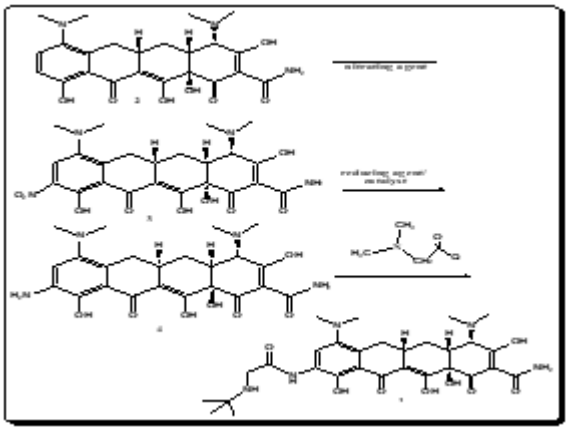
Tigecycline, which is a minocycline derivative, is the first antibiotic in the new glycylcycline class to have a wider range of actions in vitro. It has some advantages, like being an analog of the semi-synthetic antibiotic minocycline, and is an effective, broad-spectrum antibiotic that functions by blocking bacteria from synthesizing their proteins(5). Some of the common side effects of tigecycline are nausea, vomiting, stomach pain, diarrhea, and headache, and some of the serious side effects are increased pressure inside the brain or liver problems(6).

Application of tigecycline is used for the treatment of complicated skin infections, skin structure, intra- and post-surgical infections, and intra-abdominal infections and sometimes is used for treating community-acquired pneumonia(7). The dosage that is required for the treatment of complicated intra-abdominal and skin/skin-structure infections is, in adults, starting with 100 mg and then followed by 50

mg every 12 h unless the patient has severe hepatic impairment, in which case the dosage is 25mg every 12 h after the 100mg starting dosage(8). The cost of tigecycline is $90 per day, which is less costly than intravenous linezolid, daptomycin, or meropenem but more costly than ertapenem and piperacillin/tazobactam(9).



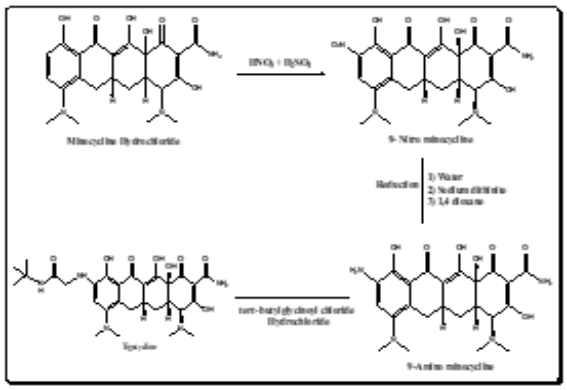
In the past few years, one of these methods has been used to synthesize tigecycline. In giving a reaction, the starting material is minocycline (compound 2) or a minocycline derivative. Reaction of minocycline with one nitrating agent results in a —NO_2 substituent to compound 3. The NO_2 substituent in formula 3 can be subsequently reduced to an amino, such as by hydrogenation, to form the compound of formula 4 as the sulfuric acid salt, which is optionally converted to the HCL salt. Finally, acylation of the compound of formula 4 generates the compound of formula 1, tigecycline(10).



Scheme 1-synthesis of tigecycline from minocycline

Research gap is giving a reaction could be low-cost, high-yield, safer catalysts, and sustainable methods.

In recent times, conventional inorganic salt use for synthesized tigecycline. In this reaction, it gives a practical and efficient route for synthesizing tigecycline, using minocycline hydrochloride as the starting material. Convert minocycline hydrochloride to 9-nitro minocycline in the presence of HNO_3 and H_2SO_4. The yield of 9-nitro minocycline is 97%, and its purity is 99.5%. In the next step, add water, sodium dithionite, and 1,4-dioxane, which convert 9-nitro minocycline to 9-amino minocycline. The product yield is 65%, and purity is 94%. Now, for producing the final product, add tert-butylglycinoyl chloride hydrochloride to 9-amino minocycline that gives tigecycline. The final product yields 85% with 99.7% purity(11).

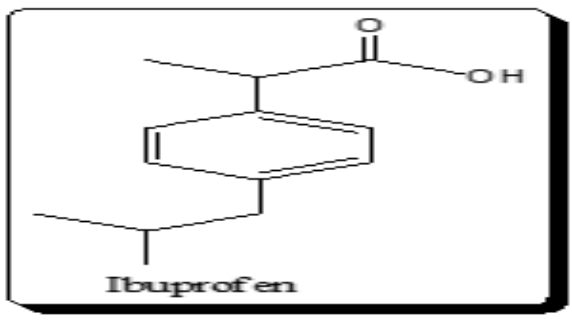


Scheme 2- Synthesis of tigecycline by conventional inorganic salt

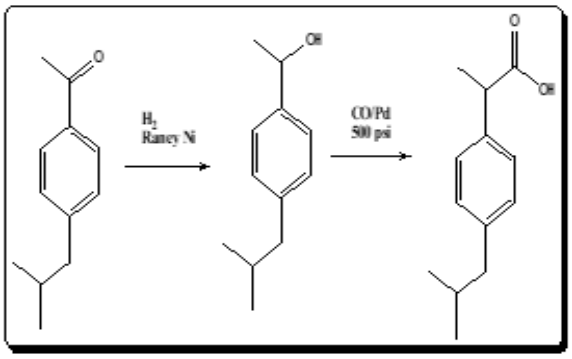
Ibuprofen

Ibuprofen is one of the most widely used analgesic–antipyretic–anti-inflammatory drugs in recent times. Ibuprofen is the first member of propionic acid derivatives. The reason for inventing this drug is to replace aspirin. It also has some side effects like gastrointestinal issues**,** kidney problems, allergic reactions**,** heart issues, etc(12,13).

The application of ibuprofen is that it is used for the treatment of moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, osteoarthritis, rheumatoid arthritis, and soft tissue disorder(14). In early times, the dosage of ibuprofen is 600-800 mg, but it is low to control symptoms of many patients, After further clinical experience, the dosage of ibuprofen increases to 1200-1800mg(15).



One of the methods where precious metal is used for the synthesis of ibuprofen in the first step, 4-isobutylacetophenone was hydrogenated using a Raney nickel catalyst to alcohol and finally carbonylated using palladium to form its product, ibuprofen(16).

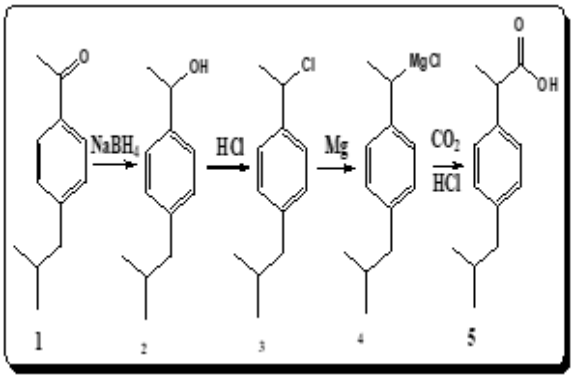


Scheme 3-synthesis of ibuprofen by Pd/CO

The precaution that should be taken while performing this method is to avoid inhalation, eye contact, or contact with any chemical used in this method. For safety, wear eye protection, rubber gloves, and protective gear that is worn at all times(16).

Environmentally friendly synthesis of ibuprofen

Ibuprofen (5) has been synthesized by reducing compound (1) with sodium borohydride in methanol it gives compound (2) 1-(4-isobutylphenyl)ethan-1-ol. Then add HCl to compound (2) it gives 1-(1-chloroethyl)-4-isobutylbenzene (3). It requires a Grignard reagent using magnesium in dry THF to convert compound (3) to compound (4) in the last step; addition of 1,2-dibromoethane and CO_2 gives pure ibuprofen(17).

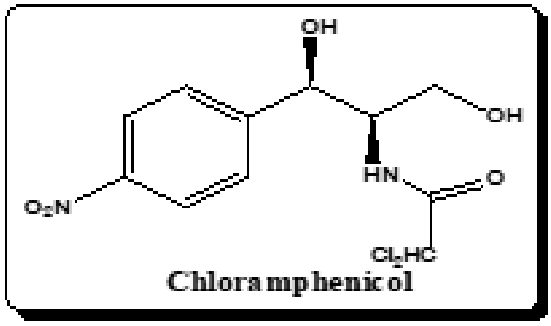


Scheme 4- Synthesis of ibuprofen by conventional inorganic salt

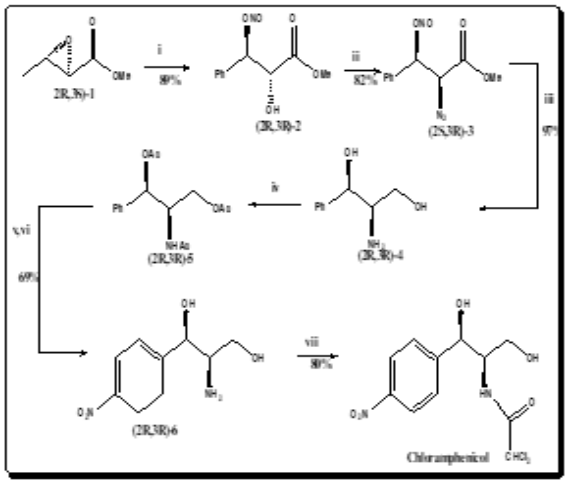
Chloramphenicol

Chloramphenicol is an antibiotic drug that was found in 1949. It is available in many forms, like oral tablets, intravenous formulations, and eye drops. Chloramphenicol has some side effects: vomiting, diarrhea, grey baby syndrome, childhood leukemia, etc(18,19).

The application of chloramphenicol is that it is used in the treatment of bacterial meningitis; after the invention of chloramphenicol, it was mainly used in the cure of typhoid fever and the treatment of eye infections(20,21).

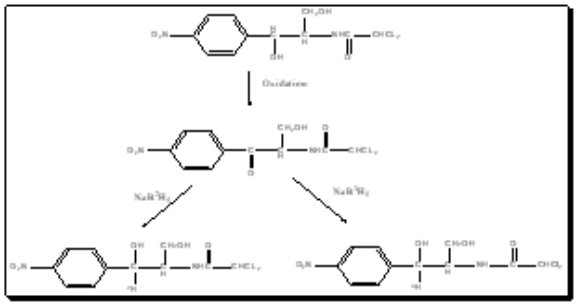


synthesis of Chloramphenicol where precious metal pd is used where in the synthesis of chloramphenicol requisite epoxide (+)-1 made out of cinnamate. In the next step, the addition of $NaNO_2$ and acetic acid in water gave diol (+)-2 in 89% yield. Then (+)-2 was treated with diphenyl phosphoryl azide (DPPA) in the presence of DEAD and PPh_3 in THF at 0°C, and then the temperature was increased to room temperature, and azide (+)-3 formed with an 82% yield. Catalytic hydrogenation of (+)-3 using 10% Pd–C at 1 atm in methanol gives (+)-4 in 97% yield. The next step is followed by acetylation under standard conditions to give product 5 and The free amine is formed by nitration of the aromatic ring and acid hydrolysis of the acetyl protecting group. in the last step The synthesis was finished by applying $Cl_2CHCOOMe$ to 6 to form chloramphenicol(22).



Scheme 5- Reagents and conditions: (i) NaNO2, AcOH, H2O, 0C to rt, 2 h; (ii) DPPA, DEAD, PPh3, THF, 0 _C to rt, 12 h; (iii) 10% Pd–C, MeOH,1 atm, rt, 12 h; (iv) Ac2O, DMAP, pyridine; (v) HNO3, H2SO4, _20 _C to rt, 1.5 h; (vi) aqueous 5% HCl, 90 _C; (vii) Cl2CHCOOCH3, 90oC, 1 h.

synthesis of Chloramphenicol where conventional inorganic salt is used to prepare labeled chloramphenicols, the oxidation of non-labeled antibiotics to form their 0xo derivative. Then it undergoes reduction with 3 H-sodium borohydride and forms chloramphenicol(23).

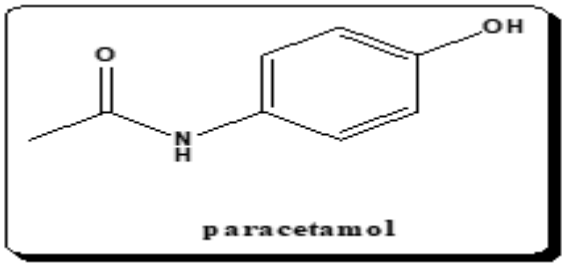


Scheme 6- Synthesis of Chloramphenicol by conventional inorganic salt

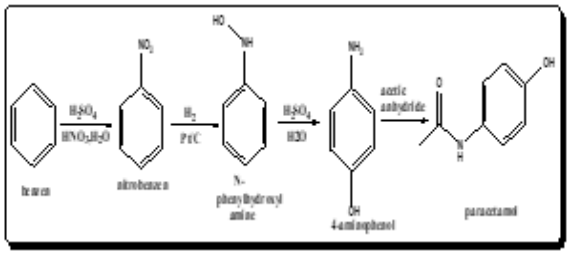
Paracetamol

Paracetamol, also known as acetaminophen, is an analgesic drug. was firstly synthesized in 1878; at that time, it was initially used in treatment for pain and fever Paracetamol is the most commonly used drug worldwide in today's time(24). Paracetamol is available in various forms, like tablets, capsules, and liquid suspensions(25). Some side effects of paracetamol are allergic reactions, gastrointestinal effects, liver damage, etc(26,27).

Application of paracetamol is commonly used for pain relief, Paracetamol is safe to use in pregnancy and lactation because only a small amount of the drug reaches breast milk, treatment of lower back pain, cold and flu treatments, etc(27,28).

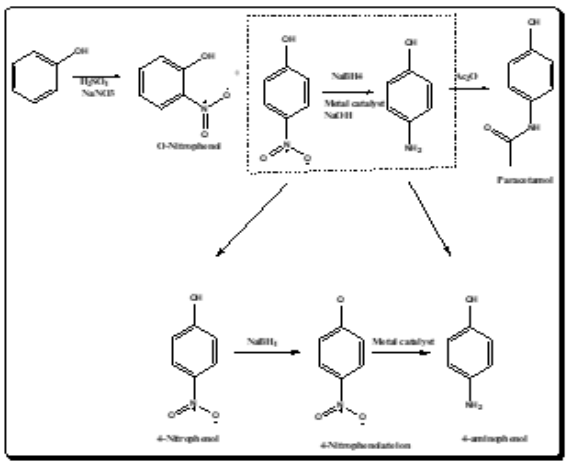


Synthesis of paracetamol where precious metal pt is used. This method is the Bamberger rearrangement of phenylhydroxylamine, where in the first step benzene undergoes nitration in the presence of HNO_3 and H_2SO_4 to give nitrobenzene, and then nitrobenzene undergoes reduction by reducing agent Pt/C and gives N-phenylhydroxylamine. Now in the presence of sulfuric acid, N-phenylhydroxylamine undergoes rearrangement and forms 4-aminophenol. Acetylation of 4-aminophenol gives the final product, paracetamol(29).



Scheme 7-Synthesis of paracetamol by Pt/C

Synthesis of paracetamol where conventional salt is used where in the the given synthesis of paracetamol, phenol is used as the starting material. In the first step, nitration of phenol occurs, and then reduction by reducing agent $NaBH_4$ converts it into p-aminophenol. At the last step of synthesis, acetylate the product (p-aminophenol) to form paracetamol(30).

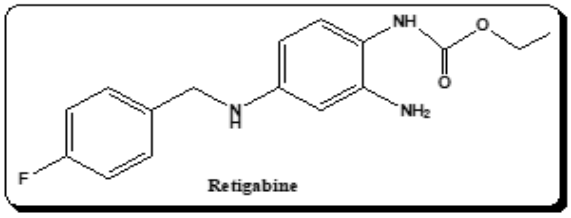


Scheme 8-Synthesis of paracetamol by conventional inorganic salt

Retigabine

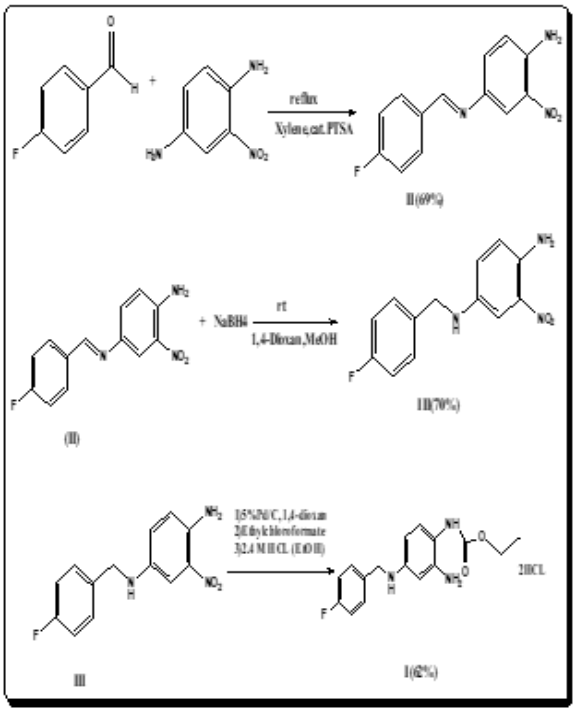
Retigabine is also known as ezogabine, which is a novel antiepileptic drug. Retigabine is a crystalline powder whose colour is white to barely shaded, odorless, tasteless, and non-hygroscopic, and its

melting point is 138–145°C(31). Some of the side effects of retigabine are dizziness, vision disturbances, including blue or blurred vision, somnolence, and fatigue, but it is mainly used for the cure of epilepsy(32,33)



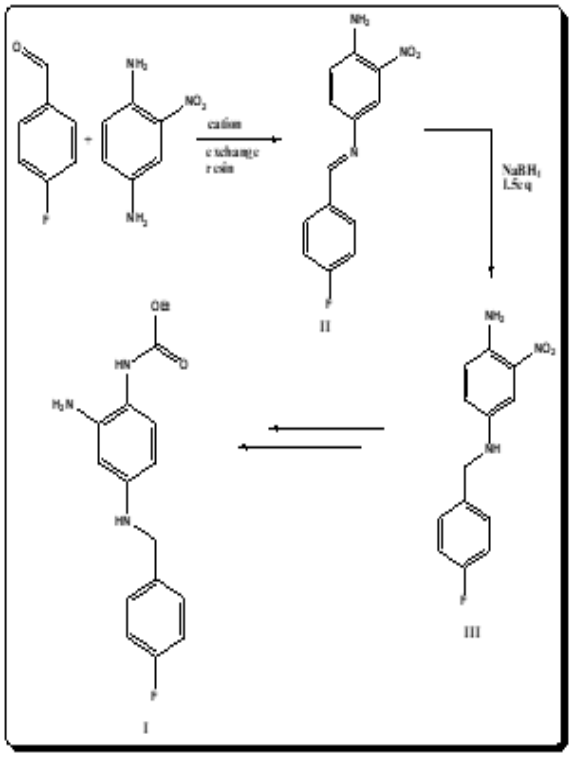
The application of retigabine is its use for the treatment of focal seizures and epilepsy. It is a neurological disorder. The antiepileptic drugs are continuously used for treatment, but retigabine is the most effective drug(34–36).

Synthesis of Retigabine where precious metal is used where in starting material 2-nitro-1,4-phenylenediamine is reacted with other material 4-fluorobenzaldehyde under specific Dean Stark conditions to form imine. After extraction, this amine is reduced using metal hydride to give III. And then nitro compound III is reduced using palladium on carbon to convert aryldiamine. Then a simple "one-pot" derivatization to ethyl carbamate: I add alcoholic hydrogen chloride to it from retigabine(37).



Scheme 9- 2-nitro-1,4-phenylenediamine to retigabine by Pd/c metal

Synthesis of Retigabine where conventional inorganic salt is used where in this synthesis of Retigabine was patented by Asta Medica. In this synthesis, 2-nitro-1,4-phenylenediamine and 4-fluorobenzaldehyde are used as starting material. Schiff base compound II is prepared by a cation-exchange resin. Then the reduction of compound II by $NaBH_4$ forms compound III at a yield of 80%. At the last, 21 g of the product I (50% RME) were obtained from reaction(38).

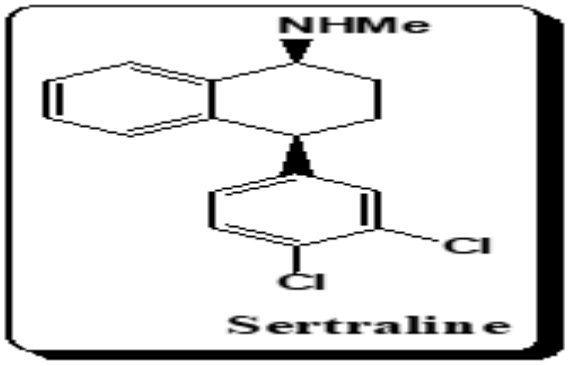


Scheme 10-synthesis of Retigabine from 2-nitro-1,4-phenylenediamine and 4-fluorobenzaldehyde by conventional inorganic salt

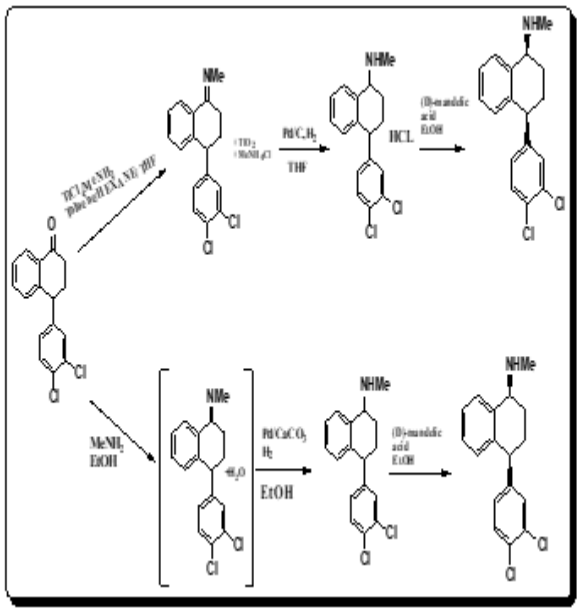
Sertraline

In today's time, depression and anxiety are the most common psychiatric disorders and are increasing in recent years(39).Sertraline is an antidepressant agent that is mainly used in the treatment of depression, Sertraline increases serotonin in the brain, which helps with good mood, emotion, and sleep(40). Also, sertraline has some side effects like gastrointestinal issues, sleep disturbances, headaches, dizziness, or light headedness, etc(41).

The application of sertraline is that it is used in the treatment of panic disorder, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, specific phobia, etc(42,43).

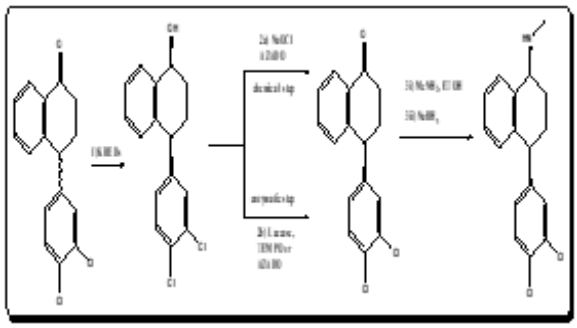


Synthesis of Sertraline where precious metal is used where in this synthesis of sertraline is presented by Colberg et al. in 2004, This synthesis is the first commercial reaction of sertraline, which includes the condensation reaction of sertraline tetralone with an excess of monomethylamine then it is catalyzed by titanium tetrachloride to form imine the reduction by reducing agent Pd/c forms racemic syn- and anti-diastereomers of the amine; then the form amine undergoes selective crystallization and produces sertraline hydrochloride(44).



Scheme 11- Synthesis of Sertraline by Pd/C

Synthesis of sertraline where conventional inorganic salt is used where in synthesis of the API sertraline: in the first step of synthesis, KRED catalyzes the selective bioreduction of sertraline tetralone to the alcohol precursor; the second step is achieved chemically or enzymatically; the chemical step occurs by 2a) NaOCl/AZADO, and the enzymatic step occurs by 2b) Trametes versicolor laccase/AZADO; the last step involves methylamine-based direct amination followed by $NaBH_4$ reduction(45).

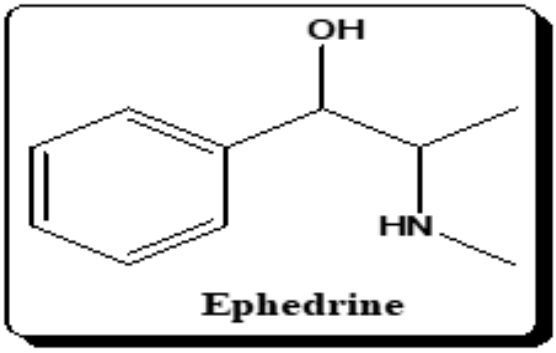


Scheme 12-Synthesis of sertraline by conventional inorganic salt

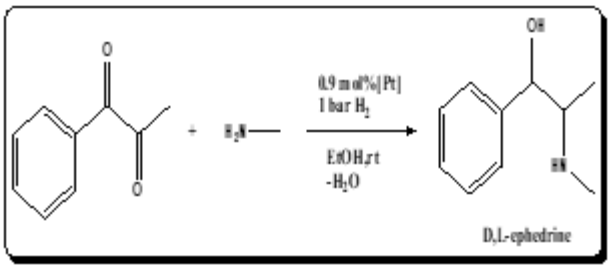
Ephedrine

Ephedrine is derived from the Ephedra plant. It is an adrenergic drug usually marketed as hydrochloride or a sulphate salt. Ephedrine is mainly used as a product of weight loss, and some athletes use ephedrine because they believe it can improve their performance(46). It is safe to use ephedrine under doctor supervision, but it has some side effects like elevated blood pressure, nausea, heart attack, headache, stroke, psychiatric disturbance, etc(47).

Application of ephedrine is its use in the treatment of asthma because ephedrine possesses anti-asthmatic properties. Treatment of skin diseases, used as a weight loss product, to improve athletic performance and used as an analgesic(48–51).

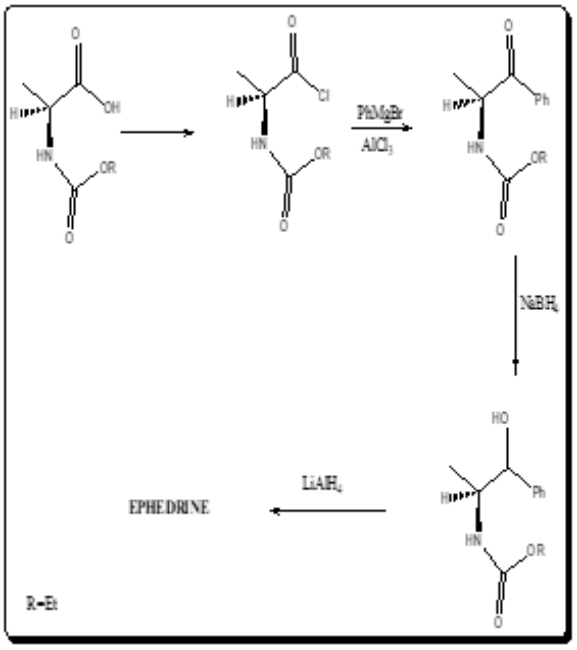


Synthesis of ephedrine by Pt catalyst where in Synthesis of Ephedrine, Manske and Johnson take 1-phenyl-1,2-propanedione as starting material; then it undergoes reductive amination in the presence of 1 equiv of methylamine to form 40% ephedrine using a Pt catalyst(52).



Scheme 13- Synthesis of ephedrine by Pt

Synthesis of ephedrine by conventional inorganic salt where in This method is first, which converts an α-amino acid derivative to the corresponding acid chloride and then further undergoes Friedel-Crafts acylation presence of phenyl magnesium bromide to form ketone, then reduction of (S)-2((ethoxycarbonyl)amino) -1-phenyl-propanone by $NaBH_4$ followed by reduction with lithium aluminum hydride, which forms secondary amino alcohol. This method yields90%(53).



Scheme 14- Synthesis of ephedrine by conventional inorganic salt

II. CONCLUSION

In today's time, various methods are available for synthesizing drugs, but these methods are costly and environmentally harmful. That's why we are required to develop new methods that are cost-free and ecologically friendly. In most reduction reactions, precious metals like Pd, Pt, and Rh are used, which is hazardous and costly; therefore, the use of conventional inorganic salts in reduction comes into action. The use of conventional inorganic salt is beneficial in many ways, like reducing the use of organic solvents, the cost of the method, and metal-free or low-metal catalysts to reduce environmental impact. The conclusion of this research is that developing the new method for easily synthesizing.

REFERENCES

[1] Jones AW. Early drug discovery and the rise of pharmaceutical chemistry. Drug Test Anal. 2011;3(6):337–44.
[2] Chodankar N. Use of Catalysis for API Manufacturing. In: Industrial Catalytic Processes for Fine and Specialty Chemicals. Elsevier Inc.; 2016. p. 509–95.
[3] Blaser HU, Indolese A, Schnyder A, Steiner H, Studer M. Supported palladium catalysts for fine chemicals synthesis. Vol. 173, Journal of Molecular Catalysis A: Chemical. 2001.
[4] Zhou ZH, Xu YB, Wu SM, Ling WJ, Zhang L, Wang ZQ. Selective Nitro Reduction of Ester Substituted Nitroarenes by NaBH 4-FeCl 2. Pharmaceutical Fronts. 2022 Sep 1;4(3):E151–6.
[5] Peterson LR. A review of tigecycline - the first glycylcycline. Int J Antimicrob Agents. 2008 Dec;32(SUPPL. 4).
[6] Xiong Y, Liu G, Tang X, Xia B, Yu Y, Fan G. Prediction and analysis of toxic and side effects of tigecycline based on deep learning. Front Microbiol. 2024;15.
[7] Magalhães Da Silva L, Regina H, Salgado N. Tigecycline: A Review of Properties, Applications, and Analytical Methods.
[8] Greer ND. Tigecycline (Tygacil): The First in the Glycylcycline Class of Antibiotics. Baylor University Medical Center Proceedings. 2006 Apr;19(2):155–61.
[9] Stein GE, Craig WA. Tigecycline: A Critical Analysis Downloaded from [Internet]. Vol. 43, Clinical Infectious Diseases. 2006. Available from: http://cid.oxfordjournals.org/
[10] US20090099376A1.
[11] Bhupatray Sompura V, Ghumara RY, RanajiKiri N, Akhaja TN, RavjibhaiSutariya T, Rama Ram S,

et al. Novel, Low-Cost, And Environmentally Friendly Pathway for Synthesizing Tigecycline.

[12] Rainsford KD. Ibuprofen: Pharmacology, efficacy and safety. Vol. 17, Inflammopharmacology. Birkhauser Verlag AG; 2009. p. 275–342.

[13] Bushra R, Aslam N. An overview of clinical pharmacology of ibuprofen. Vol. 25, Oman Medical Journal. Oman Medical Specialty Board; 2010. p. 155–61.

[14] Krasniqi D, Thaqi E, Berisha D, Bibaj G, Kryeziu F. The use of Ibuprofen and our knowledge about it [Internet]. Available from: https://knowledgecenter.ubt-uni.net/conference

[15] busson1986.

[16] Kjonaas RA, Williams PE, Counce DA, Crawley LR. Synthesis of ibuprofen in the introductory organic laboratory. J Chem Educ. 2011 Jun 1;88(6):825–8.

[17] Improve the Role of Ibuprofen in the Biological Field: Short Review. International Journal of Advanced Research in Chemical Science. 2020;7(6).

[18] Feder HM, Osier C, Maderazo EG. Chloramphenicol: A Review of Its Use in Clinical Practice [Internet]. Vol. 3, REVIEWS OF INFECTIOUS DISEASES. Available from: http://cid.oxfordjournals.org/

[19] Mock DM, Perman JA, Thaler MM. Chronic fructose intoxication after infancy in children with hereditary fructose intolerance. Vol. 309, Am J Dis Child. McGraw-Hill; 1983.

[20] wareham20022.

[21] Enterococcus VR, Lautenbach E, Schuster MG, Bilker WB, Brennan PJ. The Role of Chloramphenicol in the Treatment of Bloodstream Infection Due to. Vol. 27. 1998.

[22] Boruwa J, Borah JC, Gogoi S, Barua NC. A short asymmetric total synthesis of chloramphenicol using a selectively protected 1,2-diol. Tetrahedron Lett. 2005 Mar 7;46(10):1743–6.

[23] Al-badr AA, El-obeid HA. 5.3 Half-life 5.4 Metabolism Acknowledgement.

[24] Roberts E, Nunes VD, Buckner S, Latchem S, Constanti M, Miller P, et al. Paracetamol: Not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis. 2016 Mar 1;75(3):552–9.

[25] Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S. Paracetamol: New vistas of an old drug. Vol. 12, CNS Drug Reviews. 2006. p. 250–75.

[26] McCrae JC, Morrison EE, MacIntyre IM, Dear JW, Webb DJ. Long-term adverse effects of paracetamol – a review. Vol. 84, British Journal of Clinical Pharmacology. Blackwell Publishing Ltd; 2018. p. 2218–30.

[27] Pini LA, Guerzoni S, Cainazzo M, Ciccarese M, Prudenzano MP, Livrea P. Comparison of tolerability and efficacy of a combination of paracetamol + caffeine and sumatriptan in the treatment of migraine attack: A randomized, double-blind, double-dummy, cross-over study. Journal of Headache and Pain. 2012 Nov;13(8):669–75.

[28] Sharma C V., Mehta V. Paracetamol: Mechanisms and updates. Continuing Education in Anaesthesia, Critical Care and Pain. 2014;14(4):153–8.

[29] Park J, Evans C, Maier J, Hatzell M, France S, Sievers C, et al. Renewables-Based Routes to Paracetamol: A Green Chemistry Analysis. ACS Sustain Chem Eng. 2024 Nov 4;

[30] Mejía YR, Reddy Bogireddy NK. Reduction of 4-nitrophenol using green-fabricated metal nanoparticles. Vol. 12, RSC Advances. Royal Society of Chemistry; 2022. p. 18661–75.

[31] j.nurt.2006.11.012.

[32] Baulac M, Ch NH, Nh FO. The Treatment of Epilepsy. 2016.

[33] Tomson T, Rask O. Pharmacotherapy of epilepsy. Lakartidningen. 2018;115(21):918.

[34] Czuczwar P, Wojtak A, Cioczek-Czuczwar A, Parada-Turska J, Maciejewski R, Czuczwar SJ. Retigabine: the newer potential antiepileptic drug. 2010.

[35] Rostock A, Tober C, Rundfeldt C, Bartsch R, Engel J, Polymeropoulos EE, et al. a new anticonvulsant with a broad spectrum activity in animal models of epileptic seizures. Vol. 23, Epilepsy Research. 1996.

[36] Hermann R, Ferron GM, Erb K, Knebel N, Ruus P, Paul J, et al. Effects of age and sex on the disposition of retigabine. Clin Pharmacol Ther. 2003 Jan 1;73(1):61–70.

[37] Blackburn-Munro G, Dalby-Brown W, Mirza NR, Mikkelsen JD, Blackburn-Munro RE. Retigabine: Chemical synthesis to clinical application. Vol.

11, CNS Drug Reviews. Neva Press Inc.; 2005. p. 1–20.

[38] Afanasyev OI, Kuchuk E, Usanov DL, Chusov D. Reductive Amination in the Synthesis of Pharmaceuticals. Vol. 119, Chemical Reviews. American Chemical Society; 2019. p. 11857–911.

[39] Kubanek A, Paul P, Przybylak M, Kanclerz K, Rojek JJ, Renke M, et al. medicina Use of Sertraline in Hemodialysis Patients. 2021; Available from: https://doi.org/10.3390/medicina

[40] Sertraline B, McRae AL, Brady KT. Review of sertraline and its clinical applications in psychiatric disorders [Internet]. Available from: http://www.ashley-pub.com

[41] Sheehan D V., Kamijima K. An evidence-based review of the clinical use of sertraline in mood and anxiety disorders. Vol. 24, International Clinical Psychopharmacology. 2009. p. 43–60.

[42] McGuire JF, Lewin AB, Storch EA. Enhancing exposure therapy for anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder. Vol. 14, Expert Review of Neurotherapeutics. Expert Reviews Ltd.; 2014. p. 893–910.

[43] Bautovich A, Katz I, Smith M, Loo CK, Harvey SB. Depression and chronic kidney disease: A review for clinicians. Vol. 48, Australian and New Zealand Journal of Psychiatry. SAGE Publications Ltd; 2014. p. 530–41.

[44] Taber GP, Pfisterer DM, Colberg JC. A new and simplified process for preparing N-[4-(3,4-dichlorophenyl)-3,4- dihydro-1(2H)-naphthalenylidene]methanamine and a telescoped process for the synthesis of (1S-cis)-4-(3,4-dichlorophenol)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine mandelate: Key intermediates in the synthesis of sertraline hydrochloride. Org Process Res Dev. 2004 May;8(3):385–8.

[45] Marx L, Ríos-Lombardía N, Süss P, Höhne M, Morís F, González-Sabín J, et al. Chemoenzymatic Synthesis of Sertraline. European J Org Chem. 2020 Jan 31;2020(4):510–3.

[46] Dnyanadev TS, Nikhil M, Shete A, Dnyaneshwari N, Mayuri P, Priya P. A REVIEW ON: EPHEDRINE. Pharmaceutical Resonance. 2022.

[47] Mandal P, Jain P, Ujjainia P, Singh A, Sharma K, Chaudhary M, et al. Ephedrine and Pseudoephedrine: A Comprehensive Review of Their Pharmacology and Clinical Applications. Journal of Chemical Health Risks [Internet]. Available from: www.jchr.org

[48] Shenefelt PD. Herbal Medicine: Biomolecular and Clinical Aspects.

[49] Wang Y, Chen YJ, Xiang C, Jiang GW, Xu YD, Yin LM, et al. Discovery of potential asthma targets based on the clinical efficacy of Traditional Chinese Medicine formulas. J Ethnopharmacol. 2020 Apr 24;252.

[50] Miller Bohn A, Khodaee M, Schwenk TL. Ephedrine and Other Stimulants As Ergogenic Aids. Vol. 2, Current Sports Medicine Reports. 2003.

[51] Dasgupta A. Review of abnormal laboratory test results and toxic effects due to use of herbal medicines. Vol. 120, American Journal of Clinical Pathology. American Society of Clinical Pathologists; 2003. p. 127–37.

[52] Irrgang T, Kempe R. Transition-metal-catalyzed reductive amination employing hydrogen. Vol. 120, Chemical Reviews. American Chemical Society; 2020. p. 9583–674.

[53] Mullen AJ, Mici G. The Synthesis and Pharmacology of Ephedrine Analogues Under the Direction and Supervision of Paraic James BSc PhD. 1991.