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A REVIEW ON SYNTHESIS, CHARACTERIZATION AND GENOTOXIC EVALUATION OF DRUG IMPURITIES

Shebin John* and Pramila T.

Department of Pharmaceutical Chemistry, Bharathi College of Pharmacy, Bharathinagar-571422, Maddur Taluk, Mandya District, Karnataka, India.

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***Corresponding Author**
Shebin John
Department of Pharmaceutical Chemistry, Bharathi College of Pharmacy, Bharathinagar-571422, Maddur Taluk, Mandya District, Karnataka, India.

ABSTRACT

The impurities in pharmaceuticals are unwanted chemicals that remain with the active pharmaceutical ingredients (APIs) or develop during formulation or upon aging of both API and formulation. The presence of these unwanted chemicals even in trace amount might influence the efficacy and safety of pharmaceutical product. The control of impurities is currently a critical issue to the pharmaceutical industry. International Conference on Harmonization (ICH) formulated guidelines regarding the control of impurities. This review outlines the description of different types and origins of impurities and degradation routes with specific examples.

KEYWORDS: Impurities, Efficacy, Formulation.

INTRODUCTION

Impurities in pharmaceuticals are undesirable chemical compounds that continue to be with the lively pharmaceutical components (APIs), or expand at some stage in balance testing, or develop in the course of components or upon ageing of each APIs and formulated APIs in drug treatments. The presence of those unwanted chemical substances even in small quantities can also influence the fine, safety and efficacy of the prescription drugs.

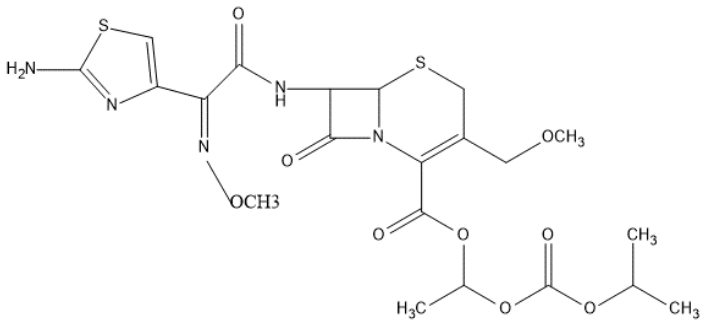
An impurity as described by using the ICH (The global Council for Harmonisation of Technical requirements for pharmaceuticals for Human Use) recommendations is "any element of the medicinal product which isn't the chemical entity defined because the energetic substance or an excipient in the product". The presence of impurities in hint quantity in drug substances or drug products is inevitable. Therefore, their level needs

to be controlled and monitored. They are able to improve or diminish the pharmacological efficacy of the APIs and Formulations. Occasionally, the effect produced by means of impurities can be teratogenic, mutagenic or carcinogenic. This can jeopardize the human health through affecting satisfactory, safety and efficacy of the prescription drugs.

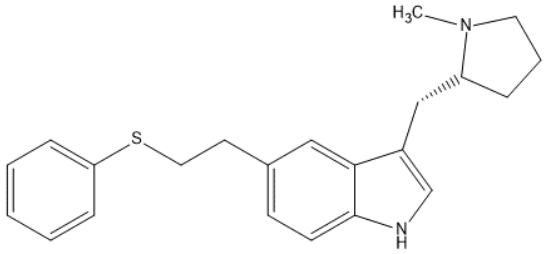
Impurity profiling (i.e., the identification as well as the quantity of impurity in the pharmaceuticals), is now getting receiving crucial essential interest from regulatory government. The exceptional pharmacopoeias, inclusive of the Indian Pharmacopoeia (IP) the British Pharmacopoeia (BP) and the USA Pharmacopoeia (USP), are slowly incorporating limits to allowable tiers of impurities gift in the APIs or formulations.

Genotoxicity, a word used in the genetic that has destructive effect on the genetic material of the cell (DNA & RNA). It effects integrity of the cell. Genotoxicity is mainly caused by genotoxin which is a mutagen which leads to damage of genetic materials and thus cause to mutation. Damage of genetic material in the somatic cell leads mutagenesis to cancer and damage of genetic material in germ cells leads to heritable mutation. One of the best ways to control the damage due to mutagens is to identify the substance or chemical, i.e., antimutagens (inhibit or suppress the mutagenesis process). The purpose of genotoxicity assay is to detect wide variety of genotoxic endpoints and also allows detection of a drug's potential to cause genotoxicity even in the early stage of drug development.

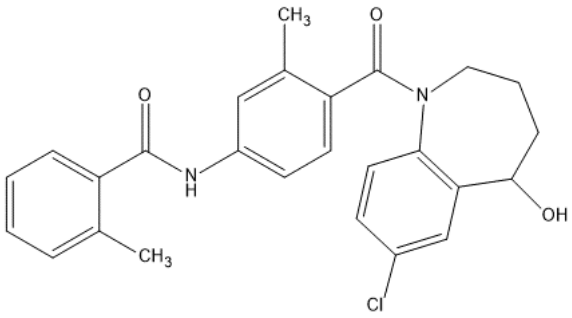
1. **Srinivasa garga *et al.*,** have studied the identification synthesis and characterization of new impurity in cefpodoxime proxetil. Cefpodoxime is a potent 3rd generation antibiotic for oral use. An unknown impurity was detected along with known impurity. Structure was assumed using LC-MS and mass fragmentation i.e.; desmethyl cefpodoxime proxetil. The unknown impurity was synthesized and characterization was done by ^{1}H NMR,^{13}C NMR AND IR.



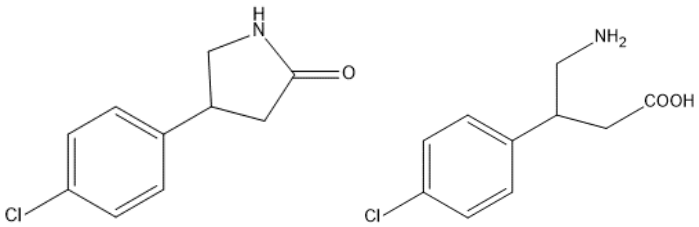
2. **Moovi nemma *et al.*,** have studied the synthesis and characterization of impurities of eletriptan & its HPLC development and validation. Some impurities are formed during the synthesis of eletriptan which is named as *N*-acetyl 5- (phenyl sulfonyl ethen 2-yl) indole and 5- (phenyl sulfonyl ethen2-yl)-1H-indole. These impurities are identified using HPLC method. The synthesis and characterization done by GC-MS, NMR & FT-IR. Validation is done as per ICH guidelines.



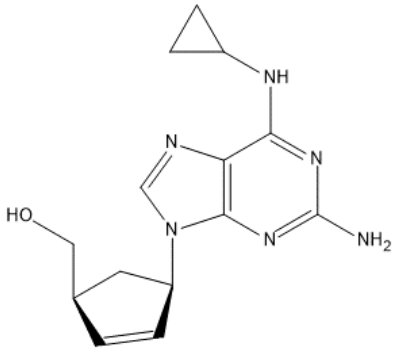
3. **Madhuresh kumar sethi *et al.*,** have studied the synthesis & characterization of tolvaptan impurities. During the synthesis of tolvaptan, 26 observed impurities have been identified & synthesized. Characterization of these impurities done by HPLC, NMR & Mass spectra.



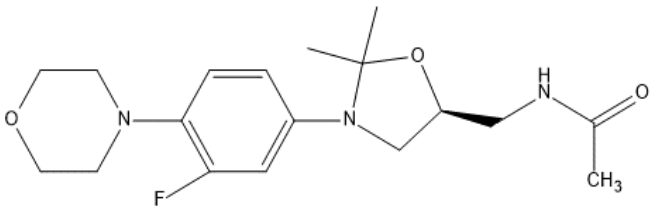
4. **Utpal nandi *et al.*,** have studied the synthesis & characterization of RS-4-amino-3-(4-chlorophenyl)-butyric acid: baclofen impurity A as per Indian pharmacopoeia. Baclofen is a drug which is used for the treatment of spacisity, alcoholism & hiccups. Baclofen is a GABA derivative. The intension of the study was synthesis & characterization of RS-4-amino-3-(4-chlorophenyl)-butyric acid which is a baclofen impurity A. it was done with the help of analytical technique such as FT-IR, DSC, TGA, NMR, LC-MS, HPLC & GC-HS. The result conclude that impurity of baclofen obtained in pure form (>99.0%).



5. **Sathyanarayana G *V et al.,*** have studied the Synthesis and characterization of potent Abacavir impurities. Abacavir is a drug used to treat HIV/AIDS. It is similar to other nucleoside reverse transcriptase inhibitor. Carbocyclic & hexenopyranosyl nucleoside was developed. Abacavir & the derivative of abacavir as well as hexapyranosyl nucleoside analogue was synthesized & purification of these compound was done by chromatography. Its characterization was done by IR, ^{1}H NMR, ^{13}C NMR & MASS spectral analysis.

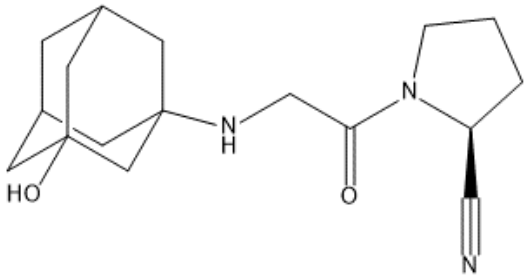


6. **Mura reddy gadisela *et al.,*** have studied the synthesis & characterization of degradation impurities of an antibiotic drug linezolid. Linezolid is a class of antibacterial called oxazolidinones and it is used to treat infections including pneumonia & infection of skin. In this study, it includes synthesis of degradation impurities of linezolid such as (*R*)-N-(3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl) acetamide and (*S*)-1-amino-3-(3-fluoro-4-morpho lino phenylamino) propan-2-yl acetate. (*R*)-N-(3-(3-fluoro-4-morpholinophenylamino)-2-hydroxypropyl) acetamide was synthesized starting from3-fluoro-4-morpholinylaniline with epichlorohydrin followed by 4 steps. (*S*)-1-amino-3-(3-fluoro-4-morpholinophenylamino) propan-2-yl acetate was synthesized starting from 3-fluoro-4-morpholinyl aniline with epichlorohydrin followed by 6 steps. All synthesized compound was characterized by ^{1}H, ^{13}C NMR & MASS spectral analysis.

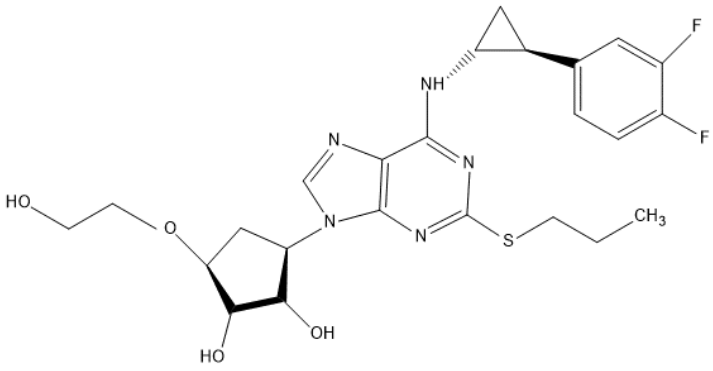


7. **Neeraj kumar *et al.,*** have studied the identification isolation & characterization of potential process related impurity & its degradation product in vildagliptin. Vildagliptin is an oral hyperglycaemic agent of dipeptidyl peptidase-4-inhibitor class of drug. An

unknown impurity of vildagliptin was identified along with the known impurities by HPLC analysis. The unknown impurity was detected in the range of 0.01-0.06%. using LC/ESI-MS^n study, the structure of the unknown impurity was proposed as (2S)-1- [2-[(3-hydroxyadamantan-1-yl) imino] acetyl] pyrrolidine-2-carbonitrile (Impurity-E). the degraded stable impurity was isolated by semi preparative liquid chromatography. Characterization of stable impurity was done using by FT-IR, NMR (^{1}H NMR,^{13} C NMR & DEPT), 2D NMR (HSQC, HMBC & COSY) & MASS spectral analysis.

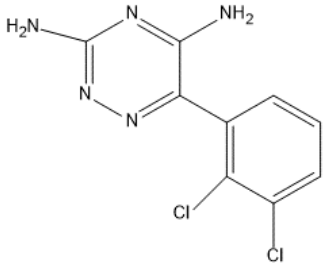


8. **Neeraj kumar *et al.*,** have studied four process related potential impurities in ticagrelor: identification, isolation, characterization using LC/ESI-MS^n, NMR & their synthesis. Using LC-MS & HPLC method some of the process related impurities were detected in the range of 0.08-0.22% in ticagrelor which is named as Tic imp 1,2,3,4 & 5. Out of five impurities four impurities were unknown. Using LC-ESI/MS^n study, Chemical structure of these impurities was proposed and isolation of unknown impurity was done by column chromatography & preparative HPLC. The proposed structure was confirmed by complete spectral analysis such as MS, 1D NMR (^{1}H, ^{13}C &DEPT), 2D NMR (HSQC, HMQC) & IR.

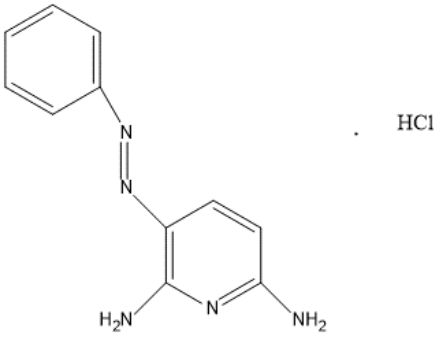


9. **Somesetti narender RAO *et al.*,** have studied the synthesis and characterization of an anticonvulsant drug lamotrigine. Lamotrigine is a benzodiazepine derivative used the treat epilepsy & in regards to mental health. During the synthesis of lamotrigine, five related unknown peaks are identified using the HPLC analysis. Identified impurities are

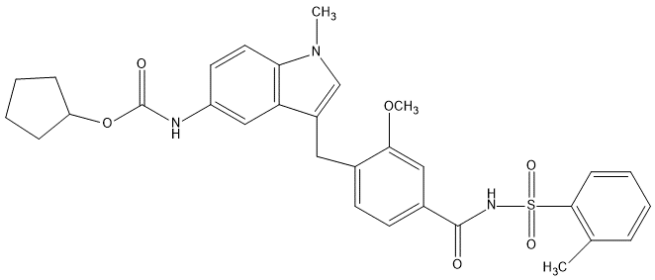
synthesized & characterized using IR, MASS & NMR spectral data. Proposed structure of the impurities is 2-(2,3-dichlorophenyl)-2-(guanidiny limino) acetonitrile, *N*-guanidinyl-2,3- dichlorobenzamide, 3-amino-6-(2,3-dichlorophenyl)- 4H-1,2,4-triazin-5-one, *N*- [5-amino-6-(2,3-dichloro phenyl)-1,2,4-triazin-3-yl]-2,3-dichloro benzamide and 3,5-bis-(2,3-dichloro benzamido)-6-(2,3-dichloro phenyl)-1,2,4-triazine.



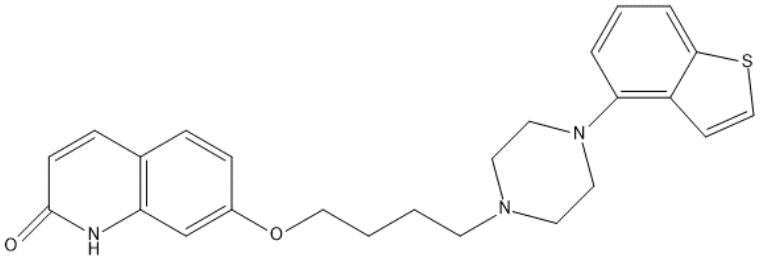
10. **Nageswara rao R *et al.,*** studied the Isolation and characterization of a potential process related impurity of phenazopyridine HCl by preparative HPLC followed by MS–MS and 2D-NMR spectroscopy. Some impurities were detected during the development of phenazopyridine HCl using HPLC analysis, impurity was isolated & synthesized. Theunknown impurity was formed at a level of 0.2%. Characterization of the impurity was done by MS-ESI/MS & 2D NMR.



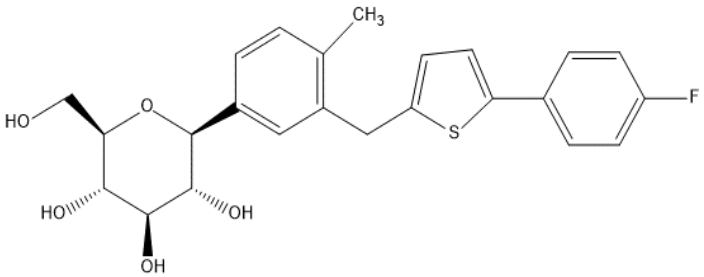
11. **Gilla goverdhan *et al.,*** have studied the identification, characterization and synthesis of impurities of zafirlukast. Zafirlukast is an orally administered leukotriene receptor antagonist used for chronic treatment of asthma. Some unknown impurities were detected in the process development of zafirlukast in reverse HPLC. These impurities are isolated using reverse phase preparative HPLC & synthesized. Using the spectral data, the structure of these impurities was proposed. Proposed structure is confirmed by IR, MS, & NMR spectra.



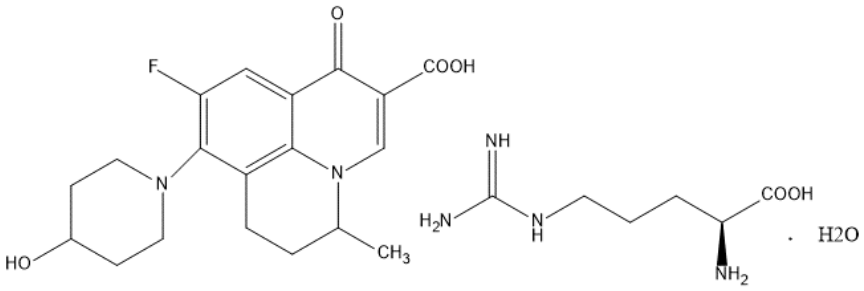
12. **Rahul tyagi *et al.,*** studied on the identification, synthesis & control of process related impurities in antipsychotic drug substance brexpiprazole. Brexpiprazole is an antipsychotic. It involves identification synthesis & process related impurities. Impurities are confirmed by LC-MS. The proposed structure was established using spectroscopic technique.



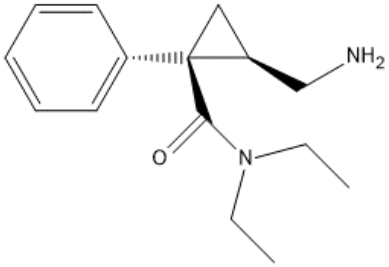
13. **Sharad pachore R *et al.,*** have studied the synthesis & characterization of potential impurities of canagliflozin. Six impurities of canagliflozin were detected using HPLC & LC-MS analysis. It includes three potential impurities such as impurity A, impurity B, impurity C, impurity D, impurity E & impurity F were synthesized and established their structures. Characterization of these identified impurities was done by HRMS, IR spectroscopy & co-injection in LC-MS.



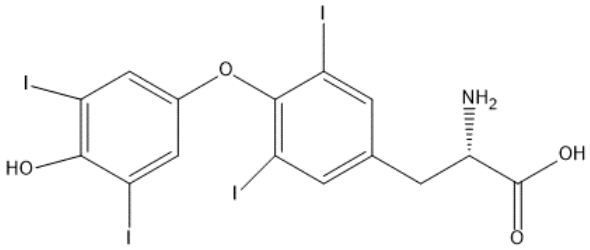
14. **Jeydeo kilbile T *et al.,*** have studied on Efficient Synthesis of Potential Impurities Levonadifloxacin (WCK771). Levanodifloxacin is used for the treatment of acute bacterial skin and skin structure infection with concurrent bacteraemia & diabetic foot infection. Five process related impurities and one degradation impurity of levanodifloxacin were synthesized using HPLC technique.



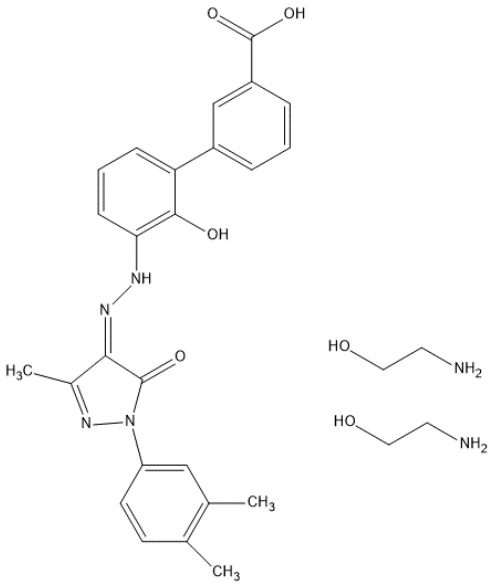
15. **Raja gopal P *et al.,*** have studied on Identification, Synthesis and Characterisation of process related impurities of Milnacipran. Milnacipran is a cyclopropane derivative used to treat a condition called fibromyalgia. Four process related impurities of milnacipran were identified in HPLC which are synthesized & characterized using spectral data by IR, LC-MS, ^{1}H NMR & ^{13}C NMR.



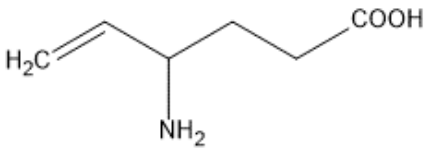
16. **Deepak panmanad *et al.,*** have studied on the Synthesis and Characterization of Potential Impurities in Levothyroxine. Five potential impurities of levothyroxine were synthesized & characterized. The proposed impurities of levothyroxine are *N*-methyl amide, T4-amine *O*-methyl, T4-acetamide, *N*-acyl-T4 and *N*-formyl-T4. Characterization was done by IR, ^{1}H NMR & mass spectroscopy.



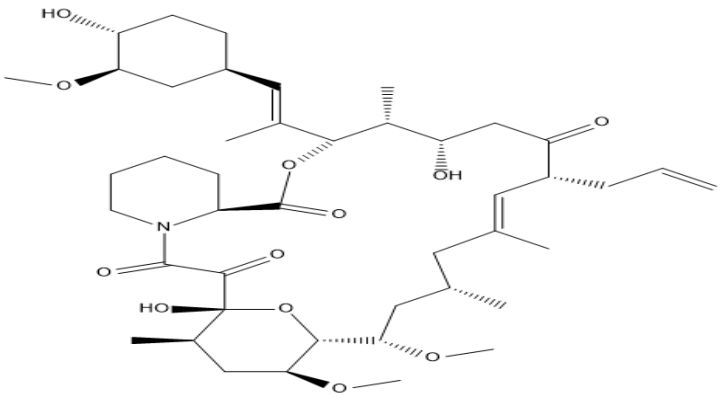
17. **Katuroju srinivasachary *et al.,*** have studied on the Synthesis and Characterization of Potential Impurities of Eltrombopag Olamine. This work detected four potential impurities of eltrombopag olamine, namely eltrombopag olamine ester, 2-aminophenol analogue of eltrombopag, 3,3′-(2-amino-3-oxo-3*H*-phenoxazine-4,6-diyl dibenzoic acid, 2′-hydroxy[1,1-biphenyl]-3-carboxylic acid. Characterization was done by ^{1}H, ^{13}C NMR & 13C NMR & mass spectroscopy.



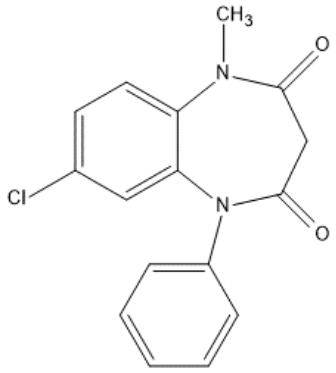
18. **Kishore karumanchi *et al.*,** have studied on the Synthesis and characterization of potential impurities of Vigabatrin-An antiepileptic drug. This work explains the synthesis & characterization of four potential impurities of vigabatrin such as 2-(2-aminobut-3-enyl) malonic acid (Vigabatrin USP impurity-E), 2-(2-oxo-5-vinylpyrrolidin-1-yl) acetic acid (USP Tablets impurity), 4-aminohexanoic acid and 2,20-oxo-5,50-bispyrrolidinyl ether.



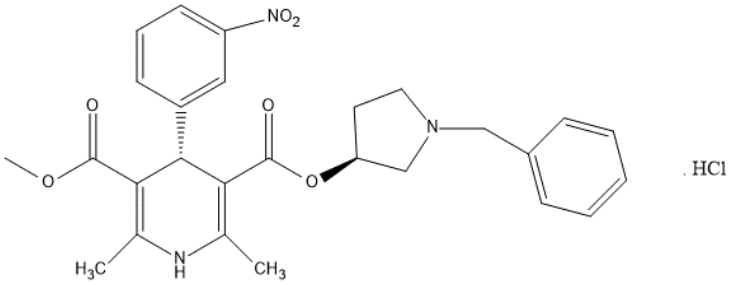
19. **Patrizia ferraboschi *et al.*,** have studied the Evaluation, synthesis and characterization of tacrolimus impurities. Tacrolimus is used as immunosuppressant drug. The main impurities of tacrolimus were identified, synthesized & characterized using HPLC, LC-MS & NMR analysis.



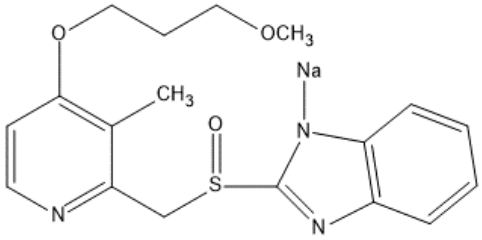
20. **Neeraj kumar *et al.,*** studied on the Potential Impurities of the Anti-epileptic Drug, Clobazam: Synthesis and Characterization. Clobazam is a benzodiazepine class of drug, used as anxiolytic. It is a study about the synthetic approaches & structural elucidation using the analytical technique such as IR & NMR (^{1}H, ^{13}C & DEPT) of clobazam related impurities such as impurity A, B, C, D, E & F.



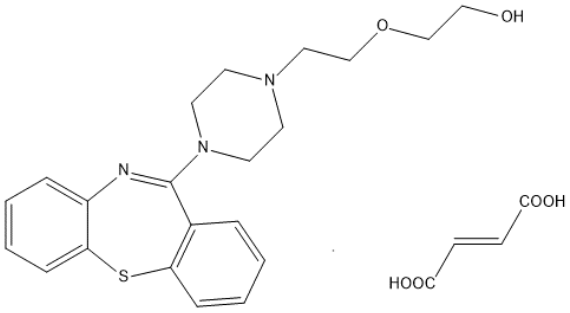
21. **Zhi-gang cheng *et al.,*** have studied the synthesis and characterization of impurities of barnidipine hydrochloride, an antihypertensive drug substance. Barnidipine hydrochloride is a calcium channel blocker used in the treatment of hypertension. Some of the impurities were identified during the process development of barnidipine HCl. These impurities were synthesized & characterization was done by spectral data (MS, ^{1}H NMR & ^{13}C NMR)



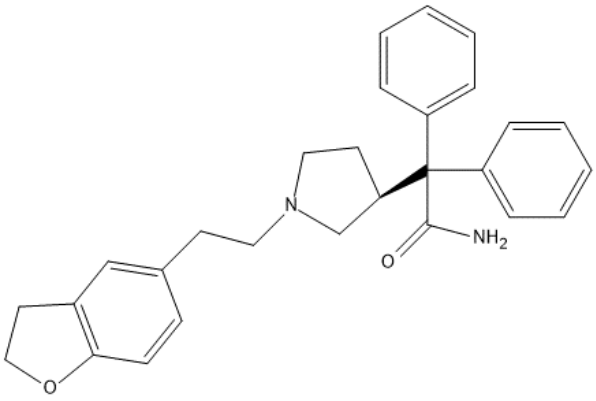
22. **Vijaya bhaskar B *et al.,*** have studied the identification & synthesis of potential impurities od rabeprazole sodium. Rabeprazole sodium is a gastric proton pump inhibitor, used to treat certain stomach & oesophagus problems. Two potential impurities were detected in HPLC during the preparation of rabeprazole sodium. And it is characterized as 2- {[(4 chloro-3-methyl-2-pyridinyl) methyl] sulfinyl}-1H-bezimidazole (2, chloro analogue of rabeprazole) and 2-[{(4-methoxy-3-methyl-2-pyridinyl) methyl} sulfinyl]-1H-benzimidazole (3, methoxy analogue of rabeprazole). And it is synthesized.



23. Bharathi ch *et al.,* have studied the identification, isolation, synthesis & characterization of quetiapine fumarate. Six unknown & one known impurities of quetiapine fumarate were identified during in the preparation of quetiapine fumarate ranging from 0.05-0.15% in the reverse HPLC. All these impurities were synthesized & structural elucidation was done using spectral data (^{1}H NMR, ^{13}C NMR, MS & IR).

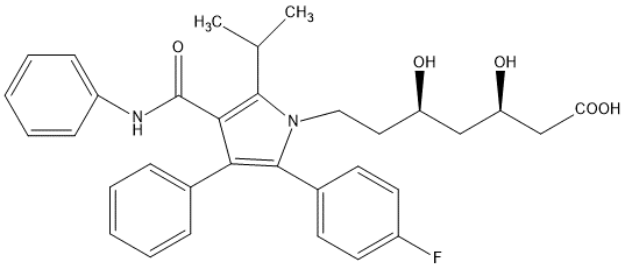


24. Srinivasa K *et al.,* have studied on the synthesis & characterization of novel & potential impurities of darifenacin, a potent muscarinic M3 receptor antagonist. Four potential impurities were identified during the synthesis of darifenacin hydrobromide such as darifenacin acid, darifenacin desnitile, darifenacin vinyl phenol & darifenacin ether. All these impurities of darifenacin were synthesized & characterized using mass, LC-MS, IR & NMR technique.

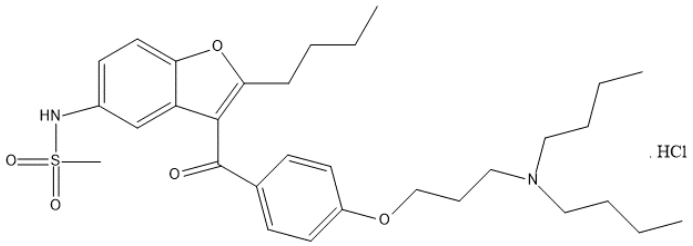


25. Appala naidu A *et al.,* have done the synthesis of novel impurities in 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenyl pentanamide; an

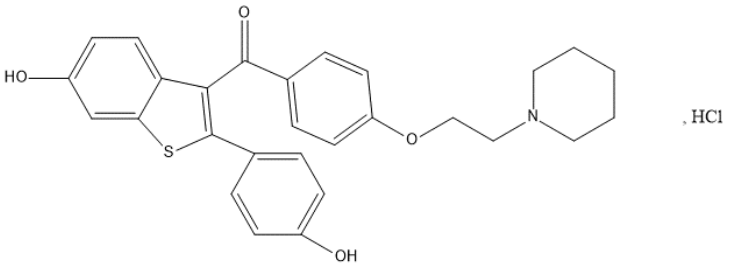
atorvastatin intermediate. Two impurities of atorvastatin intermediate were identified during the manufacture of 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenyl pentanamide. Those impurities were named as 2-acetyl-4-(4-fluorophenyl)-4-oxo-N, 3-diphenyl butamide & 2-(2-(3-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxo-N-phenyl pentanamide. Characterization of these impurities were done by spectroscopic techniques.



26. Mahender M *et al.,* have studied the identification & characterization of potential impurities of dronedarone hydrochloride. Total six potential impurities were detected using the HPLC & LC-MS during the impurity profile study of dronedarone. These impurities were synthesized & characterized using spectroscopic technique such as MS, IR,^{1}H NMR, ^{13}CNMR & DEPT.



27. Reguri buchi reddy *et al.,* have studied on the identification & characterization of potential impurities in raloxifene hydrochloride. During the synthesis of raloxifene hydrochloride. Eight impurities were detected using HPLC method. These impurities were synthesized using spectral data (IR, NMR & Mass).



CONCLUSION

This review provides a perspective on impurities in drug substance and drug product. Impurity profile of pharmaceuticals is an increasing importance and drug safety receives more and more attention from the public and from the media. This article provides the valuable information about the impurity's types and various techniques of characterization and analytical techniques for the determination, qualification of impurities.

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