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PRESENCE OF ORGANIC IMPURITIES INTO ACTIVE PHARMACEUTICAL INGREDIENTS: A REVIEW

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Keywords:

Active Pharmaceutical Ingredient (API), Chromatography, Impurity profile, Organic impurity, Spectroscopy

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ABSTRACT: The presence of an excess amount of pharmaceutical impurities in active pharmaceutical ingredients and control of these are a major issue for all pharmaceutical companies. It is essential to know the presence of impurities in the drug substances and control them up to a certain level to avoid adverse effects. Impurities in organic drug molecules can be developed during organic synthesis, formulation or upon aging of active pharmaceutical ingredients, which may affect the quality, safety, and efficacy of drugs. Impurity profile is defined as the description of identified and unidentified impurities present in new drugs as per ICH guidelines. The identification of the impurities of different drugs is done by a variety of available Chromatographic and Spectroscopic techniques. The different analytical methods are utilized for characterization and identification of impurities such as Capillary Electrophoresis (CE), Gas Chromatography (GC), Supercritical Fluid Chromatography (SFC), Thin Layer Chromatography (TLC), High Performance Thin Layer Chromatography (HPTLC), High Performance Liquid Chromatography (HPLC), UV-Visible, IR, Mass, NMR and Raman spectroscopy. In this review article, a study has been done on various well known marketed drugs for their organic impurities, those were reported by various researchers, and a list of few drugs is prepared, those were obtained from British Pharmacopeia 2007.

INTRODUCTION: The quality, safety, and efficacy of drug products are directly dependent on their toxicological properties and the presence of impurities. Various regulatory authorities like ICH, USFDA, Canadian Drug, and Health Agency are emphasizing on the significance of purity detection and the identification of impurities in Active Pharmaceutical Ingredients.

Biological safety can be achieved by evaluating and obtaining data on the presence of impurities in drug substances. That's why impurity profiling is required to get an appropriate result from drug substances¹. The term 'impurity' can be defined as something that is impure or makes something else impure.

In the field of pharmaceutical sciences, mostly impurities in drug substances mean the presence of organic materials, inorganic residues, and residual solvents, besides the drug substance. Impurity profile is the description of identified and unidentified impurities present in new drug substances as per ICH guidelines.

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It includes identification, structure elucidation, and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulations.

It helps in identifying and quantifying the impurities present in drug substances (APIs) or pharmaceutical formulations¹⁻⁴.

Impurities have been named differently or classified as follows:

- a) **Common Impurities:** By-products, Degradation products, Interaction products, Intermediates, Penultimate intermediates, Related products, Transformation products.
- b) **Various Pharmacopeia listed Impurities:** Pharmacopoeias of various countries also mention impurities in various sections; Impurities in Official Articles, Ordinary Impurities, Organic Volatile Impurities, etc.
- c) **As per ICH Terminology:** According to ICH guidelines, impurities in the drug substances produced by chemical synthesis can broadly be classified into the following three categories;
 - i. Organic Impurities (Process and Drug-related)
 - ii. Inorganic Impurities
 - iii. Residual Solvents¹

Organic Impurities: Organic impurities can arise in APIs or drug product formulations during the manufacturing process or during the storage of drug substances. They may be known, unknown, volatile, or non-volatile compounds with sources including starting materials, intermediates, unintended by-products, and degradation products. They may also arise from racemization or contamination of one enantiomeric form with another. In all cases, they can result in undesired biological activity.

- a) **Starting Materials or Intermediates:** These are the most common impurities found in every API unless proper care is taken in every step involved throughout the multi-step synthesis. In Paracetamol bulk, there is a limit test for p-aminophenol, which could be a

starting material for one manufacturer or be an intermediate for another.

- b) **By-products:** In synthetic organic chemistry, getting a single end product with 100% yield is very rare; there is always a chance of having by-products. In the case of Paracetamol bulk, diacetylated paracetamol may form as a by-product.
- c) **Degradation Products:** Impurities can also be formed by degradation of the end product during the manufacturing of bulk drugs, storage or formulation to different dosage forms or aging. The degradation of Penicillins and Cephalosporins is a well-known example of degradation products. The presence of a β -lactam ring, as well as that of an α -amino group in the C6/C7 side chain, plays a critical role in their degradation^{4,5}.

Inorganic Impurities: Inorganic impurities can arise from raw materials, synthetic additives, excipients, and production processes used when manufacturing drug products. Sources of inorganic impurities include manufacturing process reagents such as ligands, catalysts (*e.g.*, platinum group elements), metals derived from other stages of production (*e.g.*, process water and stainless steel reactor vessels), charcoal, and elements derived from other materials used in filtration.

Residual Solvents: Residual solvents are the volatile organic chemicals used during the manufacturing process or generated during drug production. Several organic solvents used in the synthesis of pharmaceutical products have toxic or environmentally hazardous properties, and their complete removal can be very difficult⁶.

Sources of Impurities: From the preceding discussion, it is clear that impurities can be originated from several sources such as; Crystallization-related impurities, Stereochemistry-related impurities, Residual solvents, Synthetic intermediates and by-products, Formulation-related impurities, Impurities arising during storage, Method related impurity, Mutual interaction amongst ingredients, Functional group-related typical degradation¹.

Different Methods to Identify Impurities:

- 1. Spectroscopic Method:** The UV-Visible, IR, Mass, NMR, and Raman spectroscopic methods are routinely being used for characterizing impurities.
- 2. Separation Method:** Capillary Electrophoresis (CE), Gas Chromatography (GC), Supercritical Fluid Chromatography (SFC), Thin Layer Chromatography (TLC), High-Performance Thin Layer Chromatography (HPTLC), High-Performance Liquid Chromatography (HPLC) are regularly being used for separation of impurities and degradation products⁴.

Identification of Impurities by Researchers:

Thomas *et al* reported an unknown impurity in the drug Deferasirox. HPLC detected it and identified by (LC-ESI-QT/MS/MS). The impurity was confirmed as 2-[3,5-bis(2-hydroxy-phenyl)-[1,2,4]-triazol-1-yl]-benzoic acid⁷.

3- [1- (dimethylamino) ethyl] phenyl N-ethyl-N-methyl carbamate N-oxide, Ethyl-methyl-carbamic acid 4-(1-dimethylamino-ethyl)-phenyl ester, ethyl-methyl-carbamic acid 2-(1-dimethylamino-ethyl)-phenyl ester impurities were reported by Thomas *et al.* in the drug Rivastigmine tartrate by using HPLC and LC/MS/MS method⁸.

Gazdag M *et al.*, confirmed the presence of 17 α -Hydroxy-17-oic acid and 17 α ,20-Dihydroxy-21-oic acid impurities in Mazipredone by using HPLC-(APCI)-MS and HPLC- diode-array UV method⁹.

Makino Y *et al.*, determined the presence of (1R,2S)-(1)-ephedrine and (1S,2S)-(1) pseudo-ephedrine impurities in bulk Methamphetamine with the help of HPLC using two different columns: a phenyl- β -cyclodextrin- type column and an ODS-type column¹⁰.

Choe S *et al.*, identified the presence of pharmaceutical impurities such as Acetaminophen, Caffeine, Chlorpheniramine, Phenacetin, Ambroxol, *etc.* in the drug Methamphetamine crystals seized in Korea by using the GC-FID and GC-MS method¹¹.

The presence of benzaldehyde and benzyl alcohol in the drug Methamphetamine was identified by

Kuwayama K *et al.*, by using the HS-SPME & GC-MS¹².

Trefi S *et al.*, investigated different impurity profiles in generic Ciprofloxacin formulations collected from different countries by using ¹⁹F, ¹H and DOSY NMR techniques. The impurities were 7- chloro- 1- cyclopropyl- 6- fluoro- 4-oxo-1, 4-dihydroquinoline-3-carboxylic acid (fluoro-quinolonic acid), 1-cyclopropyl-4-oxo-7-(piperazin -1-yl)-1,4-dihydroquinoline-3-carboxylic acid (des-fluoro compound), 7- [(2- aminoethyl) amino]-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid (ethylenediamine compound) and 7-chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid¹³.

The presence of impurities in the antiparkinsonian drugs such as Levodopa, Carbidopa, Entacapone was identified by Vemić A *et al.*, by using reversed-phase LC method. The identified impurities were (2S)-2-amino-3-(4-hydroxyphenyl) propanoic acid and (2RS)-2-amino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid for Levodopa, Methylodopa, 3-O-methylcarbidopa for Carbidopa and (2Z)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N, N-diethyl-2-propenamide, and 3,4-dihydroxy-5-nitrobenzaldehyde for Entacapone¹⁴.

Sun C *et al.*, reported a novel impurity in bulk drug Eprosartan by a simple and sensitive HPLC/MSⁿ and NMR method. The identified impurity was 4, 4'-(5,5'-(1E,1'E)-3,3-(4,4'-methylenebis (thiophene-4, 2-diyl))bis(2-carboxyprop-1-ene-3, 1-diyl) bis(2-butyl- 1H -imidazole-5, 1-diyl)) bis (methylene) dibenzoic acid¹⁵.

Zhang D *et al.*, isolated and identified three impurities 5-((4-fluorobenzyl)amino)- 2-oxo- 1H-imidazo[4,5-b]pyridine-1, 3(2H)-dicarboxylate, diethyl(6-((4-fluorobenzyl)amino)pyridine-2,3-diyl) dicarbamate and 5-((4-fluorobenzyl)amino)-1H imidazo[4,5-b]pyridin-2(3H)-one in the drug Flupirtine maleate, a centrally acting, non-opioid, nonsteroidal anti-inflammatory analgesic by using MS, ¹H, ¹³C, 2D NMR and IR¹⁶.

Kadivar MH *et al.*, prepared impurity profile on Febuxostat drug substance by LC-MS/MS technique. The impurities were first identified with the help of LC-MS/MS and characterized by IR and NMR. The impurities 2-(3-carbamoyl-4-iso butoxy

phenyl)-4-methyl-1,3-thiazole-5-carboxylic acid, 2-[4-(butan-2-yloxy)-3-cyano phenyl]-4-methyl-1,3-thiazole-5-carboxylic acid, 4-methyl-2-[4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylic acid, 2-(2-methylpropoxy)-5-(4-methyl-1,3-thiazol-2-yl)benzotrile were found¹⁷.

Volk KJ *et al.*, mentioned the presence of impurities such as Norbutorphanol, 9-hydroxy-butorphanol, 9-keto-butorphanol, Ring-contracted butorphanol, $\Delta 1$, 10a-butorphanol in the drug

Butorphanol tartrate by using LC-MS & LC-Tandem MS¹⁸.

A list of several impurities present in various drugs identified by different methods is shown in **Table 1**, and a list of some well-known marketed drugs and their impurities mentioned in British Pharmacopoeia¹⁹ is discussed in **Table 2**.

The structures of the aforementioned impurities are shown in **Fig. 1**.

TABLE 1: LIST OF IMPURITIES IDENTIFIED BY DIFFERENT METHODS

Author	Method	Drug	Impurity	Structure
Thomas S <i>et al.</i> , ⁷	HPLC & (LC-ESIQT/MS/MS)	Deferasirox	i) 2-[3,5-bis(2-hydroxy-phenyl)-[1,2,4]-triazol-1-yl]-benzoic acid	1a
Thomas S <i>et al.</i> , ⁸	HPLC & LC/MS/MS	Rivastigmine tartrate	ii) 3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methyl carbamate N-oxide iii) Ethyl-methyl-carbamic acid 4-(1-dimethylamino-ethyl)-phenyl ester iv) ethyl-methyl-carbamic acid 2-(1-dimethylamino-ethyl)-phenyl ester	2a 3a 4a
Gazdag M <i>et al.</i> , ⁹	HPLC-(APCI)-MS & HPLC-diode-array UV	Mazipredone	v) 17 α -Hydroxy-17-oic acid vi) 17 α ,20-Dihydroxy-21-oic acid	5a 6a
Makino Y <i>et al.</i> , ¹⁰	HPLC	Methamphetamine	vii) (1R,2S)-(-)-ephedrine viii) (1S,2S)-(+)-pseudoephedrine	7a 8a
Choe S <i>et al.</i> , ¹¹	GC-FID & GC-MS	Methamphetamine	ix) Acetaminophen x) Caffeine xi) Chlorpheniramine	9a 10a 11a
Kuwayama K <i>et al.</i> , ¹²	HS-SPME/GC-MS	Methamphetamine	xii) Benzaldehyde xiii) Benzyl alcohol	12a 13a
Trefi S <i>et al.</i> , ¹³	¹⁹ F, ¹ H & DOSY NMR	Ciprofloxacin	xiv) 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (fluoroquinolonic acid) xv) 1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (desfluoro compound)	14a 15a
Vemi'c A <i>et al.</i> , ¹⁴	RP-HPLC	Levodopa Carbidopa, Entacapone	xvi) ((2S)-2-amino-3-(4-hydroxyphenyl) propanoic acid xvii) (2RS)-2-amino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid xviii) Methyl dopa xix) 3-O-methylcarbidopa xx) (2Z)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide xxi) 3,4-dihydroxy-5-nitrobenzaldehyde xxii) 4,4'-(5,5'-(1E,1'E)-3,3-(4,4'-methylenebis(thiophene-4,2-diyl)) bis (2-carboxyprop-1-ene 3,1-diyl)bis(2-butyl-1H-imidazole-5,1-diyl))bis(methylene)dibenzoic acid	16a 17a 18a 19a 20a 21a 22a
Sun C <i>et al.</i> , ¹⁵	HPLC/MS ⁿ & NMR	Eprosartan	xxiii) 5-((4-fluorobenzyl)amino)-2-oxo-1H-imidazo[4,5-b]pyridine-1,3(2H)-dicarboxylate xxiv) diethyl(6-((4-fluorobenzyl)amino)pyridine-2,3-diyl)dicarbamate xxv) 5-((4-fluorobenzyl)amino)-1H-imidazo[4,5-b]pyridin-2(3H)-one	23a 24a 25a

Kadivar MH <i>et al.</i> , ¹⁷	LC-MS/MS	Febuxostat	xxvi) 2-(3-carbamoyl-4-isobutoxyphenyl)-4-methyl-1,3-thiazole-5-carboxylic acid	26a
			xxvii) 2-[4-(butan-2-yloxy)-3-cyanophenyl]-4-methyl-1,3-thiazole-5-carboxylic acid	27a
			xxviii) 4-methyl-2-[4-(2-methylpropoxy)phenyl]-1,3-thiazole-5-carboxylic acid	28a
			xxix) 2-(2-methylpropoxy)-5-(4-methyl-1,3-thiazol-2-yl)benzotrile	29a
			xxx) Norbutorphanol	30a
Volk KJ <i>et al.</i> , ¹⁸	LC-MS & LC-Tandem MS	Butorphanol tartrate	xxxi) 9-hydroxy-butorphanol	31a
			xxxii) 9-keto-butorphanol	32a
			xxxiii) Ring-contracted butorphanol	33a
			xxxiv) Δ 1, 10a-butorphanol	34a

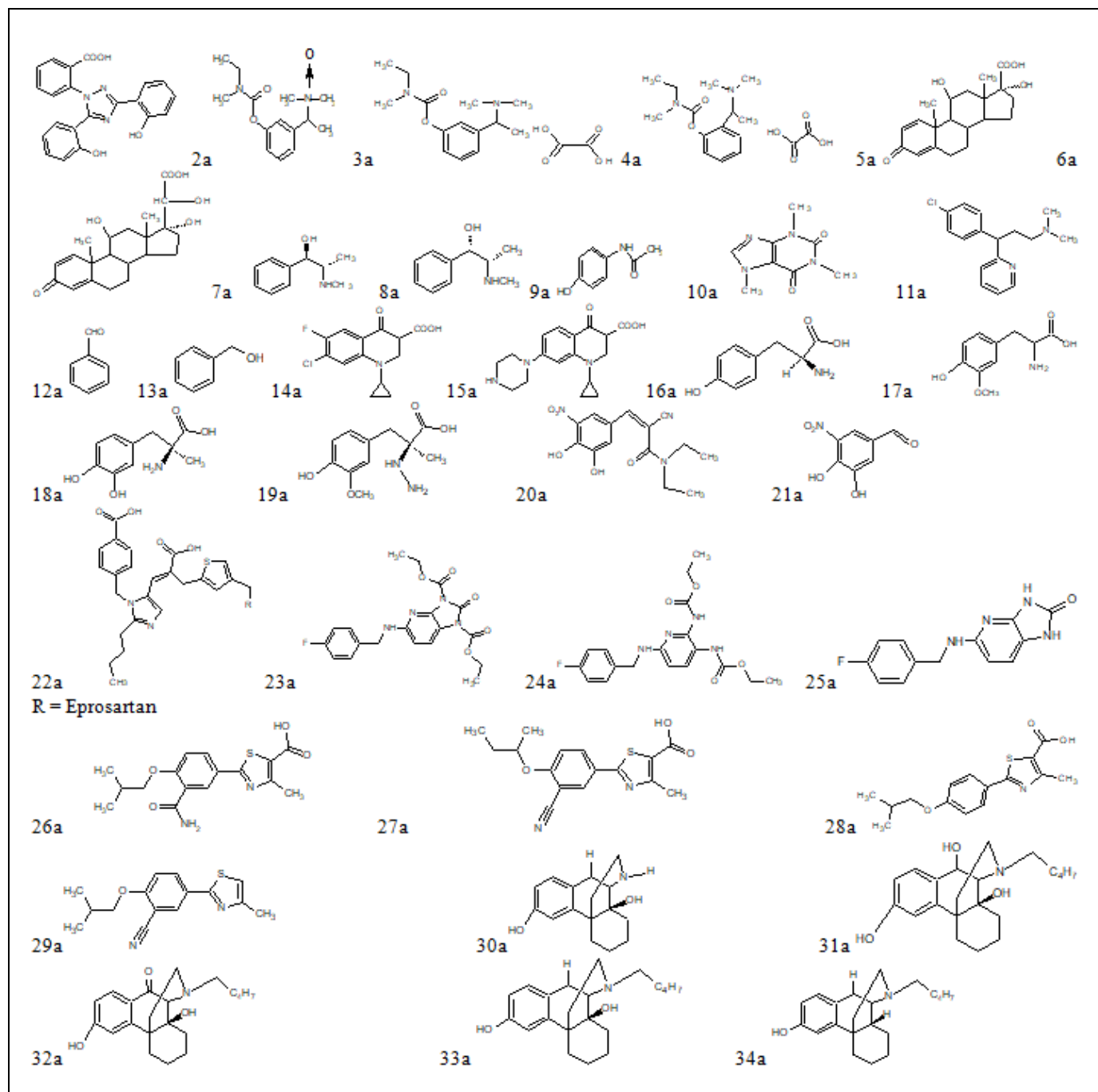
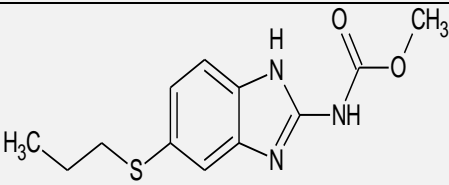
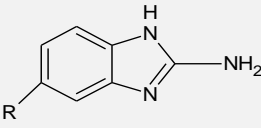


FIG. 1: STRUCTURE OF IMPURITIES

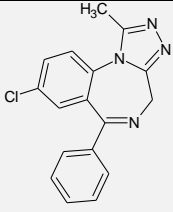
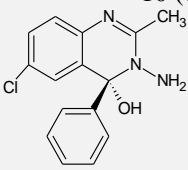
TABLE 2: IMPURITIES OF FEW WELL-KNOWN MARKETED DRUGS AS PER BRITISH PHARMACOPOEIA: DRUG NO. 01

Drug's Name	Aceclofenac
Drug's structure	
Activity Total impurities Structures of impurities	Analgesic, Anti-inflammatory 09 (Nine)
Impurity A	
Impurity B	
Impurity C	R = H: [2-[(2,6-dichlorophenyl)amino]phenyl]acetic acid (diclofenac)
	R = CH ₃ : methyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (methyl ester of diclofenac)
	R = C ₂ H ₅ : ethyl [2-[(2,6-dichlorophenyl)amino]phenyl]acetate (ethyl ester of diclofenac)
Impurity D	
Impurity E	
Impurity F	R = CH ₃ : methyl [[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (methyl ester of aceclofenac)
Impurity G	R = C ₂ H ₅ : ethyl [[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (ethyl ester of aceclofenac)
Impurity H	R = CH ₂ -C ₆ H ₅ : benzyl [[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (benzyl ester of aceclofenac)
	R = CH ₂ -CO ₂ H: [[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac)
	R = CH ₂ -CO-O-CH ₂ -CO ₂ H: [[[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetyl]oxy]acetic acid (diacetic aceclofenac)
Impurity I	
	1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one

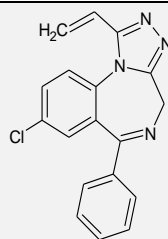
DRUG NO. 02

Drug's Name	Albendazole
Drug's structure	
Activity	Anthelmintic
Total impurities	06 (Six)
Structures of impurities	
Impurity A	R = S-CH ₂ -CH ₂ -CH ₃ : 5-(propylsulphonyl)-1 <i>H</i> -benzimidazol-2-amine
Impurity D	R = SO ₂ -CH ₂ -CH ₂ -CH ₃ : 5-(propylsulphonyl)-1 <i>H</i> -benzimidazol-2-amine
Impurity B	R = SO-CH ₂ -CH ₂ -CH ₃ : methyl [5-(propylsulphonyl)-1 <i>H</i> -benzimidazol-2-yl]carbamate
Impurity C	R = SO ₂ -CH ₂ -CH ₂ -CH ₃ : methyl [5-(propylsulphonyl)-1 <i>H</i> -benzimidazol-2-yl]carbamate
Impurity E	R = H: methyl (1 <i>H</i> -benzimidazol-2-yl)carbamate
Impurity F	R = S-CH ₃ : methyl [5-(methylsulphonyl)-1 <i>H</i> -benzimidazol-2-yl]carbamate

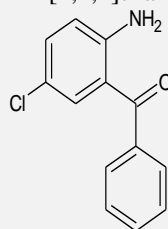
DRUG NO. 03

Drug's Name	Alprazolam
Drug's structure	
Activity	Anxiolytic
Total impurities	10 (Ten)
Structures of impurities	
Impurity A	and enantiomer (4 <i>RS</i>)-3-amino-6-chloro-2-methyl-4-phenyl-3,4-dihydroquinazolin-4-ol
Impurity B	R = CH ₂ OH: [5-chloro-2-[3-(hydroxymethyl)-5-methyl-4 <i>H</i> -1,2,4-triazol-4-yl]phenyl]phenylmethanone
Impurity C	R = H: [5-chloro-2-[3-methyl-4 <i>H</i> -1,2,4-triazol-4-yl]phenyl]phenylmethanone
Impurity F	R = CH ₂ Cl: [5-chloro-2-[3-(chloromethyl)-5-methyl-4 <i>H</i> -1,2,4-triazol-4-yl]phenyl]phenylmethanone

Impurity D

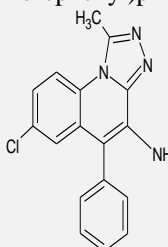
8-chloro-1-ethenyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine

Impurity E

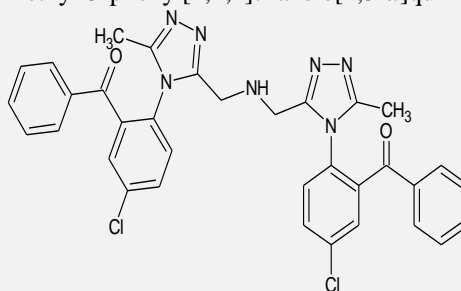


(2-amino-5-chlorophenyl)phenylmethanone

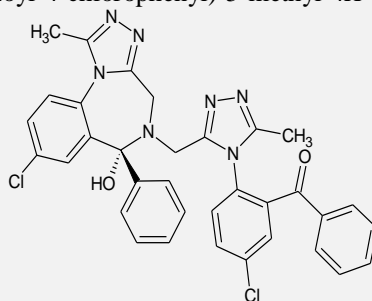
Impurity G

7-chloro-1-methyl-5-phenyl[1,2,4]triazolo[4,3-*a*]quinolin-4-amine

Impurity H

bis[[4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazol-3-yl]methyl]amine

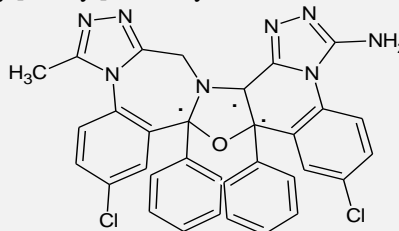
Impurity I



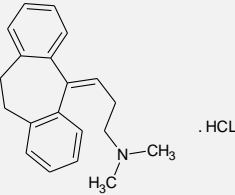
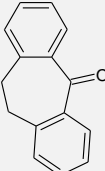
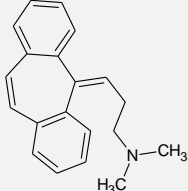
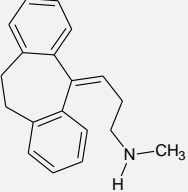
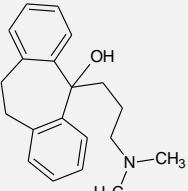
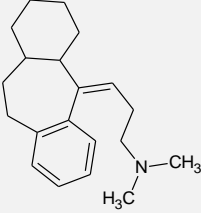
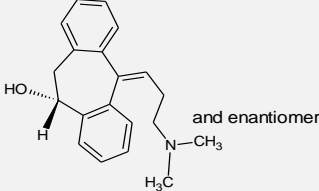
and enantiomer

[5-chloro-2-[3-[[4-(6-chloro-6-hydroxy-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-5(6*H*)-yl]methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone

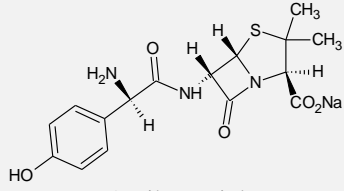
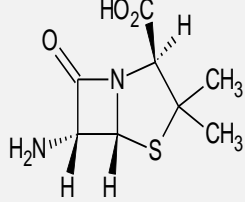
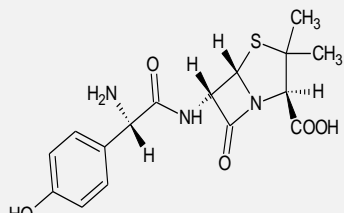
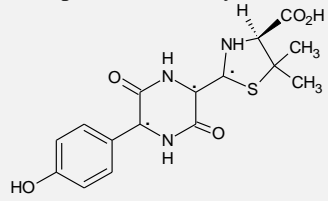
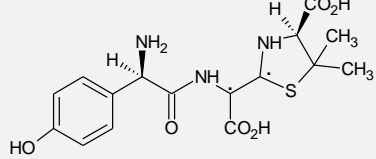
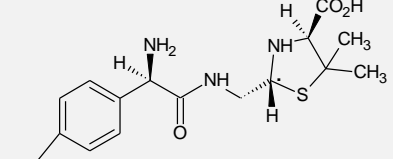
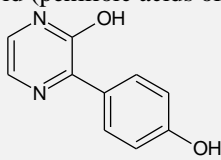
Impurity J

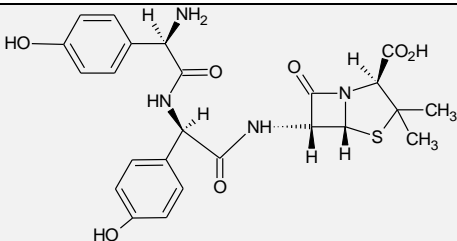
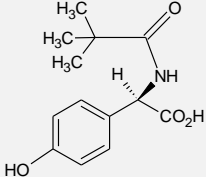
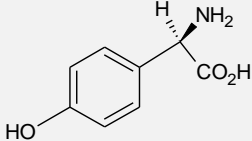
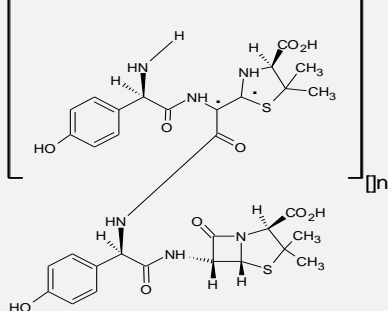
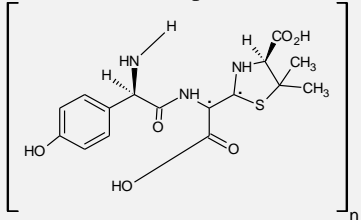
2,17-dichloro-6,13-dimethyl-18*b*,19*a*-diphenyl-8*b*,19*a*-dihydro-10*H*,18*bH*-[1,2,4]triazolo[4''',3''':1'',2''']quinolo[3'',4''':4'',5']oxazolo[3',2'-*d*]-1,2,4-triazolo[4,3-*a*][1,4]benzodiazepine.

DRUG NO. 04

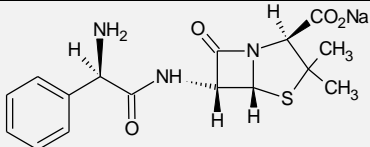
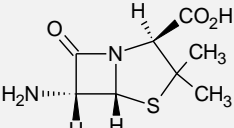
Drug's Name	Amitriptyline Hydrochloride
Drug's structure	 <p style="text-align: right;">.HCL</p>
Activity Total impurities Structures of impurities	<p style="text-align: center;">Antidepressant 06 (Six)</p> 
Impurity A	10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-one (dibenzosuberone)
Impurity B	 <p>3-(5H-dibenzo[a,d][7]annulen-5-ylidene)-N,N-dimethylpropan-1-amine (cyclobenzaprine)</p>
Impurity C	 <p>3-(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-N-methylpropan-1-amine</p>
Impurity D	 <p>5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-ol</p>
Impurity E	 <p>3-(1,2,3,4,4a,10,11,11a-octahydro-5H-dibenzo[a,d][7]annulen-5-ylidene)-N,N-dimethylpropan-1-amine</p>
Impurity F	 <p>and enantiomer</p> <p>(10RS)-5-[3-(dimethylamino)propylidene]-10,11-dihydro-5H-dibenzo[a,d][7]annulen-10-ol</p>

DRUG NO. 05

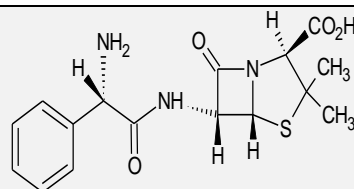
Drug's Name	Amoxicillin Sodium
Drug's structure	
Activity Total impurities Structures of impurities	Antibacterial 11 (Eleven)
Impurity A	 <p>(2<i>S</i>,5<i>R</i>,6<i>R</i>)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid)</p>
Impurity B	 <p>(2<i>S</i>,5<i>R</i>,6<i>R</i>)-6-[[[(2<i>S</i>)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-amoxicillin)</p>
Impurity C	 <p>(4<i>S</i>)-2-[5-(4-hydroxyphenyl)-3,6-dioxopiperazin-2-yl]-5,5-dimethylthiazolidine-4-carboxylic acid (amoxicillin diketopiperazines)</p>
Impurity D	 <p>(4<i>S</i>)-2-[[[(2<i>R</i>)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of amoxicillin)</p>
Impurity E	 <p>(2<i>RS</i>,4<i>S</i>)-2-[[[(2<i>R</i>)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of amoxicillin)</p> <p>and epimer at C*</p>
Impurity F	 <p>3-(4-hydroxyphenyl)pyrazin-2-ol</p>

Impurity G	
Impurity H	<p data-bbox="558 386 1471 474">2<i>S</i>,5<i>R</i>,6<i>R</i>)-6-[[[(2<i>R</i>)-2-[[[(2<i>R</i>)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (D-(4-hydroxyphenyl)glycylamoxicillin)</p>  <p data-bbox="558 653 1333 684">(2<i>R</i>)-2-[(2,2-dimethylpropanoyl)amino]-2-(4-hydroxyphenyl)acetic acid</p>
Impurity I	 <p data-bbox="699 827 1190 856">(2<i>R</i>)-2-amino-2-(4-hydroxyphenyl)acetic acid</p>
Impurity J	 <p data-bbox="602 1171 1279 1203">co-oligomers of amoxicillin and penicilloic acids of amoxicillin</p>
Impurity K	 <p data-bbox="704 1423 1177 1457">oligomers of penicilloic acids of amoxicillin</p>

DRUG NO. 06

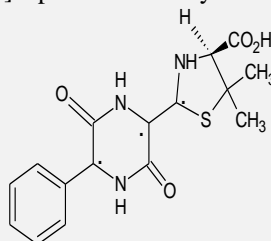
Drug's Name	Ampicillin Sodium
Drug's structure	
Activity Total impurities Structures of impurities Impurity A	<p data-bbox="883 1709 1029 1772">Antibacterial 14 (Fourteen)</p>  <p data-bbox="440 1913 1471 1969">(2<i>S</i>,5<i>R</i>,6<i>R</i>)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid)</p>

Impurity B



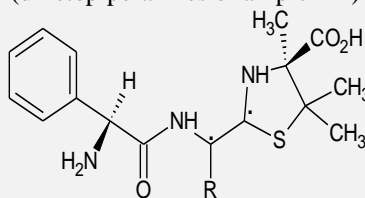
(2*S*,5*R*,6*R*)-6-[[[(2*S*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-ampicillin)

Impurity C



(4*S*)-2-(3,6-dioxo-5-phenylpiperazin-2-yl)-5,5-dimethylthiazolidine-4-carboxylic acid (diketopiperazines of ampicillin)

Impurity D

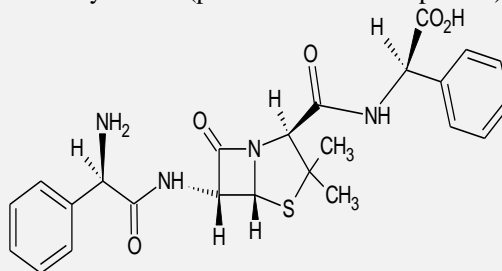


R = CO₂H: (4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of ampicillin)

Impurity F

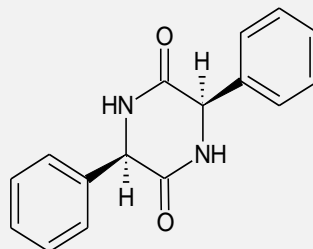
R = H: (2*R*,4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of ampicillin)

Impurity E



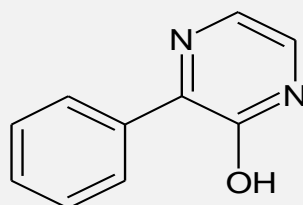
(2*R*)-2-[[[(2*S*,5*R*,6*R*)-6-[[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]-2-phenylacetic acid (ampicillinyl-D-phenylglycine)

Impurity G



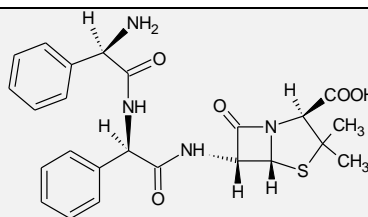
(3*R*,6*R*)-3,6-diphenylpiperazine-2,5-dione

Impurity H



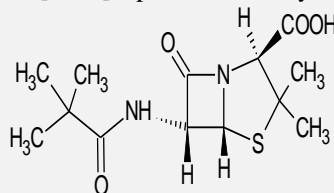
3-phenylpyrazin-2-ol

Impurity I



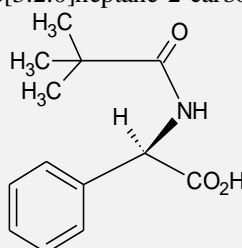
(2*S*,5*R*,6*R*)-6-[[[(2*R*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (D-phenylglycylampicillin)

Impurity J



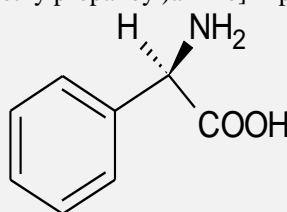
(2*S*,5*R*,6*R*)-6-[(2,2-dimethylpropanoyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Impurity K



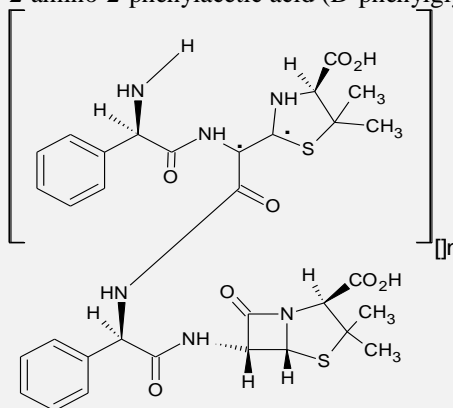
(2*R*)-2-[(2,2-dimethylpropanoyl)amino]-2-phenylacetic acid

Impurity L



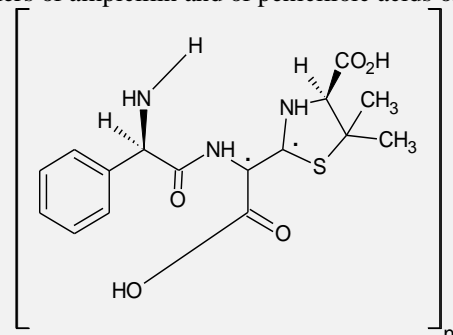
(2*R*)-2-amino-2-phenylacetic acid (D-phenylglycine)

Impurity M



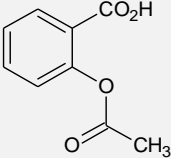
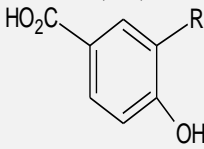
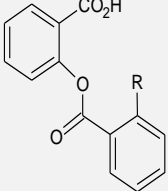
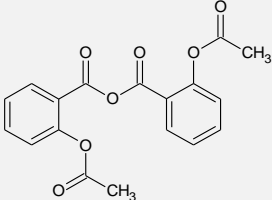
co-oligomers of ampicillin and of penicilloic acids of ampicillin

Impurity N

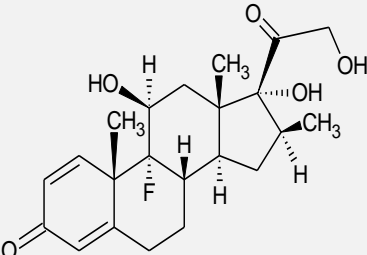


oligomers of penicilloic acids of ampicillin

DRUG NO. 07

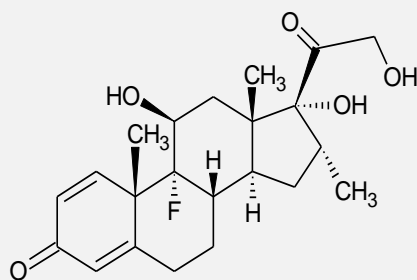
Drug's Name	Aspirin
Drug's structure	
Activity	Analgesic, antipyretic
Total impurities	06 (Six)
Structures of impurities	
Impurity A	R = H: 4-hydroxybenzoic acid
Impurity B	
Impurity C	R = CO ₂ H: 4-hydroxybenzene-1,3-dicarboxylic acid (4-hydroxyisophthalic acid)
Impurity D	salicylic acid 
Impurity E	R = O-CO-CH ₃ : 2-[[2-(acetyloxy)benzoyl]oxy]benzoic acid (acetylsalicylsalicylic acid)
Impurity F	R = OH: 2-[(2-hydroxybenzoyl)oxy]benzoic acid (salicylsalicylic acid)
	
	2-(acetyloxy)benzoic anhydride (acetylsalicylic anhydride)

DRUG NO. 08

Drug's Name	Betamethasone
Drug's structure	
Activity	Corticosteroid
Total impurities	10 (Ten)

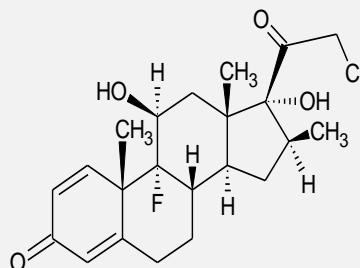
Structures of impurities

Impurities A



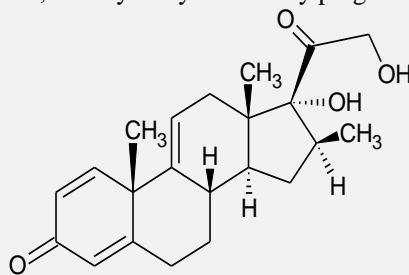
Dexamethasone

Impurities B



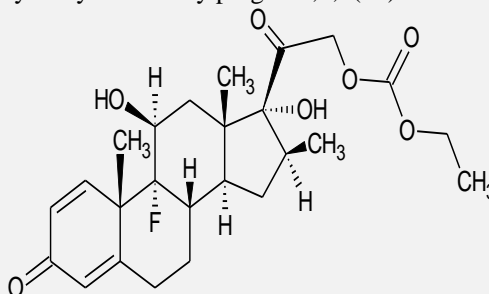
21-chloro-9-fluoro-11',17-dihydroxy-16'-methylpregna-1,4-diene-3,20-dione

Impurities C



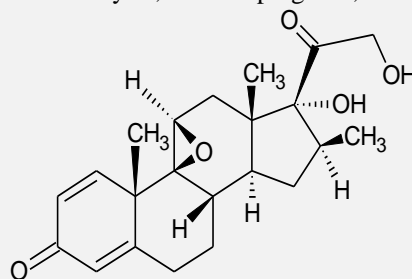
17,21-dihydroxy-16'-methylpregna-1,4,9(11)-triene-3,20-dione

Impurities D



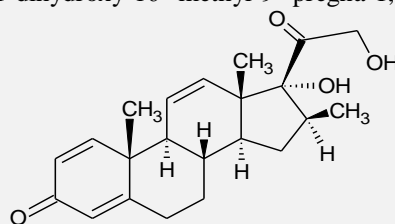
9-fluoro-11',17-dihydroxy-16'-methyl-3,20-dioxopregna-1,4-dien-21-yl ethoxycarboxylate

Impurities E

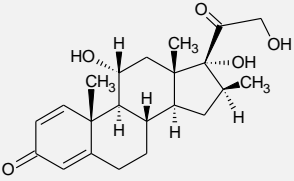
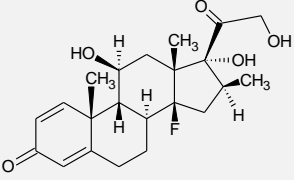
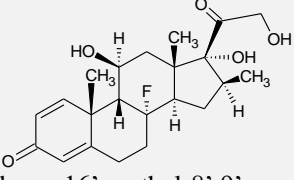
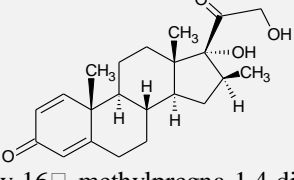


9,11'-epoxy-17,21-dihydroxy-16'-methyl-9'-pregna-1,4-diene-3,20-dione

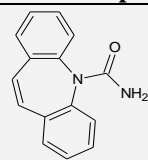
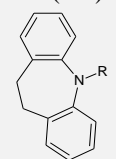
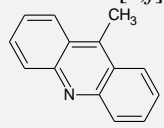
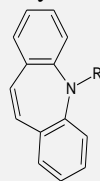
Impurities F



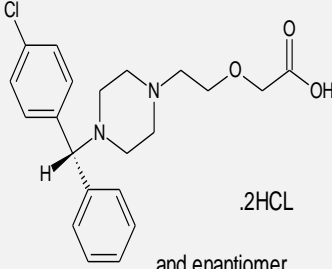
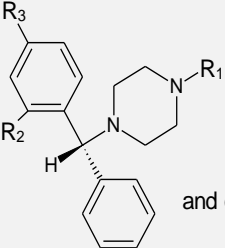
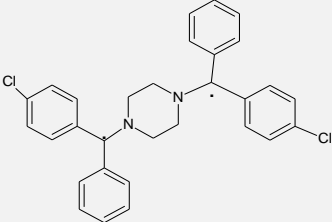
17,21-dihydroxy-16'-methylpregna-1,4,11-triene-3,20-dione

Impurities G	
	11',17,21-trihydroxy-16'-methylpregna-1,4-diene-3,20-dione
Impurities H	
	14-fluoro-11',17,21-trihydroxy-16'-methyl-8',9',14'-pregna-1,4-diene-3,20-dione
Impurities I	
	8-fluoro-11',17,21-trihydroxy-16'-methyl-8',9'-pregna-1,4-diene-3,20-dione
Impurities J	
	17,21-dihydroxy-16-methylpregna-1,4-diene-3,20-dione

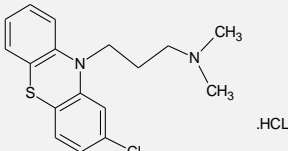
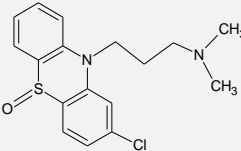
DRUG NO. 09

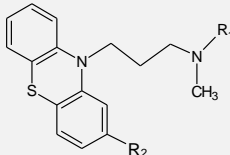
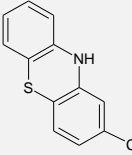
Drug's Name	Carbamazepine
Drug's Structure	
Activity	Anticonvulsant
Total Impurities	06 (Six)
Structures of Impurities	
Impurity A	R = CONH ₂ : 10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide (10,11-dihydrocarbamazepine)
Impurity E	R = H: 10,11-dihydro-5H-dibenzo[b,f]azepine(iminodibenzyl)
Impurity B	
	9-methylacridine
Impurity C	
Impurity D	R = CO-NH-CO-NH ₂ : (5H-dibenzo[b,f]azepin-5-ylcarbonyl)urea(N-carbamoylcarbamazepine)
	R = H: 5H-dibenzo[b,f]azepine(iminostilbene)
Impurity F	R = CO-Cl: 5H-dibenzo[b,f]azepine-5-carbonyl chloride (5-chlorocarbonyliminostilbene)

DRUG NO. 10

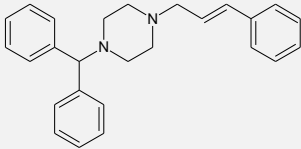
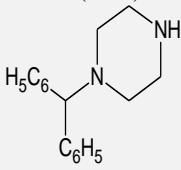
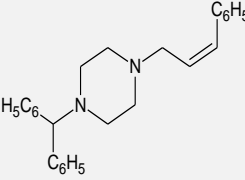
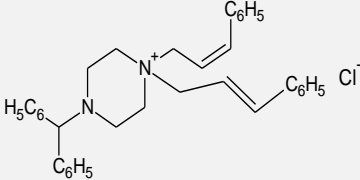
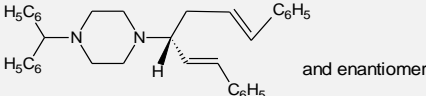
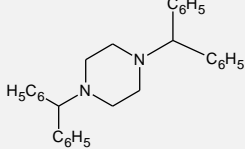
Drug's Name	Cetirizine Hydrochloride
Drug's Structure	 <p data-bbox="1045 401 1097 426">.2HCL</p> <p data-bbox="959 464 1089 489">and enantiomer</p>
Activity Total Impurities Structures of Impurities	<p data-bbox="797 489 1149 514">Histamine H₁ receptor antagonist</p> <p data-bbox="915 516 1031 541">07 (Seven)</p>
Impurity A	 <p data-bbox="987 737 1138 762">and enantiomer</p>
Impurity B	
Impurity C	R1 = R2 = H, R3 = Cl: (<i>RS</i>)-1-[(4-chlorophenyl)phenylmethyl]piperazine
Impurity E	R1 = CH ₂ -CO ₂ H, R2 = H, R3 = Cl: (<i>RS</i>)-2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]acetic acid
Impurity F	R1 = CH ₂ -CH ₂ -O-CH ₂ -CO ₂ H, R2 = Cl, R3 = H: (<i>RS</i>)-2-[2-[4-[(2-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid
Impurity G	R1 = CH ₂ -[CH ₂ -O-CH ₂] ₂ -CO ₂ H, R2 = H, R3 = Cl: (<i>RS</i>)-2-[2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]ethoxy]acetic acid (ethoxycetirizine)
	R1 = CH ₂ -CH ₂ -O-CH ₂ -CO ₂ H, R2 = R3 = H: [2-[4-(diphenylmethyl)piperazin-1-yl]ethoxy]acetic acid
	R1 = CH ₂ -CH ₂ -OH, R2 = H, R3 = Cl: 2-[4-[(<i>RS</i>)-(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethanol
Impurity D	 <p data-bbox="711 1409 1235 1434">1,4-bis[(4-chlorophenyl)phenylmethyl]piperazine</p>

DRUG NO. 11

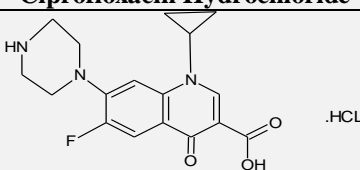
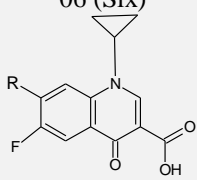
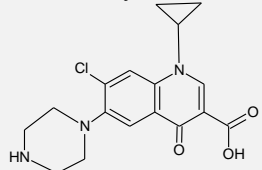
Drug's Name	Chlorpromazine Hydrochloride
Drug's Structure	 <p data-bbox="1089 1646 1127 1671">.HCL</p>
Activity Total Impurities Structures of Impurities	<p data-bbox="834 1692 1127 1717">Antipsychotic, Anti-emetic</p> <p data-bbox="932 1724 1029 1749">05 (Five)</p>
Impurity A	 <p data-bbox="483 1913 1479 1967">3-(2-chloro-10<i>H</i>-phenothiazin-10-yl)-<i>N,N</i>-dimethylpropan-1-amine <i>S</i>-oxide (chlorpromazine sulphoxide)</p>

	
Impurity B	R1 = [CH ₂] ₃ -N(CH ₃) ₂ , R2 = Cl: <i>N</i> -[3-(2-chloro-10 <i>H</i> -phenothiazin-10-yl)propyl]- <i>N,N,N'</i> -trimethylpropane-1,2-diamine
Impurity C	
Impurity D	R1 = CH ₃ , R2 = H: promazine
Impurity E	R1 = H, R2 = Cl: 3-(2-chloro-10 <i>H</i> -phenothiazin-10-yl)- <i>N</i> -methylpropan-1-amine (desmethylchlorpromazine)
	
	2-chloro-10 <i>H</i> -phenothiazine

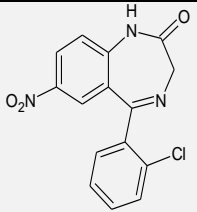
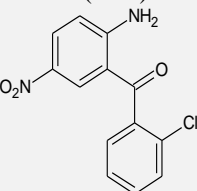
DRUG NO. 12

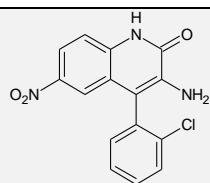
Drug's Name	Cinnarizine
Drug's structure	
Activity	Histamine H ₁ -receptor antagonist.
Total impurities	05 (Five)
Structures of impurities	
Impurities A	 1-(diphenylmethyl)piperazine
Impurities B	 (<i>Z</i>)-1-(diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine
Impurities C	 (4-(diphenylmethyl)-1,1-bis[(<i>E</i>)-3-phenylprop-2-enyl]piperazinium chloride
Impurities D	 1-(diphenylmethyl)-4-[(1 <i>R</i> ,3 <i>E</i>)-4-phenyl-1-[(<i>E</i>)-2-phenylethenyl]but-3-enyl]piperazine and enantiomer
Impurities E	 1,4-bis(diphenylmethyl)piperazine

DRUG NO. 13

Drug's Name	Ciprofloxacin Hydrochloride
Drug's Structure	
Activity	Antibacterial
Total Impurities	06 (Six)
Structures of Impurities	
Impurity A	R = Cl: 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (fluoroquinolonic acid)
Impurity C	R = NH-[CH ₂] ₂ -NH ₂ : 7-[(2-aminoethyl)amino]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (ethylenediamine compound)
Impurity B	R = CO ₂ H, R' = H: 1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (desfluoro compound),
Impurity E	R = H, R' = F: 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1H)-one (decarboxylated compound),
Impurity F	R = CO ₂ H, R' = OH: 1-cyclopropyl-6-hydroxy-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid,
Impurity D	 7-chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

DRUG NO. 14

Drug's Name	Clonazepam
Drug's structure	
Activity	Anticonvulsant
Total impurities	02 (Two)
Structures of impurities	
Impurities A	2-amino-5-nitrophenyl(2-chlorophenyl)methanone



Impurity B

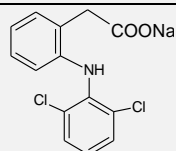
3-amino-4-(2-chlorophenyl)-6-nitroquinolin-2(1H)-one

DRUG NO. 15

Drug's Name

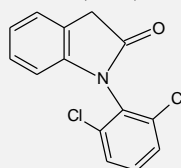
Diclofenac Sodium

Drug's Structure

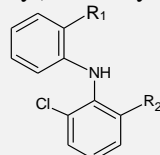


Activity
Total Impurities
Structures of
Impurities
Impurity A

Analgesic, Anti-inflammatory
05 (Five)



1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one



Impurity B

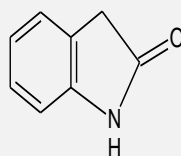
R1 = CHO, R2 = Cl: 2-[(2,6-dichlorophenyl)amino]benzaldehyde,

Impurity C

R1 = CH₂OH, R2 = Cl: [2-[(2,6-dichlorophenyl)amino]phenyl]methanol

Impurity D

R1 = CH₂-CO₂H, R2 = Br: 2-[2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid



Impurity E

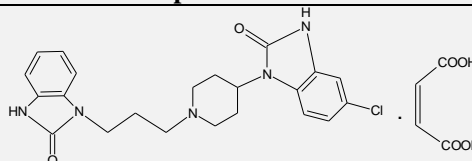
1,3-dihydro-2H-indol-2-one

DRUG NO. 16

Drug's Name

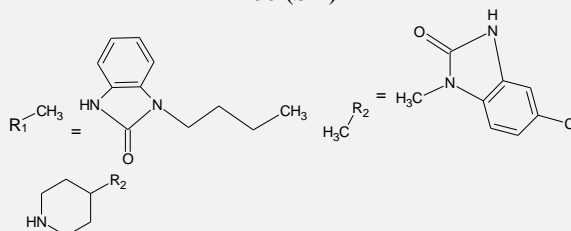
Domperidone maleate

Drug's Structure



Activity
Total Impurities
Structures of
Impurities

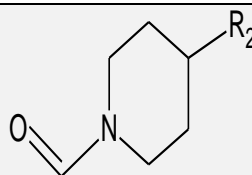
Antiemetic
06 (Six)



Impurity A

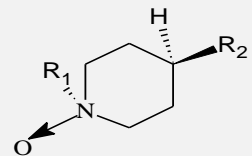
5-chloro-1-(piperidin-4-yl)-1,3-dihydro-2H-benzimidazol-2-one

Impurity B

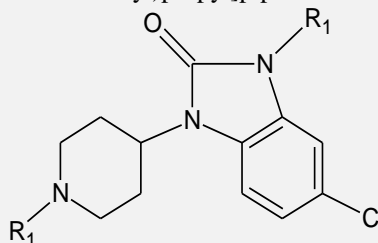


4-(5-chloro-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-formylpiperidine

Impurity C

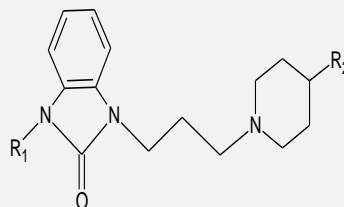
*cis*-4-(5-chloro-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)-1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidine 1-oxide

Impurity D



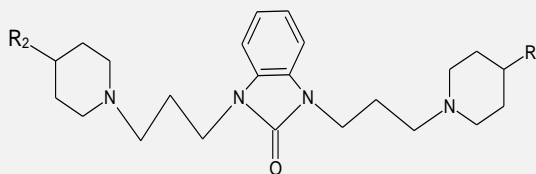
5-chloro-3-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2H-benzimidazol-2-one

Impurity E



1-[3-[4-(5-chloro-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]propyl]-3-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]-1,3-dihydro-2H-benzimidazol-2-one

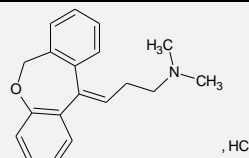
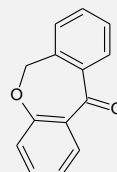
Impurity F



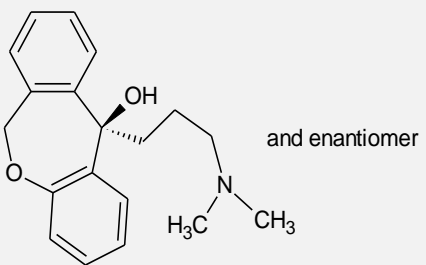
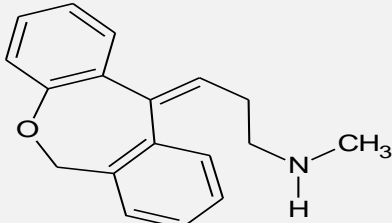
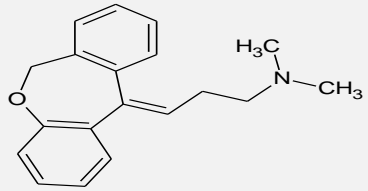
1,3-bis[3-[4-(5-chloro-2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)piperidin-1-yl]propyl]-1,3-dihydro-2H-benzimidazol-2-one

DRUG NO. 17**Drug's Name****Doxepin Hydrochloride**

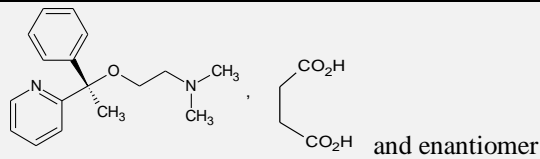
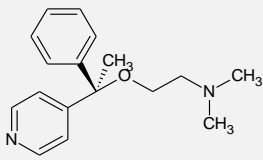
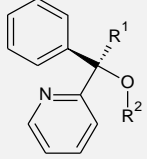
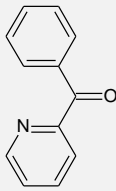
Drug's structure

Antidepressant
04 (Four)Activity
Total impurities
Structures of impurities
Impurities A

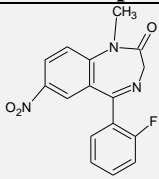
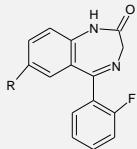
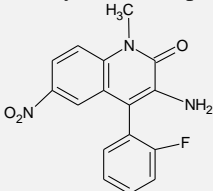
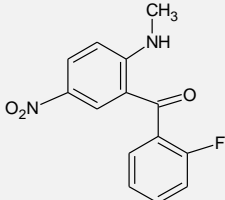
dibenzo[b,e]oxepin-11(6H)-one

Impurities B	 <p>and enantiomer</p>
Impurities C	<p>(11RS)-11-[3-(dimethylamino)propyl]-6,11-dihydrodibenzo[b,e]oxepin-11-ol</p> 
Impurities D	<p>(E)-3-(dibenzo[b,e]oxepin-11(6H)-ylidene)-N-methylpropan-1-amine</p>  <p>(Z)-3-(dibenzo[b,e]oxepin-11(6H)-ylidene)-N,N-dimethylpropan-1-amine</p>

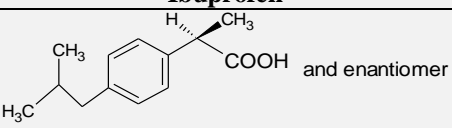
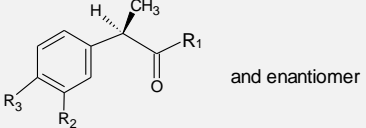
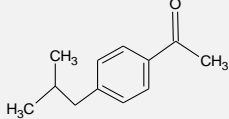
DRUG NO.18

Drug's Name	Doxylamine Succinate
Drug's structure	 <p>and enantiomer</p>
Activity	Histamine H ₁ -receptor antagonist
Total impurities	04 (Four)
Structure of impurities	
Impurities A	 <p>and enantiomer</p> <p>N,N-dimethyl-2-[1(RS)-1-phenyl-1-(pyridin-4-yl)ethoxy]ethanamine</p>
Impurities B	 <p>and enantiomer</p> <p>R1 = CH₃, R2 = H: (1RS)-1-phenyl-1-(pyridin-2-yl)ethanol</p>
Impurities C	<p>R1 = H, R2 = CH₂-CH₂-N(CH₃)₂: N,N-dimethyl-2-[(RS)-1-phenyl(pyridin-2-yl)methoxy]ethanamine</p>
Impurities D	 <p>Phenyl(pyridin-2-yl)methanone (2-benzoylpyridine)</p>

DRUG NO. 19

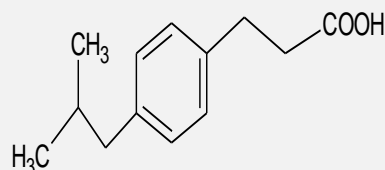
Drug's Name	Flunitrazepam
Drug's Structure	
Activity	Hypnotic
Total Impurities	04 (Four)
Structures of Impurities	
Impurity A	R = NH ₂ : 7-amino-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (7-aminodemethylflunitrazepam)
Impurity B	R = NO ₂ : 5-(2-fluorophenyl)-7-nitro-1,3-dihydro-2H-1,4-benzodiazepin-2-one (demethylflunitrazepam)
Impurity C	
Impurity D	3-amino-4-(2-fluorophenyl)-1-methyl-6-nitroquinolin-2(1H)-one  (2-fluorophenyl)[2-(methylamino)-5-nitrophenyl]methanone

DRUG NO. 20

Drug's Name	Ibuprofen
Drug's Structure	
Activity	Analgesic, Anti-inflammatory
Total Impurities	18 (Eighteen)
Structures of Impurities	
Impurity A	R1 = OH, R2 = CH ₂ -CH(CH ₃) ₂ , R3 = H: (2RS)-2-[3-(2-methylpropyl)phenyl]propanoic acid
Impurity B	R1 = OH, R2 = H, R3 = [CH ₂] ₃ -CH ₃ : (2RS)-2-(4-butylphenyl)propanoic acid
Impurity C	R1 = NH ₂ , R2 = H, R3 = CH ₂ -CH(CH ₃) ₂ : (2RS)-2-[4-(2-methylpropyl)phenyl]propanamide
Impurity D	R1 = OH, R2 = H, R3 = CH ₃ : (2RS)-2-(4-methylphenyl)propanoic acid
Impurity E	

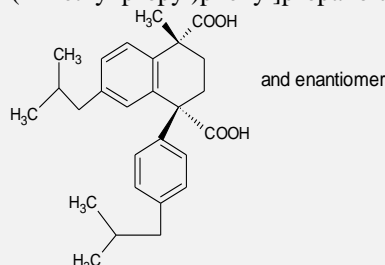
1-[4-(2-methyl propyl)phenyl]ethanone

Impurity F

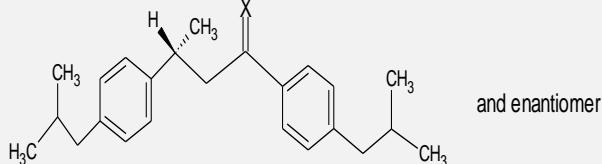


3-[4-(2-methyl propyl)phenyl]propanoic acid

Impurity G

*cis*-7-(2-methylpropyl)-1-[4-(2-methylpropyl)phenyl]-1,2,3,4-tetrahydronaphthalene-1,4-dicarboxylic acid

Impurity H



Impurity I

X = O: (3*RS*)-1,3-bis[4-(2-methylpropyl)phenyl]butan-1-oneX = H₂: (3*RS*)-1,3-bis[4-(2-methylpropyl)phenyl]butane

Impurity J

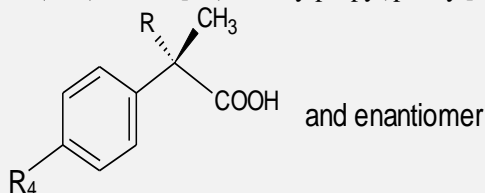
Impurity K

Impurity L

Impurity M

Impurity N

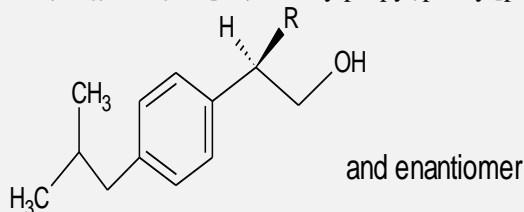
Impurity O



- R = H, R₄ = CO-CH(CH₃)₂: (2*RS*)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid
 R = H, R₄ = CHO: (2*RS*)-2-(4-formylphenyl)propanoic acid
 R = H, R₄ = CHOH-CH(CH₃)₂: 2-[4-(1-hydroxy-2-methylpropyl)phenyl]propanoic acid
 R = OH, R₄ = CH₂-CH(CH₃)₂: (2*RS*)-2-hydroxy-2-[4-(2-methylpropyl)phenyl]propanoic acid
 R = H, R₄ = C₂H₅: (2*RS*)-2-(4-ethylphenyl)propanoic acid
 R = H, R₄ = CH(CH₃)-C₂H₅: 2-[4-(1-methylpropyl)phenyl]propanoic acid

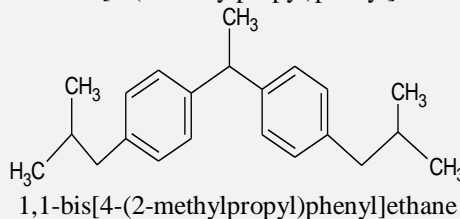
Impurity P

Impurity Q

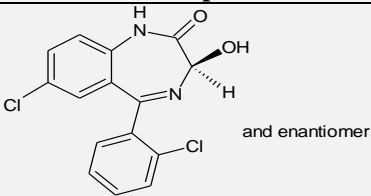
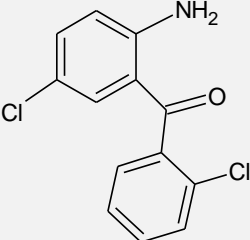
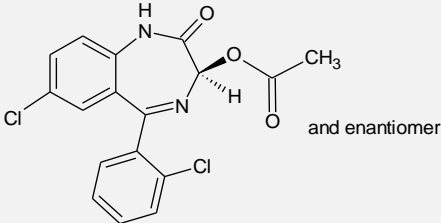
R = CH₃: (2*RS*)-2-[4-(2-methylpropyl)phenyl]propan-1-ol

R = H: 2-[4-(2-methylpropyl)phenyl]ethanol

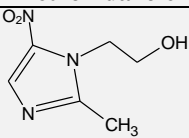
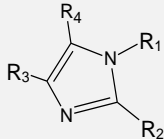
Impurity R



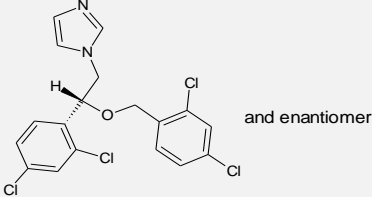
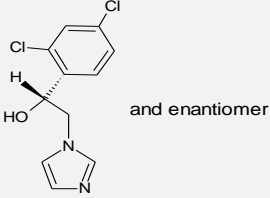
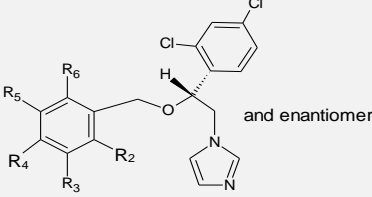
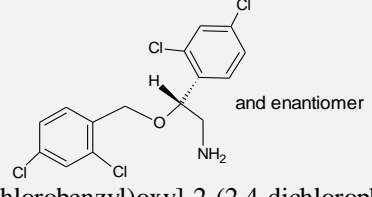
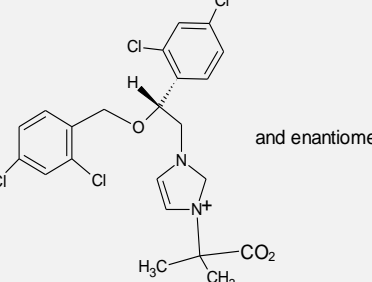
DRUG NO. 21

Drug's Name	Lorazepam
Drug's structure	 and enantiomer
Activity	Anxiolytic
Total impurities	02 (Two)
Structures of impurities	
Impurities A	(2-amino-5-chlorophenyl)(2-chlorophenyl)methanone,
Impurities B	 and enantiomer
Impurities B	(3RS)-7-chloro-5-(2-chlorophenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl acetate

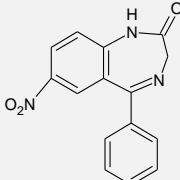
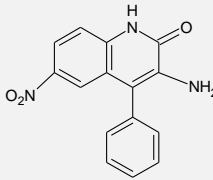
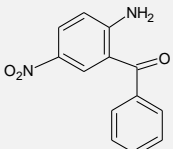
DRUG NO. 22

Drug's Name	Metronidazole
Drug's Structure	
Activity	Antibacterial
Total Impurities	07 (Seven)
Structures of Impurities	
Impurity A	
Impurity B	R1 = R4 = H, R2 = CH ₃ , R3 = NO ₂ : 2-methyl-4-nitroimidazole
Impurity C	R1 = R2 = R4 = H, R3 = NO ₂ : 4-nitroimidazole
Impurity D	R1 = CH ₂ -CH ₂ -OH, R2 = R4 = H, R3 = NO ₂ : 2-(4-nitro-1H-imidazol-1-yl)ethanol R1 = CH ₂ -CH ₂ -OH, R2 = R3 = H, R4 = NO ₂ : 2-(5-nitro-1H-imidazol-1-yl)ethanol
Impurity E	R1 = CH ₂ -CH ₂ -OH, R2 = CH ₃ , R3 = NO ₂ , R4 = H: 2-(2-methyl-4-nitro-1H-imidazol-1-yl)ethanol
Impurity F	R1 = CH ₂ -CH ₂ -O-CH ₂ -CH ₂ -OH, R2 = CH ₃ , R3 = H, R4 = NO ₂ : 2-[2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethoxy]ethanol
Impurity G	R1 = CH ₂ -CO ₂ H, R2 = CH ₃ , R3 = H, R4 = NO ₂ : 2-(2-methyl-5-nitro-1H-imidazol-1-yl)acetic acid

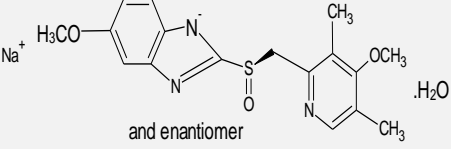
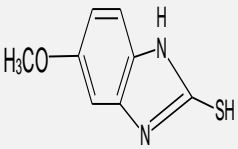
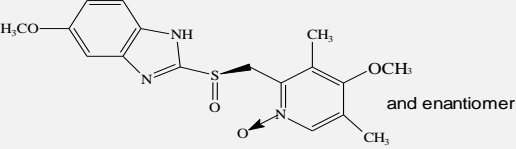
DRUG NO. 23

Drug's Name	Miconazole
Drug's Structure	 <p style="text-align: right;">and enantiomer</p>
Activity Total Impurities Structures of Impurities	<p style="text-align: center;">Antifungal 09 (Nine)</p>
Impurity A	 <p style="text-align: right;">and enantiomer</p> <p style="text-align: center;">(1RS)-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol</p>
Impurity B	 <p style="text-align: right;">and enantiomer</p> <p style="text-align: center;">R2 = R3 = R5 = R6 = H, R4 = Cl: 1-[(2RS)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole</p>
Impurity D	<p style="text-align: center;">R2 = R6 = Cl, R3 = R4 = R5 = H: 1-[(2RS)-2-[(2,6-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole</p>
Impurity F	<p style="text-align: center;">R2 = R5 = R6 = H, R3 = R4 = Cl: 1-[(2RS)-2-[(3,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole</p>
Impurity G	<p style="text-align: center;">R2 = R5 = Cl, R3 = R4 = R6 = H: 1-[(2RS)-2-[(2,5-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole</p>
Impurity H	<p style="text-align: center;">R2 = R3 = R4 = R5 = R6 = H: 1-[(2RS)-2-benzyl-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole</p>
Impurity I	<p style="text-align: center;">R2 = Cl, R3 = R4 = R5 = R6 = H: 1-[(2RS)-2-[(2-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole</p>
Impurity C	 <p style="text-align: right;">and enantiomer</p> <p style="text-align: center;">(2RS)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethanamine</p>
Impurity E	 <p style="text-align: right;">and enantiomer</p> <p style="text-align: center;">2-[1-[(2RS)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazol-3-yl]-2-methylpropanoate</p>

DRUG NO. 24

Drug's Name	Nitrazepam
Drug's Structure	
Activity	Hypnotic
Total Impurities	02 (Two)
Structures of Impurities	
Impurity A	3-amino-6-nitro-4-phenylquinolin-2(1H)-one
Impurity B	 (2-amino-5-nitrophenyl)phenyl methanone

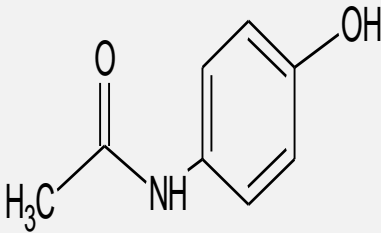
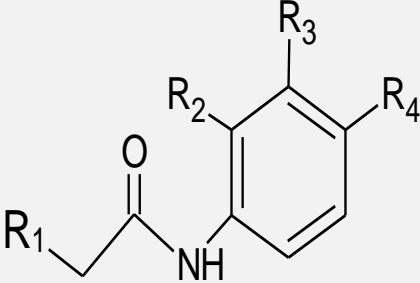
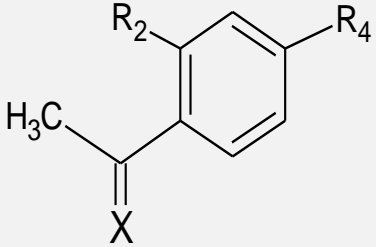
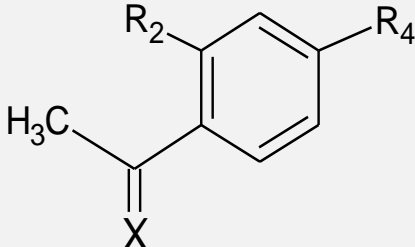
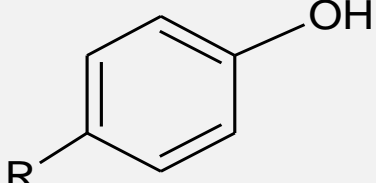
DRUG NO. 25

Drug's Name	Omeprazole Sodium
Drug's Structure	 and enantiomer
Activity	Treatment of Peptic ulcer
Total Impurities	05 (Five)
Structures of Impurities	
Impurity A	5-methoxy-1H-benzimidazole-2-thiol
Impurity B	R = H, X = SO: 2-[(RS)-[(3,5-dimethylpyridin-2-yl)methyl]sulphonyl]-5-methoxy-1H-benzimidazole
Impurity C	R = OCH ₃ , X = S: 5-methoxy-2-[[4-methoxy-3,5-dimethylpyridin-2-yl)methyl]thio]-1H-benzimidazole (ufiprazole)
Impurity D	R = OCH ₃ , X = SO ₂ : 5-methoxy-2-[[4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1H-benzimidazole (omeprazole-sulphone)
Impurity E	 and enantiomer 4-methoxy-2-[[RS)-(5-methoxy-1H-benzimidazol-2-yl)sulphonyl]methyl]-3,5-dimethylpyridine 1-oxide

DRUG NO. 26

Drug's Name	Oxazepam
Drug's structure	
Activity Total impurities	<p>and enantiomer Anxiolytic 05 (Five)</p>
Structures of impurities	
Impurities A	<p>and enantiomer (5RS)-7-chloro-5-phenyl-4,5-dihydro-1H-1,4-benzodiazepine-2,3-dione</p>
Impurities B Impurities C	
Impurities B Impurities C	<p>and enantiomer (3RS)-7-chloro-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl acetate</p>
Impurities D	
Impurities D	<p>6-chloro-4-phenylquinazoline-2-carbaldehyde</p>
Impurities E	
Impurities E	<p>(2-amino-5-chlorophenyl)phenylmethanone</p>
	<p>7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one 4-oxide</p>

DRUG NO. 27

Drug's Name	Paracetamol
Drug's Structure	
Activity Total Impurities Structures of Impurities	Analgesic, Antipyretic 11 (Eleven)
Impurity A Impurity B Impurity C Impurity D Impurity H Impurity J	 <p data-bbox="565 808 1393 989"> R1 = R3 = R4 = H, R2 = OH: <i>N</i>-(2-hydroxyphenyl)acetamide R1 = CH₃, R2 = R3 = H, R4 = OH: <i>N</i>-(4-hydroxyphenyl)propanamide R1 = R2 = H, R3 = Cl, R4 = OH: <i>N</i>-(3-chloro-4-hydroxyphenyl)acetamide R1 = R2 = R3 = R4 = H: <i>N</i>-phenylacetamide R1 = R2 = R3 = H, R4 = O-CO-CH₃: 4-(acetamino)phenyl acetate R1 = R2 = R3 = H, R4 = Cl: <i>N</i>-(4-chlorophenyl)acetamide (chloroacetanilide) </p>
Impurity E Impurity G	 <p data-bbox="678 1241 1279 1276">X = O, R₂ = H, R₄ = OH: 1-(4-hydroxyphenyl)ethanone</p> <p data-bbox="618 1297 1336 1331">X = N-OH, R₂ = H, R₄ = OH: 1-(4-hydroxyphenyl)ethanone oxime</p>
Impurity I	 <p data-bbox="678 1583 1279 1619">X = O, R₂ = OH, R₄ = H: 1-(2-hydroxyphenyl)ethanone</p>
Impurity F Impurity K	 <p data-bbox="849 1822 1105 1856">R = NO₂: 4-nitrophenol</p> <p data-bbox="841 1885 1114 1919">R = NH₂: 4-aminophenol</p>

CONCLUSION: Impurity profiling of a pharmaceutical substance under investigation gives a maximum possible description of impurities present in it. The establishment of regulatory guidelines for impurity levels in drug substances and products provides the quality criteria for manufacturers. These impurities are developed in pharmaceutical products during the manufacturing process, chemical synthesis, formulation, storage, etc. Various analytical tools have been used for the detection, identification, and characterization of various impurities in active pharmaceutical ingredients. From the above discussion, it has been observed that there are lots of impurities present in several well-known marketed drugs whose successful identification and control of the individual or total content as per pharmacopeias are needed to render biological safety and efficacy.

The present study throws the attention to the future researchers to set the impurity profiling as a paramount step in the process of quality control and to develop more sophisticated analytical techniques to detect the level of potent impurities present in drugs more accurately. Even in this article, we have tried to give a brief list of impurities of well-known marketed drugs, mentioned into British pharmacopeia. In the future, we would like to make a more improvised list of impurities with their content limits along with APIs of all well-known marketed drugs, listed in other pharmacopeias also.

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CONFLICT OF INTEREST: Nil

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