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PRESENCE OF ORGANIC IMPURITIES INTO ACTIVE PHARMACEUTICAL INGREDIENTS: A REVIEW

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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.

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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 substances [1]. 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.

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 formulations [1-4].

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 Solvents [1]

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 ß-lactam ring, as well as that of an a-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 difficult [6].

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 degradation [1].

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 products [4].

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 acid [7].

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 method [8].

Gazdag M *et al.,* confirmed the presence of 17α-Hydroxy-17-oic acid and 17α,20-Dihydroxy-21-oic acid impurities in Mazipredone by using HPLC-(APCI)-MS and HPLC- diode-array UV method [9].

Makino Y *et al.,* determined the presence of (1*R*,2*S*)-(1)-ephedrine and (1*S*,2*S*)-(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 column [10].

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 method [11].

The presence of benzaldehyde and benzyl alcohol in the drug Methamphetamine was identified by Kuwayama K *et al.,* by using the HS-SPME & GC-MS [12].

Trefi S *et al.,* investigated different impurity profiles in generic Ciprofloxacin formulations collected from different countries by using ^{19}F, ^{1}H 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 acid [13].

The presence of impurities in the antiparkinsonian drugs such as Levodopa, Carbidopa, Entacapone was identified by Vemi´c 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, Methyldopa, 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 Entacapone [14].

Sun C *et al.,* reported a novel impurity in bulk drug Eprosartan by a simple and sensitive HPLC/MS^n 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 acid [15].

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, ^{1}H,^{13}C, 2D NMR and IR [16].

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)benzonitrile were found [17].

Volk KJ *et al.*, mentioned the presence of impurities such as Norbutorphanol, 9-hydroxy-butorphanol, 9-keto-butorphanol, Ring-contracted butorphanol, Δ1, 10*a*-butorphanol in the drug Butorphanol tartrate by using LC-MS & LC-Tandem MS [18].

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 Pharmacopoeia [19] 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 *et al.,* [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 *et al.,* [8]	HPLC & LC/MS/MS	Rivastigmine tartrate	ii)3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methyl carbamate N-oxide	2a
			iii)Ethyl-methyl-carbamic acid 4-(1-dimethylamino-ethyl)-phenyl ester	3a
			iv)ethyl-methyl-carbamic acid 2-(1-dimethylamino-ethyl)- phenyl ester	4a
Gazdag M *et al.,* [9]	HPLC-(APCI)-MS & HPLC-diode-array UV	Mazipredone	v) 17α-Hydroxy-17-oic acid	5a
			vi) 17α,20-Dihydroxy-21-oic acid	6a
Makino Y *et al.,* [10]	HPLC	Methamphetamine	vii) (1*R*,2*S*)-(-)-ephedrine	7a
			viii) (1*S*,2*S*)-(+)-pseudoephedrine	8a
Choe S *et al.,* [11]	GC-FID & GC-MS	Methamphetamine	ix) Acetaminophen	9a
			x) Caffeine	10a
			xi) Chlorpheniramine	11a
Kuwayama K *et al.,* [12]	HS-SPME/GC–MS	Methamphetamine	xii) Benzaldehyde	12a
			xiii) Benzyl alcohol	13a
Trefi S *et al.,* [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)	14a
			xv) 1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (desfluoro compound)	15a
Vemi'c A *et al.,* [14]	RP-HPLC	Levodopa	xvi) ((2S)-2-amino-3-(4-hydroxyphenyl) propanoic acid	16a
			xvii) (2RS)-2-amino-3-(4-hydroxy-3-methoxyphenyl)propanoic acid	17a
		Carbidopa,	xviii) Methyldopa	18a
			xix)3-O-methylcarbidopa	19a
		Entacapone	xx) (2Z)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide	20a
			xxi) 3,4-dihydroxy-5-nitrobenzaldehyde	21a
Sun C *et al.,* [15]	HPLC/MS^{n} & NMR	Eprosartan	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	22a
Zhang D *et al.,* [16]	MS, ^{1}H, ^{13}C, 2D NMR & IR	Flupirtine maleate	xxiii) 5-((4-fluorobenzyl)amino)-2-oxo-1H-imidazo[4,5-b]pyridine-1,3(2H)-dicarboxylate	23a
			xxiv) diethyl(6-((4-fluorobenzyl)amino)pyridine-2,3-diyl)dicarbamate	24a
			xxv)5-((4-fluorobenzyl)amino)-1H-imidazo[4,5-b]pyridin-2(3H)-one	25a

Kadivar MH *et al.,* [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)benzonitrile	29a
Volk KJ *et al.,* [18]	LC-MS & LC-Tandem MS	Butorphanol tartrate	xxx) Norbutorphanol	30a
			xxxi) 9-hydroxy-butorphanol	31a
			xxxii)9-keto-butorphanol	32a
			xxxiii)Ring-contracted butorphanol	33a
			xxxiv) Δ1, 10*a*-butorphanol	34a

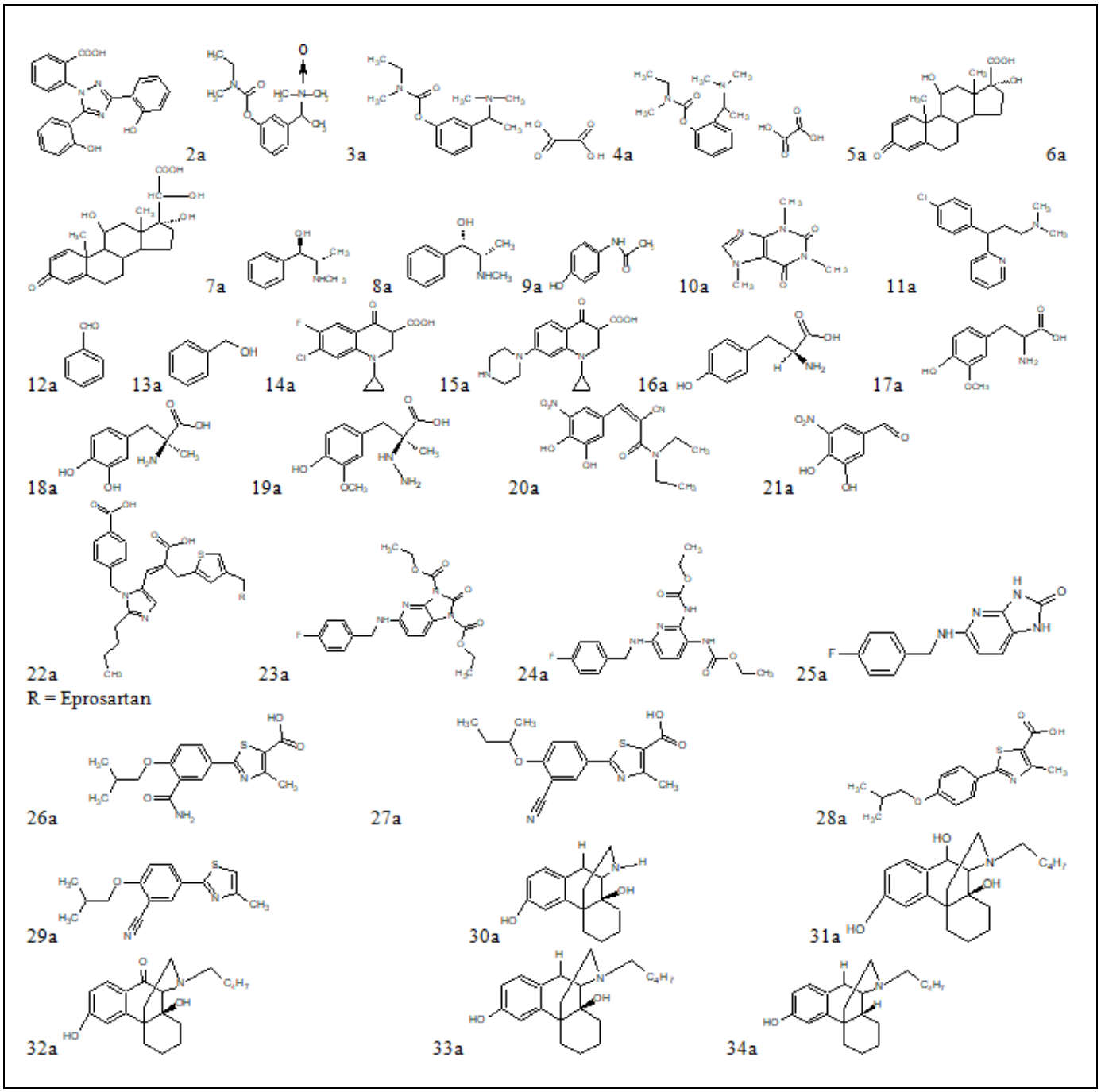
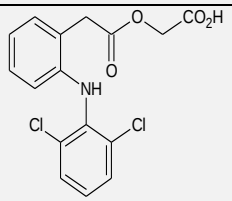
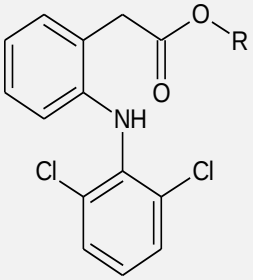
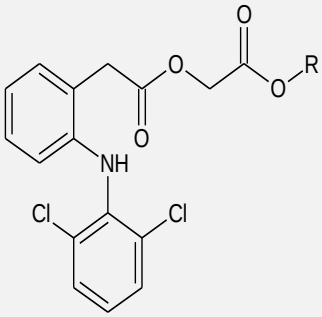
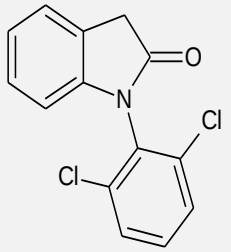
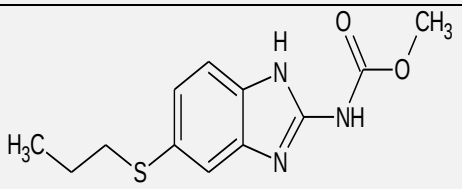
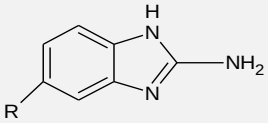
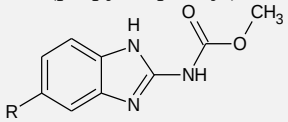


FIG. 1: STRUCTURE OF IMPURITIES

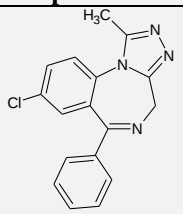
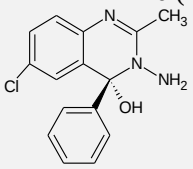
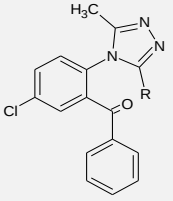
TABLE 2: IMPURITIES OF FEW WELL-KNOWN MARKETED DRUGS AS PER BRITISH PHARMACOPOEIA: DRUG NO. 01

Drug's Name	**Aceclofenac**
Drug's structure	
Activity	Analgesic, Anti-inflammatory
Total impurities	09 (Nine)
Structures of impurities	
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_2H_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_2H_5: ethyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (ethyl ester of aceclofenac)
Impurity H	R = CH_2-C_6H_5: benzyl [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetate (benzyl ester of aceclofenac) R = CH_2-CO_2H: [[[[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetyl]oxy]acetic acid (acetic aceclofenac) R = CH_2-CO-O-CH_2-CO_2H: [[[[[[[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-2*H*-indol-2-one

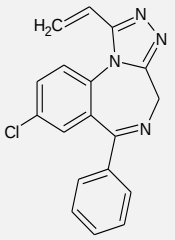
DRUG NO. 02

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-(propylsulphanyl)-1*H*-benzimidazol-2-amine
Impurity D	R = SO_2-CH_2-CH_2-CH_3: 5-(propylsulphonyl)-1*H*-benzimidazol-2-amine
Impurity B	 R = SO-CH_2-CH_2-CH_3: methyl [5-(propylsulphinyl)-1*H*-benzimidazol-2-yl]carbamate
Impurity C	R = SO_2-CH_2-CH_2-CH_3: methyl [5-(propylsulphonyl)-1*H*-benzimidazol-2-yl]carbamate
Impurity E	R = H: methyl (1*H*-benzimidazol-2-yl)carbamate
Impurity F	R = S-CH_3: methyl [5-(methylsulphanyl)-1*H*-benzimidazol-2-yl]carbamate

DRUG NO. 03

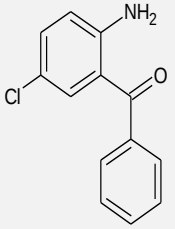
Drug's Name	**Alprazolam**
Drug's structure	
Activity	Anxiolytic
Total impurities	10 (Ten)
Structures of impurities	
Impurity A	and enantiomer (4*RS*)-3-amino-6-chloro-2-methyl-4-phenyl-3,4-dihydroquinazolin-4-ol
Impurity B	 R = CH_2OH: [5-chloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone
Impurity C	R = H: [5-chloro-2-[3-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone
Impurity F	R = CH_2Cl: [5-chloro-2-[3-(chloromethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone

Impurity D



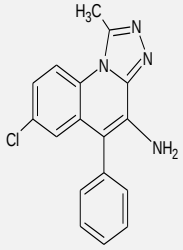
8-chloro-1-ethenyl-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine

Impurity E



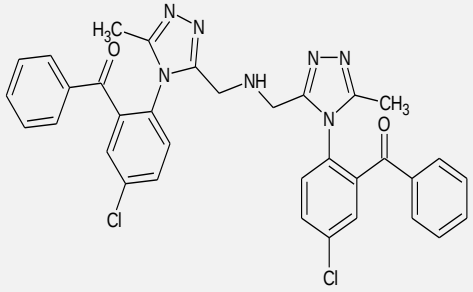
(2-amino-5-chlorophenyl)phenylmethanone

Impurity G



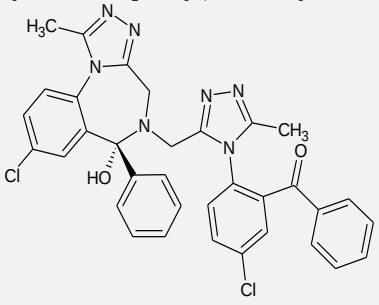
7-chloro-1-methyl-5-phenyl[1,2,4]triazolo[4,3-*a*]quinolin-4-amine

Impurity H



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

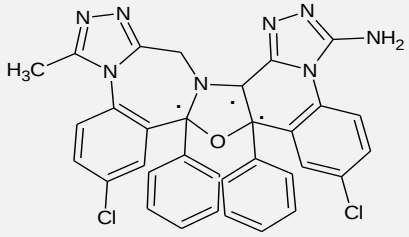
Impurity I



and enantiomer

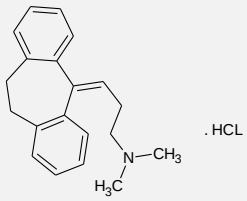
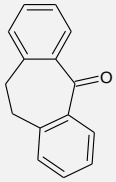
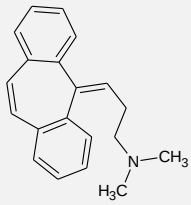
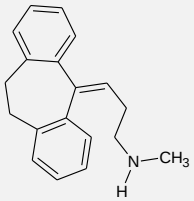
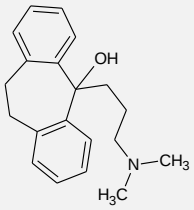
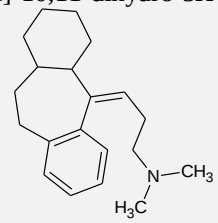
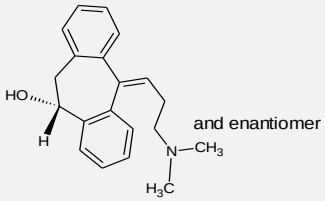
[5-chloro-2-[3-[[(6*RS*)-8-chloro-6-hydroxy-1-methyl-6-phenyl-4*H*-[1,2,4]triazolo[4, 3-*a*][1,4]benzodiazepin-5(6*H*)-yl]methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]phenyl]phenylmethanone

Impurity J

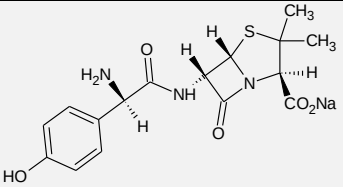
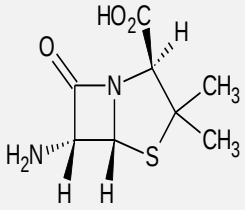
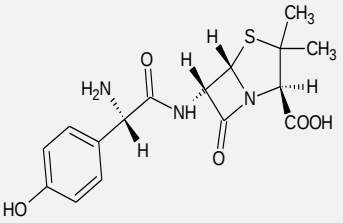
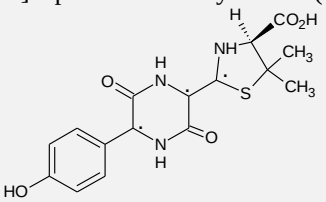
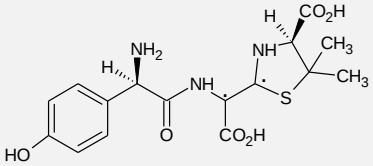
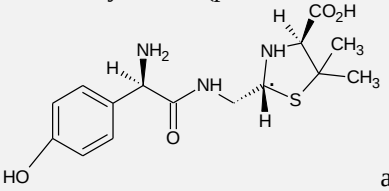
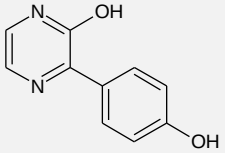


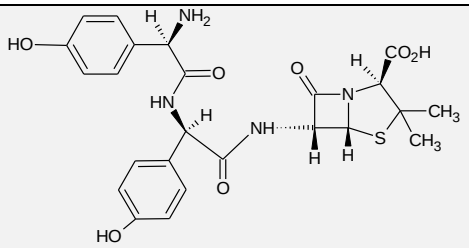
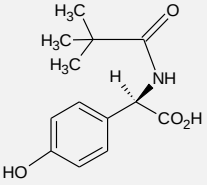
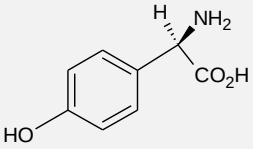
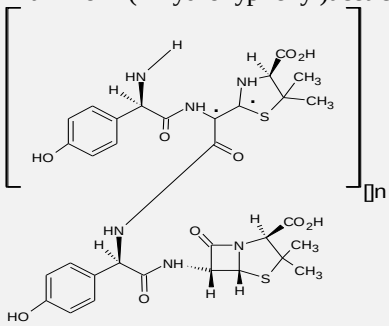
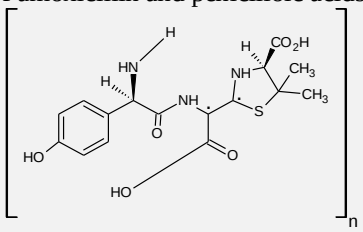
2,17-dichloro-6,13-dimethyl-18b,19a-diphenyl-8b,19a-dihydro-10*H*,18b*H*-[1,2, 4]triazolo[4‘‘‘,3‘‘‘:1‘‘,2‘‘]quinolo[3‘‘,4‘‘:4’,5’]oxazolo[3’,2’-*d*]-1,2,4-triazolo[4,3-*a*][1,4]benzodiazepine.

DRUG NO. 04

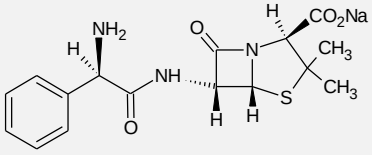
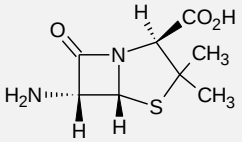
Drug's Name	**Amitriptyline Hydrochloride**
Drug's structure	
Activity	Antidepressant
Total impurities	06 (Six)
Structures of impurities	
Impurity A	 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-one (dibenzosuberone)
Impurity B	 3-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-amine (cyclobenzaprine)
Impurity C	 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*-methylpropan-1-amine
Impurity D	 5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ol
Impurity E	 3-(1,2,3,4,4a,10,11,11a-octahydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-*N*,*N*-dimethylpropan-1-amine
Impurity F	 (10*RS*)-5-[3-(dimethylamino)propylidene]-10,11-dihydro-5*H*-dibenzo[*a*,*d*] [7]annulen-10 ol

DRUG NO. 05

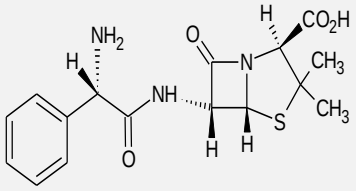
Drug's Name	**Amoxicillin Sodium**
Drug's structure	
Activity	Antibacterial
Total impurities	11 (Eleven)
Structures of impurities	
Impurity A	 (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid)
Impurity B	 (2*S*,5*R*,6*R*)-6-[[(2*S*)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-ox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

Impurity G	
	2*S*,5*R*,6*R*)-6-[[(2*R*)-2-[[(2*R*)-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)
Impurity H	
	(2*R*)-2-[(2,2-dimethylpropanoyl)amino]-2-(4-hydroxyphenyl)acetic acid
Impurity I	
	(2*R*)-2-amino-2-(4-hydroxyphenyl)acetic acid
Impurity J	
	co-oligomers of amoxicillin and penicilloic acids of amoxicillin
Impurity K	
	oligomers of penicilloic acids of amoxicillin

DRUG NO. 06

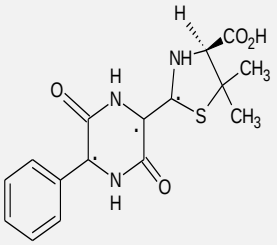
Drug's Name	**Ampicillin Sodium**
Drug's structure	
Activity	Antibacterial
Total impurities	14 (Fourteen)
Structures of impurities	
Impurity A	
	(2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid)

Impurity B



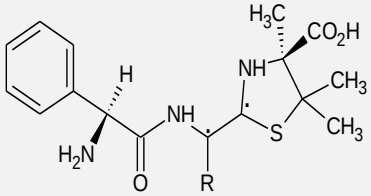
(2*S*,5*R*,6*R*)-6-[[(2*S*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (L-ampicillin)

Impurity C



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

Impurity D

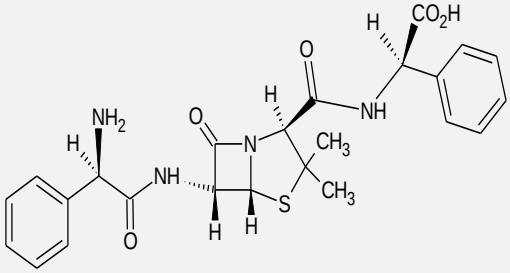


R = CO_2H: (4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]carboxymethyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of ampicillin)

Impurity F

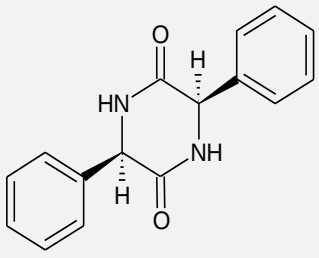
R = H: (2*RS*,4*S*)-2-[[[(2*R*)-2-amino-2-phenylacetyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of ampicillin)

Impurity E



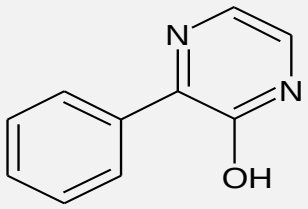
(2*R*)-2-[[[(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]-2-phenylacetic acid (ampicillinyl-D-phenylglycine)

Impurity G



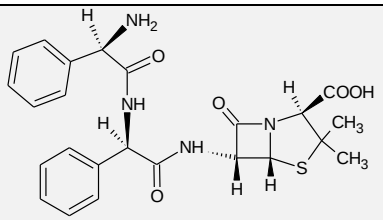
(3*R*,6*R*)-3,6-diphenylpiperazine-2,5-dione

Impurity H



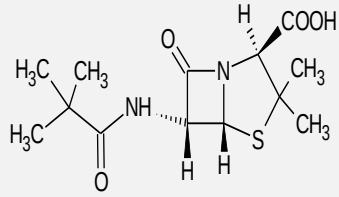
3-phenylpyrazin-2-ol

Impurity I



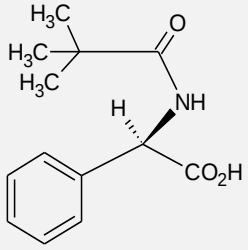
(2*S*,5*R*,6*R*)-6-[[(2*R*)-2-[[(2*R*)-2-amino-2-phenylacetyl]amino]-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (D-phenylglycylampicillin)

Impurity J



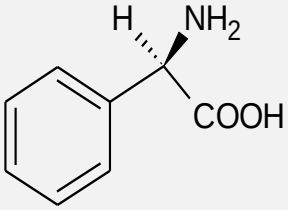
(2*S*,5*R*,6*R*)-6-[(2,2-dimethylpropanoyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

Impurity K



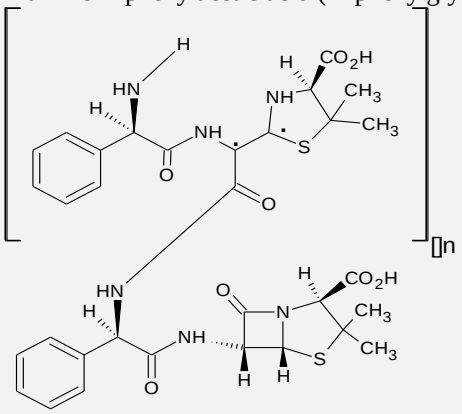
(2*R*)-2-[(2,2-dimethylpropanoyl)amino]-2-phenylacetic acid

Impurity L



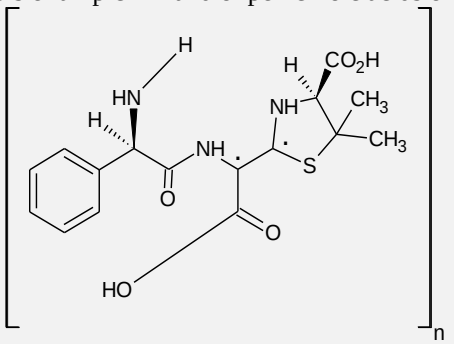
(2*R*)-2-amino-2-phenylacetic acid (D-phenylglycine)

Impurity M



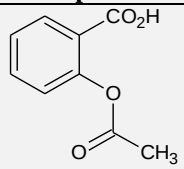
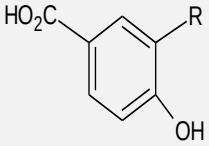
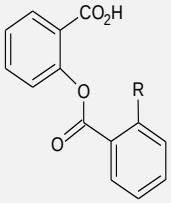
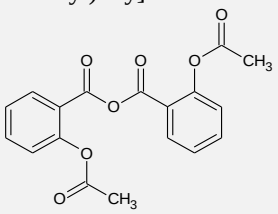
co-oligomers of ampicillin and of penicilloic acids of ampicillin

Impurity N

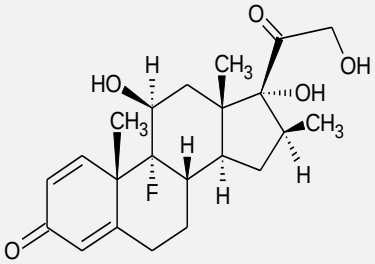


oligomers of penicilloic acids of ampicillin

DRUG NO. 07

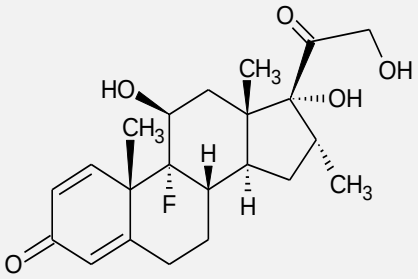
Drug's Name	**Aspirin**
Drug's structure	
Activity	Analgesic, antipyretic
Total impurities	06 (Six)
Structures of impurities	
Impurity A	
Impurity B	R = H: 4-hydroxybenzoic acid
Impurity C	R = CO_2H: 4-hydroxybenzene-1,3-dicarboxylic acid (4-hydroxyisophthalic acid)
Impurity D	salicylic acid 
Impurity 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)

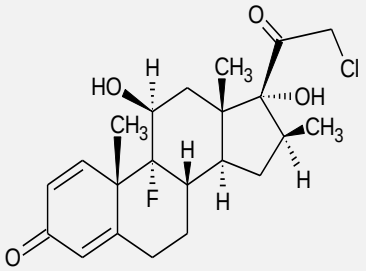
Structures of impurities

Impurities A



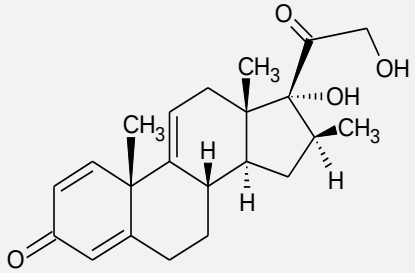
Dexamethasone

Impurities B



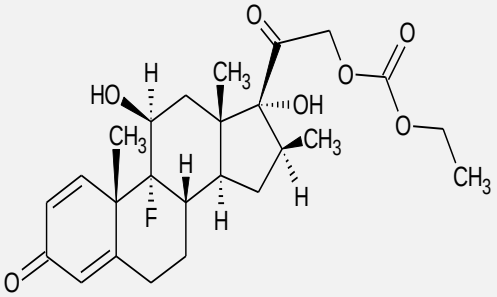
21-chloro-9-fluoro-11',17-dihydroxy-16'-methylpregna-1,4-diene-3,20-dione

Impurities C



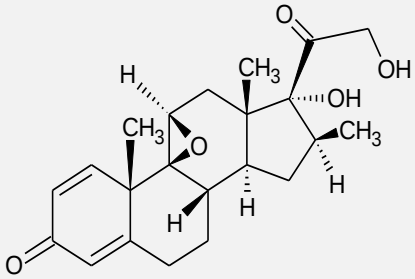
17,21-dihydroxy-16'-methylpregna-1,4,9(11)-triene-3,20-dione

Impurities D



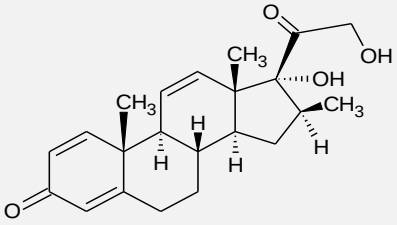
9-fluoro-11',17-dihydroxy-16'-methyl-3,20-dioxopregna-1,4-dien-21-yl ethoxycarboxylate

Impurities E

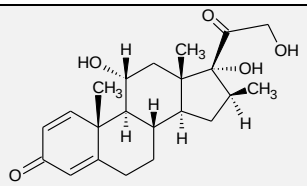
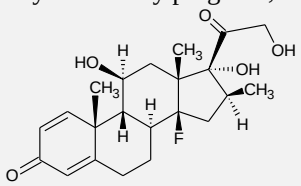
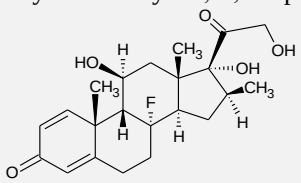
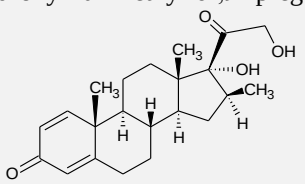


9,11'-epoxy-17,21-dihydroxy-16'-methyl-9'-pregna-1,4-diene-3,20-dione

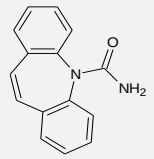
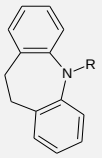
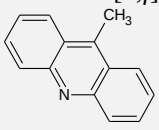
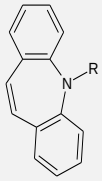
Impurities F



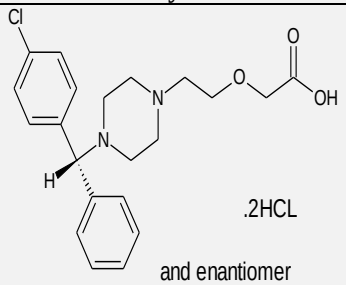
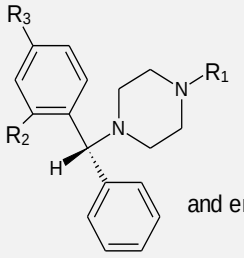
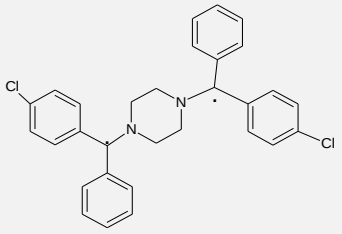
17,21-dihydroxy-16'-methylpregna-1,4,11-triene-3,20-dione

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

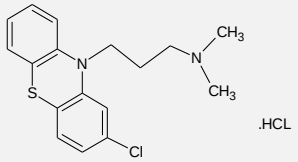
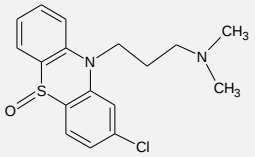
DRUG NO. 09

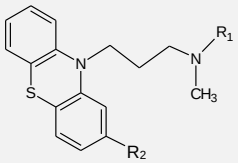
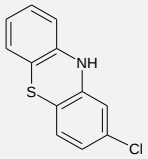
Drug's Name	**Carbamazepine**
Drug's Structure	
Activity	Anticonvulsant
Total Impurities	06 (Six)
Structures of Impurities	
Impurity A	R = $CONH_2$: 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide (10,11-dihydrocarbamazepine)
Impurity E	R = H: 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine(iminodibenzyl)
Impurity B	 9-methylacridine
Impurity C	
Impurity D	R = CO-NH-CO-NH_2: (5*H*-dibenzo[*b*,*f*]azepin-5-ylcarbonyl)urea(*N*-carbamoylcarbamazepine)
	R = H: 5*H*-dibenzo[*b*,*f*]azepine(iminostilbene)
Impurity F	R = CO-Cl: 5*H*-dibenzo[*b*,*f*]azepine-5-carbonyl chloride (5-chlorocarbonyliminostilbene)

DRUG NO. 10

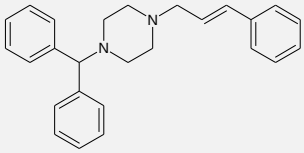
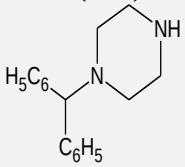
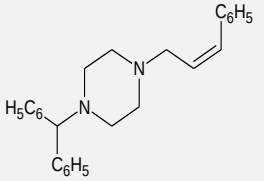
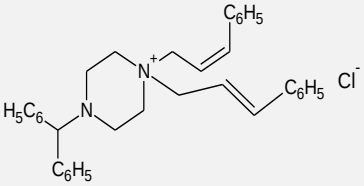
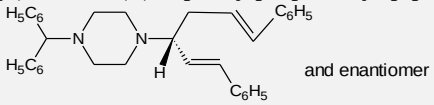
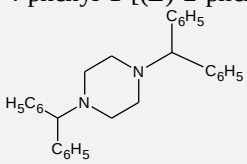
Drug's Name	**Cetirizine Hydrochloride**
Drug's Structure	 .2HCL and enantiomer
Activity	Histamine H_1 receptor antagonist
Total Impurities	07 (Seven)
Structures of Impurities	 and enantiomer
Impurity A	R1 = R2 = H, R3 = Cl: (*RS*)-1-[(4-chlorophenyl)phenylmethyl]piperazine
Impurity B	R1 = CH_2-CO_2H, R2 = H, R3 = Cl: (*RS*)-2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]acetic acid
Impurity C	R1 = CH_2-CH_2-O-CH_2-CO_2H, R2 = Cl, R3 = H: (*RS*)-2-[2-[4-[(2-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid
Impurity E	R1 = CH_2-[CH_2-O-CH_2]$_2$-CO_2H, R2 = H, R3 = Cl: (*RS*)-2-[2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]ethoxy]acetic acid (ethoxycetirizine)
Impurity F	R1 = CH_2-CH_2-O-CH_2-CO_2H, R2 = R3 = H: [2-[4-(diphenylmethyl)piperazin-1-yl]ethoxy]acetic acid
Impurity G	R1 = CH_2-CH_2-OH, R2 = H, R3 = Cl: 2-[4-[(*RS*)-(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethanol
Impurity D	 1,4-bis[(4-chlorophenyl)phenylmethyl]piperazine

DRUG NO. 11

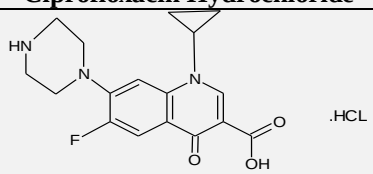
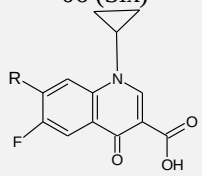
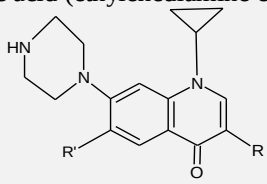
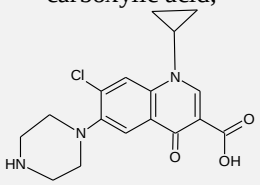
Drug's Name	**Chlorpromazine Hydrochloride**
Drug's Structure	 .HCL
Activity	Antipsychotic, Anti-emetic
Total Impurities	05 (Five)
Structures of Impurities	
Impurity A	3-(2-chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine *S*-oxide (chlorpromazine sulphoxide)

	
Impurity B	R1 = $[CH_2]_3$-$N(CH_3)_2$, R2 = Cl: *N*-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-*N*,*N*',*N*'-trimethylpropane-1,2-diamine
Impurity C	R1 = CH_3, R2 = H: promazine
Impurity D	R1 = H, R2 = Cl: 3-(2-chloro-10*H*-phenothiazin-10-yl)-*N*-methylpropan-1-amine (desmethylchlorpromazine)
Impurity E	 2-chloro-10*H*-phenothiazine

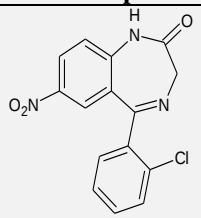
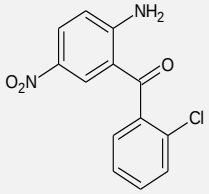
DRUG NO. 12

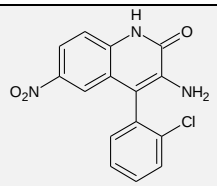
Drug's Name	**Cinnarizine**
Drug's structure	
Activity	Histamine H_1-receptor antagonist.
Total impurities	05 (Five)
Structures of impurities	
Impurities A	 1-(diphenylmethyl)piperazine
Impurities B	 (*Z*)-1-(diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine
Impurities C	 (4-(diphenylmethyl)-1,1-bis[(*E*)-3-phenylprop-2-enyl]piperazinium chloride
Impurities D	 and enantiomer 1-(diphenylmethyl)-4-[(1*RS*,3*E*)-4-phenyl-1-[(*E*)-2-phenylethenyl]but-3-enyl]piperazine
Impurities E	 1,4-bis(diphenylmethyl)piperazine

DRUG NO. 13

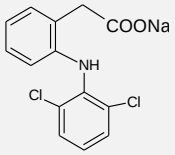
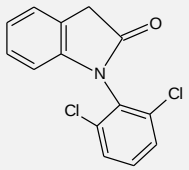
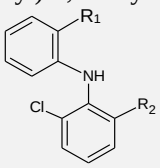
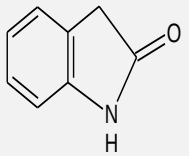
Drug's Name	**Ciprofloxacin Hydrochloride**
Drug's Structure	
Activity	Antibacterial
Total Impurities	06 (Six)
Structures of Impurities	
Impurity A	R = Cl: 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (fluoroquinolonic acid)
Impurity C	R = NH-$[CH_2]_2$-NH_2: 7-[(2-aminoethyl)amino]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (ethylenediamine compound)
Impurity B	
Impurity E	R = CO_2H, R' = H: 1-cyclopropyl-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (desfluoro compound),
Impurity F	R = H, R' = F: 1-cyclopropyl-6-fluoro-7-(piperazin-1-yl)quinolin-4(1*H*)-one (decarboxylated compound),
	R = CO_2H, 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

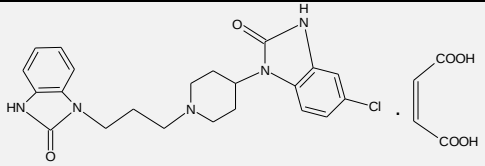
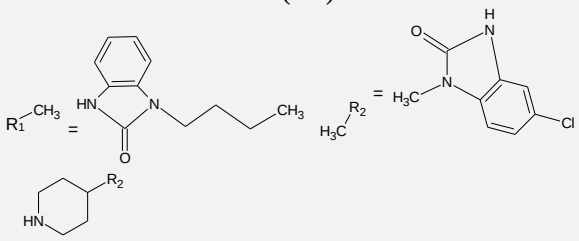
Drug's Name	**Clonazepam**
Drug's structure	
Activity	Anticonvulsant
Total impurities	02 (Two)
Structures of impurities	
Impurities A	2-amino-5-nitrophenyl)(2-chlorophenyl)methanone

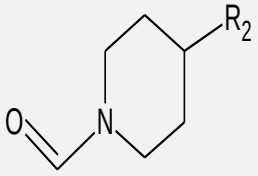
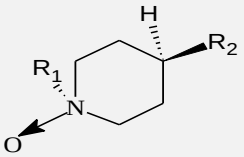
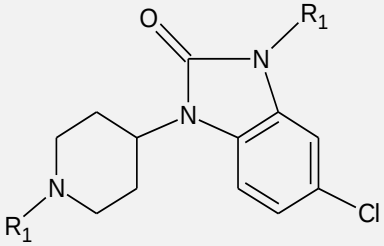
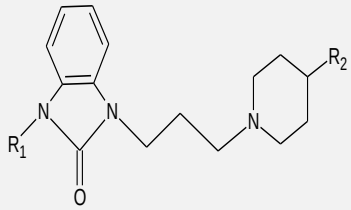
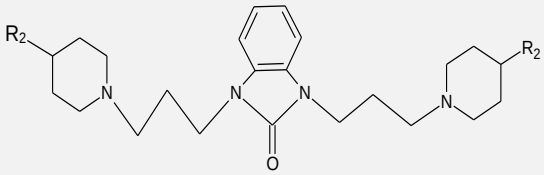
	
Impurity B	3-amino-4-(2-chlorophenyl)-6-nitroquinolin-2(1*H*)-one

DRUG NO. 15

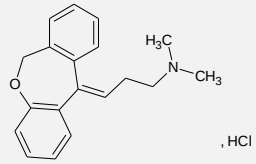
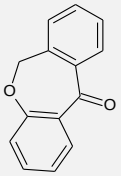
Drug's Name	**Diclofenac Sodium**
Drug's Structure	
Activity	Analgesic, Anti-inflammatory
Total Impurities	05 (Five)
Structures of Impurities	
Impurity A	
	1-(2,6-dichlorophenyl)-1,3-dihydro-2*H*-indol-2-one
	
Impurity B	R1 = CHO, R2 = Cl: 2-[(2,6-dichlorophenyl)amino]benzaldehyde,
Impurity C	R1 = CH_2OH, R2 = Cl: [2-[(2,6-dichlorophenyl)amino]phenyl]methanol
Impurity D	R1 = CH_2-CO_2H, R2 = Br: 2-[2-[(2-bromo-6-chlorophenyl)amino]phenyl]acetic acid
	
Impurity E	1,3-dihydro-2*H*-indol-2-one

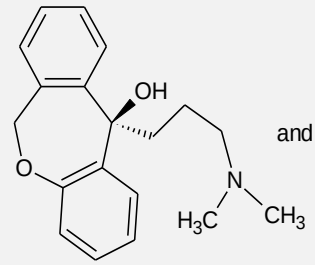
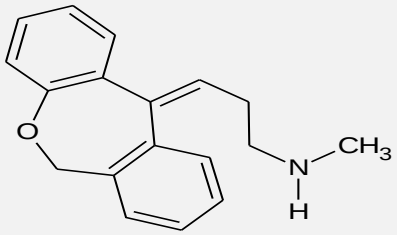
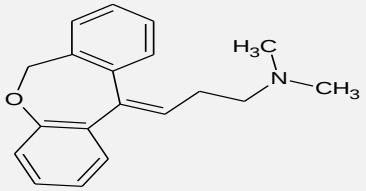
DRUG NO. 16

Drug's Name	**Domperidone maleate**
Drug's Structure	
Activity	Antiemetic
Total Impurities	06 (Six)
Structures of Impurities	
	
Impurity A	5-chloro-1-(piperidin-4-yl)-1,3-dihydro-2*H*-benzimidazol-2-one

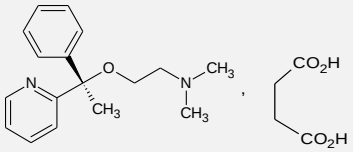
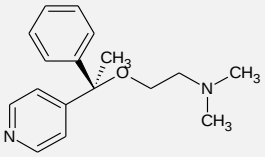
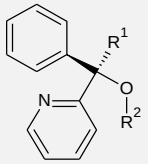
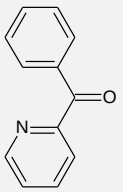
Impurity B	 4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-formylpiperidine
Impurity C	 *cis*-4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidine 1-oxide
Impurity D	 5-chloro-3-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one
Impurity E	 1-[3-[4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]propyl]-3-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)propyl]-1,3-dihydro-2*H*-benzimidazol-2-one
Impurity F	 1,3-bis[3-[4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidin-1-yl]propyl]-1,3-dihydro-2*H*-benzimidazol-2-one

DRUG NO. 17

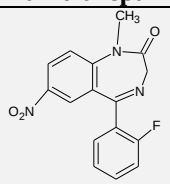
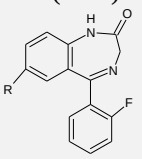
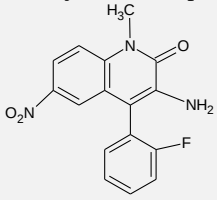
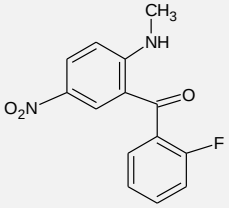
Drug's Name	**Doxepin Hydrochloride**
Drug' structure	
Activity	Antidepressant
Total impurities	04 (Four)
Structures of impurities	
Impurities A	 dibenzo[*b*,*e*]oxepin-11(6*H*)-one

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

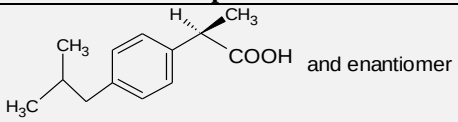
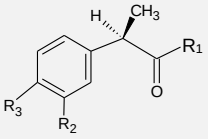
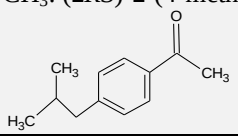
DRUG NO.18

Drug's Name	**Doxylamine Succinate**
Drug's structure	 and enantiomer
Activity	Histamine H_1-receptor antagonist
Total impurities	04 (Four)
Structure of impurities	
Impurities A	 and enantiomer *N*,*N*-dimethyl-2-[1(*RS*)-1-phenyl-1-(pyridin-4-yl)ethoxy]ethanamine
Impurities B	 and enantiomer R1 = CH_3, R2 = H: (1*RS*)-1-phenyl-1-(pyridin-2-yl)ethanol
Impurities C	R1 = H, R2 = CH_2-CH_2-N(CH_3)$_2$: *N*,*N*-dimethyl-2-[(*RS*)-1-phenyl(pyridin-2-yl)methoxy]ethanamine
Impurities D	 Phenyl(pyridin-2-yl)methanone (2-benzoylpyridine)

DRUG NO. 19

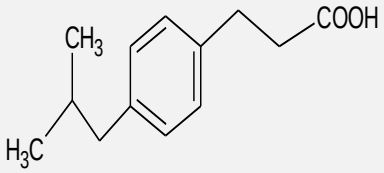
Drug's Name	**Flunitrazepam**
Drug's Structure	
Activity	Hypnotic
Total Impurities	04 (Four)
Structures of Impurities	
Impurity A	R = NH_2: 7-amino-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (7-aminodemethylflunitrazepam)
Impurity B	R = NO_2: 5-(2-fluorophenyl)-7-nitro-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (demethylflunitrazepam)
Impurity C	 3-amino-4-(2-fluorophenyl)-1-methyl-6-nitroquinolin-2(1*H*)-one
Impurity D	 (2-fluorophenyl)[2-(methylamino)-5-nitrophenyl]methanone

DRUG NO. 20

Drug's Name	**Ibuprofen**
Drug's Structure	 and enantiomer
Activity	Analgesic, Anti-inflammatory
Total Impurities	18 (Eighteen)
Structures of Impurities	 and enantiomer
Impurity A	R1 = OH, R2 = CH_2-$CH(CH_3)_2$, R3 = H: (2*RS*)-2-[3-(2-methylpropyl)phenyl]propanoic acid
Impurity B	R1 = OH, R2 = H, R3 = $[CH_2]_3$-CH_3: (2*RS*)-2-(4-butylphenyl)propanoic acid
Impurity C	R1 = NH_2, R2 = H, R3 = CH_2-$CH(CH_3)_2$: (2*RS*)-2-[4-(2-methylpropyl)phenyl]propanamide
Impurity D	R1 = OH, R2 = H, R3 = CH_3: (2*RS*)-2-(4-methylphenyl)propanoic acid
Impurity E	

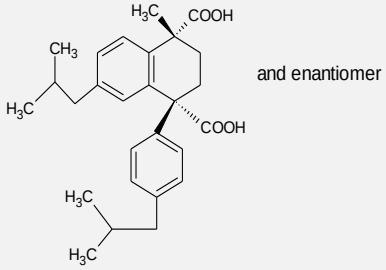
1-[4-(2-methyl propyl)phenyl]ethanone

Impurity F



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

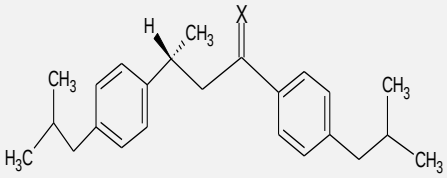
Impurity G



and enantiomer

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

Impurity H



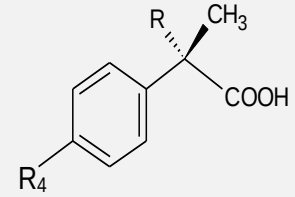
and enantiomer

Impurity I

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

X = H_2: (3*RS*)-1,3-bis[4-(2-methylpropyl)phenyl]butane

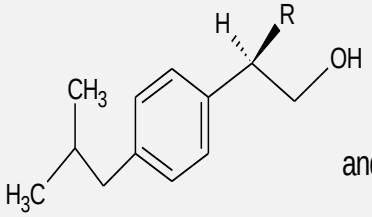
Impurity J
Impurity K
Impurity L
Impurity M
Impurity N
Impurity O



and enantiomer

R = H, R4 = CO-$CH(CH_3)_2$: (2*RS*)-2-[4-(2-methylpropanoyl)phenyl]propanoic acid
R = H, R4 = CHO: (2*RS*)-2-(4-formylphenyl)propanoic acid
R = H, R4 = CHOH-$CH(CH_3)_2$: 2-[4-(1-hydroxy-2-methylpropyl)phenyl]propanoic acid
R = OH, R4 = CH_2-$CH(CH_3)_2$: (2*RS*)-2-hydroxy-2-[4-(2-methylpropyl)phenyl]propanoic acid
R = H, R4 = C_2H_5: (2*RS*)-2-(4-ethylphenyl)propanoic acid
R = H, R4 = $CH(CH_3)$-C_2H_5: 2-[4-(1-methylpropyl)phenyl]propanoic acid

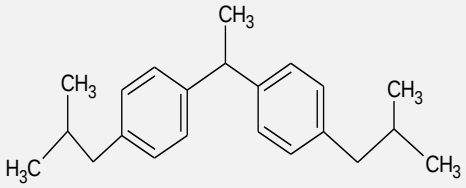
Impurity P
Impurity Q



and enantiomer

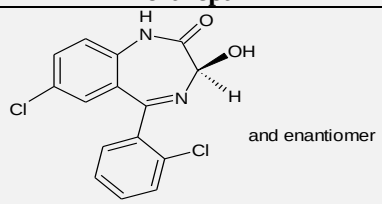
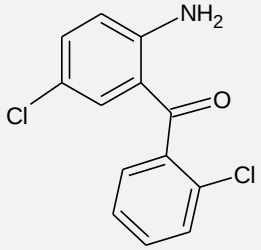
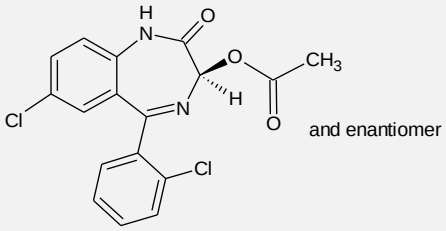
R = CH_3: (2*RS*)-2-[4-(2-methylpropyl)phenyl]propan-1-ol
R = H: 2-[4-(2-methylpropyl)phenyl]ethanol

Impurity R

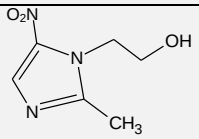
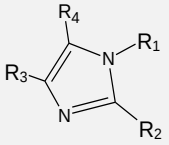


1,1-bis[4-(2-methylpropyl)phenyl]ethane

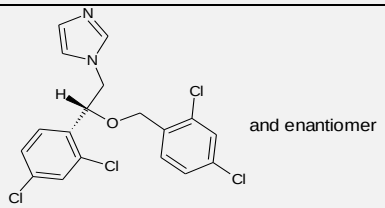
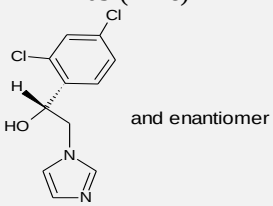
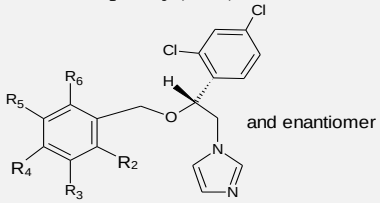
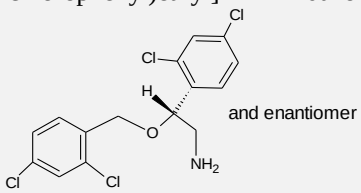
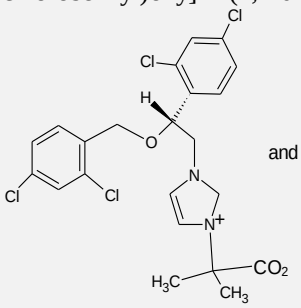
DRUG NO. 21

Drug's Name	**Lorazepam**
Drug' 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 (3*RS*)-7-chloro-5-(2-chlorophenyl)-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl acetate

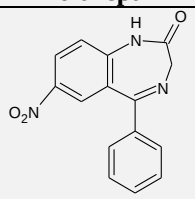
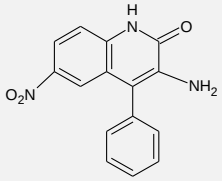
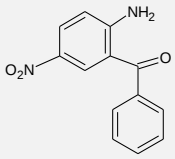
DRUG NO. 22

Drug's Name	**Metronidazole**
Drug's Structure	
Activity	Antibacterial
Total Impurities	07 (Seven)
Structures of Impurities	
Impurity A	R1 = R4 = H, R2 = CH_3, R3 = NO_2: 2-methyl-4-nitroimidazole
Impurity B	R1 = R2 = R4 = H, R3 = NO_2: 4-nitroimidazole
Impurity C	R1 = CH_2-CH_2-OH, R2 = R4 = H, R3 = NO_2: 2-(4-nitro-1*H*-imidazol-1-yl)ethanol R1 = CH_2-CH_2-OH, R2 = R3 = H, R4 = NO_2: 2-(5-nitro-1*H*-imidazol-1-yl)ethanol
Impurity D	R1 = CH_2-CH_2-OH, R2 = CH_3, R3 = NO_2, R4 = H: 2-(2-methyl-4-nitro-1*H*-imidazol-1-yl)ethanol
Impurity E	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-1*H*-imidazol-1-yl)ethoxy]ethanol
Impurity F	R1 = CH_2-CO_2H, R2 = CH_3, R3 = H, R4 = NO_2: 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)acetic acid
Impurity G	

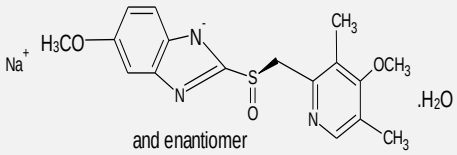
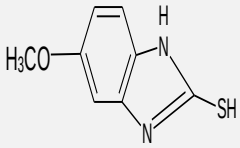
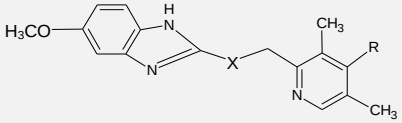
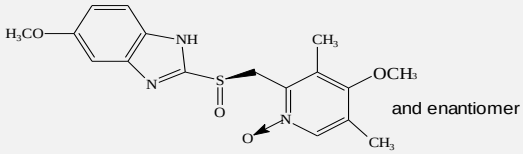
DRUG NO. 23

Drug's Name	**Miconazole**
Drug's Structure	 and enantiomer
Activity	Antifungal
Total Impurities	09 (Nine)
Structures of Impurities	 and enantiomer
Impurity A	(1*RS*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol
Impurity B	 and enantiomer R2 = R3 = R5 = R6 = H, R4 = Cl: 1-[(2*RS*)-2-[(4-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole
Impurity D	R2 = R6 = Cl, R3 = R4 = R5 = H: 1-[(2*RS*)-2-[(2,6-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole
Impurity F	R2 = R5 = R6 = H, R3 = R4 = Cl: 1-[(2*RS*)-2-[(3,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole
Impurity G	R2 = R5 = Cl, R3 = R4 = R6 = H: 1-[(2*RS*)-2-[(2,5-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole
Impurity H	R2 = R3 = R4 = R5 = R6 = H: 1-[(2*RS*)-2-benzyloxy-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole
Impurity I	R2 = Cl, R3 = R4 = R5 = R6 = H: 1-[(2*RS*)-2-[(2-chlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole
Impurity C	 and enantiomer (2*RS*)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethanamine
Impurity E	 and enantiomer 2-[1-[(2*RS*)-2-[(2,4-dichlorobenzyl)oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazol-3-io]-2-methylpropanoate

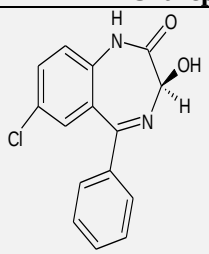
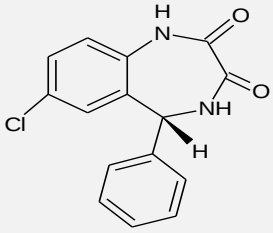
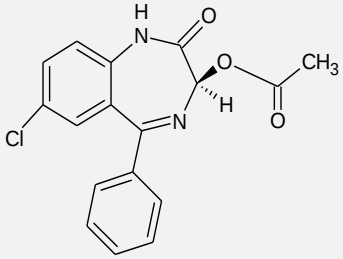
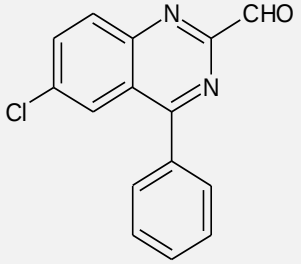
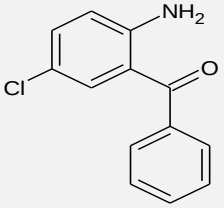
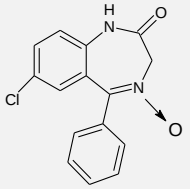
DRUG NO. 24

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(1*H*)-one
Impurity B	 (2-amino-5-nitrophenyl)phenyl methanone

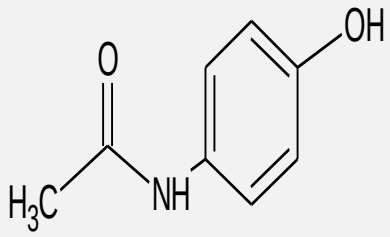
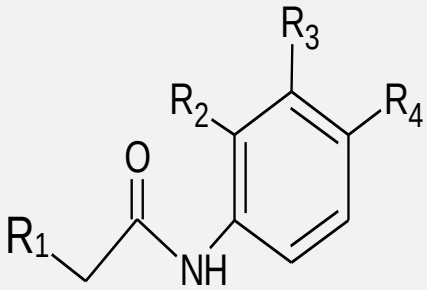
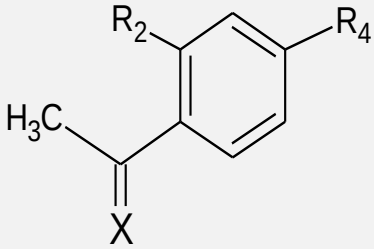
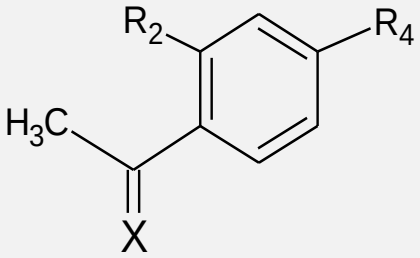
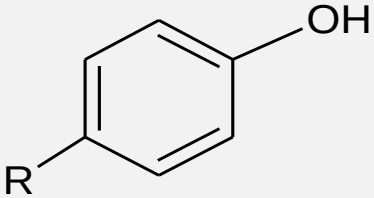
DRUG NO. 25

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-1*H*-benzimidazole-2-thiol
Impurity B	 R = H, X = SO: 2-[(*RS*)-[(3,5-dimethylpyridin-2-yl)methyl]sulphinyl]-5-methoxy-1*H*-benzimidazole
Impurity C	R = OCH_3, X = S: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]thio]-1*H*-benzimidazole (ufiprazole)
Impurity D	R = OCH_3, X = SO_2: 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfonyl]-1*H*-benzimidazole (omeprazole-sulphone)
Impurity E	 4-methoxy-2-[[(*RS*)-(5-methoxy-1*H*-benzimidazol-2-yl)sulphinyl]methyl]-3,5-dimethylpyridine 1-oxide

DRUG NO. 26

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

DRUG NO. 27

Drug's Name	**Paracetamol**
Drug's Structure	
Activity	Analgesic, Antipyretic
Total Impurities	11 (Eleven)
Structures of Impurities	
Impurity A Impurity B Impurity C Impurity D Impurity H Impurity J	 R1 = R3 = R4 = H, R2 = OH: *N*-(2-hydroxyphenyl)acetamide R1 = CH_3, R2 = R3 = H, R4 = OH: *N*-(4-hydroxyphenyl)propanamide R1 = R2 = H, R3 = Cl, R4 = OH: *N*-(3-chloro-4-hydroxyphenyl)acetamide R1 = R2 = R3 = R4 = H: *N*-phenylacetamide R1 = R2 = R3 = H, R4 = O-CO-CH_3: 4-(acetylamino)phenyl acetate R1 = R2 = R3 = H, R4 = Cl: *N*-(4-chlorophenyl)acetamide (chloroacetanilide)
Impurity E Impurity G	 X = O, R_2 = H, R_4 = OH: 1-(4-hydroxyphenyl)ethanone X = N-OH, R_2 = H, R_4 = OH: 1-(4-hydroxyphenyl)ethanone oxime
Impurity I	 X = O, R2 = OH, R4 = H: 1-(2-hydroxyphenyl)ethanone
Impurity F Impurity K	 R = NO_2: 4-nitrophenol R = NH_2: 4-aminophenol

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

REFERENCES:

1. Impurity profile: Significance in Active Pharmaceutical Ingredient. Eurasian Journal of Analytical Chemistry 2007; 2(1): 32-53.
2. Ayre A, Varpe D, Nayak R and Vasa N: Impurity profiling of Pharmaceuticals. Advance Research in Pharmaceuticals and Biologicals 2011; 1(2): 76-90.
3. Manasa P, Vasanth PM, Ramesh T and Ramesh M: Development and validation of new RP- HPLC method for the quantification of degradation impurities in Levofloxacin tablet dosage form. International Journal of Biological & Pharmaceutical Research 2012; 3(7): 918-28.
4. Solanki R: Impurity profiling of Active Pharmaceutical Ingredients and finished drug products. International Journal of Drug Rese and Technology 2012; 2(3): 231-38.
5. Roy J: Pharmaceutical Impurities - A Mini-Review. AAPS Pharm Sci Tech 2002; 3(2): 1-8.
6. ICH harmonized tripartite guideline impurities in new drug substances Q3A(R2).
7. Thomas S, Joshi SC, Vir D, Agarwal A, Rao RD and Sridhar I: Identification, characterization and quantification of a new impurity in Deferasirox active pharmaceutical ingredient by LC–ESI–QT/MS/MS. Journal of Pharmaceutical and Biomedical Analysis 2012; 63: 112-19.
8. Thomas S, Shandilya S, Bharati A, Paul SK, Agarwal A and Mathela CS: Identification, characterization and quantification of new impurities by LC–ESI/MS/MS and LC–UV methods in Rivastigmine tartrate active pharmaceutical ingredient. Journal of Pharmaceutical and Biomedical Analysis 2012; 57: 39-51.
9. Gazdag M, Babja´k M, Brlik J, Maho S, Tuba Z and Gorog S: Estimation of impurity profiles of drugs and related materials Part 18. Impurities and degradation products of Mazipredone. Journal of Pharmaceutical and Biomedical Analysis 1998; 17: 1029-36.
10. Makino Y, Urano Y and Nagano T: Impurity profiling of Ephedrines in Methamphetamine by High-performance liquid chromatography. Journal of Chromatography A 2002; 947: 151-54.
11. Choe S, Heo S, Choi H, Kim E, Chung H and Lee J: Analysis of pharmaceutical impurities in the Methamphetamine crystals seized for drug trafficking in Korea. Forensic Science International 2013; 227: 48-51.
12. Kuwayama K, Tsujikawa K, Miyaguchi H, Kanamori T, Iwata Y and Hiroyuki I: Identification of impurities and the statistical classification of Methamphetamine using headspace solid phase microextraction and gas chromatography-mass spectrometry. Forensic Science International 2006; 160: 44-52.
13. Trefi S, Gilard V, Martino MM and Martino R: Generic Ciprofloxacin tablets contain the stated amount of drug and different impurity profiles: A 19F, 1H and DOSY NMR analysis. Journal of Pharmaceutical and Biomedical Analysis 2007; 44: 743-54.
14. Vemi´ca A, Stojanovi´ca BJ, Stamenkovi´cb I and Malenovi´c A: Chaotropic agents in liquid chromatographic method development for the simultaneous analysis of Levodopa, Carbidopa, Entacapone and their impurities. Journal of Pharmaceutical and Biomedical Analysis 2013; 77: 9-15.
15. Sun C, Wu J, Wang D and Pan Y: Characterization of a novel impurity in bulk drug Eprosartan by ESI/MSn and NMR. Journal of Pharmaceutical and Biomedical Analysis 2010; 51: 778-83.
16. Zhang D, Song X and Su J: Isolation, identification and characterization of novel process-related impurities in Flupirtine maleate. Journal of Pharmaceutical and Biomedical Analysis 2014; 90: 27-34.
17. Kadivar MH, Sinha PK, Kushwaha D, Kushwaha D, Jana P and Sharma H: Study of impurity carryover and impurity profile in Febuxostat drug substance by LC–MS/MS technique. Journal of Pharmaceutical and Biomedical Analysis 2011; 56: 749-57.
18. Volk KJ, Klohr SE, Rourick RA, Kerns EH and Lee MS: Profiling Impurities and Degradants of Butorphanol tartrate Using Liquid Chromatography/Mass Spectrometry and Liquid Chromatography/Tandem Mass Spectrometry substructural techniques. Journal of Pharmaceutical and Biomedical Analysis 1996; 14: 1663-1674. British Pharmacopoeia 2007.

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