RESEARCH PAPER

CHIRAL DRUGS BIOACCUMULATION IN AQUATIC ENVIRONMENT AND THE OPPORTUNITIES, CHALLENGES IN BIOANALYSIS

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ABSTRACT

Chiral compounds are asymmetric three-dimensional molecules that have one or more stereogenic centers or asymmetry that is caused by planes or axes and results in two molecules that cannot be superimposed on one another. Chiral separation has become more important in forensic chemistry and has been used in the examination of biological fluids, environmental samples, and the examination of illicit drug mixtures. Most of the molecules at the center of life, including DNA, amino acids (AAs), and sugars, are chiral compounds. The investigated compounds included synthetic psychoactive drugs (stimulants), synthetic opioids, β-blockers, antidepressants, anticoagulants, bronchodilators, and dissociative anesthetics. Racemate use frequently causes stereoselective pharmacological activity and pharmacokinetic effects on absorption, metabolism, and excretion that may raise the risk of death or have major side consequences such as poisoning. Many medications are still delivered as racemates, despite the trend towards making pharmaceuticals as single enantiomers. Chiral analysis in biological fluids can provide details about use and help distinguish between legitimate medications and illicit substances that only contain one enantiomer. Additionally, it has been demonstrated that the presence of these substances in wastewater can be used as a tool for community-level drug consumption monitoring. Pharmaceuticals and illicit drugs may enter the aquatic environment by direct sewage discharge or effluents from WWTPs that are unable to completely remove these micro-pollutants. Studies of the presence of chiral medicines in environmental matrices are motivated by the potential negative effects of enantiomers on aquatic and human life. This study reviewed 90 articles that have been published between 1996 and 2022 based on ScienceDirect and ISI Web of Knowledge databases. In this review discussed about the challenges and opportunities of the application of chiral analysis in biological, environmental samples and their relevance in the forensic field.

Keywords: Chiral compounds, biological fluids, environmental samples, forensic chemistry.

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Introduction:

Chiral compounds are asymmetric three-dimensional molecules that have one or more stereo genic centers or asymmetry that is caused by planes or axes and results in two molecules that cannot be superimposed on one another. These molecules are known as enantiomers(1). When he first manually separated the two isomers of sodium ammonium tartrate in 1848, French chemist and biologist Louis Pasteur made the discovery of chiral chemistry(2). The in-depth study of enantiomers has demonstrated that the spatial arrangements of the two enantiomers are not identical and resemble the left and right hands in terms of their interaction. Chiral molecules, which involves that a molecule whose arrangement differs from that of its

mirrors(3, 4). Chemical, physical, pharmacological, and biological systems all depend on chirality, which encourages fresh biomimetic discoveries(5). Most of the molecules at the center of life, including DNA, amino acids (AAs), and sugars, are chiral compounds(6). In addition to being a crucial component of scientific research, the resolution and analysis of chiral substances has potential applications in the fields of pharmaceutical analysis, food, environmental, therapeutic, synthetic, and analytical chemistry(7).Enantiomers have comparable physical and chemical properties in achiral environments, but in chiral environments, such as those found in living things, enantiomers may have differing biological activity and/or toxicity due to enantioselective interactions(2, 8). Enantiomer separation has become more important in forensic chemistry and has been used in the examination of biological fluids, the examination of environmental samples, and the examination of illicit drug mixtures(9).The majority of alkaloids, hormones, nucleosides, proteins, enzymes, amino acids, carbohydrates, and carbohydrates are all chiral substances. In pharmaceutical sectors, 88% of the most recent pharmaceuticals are marketed as racemates, which are composed of an equimolar mixture of two enantiomers, and 56% of the drugs currently in use are chiral products(10).

Pharmaceuticals and other classes of illegal medications that are overused for improving athletic performance or because of their psychotropic effects are among the substances of forensic interest. Consuming these chemicals increases the chance of death and has toxicological effects(11). These drugs are available as racemates or as a single enantiomer, and they can be used either legally or illegally. The control of illicit drug production, consumption, or the establishment of links between illicit drug preparations, users, and traffickers can all benefit from data from chiral analysis in both biological samples and illicit drug preparations(12). Chiral analysis in bodily fluids can provide details about use and help distinguish between legitimate medications and illicit substances that only contain one enantiomer(13). For instance, use of dexedrine (S-(+)-amphetamine (AM)), which is used to treat children with narcolepsy, attention deficit disorders, and hyperactivity, only causes blood concentrations of S-(+)-AM, as opposed to consumption of illegal AM, which results in both enantiomers(14). Additionally, it has been demonstrated that the presence of these substances in wastewater can be used as a tool for community-level drug consumption monitoring.

2.Nomenclature of chiral compounds:

The following is a recap of the vocabulary used to define various stereochemical characteristics. Chirality is the quality of an object that prevents it from superimposing with its mirror image. It is also sometimes referred to as stereoisomerism, enantiomerism, or dissymmetry(15). The word "chiral" derives from the Greek word "cheir," which meaning "handedness." When a molecule's mirror image cannot be overlaid upon it, the molecule and its image are known as chiral. It's comparable to left and right hands. Enantiomers are the two non-superimposable mirror-image forms of chiral compounds. the enantiomers most frequently created when four distinct substituents are present on a carbon atom(16, 17). Not just carbon can function as an asymmetric centre. Sometimes, phosphorus, nitrogen, and sulphur can combine to generate chiral compounds such respectively, omeprazole, cyclophosphamide, and methaqualone. Enantiomers are also sometimes referred to as optical isomers since chiral compounds have optical activity. Such substances' two enantiomers can be categorised. Depending on whether they rotate plane-polarized light with their left (-) or right (+) hands, they are referred to as levorotary (l-isomer) or dextrorotary (d-isomer), respectively(18).

A racemic mixture (racemate) with sign (+, _) or (d, l) that does not display optical properties is a mixture of two chiral compounds that are equimolar (50/50) activity. Molecules that have the same chemical formula, the same physical and chemical characteristics, but differ in their optical activity and spatial arrangement are known as optical isomers or enantiomers. Nowadays, the spatial arrangement of substituents in a molecule's chiral centre serves to distinguish enantiomers. This configuration uses the Cahn-Ingold-Prelog (CIP) protocol (11) to assign substituent groups priorities. This system's foundation is a set of guidelines for prioritising the substituents attached to the asymmetric atom according to sequence criteria(2) (19).Additionally, it has been demonstrated that the presence of these substances in wastewater can be used as a tool for community-level drug consumption monitoring. In reality once expelled, chiral drug residues, primarily in the form of parent chemicals and metabolites, enter the aquatic environment(13, 20).

3.Chromatography in chiral analysis:

Currently, liquid chromatography (LC), gas chromatography (GC), capillary electrophoresis (CE), and supercritical fluids chromatography are used to separate enantiomers. Indirect and direct chromatographic methods are available for enantiomer resolution. The indirect method relies on the creation of diastereoisomers, which have different

physico-chemical properties and may be distinguished using standard techniques like chromatography, when the enantiomers react with chiral derivatization reagents (CDRs)(21, 22). Chiral stationary phases (CSPs), which are often used in liquid chromatography (LC), or chiral mobile phase additives can be used to achieve the direct technique. Both indirect and direct GC and LC procedures are available(23-26). However, there aren't many chiral columns accessible for GC. As a result, the majority of GC studies employed indirect strategies with CDRs, which are subsequently divided by achiral columns.S-(-)-N-(trifluoro acetyl)propyl chloride (S-TPC), R-(-)--methoxy--(trifluoromethyl)phenylacetyl (R-MTPCl), and S-(-)-N-(heptafluorobutyryl)propyl chloride (S-HFBPrCl) are a few examples of the most often utilized CDRs(27-31). There are many different types of CSP accessible for direct approaches, but the most popular ones include cyclodextrin (CD), Pirkle-type, polysaccharide derivatives, antibiotics-based, and polymeric-based(32-34). Enantioselective analyses of many kinds of illicit drugs in biological fluids have been performed using both GC and LC techniques, while LC techniques are more frequently utilized with environmental samples(35, 36).

In recent years, many effective and adaptable chiral derivatizing and solvating agents have appeared. Because the structure and environmental factors can be altered to enhance molecular interactions, these substances exhibit various chiral recognition capabilities. Using multinuclear NMR spectroscopy offers new opportunities for chiral investigations and the clarification of their chiral recognition mechanisms with the prospect of increasing the chiral probes. The nuclear characteristics of the 19F, 31P, 13C, and 77Se nuclei, as well as their integration into organic molecules via organic synthesis processes, have exhibited effective outcomes(37, 38).

4.Chiral drug analysis in biological samples:

The investigated compounds included syntheticpsychoactive drugs (stimulants), synthetic opioids, β-blockers, antidepressants, anticoagulants, bronchodilators and dissociative anesthetics(39).Racemate use frequently causes stereoselective pharmacological activity and pharmacokinetic effects on absorption, metabolism, and excretion that may raise the risk of death or have major side consequences such as poisoning. Many medications are still delivered as racemates, despite the trend towards making pharmaceuticals as single enantiomers(36, 40, 41).Depending on the manufacturing process, these substances can also be found as racemates or single enantiomers in illicit drugs(9). Consumption of pure enantiomers (eutomers) in clandestine administrations could occasionally result in overdose or even fatal situations. Because it is now possible to establish whether a drug of concern is produced from a controlled or illicit material, the importance of chiral analysis has increased(41-43). Because of their advantages in medicinal activities, several restricted drugs are sold in their pure enantiomeric form. On the other side, unauthorized medication manufacture results in either.

Depending on the manufacturing process, such as racemic or enantiomer pure precursors, the product may be either single enantiomer or racemic. As a result, in forensic chemistry, EF evaluation can help distinguish between the use of legal and illegal chemicals, provide details about the synthesis process, or profile various seizures to identify consumers and traffickers among them. The International Olympic Committee clearly forbids the use of levorphanol, although the use of preparations containing dextromethorphan is permitted by athletes. This is only one example of how chiral analysis might be used in the fight against doping(44).Despite the fact that a number of articles have been published on the chiral separation of various kinds of pharmaceuticals and illegal drugs with forensic interest in biological matrices, the majority of these articles do not specify the enantiomeric composition. It is crucial to have information on the enantiomeric makeup of parent substances and metabolites in order to interpret data correctly and conduct further study on the outcomes(45, 46). Additionally, chiral achiral chemical metabolites should be considered in biological samples.

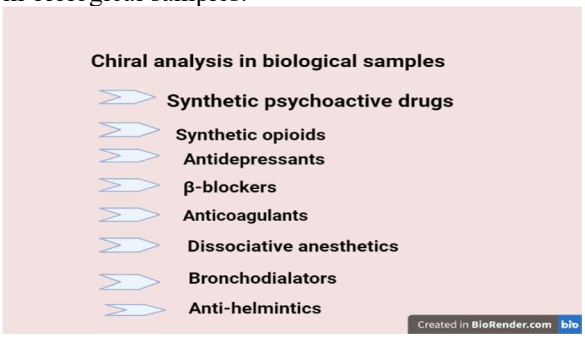


Figure:I. Chiral analysis in biological samples.

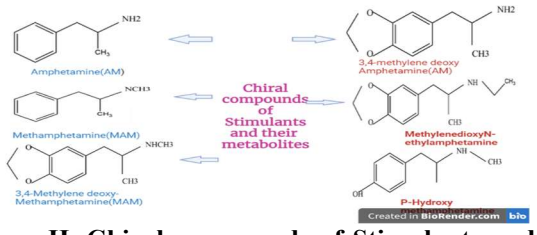


Figure:II. Chiral compounds of Stimulants and their metabolites.

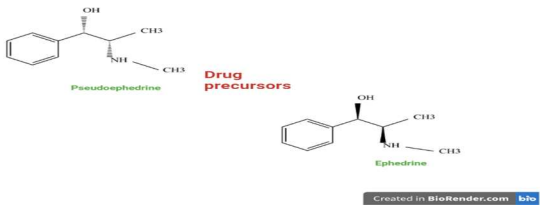


Figure:II Drug precursors.

4.1. Synthetic psychoactive drugs:

This class of chiral drugs was the most studied (fig:II).The amphetamine-like substances are a class of synthetic psychoactive chemicals that share structural similarities and have a high potential for abuse, addiction, and toxicity(47). Among most studied compounds are amphetamine AM, methamphetamine (MA), 3,4-methylenedioxymethylamphetamine (MDMA), 3,4-methylenedioxy-ethylamphetamine (MDEA) and methylphenidate (MPH). These drugs enantiomers have been identified in plasma, urine, blood, and hair. The enantiomers of these medications were separated using analytical techniques such as LC-MS, GC-FID, and GC-MS and CE. Some disorders can be treated with substances that resemble amphetamines, such as Parkinson's disease can be treated with selegiline (L-deprenyl, SG), ADHD can be treated with Adderall or Elvanse, and pain can be controlled with famprofazone, a nonsteroidal anti-inflammatory drug. S-MA and its metabolite S-AM are produced in the body when SG is consumed, whereas R-MA and S-MA and their metabolites are produced in the body when famprofazone is taken(48). As a result, users and consumers have found alternate ways to get these medications through illicit formulations. In the Leuckart procedure, which is used to produce AM illegally and results in a racemic product, 1-phenyl-2-propanone and additional reagents such formic acid, ammonium formate, or formamide are sometimes utilised(49, 50).

Safrole, isosafrole, piperonal, or 3,4-methylenedioxyphenyl-2-propanone (PMK) can be used to make MDMA and similar substances. Many illegal drug syntheses begin with PMK and produce racemic MDMA through the Leuckart pathway or different reductive aminations(51-53). Therefore, research focused on figuring out the ratios of the parent chemicals' and metabolites' R- and S-isomers are crucial for distinguishing medical drug administration or illicit drug use(54). Additionally, chiral information is important and valuable for determining the precursor, the synthesis pathway, and the inherent properties of the samples that were seized.

For determining the enantiomers of MA, AM, SG, and its metabolite, desmethylselegiline (DMSG), in hair samples, Nishida et al. described an LC-MS approach. The authors of this study demonstrated differences between MA abusers and SG consumers as well as in the enantiomer ratios of MA and AM(42). Additionally, it was revealed that DMSG, which is not often present in urine, can be used to distinguish between MA abusers and those who use SG for therapeutic purposes. In their description of a GC-MS technique for separating the enantiomers of MA, AM, MDMA, and MDA in urine samples, Fujii et al. used CDR TPC to create diastereoisomers.(55) This technique can be used to distinguish between the use of these medications for legal and illicit purposes. For the first time, a GC-MS enantioselective approach for the separation of AM, MA, MDA, MDMA, and MDEA in whole blood based on the creation of diastereomers was established by Rasmussen et al.(50)

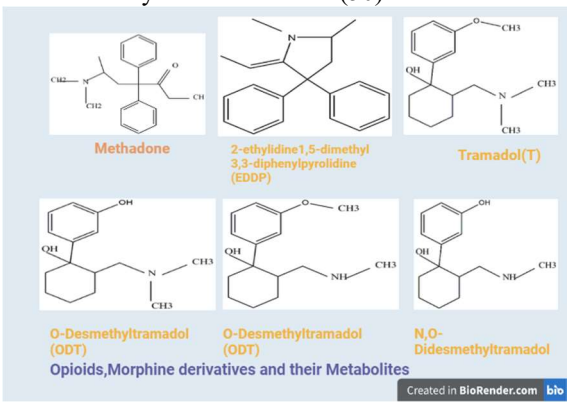


Figure:IV. Opioids,Morphine derivatives and their Metabolites.

4.2. SYNTHETIC OPIOIDS:

The second most studied class of chiral compounds are the synthetic opioids (Fig:IV). There have been reports of tramadol, methadone, and methorphan. Overdose, addiction, and abuse of opioids are all severe public health issues(56, 57). According to the 2017 European Monitoring Centre of Drug and Drug Addiction report, opioids were the third most commonly abused drug class in Europe and the one with the highest number of fatal overdose incidents(58). Tramadol is a synthetic opioid that selectively binds to opioid receptors and acts as an agonist. It is sold as a racemate of the more active 1R,2R-enantiomer ((+)-tramadol) and the less active 1S,2S-enantiomer ((-)-tramadol), with both enantiomers acting in a synergistic manner. However, there are significant variances in their pharmacological activity due to differences in their binding characteristics(59). O-desmethyltramadol (ODT) and N-desmethyltramadol (NDT) are the products of the metabolism of tramadol. Tramadol is O-demethylated by the polymorphically produced

enzyme CYP2D6(60). Polymorphisms play an important role in inter-individual drug response(61).The metabolite ODT is more powerful than the parent chemicals, has a longer half-life, and is pharmacologically active. Because of its euphoric and mood-enhancing properties, tramadol has been utilized for non-medical uses(62). Abusers of tramadol develop physiological dependence, which can have adverse consequences like convulsions and seizures(63). Additionally, genetic variations can affect biological characteristics, such as toxicity. For pharmacokinetic applications in plasma samples, an LC-MS/MS technique for separating tramadol and its main metabolites, ODT and NDT, was reported(64). The pharmacokinetics of ODT was not enantioselective in patients with neuropathic pain who were phenotypic as extensive CYP2D6 metabolizers, the authors demonstrated, but tramadol and its NDT metabolite's kinetic disposition were enantioselective, with plasma accumulation of (+)-tramadol and (+)-NDT. Therefore, for a precise assessment of tramadol's biological characteristics and toxicity, enantioselective approaches for both tramadol and its metabolites are necessary. Often used to treat opiate addicts, methadone is a synthetic opioid that is pharmacologically comparable to morphine but lacks the euphoric effects(65). Methadone can be lethal on its own or when combined with other medicines, such as CNS depressants. Methadone is a substrate for the stereoselective CYP2B6 and CYP2C19 enzymes. Additionally, polymorphisms in CYP P450 isoenzymes are known to cause individual variability, resulting in poor, rapid, and ultra-rapid metabolizers(66). For the detection of methadone and EDDP in human plasma, urine, and liver microsomes, Moody et al. devised an enantioselective technique using LC-MS/MS.This study showed variations in the pharmacokinetics of methadone's primary metabolite, EDDP, and its two enantiomers, suggesting that S-EDDP is produced in higher amounts and cleared from the body at a slower rate (67).The R- and R- isomers of 3-methoxy-N-methylmorphinan are the antitussive dextromethorphan (approved drug) and the narcotic analgesic levomethorphan (barred substance, not commercially available). For the separation of methorphan (a racemate of dextromethorphan and levomethorphan), Aumatell and Wells created a CE chiral technique(68).

The differentiation of these substances is important for treating patients who are drunk as well as for forensic research (such as determining the cause of death following levomethorphan consumption). Additionally, athletes are permitted to use dextromethorphan-containing products, whereas the International Olympic Committee expressly forbids the use of levorphanol(44).

4.3. Antidepressants:

Considering the fact that antidepressants are thought to be non-addictive, many people abuse these medications(69).Users may develop physical dependence, which may lead to noncompliance and, in certain cases, catastrophic outcomes(70). Fluoxetine (FLX), citalopram, reboxetine, venlafaxine (VNF), and its metabolites are some of the antidepressants that have been researched. FLX is an example of an antidepressant that is administered as a racemate and has the same pharmacological activity in both enantiomers. Serotonin, dopamine, and norepinephrine are increased in the extracellular space by specifically inhibiting the serotonin reuptake pump. It is transformed into norfluoxetine (NFLX) in the human body. The 5-HT reuptake is almost equally blocked by FLX and NFLX enantiomers, however their pharmacological activities differ substantially. Both in vitro and in vivo, the enantiomer S-NFLX exhibits roughly 20 times the potency of the R-enantiomer as a 5-HT reuptake inhibitor(71-73). To examine potential sources of fluctuation in the amounts of FLX and NFLX and their enantiomers in rats receiving long-term therapy, Unceta et al. devised an LC-FD approach for simultaneous separation of FLX and NFLX enantiomers. R-NFLX plasma levels were significantly higher than those of the S-enantiomer. Contrary to NFLX R/S ratios, which were 1.81 in plasma and 1.5 in the cerebral cortex, FLX R/S ratios in plasma were of 1.02 compared to 1.05 in the cerebral cortex.

Citalopram is marketed as a racemate and is used to treat depression. Compared to R-(-)-citalopram, its enantiomer S-(+)-citalopram (also known as escitalopram, is sold in its enantiomerically pure form) has 100 times higher potency as a serotonin reuptake inhibitor. VNF, a phenylethylamine derivative, influences brain neurotransmission by preventing serotonin and noradrenaline from being reabsorbed presynaptically(74, 75).

VNF, a phenylethylamine derivative used to treat psychiatric illnesses, interferes with brain neurotransmission by inhibiting serotonin and noradrenaline presynaptic reuptake(74). By way of extensive first-pass metabolism, VNF is converted into two minor metabolites, N-desmethylvenlafaxine (ND-VNF) and N, O-didesmethylvenlafaxine (N,O-DD-VNF), as well as its main active metabolite, O-desmethylvenlafaxine (OD-VNF). Like VNF, OD-VNF inhibits serotonin and noradrenaline reuptake in a potent manner. The median S, S/R, R ratio in steady state, according to the authors, was 0.5 and varied

from 0.22 to 0.88. It was also discovered that women had an S, S/R, R ratio that is almost 30% higher than that of men. Reboxetine concentrations were not found to correlate with S, S/R, R ratios. A association between selective noradrenaline reuptake inhibitor activity, which is stronger in women than in males and may change the enantiomeric ratio, was also discovered by the authors.

4.4.β-blockers:

A class of chiral medications called "β-blockers," also referred to as "β-adrenergic blocking agents," is used to treat cardiac arrhythmias. The potency of one enantiomer is typically higher than that of the other. S-(-)-propranolol (PHO) is 100 times more potent than R-(+)-PHO, for example. Most beta-blockers are sold as racemates, including acebutolol, atenolol (ATE), alprenolol, betaxolol, carvediol, metoprolol (MET), labetalol, pindolol, and sotalol. Timolol is the exception because it is the S-isomer(2). Along with their medicinal benefits, these substances provide relaxing neurological effects that reduce anxiety and nervousness while stabilising motor function. Because of the enhanced psychomotor performance that may be advantageous in sports requiring precision and accuracy like shooting and archery, among others, these substances are listed as illegal under World Anti-Doping Agency (WADA) regulations(44). In plasma and urine, only the β-blockers PHO, MET, carvedilol, verapamil, and its metabolite enantiomers were differentiated(76). LC-MS and GC-MS were two analytical techniques utilised for the separation of these medicines' enantiomers. Racemate PHO is used to treat hypertension and normalise tachycardia response, however the S-enantiomer has stronger cardiosympatholytic action.

Siluk et al. developed an analytical method for separation of *R*,*S*-PHO in human plasma for determination of pharmacokinetic difference among the two enantiomers and even drugs interaction. According to this study's authors, R-PHO is excreted more quickly than S-PHO. An analytical technique for enantioseparating MET's enantiomers in urine was created by Kim et al. This technique can be used in biological sample pharmacological and pharmacokinetic research of both enantiomers(77). There are no investigations on the enantioseparation of other commonly used -blockers in biological samples than carvedilol and verapamil. For these medications, enantioseparation techniques are crucial to assess pharmacological and pharmacokinetic variations across enantiomers as well as potential toxicity resulting from interactions with other pharmaceuticals.

4.5. Anticoagulants:

One of the most often given cardiovascular medications for managing thromboembolic illness is warfarin (WFN). Although the S-enantiomer of WFN has greater activity than the R-enantiomer, WFN is taken orally as a racemate. Age, sex, histories of smoking and alcohol consumption, diets high in vitamin K, and genetic polymorphisms are among the factors that raise the risk of over-anticoagulation(78). The risk of excessive anticoagulation is mostly caused by genetic factors and medication interactions. In addition to ensuring effectiveness and safety, understanding enantioselective pharmacodynamic and pharmacokinetic processes is crucial since genetic polymorphisms can significantly affect biological features, including toxicity. Different analytical techniques were used to separate WFN enantiomers: LC-MS/MS, Micellar electrokinetic chromatography, and SFC-MS/MS MEKC-MS plasma levels(79). Understanding the pharmacokinetics of WFN's enantiomers and its metabolites may help with investigations on the potential toxicology and interactions of WFN with other medications that are delivered concurrently as well as the creation of enantiopure commercial variants of WFN that may be safer. In addition to its usage as an anticoagulant, WFN was also a poison and is currently sold as a pesticide for use against rats and mice.

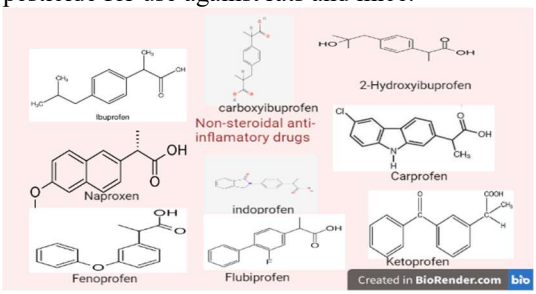


Figure:V. Non- steroidal anti-inflamatory drugs.

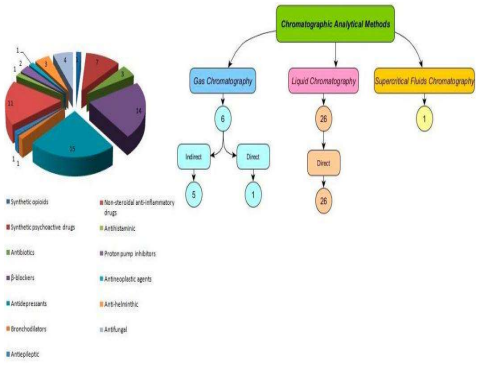
4.6. Dissociative anesthetics:

In several nations, ketamine (K) started to be abused frequently and was mostly obtained illegally. This medication induces hallucinations at subanesthetic levels. Due to these desired effects, K is frequently used for recreational activities and is especially risky for workplace and traffic safety. K can actually be purchased online from alleged veterinary distributors and hospitals(80). Plasma and hair were used to perform chiral discrimination between K and its primary metabolite norketamine (NK)(81). S-(+)-K is an anaesthetic and analgesic, but R-(-)-K is linked to agitation and hallucinations. K is a dissociative anaesthetic that causes amnesia, immobility, loss of consciousness, and to a lesser extent, analgesia. Due to its lower propensity to cause

respiratory depression, it is employed in veterinary surgery and paediatric emergency retrieval(82). Its principal advantage is that it causes severe analgesia and forgetfulness while stabilising the heart, lungs, and protective airway reflexes(83). K undergoes extensive first-pass metabolism to produce various free and glucurinated hydroxylated derivatives. However, its primary metabolic pathway involves N-demethylation, leading to NK, which appears to have 20–30% of the parent drug's action.

4.7. Bronchodialators:

Among bronchodilators are β-adrenoreceptor agonists are the drugs commonly used for asthma and pulmonary disorders. They have anabolic and bronchodilator properties. The use of these substances by athletes to improve performance and as a safer alternative to anabolic steroids is permitted due to their qualities, while it is not prohibited for athletes who have asthma. In this regard, the WADA's Prohibit List schedules -adrenergic substances with -blockers.(44) There is only one report that discusses the enantioseparation of salbutamol (SBT), a bronchodilator. Although this substance is sold as a racemate, the R-enantiomer of SBT has a stronger affinity for binding to 2-adrenergic receptors than the S-enantiomer, which doesn't work by activating -adrenergic receptors. S-SBT has negative side effects, including increased bronchospasm and pro-inflammatory activity. Studies have shown that the S-enantiomer can increase the effects of spasmogens in human and guinea pig airway smooth muscle, and a number of clinical studies have also shown an increase in the hyperresponsiveness of the airways in both animals and asthmatic individuals(84). Sulphate conjugation, a stereoselective process that takes place in human airway epithelial cells as well as other cells and tissues, is the first stage in the metabolism of both enantiomers(85). Lower plasma levels of the R- than the S-enantiomer in human subjects may result from



the higher rate of sulphate conjugation of R-SBT, which may increase the side effects associated with the latter. The development of enantioselective bronchodilator methodologies is crucial for stereo-pharmacokinetics and enantioselective safety investigations since the pharmacodynamics of bronchodilators are enantioselective. The creation of enantiopure broncodilators therapeutic medications that are safer and can be used to control broncodilators abuse can benefit from the data from pharmacokinetic studies(84).

4.8. Anti-helmintics:

Due to its toxicity, levamisole and dexamisol [(phenyltetrahydroimidazothiazole (PTHIT)] are no longer recognised for use in the United States or Canada as anti-worm medications for both humans and animals.(11) PTHIT has been known to be added to cocaine formulations in South American illicit cocaine labs in order to prolong the effects of the drug. An analytical technique for GC-FID was developed by Casale et al. to determine the PTHIT enantiomers. Specifically, levamisole and dexamisole have been found in illicit cocaine seizures and cocaine users' urine.(11) Beyond the potential correlation between cocaine usage and seizures, it has been demonstrated that cocaine addicts who get addicted to PTHIT develop agranulocytosis and neutropenia, intensifying the negative effects of the drug's use. PTHIT was present in approximately 78% of cocaine samples, with an average concentration of 23%. Dexamisole and levamisole sample enantiomeric compositions varied. Levamisole, racemate, and greater amounts of levamisole were all present in 66%, 19%, and 15% of the samples, respectively. Samples with simply dexamisole in them were not found. Tetramisole and levamisole may have been added to the cocaine by traffickers, or levamisole may have been prepared illegally, explaining the increased content in levamisole. When taking into account urine samples, the majority of urine extracts (46%), levamisole improved enrichment (20%), and dexamisole enhanced enrichment (26%), all included levamisole. Levamisole is very poisonous and affects all organ systems.(11)

5. Chiral drug analysis in aquatic environment:

33 publications published between 2005 and 2020 were examined for this study using the ScienceDirect and ISI Web of Knowledge databases. Antidepressants, -blockers, nonsteroidal anti-inflammatories (NSAIDs), synthetic psychoactive substances, antibiotics, synthetic opioids, antiepileptics, and antihistamines were among the target substances. Other chemicals included bronchodilators, antineoplastic medicines, and proton pump inhibitors.

Figure1: Relative number of each class of chiral drug referred in the reviewed enantioselective published studies and the analytical methods for the separation of chiral drugs in environmental samples.

Pharmaceuticals and illicit drugs may enter the aquatic environment by direct sewage discharge or effluents from WWTPs that are unable to completely remove these micro-pollutants. Given that microbial action is typically stereoselective, biological therapies at WWTPs can change the EF of the enantiomers present in the influent.(86, 87) Drugs that have been disposed of are typically discovered in their parent form, either as racemate or as single enantiomers. On the other hand, expelled medications will typically be discovered as metabolites of the original substance, frequently chiral. Studies of the presence of chiral medicines in environmental matrices are motivated by the potential negative effects of enantiomers on aquatic and human life(88, 89).

The quantities of these chemicals in wastewater can be used to estimate the intake of illegal drugs and abused substances. Drugs are ingested, metabolised, and expelled by humans as parent chemicals or metabolites before being dumped into wastewater treatment plants (WWTPs).(89) Environmental samples can contain illicit drugs as well, and environmental data are crucial sources for a forensic approach. This involves using environmental data to: (1) confirm patterns of illegal and legal drug use in the area; (2) apply drugs as chemical indicators of faecal water contamination with (human) sewage; and (3) confirm the source of illicit or legal drug use.(89) Enantioselectivity must be acknowledged in order to provide a more accurate risk assessment of chiral chemicals with regard to biodegradation, ecotoxicity, and environmental destiny. By keeping track of their EF during biological processes, it is possible to research how chiral medicines behave in the environment.(90) Both abiotic and biotic mechanisms are necessary for the degradation of these substances.It is anticipated that biodegradation in WWTP will be stereoselective, which modifies the EF of a particular molecule in the sample and results in a range of removal/degradation rates.(91) The amount of research that has been published in chiral environmental analysis during the past five years has been rising quickly. Understanding the behaviour of chiral micropollutants in the environment, particularly in water samples of wastewater or surface water, has proved helpful for risk assessment and improving the effectiveness of WWTPs.(91) The EF of several drugs, including PHO, alprenolol, VNF, and climbazole in surface waters, can show how effective various WWTPs are.These substances have also been suggested as markers to distinguish between treated and untreated water. An overview of the efficiency and of the WWTPs is provided by comparing the EF of the influent and effluent of the target analytes during the analysis of wastewater samples.(92-94)

Since fresh sewage is what feeds WWTPs, Kasprzyk-Hordern et al. claim that a long-term drug monitoring programme could disclose how drugs are used locally and how that usage varies over time.This is the primary pathway by which chiral medicines enter the environment, where they may be discovered in metabolised form (as metabolites) or with altered enantiomeric EFs as a result of human metabolism.(88) In the first attempt to apply chirality to sewage epidemiology, Kasprzyk-Hordern et al. quantified the amounts of AM, MA, MDMA, MDA, ephedrine, and pseudoephedrine enantiomers in wastewater samples collected over an 8-month period from seven WWTPs in London during five sampling campaigns.(95) However, when it comes to MDMA and MDA, enantiomeric profiling has proven invaluable in distinguishing between MDA abuse and its formation due to MDMA metabolism, indicating that this profiling could also help in differentiating between actual consumption and direct disposal.

The use of wastewater enantiomeric profiling indicated regional trends in the use of chiral medicines, with consumption of AM displaying an erratic pattern over the course of the two-week sampling campaign and MA displaying a minor rise in daily loads over the course of the weekend in one of the WWTPs. Weekends were when MDMA showed a definite weekly pattern of higher daily doses.

9.GENERAL CONCLUSIONS AND FURTHER PERSPECTIVES

Given its low quantification limits, selectivity, and unmistakable identification, LC-MS/MS is the method of choice for studies of biological and environmental matrices. Environmental analysis is primarily described using the direct method developed by LC employing CSP. However, there are still few approaches for chiral medication mixtures that are complex. Chiral analysis in biological matrices include a number of indirect approaches by GC, but the direct method by LC is currently in vogue.

Despite the significance of chiral analysis in forensic chemistry, certified laboratories do not currently employ this kind of information for chiral drug control in general, criminal offence detection, environmental monitoring, or doping control. In order to establish the significance of the chiral analysis in forensic chemistry, more research is required about new enantioselectivity methods with various CSP and demonstrations with practical applications.

Enantioselective chromatography has evolved into a crucial tool in all phases of drug development,

particularly in the early stages, when taking into account chiral compounds. Some conclusions may be derived from this when looking at medicinal chemistry from the perspective of the huge number of chiral pharmaceuticals.The need for more efficient procedures was sparked by the need for quicker analytical and preparative enantioresolution approaches for bioactive chemicals.

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