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*Review*

# Survey on the Integration of Molecularly Imprinted Polymers as Artificial Receptors in Potentiometric Transducers for pharmaceutical Drugs

*Ayman H. Kamel*[1,*], *Somaia G. Mohammad* [2], *Nasser S. Awwad*[3], *Yomna Y. Mohammed*[4]

[1] Department of Chemistry, Faculty of Science, Ain Shams University,11566 Abbassia, Cairo, Egypt.
[2] Central Agricultural Pesticides Laboratory, Agriculture Research Center (ARC), 12618, Dokki, Egypt.
[3]Department of Chemistry, Faculty of Science, King Khalid University, P.O. Box 9004, Abha, Saudi Arabia
[4] Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Ain Shams University, 11566 Abbassia, Cairo, Egypt.
[*]E-mail:ahkamel76@sci.asu.edu.eg (Coressponding author, Ayman H. Kamel)

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Molecular imprinted polymers (MIPs) became a very important part within the preparation of artificial and strong recognition materials. MIPs bring several advantages, when integrated with potentiometric sensors for pharmaceutical analysis, especially enhanced selectivity for analytes (drugs) in different pharmaceutical or biological matrices. An overview on the use of MIPs as recognition element in potentiometric sensors for pharmaceutical assay is presented covering different synthesis procedures, sensor assembly, and selectivity coefficients for interferences. Also, summary of linearity range, lower limit of detection, slope and working pH for each sensor are presented.

**Keywords:** Molecularly imprinted polymers, Potentiometric sensors, Drugs, Pharmaceuticals, Biological fluids, Application.

**ABBREVATIONS**

Acetonitrile (ACN)
Acrylamide grafted MWCNTs with vinyl group (MWCNTs-g-AAm-CH=$CH_2$)
2-acrylamido-2-methyl-1-propanesulfonic acid (AAMPSO)
Acrylic acid (AA)
Acrylonitrile (AN)
3- aminopropyltriethoxysilane (APTES)
Atomic force microscopy (AFM)
2,2'-azobisisobutyronitrile (AIBN)
Bio-mimetic bulk acoustic wave (BAW)
Benzoyl peroxide (BPO)

Bis (2-ethyl hexyl) sebacate (BEHS)
Bis (2-ethylhexyl) phthalate (BEPH)
Brunauere Emmette Teller (BET)
1-Butyl-1-methyl pyrrolidinium bis (trifluoromethylsulfonyl) imide ([BMP]$Tf_2N$)
Di-butyl phosphate (DBP)
Di-butyl sebacate (DBS)
Di-butyl phthalate (DBPH)
Differential scanning calorimetry
Di-octyl phthalate (DOP)
Di-octylsebacate (DOS)
Dimethyl formamide (DMF)
Dimethyl sulfoxide (DMSO)
Diphenyldimethoxysilan (DPTS)
Divinyl benzene (DVB)
Fixed interference method (FIM)
Imprinted sol–gel (ISG)
Molecular imprinted polymer (MIP)
Non imprinted polymer (NIP)
Ethylene glycol dimethacrylate (EGDMA)
Fourier transform infrared (FT-IR)
Itaconic acid (IA)
Ion Selective electrode (ISE)
Lanthanum nitrate $La(NO_3)_3.6H_2O$
Matched potential method (MPM)
Methacrylic acid (MAA)
Mixed solution method (MSM)
Molecular imprinted polymer (MIP)
Multi-walled carbon nanotubes (MWCNTs)
2-Nitrophenylphenyl ether (NPPE)
*o*,Nitophenyloctyl ether (*o*, NPOE)
Non imprinted polymer (NIP)
Oleic acid (OA)
Polyvinyl chloride (PVC)
Potassium tetrakis (4- chlorophenyl) borate (TpClPB)
Scanning electron microscopy (SEM)
Separate solution method (SSM)
Sodium tetraphenylborate (NaTPB)
Tetraethyl orthosilicate (TEOS)
Tetrahydrofuran (THF)
Tretraoctylammonium bromide (TOABr)
p-tert-octylphenol (TOP)
Thermogravimetric analysis (TGA)
Trifluoroacetic acid (TFA)
Tridodecylmethyl ammonium ($TDMA^+$)
Transmission electronmicroscopy (TEM)
Trimethylolpropanetrimethacrylate (TRIM)
2-vinyl pyridine (VP)
X-ray diffraction (XRD)
Below the detection limit (BDL)

## 1. INTRODUCTION

Nowadays, one of the most interesting research fields in sensors' field is electrochemical sensors. There are three important factors should be considered before construction of an electrochemical sensor: (a) Good selection of the recognition element receptor; (b) choice of the transducer; and, (c) the integration of both elements. Molecular imprinted polymers (MIPs) are the most promising materials in the preparation of artificial molecular recognition systems. The advantages of using of molecular imprinted technologies that they have high selectivity and sensitivity, which can be used in combination with suitable transducer for desired application [1]. The theory behind this method involves moulding a fabric (with the required chemical recognition properties) around individual molecules (template). By removal of the molecular template, the material preserves its molded shape to fit with that of the template molecules. Thus, molecular imprinting can provide materials that can selectively bind to molecules of interest [1].

The technology of molecular imprinting had increased interest in the recent years [2], that was reflected in several reviews [3], and discussed the application of MIPs in solid phase extraction, chromatographic separations or as drug delivery systems. Regarding chemical sensing, Haupt and Mosbach [4], presented a review about MIPs and their use in biomimetic sensors. Al-Kindy [5], gave an outline of MIPs and their applications in optical sensing, an area showing the vital applications of MIPs within the chemical sensing field. Other works covered the applications of MIPs as recognition element in pharmaceutical, environmental and food quality control connected with various transducers [6]. Wide applications using potentiometric ion selective electrodes (ISEs) have been observed in drug pharmaceutical analysis as summarized in Table 1. Incorporation of MIPs in the membrane of ISEs combines the advantages of MIPs of selectivity and specificity to template. These are needed in quantitative analysis of the analyte in different complex matrices that represent high degree of interference. No review has summarized different MIPs used in potentiometric sensors applied for quantitative pharmaceutical analysis and these work overviews different ISEs based on incorporation of MIPs in as selective recognition element.

## 2. PREPARATION of MIPs

### *2.1. Optimization of MIP synthesis procedures*

Different parameters, such as amount and nature of monomer, cross-linker, and porogenic solvent, have to be optimized to obtain the final desired characteristics of the prepared MIPs in terms of affinity, capacity, and selectivity for the target analyte. Thus, different trials should be carried out to reach the optimum mixture of cross-linker and functional monomer. This is to minimize the nonspecific binding as possible. Essentially, proper molar ratios of functional monomer to template are very important to achieve the specific affinity of prepared polymers and number of recognition sites in MIPs. High ratios of functional monomer to template would result in a high nonspecific affinity, while low ratios will limit complexation opportunity due to inadequate functional groups [7].

The synthesis of MIPs was done by three different imprinting methods [8], as follows: *i) The non-covalent approach:* It is considered the most widely used method of imprinting due to its relative simplicity on experimental level. The complexation step throughout the synthesis is achieved by mixing the template with the appropriate functional monomer (s), in a suitable solvent that is called porogen [9]. After preparation, the template is removed from the formed polymer mainly by washing and extracting it with a solvent or a mixture of solvents. The rebinding step is based on non-covalent interactions between the prepared MIPs and the template (Fig. 1). *ii) The covalent approach:* It depends on the formation of covalent bonds between the template and the functional monomer prior to polymerization. Removal of the template from the polymer matrix after preparation is done after the cleavage of the formed covalent bonds. The polymer is then refluxed in a Soxhlet extraction or treated with reagents in solution [10]. *iii) The semi-covalent approach:* It is a hybrid of the two previous approaches. The rebinding of the template to the MIP is based on non-covalent interactions, as the non-covalent imprinting protocol [11].

In general, the production of molecular-sensing polymer includes the following steps: (i) Selection and preparation of required monomer(s), cross-linker, porogen (ii) Synthesis of the MIPs, (iii) Washing of MIPs and template removal (iv) Optimization to achieve molecular selectivity, and (v) construction of MIP-based membrane sensors using the prepared polymers [12].

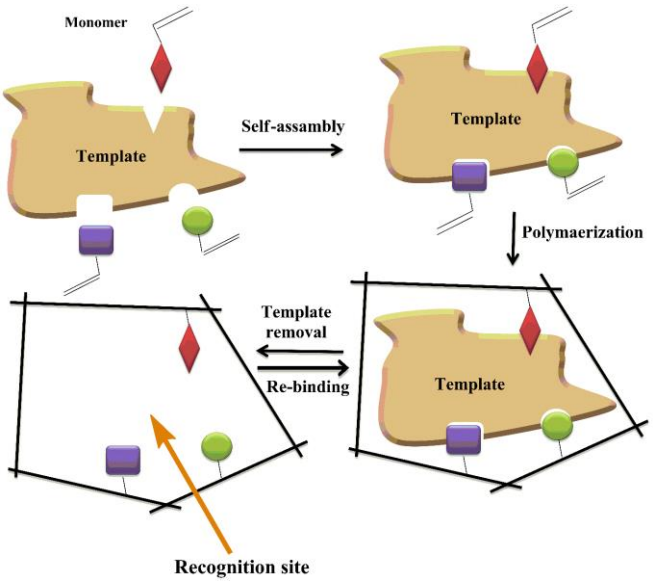



**Figure 1.** Schematic overview of the MIP imprinting.

The nature of formed binding sites during molecular imprinting shows variable characteristics, depending on the interactions established during polymerization stage. The majority of binding sites are using bonding by non-covalent forces that show average weaker affinity than those prepared using covalent methods. That is explained by the electrostatic, hydrogen bonding, π-π and hydrophobic interactions between the template and the functional monomers used mainly in formation of the MIPs [13]. In addition, presence of excess functional monomer relative to the template is generally required to enhance complex formation (between template and functional monomer) and to preserve its

integrity during polymerization. Obviously, when covalent bonds are formed between the template and the functional monomer before polymerization stage, this establish better structured and more homogeneous binding sites than the non-covalent approach, as the template-functional monomer interactions are more stable and well-defined during the imprinting process [11]. But, non-covalent imprinting protocol is still the most important method used method to prepare MIP referring to its advantage over the covalent approach of practical simplicity.

### *2.2. Characterization of molecularly imprinted polymers*

The characterization of imprinted polymer particles by FT-IR usually measure changes in O-H and C=O stretching vibration in the leached MIP than un-leached MIP (shifted to lower frequencies). The lower frequencies in FTIR is explained by the interaction of hydrogen of O-H and C=O groups in either monomer or cross linker with the template. Also, MIPs with well-controlled physical forms in different size ranges are highly desirable, for example, MIP nano-spheres are desired for use in developing binding assays.

SEM is utilized to determine surface morphology and shape of the produced polymer particles. The characterization of molecular imprinted polymer by particle size was carried by photon correlation spectroscopy, BET surface area, TGA and DSC [11,14,15] .

## 3. APPLICATIONS of MIPs

Molecular imprinting has now become a well-known process and has also been applied in different areas of biomedical and analytical chemistry. Several papers described usage of MIP as chromatographic stationary phases [16] and for enantiomeric separations [17]. Also, they showed a great advance in fields of solid-phase extraction [18], catalysis [19] and sensor design [20], as well as for protein separation [21]. MIPs have the ability to act as receptor [22], antibody [23] and enzyme mimics [24], and recently as drug delivery systems (DDS) [25]. MIPs were integrated as recognition receptors in potentiometric ISEs for quantitative determination of different organic and inorganic ions [26-37]. In this review, we focus on the MIPs integrated in potentiometric sensor devices developed for selective and quantitative assay of drugs in pharmaceuticals formulations and biological fluids.

## 4. POTENTIOMETRIC SENSORS

### *4.1. Principle*

Potentiometric sensors are considered the most widely used analytical technique in many fields, including clinical and environmental analysis and process control. The imprinted polymers become point of interest for scientists focused in the development of the electrochemical sensor [1, 4, 38]. Using MIPs offers many benefits such as their better stability, low cost, high selectivity, and ease of

preparation. Moreover, MIPs are much more stable to organic solvents, pH, high temperature, and pressure than ordinary membranes. The cost of producing MIPs is relatively low, and they can be stored in the dry state at room temperature for long periods of time.

With the increasing of number of MIP based electrochemical sensors with different electrochemical transducers (capacitive, conductometric, amperometric, and voltammetric), it is observed that only a few MIP-based sensors have been reported using a potentiometric transducer (in spite of the relatively simple transduction of the potentiometric signal) [26-37,39]. Especially, the areas of environmental monitoring and food and drug analysis require analytical tools facilitate detection of chemicals with high molecular specificity, considering complex biological fluids that resemble high interference. The possibility of incorporating tailor-made, highly selective artificial MIPs makes these synthetic polymers the ideal recognition elements in electrochemical sensors [40,41].

### *4.2. Incorporation of MIPs*

MIPs play an outstanding role when associated with potentiometric sensors. These electrodes utilize membranes to enable the recognition of a specific ion by transferring it (selectively) across the interface between the sample and membrane phase. This transfer across generates a potential difference that indicate the activity of the transferred ion.

Regarding sensor assembly, there are various MIP-based potentiometric sensors that are described by dispersing MIP particles in plasticizer and embedding in PVC matrix [42,43], forming a glassy membrane [44] or assembling the template on the polar surface of indium tin oxide (ITO) glass plate [45]. Depositing a MIP polymeric film on the gate surface of an ion-sensitive field-effect transistor (ISFET) [46], and preparing the chemically modified carbon paste electrodes (CMCPEs) by mixing graphite/binder paste and MIP as modifier [47,48] can be an alternative pathway. In MIP-based potentiometric sensors, incorporation of the imprinted polymer as the active ingredient in a membrane of an ISE provides new electrochemical transduction by chemical recognition which can be practical in analytical objectives.

### *4.3. Mechanism of response*

Until now, several mechanisms have been proposed for the response mechanism of these types of electrodes. One of these mechanisms is based on the phase boundary theory [49]. For operation of ion selective electrode, ions in an aqueous phase must transfer into an organic medium and interact with the active ingredients in the membrane [50]. The electromotive force (*emf*) across the cell is the sum of all individual potential contributions. Many of these developed potentials are sample-independent, and the measured emf, *E* can usually be described as:

$$E = E_{const} + E_J + E_M \qquad \text{Eq. (1)}$$

where $E_M$ is the membrane potential, $E_{const}$ stands for reference electrode, and $E_J$ is the liquid junction potential at the sample/bridge electrolyte interface, which can either be kept reasonably small and constant under well-defined conditions.

Typically, the membrane potential is divided into three separate potential contributions: the phase boundary potentials at both interfaces and the diffusion potential within the ion-selective membrane. The membrane's internal diffusion potential can be assumed to be equal zero, if there is no concentration gradient within the membrane.

$$E_M = E_{const} + E_{PB} \quad \text{Eq. (2)}$$

$$E_{PB} = \Delta\phi = -\frac{\mu^0(org)-\mu^0(aq)}{zF} + \frac{RT}{zF}\ln\frac{a_I(aq)}{a_I(org)} \quad \text{Eq. (3)}$$

$$E_M = E_{const} - \frac{\mu^0(org)-\mu^0(aq)}{zF} - \frac{RT}{zF}\ln a_I(org) + \frac{RT}{zF}\ln a_I(aq) \quad \text{Eq. (4)}$$

where $E_{PB}$ is the phase boundary potential at the membrane-sample interface, which can be derived from basic thermodynamic considerations, $\mu$ is the chemical potential ($\mu^0$ under standard conditions), $z$ is the valence of analyte and $a_I$ the activity of the un-complexed ion $I$, $\phi$ is the electrical potential, and $R$, $T$ and $F$ are the universal gas constant, the absolute temperature and the faraday's constant. Under equilibrium conditions, $a_{I(org)}$ remains unaltered so it can, together with all other sample-independent potential contributions, be included in one term ($E^0$) and Eq. (4) is reduced to the well-known Nernst equation (Eq. 5):

$$E_M = E^0 + \frac{RT}{zF}\ln a_I(aq) \quad \text{Eq. (5)}$$

Assuming that the interfacial ion transfer and the complexation processes are relatively fast, so, the equilibrium for analyte ion is held at the interface. Response mediated through complex formation between analyte and MIPs may be assumed to be based on neutral carrier mechanism as MIPs have a neutral net charge and their electrochemical behaviors show big similarity with neutral carriers (Fig. 2). The enhanced response shown for MIPs over obtained with NIPs gives an evidence on the inclusion of the template inside the cavity of MIPs and formation of physicochemical interactions through membrane. This can lead to potential development after transfer of ions across the membrane and binding with MIPs. Ionic additives [$R^+$ or $R^-$] should be also added to ensure that ISE membranes are perm-selective [51], reducing the ionic interferences and lowering the electrical resistance of the membranes [52].

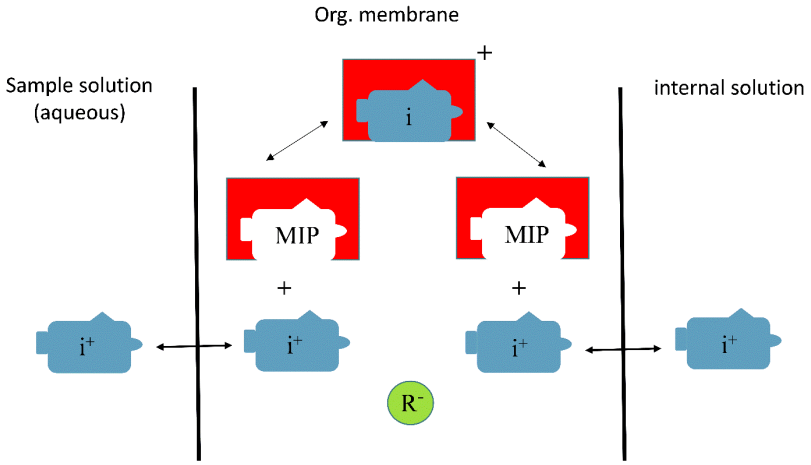



**Figure 2.** Schematic representation of phase boundary theory for MIP-based potentiometric sensors.

Comparison between the membranes with and without ionic additives showed that incorporation of anionic site additive (i.e. $TPB^-$) to MIPs membrane based sensor for cationic drug caused a remarkable improvement in the potentiometric response properties (slope, lower limit of linear range and the detection limit) while the incorporation of cationic site additive (i.e. $TDMA^+$) dramatically deteriorated the potentiometric response characteristics [53]. The common used ionic additives are either to be anionic additives as TpCIPB [54-57], or NaTPB [58-62] or anionic sites in PVC polymer structure itself that comes from impurities [48, 52, 63-66]. In terms of analytical performance, the addition of lipophilic additives is expected to augment the ISE performance, widening the linear range with theoretical slope and stable sensor response.

At the same time, the incorporation of a selectively binding ionophore (MIPs) into the ISE sensing layer will lower the overall free energy for ion transfer into the organic phase (the membrane) for those ions to which the MIPs binds [49], therefore for analyte ions complexed by the MIPs, a great difference in the magnitude of selectivity coefficients is observed against the lipophilicity series expected behavior [51]. So partitioning of analyte between the organic membrane containing MIPs and the aqueous sample solutions can be a base for explanation of MIPs mediated response especially the high selectivity obtained. The overall response will depend on *K* (partition coefficient of analyte *I* and interfering ion *J*) and their β (complex formation coefficient toward MIPs). So, the selectivity of the membrane sensor is expressed in one term called "selectivity coefficient $(K_{I,J}^{pot})$".

Determination of Selectivity Coefficients for analyte ion and other interferences can be performed according to IUPAC 1976 by using two different procedures one called separate solution method (SSM) and the other called fixed interference method (FIM) [67,68]. The SSM involves the measurement of two separate solutions, each containing a salt of the primary or interfering ion only both are of same activity. The calculation of Nicolskii Selectivity coefficient from the two observed values of emf (E) can be calculated from Eq. (6) as follows:

$$K_{I,J}^{pot} = a_I^{(1-1/z_J)} e^{(E_J - E_I)/S} \qquad \text{Eq. (6)}$$

where *S* is the practical slope calculated after the calibration experiments.

In the FIM which is a mixed solution method, an entire calibration curve is measured for the primary ion in a constant interfering ion background ($a_J$). The linear (i.e., Nernstian) response curve of the electrode as a function of the primary ion activity is extrapolated until, at the lower detection limit $a_{I(DL)}$, it intersects with the observed potential for the background alone. The calculation of Nicolskii coefficient from these two extrapolated linear segments of the calibration curve, each relating the analytical response of the ISE to one respective ion only [69,70].

The introduction of the matched potential method (MPM) was within the mid 1980s by Gadzekpo and Christian [71]. A specified amount of the primary ions is added to a reference solution and the membrane potential is then measured. In a separate experiment, the interfering ion is successively added to an identical reference solution until the membrane potential matches the one obtained before with the primary ion. The definition of the matched potential method selectivity coefficient is the ratio of the primary ion and interfering ion activity increases in the two experiments as in Eq.(7):

$$K_{I,J}^{pot} = \frac{a_I}{(a_J)^{z_I/z_J}} \qquad \text{Eq. (7)}$$

Another assumption that MIPs may have some ionic exchanger properties due to the extremities of monomers after polymerization especially free acidic groups (as of MAA). MIPs would gain the ability to attract ionic $I^+$ analytes that explains why in some cases NIPs itself show a response and reasonable potential but when this response is compared with MIPs it can be neglected. It can simulate the activity of PVC-COOH that gives potentiometric response with ephedrine with ion exchange mechanism [72]. So the activity of MIPs as neutral ionophore recognition element in the sensor membrane would be the main theory that can explain mechanism of response of MIPs as recognition element. Another unique feature of potentiometry is that the creation of a membrane potential does not required the extraction of template from the membrane, and ionic species do not have to diffuse through the membrane, providing no size restrictions on the template compound [38].

## 5. PHARMACEUTICAL ANALYSIS

Different articles were reported as analytical method using MIP based potentiometric sensors for quantitation of drug content in different pharmaceutical formulations and/or biological fluids. Table 1 summarizes published papers utilized MIPs based sensors in terms of assembly, sensitivity and selectivity parameters. Synthesis and preparation of MIPs Potentiometric based sensors are also presented in Table (1).

### *5.1. Antihistaminic drugs*

Different three antihistaminic drugs were used as a template in the synthesis of molecularly imprinted polymers. These polymers were integrated in potentiometric carbon-paste sensors for drug monitoring. The structures of these drugs are shown in Fig. 3.

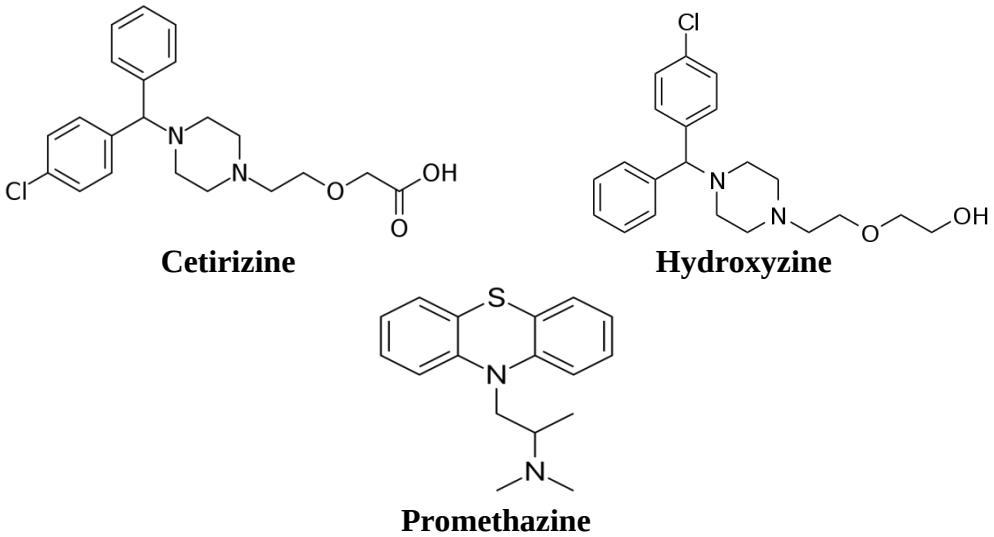



**Figure 3.** Structures of Cetirizine, Hydroxyzine and Promethazine as Antihistaminic drugs

*5.1.1. Cetirizine*

MIPs were integrated in a potentiometric detector for cetirizine determination [48]. EGDMA (3.82 mmol) was used as a cross-linker and MAA (0.915 mmol) as a functional monomer. The potentiometric sensor type used was carbon paste electrode consisted of graphite powder, paraffin oil and the ratio of MIP used was in proportions of 5, 10, 12 and 15% (w/w). The sensor revealed a Nernstian response slope of 28.0 mV/decade with a detection limit $7.0\times10^{-7}$ at pH 1.9-4.5. Different organic compounds and drugs were tested for selectivity measurements using matched potential method (MPM). The sensor exhibited a lower selectivity coefficient values towards Hydroxyzine (-2.2), Piperazine (-3.2), Triethylamine (-3.3) Pyrrole (-3.9 ), and Salbutamol (-4.0).

*5.1.2. Hydroxyzine*

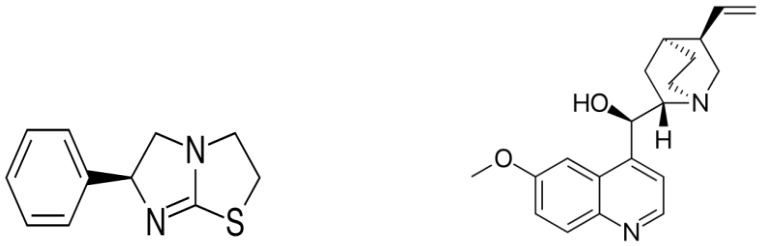
A carbon paste electrode integrated with MIPs for hydroxyzine determination [47]. MAA (0.915 mmol) and EGDMA (3.82 mmol) were used for the preparation of imprinted polymer. Different ratios of MIP (i.e. 5, 10, 12 and 15% (w/w)) were tested. The sensor exhibited a detection limit $7.0\times10^{-7}$ M with a slope of 29.4 mV/decade within the pH 1.7-4.2. The calculation of selectivity coefficient values was done by using MPM and FIM methods. Interference from cetrizine (-1.8) over hydroxyzine was reported.

*5.1.3. Promethazine*

Polymeric PVC membrane sensors based on molecular imprinted polymer for the analysis of promethazinedrugs were fabricated [73]. MAA and 4-VP (7.0 mmol) were used as a functional monomers in presence of DVB or EGDMA (32 mmol) as a cross-linker for all MIP and NIP synthesis. The MIP/NIP polymer particles were dispersed in plasticized PVC matrix. The analytical performances of the sensors were evaluated in different plasticizers namely, *o,NPOE,* DOP, BEHS and DBP. In the high polar plasticizer *o,*NPOE, the sensor revealed a cationic slope 35.1 mV/decade with a detection limit $1.0\times10^{-7}$ M and linearity starts from $5x10^{-7}$ M at pH 2.0-5.0. The Selectivity of the sensor over different common organic and inorganic cations was checked and the calculation of selectivity coefficient values was done by using MPM.

*5.2. Antiparasitic drugs*

Antiparasitics are a category of medications which are indicated for the treatment of parasitic diseases, such as those caused by helminthes, amoeba, ectoparasites, parasitic fungi, and protozoa, among others. Only two antihistaminic drugs were used as a template in the synthesis of molecularly imprinted polymer which integrated in potentiometric sensors, levamisole and quinine (Fig. 4).




**Levamisole** **Quinine**

**Figure 4.** Structures of Levamisole and Quinne as antiparasitic drugs

*5.2.1. Levamisole*

Levamisol as an anthelmintic drug was imprinted and used for drug determination using polymeric PVC membrane sensor [63]. The preparation of MIP was done by using (0.0833 mmol) levamisol as a template, (0.33 mmol) MAA as a functional monomer, (1.26 mmol) DVB as a cross-linker and (0.023 mmol) AIBN as an initiator in 3 mL DMSO: AN (2:8) porgenic solvent. The membrane composition was 29.5 mg of PVC powder, 30 mg MIP/NIP and 0.2 mL of a plasticizer. The mixture was stirred and dispersed in 3.0 mL THF. The sensor revealed a Nernstian slope of 57.0 mV/decade with LLLR $2.5x10^{-6}$ M and detection Limit $1.0x10^{-6}$ at pH range 5.0-9.0. Sever interferences were noticed from imidazole (-0.6), $Ni^{2+}$(-0.2), benzoic acid (-1.7), oxalic acid (-0.8) and salicylic acid (-0.1). The method used for selectivity measurements were SSM.

*5.2.2. Quinine*

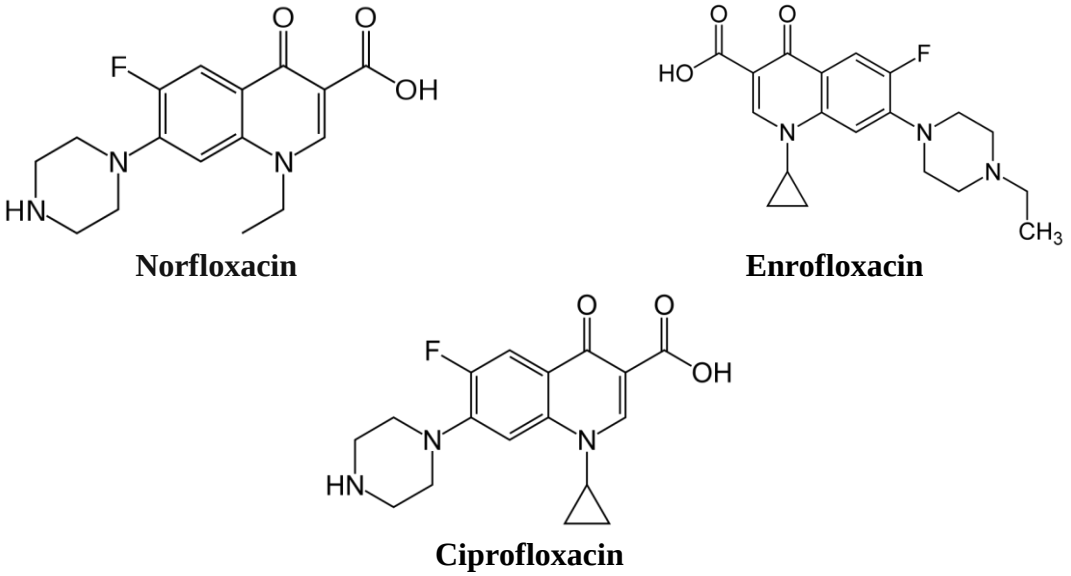
Miniaturized potentiometric membrane sensors for quinine incorporated with molecular imprinted polymer (MIP) were synthesized and implemented [54]. Planar PVC based polymeric membrane sensors containing quinine-methacrylic and/or acrylic acid-ethylene glycol methacrylate were dispensed into anisotropically etched wells on polyimide wafers. The membrane composition was 1.0 wt% MIP/NIP, 64.0wt% BEHS, 33.0 wt% PVC and 30.0 % mole of TpCIB or TDMAC. The performance characteristics for this type of potentiometeric sensor were slope 47.7-61.3 (mV/ decade), detection limit of $1.2x10^{-6}$ M, LLLR of $4.0x10^{-6}$ M at pH range 4.8-8.0. The sensors exhibited good selectivity and selectivity coefficients towards common organic and inorganic cations such as $K^+$ (~ -4.0), $Mg^{2+}$ (~ -4.0), $Ca^{2+}$ (-4.5), cinchonidine (~ -2.5), quinolone (-2.5), ephedrine (-3.5), caffeine (-3.5), creatinine (-4.0), urea (-3.5) and urate. All values of selectivity coefficient were calculated using the selectivity method SSM.

*5.3. Antibiotics*

*5.3.1. Fluoroquinolones*

A quinolone antibiotic is any member of a large group of broad-spectrum bactericides that share a bicyclecore structure related to the compound 4-quinolone. They are used for both human and

veterinary medicine to treatbacterial infections, as well as in animal husbandry. Nearly al lquinolone antibiotics in use are fluoroquinolones, which contain a fluorine atom in their chemical structure and are effective against both Gram-negative and Gram-positive bacteria. Some of these fluoroquinolone drugs are shown in Fig. 5.




**Norfloxacin** **Enrofloxacin**

**Ciprofloxacin**

**Figure 5.** Structures of Norfloxacin, Enrofloxacin and Ciprofloxacin as fluoroquinolone drugs

*5.3.1.1. Norfloxacin*

Norfloxacin as a fluoroquinolone antibiotic, is used for urinary tract infections treatment, gynecological infections, inflammation of the prostate gland, gonorrhea and bladder infection. Solid contact potentiometric sensor integrated with MIP particles was prepared for the drug determination [55]. The MIP synthesis was performed using (20.0 mmol) EGDMA as a cross-linker and (1.0 mmol) Norfloxacin as a template in presence of (5.0 mmol) MAA/4-VP as functional monomers. The composition of the membrane consisted of 200 mg PVC, 400 mg of *o*,NPOE plasticizer and 7 mg of MIP/NIP particles. A 2 mg of TpClPB was added as anionic additive. The mixture was stirred, and dispersed in 3.0 mL THF. The sensor revealed a slope response of 67.1 mV/decade with a LLLR $4.0x10^{-6}$ M and a detection limit $1.0x10^{-6}$ M over the pH range 2.0-6.0. Different common drugs and inorganic cations were tested to evaluate the selectivity behavior of the senor. The calculation of selectivity coefficient values by MSM were: enrofloxacin (-0.9), tetracycline (-1.0), dopamine (-1.1), hydroxylamine (-1.1), creatinine (-1.4), sulfadiazine ( -1.3), glucose (~ -1.2), $Li^+$ (-1.0) and $NH_4^+$ (-1.2).

*5.3.1.2. Enrofloxacin*

Enrofloxacin is a fluoroquinolone antimicrobial antibiotic used both in humans and in food producing species. Its control is required in farmed species and their surroundings in order to reduce

the prevalence of antibiotic resistant bacteria. An artificial host was imprinted in specific polymers using both MAA and MAA/4-VP as functional monomers in presence of the cross-linker EGDMA [74]. The synthesized polymeric particles were dispersed in 2-nitrophenyloctyl ether and entrapped in a PVC matrix. The potentiometric sensors revealed a near-Nernstian slope response varied within 47.4-65.2 mV/decade. The detection limits ranged from 0.28 to 1.01 µg/mL with a LLLR $4.0x10^{-7}$ M at pH 4-7. The proposed sensors exhibited good selectivity behavior towards enrofloxacine in many common organic and inorganic cations, such as $K^+$ (-3.0), $Ca^{2+}$ (-3.0), glycine (-3.0), ascorbic acid (-3.0), norfloxacin (-2.5), ciprofloxacin (-1.0) and tetracycline (-1.0).

*5.3.1.3. Ciprofloxacin*

Ciprofloxacin antibiotic is used for bacterial infections treatment. It can stop the production of bacteria by inhibiting the reproduction and repair of their genetic material (DNA). It is used to treat infections of the bones, airways, skin, lungs, and joints caused by susceptible bacteria. The preparation of molecularly imprinted polymer (MIP) for special molecule recognition by thermal polymerization is done [64]. Ciprofloxacin acted as the template molecule, methacrylic acid (MAA) (3.0 mmol) or 4-vinylpyridine (4-VP) (3.0 mmol) acted as the functional monomer and ethylene glycol dimethacrylate (EGDMA) (15.0 mmol) acted as the cross-linker. The field of biomimetic potentiometric device was developed for the assessment of antibiotics cirofloxacin (CIP) based on these newly synthesized imprinted polymers. The sensing elements were fabricated by the inclusion of CIP imprinted polymers in polyvinyl chloride (PVC) matrix. The membrane composition consisted of 200 mg PVC, 200 mg of PVC, 350 mg of plasticizer *o*,NPOE and 15 mg of the sensing polymer MIP/NIP. The limit of detection of this sensor is $1.0x10^{-5}$ and the pH is 3.0-4.5. The interferences and selectivity using MIP/MAA towards some sugars such as galactose (-2.5), sucrose (-2.6), glucose (-2.6), and the selectivity method used was MSM. Moreover, the sensor have found sever interferences from trimethoprim (+1.6), enrofloxacin (-0.9), tetracycline (-0.7), sulphamerazine (-0.1), hydroxylamine (-1.0), sucrose (-1.0) and sulfadiazine (-2.3).

For selectivity improvement, Kamel's group [58] prepared a new potentimetric sensor for ciprofloxacin determination using MIP particles dispersied in plasticized PVC membrane. The preparation of MIP particles was done by using Ciprofloxacin (0.11 mmol), methacrylic acid (MAA) (0.88 mmol), 2-vinylpyridine (2-VP) (0.88 mmol) or acrylonitril (AN) (0.88 mmol), acted as the functional monomer and ethylene glycol dimethacrylate (EGDMA) (2.2 mmol) acted as the cross-linker. The effect of membrane and type of plasticizers were tested. It was found that the sensitivity and the linearity of the sensor increased as the amount of the MIP increased from 10 to 15 mg. From 15 to 20 mg of the MIP, there was no effect on either the sensitivity or linearity and both reached a maximum. The sensors made using DOP as solvent mediator showed the best characteristics. The sensors displayed a linear response start from $3.2x\ 10^{-5}$ M with a cationic slope of 29.2±1.2, 25.4±0.8 and 20.2±0.9 mV/decade and the order of the detection limit were 35.5, 40.4 and 44.7 µg/mL for sensor MIP/MAA, MIP/AN and MIP/2-VP respectively. The selectivity coefficient values calculated by FIM showed a good selectivity towards ciprofloxacin over cystien (-2.5), glutamine (-2.1), histidine

(-2.0), phenylalanine (-2.3), $Na^+$ (-2.8), $K^+$ (-2.5) and $Mg^{2+}$ (-2.0). Sever interference is coming from norfloxacine (+0.3), ofloxacine (+0.3) and enrofloxacine (+0.4).

### *5.3.2. Tetracyclines*

Tetracyclines are broad-spectrum antibiotics whose general usefulness has been reduced with the onset of antibiotic resistance. They are generally used in the treatment of infections of the urinary tract, respiratory tract, and the intestines and are also used in the treatment of chlamydia, especially in patients allergic to β-lactams and macrolides; however, their use for these indications is less popular than it once was due to widespread development of resistance in the causative organisms. Their most common current use is in the treatment of moderately severe acne and rosacea (tetracycline, oxytetracycline, doxycycline or chlorotetracycline) (Fig. 6).

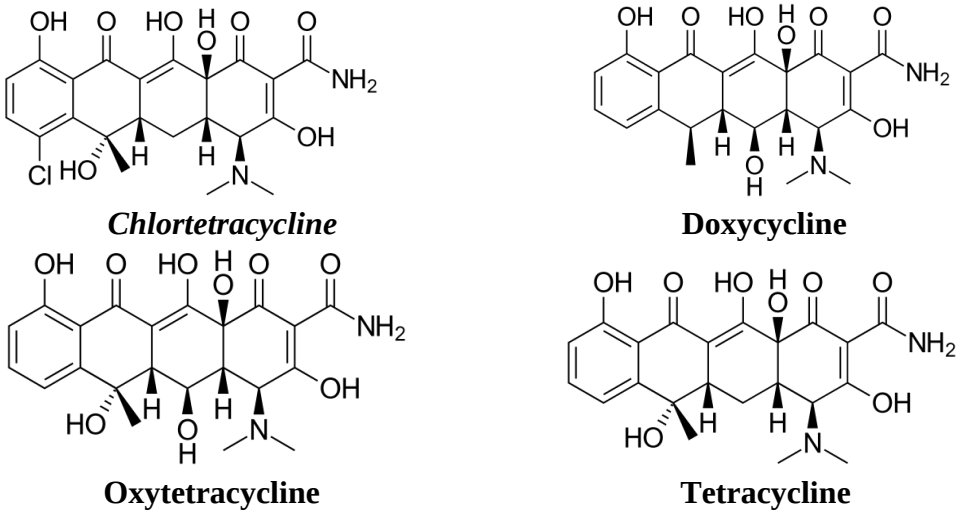



**Figure 6.** Structures of tetracycline, oxytetracycline, doxycycline and chlorotetracycline drugs

#### *5.3.2.1. Chlortetracycline*

A graphite based sensor integrated with MIP particles was prepared and characterized by Sales' group for the analysis of chlorotetracycline [75]. MAA and AA were used as functional monomers in addition to EGDMA as a cross-linker fir the synthesis of the MIP particles. The sensor exhibited a detection limit $4.1x10^{-5}$ M with a response slope range from 48.6 to 68.6 mV/ decade at pH 2.5-13. For sensors based on MIP/MAA, they revealed a selectivity battern towards chlorotetracycline over other ions as: Glucose (-1.6), cysteine (-1.6), sacarose (-1.6), $Ca^{2+}$ (-1.6), $Li^+$ (-2.6), $Mg^{2+}$ (-4.1), $Na^+$ (-2.1) using the selectivity method SSM. On the other hand, for the selectivity method MSM, they found the Interferences towards Ciprofloxacin (~ -1.8), Sulfamethazine (~ -2.8), Sulfathiazole (~ -3.3), Creatinine (~ -2.8).

*5.3.2.2. Doxycycline*

Doxycycline (DOX) is a tetracycline antibiotic that possesses broad-spectrum activity. The properties of bactericidal are based on the inhibition of bacteria cell protein synthesis in Gram-positive and Gram-negative bacteria, spirochetes, mycoplasmas, Nocardia, Coxiella, Rickettsia and Chlamydia. Sales' group [65] described doxycycline sensitive ISEs based on DOX/MIP particles dispersed in 2-nitrophenyloctyl ether (*o*,NPOE) and embedded in polyvinylchloride (PVC) matrix, for the monitoring of DOX and its application to the analysis of pharmaceuticals under static and hydrodynamic mode of operations. The synthesis of molecularly imprinted polymer (MIP) by using doxycycline as a template molecule, acrylamide (AA) and/or methacrylic acid (MAA) as a functional monomer and ethylene glycol dimethacrylate (EGDMA) as a cross-linking agent. The sensors exhibited linear potentiometric response towards DOX ions with lower limit of linear range $7.9\times10^{-6}$, $7.92\times10^{-6}$ and $5.01\times10^{-6}$ M, and detection limits of 3.55, 2.5 and 0.71$\mu$g $mL^{-1}$, for sensors based on MAA, AA and MAA/AA polymers, respectively. All sensors exhibited near-Nernstian slopes of 54.8±0.5 ($r^2$=0.998), 50.1±0.8 ($r^2$=0.997) and 52.4±0.6 ($r^2$= 0.997) mV/decade, respectively. The order of selectivity order of MIP/MAA and MIP/AA based sensors is: Doxycycline >Chlortetracycline > tetracycline > lactose > creatinine > oxytetracycline > glucose > sulfadiazine > glycin. For MIP/AA based sensors the selectivity order is: Doxycycline > chlortetracycline > tetracycline > lactose > creatinine > oxytetracycline > glucose ~ sulfadiazine > glycin. The selectivity order of MIP/MAA-AA based sensor is: Doxycycline > chlortetracycline > lactose > tetracycline > creatinine > sulfadiazine > glucose > oxytetracycline > glycine. In general, sensors based on MIP/MAA are less affected by oxytetracycline, sulfadiazine and creatinine than that of MIP/AA and MIP/MAA-AA based membrane sensors. On the other hand, a sensor based on MIP/AA is less affected by tetracycline only than sensors based on MIP/MAA and MIP/MAA-AA.

*5.3.2.3. Oxytetracycline*

Biomimetic sensor for the potentiometric transduction of oxytetracycline is presented [56]. The artificial host was imprinted in methacrylic acid and/or acrylamide based polymers. Different amounts of molecularly imprinted and non-imprinted polymers were dispersed in different plasticizing solvents and entrapped in a poly(vinyl chloride) matrix. These sensors exhibited a near-Nernstian response in steady state evaluations; slopes and detection limits ranged 42-63 mV/decade and 2.5-31.3µg/mL, respectively. Sensors were independent from the pH of test solutions within 2-5. Under flow analysis, the sensors revealed good reproducibility (RSD of ±0.7%), fast response, good sensitivity (65 mV/decade), wide linear range ($5.0\times10^{-5}$ to $1.0\text{x}10^{-2}$ M) and low detection limit (19.8µg/mL). Using SSM, the sensors exhibited good selectivity for oxytetracycline towards glycine (-1.7), hydrxylamine (-1.7), lactose (-2.0), creatinine (-1.5), and sulfadiazin (-1.7). High interference is presented from ciprofloxacin (-0.5).

*5.3.2.4. Tetracycline*

Potentiometric membrane sensors with cylindrical configuration for tetracycline (TC) were presented by Sales' group [57]. The membrane sensors based on the use of a newly designed molecularly imprinted polymer (MIP) material consisting of 2-vinylpyridine (5.0 mmol) as a functional monomer and EGDMA (24.5 mmol) as across-linker in a plasticized PVC membrane. The template amount was 0.5 mmol. The sensor exhibited significantly enhanced response towards TC over the concentration range $1.6x10^{-5}$-$1.0x10^{-3}$ M at pH 3-5 with a lower detection limit of $1.3x10^{-5}$ M. The response was near-Nernstian, with average slopes of 63.9 mV/decade. The effect of various foreign common ions was tested using SSM. The typical selectivity order was: Tetracycline > oxycycline (-0.6) ~ alanine (-0.6) ~ $NH_2OH.HCl$ (-0.6) > cysteine (-0.7) > creatinine (-1.0) > citric acid (-1.1) > tartaric acid (-1.2) > $K^+$ (-1.4) ~ $NH_4^+$ (-1.4) > naldixic acid (-1.7) > $Na^+$ (-1.8) > glycine (-1.9) > $Ca^{2+}$ (-3.5) > $Ba^{2+}$ (-3.6) > $Mg^{2+}$(-3.8).

Another biomimetic sensor for the potentiometric transduction of tetracycline is presented [66]. The MIP particles was synthesized using bulk precipitation method using (0.1 mmol) TC, (0.1 mmol) La $(NO_3)_3$, (0.066 mL) MAA and (0.944 mL) EGDMA. The polymeric PVC membrane consisted of 100 mg of PVC, MIP/NIP particles (122 mg), DBP (128 mg) were added into 2 mL of THF and stirred for 1 h. The sensor revealed a limit of detection $2.5\times10^{-8}$ M over a potentiometric slope of 57.6 mV/ decade. The LLLR was $6.0x10^{-8}$ M over a pH range 2.0-4.0. Good selectivity coefficients calculated by SSM were found towards some common compounds such as, glucose (< -4.0), lactose (< -4.0), alanine (<-4.0), valine (<-4.0) and maltose (< -4.0).

Using (0.1 mmol) TC, (0.1 mmol) La $(NO_3)_3$, (0.088 mL) MAA and (0.944 mL) EGDMA, another MIP particles were synthesized and dispersed in plasticized PVM membrane for potentiometric determination of tetracycline [59]. The polymeric PVC membrane consisted of MIP/NIP particles, NaTFPB, plasticizers and PVC (total 960 mg) were added into 6 mL of THF and stirred for 1 h. The detection limits for this sensor was $1.0\times10^{-8}$ and LLLR $2.0x10^{-8}$ M with a potentiometric slope 59.8 mV/decade over the pH range 2.0-4.0. Only interference was produced from oxytetracyline (-1.2) and chlorotetracylcine (-1.3).

*5.3.3. Macrolides*

The macrolides are a class of natural products that consist of a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. Some macrolides have antibiotic or antifungal activity and are used as pharmaceutical drugs.

*5.3.3.1. Azithromycin*

Azithromycin (Fig.7) is an antibiotic useful for the treatment of a number of bacterial infections. Biomimetic-potentiometric sensor for the determination of this antibiotic is presented [76]**.** The MIP particles were synthesized using bulk precipitation method using (0.5 mmol) azithromycin, (3.0 mmol) AA or 2-VP and (15.0 mmol) EGDMA. The MIP particles were integrated with a coated

graphite electrode for azithromycin monitoring. The graphite coated membrane consisted of 0.17g PVC, 0.4g of two plasticizers (DBP or DBP) and 0.02 gm of the sensing polymer (MIP/NIP). The sensor revealed a potentiometric response of a slope 57.1 mV/decade with a LLLR $5.0x10^{-7}$ M and limit of detection $2.0x10^{-7}$ M. A stable potential response was obtained over the pH range 3.0-8.0. The selectivity coefficient values obtained using SSM reflects good selectivity behavior for the sensors over most common carbohydrates such as, glucose (-3.6), sucrose (-3.2 ), lactose (-3.1) and starch (-4.1), and inorganic cations such as $Na^+$ (-2.5), $K^+$ (-2.1), $Ca^{2+}$ (-2.3), $Mg^{2+}$ (-3.9), $Zn^{2+}$ (-2.4), $Cd^{2+}$ (-2.3) and $Fe^{3+}$ (-3.0).

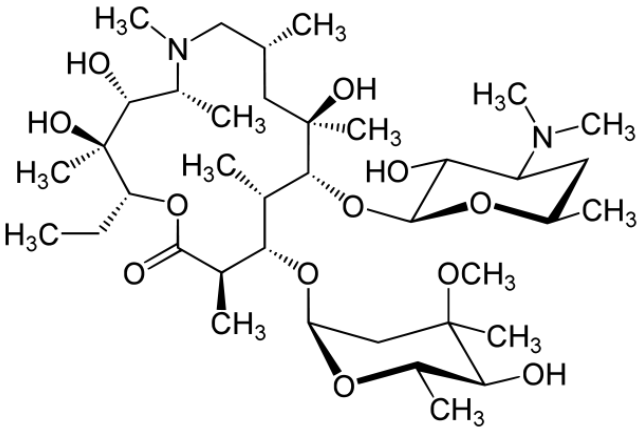


**Figure 7.** Azithromycin

*5.3.4. Penicillins*

Penicillin is considered the first and effective medications against many bacterial infections caused by staphylococci and streptococci. They are still widely used today, though many types of bacteriahave developed resistance following extensive use.

*5.3.4.1. Amoxicillin*

Amoxicillin (Fig. 8) is an antibiotic useful for the treatment of a number of bacterial infections. It is the first line treatment for middle ear infections and used for strep throat, pneumonia, skin infections, and urinary tract infections among others. Amoxicillin wasimprinted and the MIP particleswereused for drug détermination usingpolymeric PVC membrane sensor [77]. The MIP particles were prepared using (0.5 mmol) amoxicillin as a template, (5.0 mmol) MAA or (5.0 mmol) AAMPSO as a functional monomers, (24.5 mmol) EGDMA as a cross-linker and (0.32 mmol) BPO as an initiator in 3 mL methanol porgenic solvent. The potentiometric sensor used was graphite coated electrode. The graphite coated electrode consisted of 200 mg of PVC, 350 mg of *o*,NPOE and 15 mg of the sensing polymer (MIP/NIP) and also added of 7.5 mg of (TpClPB) membrane acting as anionic additive. The limit of detection and slope for the sensor were 1.8 $x10^{-5}$ M and 73.4 mV/decade, respectively. It revealed a stable potential over the pH range 4.0-5.0. The lower limit of linear range

(LLLR) was $3.3x10^{-5}$ M. The selectivity coefficients calculated by SSM were sucrose (-1.5), fructose (-1.6), cystiene (-0.5), creatinine (-1.0) and glucose (-1.6).

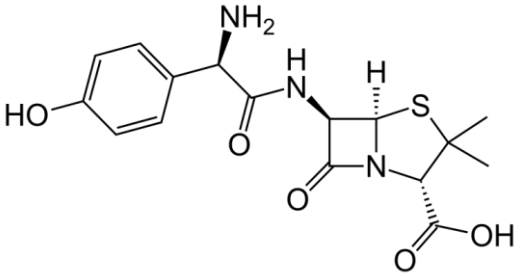
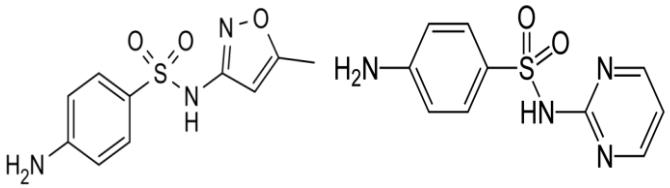



**Figure 8.** Amoxicillin

*5.3.6. Sulpha (sulphonamides) drugs*

Sulfonamide drugs (Fig. 9) were the first effective chemotherapeutic agents employed for preventing bacteria from synthesizing folic acid, a chemical that was essential to their growth. They are also used to treat allergies and cough, as well as antifungal and anti-malarial functions.




Sulfamethoxazole Sulfadiazine

**Figure 9.** Some sulphonamide drugs

Inorganic imprinted technique was used for sulfamethoxazole and sulfadiazine [60]. The imprinted polymer beads were synthesized using (12.5 mg) sulfamethoxazole or sulfadiazine as templates, (1.5 mL) APTES, (1.5 mL) DPTS as a functional monomers and (0.5mL) TEOS as a cross-linker. The prepared molecular imprinted beads were integrated in a graphite electrode for potntiometric determination of sulfamethoxazole. The composition of this electrode was 210 mg of PVC, 15.0 mg of the imprinted particles, 350 mg plasticizer (*o*,NPOE, BEHS or DPB), TOABr, TOP and NaTPB as ionic additives. The corresponding average slope was −51.4 and −52.4 mV/decade, linear responses were $9.0x10^{-6}$ and $1.7x10^{-5}$ M, and limits of detection were 0.74 and 1.3 μg/mL for sulfadiazine and for sulfamethoxazole, respectively. The sensors showed sever interferences from $NO_3^-$, $SO_4^{2-}$, persulphate, ciprofloxacin, creatinine, dopamine, galactose, sulfathiazole and tetracycline. The selectivity coefficient values ($log\ K^{POT}$) values lying within a narrow range: −0.20 to −3.9 and-0.29 to -3.8 for SDZ and SMX selective electrodes, respectively.

Another imprinted polymer was prepared for sulfamethoxazole using (0.195 mmol) template, (0.915 mmol) MAA, (3.82 mmol) EGDMA and (0.198 momol) AIBN [79]. The polymer was integrated in a potentiometeric PVC membrane sensor for the drug determination. The sensor revealed

a slope response 5.8-64.2 mV/decade with a LLLR $1.0x10^{-7}$ M and a detection limit $6.3x10^{-8}$M. The selectivity coefficients of sulfamethoxazole sensor using SSM were: sulfasalazine (-3.8), sulfacetamide (-3.1), sulfadiazine (SDZ) (-1.6), $Ca^{2+}$(-2.3), $Ni^{2+}$(-2.4), $Sn^{+2}$ (-2.7) and $Zn^{2+}$ (-2.0). By using the MPM, the selectivity values were: sulfasalazine (-2.9), sulfacetamide (-3.1) and sulfadiazine (-1.5).

A new biomimetic sensor material for sulfamethoxazole [80]. It is prepared by means of radical polymerization, having ethylene glycol dimethacrylate as a cross-linker, 2,2'-azobisisobutyronitrile as radical initiator, methacrylic acid as a functional monomer and acetonitrile as porogenic solvent. Carbon-paste sulfamethoxazole sensor with 10.9% of imprinted particles showed the best response in terms of slope -58.3 mV/decade and detection limit $6.3x10^{-8}$ M. The sensor revealed selectivity towards the sulfonamide antibiotics, glucose, calcium, ammonium, nickel, sodium and zinc. The sensor was not affected by pH < 2.2 and pH > 6.

### *5.3.7. Others*

#### *5.3.7.1. Trimethoprim*

Trimethoprim (TMP) (Fig. 10) is an antibiotic used mainly in the treatment of bladder infections. Other uses include for middle ear infections and travelers' diarrhea. It belongs to the group of dihydrofolate reductase inhibitor types. An artificial host was imprinted in specific polymers using both MAA and 4-VP as functional monomers in presence of the cross-linker TRIM [78]. The MIP particles were dispersed in a plasticized PVC membrane and coated over a graphite solid contact. The sensor revealed a linear range starts from $4.0x10^{-7}$ M with a detection limit $3.0x10^{-7}$ M with a potentiometric response slope 49.4-99.7 mv/decade. The sensors exhibited a stable potential response over the pH range 2.0-6.0. Selectivity values were evaluated using MPM for sulfadiazine, tryptophan, cystiene, valine, alanine and glycine. For inorganic cations such as $Fe^{2+}$, $Cr^{3+}$, $K^{+}$, $Na^{+}$, $NH_4^{+}$, $Ni^{2+}$, $Mn^{2+}$, $Al^{3+}$ and $Pb^{2+}$, SSM method was used for calculating the selectivity coefficient values.

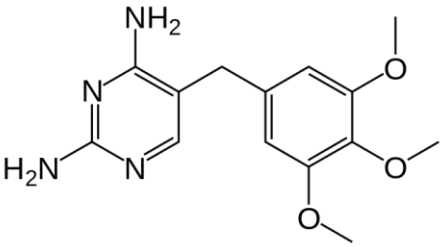



**Figure 10.** Trimethoprim

#### *5.3.6.2. Chloramphenicol*

Chloramphenicol (Fig.11) is an antibiotic useful for the treatment of a number of bacterial infections. This includes as an eye ointment to treat conjunctivitis. A nano-composite carbon paste electrode was prepared for chloramphenicol determination using MIP receptors [81]. The composition of MIP includes (1.0 mmol) chloramphenicol, (5.0 mmol) MAA, 30.0 mmol) EGDMA and (0.2 mmol)

AIBN im 50 mL chloroform. The Nano-composite carbon paste electrode consisted of 20% MIP/NIP, 54% graphite powder, 20% paraffin oil, 1% nano-silica and 5% of multi-walled carbon nanotubes. The sensor exhibited a LLLR $1.0x10^{-6}$ M with a Nernstian slope of 59.1 mV/decade and a limit of detection of $1.0 \times 10^{-6}$ M. The pH range for a stable potential response was 3.0-5.0. Using MPM for selectivity coefficient values, the sensor revealed a good selectivity towards chloramphenicol over glucose (-3.8), $Na^+$ (< -4.0), $Co^{2+}$ (-3.8), $K^+$ (< -4.0), $Mg^{2+}$ (-3.9), $Ca^{2+}$ (< -4.0), $Cl^-$ (< -4.0) and $CO_3^{2-}$ (< -4.0).

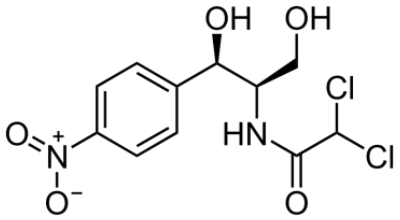


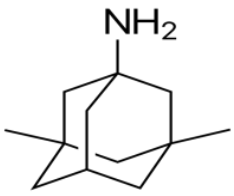

**Figure 11.** Chloramphenicol antibiotic

*5.4. Central nervous system drugs*

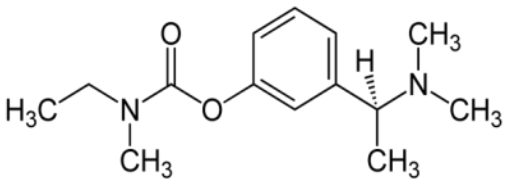
*5.4.1. Alzheimer's disease drugs*

*5.4.1.1. Memantine*

Memantine (Fig.12) is used to treat moderate to severe Alzheimer's disease. It acts on the glutamatergic system by blocking NMDA receptors. Syntheses of molecular imprinted polymer for memantine were presented in the literature [61]. The prepa,red MIP using (0.915 mmol) MAA, (0.238 mmol) memantine, (3.82 mmol) EGDMA and (0.088 mmol) AIBN. The potentiometeric membrane sensor consisted of 90 mg PVC powder with 45 mg MIP/ NIP, 25.0 mg NaTPB and 0.2 ml DBS were dissolved in 3.0 mL THF. The sensor developed showed a linear range starts from $1.0 \times 10^{-5}$ with a detection limit $6.0 \times 10^{-6}$. A stable potential is obtained at pH 5.0 -.9.0 with fast response time (~15 s). The selectivity for the sensor includes nicotinic acid (-3.2), oxalic acid (-2.7), $Na^+$ (-3.9), $Sn^{2+}$ (-3.6), $Ca^{2+}$ (-4.0), $K^+$ (-3.2). The selectivity method used SSM and MPM.




Memantine




Rivastigmine

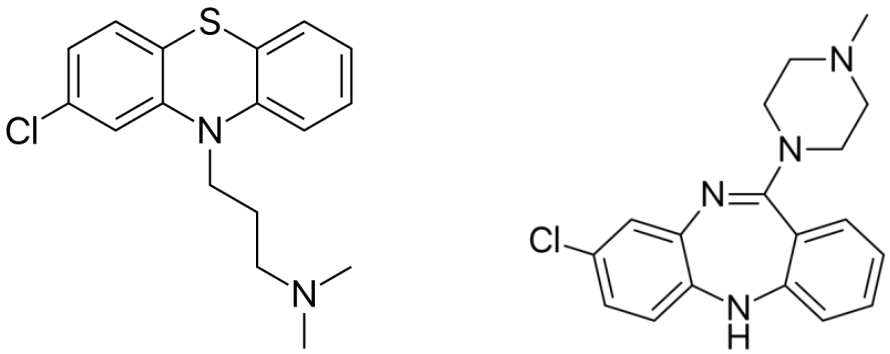
**Figure 12.** Chemical structures of Memantine and Rivastigmine

*5.4.1.2. Rivastigmine*

Rivastigmine *(Fig. 12)* is an acetylcholinesterase inhibitor used for the treatment of mild to moderate Alzheimer's disease and Parkinson's. The drug can be administered orally or via a transdermal patch; the latter form reduces the prevalence of side effects, which typically include nausea and vomiting. Polymeric PVC membrane sensor was prepared and characterized [82]. Molecularly imprinted polymer was synthesized for rivastigmine and integrated in the sensor. The MIP particles were prepared via thermal polymerization process using (0.198 mmol) template, (0.915 mmol) MAA, (3.82 mmol) EGDMA and (0.088 mmol) AIBN. The membrane based sensor consisted of MIP/NIP (10.5 mg), DBS (63.0 mg), and PVC (31.5 mg) dispersed in 3 mL of THF. The characteristic performances of the sensor were evaluated and the revealed a LLLR 1.0 $x10^{-5}$ M with detection limit $6.3x10^{-6}$ M. The potentiometric response slope of the sensor was 30.7 mV/decade and pH measuring range 4.0-8.0. The selectivity of the sensors was tested using both SSM and MPM. The sensor suffered from severe interference from gabapentin (-0.7), sertraline (-0.6) and citalopram (-0.6).

*5.4.2. Antipsychotic drugs*

Antipsychotic drugs (Fig. 13) are known as neuroleptics or major tranquilizers. They are belongs as a class of medication to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia and bipolar disorder. They are increasingly being used in the management of non-psychotic disorders. Antipsychotics are usually effective in relieving symptoms of psychosis in the short term.




Chlorpromazine Clozapine

**Figure 13.** Chemical structures of some Antipsychotic drugs

*5.4.2.1. Chlorpromazine*

Sales' group [83] was prepared a new molecular imprinted polymer and used it for the determination of Chlorpromazine in fish samples. The artificial polymer was synthesized by using (0.25 mmol) chlorpromazine template, (2.0 mmol) MAA, AAMPSO or 4-VP as monomers, (10.0 mmol) EGDMA or TRIM as cross-linkers and (0.5mmol) BPO initiator. The membrane based sensor

was added to conductive graphite base via drop-casting. The composition of the membrane was 200 mg of PVC, 400 mg *o*,NPOE, 7 mg MIP/ NIP, 2 mg TpClPB and 3.0 mL THF. The sensor revealed a good characteristic features towards chlorpromazine detection. The slope of this sensor ranged between 47.8-67.4 mV/decade with a LLLR $4.1x10^{-6}$ M and detection limit $1.3x10^{-6}$ mV/decade. The pH range for measuring was 2.0-5.5. Different common drugs were tested in this work for selectivity measurements. Slight interferences were noticed from creatinine (-1.5), doxycyline (-1.4), oxycycline (-1.6)trimethoprim (-1.1) and nalidixic acid (-1.4). The method used for selectivity measurements was SSM.

*5.4.2.2. Clozapine*

Clozapine nano-composite carbon paste electrode integrated with MIP particles was evaluated and characterized [84]. The composition of nano-composite carbon paste was 20% MIP/NIP, 54% graphite powder, 20% paraffin oil, 1% nano-silica and 5% of multi-walled carbon nanotubes. This solid sensor revealed good response towards Clozapine with a slope response of 28.8 mV/decade over a linearity starts from $1.0x10^{-6}$ M and detection limit $1.0x10^{-6}$ M. The sensor exihibited a stable potential response at pH range 3.5-5.0. The sensor revealed good selectivity behavior over lactose (-3.3), glucose (-3.2), $K^+$ (< -4.0), $Mg^{2+}$ (-4.0) and $Ca^{2+}$ (< -4.0). No studies were presented for testing the selectivity over most common drugs. The method used for selectivity measurements were MPM.

*5.4.3. Anticonvulsant drugs*

*5.4.3.1. Lamotrigine*

Lamotrigine (Fig. 14) is an anticonvulsant medication used to treat epilepsy and bipolar disorder. Novel potentiometric sensor based on man-tailored polymer for the determination of lamotrigine was developed [62]. The prepared MIP (0.4 mmol) lamotrigine template, (2.0 mmol) MAA as a functional monomer and (8.0 mmol) EGDMA as a cross- linker. The membrane based sensor was drop-casted on a graphite solid support. It consisted of 6.0 mg MIP/NIP, 1.0 mg of NaTPB ionic additive, 61 mg of DOP as plasticize and 32 mg of PVC in 2.0 ml THF. The sensor showed a wide linear range starts from $1.0\times10^{-6}$ with a limit of detection $8.0x10^{-7}$and potential response slope of 30.8 mV/decade. The sensor revealed a wide pH range for measurements starts from pH 1.0 to pH 5.0 and a response time of ~30 s. The sensor exhibited a good selectivity behavior towards some of different drugs such as phenobarbital (-3.1), 3-Amino-1,2,4triazin (-3.1), 2,4-Diamino-6 phenyl-1,2,4 triazin (-2.7) and common cations such as $Na^+$ (-2.8), $Mg^{2+}$ (-3.0) and $Ca^{2+}$(-2.9). The method used for selectivity measurements was MPM.

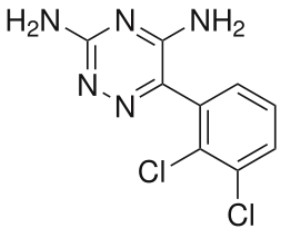



**Figure 14.** Lamotrigine anticonvulsant drug

*5.4.4. Antidepressant drugs*

*5.4.4.1. Sertraline*

Sertaline (Fig.15) is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. It is primarily used for major depressive disorder, obsessive-compulsive disorder, panic disorder, and social anxiety disorder. Effectiveness is similar to other antidepressants. Hashemi's et al., reported a new potentiometric sensor for sertaline determination using MIP as a recognition element [85]. The MIP particles were prepared from (0.088 mmol) sertraline template, (0.915 mmol) MAA as a functional monomer and (3.82 mmol) EGDMA as a cross- linker in 40 mL chloroform as a solvent. The proposed sensor revealed good performance characteristics for measuring sertraline. The slope of the potentiometric response was 63.7 mv/decade with a LLLR $1.0x10^{-6}$ M and detection limit $8.0x10^{-7}$ M. The selectivity coefficients of the sensor towards sertraline over different drugs were: fluoxetine (-3.1), Fluvoxamine (-3.1), mirtazapine (-3.3), trazodone (-3.5), $Ca^{2+}$(-3.2), $K^{+}$( -3.4), $Ba^{2+}$( -3.3) and $Zn^{2+}$ ( -3.2).

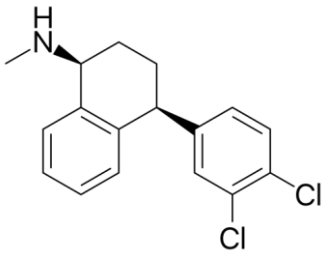



**Figure 15.** Sertraline antidepressant drug

*5.4.5. Neurotransmitter drugs*

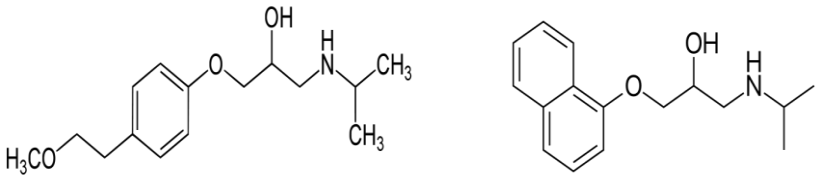
*5.4.5.1. Dopamine*

As presented in [86], the scientific group have prepared multi-walled carbon nanotube grafted with vinyl group based molecular imprinted polymer and use it for the determination of dopamine (DA) in different samples of blood and urine. The selectivity method used in this study was SSM. The limit of detection and the response time were $1.0x10^{-9}$ and 2 min. The selectivity coefficients of the sensor towards some acid such as uric acid (-0.2), citric acid (BDL) and ascorbic acid (BDL).

*5.5. Antihypertensive*

*5.5.1. Beta-blockers*

β-blockers, are a class of medications that are predominantly used to manage abnormal heart rhythms, and to protect the heart from a second heart attack (myocardial infarction) after a first heart attack (secondary prevention). They are also widely used to treat high blood pressure (hypertension). Some of these compounds are metoprolol and propranolol (Fig. 16).




**Metoprolol** **Propranolol**

**Figure 16.** Metoprolol and propranolol

Metoprolol imprinted polymer was synthesized and used as a potentiometric sensor for drug determination [87]. The MIP particles were prepared from (0.25 mmol) metoprolol template, (0.5 mmol) MAA as a functional monomer and (10.0 mmol) EGDMA as a cross-linker in 20 mL chloroform. The PVC membrane was drop-casted on a conductive graphite base. The membrane sensor consisted of 60.0 mg of PVC and 40.0 mg of MIP particles and were dispersed in 0.2 mL of DOP and dissolved in 2.5 mL of THF. The sensor revealed a fast response time of about 14 seconds and life-span of least 6 months. The detection limit of the sensor and its LLLR were $1.0\times10^{-7}$ and $1.3x10^{-7}$M, respectively. The pH range for measurements was 3.5 and 10.5. The selectivity coefficients were calculated using SSM towards benzoic acid (-1.6), oxalic acid (-0.68), $Mg^{2+}$ (-4.1), $Ca^{2+}$ (-3.7), $Pb^{2+}$ (-3.5), $Na^{+}$ (-3.0), $Cu^{2+}$ (-4.0), and $K^{+}$ (-3.3).

Propranolol as a medication of the beta blocker class was measured using a polymeric PVC membrane sensor integrated with MIP particles [88]. The MIP particles were prepared using bulk precipitation method with a (0.53 mmol) propranolol template, (1.31 mmol) MAA and (2.63 mmol) DVB in 40 mL acetonitril (ACN). The prepared sensor has a potentiometric slope of 56.7 mV/decade with LLLR $1.0x10^{-5}$ M and detection limit of $1.0x10^{-5}$ M. The pH value for measurements was 6.0. Sever interference appeared from metoprolol (-0.1) and atenolol (-0.7) using SSM for selectivity measurements.

*5.5.2. Angiotensin receptor blockers*

They are a group of pharmaceuticals that modulate the renin–angiotensin system. Their main uses are in the treatment of hypertension (high blood pressure), diabetic nephropathy (kidney damage due to diabetes) and congestive heart failure. They block the activation of $AT_1$ receptors, preventing the binding of angiotensin II.

Losartan (Fig.17) is a medication mainly used to treat high blood pressure. Other uses include for diabetic kidney disease, heart failure, and left ventricular enlargement. A new molecular imprinted polymer nano-graphene for the determination of losartan by using carbon paste electrode was designated and prepared [89]. MAA (2.0 mmol) and (13.6 mmol) EGDMA were used for MIP preparation. The composition of carbon paste electrode consisted of graphite powder and paraffin oil. The sensor revealed a lower detection limit of $1.8x10^{-9}$ and response time of about 6 second. The potentiometric response slope was 59.6 mV/decade with LLLR $3.0x10^{-9}$ M. The pH range for potentiometric response was 6.0-8.5. The selectivity values calculated by MPM for the proposed sensor over trazodone (-3.3), amlodipine (-4.1) were presented.

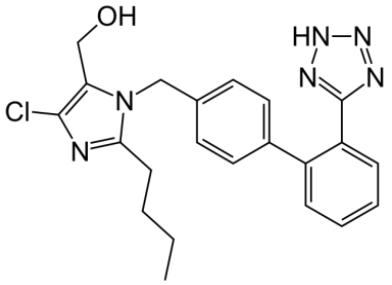



**Figure 17.** Losartan

*5.6. Antitussive and drug of abuse*

*5.6.1. Dextromethorphan*

Dextromethorphan (DXM) (Fig. 18) is a drug of the morphinan class with sedative, dissociative, and stimulant properties (at lower doses). It is a cough suppressant in many over-the counter cold and cough medicines. DXM sensitive potentiometric sensors based on DXM/MIP particles dispersed in DOP and embedded in polyvinylchloride (PVC) matrix, for the monitoring of DXM. MAA or AN (0.1 mmol) and (20.0 mmol) EGDMA were used for MIP preparation [53]. The sensing membranes were prepared by mixing 15 mg of the sensing polymer, 350 mg of the plasticizer and 195 mg of PVC and dissolved in ~ 3 mL THF. Electrochemical evaluation of these sensors revealed near-Nernstian response with slopes of 49.6 ± 0.5 and 53.4 ± 0.5 mV/decade with a detection limit of $1.9x10^{-6}$, and $1.0x10^{-6}$ M DXM with MIP/MAA and MIP/ AN membrane based sensors, respectively. The order of selectivity MIP/MAA and NIP/MAA based sensors with membrane plasticized with DOP is: DXM > ethylmorphine > ketamine > ephedrine > codeine > phenylpropanolamine > morphine and DXM > ethylmorphine > ketamine ~ ephedrine > morphine > phenylpropanolamine > codeine, respectively. For MIP/AN and NIP/AN based sensors with membrane plasticized with DOP is: DXM > ephedrine > ethylmorphine > ketamine ~ codeine > phenylpropanolamine > morphine and DXM > ethylmorphine ~ ketamine > morphine > phenylpropanolamine > ephedrine > codeine, respectively. Glucose, starch, maltose, , talc, and tween-80 used as drug excipients at concentration level as high as 1000-fold excess over DXM have no diverse effect on the accuracy of the results.

A graphite coated wire electrode integrated with MIP beads was prepared for dextromethorphan determination [90]. The preparation of MIP particles were (0.5 mmol) dextromethorphan template, (3.0 mmol) AA or VP as functional monomers and (15.0 mmol) EGDMA as a cross- linker. The preparation of membrane sensor was done by dissolving 0.17 mg of PVC, 0.4 gm DOP or BEHS as plasticizers, 0.02 gm of MIP and dispersed into 2.0-3.0 mL of THF. The response time of the proposed sensor was 1.0 min at pH 2.0-9.0. The LLLR and detection limit of the proposed sensor were $5.0x10^{-7}$ and 1.0 $x10^{-7}$ M mV/decade. Paracetamol (-1.9), ketorolac (-1.9), amoxicillin (-2.1), glucose (-1.8), $Ba^{2+}$ (-1.6), $K^{+}$ (-2.1) and $Na^{+}$ (-2.1) ions were tested for selectivity measurements using the separate solution method (SSM).

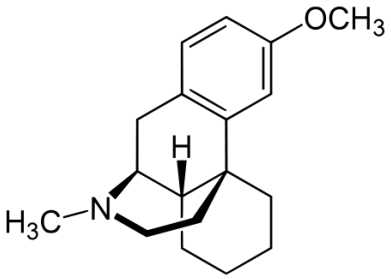



**Figure 18.** Dextromethorphan

*5.7. Antiasthmatic*

Clenbuterol (Fig. 19) is a sympathomimetic amine used by sufferers of breathing disorders as a decongestant and bronchodilator. People with chronic breathing disorders such as asthma use this as a bronchodilator to make breathing easier. A potentiometeric sensor was prepared and characterized for the determination of Clenbuterol in urine samples [91]. The MIP particles were prepared from (0.4 mmol) clenbuterol template, (2.5 mmol) methacrylic acid (MAA) or (0.83 mmol) methyl methacrylic acid (MMA) as functional monomers and (0.4 mmol) DVB as a cross- linker. The sensor revealed a detection limit of $7.0 \times 10^{-8}$ with a potentiometric slope range from 32.2 to 56.3 mV/decade over the pH range 7.0-8.5. The sensor reached its equilibrium in time < 3 min. The selectivity coefficient values were evaluated using the so called' modified separate solution method" (MSSM). No observed interference from the tested ions.

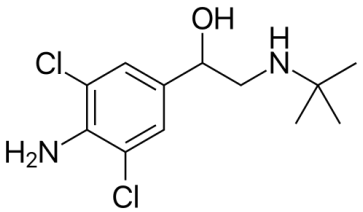



**Figure 19.** Clenbuterol

*5.8. Antihyperglycemic*

Sitagliptin is a relatively new oral anti-hyperglycemic drug used to treat type II diabetes. Kamel et. al [92] synthesized the potentiometeric solid contact potentiometric membrane sensors for sitagliptin (STG) incorporated with molecular imprinted polymer (MIP). The selective MIP particles consist of sitagliptin (1.5 mmol), methacrylic (MIP/MAA) or 2-vinyl pyridine (MIP/2-VP) (4.0 mmol) and ethylene glycol methacrylate (EGDMA) (20.0 mmol). At pH 5, wide range of concentration of sensors of $5.0x10^{-6}$-$1.0x10^{-2}$ M and $1.0x10^{-5}$- $1.0x10^{-2}$ M with slopes of about 52.7 - 40.5 mV/decade. The sensors revealed detection limits of $2.6x10^{-6}$ and $5.3x10^{-6}$ M upon the use of MAA and 2-VP monomers in the imprinted polymer, respectively. The selectivity coefficients for the Sitagliptin by fixed interference method towards inorganic cations such as $K^+$ (-2.1), $Na^+$ (-4.1) and commonly additives used in the preparation of drugs such as caffeine (-2.7) pheniramine (-1.9), creatine (-2.7), glutamine (-2.6) and dextromethorphan (-1.7) were reported.

### *5.9. Anticoagulant*

#### *5.9.1. Heparin*

Heparin (Fig. 20), is a medication which is used as an anticoagulant (blood thinner). Specifically it is used to treat and prevent deep vein thrombosis, pulmonary embolism, and arterial thromboembolism. It is also used in the treatment of heart attacks and unstable angina. It is given by injection into a vein. The anticoagulant heparin was imprinted using (0.1 mmol) heparin as a template, (0.8 mmol) methacrylic acid and (2.4 mmol) EGDMA as a functional monomer and cross-linker, respectively [93]. The sensing membrane was coated above a glassy carbon rod. The sensor revealed a potentiometric slope 148.1 mV/decade with a LLLR $3.0x10^{-9}$ M and a detection limit $1.0x10^{-9}$ M. Glucose (-1.6), epinephrine (-1.3), uric acid (1.3), glutamate (-1.1), fructose (-1.6), lysine (-1.3), salicylate(1.6) andascorbic acid (-1.3) were tested for selectivity measurements.

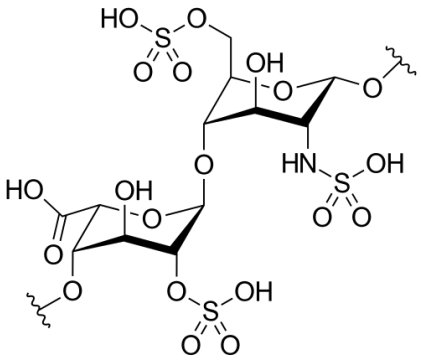



**Figure 20.** Heparin

L-ascorbic acid (Fig. 21), is a vitamin used as a dietary supplement and found in food. The disease scurvy is prevented and treated with vitamin C-containing foods or dietary supplements. A new potentiometeric based glassy carbon sensor for the determination of ascorbic acid (Vitamin C) in food and pharmaceutical samples was evaluated [94]. Pyrrol (50 mM) is electropolymerized in presence of

20 mM ascorbic acid over a glassy carbon surface. The sensor revealed a potentiometric slope 42.2-56.8 mV/decade with a LLLR $5.0x10^{-6}$ M with a detection limit $3.0x10^{-6}$ M. The pH of the tested solutions was adjusted at 5.5. The selectivity coefficients for ascorbate toward some anions such as, chloride (-2.3), hydrogen carbonate (-1.6), nitrate (-2.6), acetylsalicylate (-0.7) and acetate (-0.4) were evaluated. Matched potential method (MPM) was also reported for comparison.

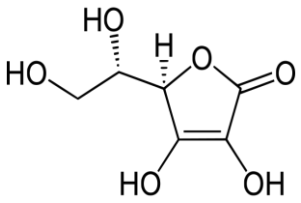



**Figure 21.** L-ascorbic acid

*5.11. Veterinary drug*

Imidocarb (Fig. 22), is a urea derivative used in veterinary medicine as an antiprotozoal agent for the treatment of infection with *Babesia* (babesiosis) and other parasites. A novel potnetiometric sensor integrated with MIP beads was prepared and characterized for Imidocarb determination [95]. MIP was synthesized using (0.1 mM) imidocarb, (1.0 mmol) MAA and (10 mM) EGDMA in 3 mL ACN. The PVC membrane sensor was prepared by dissolving 24.6 mg of PVC, 1.296 mg MIP, 45.3 mg *o*,NPOE or NPPE dispersed in 3.0 mL of THF. The slope, LLLR and limit of detection of the proposed sensor were 24.71 mV/decade, $1.0x10^{-5}$ and $2\times10^{-6}$ M, respectively. The pH range for measurements was 6.0-7.0.The selectivity coefficients towards imidocarb over $SO_4^{2-}$ (-2.0), $Cl^-$ (-2.1) $K^+$ (-2.1), $Fe^{3+}$ (-1.0) and glycine (-1.0) were reported.

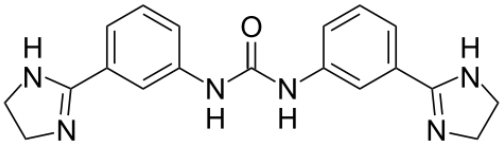



**Figure 22.** Imidocarb

## 6. CONLUSIONS

This review has attempted to summarize different molecular imprinting techniques especially in potentiometric sensors for pharmaceutical analysis within recent years. The recognition ability of MIPs for drugs, their stability, ease and low cost preparation make them very appealing for their use instead of traditional analytical techniques. Although most of the development of MIPs has been carried out in the biological and the clinical fields, their potential as selective approach in analytical techniques dedicated to the pharmaceutical field has been illustrated by many papers already published

as mentioned and in the future there will be a large number of different systems and companies using this exciting new technology, invading the analytical area.

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**Table 1**. Summary of MIPs Potentiometric based sensors

| Drugs | Synthesis and Preparation of MIP | Potentiometric sensor | LLLR (M) | LOD (M) | Slope (mV/ decade) | pH | Interferences and Selectivity coefficients (log K) | Selectivity methods | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| Antihistaminic | | | | | | | | | |
| *Cetirizine* | -MAA (0.915 mmol)<br>-EGDMA (3.82 mmol)<br>-Cetirizine (0.198 mmol)<br>-AIBN (0.088 mmol)<br>-40 ml $H_2O$:ACN (1:19)<br>Elution: 15 ml of methanol/acetic | Carbon paste electrode | $1.0\times10^{-6}$ | $7.0\times10^{-7}$ | 10.7-28.0 | 1.9 - 4.5 | Hydroxyzine (-2.2), Pyrrole (-3.9 ), Promethazine (-4.2), Aniline (-4.0), Salbutamol (-4.0), Piperazine (-3.2), Difenhydramine (-4.6), Pipyridine (-3.5), Triethyl amine (-3.3), Terfenadine (-4.4), $K^+$(-3.4), $NaNO_3$ (-4.8), NaCl (-4.8),$NaH_2PO_4$ (-4.3), $Ca^{+2}$(-3.6), $Mg^{2+}$(-3.8) | MPM | [36] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | acid (10:1, v/v) then 15 ml pure water | | | | | | | | |
| *Hydroxyzine* | -MAA (0.915 mmol) -EGDMA (3.82 mmol), -Hydroxyzine (0.198 mmol) -AIBN (0.088 mmol) of -40 ml chloroform Elution: 15 ml of methanol/acetic acid (10:1, v/v) then 15 ml pure water | Carbon paste electrode | $1.0\times10^{-6}$ | $7.0\times10^{-7}$ | 10.7-29.4 | 1.7 - 4.2 | Cetrizine(−1.8), Pyrrole(−4.2), Promethazine (−3.9) , Aniline (−4.2),Salbutamol sulfate (−4.1), Piperazine (-3.3), Pipyridine (-3.4), Metochlorpramide (-4.1), Terazosine (-4.5) , $K^+$ (-3.3) , $NaNO_3$ (-4.8), NaCl (-4.8), $Ca^{2+}$ (-3.5)$N(CH_2CH_3)_3Cl$ (-3.5), $Mg^{2+}$ (-4.0)<br><br>Cetrizine (-1.9), Pyrrole (4.3), Promethazine (-4.1), Aniline(−4.2),Salbutamol sulfate (−4.2), Piperazine(−3.3), Pipyridine(−3.5), Metochlorpramide(−4.4), Terazosine(−4.6), $K^+$(−3.5), $NaNO_3$ (−4.1), NaCl(−5.0), $Ca^{2+}$(−3.6) $N(CH_2CH_3)_3Cl$ (−3.7), $Mg^{2+}$(−4.2) | MPM<br><br>FIM | [35] |
| *Promethazine* | -Promethazine (1 mmol) -MAA or VP (7 mmol) -EGDMA or DVB (32mmol) -AIBN (0.1 g) Elution: acetone | Polymeric PVC membrane | $5.0\times10^{-7}$ | $1.0\times10^{-7}$ | 19.4-35.1 | 2.0 – 5.0 | Chloropromethazine(−2.1), Methylene blue (−2.9), Clozapine (−3.1), Salbutamol(−4.3), Methochlorpramide (−3.7), Hydroxyzine (−3.4), Aniline (−5.0), Pyrrole (−4.9), $Al^{3+}$(−4.9), $Zn^{2+}$ (−3.3), $Cu^{2+}$(−4.3), $Mg^{2+}$(−3.6) | MPM | [61] |
| Antiparasitic<br>Anthelmintic<br>*Levamisole* | -levamisole (0.0833 mmol) -MAA (0.33 mmol) -DVB (1.26 mmol) -AIBN (0.023 mmol) - 3 ml DMSO:ACN (2:8) Elution: methanol, ACN and alkaline solutions | Polymeric PVC membrane | $2.5\times10^{-6}$ | $1.0\times10^{-6}$ | 57.0 | 5.0–9.0 | 2-Aminobenzothiazole (−3.6), 2-Methyl-thiobenzothiazole (−3.9) Thiabendazole (−4.1),Urea (−4.6), Imidazole (−0.6), Benzoic acid (−1.7), Oxalic acid (−0.8), Salicylic acid (−0.1), Glucose (−5.3), $Ni^{2+}$(−0.2), $Na^+$ (−3.9), $Ca^{2+}$(−3.9), $K^+$(−5.4), $Mg^{2+}$(−4.6), $Ba^{2+}$(−5.4), $Pb^{2+}$(−5.6) , $NH_4$(−4.2), $Zn^{2+}$(−5.0) | SSM | [51] |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Antimalarial | | | | | | | | | |
| *Quinine* | -MAA or AA (5 mmol)<br>-EGDMA (30 mmol)<br>-BPO (0.5 mmol),<br>-Quinine (1mmol)<br>-3 ml CAN<br>Elution: methanol/acetic acid (9:1, v/v) then pure water | Gold base electrode solid contact | $4.0\times10^{-6}$ | $1.2\times10^{-6}$ | 47.7-61.3 | 4.8–8.0 | *Using MIP/MAA*<br>Cinchonidine (~ -2.5), Quinolone (~ -2.5), Ephedrine (~ -3.5), Caffeine (~ -3.5), Creatinine (~ -4.0), Urea (~ -3.5), Urate (~ -4.0), $NH_4^+$(~ -4.0), $K^+$(~ -4.0), $Mg^{2+}$ (~ -4.0), $Ca^{2+}$ (~ -4.5) | SSM | [42] |
| Antibiotic<br>Fluoroquinolones | | | | | | | | | |
| *Norfloxacin* | -Norfloxacin(1.0 mmol))<br>-MAA/VP (5.0 mmol)<br>-EGDMA (20.0 mmol)<br>-BPO (0.32 mmol)<br>-3.5 ml MeOH<br>Elution: methanol/acetic acid (5:1, v/v) | Graphite electrode | $4.0x10^{-6}$ | $1.3x10^{-6}$ | 20.0-67.1 | 2.0–6.0 and 8.0-11.0 | *Using MIP/MAA*<br>Enrofloxacin (~ -0.9), Tetracycline (~ -1.0), Sulfadiazine (~ -1.3), Dopamide (~ -1.1), Glucose (~ -1.2), hydroxylamine (~ -1.1), Creatinine (~ -1.4), $NH_4^+$ (~ -1.2), $Li^+$ (~ -1.0) | MSM | [43] |
| *Enrofloxacin* | −Enrofloxacin(0.5 mmol)<br>-MAA (5.0 mmol) or VP/MAA(2.5 mmol) each<br>-EGDMA (24.5 mmol)<br>- BPO (0.32 mmol)<br>- 3ml MeOH.<br>Elution: methanol/acetic acid (5:1, v/v) | Graphite solid contact | $4.0x10^{-7}$ | $2.0\times10^{-7}$ | 47.4-65.2 | 4.0–7.0 | *Using MIP/MAA*<br>Glycine (~ -3.0), Ascorbic acid (~ -3.0), Creatinine (~ -2.5), Norfloxacin (~ -2.5), Ciprofloxacin (~ -1.0), Tetracycline (~ −1.0), $K^+$ (~ −3.0), $Ba^+$ (~ -4.5), $Mg^{2+}$(~ -4.5), $Ca^{2+}$ (~ -4.5) | SSM | [62] |
| *Ciprofloxacin* | -Ciprofloxacin (0.5 mmol)<br>-MAA or VP (3.0 mmol)<br>-EGDMA (15.0 mmol)<br>-BPO (0.32 mmol)<br>-3 ml Methanol/water (7:3)<br>Elution: methanol/acetic acid (5:1, v/v) | Graphite electrode | $2.0\times10^{-5}$ | $1.0\times10^{-5}$ | 26.8-50.0 | 3.0–4.5 and pH > 9 | *Using MIP/MAA*<br>Trimethoprim (−2.8), Enrofloxacin(−1.9), Tetracycline (−2.6), Cysteine (−2.4), Galactose (−2.5), Hydroxylamine (−2.4), Creatinine (−2.4), $NH_4^+$(−2.51), Sucrose (−2.6), Glucose (−2.6), Sulphamerazine(−2.3), Sulfadiazine (−2.2) | MSM | [52] |
| | | | | | | | Trimethoprim (1.6), Enrofloxacin (-.0.9), Tetracycline (-0.7), Cysteine (-1.0), Galactose (-1.9), Hydroxylamine (-1.0), Creatinine (-1.9), $NH_4^+$(-2.3), Sucrose (-1.0), Glucose (-0.6), Sulphamerazine (-0.1), Sulfadiazine (-2.3 | SSM | |
| | -Ciprofloxacin (0.11 mmol)<br>-MAA or VP or AN (0.88 mmol)<br>-EGDMA (2.2 mmol)<br>-BPO (0.25 mmol)<br>-5 ml ACN<br>Elution: methanol:acetic acid and ACN:acetic acid (1:1v/v) | Electrode glass body | $3.2\times10^{-5}$ | $2.1\times10^{-5}$ | 9.85-30.3 | 3.0-5.0 | Cysteine (-2.5), Glutamine (-2.1), Phenylalanine (-2.3), Histidine (-2.0), Norfloxacin (0.3), Ofloxacin (0.3), Enrofloxacin (0.4), $Na^+$ (-2.8), $K^+$ (-2.5), $Ca^{2+}$ (-2.2), $Mg^{2+}$(-2.0). | FIM | [46] |
| Tetracyclines | | | | | | | | | |
| *Chlortetracycline* | -Chlortetracycline (0.5mmol)<br>-MAA or AA (5.0 mmol)<br>-EGDMA (20.0 | Graphite electrode | $4.6\times10^{-5}$ | $4.1\times10^{-5}$ | 48.6-68.6 | 2.5-13.0 | *Using MIP/MAA*<br>Ciprofloxacin(~ -0.6), Sulfamethazine (~ -0.6), Sulfathiazole (~ -2.1), Creatinine (~ -1.8), Dopamine (~ -1.6), | SSM | [63] |

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|---|---|---|---|---|---|---|---|---|---|
| | mmol)<br>-BPO (0.32 mmol)<br>-3 ml ACN<br>Elution: ACN | | | | | | Glucose (~ -1.6), Cysteine (~ -1.6),Sacarose (~ -1.6), $Ca^{2+}$(~ -1.6), $Li^{+}$ (~ -2.6), $Mg^{2+}$(~ -4.1), $Na^{+}$ (~ -2.1),<br>$Ba^{2+}$ (~ -3.6) | | |
| | | | | | | | Ciprofloxacin(~ -1.8), Sulfamethazine (~ -2.8), Sulfathiazole (~ -3.3), Creatinine (~ -2.8), Dopamine (~ -0.3), Glucose (~ -3.5),Cysteine (~ -3.3), Sacarose (~ -3.5), $Ca^{2+}$ (~ -3.5), $Li^{+}$ (~ -4.0), $Mg^{2+}$ (~ -2.8), $Na^{+}$ (~ -2.8), $Ba^{2+}$ (~ -3.3) | MSM | |
| *Doxyxycline* | -MAA or Acrylamide (4 mmol), or MAA and AA (2 mmol each)<br>-EGDMA (20 mmol)<br>-3 ml ACN<br>-BPO (80 mg)<br>Acrylamide<br>Elution: methanol/acetic acid (5:1 v/v) | Graphite electrode | $5.0\times10^{-6}$ | $1.6\times10^{-6}$ | 50.1-54.8 | 2.0–3.5 | *Using MIP/MAA*<br>Lactose (~ -1.2), Creatinine(~ -1.3), Glucose (~ -1.5), Glycin(~ -1.8), Chlorotetracycline(~ -0.1), Oxytetracycline(~-1.4), Sulfadiazine (~ -1.6), Tetracycline (~ -0.5) | SSM | [53] |
| *Oxytetracycline* | -Oxytetracycline(0.5 mmol)<br>-MAA or AA (5.0mmol)<br>-EGDMA (24.5 mmol)<br>-BPO (0.32 mmol)<br>-3mL Methanol<br>Elution: ACN/acetic acid (5:1, v/v). | Graphite paste | $7.6\times10^{-6}$ | $1.0\times10^{-6}$ | 39.8–64.8 | 2.0-5.0 | *Using MIP/MAA*<br>Ciprofloxacin(~ -0.2), Creatinine (~ -1.2), Nalidixic acid (~ -1.2), Sulfadiazine(~ -1.7), Cysteine (~ -1.3), Hydroxylamine(~ -1.5), Lactose (~ -2.0), Glycine(~ -1.7) | MSM | [44] |
| | | | | | | | Ciprofloxacin(~ -0.5), Creatinine (~ -1.5), Nalidixic acid (~ -1.7), Sulfadiazine(~ -1.7), Cysteine (~ -1.3), Hydroxylamine(~ -1.7), Lactose(~ -2.0), Glycine(~ -1.7) | SSM | |
| *Tetracycline* | -Tetracycline (0.5 mmol)<br>-VP (5 mmol)<br>-EGDMA (24.5 mmol)<br>-BPO (0.32 g)<br>-3 ml ACN<br>Elution: ACN/water/acetic acid (92.5/2.5/5, v/v/v) | Graphite electrode | $1.6\times10^{-5}$ | $1.3\times10^{-5}$ | 24.9-76.9 | 3.0-5.0 | Oxycycline (-0.6), Creatinine (-1.0), Naldixic acid (-1.7), Glycine (-1.9), $NH_2OH.HCl$ (-0.6), Cysteine (-0.7), Alanine (-0.6), Tartaric acid (-1.2), Citric acid (-1.1), $NH_4^{+}$ (-1.4), $Na^{+}$ (-1.8), $K^{+}$(-1.4), $Ba^{2+}$(-3.6), $Ca^{2+}$ (-3.5), $Mg^{2+}$ (-3.8) | SSM | [45] |
| | -Tetracycline (0.1 mmol)<br>-$La(NO_3)_3.6H_2O$ (0.1 mmol)<br>-MAA (0.066ml)<br>-5 ml of methanol–water (9:1, v/v).<br>-EGDMA (0.944 ml)<br>-AIBN (12 mg)<br>Elution: methanol–acetic acid (9:1, v/v) | Polymeric PVC membrane | $6.0\times10^{-8}$ | $2.5\times10^{-8}$ | 57.6 | 2.0-4.0 | Alanine (< -4.0), Valine (< -4.0), Lysine (< -4.0), Maltose (< -4.0), Glucose (< -4.0), Lactose (< -4.0) | SSM | [54] |

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|---|---|---|---|---|---|---|---|---|---|
| | -Tetracycline (0.1 mmol)<br>-$La(NO_3)_3.6H_2O$ (0.1 mmol)<br>-MAA (0.088 ml)<br>-5 ml of methanol–water (9:1, v/v).<br>-EGDMA (0.944 ml)<br>-AIBN (12 mg)<br>Elution: methanol–acetic acid (9 : 1, v/v) | PVC tube | $2.0\times10^{-8}$ | $1.0\times10^{-8}$ | 12.6-59.8 | 2.0–4.0 | Glycine (-4.6), Alanine (-4.4), Valine (-4.1), Leucine (-4.7), Lysine (-4.3), Maltose (-4.7), Glucose (-4.2), Lactose (-4.1), Oxytetracycline (-1.2), Chlortetracycline (-1.3), Doxycycline (-1.2), $Na^+$ (-5.5), $Al^{3+}$ (-4.1), $K^+$(-5.2), $Fe^{3+}$ (-4.6), $NH_4^+$ (-5.3), $Zn^{2+}$ (-5.0), $Co^{2+}$ (-4.2), $Ca^{2+}$ (-4.1), $Ni^{2+}$ (-4.6), $Sr^{2+}$ (-4.1), $Mg^{2+}$ (-4.6), $Cu^{2+}$ (-4.9), $Fe^{2+}$ (-4.6), $Mn^{2+}$ (-4.4), $Ba^{2+}$(-4.8) | SSM | [47] |
| Macrolides<br>*Azithromycin* | -0.5 mmol Azithromycin<br>-3.0 mmol (AA or VP)<br>-15 mmol EGDMA - 0.32 mmol BPO<br>-4 ml methanol<br>Elution: 30% acetic acid in water | Coated graphite electrode | $5.0\times10^{-7}$ | $2.0\times10^{-7}$ | 12.2-57.1 | 3.0 - 8.0 | Glucose (-3.6), Sucrose (-3.2), Lactose (-3.1), Glycine (-3.4), Starch (-4.1),Magnesium stearate (-4.2), $Na^+$ (-2.5), $K^+$ (-2.1),$Ca^{2+}$ (-2.3), $Mg^{2+}$ (-3.9), $Zn^{2+}$(-2.4), $Cd^{2+}$ (-2.3), $Fe^{3+}$(-3.0) | SSM | [64] |
| Penicillins<br>*Amoxicillin* | -Amoxicillin (0.5 mmol)<br>-MAA (5.0 mmol), VP (5.0 mmol) and AAMPSO (5.0 mmol)<br>-EGDMA (24.5 mmol)<br>-BPO (0.32 mmol)<br>-3 ml methanol<br>Elution: methanol/acetic acid (4:1, v/v) | Graphite electrode | $3.3\times10^{-5}$ | $1.8\times10^{-5}$ | 11.9-73.4 | 4.0-5.0 | *Using MIP/MAA*<br>Dopamine (~ 0.5),Sacarose(~ -1.5), Fructose(~ -1.6), Glucose(~ -1.6), Cysteine(~ -0.5), Creatinine(~ -1.0) | SSM | [65] |
| Dihydrofolate reductaseinhibitor*Trimethoprim* | -Trimethoprim ( 0.26 g)<br>-MAA or VP (0.35 g)<br>-TRIM (4 g)<br>-BPO (0.096 g)<br>-3 mL of chloroform<br>Elution: methanol/acetic acid (50:50, v/v) | Graphite solid contact | $4.0\times10^{-7}$ | $3.0\times10^{-7}$ | 49.4-99.7 | 2.0–6.0 | *Using MIP/MAA*<br>Sulfadiazine (< 2700), Tryptophan (< 2040), Cysteine(<1750), Valine(<1170),Alanine(<900),Glycine(<750)<br>$Fe^{+2}$ (~ -5.0), $Cr^{+3}$(~ -4.5), $K^+$ (~ -3.6), $Na^+$(~ -4.0), $NH_4^+$(~ -4.5), $Ni^{2+}$(~ -3.0), $Mn^{2+}$(~ -5.0), $AL^{3+}$ (~ -5.6), $Pb^{2+}$(~ -4.5) | MPM (expressed as tolerance level $mgL^{-1}$)<br>FIM | [66] |

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|---|---|---|---|---|---|---|---|---|---|
| Sulphonamides*Sulfadiazine (SDZ) Sulfamethoxazole (SMX)* | - Sulphonamides (12.5 mg)<br>- APTES (1.5 ml)<br>- DPTS (1.5 ml)<br>- Methanol (4.0 ml)<br>-TEOS (0.5 mL)<br>-HCl (0.1 M, 0.3 mL)<br>-desionized water (2.5 mL) Elution: water | Sol-gel Graphite electrode | SDZ $9.0\times10^{-6}$<br>SMX $5.1\times10^{-6}$ | SDZ $2.7\times10^{-6}$<br>SMX $1.7\times10^{-5}$ | SDZ 12.0-60.2<br>SMX 36.1-59.5 | SDZ $9.0\times10^{-6}$<br>SMX $5.1\times10^{-6}$ | *Using MIP/ISG*<br>SDZ<br>$CO_3^{2-}$(−1.5), $Cl^-$ (−1.7), $F^-$ (−1.5), $HCO_3^-$(−1.6), $NO_3^-$ (−0.95), $NO_2^-$ (−1.02), $PO_4^{3-}$(−3.9), $CN^-$ (−1.2) $SO_4^{2-}$(−0.51) , Borate (−2.9), Persulphate(−0.41), Citrate (−2.8), Tartrate (−2.7), Salicylate (−1.7) , Ciprofloxacin (−0.70), Creatinine (−1.0), Cysteine (−1.2), Dopamine (−1.1), Galactose(−1.0), Glucose (−1.3) , Sulphamerazine(−1.1), Sulfathiazole (−0.50), Tetracycline (−0.90)<br><br>SMX<br>$CO_3^{2-}$ (−1.6), $Cl^-$( −1.9), $F^-$ (−1.7), $HCO_3^-$ ( −1.8), $NO_3^-$ (−1.3), $NO_2^-$ (−1.5), $PO_4^{3-}$ (−3.8), $CN^-$ (−1.3), $SO_4^{2-}$ (−3.2), Borate (−3.0), Persulphate(−0.42), Citrate (−2.2),Tartrate (−2.5), Salicylate (−1.7) | MSM | [48] |
| *Sulfamethoxazole* | -MAA (0.915 mmol)<br>-EGDMA (3.82 mmol)<br>-Sulfamethoxazole (0.198 mmol)<br>-AIBN (0.088 mmol)<br>-40 ml ACN.<br>Elution: 15 ml methanol/acetic acid (10:1, v/v) then 15 ml pure water | Polymeric PVC membrane | $1.0\times10^{-7}$ | $6.3x10^{-8}$ | 5.8-64.2 | pH< 2.2 and pH >6 | Sulfasalazine (~ -3.8), Sulfacetamide (~ -3.1), Sulfadiazine (~ -1.6), Cefixime (~ -3.5), Ceftriaxone (~ -3.6), Trimethoprim (~ -3.0), Glucose (~ -4.0), $Na^+$ (~ -2.0), $NH_4^+$ (~ -2.5), $Ca^{2+}$(~ -2.3), $Ni^{2+}$(~ -2.4), $Sn^{+2}$(~ -2.7), $Zn^{2+}$ (~ -2.0)<br><br>Sulfasalazine (~ -2.9), Sulfacetamide (~ -3.1), Sulfadiazine (~ -1.5), Cefixime (~ -3.8), Ceftriaxone (~ -4.5), Trimethoprim (~ -3.5), Glucose (~ -3.5), $Na^+$ (~ -3.7), $NH_4^+$ (~ -2.6), $Ca^{2+}$(~ -2.7), $Ni^{2+}$(~ -2.5), $Sn^{+2}$ (~ -3.0), $Zn^{2+}$(~ -3.0) | SSM<br>MPM | [67] |
| | -MAA (0.915 mmol)<br>-EGDMA (3.82 mmol)<br>-Sulfamethoxazole (0.198 mmol)<br>-AIBN (0.088 mmol)<br>-40ml ACN<br>Elution: methanol/acetic acid (10:1, v/v) | Carbon paste electrode | $6.0\times10^{-8}$ | $3.5 \times 10^{-9}$ | 34.7-57.2 | 1.5-2.5 and pH >5.5 | Sulfamerazine(~ -0.5), Sulfathiazole (~ -0.5), Sulfadiazine (~ -0.5), Sulfasalazine (~ -2.1),Sulfacetamide (~ -1.9), Cefixime(~ -2.5), Ceftriaxone (~ -1.9), Glucose (~ -2.9), $Na^+$ (~ -1.0), $NH_4^+$ (~ -2.0), $Ca^{2+}$(~ -2.0), $Li^+$(~ -1.0), $K^+$(~ -1.5)<br><br>Sulfamerazine(~ -0.5), Sulfathiazole (~ -0.5), Sulfadiazine (~-1.0), Sulfasalazine (~ -2.0),Sulfacetamide (~ -2.0),Cefixime(~ -2.5), Ceftriaxone (~ -1.5), Glucose (~ -1.0),$Na^+$ (~ -1.1), $NH_4^+$ (~ -1.5), $Ca^{2+}$(~ -1.9), $Li^+$(~ -1.0), $K^+$ (~ -2.0) | SSM<br>MSM | [68] |

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| Others<br>*Chloramphenicol* | -Chloramphenicol (1.0mmol)<br>-MAA (5.0 mmol)<br>-50 ml Chloroform<br>-EGDMA (30.0 mmol)<br>-AIBN (0.2 mmol)<br>Elution: methanol then ACN | Nano-composite carbon paste electrode | 1.0 $\times10^{-6}$ | 1.0 $\times10^{-6}$ | 6.5-59.1 | 3.0-5.0 | Glucose (-3.8), $Na^+$ (< -4.0), $K^+$ (< -4.0), $Mg^{2+}$ (-3.9), $Ca^{2+}$ (< -4.0), $Cl^-$ (< -4.0), $CO_3^{-2}$ (< -4.0), $Co^{2+}$ (-3.8) | MPM | [69] |
| Central nervous system<br>Alzheimer's disease<br>*MemantineHCl* | | | | | | | | | |
| | -MAA (0.915 mmol)<br>-EGDMA (3.82 mmol)<br>-Memantine (0.238 mmol)<br>-AIBN (0.088 mmol)<br>-10 ml chloroform.<br>Elution:15 ml methanol/acetic acid solution (10:1, v/v) | Pyrex tube | $1.0\times10^{-5}$ | $6.0\times10^{-6}$ | 3.5-57.4 | 5.0-9.0 | Oxalic acid (-2.7), Glucose (-3.4), Citalopram HBr (-3.2), Sertraline HCl(-2.6), Gabapentin HCl (-3.3), Chlordiazepoxide (-3.2), Nicotinic acid (-3.2) , $Na^+$ (-3.9), $Sn^{2+}$(-3.6), $Ca^{2+}$(-4.0), $K^+$ (-3.2), $NH_4^+$ (-3.2), $Zn^{2+}$(-3.3), $Ni^{2+}$(-4.9), $Mg^{2+}$(-4.1), $Ba^{2+}$(-3.8) | SSM | [49] |
| | | | | | | | Oxalic acid (-3.0), Glucose (-3.6), Citalopram HBr (-3.1), Sertraline HCl(-2.7), Gabapentin HCl (-1.3), Chlordiazepoxide (-2.9), Nicotinic acid (-2.5),$Na^+$ (-3.5), $Sn^{2+}$ (-2.9), $Ca^{2+}$(-3.1), $K^+$ (-3.2), $NH_4^+$ (-3.1), $Zn^{2+}$ (-3.4), $Ni^{2+}$(-3.4), $Mg^{2+}$(-3.2), $Ba^2$ (-3.5) | MPM | |
| *Rivastigmine* | -MAA (0.915 mmol)<br>-EGDMA (3.82 mmol)<br>-Rivastigmine (0.198 mmol)<br>-AIBN (0.088 mmol)<br>-40 ml CAN<br>Elution: 15 mL methanol/acetic acid (10:1, v/v) then 15 mL pure water | Polymeric PVC membrane | $1.0\times10^{-5}$ | $6.3x10^{-6}$ | 5.0-30.7 | 4.0–8.0 | 3-(1-dimethyl amino ethyl) phenol (-0.1), $Na^+$ (-3.5), $K^+$(-3.2), $Ca^{+2}$ (-3.1)Alanine (-2.2), Glycine (-1.5), Oxalic acid (-2.6), Gabapentin (-0.7), Sertraline HCl (-0.6), Citalopram (-0.6) | SSM | [70] |
| | | | | | | | 3-(1-dimethyl amino ethyl) phenol (-0.3), $Na^+$ (NI), $K^+$(NI), $Ca^{+2}$(NI), Alanine (NI), Glycine (NI), Oxalic acid (NI), Gabapentin (-1.3), Sertraline HCl (-1.1), Citalopram (-1.1) | MPM | |
| Antipsychotic<br>*Chlorpromazine* | -Chlorpromazine (0.25 mmol)<br>-MAA, AAMPSO or VP (2.0 mmol)<br>-EGDMA or TRIM (10.0 mmol)<br>-BPO ( 0.50 mmol)<br>-3 ml of Methanol, ethanol, ACN or THF.<br>Elution: Methanol/acetic acid (5:1, v/v) | Graphite electrode | $4.1\times10^{-6}$ | $1.3\times10^{-6}$ | 47.8-67.4 | 2.0–5.5 | *Using MIP/MAA*<br>Oxytetracycline (~ -2.8), Doxytetracycline (~ -2.9), Ciprofloxacin (~ -2.3),Enrofloxacin (~ -3.0), Nalidixic acid (~ -3.5), Sulfadiazine (~ -2.6), Trimethoprim (~ -2.9), Glycine (~ -2.1), Hydroxylamine (~ -2.6), Cysteine (~ -2.3), Creatinine (~ -1.5) | SSM | [71] |
| | | | | | | | Oxytetracycline (~ -1.6), Doxytetracycline (~ -1.4), Ciprofloxacin (~ -1.7), Enrofloxacin (~ -1.4), Nalidixic acid (~ -1.4), Sulfadiazine (~ -2.5), Trimethoprim (~ -1.1), Glycine (~ -1.7), Hydroxylamine (~ -1.8), Cysteine | MSM | |

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| | | | | | | | (~ -1.4), Creatinine (~ -1.5) | | |
| *Clozapine* | -Clozapine (0.25-0.5 mmol)<br>-MAA (2.5 mmol)<br>-5 ml Chloroform<br>-EGDMA (12.5 mmol)<br>-AIBN<br>Elution: methanol–acetic acid (8:2, v/v) | Nano-composite carbon paste electrode | $1.0 \times 10^{-6}$ | $1.0 \times 10^{-6}$ | 5.2-28.8 | 3.5-5.0 | Lactose (-3.3), Glucose (-3.2), $Na^+$ (< -4.0), $K^+$ (< -4.0), $Mg^{2+}$ (-4.0), $Ca^{2+}$ (< -4.0), $Cl^-$ (< -4.0), $CO_3^{-2}$ (< -4.0), $Co^{2+}$ (-3.9), $NH_4^+$ (-3.3) | MPM | [72] |
| Anticonvulsant | | | | | | | | | |
| *Lamotrigine* | -Lamotrigine(0.4 mmol)<br>-MAA (2 mmol)<br>-EGDMA (8 mmol)<br>-AIBN (0.06 mmol)<br>-7 ml THF/ACN (4:3 v/v)<br>Elution: THF/TFA 90% (50–50 v/v) | Pyrex tube | $1.0 \times 10^{-6}$ | $8.0 \times 10^{-7}$ | 3.0-30.8 | 1.0-5.0 | Phenobarbital (-3.1), 3-Amino-1,2,4 triazin (-3.1), 2,4-Diamino-6 phenyl-1,2,4 triazin (-2.7), 3-Amino-5,6 dimethyl-1,2,4 triazin (-2.7), $Cu^{2+}$ (-2.4), $Na^{2+}$ (-2.8), $Mg^{2+}$ (-3.0), $Ca^{2+}$(-2.9) | MPM | [50] |
| Antidepressant | | | | | | | | | |
| *Sertraline HCl* | -Sertraline hydrochloride (0.088 mmol)<br>-MAA (0.915 mmol)<br>-EGDMA (3.82 mmol)<br>-AIBN (0.198 mmol)<br>-40 ml chloroform.<br>Elution: acetone/methanol then methanol/acetic acid (10:1, v/v, of 98% methanol and pure acetic acid) | Pyrex tube | $1.0 \times 10^{-6}$ | $8.0 \times 10^{-7}$ | 12.3-63.7 | 2.0-7.0 | Alprazolam (~ -2.9), Amitriptyline (~ -3.2), Bupropion (~ -2.9), Citalopram (~ -3.0), Duloxetine (~ -3.1), Fluoxetine (~ -3.1), Fluvoxamine (~ -3.1), Mirtazapine (~ -3.3),Trazodone (~ -3.5), Venlafaxine (~ -2.8), $Na^+$ (~ -3.6), $Mg^{2+}$(~ -3.2), $Ca^{2+}$(~ -3.2), $K^+$ (~ -3.4), $Ba^{2+}$(~ -3.3), $Zn^{2+}$ (~ -3.2), $Ni^{2+}$ (~ -3.1), $Sn^{2+}$ (~ -3.0), $NH_4^+$ (~ -3.3) | SSM | [73] |
| Neurotransmitter | | | | | | | | | |
| *Dopamine* | -MWCNTs-g-AAm-CH=$CH_2$ with IA<br>-EGDMA<br>-AIBN<br>-5 ml of DMF<br>Elution: methanol and acetic acid (9:1, v/v) | MWCNTs | $1.0 \times 10^{-9}$ | $1.0 \times 10^{-9}$ | 7.9-54.0 | 7.0 | $NH_4^+$ (-0.6), $Na^+$ (-1.6), $K^+$ (-0.4), $Ca^{2+}$ (-0.2), $Mg^{2+}$ (-1.4), Glucose (-0.9), Uric acid (-0.2), Cysteine (BDL), Citric acid (BDL), Ascorbic acid (BDL) | SSM | [74] |

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| Antihypertensive<br>Beta-blocker<br>*Metoprolol tartarate* | -Metoprolol (0.25 mmol)<br>-MAA (0.5 mmol)<br>-EGDMA (10 mmol)<br>-AIBN (0.25 mmol)<br>-20 ml chloroform methanol/acetic acid (70 :30, v/v) | Graphite Electrode | $1.0 \times 10^{-7}$ | $1.3 \times 10^{-7}$ | 18.1-55.9 | 3.5-10.5 | Urea (-4.4), Benzoic acid (-1.6), Glucose (-5.2), Oxalic acid (-0.68), $Mg^{2+}$ (-4.1), $Ca^{2+}$ (-3.7), $Ba^{2+}$ (-4.5), $Pb^{2+}$ (-3.5), $Na^{+}$ (-3.0), $Cu^{2+}$ (-4.0), $K^{+}$ (-3.3), $Ni^{2+}$ (-2.7), $NH_4^{+}$ (-3.1), $Zn^{2+}$ (-3.0) | SSM | [75] |
| *Propranolol* | -Propranolol (0.53 mmol)<br>-ACN (40 mL)<br>-MAA (1.31 mmol)<br>-DVB (2.63 mmol)<br>-TRIM(1.01 mmol)<br>-AIBN (2 %)<br>Elution: methanol containing 10 % acetic acid (v/v) | Polymeric PVC membrane | $1.0\times10^{-5}$ | $1.0\times10^{-5}$ | 32.8-56.7 | 6.0 | $K^{+}$ (-1.6), $NH_4^{+}$ (-2.1), Naacetate (-2.3), $NaNO_3$ (-2.4), $Mg^{+2}$ (-3.5), $Ca^{+2}$(-3.5),Urea (-1.6), Metoprolol (-0.1), Atenolol (-0.7) | SSM | [76] |
| Angiotensin receptor blocker<br>*Losartan* | -MAA (2.0mmol)<br>-EGDMA (13.6mmol)<br>-Losartan (0.2 mmol)<br>-AIBN (0.76 mmol)<br>-30 ml chloroform<br>Elution:methanol:acetic acid (9:1, v: v). | Carbon paste electrode | $3.0\times10^{-9}$ | $1.8\times10^{-9}$ | 7.2-59.6 | 6.0-8.5 | Trazodone (-3.3), Valsartan (-3.1), Povidone (-5.8), Hydrochlorothiazide (-4.6), Ramipril (-4.1), Amlodipine (-4.1) | MPM | [77] |
| Antitussive and Drug of abuse<br>*Dextromethorphan* | - Dextromethorphan (0.1 mmol)<br>- MAA or AN (2.0 mmol)<br>- EGDMA (20 mmol)<br>- BPO (70 mg)<br>-3 ml ACN<br>Elution: methanol: acetic acid (9:1) then ACN: acetic acid (1:1) | Polymeric PVC membrane | $1.8\times10^{-6}$ | $6.3 \times 10^{-7}$ | 40.4-57.9 | 4.0-10.0 | *Using MIP/MAA* Morphine (-2.0), Codeine (-1.8), Ethylmorphine (-1.5), Ketamine (-1.6), Ephedrine (-1.7),Phenyl propanolamine (-1.9) | FIM | [41] |
| | - Dextromethorphan (0.5 mmol)<br>- AA or VP (3.0 mmol)<br>- EGDMA (15 mmol)<br>- BPO (0.3 mmol)<br>-3 ml chloroform<br>Elution: 30% acetic acid in water | Polymeric PVC membrane and Graphite Coated Electrode | $5.0\times10^{-7}$ | $1.0 \times 10^{-7}$ | 19.9-78.1 | 2.0-9.0 | Glucose (-1.8), Paracetamol (-1.9), Ketorolac (-1.9),Amoxicillin (-2.1), $Na^{+}$(-2.1), $K^{+}$ (-2.1), $Ba^{2+}$ (-1.6) | SSM | [78] |
| Antiasthmatic<br>*Clenbuterol* | -Clenbuterol (0.4 mmol)<br>-MAA (2.5 mmol)<br>-MMA (0.83mmol)<br>-DVB 80 (0.4 mmol)<br>-TRIM (1.0 mmol)<br>-AIBN (0.5 mmol)<br>-40 ml of methanol<br>Elution: methanol/acetic acid (9:1, *vlv*) and methanol | Polymeric PVC membrane | $1.0\times10^{-7}$ | $7.0 \times 10^{-8}$ | 32.2-56.3 | 7.0–8.5 | Ethylenediamine$^{2+}$(-6.1), Ractopamine$^{+}$ (-2.5), $Na^{+}$ (-7.6), $Cu^{2+}$(-7.4), $K^{+}$ (-5.9), $Zn^{2+}$ (-7.8), $H^{+}$ (-6.9), $Mg^{2+}$ (-7.8), $NH_4^{+}$ (-6.2), $Ca^{+2}$(-7.4) | Bakker's method | [79] |

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| Antihyperglycemic | | | | | | | | | |
| *Sitagliptin* | -Sitagliptin (1.5 mmol)<br>-MAA or VP (4 mmol)<br>-EGDMA (20 mmol)<br>-BPO (80 mg)<br>-3 ml ACN<br>Elution: methanol/acetic acid (1:1) and ACN : acetic acid (1:1) | Graphite solid contact | $2.5\times10^{-6}$ | $2.0\times10^{-6}$ | 40.5-64 | 4.4 - 6.5 | *Using MIP/MAA*<br>Fluoxetine (-2.8), Caffeine (-2.7) Pheniramine (-1.9), Dextromethorphan (-1.7), Nicotine (-1.7), Pseudoephedrine (-1.8), Diphenhydramine (-3.0), Metformin (-2.1), Creatine (-2.7), Glutamine (-2.6), Creatinine (-2.9), Histidine (-2.4), Quinine (-1.5), $K^+$ (-2.1), $Na^+$ (-4.1) | FIM | [80] |
| Anticoagulant | | | | | | | | | |
| *Heparin* | -Heparin (0.1 mmol)<br>-MAA (0.8 mmol)<br>-EGDMA (2.4 mmol)<br>-AIBN (1 mmol)<br>-Benzene (50 ml)<br>Elution: methanol/acetic acid (9:1, v/v) | glassy carbon rod | $3.0\times10^{-9}$ | $1.0\times10^{-9}$ | 148.1 | 6.0 - 8.5 | Glucose (-1.6), epinephrine (-1.3), uric acid (1.3), glutamate (-1.1), fructose (-1.6), lysine (-1.3), salicylate(1.6),ascorbic acid (-1.3) | NR | [81] |
| Vitamin C | | | | | | | | | |
| *Ascorbic acid* | -50 mMpyrrole<br>-20 mM ascorbic acid | Glassy carbon | $5.0\times10^{-6}$ | $3.0\times10^{-6}$ | 42.2-56.8 | 5.5 | Tartrate (-2.4), Citrate (-0.5), $CH_3COO^-$ (-0.4), Acetylsalicylate (-0.7), $SO_4^{2-}$ (-28), $C_2O_4^{2-}$(-2.3), $NO_3^-$ (-2.6), $Cl^-$(-2.6), $HCO_3^-$ (-1.6) | SSM | [82] |
| | | | | | | | Tartrate (NI), Citrate (-2.0), $CH_3COO^-$ (-1.9), Acetylsalicylate (-1.1), $SO_4^{2-}$ (NI), $C_2O_4^{2-}$(NI), $NO_3^-$(NI), $Cl^-$ (NI), $HCO_3^-$ (-2.1) | MPM | |
| Veterinary drug | | | | | | | | | |
| *Imidocarbdipropionate* | -0.1 mMimidocarb<br>-1.0 mM MAA<br>-10.0 mM EGDMA<br>- 0.06 g BPO<br>-3 mL ACN<br>Elution: methanol, acetic acid and alkaline solutions | Polymeric PVC membrane | $1.0\times10^{-5}$ | $2\times10^{-6}$ | 24.71 | 6.0-7.0 | $NaSO_4$(-2.0), $Mg^{+2}$(-2.1), NaCl (-2.1), $K^+$(-2.1), $Ca^{+2}$(-2.1), $Fe^{+3}$ (-1.0), Diminazeneaceturate(-2.1), Glycine(-1.0) | NR | [83] |

*NR: Not reported, NI: Non-interferent, BDL: Below detection limit