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Fighting against Bacterial Resistance to Penicillins with CDs

Introduction

Penicillin antibiotics were amongst of the earliest discovered drugs effective against bacterial infections. Penicillins are widespread in nature and lethal to growing bacteria because they inhibit their cell wall synthesis. The penicillin was accidentally discovered by Scottish scientist and Nobel laureate Alexander Fleming in 1928. Penicillins are still widely used today, though many types of bacteria developed resistance. It has become a major healthcare problem nowadays that bacteria resistant to commonly used antibiotics infect large communities [1]. Bacteria have been extremely creative in developing various mechanisms of resistance. The simple structure of bacterial DNA enables fast mutations adapting to the environment.

All penicillins belong to β-lactam antibiotics. The common element of the structure is the 4-membered β-lactam ring. The structure of some representatives of the penicillin family can be seen in Fig. 1.

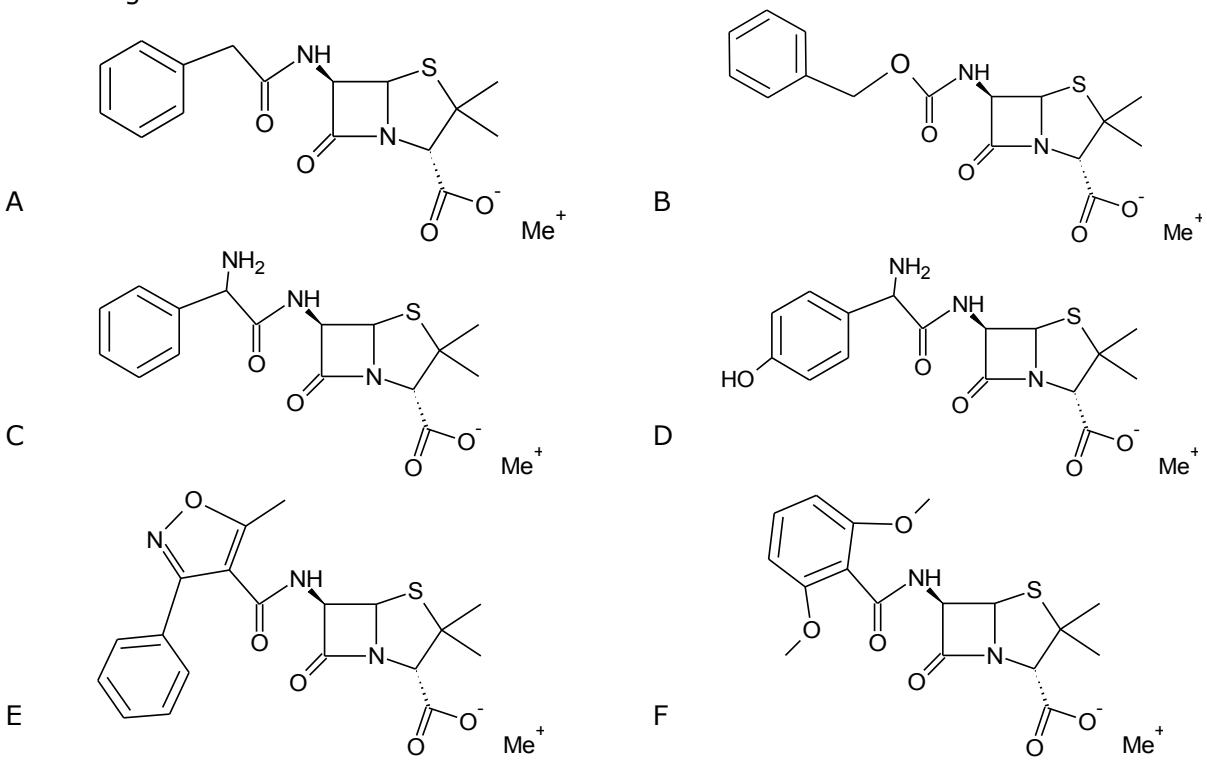

Fig.1: The structure of penicillin G (benzylpenicillin) (A), penicillin V (phenoxymethylpenicillin) (B), ampicillin (C), amoxicillin (D), dicloxacillin (E), meticillin (F). Me is usually Na or K

In the case of penicillins the resistance is ascribed to the cleavage of β-lactam ring by penicillinases (class A β-lactamases) [2]. That is why penicillins are used in combination with agents inhibiting β-lactamases. In this editorial we overview how various CDs influence the stability of the β-lactam ring.

Catalysis and inhibition of ring opening by CDs under various conditions

CD complexation may either catalyze or inhibit the cleavage of β-lactam rings depending on the pH.

Under weakly alkaline conditions both α- and βCD accelerate the β-lactam cleavage of various penicillins as much as 20-80 fold compared to alkaline hydrolysis without CDs [3,4,5]. The NMR study of penicillin V/αCD complex proved that the phenyl ring is included into the cavity leaving the β-lactam ring exposed to the alkaline solution [5]. The reaction proceeds in several consecutive steps: first the penicillin/CD complex is formed, next the βCD alkoxide ions attack the β-lactam ring, forming an acyl intermediate, and then the intermediate is hydrolyzed and the product is released [3,4]. The rate of acceleration depends on the structure of the penicillin. These inclusion complexes can serve as a model for the β-lactamase enzyme-substrate complex, so the use of CDs as biomimetic models was suggested. This catalytic effect was demonstrated also *in vivo* using βCD-producing alkalophile (ATCC 21594) [6]. These bacteria show penicillin resistance and βCD-mediated β-lactamase activity. This catalytic activity might contribute to the antibiotic resistance of a bacterium that can synthesize βCD.

Under neutral conditions lower catalytic effect was observed: the hydrolysis of penicillin V was accelerated by βCD only 5 fold. Other βCD derivatives, however, exhibited better catalytic activities under both neutral and alkaline conditions. For instance, amino-βCD had 165 fold acceleration of the hydrolysis of penicillin V at neutral pH [7]. ROESY NMR studies proved that ampicillin, amoxicillin and dicloxacillin formed inclusion complexes with β- and γCD and their anionic derivatives, heptakis(6-oxycarbonylethylthio-6-deoxy)-βCD (OCET-βCD) and octakis(6-oxycarbonylethylthio-6-deoxy)-γCD (OCET-γCD, commercialized as Sugammadex) at neutral pH, but the complexation had no influence on the hydrolysis [8].

On the other hand, under weak acidic conditions the degradation of penicillins was slightly retarded by βCD [9]. Also α- and γCDs were found to reduce the acidic hydrolysis of penicillin G the latter showing higher protection [10]. The complex association constants of penicillin G/CD systems at pH 5.7 were calculated 2.6, 30 and 179 M^{-1} for α-, β- and γCDs, respectively. The high stability of the γCD complex was ascribed to the fact that penicillin G was shown to form dimer, which can be incorporated into γCD, but not into α- and βCDs.

A single-molecule investigation of pH- and voltage-dependent reversible interactions between ampicillin and γCDs monitored the ionic current signatures across an α-hemolysin protein entrapping a γCD molecule [11]. It was found that at close to neutral pH more unstable

ampicillin/γCD complexes are formed as compared to that formed at acidic pH.

For dicloxacillin the highest stability constants of the inclusion complexes were obtained also with γCD compared to α-, βCDs and HPBCD at pH 1 and 2 while at pH 3 HPBCD was found the best stabilizer [12].

HPBCD showed stabilizing effect on penicillin G under strong acidic conditions (pH 2.2) [13]. Penicillin G complexed with HPBCD was degraded approx. 9-fold slower than the uncomplexed drug. Hydroxyethyl βCD (HEBCD) behaved similarly [14]. HPBCD was found to form two types of complexes with a 1:1 stoichiometry with ampicillin, amoxicillin and penicillin G in strong acidic solutions (where the drugs are cations): either the phenyl ring was included or the penam (β-lactam ring fused to a 5-membered ring) [15,16]. The latter, however, had lower association constants. At pH 4.5 (where the drugs are in zwitterionic form), only the complex with inclusion of phenyl ring was formed according to NMR investigations.

Molecular dynamic simulation studies of these two types of complexes for βCD gave similar results: a complex with the hydrophobic phenyl moiety of ampicillin included through the narrow rim of βCD is the preferred arrangement for the 1:1 complex [17]. The structures with the polar moiety of ampicillin inside the cavity were not stable, even when two CDs were considered in a 2:1 complex. The hydrogen bonds between the ionized carboxyl group on the penam ring and the secondary hydroxyl groups of another βCD contribute to the complex association [18].

Effect of CDs on the enzymatic hydrolysis of penicillins

The elongated cavity of OCET-γCD (Sugammadex), which was found to form 1:2 guest : host complexes, resulted in superior protection against enzymatic hydrolysis [7]. In the presence of β-lactamase enzymes ampicillin complexed with OCET-γCD degraded twice as slowly as the free drug.

Another approach to avoid the cleavage by β-lactamase is the conjugation of penicillins, such as methicillin to CD [19].

Effect on the antimicrobial activity

The bioavailability of ampicillin was improved when administered to humans in the form of βCD complex [20].

The 1:2 penicillin/CD complex resulted in enhanced antimicrobial activity: the concentration necessary to inhibit 50% of bacterial isolates of the same strain (MIC_{50}) decreased at least to the half for both βCD and HPBCD complexes [21]. Even the highest resistance to ampicillin shown by *Klebsiella* spp. was reduced (Fig. 2). Similar results were obtained for the amoxicillin complexes. In these experiments *Staphylococcus aureus* was especially sensitive to both

ampicillin and amoxicillin (MIC_{50} 2 mg/mL). This high antimicrobial effect was doubled when the drugs were applied in complexed form (MIC_{50} 1 mg/mL for both βCD and HPBCD complexes of both drugs). The enhanced antimicrobial activity is explained by two reasons: i) β-lactames in complexed form do not fit into the active site of β-lactamases; ii) complexed drugs can penetrate the bacterial cell wall faster than the free drug. The faster diffusion through the enterobacterial outer membrane might be the consequence of the changed membrane fluidity upon the effect of CDs on the membrane lipid components [22]. On the other hand, it was suggested that porins specific for cyclodextrins detected in *Klebsiella oxytoca* and *Bacillus subtilis* strains could be present in the bacteria studied [23,24]. These pore-forming membrane proteins (CymA and CycB, respectively) are able to bind CDs and behave as transporters helping CDs to get through the cell wall.

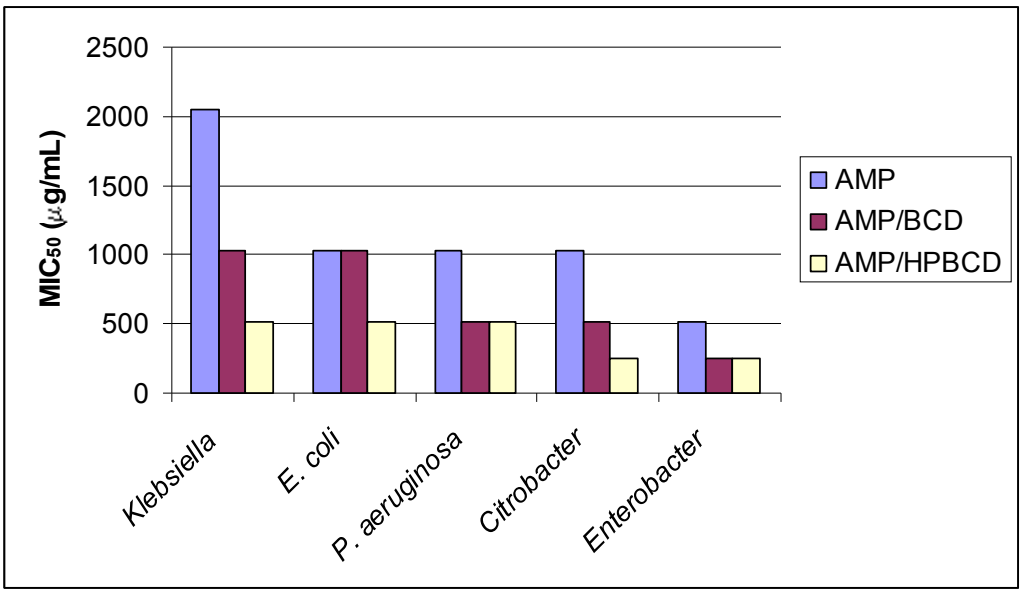

Fig. 2: Minimum inhibitory concentration (MIC_{50}) at which 50% of bacteria are inhibited in the presence of free ampicillin (AMP), and its 1:2 complex with βCD and HPBCD [21]

A designed βCD derivative, per-6-(4-methoxylbenzyl)-amino-6-deoxy-βCD HCl salt (MBABCD), was synthesized. The formation and the conformation of 1:1 (molar ratio) complex with methicillin were determined by NMR. The *in vitro* MIC values of methicillin combined with MBABCD against two methicillin-resistant *Staphylococcus aureus* strains were decreased 30-60-fold, compared to those for the antibiotic alone, and 1:1 methicillin/HPBCD complex [25].

Drug formulations

Several examples of drug formulations containing penicillins have been studied. Some examples:

- Sustained-release formulations containing penicillins included in αCD polymer were developed [26].

- Controlled release formulations were obtained by attaching ampicillin and amoxicillin to βCD-polyethylene glycol conjugate [27].
- Gels containing β-lactam antibiotics, such as penicillin G included in CDs were patented as surgical devices, e.g. a protective corneal mask or ablatable mask useful in laser keratectomy [28].

The potential of sugammadex to selectively remove allergenic drugs, such as penicillins and cephalosporins, was suggested by Baldo *et al.* [29]. Sugammadex is used in anaesthesia as an innovative and useful agent for rapid reversal of rocuronium-induced neuromuscular block by sequestering the drug as an inclusion complex. The removal of pencillins and cephalosporins in cases of difficult-to-reverse anaphylaxis to these drugs would be of great importance.

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Crystal structure, Supramolecular chemistry, X-ray crystallography, NMR spectroscopy

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Solvatochromic azo-dyes, Rotaxanes, Cyclodextrins, Pentacyanoferrate(II) complexes, Metal-to-ligand-charge-transfer (MLCT), Push–pull system

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Pyrazoline, Synthesis, Charge-transfer character, Solvent effect, Fluorescence anisotropy, Labeled drug, Phenylephrine

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Sensitizing effect, Fluorescence-quenching, Stern–Volmer equation

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Supramolecular hydrogels, Complex with α-cyclodextrins

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Carrier, Cytotoxicity, Human colon cancer cell lines

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Inclusion complex, NMR spectroscopy, Phase solubility studies, Pharmacokinetics, Beagle dogs

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Solubility, Antitumor agent, Thermodynamics, 2HP-β-CD–methylium, Tris(1-pentyl-1H-indol-3-yl)-, chloride

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Inclusion compounds, Spin–spin relaxation time, Nuclear magnetic resonance, Atom–atom potential method

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Magnetic properties, Up-conversion luminescence, Microwave-triggered, Controlled drug release, Noninvasive, Externally controlled drug-delivery system, Etoposide

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Solubilization studies, Bidimensional ^{1}H NMR, Molecular docking, NOESY

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Biodegradable stabilizer, Stability, Antibacterial activity, Escherichia coli, Staphylococcus aureus

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Inclusion complex, Self-assembly, Nano particles, Microtubular structures, α-CD, β-CD, Micro-sized tubular structures

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Manipulation the behavior of supramolecular hydrogels of α-cyclodextrin/star-like block copolymer/carbon-based nanomaterials

Graphene, Graphene oxide, Hydrogel, biomedical applications

Carbohydrate Polymers, 2015, 117, 592-599; DOI:10.1016/j.carbpol.2014.10.011

Shringirishi, M.; Prajapati, S. K.; Mahor, A.; Alok, S.; Yadav, P.; Verma, A.

Nanosponges: a potential nanocarrier for novel drug delivery – A review

Cross linking agent, Cross linking different types of cyclodextrins with a carbonyl or a dicarboxylate compound as a cross linker

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Methionine aminopeptidase, Inhibition, Cyclodextrin–substrate complex, Molecular modeling, Antibiotic agents

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Evaluation of sorption capacity of antibiotics and antibacterial properties of a cyclodextrin-polymer functionalized hydroxyapatite-coated titanium hip prosthesis

Infection, Drug delivery system, Antibiotics, Tobramycin, Rifampicin, Prolonged antibacterial activity

International Journal of Pharmaceutics, 2014, 477, 380-389; DOI:10.1016/j.ijpharm.2014.10.026

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Surface modification, Visceral mesh textile, Local anesthetic, Prolonged delivery, Crosslinked polymer of hydroxypropyl-β-cyclodextrin

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Anti-tumour activity, Phase-solubility studies

Carbohydrate Research, 2014, 396, 54-61; DOI:10.1016/j.carres.2014.07.015

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Solubility, Bioavailability, Ethyl acetate, Antioxidant capacity

International Journal of Pharmaceutics, 2014, 477, 148-158; DOI:10.1016/j.ijpharm.2014.10.027

4. CDs in Cell Biology

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How to reduce the accumulation of autophagic vacuoles in NPC1-deficient neurons: A comparison of two pharmacological strategies

Neurons, Niemann-Pick type C disease, Autophagy, PI3K-inhibitor, (2-Hydroxy)propyl-β-cyclodextrin

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Successful yellow head virus infection of *Penaeus monodon* requires clathrin heavy chain

Endocytosis, Double stranded RNA, RNAi, Black tiger shrimp, Endocytosis inhibitors, Methyl-β-cyclodextrin, Cellular entry pathway

Aquaculture, 2015, 435, 480-487; DOI:10.1016/j.aquaculture.2014.10.018

5. CDs in Food, Cosmetics and Agrochemicals

Izutani, Y.; Kanaori, K.; Oda, M.

Aggregation property of glycyrrhizic acid and its interaction with cyclodextrins analyzed by dynamic light scattering, isothermal titration calorimetry, and NMR

Binding thermodynamics, Dispersion, Multimodal inclusion complex, γ-cyclodextrin

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Phenylpropanoid pathway, Vitis vinifera cv. Monastrell, elicitors

Plant Physiology and Biochemistry, 2014, 84, 271-276; DOI:10.1016/j.plaphy.2014.09.019

6. CDs for other Industrial Applications

Clements, A. R.; Pattabiraman, M.

γ-Cyclodextrin mediated photo-heterodimerization between cinnamic acids and coumarins

Photochemistry, Host–guest, Supramolecular, Photodimerization, Weak interactions, Ternary inclusion complexes

Journal of Photochemistry and Photobiology A: Chemistry, 2015, 297, 1-7; DOI:10.1016/j.jphotochem.2014.10.001

Gull, N.; Khan, J. M.; Ishtikhar, M.; Qadeer, A.; Khan, R. A.; Gul, M.; Khan, R. H.

Secondary structural changes in guanidinium hydrochloride denatured mammalian serum albumins and protective effect of small amounts of cationic gemini surfactant pentanediyl-α, ω-bis(cetyldimethylammonium bromide) and methyl-β-cyclodextrin: A spectroscopic study

Sheep serum albumin, Rabbit serum albumin, Porcine serum albumin, Pentanediyl-α,ω-bis(cetyldimethylammonium bromide, Circular dichroism and dynamic light scattering, Protein refolding

Journal of Colloid and Interface Science, 2015, 439, 170-176; DOI:10.1016/j.jcis.2014.10.012

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Acid-catalyzed conversion of C6 sugar monomer/oligomers to levulinic acid in water, tetrahydrofuran and toluene: Importance of the solvent polarity

Solvent polarity, Levulinic acid, Polymerization

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Predicting PAH bioremediation efficacy using bioaccessibility assessment tools: Validation of PAH biodegradation–bioaccessibility correlations

Bioaccessibility, Biodegradation, Bioremediation, Cyclodextrin, Polycyclic aromatic hydrocarbons, Validation, HP-β-CD, PAH-contaminated soils, Linear regression models

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P-nitrophenol, 1,6-diisocyanatohexane, β-cyclodextrin

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Iron(III)-porphyrin, Humic acid, Catalytic oxidation, Tetrabromobisphenol A, Soil organic matter

Journal of Molecular Catalysis B: Enzymatic, 2014, 110, 147-153; DOI:10.1016/j.molcatb.2014.10.003

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Hydrophobic interaction chromatography HIC, Antibody purification, Salt-independent, Host–guest interaction, Phenyl ligands, Human IgG

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Contaminated soil, Mineralisation, Diuron, Bioremediation, Compost, Sewage sludge, Urban solid residues

Science of The Total Environment, 2015, 502, 699-705; DOI:10.1016/j.scitotenv.2014.09.052

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Synthesis, characterization and sorption properties of silica modified with some derivatives of β-cyclodextrin

Cadmium nitrate, Hardness salts, Cadmium (II) sorption, Inclusion complexes "β-cyclodextrin–nitrate-anion"

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Phosphate ester hydrolysis catalyzed by a dinuclear cobalt(II) complex equipped with intramolecular β-cyclodextrins

Kinetic, Hydrophobic microenvironment, Phosphate esterase activities

Journal of Molecular Catalysis A: Chemical, 2015, 396, 346-352; DOI:10.1016/j.molcata.2014.10.020

7. CDs in Sensing and Analysis

Baruah, U.; Gogoi, N.; Majumdar, G.; Chowdhury, D.;

β-Cyclodextrin and calix[4]arene-25,26,27,28-tetrol capped carbon dots for selective and sensitive detection of fluoride

Chitosan, Capping, Fluorescence quenching, Fluorescence enhancement, Sensing

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One-pot green synthesis of Prussian blue nanocubes decorated reduced graphene oxide using mushroom extract for efficient 4-nitrophenol reduction

Electrochemical sensor, Mushroom, 4-Nitrophenol, Introduction of beta-cyclodextrin

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β-Cyclodextrin, Naphthalenediols, Chemosensor, Inclusion complex, Color change

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Venlafaxine, Drug delivery, Magnetite nano-particles, Solid phase extraction, Antidepressant

International Journal of Pharmaceutics, 2014, 476, 178-184; DOI:10.1016/j.ijpharm.2014.09.051

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Ultrafast torsional dynamics of Thioflavin-T in an anionic cyclodextrin cavity

Sulphobutylether-beta-Cyclodextrin, Fluorescence, Confinement, Amyloid fibril sensing dye

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A novel sandwich–type noncompetitive immunoassay of diethylstilbestrol using β-cyclodextrin modified electrode and polymer-enzyme labels

EnVision™ polymerase, Diethylstilbestrol, Milk, Platinum nanoparticles, Electrochemical immunosensor, Two-step recognition, Food safety

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Electrochemical simultaneous determination of hydroquinone and *p*-nitrophenol based on host-guest molecular recognition capability of dual β-cyclodextrin functionalized Au@graphene nanohybrids

Gold nanoparticles@graphene, SH/NH_2-β-cyclodextrin, Supramolecular recognition, Nanohybrid, Interference study

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An ultra-sensitive acetylcholinesterase biosensor based on reduced graphene oxide-Au nanoparticles-β-cyclodextrin/Prussian blue-chitosan nanocomposites for organophosphorus pesticides detection

Acetylcholinesterase, Electrochemical reduced graphene oxide, Au nanoparticles, Oxidation of thiocholine

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Fast preparation of fluorescent carbon nanoparticles from β-cyclodextrin via precursor design treatment

Biomaterials, Bio-imaging, Calcining β-cyclodextrin

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