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Immobilization of Chondroitin Sulfate A onto Monolithic Epoxy Silica Column as a New Chiral Stationary Phase for High-Performance Liquid Chromatographic Enantioseparation

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Abstract: Chondroitin sulfate A was covalently immobilized onto a monolithic silica epoxy column involving a Schiff base formation in the presence of ethylenediamine as a spacer and evaluated in terms of its selectivity in enantioseparation. The obtained column was utilized as a chiral stationary phase in enantioseparation of amlodipine and verapamil using a mobile phase consisting of 50 mM phosphate buffer pH 3.5 and UV detection. Sample dilution by organic solvents (preferably 25% *v*/*v* acetonitrile-aqueous solution) was applied to achieve baseline enantioresolution (*R*s > 3.0) of the individual drug models within 7 min, an excellent linearity (R^2 = 0.999) and an interday repeatability of 1.1% to 1.8% RSD. The performance of the immobilized column for quantification of racemate in commercial tablets showed a recovery of 86–98% from tablet matrices. Computational modeling by molecular docking was employed to investigate the feasible complexes between enantiomers and the chiral selector.

Keywords: amlodipine; chiral stationary phase; chondroitin sulfate A; enantioseparation; immobilization; monolithic column; Schiff base; verapamil

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1. Introduction

Polysaccharide-based chiral stationary phases (CSPs) play an important role in enantioseparations of chiral compounds by high-performance liquid chromatography (HPLC) [1]. Due to the asymmetric and long-range helical structures, polysaccharides offer high recognition capacity and enantioselectivity toward broad types of chiral substances [2,3]. As one of the most prominent separation methods in analysis and preparative purposes, HPLC using amylose-based and cellulose-based columns delivers excellent performance [4–7]. In the beginning, the utilization of polysaccharide-based CSPs faced a restriction in the enantioselectivity improvement due to their low compatibility toward polar organic modifiers [8,9]. Therefore, immobilized CSPs are developed to achieve an expansion of column compatibility with a wide range of solvent polarity [9,10]. Immobilized CSPs typically could be applied in normal phase (NP)-, reversed-phase (RP)-, and polar-elution mode with a large diversity of organic solvents as mobile phases [1,11]. On the other hand, coated CSPs can only be used as a single mode in NP or RP.

Immobilization of a chiral selector onto macroporous silica has been conducted through a radical copolymerization reaction [12] and a photochemical technique [9]. In 2017, Bezhitashvili et al. reported highly efficient separation using a wide pore silica surface as the backbone for high molecular weight polysaccharide-based chiral selectors [12,13] by

providing loading capacity [14]. In line with these achievements, a previous study on the covalent immobilization of monolithic silica via epoxide moiety has improved separation efficiency and compatibility with numerous organic solvents [15].

Among polysaccharides, chondroitin sulfates have been found to be potential chiral selectors in capillary electrophoresis (CE) [16]. As charged molecules, they possess different mobility under an electrical field compared to neutral polysaccharides. In addition to their charges, chondroitin sulfates afford ionic and hydrophobic interactions as well as hydrogen bonds. Therefore, chondroitin sulfate A (CSA) with the sulfate group at carbon number four (Figure 1) has been successfully utilized as a chiral selector in CE [17]. Since then, chondroitin sulfate B [18], D, and E [19] have been employed as chiral selectors for various chiral substances.

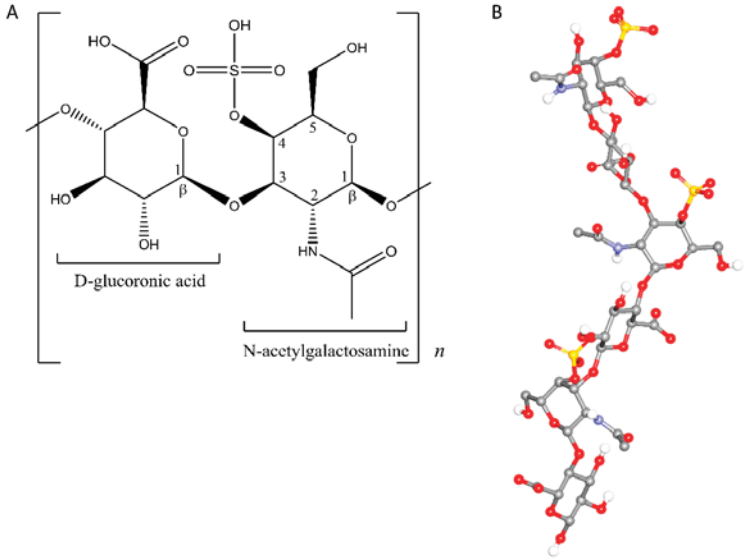

Figure 1. Repeating unit of chondroitin sulfate A (CSA): 2-D monomer (**A**) and 3-D helical representation consisting of three monomer units, extracted from its crystal structure entry 4N8W [20] (**B**).

Monolithic silica columns showed successful applications as one current approach for fast HPLC analysis [3,21–23]. A combination of the broad enantiomers recognition ability of CSA and the benefits of the monolith backbone is interesting for further investigation of chromatographic enantioseparations. The immobilization of a chiral selector on a monolithic chromatographic support through epoxy and Schiff base formations have been established [24–27]. Particularly, its application on monolithic epoxy support in capillary liquid chromatography (CLC) [28] and HPLC via in situ modification has been successfully obtained [15,27]. Moreover, in general, immobilization through a Schiff base formation proves to be the best approach [24]. Based on our best knowledge, the usage of CSA as a chiral selector in HPLC either as a mobile phase additive or a CSP has not been reported.

Molecular docking is commonly used in chiral separation studies to clarify the chiral recognition mechanism [29,30]. A docking approach might be employed to simulate the interactions between a chiral selector and the individual enantiomers. The most stable intermolecular conformation could be simulated with regard to the lowest binding energy [30].

In this study, the immobilization of CSA onto a monolithic column by sequential Schiff base formation and reduction was developed to provide an alternative polysaccharide-based CSP for chromatographic enantioseparation. The enantioseparation capability of the immobilized CSA column was evaluated by using amlodipine (AML) and verapamil (VER) in their racemic form as chiral analytes. Both compounds are calcium channel antagonist drugs, belonging to the classes of dihydropyridines and non-dihydropyridines, respectively. Further evaluation of the column performance in enantioseparation was

carried out using commercial tablet matrices. Additionally, molecular docking was utilized to simulate the enantiorecognition and visualize the feasible interaction between CSA and the individual enantiomers.

2. Results

2.1. Organic Modifier Effects

The polarity of the mobile phase can be tuned by changing the type and concentration of an organic additive. Consequently, the recognition mechanism can be strongly influenced [31–33]. The organic solvent can be added in the mobile phase or as sample diluent. In order to enhance the enantioresolution of amlodipine (AML) and verapamil (VER), the addition of an organic modifier in the sample solvent was applied. The concentrations of methanol (MeOH) and acetonitrile (MeCN) in aqueous solution as sample solvents were optimized, while the mobile phase composition was kept constant. The effect of organic modifier content on enantioseparation was investigated at 10–100% v/v MeOH (in water) and 10–100% v/v MeCN (in water).

The increases of MeOH concentrations in the sample solvent gradually improved the resolution (R_s) of AML and VER. However, up to the solvent composition of 100% v/v MeOH, only partial enantioseparations of AML and VER were reached with R_s = 0.8 and R_s = 1.1, respectively. The appearances of peak plateaus and coalescence indicate competition between chromatographic resolution and on-column stereoisomerism [34], known as dynamic interconversion HPLC [35]. The racemization of the analyte during passing throughout the column drives the rise of the baseline pattern [36]. In some cases, low-temperature conditions in chromatographic separations were applied to prevent interconversion by conducting a slow exchange system [34,35]. In this study, the addition of 10% v/v to 25% v/v MeCN (in water) as a sample solvent significantly increased the response of the first eluted enantiomer and led to complete peak decoalescence. The influence of organic modifiers as the sample diluent toward enantiomeric separation profiles is shown in Figure 2.

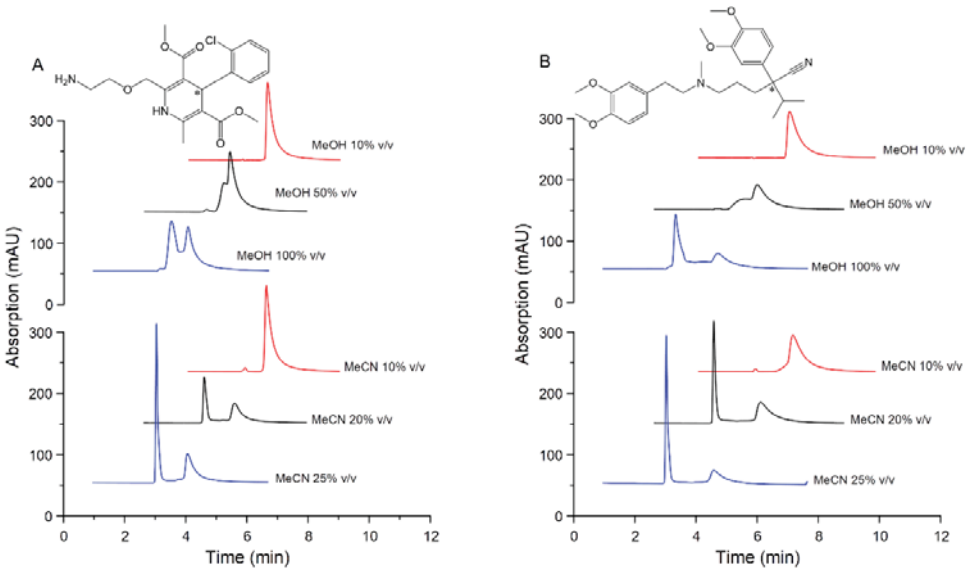

Figure 2. Influence of methanol (MeOH) and acetonitrile (MeCN) as organic solvents in various concentrations of sample diluent towards enantioseparation profiles of (**A**) amlodipine, AML and (**B**) verapamil, VER, as racemic mixtures. Stationary phase: CSA column; mobile phase: 50 mM phosphate buffer pH 3.5; flow rate 0.8 mL/min; UV detection (**A**) 240 nm and (**B**) 230 nm. The organic solvent was prepared in water (aqueous solution).

2.2. Resolution and Selectivity

Resolution (R_s) of AML and VER was obtained at R_s = 3.2 and R_s = 3.6, respectively. Furthermore, the enantioselectivity of α = 1.8 for AML and α = 2.1 for VER, was achieved as shown in Table 1.

Table 1. Evaluation of CSA column.

Parameter	AML	VER
t_1 (min)	$2.2 \pm 3.3 \times 10^{-3}$	$2.2 \pm 2.0 \times 10^{-3}$
t_2 (min)	$3.2 \pm 3.7 \times 10^{-2}$	3.6 ± 0.2
R_s	$3.2 \pm 8.5 \times 10^{-2}$	$3.6 \pm 8.5 \times 10^{-2}$
k_1	$1.4 \pm 3.0 \times 10^{-3}$	$1.4 \pm 3.0 \times 10^{-3}$
k_2	$2.5 \pm 7.4 \times 10^{-2}$	2.9 ± 0.2
α	$1.8 \pm 2.8 \times 10^{-2}$	2.1 ± 0.1
N_1	4532 ± 408	4407 ± 368
N_2	1049 ± 92	589 ± 36

t_1: first eluted enantiomer; t_2: second eluted enantiomer. Separation conditions: mobile phase: 50 mM phosphate buffer pH 3.5; flow rate 0.8 mL/min; sample solvent: 25% *v*/*v* MeCN (in water); injection volume: 20 µL; UV detections: 240 nm (AML) and 230 nm (VER). N_1: number of theoretical plates of first eluted enantiomer; N_2: number of theoretical plates of second eluted enantiomer.

2.3. Method Validation

Proportional responses of the analyte in triplicate injections of five concentrations have shown decent linearity for both drug models. Intraday and interday repeatabilities of peak area ratio were obtained at 0.5–1.3% and 1.1–1.8% RSD, respectively. The RSD values are indicating satisfactory precision of the separation method. Method accuracy by adding a respective amount of analyte at 50 µg/mL, 80 µg/mL, and 100 µg/mL was achieved at 98–102% and 95–104% for AML and VER, respectively. Validation parameters are shown in Table 2.

Table 2. Validation of the enantioseparation method using immobilized-CSA column.

Parameter	AML		VER	
	t_1	t_2	t_1	t_2
Range (µg/mL)	50–120	50–120	50–200	50–200
Linearity (R^2)	0.9995	0.9985	0.9989	0.9988
Regression	$y = 95.3 \times 10^3 x + 132.6 \times 10^4$	$y = 102.9 \times 10^3 x - 373.7 \times 10^4$	$y = 90.5 \times 10^3 x + 147.5 \times 10^4$	$y = 80.8 \times 10^3 x - 102.3 \times 10^4$
LOD [a] (µg/mL)	2	3	4	6
LOQ [b] (µg/mL)	6	10	11	17
Intraday precision *	1.0–1.3%	1.0–1.3%	0.5–1.2%	0.5–1.2%
Interday precision **	1.2–1.8%	1.2–1.8%	1.1–1.2%	1.1–1.2%
Accuracy	99–102%	98–102%	95–102%	98–104%

[a] based on 3.3 RMSE/slope. [b] based on 10 RMSE/slope; RMSE: root mean square error. * repeatability of peak area ratio (*n*: samples = 9; *df*: degrees of freedom = 6). ** repeatability of peak area ratio (days: 3). t_1: first eluted peak. t_2: second eluted peak.

2.4. Enantioseparation in Commercial Tablet Matrices

The modified column also proved its selectivity towards commercial tablets' matrices of A (5 mg AML) and B (80 mg VER). Sample pretreatment through solvent addition (25% *v*/*v* MeOH in water) and ultrasonication was taken to release the analyte from its matrix and followed by filtration. The proposed method was able to determine the active substance of selected pharmaceutical dosage form in triplicate with an average of 86% (2.5% RSD, n = 9, df = 6) and 98% (3.0% RSD, n = 9, df = 6) for AML and VER, respectively. Separation profile of the enantiomers in tablet matrices is given in Figure 3.

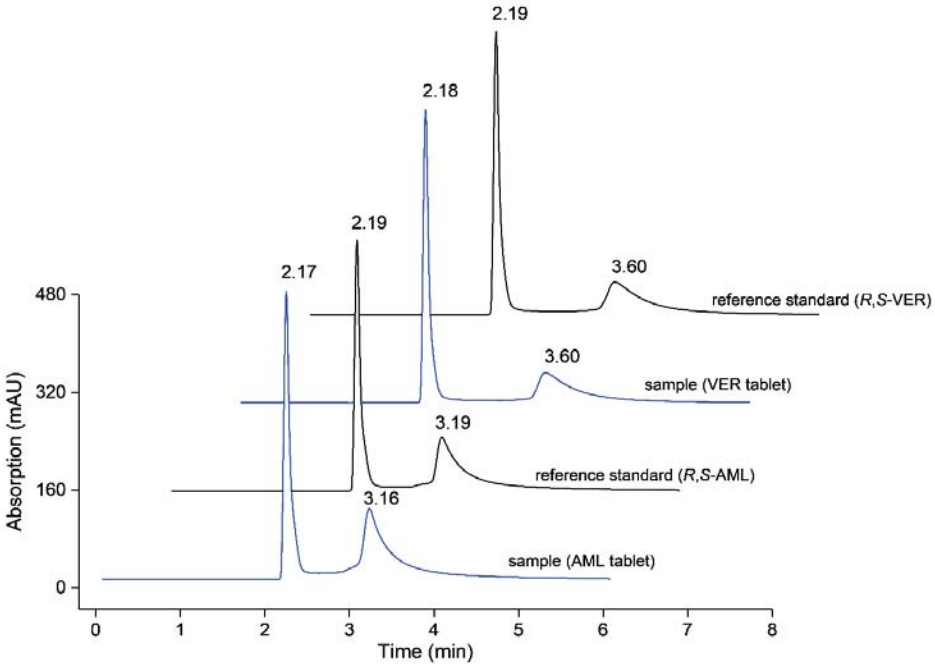

Figure 3. Determination of active pharmaceutical ingredients in commercial tablet matrices. The chromatograms represent amlodipine (AML) 80 μg/mL and verapamil (VER) 100 μg/mL with their individual reference standards at the corresponding concentrations.

2.5. Intermolecular Interactions Revealed by Molecular Docking

As per molecular docking, the interactions between CSA and enantiomers seem to be driven by hydrogen bonding. The interactions of CSA towards *R*-(+)-amlodipine were dominated by hydrogen bonding between (SO···) and (···HN) of the primary amine, among two electrostatic binding forces. In contrast, other than a conventional hydrogen bond and an electrostatic interaction, the primary amine of *S*-(−)-amlodipine possessed electrostatic π-anion (chlorophenyl ring··· and ···O-S) interaction, which were not found in its antipode. The different types of interactions, along with the resulted binding affinities, may lead to the enantioseparation of AML.

In the case of VER, the secondary amine plays an important role in the molecular interaction. *R*-(+)-verapamil formed a hydrogen bond from the interaction between the ionized tertiary amine and (····O-) group of CSA. On the other hand, *S*-(−)-verapamil formed an hydrogen bond from the interaction between the ionized tertiary amine (NH···) and (···O=S) group of CSA. Two π-sulfur interactions were found in the *R*-(+)-enantiomer and only one in the *S*-(−)-enantiomer. Additionally, an electrostatic interaction was only present in by *S*-(−)-verapamil. Thus, the differences in the complexes of VER enantiomers might occur. The populations in the best clusters from 250 docking runs for each enantiomer were 44 for *R*-(+)-amlodipine, 67 for *S*-(−)-amlodipine, 28 for *R*-(+)-verapamil, and 19 for *S*-(−)-verapamil. The estimated lowest binding energies in the best clusters are listed in Table 3, which correspond to the complexes and the molecular interactions briefly depicted in Figure 4.

Table 3. Proposed interactions by molecular docking and binding energies.

Enantiomer	Type of Interaction	Functional Group	Distance (Å)	ΔG [a] (kcal/mol)	$\Delta\Delta G$ [b] (kcal/mol)
R-(+)-amlodipine	Electrostatic *	S-O···N	4.42	−4.84	0.96
	Electrostatic *	-O···N	4.48		
	Hydrogen bond	-OH···O-	2.09		
	Hydrogen bond	-O-···HN	2.13		
	Hydrogen bond	S=O···HN	1.80		
	Hydrogen bond	S=O···HN	2.33		
S-(−)-amlodipine	Electrostatic *	S=O···N	3.71	−3.88	
	Hydrogen bond	-O-···HN	2.03		
	Hydrogen bond	S=O···HN	1.61		
	Electrostatic **	S-O···chlorophenyl ring	3.59		
R-(+)−verapamil	Hydrogen bond	-O-···HN	2.20	−3.81	0.73
	π-Sulfur	S···dimetoxyphenyl ring	5.92		
	π-Sulfur	S···dimetoxyphenyl ring	5.53		
S-(−)-verapamil	Hydrogen bond	S=O···HN	2.35	−3.08	
	Electrostatic *	S-O···N	4.53		
	π-Sulfur	S···dimetoxyphenyl ring	4.48		

[a] ΔG: the lowest docking energy of the best cluster; [b] $\Delta GG = |\Delta G_R - \Delta G_S|$; * attractive charge; ** π-anion.

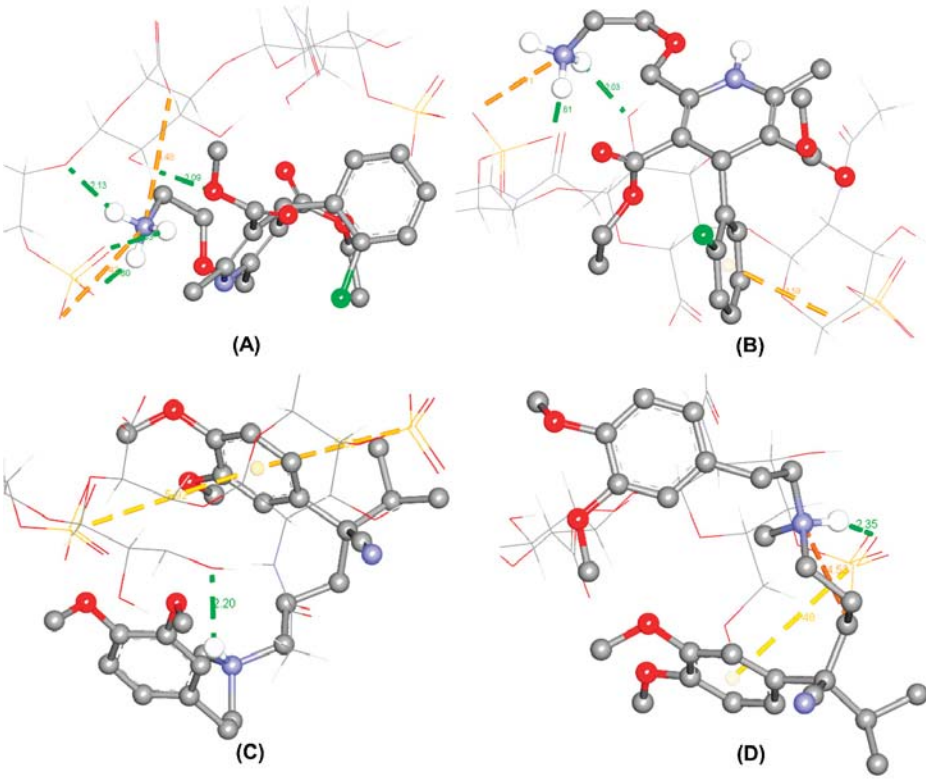

Figure 4. Prediction of the most stable complexes between CSA and the enantiomers of amlodipine and verapamil. CSA is drawn in the wire form and enantiomers are illustrated in the ball-stick form as *R*-(+)-amlodipine (**A**); *S*-(−)-amlodipine (**B**); *R*-(+)-verapamil (**C**); *S*-(−)-verapamil (**D**). Green dotted lines represent hydrogen bonds; yellow and orange dotted lines represent π-sulfur interactions and electrostatic interactions, respectively. The numbers indicate the distances between two functional groups in the predicted interactions.

3. Discussion

3.1. Immobilized CSA Column

A protocol of stepwise immobilization onto monolithic epoxy HPLC column via reductive amination has been proposed by Merck. This approach is applicable for immobilization of various ligands, including performing in house generation of CSA-based CSP. The strategy of CSA immobilization onto the monolithic epoxy column was initialized by opening the epoxy ring through hydrolyzation to a diol. The oxidizing agent $NaIO_4$ was utilized to cleave the diol groups to an aldehyde. The formation of aldehydes was intended to provide an active surface for the attachment of diamine-spacer. The primary amines of the spacer were expected to bind to aldehydes by forming a Schiff base linkage (imine formation) under alkaline conditions. Ethylenediamine, as the selected diamine-spacer, was introduced into the column in a continuous flow system with a reductant ($NaCNBH_3$, 5 mM) under mildly basic conditions ($(NH_4)_2SO_4$, 1.9 M) at pH 8.0. In the next step, $NaCNBH_3$ (20 mM) was utilized at pH 3.0 to drive the immobilization of ethylenediamine to completion by quenching the remaining residual aldehydes on the monolithic surface. In order to neutralize the immobilized column, a phosphate buffer was employed at pH 7.4 (Figure 5A). A solution of 100 mM $NaIO_4$ in 20% v/v MeOH (aqueous solution) was prepared to conduct the oxidative cleavage of CSA, prior to introducing to the column (Figure 5B). The immobilization of CSA (Figure 5C) was carried out via Schiff base formation using reductant $NaCNBH_3$ (5 mM) under a mild basic condition of $(NH_4)_2SO_4$ (1.9 M) pH 8.0 in a continuous flow system. A subsequent process of quenching the remaining aldehydes employing $NaCNBH_3$ (20 mM) at pH 3.0 and column neutralization using phosphate buffer pH 7.4 led to the completion of CSA immobilization.

In this protocol, the primary amine as a spacer was expected to bind to aldehydes via Schiff base linkage. However, the Schiff base linkage is susceptible to hydrolysis and can revert to the aldehyde and primary amine. Thus, the linkage needs to be stabilized by reduction to a secondary amine bond. Therefore, the reaction was conducted using reductant $NaCNBH_3$ (5 mM) to perform an in situ reductive amination reaction. The reaction between diamine groups and aldehydes might also give side products such as imidazolines, formed as aminal from the diamine, or diimines from reactions of neighboring aldehydes of the stationary phase [37]. Nevertheless, the immobilization process of ethylenediamine in this scheme was focused on the formation of imines as the main product.

In order to conduct applicability and simplicity, the immobilization was performed on a monolithic analytical column. The immobilization was carried out in a closed continuous flow system to carry out a constant and stable process. In the applied protocol, an in-process determination of yields and column characterization was not possible. Therefore, subsequent rinsing was employed using $NaIO_4$ at an alkaline pH as a control strategy to minimize unwanted side products and stabilize the intended reaction. However, the presence of $NaIO_4$ in the overnight immobilization system led to gradual oxidation of the remaining solution containing CSA. Thus, after the overnight immobilization process, the determination of the remaining yield less represents the main reaction involved due to gradual oxidation. Likewise, a characterization of the column surface by taking out the monolith from the column housing and a cross-section cutting was not feasible. Due to these restrictions, the immobilized column was evaluated through its performance in enantioseparation. Investigation of the immobilization process reproducibility becomes a further step that follows the column evaluation results. This initial report proposed an immobilization method of CSA onto a monolithic column and its performance in enantioseparation.

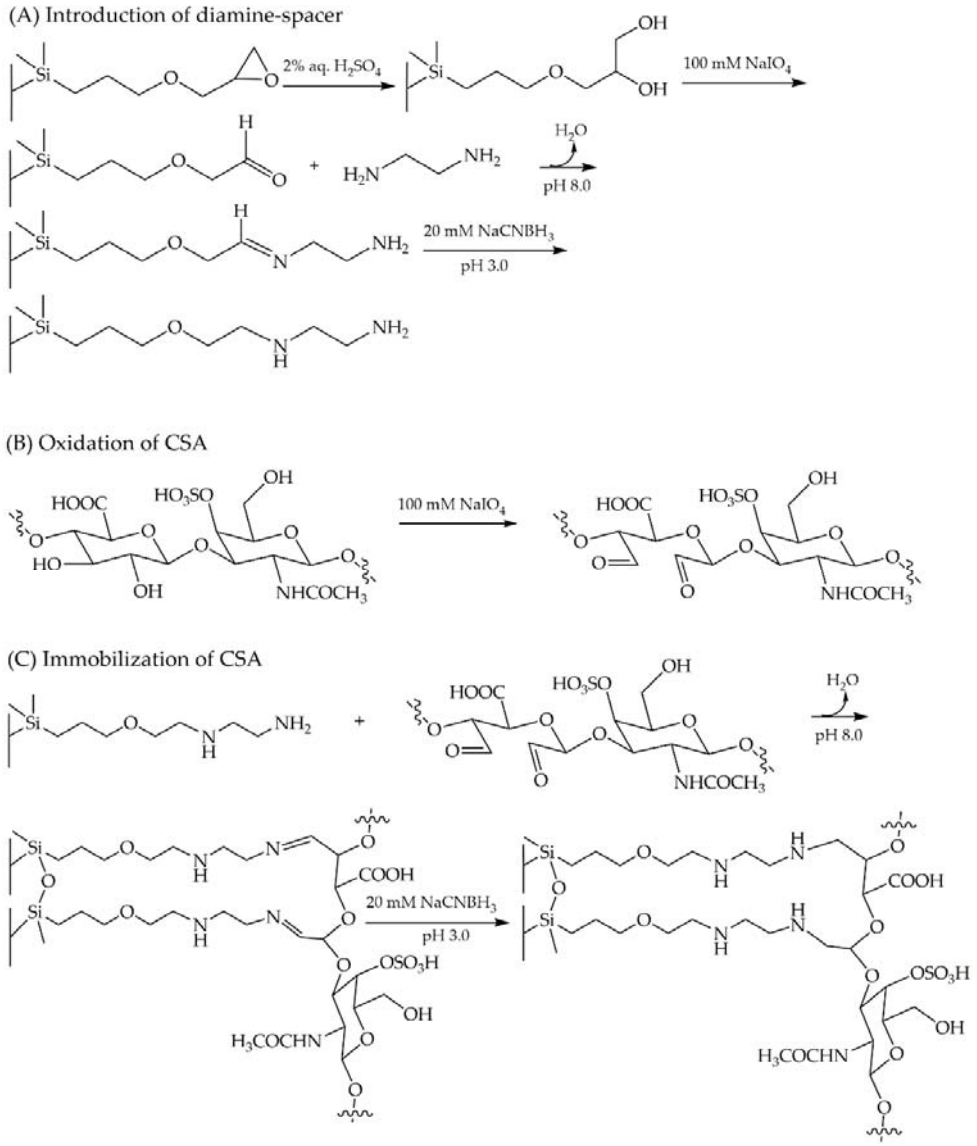

Figure 5. Schematic immobilization of CSA onto the monolithic epoxy column. Introduction of diamine-spacer (**A**), oxidation of chondroitin sulfate A (CSA) (**B**), and immobilization of CSA (**C**).

3.2. Enantioseparation

The enantiomeric separation was optimized using phosphate buffer, considering the final solution for the column washing. An acidic pH at 3.5 was applied to achieve fully ionized basic drugs. Hence, the sulfate group of CSA as an anionic chiral selector was predicted to be the most important for enantiorecognition by providing electrostatic interactions with the cationic analyte [38]. Apparently, the addition of organic solvent in the mobile phase progressively decreased the retention time and resulted in poor resolution (data not shown). This typical separation behavior is known in an RP system [32]. However, the presence of an organic solvent in a small amount was found to be required to achieve baseline resolution. Therefore, the mobile phase of 50 mM phosphate buffer pH 3.5 was selected for further study with a small volume addition of organic modifier in the sample solvent. Interestingly, the resolution of the enantiomers was remarkably improved in the presence of MeCN (25% v/v in water). It might correspond to the higher polarity of MeCN, which elevates enantioselectivity with less competition in hydrogen-bonding

interaction compared to MeOH [39]. The immobilized CSA column performed initial enantioseparation on RP mode HPLC. Thus, expansion of the CSA column applicability in NP mode separation remains an interesting aspect of future research.

3.3. Molecular Docking and Chromatographic Enantioseparation

HPLC analysis is known to have a limitation in providing direct evidence of the specific binding sites of analytes with the chiral selector. On the other hand, computational docking offers further insights into the detailed geometry information and binding energy of the chiral selector-analyte complex [40]. Thus, computational docking has been proposed as simple approaches for understanding the chiral recognition mechanism on CSPs [41–44]. A comprehensive docking study on the factors affecting enantioseparation such as solvent effect and other achiral influence was appointed as quantitative approach along with more complex interaction model. However, a molecular docking study was often performed in a vacuum without considering the effect of the medium in the actual separation condition. Consequently, a difference in the predicted energy by molecular modeling and the result from the HPLC analysis might occur. Despite that fact, docking approach delivers a close qualitative estimation regarding the nature of intermolecular forces responsible for the complexes. Although molecular docking does not account for the actual separation conditions, strong correlations of binding affinity scores with chromatography elution orders have been reported [45,46]. In order to assess feasible molecular interactions between the immobilized CSA stationary phase and the analyte, a basic docking approach using AutoDock 4.2.6 was applied.

In this study, the molecular docking was simulated on the three-dimensional structure of CSA and the individual enantiomers at acidic pH. The molecules of CSA and enantiomers were set up as a rigid selector and flexible ligands, respectively. The most stable complexes result in binding energies (ΔG) that do not take solvation effects into account. Even though these limitations might lead to the differences between the calculated binding energies and experimental results [29], the applied method offers preliminary insights into enantiomer-specific interactions of the study-related structures [45]. Herein, the sulfate group of CSA was found to play an important role in the chiral recognition of both drug models. It showed a close agreement with the previous study by Nishi et al. using capillary electrophoresis [17]. The difference in binding forces and the ΔG values between two enantiomers might define their separation on CSA column chromatography. Based on the predicted binding energies, *R*-(+)-amlodipine and *R*-(+)-verapamil might have retained longer in the column than their counterparts.

4. Materials and Methods

4.1. Chemicals and Reagents

Methanol and acetonitrile (gradient grade for liquid chromatography) were obtained from Merck (Darmstadt, Germany). Sulfuric acid (H_2SO_4) 96%, *ortho*-phosphoric acid (H_3PO_4, 85%), sodium periodate ($NaIO_4$), sodium cyanoborohydride ($NaCNBH_3$), ethylenediamine ($NH_2CH_2CH_2NH_2$), disodium hydrogen phosphate (Na_2HPO_4), chondroitin sulfate A sodium salt from bovine trachea, (*R*,*S*)-amlodipine as amlodipine besylate, and (*R*,*S*)-verapamil (pharmaceutical secondary standard) were acquired from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Water was purified by Arium® pro UF/VF-Sartophore 0.22 µm water purification system from Sartorius Weighing Technology GmbH (Göttingen, Germany).

4.2. Instrumentation and Chromatographic Conditions

HPLC analysis was conducted using a VWR™-Hitachi (VWR International GmbH, Darmstadt, Germany) consisting of an L-2455 DAD detector, an L-2130 pump, and an L-2200 autosampler. System management and data acquisition were performed by EZChrom Elite® 3.3.2 SP2 Software (VWR International GmBH, Darmstadt, Germany) involving integration parameters of peak area, retention time, and resolution. A Chromolith® Widepore

300 Epoxy 100-4.6 mm HPLC column was kindly provided by Merck KGaA, Germany. Enantiomer separations were performed at ambient column temperature and flow rate of 0.8 mL/min with a mobile phase 50 mM Na_2HPO_4 pH 3.5 (adjusted by addition of about 4 mL H_3PO_4 85% in 1 L buffer solution). An injection volume of 20 µL was set up at detection wavelengths of 230 nm and 240 nm.

4.3. Preparation of the Immobilized CSP

4.3.1. Conversion of Epoxy Groups and Immobilization of Diamine Spacer

An immobilization approach was applied to develop a CSA-based CSP via a Schiff base formation. A Chromolith® Widepore 300 Epoxy 100-4.6 mm monolithic HPLC column was used as a backbone of the immobilized CSA. Epoxy groups of the monolithic column were first converted to diol groups by hydrolyzation. This step was applied at a flow rate of 0.2 mL/min using 2% *v*/*v* H_2SO_4 in water for 24 h. In order to cleave the diol groups to an aldehyde, the process was continued by rinsing the column with 100 mM $NaIO_4$ in 20% *v*/*v* MeOH (aqueous solution) at a flow rate of 0.2 mL/min for 15 h. At the following step, 83 mM ethylenediamine in 50 mM Na_2HPO_4 containing a mixture of 1.9 M $(NH_4)_2SO_4$ pH 8.0 and 5 mM $NaCNBH_3$ was introduced into the column at a flow rate of 0.2 mL/min for 20 h. The immobilization of diamine-spacer was ended by flushing the column with 20 mM $NaCNBH_3$ in 50 mM Na_2HPO_4 pH 3.0 at a flow rate of 0.2 mL/min for 8 h, and neutralizing with 100 mM Na_2HPO_4 pH 7.4 at a flow rate 0.2 mL/min for 5 h. All of the employed solutions in this step were prepared in water as solvent.

4.3.2. Oxidation of CSA

The oxidation of 1% *w*/*v* CSA was applied by converting the hydroxy groups to the aldehyde groups using 100 mM $NaIO_4$ in 20% *v*/*v* MeOH (aqueous solution).

4.3.3. Immobilization of CSA

The immobilization via Schiff base formation was conducted by introducing a mixture of the oxidized CSA (1% *w*/*v*) and 5 mM $NaCNBH_3$ as a reductant containing 1.9 M $(NH_4)_2SO_4$ pH 8.0 in 50 mM Na_2HPO_4, at a constant low flow rate of 0.1 mL/min for 20 h. In the following step, solution of 20 mM $NaCNBH_3$ in 50 mM Na_2HPO_4 pH 3.0 was employed at a flow rate of 0.2 mL/min for 8 h. As the last step, the column was flushed using 50 mM Na_2HPO_4 pH 7.4 at 0.2 mL/min for 5 h.

4.4. Preparation of Bulk Samples

Stock solutions of AML and VER were prepared individually at the concentration of 1.0 mg/mL in 5% *v*/*v* MeOH (aqueous solution). The samples were freshly prepared by diluting each stock solution into 30 µg/mL in various ratios of MeOH as well as acetonitrile (MeCN) as solvent.

4.5. Method Validation

Validation of enantioseparation method on the immobilized CSA-based column was performed in the range concentration of AML (50–120 µg/mL) and VER (50–200 µg/mL) at a wavelength of 240 nm and 230 nm, respectively. Phosphate buffer 50 mM at acidic pH 3.5 was chosen at a flow rate 0.8 mL/min. Limit of detection (LOD) and limit of quantitation (LOQ) were calculated as 3.3 times and 10 times the root mean square error (RMSE) divided by the slope of the calibration curve, respectively. Intraday and interday precision of the peak area ratio were determined at three concentrations within 50–100 µg/mL.

4.6. Determination of Enantiomers in Commercial Tablets

A further step was taken in order to perform enantioseparation on the immobilized column using commercial tablet matrices of AML (5 mg amlodipine besylate) and VER (80 mg verapamil HCl). Series concentrations of grounded AML and VER tablets were treated individually and dissolved in 5% *v*/*v* MeOH (aqueous solution) by ultrasonication

for 5 min at room temperature. Finally, the samples were filtered through a 0.22 µm filter membrane to obtain a clear solution and diluted in 25% v/v MeCN (aqueous solution) to final concentrations of 60–100 µg/mL of the active substance. Three samples were prepared for each drug and injected in triplicate.

4.7. Data Evaluation

Resolution (R_s) between two enantiomers was determined by the mid-height of the peaks, where t_1 and t_2 represent the retention times of the first and second eluted peaks, respectively, while w_1 and w_2 correspond to widths at the mid-height of the peaks. Retention factors of k_1 and k_2 are described as the ratio of Δt between two enantiomers with void value (t_0). *R*s and enantioselectivity (α) were calculated using Equation (1) and Equation (2), respectively.

$$R_s = 1.18\frac{t_1 - t_2}{w_1 + w_2} \quad (1)$$

$$\alpha = \frac{k_2}{k_1} \quad (2)$$

4.8. Molecular Docking

In general, as a polysaccharide, CSA exposes many types of chiral binding sites. However, the determination is challenging [40]. Thus, a computational method using molecular docking was employed to figure out the feasible complexes. The simulation was conducted using a 3D conformer of the CSA structure taken from the Protein Data Bank (PDB) server entry 4N8W (rcsb.org/structure/4N8W) [20]. The selected CSA consisting of three monomer units was extracted from its crystal structure 4N8W (cathepsin K-chondroitin sulfate complex). Drug structures of *R*-(+)-amlodipine CID_9801597, *S*-(−)-amlodipine CID_9822750, *R*-(+)-verapamil CID_65808, *S*-(−)-verapamil CID_92305 were selected from Pubchem. The structures of the enantiomers were stabilized through MMFF94 geometry optimization using Avogadro version 1.2.0 software and finalized in mol2 format. AutoDock 4.2.6 software (The Scripps Research Institute, La Jolla, CA, USA) was employed to accomplish docking calculations using the Lamarckian Genetic algorithm. In order to involve the charges of drug-related structures, the Gasteiger–Hückel calculation was applied. Grid box size of 30 × 30 × 30 Å was set up with a spacing of 0.375 Å. For each final structure of complexes of 250 independent docking runs was performed. The lowest binding energies represent the most stable analyte-selector complex. Biovia Discovery Studio Visualizer v20.1.0.19295, copyright © 2019 (Dassault Systèmes Biovia Corp, Vélizy-Villacoublay, France) was utilized to visualize the complexes.

5. Conclusions

This preliminary study reports the in house generation of an immobilized CSA-based CSP and its performance in chromatographic enantioseparation. CSA immobilization was successfully conducted onto a Chromolith® Widepore 300 Epoxy 100-4.6 mm HPLC column via a reductive amination strategy involving Schiff base formation in the presence of a diamine-spacer. The modified column exhibited chiral separation toward AML and VER in bulk samples and tablet matrices. Molecular docking projected insights into feasible complexes along with the molecular interaction between CSA and the individual enantiomers, which were found to be dominated by hydrogen bonding. The difference of binding energy (ΔG) of two enantiomers might correspond to their retention on the CSA-based chromatography column. A study on the immobilized CSA column applicability in various HPLC modes remains attractive for future research.

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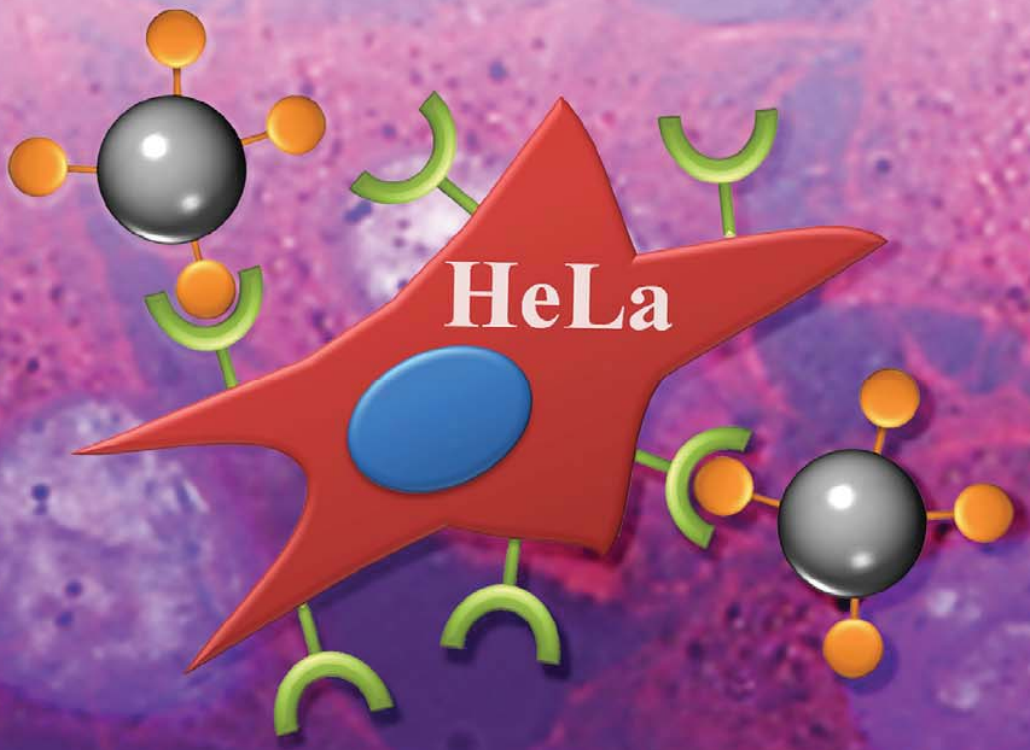

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Pharmaceuticals, Volume 14, Issue 2 (February 2021) – 100 articles

Cover Story (**view full-size image (/files/uploaded/covers/pharmaceuticals/big_cover-pharmaceuticals-v14-i2.png)**): We have demonstrated that the electrochemical method gives rise to stoichiometric cobalt ferrite nanoparticles in an easy and reproducible way, with good magnetic properties. The nanoparticles (NPs) were vectorized with folic acid to render a high uptake dose in the HeLa cancer cell line without a decrease in cell survival, up to 3 mM of Co + Fe concentration. In addition, the cytoskeleton retains its structure and morphology when nanoparticles are internalized at high doses. Relaxivity measurements of the NP-FA colloidal solution up to concentrations of 1 mM result in a high r_2 value of 479 Fe+Co $mM^{-1}s^{-1}$. Finally, in vitro analysis with the HeLa cell line of phantom T2-weighted images present a progressive negative enhancement with the increase of concentration dose, in accordance with the high r_2 value obtained. **View this paper (https://www.mdpi.com/1424-8247/14/2/124)**

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by **Joana Magalhães (https://sciprofiles.com/profile/author/emg2czhsNEdwYmJ3SzEvR0pTbXNJbHhSOUFzTElhekhMbnhRUXNOOVVacz0=)**, **Nina Franko (https://sciprofiles.com/profile/author/VVB2VExKcFBWNEY5QlNnWWZDaGxtYWx4M1VrTE54bjE1K3QyRjloTXlyUT0=)**, **Samanta Raboni (https://sciprofiles.com/profile/1361819)**, **Giannamaria Annunziato (https://sciprofiles.com/profile/763417)**, **Päivi Tammela (https://sciprofiles.com/profile/61440)**, **Agostino Bruno (https://sciprofiles.com/profile/2280554)**, **Stefano Bettati (https://sciprofiles.com/profile/834552)**, **Stefano Armao (https://sciprofiles.com/profile/author/VmNmT2NxWDZuVlpMbHRDVE1hQytuaFZUTHkzWlVRRmdMRnlBNEZ4ZVdrRT0=)**, **Costanza Spadini (https://sciprofiles.com/profile/1519303)**, **Clotilde Silvia Cabassi (https://sciprofiles.com/profile/1132612)**, **Andrea Mozzarelli (https://sciprofiles.com/profile/139511)**, **Marco Pieroni (https://sciprofiles.com/profile/265645)**, **Barbara Campanini (https://sciprofiles.com/profile/466601)** and **Gabriele Costantino (https://sciprofiles.com/profile/2713112)**

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Abstract Many bacteria and actinomycetales use L-cysteine biosynthesis to increase their tolerance to antibacterial treatment and establish a long-lasting infection. In turn, this might lead to the onset of antimicrobial resistance that currently represents one of the most menacing threats to public health worldwide. **[...] Read more.**

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Preclinical Pharmacokinetics and Biodistribution of Anticancer Dinuclear Palladium(II)-Spermine Complex (Pd_2Spm) in Mice (/1424-8247/14/2/173)

by **Martin Vojtek (https://sciprofiles.com/profile/868379)**, **Salomé Gonçalves-Monteiro (https://sciprofiles.com/profile/1382683)**, **Edgar Pinto (https://sciprofiles.com/profile/922272)**, **Sára Kalivodová (https://sciprofiles.com/profile/author/b21YTXp4SzJlZE1rQjRqL3R3VEFCaEVDaHZJMW1OY2Q4NUdNOHoyenVhOD0=)**, **Agostinho Almeida (https://sciprofiles.com/profile/257139)**, **Maria P. M. Marques (https://sciprofiles.com/profile/570243)**, **Ana L. M. Batista de Carvalho (https://sciprofiles.com/profile/916395)**, **Clara B. Martins (https://sciprofiles.com/profile/1901173)**, **Helder Mota-Filipe (https://sciprofiles.com/profile/1988305)**, **Isabel M. P. L. V. O. Ferreira (https://sciprofiles.com/profile/1002723)** and **Carmen Diniz (https://sciprofiles.com/profile/254229)**

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Abstract Palladium-based compounds are regarded as potential analogs to platinum anticancer drugs with improved properties. The present study assessed the pharmacokinetics and biodistribution of a dinuclear palladium(II)-spermine chelate (Pd_2Spm), which has previously been shown to possess promising in vitro activity against several **[...] Read more.**

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Up-Regulated Vitamin D Receptor by *Pelargonium sidoides* Extract EPs® 7630 Contributes to Rhinovirus Defense in Bronchial Epithelial Cells (/1424-8247/14/2/172)

by **Michael Roth (https://sciprofiles.com/profile/605017)**, **Qingzhu Sun (https://sciprofiles.com/profile/author/cHM5b2hXTE9TU3J1Y21OY3pXS09WVlpaTE9GSkVvYXc1UlFpbEdudnovbz0=)** and **Michael Tamm (https://sciprofiles.com/profile/author/T1dzdHZpR0pHRVp1QnJmK096VVBmVmhFT3U5Sjk4em4yaDVMSDhPL3VNZz0=)**

Pharmaceuticals **2021**, *14*(2), 172; **https://doi.org/10.3390/ph14020172 (https://doi.org/10.3390/ph14020172)** - 22 Feb 2021
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Abstract EPs®7630, extracted from *Pelargonium sidoides*, reduces the severity of viral upper respiratory tract infections. Vitamin D also improves anti-viral host defense through similar signaling pathways. This study assessed if EPs®7630 modifies vitamin D receptor (VDR) expression and function **[...] Read more.**
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***Cannabis*-Based Oral Formulations for Medical Purposes: Preparation, Quality and Stability (/1424-8247/14/2/171)**

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Pharmaceuticals **2021**, *14*(2), 171; **https://doi.org/10.3390/ph14020171 (https://doi.org/10.3390/ph14020171)** - 22 Feb 2021
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Abstract Current legislation in Italy provides that medical *Cannabis* may be administered orally or by inhalation. One of the fundamental criteria for the administration of oral formulations is that they deliver a known consistent quantity of the active ingredients to ensure uniform therapies leading **[...] Read more.**
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PARP Traps Rescue the Pro-Inflammatory Response of Human Macrophages in the In Vitro Model of LPS-Induced Tolerance (/1424-8247/14/2/170)

by **Julita Pietrzak (https://sciprofiles.com/profile/1331359)**,
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Abstract Secondary infections cause sepsis that lead to patient disability or death. Contact of macrophages with bacterial components (such as lipopolysaccharide—LPS) activates the intracellular signaling pathway downstream of Toll-like receptors (TLR), which initiate an immune proinflammatory response. However, the expression of nuclear factor-kappa B **[...] Read more.**
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Synthesis and Biological Evaluation of 1-(Diarylmethyl)-1*H*-1,2,4-triazoles and 1-(Diarylmethyl)-1*H*-imidazoles as a Novel Class of Anti-Mitotic Agent for Activity in Breast Cancer (/1424-8247/14/2/169)

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Abstract We report the synthesis and biochemical evaluation of compounds that are designed as hybrids of the microtubule targeting benzophenone phenstatin and the aromatase inhibitor letrozole. A preliminary screening in estrogen receptor (ER)-positive MCF-7 breast cancer cells identified 5-((2*H*-1,2,3-triazol-1-yl)(3,4,5-trimethoxyphenyl)methyl)-2-methoxyphenol **24** as a **[...] Read more.**
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Non-Coding RNAs: The “Dark Side Matter” of the CLL Universe (/1424-8247/14/2/168)

by Marcello Francesco Lingua (https://sciprofiles.com/profile/1447088), Giovanna Carrà (https://sciprofiles.com/profile/569893), Beatrice Maffeo (https://sciprofiles.com/profile/1468663) and Alessandro Morotti (https://sciprofiles.com/profile/204349)

Pharmaceuticals **2021**, *14*(2), 168; https://doi.org/10.3390/ph14020168 (https://doi.org/10.3390/ph14020168) - 21 Feb 2021

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Abstract For many years in the field of onco-hematology much attention has been given to mutations in protein-coding genes or to genetic alterations, including large chromosomal losses or rearrangements. Despite this, biological and clinical needs in this sector remain unmet. Therefore, it is not **[...] Read more.**

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Advances in Development of Radiometal Labeled Amino Acid-Based Compounds for Cancer Imaging and Diagnostics (/1424-8247/14/2/167)

by Mária Bodnár Mikulová (https://sciprofiles.com/profile/1093339) and Peter Mikuš (https://sciprofiles.com/profile/288443)

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Abstract Radiolabeled biomolecules targeted at tumor-specific enzymes, receptors, and transporters in cancer cells represent an intensively investigated and promising class of molecular tools for the cancer diagnosis and therapy. High specificity of such biomolecules is a prerequisite for the treatment with a lower burden **[...] Read more.**

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Losartan Improves Memory, Neurogenesis and Cell Motility in Transgenic Alzheimer’s Mice (/1424-8247/14/2/166)

by Henning Johannes Drews (https://sciprofiles.com/profile/1468331), Roman Klein (https://sciprofiles.com/profile/author/azE1cERUOFhJN2NiT05ZTWkzbCtWdWdORmhGZWZEbHcrSHlHTjl4OWJvND0=), Ali Lourhmati (https://sciprofiles.com/profile/author/TlVuSC93NHR6WC9Xc3NoMjE0SEY3Sm82WndmMWFZYUkwQ1lRSEFNQXRPST0=), Marine Buadze (https://sciprofiles.com/profile/author/NFdWNHQ1cjhRZk1hNWhNRDl2WVNUMmsxQ3o3aFFydkl5RnRzb1h5bWs3TT0=), Elke Schaeffeler (https://sciprofiles.com/profile/author/Vms2Y2dMRWx6d3B2R1IyRUszK2Y5TDEya1NxcjE5WUk1T2xlZGo5L0h5dUpBVXJYd0hwQXRITzZ6RW5ibEFqQQ==), Thomas Lang (https://sciprofiles.com/profile/author/Zm5oVytSRTB5ak1WN0RKVk1DVUtPdmVUdXBrTFRxdEdhSXAyUTVwTWY1OD0=), Torgom Seferyan (https://sciprofiles.com/profile/author/Z2xjUXpOOWtkSk1wRmtleUNtWUpVYjdqNzNselowcDcySHJHczVVMVovRT0=), Leah R. Hanson (https://sciprofiles.com/profile/author/ai9SSUZJMUJVUGhBTFlyN214VndwSER6d0hpVVNOWksweUNsRkhWY3JHZzNhV05GbHE1d2NaSEtMaXZMcTNhQg==), William H. Frey II (https://sciprofiles.com/profile/986077), Tom C.G.M. de Vries (https://sciprofiles.com/profile/1492139), Inge A.E.W. Thijssen-van Loosdregt (https://sciprofiles.com/profile/author/VG1KY0ttOXVGKzdyS2VmdzVUUElOYXJYZWdyT0ZORUtxSWN1OE5DWGdScz0=), Christoph H. Gleiter (https://sciprofiles.com/profile/author/cFJXMXhJK1FqZlMveDcyc3J6dTNQL2U5YzdQZHZHNFVldGxMRXdYY05DdVFmSUxSeTBha2JvbFQ5VG1WTFhzQg==), Matthias Schwab (https://sciprofiles.com/profile/6686) and Lusine Danielyan (https://sciprofiles.com/profile/1148962)

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Abstract Angiotensin receptor blockers (ARBs) have demonstrated multiple neuroprotective benefits in Alzheimer's disease (AD) models. However, their beneficial effects on memory deficits, cholinergic activity, neurogenesis and Amyloid beta (Aβ) clearance reveal significant interstudy variability. The delivery route can impact not only delivery but also **[...] Read more.**

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Open Access Article **(/1424-8247/14/2/165/pdf?version=1614136382)**

A Multicenter Retrospective Study Evaluating Brivaracetam in the Treatment of Epilepsies in Clinical Practice (/1424-8247/14/2/165)

by **Maria Stefanatou (https://sciprofiles.com/profile/1241756)**, **Eirini Vasileiadou Kapetanou (https://sciprofiles.com/profile/1477936)**, **Vasilios K. Kimiskidis (https://sciprofiles.com/profile/2524304)**, **Vasileios Papaliagkas (https://sciprofiles.com/profile/1457275)**, **Panagiotis Polychronopoulos (https://sciprofiles.com/profile/author/Z1Y2T3FjYklXUHRpOUszeWppM0dZcXFNY3E5dFJNNzVJakFUT2JyMk9Baz0=)**, **Sofia Markoula (https://sciprofiles.com/profile/author/ZVU5V1Vwc1A5V2xyZWZFbk8yVUlCZUFJcHZtTzJIVlRKQ0h6ajc1V1FHVT0=)**, **Kleoniki Charisiou (https://sciprofiles.com/profile/author/UGh4c2x0TG0wT2tFZ1hrMXdRdExuRkNyYUhJTDhGNXhrUFArSVU0R21nND0=)**, **Dimitrios Kazis (https://sciprofiles.com/profile/author/N2p3bm15N0JkdmdwRzY3ZFF1eXdKUCs0WHduNkJyRGtVZnVScDFrSXRmQT0=)**, **Anastasia Verentzioti (https://sciprofiles.com/profile/3019629)**, **Panayiotis Patrikelis (https://sciprofiles.com/profile/1731988)**, **Athanasia Alexoudi (https://sciprofiles.com/profile/2579429)** and **Stylianos Gatzonis (https://sciprofiles.com/profile/1789880)**

Pharmaceuticals **2021**, *14*(2), 165; **https://doi.org/10.3390/ph14020165 (https://doi.org/10.3390/ph14020165)** - 19 Feb 2021

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Abstract Brivaracetam (BRV) is the latest approved antiepileptic drug. The aim of the study was to evaluate the efficacy and tolerability of BRV in everyday clinical practice. In this retrospective, observational, multicenter study, data from epilepsy patients receiving BRV from January 2018 to July **[...] Read more.**

(This article belongs to the Special Issue **Therapeutic Agents for Neurological Disorders (/journal/pharmaceuticals/special_issues/Therapeutic_Neurological_Disorder)**)

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Open Access Article **(/1424-8247/14/2/164/pdf?version=1613800931)**

In Vitro Characterization of Inhalable Cationic Hybrid Nanoparticles as Potential Vaccine Carriers (/1424-8247/14/2/164)

by **Iman M. Alfagih (https://sciprofiles.com/profile/1260515)**, **Kan Kaneko (https://sciprofiles.com/profile/author/UXFYUk43ODdWc2ozZWxDQ2MyQk9BdWJleUNPcjEvQmpqb21YMjJ4ZlE3bz0=)**, **Nitesh K. Kunda (https://sciprofiles.com/profile/448927)**, **Fars Alanazi (https://sciprofiles.com/profile/788642)**, **Sarah R. Dennison (https://sciprofiles.com/profile/3068631)**, **Hesham M. Tawfeek (https://sciprofiles.com/profile/1481384)** and **Imran Y. Saleem (https://sciprofiles.com/profile/729861)**

Pharmaceuticals **2021**, *14*(2), 164; **https://doi.org/10.3390/ph14020164 (https://doi.org/10.3390/ph14020164)** - 18 Feb 2021

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Abstract In this study, PGA-co-PDL nanoparticles (NPs) encapsulating model antigen, bovine serum albumin (BSA), were prepared via double emulsion solvent evaporation. In addition, chitosan hydrochloride (CHL) was incorporated into the external phase of the emulsion solvent method, which resulted in surface adsorption onto the **[...] Read more.**

(This article belongs to the Special Issue **Nano Drug Carriers 2021 (/journal/pharmaceuticals/special_issues/NanoDrugCarriers_2)**)

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Open Access Article **(/1424-8247/14/2/163/pdf?version=1613647722)**

Development and Validation of an LC-MS/MS Method for Quantification of the Novel Antibacterial Candidate DA-7010 in Plasma and Application to a Preclinical Pharmacokinetic Study (/1424-8247/14/2/163)

by **Mi Hye Kwon (https://sciprofiles.com/profile/author/QjFYTStzVVhnWFAzMTlzODRHQWgwUkVNNTNJSzltRmdMUnZ6V3puMFlBVT0=)**, **Dae Young Lee (https://sciprofiles.com/profile/author/WmNNSTlJcktBY1lLUHJpVDFldG9VdnFUKzZtbUJNVmxhcnNQRGkwd2R5ST0=)** and **Hee Eun Kang (https://sciprofiles.com/profile/100568)**

Pharmaceuticals **2021**, *14*(2), 163; **https://doi.org/10.3390/ph14020163 (https://doi.org/10.3390/ph14020163)** - 18 Feb 2021

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Abstract DA-7010 is a new candidate for an antibacterial agent that targets Gram-negative pathogens by acting as a leucyl-tRNA synthetase inhibitor. In this study, a simple and rapid liquid chromatography tandem mass spectrometry (LC-MS/MS) method was developed to determine DA-7010 levels in the plasma **[...] Read more.**

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Open Access Article (/1424-8247/14/2/162/pdf?version=1614301767)

Limited Sampling Strategy for Determination of Ibrutinib Plasma Exposure: Joint Analyses with Metabolite Data (/1424-8247/14/2/162)

by Félicien Le Louedec (https://sciprofiles.com/profile/1272484), Fanny Gallais (https://sciprofiles.com/profile/1484246), Fabienne Thomas (https://sciprofiles.com/profile/1314802), Mélanie White-Koning (https://sciprofiles.com/profile/1482735), Ben Allal (https://sciprofiles.com/profile/1428074), Caroline Protin (https://sciprofiles.com/profile/author/Z0poNGJ1bjJCYkxZdWhVc1A3YkRyNk94dnA3WVRrOXpld0NKUXdiUi9BZGQwTU01dUYwNUFvVHFyMXJ5V1FWQQ==), Loïc Ysebaert (https://sciprofiles.com/profile/author/b0dlNXFkaXowR2tEN3R6eWdLM3plQmt4ZTY4OVFIL2ZqTmJMQTY1aGRPcz0=), Étienne Chatelut (https://sciprofiles.com/profile/1268537) and Florent Puisset (https://sciprofiles.com/profile/2577272)

Pharmaceuticals **2021**, *14*(2), 162; https://doi.org/10.3390/ph14020162 (https://doi.org/10.3390/ph14020162) - 18 Feb 2021

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Abstract Therapeutic drug monitoring of ibrutinib is based on the area under the curve of concentration vs. time (AUC_{IBRU}) instead of trough concentration ($C_{min,ss}$) because of a limited accumulation in plasma. Our objective was to identify a limited sampling strategy **[...] Read more.**

(This article belongs to the Special Issue **Precision Medicine in Oncology: Controlling the Pharmacokinetics Variability (/journal/pharmaceuticals/special_issues/Oncology_Pharmacokinetics)**)

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Open Access Review (/1424-8247/14/2/161/pdf?version=1614304246)

Bacteriophages as Therapeutic and Diagnostic Vehicles in Cancer (/1424-8247/14/2/161)

by Valentina Foglizzo (https://sciprofiles.com/profile/1568311) and Serena Marchiò (https://sciprofiles.com/profile/937955)

Pharmaceuticals **2021**, *14*(2), 161; https://doi.org/10.3390/ph14020161 (https://doi.org/10.3390/ph14020161) - 17 Feb 2021

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Abstract Evolution of nanomedicine is the re-design of synthetic and biological carriers to implement novel theranostic platforms. In recent years, bacteriophage research favors this process, which has opened up new roads in drug and gene delivery studies. By displaying antibodies, peptides, or proteins on **[...] Read more.**

(This article belongs to the Special Issue **Bacteriophages as Therapeutic Delivery Vehicles (/journal/pharmaceuticals/special_issues/Bacteriophages_Therapeutic_Delivery_Vehicles)**)

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Open Access Article (/1424-8247/14/2/160/pdf?version=1614080747)

Design and Mechanism of Action of a New Prototype of Combi-Molecule "Programed" to Release Bioactive Species at a pH Range Akin to That of the Tumor Microenvironment (/1424-8247/14/2/160)

by Anne-Laure Larroque-Lombard (https://sciprofiles.com/profile/author/YTRzN0pGdkxYREhob0JEc2hQTkdNOGlCL215bCt5OFExMWRYVmxTSHZ2dXBGSlhOMFhEZ3lZQWQySFFI), Etienne Chatelut (https://sciprofiles.com/profile/1268537), Jean-Pierre Delord (https://sciprofiles.com/profile/2214179), Diane-Charlotte Imbs (https://sciprofiles.com/profile/author/a3ZMM0QwRU45a3g3L04rT0M3N3lYeTZ0bmZodTRrSEhtQlBvYXhrbzhwRVFmOFpUM2VpSGRVUHlZcjJjZDBTbQ==), Philippe Rochaix (https://sciprofiles.com/profile/author/aWdDY25QKzIxYmNQWEhVY29OcU8rZDBYNU9sc1pTd2tEeHBhNmp6akJZNUxkL21KRVFxeXpMaG5uSUczNWlpTg==), Bertrand Jean-Claude (https://sciprofiles.com/profile/271068) and Ben Allal (https://sciprofiles.com/profile/1428074)

Pharmaceuticals **2021**, *14*(2), 160; https://doi.org/10.3390/ph14020160 (https://doi.org/10.3390/ph14020160) - 16 Feb 2021

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Abstract The clinical use of cytotoxic agents is plagued by systemic toxicity. We report a novel approach that seeks to design a "combi-molecule" to behave as an alkylating agent on its own and to undergo acid-catalyzed conversion to two bioactive species at a pH **[...] Read more.**

(This article belongs to the Special Issue **Precision Medicine in Oncology: Controlling the Pharmacokinetics Variability (/journal/pharmaceuticals/special_issues/Oncology_Pharmacokinetics)**)

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Open Access Case Report (/1424-8247/14/2/159/pdf?version=1614268726)

Tumor Type Agnostic Therapy Carrying BRAF Mutation: Case Reports and Review of Literature (/1424-8247/14/2/159)

by Ottavia Bernocchi (https://sciprofiles.com/profile/1382087), Marianna Sirico (https://sciprofiles.com/profile/1312937), Silvia Paola Corona (https://sciprofiles.com/profile/author/K3M1RXcrR3lDbURWU2hob0J2UjlERFY2RDF0c3pQZnBheFdGVU5NMUJicz0=), Carla Strina (https://sciprofiles.com/profile/author/czRybWdlN0hUejlPdGtsQ25VS0FGVXFUK1dMQnlSeXYweDY4VmQ2UjBWST0=), Manuela Milani (https://sciprofiles.com/profile/author/VGMzWWpDQkFQNU14c1g5Q2ViQkFZTHZPYXVVNzRER2x0WHdEL1YxTjlucz0=), Maria Rosa Cappelletti (https://sciprofiles.com/profile/2443422), Giuseppina Ferrero (https://sciprofiles.com/profile/author/clkzaXpGZlJvTUxYSFVlZGw4ZDBPZGtwM3dpZWlpUG43R1dEekdHV0NEVT0=), Nicoletta Ziglioli (https://sciprofiles.com/profile/author/V0NhM0o3WkMyNkljWjZvMjFmVnV0ZlRDakZzK3RVaHNhbEQrTStNajBHST0=), Valeria Cervoni (https://sciprofiles.com/profile/author/YmZ0WE5STnVTY3ZNQ0dpSEVqcGNRaERybEJCZDc4dDlIbkswM3FUZGpkbz0=), Andrea Macchiavelli (https://sciprofiles.com/profile/author/SXU3WlIreTRRZ3VNa0d6TVdOTUZKdkNaMVhNUTM0cjJHZTNOc25aWlppcz0=), Giandomenico Roviello (https://sciprofiles.com/profile/1246038) and Daniele Generali (https://sciprofiles.com/profile/1531980)

Pharmaceuticals **2021**, *14*(2), 159; https://doi.org/10.3390/ph14020159 (https://doi.org/10.3390/ph14020159) - 16 Feb 2021

Cited by 4 (/1424-8247/14/2/159#metrics) | Viewed by 2649

Abstract Background: Precision medicine is based on molecular and genotypic patient characterization to define specific target treatment. BRAF mutation is an oncogenic driver, and the Cancer Genome Atlas has identified BRAF mutations in different cancer types. Tumor type agnostic therapy is based on targeting **[...] Read more.**

(This article belongs to the Special Issue **Cancer Translational Biomarkers and Targeted Therapies (/journal/pharmaceuticals/special_issues/Cancer_Biomarkers_Targeted_Therapies)**)

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Open Access Article (/1424-8247/14/2/158/pdf?version=1613388880)

Preparation and Bioevaluation of Novel ^{99m}Tc-Labeled Complexes with a 2-Nitroimidazole HYNIC Derivative for Imaging Tumor Hypoxia (/1424-8247/14/2/158)

by **Qing Ruan (https://sciprofiles.com/profile/1433699)**, **Qianqian Gan (https://sciprofiles.com/profile/author/Rkt6VUozUmxFdUhlUHRaT1I3T2RxMzVha2srR0Y2VkZzSHB2d2lxUXdVST0=)**, **Xuran Zhang (https://sciprofiles.com/profile/author/dkFYMlFMNlFKd3N1TEVEVTlka2lOM1lLZVlMaVk5NzQ4TjNSQXVBdG8xWT0=)**, **Si'an Fang (https://sciprofiles.com/profile/1373067)** and **Junbo Zhang (https://sciprofiles.com/profile/150552)**

Pharmaceuticals **2021**, *14*(2), 158; **https://doi.org/10.3390/ph14020158 (https://doi.org/10.3390/ph14020158)** - 15 Feb 2021

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Abstract To develop novel ^{99m}Tc-labeled single-photon emission computed tomography (SPECT) radiotracers for imaging hypoxia, a novel HYNICNM ligand (6-hydrazinonicotinamide (HYNIC) 2-nitroimidazole derivative) was designed and synthesized. It was radiolabeled with technetium-99m using tricine/trisodium triphenylphosphine-3,3′,3″-trisulfonate (TPPTS), tricine/sodium triphenylphosphine-3-monosulfonate (TPPMS) and tricine as co-ligands to **[...] Read more.**

(This article belongs to the Special Issue **Forward Thinking towards Theranostic (Radio)ligands Targeting the Tumor Microenvironment (TME) (/journal/pharmaceuticals/special_issues/radio_TEM)**)

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Open Access Review (/1424-8247/14/2/157/pdf?version=1613784153)

Status and Challenges of Plant-Anticancer Compounds in Cancer Treatment (/1424-8247/14/2/157)

by **Paula Garcia-Oliveira (https://sciprofiles.com/profile/1138017)**, **Paz Otero (https://sciprofiles.com/profile/285392)**, **Antia Gonzalez Pereira (https://sciprofiles.com/profile/991297)**, **Franklin Chamorro (https://sciprofiles.com/profile/1293681)**, **Maria Carpena (https://sciprofiles.com/profile/1019959)**, **Javier Echave (https://sciprofiles.com/profile/1431323)**, **Maria Fraga-Corral (https://sciprofiles.com/profile/948109)**, **Jesus Simal-Gandara (https://sciprofiles.com/profile/39954)** and **Miguel Angel Prieto (https://sciprofiles.com/profile/607720)**

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Abstract Nowadays, cancer is one of the deadliest diseases in the world, which has been estimated to cause 9.9 million deaths in 2020. Conventional treatments for cancer commonly involve mono-chemotherapy or a combination of radiotherapy and mono-chemotherapy. However, the negative side effects of these **[...] Read more.**

(This article belongs to the Special Issue **Anticancer Compounds in Medicinal Plants (/journal/pharmaceuticals/special_issues/anticancer_Medicinal_Plants)**)

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Open Access Article (/1424-8247/14/2/156/pdf?version=1613644686)

Quetiapine-Induced Place Preference in Mice: Possible Dopaminergic Pathway (/1424-8247/14/2/156)

by **Yusuf S. Althobaiti (https://sciprofiles.com/profile/656493)**

Pharmaceuticals **2021**, *14*(2), 156; **https://doi.org/10.3390/ph14020156 (https://doi.org/10.3390/ph14020156)** - 14 Feb 2021

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Abstract Quetiapine, an atypical antipsychotic, is effective in the management of schizophrenia, depression, and anxiety. Although quetiapine overdosage and misuse have been reported, its abuse potential has not been investigated in animals. In this study, the abuse potential of quetiapine was assessed based on **[...] Read more.**

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Synthesis, Characterization, and Biological Evaluation of New Derivatives Targeting MbtI as Antitubercular Agents (/1424-8247/14/2/155)

by **Matteo Mori (https://sciprofiles.com/profile/933478)**, **Giovanni Stelitano (https://sciprofiles.com/profile/994802)**, **Laurent R. Chiarelli (https://sciprofiles.com/profile/194424)**, **Giulia Cazzaniga (https://sciprofiles.com/profile/1482861)**, **Arianna Gelain (https://sciprofiles.com/profile/1264252)**, **Daniela Barlocco (https://sciprofiles.com/profile/271438)**, **Elena Pini (https://sciprofiles.com/profile/453200)**, **Fiorella Meneghetti (https://sciprofiles.com/profile/290715)** and **Stefania Villa (https://sciprofiles.com/profile/582863)**

Pharmaceuticals **2021**, *14*(2), 155; **https://doi.org/10.3390/ph14020155 (https://doi.org/10.3390/ph14020155)** - 13 Feb 2021

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Abstract Tuberculosis (TB) causes millions of deaths every year, ranking as one of the most dangerous infectious diseases worldwide. Because several pathogenic strains of *Mycobacterium tuberculosis* (Mtb) have developed resistance against most of the established anti-TB drugs, new therapeutic options are urgently needed. An **[...] Read more.**

(This article belongs to the Special Issue **Novel Antibacterial Agents (/journal/pharmaceuticals/special_issues/Antibacterial_Agents)**)

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Open Access Review (/1424-8247/14/2/154/pdf?version=1614130353)

The Treatment of Lung Involvement in Systemic Sclerosis (/1424-8247/14/2/154)

by Barbara Ruaro (https://sciprofiles.com/profile/1139879), Marco Confalonieri (https://sciprofiles.com/profile/646766), Marco Matucci-Cerinic (https://sciprofiles.com/profile/2565491), Francesco Salton (https://sciprofiles.com/profile/230995), Paola Confalonieri (https://sciprofiles.com/profile/1139880), Mario Santagiuliana (https://sciprofiles.com/profile/author/a2g2MWJLMUx5dHdWTlZ4RFlMV2NVUTZVL25nZFRUNW14NmVXSkZ1K1BNST0=), Gloria Maria Citton (https://sciprofiles.com/profile/1485097), Elisa Baratella (https://sciprofiles.com/profile/749110) and Cosimo Bruni (https://sciprofiles.com/profile/1383151)

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Abstract Systemic sclerosis (SSc) patients are often affected by interstitial lung disease (ILD) and, although there have been recent treatment advances, it remains the leading cause of death among SSc, with a 10-year mortality up to 40%. African Americans and subjects with diffuse cutaneous **[...] Read more.**

(This article belongs to the Special Issue **Rheumatic Diseases: Pathophysiology, Targeted Therapy, Focus on Vascular and Pulmonary Manifestations (/journal/pharmaceuticals/special_issues/Rheumatic_Diseases)**)

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Pharyngeal Pumping and Tissue-Specific Transgenic P-Glycoprotein Expression Influence Macrocyclic Lactone Susceptibility in *Caenorhabditis elegans* (/1424-8247/14/2/153)

by Alexander P. Gerhard (https://sciprofiles.com/profile/1423265), Jürgen Krücken (https://sciprofiles.com/profile/1462346), Cedric Neveu (https://sciprofiles.com/profile/1601607), Claude L. Charvet (https://sciprofiles.com/profile/1070604), Abdallah Harmache (https://sciprofiles.com/profile/author/WlYyalpCUkF4UHhGbkFzVzhrR1MzUVF5VUdHVnNjblk5OXpaeE5tVERjbz0=) and Georg von Samson-Himmelstjerna (https://sciprofiles.com/profile/1244122)

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Abstract Macrocyclic lactones (MLs) are widely used drugs to treat and prevent parasitic nematode infections. In many nematode species including a major pathogen of foals, *Parascaris univalens*, resistance against MLs is widespread, but the underlying resistance mechanisms and ML penetration routes into nematodes **[...] Read more.**

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Therapeutic Applications of Type 2 Diabetes Mellitus Drug Metformin in Patients with Osteoarthritis (/1424-8247/14/2/152)

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Abstract Type 2 diabetes mellitus (T2DM) and osteoarthritis (OA) are common chronic diseases that frequently co-exist. The link between OA and T2DM is attributed to common risk factors, including age and obesity. Several reports suggest that hyperglycemia and accumulated advanced glycosylation end-products might regulate **[...] Read more.**

(This article belongs to the Special Issue **Drug and Therapy for Osteoarthritis (OA) (/journal/pharmaceuticals/special_issues/Drug_Osteoarthritis)**)

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Immune Checkpoint Inhibition in Oesophago-Gastric Carcinoma (/1424-8247/14/2/151)

by Anica Högner (https://sciprofiles.com/profile/1433073) and Peter Thuss-Patience (https://sciprofiles.com/profile/1433639)

Pharmaceuticals **2021**, *14*(2), 151; https://doi.org/10.3390/ph14020151 (https://doi.org/10.3390/ph14020151) - 12 Feb 2021

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Abstract Immune checkpoint inhibitors enrich the therapeutic landscape in oesophago-gastric carcinoma. With regard to oesophageal squamous cell carcinoma (ESCC), the selective PD-1 (programmed cell death receptor 1)-inhibitor nivolumab improves disease-free survival in the adjuvant therapy setting (CHECKMATE-577). In first-line treatment, ESCC patients (pts) benefit **[...] Read more.**

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Assessment of Novel Inhaler Technique Reminder Labels in Image Format on the Correct Demonstration of Inhaler Technique Skills in Asthma: A Single-Blinded

Randomized Controlled Trial (/1424-8247/14/2/150)

by Iman Basheti (https://sciprofiles.com/profile/1393176),
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Pharmaceuticals **2021**, *14*(2), 150; https://doi.org/10.3390/ph14020150 (https://doi.org/10.3390/ph14020150) - 12 Feb 2021

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Abstract Background: Prevalence of asthma in the United Arab Emirates (UAE) is high, and training patients on correct inhaler technique is vital. Objectives: To assess the effectiveness of inhaler technique labels incorporating the individual technique steps in image format on the retention of correct **[...] Read more.**

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The Role of miRNA-7 in the Biology of Cancer and Modulation of Drug Resistance (/1424-8247/14/2/149)

by Ewa Gajda (https://sciprofiles.com/profile/820998), Małgorzata Grzanka (https://sciprofiles.com/profile/624572),
Marlena Godlewska (https://sciprofiles.com/profile/383995) and Damian Gawel (https://sciprofiles.com/profile/690508)

Pharmaceuticals **2021**, *14*(2), 149; https://doi.org/10.3390/ph14020149 (https://doi.org/10.3390/ph14020149) - 12 Feb 2021

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Abstract MicroRNAs (miRNAs, miRs) are small non-coding RNA (ncRNA) molecules capable of regulating post-transcriptional gene expression. Imbalances in the miRNA network have been associated with the development of many pathological conditions and diseases, including cancer. Recently, miRNAs have also been linked to the phenomenon **[...] Read more.**

(This article belongs to the Special Issue MiRNA-Based Therapeutics in Cancer (/journal/pharmaceuticals/special_issues/miRNA_Cancer))

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Modulation of the Serotonergic Receptosome in the Treatment of Anxiety and Depression: A Narrative Review of the Experimental Evidence (/1424-8247/14/2/148)

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Abstract Serotonin (5-HT) receptors are found throughout central and peripheral nervous systems, mainly in brain regions involved in the neurobiology of anxiety and depression. 5-HT receptors are currently promising targets for discovering new drugs for treating disorders ranging from migraine to neuropsychiatric upsets, such **[...] Read more.**

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Application of RP-18 TLC Retention Data to the Prediction of the Transdermal Absorption of Drugs (/1424-8247/14/2/147)

by Anna W. Sobańska (https://sciprofiles.com/profile/639722), Jeremy Robertson (https://sciprofiles.com/profile/2907074) and
Elżbieta Brzezińska (https://sciprofiles.com/profile/2708211)

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Abstract Several chromatographic parameters (R_M^0 and S obtained from RP-18 TLC with methanol—pH 7.4 phosphate buffer mobile phases by extrapolation to zero concentration of methanol; R_f and R_M obtained from RP-18 TLC with acetonitrile—pH 7.4 phosphate buffer 70:30 *v* **[...] Read more.**

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Zingerone Targets Status Epilepticus by Blocking Hippocampal Neurodegeneration via Regulation of Redox Imbalance, Inflammation and Apoptosis (/1424-8247/14/2/146)

by Summya Rashid (https://sciprofiles.com/profile/2648758), Adil Farooq Wali (https://sciprofiles.com/profile/929965), Shahzada Mudasir Rashid (https://sciprofiles.com/profile/author/UGFnUk1aaytlamRlRmJleGh0WG9YaEo4d0ZPWTBwYlpYeDd6cnlwVHVubz0=), Rana M. Alsaffar (https://sciprofiles.com/profile/author/QUZBNGVCbmxaMkpMQVR5YWNlczAvS3RJL2tCbm4vSWFtb3VYZk9sdWkyST0=), Ajaz Ahmad (https://sciprofiles.com/profile/2207453), Basit L. Jan (https://sciprofiles.com/profile/author/YnUvY0hHdys1cGtqdUJvbFdjNEszUT09), Bilal Ahmad Paray (https://sciprofiles.com/profile/1399345), Saeed M. A. Alqahtani (https://sciprofiles.com/profile/author/Smk4N0crVWJiNEdMNkd6ZnZMdXNhWDhkcmdQNHhhNDd3VmFlVzVETTE1Zz0=), Azher Arafah (https://sciprofiles.com/profile/2676276) and Muneeb U. Rehman (https://sciprofiles.com/profile/849683)

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Abstract Epilepsy is an intricate neurological disease where the neurons are severely affected, leading to the mortality of millions worldwide. Status epilepticus (SE), induced by lithium chloride (LiCl) and pilocarpine, is the most accepted model for epilepsy. The current work aims to unravel the **[...] Read more.**

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2020 FDA TIDES (Peptides and Oligonucleotides) Harvest (/1424-8247/14/2/145)

by Othman Al Musaimi (https://sciprofiles.com/profile/426594), Danah Al Shaer (https://sciprofiles.com/profile/434145), Fernando Albericio (https://sciprofiles.com/profile/11221) and Beatriz G. de la Torre (https://sciprofiles.com/profile/328218)

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Abstract 2020 has been an extremely difficult and challenging year as a result of the coronavirus disease 2019 (COVID-19) pandemic and one in which most efforts have been channeled into tackling the global health crisis. The US Food and Drug Administration (FDA) has approved **[...] Read more.**

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Open Access Article (/1424-8247/14/2/144/pdf?version=1614160561)

Novel Potent and Selective DPP-4 Inhibitors: Design, Synthesis and Molecular Docking Study of Dihydropyrimidine Phthalimide Hybrids (/1424-8247/14/2/144)

by Ahmed A. E. Mourad (https://sciprofiles.com/profile/1384759), Ahmed E. Khodir (https://sciprofiles.com/profile/1452692), Sameh Saber (https://sciprofiles.com/profile/1626678) and Mai A. E. Mourad (https://sciprofiles.com/profile/1384865)

Pharmaceuticals **2021**, *14*(2), 144; https://doi.org/10.3390/ph14020144 (https://doi.org/10.3390/ph14020144) - 11 Feb 2021

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Abstract Background: Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as anti-hyperglycemic agents that improve glycemic control in type 2 diabetic patients, either as monotherapy or in combination with other antidiabetic drugs. Methods: A novel series of dihydropyrimidine phthalimide hybrids was synthesized and evaluated for their **[...] Read more.**

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Open Access Feature Paper Article (/1424-8247/14/2/143/pdf?version=1614133887)

3D Printing of Mini Tablets for Pediatric Use (/1424-8247/14/2/143)

by Julius Krause (https://sciprofiles.com/profile/2434449), Laura Müller (https://sciprofiles.com/profile/2529181), Dorota Sarwinska (https://sciprofiles.com/profile/1503089), Anne Seidlitz (https://sciprofiles.com/profile/1654191), Malgorzata Sznitowska (https://sciprofiles.com/profile/489595) and Werner Weitschies (https://sciprofiles.com/profile/540846)

Pharmaceuticals **2021**, *14*(2), 143; https://doi.org/10.3390/ph14020143 (https://doi.org/10.3390/ph14020143) - 11 Feb 2021

Cited by 24 (/1424-8247/14/2/143#metrics) | Viewed by 3199

Abstract In the treatment of pediatric diseases, suitable dosages and dosage forms are often not available for an adequate therapy. The use of innovative additive manufacturing techniques offers the possibility of producing pediatric dosage forms. In this study, the production of mini tablets using **[...] Read more.**

(This article belongs to the Special Issue **Advances in 3D Printed Drug Controlled Delivery Systems and Biomedical Applications (/journal/pharmaceuticals/special_issues/3D_Drug)**)

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Open Access Article (/1424-8247/14/2/142/pdf?version=1613791087)

Herbal-Based Formulation Containing *Eurycoma longifolia* and *Labisia pumila* Aqueous Extracts: Safe for Consumption? (/1424-8247/14/2/142)

by Bee Ping Teh (https://sciprofiles.com/profile/1242103), Norzahirah Ahmad (https://sciprofiles.com/profile/444572), Elda Nurafnie Ibnu Rasid (https://sciprofiles.com/profile/1394656), Nor Azlina Zolkifli (https://sciprofiles.com/profile/author/TzdJN29MZGREbDVsSDhqRXJJQ2ZUYTBzekJkYzJ1WllML0NBaDk5TDFtOD0=), Umi Rubiah Sastu@Zakaria (https://sciprofiles.com/profile/1392406), Norliyana Mohamed Yusoff (https://sciprofiles.com/profile/author/RzJoYkZqeUxYSDZkR0thSERCTHVYOXl2dW1uRTF4dW9reTJTQjBDNms2ST0=), Azlina Zulkapli (https://sciprofiles.com/profile/1366508), Norfarahana Japri (https://sciprofiles.com/profile/author/QkRBMzUxU2FEMkR3VFVKUlhsTXBxdTBlU2VHR05lV255Z01oT1piNXBwRT0=), June Chelyn Lee (https://sciprofiles.com/profile/1369762) and Hussin Muhammad (https://sciprofiles.com/profile/1390284)

Pharmaceuticals **2021**, *14*(2), 142; https://doi.org/10.3390/ph14020142 (https://doi.org/10.3390/ph14020142) - 10 Feb 2021

Cited by 3 (/1424-8247/14/2/142#metrics) | Viewed by 2292

Abstract A combined polyherbal formulation containing tongkat ali (*Eurycoma longifolia*) and kacip fatimah (*Labisia pumila*) aqueous extracts was evaluated for its safety aspect. A repeated dose 28-day toxicity study using Wistar rats was conducted where the polyherbal formulation was administered **[...] Read more.**

(This article belongs to the Special Issue **Medicinal Plants 2020 (/journal/pharmaceuticals/special_issues/med_plants_2020)**)

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Open Access Article (/1424-8247/14/2/141/pdf?version=1612965440)

A New Computer Model for Evaluating the Selective Binding Affinity of Phenylalkylamines to T-Type Ca^{2+} Channels (/1424-8247/14/2/141)

by You Lu (https://sciprofiles.com/profile/author/K05GR2VHdHBsTXBLbHhzTG1nNDJRdz09) and Ming Li (https://sciprofiles.com/profile/1406936)

Pharmaceuticals **2021**, *14*(2), 141; https://doi.org/10.3390/ph14020141 (https://doi.org/10.3390/ph14020141) - 10 Feb 2021

Cited by 4 (/1424-8247/14/2/141#metrics) | Viewed by 1516

Abstract To establish a computer model for evaluating the binding affinity of phenylalkylamines (PAAs) to T-type Ca^{2+} channels (TCCs), we created new homology models for both TCCs and a L-type calcium channel (LCC). We found that PAAs have a high affinity for domains **[...] Read more.**

(This article belongs to the Special Issue **In Silico Approaches in Drug Design (/journal/pharmaceuticals/special_issues/Silico_Approaches_Drug)**)

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Special Issue "Adenosine Receptors as Attractive Targets in Human Diseases" (/1424-8247/14/2/140)

by Daniela Catarzi (https://sciprofiles.com/profile/466316), Flavia Varano (https://sciprofiles.com/profile/466317) and Vittoria Colotta (https://sciprofiles.com/profile/466315)

Pharmaceuticals **2021**, *14*(2), 140; https://doi.org/10.3390/ph14020140 (https://doi.org/10.3390/ph14020140) - 10 Feb 2021

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Abstract The idea of promoting this Special Issue arises from the desire to witness the multidisciplinary efforts that are currently in progress to provide new insights into the pathophysiological role of adenosine [...] **Full article (/1424-8247/14/2/140)**

(This article belongs to the Special Issue **Adenosine Receptors as Attractive Targets in Human Diseases (/journal/pharmaceuticals/special_issues/adenosine_receptors)**)

Open Access Article (/1424-8247/14/2/139/pdf?version=1613726478)

Biofabricated Fatty Acids-Capped Silver Nanoparticles as Potential Antibacterial, Antifungal, Antibiofilm and Anticancer Agents (/1424-8247/14/2/139)

by Mohammad Azam Ansari (https://sciprofiles.com/profile/471276), Sarah Mousa Maadi Asiri (https://sciprofiles.com/profile/author/aDZqUkN1SmswODJPUml2djVsVGtRY0t4c0t5MEZWRFV6NXAwcXUxcG10Zz0=), Mohammad A. Alzohairy (https://sciprofiles.com/profile/author/NURaRjh6MVJHTlFFTHRDSnByZVpRbFJkWlN4YVdQTmZneng3Uit6d2ZMST0=), Mohammad N. Alomary (https://sciprofiles.com/profile/741018), Ahmad Almatroudi (https://sciprofiles.com/profile/634526) and Firdos Alam Khan (https://sciprofiles.com/profile/396849)

Pharmaceuticals **2021**, *14*(2), 139; https://doi.org/10.3390/ph14020139 (https://doi.org/10.3390/ph14020139) - 09 Feb 2021

Cited by 20 (/1424-8247/14/2/139#metrics) | Viewed by 2948

Abstract The current study demonstrates the synthesis of fatty acids (FAs) capped silver nanoparticles (AgNPs) using aqueous poly-herbal drug Liv52 extract (PLE) as a reducing, dispersing and stabilizing agent. The NPs were characterized by various techniques and used to investigate their potent antibacterial, antibiofilm, **[...] Read more.**

(This article belongs to the Special Issue **Metal-Based Drugs: Updates and Perspectives (/journal/pharmaceuticals/special_issues/metaldrugs)**)

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Open Access Editor's Choice Article (/1424-8247/14/2/138/pdf?version=1614260878)

Photophysical Properties of Protoporphyrin IX, Pyropheophorbide-a, and Photofrin® in Different Conditions (/1424-8247/14/2/138)

by
Bauyrzhan Myrzakhmetov (https://sciprofiles.com/profile/author/ZTFXL2xTcUpkckViUmZSUnBGbzJIT3dkdFNlTmYxdW9CQTF0OThEQm9zSFBVSkZoTGlLOEhndDB3bURlbytjeg==),
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Samir Acherar (https://sciprofiles.com/profile/466663),
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Céline Frochot (https://sciprofiles.com/profile/453906)

Pharmaceuticals **2021**, *14*(2), 138; https://doi.org/10.3390/ph14020138 (https://doi.org/10.3390/ph14020138) - 09 Feb 2021
Cited by 27 (/1424-8247/14/2/138#metrics) | Viewed by 3529

Abstract Photodynamic therapy (PDT) is an innovative treatment of malignant or diseased tissues. The effectiveness of PDT depends on light dosimetry, oxygen availability, and properties of the photosensitizer (PS). Depending on the medium, photophysical properties of the PS can change leading to increase or **[...] Read more.**
(This article belongs to the Special Issue Photodynamic Therapy 2021 (/journal/pharmaceuticals/special_issues/photodynamic_therapy_2021))

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Open Access Article (/1424-8247/14/2/137/pdf?version=1612853200)

miR-16-5p Promotes Erythroid Maturation of Erythroleukemia Cells by Regulating Ribosome Biogenesis (/1424-8247/14/2/137)

by Christos I. Papagiannopoulos (https://sciprofiles.com/profile/author/K3l6dlgra0xmT1d5NW13SVRqL3EveElob1poSHF6NHVmdnNqMk5LR09Taz0=),
Nikoleta F. Theodoroula (https://sciprofiles.com/profile/author/SFB6NFdOdWoreWorQ2FMUmJPR0E1Szl1NkcxcVhJSndqbUVzNTRYTjFVbz0=) and
Ioannis S. Vizirianakis (https://sciprofiles.com/profile/1426376)

Pharmaceuticals **2021**, *14*(2), 137; https://doi.org/10.3390/ph14020137 (https://doi.org/10.3390/ph14020137) - 09 Feb 2021
Cited by 4 (/1424-8247/14/2/137#metrics) | Viewed by 2018

Abstract miRNAs constitute a class of non-coding RNA that act as powerful epigenetic regulators in animal and plant cells. In order to identify putative tumor-suppressor miRNAs we profiled the expression of various miRNAs during differentiation of erythroleukemia cells. RNA was purified before and after **[...] Read more.**
(This article belongs to the Special Issue siRNA Therapeutics: From Bench Lab to Clinics (/journal/pharmaceuticals/special_issues/sirna))

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Open Access Review (/1424-8247/14/2/136/pdf?version=1612898720)

MicroRNA-Based Therapeutics for Drug-Resistant Colorectal Cancer (/1424-8247/14/2/136)

by Eunsun Jung (https://sciprofiles.com/profile/1449670),
Jinhyeon Choi (https://sciprofiles.com/profile/author/R1E3YlFFSlhUWFJTRjdsdTE2bUpjVjZsQ2d2YUpXSGU1cVFBbkRiVGcwYz0=),
Jang-Seong Kim (https://sciprofiles.com/profile/1412079) and Tae-Su Han (https://sciprofiles.com/profile/563011)

Pharmaceuticals **2021**, *14*(2), 136; https://doi.org/10.3390/ph14020136 (https://doi.org/10.3390/ph14020136) - 08 Feb 2021
Cited by 10 (/1424-8247/14/2/136#metrics) | Viewed by 2119

Abstract Although therapeutic approaches for patients with colorectal cancer (CRC) have improved in the past decades, the problem of drug resistance still persists and acts as a major obstacle for effective therapy. Many studies have shown that drug resistance is related to reduced drug **[...] Read more.**
(This article belongs to the Special Issue MiRNA-Based Therapeutics in Cancer (/journal/pharmaceuticals/special_issues/miRNA_Cancer))

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Ameliorative Effects of Loganin on Arthritis in Chondrocytes and Destabilization of the Medial Meniscus-Induced Animal Model (/1424-8247/14/2/135)

by Eunkuk Park (https://sciprofiles.com/profile/94102), Chang Gun Lee (https://sciprofiles.com/profile/2102457), Seung Hee Yun (https://sciprofiles.com/profile/author/UDlZUVl0RVlaa2tPcWpiOUhKWUV1T3AzcitpUlZ4NHFkNXJyOXkzR2VGMD0=), Seokjin Hwang (https://sciprofiles.com/profile/author/eDE5dXhIVEVtb2lNb3B1eVFCZ2xvd3RuQit2VlRsVHRNUGttRGl6aHQ0Yz0=), Hyoju Jeon (https://sciprofiles.com/profile/author/K1FQMXFod1NJc0VWazN3Yys0UThjN21Pc0VDVGNycXFCN0V2VVZWcGxFbz0=), Jeonghyun Kim (https://sciprofiles.com/profile/author/MnJFM3pXQ0tSWUhtN1dETEpSQ3pqN3JtZG9QdUQxQXBBVUZUZkViZ1dQMD0=), Subin Yeo (https://sciprofiles.com/profile/author/WHpSUVBXZmZRbWJ0WTRTRlpXTzlMbVhhYzhCSTVlQVQrRDg1UGFNYlpMND0=), Hyesoo Jeong (https://sciprofiles.com/profile/author/RXhyeXFLMTlZc280TllobUpPb2hPVzBkMmw4U3dQL0lYTDdFZVh3TzVQZz0=), Seong-Hoon Yun (https://sciprofiles.com/profile/author/aDAwWVpPaVFQY3JXY2Zid0JSc0UxMEZXNXJuQmwyQ1NwOHNyTWxmdzMvVT0=) and Seon-Yong Jeong (https://sciprofiles.com/profile/88263)

Pharmaceuticals **2021**, *14*(2), 135; https://doi.org/10.3390/ph14020135 (https://doi.org/10.3390/ph14020135) - 08 Feb 2021
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Abstract Arthritis is a common inflammatory disease that causes pain, stiffness, and joint swelling. Here, we investigated the ameliorative effects of loganin on arthritis in vitro and in vivo. A single bioactive compound was fractionated and isolated from *Cornus officinalis* (CO) extract to screen **[...] Read more.**
(This article belongs to the Special Issue **Drug and Therapy for Osteoarthritis (OA) (/journal/pharmaceuticals/special_issues/Drug_Osteoarthritis)**)

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Open Access Article (/1424-8247/14/2/134/pdf?version=1612765185)

Liquid and Vapor Phase of Four Conifer-Derived Essential Oils: Comparison of Chemical Compositions and Antimicrobial and Antioxidant Properties (/1424-8247/14/2/134)

by Stefania Garzoli (https://sciprofiles.com/profile/116660), Valentina Laghezza Masci (https://sciprofiles.com/profile/946078), Valentina Caradonna (https://sciprofiles.com/profile/1477115), Antonio Tiezzi (https://sciprofiles.com/profile/422815), Pierluigi Giacomello (https://sciprofiles.com/profile/946535) and Elisa Ovidi (https://sciprofiles.com/profile/754055)

Pharmaceuticals **2021**, *14*(2), 134; https://doi.org/10.3390/ph14020134 (https://doi.org/10.3390/ph14020134) - 08 Feb 2021
Cited by 19 (/1424-8247/14/2/134#metrics) | Viewed by 2458

Abstract In this study, the chemical composition of the vapor and liquid phase of *Pinus cembra* L., *Pinus mugo* Turra, *Picea abies* L., and *Abies Alba* M. needles essential oils (EOs) was investigated by Headspace-Gas Chromatography/Mass Spectrometry (HS-GC/MS). In the examined EOs, a total **[...] Read more.**
(This article belongs to the Special Issue **Novel Antibacterial Agents (/journal/pharmaceuticals/special_issues/Antibacterial_Agents)**)

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Open Access Editor's Choice Review (/1424-8247/14/2/133/pdf?version=1612691717)

Monofunctional Platinum(II) Anticancer Agents (/1424-8247/14/2/133)

by Suxing Jin (https://sciprofiles.com/profile/author/RnJ4ZitkWW15UlMyQjBCNmRDbzdvK0dwUUZBVHFHQ0VXcVUveE5aaUJ6RT0=), Yan Guo (https://sciprofiles.com/profile/author/ajVkQXA4MG5vM2kvVFg2SGRyVXY1T1pweVlvTURQSGk5Vm1qOG11cWhDdz0=), Zijian Guo (https://sciprofiles.com/profile/2483768) and Xiaoyong Wang (https://sciprofiles.com/profile/1432633)

Pharmaceuticals **2021**, *14*(2), 133; https://doi.org/10.3390/ph14020133 (https://doi.org/10.3390/ph14020133) - 07 Feb 2021
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Abstract Platinum-based anticancer drugs represented by cisplatin play important roles in the treatment of various solid tumors. However, their applications are largely compromised by drug resistance and side effects. Much effort has been made to circumvent the drug resistance and general toxicity of these **[...] Read more.**
(This article belongs to the Special Issue **Applications of Medicinal Bioinorganic Chemistry (/journal/pharmaceuticals/special_issues/bioinorgani)**)

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Open Access Article (/1424-8247/14/2/132/pdf?version=1612774922)

Development of Controlled-Release Carbamide Peroxide Loaded Nanoemulgel for Tooth Bleaching: In Vitro and Ex Vivo Studies (/1424-8247/14/2/132)

by Siriporn Okonogi (https://sciprofiles.com/profile/422726), Adchareeya Kaewpinta (https://sciprofiles.com/profile/1293456), Sakornrat Khongkhunthian (https://sciprofiles.com/profile/author/SmlGOE9OMlc3Yk9vRnR4MHlQeTBqcVphZjBjakRHcjJuQ0l6T1M5Z2VFdz0=) and Pisaisit Chaijareenont (https://sciprofiles.com/profile/author/THJDS3ZhUmhTZ0MzVlNUWTAvR01CMWQxY085NDFSNlVubXBBWXNXR1dFTT0=)

Pharmaceuticals **2021**, *14*(2), 132; https://doi.org/10.3390/ph14020132 (https://doi.org/10.3390/ph14020132) - 07 Feb 2021
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Abstract Burst release of carbamide peroxide (CP) from traditional hydrogels causes severe inflammation to periodontal tissues. The present study explores the development of a novel CP nanoemulgel (CP-NG), an oil-in-water nanoemulsion-based gel in which CP was loaded with a view to controlling CP release. **[...] Read more.**
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Open Access Review **(/1424-8247/14/2/131/pdf?version=1612680121)**

Therapeutic Single Compounds for Osteoarthritis Treatment (/1424-8247/14/2/131)

by **Hyemi Lee (https://sciprofiles.com/profile/649564)**, **Xiangyu Zhao (https://sciprofiles.com/profile/1424450)**, **Young-Ok Son (https://sciprofiles.com/profile/1168897)** and **Siyoung Yang (https://sciprofiles.com/profile/794386)**
Pharmaceuticals **2021**, *14*(2), 131; **https://doi.org/10.3390/ph14020131 (https://doi.org/10.3390/ph14020131)** - 06 Feb 2021
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Abstract Osteoarthritis (OA) is an age-related degenerative disease for which an effective disease-modifying therapy is not available. Natural compounds derived from plants have been traditionally used in the clinic to treat OA. Over the years, many studies have explored the treatment of OA using **[...] Read more.**
(This article belongs to the Special Issue **Drug and Therapy for Osteoarthritis (OA) (/journal/pharmaceuticals/special_issues/Drug_Osteoarthritis)**)

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Open Access Review **(/1424-8247/14/2/130/pdf?version=1612765957)**

MERTK Inhibition: Potential as a Treatment Strategy in EGFR Tyrosine Kinase Inhibitor-Resistant Non-Small Cell Lung Cancer (/1424-8247/14/2/130)

by **Chao-Ju Chen (https://sciprofiles.com/profile/573350)** and **Yu-Peng Liu (https://sciprofiles.com/profile/698676)**
Pharmaceuticals **2021**, *14*(2), 130; **https://doi.org/10.3390/ph14020130 (https://doi.org/10.3390/ph14020130)** - 06 Feb 2021
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Abstract Epidermal growth factor tyrosine kinase inhibitors (EGFR-TKIs) are currently the most effective treatment for non-small cell lung cancer (NSCLC) patients, who carry primary EGFR mutations. However, the patients eventually develop drug resistance to EGFR-TKIs after approximately one year. In addition to the acquisition **[...] Read more.**
(This article belongs to the Special Issue **Treatment Options and Therapeutics for Non-small Cell Lung Cancer (/journal/pharmaceuticals/special_issues/treatment_lung_cancer)**)

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An Angiopep2-PAPTP Construct Overcomes the Blood-Brain Barrier. New Perspectives against Brain Tumors (/1424-8247/14/2/129)

by **Sofia Parrasia (https://sciprofiles.com/profile/1371740)**, **Andrea Rossa (https://sciprofiles.com/profile/1445004)**, **Tatiana Varanita (https://sciprofiles.com/profile/author/SDRzbm4vNXlaaGRpNktEQ3FHZkplZGJHOURLWGI2UEp3a0ZDenkyMGdFbz0=)**, **Vanessa Checchetto (https://sciprofiles.com/profile/718807)**, **Riccardo De Lorenzi (https://sciprofiles.com/profile/author/c1VyOU5PWWI0L29CVitUR01kSHVsSlk4V29xTnFXSHJvbm9MQlAxRW11WT0=)**, **Mario Zoratti (https://sciprofiles.com/profile/1041)**, **Cristina Paradisi (https://sciprofiles.com/profile/1068)**, **Paolo Ruzza (https://sciprofiles.com/profile/44315)**, **Andrea Mattarei (https://sciprofiles.com/profile/127447)**, **Ildikò Szabò (https://sciprofiles.com/profile/author/MGZYQzdqRWVGWnhEWFc0TXJwc1ZnYVRya3BOcDhtUWxwUjZxV3dXN3NzUT0=)** and **Lucia Biasutto (https://sciprofiles.com/profile/86609)**
Pharmaceuticals **2021**, *14*(2), 129; **https://doi.org/10.3390/ph14020129 (https://doi.org/10.3390/ph14020129)** - 06 Feb 2021
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Abstract A developing family of chemotherapeutics—derived from 5-(4-phenoxybutoxy)psoralen (PAP-1)—target mitochondrial potassium channel mtKv1.3 to selectively induce oxidative stress and death of diseased cells. The key to their effectiveness is the presence of a positively charged triphenylphosphonium group which drives their accumulation in the organelles. **[...] Read more.**
(This article belongs to the Special Issue **Selected Papers from the 6th International Electronic Conference on Medicinal Chemistry (ECMC2020) (/journal/pharmaceuticals/special_issues/ECMC_2020)**)

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Small EVs-Associated DNA as Complementary Biomarker to Circulating Tumor DNA in Plasma of Metastatic Colorectal Cancer Patients (/1424-8247/14/2/128)

by Silvia Galbiati (https://sciprofiles.com/profile/729764), Francesco Damin (https://sciprofiles.com/profile/1361433), Dario Brambilla (https://sciprofiles.com/profile/1397027), Lucia Ferraro (https://sciprofiles.com/profile/author/UndFS2d6L3JGajJsTjFoUnZLUUhBQXUzcVBwR2VLTHVTaUdrTlh3aSt2bz0=), Nadia Soriani (https://sciprofiles.com/profile/author/cFk5QkVtdkJYNXdadHYrWUpNTHQ0WTRWdUY3dnRRUk9pK1hHcEtGRGFRaz0=), Anna M. Ferretti (https://sciprofiles.com/profile/321706), Valentina Burgio (https://sciprofiles.com/profile/author/V1dkVk1lc1pBK1owVVVweW9SMDBvNThmY0hmNFQwSkFqd1dLUm1qdlFWOD0=), Monica Ronzoni (https://sciprofiles.com/profile/author/aGtDWEtpYTZmYzJ1WTUyYkNyVDJUZ29vMXMvU1dnUjhSeWowT1ErajhWRT0=), Riccardo Vago (https://sciprofiles.com/profile/39598), Laura Sola (https://sciprofiles.com/profile/1395028) and Marcella Chiari (https://sciprofiles.com/profile/2063988)

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Abstract It is widely accepted that assessing circular tumor DNA (ctDNA) in the plasma of cancer patients is a promising practice to evaluate somatic mutations from solid tumors noninvasively. Recently, it was reported that isolation of extracellular vesicles improves the detection of mutant DNA **[...] Read more.**
(This article belongs to the Special Issue **Exosomes as a Tool for Disease Progression Monitoring in Humans and Animals (/journal/pharmaceuticals/special_issues/exosomes_as_a_tool_for_disease_progression_monitoring)**)

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Relationship between Delta Rhythm, Seizure Occurrence and Allopregnanolone Hippocampal Levels in Epileptic Rats Exposed to the Rebound Effect (/1424-8247/14/2/127)

by Anna-Maria Costa (https://sciprofiles.com/profile/1572604), Chiara Lucchi (https://sciprofiles.com/profile/2988656), Asiye Malkoç (https://sciprofiles.com/profile/author/TUczN3UyOWpkVy9NZVNBckI5TVZ6OElNMkxKeCtocnQ1NS9ydC9MbWNsaz0=), Cecilia Rustichelli (https://sciprofiles.com/profile/1249034) and Giuseppe Biagini (https://sciprofiles.com/profile/258520)

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Abstract Abrupt withdrawal from antiepileptic drugs is followed by increased occurrence of epileptic seizures, a phenomenon known as the “rebound effect”. By stopping treatment with levetiracetam (LEV 300 mg/kg/day, *n* = 15; vs. saline, *n* = 15), we investigated the rebound effect in adult **[...] Read more.**
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Open Access Review (/1424-8247/14/2/126/pdf?version=1612712049)

Targeting Cartilage Degradation in Osteoarthritis (/1424-8247/14/2/126)

by Oliver McClurg (https://sciprofiles.com/profile/1391162), Ryan Tinson (https://sciprofiles.com/profile/author/dmppRmJVRlBGOHJlby9SRzI5bTY5S1hQSVpudEVRZlEzK0ZtM2lZT0pGZz0=) and Linda Troeberg (https://sciprofiles.com/profile/1377879)

Pharmaceuticals **2021**, *14*(2), 126; https://doi.org/10.3390/ph14020126 (https://doi.org/10.3390/ph14020126) - 05 Feb 2021
Cited by 12 (/1424-8247/14/2/126#metrics) | Viewed by 3092

Abstract Osteoarthritis is a common, degenerative joint disease with significant socio-economic impact worldwide. There are currently no disease-modifying drugs available to treat the disease, making this an important area of pharmaceutical research. In this review, we assessed approaches being explored to directly inhibit metalloproteinase-mediated **[...] Read more.**
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Methyl Jasmonate and Methyl-β-Cyclodextrin Individually Boost Triterpenoid Biosynthesis in *Chlamydomonas Reinhardtii* UVM4 (/1424-8247/14/2/125)

by Audrey S. Commault (https://sciprofiles.com/profile/920762), Unnikrishnan Kuzhiumparambil (https://sciprofiles.com/profile/187478), Andrei Herdean (https://sciprofiles.com/profile/1455264), Michele Fabris (https://sciprofiles.com/profile/471527), Ana Cristina Jaramillo-Madrid (https://sciprofiles.com/profile/author/UnBmdnRuRE41dTd3S05YZU44WFhkZ3orUVVFU0FxZXN5QTM1djFDQ2xGK1I6S3pEY2sxd3VzMUxFM2FIeW, Raffaela M. Abbriano (https://sciprofiles.com/profile/977143), Peter J. Ralph (https://sciprofiles.com/profile/author/WEdGY25YeFIxNUdDbWoxSUh0NE94Nk1SNHN3YVc3czBReVlETlM5Nkxsaz0=) and Mathieu Pernice (https://sciprofiles.com/profile/982066)

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Cited by 6 (/1424-8247/14/2/125#metrics) | Viewed by 1887

Abstract The commercialisation of valuable plant triterpenoids faces major challenges, including low abundance in natural hosts and costly downstream purification procedures. Endeavours to produce these compounds at industrial scale using microbial systems are gaining attention. Here, we report on a strategy to enrich the **[...] Read more.**
(This article belongs to the Special Issue **Terpenes – Pharmaceutics and Biotechnology (/journal/pharmaceuticals/special_issues/Terpenes_Pharmaceutics_Biotechnology)**)

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Highly Efficient T2 Cobalt Ferrite Nanoparticles Vectorized for Internalization in Cancer Cells (/1424-8247/14/2/124)

by Eva Mazario (https://sciprofiles.com/profile/843101), Magdalena Cañete (https://sciprofiles.com/profile/89949), Fernando Herranz (https://sciprofiles.com/profile/559162), Jorge Sánchez-Marcos (https://sciprofiles.com/profile/author/LzNLczVLQ3FYYUlybUo4dVF0SGhhMXQzRkdoT3Jqb1NJWnBvSnpsZXlTYz0=), Jesús M. de la Fuente (https://sciprofiles.com/profile/195196), Pilar Herrasti (https://sciprofiles.com/profile/843115) and Nieves Menéndez (https://sciprofiles.com/profile/1442858)

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Abstract Uniform cobalt ferrite nanoparticles have been synthesized using an electrochemical synthesis method in aqueous media. Their colloidal, magnetic, and relaxometric properties have been analyzed. The novelty of this synthesis relies on the use of iron and cobalt foils as precursors, which assures the **[...] Read more.**

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Open Access Review (/1424-8247/14/2/123/pdf?version=1612660506)

Mercury Toxicity and Detection Using Chromo-Fluorogenic Chemosensors (/1424-8247/14/2/123)

by Vinita Bhardwaj (https://sciprofiles.com/profile/1474283), Valeria M. Nurchi (https://sciprofiles.com/profile/306666) and Suban K. Sahoo (https://sciprofiles.com/profile/1305677)

Pharmaceuticals **2021**, *14*(2), 123; https://doi.org/10.3390/ph14020123 (https://doi.org/10.3390/ph14020123) - 05 Feb 2021

Cited by 21 (/1424-8247/14/2/123#metrics) | Viewed by 2813

Abstract Mercury (Hg), this non-essential heavy metal released from both industrial and natural sources entered into living bodies, and cause grievous detrimental effects to the human health and ecosystem. The monitoring of Hg^{2+} excessive accumulation can be beneficial to fight against the risk **[...] Read more.**

(This article belongs to the Special Issue **Applications of Medicinal Bioinorganic Chemistry (/journal/pharmaceuticals/special_issues/bioinorgani)**)

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Open Access Editor's Choice Review (/1424-8247/14/2/122/pdf?version=1612509428)

The Current and Potential Therapeutic Use of Metformin—The Good Old Drug (/1424-8247/14/2/122)

by Józef Drzewoski (https://sciprofiles.com/profile/536777) and Markolf Hanefeld (https://sciprofiles.com/profile/author/dEt4cnI3UGRJTDdyZDNVWEJEM21pNTRaTXBhelltUjdzb3R6bE0vRndaND0=)

Pharmaceuticals **2021**, *14*(2), 122; https://doi.org/10.3390/ph14020122 (https://doi.org/10.3390/ph14020122) - 05 Feb 2021

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Abstract Metformin, one of the oldest oral antidiabetic agents and still recommended by almost all current guidelines as the first-line treatment for type 2 diabetes mellitus (T2DM), has become the medication with steadily increasing potential therapeutic indications. A broad spectrum of experimental and clinical [...] Read more.

(This article belongs to the Special Issue Metformin: Mechanism and Application 2022 (/journal/pharmaceuticals/special_issues/metformin_2022))

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Locking up the AS1411 Aptamer with a Flanking Duplex: Towards an Improved Nucleolin-Targeting (/1424-8247/14/2/121)

by André Miranda (https://sciprofiles.com/profile/1222652), Tiago Santos (https://sciprofiles.com/profile/1472898), Eric Largy (https://sciprofiles.com/profile/2547379) and Carla Cruz (https://sciprofiles.com/profile/43121)

Pharmaceuticals **2021**, *14*(2), 121; https://doi.org/10.3390/ph14020121 (https://doi.org/10.3390/ph14020121) - 04 Feb 2021

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Abstract We have designed AS1411-N6, a derivative of the nucleolin (NCL)-binding aptamer AS1411, by adding six nucleotides to the 5′-end that are complementary to nucleotides at the 3′-end forcing it into a stem-loop structure. We evaluated by several biophysical techniques if AS1411-N6 can adopt [...] Read more.

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Open Access Article (/1424-8247/14/2/120/pdf?version=1612515421)

Electrochemical and Mechanistic Study of Superoxide Elimination by Mesalazine through Proton-Coupled Electron Transfer (/1424-8247/14/2/120)

by Tatsushi Nakayama (https://sciprofiles.com/profile/904475) and Ryo Honda (https://sciprofiles.com/profile/author/bkM4U2J3VEdnRkF0cnhyRlNZbWRaemtSVW55bnQxckpTeEgvVldsc2lCaz0=)

Pharmaceuticals **2021**, *14*(2), 120; https://doi.org/10.3390/ph14020120 (https://doi.org/10.3390/ph14020120) - 04 Feb 2021

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Abstract The elimination of superoxide radical anions ($O_2^{\bullet-}$) by 5-amino-2-hydroxybenzoic acid (mesalazine, 5-ASA), 4-amino-2-hydroxybenzoic acid (4-ASA), and related compounds used for ulcerative colitis treatment was investigated using cyclic voltammetry and electron spin resonance (ESR) analyses aided by density functional theory (DFT) [...] Read more.

(This article belongs to the Section Medicinal Chemistry (/journal/pharmaceuticals/sections/pharm_medicinal_chemistry))

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Open Access Article (/1424-8247/14/2/119/pdf?version=1612432973)

Feasibility of Extrapolating Randomly Taken Plasma Samples to Trough Levels for Therapeutic Drug Monitoring Purposes of Small Molecule Kinase Inhibitors (/1424-8247/14/2/119)

by Ruben A. G. van Eerden (https://sciprofiles.com/profile/1432063), Esther Oomen-de Hoop (https://sciprofiles.com/profile/555540), Aad Noordam (https://sciprofiles.com/profile/author/QWp1eW54RDAzU1dOMkRaMFJZdnNxelpFVmdSYThkc3pZRzNHYVdrRmhXdz0=), Ron H. J. Mathijssen (https://sciprofiles.com/profile/555496) and Stijn L. W. Koolen (https://sciprofiles.com/profile/author/aFEzeFlLODRtZFJxQWQrVmZpMXYxbXpqbVQrSVA2aEsrSU42czZxMmkvVT0=)

Pharmaceuticals **2021**, *14*(2), 119; https://doi.org/10.3390/ph14020119 (https://doi.org/10.3390/ph14020119) - 04 Feb 2021

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Abstract Small molecule kinase inhibitors (SMKIs) are widely used in oncology. Therapeutic drug monitoring (TDM) for SMKIs could reduce underexposure or overexposure. However, logistical issues such as timing of blood withdrawals hamper its implementation into clinical practice. Extrapolating a random concentration to a trough [...] Read more.

(This article belongs to the Special Issue Precision Medicine in Oncology: Controlling the Pharmacokinetics Variability (/journal/pharmaceuticals/special_issues/Oncology_Pharmacokinetics))

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Integrative Genomic–Epigenomic Analysis of Clozapine-Treated Patients with Refractory Psychosis (/1424-8247/14/2/118)

by Yerye Gibrán Mayén-Lobo (https://sciprofiles.com/profile/author/M3RjOHFLcWxkMnFybGpFWS9vVHBXenNnMjJnNTlFQzY3dlFPY2lQREJtST0=), José Jaime Martínez-Magaña (https://sciprofiles.com/profile/317866), Blanca Estela Pérez-Aldana (https://sciprofiles.com/profile/author/djFGcXF1OGhURWZVekI1MkNxS2RBQlBsaTZ2SklXZHV5Wi9INGxtMVhlcz0=), Alberto Ortega-Vázquez (https://sciprofiles.com/profile/author/REk5WVlCYURyTzl3L2ZUZXEzajRrcER0alNja1RnWWsvdDF6NWhpSkVBZz0=), Alma Delia Genis-Mendoza (https://sciprofiles.com/profile/316918), David José Dávila-Ortiz de Montellano (https://sciprofiles.com/profile/1456634), Ernesto Soto-Reyes (https://sciprofiles.com/profile/2876161), Humberto Nicolini (https://sciprofiles.com/profile/515237), Marisol López-López (https://sciprofiles.com/profile/979599) and Nancy Monroy-Jaramillo (https://sciprofiles.com/profile/1363920)

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Abstract Clozapine (CLZ) is the only antipsychotic drug that has been proven to be effective in patients with refractory psychosis, but it has also been proposed as an effective mood stabilizer; however, the complex mechanisms of action of CLZ are not yet fully known. [...] Read more.

(This article belongs to the Special Issue The Pharmacogenomics of Mood Stabilizers (/journal/pharmaceuticals/special_issues/mood_stabilizer))

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Informing Patients about Biosimilar Medicines: The Role of European Patient Associations (/1424-8247/14/2/117)

by Yannick Vandenplas (https://sciprofiles.com/profile/1166667), Steven Simoens (https://sciprofiles.com/profile/1070064), Philippe Van Wilder (https://sciprofiles.com/profile/1467857), Arnold G. Vulto (https://sciprofiles.com/profile/1070063) and Isabelle Huys (https://sciprofiles.com/profile/645425)

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Abstract Biosimilar medicines support the sustainability of national healthcare systems, by reducing costs of biological therapies through increased competition. However, their adoption into clinical practice largely depends on the acceptance of healthcare providers and patients. Patients are different from health care professionals (HCPs), who [...] Read more.

(This article belongs to the Special Issue Biosimilars in Europe (/journal/pharmaceuticals/special_issues/biosimilars_Europe))

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Open Access Review (/1424-8247/14/2/116/pdf?version=1612514601)

Pharmacokinetics and Pharmacodynamics of Salvinorin A and *Salvia divinorum*: Clinical and Forensic Aspects (/1424-8247/14/2/116)

by Andreia Machado Brito-da-Costa (https://sciprofiles.com/profile/1264030), Diana Dias-da-Silva (https://sciprofiles.com/profile/1345999), Nelson G. M. Gomes (https://sciprofiles.com/profile/65306), Ricardo Jorge Dinis-Oliveira (https://sciprofiles.com/profile/490770) and Áurea Madureira-Carvalho (https://sciprofiles.com/profile/411838)

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Abstract *Salvia divinorum* Epling and Játiva is a perennial mint from the Lamiaceae family, endemic to Mexico, predominantly from the state of Oaxaca. Due to its psychoactive properties, *S. divinorum* had been used for centuries by Mazatecans for divinatory, religious, and medicinal purposes. In [...] Read more.

(This article belongs to the Special Issue Pharmacokinetics and Pharmacodynamics of Psychoactive Substances: Clinical and Forensic Aspects (/journal /pharmaceuticals/special_issues/Pharmacokinetics_Pharmacodynamics_Psychoactive))

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Simulation-Based Assessment of the Impact of Non-Adherence on Endoxifen Target Attainment in Different Tamoxifen Dosing Strategies (/1424-8247/14/2/115)

by Anna Mueller-Schoell (https://sciprofiles.com/profile/author/RndNNEs3QWNpcDJOems2MVZKeGdqQ2VZNlV3ckV2dm1PbC9ScCtORFF0NTJaSldqNHp1MVVSWE80QXFQRHZqZ/

, Lena Klopp-Schulze (https://sciprofiles.com/profile/author/SkNCRjY3aWtubXc3MzdOWU1ydHBHdUpMZ3l3N3NlV3Urd3k3MEErSjdrND0=), Robin Michelet (https://sciprofiles.com/profile/1434194), Madelé van Dyk (https://sciprofiles.com/profile/1996748), Thomas E. Mürdter (https://sciprofiles.com/profile/757469), Matthias Schwab (https://sciprofiles.com/profile/6686), Markus Joerger (https://sciprofiles.com/profile/134779), Wilhelm Huisinga (https://sciprofiles.com/profile/author/SWF0SVNDbk1GVFRPb0k4VDRTa1dqRW1yeWErb3hYM0pxaE1OKzF4dUFGdz0=), Gerd Mikus (https://sciprofiles.com/profile/1468081) and Charlotte Kloft (https://sciprofiles.com/profile/417429)

Pharmaceuticals **2021**, *14*(2), 115; https://doi.org/10.3390/ph14020115 (https://doi.org/10.3390/ph14020115) - 03 Feb 2021

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Abstract Tamoxifen is widely used in breast cancer treatment and minimum steady-state concentrations of its active metabolite endoxifen ($C_{SS,min\ ENDX}$) above 5.97 ng/mL have been associated with favourable disease outcome. Yet, about 20% of patients do not reach target $C_{SS,min\ ENDX}$ [...] Read more.

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Population Pharmacokinetic Method to Predict Within-Subject Variability Using Single-Period Clinical Data (/1424-8247/14/2/114)

by Won-ho Kang (https://sciprofiles.com/profile/1327295), Jae-yeon Lee (https://sciprofiles.com/profile/1461948), Jung-woo Chae (https://sciprofiles.com/profile/645913), Kyeong-Ryoon Lee (https://sciprofiles.com/profile/1410156), In-hwan Baek (https://sciprofiles.com/profile/517159), Min-Soo Kim (https://sciprofiles.com/profile/94964), Hyun-moon Back (https://sciprofiles.com/profile/author/NHZNQ2x0VlJZRkJOV2JGVi9XaXVtbHBab1F2UWJRRGlHb3F6OVBRL2MwWT0=), Sangkeun Jung (https://sciprofiles.com/profile/author/M3ArZXUxT2pta0d2cGJoME1LbEt2NXg2TEl0RCtyWkVZK3NjVkNlR1ZuTT0=), Craig Shaffer (https://sciprofiles.com/profile/author/Q29lSzcrTzFTV2FjRlRDMEZ0dGpUdGdqRHJsU0hndVJhc1NzcitKNG9sUT0=), Rada Savic (https://sciprofiles.com/profile/1430753) and Hwi-yeol Yun (https://sciprofiles.com/profile/536934)

Pharmaceuticals **2021**, *14*(2), 114; https://doi.org/10.3390/ph14020114 (https://doi.org/10.3390/ph14020114) - 03 Feb 2021

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Abstract Sample sizes for single-period clinical trials, including pharmacokinetic studies, are statistically determined by within-subject variability (WSV). However, it is difficult to determine WSV without replicate-designed clinical trial data, and statisticians typically estimate optimal sample sizes using total variability, not WSV. We have developed [...] Read more.

(This article belongs to the Special Issue **The Prediction of Pharmacokinetics/Pharmacodynamics Using In-Silico Modeling (/journal/pharmaceuticals/special_issues/Pharmacokinetics_Pharmacodynamics_Modeling)**)

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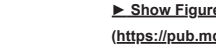

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Open Access Article (/1424-8247/14/2/113/pdf?version=1612179998)

Design, Synthesis, Anticancer Activity, and Solid Lipid Nanoparticle Formulation of Indole- and Benzimidazole-Based Compounds as Pro-Apoptotic Agents Targeting Bcl-2 Protein (/1424-8247/14/2/113)

by **Manar I. Nagy (https://sciprofiles.com/profile/author/eUpSR0lsUjcrQ1N0SUd5WXMxMkFsZ0dGdGcxU084K1p2bDhXUnVrQjdORT0=)**, **Khaled M. Darwish (https://sciprofiles.com/profile/1339518)**, **Safaa M. Kishk (https://sciprofiles.com/profile/1055649)**, **Mohamed A. Tantawy (https://sciprofiles.com/profile/1510483)**, **Ali M. Nasr (https://sciprofiles.com/profile/133203)**, **Mona Qushawy (https://sciprofiles.com/profile/358200)**, **Shady A. Swidan (https://sciprofiles.com/profile/378025)**, **Samia M. Mostafa (https://sciprofiles.com/profile/author/cys0RXZ4NGFiU2JSMzRRZ0VXcmlhT3ZoTEJhLzRjQUtKSTh1WUR6d2hZcz0=)** and **Ismail Salama (https://sciprofiles.com/profile/1194403)**

Pharmaceuticals **2021**, *14*(2), 113; **https://doi.org/10.3390/ph14020113 (https://doi.org/10.3390/ph14020113)** - 01 Feb 2021

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Abstract Cancer is a multifactorial disease necessitating identification of novel targets for its treatment. Inhibition of Bcl-2 for triggered pro-apoptotic signaling is considered a promising strategy for cancer treatment. Within the current work, we aimed to design and synthesize a new series of benzimidazole- **[...] Read more.**

(This article belongs to the Special Issue **Anticancer Drugs 2021 (/journal/pharmaceuticals/special_issues/Anticancer_Drugs_2)**)

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Open Access Review (/1424-8247/14/2/112/pdf?version=1612235507)

Mirogabalin—A Novel Selective Ligand for the α2δ Calcium Channel Subunit (/1424-8247/14/2/112)

by **Renata Zajączkowska (https://sciprofiles.com/profile/402296)**, **Joanna Mika (https://sciprofiles.com/profile/1282627)**, **Wojciech Leppert (https://sciprofiles.com/profile/383601)**, **Magdalena Kocot-Kępska (https://sciprofiles.com/profile/660648)**, **Małgorzata Malec-Milewska (https://sciprofiles.com/profile/author/RVl4SjFtdlpjbUhoRC9GZkpqNFRocUpOdzZ3NWpHdkRzeFBnS1lQdVA5WT0=)** and **Jerzy Wordliczek (https://sciprofiles.com/profile/2939500)**

Pharmaceuticals **2021**, *14*(2), 112; **https://doi.org/10.3390/ph14020112 (https://doi.org/10.3390/ph14020112)** - 31 Jan 2021

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Abstract The efficacy of neuropathic pain control remains unsatisfactory. Despite the availability of a variety of therapies, a significant proportion of patients suffer from poorly controlled pain of this kind. Consequently, new drugs and treatments are still being sought to remedy the situation. One **[...] Read more.**

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In Vitro Modulation of P-Glycoprotein Activity by *Euphorbia intisy* Essential Oil on Acute Myeloid Leukemia Cell Line HL-60R (/1424-8247/14/2/111)

by **Paola Poma (https://sciprofiles.com/profile/276634)**, **Manuela Labbozzetta (https://sciprofiles.com/profile/609624)**, **Aro Vonjy Ramarosandratana (https://sciprofiles.com/profile/768993)**, **Sergio Rosselli (https://sciprofiles.com/profile/27473)**, **Marco Tutone (https://sciprofiles.com/profile/623930)**, **Maurizio Sajeva (https://sciprofiles.com/profile/362435)** and **Monica Notarbartolo (https://sciprofiles.com/profile/364215)**

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Abstract *Euphorbia* species have a large spectrum of traditional medicinal uses. We tested the biological activities of the essential oil (EO) of *Euphorbia intisy* Drake in an acquired multidrug resistance leukemia model to assess whether the EO obtained by hydrodistillation of stems was able **[...] Read more.**

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Tauvid™: The First FDA-Approved PET Tracer for Imaging Tau Pathology in Alzheimer's Disease (/1424-8247/14/2/110)

by Caitlin V. M. L. Jie (https://sciprofiles.com/profile/1525856), Valerie Treyer (https://sciprofiles.com/profile/2081385), Roger Schibli (https://sciprofiles.com/profile/120760) and Linjing Mu (https://sciprofiles.com/profile/1428361)
Pharmaceuticals **2021**, *14*(2), 110; https://doi.org/10.3390/ph14020110 (https://doi.org/10.3390/ph14020110) - 30 Jan 2021
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Abstract Tauvid has been approved by the U.S. Food and Drug Administration (FDA) in 2020 for positron emission tomography (PET) imaging of adult patients with cognitive impairments undergoing evaluation for Alzheimer's disease (AD) based on tau pathology. Abnormal aggregation of tau proteins is one **[...] Read more.**
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Think Big, Start Small: How Nanomedicine Could Alleviate the Burden of Rare CNS Diseases (/1424-8247/14/2/109)

by Abdelfattah Faouzi (https://sciprofiles.com/profile/1205643) and Valérie Gaëlle Roullin (https://sciprofiles.com/profile/784871)
Pharmaceuticals **2021**, *14*(2), 109; https://doi.org/10.3390/ph14020109 (https://doi.org/10.3390/ph14020109) - 30 Jan 2021
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Abstract The complexity and organization of the central nervous system (CNS) is widely modulated by the presence of the blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier (BCSFB), which both act as biochemical, dynamic obstacles impeding any type of undesirable exogenous exchanges. The disruption **[...] Read more.**
(This article belongs to the Special Issue **Targeted and Stimulus-Responsive Nanomedicines for the Treatment of Central Nervous System (CNS) Disorders (/journal /pharmaceuticals/special_issues/Nanomedicines_CNS)**)

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Open Access Feature Paper Review (/1424-8247/14/2/108/pdf?version=1612408924)

Characterization and Applications of Colloidal Systems as Versatile Drug Delivery Carriers for Parenteral Formulations (/1424-8247/14/2/108)

by Lakshmi Prasanna Kolluru (https://sciprofiles.com/profile/1457154), Prachi Atre (https://sciprofiles.com/profile/1461011) and Syed A. A. Rizvi (https://sciprofiles.com/profile/533004)
Pharmaceuticals **2021**, *14*(2), 108; https://doi.org/10.3390/ph14020108 (https://doi.org/10.3390/ph14020108) - 29 Jan 2021
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Abstract Preparing a suitable formulation for parenteral administration is already a difficult task; this, coupled with poor water-soluble new chemical entity (NCE), complicates this situation even further. There are several methodologies available to enhance water solubility, but this alone does not entail successful formulation. **[...] Read more.**
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Heat Shock Protein Inhibitor 17-Allyamino-17-Demethoxygeldanamycin, a Potent Inductor of Apoptosis in Human Glioma Tumor Cell Lines, Is a Weak Substrate for ABCB1 and ABCG2 Transporters (/1424-8247/14/2/107)

by Nikola Pastvova (https://sciprofiles.com/profile/author/RmdJbUM5dE1zbERZK1hWMDF5a1hDRTg0S25idkZaU2hTZjB4cDlrN1hmZz0=), Petr Dolezel (https://sciprofiles.com/profile/author/RnN6dHFtZWpObkpheUdOdnY4V0p5bTZWZlNWd0h0Mi9aTFNrbWxkeXpJND0=) and Petr Mlejnek (https://sciprofiles.com/profile/266823)
Pharmaceuticals **2021**, *14*(2), 107; https://doi.org/10.3390/ph14020107 (https://doi.org/10.3390/ph14020107) - 29 Jan 2021
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Abstract Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults and has a poor prognosis. Complex genetic alterations and the protective effect of the blood–brain barrier (BBB) have so far hampered effective treatment. Here, we investigated the cytotoxic effects of heat **[...] Read more.**
(This article belongs to the Special Issue **Malignant Glioma: Novel Therapeutic Strategies (/journal/pharmaceuticals/special_issues/malignant_glioma)**)

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Monitoring of Peripheral Blood Leukocytes and Plasma Samples: A Pilot Study to Examine Treatment Response to Leflunomide in Rheumatoid Arthritis (/1424-8247/14/2/106)

by João F. S. Rodrigues (https://sciprofiles.com/profile/author/UmRjVm94WEx5WHV5QnRBZTEydmk0VE13blg0RGlpVDg0L0NvRjVtZUs4RT0=),
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Pharmaceuticals **2021**, *14*(2), 106; https://doi.org/10.3390/ph14020106 (https://doi.org/10.3390/ph14020106) - 29 Jan 2021
Cited by 1 (/1424-8247/14/2/106#metrics) | Viewed by 1805

Abstract Rheumatoid arthritis (RA) is a painful inflammatory disease of the joints which affects a considerable proportion of the world population, mostly women. If not adequately treated, RA patients can become permanently disabled. Importantly, not all the patients respond to the available anti-rheumatic therapies, **[...] Read more.**
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The Role of Imaging in Planning Treatment for Central Serous Chorioretinopathy (/1424-8247/14/2/105)

by Stefano Da Pozzo (https://sciprofiles.com/profile/1342012), Pierluigi Iacono (https://sciprofiles.com/profile/1022501),
Alessandro Arrigo (https://sciprofiles.com/profile/748242) and Maurizio Battaglia Parodi (https://sciprofiles.com/profile/766658)
Pharmaceuticals **2021**, *14*(2), 105; https://doi.org/10.3390/ph14020105 (https://doi.org/10.3390/ph14020105) - 29 Jan 2021
Cited by 2 (/1424-8247/14/2/105#metrics) | Viewed by 1755

Abstract Central serous chorioretinopathy (CSC) is a controversial disease both in terms of clinical classification and choice of therapeutic strategy. Choroidal layers, retinal pigment epithelium (RPE), photoreceptors, and retina are involved to varying degrees. Beyond well-known symptoms raising the clinical suspect of CSC and **[...] Read more.**
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The Protein-Binding Behavior of Platinum Anticancer Drugs in Blood Revealed by Mass Spectrometry (/1424-8247/14/2/104)

by Jingchen Wang (https://sciprofiles.com/profile/1419242),
Jianmei Tao (https://sciprofiles.com/profile/author/d053Qk9wbjBXaHYrd3BhMHBhZ1lUdzdXc2wrN2lHZS84OG9DTUtsL2lFbz0=),
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Meiqin Wang (https://sciprofiles.com/profile/1449639), Hongliang Jiang (https://sciprofiles.com/profile/481518) and
Zhifeng Du (https://sciprofiles.com/profile/610475)
Pharmaceuticals **2021**, *14*(2), 104; https://doi.org/10.3390/ph14020104 (https://doi.org/10.3390/ph14020104) - 29 Jan 2021
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Abstract Cisplatin and its analogues are widely used as chemotherapeutic agents in clinical practice. After being intravenously administrated, a substantial amount of platinum will bind with proteins in the blood. This binding is vital for the transport, distribution, and metabolism of drugs; however, toxicity **[...] Read more.**
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Cytostatic Action of Novel Histone Deacetylase Inhibitors in Androgen Receptor-Null Prostate Cancer Cells (/1424-8247/14/2/103)

by Zohaib Rana (https://sciprofiles.com/profile/941303), Joel D. A. Tyndall (https://sciprofiles.com/profile/649949),
Muhammad Hanif (https://sciprofiles.com/profile/79718), Christian G. Hartinger (https://sciprofiles.com/profile/11314) and
Rhonda J. Rosengren (https://sciprofiles.com/profile/909443)

Pharmaceuticals **2021**, *14*(2), 103; **https://doi.org/10.3390/ph14020103 (https://doi.org/10.3390/ph14020103)** - 29 Jan 2021
Cited by 9 (/1424-8247/14/2/103#metrics) | Viewed by 1725

Abstract Androgen receptor (AR)-null prostate tumors have been observed in 11–24% of patients. Histone deacetylases (HDACs) are overexpressed in prostate tumors. Therefore, HDAC inhibitors (Jazz90 and Jazz167) were examined in AR-null prostate cancer cell lines (PC3 and DU145). Both Jazz90 and Jazz167 inhibited the **[...] Read more.**
(This article belongs to the Special Issue **Cancer Translational Biomarkers and Targeted Therapies (/journal/pharmaceuticals/special_issues /Cancer_Biomarkers_Targeted_Therapies)**)

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Open Access Review **(/1424-8247/14/2/99/pdf?version=1611902473)**

Reuse of Molecules for Glioblastoma Therapy (/1424-8247/14/2/99)

by **Abigail Koehler (https://sciprofiles.com/profile/1347954)**, **Aniruddha Karve (https://sciprofiles.com/profile/1445337)**, **Pankaj Desai (https://sciprofiles.com/profile/3067914)**, **Jack Arbiser (https://sciprofiles.com/profile/490131)**, **David R. Plas (https://sciprofiles.com/profile/author/V3dXOWRpSWduR2hCU0RaTkorYzJtR2ZYKzlCdE1UQjVnNFdlNVVtZWp6TT0=)**, **Xiaoyang Qi (https://sciprofiles.com/profile/2153441)**, **Renee D. Read (https://sciprofiles.com/profile/author/UWtmaFRUYXNLM2RhTHY1VlhmcUxCcjl4RXRQS1p3Q0d6WlhQR1lsUlBEND0=)**, **Atsuo T. Sasaki (https://sciprofiles.com/profile/author/Q0h1WTArbXhTQ1A1TTUyb09HSlB5ckd2T3NrOG9Pd2l1WitrdHhhQ0RhND0=)**, **Vaibhavkumar S. Gawali (https://sciprofiles.com/profile/1542278)**, **Donatien K. Toukam (https://sciprofiles.com/profile/2168506)**, **Debanjan Bhattacharya (https://sciprofiles.com/profile/2113022)**, **Laura Kallay (https://sciprofiles.com/profile/1348044)**, **Daniel A. Pomeranz Krummel (https://sciprofiles.com/profile/2092979)** and **Soma Sengupta (https://sciprofiles.com/profile/1367798)**
Pharmaceuticals **2021**, *14*(2), 99; **https://doi.org/10.3390/ph14020099 (https://doi.org/10.3390/ph14020099)** - 28 Jan 2021
Cited by 3 (/1424-8247/14/2/99#metrics) | Viewed by 3355

Abstract Glioblastoma multiforme (GBM) is a highly malignant primary brain tumor. The current standard of care for GBM is the Stupp protocol which includes surgical resection, followed by radiotherapy concomitant with the DNA alkylator temozolomide; however, survival under this treatment regimen is an abysmal **[...] Read more.**
(This article belongs to the Special Issue **Malignant Glioma: Novel Therapeutic Strategies (/journal/pharmaceuticals/special_issues/malignant_glioma)**)

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Open Access Article **(/1424-8247/14/2/102/pdf?version=1612156116)**

Metabolite Profiling of Methanolic Extract of *Gardenia jaminoides* by LC-MS/MS and GC-MS and Its Anti-Diabetic, and Anti-Oxidant Activities (/1424-8247/14/2/102)

by **Kandasamy Saravanakumar (https://sciprofiles.com/profile/656584)**, **SeonJu Park (https://sciprofiles.com/profile/1403876)**, **Anbazhagan Sathiyaseelan (https://sciprofiles.com/profile/1312284)**, **Kil-Nam Kim (https://sciprofiles.com/profile/106810)**, **Su-Hyeon Cho (https://sciprofiles.com/profile/author/bXJkOVZ4aEgyeTFFdWUrb1BXRUNlSFErYVUvWFl5ZHJ5Yzk4ZHBaWnhRaz0=)**, **Arokia Vijaya Anand Mariadoss (https://sciprofiles.com/profile/1425520)** and **Myeong-Hyeon Wang (https://sciprofiles.com/profile/651399)**
Pharmaceuticals **2021**, *14*(2), 102; **https://doi.org/10.3390/ph14020102 (https://doi.org/10.3390/ph14020102)** - 28 Jan 2021
Cited by 34 (/1424-8247/14/2/102#metrics) | Viewed by 3927

Abstract In this study, the methanolic extract from seeds of *Gardenia jasminoides* exhibited strong antioxidant and enzyme inhibition activities with less toxicity to NIH3T3 and HepG2 cells at the concentration of 100 μg/mL. The antioxidant activities (DPPH and ABTS), α-amylase, and α-glucosidase inhibition activities **[...] Read more.**
(This article belongs to the Special Issue **Applications of Liquid Chromatography in Analysis of Pharmaceuticals and Natural Products (/journal/pharmaceuticals /special_issues/Liquid_Chromatography_Natural_Products)**)

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Open Access Article **(/1424-8247/14/2/101/pdf?version=1612162120)**

Hyaluronic Acid-Modified and Doxorubicin-Loaded Gold Nanoparticles and Evaluation of Their Bioactivity (/1424-8247/14/2/101)

by **Lin-Song Li (https://sciprofiles.com/profile/author/WHRyK0FvVjJ5ZlFSSzJjeTNRamgzMElLTS96ellhYUlxNnZLZk9Fek5LQT0=)**, **Bin Ren (https://sciprofiles.com/profile/author/QVl0WjdxdzhpVXlMaUxoSThHTU1VMHpoOHJCcDJFVVpMeitLa3hQK2piWT0=)**, **Xiaojing Yang (https://sciprofiles.com/profile/517809)**, **Zhong-Chao Cai (https://sciprofiles.com/profile/author/ZTlrbFJ0OEFNcllPR29kbllad1JnY1NJUUlBVFVLNHlqTTdVU3hzRW0xcz0=)**, **Xue-Jie Zhao (https://sciprofiles.com/profile/author/QytEUEdYSDVHWlNweTE5NXF4R0hqbGw5MGVTRWkvZUlNekdDUVR3SU1laz0=)** and **Mei-Xia Zhao (https://sciprofiles.com/profile/1414526)**
Pharmaceuticals **2021**, *14*(2), 101; **https://doi.org/10.3390/ph14020101 (https://doi.org/10.3390/ph14020101)** - 28 Jan 2021
Cited by 12 (/1424-8247/14/2/101#metrics) | Viewed by 2077

Abstract Functionalized gold nanoparticles (AuNPs) have been successfully used in many fields as a result of having low cytotoxicity, good biocompatibility, excellent optical properties, and their ability to target cancer cells. Here, we synthesized AuNP carriers that were modified by hyaluronic acid (HA), polyethylene **[...] Read more.**
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Open Access Article (/1424-8247/14/2/100/pdf?version=1611903059)

Acute Pharmacological Effects of Oral and Intranasal Mephedrone: An Observational Study in Humans (/1424-8247/14/2/100)

by Esther Papaseit (https://sciprofiles.com/profile/1397122), Eulalia Olesti (https://sciprofiles.com/profile/695477), Clara Pérez-Mañá (https://sciprofiles.com/profile/1140193), Marta Torrens (https://sciprofiles.com/profile/835108), Francina Fonseca (https://sciprofiles.com/profile/1153408), Marc Grifell (https://sciprofiles.com/profile/1798747), Mireia Ventura (https://sciprofiles.com/profile/author/Tnd2dHlxSFNoaDZxSmk1Q29SYVZVRG93eE9zdkhLMlIRZForSW5TaUpaMD0=), Rafael de la Torre (https://sciprofiles.com/profile/480633) and Magí Farré (https://sciprofiles.com/profile/1072386)

Pharmaceuticals **2021**, *14*(2), 100; https://doi.org/10.3390/ph14020100 (https://doi.org/10.3390/ph14020100) - 28 Jan 2021

Cited by 10 (/1424-8247/14/2/100#metrics) | Viewed by 3301

Abstract Mephedrone (4-methylmethcathinone) is a synthetic cathinone with psychostimulant properties which remains one of the most popular new psychoactive substances (NPS). It is frequently used orally and/or intranasally. To date, no studies have evaluated the acute effects and pharmacokinetics after self-administration of mephedrone orally **[...] Read more.**

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Open Access Article (/1424-8247/14/2/98/pdf?version=1611894978)

Immobilization of Chondroitin Sulfate A onto Monolithic Epoxy Silica Column as a New Chiral Stationary Phase for High-Performance Liquid Chromatographic Enantioseparation (/1424-8247/14/2/98)

by Ratih Ratih (https://sciprofiles.com/profile/author/ZUNOV29BZ0ZNcnkzbTBlTjZ6SjYxMGV3VGc0aEt1eTdlOGMrTitCK2RLaz0=), Hermann Wätzig (https://sciprofiles.com/profile/2907935), Azminah Azminah (https://sciprofiles.com/profile/1452627), Mufarreh Asmari (https://sciprofiles.com/profile/1452308), Benjamin Peters (https://sciprofiles.com/profile/author/Wi91NTc2V3huMk9YUWx0RDZpcHdlVkJRU2dkQW9CTUtOY0V6ZzJ3ZEZXQT0=) and Sami El Deeb (https://sciprofiles.com/profile/1403627)

Pharmaceuticals **2021**, *14*(2), 98; https://doi.org/10.3390/ph14020098 (https://doi.org/10.3390/ph14020098) - 27 Jan 2021

Cited by 7 (/1424-8247/14/2/98#metrics) | Viewed by 2124

Abstract Chondroitin sulfate A was covalently immobilized onto a monolithic silica epoxy column involving a Schiff base formation in the presence of ethylenediamine as a spacer and evaluated in terms of its selectivity in enantioseparation. The obtained column was utilized as a chiral stationary **[...] Read more.**

(This article belongs to the Special Issue **Analytical Techniques in the Pharmaceutical Sciences (/journal/pharmaceuticals/special_issues/analytical_techniques_pharm)**)

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Open Access Article (/1424-8247/14/2/97/pdf?version=1611825149)

Repeated Administration of Clinically Relevant Doses of the Prescription Opioids Tramadol and Tapentadol Causes Lung, Cardiac, and Brain Toxicity in Wistar Rats (/1424-8247/14/2/97)

by Joana Barbosa (https://sciprofiles.com/profile/1127808), Juliana Faria (https://sciprofiles.com/profile/1147348), Fernanda Garcez (https://sciprofiles.com/profile/author/QXBWNGdwWkpJSklzakZmMFA1WCtCdjc3MmRFNmc3Uk5URUFCNXZ1N1NTRT0=), Sandra Leal (https://sciprofiles.com/profile/1620982), Luís Pedro Afonso (https://sciprofiles.com/profile/author/ajlsWFVvRFpObkx6ZHVjL2VFMWxWNlJONHFra0JCejFLdG1BdVVZbHN4RT0=), Ana Vanessa Nascimento (https://sciprofiles.com/profile/author/WU1Ya2x2UDY3TDl2bnM0OHlyNnhzalVQb2s2RjJ5UkFrdmZ5TVMreHFPTT0=), Roxana Moreira (https://sciprofiles.com/profile/1147943), Frederico C. Pereira (https://sciprofiles.com/profile/1396260), Odília Queirós (https://sciprofiles.com/profile/1167488), Félix Carvalho (https://sciprofiles.com/profile/777248) and Ricardo Jorge Dinis-Oliveira (https://sciprofiles.com/profile/490770)

Pharmaceuticals **2021**, *14*(2), 97; https://doi.org/10.3390/ph14020097 (https://doi.org/10.3390/ph14020097) - 27 Jan 2021

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Abstract Tramadol and tapentadol, two structurally related synthetic opioid analgesics, are widely prescribed due to the enhanced therapeutic profiles resulting from the synergistic combination between μ-opioid receptor (MOR) activation and monoamine reuptake inhibition. However, the number of adverse reactions has been growing along with **[...] Read more.**

(This article belongs to the Special Issue **Pharmacokinetics and Pharmacodynamics of Psychoactive Substances: Clinical and Forensic Aspects (/journal/pharmaceuticals/special_issues/Pharmacokinetics_Pharmacodynamics_Psychoactive)**)

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The i-Motif as a Molecular Target: More Than a Complementary DNA Secondary Structure (/1424-8247/14/2/96)

by Susie L. Brown (https://sciprofiles.com/profile/1502739) and Samantha Kendrick (https://sciprofiles.com/profile/1402169)

Pharmaceuticals **2021**, *14*(2), 96; https://doi.org/10.3390/ph14020096 (https://doi.org/10.3390/ph14020096) - 27 Jan 2021

Cited by 37 (/1424-8247/14/2/96#metrics) | Viewed by 5651

Abstract Stretches of cytosine-rich DNA are capable of adopting a dynamic secondary structure, the i-motif. When within promoter regions, the i-motif has the potential to act as a molecular switch for controlling gene expression. However, i-motif structures in genomic areas of repetitive nucleotide sequences **[...] Read more.**

(This article belongs to the Special Issue **Quadruplex Nucleic Acid Ligands (/journal/pharmaceuticals/special_issues /Quadruplex_Nucleic_Acid_Ligands)**)

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Open Access Feature Paper Review (/1424-8247/14/2/95/pdf?version=1611736027)

Mechanisms of Intranasal Deferoxamine in Neurodegenerative and Neurovascular Disease (/1424-8247/14/2/95)

by Jacob Kosyakovsky (https://sciprofiles.com/profile/1436445), Jared M. Fine (https://sciprofiles.com/profile/1413345), William H. Frey (https://sciprofiles.com/profile/986077) and Leah R. Hanson (https://sciprofiles.com/profile/author/ai9SSUZJMUJVUGhBTFlyN214VndwSER6d0hpVVNOWksweUNsRkhWY3JHZzNhV05GbHE1d2NaSEtMaXZMcTNhQg==)

Pharmaceuticals **2021**, *14*(2), 95; https://doi.org/10.3390/ph14020095 (https://doi.org/10.3390/ph14020095) - 27 Jan 2021

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Abstract Identifying disease-modifying therapies for neurological diseases remains one of the greatest gaps in modern medicine. Herein, we present the rationale for intranasal (IN) delivery of deferoxamine (DFO), a high-affinity iron chelator, as a treatment for neurodegenerative and neurovascular disease with a focus on **[...] Read more.**

(This article belongs to the Special Issue **New Drugs and Biologics For Treatment of Central Nervous Dysfunction (/journal/pharmaceuticals/special_issues/Drugs_CND)**)

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Open Access Article (/1424-8247/14/2/94/pdf?version=1611731043)

Influence of Estrogenic Metabolic Pathway Genes Polymorphisms on Postmenopausal Breast Cancer Risk (/1424-8247/14/2/94)

by Micaela Almeida (https://sciprofiles.com/profile/1453005), Mafalda Soares (https://sciprofiles.com/profile/1454178), José Fonseca-Moutinho (https://sciprofiles.com/profile/author/TGVyRUJpREV5WXM5aXRiMFRwUnR4eWtkblAzZzBWcGMveHlQenFXK0hRTT0=), Ana Cristina Ramalhinho (https://sciprofiles.com/profile/2185405) and Luiza Breitenfeld (https://sciprofiles.com/profile/274116)

Pharmaceuticals **2021**, *14*(2), 94; https://doi.org/10.3390/ph14020094 (https://doi.org/10.3390/ph14020094) - 27 Jan 2021

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Abstract Estrogen metabolism plays an important role in tumor initiation and development. Lifetime exposure to high estrogens levels and deregulation of enzymes involved in estrogen biosynthetic and metabolic pathway are considered risk factors for breast cancer. The present study aimed to evaluate the impact **[...] Read more.**

(This article belongs to the Special Issue **Cancer Translational Biomarkers and Targeted Therapies (/journal/pharmaceuticals/special_issues /Cancer_Biomarkers_Targeted_Therapies)**)

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Open Access Feature Paper Article (/1424-8247/14/2/93/pdf?version=1611721689)

Extracts of the Tiger Milk Mushroom (*Lignosus rhinocerus*) Enhance Stress Resistance and Extend Lifespan in *Caenorhabditis elegans* via the DAF-16/FoxO Signaling Pathway (/1424-8247/14/2/93)

by Parinee Kittimongkolsuk (https://sciprofiles.com/profile/1416183), Mariana Roxo (https://sciprofiles.com/profile/1053055), Hanmei Li (https://sciprofiles.com/profile/376350), Siriporn Chuchawankul (https://sciprofiles.com/profile/1191707), Michael Wink (https://sciprofiles.com/profile/93367) and Tewin Tencomnao (https://sciprofiles.com/profile/7057)

Pharmaceuticals **2021**, *14*(2), 93; https://doi.org/10.3390/ph14020093 (https://doi.org/10.3390/ph14020093) - 27 Jan 2021

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Abstract The tiger milk mushroom, *Lignosus rhinocerus* (LR), exhibits antioxidant properties, as shown in a few in vitro experiments. The aim of this research was to study whether three LR extracts exhibit antioxidant activities in *Caenorhabditis elegans*. In wild-type N2 nematodes, we determined **[...] Read more.**

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Monoclonal Antibodies as Neurological Therapeutics (/1424-8247/14/2/92)

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Dimos D. Mitsikostas (https://sciprofiles.com/profile/1148965) and Dimitrios Papadopoulos (https://sciprofiles.com/profile/506123)
Pharmaceuticals **2021**, *14*(2), 92; https://doi.org/10.3390/ph14020092 (https://doi.org/10.3390/ph14020092) - 26 Jan 2021
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Abstract Over the last 30 years the role of monoclonal antibodies in therapeutics has increased enormously, revolutionizing treatment in most medical specialties, including neurology. Monoclonal antibodies are key therapeutic agents for several neurological conditions with diverse pathophysiological mechanisms, including multiple sclerosis, migraines and neuromuscular **[...] Read more.**
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Open Access Article (/1424-8247/14/2/91/pdf?version=1612160353)

Ursolic Acid Inhibits Collective Cell Migration and Promotes JNK-Dependent Lysosomal Associated Cell Death in Glioblastoma Multiforme Cells (/1424-8247/14/2/91)

by Gillian E. Conway (https://sciprofiles.com/profile/1393800),
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Orla Howe (https://sciprofiles.com/profile/1255633) and James F. Curtin (https://sciprofiles.com/profile/1062029)
Pharmaceuticals **2021**, *14*(2), 91; https://doi.org/10.3390/ph14020091 (https://doi.org/10.3390/ph14020091) - 26 Jan 2021
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Abstract Ursolic acid (UA) is a bioactive compound which has demonstrated therapeutic efficacy in a variety of cancer cell lines. UA activates various signalling pathways in Glioblastoma multiforme (GBM) and offers a promising starting point in drug discovery; however, understanding the relationship between cell **[...] Read more.**
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Protopine/Gemcitabine Combination Induces Cytotoxic or Cytoprotective Effects in Cell Type-Specific and Dose-Dependent Manner on Human Cancer and Normal Cells (/1424-8247/14/2/90)

by Mercedes Garcia-Gil (https://sciprofiles.com/profile/472299),
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Silvia Marracci (https://sciprofiles.com/profile/670271)
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Abstract The natural alkaloid protopine (PRO) exhibits pharmacological properties including anticancer activity. We investigated the effects of PRO, alone and in combination with the chemotherapeutic gemcitabine (GEM), on human tumor cell lines and non-tumor human dermal fibroblasts (HDFs). We found that treatments with different **[...] Read more.**
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miRNA-Based Therapeutics in the Era of Immune-Checkpoint Inhibitors (/1424-8247/14/2/89)

by Florian Huemer (https://sciprofiles.com/profile/976956), Michael Leisch (https://sciprofiles.com/profile/2035570), Roland Geisberger (https://sciprofiles.com/profile/1026053), Nadja Zaborsky (https://sciprofiles.com/profile/1388927) and Richard Greil (https://sciprofiles.com/profile/633681)

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Abstract MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by binding to complementary target regions on gene transcripts. Thus, miRNAs fine-tune gene expression profiles in a cell-type-specific manner and thereby regulate important cellular functions, such as cell growth, proliferation and cell death. [...] Read more.

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Effects of Selective Peroxisome Proliferator Activated Receptor Agonists on Corneal Epithelial Wound Healing (/1424-8247/14/2/88)

by Yutaro Tobita (https://sciprofiles.com/profile/1127207), Takeshi Arima (https://sciprofiles.com/profile/1116459), Yuji Nakano (https://sciprofiles.com/profile/1126460), Masaaki Uchiyama (https://sciprofiles.com/profile/2354666), Akira Shimizu (https://sciprofiles.com/profile/560492) and Hiroshi Takahashi (https://sciprofiles.com/profile/2354667)

Pharmaceuticals **2021**, *14*(2), 88; https://doi.org/10.3390/ph14020088 (https://doi.org/10.3390/ph14020088) - 25 Jan 2021

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Abstract The effects of each subtype-selective peroxisome proliferator activated receptor (PPAR) agonist (α, β/δ, γ) on corneal epithelial wound healing were investigated using a rat corneal alkali burn model. After the alkali burn, each PPAR agonist or vehicle ophthalmic solution was instilled topically onto [...] Read more.

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Identification of 37 Heterogeneous Drug Candidates for Treatment of COVID-19 via a Rational Transcriptomics-Based Drug Repurposing Approach (/1424-8247/14/2/87)

by Andrea Gelemanović (https://sciprofiles.com/profile/805350), Tinka Vidović (https://sciprofiles.com/profile/1417105), Višnja Stepanić (https://sciprofiles.com/profile/813623) and Katarina Trajković (https://sciprofiles.com/profile/1417097)

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Abstract A year after the initial outbreak, the COVID-19 pandemic caused by SARS-CoV-2 virus remains a serious threat to global health, while current treatment options are insufficient to bring major improvements. The aim of this study is to identify repurposable drug candidates with a [...] Read more.

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Natural Marine and Terrestrial Compounds as Modulators of Matrix Metalloproteinases-2 (MMP-2) and MMP-9 in Alzheimer's Disease (/1424-8247/14/2/86)

by Lidia Ciccone (https://sciprofiles.com/profile/1074772), Jennifer Vandooren (https://sciprofiles.com/profile/590212), Susanna Nencetti (https://sciprofiles.com/profile/1423943) and Elisabetta Orlandini (https://sciprofiles.com/profile/1358112)

Pharmaceuticals **2021**, *14*(2), 86; https://doi.org/10.3390/ph14020086 (https://doi.org/10.3390/ph14020086) - 24 Jan 2021

Cited by 22 (/1424-8247/14/2/86#metrics) | Viewed by 2987

Abstract Several studies have reported neuroprotective effects by natural products. A wide range of natural compounds have been investigated, and some of these may play a beneficial role in Alzheimer's disease (AD) progression. Matrix metalloproteinases (MMPs), a family of zinc-dependent endopeptidases, have been implicated [...] Read more.

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(2-Aminobenzothiazole)-Methyl-1,1-Bisphosphonic Acids: Targeting Matrix Metalloproteinase 13 Inhibition to the Bone (/1424-8247/14/2/85)

by Antonio Laghezza (https://sciprofiles.com/profile/237765), Luca Piemontese (https://sciprofiles.com/profile/150581), Leonardo Brunetti (https://sciprofiles.com/profile/1198617), Alessia Caradonna (https://sciprofiles.com/profile/author/aTdPSGVWRTUvc3pSRHRjeDNmaUd6ZW1QWW9pOGZucXdFMm1mMkFBRldBcz0=), Mariangela Agamennone (https://sciprofiles.com/profile/195316), Fulvio Loiodice (https://sciprofiles.com/profile/1084564) and Paolo Tortorella (https://sciprofiles.com/profile/924201)

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Cited by 1 (/1424-8247/14/2/85#metrics) | Viewed by 1473

Abstract Matrix Metalloproteinases (MMPs) are a family of secreted and membrane-bound enzymes, of which 24 isoforms are known in humans. These enzymes degrade the proteins of the extracellular matrix and play a role of utmost importance in the physiological remodeling of all tissues. However, [...] Read more.

(This article belongs to the Special Issue Novel Approaches for Targeting Metalloproteinases (/journal/pharmaceuticals/special_issues/Targeting_Metalloproteinases))

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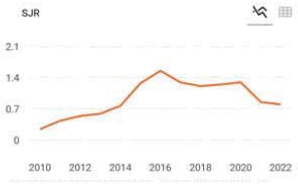

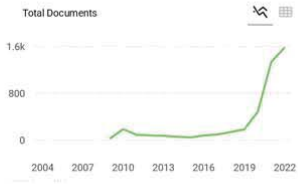

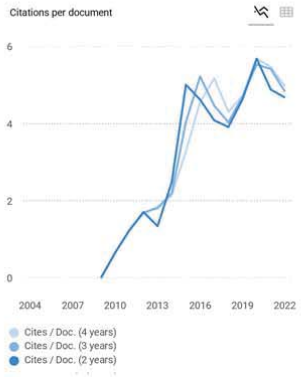

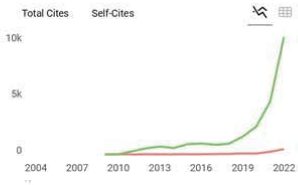

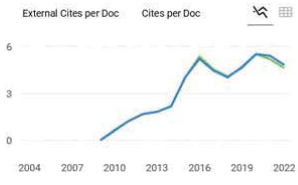

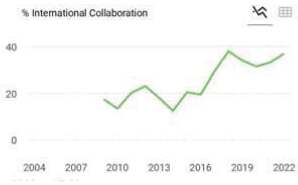

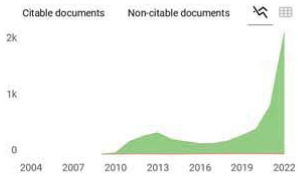

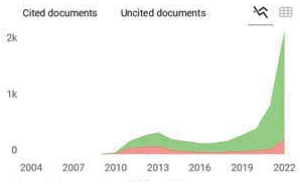

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