Chiral Separation of Cathinone Derivatives Used as Recreational Drugs by HPLC-UV Using a CHIRALPAK® AS-H Column as Stationary Phase

STEFAN MOHR,[1,2] MAGDALENA TASCHWER,[1] AND MARTIN G. SCHMID [1]*

[1]*Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Karl-Franzens-University Graz, A-8010 Graz, Austria*
[2]*Research Center Pharmaceutical Engineering, Graz, Austria*

ABSTRACT Cathinone derivatives gained high popularity on the recreational drugs market during the past 10 years. All these compounds are chiral, and the pharmacological potency of the enantiomers of these stimulants is supposed to differ. The goal of this research was to develop a reliable and easy-to-perform high-performance liquid chromatography ultraviolet method for the chiral separation of a set of 24 cathinone derivatives. A commercially available CHIRALPAK® AS-H column consisting of amylose tris [*(S)*-α-methylbenzylcarbamate] coated on 5-μm silica gel was found to be suitable to resolve a majority of the tested compounds. High-performance liquid chromatography measurements were performed in normal phase mode under isocratic conditions with a mobile phase consisting of hexane, isopropanol, and triethylamine at a flowrate of 1 ml/min. The ratio between hexane and isopropanol was optimized by means of three model substances. Under final conditions with a mobile phase of hexane, isopropanol, and triethylamine (97:3:0.1), 19 out of 24 compounds were successfully resolved into their enantiomers and detected at a wavelength of 254 nm. A correlation between the substituents of the nitrogen atom and the separation results are shown. Furthermore, enantiomer separation results of four cathinone derivatives were compared with the results of their amphetamine analogs. *Chirality 00:000–000, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: mephedrone; legal highs; amphetamines; polysaccharide-based stationary phase

INTRODUCTION

During the past 5 years, new chemical compounds structurally related to the naturally occuring phenylpropane alkaloid or beta-keto-amphetamine, cathinone gained high popularity on the recreational drugs market. Among them, mephedrone (4-methyl-methcathinone) is the most popular substance still being merchandised via the Internet as plant food, bath salt, or research chemical. Because it is easy and nearly anonymous to procure these compounds, combined with the low price and the high purity, mephedrone became a very popular legal alternative to the well-known party drugs amphetamine (Speed) or methylendioxymethamphetamine (Ecstasy). In 2009, the mephedrone hype was on its top in Europe, and authorities were forced to react. Since the beginning of 2011, mephedrone is prohibited in nearly entire Europe, leading to a swap of other cathinone derivatives onto the drug market. The backbone of the beta-keto-amphetamines can be modified by various substituents. Only a few countries, for example, Great Britain, prohibited the entire class of cathinone substances to avoid the shift of the market to analogs with nearly the same spectrum of effects.

Because it is well known that the enantiomers of a chiral active pharmaceutical ingredient may exhibit different pharmacological effects, different potency, or an effect limited to only one optical isomer of the molecule, the development of chiral separation methods in analytical and preparative scale is a big field of interest. During the development process of a new racemic drug substance, pharmacological and toxicological tests are performed for each enantiomer to avoid scenarios known from thalidomide. All new designer drugs derived from cathinone have an asymmetric substituted carbon atom yielding in two stereoisomers. Because of the novelty of these compounds, limited pharmacological and toxicological data of the racemic mixture and nearly no data about the single enantiomers are available. It was found out that the *S*(−) enantiomer of methcathinone and the *S*(+) enantiomer of amphetamine are more potent stimulants than their *R*(+) and *R*(−) antipodes, respectively.[1–4] This potency differences and the possibility to collect information about the lab of origin may be subject to the development of analytical methods for the determination of the enantiomer purity of this substance class.

Some articles dealing with the chiral separation of compounds related to amphetamine can be found in literature including capillary electrophoresis,[5–10] gas chromatography,[4,11–13] and high-performance liquid chromatography (HPLC) methods.[14–18] Recently, our group succeeded in separating 19 cathinone derivatives by cyclodextrin-modified capillary electrophoresis.[10] Mathys' group performed indirect chiral separation of cathinone by derivatization with *S*(−)-phenylethyl isocyanate on a 5-μm normal phase column.[15] Direct chiral separation of cathinone and some analogs was performed by using a (3,3-diphenyl-1,1-binaphtyl)-20-crown-6 dynamically coated

*Correspondence to: Martin Schmid, Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Karl-Franzens-University Graz, A-8010 Graz, Austria. E-mail: martin.schmid@uni-graz.at
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on octadecylsilica gel[18] and covalently bond to silica gel, respectively.[14,17] Further chiral stationary phases (CSPs) based on cellobiohydrolase (CBH-I)[20] and (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid[19] were reported to be successful. Because the use of crown ether-based CSPs is limited to primary amines, our goal was to find a CSP suitable to resolve most of the new synthetic drug substances of abuse, which mainly consist of secondary amines.

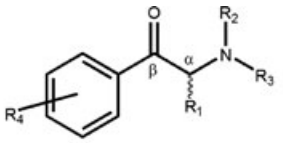
The goal of this work was to develop a chiral separation method for cathinone derivatives available on the street market. Four cathinone derivatives were compared with their amphetamine analogs regarding the chiral resolution. To our knowledge, it was the first time that such a broad spectrum of cathinone derivatives was investigated by HPLC.

MATERIALS AND METHODS

Chromatographic Conditions

Analysis was performed on an Agilent (Waldbronn, Germany) HP 1090 series II HPLC System equipped with an autosampler and a diode array detector. Ultraviolet (UV)-detection was performed at 254 nm. The UV-spectra of all compounds were collected in a range from 200 to 400 nm. Measurements were performed at room temperature with a mobile phase consisting of hexane, isopropanol, and triethylamine (TEA) under isocratic conditions with a flow of 1 ml/min. A commercially available CHIRALPAK® AS-H column, 150 × 4.6 mm, coated on 5-μm silica gel was used as CSP. The injection volume was set to 5 μl. Prior to injection, the needle was flushed with 10 μl of the mobile phase. Data analysis was performed with Chem Station for LC 3D Rev. A. 10.01 (Agilent Technologies, CA, USA).

For the reproducibility studies, a modular HPLC system consisting of a D-7000 interface (Merck Hitachi, Darmstadt, Germany), a LaChrom



Compound	R_1	R_2	R_3	R_4
4-Bromomethcathinone (4-BMC)	Me	H	Me	4-Br
Buphedrone	Et	H	Me	H
Butylone	Et	H	Me	3,4-methylenedioxy
Cathinone	Me	H	H	H
3,4-Dimethylmethcathinone (3,4-DMMC)	Me	H	Me	3,4-dimethyl
N,N-Dimethylbutylone	Et	Me	Me	3,4-methylenedioxy
Ethcathinone	Me	H	Et	H
Ethylone	Me	H	Et	3,4-methylenedioxy
Ethylbuphedrone	Et	H	Et	H
2-Fluoromethcathinone (2-FMC)	Me	H	Me	2-F
3-Fluoromethcathinone (3-FMC)	Me	H	Me	3-F
4-Fluoromethcathinone (4-FMC)	Me	H	Me	4-F
Methylendioxypyrovalerone (MDPV)	Pr	pyrrolidinyl		3,4-methylenedioxy
4-Methylbuphedrone	Et	H	Me	4-Me
4-Methylethcathinone (4-MEC)	Me	H	Et	4-Me
4-Methyl-alpha-Pyrrolidinopropiophenone (MPPP)	Me	pyrrolidinyl		4-Me
Mephedrone (4-MMC)	Me	H	Me	4-Me
Methcathinone	Me	H	Me	H
Methedrone	Me	H	Me	4-MeO
Methylone	Me	H	Me	3,4-methylenedioxy
Naphyrone	Pr	pyrrolidinyl		β-naphtyl instead of phenyl
Pentedrone	Pr	H	Me	H
Pentylone	Pr	H	Me	3,4-methylenedioxy
α-Pyrrolidinopropiophenone	Me	pyrrolidinyl		H

Fig. 1. Structures of the tested cathinone derivatives.

L-7100 pump (Merck Hitachi), and a L-7400 single wavelength detector was used. Samples were injected manually with a loop size of 20 µl. For data collection and analysis, a D-7000 HPLC system manager (Merck Hitachi) was used.

Chemicals and Solutions

All chemicals were of analytical grade. Hexane, methylene chloride, and isopropanol were purchased from Carl Roth (Karlsruhe, Germany). TEA and ethcathinone were from Sigma-Aldrich Chemicals (St Louis, MO, USA). Sodium sulfate and sodium hydroxide were obtained from VWR (Darmstadt, Germany). Water was deionized and double-distilled. Amphetamine HCl, methamphetamine HCl, 3,4-methylendioxymethamphetamine HCl, 3,4-methylendioxyethylamphetamine HCl, and methylbenzodioxolylbutanamine HCl were purchased from LGC Standards (Wesel, Germany).

Because of their novelity, most analytes were not available from official suppliers and therefore bought in relevant online stores.

4-Methylmethcathinone (mephedrone) and butylone were purchased from http://naughtyplantfood.com. 3-Fluoromethcathinone (3-FMC) and 3,4-dimethylmethcathinone (3,4-DMMC) were obtained from http://research-chemicals24.hu. Methylone, 4-methylethcathinone (4-MEC), naphyrone, and 4-fluoromethcathinone (4-FMC) were purchased from http://get-rc.to. Methylendioxypyrovalerone (MDPV) was bought from http://RCshop.es. Pentedrone, ethylone, and 4-methyl-alpha-pyrrolidinopropiophenon were purchased from http://buybestrc.com. 4-Bromomethcathinone (4-BMC), methedrone, buphedrone, alpha-pyrrolidinopropiophenone (α-PPP), and *N*-ethylbuphedrone were obtained from http://labamin.pl. 4-Methyl-buphedrone and 2-fluoromethcathinone were from http://sensearomatic.com. Pentylone was purchased from http://jollyeffects.com and dimethylbutylone from http://chem-guru.com. Prior to use, the compounds were characterized by GC-EI-MS and NMR if necessary. Figures 1 and 2 show the structure of all used analytes. The single enantiomers of cathinone and methcathinone were synthesized by oxidation of (1*R*,2*S*)-(−) and (1*S*,2*R*)-(+)-norephedrine and ephedrine with potassium permanganate.

The mobile phase was prepared by mixing hexane, isopropanol, and TEA in required ratios. The solution was degassed for 2 min with helium 5.0.

Sample Preparation

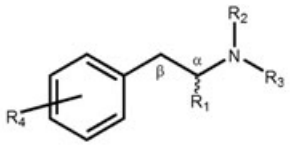
For sample preparation, 1.5 mg of the substance was dissolved in 1.5 ml of water, 20 µl of a 1 M sodium hydroxide solution was added, and the free base was extracted with 1.5 ml methylenchloride. The methylene chloride layer was dried over anhydrous sodium sulfate, and methylene chloride was evaporated under a soft nitrogen stream. The remaining free base of the compounds was reconstituted in a mixture of hexane and isopropanol (97:3).

RESULTS AND DISCUSSION

Even though it was found out that polysaccharide-based CSPs first introduced by Okamoto and co-workers [21] are able to separate up to 95% of low and medium weight chiral molecules from pharmaceutical interest, it is not predictable which type of CSP is able to enantioseparate a specific molecule or class of molecules. Mostly, the optimal CSP has to be found out empirically by screening different types of polysaccharide CSPs under different conditions. In general, chiral resolution of enantiomers is based on different interactions of each enantiomer with the immobilized CSP. Therefore, the enantiomer with the weaker interaction to the CSP passes the detector first. Spatial effects of cavities built by the polysaccharide are mainly responsible for the enantiomer–CSP interplay. Secondary interactions to be taken into account are hydrogen bondings, π–π interactions, dipole–dipole interactions, and steric effects.

On the basis of previous experiences with polysaccharide CSPs in our group, a CHIRALPAK® AS-H column consisting of amylose tris [(S)-α-methylbenzylcarbamate] coated on 5-µm silica gel was chosen as stationary phase. A mobile phase consisting of hexane/isopropanol (90:10) with 0.1% TEA as basic modifier was used as mobile phase for the optimization procedure. With the use of mephedrone, butylone, and MDPV as model compounds, the isopropanol content of the mobile phase was reduced successively. The effect of different ratios between hexane and isopropanol on the retention time and the resolution of the enantiomers is shown in Table 1.

With the use of mobile phases with a specific content of isopropanol ranging from 10% to 2%, mephedrone and butylone were resolved successfully into their enantiomers. According to the instruction manual of the column, retention times decreased with increasing alcohol content. With decreasing retention times, lower resolution was observed because the interaction with the CSP is weaker. The resolution for mephedrone was ranging from 1.3 with 10% to 3.5 with 2% isopropanol and for butylone from 3.2 to 6.1. MDPV did not show any chiral discrimination with an isopropanol consisting mobile phase. By using 100% hexane with 0.1% TEA, butylone and MDPV were partially separated, whereas enormous peak tailing was observed. With mephedrone, no peak was detected within 1 h



Compound	R_1	R_2	R_3	R_4
Amphetamine	Me	H	H	H
3,4-Methylendioxymethamphetamine (MDMA)	Me	H	Me	3,4-methylenedioxy
3,4-Methylendioxyethamphetamine (MDEA)	Me	H	Et	3,4-methylenedioxy
Methylbenzodioxolylbutanamine (MBDB)	Et	H	Me	3,4-methylenedioxy

Fig. 2. Structures of the tested amphetamine analogs.

TABLE 1. Effect of different isopropanol contents of the mobile phase on the resolution and the retention time

	Mephedrone				Butylone				Methylendioxypyrovalerone			
Isopropanol vol %	t_1 (min)	t_2 (min)	α	R_s	t_1 (min)	t_2 (min)	α	R_s	t_1 (min)	t_2 (min)	α	R_s
10	3.22	4.50	1.875	1.3	4.31	6.58	1.897	3.2	2.82	–	–	–
5	4.25	6.41	1.908	2.0	6.01	9.68	1.883	3.2	3.25	–	–	–
3	4.85	7.94	2.047	2.6	7.05	12.07	1.972	5.1	3.55	–	–	–
2	5.82	10.62	2.228	3.5	8.45	16.13	2.170	6.1	3.88	–	–	–
0	>60	–	–	–	9.66	9.87	1.027	0.0	10.87	11.73	1.100	0.4

Conditions: column: CHIRALPAK® AS-H, mobile phase: hexane/isopropanol + 0.1% triethylamine, ambient temperature, flow: 1.0 ml/min, UV: 254 nm, injection: 5 µl.

because the mobile phase was not polar enough for the elution from the column. Even if MDPV could not be separated, with respect to retention time and resolution, a mobile phase consisting of hexane/isopropanol/TEA (97:3:0.1) was chosen for the screening of all 24 cathinone derivatives. Under these conditions, 19 compounds were baseline-separated within 25 min with resolution factors ranging from 0.7 for 4-BMC to 4.2 for methylone. As it was expectable from the experiments with the model substances, MDPV, MPPP, α-PPP, and naphyrone could not be separated into their enantiomers, as shown in Table 2. It seems that under these conditions, the CHIRALPAK® AS-H column is not suitable for enantioseparation of beta-keto amphetamines with the nitrogen atom included in a ring structure. This might be due to inability of the tertiary amino group to form hydrogen bondings with the chiral selector. The separation result of *N,N*-dimethylbutylone confirms this hypothesis because the resolution result was inferior to the, apart from the second methyl group on the nitrogen, identical primary amine butylone. *N,N*-dimethylbutylone was only partially separated, whereas butylone was baseline-separated. The bulky pyrrolidinyl moiety seems to represent a steric hindrance as well. Figure 3 shows a comparison of the chromatograms of butylone, *N,N*-dimethylbutylone, and MDPV.

TABLE 2. Chiral separation results of a set of 24 cathinone derivatives

	t_1 (min)	t_2 (min)	α	R_s
4-BMC	5.53	6.53	1.272	0.7
Buphedrone	3.26	5.22	2.438	1.9
Butylone	6.98	13.07	2.200	3.8
Cathinone	13.91	23.08	1.764	3.4
3,4-DMMC	4.71	11.91	3.550	4.5
N,N-Dimethylbutylone	3.85	4.03	1.091	0.5
Ethcathinone	3.14	3.73	1.474	1.2
Ethylone	7.17	9.75	1.489	2.1
Ethylbuphedrone	2.54	2.91	1.560	1.0
2-Fluoromethcathinone	4.06	4.83	1.361	1.6
3-Fluoromethcathinone	4.12	5.81	1.764	2.0
4-Fluoromethcathinone	4.76	7.71	2.033	3.0
MDPV	3.54	3.54	1.000	–
4-Methylbuphedrone	3.36	5.57	2.510	2.3
4-MEC	3.24	4.16	1.690	1.0
MPPP	2.95	2.95	1.000	–
Mephedrone	4.95	8.53	2.177	2.9
Methcathinone	4.58	7.36	2.034	2.5
Methedrone	10.37	16.92	1.772	3.3
Methylone	12.70	21.67	1.830	4.2
Naphyrone	2.59	2.59	1.000	–
Pentedrone	2.92	4.15	2.195	1.9
Pentylone	5.69	9.60	2.030	3.5
α-Pyrrolidinopropiophenone	2.85	2.85	1.000	–

Conditions: column: CHIRALPAK® AS-H, mobile phase: hexane/isopropanol/triethylamine (97:3:0.1), ambient temperature, flow: 1.0 ml/min, UV: 254 nm, injection: 5 µl.

The enantiomer elution order was checked by injecting a methcathinone solution with an excess of the *S*(−) enantiomer. As shown in Figure 4, the *R*(+) enantiomer elutes first followed by the *S*(−) enantiomer. The same enantiomer elution order was obtained with a cathinone sample.

Furthermore, it was tried out to achieve simultaneous enantioseparation for more racemic compounds per run; therefore, samples consisting of different cathinone derivatives were injected. A maximum of five cathinones (3-FMC, 4-FMC, methedrone, buphedrone, and cathinone) were separated simultaneously in one run (Fig. 5).

It can be emphasized here that, within this run, the structural isomers 3-FMC and 4-FMC, which are only different by the position of the fluoro atom on the phenyl ring, were separated into its stereoisomers.

Another interesting sample consisted of methcathinone, buphedrone, and pentedrone. The only difference between this compounds is the length of the α carbon substituent as seen in Figure 1. In Figure 6, the enantioseparation of all three compounds in one run is shown, whereby the elution order was pentedrone, buphedrone, and methcathinone.

Additionally, the chromatographic separation behavior of four cathinones was compared with their amphetamine analogs. Because cathinones represent beta-keto amphetamines, for each cathinone, an amphetamine analog exists, for example, cathinone and amphetamine or methylone and MDMA (Ecstasy), respectively. It was found out that separation results of amphetamines are poor compared with the cathinones (Table 3). Amphetamine could not be detected within 1 h. The other four amphetamines were only partially separated. Figure 7 shows the overlaid chromatograms of MDMA and methylone. It seems that the carbonyl oxygen with its two free electron pairs plays a key role in promoting sufficient interaction between the compounds and the CSP to obtain baseline separation of the enantiomers.

The introduced method was validated with regard to repeatability and reproducibility concerning the retention time

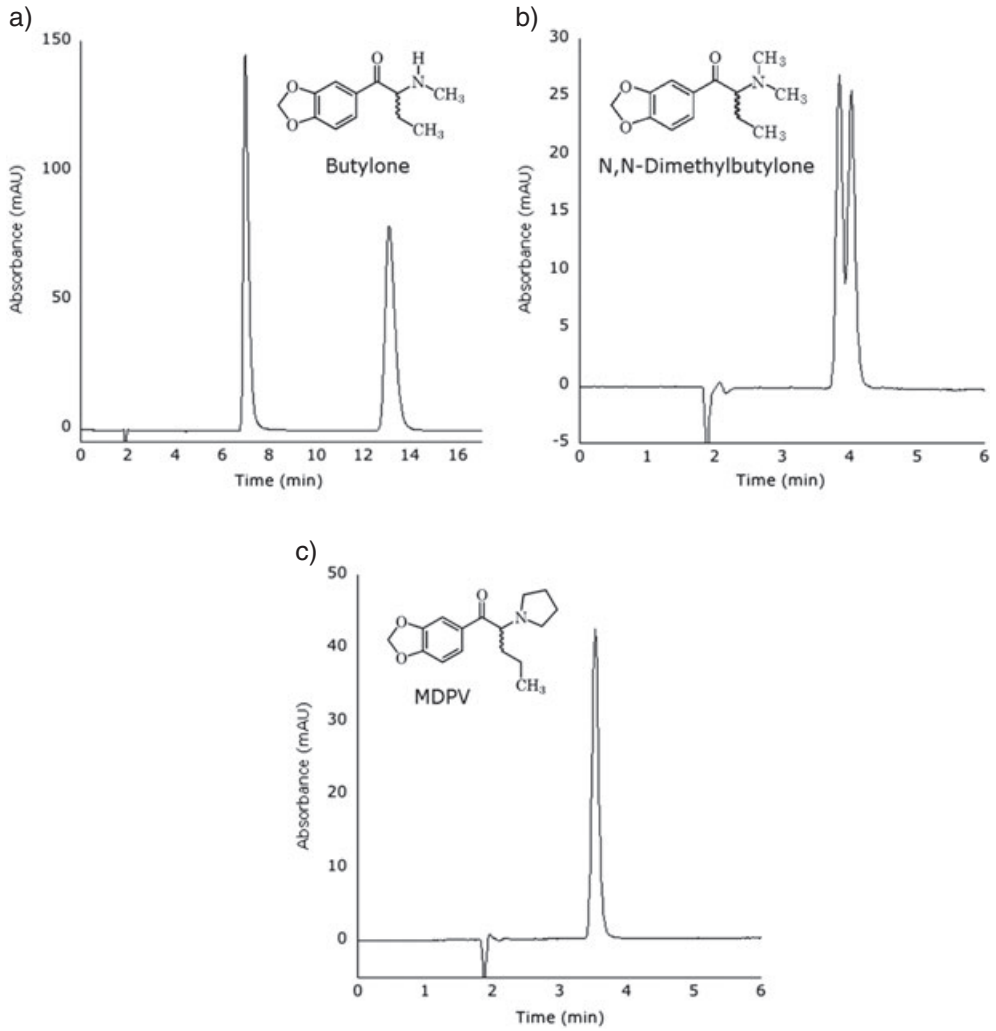


Fig. 3. Comparison of the chromatograms of (**a**) butylone, (**b**) *N,N*-dimethylbutylone, and (**c**) MDPV. Conditions: column: CHIRALPAK® AS-H, mobile phase: hexane/isopropanol/triethylamine (97:3:0.1), ambient temperature, flow: 1.0 ml/min, UV: 254 nm, injection: 5 µl.

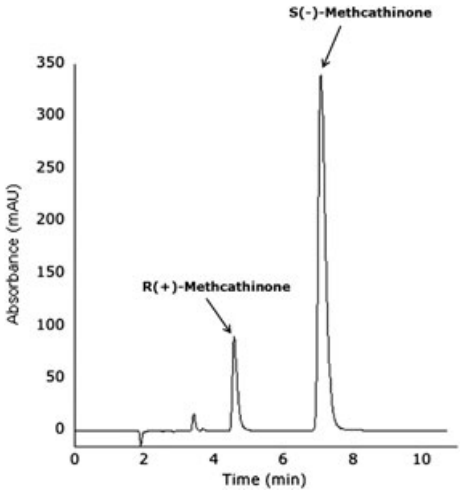


Fig. 4. Determination of the enantiomer migration order by means of methcathinone. Conditions: column: CHIRALPAK® AS-H, mobile phase: hexane/isopropanol/triethylamine (97:3:0.1), ambient temperature, flow: 1.0 ml/min, UV: 254 nm, injection: 5 µl.

of the two enantiomers and the resolution factor (Table 4). For the validation, a mephedrone sample was used. The intraday repeatability for all three parameters is quite good with relative standard deviation (RSD) for the resolution factor of 2.15% and for the retention times less than 0.15%. The day-to-day repeatability for the retention times is below 1.6%, whereas the high RSD value for the resolution factor can be explained by an increase of the peak efficiency from one day to the other. Reproducibility test was performed using different HPLC equipment in another laboratory, and measurements were conducted by another person. Although retention times were very reproducible with an RSD below 1.33%, a relatively high RSD of 18.3% for the resolution was obtained because of the change in peak shape.

CONCLUSION

Because cathinone derivatives reached high popularity on the recreational drugs market as a legal alternative to the scheduled amphetamines, such as MDMA (Ecstasy) and amphetamine (Speed), the development of achiral and chiral analytical methods is of great interest. Cathinone derivatives are a relatively new substance class on the drugs market, and therefore, data about the prolonged abuse are not available for most of the compounds.

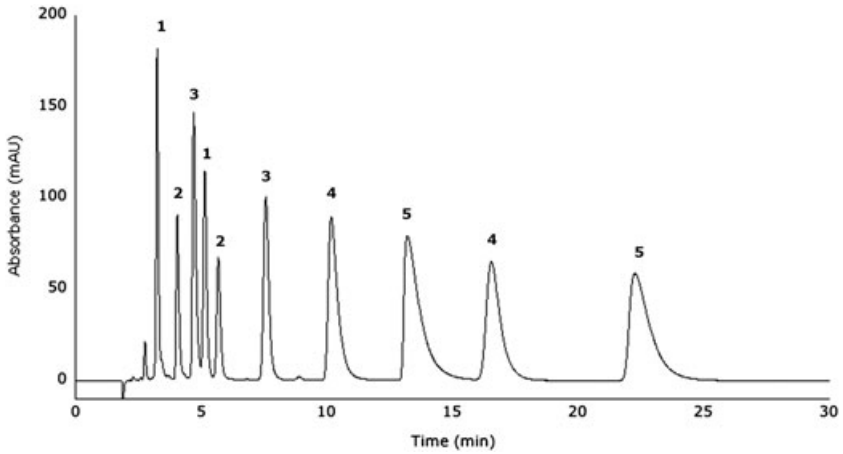


Fig. 5. Simultaneous chiral separation of (1) buphedrone, (2) 3-FMC, (3) 4-FMC, (4) methedrone and (5) cathinone. **Conditions**: Column: CHIRALPAK® AS-H, mobile phase: hexane/isopropanol/TEA (97:3:0.1), ambient temperature, flow: 1,0 ml/min, UV: 254 nm, injection: 5µl.

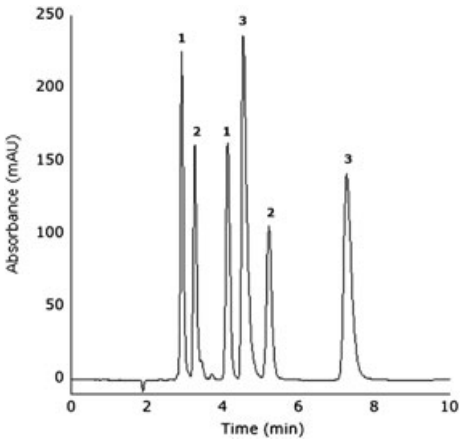


Fig. 6. Simultaneous chiral separation of (1) pentedrone, (2) buphedrone and (3) methcathinone. **Conditions**: Column: CHIRALPAK® AS-H, mobile phase: hexane/isopropanol/TEA (97:3:0.1), ambient temperature, flow: 1,0 ml/min, UV: 254 nm, injection: 5µl.

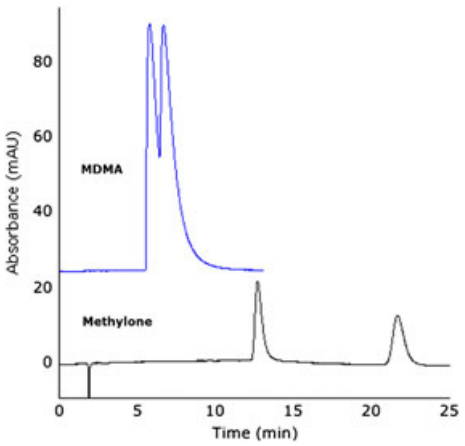


Fig. 7. Comparison of the chromatograms of MDMA and methylone. **Conditions**: Column: CHIRALPAK® AS-H, mobile phase: hexane/isopropanol/TEA (97:3:0.1), temperature: room temperature, flow: 1,0 ml/min, UV: 254 nm, injection: 5µl.

TABLE 3. Comparison of the separation results of cathinones and their amphetamine analogs

	t_1 (min)	t_2 (min)	α	R_s
Cathinone	13.91	23.08	1.764	3.4
Amphetamine	>60	>60	–	–
Butylone	6.98	13.07	2.200	3.8
MBDB	4.44	5.24	1.306	0.5
Ethylone	7.17	9.75	1.489	2.1
MDEA	3.75	4.12	1.185	0.3
Methylone	12.70	21.67	1.830	4.2
MDMA	5.79	6.67	1.229	0.4

Conditions: column: CHIRALPAK® AS-H, mobile phase: hexane/isopropanol/triethylamine (97:3:0.1), ambient temperature, flow: 1.0 ml/min, UV: 254 nm, injection: 5 µl.

With the introduced isocratic normal phase HPLC method, 19 out of 24 cathinone derivatives were baseline-separated into their enantiomers. All five not baseline-separated compounds bear a tertiary amino group, whereas *N,N*-dimethylbutylone was partially separated and the four compounds with the nitrogen atom included into a pyrrolidine heterocycle were not separated anyway. Nevertheless, this leads to the assumption that the ability of primary and secondary amines to build out hydrogen bondings is compulsory for proper solute–CSP interaction. CHIRALPAK® AS-H columns are well established in the field of chiral separations; this research enables a broader spectrum of the areas of application. The method was validated with respect to intraday and interday repeatability and reproducibility, respectively. Moreover, the simultaneous chiral resolution of a mix of five compounds in one run was shown. Additionally, the chiral resolution of four cathinone derivatives was compared with the resolution of their amphetamine analogs. In all cases amphetamines where worse separated. As a minor drawback, the sample preparation step to obtain the free nitrogen base has to be taken into account.

TABLE 4. Repeatability and reproducibility data including retention time and resolution by means of mephedrone

	t_1 (min)	t_2 (min)	R_s
Repeatability			
Intraday $n = 5$	4.80 ± 0.00, RSD = 0.08%	8.27±0.01 RSD = 0.11%	2.63±0.06 RSD = 2.15%
Day-to-day $n = 10$	4.81 ± 0.00, RSD = 0.06%	8.15 ±0.12, RSD = 1.50%	2.88±0.27 RSD = 9.43%
Reproducibility			
Intraday $n = 20$	4.76 ± 0.05, RSD = 1.15%	8.19±0.11 RSD = 1.33%	3.45±0.63 RSD = 18.30%

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