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ENANTIOMER PURIFICATION THROUGH ACHIRAL CHROMATOGRAPHY: INTEGRATING SIMULATED MOVING BED AND SELF-DISPROPORTIONATION OF ENANTIOMERS.

Alicja Wzorek,[1] Karel D. Klika,[2] Jianlin Han,[3] Alexander E. Sorochinsky,[4] Taizo Ono,[5] Vadim A. Soloshonok [*6,7]

[1] *Institute of Chemistry, Jan Kochanowski University in Kielce, Uniwersytecka 7, 25–406 Kielce, Poland;*
[2] *Research and Development Center, Archer Daniels Midland, 1001 N Brush College Rd., Decatur, IL 62521, USA;*
[3]*Jiangsu Co-Innovation Center of Efficient Processing and Utilization of Forest Resources, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China;*
[4] *V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, The National Academy of Sciences of Ukraine, Kyiv 02094, Ukraine;*
[5] *National Institute of Advanced Industrial Science and Technology (AIST), 2266–98, Anagahora, Shimoshidami, Moriyama-ku, Nagoya, 463–8560, Japan;*
[6] *Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, Paseo Manuel Lardizábal 3, 20018 San Sebastián, Spain;*
[7] *IKERBASQUE, Basque Foundation for Science, María Díaz de Haro 3, Plaza Bizkaia, 48013 Bilbao, Spain*
**email: vadimsoloshonok@gmail.com*

Enantiomer purification is a critical process in the pharmaceutical, agrochemical, and food industries, where chiral compounds often exhibit distinct biological activities. Traditional chiral chromatography is effective but costly due to the use of expensive chiral stationary phases. This review article highlights a recent breakthrough in enantiomer purification under entirely achiral conditions. Specifically, it focuses on the convergence of achiral simulated moving bed chromatography and the phenomenon of self-disproportionation of enantiomers (SDE). Experimental validation using scalemic methyl p-tolyl sulfoxide as a model compound enabled the isolation of the excess enantiomer with high purity (~99% ee) and a respectable yield (~50%). This innovative process features exceptional productivity (up to 99 grams per liter of column volume per day), reproducibility, and reliability. This breakthrough presents the first practical example of enantiomer purification based on SDE, offering a scalable and economically viable alternative to conventional chiral separations. Given that SDE is an inherent property of all chiral compounds, this innovative approach is anticipated to become the method of choice for practical enantiomer purification in both research and industrial production.

Key words: Chirality, Enantiomers, Purification, Self-Disproportionation of Enantiomers (SDE), Achiral Chromatography, Simulated Moving Bed Chromatography.

INTRODUCTION. Chiral compounds play a crucial role in the pharmaceutical, agrochemical, and food industries [1–6]. Incorporating elements of chirality, particularly a stereogenic carbon, in compounds under development enhances the success rate of these molecules as they progress from the discovery phase to approval [7]. Approximately 70% of approved drugs on the pharmaceutical market contain at least one element of chirality [8]. Following the Thalidomide tragedy [9–11], the FDA mandates a separate full biological study for each enantiomer of submitted chiral compounds. Asymmetric synthesis, whether stoichiometric, catalytic, or enzymatic, very rarely affords chiral compounds with the level of enantiomeric purity required for the FDA-mandated biological study [12]. Incredibly, the final enantiomer purification stage can be the most laborious and costly phase of the entire chemical procedure [13, 14]. Therefore, the ability to isolate pure enantiomers becomes an absolutely essential part of successful drug development, ensuring reasonable time and cost structures.

Traditional enantiomer separation techniques, such as chiral chromatography (CCh) and diastereoisomeric crystallization, grapple with challenges like high costs and the unpredictably complex selection of resolving agents and conditions [15–18]. However, a recent study led by Professor Dorota Antos [19] has achieved a significant breakthrough by merging two previously orthogonal innovations in the fields of chirality and chromatographic separations.

The first innovation is the self-disproportionation of enantiomers (SDE) [20, 21], which allows for the separation of excess enantiomers from the racemic portion under completely achiral conditions. The second is simulated moving bed (SMB) chromatography, currently the most efficient solution for continuous chromatographic separation [2, 23].

This newly reported approach – achiral SMB (ACh-SMB) – undoubtedly deserves special attention and widespread dissemination among practitioners in the areas of chirality, chromatography, asymmetric synthesis, and drug development in academic and industrial research institutions. Given the high methodological and practical potential of these results, this brief Perspective aims to highlight the reported methodological and technological advances, situating them within the greater concept of the SDE phenomenon. These recent developments bode well for the future general applications of ACh-SMB-SDE as an approach of choice in enantiomer purifications.

Self-disproportionation of enantiomers (SDE). As illustrated in Fig. 1, a scalemic mixture of 6 red and 3 blue enantiomers can adopt five general configurations based on intermolecular interactions. In configuration **A**, where such interactions are absent or very weak, all nine molecules in an achiral environment will behave congruently, requiring a chiral selector to distinguish between red and blue enantiomers. However, when intermolecular interactions occur, describing a scalemic compound merely as a mixture of enantiomers becomes conceptually incorrect and methodologically misleading. Thus, if there is a preference for heterochiral interactions, the sample should be described as a collection of dimers (**B**) or oligomers (**E**) along with the corresponding monomers. Conversely, if homochiral intermolecular interactions dominate, the molecular configurations will include dimers versus monomers (**C**) and a mixture of oligomers (**D**)

with molecular weight distributions reflecting the ratio of the original enantiomers. These four molecular configurations, driven by intermolecular interactions, are essentially mixtures of compounds with different molecular weights and distinct physicochemical properties, resulting in their separation in a completely achiral environment. This spontaneous separation of scalemic samples into fractions with proportions of enantiomers different from the original mixture is termed Self-Disproportionation of Enantiomers (SDE) [24–26].

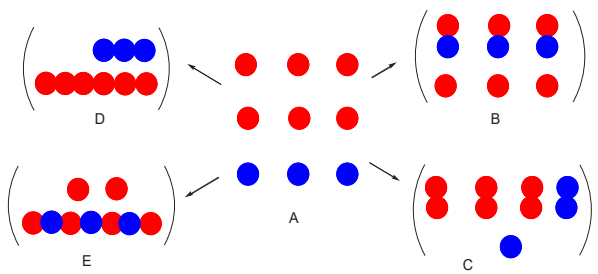


Fig. 1. Scalemic mixture of 33.33% ee and four general configurations: absence of any intermolecular interactions (A); intermolecular interactions leading to the formation of heterochiral dimers (B), homochiral dimers (C), homochiral oligomers (D), and heterochiral oligomers (E).

Since intermolecular interactions are an inherent property of all chemical compounds, one can deduce that SDE is similarly an inherent property of all chiral compounds. Systematic research into SDE began only about 20 years ago, generating a wealth of SDE data for compounds of various chemical structures and all common types of chirality, including helical [27], axial [28–34] chirality, central chirality on carbon [35–37], sulfur [38–41], as well as compounds possessing multiple stereogenic centers and C_2 symmetry [42]. A similar wide generality is also reported for areas of SDE manifestation, particularly in crystallization [43, 44], sublimation [45–48], distillation [49–51], density gradient ultracentrifugation [52] or suspension precipitation [53], and chromatography – including simple gravity-driven columns [54–56], flash chromatography [38], MPLC [57–59], HPLC [28], size-exclusion [51], and even gas chromatography [60].

Among the wider implications of the ubiquitous nature of SDE is the problem of accurately reporting the enantiomeric purity of chiral compounds isolated from natural sources or prepared in the laboratory [61–63]. SDE is highly relevant to the field of chirality and asymmetric synthesis. Understanding SDE is crucial for accurately reporting the stereochemical outcomes of enantioselective reactions. SDE presents both a challenge and an opportunity in chemistry, requiring careful consideration and control to avoid errors in experimental results and interpretation [64–66].

A particularly exciting implication of SDE is related to the origin of prebiotic homochirality. Among various theories proposed, SDE is the only experimentally proven mechanism for the formation and maintenance of enantiomerically pure or highly enriched samples [67–69].

SDE and enantiomer purifications. In essence, the SDE phenomenon is the spontaneous separation of the excess enantiomer from the racemic portion. Therefore, enantiomer purification is an innate property and the way of SDE manifestation. Thus, the primary question is how to amplify this spontaneous, innate enantiomer purification to a practical application level. Research conducted on numerous chiral compounds has identified certain structural classes and functional groups, known as SE-phoric groups [21, 70], that allow for high magnitudes of SDE, reaching prac-

tical levels. As SDE can be used as a method to obtain enantiopure samples from scalemic mixtures, it can lead to the development of unconventional and superior methods for enantiopurification. Particularly exciting results were reported for the SDE-driven enantiomer purification via sublimation [71–75] and achiral column chromatography. Figure 2 and Table 1 present several examples of various types of chiral organic compounds.

Table 1. Examples of SDE-driven enantiomer purifications via achiral chromatography.

Entry	**Cmpd.**	**Starting ee [%]**	**Type of chromatography**	**Eluent**	**First fraction [%]**	**Last fraction [%]**	**Δee**	**Yields [%]**
1	**1**	75.0 (*S*)	flash	*c*-Hex–benzene–di-*tert*-butyl ether (1:1:0.1)	28.0	>99	63.3	44.0
2	**2**	78.9 (*S*)	gravity	*c*-Hex/MTBE (1:2)	>99	56.6	43.3	24.0
3	**2**	71.0 (*S*)	MPLC	*n*-Hex–EtOAc (1:1)	>99	28	71	66.0
4	**3**	64.9 (*R*)	gravity	*c*-hex/MTBE (1:2)	>99	33.2	66.7	21.7
5	**4**	72.6 (*S*)	gravity	*c*-hex/MTBE (1:2)	80.3	79.9	12.6	–
6	**4**	69.0 (*S*)	MPLC	*n*-Hex–EtOAc (2:1)	>99	52.0	47	40.0
7	**5**	64.2 (*P*)	gravity	CH_2CL_2	>99	44.6	55.3	0.7
8	**5**	65.8 (*P*)	MPLC	*n*-Hex–EtOAc	>99	35.4	63.6	53.6
9	**6**	34.6 (*R*)	gravity	*n*-Hex–EtOAc (5:1)	8.1	>99	91.8	4.3
10	**7**	34.6 (*R*)	gravity	*c*-Hex/EtOAc (1:5)	>99	13.0	86	0.5
11	**8**	81.4 (S)	flash	*n*-Hex–EtOAc	93.5	62.3	31.2	–
12	**9**	72.4 (*S*)	gravity	*n*-Hex–EtOAc (1:13)	97.0	47.4	49.6	–
13	**10**	82 (*M*)	gravity	*n*-Hex–EtOAc (3:1)	69	89	20	–

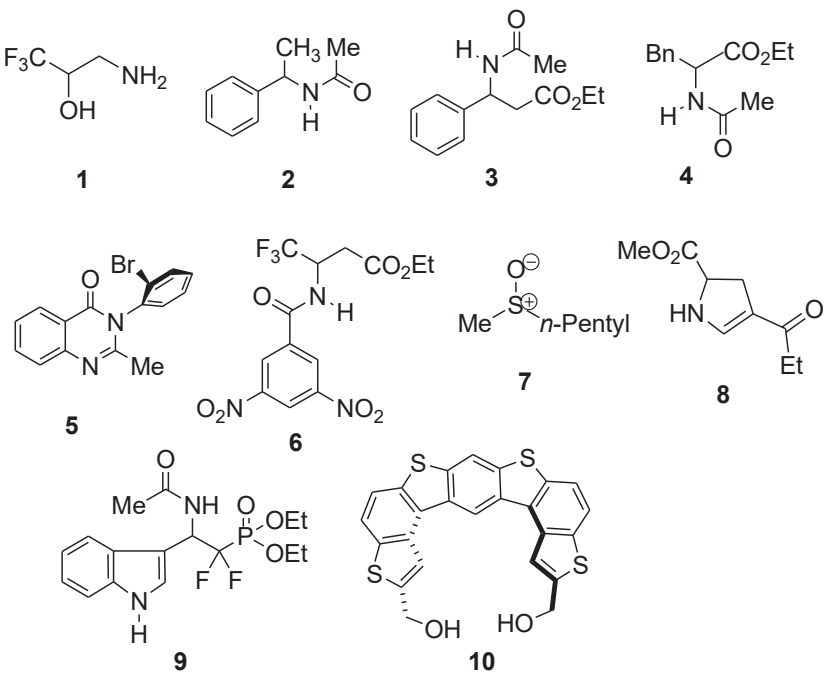


Fig. 2. Examples of compounds exhibiting a high magnitude of self-disproportionation of enantiomers (SDE) under achiral chromatography conditions.

Examples **1**–**10** (Fig.1) were selected to showcase the structural variety of chiral compounds demonstrating significant SDE magnitudes, leading to laboratory-scale enantiomer purifications. These examples include unprotected amino alcohol **1** [76], amide-protected amine **2** [55, 77, 78], α-amino acid **4** [79], β-amino acids **3** [54, 57, 80] and **6** [37], phosphorus analog of β-amino acid **9** [81], unprotected α-amino ester **8** [82], sulfoxide **7** [39], compound with axial chirality **5** [83], and helicine **10** [27].

For each compound (**1**–**10**), Table 1 provides data on initial enantiomeric purity, type of achiral chromatography, eluent, enantiomeric excess in the first and last fractions, the difference in enantiomeric excess (Δee), and the yields of isolated enantiomerically pure compounds. These data overwhelmingly highlight the prowess of SDE via achiral chromatography as a general approach for the enantiopurification of scalemic organic compounds. However, practical application has been severely hindered by difficulties in scaling up from gram to a practically useful level of 100 g or more. This is why the breakthrough reported by Dorota Antos' group [19] represents a critically needed advancement in this field.

Simulated moving bed chromatography. Simulated Moving Bed (SMB) chromatography is an advanced technique used to separate and purify different components from a mixture [84-87]. Unlike traditional batch chromatography, which processes samples in fixed amounts, SMB operates continuously, making it more efficient and cost-effective for large-scale separations. SMB chromatography consists of several interconnected columns filled with a sta-

tionary phase that interacts uniquely with each component of the mixture. A liquid containing the mixture flows through the system, and the continuous alternation of input and output positions facilitates the separation process, replicating the effect of a moving solid phase. The number of columns typically used can vary depending on the specific application and scale of the process. Generally, 8, 12, or 16 columns are commonly employed. Simplified version of the SMB system is illustrated in Fig. 2.

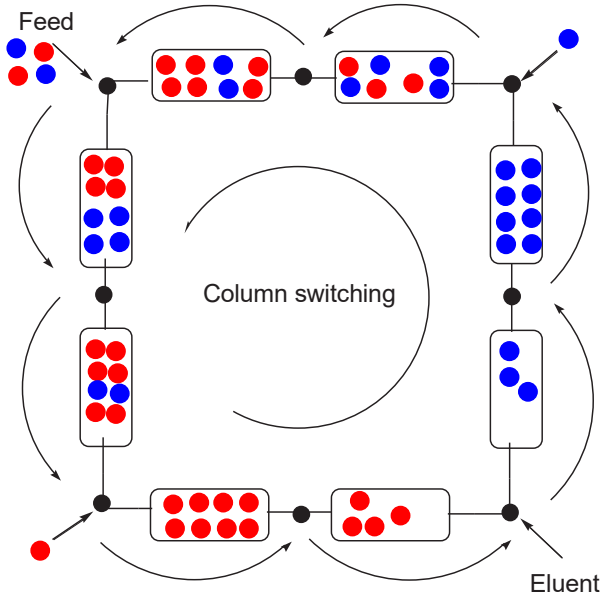
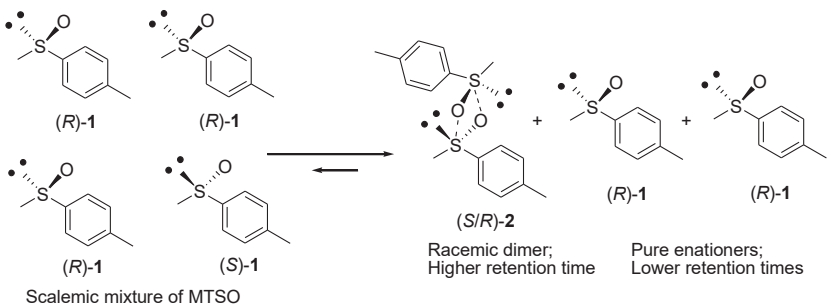


Fig. 2. Schematic of SMB units separating a binary mixture.

SMB consists of several connected columns filled with a stationary material that interacts differently with each component of the mixture. A liquid carrying the mixture flows through the system, and due to the constant switching of input and output positions, the separation process mimics the effect of a moving solid phase [88–90].

SMB is widely used in industries like pharmaceuticals, food processing, and petrochemicals [91-95]. It offers several benefits such as higher efficiency, better purity, and cost-effectiveness. SMB is widely used in pharmaceutical industry for large-scale isolation/purification of drug components, especially enantiomers in chiral drugs. In food industry for refining sugars, amino acids, and other food additives. More generally, in chemical industry for separation of petrochemical products and bio-based chemicals. Overall, while SMB chromatography may seem complex, it is essentially a smart way of continuously filtering out desired compounds from mixtures. By improving efficiency and reducing waste, it plays a crucial role in modern industry and scientific research.

Case of methyl p-tolyl sulfoxide. The study under discussion [19] focused on developing an SDE-driven Achiral Simulated Moving Bed (SDE-ACh-SMB) process for the separation of enantiomers of (*S*)-MTSO (Scheme 1).



Scheme 1. SDE-driven enantiopurification of scalemic S-MTSO.

Due to identical Henry constants for enantiomers in an achiral environment, conventional design methods like triangle theory were inapplicable [96–98]. Instead, the approach involved three steps, including batch-column separation for model calibration, model-aided selection of operational variables, and experimental adjustment.

Elution experiments helped determine key parameters such as total column porosity (εt), apparent dispersion coefficient (Da), and isotherm coefficients (qm, KI, KII). The porosity (εt) averaged 0.70 with minimal deviations between columns. The number of theoretical plates (N ≈ 1000) was used to calculate Da, and the isotherm coefficients were estimated using peak fitting techniques. These parameters ensured accurate predictions of migration velocities for the enantiomers' fronts during the separation process.

Initial experiments in batch columns demonstrated the SDE phenomenon, allowing the formation of homochiral and heterochiral associates with different retention properties.

Optimal conditions for batchwise achiral separation were determined, providing a baseline for further SMB experiments.

A series of SMB runs were conducted with varying zone flowrates, switching times, and feed conditions. The initial scouting run failed due to incorrect predictions of enantiomer migration velocities.

Subsequent runs adjusted flowrates and switching times, achieving high-purity separation of S-MTSO enantiomer with improved productivity and yield. Specifically, run 3 reached approximately 100% purity with a productivity of 28 grams of (*S*)-MTSO per liter of column volume per day.

Variations in feed concentration and enantiomeric excess were investigated. Higher ee improved product purity and productivity by enhancing the migration velocity difference between enantiomers. Increased feed concentration intensified the SDE effect, beneficial for separation performance, but also made maintaining product purity more challenging due to the sharper concentration fronts of enantiomers.

The dynamic model was verified against experimental data, confirming its accuracy and reliability in predicting SMB separation performance. The model parameters were adjusted based on experimental results to ensure precise predictions.

The ACh-SMB system used for the enantiopurification was equipped with four Smartline Pumps (model 100 V.5010), a pair of UV detectors (K-2501), an SMB-Control unit, and a multifunctional valve (CSEP C9 Series Simulated Moving Bed and Chromatography Systems V0499, 12/2000). All components were sourced from Knauer.

In showcase experiments the enantiomeric excess (ee) of the enantioenriched MTSO stream was maintained at 50%. The yield of the target enantiomer (S-MTSO) was approximately 26%. The productivity was 28 grams of S-MTSO per liter of total column volume per day. These experiments clearly highlighted the key benefits and effectiveness of the method, providing clear and compelling evidence of its capabilities. The reproducibility of the ACh-SMB process was confirmed through repeated runs, yielding consistent performance indicators.

The developed ACh-SMB process offers a cost-effective alternative for separating non-racemic mixtures with high ee, common in asymmetric synthesis. This method can reduce reliance on expensive chiral chromatography. For mixtures with low ee, a tandem configuration with chiral chromatography can improve

process economy by recycling the waste fraction.

CONCLUSIONS. A novel SDE-ACh-SMB process was developed and verified for the continuous separation of enantiomers from nonracemic mixtures [19]. The process is feasible, reproducible, and predictable, demonstrating high potential for industrial applications. Optimal conditions achieved product purity of 96–100% and productivity up to 99 grams per liter of column volume per day. The only drawback of this method is the remaining racemic compound, which must be discarded or resolved using an external chiral selector. In this regard, one can envision an advanced methodology presented in Fig. 3. The process starts with a racemic compound. Using low-cost chiral chromatography, the racemate is transformed into two fractions of scalemic compounds, enantiomerically enriched in (R)- and (S)-enantiomers, respectively. Next, the SDE-SMB approach is used to separate the target enantiomers, and the remaining portion is fed back to the racemate injector port. Properly designed and working continuously, such a process will revolutionize the separation of enantiomers.

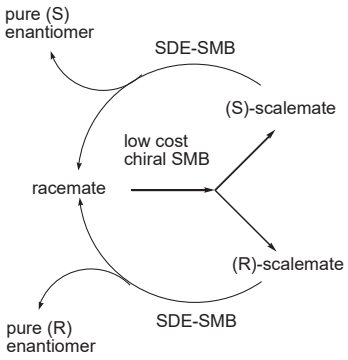


Fig. 3. Proposed advanced process for resolution of racemates using low-cost chiral chromatography and the SDE-SMBCh.

Since SDE is an inherent property of all chiral compounds, the SDE-ACh-SMB process is expected to have the broadest possible applicability in the field of enantiomer purifications.

ОЧИЩЕННЯ ЕНАНТІОМЕРІВ ЗА ДОПОМОГОЮ АХІРАЛЬНОЇ ХРОМАТОГРАФІЇ: ІНТЕГРАЦІЯ СИМУЛЬОВАНОГО РУХОМОГО ШАРУ ТА САМОДИСПРОПОРЦІОНУВАННЯ ЕНАНТІОМЕРІВ

Аліція Взорек,[1] Карел Д. Кліка,[2] Джіанлін Хань,[3] Олександр Е. Сорочинський,[4] Тайзо Оно,[5] Вадим А. Солошонок[6,7]*

[1] Інститут хімії, Університет Яна Кохановського в Кельцях, вул. Університетська 7, 25–406 Кельце, Польща;

[2] Центр досліджень і розроблень, Archer Daniels Midland, 1001 N Brush College Rd., Декейтер, Іллінойс 62521, США;

[3] Цзянсу Співдружній центр ефективного оброблення і використання лісових ресурсів, Коледж хімічного машинобудування, Нанкінський лісовий університет, Нанкін 210037, Китай;

[4] Інститут біоорганічної хімії та нафтохімії ім. В. П. Кухаря, Національна академія наук України, вул. Академіка Кухаря, 1, Київ 02094, Україна;

[5] Національний інститут передових промислових наук і технологій (AIST), 2266–98, Анагагора, Шимошидамі, Моріяма-ку, Нагоя, 463–8560, Японія;

[6] Кафедра органічної хімії I, Факультет хімії, Університет Країни Басків UPV/EHU, Пасаео Мануель Лардісабаль 3, 20018 Сан Себастьян, Іспанія;

[7] IKERBASQUE, Баскський фонд науки, вул. Марія Діас де Харо 3, площа Бізкая, 48013 Більбао, Іспанія

Очищення енантіомерів є важливим процесом у фармацевтичній, агрохімічній та харчовій промисловості, де хіральні сполуки часто виявляють різну біологічну активність. Традиційна хіральна хроматографія є ефективною, але дорогою через використання дорогих хіральних стаціонарних фаз. Ця оглядова стаття висвітлює останній прорив у очищенні енантіомерів в умовах повністю ахіральних умов. Зокрема, акцент зроблено на поєднанні ахіральної симульованої рухомої шарової хроматографії та феномена самодиспропорціонування енантіомерів (SDE). Експериментальна перевірка з використанням скалемічного метил-р-толуїлсульфоксиду як модельної сполуки дозволила ізолювати надлишковий енантіомер із високою чистотою (~99% ее) та поважним виходом (~50%). Цей інноваційний процес характеризується винятковою продуктивністю (до 99 грамів на літр об'єму колони на день), відтворюваністю та надійністю. Цей прорив являє собою перший практичний приклад очищення енантіомерів на основі SDE, пропонуючи масштабовану та економічно доцільну альтернативу традиційним хіральним розділенням. Враховуючи, що SDE є властивістю всіх хіральних сполук, цей інноваційний підхід очікувано має стати пріоритетним методом для практичного очищення енантіомерів як у дослідженнях, так і в промисловому виробництві.

Ключові слова: хіральність, енантіомери, очищення, самодиспропорціонування енантіомерів (SDE), ахіральна хроматографія, симульована рухома шарова хроматографія.

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