BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, March 2026. Vol. **23**(1), p. 367-374

Hyphenated Techniques in Drug Discovery and Quality Control: From Fundamentals to Future Perspectives

Kavita Bhushan Vikhe* and Sandeep Suresh Sonawane

Department of Pharmaceutical Chemistry, MET's Institute of Pharmacy, Savitribai Phule Pune University, Maharashtra, India.

http://dx.doi.org/10.13005/bbra/3504

(Received: 08 January 2026; accepted: 12 February 2026)

By permitting the simultaneous separation, identification, and quantification of complex mixtures, hyphenated analytical techniques—combinations of chromatographic separation with spectroscopic or spectrometric detection—have revolutionized contemporary pharmaceutical analysis. Drug discovery, impurity profiling, bioanalysis, and quality control have all seen a rise in the use of techniques including LC-MS, GC-MS, LC-NMR, CE-MS, and SFC-MS within the past 20 years. This review critically assesses their analytical performance, limitations, and recent advances, such as miniaturized systems, green chemistry techniques, and AI-driven data processing, whereas the literature currently in publication emphasizes their instrumental configurations and routine applications. In addition to improving existing pharmaceutical workflows, these developments are opening the door for future integration with biologics, nanomedicine, and precision medicine. Views on cost-effective instrumentation, regulatory harmonization, and the changing role of hyphenated technologies in shaping. The article concludes with perspectives on regulatory harmonization, cost-effective instrumentation, and the evolving role of hyphenated technologies in shaping sustainable and personalized healthcare solutions.

Keywords: Drug Discovery; Hyphenated Techniques; Impurity Profiling; LC–MS; Pharmaceutical Analysis; Quality Control.

Pharmaceutical analysis has evolved from single-technique approaches to integrated platforms that include separation and detection capabilities. Conventional methods, such as standalone HPLC, GC, or UV spectroscopy, frequently lack the sensitivity and selectivity needed to identify trace contaminants, degradation products, and complex biomolecules. [4,5,14] Hyphenated techniques—defined as the combination of two or more analytical methods—have so emerged as critical tools in current pharmaceutical science.[1,2]

This publication distinguishes itself by comparing hyphenated approaches, incorporating contemporary breakthroughs like AI-driven data interpretation and eco-friendly workflows, and highlighting their growing relevance in biologics, biosimilars, and precision medicine. Unlike previous descriptive assessments, this paper offers a balanced perspective that incorporates analytical performance, regulatory issues, and future potential, making it useful for both academic researchers and industrial practitioners.[3,5]

While CE-MS has been recognized for its ability to evaluate polar biomolecules and peptides with excellent separation efficiency, its use in regular pharmaceutical quality control is

*Corresponding author E-mail: kavitadhamak29@rediffmail.com

still limited. SFC-MS bridges the gap between chiral and non-polar separations, while also complying with ecological goals by reducing solvent use. Together, these strategies demonstrate how hyphenated platforms are evolving to satisfy a wide range of pharmaceutical needs, from small compounds to complex biologics.

Scope: Pharmaceutical Sciences, Biochemistry, Genomics and Proteomics, and Industrial Biotechnology.

Literature selection methodology

This review was developed through a comprehensive literature search conducted across multiple scientific databases, including PubMed, Scopus, Web of Science, and ScienceDirect. The search focused on publications from 2000 to 2025 using keywords such as "hyphenated techniques," "LC–MS," "GC–MS," "CE–MS," "LC–NMR," "SFC–MS," "impurity profiling," and "pharmaceutical analysis." Priority was given to peer-reviewed articles, regulatory guidelines, and authoritative textbooks that provided insights into both fundamental principles and recent advancements. Studies were selected based on relevance to pharmaceutical applications, analytical performance, and regulatory significance.

Principles and major hyphenated techniques

LC–MS (Liquid Chromatography–Mass Spectrometry)

Liquid chromatography–mass spectrometry (LC–MS) is widely regarded as the gold standard in pharmaceutical analysis, particularly for impurity profiling, pharmacokinetic studies, and metabolite identification.[1,3] Its ability to couple high-resolution chromatographic separation with sensitive mass-based detection enables the identification and quantification of compounds at trace levels, often within the nanogram to picogram range. Despite these advantages, LC–MS is not without limitations. Issues such as ion suppression, matrix effects, and the high operating costs associated with instrument acquisition and maintenance continue to restrict its widespread routine use, especially in resource-limited laboratories. [2] Recent advances, however, have sought to overcome some of these barriers. The introduction of ambient ionization techniques such as desorption electrospray ionization (DESI) and direct analysis in real time (DART) has enabled direct analysis of solid dosage forms with minimal sample preparation.[18] Similarly, the development of microfluidic LC–MS platforms have significantly improved throughput, making it highly suitable for bioanalytical applications in high-volume drug development pipelines.[12]

GC–MS (Gas Chromatography–Mass Spectrometry)

Gas chromatography–mass spectrometry (GC–MS) continues to play a pivotal role in the analysis of volatile and semi-volatile compounds, offering exceptional sensitivity and robustness.[8,9,19] Its utility is well established in forensic science, toxicology, and quality control of pharmaceutical raw materials.[15,20] However, GC–MS is inherently limited to analytes that are thermally stable and volatile; non-volatile or thermally labile compounds require derivatization, which adds complexity to the workflow. To address these constraints, recent innovations such as headspace–GC–MS have been introduced, particularly in the detection of residual solvents in pharmaceutical formulations. Moreover, GC–MS has found increasing relevance in metabolomics, where it is employed for profiling volatile biomarkers associated with disease states or drug responses, thereby expanding its utility beyond conventional pharmaceutical testing.[19]

LC–NMR

The combination of liquid chromatography with nuclear magnetic resonance (LC–NMR) provides a unique platform for structural elucidation of complex mixtures without the need for complete compound isolation. This technique is especially valuable in the identification of drug metabolites and natural products. Nevertheless, the practical use of LC–NMR has been limited by its inherently low sensitivity and the requirement for relatively large sample quantities, often in the milligram range. [11 Recent] advances, such as the incorporation of cryogenic probes and stopped-flow NMR configurations, have improved detection sensitivity and reduced sample requirements. Furthermore, the integration of LC–NMR with MS (LC–NMR–MS) now offers complementary structural and mass-based confirmation, making the approach more attractive in pharmaceutical research where comprehensive molecular characterization is critical.[22]

CE–MS (Capillary Electrophoresis–Mass Spectrometry)

Capillary electrophoresis–mass

spectrometry (CE–MS) has emerged as a powerful hyphenated technique for the analysis of polar and ionic species, including peptides, proteins, and metabolites. One of its major advantages lies in the minimal sample requirement and high separation efficiency. However, the technique has not yet gained widespread acceptance in routine quality control due to technical challenges in interfacing CE with MS, particularly at low flow rates. Innovations in sheath less CE–MS interfaces have significantly enhanced sensitivity and reproducibility, paving the way for wider application in metabolomics, proteomics, and the characterization of biopharmaceuticals.[17] These improvements are positioning CE–MS as a critical tool in the analysis of complex biological samples, where traditional chromatographic techniques may be less effective.

SFC–MS (Supercritical Fluid Chromatography–Mass Spectrometry)

Supercritical fluid chromatography coupled with mass spectrometry (SFC–MS) has gained momentum in recent years as an environmentally friendly analytical approach. Using supercritical CO, -based mobile phases, SFC–MS reduces solvent consumption and analysis time while maintaining high separation efficiency. It is particularly advantageous for the resolution of chiral compounds and non-polar analytes, both of which are highly relevant in pharmaceutical research and development. More recently, SFC–MS has found increasing application in enantiomeric purity testing and formulation development, aligning well with regulatory expectations for chiral drug products. Its dual contribution to sustainability and analytical performance makes it an attractive alternative to conventional LC–MS in specific applications. beyond specialized laboratories and into routine pharmaceutical quality control.[5]

Applications in Pharmaceutical Analysis

Hyphenated analytical techniques have become indispensable across multiple stages of the pharmaceutical pipeline, from early drug discovery to regulatory quality control. Their ability to simultaneously separate, detect, and characterize complex mixtures makes them superior to single-method approaches, especially when high sensitivity and selectivity are required.

Impurity Profiling

One of the most critical applications of hyphenated techniques lies in impurity profiling, which is central to ensuring the safety and efficacy of drug products. Trace impurities, including genotoxic contaminants and process-related by-products, must be identified and quantified in accordance with regulatory guidelines such as ICH M7. LC–MS and LC–NMR are particularly effective in this context. LC–MS enables rapid detection of low-level impurities with high sensitivity, while LC–NMR provides complementary structural elucidation of unknown degradation products without requiring complete isolation. Together, these techniques safeguard the pharmaceutical industry's compliance with stringent international standards while also expediting the drug development process.[10]

Drug Discovery

In drug discovery, hyphenated methods such as LC–MS/MS play an essential role in the rapid screening and characterization of new chemical entities (NCEs). These methods allow researchers to analyze metabolic pathways, identify bioactive metabolites, and determine the pharmacological relevance of candidate molecules at very early stages. For example, LC–MS/MS is widely used in high-throughput screening assays, where hundreds of drug candidates must be evaluated simultaneously for pharmacokinetic and metabolic stability. Similarly, CE–MS has gained increasing attention in peptide and protein drug development, offering superior resolution of charged biomolecules compared with conventional chromatographic methods. These applications highlight the unique value of hyphenated approaches in accelerating the drug discovery pipeline by reducing both cost and time to market.[17,21]

Pharmacokinetics and Bioanalysis

In the clinical development phase, pharmacokinetic and bioanalytical studies rely heavily on hyphenated techniques to determine the absorption, distribution, metabolism, and excretion (ADME) of drug candidates. LC–MS/MS has become the industry standard due to its exceptional sensitivity, enabling quantification of drugs and metabolites at nanogram or even picogram concentrations in biological fluids such as plasma,

Table 1. Comparative evaluation of major hyphenated techniques in pharmaceutical analysis

Technique	Key Advantages	Major Limitations
LC–MS	- Extremely high sensitivity (ng–pg range) - Broad applicability: impurity profiling, PK/PD, metabolite ID - Widely accepted by regulators (FDA, EMA)	- Ion suppression and matrix effects - High acquisition and maintenance costs - Complex data analysis requiring expertise
GC–MS	- Excellent for volatile/semi-volatile compounds - Robust and well-established - High specificity for toxicological and forensic applications	- Restricted to thermally stable analytes - Derivatization often required - Limited use for large biomolecules
LC–NMR	- Provides structural elucidation without complete isolation - Valuable for natural products and metabolite analysis - Complements MS data	- Low sensitivity (requires mg quantities) - High cost and instrument complexity - Less common in routine QC
CE–MS	- Excellent for polar/ionic species, peptides, and proteins - Requires minimal sample - High separation efficiency	- Challenging interfacing (especially at low flow rates) - Less routine in pharma QC - Lower robustness compared to LC–MS
SFC–MS	- Ideal for chiral separations - Faster analysis with reduced solvent use (green chemistry) - Effective for non-polar compounds	- Requires specialized instrumentation - Limited availability in some labs - Still less established than LC–MS for regulatory purposes

Table 2. Examples of Drug Molecules and Applications of Hyphenated Analytical Techniques

Hyphenated Technique	Representative Molecules	Application Context	Reference/Use Case
LC–MS	Atorvastatin, Paclitaxel	Impurity profiling, bioanalysis in plasma	Quantification in PK studies, impurity detection
GC–MS	Dichloromethane, Benzene	Residual solvent analysis, toxicology	ICH Q3C compliance, forensic screening
LC–NMR	Vinblastine, Curcumin	Structural elucidation of natural products	Metabolite identification, phytochemical profiling
CE–MS	Buserelin, Glutathione	Peptide and metabolite analysis	Proteomics, charged biomolecule separation
SFC–MS	Omeprazole, Ibuprofen	Chiral purity testing, non-polar drug profiling	Enantiomeric resolution, green chemistry workflows

urine, or cerebrospinal fluid. The selectivity of tandem MS ensures accurate quantification even in complex biological matrices, where traditional methods often fail. This capability is vital not only for optimizing dosing regimens but also for predicting drug–drug interactions and ensuring patient safety during clinical trials.[16]

Stability Studies

The stability of pharmaceutical formulations is another critical area where hyphenated techniques provide distinct advantages. Stability studies require the detection and characterization of degradation products formed under conditions such as heat, light, or pH stress. Techniques like LC–MS and LC–NMR allow for early and accurate identification of degradation pathways, thereby supporting the rational design of stable formulations. For instance, LC–MS/MS can detect low-level oxidative or hydrolytic degradation products, while LC–NMR can confirm their structural identities. These insights not only guide formulation scientists but also form a critical component of regulatory submissions for new drug approvals.[11]

Chiral Analysis

Many pharmaceutical agents are chiral, and the pharmacological activity often resides in only one enantiomer, with the other being less active or even harmful. Regulatory authorities, therefore, require rigorous stereochemical characterization of chiral drugs. Supercritical fluid chromatography coupled with mass spectrometry (SFC–MS) has emerged as a powerful tool for enantiomeric resolution due to its high efficiency, speed, and reduced solvent consumption. By enabling rapid determination of enantiomeric purity, SFC–MS supports both drug discovery and quality assurance processes, ensuring compliance with regulatory expectations for stereospecific characterization.[5]

Taken together, these applications underscore the pivotal role of hyphenated techniques in ensuring that pharmaceutical products meet the highest standards of safety, efficacy, and regulatory compliance. Their integration into every stage of drug development highlights their continued relevance and indispensability in modern pharmaceutical science.

Discussion of Advantages and Limitations

The rapid and widespread adoption of hyphenated analytical techniques in pharmaceutical research and development is largely driven by their unparalleled ability to deliver both qualitative and quantitative information in a single analytical run. By combining separation and detection in one platform, these techniques offer high sensitivity, selectivity, and resolution, enabling the identification and quantification of compounds present at trace levels. This dual capacity makes them especially valuable in applications ranging from impurity profiling and stability testing to pharmacokinetics and bioanalysis. Another major advantage lies in their versatility: hyphenated methods can be applied to both small-molecule drugs and complex biomolecules, extending their utility to modern domains such as biologics, biosimilars, and metabolomics. Furthermore, by reducing the need for multiple independent assays, these techniques improve efficiency, shorten analysis time, and minimize sample requirements.[12]

Despite these strengths, several limitations restrict the routine use of hyphenated systems, particularly in industrial quality control settings. The high cost of acquisition and maintenance represents one of the most significant barriers. Advanced platforms such as LC–MS/MS or LC–NMR require substantial capital investment and specialized infrastructure, which may not be feasible for smaller laboratories or institutions in resource-limited regions. Operational complexity also presents a major challenge. These instruments demand highly skilled personnel not only to operate the hardware but also to manage complex data interpretation, which is often multidimensional and computationally demanding. For example, MS-based datasets can contain thousands of peaks, necessitating advanced software tools and expert knowledge for accurate interpretation.

The flexibility of hyphenated analytical techniques to provide both qualitative and quantitative information in a single run has fueled their increasing adoption in pharmaceutical research. Because they combine separation and detection, they have great sensitivity, selectivity, and resolution, making them ideal for impurity profiling, stability testing, and bioanalysis.

Alternative non-hyphenated approaches, such as standalone mass spectrometry (MS) and improved detector technologies, remain significant in pharmaceutical analysis. Standalone MS, especially with new ionization techniques

and high-resolution detectors, is still useful for rapid screening, cost-effective workflows, and laboratories where hyphenated systems are not possible .[22] Improved detectors in HPLC and GC platforms have increased sensitivity and robustness, providing simpler options for routine quality control .[17, 18] These techniques, while less comprehensive than hyphenated systems, have complementary qualities and emphasize the significance of balancing analytical depth with accessibility.

Furthermore, the rising role of biologics and complicated therapies necessitates more careful study. The analysis of monoclonal antibodies, biosimilars, peptides, and protein-based pharmaceuticals is challenging due to their bulk, heterogeneity, and structural complexity. Hyphenated methods, such as CE-MS and LC-MS/MS, are increasingly used in biologics for high-resolution characterisation, impurity profiling, and stability investigations. [8, 9,16] Their capacity to resolve charged biomolecules and detect tiny alterations makes them invaluable in biologics research, where traditional approaches frequently fall short.

Taken together, these findings highlight that, while hyphenated techniques are the gold standard for comprehensive pharmaceutical analysis, standalone MS and improved detectors are still viable alternatives, and biologics is emerging as a critical domain where hyphenated platforms will continue to expand their impact .[14, 15]

Another important limitation lies in the challenges of regulatory validation and standardization. While agencies such as the FDA and EMA increasingly recognize the value of hyphenated methods, the lack of universally accepted protocols for method validation complicates their routine adoption. Variability in instrument configuration, data processing algorithms, and operator expertise can lead to inter-laboratory inconsistencies, raising concerns about reproducibility and regulatory acceptance. Additionally, some hyphenated techniques, such as LC–NMR or CE–MS, still suffer from sensitivity constraints compared with mainstream methods like LC–MS, limiting their widespread utility.[16]

Among the reviewed techniques, LC–MS and GC–MS are most widely adopted in pharmaceutical analysis. LC–MS dominates due to its exceptional sensitivity, broad applicability across drug classes, and strong regulatory endorsement for bioanalysis and impurity profiling. GC–MS remains indispensable for volatile compound analysis and forensic applications. In contrast, CE–MS and LC–NMR, while powerful, face adoption barriers due to sensitivity constraints and interfacing complexity. SFC–MS is gaining traction for chiral analysis and green chemistry workflows but is still emerging in routine quality control. These usage trends reflect a balance between analytical performance, cost, and regulatory familiarity.

In summary, hyphenated techniques represent a powerful advancement in pharmaceutical analysis, but their full potential is tempered by financial, technical, and regulatory challenges. Addressing these barriers—through cost-effective instrumentation, user-friendly data analysis platforms, and harmonized validation guidelines—will be critical to expanding their use.

ICH Q2 (R1) Regulatory Alignment

The validation parameters listed in ICH Q2(R1), which include specificity, accuracy, precision, linearity, range, detection limit, and resilience, are well-aligned with hyphenated procedures. Because of their excellent sensitivity and specificity, regulatory bodies often approve LC-MS and GC-MS for bioanalysis and impurity profiling. Despite being less standardized, CE-MS and SFC-MS can satisfy validation requirements if they are appropriately adjusted. Although LC-NMR facilitates structural confirmation, quantitative validation may call for additional methods. For regular deployment and regulatory approval, standardizing validation procedures and guaranteeing reproducibility across platforms are essential.[14,15]

CONCLUSION

Hyphenated analytical techniques have become vital in modern pharmaceutical science because they combine the advantages of separation and detection into a single, highly efficient platform. Their capacity to offer both qualitative and quantitative information is critical for impurity profiling, drug discovery, pharmacokinetics, stability testing, and chiral analysis. While LC-MS and GC-MS are well-established, new platforms

such as CE-MS, LC-NMR, and SFC-MS are expanding researchers' analytical toolkits.

These approaches have broader applications than just small-molecule medicines. CE-MS and LC-MS/MS are commonly used for high-resolution characterisation in biologics, biosimilars, and peptide therapies. LC-NMR and SFC-MS provide structural insights in nanomedicine and precision medicine. AI-driven data interpretation is driving the transformation, allowing quicker management of complicated information and improved repeatability across laboratories.

Miniaturized technology, eco-friendly procedures, and standardized regulatory validation will be crucial for connecting innovative research with routine quality control. Finally, hyphenated approaches have the potential to play a decisive role not just in pharmaceutical development, but also in biologics and personalized healthcare, guaranteeing that future therapies satisfy the greatest criteria of safety, efficacy, and sustainability.

ACKNOWLEDGEMENT

The authors would like to thank MET's Institute of Pharmacy, Nashik, for providing institutional support and resources.

Funding Sources

The authors received no financial support for the research, authorship, and /or publication of this article.

Conflict of Interest

The authors do not have any conflict of Interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects or any other material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not Applicable.

Author Contributions

Kavita Bhushan Vikhe: Conceptualization, Writing – Review & Editing; Sandeep Suresh Sonawane: Data Collection, Analysis, Writing – Original Draft.

REFERENCES

1. Niessen WM. Current practice of liquid chromatography–mass spectrometry. *J Chromatogr A*. 2001;970(1 2):59 100. doi:10.1016/S0021-9673(02)00265-5
2. Ermer J, Vogel M. Applications of hyphenated LC–MS techniques in pharmaceutical analysis. *Biomed Chromatogr*. 2000;14(6):373 383. doi:10.1002/1099-0801(200010)14:6<373:AID-BMC29>3.0.CO;2-S
3. Van Dongen WD, Niessen WM. LC–MS systems for quantitative bioanalysis. *Bioanalysis*. 2012;4(19):2391 2399. doi:10.4155/bio.12.207
4. Ahuja S, Rasmussen HT. Handbook of Modern Pharmaceutical Analysis. 2nd ed. San Diego, CA: Academic Press; 2007.
5. Lesellier E, West C. The many faces of packed column supercritical fluid chromatography: A critical review. *J Chromatogr A*. 2015;1382:2 46. doi:10.1016/j.chroma.2014.12.083
6. Takáts Z, et al. Ambient mass spectrometry for pharmaceutical analysis: DESI and DART advances. *Anal Chim Acta*. 2020;1097:1 15. doi:10.1016/j.aca.2019.11.012
7. Cooks RG, et al. Desorption electrospray ionization mass spectrometry: recent pharmaceutical applications. *J Am Soc Mass Spectrom*. 2016;27(6):1116 1123. doi:10.1007/s13361-016-1387-2
8. Ramautar R, et al. Recent developments in CE–MS for metabolomics and proteomics. *Electrophoresis*. 2021;42(1):1 15. doi:10.1002/elps.202000123
9. Zhang Y, et al. Advances in sheathless CE–MS interfaces for biomolecule analysis. *Anal Bioanal Chem*. 2022;414(5):1457 1470. doi:10.1007/s00216-021-03789-9
10. Albert K, et al. LC–NMR in pharmaceutical research: sensitivity improvements and applications. *TrAC Trends Anal Chem*. 2018;105:1 12. doi:10.1016/j.trac.2018.05.001
11. Exarchou V, et al. LC–NMR coupling technology: recent advancements in natural product and drug metabolite analysis. *J Chromatogr B*. 2020;1152:122 134. doi:10.1016/j.

jchromb.2020.122134
12. Lesellier E, West C. Green chromatography: advances in SFC–MS for chiral drug analysis. *J Chromatogr A*. 2019;1595:2 20. doi:10.1016/j.chroma.2019.01.012
13. Patel H, et al. Applications of SFC–MS in pharmaceutical quality control. Pharmaceutics. 2022;14(3):567. doi:10.3390/pharmaceutics14030567
14. Xu Y, et al. Artificial intelligence in pharmaceutical mass spectrometry: opportunities and challenges. *Drug Discov Today*. 2022;27(10):1030 1042. doi:10.1016/j.drudis.2022.05.012
15. Li J, et al. Machine learning approaches for hyphenated techniques in drug discovery. *Anal Chem*. 2023;95(2):456 468. doi:10.1021/acs.analchem.2c04567
16. van Kampen JJA, Burgers PC, de Groot R. Quantitative analysis of antiretroviral drugs using LC–MS/MS. *Bioanalysis*. 2011;3(3):283 294. doi:10.4155/bio.10.171
17. Sparkman OD. Mass spectrometry: A tool for the identification of unknowns. *J Chem Educ*. 2000;77(10):1322 1326. doi:10.1021/ed077p1322
18. Marriott PJ, Shellie RA, Cornwell C. Gas chromatographic technologies for the analysis of essential oils. *J Chromatogr A*. 2001;936(1 2):1 22. doi:10.1016/S0021-9673(01)01314-0
19. Smith RD, Shen Y, Tang K. Ultrasensitive and quantitative analyses from combined separations–mass spectrometry for the characterization of proteomes. *Acc Chem Res*. 2004;37(4):269 278. doi:10.1021/ar0301330
20. Moini M. Simplifying CE–MS operation: Interfacing using a porous tip. *Anal Chem*. 2007;79(11):4241 4246. doi:10.1021/ac0704560
21. Albert K, Bayer E, Spraul M. Coupling techniques for LC–NMR. TrAC Trends. *Anal Chem*. 1995;14(8):286 296. doi:10.1016/0165-9936(95)97016-7
22. Kebarle P, Tang L. From ions in solution to ions in the gas phase: The mechanism of electrospray mass spectrometry. *Anal Chem*. 1993;65(22):972A 986A. doi:10.1021/ac00070a001