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Flow Chemistry Highlights

A CHIMIA Column

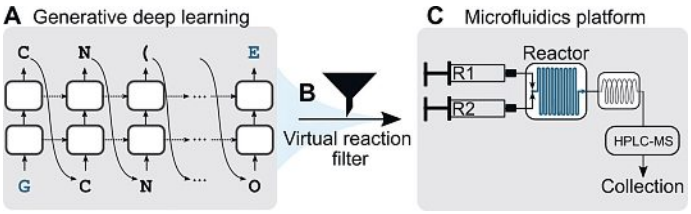
Review of Recent Literature on Flow Chemistry. Selected Topic: Automation

Combining generative artificial intelligence and on-chip synthesis for de novo drug design

F. Grisoni, B. J. H. Huisman, A. L. Button, M. Moret, K. Atz, D. Merk, G. Schneider*, *Sci. Adv.* **2021**, *7*, https://doi.org/10.1126/sciadv.abg3338

An automated design-make-test-analyze cycle remains an important goal of the fine chemical industry and has prompted many recent scientific developments. In this contribution, the authors combine an automated synthesis platform with a generative deep learning model to design liver X receptor agonists. The investigated chemical space was defined by 17 one-step reactions which could be performed automatically in a microfluidic device coupled to HPLC-MS. Out of 41 selected molecules, 25 were successfully synthesized using three reaction types: sulfonamide formation, amide bond formation and ester bond formation. To complete the set, three additional compounds were purchased.
In vitro activity testing performed with crude reaction mixtures revealed 17 hits. To confirm the results, 14 compounds were re-synthesized and purified in batch, and the bioactivity was confirmed for 12 molecules. This work demonstrates how recent advances in miniaturization, automation and computational algorithms can speed up and simplify drug design efforts.

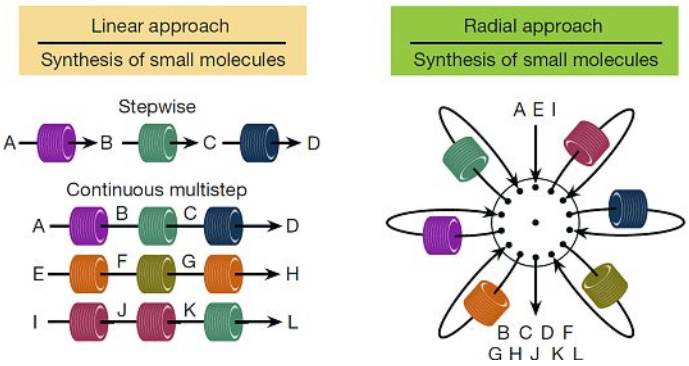
Author's comments*:
"In our method, decision making is partially transferred from the human science manager to a virtual chemist which is able to generate new molecules autonomously. By learning from experience, the artificial intelligence designs new molecules from scratch, and eliminates the need for screening huge numbers of chemical substances in costly experiments. Our closed-loop prototype demonstrates the practical applicability of this discovery concept."



Automated radial synthesis of organic molecules

S. Chatterjee, M. Guidi, P. H. Seeberger, K. Gilmore, *Nature* **2020**, *579*, 379-384, https://doi.org/10.1038/s41586-020-2083-5

Today biopolymers such as peptides and oligo-nucleotides are synthesized by iterative cycles of steps in an automated synthesiser relying in part on continuous flow operations. The authors take an intriguing step towards the automation of non-polymeric small molecules by exploiting a radial synthesis concept. For this, a series of reactors are arranged around a central switching station such that sequential, but non simultaneous, continuous multistep operations can deliver the desired compounds. Inline analytical monitoring provides the necessary reaction analysis and feedback, and the entire setup requires only milligrams of materials moving in liquid slugs shunted forward by pressurized nitrogen gas.
To showcase the versatility of the ingenious setup, the 3-step synthesis of the anticonvulsant drug rufinamide is demonstrated with 70% yield according to a convergent route. In extension, the authors prepare 12 derivatives of the drug using the same miniaturized setup. Since transparent tubing was used as reactor, a dual photoredox catalyzed C-N coupling was also demonstrated to provide four orthogonally substituted products. All of the above could take place without reconfiguration of the unit.



Would you like to propose a Flow Chemistry Highlight topic here?
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