How should we teach medicinal chemistry in higher education to prepare students for a future career as medicinal chemists and drug designers?

- A teacher´s perspective.

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ABSTRACT

In the recent two decades, the multidisciplinary field of medicinal chemistry has undergone several conceptual and technology-driven paradigm changes with significant impact on the skill set medicinal chemists need to acquire during their education. Considering the need for academic medicinal chemistry teaching, this article aims at identifying important skills, competences, and basic knowledge as general learning outcomes based on an analysis of the relevant stakeholders and concludes effective teaching strategies preparing students for a future career as medicinal chemists and drug designers.

1. Introduction

The multidisciplinary field of medicinal chemistry has experienced emerging innovation in associated technologies, ongoing digitalization, and drastic conceptual paradigm changes in drug discovery. The changing scope and landscape of medicinal chemistry leads to changes in the skills sets students in medicinal chemistry education need to acquire to be successful as medicinal chemists. This has also impact on the question: "How should we teach medicinal chemistry in higher education to prepare students for a future career as medicinal chemists and drug designers?"

Within this work I aim to:

- summarize the changes in the field of medicinal chemistry,
- derive a basic skill set for medicinal chemists based on an analysis of stakeholders in medicinal chemistry teaching in higher education,
- and derive suggestions for strategies and methods on how to teach medicinal chemistry to enable students to learn these required skills and be successful as medicinal chemist and drug designer.

Medicinal chemistry – An interdisciplinary field

In 1998 medicinal chemistry has been defined by Medicinal Chemistry Section (now part of Division VII: Chemistry and Human Health)[1] of the International Union of Pure and Applied Chemistry (IUPAC) as "Medicinal chemistry is a chemistry-based discipline, also involving aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships."[2] Although, there has been formulated the need for new and in particular more specific definitions,[3] this early general definition holds true and underlines two important but somewhat contradictory aspects of medicinal chemistry: the clear allocation as a historically chemistry-based discipline and the highly interdisciplinary nature of medicinal chemistry comprising multiple methods from a broad variety of different associated natural science disciplines. This makes teaching medicinal chemistry challenging as teachers coming from the organic chemistry field must provide a broad range of knowledge from outside their field. In the last decades, the interdisciplinary nature of medicinal chemistry has expanded significantly comprising a growing influence of structural biology, genetic

modulation techniques, virtual screening, and modeling techniques, computer-aided drug design, and data sciences including artificial intelligence and machine learning tools for bioinformatic analysis.[4,5] Furthermore, technological advances in all disciplines involved in the drug discovery and development process have boosted new developments in the field of medicinal chemistry and initiated several paradigm shifts currently changing the field drastically.

Driven by technology innovation - From pharmacology-guided to rational drug-discovery

While still part of the methodology portfolio in drug discovery, pure pharmacology-guided approaches significantly lost ground in favor for more rational "Target-First, Pharmacology-Second" drug design approaches[6,7] enabled by a growing knowledge feed from genome-wide association studies (GWAS)[7–11] and deep sequencing[12,13] of DNA. As a consequence, the target space in drug discovery has significantly expanded and beyond classical drug targets such as enzymes and receptors, now regulatory or structural proteins are on the drug discovery menu list often targeted by modulation or inhibition of their protein-protein interactions.[6] New hit-finding technologies (e.g. new High-Throughput Screening (HTS) technologies,[14,15] virtual screening (VS),[16] focused screens,[17,18] fragment-based drug discovery,[19,20] DNA-encoded library screens,[21–25] MS-based affinity selection[26,27]) have emerged boosting the success of medicinal chemistry projects. These drastic changes and the broadening of the scope of drug discovery campaigns need to be reflected in the teaching of medicinal chemistry in higher education, which raises challenges to select content for teaching without overwhelming students and provoke them to avoid too difficult courses.

Paradigm changes in drug discovery – Rethinking drug discovery

Furthermore, two major design rules in medicinal chemistry have been questioned in the last decade leading to paradigm changes following a dramatic expansion of the scope of medicinal chemistry. Historically and based on hepatotoxic properties of covalent binding metabolites of drugs such as acetaminophen (Paracetamol), investigated in the 1970s, drugs binding covalently to their targets were associated with concerns about potential for off-target activity and for years controversy discussed for their role in the pathogenesis of idiosyncratic drug-related toxicity.[28] Despite multiple successful examples (e.g. esomeprazol[29]/Nexium; AstraZeneca, clopridogrel[30]/Plavix; Sanofi-Aventis/Bristol-Myers Squibb) of selective and safe drugs beyond antimicrobial compounds such as β-lactam antibiotics or conventional chemotherapeutics, covalent binding had been considered a risk factor and, as a consequence, covalent mode-of-actions were avoided in drug discovery programs. In the 2000s, the distinct strength of the combination of covalent and non-covalent modes of actions was recognized and the concept of targeted covalent inhibitors (TCIs) evolved rapidly with rational drug design approaches with nowadays multiple examples of successfully market drugs,[28,31,32] especially in the area of kinase inhibitors.[33]

The second paradigm change was an even more pronounced drumbeat as the long standing *Lipinsky's Rule of Five* (Ro5)[34] was overthrown, which had influenced the drug designers for over 25 years. In 1997, *Lipinsky* and coworkers analyzed 2245 drug candidates, which had progressed beyond early clinical trials and therefore were assumed to have achieved sufficient levels of systemic exposure in early clinical trials. They assessed four selected physicochemical properties of these compounds, defined cut-offs so that 90% of the compounds fall inside them and introduced the *Rule of Five* (Ro5) predicting that poor gastrointestinal absorption and membrane permeation for small molecules (SMOLs) is more likely with more than 5 hydrogen bond donors (expressed as the sum of OHs and NHs), more than 10 hydrogen bond acceptors (expressed as the sum of Ns and Os), a molecular weight over 500 g/mol and a LogP over 5.[34] Although, *Lipinsky* and coworkers cautioned that the Ro5 should merely be used as an alert tool for newly synthesized SMOLs rather than a hard rule and already made exclusion for certain compound classes as well as noticed that natural product like drug classes did not comply with the Ro5, it quickly gained attention in the industrial and also academic medicinal chemistry

community and became an overinterpreted rule shaping the thinking of a generation of medicinal chemists.[35] In some pharma companies the Ro5 became dogma introducing an era of property-based drug design.[36] Early concerns on the general validity of the Ro5[37] led to expansions and variants of Ro5 such as the *Ghose's*[38] or *Egan's* filter[39] for the prediction of "*druglikeness*", *Veber's* rule[40], particularly questioning the hard molecular weight cut-off and accounting for the influence of polar surface area (PSA), *Muegge's* drug like criteria[41] and the truncation to the *Rule of 3* (Ro3) for fragment-based lead discovery by *Jhoti* and coworkers. However, all these approaches were not considering metabolization of drugs, compensating effects between different drug properties or the impact of high potency and the corresponding rules were applied too restrictively. Even in recent years, medicinal chemist desperately try to find standardized criteria for "druglikeness"[42,43] but all these rigorous models narrow the available chemical space and should only be used in *Lipinsky's* original intention as an alert tool for drug design.[35] The physicochemical understanding[44] and acceptance of drug space "*beyond rule of 5*" (bRo5)[35–37,45,46] in the medicinal chemistry community in recent years have culminated in the development of protein-targeting chimeras (PROTACs).[47,48] These bifunctional SMOLs occupy bRo5 drug space and consist of a high affinity binder for a protein target and E3-ligase active war head, which induce proximity between the protein of interest (POI), the PROTAC and an E3-ligase by formation of a ternary complex inducing ubiquitination.[49–51] The ubiquitylated POI then gets degraded intracellularly by the proteasome. The PROTAC concept has been demonstrated to be particularly successful in addressing difficult targets and although no PROTACs have been approved yet, several clinical studies are ongoing.[52–56] Carefully designed PROTACs can be orally active and even pass the blood-brain barrier[57] convincing experts in the field that PROTACs can be a game changers for several diseases.[58] Considering that not too long ago it seemed that SMOL drugs were on the decline as advances in biotechnology enabled pharma companies to cost-effectively[59] generate a range biologics such as large peptides, recombinant proteins, monoclonal antibodies, fusion proteins and vaccines, now SMOL drug discovery is having its moment[60] and the rise of an excitingly innovative time is tangible.

Although Ro5 complaint SMOLs remain a corner stone of modern drug discovery, new chemical modalities[52,61,62] (such as PROTACs, other bRo5 SMOLs and peptides (e.g. cyclopeptides and macrocycles[63]), oligonucleotide therapeutics[64–69] (including small interfering RNA (siRNAs), antisense oligonucleotides (ASOs), microRNAs and aptamers), biologics (e.g. antibodies), CRISPR-cas9-based therapeutics,[70–73] SMOL-radionuclide conjugates and mixed molecular conjugates for extracellular-targeted drug delivery (e.g. antibody-drug conjugates[74,75], antibody-degrader conjugates[76–78] and peptide-drug conjugates)) have emerged with successful Proof-of-Principles (PoPs), initiated clinical studies and approved drugs now significantly expanding the scope of medicinal chemistry. A new era of drug design has been heralded and it seems that terms like "undruggable" or "non-ligandable" are terms of the past.

Our excitement about these new opportunities is something we should transport when teaching medicinal chemistry in higher education to facilitate intrinsic learning motivation[79] and foster creative thinking in students.[80,81] This makes it also fundamental to create an inclusive,[82,83] safe and autonomy-supportive[84] learning atmosphere allowing students to be creative, to think out of the box and expand the binderies of the state-of-the-art. However, a deep understanding of physicochemical guidelines and their limitations seems to be key to support the students in considering pharmacodynamic and pharmacokinetic safety aspects of drugs.

New synthetic methods and the digitalization of medicinal chemistry.

The discussed changes in the drug discovery landscape are accompanied by an increasing synthetic complexity of lead compounds with a growing share of 3-dimentionality and chirality, which has also triggered the implementation of new synthetic methods such as direct C-H-functionalization of advanced lead compounds, photo-redox-catalysis, electro chemical transformations, flow chemistry and high-throughput experimentation for reaction condition screening and optimization.[85]

Furthermore, there is a growing importance of sustainable medicinal chemistry with greener active pharmaceutical ingredients (APIs).[86] Teaching in medicinal chemistry always needs to be anchored in organic synthesis aimed to provide methodology to synthesize the targeted compounds and best allow the students to develop retrosynthetic routes on their own.

Finally, in terms of automation and digitalization, the paradigm shift in pharmaceutical industry seems to be on-going[87,88] as digital tools such as machine learning (ML) supported prediction of physicochemical compounds properties, *in vitro* and *in vivo* absorption-distribution-metabolism-excretion-toxicity (ADMET) properties and artificial intelligence (AI)-based retrosynthesis tools[89–92] find first application in medicinal chemistry projects and being further developed, while tools like AlphaFold,[93,94] clearly start to make differences in the accuracy of protein folding predictions. Medicinal chemistry teaching in higher education needs to reflect these changes in automation and digitalization by training students on automated devices and in the use of AI based tools without neglecting the teaching of the underlaying manual analog principles and concepts.

The described changes in medicinal chemistry have led to an evolving skill set of distinct soft and hard skills for scientists in medicinal chemistry, which need to be considered when teaching medicinal chemistry to the next generation. However, this task goes way beyond the continuous adaptation of medicinal chemistry education to changes, and the obvious challenge to select the content for a time limited lecture from this broadened variety of topics. As current academic medicinal chemistry education seems not to meet the needs of pharmaceutical industry, one of the most important stakeholders,[45,95–97] it is time to rethink the way we teach medicinal chemistry!

2. Stakeholders of medicinal chemistry education and their expectations to the skill set and competencies of medicinal chemists.

To provide a comprehensive picture and analyze which skill sets and learning outcomes need to be aimed at in medicinal chemistry teaching, it is important to identify the different stakeholder groups in medicinal chemistry teaching in higher education. The results of this analysis are summarized in Figure 1. The following analysis is structured by the different stakeholder groups identified in literature[3,45,96–98] or by my practice as teacher as well as academic and industrial researcher in the field. Skills derived from the needs of the different stakeholders are highlighted in bold. The term *stakeholders* refer to groups with relevant interests which need to be considered in teaching of medicinal chemistry in higher education. It is however important to note that this analysis is not meant to be complete. Its primary aim is to be thought provoking, stimulating further inquiry and discussion in the scientific community and among medicinal chemistry teachers.

Students pursuing medicinal chemistry education

Within a constructivist student-centered learning approach for medicinal chemistry teaching,[99–101] the primary stakeholder group to mention should be the students pursuing a medicinal chemistry education. In general, this group is highly diverse in terms of educational background coming from first, second and third cycle chemistry, medicinal chemistry, pharmacy, and chemical biology study programs. Although the expectations of medicinal chemistry students can vary based on their academic experience, career goal, and depth of knowledge they seek, all might have a direct interest in the quality of education, the curriculum content, and the relevance of the teaching material to their future careers.[102] First cycle students seek to be introduced to fundamental concepts of medicinal chemistry and the drug discovery process and aim to learn **basic laboratory skills including commonly used techniques** to lay the groundwork for further second cycle studies. Second cycle students might already have a more distinct perception of their areas of interest looking for a broader variety of advanced topics such as specific **computational methods** or more specialized therapeutic areas.

Second cycle students often aim to gain **hands-on experience in medicinal chemistry research** to prepare for internships in both academic and industrial medicinal chemistry. Furthermore, expectations of this stakeholder group might include opportunities to network with medicinal chemistry professionals from industry. This wish for network opportunities seems to increase among third cycle students. Many of them are becoming experts in specific areas of medicinal chemistry on their own. However, their expectations might be related to future career preparation, including the expansion of knowledge in areas beyond their thesis topic and **transferable skills for both academic and industry postdoctoral or industrial entry-level positions**. Although the overall expectations on "How medicinal chemistry should be taught?" from the perspective of the stakeholder groups of students might be less defined, it has been demonstrated that students in higher education clearly prefer students-centered interactive teaching activities over classical information-transmitting teacher-centered approaches.[102–104]

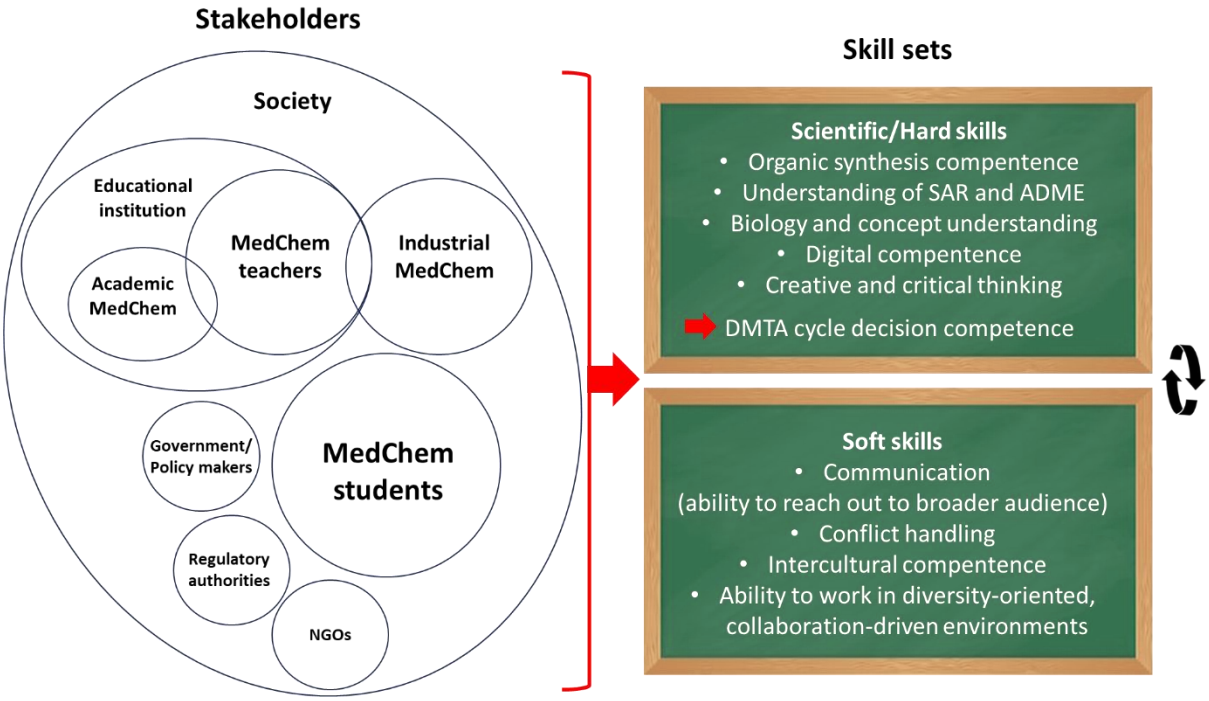

Figure 1: Stakeholders of medicinal chemistry teaching in higher education and the basic skills set deriving from their needs. MedChem = Medicinal Chemistry, NGO = non-governmental organization, DMTA = Design-Make-Test-Analyze. On the left side of the figure the different stakeholders of medicinal chemistry teaching in higher education are listed and arranged graphically according to their relation towards each other. On the right side distinct scientific hard skills and required soft skills for a medicinal chemist derived from the stakeholder analysis are summarized. The hard and soft skills thereby represent to sides of the skill set equally important for medicinal chemists.

Teachers of medicinal chemistry in higher education and academic MedChem community

The faculty and instructors responsible for teaching medicinal chemistry are crucial stakeholders as they are directly involved in designing the curriculum and associated teaching activities in medicinal chemistry in higher education. Teachers in medicinal chemistry education do not only have to address the pedagogical challenges arising with the multidisciplinary field but also hold the important role to mediate and address the needs of all stakeholder groups within the curriculum off medicinal chemistry courses. They should have an interest in providing relevant topics, practical lab course experiences and teaching relevant skills to their students, preparing them for future tasks as medicinal chemists and drug designers. Therefore, they need access to state-of-the-art laboratories and teaching facilities, cutting-edge technologies, and proper equipment to enable effective teaching. In addition, this group should have an emphasis on engaging effective teaching methods to capture students' interest,

facilitate understanding of complex medicinal chemistry concepts and create an inclusive[83] and supportive learning environment for the subject. One challenge for the teachers in medicinal chemistry in higher education might also be to balance out the interest of some of the other stakeholder groups by alignment of their individual teaching goals with the evolving needs of pharmaceutical industry, broader society-derived needs, and goals of the educational institution they are representing to ensure a cohesive and effective educational experience for the students. As they often conduct medicinal chemistry projects in their own academic research groups, this stakeholder group of academic teachers of medicinal chemistry has a huge overlap with the academic medicinal chemistry community. Both share a strong interest in the proper education of future PhDs and coworkers with **creative and critical thinking driving** future innovation in their labs. In their role within the higher education system, medicinal chemistry teachers strongly depend on their educational institutions.

Educational institutions

Therefore, educational institutions such as universities and technical colleges offering medicinal chemistry programs are stakeholders closely connected to the stakeholder group of medicinal chemistry teachers. They have an interest in maintaining the quality and reputation of their educational programs, attracting students, and meeting accreditation standards. Within this role they are responsible for providing the required facilities, equipment, and proper framework for teaching.

Future employers and the pharmaceutical industry

A further very important stakeholder group are the future employers of graduates of medicinal chemistry study programs, a group being strongly dominated by the pharmaceutical industry.[3,45,95–97] The pharma discovery ecosystem has faced major changes[105] from mainly big pharma companies in the 1990s towards a pharma landscape today comprised of big and medium sized pharma companies, contract research organizations (CROs) providing top-notch lab infrastructure and scientific expertise, and a broad range of biotech companies and start-ups. Therefore, this stakeholder group might be even more divers than expected on the first glance and expectations of this stakeholder group towards medicinal chemistry education might differ based on actual work tasks and structural frameworks within these organizations. While the actual responsibility of a medicinal chemist within bigger pharma companies with more employees might be more specialized or strongly centered around pure synthetic chemistry, in mid-size pharma and biotech companies who have overall smaller medicinal chemistry departments or less coworkers, the expected skill set for a medicinal chemist might be even broader, simply as it cannot be afforded to exclusively dedicate internal chemist to synthetic chemistry task only.[45] The basic skill sets for medicinal chemists in industry have been controversy discussed multiple times, especially in the context of the reorganization of European study programs within the Bologna process.[3,95,96,98]

The participants of the European Medicinal Chemistry Leaders in Industry (EMCL) meeting, despite all the differences, represent a substantial part of this stakeholder group[45] and identified as key competences for medicinal chemists a **solid education in organic synthesis with the ability to efficiently access complex molecules** and a **clear understanding how drug properties are linked to a molecular structure**. In addition, an **understanding of the fundamental biology and new treatments concepts** is of growing importance[45,95–97] to be able to navigate securely through the broadened scope of medicinal chemistry and make valuable decisions within drug discovery's **Design-Make-Test-Analyze (DMTA) Cycles**.[106,107] Furthermore, **digital competence** in the use of tools for prediction of binding interaction or physicochemical chemical properties or even hands-on digital capabilities such as coding skills will gain more importance in the future.[45]

Beyond that, a distinct set of soft skills is of growing importance for industrial medicinal chemists working in highly diverse and interdisciplinary teams. These include **good communication skills**, being able to reach out to diverse audience, **the ability to work in an intercultural, diversity-oriented,**

collaboration-driven environment, and **management skills** are seen as important as the scientific know-how listed above.[45] Teachers in medicinal chemistry need to review if and how such skills are reflected in the curricula and should aim for appropriate teaching activities fostering students' development towards these highly ambitious learning outcomes.

The society

The stakeholder group of the future employers, particularly the pharmaceutical industry, is of special importance and a medicinal chemistry education ignoring the needs and interest of these stakeholders would probably fail to educate the next generation of drug designers. However, it also needs to be considered that the needs of society and the aims of economically driven companies do not necessarily always match.

One specific example underlying this mismatch situation is the current antibiotic crisis.[108–112] After the "*golden era of antibiotic drug discovery*" from the 1930s to mid-1960s[113] in which the most of the antibiotics used today have been discovered and developed to enter the drug market, a huge innovation gap of over 40 years followed in which no new antibiotics have been developed. At the same time, the occurrence and spread of resistances against market antibiotics has risen tremendously leading to a situation today in which we see ourselves confronted with nosocomial infections with multi-drug-resistant (MDR) bacterial pathogens where there are no effective treatments available anymore.[114] This situation has been amplified by the fact that most big pharma companies have stopped their antimicrobial research programs and stepped out of the non-lucrative business of the development of antibiotics for economic reasons.[115] From a purely economic standpoint of view, an understandable decision. While the development cost and time of an antibiotic is comparable to those of a cardiovascular or anticancer drug, the economic risks for the company are significantly higher. Not only that in pronounced contrast to other medical indications, the efficacy of antibacterial drugs deteriorates over time as bacterial resistance is an intrinsic factor of bacterial evolution in consequence to the antibiotics impact on the bacterial resistome[109]. Furthermore, additional limitations such as reduced prescription for drugs classified as antibiotics of last resort or comparably short treatment times of infections contribute to a difficult economic exploitation of antibiotics. Despite all understanding of the problematic situation, despite the clear need for a political solution addressing the requirements of functional business models for the pharmaceutical industry,[116] and despite recent single positive examples of antibiotic drugs entering the marked,[109,117,118] the social responsibility of the pharma industry as key player in the development of new antibiotics to counteract the antibiotic crisis is, from ethical stand point of view, currently not fulfilled.[119]

Therefore, the **society** needs to be considered as a stakeholder with a strong interest in medicinal chemistry to maintain public health through development of effective, safe, and more sustainable drugs. In medicinal chemistry teaching in higher education, we need to identify these conflicts of interest and balance them out by incorporating the needs of society into an industry-oriented teaching of medicinal chemistry. Finally, society has a strong interest in the education of creative and critical thinkers, challenging the status quo and being able to provide innovative solutions for current and future problems of humanity.

Miscellaneous stakeholders

Furthermore, partially overlapping additional stakeholder groups are **governments and policymakers** providing support for educational programs with an interest in workforce development, **regulatory authorities** providing framework for drug development, or **non-governmental organizations** such as patience associations or professional organizations related to medicinal chemistry setting standards and advocating for their fields. Each of these stakeholders plays a role in shaping and influencing the landscape of medicinal chemistry education and defining the educational

mandate with a distinct skill set of scientific hard skills and required soft skills to succeed as future drug designers.

3. How should we teach medicinal Chemistry in the future?

Unfortunately, traditional lecture formats are still a very common approach in teaching natural sciences. Although this teacher-centered format can work reasonably well with certain charismatic teachers and highly self-motivated students, who are both attentive in class and additionally invest the required hours after lectured to revise and learn the material, most classroom realities look different. Even if we assume all teachers were charismatic and all students were highly self-motivated, it is highly questionable whether it is an efficient use of classroom time when we "read out" information to students considering that large amounts of information are easily available. Beyond that, it is unquestionable that this approach neither improve student's scientific communication and collaboration abilities nor help them to develop scientific and critical thinking and problem-solving skills. Looking at the skills sets for medicinal chemists identified in Section 2 and summarized in Figure 1, this seems to be a clearly mismatching approach to teach medicinal chemistry and science in general. Ergo, we need to adjust the way we are teaching medicinal chemistry to meet the learning outcomes required for the next generation of medicinal chemists to tackle the problems of our future.

A constructivist active-learning approach for teaching medicinal chemistry will foster critical thinking and understanding.

The learning theory has been long established, the teaching tools and their functional evidence exists. Constructivism learning theory[101,120] tells us that learning is depending on understanding and that learners actively need to construct their own meaning to understand taught subjects.[101] Learning is an active process and more than passive listening to fact-based lectures. Thus, a learning environment must provide opportunities for active learning.[121] Learners need to challenge and adjust their current understanding depending on what they encounter in the new learning situation. If the encounter is inconsistent with their current understanding, their understanding can change to accommodate new experience. Learners remain active throughout this process: they apply current understandings, note relevant elements in new learning experiences, judge the consistency of prior and emerging knowledge, and based on that judgment, they can modify knowledge.[122] Constructivist active learning activities such as flipped classroom settings,[123–126] problem-based learning (PBL) approaches[127–130] or interrupted case-studies[131,132] put the focus of learning on critical thinking[133] and understanding rather than on basic memorization, which allow the students to create organizing principles that they transfer more easily to other learning settings and subjects. Problem solving is furthermore fostering creative thinking.[134]

Learning in medicinal chemistry needs to be collaborative and cooperative.

We have known for decades that social interactions (between students and teachers as well as among students) play a key role in the learning process. Learning situations therefore should be social, cooperative and collaborative.[135] Creating a class room environment that emphasizes collaboration and exchange of ideas promotes social and communication skills as students learn how to articulate ideas clearly, negotiate with peers and evaluate their contributions in a socially acceptable manner to collaborate effectively on a task. In most medicinal chemistry classes we can take advantage of the usually highly diverse student body to mimic the diverse and intercultural teams in medicinal chemistry departments of the pharmaceutical industry if we actively involve the students into the teaching and learning process by fostering group discussions and peer-to-peer teaching activities.[136]

Looking at the teaching body for highly interdisciplinary medicinal chemistry courses, which is usually less diverse, it might help to incorporate multiple teachers into the course to break stereotyped role models, make teaching more inclusive[82] and take advantage of specific expertise by incorporating

colleagues from theoretical chemistry or biology. Furthermore, embedding of course parts led by researchers from industry is a valuable opportunity to include very specialized medicinal chemistry expertise, promote exchange between industry representatives and students, and align educational aims with industry needs.

Finally, authentic learning tasks are crucial for meaningful learning as they stimulate students natural curiosity to the matter and engage students into critical thinking.[101] Teachers will support the understanding of, for example, physicochemical values of drug candidates way better if students can experience their effects in real-world examples of interrupted case-studies on e.g. Hit-to-Lead optimizations taken from recent industry or academic medicinal research examples.

The functional, scientific evidence of active student-centered learning is massive[137,138] and, as phrased perfectly by Clarissa Dirks, former co-chair of the US National Academies Scientific Teaching Alliance: "At this point it would be unethical to teach any other way."[139] As implication for teaching medicinal chemistry courses, it should be our priority aim to design a comprehensive education in a constructivist active way that students can learn and apply the mandatory scientific hard skills and train the required soft skills in collaborative student-centered active learning settings.

A common counter argument against the implementation of collaborative active learning activities is that they consume more classroom time compared to classical lecture formats and would limit the content which could be covered in class. However, for example flipped classroom events can actually help to provide both time to cover course content and getting sufficient time to work through more complex problems in class by refreshing existing knowledge prior to class and reduce the in-class cognitive load for the students.[123,124,140]

A more holistic approach: Teaching of concepts and train DMTA-cycle competence

The course content of medicinal chemistry lectures needs to be reduced, we need to leave such boring pharmacy lectures behind us which consist of getting lost in detail and reading through hundreds of examples of marked drug classes. On the contrary, we should concentrate on overarching principles and concepts[141] to create room for topics like new modalities, covalent drugs, or compound classes bRo5. Therefore, a solid introduction into the general concepts of pharmacodynamics, pharmacokinetics and general design strategies is important at the beginning of the course. This might even be partially achieved using lecture style formats, but with implementation of flipped classroom events and significant interruption by active exercises enabling the students to apply and thereby understand the content. During such an introduction, the market drug classes still find their place but as perfect examples for the taught, general concepts. Course accompanying tutorials might give an additional focus on the synthesis of specific market drug classes.

The major part of the courses should have a clear focus on design and synthesis of current drugs utilizing multiple active learning events to cover different topics. Thus, interrupted case studies based on recent industry and academic medicinal chemistry campaigns hold potential to enable both the coverage of different drug classes (e.g. SMOLs, PROTACs, cyclopeptide drugs, natural product derived antibiotics, etc.) as well as aspects of pharmacokinetic and drug design problems at different stages of the drug discovery process (e.g. Hit finding, Hit-to-Lead optimization, Lead optimization, etc.). All case studies should, first, challenge the students to retrosynthetically dissect the discussed molecules and suggest synthesis routes to facilitate the understanding on how drugs can be made and, further, embed the medicinal chemistry course as essential within organic chemistry. A smart selection of examples can ensure that multiple synthetic aspects and strategies (e.g. photo-redox catalysis, electro chemical late-stage derivatization, CH-activation, combinatorial chemistry, solid-phase supported synthesis or flow chemistry) are covered sufficiently. Such a more holistic approach would allow the students to explore effects of physicochemical compound properties and structural modifications and gain a clear understanding of DMTA cycles by evaluating their own decisions and strategies while discussing with their peers. Short introductions to the general field, the targeted diseases or bio

pathological mechanism and market drugs in the indication could provide context for the case studies and might also give opportunities to visualize drug-target interactions based on available co-crystal structures using 3D-illustration software.

Recently, *Lewis D. Pennington* published an article[142] in which he outlined the analogues conceptual frameworks of total synthesis and medicinal chemistry stating that total synthesis and the retrosynthetic disconnection of natural products might be the perfect training for medicinal chemistry. Considering this case study examples derived from active natural products might be smoothly integrated into the teaching approach described above.

Additionally, a flipped classroom type case study in which groups of students dissect a given publication on a drug discovery campaign guided by questions into a digestible core and present the result to their peers could not only help to manifest understanding and prepare the students for examinations but further help the teacher to identify aspects which need more clarification.

Real-problem laboratories with hands-on DMTA cycle decisions

Laboratory parts should be mandatory for medicinal chemistry classes to connect theory with practice. However, although lab courses are by definition active, often they are conducted as classical cook-book laboratories in which students follow a given procedure to conduct an experiment, collect data and partially draw conclusions from it. Certainly, students might learn how to conduct a specific experiment in such settings, but cook-book labs leave out important parts of the scientific research process such as the definition of the research question, the background research, the formulation of a hypothesis, and the design of the experiment to prove the hypothesis.[143–146]

If we aim to teach students how design and synthesize drugs and justify expensive lab courses, we need to provide a more comprehensive lab experience allowing students to experience at least a glance of what drug discovery means and how DMTA cycles in industry work in a more holistic scenario. A good set up for such a lab course could be problem-based learning (PBL)[147,148] or guided inquiry-based lab (IBL)[129,149] approaches, in which groups of students are confronted with structures and biological data of compounds in fictional drug discovery campaign as a real-life and contextual problem to solve motivating them to fill the knowledge gap through collaborative knowledge building.[150,151] As such approaches emphasize both process and content as the learning objectives, they are often perceived by students as more useful,[127,152,153] and substantial evidence exists that such lab courses increase students' motivation and outcomes with respect to data analysis and experimental design[154–156] as well as their ability to ask questions.[157] Furthermore, there are multiple successful implementations of such lab courses across different areas of chemistry underlining their efficacy.[127,129,158–161]

Thus, using PBL or guided IBL lab course design, a clear focus on DMTA cycles and the connection of structure and physicochemical properties can be set to connect to the medicinal chemistry content of the theoretical part of the medicinal chemistry course. The synthesis of potential drug candidates should be a central element in such lab courses, but embedded in a Hit-finding, Hit-to-Lead optimization, or Lead-optimization context, in which students must collaboratively work together in groups to:

1. derive a hypothesis/identifying a research question from on given structure of potential drug candidates and their biological data
2. identify proper assays to access derivative's performance
3. design modified compounds based on structural information of a biological target
4. synthesize/make modified compounds through retrosynthetic analysis, literature research, planning and conducting of a synthesis route
5. test the compounds in simple biochemical, biological or spectroscopic assays
6. and critically analyze their results to make recommendations/decisions

thus, going through a complete DMTA cycle, giving students to a realistic view of collaborative work in drug discovery projects and allowing for intentional development of team-working skills.[162]

By this means, it is less important if the individual student groups have designed substantially improved compounds, as positive as well as negative DMTA cycle decision will support understanding of the overall drug discovery process once properly discussed and reflected upon. A good level of creative freedom in this process might even be an incentive to facilitate the students' engagement in the task. This should further be supported engaging students in the use of state-of-the-art virtual screening techniques and molecular docking utilizing available co-crystal target structures to help the students to understand the structure and functionality of the biological target and promote their understanding of drug-target interactions.

Students in a medicinal chemistry lab course should learn how they can plan and conduct the synthesis of new derivatives. A clear understanding of retrosynthesis aspects from earlier advanced organic chemistry courses should be the basis for own retrosynthetic analysis of envisaged compounds. Thereby the use of chemical reaction research tools and databases like Scifinder or Reaxys, but also AI-supported retrosynthesis software like (Synthia or others) should encourage students to touch base with these tools and enable critical reflection of opportunities such as evaluation of the environmental sustainability of selected synthesis routes.

Due to time restrictions or cost limitations in medicinal chemistry lab courses, it might not always be possible to conduct complex biological assays within lab courses. An alternative could be simple colorimetric or fluorometric assays (e.g. GOD-PAP or PUB assays[163,164]) conducted with plate readers in well plates giving the students the opportunity to access the properties of the compounds they aim to change first-hand. Additionally, data of more complex assays could be provided by the teacher to enable the simulation of complex, multi-parametric DMTA cycles in drug discovery. Medicinal chemistry relevance of the lab course will be key to fostering the student's engagement and deepening the taught knowledge. Easy to implement and simple experiments such as NMR-based LogP determination experiments[165] in combination with property prediction by virtual property prediction tools could help students to understand the link between structural moieties in the drug candidate and observed ADME properties. Furthermore, the introduction of combined activity, physicochemical and pharmacokinetic properties profiles might assist students to orientate within a multiparametric optimization study.[166]

During the lab course, groups of students should make decisions collaboratively based on scientific discussions guided by the lab assistant. Thereby, we can take advantage of the high diversity of current student bodies to train communication skills in intercultural and diverse teams.[162] Finally, results of the lab courses might be documented by the students in publication style or even as scientific posters[167] with incorporation of peer-review cycles to improve scientific writing and proper communication.[168]

State-of-the-Art lab equipment is key for good medicinal chemistry education.

For such lab courses it will be of great importance to provide access to state-of-the-art educational laboratories equipped with appropriate research devices (e.g. microwave or photo reactors, peptide synthesizers and automated chromatography devices for synthesis, or pipettes, plate readers, gel electrophoresis devices for the conduction of biochemical and biological assays) and student licenses for modelling, prediction, and retrosynthesis software. Beyond the associated cost, a common challenge in this regard might be that often educational laboratories are used for different lab courses and therefore need to be flexible in their equipment and the arrangement of lab and hood space. A simple win-win solution to reduce equipment associated cost and retain flexibility might be to involve suppliers of synthesis and analytical devices providing the equipment during the lab course chargeless for demonstration. For the supplier, the chance to get future decision makers trained on company

devices seems to be reward enough to engage in such deals. A recent example at the University of Gothenburg showed that this can lead to high-end, automated equipment for course labs, very much appreciated by students and finally enabling time and space for additional biological experiments in the course.

4. Conclusions

Following the recognition of the discussed paradigm changes in medicinal chemistry, it is time to not only adjust the curricula of medicinal chemistry courses with regard to their content but furthermore revise courses towards constructivist teaching approaches fostering active and sustainable learning techniques justifying in class time and lab courses by additional value beyond pure knowledge resources. Medicinal chemistry teaching should be embedded in organic chemistry to address the core requirements of industry as the main stakeholder. Student-centered, collaborative active learning techniques can make the crucial difference in medicinal chemistry teaching enabling the learning of mandatory scientific hard skills while applying and training the industry-required soft skills.

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