General description
Truly being about chemistry in an interdisciplinary drug context, in the specialization Drug Design and Synthesis you will focus on the organic chemistry of novel biologically active compounds, peptides/peptidomimetics, radiolabeled molecules or novel synthetic methodologies. You will work with the newest synthesis, purification and compound characterization equipment. Your classes will reveal how to reap the fruits of life science research and will guide you along the way to become an innovative synthetic chemist in a life science context. Opportunities to incorporate molecular modeling angles in your programme are plentiful and highly supported with state-of-the-art computational approaches. Indeed, uniquely you can choose to devote your main attention to organic synthesis, to computational design, or to a combination of both.

Programme components (EC)
The Master’s programme in Drug Discovery and Safety is a two-year programme starting in September. The specialization Drug Design And Synthesis contains the following components (EC):

- Compulsory (core) courses (30-36)
- Major research project (42-60)
- Literature thesis and colloquium (12)
- Ethics and academic skills (6)
- Elective: minor research project; traineeship abroad/company; optional courses (6-30)

Course overview

<table>
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<tr>
<th>Period</th>
<th>Month</th>
<th>Course (EC)</th>
<th>Category</th>
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<tbody>
<tr>
<td>1*</td>
<td>Sep – Oct</td>
<td>Chemical biology (6)</td>
<td>Compulsory core course**</td>
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<td>ADMET (6)</td>
<td>Compulsory core course**</td>
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<td></td>
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<td>Principles of pharmacochemistry (6)</td>
<td>Introductory course***</td>
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<td></td>
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<td>Physical-organic chemistry (6)</td>
<td>Compulsory course</td>
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<td>2</td>
<td>Nov – Dec</td>
<td>Synthetic Approaches in Medicinal Chemistry</td>
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<td>3</td>
<td>Jan</td>
<td>Ethics and academic skills courses (6 total)</td>
<td>Compulsory course</td>
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<td>Feb – Mar</td>
<td>Computational design and synthesis of drugs (6), Drug action (6)</td>
<td>Compulsory core course**</td>
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<td>5</td>
<td>Apr – May</td>
<td>Traineeship, literature study, optional course</td>
<td>Compulsory core course**</td>
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<tr>
<td>6</td>
<td>Jun-</td>
<td>Traineeship</td>
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More information: www.vu.nl/dds

* Not necessarily all in year one
** At least 3 out of 4 compulsory core courses are obligatory.
***Principles of pharmacochemistry only compulsory for students without prior background in pharmaceutical sciences.
Master’s programme in Drug Discovery and Safety

Drug Design and Synthesis

Research topics

Medicinal Chemistry: Dr. Maikel Wijtmans; Prof. Dr. Iwan de Esch

Synthesis of organic compounds for fundamental and applied medicinal research

Our synthetic chemists use state-of-the-art synthetic equipment and a large diversity of reaction types to prepare novel organic molecules, many of which are heterocyclic compounds. Collaborations with pharmacologists allow elucidation of the biological activity of these compounds. The resulting insights pave the way to further synthesis of exciting new organic compounds that help in unraveling cell processes and may serve as potential medicines.

Computational modeling of organic compounds and their interaction with protein targets

Our computational chemists use protein sequences, protein crystal structures, molecular dynamics and conformations of organic molecules to generate three-dimensional models of protein-ligand complexes with state-of-the-art computational chemistry technologies. These in silico models lead to a better molecular understanding of ligand-protein interactions. In turn, this enables virtual screening for new organic ligands, paving the way for improved medicines.

Efficiently traveling in ‘chemical space’: Fragment-Based Drug Discovery (FBDD)

In FBDD, the synergy between computational design and organic synthesis is at its finest. Small molecules (fragments) that bind to the biological target are identified and the fragments are grown step-by-step into new efficient ligands through an intimate design and synthesis process. We apply FBDD to a variety of protein targets (G-protein coupled receptors, kinases, ion channels, etc.) that are important in a range of therapeutic areas (inflammation, cancer, neglected third-world diseases, flu and antibiotics).

Design and synthesis of light-responsive organic molecules to study biochemical processes

We have launched a research line addressing the design and synthesis of novel photoresponsive organic molecules that are being used in chemical biology approaches. Upon irradiation with light, these molecules change their 3D shape and hence physiochemical and biological properties, giving the potential to perturb biochemical processes differently in the light and in the dark. This in turn allows for the exciting opportunity to modulate biochemical processes with spatial and temporal precision simply using light.
Master’s programme in Drug Discovery and Safety
Drug Design and Synthesis

Research topics

Synthetic & Bioorganic Chemistry: Dr. Eelco Ruijter, Prof. Dr. Romano Orru

**Sustainable synthesis of complex pharmaceuticals**
Modern drug molecules are increasingly complex compounds. As a result, their production often involves long synthetic routes with the concomitant production of a lot of waste. Synthetic process optimization is therefore crucial for sustainable pharmaceutical production. We exploit our expertise in biocatalysis and multicomponent reactions to make drug molecules with unprecedented efficiency.

**Multicomponent reactions**
The drug discovery process relies on access to large arrays of drug-like compounds for high-throughput screening, which in turn depends on synthetic organic chemistry to make these compounds. Traditional approaches typically involve lengthy, stepwise synthetic routes, limiting the overall efficiency of the process. We develop flexible and robust multicomponent reactions combining three or more reactants to make complex drug-like compounds in a single operation.

**Catalytic synthesis of drug-like heterocycles**
Nitrogen heterocycles, omnipresent in small-molecule drugs, are traditionally constructed using condensation of highly activated precursors under harsh conditions. We use transition metal catalysis to construct pharmaceutically important heterocyclic systems under benign conditions by isocyanide insertion and allyl transfer reactions.

**Cascade reactions in natural product synthesis**
Naturally occurring alkaloids display potent and diverse biological activities, making them interesting leads for drug development. However, their complex molecular architecture presents a formidable synthetic challenge. We develop novel cascade reactions (forming multiple bonds, ring systems and stereocenters in a single process) to efficiently access natural and non-natural alkaloid frameworks.
Synthesis of peptidomimetics
Our synthetic efforts focus on the synthesis of non-natural amino acids and peptide-derived molecules. We aim for the expansion of the repertoire of reactions that can be applied for the synthesis of such molecules directly on solid-phase. In particular, we focus on the design of inhibitors of important therapeutic targets.

Biocompatible reactions and protein stabilization
We apply biocompatible reactions for the functionalization of native proteins. For that purpose, proximity-induced reactions are applied in which a ligand directs the reactive group towards a particular amino acid. In addition, we seek electrophilic groups that show high sensitivity towards the amino acid micro-environment. Those reactions are applied to label protein in cells and to improve enzymes for biotechnological applications.

Biophysical characterization of target binding
The characterization of interactions between our designed ligands (peptides and peptidomimetics) and their biological targets (proteins and RNA) is central for the follow-up design of improved inhibitors. For this purpose, the following techniques are used: fluorescence polarization assays, isothermal titration calorimetry (ITC) and cellular pull-down assays (among others).
General radiopharmaceutical sciences
Radiopharmaceutical sciences is a truly translational discipline in which radiochemistry, organic chemistry, medicinal chemistry, molecular pharmacology and imaging come together and where new radiopharmaceuticals are developed from bench-to-bedside. Your classes will reveal how to design, synthesize and evaluate radiopharmaceuticals and will develop you into a radiopharmaceutical chemist/scientist.

Development of new radiochemistry methodology to enlarge the radiochemistry toolbox
Our radiochemists develop new synthetic methods to be able to radiolabel any molecule of interest in the future. Right now the radiochemistry methodology available to synthesize radiopharmaceuticals is limited. The short physical half-life limits the chemical possibilities and fast, high yielding reactions therefore need to be developed. To this end, our radiochemists work in lead-shielded isolators developing new automated synthetic procedures for new radiolabelled building blocks and apply them in the synthesis of new imaging agents.

Synthesis of new PET tracers for imaging
Our radiochemists synthesize new lead compounds for PET imaging of a target of interest. After lead finding, lead optimization on a small scale is performed. The optimal compounds are radiolabelled and investigated in vivo in collaboration with the radiopharmaceutical scientists. If no suitable PET tracer can be identified in vivo, new tracers will be designed and synthesized.