TCG Lifesciences | Chembiotek

PROTAC & MG Chemistry

Our Core Capabilities

❖ **Custom PROTAC, MG Design & Synthesis**

- Extensive experience in synthesizing all individual components—POI ligands, E3 ligase ligands, and linkers—with tailored modifications.
- Flexible assembly strategies including:
  - Linker-first or warhead-first conjugation
  - Fragment stitching through Click chemistry
  - Pre-assembled linker-ligand conjugates
- Capability to produce and purify PROTAC molecules and MGs from mg to multigram scale.

❖ **In-House Ligand-Linker Toolbox**

- Large inventory of over 200 E3 ligase ligand–linker conjugates featuring:
  - CRBN (Thalidomide, Lenalidomide, Pomalidomide, PG, DHU)
  - VHL (Hydroxyproline derivatives)
  - IAP, LAP, and MDM2 ligands
- Multiple exit vectors and reactive sites for rapid library generation
- >300 linkers of diverse chemical space (alkyl, PEG, glycols, triazoles, heteroaryls, spirocycles, azetidines, piperidines, etc.)

❖ **Linker Chemistry Expertise**

- Tailored design and synthesis of linkers with defined length, rigidity, flexibility, and attachment sites
- Broad experience with:
  - Triazole-containing linkers via Click chemistry
  - Rigid N-heterocycles (e.g., piperazine, piperidine)
  - PhotoPROTAC frameworks and photo-switchable linkers

  - Amide bioisosteres to enhance solubility and pharmacokinetics
- In-house linker inventory curated with diverse chemical compositions designed to support favourable ADME/PK profiles

❖ CRBN Ligand Chemistry

- Robust multistep synthesis (14–15 steps) of novel substituted glutarimides, PG-based, and DHU ligands
- Custom ligand design with diverse attachment modes (C, N, O, S) at C4/C5 of the phthalimide ring
- Synthesis of novel CRBN cores at multigram scale with optimized SAR and exit vectors
- Availability of benzimidazolone-based imide ligands

❖ VHL Ligand Expertise

- Design and synthesis of hydroxyproline analogs with customized exit vectors
- Exploration of alternate linkage positions (e.g., benzylic site, phenyl group, and C3 of proline)
- Replacement of N-terminal acetyl with fluorocyclopropyl groups
- Comprehensive SAR analysis of N- and C-terminal fragments

❖ IAP and Other E3 Ligase Ligands

- In-house synthesis of cIAP ligands and availability for library production
- Capability to prepare multigram quantities for extended synthesis campaigns
- Stock of ligands for LAP and MDM2 E3 ligases available for conjugation

❖ Focused PROTAC Libraries

- Proven track record of >3000 compounds delivered as part of collaborative library programs
- In-house expertise in virtual library design, compound tracking, and assay-ready delivery
- High-throughput platforms for synthesis, purification, and compound management:
  - Mass-directed auto purification
  - Work-up and filtration systems
  - Solvent evaporation and DMSO plate formatting under dry ice
- Success rate of >95% in synthesizing custom PROTAC arrays (>600 molecules)

❖ Strategic PROTAC Assembly Approaches

- Expertise in three PROTAC assembly approaches:
  - Approach A: Linker–E3 conjugation followed by POI ligand
  - Approach B: Linker–POI conjugation followed by E3 ligand
  - Approach C: Convergent strategy joining pre-functionalized fragments
- Approach selection based on synthetic feasibility, building block availability, and cost efficiency

More Information
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