

## Dr. Steven BALLET

### Academic CV

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### Personal Data

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Date of Birth June 5, 1979  
Place of Birth Brussels, Belgium

### Education

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1997 - 2001 Vrije Universiteit Brussel, Brussels, Belgium (*M.Sc. Chemistry*)  
2001 - 2002 CREPUQ Exchange (Graduate program, Université de Montréal, P.I. W. D. Lubell)  
2002 - 2007 Vrije Universiteit Brussel, Brussels, Belgium (*Ph.D. Chemistry*)

### Main Areas of Research

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**Research areas** Organic and peptide chemistry, medicinal chemistry, drug design, biomaterial synthesis  
**Specific interests** Neuropeptides, pain research, molecular medical imaging, drug development

### Career History and Positions Held

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2007 - 2008 *Post-Doctoral Research Fellow*, School of Chemistry and Physics, University of Adelaide, Adelaide, Australia (P.I. Andrew. D. Abell)  
2008 - 2009 *Post-Doctoral Research Fellow*, Department of Chemistry, Vrije Universiteit Brussel, Brussels, Belgium  
2009 - 2010 *Post-Doctoral Research Fellow*, Department of Peptide Research and Chemical Biology, Institut de Recherches Cliniques de Montréal, Mtl, Canada (P.I. Peter W. Schiller)  
2010 - present *Associate Professor in Bioorganic Chemistry*, Department of Chemistry and Department of Bio-engineering Sciences, Vrije Universiteit Brussel, Brussels, Belgium  
2010 - present *Head of the 'Laboratory for Organic Chemistry'*, Department of Chemistry and Department of Bio-engineering Sciences, Vrije Universiteit Brussel, Brussels, Belgium

## Memberships

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Scientific Organizations      Royal Flemish Chemical Society, American Chemistry Society, European Peptide Society

Scientific Committees      Member of the organizing committee of the *1<sup>st</sup> and 2<sup>nd</sup> Belgian Peptide Group Meeting (Brussels 2012; Ghent 2014; +/- 175 participants)*;  
Member of the organizing committee of the *Medicinal Chemistry Symposium (2013 & 2014)*, organized by the Royal Flemish Chemical Society;  
Member of the Scientific Advisory Committee of the *Frontiers in Medicinal Chemistry Symposium 2015*, organized by the European Federation for Medicinal Chemistry (EFMC), the MediDivision of the American Chemical Society (ACS) and the local Dutch and Belgian organizers: the Medicinal and Bioorganic Chemistry Division of the Royal Flemish Chemical Society (KVCV, Belgium), the Société Royale de Chimie (SRC, Belgium), and the Section Medicinal Chemistry of the Royal Netherlands Chemical Society (KNCV, The Netherlands).

## Peer Review Activities

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Journals      Journal of Medicinal Chemistry, Journal of Peptide Science, Expert Opinion on Drug Discovery, Future Medicinal Chemistry, Organic Letters, ...

Grants      Austrian Research Fund (FWF), Agency for Innovation through Science and Technology (IWT Vlaanderen)

## Invitations at Academic Conferences

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2011      Groupe Français des Peptides et Protéines, Aussois, France  
2012      International Narcotics Research Conference (INRC), Kansas City, MI, USA  
2013      Drug Discovery Chemistry Conference, San Diego, CA, USA  
2013      10<sup>th</sup> Australian Peptide Conference, Penang, Malaysia  
2015      Florida Heterocyclic and Synthetic Conference, Gainesville, FL, USA

## International Cooperation Partners

Name	Country	Institution
Mariana Spetea	Austria	University of Innsbruck, Innsbruck
Peter W. Schiller	Montreal	Clinical Research Institute Montreal, Montreal
Csaba Tomböly	Hungary	Biological Research Center, Szeged

Barbara Przewlocka	Poland	Polish Academy of Sciences, Krakow
Aleksandra Misicka	Poland	Polish Academy of Sciences, Warsaw
Daniel Sejer Pedersen	Copenhagen	University of Copenhagen, Copenhagen
Birger Brodin	Copenhagen	University of Copenhagen, Copenhagen
Bruno Mégarbane	France	Université Paris – Diderot, Paris
Maurits Kleijnen	UK	Imperial College London, London
Rebecca Goss	UK	University of St Andrews, St Andrews
James Gardiner	Australia	Commonwealth Scientific and Industrial Research Organization, Melbourne
Paul Alewood	Australia	University of Queensland, Brisbane
Ray Stevens	USA	The Scripps Research Institute, La Jolla, CA
Brian Kobilka	USA	Stanford University, Stanford

### Publication List

#### Publications: Overview

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- 45 Research articles (peer-reviewed)
- 2 Review articles
- 1 Book chapters
- 53 Abstracts
- 14 Meeting proceedings
- 5 Invited lectures at academic and research institutes
- 11 Oral communications at national and international scientific meetings

#### Publications during the last 5 years

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1. Kleczkowska P., Kosson P., **Ballet S.**, Van den Eynde I., Tsuda Y., Tourwé D., Lipkowski A.W. PK20, a new opioid-neurotensin hybrid peptide that exhibits central and peripheral antinociceptive effects. *Mol. Pain.* 6:86 (2010). doi: 10.1186/1744-8069-6-86.
2. **Ballet S.**, Feytens D., Marczak E.D., Salvadori S., Lazarus L.H., Sasaki Y., Abell A.D., Balboni G., Tourwé D. Novel multiple opioid ligands based on 4-aminobenzazepinone (Aba), azepinoindole (Aia) and tetrahydroisoquinoline (Tic) scaffolds. *Bioorg. Med. Chem. Lett.* 20, 1610-1613 (2010). doi: 10.1016/j.bmcl.2010.01.055.
3. **Ballet S.**, Feytens D., Buysse K., Chung N.N., Lemieux C., Tumati S., Keresztes A., Van Duppen J., Lai J.; Varga E., Porreca F., Schiller P.W., Vanden Broeck J., Tourwé D., Design of novel neurokinin 1 receptor antagonists based on conformationally constrained aromatic amino acids and discovery of a potent chimeric opioid agonist-neurokinin 1 receptor antagonist. *J. Med. Chem.* 2467-2476 (2011). doi: 10.1021/jm1016285.

4. Vandormael B., De Wachter R., Martins J.C., Hendrickx P.M.S., Keresztes A., **Ballet S.**, Mallareddy J.R., Toth F., Toth G., Tourwé D. Asymmetric Synthesis and Conformational Analysis by NMR Spectroscopy and MD of Aba- and alpha-MeAba-Containing Dermorphin Analogues. *Chem. Med. Chem.* 6, 2035-2047 (2011) doi: 10.1002/cmdc.201100314.
5. De Wachter R., de Graaf C., Keresztes A., Vandormael B., **Ballet S.**, Tóth G., Rognan D., Tourwé D. Synthesis, biological evaluation and automated docking of constrained analogs of the opioid peptide H-Dmt-D-Ala-Phe-Gly-NH<sub>2</sub> using the 4- or 5-methyl substituted 4-amino-1,2,3,4-tetrahydro-2-benzazepin-3-one scaffold. *J. Med. Chem.* 54, 6538-6547 (2011). doi: 10.1021/jm2003574.
6. Buysse K., Farard J., Nicolaou A., Vanderheyden P., Vauquelin G., Sejer Pedersen D., Tourwé D., **Ballet S.** Amino Triazolo Diazepines (Ata) as histidine mimetics. *Org. Lett.* 13, 6468-6471 (2011). doi: 10.1021/ol202767k.
7. Guillemyn, K., Kleczkowska P., Novoa A., Vandormael B., Van den Eynde I., Kosson P., Asim M.F., Schiller P.W., Spetea M., Lipkowski A.W., Tourwé D., **Ballet S.** In vivo antinociception of potent mu opioid agonist tetrapeptide analogues and comparison with a compact opioid agonist – NK1 receptor antagonist chimera. *Mol. Brain* 5:4. (2012) doi: 10.1186/1756-6606-5-4.
8. Novoa A., Van Dorpe S., Wynendaele E., Spetea M., Bracke N., Stalmans S., Betti C., Chung N.N., Lemieux C., Zuegg J., Coope, M.A., Tourwé D., De Spiegeleer B., Schiller P.W., **Ballet, S.** Variation of the Net Charge, Lipophilicity, and Side Chain Flexibility in Dmt(1)-DALDA: Effect on Opioid Activity and Biodistribution. *J. Med. Chem.* 55, 9549-9561. (2012) doi: 10.1021/jm3008079.
9. Frankiewicz L., Betti C., Tourwé D., Jaquo, Y., **Ballet S.** Stabilization of a short alfa-helical VIP fragment by side chain-to-side-chain cyclization: A comparison of common cyclization motifs by circular dichroism. *J. Pept. Sci.* 19, 423-432. (2013) doi: 10.1002/psc.2515.
10. Kleczkowska P., Engin B., Lesniak A., Kosso, P., Van den Eynde I., **Ballet S.**, Benyhe S., Tourwé D., Lipkowski A.W. Identification of Dmt-DLys-Phe-Phe-OH as a highly antinociceptive tetrapeptide metabolite of the opioid-neurotensin hybrid peptide PK20. *Pharmacol. Reports.* 65, 836-846. (2013) doi: [10.1016/S1734-1140\(13\)71064-8](https://doi.org/10.1016/S1734-1140(13)71064-8).
11. Jida M., Betti C., Urbanczyk-Lipkowska Z., Tourwé D., **Ballet S.** Highly Diastereoselective Synthesis of 1-Carbamoyl-4-aminoindolazepinone Derivatives via the Ugi Reaction. *Org. Lett.* 15, 5866-5869. (2013) doi: 10.1021/ol402940x.
12. Van Bouchaute P., Novoa A., **Ballet S.**, Rogens S., Angenon G. Regulatory mechanisms after short-term and long-term perturbed lysine biosynthesis in the aspartate pathway : The need for

- isogenes in «*Arabidopsis thaliana*». *Physiologia Plantarum*. 149, 449-460. (2013) doi: 10.1111/ppl.12053.
13. Kleczkowska P., Lipkowski A.W., Tourwé D., **Ballet S.** Hybrid opioid/non-opioid ligands in pain research. *Curr. Pharm. Des.* 19, 7435-7450. (2013) doi: [10.2174/138161281942140105165646](https://doi.org/10.2174/138161281942140105165646).
  14. Ye L., **Ballet S.**, Hildebrand F., Laus, G., Guillemyn K., Raes J., Matthijs S., Martins J., Cornelis P. A combinatorial approach to the structure elucidation of a pyoverdine siderophore produced by a *Pseudomonas putida* isolate and the use of pyoverdine as a taxonomic marker for typing *P. putida* subspecies. *Biomaterials*. 26, 561-575. (2013) doi: 10.1007/s10534-013-9653-z.
  15. **Ballet S.**, Betti C., Novoa A., Tomboly Cs., Uhd Nielsen C., Helms H.C., Lesniak A., Kleczkowska P., Chung N.N., Lipkowski A.W., Brodin, B. Tourwé, D. Schiller P.W. In Vitro Membrane Permeation Studies and in Vivo Antinociception of Glycosylated Dmt1-DALDA Analogues. *ACS Med. Chem. Lett.* 5, 352-357. (2014) doi: 10.1021/ml4004765.
  16. Ye L.M., Cornelis P., Guillemyn K., **Ballet S.**, Christophersen C., Hammerich O. Structure Revision of N-mercapto-4-formylcarbostyryl produced by *pseudomonas fluorescens* G308 to 2-(2-hydroxyphenyl)thiazole-4-carbaldehyde [aeruginaldehyde]. *Nat. Prod. Commun.* 9, 789-794. (2014) doi: c00f54ef-a5bf-4671-8853-03609dd2b671.
  17. Smith D.R.M., Willemse T., Gkotski D.S., Schepens W., Maes B.U.W., **Ballet S.**, Goss R.J.M. The first one-pot synthesis of L-7-iodotryptophan from 7-iodoindole and serine, and an improved synthesis of other L-7-halotryptophans. *Org. Lett.* 16, 2622-2625. (2014) doi: 10.1021/ol5007746.
  18. Jida M., Betti C., Schiller P.W., Tourwé D., **Ballet S.** One-pot isomerization – Cross metathesis – reduction (ICMR) Synthesis of lipophilic tetrapeptides. *ACS Comb. Sci.* 16, 342-351. (2014) doi: 10.1021/co500020a.
  19. Schurgers B., Brigou B., Urbanczyk-Lipkowska Z., Tourwé D., **Ballet S.**, De Proft F., Van Lommen G., Verniest G. Synthesis of Fused 3-Aminoazepinones via Trapping of a New Class of Cyclic Seven-Membered Allenamides with Furan. *Org. Lett.* 16, 3712-3715. (2014) doi: 10.1021/ol501529z.
  20. Barlow T.M.A., Jida M., Tourwé D., **Ballet S.** Efficient synthesis of conformationally constrained, amino-triazoloazepinone-containing di- and tripeptides via a one-pot Ugi-Huisgen tandem reaction. *Org. Biomol. Chem.* 12, 6986-6989. (2014) doi: 10.1039/C4OB01381F.
  21. Jida M., Tourwé D., **Ballet S.** Highly stereoselective one-pot construction of trisubstituted tetrahydro-diketopiperazines: A synthetic route towards cialis analogues. *RSC Advances*. 4, 38159-38163. (2014) doi: 10.1039/C4RA05981F.
  22. Ye L., Hildebrand F., Dingemans J., **Ballet S.**, Laus G., Matthijs S., Berendsen R., Cornelis P. Draft Genome Sequence of a *Pseudomonas putida* W15Oct28 Strain with Antagonistic Activity to

- Gram-Positive and Pseudomonas sp Pathogens. *Plos ONE*. 9, e110038. (2014) doi: 10.1371/journal.pone.0110038.
23. Van der Poorten O., Fehér K., Buysse K., Feytens D., Zoi I., Schwartz S.D., Martins J.C., Cai M., Hruby V.J.; **Ballet S.** Azepinone-containing tetrapeptide analogues of melanotropin lead to selective hMC4R agonists and hMC5R antagonist. *ACS Med. Chem. Lett.* 6, 192-197. (2015) doi: 10.1021/ml500436s.
24. Guillemyn K., Kleczkowska P., Lesniak A., Dyniewicz J., Van der Poorten O., Van den Eynde I., Keresztes K., Varga E., Lai J., Porreca F., Chung N.N., Lemieux C., Mika J., Rojewska E., Makuch W., Van Duppen J., Przewlocka B., Vanden Broeck J., Lipkowski A.W., Schiller P.W., Tourwé D., **Ballet S.** Synthesis and biological evaluation of compact, conformationally constrained bifunctional opioid agonist – Neurokinin 1 antagonist peptidomimetics. *Eur. J. Med. Chem.* 92, 64-77. (2015) doi: 10.1016/j.ejmech.2014.12.033.
25. Bibian M., Mangelschots J., Gardiner J., Waddington L., Acevedo M.M.D., De Geest B., Van Mele B., Madder A., Hoogenboom R., **Ballet S.** Rational Design of hexapeptide hydrogelator for controlled-release drug delivery. *J. Mater. Chem. B* 3, 759-765. (2015) doi: 10.1039/C4TB01294A.
26. Fenalti G., Zatspein N.A., Betti C., Giguere P., Han G.W., Ishchenko A., Liu W., Guillemyn K., Zhang H., James D., Wang D., Weierstall U., Spence J.C.H., Boutet S., Messerschmidt M., Williams G.J. Gati C., Yefanov O.M., White T.A., Oberthuer D., Metz M., Yoon C.H., Barty A., Chapman H.N., Basu S., Coe J., Conrad C.E., Fromme R., Fromme P., Tourwé D., Schiller P.W., Roth B.L., **Ballet S.**, Katritch V., Stevens R.C., Cherezov V. Structural basis for bifunctional peptide recognition at human  $\delta$ -opioid receptor. *Nat. Struct. Mol. Biol.* 22, 265-268. (2015) doi: 10.1038/nsmb.2965.
27. Verlinden, S.; Geudens, N.; Martins, J.C.; Tourwé, D.; Ballet, S.; Verniest, G. Oxidative a,w-diyne coupling as an approach towards novel peptidic macrocycles. *Org. Biomol. Chem.*, 13, 9398-9404 (2015) doi: 10.1039/C5OB01153A.
28. Willemse, T.; Van Imp, K.; Goss, R.J.M.; Van Vlijmen, H.W.T.; Schepens, W.; Maes, B.U.W.; Ballet, S. Suzuki-Miyaura Diversification of Amino Acids and Dipeptides in Aqueous Media. *ChemCatChem*, 7, 2055-2070 (2015) doi: 10.1002/cctc.201500190.
29. Jida, M.; Van der Poorten, O.; Guillemyn, K.; Urbanczyk-Lipkowska, Z.; Tourwé, D.; Ballet, S. T3P-Promoted, Mild, One-Pot Synthesis of Constrained Polycyclic Lactam Dipeptide Analogues via Stereoselective Pictet-Spengler and Meyers Lactamization Reactions. *Org. Lett.* Asap 2015 doi: 10.1021/acs.orglett.5b02145

30. Ballet, S.; Guillemyn, K.; Van der Poorten, O.; Schurgers, B.; Verniest, G.; Tourwé, D. Azpinone-Constrained Amino Acids in Peptide and Peptidomimetic Design. *Top. Heterocycl. Chem.*, in press.

### 10 Most Important Publications

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1. Buysse K., Farard J., Nicolaou A., Vanderheyden P., Vauquelin G., Sejer Pedersen D., Tourwé D., **Ballet S.** Amino Triazolo Diazepines (Ata) as histidine mimetics. *Org. Lett.* 13, 6468-6471 (2011). doi: 10.1021/ol202767k.
2. **Ballet S.**, Misicka A., Kosson P., Lemieux C., Chung N.N., Schiller P.W., Lipkowski A.W., Tourwé D. Blood-Vrain Barrier penetration by Two Dermorphin Tetrapeptide Analogues: Role of Lipophilicity vs. Structural Flexibility. *J. Med. Chem.* 51, 2571-2574. (2008) doi: 10.1021/jm701404s.
3. **Ballet S.**, Feytens D., Buysse K., Chung N.N., Lemieux C., Tumati S., Keresztes A., Van Duppen J., Lai J.; Varga E., Porreca F., Schiller P.W., Vanden Broeck J., Tourwé D., Design of novel neurokinin 1 receptor antagonists based on conformationally constrained aromatic amino acids and discovery of a potent chimeric opioid agonist-neurokinin 1 receptor antagonist. *J. Med. Chem.* 2467-2476 (2011). doi: 10.1021/jm1016285.
4. Guillemyn, K., Kleczkowska P., Novoa A., Vandormael B., Van den Eynde I., Kosson P., Asim M.F., Schiller P.W., Spetea M., Lipkowski A.W., Tourwé D., **Ballet S.** In vivo antinociception of potent mu opioid agonist tetrapeptide analogues and comparison with a compact opioid agonist – NK1 receptor antagonist chimera. *Mol. Brain* 5:4. (2012) doi: 10.1186/1756-6606-5-4.
5. Jida M., Betti C., Urbanczyk-Lipkowska Z., Tourwé D., **Ballet S.** Highly Diastereoselective Synthesis of 1-Carbamoyl-4-aminoindolazepinone Derivatives via the Ugi Reaction. *Org. Lett.* 15, 5866-5869. (2013) doi: 10.1021/ol402940x.
6. Novoa A., Van Dorpe S., Wynendaele E., Spetea M., Bracke N., Stalmans S., Betti C., Chung N.N., Lemieux C., Zuegg J., Coope, M.A., Tourwé D., De Spiegeleer B., Schiller P.W., **Ballet, S.** Variation of the Net Charge, Lipophilicity, and Side Chain Flexibility in Dmt(1)-DALDA: Effect on Opioid Activity and Biodistribution. *J. Med. Chem.* 55, 9549-9561. (2012) doi: 10.1021/jm3008079.
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8. Guillemyn K., Kleczkowska P., Lesniak A., Dyniewicz J., Van der Poorten O., Van den Eynde I., Keresztes K., Varga E., Lai J., Porreca F., Chung N.N., Lemieux C., Mika J., Rojewska E.,

- Makuch W., Van Duppen J., Przewlocka B., Vanden Broeck J., Lipkowski A.W., Schiller P.W., Tourwé D., **Ballet S.** Synthesis and biological evaluation of compact, conformationally constrained bifunctional opioid agonist – Neurokinin 1 antagonist peptidomimetics. *Eur. J. Med. Chem.* 92, 64-77. (2015) doi: 10.1016/j.ejmech.2014.12.033.
9. Bibian M., Mangelschots J., Gardiner J., Waddington L., Acevedo M.M.D., De Geest B., Van Mele B., Madder A., Hoogenboom R., **Ballet S.** Rational Design of hexapeptide hydrogelator for controlled-release drug delivery. *J. Mater. Chem. B.* 3, 759-765. (2015) doi: 10.1039/C4TB01294A.
10. Fenalti G., Zatschin N.A., Betti C., Giguere P., Han G.W., Ishchenko A., Liu W., Guillemyn K., Zhang H., James D., Wang D., Weierstall U., Spence J.C.H., Boutet S., Messerschmidt M., Williams G.J. Gati C., Yefanov O.M., White T.A., Oberthuer D., Metz M., Yoon C.H., Barty A., Chapman H.N., Basu S., Coe J., Conrad C.E., Fromme R., Fromme P., Tourwé D., Schiller P.W., Roth B.L., **Ballet S.**, Katritch V., Stevens R.C., Cherezov V. Structural basis for bifunctional peptide recognition at human  $\delta$ -opioid receptor. *Nat. Struct. Mol. Biol.* 22, 265-268. (2015) doi: 10.1038/nsmb.2965.