CURRICULUM VITAE

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1. EDUCATION

Year	Degree	Thesis	Institution
1985-1991	B. Sc. (Chemistry)	Synthesis of Schiff bases of heterocyclic amino-derivatives and study of their reactions with methyl-ketene	Aristotle University Greece
1991-1996	Ph.D. (Organic Chemistry)	Synthesis and study of properties of new compounds of hypervalent iodine	Aristotle University Greece

2. MILITARY SERVICE

12/1996-03/1998 Analytical Chemist, Sergeant, quality control of fuels and lubricants (ASTM), Fighter Aircrafts, Greek Air Force, Laboratory of Petroleum Distribution Command, Larisa, Greece.

3. POSTDOCTORAL TRAINING

04/1998-03/1999 Postdoctoral Fellow (Medicinal Chemistry), Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, Athens, Greece. Supervisor: Dr. Demetris P. Papahatjis.

03/1999-08/2003 Postdoctoral Fellow (Medicinal Chemistry), Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, Storrs, CT. Supervisor: Dr. Alexandros Makriyannis.

4. APPOINTMENTS

09/2003-09/2004 Research Assistant Professor, Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, Storrs, CT.

10/2004-07/2005 Senior Research Scientist, Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, Boston, MA.

08/2005-01/2008 Research Assistant Professor, Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, Boston, MA.

02/2008-04/2010 Senior Research Scientist, Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, Athens, Greece, and Center for Drug Discovery, Northeastern University, Boston, MA (joint appointment).

10/2008-04/2010 Adjunct Professor, Center for Drug Discovery, Northeastern University, Boston, MA.

05/2010-present Research Associate Professor, Center for Drug Discovery, Department of Pharmaceutical Sciences, Northeastern University, Boston, MA.

5. PUBLICATIONS (peer-reviewed; Citations: 1355, h-index: 20, i10-index: 38, as of December 2018, via Google Scholar). *Indicates my role as corresponding author)

1. **Spyros Nikas**, Nestor Rodios, Aris Terzis, Anastasios Varvoglis. The reaction between phenyliodonium bis(phenylsulfony)methanide and pyrrolidine. *Phosphorus, Sulfur Silicon Relat. Elem*., **1994**, *90*, 285-288.

2. Christopher Glidewell, George Ferguson, **Spyros Nikas**, Anastasios Varvoglis. Accurate redetermination of diiodobis(phenylsulfony)methane, $(PhSO_2)_2CI_2$. *Acta Crystallographica*., **1996**, *C52*, 1488-1490.

3. **Spyros Nikas**, Nestor Rodios, Aris Terzis, Catherine Raptopoulou, Anastasios Varvoglis. Formation and crystal structure of an exocyclic enol δ-lactone obtained from dimedone and trimethylsilylethynyl phenyliodonium triflate. *J. Heterocyclic Chem*., **1996**, *33*, 997-999.

4. **Spyros Nikas**, Nestor Rodios, Anastasios Varvoglis, Aristidis Terzis, Catherine Raptopoulou. Reactivity of cyano (phenyl)iodonium triflate towards unsaturated hydrocarbons in wet acetonitrile. *Chimica Chronica, New Series*. **1997**, *26*, 535-544.

5. **Spyros Nikas**, Nestor Rodios, Anastasios Varvoglis. The reaction of trimethylsilylethynyl (phenyl)iodonium triflate with some phenolates. Formation of substitution and sp^2C-H insertion products. *Molecules*., **2000**, *5*, 1182-1186.

6. Demetris P. Papahatjis, **Spyros Nikas**, Andrew Tsotinis, Margarita Vlachou, Alexandros Makriyannis. A new ring-forming methodology for the synthesis of conformationally constrained bioactive molecules. *Chem. Lett*., **2001**, *3*, 192-193.

7. **Spyros Nikas**, Ganesh Thakur, Alexandros Makriyannis. A convenient and effective synthesis of 3-(3,5-dimethoxyphenyl)propanal. *Synth. Comm*., **2002**, *32*, 1751-1756.

8. **Spyros P. Nikas**, Ganesh A. Thakur, Alexandros Makriyannis. Synthesis of side chain specifically deuterated (-)-Δ^9-tetrahydrocannabinols. *J. Labelled Compd. Radiopharm*., **2002**, *45*, 1-12.

9. **Spyros P. Nikas**, Ganesh A. Thakur, Alexandros Makriyannis. Regiospecifically deuterated (-)-Δ^9-tetrahydrocannabivarins. *J. Chem. Soc. Perkin Trans. 1*, **2002**, 2544-2548.

10. Demetris P. Papahatjis, **Spyros P. Nikas**, Thanos Andreou, Alexandros Makriyannis. Novel 1′,1′-chain substituted Δ^8-tetrahydrocannabinols. *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 3583-3586.

11. Demetris P. Papahatjis, **Spyros P. Nikas**, Therapia Kourouli, Ravi Chari, Wei Xu, Roger G. Pertwee, Alexandros Makriyannis. Pharmacophoric requirements for the cannabinoid side chain. Probing the cannabinoid receptor subsite at C1′. *J. Med. Chem*., **2003**, *46*, 3221-3229.

12. Jianxin Guo, Spiro Pavlopoulos, Xiaoyu Tian, Dai Lu, **Spyros P. Nikas**, De-Ping Yang, Alexandros Makriyannis. Phospholipid model membrane systems for conformational study of lipophilic ligands by solution NMR. *J. Med. Chem*., **2003**, *46*, 4838-4846.

13. **Spyros P. Nikas**, Jolanta Grzybovska, Demetris P. Papahatjis, Avgui Charalambous, Ali R. Banijamali, Ravi Chari, Pusheng Fan, Therapia Kourouli, Sonyuan Lin, Albert J. Nitowski, Gilbert Marciniak, Yan Guo, Xiuyan Li, Chia-Lin J. Wang, Alexandros Makriyannis. The role of halogen substitution in classical cannabinoids. A CB1 pharmacophore model. *AAPSJ*. **2004**, *6*(4), e30 (http://www.aapsj.org).

14. Ganesh A. Thakur, **Spyros P. Nikas**, Chen Li, Alexandros Makriyannis. Structural requirements for cannabinoid receptor probes. In *Handbook of Experimental Pharmacology*. **2005**, Vol. 168 (Cannabinoids, Pertwee R. G., ed), pp. 209-246. Springer-Verlag.

15. Ganesh A. Thakur, **Spyros P. Nikas**, Alexandros Makriyannis. CB1 selective ligands. *Mini-Rev. Med. Chem.*, **2005**, *5*, 631-640.

16. Ganesh A. Thakur, **Spyros P. Nikas**, Richard Duclos, Alexandros Makriyannis. Synthetic methods for cannabinergic ligands. In *Marijuana and cannabinoid research: Methods and protocols* (Onaivi E. S., editor). **2005**, pp. 113-148. Humana Press Inc.

17. Spiro Pavlopoulos, Ganesh A. Thakur, **Spyros P. Nikas**, Alexandros Makriyannis. Cannabinoid receptors as therapeutic targets. *Curr. Pharm. Des.*, **2006**, *12*, 1751-1769.

18. Andrew Tsotinis, Margarita Vlachou, Theodora Calogeropoulou, Demetris P. Papahatjis, **Spyros P. Nikas**, Peter J. Garratt, Vincent Piccio, Stefan Vonhoff, Kathryn Davidson, Muy-Teck Teh, David Sugden. Mapping the melatonin receptor. 7. Subtype selective ligands based on β-substituted *N*-acyl-5-methoxytryptamines and β-substituted *N*-acyl-5-methoxy-1-methyltryptamines. *J. Med. Chem*., **2006**, *49*, 3509-3519.

19. Andrew Tsotinis, Margarita Vlachou, Demetris P. Papahatjis, **Spyros P. Nikas**, David Sugden. An efficient synthesis of simple *β,β′*-cyclobisalkylated melatoninergic phenylalkylamides. *Lett. Org. Chem*., **2007**, *4*, 92-95.

20. Serdar Durdagi, Agnes Kapou, Therapia Kourouli, Thanos Andreou, **Spyros P. Nikas**, Victoria R. Nahmias, Demetris P. Papahatjis, Manthos G. Papadopoulos, Thomas Mavromoustakos. The application of 3D-QSAR studies for novel cannabinoid ligands substituted at the C1' position of the alkyl side chain on the structural requirements for binding to CB1 and CB2 receptors. *J. Med. Chem.*, **2007**, *50*, 2875-2885.

21. **Spyros P. Nikas***, Ganesh A. Thakur, Damon Parish, Shakiru O. Alapafuja, Marilyn A. Huestis, Alexandros Makriyannis*. A concise methodology for the synthesis of (-)-Δ^9-tetrahydrocannabinol and (-)-Δ^9-tetrahydrocannabivarin metabolites and their regiospecifically deuterated analogs. *Tetrahedron*, **2007**, *63*, 8112-8123.

22. Demetris P. Papahatjis, Victoria R. Nahmias, **Spyros P. Nikas**, Thanos Andreou, Shakiru O. Alapafuja, Andrew Tsotinis, Jianxin Guo, Pusheng Fan, Alexandros Makriyannis. C1´-cycloalkyl side chain pharmacophore in tetrahydrocannabinols. *J. Med. Chem.*, **2007**, *50*, 4048-4060.

23. Shakiru O. Alapafuja, **Spyros P. Nikas***, Vidyanand G. Shukla, Ioannis Papanastasiou, Alexandros Makriyannis*. Microwave assisted synthesis of sodium sulfonates precursors of sulfonyl chlorides and fluorides. *Tetrahedron Lett.* **2009**, *50*, 7028-7031.

24. Demetris P. Papahatjis, Victoria R. Nahmias, **Spyros P. Nikas**, Marion Schimpgen, Alexandros Makriyannis. Design and synthesis of (13*S*)-methyl substituted arachidonic acid analogs: Templates for novel endocannabinoids. *Chem. Eur. J.*, **2010**, *16*, 4091-4099.

25. **Spyros P. Nikas***, Shakiru O. Alapafuja, Ioannis Papanastasiou, Carol A. Paronis, Vidyanand G. Shukla, Demetris P. Papahatjis, Anna L. Bowman, Aneetha Halikhedkar, Xiuwen Han, Alexandros Makriyannis*. Novel 1′,1′-chain substituted hexahydrocannabinols: 9*β*-hydroxy-3-(1-hexyl- cyclobut-1-yl)hexahydrocannabinol (AM2389) a highly potent cannabinoid receptor 1 (CB1) agonist. *J. Med. Chem.*, **2010**, *53*, 6996-7010.
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28. Alexandros Makriyannis, **Spyros P. Nikas**. Aspirin triggered metabolites of EFAs. *Chem. Biol*. **2011**, *18*, 1208-1209.

29. Torbjörn U.C. Järbe, Sherrica Tai, Brian J. LeMay, **Spyros P. Nikas**, Alexander Zvonok, Alexandros Makriyannis. AM2389, a high-affinity, *in vivo* potent, CB1 receptor selective ligand as evidenced by drug discrimination in rats and hypothermia testing in mice. *Psychopharmacology*, **2012**, *220*, 417-426.

30. Mohammad A. Bashashati, Martin A. Storr, **Spyros P. Nikas**, JodiAnne T. Wood, Grzegorz Godlewski, Jie Liu, Winnie Ho, Catherine M. Keenan, Hong Zhang, Shakiru O. Alapafuja, Benjamin F. Cravat, Beat Lutz, Ken Mackie, George Kunos, Kamala D. Patel, Alexandros Makriyannis, Joseph S. Davison, Keith A. Sharkey. Inhibiting fatty acid amide hydrolase normalizes endotoxin-induced enhanced gastrointestinal motility in mice. *Br. J. Pharmacol*. **2012**, *165*, 1556-1571.

31. **Spyros P. Nikas***, Marsha D'Souza, Alexandros Makriyannis*. Enantioselective synthesis of (10*S*)- and (10*R*)-methyl-anandamides. *Tetrahedron*, **2012**, *68*, 6329-6337.

32. Dai Lu, **Spyros P. Nikas**, Xiu-Wen Han, Damon A. Parrish, Alexandros Makriyannis. Synthesis and characterization of a compact tricyclic resorcinol from (+)- and (-)-3-pinanol. *Tetrahedron Lett*. **2012**, *53*, 4636-4638.

33. Carol A. Paronis, **Spyros P. Nikas**, Vidyanand G. Shukla, Alexandros Makriyannis. Δ^9-Tetrahydrocannabinol acts as a partial agonist/antagonist in mice. *Behav. Pharmacol*., **2012**, *23*, 802-805.

34. Shakiru O. Alapafuja, **Spyros P. Nikas***, Indu T. Bharathan, Vidyanand G. Shukla, Mahmoud L. Nasr, Anna L. Bowman, Nikolai Zvonok, Jing Li, Xiaomeng Shi, John R. Engen, Alexandros Makriyannis*. Sulfonyl fluoride inhibitors of fatty acid amide hydrolase. *J. Med. Chem*., **2012**, *55*, 10074-10089.

35. Ozge Gunduz-Cinar, Kathryn P. MacPherson, Resat Cinar, Joyonna Gamble-George, Karen Sugden, Benjamin Williams, Teniel S. Ramikie, Adam X. Gorka, Shakiru O. Alapafuja, **Spyros P. Nikas**, Alexandros Makriyannis, Richie Poulton, Sachin Patel, Ahmad R. Hariri, Avshalom Caspi, Terrie E. Moffitt, George Kunos, Andrew Holmes. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. *Mol. Psychiatry* **2013**, *18*, 813-823.

36. Carol A. Paronis, Ganesh A. Thakur, Shama Bajaj, **Spyros P. Nikas**, V. Kiran Vemuri, Alexandros Makriyannis, Jack Bergman. Diuretic effects of cannabinoids. *J. Pharm. Exp. Ther*. **2013**, *344*, 8-14.

37. Brian D. Kangas, Marcus S. Delatte, V. Kiran Vemuri, Ganesh A. Thakur, **Spyridon P. Nikas**, Kumara V. Subramania, Vidyanand G. Shukla, Alexandros Makriyannis, Jack Berkman. Cannabinoid discrimination and antagonism by CB1 neutral and inverse agonist antagonists. *J. Pharm. Exp. Ther*. **2013**, *344*, 561-567.

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40. Rishi Sharma, **Spyros P. Nikas***, Carol A. Paronis, JodiAnne T. Wood, Aneetha Halikhedkar, Jason Jianxin Guo, Ganesh A. Thakur, Shashank Kulkarni, Othman Benchama, Jimit Girish Raghav, Roger S. Gifford, Torbjörn U.C. Järbe, Jack Bergman, Alexandros Makriyannis*. Controlled-deactivation cannabinergic ligands. *J. Med. Chem*. **2013**, *56*, 10142-10157.
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41. Ioannis Papanastasiou, Andrew Tsotinis, Nicolas Kolocouris, **Spyros P. Nikas**, Alexandre Vamvakides. New aminoadamantane derivatives with antiproliferative activity. *Med. Chem. Res*. **2014**, *23*, 1966-1975.

42. Rishi Sharma, **Spyros P. Nikas***, Jason Jianxin Guo, Srikrishnan Mallipeddi, JodiAnne T. Wood, Alexandros Makriyannis*, C-Ring cannabinoid lactones: A novel cannabinergic chemotype. *ACS Med. Chem. Lett*. **2014**, *5*, 400-404.
This work was selected for: a) the ACS Editors' Choice collection, b) inclusion in the Chemical & Engineering News, 2014, *92*(5), February 3, and c) advertisement on the Website of the National Institutes of Health (NIDA).

43. **Spyros P. Nikas**, Rishi Sharma, Carol A. Paronis, Shashank Kulkarni, Ganesh A. Thakur, Dow Hurst, JodiAnne T. Wood, Roger S. Gifford, Girija Rajarshi, Yingpeng Liu, Jimit Girish Raghav, Jason Jianxin Guo, Torbjörn U.C. Järbe, Patricia H. Reggio, Jack Bergman, Alexandros Makriyannis. Probing the carboxyester side chain in controlled deactivation (-)-Δ^8-tetrahydrocannabinols. *J. Med. Chem*. **2015**, *58*, 665-681.

44. Catherine M. Keenan, Martin A. Storr, Ganesh A. Thakur, JodiAnne T. Wood, James Wager-Miller, Alex Straiker, Marsha R. Eno, **Spyros P. Nikas**, Mohammad A. Bashashati, Huangming Hu, Ken Mackie, Alexandros Makriyannis, Keith A. Sharkey. AM841, a covalent cannabinoid ligand, powerfully slows gastrointestinal motility in normal and stressed mice in a peripherally-restricted manner. *Br. J. Pharmacol*. **2015**, *172*, 2406-2418.

45. Erin L. Shelnut, **Spyros P. Nikas**, David F. Finnegan, Nan Chiang, Charles N. Serhan, Alexandros Makriyannis. Design and synthesis of novel prostaglandin E_2 ethanolamide and glycerol ester probes for the putative prostamide receptor(s). *Tetrahedron Lett*. **2015**, *56*, 1411-1415.

46. David F. Finnegan, Erin L. Shelnut, **Spyros P. Nikas**, Nan Chiang, Charles N. Serhan, Alexandros Makriyannis. Novel tail and head group prostamide probes. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 1228-1231.

47. Shalley N. Kudalkar, **Spyros P. Nikas**, Philip Kingsley, Shu Xu, James J. Galligan, Carol A. Rouzer, Lipin Ji, Marsha R. Eno, Alexandros Makriyannis, Lawrence J. Marnett. 13-Methyl-arachidonic acid is a positive allosteric modulator of endocannabinoid oxygenation by cyclooxygenase-2. *J. Biol. Chem*. **2015**, *290*, 7897-7909.

48. Go Ogawa, Marcus A. Tius, Han Zhou, **Spyros P. Nikas**, Aneetha Halikhedkar, Srikrishnan Mallipeddi, Alexandros Makriyannis. 3'-Functionalized adamantyl cannabinoid receptor probes. *J. Med. Chem*. **2015**, *58*, 3104-3116.

49. Sherrica Tai, **Spyros P. Nikas**, Vidyanand G. Shukla, Kiran Vemuri, Alexandros Makriyannis, Torbjörn U. C. Järbe. Cannabinoid withdrawal in mice: inverse agonist vs neutral antagonist. *Psychopharmacology*, **2015**, *232*, 2751-2761.

50. Leigh V. Panlilio, Eric B. Thorndike, **Spyros P. Nikas**, Shakiru O. Alapafuja, Tiziano Bandiera, Benjamin F. Cravatt, Alexandros Makriyannis, Daniele Piomelli, Steven R. Goldberg, Zuzana Justinova. Effects of fatty acid amide hydrolase (FAAH) inhibitors on working memory in rats. *Psychopharmacology*, **2016**, *233*, 1879-1888.

51. Brian D. Kangas, Michael Z. Leonard, Vidyanand G. Shukla, Shakiru O. Alapafuja, **Spyros P. Nikas**, Alexandros Makriyannis, Jack Bergman. Comparisons of Δ^9-tetrahydrocannabinol and anandamide on a battery of cognition-related behavior in nonhuman primates. *J. Pharm. Exp. Ther*. **2016**, *357*, 125-133.

52. David S. Jacobs, Stephen J. Kohut, Shan Jiang, **Spyros P. Nikas**, Alexandros Makriyannis, Jack Bergman. Acute and chronic effects of cannabidiol on Δ^9-tetrahydrocannabinol (Δ^9-THC)-induced disruption in stop signal task. *Exp. Clin. Psychopharmacol*. **2016**, *24*, 320-330.

53. Shashank Kulkarni, **Spyros P. Nikas***, Rishi Sharma, Shan Jiang, Carol A. Paronis, Michael Z. Leonard, Bin Zhang, Chandrashekhar Honrao, Srikrishnan Mallipeddi, Jimit Girish Raghav, Othman Benchama, Torbjörn U.C. Järbe, Jack Bergman, Alexandros Makriyannis*. Novel C-ring-hydroxy-substituted controlled deactivation cannabinergic analogues. *J. Med. Chem*. **2016**, *59*, 6903-6919.

54. Thanh C. Ho, Naoyuki Shimada, Marcus A. Tius, **Spyros P. Nikas**, Wen Zhang, Alexandros Makriyannis C1'-Azacycloalkyl hexahydrocannabinols. *J. Org. Chem*., **2017**, *82*, 7839-7849.

55. Tian Hua, Kiran Vemuri[§], **Spyros P. Nikas[§]**, Robert B. Laprairie, Yiran Wu, Lu Qu, Mengchen Pu, Anisha Korde, Shan Jiang, Jo-Hao Ho, Gye Won Han, Kang Ding, Xuanxuan Li, Haiguang Liu, Michael A. Hanson, Suwen Zhao, Laura M. Bohn, Alexandros Makriyannis, Raymond C. Stevens, Zhi-Jie Liu. Crystal structures of agonist-bound human cannabinoid receptor CB1. *Nature*, **2017**, *547*, 468-471. **[§]**these authors contributed equally to this work.

56. Karen L. G. Farizatto, Sara A. McEwan, Vinogran Naidoo, **Spyros P. Nikas**, Vidyanand G. Shukla, Michael F. Almeida, Aaron Byrd, Heather Romine, David A. Karanian, Alexandros Makriyannis, Ben A. Bahr. Inhibitor of endocannabinoid deactivation protects against in vitro and in vivo neurotoxic effects of paraoxon. *J. Mol. Neurosci*., **2017**, *63*, 115-122, doi:10.1007/s12031-017-0963-4.

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58. Sally Miller, Shashank Kulkarni, Alex Ciesielski, **Spyros P. Nikas**, Ken Mackie, Alexandros Makriyannis, Alex Straiker. Controlled-deactivation CB1 receptor ligands as a novel strategy to lower intraocular pressure. *Pharmaceuticals (Basel)*, **2018**, *11(2)*, 50; doi:10.3390/ph11020050; PMID: 29786643.

59. Christos Iliopoulos-Tsoutsouvas, Rohit N. Kulkarni, Alexandros Makriyannis, **Spyros P. Nikas***. Fluorescent probes for G-protein coupled receptor drug discovery. *Expert Opin. Drug Discov*. **2018**, *13*, 933-947.

60. Yingpeng Liu,[§] Lipin Ji,[§] Marsha Eno, Shalley Kudalkar, Ai-ling Li, Marion Schimpgen, Othman Benchama, Paula Morales, Shu Xu, Dow Hurst, Simiao Wu, Khadijah A. Mohammad, JodiAnne T. Wood, Nikolai Zvonok, Demetris P. Papahatjis, Han Zhou, Chandrashekhar Honrao, Ken Mackie, Patricia Reggio, Andrea G. Hohmann, Lawrence J. Marnett, Alexandros Makriyannis*, **Spyros P. Nikas***. **(***R*)-*N*-(1-Methyl-2-hydroxyethyl)-13-(*S*)-methyl-arachidonamide (AMG315): A novel chiral potent endocannabinoid ligand with stability to metabolizing enzymes. [§]These authors contributed equally to this work. *J. Med. Chem*. **2018**, *61*, 8639-8657. PMID: 30196704.
<u>This work was advertised for one month on the Journal's Webpage</u>.

61. Girish R. Chopda, **Spyros P. Nikas**, Rishi Sharma, Shashank Kulkarni, Alexandros Makriyannis, Carol A. Paronis. Cannabinoid-induced lower lip retraction in rats. *Psychopharmacology*, **2018**, https://doi.org/10.1007/s00213-018-5125-z.

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63. Gaitán AV, Wood JT, Solomons NW, Donohue JA, Ji L, Liu Y, **Nikas SP**, Zhang F, Allen LH, Makriyannis A, Lammi-Keefe CJ. Endocannabinoid Metabolome Characterization of Breast Milk from Guatemalan Women Living in the Western Highlands. *Curr. Dev. Nutr*., **2018**, submitted.

6. PATENTS

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This invention led to pre-clinical development (Pain Program, ENDO-PHARMACEUTICALS, Malvern, PA)

In the same family
(a) Alexandros Makriyannis, **Spyridon P. Nikas**, Atmaram D. Khanolkar. EP No 1414775.
(b) Alexandros Makriyannis, **Spyridon P. Nikas**, Atmaram D. Khanolkar. AU No 2004200538.
(c) Alexandros Makriyannis, **Spyridon P. Nikas**, Atmaram D. Khanolkar. CA No. 2452881.
(d) Alexandros Makriyannis, **Spyridon P. Nikas**, Atmaram D. Khanolkar. JP No. 2003-511769.

2. Alexandros Makriyannis, **Spyridon P. Nikas**, Atmaram D. Khanolkar. Bicyclic and Tricyclic Cannabinoids. US Patent No. 7057076, **2006**.

3. Alexandros Makriyannis, **Spyridon P. Nikas**, Atmaram D. Khanolkar. Novel bicyclic and tricyclic cannabinoids. Continuation in part, US Patent No. 7285683, **2007**.
This invention led to pre-clinical development (Multiple Sclerosis Program, BIOGEN, Cambridge, MA)

4. Alexandros Makriyannis, **Spyridon P. Nikas**, Atmaram D. Khanolkar, Ganeshsingh A. Thakur, Dai Lu. Bicyclic cannabinoids. Continuation in part, US Patent No. 7446229, **2008**.

5. Alexandros Makriyannis, **Spyridon P. Nikas**, Shakiru Olajire Alapafuja, Vidyanand Shukla. Fatty acid amide hydrolase inhibitors. WO 2008/013963A2, **2008**.
This invention led to pre-clinical development (Neuroprotection Program, http://makscientific.com, MAKSCIENTIFIC, Burlington, MA).

6. Alexandros Makriyannis, **Spyridon P. Nikas**, Shakiru Olajire Alapafuja, Vidyanand Shukla. Monoacylglycerol lipase inhibitors for modulation of cannabinoid activity. WO 2009/052319 A1, **2009**.
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This work was selected for presentation in the Sci-Mix meeting-wide event.

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8. TECHNICAL REPORTS (As Analytical Chemist, Sergeant, during obligatory military service)

1. Spyros Nikas. ″Estimation of fuels' concentration (AVGAS, MOGAS, JP-4, JP-8, and DIESEL) in dual mixtures using infrared spectroscopy″. Laboratory of Petroleum Distribution Command, Greek Air force, Larisa, **1997**.

2. Spyros Nikas. ″Water analyses of nitrates, nitrites, phosphates, ammonium salts, total hardness, and chlorine″. Laboratory of Petroleum Distribution Command, Greek Air force, Larisa, **1997**.

9. RESEARCH MENTORING

a) M.S. Thesis, Post M.S., and Undergraduate, Mentor

1. 1998-1999, Thanos Andreou, Undergraduate, Chemistry, University of Athens, Greece. Current Position: University of Barcelona, Spain (Ph.D.); then, Pharmathen, Greece.
2. 1999 Bereket Mochona, Undergraduate, Chemistry, Florida A & M University.
3. 1999 Tefamichael Gebrekidan, Undergraduate, Chemistry, Florida A & M University.
4. 2000-2002, Indu T. Bharathan, M.S., Med. Chem., Current Position: Millennium, MA then, Merck, MA.
5. 2002-2005, Jianhong Zhao, M.S., Med. Chem., Current Position: Sanofi-Aventis, NJ.
6. 2003-2006, Zhang Jing, M.S., Med. Chem., Current Position: Brigham and Women's Hospital, Harvard.
7. 2008-2010, Marion Schimpgen, Post M.S., Chem./Med. Chem., Current Position: Hoffmann-La Roche Basel, Switzerland.
8. 2016-2018, Simiao Wu, Post M.S., Med. Chem., Current Position: Takeda, MA.
9. 2017-2018, Linbo Xie, Post M.S., Chem./Med. Chem., Current Position: Dana Farber, Harvard.
10. 2014-2015, Lipin Ji, Post M.S., Chem./Med. Chem., Current Position: Pursuing Ph.D. in NEU.

b) Ph.D. Thesis, Co-Advisor/Mentor

1. 1999-2000, Ravi Chari, Med. Chem., Mentor, Current Position: Graduated from UCONN, CT.
2. 2002-2007, Victoria Nahmias, Med. Chem., Mentor, Current Position: General Chemical State Laboratory of Greece.
3. 2003-2008, Shakiru O. Alapafuja, Med. Chem., Co-Advisor, Current Position: MakScientific, MA.
4. 2007-2012, Marsha D'Souza, Med. Chem., Co-Advisor, Current Position: Post-doc at Scripps, FL; then, Covance (DMPK), WI.
5. 2008-2010, George Naxakis, Med. Chem., Mentor, Current Position: PepsiCo, Greece.
6. 2012-2017, Shashank Kulkarni, Med. Chem., Co-Advisor, Current Position: EMD Serono, MA.
7. 2012-2017, Mohammed Baradwan, Med. Chem., Co-Advisor, Currently on Medical Leave.
8. 2014-contin. Shan Jiang, Chem./Med. Chem., Co-Advisor, Current Position: AstaTech, PA.
9. 2014-contin. Yingpeng Liu, Med. Chem., Co-Advisor, Current Position: Internship in GSK, MA.
10. 2015-contin. Lipin Ji, Med. Chem., Co-Advisor,
11. 2016-contin. Christos Iliopoulos-Tsoutsouvas, Med. Chem., Co-Advisor,

12. 2018-contin. Fei Tong, Med. Chem., Co-Advisor,

c) Post-doctoral fellow, Research Scientist, Faculty, Mentor

1. 2000-2003, Dr. Ganesh A. Thakur, (Project: labelled cannabinoids), Current Position: Associate Professor/Interim Chair, Department of Pharmaceutical Sciences, Northeastern University, Boston, MA.
2. 2005-2012, Dr. Vidyanand G. Shukla, Current Position: Sigma-Aldrich, MA.
3. 2010-2012, Dr. Rishi Sharma, Current Position: Charles River Labs/DMPK, U.S.A.
4. 2010-2011, Dr. Bin Zhang, Current Position: Anichem LLC, NJ; then, J-Star Research, NJ.
5. 2008-2010, Dr. Ioannis Papanastasiou, Current Position: Assistant Professor, Faculty of Pharmacy, University of Athens, Greece.
6. 2010-2011, Dr. David F. Finnegan, Current Position: Boston Biomedical, MA.
7. 2013-2014, Dr. Michael Malamas, (Projects: Short acting cannabinoids and Cannabidiol analogs) Current Position: Research Associate Professor at CDD, Northeastern, MA.
8. 2017-2018, Dr. Maria Pascual Lopez-Alberca, Current Position: Research Scientist at CDD, Northeastern, MA.
9. 2018-contd., Dr. Thanh C. Ho, Current Position: Post-doc at CDD, Northeastern, MA.

d) Graduate Student Thesis Committee

1. 2007-2012, Marsha D'Souza (Medicinal Chemistry, Ph.D.)
2. 2012-2017, Shashank Kulkarni (Medicinal Chemistry, Ph.D.)
3. 2014-contin., Shan Jiang, (Medicinal Chemistry, Ph.D.)
4. 2014-contin., Yingpeng Liu, (Medicinal Chemistry, Ph.D.)
5. 2015-contin., Lipin Ji, (Medicinal Chemistry, Ph.D.)
6. 2016-contin., Christos Iliopoulos-Tsoutsouvas, (Medicinal Chemistry, Ph.D.)
7. 2018-contin., Fei Tong, (Medicinal Chemistry, Ph.D.)

10. MEDIA

03/2004 ***Endo-Pharmaceuticals***: Endo Announces Agreement with MakScientific for Development of New Drugs for Pain. Link: investor.endo.com/news-releases/news-release-details/endo-announces-agreement-makscientific-development-new-drugs.

09/2010 ***SciBX***: *In vitro* and mouse studies identified hexahydrocannabinol-based CNR1-specific agonists that could help treat pain. https://www.nature.com/scibx/journal/v3/n38/full/scibx.2010.1157.html.

03/2012 ***Biogen***: Biogen Idec Takes Option to MAKScientific MS Program. https://www.prnewswire.com/news-releases/biogen-idec-takes-option-to-makscientific-ms-program-142619556.html.

02/2014 ***C&E News***: Short-term THC. https://cen.acs.org/articles/92/i5/Analogs-Marijuana-Active-Ingredient-Predictable.html.

03/2014 ***NIH/NIDA***: Novel THC Analogues Hold Promise for the Development of Safer, More Effective Cannabinoid Medications. https://www.drugabuse.gov/news-events/latest-science/novel-thc-analogues-hold-promise-development-safer-more-effective-cannabinoid-medications.

06/2014 ***PhysOrg***: An off-switch for drug's side effects. https://phys.org/news/2014-06-off-switch-drugs-toxic-side-effects.html.

01/2014 ***ACS***: ACS Editors' Choice, A novel cannabinergic chemotype. *ACS Med. Chem. Lett*. **2014**, *5*, 400.

10/2018 ***ACS***: J. Med. Chem. Webpage advertisement (for one month), *J. Med. Chem.* **2018**, *61*, 8639.

11. SERVICE (Greater Scientific Community)

1. United States-Israel Binational Science Foundation (BSF), ad hoc grant reviewer (2016)
2. Chilean National Commission for Scientific and Technological Research (CONICYT), external grant reviewer (2018)
3. Journal Reviewer
   (a) Journal of Medicinal Chemistry
   (b) Chemical Science
   (c) ACS Sustainable Chemistry and Engineering
   (d) Bioorganic and Medicinal Chemistry Letters
   (e) European Journal of Medicinal Chemistry
   (g) FASEB Journal
   (h) International Journal of Molecular Sciences (MDPI)
   (i) Molecules (MDPI)
   (j) PLOS One
   (k) Medicines (MDPI)
   (l) Tetrahedron Letters
   (m) ACS Chemical Neuroscience

12. MEMBERSHIP PROFESSIONAL SOCIETIES

1. American Chemical Society.
2. International Cannabinoid Research Society.
3. American Association of University Professors.
4. Hellenic (Greek) Chemical Society.

13. TEACHING EXPERIENCE

1. 1993-1995, Graduate teaching assistant, Organic Chemistry, Department of Chemistry, Aristotle University, Greece
2. 2013 (spring), Biophysical Methods in Drug Discovery (PHSC6290, graduate course, NEU), Instructor.
3. 2014 (spring), Biophysical Methods in Drug Discovery (PHSC6290, graduate course, NEU), Instructor.
4. 2015 (spring), Biophysical Methods in Drug Discovery (PHSC6290, graduate course, NEU), Instructor.
5. 2016 (spring), Bioorganic and Medicinal Chemistry (CHEM5676, graduate course, NEU), Instructor.
6. 2017 (spring), Bioorganic and Medicinal Chemistry (CHEM5676, graduate course, NEU), Instructor.
7. 2018 (spring), Bioorganic and Medicinal Chemistry (CHEM5676, graduate course, NEU), Instructor.

14. RESEARCH INTERESTS

Bioorganic, organic, and medicinal chemistry; Drug discovery; Bioactive natural products; Endogenous lipids; Bioimaging; Specialized probes for GPCRs.

Having a background in medicinal and organic chemistry, my research interests focus on the development of biologically important molecules that can serve as experimental tools to study receptor and enzyme pharmacology, and also, as potential drug candidates for pain, neurological and cardiometabolic disorders, addiction, glaucoma, and cancer.

With a special emphasis on the ubiquitous endocannabinoid system, my current projects are related to the development of: a) potent, efficacious, and selective ligands for cannabinoid receptors, b) bioactive lipids, c) inhibitors of the endocannabinoid deactivating enzymes; d) prostaglandin probe molecules end essential fatty acid metabolites; e) antiproliferative CBD and aminoadamantane derivatives; and f) melatonin receptor ligands.
More recent high priority projects include the development of fluorescent imaging agents, caged molecules, photo-switchable probes, enzymatically-/environmentally-activatable prodrugs, time-controlled receptor activators, and tissue-/organ-specific agents. These intriguing new technologies are expected to expand our pharmacological toolbox for cannabinoid receptors and enzymes and will allow us to answer more complex biological and pharmacological questions such as "when, how, where, and for how long, we need engagement of an endocannabinoid target for safer and efficacious therapeutic gain."
Examples for organic chemistry and methodology development projects include: a) biorthogonal copper-catalyzed “click” chemistry, b) methodologies for the construction of small size carbocyclic and heterocyclic rings, c) enantioselective syntheses of natural products and lipids, d) chiral resolution, e) isotope labeling, f) parallel and microwave assisted synthetic approaches, g) scale up technologies, h) hypervalent iodine reagents with emphasis on iodonium salts, and on alkylidene carbene and nitrene precursors, i) terpene carbocation and Baeyer−Villiger rearrangements, j) optimization of boron-, lithium- and coper-based coupling reactions, and k) Friedel-Crafts allylation mechanisms.

A summary of the current research projects follows.

1. Plant derived and synthetic classical and non-classical cannabinoid analogs. This is a long-lasting research project that involves the design, synthesis, and pharmacological evaluation of cannabinergic ligands structurally related to two *Cannabis* constituents, namely, (-)-Δ^9-tetrahydrocannabinol [(-)-Δ^9-THC], and cannabidiol (CBD). Classical cannabinoids are ABC-tricyclic compounds resembling the chemical structure of (-)-Δ^9-THC, while non-classical cannabinoids are AC-bicyclic compounds lacking the benzopyran (B) ring of the natural product (-)-Δ^9-THC. Both tricyclic and bicyclic cannabinoids bind to and activate the two cannabinoid receptors CB1 and CB2, while distinct structural features within each cannabinoid chemotype can impart selectivity for one receptor subtype over the other. Currently, modulation of CB1 and/or CB2 holds great promise for the treatment of pain, neurological and cardiometabolic disorders, addiction, osteoporosis, hepatic, renal, and intestinal disorders, as well as epilepsy, diabetes, glaucoma, and cancer.
In contrast, CBD does not bind significantly to cannabinoid CB1 and CB2 receptors and exert its biological and pharmacological effects through different targets that, currently, are not well defined.
With respect to chemical structure(s) this project focus on eight chemotypes: (-)-Δ^8-tetrahydrocannabinols, (-)-hexahydrocannabinols, cannabinols (CBNs), cannabilactones, coumarin derivatives, bicyclic terpenoid cannabinoids, biphenyls, and cannabidiols (CBDs) with the natural (*R*, *R*) or the unnatural (*S*, *S*) stereochemistry. The immediate goal of this project is to develop *in vitro* and *in vivo* potent and receptor selective, and/or function selective cannabinoid ligands that can be used as probes to study the biological, and (patho)physiological aspects of the endocannabinoid system. The long-term goal is to develop druggable CB2-selective agonists, CB1 agonists with functional selectivity, and CB1/CB2-agonists with limited CNS exposure. Such cannabinergic compounds may be useful as treatment agents without the unwanted side effects of classical cannabinoids.

2. Inhibitors of the endocannabinoid deactivating enzymes. As a result of their involvement in the metabolism, regulation, and function of a growing family of bioactive lipid mediators (including the

endogenously produced cannabinoids anandamide and 2-AG), and the consequences of their inhibition, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL) have emerged as two exciting targets for developing therapeutic agents for a range of conditions such as pain, cancer, anxiety, neurodegeneration, hypertension, and sleep disorders. In this project, chemical compounds have been rationally designed, synthesized, and evaluated for their ability to inhibit FAAH and MGL, by both the reversible and the irreversible modes of inhibition. The current library of inhibitors encompasses sulfonyl fluorides, fluoroketones, carbamates, α-keto-esters, saccharin derivatives, urea derivatives, and α-keto-heterocycles. The major aims of this work are: a) to discover potent and selective FAAH and MGL inhibitors, or dual FAAH/MGL inhibitors; b) to improve the druggability profiles of lead analogs; and c) to generate information on the structure and function of the two enzymes. Such inhibitors are currently been used in several pharmacological and biophysical studies. For example, to investigate the usefulness of FAAH inhibition for neuroprotection, and for the treatment of hypertension, and fear behaviors. The long-term goal is to develop potential therapeutic agents while avoiding the disadvantages (e.g., addictive and psychotropic properties) of the activation of cannabinoid receptors through Marijuana-like direct agonists, and the undesirable side effects (e.g., suicide, abuse potential, rebound insomnia) of the sedative/hypnotics such as benzodiazepines.

3. Labeled phyto-/synthetic-cannabinoids and fatty acids. Major work involves the design and synthesis of regiospecifically deuterated natural cannabinoids (e.g., THC, CBD and THCV) and their human metabolites in the *R, R* absolute configuration, and without deuterium scrambling or loss.
Formation of regioisomers, chemical instability of the double bond at the C9 of the THC/THCV structure, formation of mixtures of 6a,10a-cis/trans isomers, sensitivity of the THC scaffold to air oxidation, isotope scrambling or loss, and restrictions related to the availability of deuterated reagents, impose major synthetic challenges on this project. The objectives are to synthesize on large scale and with high optical, chemical, and isotopic purity: a) labelled analogs for studying cannabinoid pharmacokinetics, and b) markers for distinguishing between patients on *Cannabis* for legitimate use and individuals on *Cannabis* for recreational use. These deuterated analogs of *Cannabis* constituents have been provided to NIH/NIDA for clinical studies in humans.
Additional work has led to the synthesis of ^{13}C labelled THC that was used as an NMR tool to study the conformational properties of THC with biological membranes. Recently, we have expanded our work to include synthesis of deuterated essential fatty acids and their ethanolamide and glyceride derivatives that are useful as MS internal standards for quantification of endogenous lipids in tissues and organs using LC/MS methods. More recent work on labeled cannabinoids involves the development of synthetic approaches for the incorporation of radioactive isotopes (e.g., ^{18}F and ^{11}C) into the FDA approved THC structure. The goal of this work is to develop radioligands for *in vivo* imaging of cannabinoid receptors using Positron Emission Tomography (PET).

4. Bioactive lipids. The biological actions of the endogenous cannabinoid lipids (eCBs) anandamide (AEA) and 2-AG are terminated by a transport mechanism and enzymatic deactivation. In most tissues, AEA is metabolized hydrolytically by FAAH, and 2-AG is hydrolyzed by MGL, ABHD6 and other esterases. Additionally, the eCBs are metabolized by oxygenases including cyclooxygenases (COX-2), lipooxygenases (LOXs) and cytochrome P450 leading to eicosanoid products with distinct, non-CB-mediated, biological actions. COX-2 is constitutively expressed in neurons and radial glia and is upregulated in inflammatory situations where it plays a major role in eCB metabolism. The low metabolic and chemical stability of AEA and 2-AG limits their use in biological, biochemical, and pharmacological experiments. The prime goal of this project is to develop novel AEA and 2-AG analogs possessing high CB

receptor binding affinity and efficacy, and importantly, resistance to enzymatic metabolism. Such analogs may serve as experimental tools, currently lacking, to explore the biological role(s) of the eCBs and their receptors. They can, also, aid the discovery of more potent and selective cannabinergic drug candidates as well as COX-2 and LOX inhibitors. One successful design approach for such novel, potent, and metabolically resistant eCB analogs, was developed in our lab recently and encompasses the introduction of *chiral methyl groups* at judiciously chosen positions within the arachidonoyl chain of the lipid. An additional advantage that these chiral analogs have, unlike AEA and 2-AG, is that they do not generate arachidonic acid which exhibits non-CB-mediated biological actions and *in vitro* and *in vivo* toxicity. Recently we have expanded the scope of the lipids project to include prostaglandin probes for the putative prostamide receptor, allosteric modulators of COX-2 and TRPV1 channels, and, novel families of eicosapentaenoic acid (EPA), and docosaexaenoic acid (DHA) metabolites that display potent anti-inflammatory, pro-resolving and immunoregulatory actions.

5. Melatoninergic ligands. Melatonin MT_1 and MT_2 receptors have attracted interested as being possible targets for the treatment of sleep and circadian rhythm sleep disorders. In early work we designed rationally, synthesized, and pharmacologically evaluated *N*-acyl-5-methoxytryptamine analogs, to investigate the nature of the binding site of the melatonin receptor(s) and uncover structural features responsible for subtype selectivity. This work has led to one of the first examples of an MT_1 selective antagonist.

6. Controlled deactivation and activation of drugs. Modulation of the cannabinoid CB1 and CB2 receptors by the plant-derived (-)-Δ^9-tetrahydrocannabinol [(-)-Δ^9-THC], and its synthetic analogs (e.g. Nabilone) is a promising therapeutic approach to treat an array of indications including pain, inflammation, glaucoma, CNS disorders and cancer. Despite having a rapid onset of action, the magnitude and duration of *in vivo* CB1 and/or CB2 receptor modulation by many cannabinoids such as the marketed drugs Marinol [(-)-Δ^9-THC] and Nabilone are unpredictable due to pharmacokinetic liabilities and erratic pharmacodynamic profiles. For example, Marinol and Nabilone have high lipophilicity (cLog > 7), large volume of distribution (V_d), high levels of protein binding ($\geq$ 97%) and unpredictable time course of action. Marinol exhibits slow and erratic absorption (up to 2-6 h) and it is metabolized to yield active metabolites [e.g. 11-OH-(-)-Δ^9-THC], leading to unpredictable and long half-life. As a result, the dose titration of such drugs is complicated. Recently we developed a "controlled-deactivation" methodology to improve upon the poor PK/PD properties of lipophilic cannabinoids such as Δ^9-THC and Nabilone by controlling their sequestration and detoxification to inactive metabolites while maintaining or improving biological activity. Our controlled deactivation approach combines the "soft" analog/drug concept of enzymatic deactivation with the "depot effect" which is related to the compound's lipophilicity as well as its tissue distribution and retention. *In vivo* experiments in rodents and nonhuman primates confirmed that our approach can lead to novel druggable cannabinoids with predicted duration of pharmacological drug action. This includes the recent discovery of "short-acting" activators with CNS effects lasting for only 1.5 hours in monkeys. Preclinical profiling of a lead-compound shows great promise as a therapeutic agent for general pain, migraine pain and glaucoma. Optimized analogs exhibit improved safety profiles as they don't generate active metabolites and have less propensity to induce tolerance when compared to THC and Nabilone. The preclinical profile of our lead-compound demonstrates this agent's translational potential as a safe and effective medication with fewer side-effects than currently available CB1 agonists such as the FDA-approved drugs Marinol and Nabilone.

The initial success on the "controlled-deactivation" project has prompted us to extend our research work toward the "controlled-activation" of cannabinoids, utilizing the pro-drug concept. In the pro-drug

approach an active drug with poor PK profile is transformed to an inactive precursor (pro-drug) that has enhanced pharmacokinetic and/or biopharmaceutical properties. Following *in vivo* administration, the pro-drug yields the active drug upon the action of enzymes, or upon exposure to specific environmental conditions (e.g., pH). We are hopeful that this project will identify approaches to address the poor water solubility and oral absorption of lipophilic *Cannabis* constituents, and also, to probe the potential of developing tissue/organ specific cannabinoid agents.

7. Receptor probes with tight/irreversible binding profiles. It is now becoming increasingly evident that the ligand-dependent activation of cannabinoid receptors (CBRs) CB1 and CB2 is multifactorial and can activate certain signal transduction pathways relative to other signal transduction pathways [e.g., G-proteins vs arrestins]. This phenomenon is more general in GPCRs and it is referred to as "functional selectivity" or "ligand bias". Additionally, different ligands for a GPCR may have different association and dissociation kinetics which determine the residence time of the ligand on the receptor. In the case of an agonist, the duration of the ligand-receptor complex may also influence the preferential signaling mechanisms. As with other GPCRs, it is now well appreciated that functional selectivity at CBRs offers the opportunity to refine cannabinoid based therapeutic approaches, to improve beneficial properties, and reduce side-effect liability. Thus, there is an urgent need for a better understanding of the molecular basis of the ligand-CBR binding motif(s) and the complex mechanisms and kinetics through which these binding motif(s) block or enable signaling events and intracellular processes. Toward this goal, in the Center for Drug Discovery we have developed a powerful approach namely LAPS (Ligand Assisted Protein Structure). This approach is based on the combined use of: a) purpose designed, biologically active, cannabinergic probes exhibiting tight/irreversible binding characteristics for the CBRs, b) mass spectrometric analysis, and c) cannabinoid receptor mutants. LAPS allow characterization of critical receptor residues that interact with the probe at the level of specific amino acid residues. These probes belong to chemically and functionally diverse classes of cannabinoid ligands (including lipids), and their design relies on the incorporation of reactive groups (e.g., -NCS, -CN, $-N_3$, $-ONO_2$, $-NHC(O)CH=CH_2$) at judiciously chosen positions within the cannabinoid chemical structure of interest. The reactive groups can also be combined on the same molecule to produce bifunctional probes (homo- or hetero-bifunctional) potentially capable of interacting at two distinct sites within the CB1/CB2 binding domains to obtain more precise footprinting information. The synthesis of these probes is challenging (especially the hetero-bifunctional) because of the increasing number of functional groups, reactive moieties, and chiral centers that need to be incorporated in the molecule. Notwithstanding that these probes/chemical reporters can help identifying amino acid residues within the binding pocket of the *native receptor* that are critical for ligand engagement and receptor function, they are also great utility in developing crystals of the *mutant CB receptor*-ligand complex for structural analysis using x-ray crystallography as we published recently in breakthrough work.

8. Fluorescent ligands, caged molecules, and photoswitches for bioimaging and photo-pharmacology. G-protein coupled receptors (GPCRs) mediate the effects of approximately 33% of all marketed drugs. There is a growing sense that screening of millions of compounds at a given GPCR may not be the most effective way of identifying new candidate molecules, but rather that understanding the unique pharmacology of an unmodified GPCR in its native environment has a greater potential to lead to more efficient drug discovery programmes, and to development of safer and more effective medications. Toward this goal, and with the rapid development of more sensitive fluorescent technologies, small-molecule fluorescent probes are urgently required as they represent highly sensitive and safe experimental tools for real-time investigation of the functions of GPCRs, their signaling pathways, life-cycle, binding kinetics, as

well as localization and interactions with other biomolecules. Furthermore, these ligands can be used as *in vivo* imaging agents for the early diagnosis of diseases that are related to up- or down-regulation of GPCRs, or for studying receptor expression in specific tissues. Alternatively, they could be used in the development of competition binding and High-Throughput Screening (HTS) assays to facilitate drug development campaigns. However, the design and development of such probes are challenging, largely due to the low affinity/specificity of the probe for its target, inadequate photophysical properties, extensive non-specific binding, and/or low signal-to-noise ratio. With the focus on the cannabinoid GPCRs, the major goal of this project is to develop high affinity, potent, and selective fluorescent ligands for CB1 and/or CB2 to explore the *in vitro*/*in vivo* pharmacology of these druggable receptors, and ultimately, to investigate disease progression and therapeutic response in areas where the endocannabinoid system is implicated.
Moving towards expanding the armamentarium of probes with high spatial and temporal resolution to study cannabinoid receptor pharmacology/photopharmacology in real time and with a safer manner (non-radioligand based, non-invasive) we are working on the design and synthesis of caged endocannabinoids, and photo-switchable probes.