

## References

1. Gitler AD, Dhillon P, Shorter J. Neurodegenerative disease: models, mechanisms, and a new hope. The Company of Biologists Ltd; 2017.
2. Gitler AD, Dhillon P, Shorter J. Neurodegenerative disease: models, mechanisms, and a new hope. *Disease models & mechanisms*. 2017;10(5):499-502.
3. Tanner CM, Kamel F, Ross GW, Hoppin JA, Goldman SM, Korell M, et al. Rotenone, paraquat, and Parkinson's disease. *Environ Health Perspect*. 2011;119(6):866.
4. Masliah E, Rockenstein E, Veinbergs I, Mallory M, Hashimoto M, Takeda A, et al. Dopaminergic loss and inclusion body formation in  $\alpha$ -synuclein mice: implications for neurodegenerative disorders. *Science*. 2000;287(5456):1265-9.
5. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008;79(4):368-76.
6. Wijesekera LC, Nigel Leigh P. Amyotrophic lateral sclerosis. *Orphanet Journal of Rare Diseases*. 2009;4(1):3.
7. Vonsattel J-P, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP. Neuropathological classification of Huntington's disease. *J Neuropathol Exp Neurol*. 1985;44(6):559-77.
8. Walker FO. Huntington's disease. *The Lancet*. 2007;369(9557):218-28.
9. McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. *European Journal of Neurology*. 2017;25(1):24-34.
10. Englund B, Brun A, Gustafson L, Passant U, Mann D, Neary D, et al. Clinical and neuropathological criteria for frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 1994;57(4):416-8.
11. Ratnavalli E, Brayne C, Dawson K, Hodges J. The prevalence of frontotemporal dementia. *Neurology*. 2002;58(11):1615-21.
12. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR. Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*. 1981;10(2):122-6.
13. Rochais C, Lecoutey Cd, Gaven F, Giannoni P, Hamidouche K, Hedou D, et al. Novel multitarget-directed ligands (MTDLs) with acetylcholinesterase (AChE) inhibitory and serotonergic subtype 4 receptor (5-HT4R) agonist activities as potential agents against Alzheimer's disease: the design of donecopride. *J Med Chem*. 2015;58(7):3172-87.
14. Shoghi-Jadid K, Small GW, Agdeppa ED, Kepe V, Ercoli LM, Siddarth P, et al. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. *The American Journal of Geriatric Psychiatry*. 2002;10(1):24-35.
15. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev*. 2001;81(2):741-66.
16. Kuhl DE, Minoshima S, Fessler JA, Ficaro E, Wieland D, Koepp RA, et al. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*. 1996;40(3):399-410.

17. Hyman BT, Van Hoesen GW, Damasio AR. Alzheimer's disease: glutamate depletion in the hippocampal perforant pathway zone. *Ann Neurol.* 1987;22(1):37-40.
18. Everitt BJ, Robbins TW. Central cholinergic systems and cognition. *Annu Rev Psychol.* 1997;48(1):649-84.
19. Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold K-H, Mistl C, Rothacher S, et al. Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. *Proceedings of the National Academy of Sciences.* 1997;94(24):13287-92.
20. Thinakaran G, Koo EH. Amyloid precursor protein trafficking, processing, and function. *J Biol Chem.* 2008;283(44):29615-9.
21. Mattson MP, Barger SW, Cheng B, Lieberburg I, Smith-Swintosky VL, Rydel RE.  $\beta$ -Amyloid precursor protein metabolites and loss of neuronal Ca<sup>2+</sup> homeostasis in Alzheimer's disease. *Trends Neurosci.* 1993;16(10):409-14.
22. Karan E, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nature reviews Drug discovery.* 2011;10(9):698.
23. Vassar R, Kovacs DM, Yan R, Wong PC. The  $\beta$ -secretase enzyme BACE in health and Alzheimer's disease: regulation, cell biology, function, and therapeutic potential. *J Neurosci.* 2009;29(41):12787-94.
24. Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, et al. APP processing and synaptic function. *Neuron.* 2003;37(6):925-37.
25. Pasternak SH, Callahan JW, Mahuran DJ. The role of the endosomal/lysosomal system in amyloid-beta production and the pathophysiology of Alzheimer's disease: reexamining the spatial paradox from a lysosomal perspective. *J Alzheimers Dis.* 2004;6(1):53-65.
26. Roberds SL, Anderson J, Basi G, Bienkowski MJ, Branstetter DG, Chen KS, et al. BACE knockout mice are healthy despite lacking the primary  $\beta$ -secretase activity in brain: implications for Alzheimer's disease therapeutics. *Hum Mol Genet.* 2001;10(12):1317-24.
27. Butterfield DA, Drake J, Pocernich C, Castegna A. Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid  $\beta$ -peptide. *Trends Mol Med.* 2001;7(12):548-54.
28. Danbolt NC. Glutamate uptake. *Prog Neurobiol.* 2001;65(1):1-105.
29. Lauderback CM, Hackett JM, Huang FF, Keller JN, Szweda LI, Markesberry WR, et al. The glial glutamate transporter, GLT-1, is oxidatively modified by 4-hydroxy-2-nonenal in the Alzheimer's disease brain: the role of A $\beta$ 1-42. *J Neurochem.* 2001;78(2):413-6.
30. Greenamyre JT, Maragos WF, Albin RL, Penney JB, Young AB. Glutamate transmission and toxicity in Alzheimer's disease. 1988.
31. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry.* 1999;66(2):137-47.
32. Cummings JL, Vinters HV, Cole GM, Khachaturian ZS. Alzheimer's disease Etiologies, pathophysiology, cognitive reserve, and treatment opportunities. *Neurology.* 1998;51(1 Suppl 1):S2-S17.
33. Ferreira-Vieira T, M Guimaraes I, R Silva F, M Ribeiro F. Alzheimer's disease: targeting the cholinergic system. *Curr Neuropharmacol.* 2016;14(1):101-15.

34. Mufson EJ, Counts SE, Perez SE, Ginsberg SD. Cholinergic system during the progression of Alzheimer's disease: therapeutic implications. *Expert Rev Neurother.* 2008;8(11):1703-18.
35. Danysz W, Parsons CG. The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence. *Int J Geriatr Psychiatry.* 2003;18(S1):S23-S32.
36. Greenamyre JT, Young AB. Excitatory amino acids and Alzheimer's disease. *Neurobiol Aging.* 1989;10(5):593-602.
37. Selkoe DJ. The molecular pathology of Alzheimer's disease. *Neuron.* 1991;6(4):487-98.
38. de LaCoste M-C, White III CL. The role of cortical connectivity in Alzheimer's disease pathogenesis: a review and model system. *Neurobiol Aging.* 1993;14(1):1-16.
39. Green PS, Gridley KE, de Fiebre NC. Role of estrogen replacement therapy in memory enhancement and the prevention of neuronal loss associated with Alzheimer's disease. *The American journal of medicine.* 1997;103(3):19S-25S.
40. Simpkins JW, Singh M, Bishop J. The potential role for estrogen replacement therapy in the treatment of the cognitive decline and neurodegeneration associated with Alzheimer's disease. *Neurobiol Aging.* 1994.
41. Brinton RD. Cellular and molecular mechanisms of estrogen regulation of memory function and neuroprotection against Alzheimer's disease: recent insights and remaining challenges. *Learn Mem.* 2001;8(3):121-33.
42. Morris JC, Price JL. Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *J Mol Neurosci.* 2001;17(2):101.
43. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group\* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34(7):939-.
44. Birks JS. Cholinesterase inhibitors for Alzheimer's disease. Cochrane database of systematic reviews. 2006(1).
45. Nordberg A, Svensson A-L. Cholinesterase inhibitors in the treatment of Alzheimer's disease. *Drug Saf.* 1998;19(6):465-80.
46. Anand P, Singh B. A review on cholinesterase inhibitors for Alzheimer's disease. *Arch Pharm Res.* 2013;36(4):375-99.
47. Vasquez C, Rao K, Britton G. nmda Receptor Antagonist In Alzheimer's Disease Treatment: More Options Than Memantine?: Tu04-21. *J Neurochem.* 2011;118:140-1.
48. Yong VW, Forsyth PA, Bell R, Krekoski CA, Edwards DR. Matrix metalloproteinases and diseases of the CNS. *Trends Neurosci.* 1998;21(2):75-80.
49. Brkic M, Balusu S, Van Wonterghem E, Gorlé N, Benilova I, Kremer A, et al. Amyloid  $\beta$  Oligomers Disrupt Blood-CSF Barrier Integrity by Activating Matrix Metalloproteinases. *The Journal of Neuroscience.* 2015;35(37):12766-78.
50. Saravanan C, Singh SK. Status of research on MMPs in India. *Expert Opin Ther Targets.* 2011;15(6):715-28.
51. Kumar D, Kumar M, Saravanan C, Singh SK. Curcumin: a potential candidate for matrix metalloproteinase inhibitors. *Expert Opin Ther Targets.* 2012;16(10):959-72.
52. Asada T. Non-pharmacological therapy for Alzheimer's disease. *Nihon Rinsho.* 2004;62:72-5.

53. Sjögren MJ, Hellström PT, Jonsson MA, Runnerstam M, Silander HC, Ben-Menachem E. Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: A pilot study. *The Journal of clinical psychiatry*. 2002.
54. Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. *Neurosci Biobehav Rev*. 2005;29(3):493-500.
55. Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol*. 2010;68(4):521-34.
56. Smith GS, Laxton AW, Tang-Wai DF, McAndrews MP, Diaconescu AO, Workman CI, et al. Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. *Arch Neurol*. 2012;69(9):1141-8.
57. De Strooper B. Aph-1, Pen-2, and nicastrin with presenilin generate an active  $\gamma$ -secretase complex. *Neuron*. 2003;38(1):9-12.
58. Struhl G, Adachi A. Requirements for presenilin-dependent cleavage of notch and other transmembrane proteins. *Mol Cell*. 2000;6(3):625-36.
59. Takasugi N, Tomita T, Hayashi I, Tsuruoka M, Niimura M, Takahashi Y, et al. The role of presenilin cofactors in the  $\gamma$ -secretase complex. *Nature*. 2003;422(6930):438-41.
60. Hébert SS, Serneels L, Dejaegere T, Horré K, Dabrowski M, Baert V, et al. Coordinated and widespread expression of  $\gamma$ -secretase in vivo: evidence for size and molecular heterogeneity. *Neurobiol Dis*. 2004;17(2):260-72.
61. Wong PC, Zheng H, Chen H, Becher MW, Sirinathsinghji DJ, Trumbauer ME, et al. Presenilin 1 is required for Notch 1 and Dll1 expression in the paraxial mesoderm. *Nature*. 1997;387(6630):288-92.
62. Lai EC. Notch signaling: control of cell communication and cell fate. *Development*. 2004;131(5):965-73.
63. Miele L. Notch signaling. *Clin Cancer Res*. 2006;12(4):1074-9.
64. Louvi A, Artavanis-Tsakonas S. Notch signalling in vertebrate neural development. *Nature Reviews Neuroscience*. 2006;7(2):93-102.
65. Ables JL, Breunig JJ, Eisch AJ, Rakic P. Not (ch) just development: Notch signalling in the adult brain. *Nature Reviews Neuroscience*. 2011;12(5):269-83.
66. Fraering PC, Ye W, LaVoie MJ, Ostaszewski BL, Selkoe DJ, Wolfe MS.  $\gamma$ -Secretase substrate selectivity can be modulated directly via interaction with a nucleotide-binding site. *J Biol Chem*. 2005;280(51):41987-96.
67. Netzer WJ, Dou F, Cai D, Veach D, Jean S, Li Y, et al. Gleevec inhibits  $\beta$ -amyloid production but not Notch cleavage. *Proceedings of the National Academy of Sciences*. 2003;100(21):12444-9.
68. Mayer SC, Kreft AF, Harrison B, Abou-Gharbia M, Antane M, Aschmies S, et al. Discovery of begacestat, a Notch-1-sparing  $\gamma$ -secretase inhibitor for the treatment of Alzheimer's disease. *J Med Chem*. 2008;51(23):7348-51.
69. Henley DB, May PC, Dean RA, Siemers ER. Development of semagacestat (LY450139), a functional  $\gamma$ -secretase inhibitor, for the treatment of Alzheimer's disease. *Expert Opin Pharmacother*. 2009;10(10):1657-64.
70. Siemers E, Skinner M, Dean RA, Gonzales C, Satterwhite J, Farlow M, et al. Safety, tolerability, and changes in amyloid  $\beta$  concentrations after administration of a  $\gamma$ -secretase inhibitor in volunteers. *Clin Neuropharmacol*. 2005;28(3):126-32.

71. Fleisher AS, Raman R, Siemers ER, Becerra L, Clark CM, Dean RA, et al. Phase 2 safety trial targeting amyloid  $\beta$  production with a  $\gamma$ -secretase inhibitor in Alzheimer disease. *Arch Neurol.* 2008;65(8):1031-8.
72. Doody RS, Raman R, Farlow M, Iwatsubo T, Vellas B, Joffe S, et al. A phase 3 trial of semagacestat for treatment of Alzheimer's disease. *N Engl J Med.* 2013;369(4):341-50.
73. De Strooper B. Lessons from a failed  $\gamma$ -secretase Alzheimer trial. *Cell.* 2014;159(4):721-6.
74. Rosen LB, Stone JA, Plump A, Yuan J, Harrison T, Flynn M, et al. O4-03-02: The gamma secretase inhibitor MK-0752 acutely and significantly reduces CSF Abeta40 concentrations in humans. *Alzheimer's & Dementia.* 2006;2(3):79.
75. Deangelis D, Stone R, Silverman L, Stock W, Attar E, Fearon I, et al. A phase I clinical trial of the notch inhibitor MK-0752 in patients with T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) and other leukemias. *J Clin Oncol.* 2006;24(90180):6585-
76. Krop I, Demuth T, Guthrie T, Wen PY, Mason WP, Chinnaian P, et al. Phase I pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with advanced solid tumors. *J Clin Oncol.* 2012;30(19):2307-13.
77. Hoffman LM, Fouladi M, Olson J, Daryani VM, Stewart CF, Wetmore C, et al. Phase I trial of weekly MK-0752 in children with refractory central nervous system malignancies: a pediatric brain tumor consortium study. *Childs Nerv Syst.* 2015;31(8):1283-9.
78. Panza F, Frisardi V, Imbimbo BP, Capurso C, Logroscino G, Sancarlo D, et al. REVIEW:  $\gamma$ -Secretase Inhibitors for the Treatment of Alzheimer's Disease: The Current State. *CNS Neurosci Ther.* 2010;16(5):272-84.
79. McKee TD, Loureiro RM, Dumin JA, Zarayskiy V, Tate B. An improved cell-based method for determining the  $\gamma$ -secretase enzyme activity against both Notch and APP substrates. *J Neurosci Methods.* 2013;213(1):14-21.
80. Imbimbo BP. Alzheimer's disease:  $\gamma$ -secretase inhibitors. *Drug Discov Today Ther Strateg.* 2008;5(3):169-75.
81. Silva T, Reis J, Teixeira J, Borges F. Alzheimer's disease, enzyme targets and drug discovery struggles: from natural products to drug prototypes. *Ageing research reviews.* 2014;15:116-45.
82. Barten DM, Albright CF. Therapeutic strategies for Alzheimer's disease. *Mol Neurobiol.* 2008;37(2-3):171-86.
83. Tong G, Wang J-S, Sverdlov O, Huang S-P, Slemmon R, Croop R, et al. Multicenter, randomized, double-blind, placebo-controlled, single-ascending dose study of the oral  $\gamma$ -secretase inhibitor BMS-708163 (Avagacestat): tolerability profile, pharmacokinetic parameters, and pharmacodynamic markers. *Clin Ther.* 2012;34(3):654-67.
84. Crump CJ, Castro SV, Wang F, Pozdnyakov N, Ballard TE, Sisodia SS, et al. BMS-708,163 targets presenilin and lacks notch-sparing activity. *Biochemistry.* 2012;51(37):7209-11.
85. Coric V, Salloway S, van Dyck CH, Dubois B, Andreasen N, Brody M, et al. Targeting prodromal Alzheimer disease with avagacestat: a randomized clinical trial. *JAMA neurology.* 2015;72(11):1324-33.

86. Booth R, Kim H. Permeability analysis of neuroactive drugs through a dynamic microfluidic in vitro blood–brain barrier model. *Ann Biomed Eng.* 2014;42(12):2379-91.
87. Riley R, Parker A, Trigg S, Manners C. Development of a generalized, quantitative physicochemical model of CYP3A4 inhibition for use in early drug discovery. *Pharm Res.* 2001;18(5):652-5.
88. Josien H, Bara T, Rajagopalan M, Asberom T, Clader JW, Favreau L, et al. Small conformationally restricted piperidine N-arylsulfonamides as orally active  $\gamma$ -secretase inhibitors. *Bioorg Med Chem Lett.* 2007;17(19):5330-5.
89. Bursavich MG, Harrison BA, Blain J-F. Gamma Secretase Modulators: New Alzheimer's Drugs on the Horizon? *J Med Chem.* 2016.
90. Weggen S, Eriksen JL, Das P, Sagi SA, Wang R, Pietrzik CU, et al. A subset of NSAIDs lower amyloidogenic A $\beta$ 42 independently of cyclooxygenase activity. *Nature.* 2001;414(6860):212-6.
91. Kukar T, Golde TE. Possible mechanisms of action of NSAIDs and related compounds that modulate  $\gamma$ -secretase cleavage. *Curr Top Med Chem.* 2008;8(1):47.
92. Kukar T, Murphy MP, Eriksen JL, Sagi SA, Weggen S, Smith TE, et al. Diverse compounds mimic Alzheimer disease-causing mutations by augmenting A $\beta$ 42 production. *Nat Med.* 2005;11(5):545-50.
93. Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, et al. Effect of tarenfluril on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. *JAMA.* 2009;302(23):2557-64.
94. Kukar TL, Ladd TB, Bann MA, Fraering PC, Narlawar R, Maher GM, et al. Substrate-targeting & $\gamma$ -secretase modulators. *Nature.* 2008;453(7197):925-9.
95. Lleó A, Berezovska O, Herl L, Raju S, Deng A, Bacsik BJ, et al. Nonsteroidal anti-inflammatory drugs lower A $\beta$ 42 and change presenilin 1 conformation. *Nat Med.* 2004;10(10):1065-6.
96. Takeo K, Tanimura S, Shinoda T, Osawa S, Zahariev IK, Takegami N, et al. Allosteric regulation of  $\gamma$ -secretase activity by a phenylimidazole-type  $\gamma$ -secretase modulator. *Proceedings of the National Academy of Sciences.* 2014;111(29):10544-9.
97. Mitani Y, Yarimizu J, Akashiba H, Shitaka Y, Ni K, Matsuoka N. Amelioration of cognitive deficits in plaque-bearing Alzheimer's disease model mice through selective reduction of nascent soluble A $\beta$ 42 without affecting other A $\beta$  pools. *J Neurochem.* 2013;125(3):465-72.
98. Ebke A, Luebbers T, Fukumori A, Shirota K, Haass C, Baumann K, et al. Novel  $\gamma$ -secretase enzyme modulators directly target presenilin protein. *J Biol Chem.* 2011;286(43):37181-6.
99. Crump CJ, Fish BA, Castro SV, Chau D-M, Gertsik N, Ahn K, et al. Piperidine acetic acid based  $\gamma$ -secretase modulators directly bind to presenilin-1. *ACS Chem Neurosci.* 2011;2(12):705-10.
100. Ohki Y, Higo T, Uemura K, Shimada N, Osawa S, Berezovska O, et al. Phenylpiperidine-type  $\gamma$ -secretase modulators target the transmembrane domain 1 of presenilin 1. *The EMBO journal.* 2011;30(23):4815-24.
101. Kretner B, Fukumori A, Gutsmiedl A, Page RM, Luebbers T, Galley G, et al. Attenuated A $\beta$ 42 responses to low potency  $\gamma$ -secretase modulators can be overcome for many pathogenic presenilin mutants by second-generation compounds. *J Biol Chem.* 2011;286(17):15240-51.

102. Iben LG, Olson RE, Balanda LA, Jayachandra S, Robertson BJ, Hay V, et al. Signal peptide peptidase and  $\gamma$ -secretase share equivalent inhibitor binding pharmacology. *J Biol Chem.* 2007;282(51):36829-36.
103. Pozdnyakov N, Murrey HE, Crump CJ, Pettersson M, Ballard TE, am Ende CW, et al.  $\gamma$ -Secretase modulator (GSM) photoaffinity probes reveal distinct allosteric binding sites on presenilin. *J Biol Chem.* 2013;288(14):9710-20.
104. Nakano-Ito K, Fujikawa Y, Hihara T, Shinjo H, Kotani S, Suganuma A, et al. E2012-induced cataract and its predictive biomarkers. *Toxicol Sci.* 2013;kft224.
105. Hall A, Elliott RL, Giblin GM, Hussain I, Musgrave J, Naylor A, et al. Piperidine-derived  $\gamma$ -secretase modulators. *Bioorg Med Chem Lett.* 2010;20(3):1306-11.
106. Beher D, Clarke EE, Wrigley JD, Martin AC, Nadin A, Churcher I, et al. Selected non-steroidal anti-inflammatory drugs and their derivatives target  $\gamma$ -secretase at a novel site evidence for an allosteric mechanism. *J Biol Chem.* 2004;279(42):43419-26.
107. Morihara T, Chu T, Ubeda O, Beech W, Cole G. Selective inhibition of A $\beta$ 42 production by NSAID R-enantiomers. *J Neurochem.* 2002;83(4):1009-12.
108. Wilcock GK, Black SE, Hendrix SB, Zavitz KH, Swabb EA, Laughlin MA, et al. Efficacy and safety of tarenflurbil in mild to moderate Alzheimer's disease: a randomised phase II trial. *The Lancet Neurology.* 2008;7(6):483-93.
109. Albright CF, Dockens RC, Meredith JE, Olson RE, Slemon R, Lentz KA, et al. Pharmacodynamics of selective inhibition of  $\gamma$ -secretase by avagacestat. *J Pharmacol Exp Ther.* 2013;344(3):686-95.
110. Gijsen HJ, Mercken M.  $\gamma$ -Secretase modulators: can we combine potency with safety? *International journal of Alzheimer's disease.* 2012;2012:1-10.
111. Kimura T, Kawano K, Doi E, Kitazawa N, Shin K, Miyagawa T, et al. Preparation of cinnamide, 3-benzylidenepiperidin-2-one, phenylpropynamide compounds as amyloid  $\beta$  production inhibitors. *Eisai, Japan.* 2005:679.
112. Hall A, Patel TR.  $\gamma$ -Secretase Modulators: Current Status and Future Directions. *Prog Med Chem.* 2014;53:101.
113. Wager TT, Hou X, Verhoest PR, Villalobos A. Moving beyond rules: the development of a central nervous system multiparameter optimization (CNS MPO) approach to enable alignment of druglike properties. *ACS Chem Neurosci.* 2010;1(6):435-49.
114. Yu Y, Logovinsky V, Schuck E, Kaplow J, Chang Mk, Miyagawa T, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel  $\gamma$ -secretase modulator, E2212, in healthy human subjects. *The Journal of Clinical Pharmacology.* 2014;54(5):528-36.
115. Sun Z-Y, Asberom T, Bara T, Bennett C, Burnett D, Chu I, et al. Cyclic hydroxyamidines as amide isosteres: discovery of oxadiazolines and oxadiazines as potent and highly efficacious  $\gamma$ -secretase modulators in vivo. *J Med Chem.* 2011;55(1):489-502.
116. Huang X, Zhou W, Liu X, Li H, Sun G, Mandal M, et al. Synthesis and SAR Studies of Fused Oxadiazines as  $\gamma$ -Secretase Modulators for Treatment of Alzheimer's Disease. *ACS Med Chem Lett.* 2012;3(11):931-5.
117. Toyn JH, Thompson LA, Lentz KA, Meredith JE, Burton CR, Sankaranarayanan S, et al. Identification and Preclinical Pharmacology of the-

- Secretase Modulator BMS-869780. International Journal of Alzheimer's Disease. 2014;2014.
118. Rombouts FJR, Trabanco-Suarez AA, Gijsen HJM, MacDonald GJ, Bischoff FP, Alonso-de-Diego S-A, et al. Substituted pyrido [1, 2-a] pyrazines and substituted pyrido [1, 2-a][1, 4] diazepines for the treatment of (inter alia) Alzheimer's disease. Google Patents; 2015.
119. Findeis MA, Schroeder FC, Creaser SP, McKee TD, Xia W. Natural Product and Natural Product-Derived Gamma Secretase Modulators from Actaea Racemosa Extracts. Medicines. 2015;2(3):127-40.
120. Harms H, Kehraus S, Nesaei-Mosaferan D, Hufendieck P, Meijer L, König GM. A $\beta$ -42 lowering agents from the marine-derived fungus Dichotomomyces cepii. Steroids. 2015;104:182-8.
121. Lei X, Yu J, Niu Q, Liu J, Fraering PC, Wu F. The FDA-approved natural product dihydroergocristine reduces the production of the Alzheimer's disease amyloid- $\beta$  peptides. Sci Rep. 2015;5.
122. Hubbs JL, Fuller NO, Austin WF, Shen R, Creaser SP, McKee TD, et al. Optimization of a natural product-based class of  $\gamma$ -secretase modulators. J Med Chem. 2012;55(21):9270-82.
123. Goozee K, Shah T, Sohrabi HR, Rainey-Smith S, Brown B, Verdile G, et al. Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. Br J Nutr. 2016;115(03):449-65.
124. Okuda M, Hijikuro I, Fujita Y, Teruya T, Kawakami H, Takahashi T, et al. Design and synthesis of curcumin derivatives as tau and amyloid  $\beta$  dual aggregation inhibitors. Bioorg Med Chem Lett. 2016;26(20):5024-8.
125. Costa LG, Garrick JM, Roqué PJ, Pellacani C. Mechanisms of neuroprotection by quercetin: counteracting oxidative stress and more. Oxid Med Cell Longev. 2016;2016:1-10.
126. Cai Z, Wang C, Yang W. Role of berberine in Alzheimer's disease. Neuropsychiatr Dis Treat. 2016;12:2509.
127. Huang M, Chen S, Liang Y, Guo Y. The role of berberine in the multi-target treatment of senile dementia. Curr Top Med Chem. 2016;16(8):867-73.
128. Wang H, Wang H, Cheng H, Che Z. Ameliorating effect of luteolin on memory impairment in an Alzheimer's disease model. Mol Med Report. 2016;13(5):4215-20.
129. Sawmiller D, Li S, Shahaduzzaman M, Smith AJ, Obregon D, Giunta B, et al. Luteolin reduces Alzheimer's disease pathologies induced by traumatic brain injury. International journal of molecular sciences. 2014;15(1):895-904.
130. Petersen M, Simmonds MS. Rosmarinic acid. Phytochemistry. 2003;62(2):121-5.
131. Airolidi C, Sironi E, Dias C, Marcelo F, Martins A, Rauter AP, et al. Natural compounds against Alzheimer's disease: molecular recognition of A $\beta$ 1-42 peptide by salvia sclareoides extract and its major component, rosmarinic acid, as investigated by NMR. Chemistry—An Asian Journal. 2013;8(3):596-602.
132. Friedman T. The Effect of Rosmarinic Acid on Immunological and Neurological Systems: A Basic Science and Clinical Review. Journal of Restorative Medicine. 2015;4(1):50-9.
133. Wang R, Tang X. Neuroprotective effects of huperzine A. Neurosignals. 2005;14(1-2):71-82.

134. Mehta M, Adem A, Sabbagh M. New acetylcholinesterase inhibitors for Alzheimer's disease. *International Journal of Alzheimer's disease*. 2011;2012.
135. Zhang H-y. New insights into huperzine A for the treatment of Alzheimer's disease. *Acta Pharmacol Sin*. 2012;33(9):1170-5.
136. Jung JI, Ladd TB, Kukar T, Price AR, Moore BD, Koo EH, et al. Steroids as  $\gamma$ -secretase modulators. *The FASEB Journal*. 2013;27(9):3775-85.
137. Oehlrich D, Berthelot DJ-C, Gijsen HJ.  $\gamma$ -Secretase modulators as potential disease modifying anti-Alzheimer's drugs. *J Med Chem*. 2010;54(3):669-98.
138. Yager D, Watson M, Healy B, Eckman EA, Eckman CB. Natural product extracts that reduce accumulation of the alzheimer's amyloid  $\beta$  peptide. *J Mol Neurosci*. 2002;19(1-2):129-33.
139. Kukar TL, Ladd TB, Robertson P, Pintchovski SA, Moore B, Bann MA, et al. lysine 624 of the amyloid precursor protein (app) is a critical determinant of amyloid  $\beta$  peptide length support for a sequential model of  $\gamma$ -secretase intramembrane proteolysis and regulation by the amyloid  $\beta$  precursor protein (app) juxtamembrane region. *J Biol Chem*. 2011;286(46):39804-12.
140. Di Fede G, Catania M, Morbin M, Rossi G, Suardi S, Mazzoleni G, et al. A recessive mutation in the APP gene with dominant-negative effect on amyloidogenesis. *Science*. 2009;323(5920):1473-7.
141. Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, Bjornsson S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature*. 2012;488(7409):96-9.
142. Portelius E, Dean RA, Andreasson U, Mattsson N, Westerlund A, Olsson M, et al.  $\beta$ -site amyloid precursor protein-cleaving enzyme 1 (BACE1) inhibitor treatment induces A $\beta$ 5-X peptides through alternative amyloid precursor protein cleavage. *Alzheimers Res Ther*. 2014;6(9):75.
143. May PC, Dean RA, Lowe SL, Martenyi F, Sheehan SM, Boggs LN, et al. Robust central reduction of amyloid- $\beta$  in humans with an orally available, non-peptidic  $\beta$ -secretase inhibitor. *The Journal of neuroscience*. 2011;31(46):16507-16.
144. Kennedy ME, Stamford AW, Chen X, Cox K, Cumming JN, Dockendorf MF, et al. The BACE1 inhibitor verubecestat (MK-8931) reduces CNS  $\beta$ -amyloid in animal models and in Alzheimer's disease patients. *Sci Transl Med*. 2016;8(363):363ra150-363ra150.
145. May PC, Willis BA, Lowe SL, Dean RA, Monk SA, Cocke PJ, et al. The potent BACE1 inhibitor LY2886721 elicits robust central A $\beta$  pharmacodynamic responses in mice, dogs, and humans. *The Journal of Neuroscience*. 2015;35(3):1199-210.
146. Yan R. Stepping closer to treating Alzheimer's disease patients with BACE1 inhibitor drugs. *Translational Neurodegeneration*. 2016;5(1):13.
147. Godyń J, Jończyk J, Panek D, Malawska B. Therapeutic strategies for Alzheimer's disease in clinical trials. *Pharmacol Rep*. 2016;68(1):127-38.
148. Lai R, Albala B, Kaplow J, Majid O, Matijevic M, Aluri J, et al., editors. Novel BACE1 inhibitor E2609 reduces plasma and CSF amyloid in health subjects after 14 days oral administration. The 11th International Conference On Alzheimer's & Parkinson's Diseases, Florence, Italy; 2013.
149. Bernier F, Sato Y, Matijevic M, Desmond H, McGrath S, Burns L, et al. Clinical study of E2609, a novel BACE1 inhibitor, demonstrates target engagement and inhibition of BACE1 activity in CSF. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. 2013;9(4):P886.

150. Alexander R, Budd S, Russell M, Kugler A, Cebers G, Ye N, et al. AZD3293 A novel BACE1 inhibitor: safety, tolerability, and effects on plasma and CSF A $\beta$  peptides following single-and multiple-dose administration. *Neurobiol Aging*. 2014;35:S2.
151. Eketjäll S, Janson J, Kaspersson K, Bogstedt A, Jeppsson F, Fälting J, et al. AZD3293: A novel, orally active BACE1 inhibitor with high potency and permeability and markedly slow off-rate kinetics. *J Alzheimers Dis*. 2016(Preprint):1-15.
152. Eketjäll S, Janson J, Jeppsson F, Svanhagen A, Kolmodin K, Gustavsson S, et al. AZ-4217: a high potency BACE inhibitor displaying acute central efficacy in different in vivo models and reduced amyloid deposition in Tg2576 mice. *The Journal of Neuroscience*. 2013;33(24):10075-84.
153. Barão S, Moechars D, Lichtenthaler SF, De Strooper B. BACE1 Physiological Functions May Limit Its Use as Therapeutic Target for Alzheimer's Disease. *Trends Neurosci*. 2016;39(3):158-69.
154. Sala Frigerio C, De Strooper B. Alzheimer's Disease Mechanisms and Emerging Roads to Novel Therapeutics. *Annu Rev Neurosci*. 2016;39:57-79.
155. Lichtenthaler SF, Haass C. Amyloid at the cutting edge: activation of  $\alpha$ -secretase prevents amyloidogenesis in an Alzheimer disease mouse model. *The Journal of clinical investigation*. 2004;113(10):1384-7.
156. Woodward MC. Drug treatments in development for Alzheimer's disease. *Journal of Pharmacy Practice and Research*. 2012;42(1):58-65.
157. De Strooper B, Vassar R, Golde T. The secretases: enzymes with therapeutic potential in Alzheimer disease. *Nature Reviews Neurology*. 2010;6(2):99-107.
158. Tanzi RE, Bertram L. Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. *Cell*. 2005;120(4):545-55.
159. Kuhn PH, Wang H, Dislich B, Colombo A, Zeitschel U, Ellwart JW, et al. ADAM10 is the physiologically relevant, constitutive  $\alpha$ -secretase of the amyloid precursor protein in primary neurons. *The EMBO journal*. 2010;29(17):3020-32.
160. Tippmann F, Hundt J, Schneider A, Endres K, Fahrenholz F. Up-regulation of the  $\alpha$ -secretase ADAM10 by retinoic acid receptors and acitretin. *The FASEB Journal*. 2009;23(6):1643-54.
161. Holthoewer D, Endres K, Schuck F, Hiemke C, Schmitt U, Fahrenholz F. Acitretin, an enhancer of alpha-secretase expression, crosses the blood-brain barrier and is not eliminated by P-glycoprotein. *Neurodegenerative Diseases*. 2012;10(1-4):224-8.
162. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. *The Lancet Neurology*. 2010;9(7):702-16.
163. Marcade M, Bourdin J, Loiseau N, Peillon H, Rayer A, Drouin D, et al. Etazolate, a neuroprotective drug linking GABA $A$  receptor pharmacology to amyloid precursor protein processing. *J Neurochem*. 2008;106(1):392-404.
164. Etcheberrigaray R, Tan M, Dewachter I, Kuipéri C, Van der Auwera I, Wera S, et al. Therapeutic effects of PKC activators in Alzheimer's disease transgenic mice. *Proc Natl Acad Sci U S A*. 2004;101(30):11141-6.
165. Snow AD, Cummings J, Lake T, Hu Q, Esposito L, Cam J, et al. Exebryl-1: a novel small molecule currently in human clinical trials as a disease-modifying drug for the treatment of Alzheimer's disease. *Alzheimer's & Dementia*. 2009;5(4):P418.
166. Kupis W, Pałyga J, Tomal E, Niewiadomska E. The role of sirtuins in cellular homeostasis. *J Physiol Biochem*. 2016:1-10.
167. Lavu S, Boss O, Elliott PJ, Lambert PD. Sirtuins—novel therapeutic targets to treat age-associated diseases. *Nature Reviews Drug Discovery*. 2008;7(10):841-53.

168. Jiang M, Wang J, Fu J, Du L, Jeong H, West T, et al. Neuroprotective role of Sirt1 in mammalian models of Huntington's disease through activation of multiple Sirt1 targets. *Nat Med.* 2012;18(1):153-8.
169. Donmez G, Arun A, Chung C-Y, McLean PJ, Lindquist S, Guarente L. SIRT1 protects against  $\alpha$ -synuclein aggregation by activating molecular chaperones. *The Journal of Neuroscience.* 2012;32(1):124-32.
170. Kim D, Nguyen MD, Dobbin MM, Fischer A, Sananbenesi F, Rodgers JT, et al. SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. *The EMBO journal.* 2007;26(13):3169-79.
171. Dokmanovic M, Clarke C, Marks PA. Histone deacetylase inhibitors: overview and perspectives. *Mol Cancer Res.* 2007;5(10):981-9.
172. Gregoretti I, Lee Y-M, Goodson HV. Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. *J Mol Biol.* 2004;338(1):17-31.
173. Bellamacina C. The nicotinamide dinucleotide binding motif: a comparison of nucleotide binding proteins. *The FASEB Journal.* 1996;10(11):1257-69.
174. Heltweg B, Gatbonton T, Schuler AD, Posakony J, Li H, Goehle S, et al. Antitumor activity of a small-molecule inhibitor of human silent information regulator 2 enzymes. *Cancer Res.* 2006;66(8):4368-77.
175. Medda F, Russell RJ, Higgins M, McCarthy AR, Campbell J, Slawin AM, et al. Novel cambinol analogs as sirtuin inhibitors: synthesis, biological evaluation, and rationalization of activity. *J Med Chem.* 2009;52(9):2673-82.
176. Mahajan SS, Scian M, Sripathy S, Posakony J, Lao U, Loe TK, et al. Development of pyrazolone and isoxazol-5-one cambinol analogues as sirtuin inhibitors. *J Med Chem.* 2014;57(8):3283-94.
177. Bedalov A, Gatbonton T, Irvine WP, Gottschling DE, Simon JA. Identification of a small molecule inhibitor of Sir2p. *Proceedings of the National Academy of Sciences.* 2001;98(26):15113-8.
178. Neugebauer RC, Uchiechowska U, Meier R, Hruba H, Valkov V, Verdin E, et al. Structure-activity studies on splitomicin derivatives as sirtuin inhibitors and computational prediction of binding mode. *J Med Chem.* 2008;51(5):1203-13.
179. Posakony J, Hirao M, Stevens S, Simon JA, Bedalov A. Inhibitors of Sir2: evaluation of splitomicin analogues. *J Med Chem.* 2004;47(10):2635-44.
180. Gertz M, Fischer F, Nguyen GTT, Lakshminarasimhan M, Schutkowski M, Weyand M, et al. Ex-527 inhibits Sirtuins by exploiting their unique NAD $^{+}$ -dependent deacetylation mechanism. *Proceedings of the National Academy of Sciences.* 2013;110(30):E2772-E81.
181. Smith MR, Syed A, Lukacsovich T, Purcell J, Barbaro BA, Worthge SA, et al. A potent and selective Sirtuin 1 inhibitor alleviates pathology in multiple animal and cell models of Huntington's disease. *Hum Mol Genet.* 2014;ddu010.
182. Trapp J, Meier R, Hongwiset D, Kassack MU, Sippl W, Jung M. Structure-activity studies on suramin analogues as inhibitors of NAD $^{+}$ -dependent histone deacetylases (sirtuins). *ChemMedChem.* 2007;2(10):1419-31.
183. Taylor DM, Balabadra U, Xiang Z, Woodman B, Meade S, Amore A, et al. A brain-permeable small molecule reduces neuronal cholesterol by inhibiting activity of sirtuin 2 deacetylase. *ACS Chem Biol.* 2011;6(6):540-6.

184. Freitag M, Schemies J, Larsen T, El Gaghlab K, Schulz F, Rumpf T, et al. Synthesis and biological activity of splitomicin analogs targeted at human NAD+-dependent histone deacetylases (sirtuins). *Biorg Med Chem.* 2011;19(12):3669-77.
185. Zhang Y, Au Q, Zhang M, Barber JR, Ng SC, Zhang B. Identification of a small molecule SIRT2 inhibitor with selective tumor cytotoxicity. *Biochem Biophys Res Commun.* 2009;386(4):729-33.
186. Zhu F, Qian C. Berberine chloride can ameliorate the spatial memory impairment and increase the expression of interleukin-1beta and inducible nitric oxide synthase in the rat model of Alzheimer's disease. *BMC Neurosci.* 2006;7(1):78.
187. Donmez G. The effects of SIRT1 on Alzheimer's disease models. *International Journal of Alzheimer's Disease.* 2012;2012:1-3.
188. Cao D, Wang M, Qiu X, Liu D, Jiang H, Yang N, et al. Structural basis for allosteric, substrate-dependent stimulation of SIRT1 activity by resveratrol. *Genes Dev.* 2015;29(12):1316-25.
189. Kumar R, Nigam L, Singh AP, Singh K, Subbarao N, Dey S. Design, synthesis of allosteric peptide activator for human SIRT1 and its biological evaluation in cellular model of Alzheimer's disease. *Eur J Med Chem.* 2017;127:909-16.
190. Moussa C, Hebron M, Huang X, Ahn J, Rissman RA, Aisen PS, et al. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. *J Neuroinflammation.* 2017;14(1):1.
191. Park SY, Lee HR, Lee WS, Shin HK, Kim HY, Hong KW, et al. Cilostazol modulates autophagic degradation of  $\beta$ -amyloid peptide via SIRT1-coupled LKB1/AMPK $\alpha$  signaling in neuronal cells. *PLoS One.* 2016;11(8):e0160620.
192. Cavallucci V, D'Amelio M. Matter of life and death: the pharmacological approaches targeting apoptosis in brain diseases. *Curr Pharm Des.* 2011;17(3):215-29.
193. Elmore S. Apoptosis: a review of programmed cell death. *Toxicol Pathol.* 2007;35(4):495-516.
194. Rohn TT, Kokoulina P, Eaton CR, Poon WW. Caspase activation in transgenic mice with Alzheimer-like pathology: results from a pilot study utilizing the caspase inhibitor, Q-VD-OPh. *Int J Clin Exp Med.* 2009;2(4).
195. Rohn TT, Rissman RA, Head E, Cotman CW. Caspase activation in the Alzheimer's disease brain: tortuous and torturous. *Drug News Perspect.* 2002;15(9):549-57.
196. Rohn TT, Head E. Caspases as therapeutic targets in Alzheimer's disease: is it time to "cut" to the chase? *Int J Clin Exp Pathol.* 2008;2(2).
197. Kim H-S, Suh Y-H. Minocycline and neurodegenerative diseases. *Behav Brain Res.* 2009;196(2):168-79.
198. Wang J, Wei Q, Wang C-Y, Hill WD, Hess DC, Dong Z. Minocycline up-regulates Bcl-2 and protects against cell death in mitochondria. *J Biol Chem.* 2004;279(19):19948-54.
199. Choi Y, Kim H-S, Shin KY, Kim E-M, Kim M, Kim H-S, et al. Minocycline attenuates neuronal cell death and improves cognitive impairment in Alzheimer's disease models. *Neuropsychopharmacology.* 2007;32(11):2393-404.
200. Maqbool M, Mobashir M, Hoda N. Pivotal role of glycogen synthase kinase-3: A therapeutic target for Alzheimer's disease. *Eur J Med Chem.* 2016;107:63-81.
201. Grimes CA, Jope RS. The multifaceted roles of glycogen synthase kinase 3 $\beta$  in cellular signaling. *Prog Neurobiol.* 2001;65(4):391-426.

202. Woodgett JR. Judging a protein by more than its name: GSK-3. *Sci Stke*. 2001;100(12):8-12.
203. Pei J-J, Braak E, Braak H, Grundke-Iqbali I, Iqbal K, Winblad B, et al. Distribution of active glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ) in brains staged for Alzheimer disease neurofibrillary changes. *J Neuropathol Exp Neurol*. 1999;58(9):1010-9.
204. Yamaguchi H, Ishiguro K, Uchida T, Takashima A, Lemere CA, Imahori K. Preferential labeling of Alzheimer neurofibrillary tangles with antisera for tau protein kinase (TPK) I/glycogen synthase kinase-3 $\beta$  and cyclin-dependent kinase 5, a component of TPK II. *Acta Neuropathol*. 1996;92(3):232-41.
205. Hanger DP, Hughes K, Woodgett JR, Brion J-P, Anderton BH. Glycogen synthase kinase-3 induces Alzheimer's disease-like phosphorylation of tau: generation of paired helical filament epitopes and neuronal localisation of the kinase. *Neurosci Lett*. 1992;147(1):58-62.
206. Aplin AE, Gibb GM, Jacobsen JS, Gallo JM, Anderton BH. In vitro phosphorylation of the cytoplasmic domain of the amyloid precursor protein by glycogen synthase kinase-3 $\beta$ . *J Neurochem*. 1996;67(2):699-707.
207. Aplin AE, Jacobsen JS, Anderton BH, Gallo J-M. Effect of increased glycogen synthase kinase-3 activity upon the maturation of the amyloid precursor protein in transfected cells. *Neuroreport*. 1997;8(3):639-43.
208. Takashima A, Yamaguchi H, Noguchi K, Michel G, Ishiguro K, Sato K, et al. Amyloid  $\beta$  peptide induces cytoplasmic accumulation of amyloid protein precursor via tau protein kinase I/glycogen synthase kinase-3 $\beta$  in rat hippocampal neurons. *Neurosci Lett*. 1995;198(2):83-6.
209. Mines MA, Jope RS. Glycogen synthase kinase-3: a promising therapeutic target for fragile X syndrome. *Front Mol Neurosci*. 2011;4(35).
210. de Barreda EG, Pérez M, Ramos PG, de Cristobal J, Martín-Maestro P, Morán A, et al. Tau-knockout mice show reduced GSK3-induced hippocampal degeneration and learning deficits. *Neurobiol Dis*. 2010;37(3):622-9.
211. Rockenstein E, Torrance M, Adame A, Mante M, Bar-on P, Rose JB, et al. Neuroprotective effects of regulators of the glycogen synthase kinase-3 $\beta$  signaling pathway in a transgenic model of Alzheimer's disease are associated with reduced amyloid precursor protein phosphorylation. *The Journal of neuroscience*. 2007;27(8):1981-91.
212. Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. *Biol Psychiatry*. 2000;48(8):740-54.
213. Leng Y, Fessler EB, Chuang D-M. Neuroprotective effects of the mood stabilizer lamotrigine against glutamate excitotoxicity: roles of chromatin remodelling and Bcl-2 induction. *The International Journal of Neuropsychopharmacology*. 2013;16(03):607-20.
214. Alvarez G, Muñoz-Montaña JR, Satrústegui J, Avila J, Bogómez E, Díaz-Nido J. Lithium protects cultured neurons against  $\beta$ -amyloid-induced neurodegeneration. *FEBS Lett*. 1999;453(3):260-4.
215. Chiu C-T, Wang Z, Hunsberger JG, Chuang D-M. Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. *Pharmacol Rev*. 2013;65(1):105-42.

216. Cross DA, Culbert AA, Chalmers KA, Facci L, Skaper SD, Reith AD. Selective small-molecule inhibitors of glycogen synthase kinase-3 activity protect primary neurones from death. *J Neurochem.* 2001;77(1):94-102.
217. del Ser T, Steinwachs KC, Gertz HJ, Andres MV, Gomez-Carrillo B, Medina M, et al. Treatment of Alzheimer's disease with the GSK-3 inhibitor tideglusib: a pilot study. *J Alzheimers Dis.* 2013;33(1):205-15.
218. Hu S, Begum AN, Jones MR, Oh MS, Beech WK, Beech BH, et al. GSK3 inhibitors show benefits in an Alzheimer's disease (AD) model of neurodegeneration but adverse effects in control animals. *Neurobiol Dis.* 2009;33(2):193-206.
219. Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A, et al. Transmission and spreading of tauopathy in transgenic mouse brain. *Nat Cell Biol.* 2009;11(7):909-13.
220. Gómez-Ramos A, Díaz-Hernández M, Cuadros R, Hernández F, Avila J. Extracellular tau is toxic to neuronal cells. *FEBS Lett.* 2006;580(20):4842-50.
221. Boutajangout A, Sigurdsson EM, Krishnamurthy PK. Tau as a Therapeutic Target for Alzheimer's Disease. *Current Alzheimer research.* 2011;8(6):666-77.
222. Desai AK, Chand P. Tau-based therapies for alzheimer's disease: wave of the future. *Primary Psychiatry.* 2009;16(7):40-6.
223. Birks JS. Cholinesterase inhibitors for Alzheimer's disease. *The Cochrane Library.* 2006.
224. Kishimoto A, Kajikawa N, Tabuchi H, Shiota M, Nishizuka Y. Calcium-dependent neutral proteases, widespread occurrence of a species of protease active at lower concentrations of calcium. *J Biochem.* 1981;90(3):889-92.
225. Brown BA, Nixon RA, Strocchi P, Marotta CA. Characterization and comparison of neurofilament proteins from rat and mouse CNS. *J Neurochem.* 1981;36(1):143-53.
226. Nixon RA. Calcium-Activated Neutral Proteinases as Regulators of Cellular Function Implications for Alzheimer's Disease Pathogenesis. *Ann N Y Acad Sci.* 1989;568(1):198-208.
227. Seubert P, Lee K, Lynch G. Ischemia triggers NMDA receptor-linked cytoskeletal proteolysis in hippocampus. *Brain Res.* 1989;492(1):366-70.
228. Arai A, Kessler M, Lee K, Lynch G. Calpain inhibitors improve the recovery of synaptic transmission from hypoxia in hippocampal slices. *Brain Res.* 1990;532(1):63-8.
229. Siman R, Noszek JC, Kegerise C. Calpain I activation is specifically related to excitatory amino acid induction of hippocampal damage. *The Journal of Neuroscience.* 1989;9(5):1579-90.
230. Yamada KH, Kozlowski DA, Seidl SE, Lance S, Wieschhaus AJ, Sundivakkam P, et al. Targeted gene inactivation of calpain-1 suppresses cortical degeneration due to traumatic brain injury and neuronal apoptosis induced by oxidative stress. *J Biol Chem.* 2012;287(16):13182-93.
231. Chu J, Lauretti E, Praticò D. Caspase-3-dependent cleavage of Akt modulates tau phosphorylation via GSK3 $\beta$  kinase: implications for Alzheimer's disease. *Mol Psychiatry.* 2017.
232. Shukla V, Seo J, Binukumar B, Amin ND, Reddy P, Grant P, et al. TFP5, a Peptide Inhibitor of Aberrant and Hyperactive Cdk5/p25, Attenuates Pathological Phenotypes and Restores Synaptic Function in CK-p25Tg Mice. *J Alzheimers Dis.* 2017;56(1):335-49.

233. Liu S-L, Wang C, Jiang T, Tan L, Xing A, Yu J-T. The role of Cdk5 in Alzheimer's Disease. *Mol Neurobiol.* 2016;53(7):4328-42.
234. Patrick GN, Zukerberg L, Nikolic M, de La Monte S, Dikkes P, Tsai L-H. Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration. *Nature.* 1999;402(6762):615-22.
235. Nath R, Davis M, Probert AW, Kupina NC, Ren X, Schielke GP, et al. Processing of cdk5 activator p35 to its truncated form (p25) by calpain in acutely injured neuronal cells. *Biochem Biophys Res Commun.* 2000;274(1):16-21.
236. Ahlijanian MK, Barrezueta NX, Williams RD, Jakowski A, Kowsz KP, McCarthy S, et al. Hyperphosphorylated tau and neurofilament and cytoskeletal disruptions in mice overexpressing human p25, an activator of cdk5. *Proceedings of the National Academy of Sciences.* 2000;97(6):2910-5.
237. Yamashima T. Reconsider Alzheimer's disease by the 'calpain–cathepsin hypothesis'—a perspective review. *Prog Neurobiol.* 2013;105:1-23.
238. Yamashima T, Mathivanan A, Dazortsava MY, Sakai S, Kurimoto S, Zhu H. Calpain-mediated Hsp70. 1 cleavage in monkey CA1 after ischemia induces similar "lysosomal vesiculosis" to Alzheimer neurons. *J Alzheimers Dis Parkinsonism.* 2014;10:2161-0460.1000139.
239. Yamashima T. Can 'calpain-cathepsin hypothesis' explain Alzheimer neuronal death? *Ageing Research Reviews.* 2016;32:169-79.
240. Saitoh T, Masliah E, Jin L-W, Cole G, Wieloch T, Shapiro I. Protein kinases and phosphorylation in neurologic disorders and cell death. *Laboratory investigation; a journal of technical methods and pathology.* 1991;64(5):596-616.
241. Rapoport M, Ferreira A. PD98059 Prevents Neurite Degeneration Induced by Fibrillar  $\beta$ -Amyloid in Mature Hippocampal Neurons. *J Neurochem.* 2000;74(1):125-33.
242. Liang Z, Liu F, Grundke-Iqbali I, Iqbal K, Gong CX. Down-regulation of cAMP-dependent protein kinase by over-activated calpain in Alzheimer disease brain. *J Neurochem.* 2007;103(6):2462-70.
243. Medeiros R, Kitazawa M, Chabrier MA, Cheng D, Baglietto-Vargas D, Kling A, et al. Calpain Inhibitor A-705253 Mitigates Alzheimer's Disease–Like Pathology and Cognitive Decline in Aged 3xTgAD Mice. *The American journal of pathology.* 2012;181(2):616-25.
244. Nikkel AL, Martino B, Markosyan S, Brederson J-D, Medeiros R, Moeller A, et al. The novel calpain inhibitor A-705253 prevents stress-induced tau hyperphosphorylation in vitro and in vivo. *Neuropharmacology.* 2012;63(4):606-12.
245. Vengeliene V, Moeller A, Meinhardt MW, Beardsley PM, Sommer WH, Spanagel R, et al. The calpain inhibitor A-705253 attenuates alcohol-seeking and relapse with low side-effect profile. *Neuropsychopharmacology.* 2016;41(4):979-88.
246. Trinchese F, Liu S, Zhang H, Hidalgo A, Schmidt SD, Yamaguchi H, et al. Inhibition of calpains improves memory and synaptic transmission in a mouse model of Alzheimer disease. *The Journal of clinical investigation.* 2008;118(8):2796-807.
247. Fa M, Zhang H, Staniszewski A, Saeed F, Shen LW, Schiefer IT, et al. Novel selective calpain 1 inhibitors as potential therapeutics in Alzheimer's disease. *J Alzheimers Dis.* 2016;49(3):707-21.
248. Talesa VN. Acetylcholinesterase in Alzheimer's disease. *Mech Ageing Dev.* 2001;122(16):1961-9.

249. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI, et al. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. *JAMA*. 1994;271(13):985-91.
250. Watkins PB, Zimmerman HJ, Knapp MJ, Gracon SI, Lewis KW. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. *JAMA*. 1994;271(13):992-8.
251. Winkler MA. Tacrine for Alzheimer's disease: which patient, what dose? *JAMA*. 1994;271(13):1023-4.
252. Fernández-Bachiller MI, Pérez C, Campillo NE, Páez JA, González-Muñoz GC, Usán P, et al. Tacrine-melatonin hybrids as multifunctional agents for Alzheimer's disease, with cholinergic, antioxidant, and neuroprotective properties. *ChemMedChem*. 2009;4(5):828-41.
253. Mao F, Huang L, Luo Z, Liu A, Lu C, Xie Z, et al. O-Hydroxyl-or o-amino benzylamine-tacrine hybrids: multifunctional biometals chelators, antioxidants, and inhibitors of cholinesterase activity and amyloid- $\beta$  aggregation. *Biorg Med Chem*. 2012;20(19):5884-92.
254. Huang L, Su T, Shan W, Luo Z, Sun Y, He F, et al. Inhibition of cholinesterase activity and amyloid aggregation by berberine-phenyl-benzoheterocyclic and tacrine-phenyl-benzoheterocyclic hybrids. *Biorg Med Chem*. 2012;20(9):3038-48.
255. Wagstaff AJ, McTavish D. Tacrine. *Drugs Aging*. 1994;4(6):510-40.
256. Patocka J, Jun D, Kuca K. Possible role of hydroxylated metabolites of tacrine in drug toxicity and therapy of Alzheimer's disease. *Current drug metabolism*. 2008;9(4):332-5.
257. Soukup O, Jun D, Zdarova-Karasova J, Patocka J, Musilek K, Korabecny J, et al. A resurrection of 7-MEOTA: a comparison with tacrine. *Current Alzheimer Research*. 2013;10(8):893-906.
258. Hroudová J, Fisar Z, Korabecny J, Kuca K. In vitro effects of acetylcholinesterase inhibitors and reactivators on Complex I of electron transport chain. *Neuroendocrinology Letters*. 2011;32(3):259-63.
259. Ceschi MA, da Costa JS, Lopes JPB, Câmara VS, Campo LF, de Amorim Borges AC, et al. Novel series of tacrine-tianeptine hybrids: Synthesis, cholinesterase inhibitory activity, S100B secretion and a molecular modeling approach. *Eur J Med Chem*. 2016;121:758-72.
260. Benchekroun M, Romero A, Egea J, León R, Michalska P, Buendía I, et al. The antioxidant additive approach for Alzheimer's disease therapy: new ferulic (lipoic) acid plus melatonin modified tacrines as cholinesterases inhibitors, direct antioxidants, and nuclear factor (erythroid-derived 2)-like 2 activators. *J Med Chem*. 2016;59(21):9967-73.
261. Eghehdari M, Sarrafi Y, Nadri H, Mahdavi M, Moradi A, Moghadam FH, et al. New tacrine-derived AChE/BuChE inhibitors: Synthesis and biological evaluation of 5-amino-2-phenyl-4H-pyrano [2, 3-b] quinoline-3-carboxylates. *Eur J Med Chem*. 2017;128:237-46.
262. Jerábek J, Uliassi E, Guidotti L, Korabecny J, Soukup O, Sepsova V, et al. Tacrine-resveratrol fused hybrids as multi-target-directed ligands against Alzheimer's disease. *Eur J Med Chem*. 2016.
263. Liston DR, Nielsen JA, Villalobos A, Chapin D, Jones SB, Hubbard ST, et al. Pharmacology of selective acetylcholinesterase inhibitors: implications for use in Alzheimer's disease. *Eur J Pharmacol*. 2004;486(1):9-17.

264. Munoz-Torrero D, Camps P. Dimeric and hybrid anti-Alzheimer drug candidates. *Curr Med Chem.* 2006;13(4):399-422.
265. Sopkova-de Oliveira Santos J, Lesnard A, Agondanou J-H, Dupont N, Godard A-M, Stiebing S, et al. Virtual screening discovery of new acetylcholinesterase inhibitors issued from CERMN chemical library. *Journal of chemical information and modeling.* 2010;50(3):422-8.
266. Dias KST, de Paula CT, dos Santos T, Souza IN, Boni MS, Guimarães MJ, et al. Design, synthesis and evaluation of novel feruloyl-donepezil hybrids as potential multitarget drugs for the treatment of Alzheimer's disease. *Eur J Med Chem.* 2017;130:440-57.
267. Mishra CB, Kumari S, Manral A, Prakash A, Saini V, Lynn AM, et al. Design, synthesis, in-silico and biological evaluation of novel donepezil derivatives as multi-target-directed ligands for the treatment of Alzheimer's disease. *Eur J Med Chem.* 2017;125:736-50.
268. Costanzo P, Cariati L, Desiderio D, Sgammato R, Lamberti A, Arcone R, et al. Design, Synthesis, and Evaluation of Donepezil-Like Compounds as AChE and BACE-1 Inhibitors. *ACS Med Chem Lett.* 2016;7(5):470-5.
269. Gottwald MD, Rozanski RI. Rivastigmine, a brain-region selective acetylcholinesterase inhibitor for treating Alzheimer's disease: review and current status. *Expert opinion on investigational drugs.* 1999;8(10):1673-82.
270. Awasthi M, Singh S, Pandey VP, Dwivedi UN. Alzheimer's disease: An overview of amyloid beta dependent pathogenesis and its therapeutic implications along with in silico approaches emphasizing the role of natural products. *J Neurol Sci.* 2016;361:256-71.
271. Francis PT, Parsons CG, Jones RW. Rationale for combining glutamatergic and cholinergic approaches in the symptomatic treatment of Alzheimer's disease. *Expert Rev Neurother.* 2012;12(11):1351-65.
272. Johnson JW, Kotermanski SE. Mechanism of action of memantine. *Curr Opin Pharmacol.* 2006;6(1):61-7.
273. Parsons CG, Stöffler A, Danysz W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system-too little activation is bad, too much is even worse. *Neuropharmacology.* 2007;53(6):699-723.
274. Frohlich J, Van Horn JD. Reviewing the ketamine model for schizophrenia. *Journal of Psychopharmacology.* 2013;0269881113512909.
275. Willard L, Hauss-Wegerzyniak B, Danysz W, Wenk G. The cytotoxicity of chronic neuroinflammation upon basal forebrain cholinergic neurons of rats can be attenuated by glutamatergic antagonism or cyclooxygenase-2 inhibition. *Exp Brain Res.* 2000;134(1):58-65.
276. Wang C, Zhang X, Teng Z, Zhang T, Li Y. Downregulation of PI3K/Akt/mTOR signaling pathway in curcumin-induced autophagy in APP/PS1 double transgenic mice. *Eur J Pharmacol.* 2014;740:312-20.
277. Bové J, Martínez-Vicente M, Vila M. Fighting neurodegeneration with rapamycin: mechanistic insights. *Nature Reviews Neuroscience.* 2011;12(8):437-52.
278. Ravikumar B, Berger Z, Vacher C, O'Kane CJ, Rubinsztein DC. Rapamycin pre-treatment protects against apoptosis. *Hum Mol Genet.* 2006;15(7):1209-16.

279. Caccamo A, Majumder S, Richardson A, Strong R, Oddo S. Molecular interplay between mammalian target of rapamycin (mTOR), amyloid- $\beta$ , and tau effects on cognitive impairments. *J Biol Chem.* 2010;285(17):13107-20.
280. Xue Z, Zhang S, Huang L, He Y, Fang R, Fang Y. Upexpression of Beclin-1-dependent autophagy protects against beta-amyloid-induced cell injury in PC12 cells. *J Mol Neurosci.* 2013;51(1):180-6.
281. Cai Z, Yan L-J. Rapamycin, autophagy, and Alzheimer's disease. *Journal of biochemical and pharmacological research.* 2013;1(2):84.
282. Singh I, Sagare AP, Coma M, Perlmutter D, Gelein R, Bell RD, et al. Low levels of copper disrupt brain amyloid- $\beta$  homeostasis by altering its production and clearance. *Proceedings of the National Academy of Sciences.* 2013;110(36):14771-6.
283. Santos MA, Chand K, Chaves S. Recent progress in multifunctional metal chelators as potential drugs for Alzheimer's disease. *Coordination Chemistry Reviews.* 2016;327:287-303.
284. Bush AI, Tanzi RE. Therapeutics for Alzheimer's disease based on the metal hypothesis. *Neurotherapeutics.* 2008;5(3):421-32.
285. Crouch PJ, Savva MS, Hung LW, Donnelly PS, Mot AI, Parker SJ, et al. The Alzheimer's therapeutic PBT2 promotes amyloid- $\beta$  degradation and GSK3 phosphorylation via a metal chaperone activity. *J Neurochem.* 2011;119(1):220-30.
286. Adlard PA, Bica L, White AR, Nurjono M, Filiz G, Crouch PJ, et al. Metal ionophore treatment restores dendritic spine density and synaptic protein levels in a mouse model of Alzheimer's disease. *PLoS One.* 2011;6(3):e17669.
287. Wang B, Wang Z, Chen H, Lu C-J, Li X. Synthesis and evaluation of 8-hydroxyquinolin derivatives substituted with (benzo [d][1, 2] selenazol-3 (2H)-one) as effective inhibitor of metal-induced A $\beta$  aggregation and antioxidant. *Biorg Med Chem.* 2016;24(19):4741-9.
288. Zheng H, Youdim MB, Fridkin M. Site-activated chelators targeting acetylcholinesterase and monoamine oxidase for Alzheimer's therapy. *ACS Chem Biol.* 2010;5(6):603-10.
289. Oliveri V, Grasso GI, Bellia F, Attanasio F, Viale M, Vecchio G. Soluble sugar-based quinoline derivatives as new antioxidant modulators of metal-induced amyloid aggregation. *Inorganic chemistry.* 2015;54(6):2591-602.
290. Serrano MP, Herrero-Labrador R, Futch HS, Serrano J, Romero A, Fernandez AP, et al. The proof-of-concept of ASS234: Peripherally administered ASS234 enters the central nervous system and reduces pathology in a male mouse model of Alzheimer disease. *Journal of Psychiatry and Neuroscience doi.* 2016;10.
291. Marco-Contelles J, Unzeta M, Bolea I, Esteban G, Ramsay RR, Romero A, et al. ASS234, as a new multi-target directed Propargylamine for Alzheimer's Disease therapy. *Front Neurosci.* 2016;10.
292. Xie S, Chen J, Li X, Su T, Wang Y, Wang Z, et al. Synthesis and evaluation of selegiline derivatives as monoamine oxidase inhibitor, antioxidant and metal chelator against Alzheimer's disease. *Biorg Med Chem.* 2015;23(13):3722-9.
293. Porter MR, Kochi A, Karty JA, Lim MH, Zaleski JM. Chelation-induced diradical formation as an approach to modulation of the amyloid- $\beta$  aggregation pathway. *Chemical Science.* 2015;6(2):1018-26.
294. Josephy-Hernandez S, Jmaeff S, Pirvulescu I, Aboulkassim T, Saragovi HU. Neurotrophin receptor agonists and antagonists as therapeutic agents: An evolving paradigm. *Neurobiol Dis.* 2017;97:139-55.

295. Attems J, Walker L, Jellinger KA. Olfactory bulb involvement in neurodegenerative diseases. *Acta Neuropathol.* 2014;127(4):459-75.
296. Wollen KA. Alzheimer's disease: the pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. *Altern Med Rev.* 2010;15(3):223-44.
297. Slevin JT, Gash DM, Smith CD, Gerhardt GA, Kryscio R, Chebrok H, et al. Unilateral intraputamenal glial cell line-derived neurotrophic factor in patients with Parkinson disease: response to 1 year of treatment and 1 year of withdrawal. *J Neurosurg.* 2007;106(4):614-20.
298. Zhao L, Wang J-L, Liu R, Li X-X, Li J-F, Zhang L. Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model. *Molecules.* 2013;18(8):9949-65.
299. Baglietto-Vargas D, Shi J, Yaeger DM, Ager R, LaFerla FM. Diabetes and Alzheimer's disease crosstalk. *Neurosci Biobehav Rev.* 2016;64:272-87.
300. Shafi O. Inverse relationship between Alzheimer's disease and cancer, and other factors contributing to Alzheimer's disease: a systematic review. *BMC Neurol.* 2016;16(1):236.
301. Rafii MS, Baumann TL, Bakay RA, Ostrove JM, Siffert J, Fleisher AS, et al. A phase1 study of stereotactic gene delivery of AAV2-NGF for Alzheimer's disease. *Alzheimer's & Dementia.* 2014;10(5):571-81.
302. Hocquemiller M, Giersch L, Audrain M, Parker S, Cartier N. Adeno-Associated Virus-Based Gene Therapy for CNS Diseases. *Hum Gene Ther.* 2016;27(7):478-96.
303. Tuszyński MH, Yang JH, Barba D, Hoi-Sang U, Bakay RA, Pay MM, et al. Nerve growth factor gene therapy: activation of neuronal responses in Alzheimer disease. *JAMA neurology.* 2015;72(10):1139-47.
304. Thal L, Grundman M, Berg J, Ernstrom K, Margolin R, Pfeiffer E, et al. Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology.* 2003;61(11):1498-502.
305. Orsucci D, Mancuso M, Ienco EC, LoGerfo A, Siciliano G. Targeting mitochondrial dysfunction and neurodegeneration by means of coenzyme Q10 and its analogues. *Curr Med Chem.* 2011;18(26):4053-64.
306. Bruno MA, Clarke PB, Seltzer A, Quirion R, Burgess K, Cuello AC, et al. Long-lasting rescue of age-associated deficits in cognition and the CNS cholinergic phenotype by a partial agonist peptidomimetic ligand of TrkA. *J Neurosci.* 2004;24(37):8009-18.
307. Aboulkassim T, Tong X-K, Tse YC, Wong T-P, Woo S, Neet K, et al. Ligand-dependent TrkA activity in brain impacts differently on spatial learning and long-term memory. *Mol Pharmacol.* 2011;mol. 111.071332.
308. Obianyo O, Ye K. Novel small molecule activators of the Trk family of receptor tyrosine kinases. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics.* 2013;1834(10):2213-8.
309. Jang S-W, Okada M, Sayeed I, Xiao G, Stein D, Jin P, et al. Gambogic amide, a selective agonist for TrkA receptor that possesses robust neurotrophic activity, prevents neuronal cell death. *Proceedings of the National Academy of Sciences.* 2007;104(41):16329-34.

310. Ferrer I, Marín C, Rey MJ, Ribalta T, Goutan E, Blanco R, et al. BDNF and full-length and truncated TrkB expression in Alzheimer disease. Implications in therapeutic strategies. *J Neuropathol Exp Neurol.* 1999;58(7):729-39.
311. Chakravarty S, Maitra S, Reddy RG, Das T, Jhelum P, Kootar S, et al. A novel natural product inspired scaffold with robust neurotrophic, neurogenic and neuroprotective action. *Sci Rep.* 2015;5:14134.
312. Jang S-W, Liu X, Chan CB, France SA, Sayeed I, Tang W, et al. Deoxygedunin, a natural product with potent neurotrophic activity in mice. *PLoS One.* 2010;5(7):e11528.
313. Chitranshi N, Gupta V, Kumar S, Graham SL. Exploring the molecular interactions of 7, 8-dihydroxyflavone and its derivatives with TrkB and VEGFR2 proteins. *International journal of molecular sciences.* 2015;16(9):21087-108.
314. Chen J, Chua K-W, Chua CC, Yu H, Pei A, Chua BH, et al. Antioxidant activity of 7, 8-dihydroxyflavone provides neuroprotection against glutamate-induced toxicity. *Neurosci Lett.* 2011;499(3):181-5.
315. Tsai T, Klausmeyer A, Conrad R, Gottschling C, Leo M, Faissner A, et al. 7, 8-Dihydroxyflavone leads to survival of cultured embryonic motoneurons by activating intracellular signaling pathways. *Molecular and Cellular Neuroscience.* 2013;56:18-28.
316. Yang T, Knowles JK, Lu Q, Zhang H, Arancio O, Moore LA, et al. Small molecule, non-peptide p75 NTR ligands inhibit A $\beta$ -induced neurodegeneration and synaptic impairment. *PLoS One.* 2008;3(11):e3604.
317. Elshaer SL, El-Remessy AB. Implication of the neurotrophin receptor p75NTR in vascular diseases: Beyond the eye. *Expert Review of Ophthalmology.* 2017(just-accepted).
318. Shi C, Yi D, Li Z, Zhou Y, Cao Y, Sun Y, et al. Anti-RAGE antibody attenuates isoflurane-induced cognitive dysfunction in aged rats. *Behav Brain Res.* 2017;322:167-76.
319. García-Osta A, Cuadrado-Tejedor M, García-Barroso C, Oyarzábal J, Franco R. Phosphodiesterases as therapeutic targets for Alzheimer's disease. *ACS Chem Neurosci.* 2012;3(11):832-44.
320. Reneerkens OA, Rutten K, Steinbusch HW, Blokland A, Prickaerts J. Selective phosphodiesterase inhibitors: a promising target for cognition enhancement. *Psychopharmacology (Berl).* 2009;202(1-3):419-43.
321. Boland K, Moschetti V, Dansirikul C, Pichereau S, Gheyle L, Runge F, et al. A phase I, randomized, proof-of-clinical-mechanism study assessing the pharmacokinetics and pharmacodynamics of the oral PDE9A inhibitor BI 409306 in healthy male volunteers. *Human Psychopharmacology: Clinical and Experimental.* 2017;32(1).
322. Kumar A, Singh N. Inhibitor of Phosphodiesterase-4 improves memory deficits, oxidative stress, neuroinflammation and neuropathological alterations in mouse models of dementia of Alzheimer's Type. *Biomed Pharmacother.* 2017;88:698-707.
323. García-Barroso C, Ricobaraza A, Pascual-Lucas M, Unceta N, Rico AJ, Goicolea MA, et al. Tadalafil crosses the blood-brain barrier and reverses cognitive dysfunction in a mouse model of AD. *Neuropharmacology.* 2013;64:114-23.
324. Zhu L, Yang J-y, Xue X, Dong Y-x, Liu Y, Miao F-r, et al. A novel phosphodiesterase-5 inhibitor: yonkenafil modulates neurogenesis, gliosis to improve cognitive function and ameliorates amyloid burden in an APP/PS1 transgenic mice model. *Mech Ageing Dev.* 2015;150:34-45.

325. Hutson P, Finger E, Magliaro B, Smith S, Converso A, Sanderson P, et al. The selective phosphodiesterase 9 (PDE9) inhibitor PF-04447943 (6-[(3S, 4S)-4-methyl-1-(pyrimidin-2-ylmethyl) pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1, 5-dihydro-4H-pyrazolo [3, 4-d] pyrimidin-4-one) enhances synaptic plasticity and cognitive function in rodents. *Neuropharmacology*. 2011;61(4):665-76.
326. Jeffrey S. More positive data on aducanumab in Alzheimers. *Medscape*. 2015.
327. Smith R, Puschmann A, Schöll M, Ohlsson T, Van Swieten J, Honer M, et al. 18F-AV-1451 tau PET imaging correlates strongly with tau neuropathology in MAPT mutation carriers. *Brain*. 2016:aww163.
328. Bittner T, Zetterberg H, Teunissen CE, Ostlund RE, Militello M, Andreasson U, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of  $\beta$ -amyloid (1-42) in human cerebrospinal fluid. *Alzheimer's & Dementia*. 2016;12(5):517-26.
329. Gupta-Bansal R, Frederickson RC, Brunden KR. Proteoglycan-mediated inhibition of  $\alpha\beta$  proteolysis a potential cause of senile plaque accumulation. *J Biol Chem*. 1995;270(31):18666-71.
330. Gervais F, Chalifour R, Garceau D, Kong X, Laurin J, McLaughlin R, et al. Glycosaminoglycan mimetics: a therapeutic approach to cerebral amyloid angiopathy. *Amyloid: the international journal of experimental and clinical investigation: the official journal of the International Society of Amyloidosis*. 2001;8:28-35.
331. Gervais F, Paquette J, Morissette C, Krzywkowski P, Yu M, Azzi M, et al. Targeting soluble  $\text{A}\beta$  peptide with Tramiprosate for the treatment of brain amyloidosis. *Neurobiol Aging*. 2007;28(4):537-47.
332. Brener O, Dunkelmann T, Gremer L, van Groen T, Mirecka EA, Kadish I, et al. QIAD assay for quantitating a compound's efficacy in elimination of toxic  $\text{A}\beta$  oligomers. *Sci Rep*. 2015;5:13222.
333. Fawver JN, Duong KT, Wise-Scira O, Petrofes Chapa R, Schall HE, Coskuner O, et al. Probing and trapping a sensitive conformation: Amyloid- $\beta$  fibrils, oligomers, and dimers. *J Alzheimers Dis*. 2012;32(1):197-215.
334. Ma K, McLaurin J.  $\alpha$ -Melanocyte Stimulating Hormone as a Potential Therapy for Alzheimer's Disease. *Current Alzheimer Research*. 2017;14(1):18-29.
335. Rocca WA, Mielke MM, Vemuri P, Miller VM. Sex and gender differences in the causes of dementia: a narrative review. *Maturitas*. 2014;79(2):196-201.
336. Fox M, Berzuini C, Knapp LA. Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women. *Psychoneuroendocrinology*. 2013;38(12):2973-82.
337. Depypere H, Vierin A, Weyers S, Sieben A. Alzheimer's disease, apolipoprotein E and hormone replacement therapy. *Maturitas*. 2016;94:98-105.
338. Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, et al. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *The American journal of geriatric psychiatry*. 2005;13(11):950-8.
339. Tokita K, Inoue T, Yamazaki S, Wang F, Yamaji T, Matsuoka N, et al. FK962, a novel enhancer of somatostatin release, exerts cognitive-enhancing actions in rats. *Eur J Pharmacol*. 2005;527(1):111-20.
340. Watson GS, Craft S. Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease. *Eur J Pharmacol*. 2004;490(1):97-113.

341. Jaehde U, Masereeuw R, De Boer AG, Fricker G, Nagelkerke JF, Vonderscher J, et al. Quantification and visualization of the transport of octreotide, a somatostatin analogue, across monolayers of cerebrovascular endothelial cells. *Pharm Res.* 1994;11(3):442-8.
342. Zipser B, Johanson C, Gonzalez L, Berzin T, Tavares R, Hulette C, et al. Microvascular injury and blood-brain barrier leakage in Alzheimer's disease. *Neurobiol Aging.* 2007;28(7):977-86.
343. Tundo G, Ciaccio C, Sbardella D, Boraso M, Viviani B, Coletta M, et al. Somatostatin modulates insulin-degrading-enzyme metabolism: implications for the regulation of microglia activity in AD. *PLoS One.* 2012;7(4):e34376.
344. Wright JW, Harding JW. Brain renin-angiotensin—a new look at an old system. *Prog Neurobiol.* 2011;95(1):49-67.
345. Bachmeier C, Beaulieu-Abdelahad D, Mullan M, Paris D. Selective dihydropyridine compounds facilitate the clearance of  $\beta$ -amyloid across the blood-brain barrier. *Eur J Pharmacol.* 2011;659(2):124-9.
346. Kennelly S, Abdullah L, Kenny RA, Mathura V, Luis CA, Mouzon B, et al. Apolipoprotein E genotype-specific short-term cognitive benefits of treatment with the antihypertensive nilvadipine in Alzheimer's patients—an open-label trial. *Int J Geriatr Psychiatry.* 2012;27(4):415-22.
347. Birks J, López-Arrieta J. Nimodipine for primary degenerative, mixed and vascular dementia. The Cochrane Library. 2002.
348. Gengler S, McClean PL, McCurtin R, Gault VA, Hölscher C. Val (8) GLP-1 rescues synaptic plasticity and reduces dense core plaques in APP/PS1 mice. *Neurobiol Aging.* 2012;33(2):265-76.
349. Noble W, Garwood CJ, Hanger DP. Minocycline as a potential therapeutic agent in neurodegenerative disorders characterized by protein misfolding. *Prion.* 2009;3(2):78-83.
350. Ding Y, Qiao A, Wang Z, Goodwin JS, Lee E-S, Block ML, et al. Retinoic acid attenuates  $\beta$ -amyloid deposition and rescues memory deficits in an Alzheimer's disease transgenic mouse model. *J Neurosci.* 2008;28(45):11622-34.
351. Organization WH. Neurological disorders: public health challenges: World Health Organization; 2006.
352. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, et al. Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *Journal of medicinal chemistry.* 2004;47(7):1739-49.
353. Sander T, Freyss J, von Korff M, Reich JR, Rufener C. OSIRIS, an entirely in-house developed drug discovery informatics system. *Journal of chemical information and modeling.* 2009;49(2):232-46.
354. Mahajan R, Patial VP, Sharma P. Juvenile hormone like substances: Part XV—Synthesis and biological activities of some juvenile hormone analogues containing sulphonamide feature. 2002.
355. Vogel A, Tatchell A, Furnis B, Hannaford A, Smith P. Vogel's Textbook of Practical Organic Chemistry, V<sup>Ed.</sup>, 1176. ELBS, and Longman Group Ltd: Singapore(b); Bhoya, UC, & Doshi, AV (2000) J Inst Chem(Ind). 1989.
356. Kovacs G, Csizmadia I. Peptides from non-amino acid sources III. Synthesis of diketopiperazine derivatives from ketene acetal. *Tetrahedron Lett.* 1971;12(28):2599-602.

357. Berse C, Massiah T, Piché L. Tosylated Peptides and p-Nitrophenyl Esters. Canadian Journal of Chemistry. 1963;41(11):2767-73.
358. Ellman GL, Courtney KD, Andres V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol. 1961;7(2):88IN191-9095.
359. Motulsky H. Prism 5 statistics guide, 2007. GraphPad Software. 2007;31:39-42.
360. Copeland RA, Retey J. Enzymes: a practical introduction to structure, mechanism, and data analysis: VCH Publishers New York;; 1996.
361. Copeland RA. Enzymes: a practical introduction to structure, mechanism, and data analysis: John Wiley & Sons; 2004.
362. Di L, Kerns EH, Fan K, McConnell OJ, Carter GT. High throughput artificial membrane permeability assay for blood-brain barrier. Eur J Med Chem. 2003;38(3):223-32.
363. Revilla S, Ursulet S, Álvarez-López MJ, Castro-Freire M, Perpiñá U, García-Mesa Y, et al. Lenti-GDNF Gene Therapy Protects Against Alzheimer's Disease-Like Neuropathology in 3xTg-AD Mice and MC65 Cells. CNS Neurosci Ther. 2014;20(11):961-72.
364. Jin L-W, Hua DH, Shie F-S, Maezawa I, Sopher B, Martin GM. Novel tricyclic pyrone compounds prevent intracellular APP C99-induced cell death. J Mol Neurosci. 2002;19(1-2):57-61.
365. Rajasekhar K, Madhu C, Govindaraju T. Natural Tripeptide-Based Inhibitor of Multifaceted Amyloid  $\beta$  Toxicity. ACS Chem Neurosci. 2016;7(9):1300-10.
366. Rajasekhar K, Suresh S, Manjithaya R, Govindaraju T. Rationally Designed Peptidomimetic Modulators of A $\beta$  Toxicity in Alzheimer's Disease. Sci Rep. 2015;5.
367. Chen Y, Sun J, Fang L, Liu M, Peng S, Liao H, et al. Tacrine–ferulic acid–nitric oxide (NO) donor trihybrids as potent, multifunctional acetyl-and butyrylcholinesterase inhibitors. J Med Chem. 2012;55(9):4309-21.
368. Kedare SB, Singh R. Genesis and development of DPPH method of antioxidant assay. Journal of food science and technology. 2011;48(4):412-22.
369. Mathew M, Subramanian S. In vitro screening for anti-cholinesterase and antioxidant activity of methanolic extracts of ayurvedic medicinal plants used for cognitive disorders. PLoS One. 2014;9(1):e86804.
370. Modi G, Antonio T, Reith M, Dutta A. Structural Modifications of Neuroprotective Anti-Parkinsonian (–)-N 6-(2-(4-(Biphenyl-4-yl) piperazin-1-yl)-ethyl)-N 6-propyl-4, 5, 6, 7-tetrahydrobenzo [d] thiazole-2, 6-diamine (D-264): an Effort toward the Improvement of in Vivo Efficacy of the Parent Molecule. J Med Chem. 2014;57(4):1557-72.
371. Saxena G, Singh SP, Pal R, Singh S, Pratap R, Nath C. Gugulipid, an extract of Commiphora whighitii with lipid-lowering properties, has protective effects against streptozotocin-induced memory deficits in mice. Pharmacology Biochemistry and Behavior. 2007;86(4):797-805.
372. Vogel HG. Drug discovery and evaluation: pharmacological assays: Springer Science & Business Media; 2002, II Ed., 623.
373. Tota S, Hanif K, Kamat PK, Najmi AK, Nath C. Role of central angiotensin receptors in scopolamine-induced impairment in memory, cerebral blood flow, and cholinergic function. Psychopharmacology (Berl). 2012;222(2):185-202.

374. Berman SB, Hastings TG. Dopamine oxidation alters mitochondrial respiration and induces permeability transition in brain mitochondria. *J Neurochem.* 1999;73(3):1127-37.
375. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem.* 1951;193(1):265-75.
376. Huang S-G. Development of a high throughput screening assay for mitochondrial membrane potential in living cells. *Journal of biomolecular screening.* 2002;7(4):383-9.
377. Lee M-R, Yun B-S, Park S-Y, Ly S-Y, Kim S-N, Han B-H, et al. Anti-amnesic effect of Chong–Myung–Tang on scopolamine-induced memory impairments in mice. *J Ethnopharmacol.* 2010;132(1):70-4.
378. Sopher BL, Fukuchi K-I, Kavanagh TJ, Furlong CE, Martin GM. Neurodegenerative mechanisms in Alzheimer disease. *Mol Chem Neuropathol.* 1996;29(2):153-68.
379. Abbassi YA, Mohammadi MT, Foroshani MS, Sarshoori JR. Captopril and valsartan may improve cognitive function through potentiation of the brain antioxidant defense system and attenuation of oxidative/nitrosative damage in STZ-induced dementia in rat. *Advanced pharmaceutical bulletin.* 2016;6(4):531.
380. Dinamarca MC, Sagal JP, Quintanilla RA, Godoy JA, Arrázola MS, Inestrosa NC. Amyloid- $\beta$ -Acetylcholinesterase complexes potentiate neurodegenerative changes induced by the A $\beta$  peptide. Implications for the pathogenesis of Alzheimer's disease. *Mol Neurodegener.* 2010;5(1):4.
381. Mohamed T, Shakeri A, Rao PP. Amyloid cascade in Alzheimer's disease: Recent advances in medicinal chemistry. *Eur J Med Chem.* 2016;113:258-72.
382. Lee S, Liu Y, Liu Y, Lim MH. Untangling Amyloid-beta, Tau, and Metals in Alzheimer's Disease. 2013.
383. Reybier K, Ayala S, Alies B, Rodrigues JV, Bustos Rodriguez S, La Penna G, et al. Free Superoxide is an Intermediate in the Production of H<sub>2</sub>O<sub>2</sub> by Copper (I)-A $\beta$  Peptide and O<sub>2</sub>. *Angewandte Chemie International Edition.* 2016;55(3):1085-9.
384. Lim P, Huss Jr A, Eckert C. Oxidation of aqueous sulfur dioxide. 3. The effects of chelating agents and phenolic antioxidants. *The Journal of Physical Chemistry.* 1982;86(21):4233-7.
385. Atmaca G. Antioxidant effects of sulfur-containing amino acids. *Yonsei Med J.* 2004;45:776-88.
386. Lalonde R. The neurobiological basis of spontaneous alternation. *Neurosci Biobehav Rev.* 2002;26(1):91-104.
387. Bohdanecký Z, Jarvik M. Impairment of one-trial passive avoidance learning in mice by scopolamine, scopolamine methylbromide, and physostigmine. *Int J Neuropharmacol.* 1967;6(3):217-22.
388. Petersen CAH, Alikhani N, Behbahani H, Wiehager B, Pavlov PF, Alafuzoff I, et al. The amyloid  $\beta$ -peptide is imported into mitochondria via the TOM import machinery and localized to mitochondrial cristae. *Proceedings of the National Academy of Sciences.* 2008;105(35):13145-50.
389. Kumar D, Gupta SK, Ganeshpurkar A, Gutti G, Krishnamurthy S, Modi G, et al. Development of Piperazinediones as dual inhibitor for treatment of Alzheimer's disease. *European journal of medicinal chemistry.* 2018;150:87-101.
390. Palkovits M, Brownstein MJ. Maps and guide to microdissection of the rat brain: Elsevier; 1988.

391. Foyet HS, Tsala DE, Bouba AA, Hritcu L. Anxiolytic and antidepressant-like effects of the aqueous extract of Alafia multiflora stem barks in rodents. *Adv Pharmacol Sci.* 2012;2012.
392. You J-S, Peng M, Shi J-L, Zheng H-Z, Liu Y, Zhao B-S, et al. Evaluation of anxiolytic activity of compound Valeriana jatamansi Jones in mice. *BMC Complement Altern Med.* 2012;12(1):223.
393. Bagosi Z, Csabafi K, Balangó B, Pintér D, Szolomájer-Csikós O, Bozsó Z, et al. Anxiolytic-and antidepressant-like actions of Urocortin 2 and its fragments in mice. *Brain Res.* 2018;1680:62-8.
394. Carola V, D'Olimpio F, Brunamonti E, Mangia F, Renzi P. Evaluation of the elevated plus-maze and open-field tests for the assessment of anxiety-related behaviour in inbred mice. *Behav Brain Res.* 2002;134(1-2):49-57.
395. Santos P, Herrmann AP, Benvenutti R, Noetzold G, Giongo F, Gama CS, et al. Anxiolytic properties of N-acetylcysteine in mice. *Behav Brain Res.* 2017;317:461-9.
396. Nakatsuka I, Saji H, Shiba K, Shimizu H, Okuno M, Yoshitake A, et al. In vitro evaluation of radioiodinated butyrophophenes as radiotracer for dopamine receptor study. *Life Sci.* 1987;41(17):1989-97.
397. Seibenhener ML, Wooten MC. Use of the open field maze to measure locomotor and anxiety-like behavior in mice. *Journal of visualized experiments: JoVE.* 2015(96).
398. Martin EI, Ressler KJ, Binder E, Nemeroff CB. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. *Psychiatric Clinics.* 2009;32(3):549-75.
399. File SE, Gonzalez LE, Andrews N. Endogenous acetylcholine in the dorsal hippocampus reduces anxiety through actions on nicotinic and muscarinic<sub>1</sub> receptors. *Behavioral neuroscience.* 1998;112(2):352.
400. Degroot A, Treit D. Dorsal and ventral hippocampal cholinergic systems modulate anxiety in the plus-maze and shock-probe tests. *Brain Research.* 2002;949(1):60-70.
401. Degroot A, Kashluba S, Treit D. Septal GABAergic and hippocampal cholinergic systems modulate anxiety in the plus-maze and shock-probe tests. *Pharmacology Biochemistry and Behavior.* 2001;69(3-4):391-9.
402. Ciranna á. Serotonin as a modulator of glutamate-and GABA-mediated neurotransmission: implications in physiological functions and in pathology. *Curr Neuropharmacol.* 2006;4(2):101-14.
403. Gogas KR, Lechner SM, Markison S, Williams JP, McCarthy W, Grigoriadis DE, et al. 6.04 - Anxiety. In: Taylor JB, Triggle DJ, editors. *Comprehensive Medicinal Chemistry II.* Oxford: Elsevier; 2007. p. 85-115.
404. Carter M, Shieh J. Chapter 2 - Animal Behavior. In: Carter M, Shieh J, editors. *Guide to Research Techniques in Neuroscience (Second Edition).* San Diego: Academic Press; 2015. p. 39-71.
405. Commissaris RL. Chapter 17 - Conflict behaviors as animal models for the study of anxiety. In: van Haaren F, editor. *Techniques in the Behavioral and Neural Sciences.* 10: Elsevier; 1993. p. 443-74.
406. Walf AA, Frye CA. The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. *Nature protocols.* 2007;2(2):322.
407. Bailey SJ, Toth M. Variability in the benzodiazepine response of serotonin 5-HT1A receptor null mice displaying anxiety-like phenotype: evidence for genetic

- modifiers in the 5-HT-mediated regulation of GABAA receptors. *J Neurosci.* 2004;24(28):6343-51.
408. Koyama S, Matsumoto N, Kubo C, Akaike N. Presynaptic 5-HT3 receptor-mediated modulation of synaptic GABA release in the mechanically dissociated rat amygdala neurons. *The Journal of Physiology.* 2000;529(2):373-83.
409. Forchetti CM, Meek JL. Evidence for a tonic GABAergic control of serotonin neurons in the median raphe nucleus. *Brain Res.* 1981;206(1):208-12.
410. Nishikawa T, Scatton B. Evidence for a GABAergic inhibitory influence on serotonergic neurons originating from the dorsal raphe. *Brain Res.* 1983;279(1-2):325-9.
411. von R. Schleyer P. A simple preparation of adamantane. *J Am Chem Soc.* 1957;79(12):3292-.
412. Moiseev I, Doroshenko R, Ivanova V. Synthesis of amantadine via the nitrate of 1-adamantanol. *Pharm Chem J.* 1976;10(4):450-1.
413. Benson FR, Savell WL. The chemistry of the vicinal triazoles. *Chem Rev.* 1950;46(1):1-68.
414. Bhatia K, Mock S, Krishnan S, Greenberg J, Stearn B, Baldridge K, et al. Grid workflow challenges in computational chemistry. San Diego Supercomputer Center Technical Report TR-2006-7. 2006.
415. Jan A, Hartley DM, Lashuel HA. Preparation and characterization of toxic A $\beta$  aggregates for structural and functional studies in Alzheimer's disease research. *Nat Protoc.* 2010;5(6):1186.
416. Vyas NA, Singh SB, Kumbhar AS, Ranade DS, Walke GR, Kulkarni PP, et al. Acetylcholinesterase and A $\beta$  Aggregation Inhibition by Heterometallic Ruthenium (II)-Platinum (II) Polypyridyl Complexes. *Inorganic chemistry.* 2018.
417. Hartrampf FW, Barber DM, Gottschling K, Leippe P, Hollmann M, Trauner D. Development of a photoswitchable antagonist of NMDA receptors. *Tetrahedron.* 2017;73(33):4905-12.
418. Li J, Tan E, Keller N, Chen Y-H, Zehetmaier PM, Jakowitz AC, et al. Cobalt-Catalyzed Electrophilic Aminations with Anthranils: An Expedient Route to Condensed Quinolines. *J Am Chem Soc.* 2018.
419. Tseng C-H, Tung C-W, Peng S-I, Chen Y-L, Tzeng C-C, Cheng C-M, et al. Discovery of Pyrazolo [4, 3-c] quinolines Derivatives as Potential Anti-Inflammatory Agents through Inhibiting of NO Production. *Molecules.* 2018;23(5).
420. Gerster JF. 1H-imidazo [4, 5-c] quinolines and their use as bronchodilating agents. Google Patents; 1987.
421. Vu AT, Cohn ST, Mewshaw RE. Phenyl quinolines and their use as estrogenic agents. Google Patents; 2006.
422. Bergstrom F. Heterocyclic Nitrogen Compounds. Part IIA. Hexacyclic Compounds: Pyridine, Quinoline, and Isoquinoline. *Chem Rev.* 1944;35(2):77-277.
423. Furniss BS. Vogel's textbook of practical organic chemistry: Pearson Education India; 1989.
424. Zhou X, Yan W, Zhao T, Tian Z, Wu X. Rhodamine based derivative and its zinc complex: synthesis and recognition behavior toward Hg (II). *Tetrahedron.* 2013;69(46):9535-9.
425. Liu KG, Robichaud AJ. A general and convenient synthesis of N-aryl piperazines. *Tetrahedron Lett.* 2005;46(46):7921-2.

426. Sagar SR, Singh DP, Panchal NB, Das RD, Pandya DH, Sudarsanam V, et al. Thiazolyl-thiadiazines as Beta Site Amyloid Precursor Protein Cleaving Enzyme-1 (BACE-1) Inhibitors and Anti-inflammatory Agents: Multitarget-Directed Ligands for the Efficient Management of Alzheimer's Disease. *ACS Chem Neurosci.* 2018.
427. Mancini F, Naldi M, Cavrini V, Andrisano V. Multiwell fluorometric and colorimetric microassays for the evaluation of beta-secretase (BACE-1) inhibitors. *Analytical and bioanalytical chemistry.* 2007;388(5-6):1175-83.

### **List of Patent filed**

- Novel sulfonamide derivatives as selective Matrix Metallo Proteinase (MMP) and acetylcholine esterase (AChE) inhibitors as potential therapeutic agents for the treatment of Alzheimer's disease (Application No.201711041328 A).

### **List of Publications from Thesis Work**

- Biological profiling of piperazinediones for the management of anxiety. Devendra Kumar , Gupta SK, Ganeshpurkar A, Singh R, Kumar D, Das N, Krishnamurthy S, Singh SK. Pharmacology Biochemistry and Behavior. 2019 Jan 1;176:63-71.
- Development of Piperazinediones as dual inhibitor for treatment of Alzheimer's disease. Devendra Kumar, Sukesh K. Gupta, Ankit Ganeshpurkar, Gopichand Gutti, Sairam Krishnamurthy, Gyan Modi, Sushil Kumar Singh. European Journal of Medicinal Chemistry. 2018, 150;87-101.
- Biomolecular basis of matrix metallo proteinase-9 activity. Swetha Rayala, Chandrim Gayen, Devendra Kumar, Gyan Prakash Modi, Sushil Kumar Singh. Future Medicinal Chemistry. (<https://doi.org/10.4155/fmc-2017-0236>).
- Secretase inhibitors for the treatment of Alzheimer's disease: Long Road Ahead. Devendra Kumar, Ankit Ganeshpurkar, Dileep Kumar, Gyan Prakash Modi, Sanjeev Kumar Gupta, Sushil Kumar Singh. European Journal of Medicinal Chemistry. 2018, 148; 436-452 (Selected for cover page).
- Design, synthesis and collagenase inhibitory activity of some novel phenylglycine derivatives as metalloproteinase inhibitors. Ankit Ganeshpurkar, Devendra Kumar, Sushil Kumar Singh. International Journal of Biological Macromolecules, Part B. 2018, 107;1491-1500.
- Strategies for the Synthesis of Hydroxamic acids. Ankit Ganeshpurkar, Devendra Kumar, Sushil K. Singh. Current Organic Synthesis. 2018, 15;154-165.

**Presentations in Conferences and Workshops**

- Design Synthesis and Biological Evaluation of Piperazine analogues as Acetylcholinesterase Inhibitor for the Treatment of Alzheimer Disease.  
**Devendra Kumar \***, Sukesh K. Gupta, Ankit Ganeshpurkar, Gopichand Gutti, Sairam Krishnamurthy, Ashok Kumar ,Gyan Modi, Sushil Kumar Singh. **ETDDD** held at IIT BHU,Varanasi during 18-20 January 2018
- Hands-on Workshop on Human/Cancer Cell Culture Techniques & MTT Assay. International Center for Stem Cells, Cancer and Biotechnology (ICSCCB), Pune, India. 7-13 September 2016.
- 13<sup>th</sup> Swiss Course on Medicinal Chemistry in Leysin, Switzerland (07 October, 2018 to 12 October, 2018