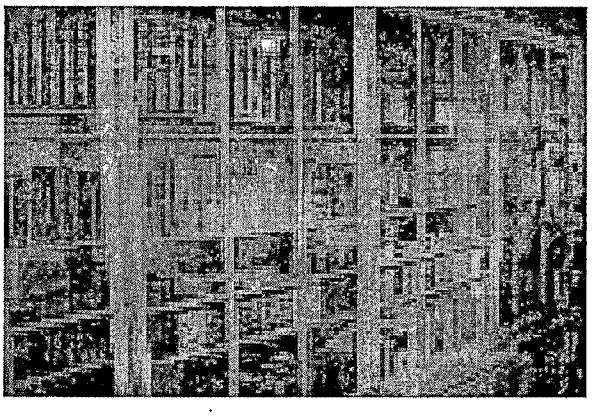

References

REFERENCES

1. Smolen, J. S.; Steiner, G. Therapeutic Strategies for Rheumatoid Arthritis. *Nature Reviews Drug Disco.* 2003, *2*, 473-88.
2. Gabriel, S. E. The epidemiology of rheumatoid arthritis. *Rheum. Dis. Clin. North Am.* 2001, *27*, 269-82.
3. Wolfe, F. E.; Hawley, D. J. The long term outcome of rheumatoid arthritis. Work disability: a prospective 18 year study of 816 patients. *J. Rheumatol.* 1998, *25*, 2108-17.
4. Kumar,V.; Dhingra, S.; Parle, M. Rheumatoid Arthritis at a glance. *Pharma Times* 2005, *37*, 53-55.
5. Dipiro, T. *Pharmacotherapy, A Pathophysiologic Approach*, 5th edition, McGraw-Hill publication, New York, 2002, pp. 1623-38.
6. Haslett, C. R.; Hunter, J. A. A.; Boon, N. A. "Diseases of the connective tissues, joints and bones", in Nuki, J.; Ralston, S.H.; Luqmani, R. (Eds.) *Davidson's Principles and Practice of Medicine*, 18th edition, Churchill Livingstone, New York, 1999, pp. 835-55.
7. American College of Rheumatology Ad Hoc Committe, Guidelines for the management of rheumatoid arthritis. *Arthritis and Rheum.* 1996, *39*, 713-22.
8. Kalden, J. R.; Manger, B. Biological agents in the treatment of inflammatory rheumatic disease. *Curr. Opin. Rheum.* 1997, *9*, 206-12.
9. Muller-Cadner, V.; Gay, R. E.; Gay S. Current pathways of joint destruction. *Curr. Opin. Rheum.* 1997, *9*, 213-20.
10. Sieger, J.; King, S. Recent advances in the pathogenesis of reactive arthritis. *Immunology Today*, 1996, *17*, 160-63.
11. Blackburn, W. D. Management of osteoarthritis and rheumatoid arthritis: prospects and possibilities. *Am J. Med.* 1996, *100 (Suppl. 2A)*, 24S-30S.
12. Smolen, J. S. Validity and reliability of the twenty-eight joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum.* 1995, *38*, 38-43.
13. www.veritasmedicine.com
14. Insel, P.A., "Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout", In Hardmann, J. G.; Limbird, L. E.; Molinoff, P. B.; Ruddon, R. W.; Gilman, A. G. (Eds.) *Goodman's & Gilman's The Pharmacological Basis of Therapeutics*, 9th edition, McGraw Hill, New York, 1996, pp. 617-47.
15. Lorenz, H.M.; Kalden, J.R. Perspectives for TNF-α targeting therapy. *Arthritis Res.* 2002, *4 (Suppl 3)*, S17-S24.
16. Oppenheim, J.J.; Feldmann, M. (Eds.) "Introduction to the role of cytokine in innate host defense and adaptive immunity" in Oppenheim, J.J.; Feldmann, M. "*Cytokine Reference*", Academic Press, New York, 2001, pp. 3-20.
17. Feldmann, M.; Brennan, F.M.; Maini, R.N. Role of cytokines in rheumatoid arthritis. *Ann. Rev. Immunol.* 1996, *14*, 397-440.

18. Odeh, M. Role of cytokines in rheumatoid arthritis. *Drug News Persp.* **1998**, *11*, 331-41.

19. Odeh, M. New insights into the pathogenesis and treatment of rheumatoid arthritis. *Clin. Immunol. Immunpathol.* **1997**, *83*, 103-16.

20. Feldmann, M.; Elliot, M.J.; Woody, J.N.; Maini, R.N. Anti tumor necrosis factor-α therapy of rheumatoid arthritis. *Adv. Immunol.* **1997**, *64*, 283-350.

21. Feldmann, M.; Bondeson, J.; Brennan, F.M.; Foxwell, B.M.J.; Maini, R.N. The rationale for the current boom in anti-TNFα treatment. Is there an active means to define therapeutic targets for drugs that provide all the benefits of anti-TNFα and minimize hazards? *Ann. Rheum. Dis.* **1999**, *58 (Suppl 1)*, 27-31.

22. Brennan, F.M.; Chantry, D.; Jackson, A; Maini, R.; Feldmann, M. Inhibitory effect of TNF-α antibodies on synovial cell interleukin-1 production in rheumatic arthritis. *Lancet* **1998**, *348*, 224-27.

23. Charles, P.; Elliot, M.J.; Davis, D.; Potter, A.; Kalden, J.R.; Antoni, C.; Breedveld, F.C.; Smolen, J.S.; Ebrel, G.; Woody, J.N.; Feldmann, M.; Maini, R.N. Regulation of cytokines and active phase proteins following TNF-α blockade in rheumatoid arthritis. *J. Immunol.* **1999**, *163*, 1521-28.

24. Carswell, E.A.; Old, L.J.; Kassel, R.L.; Green, S.; Fiore, N.; Willamson, B. An endotoxin-induced sereum factor that causes necrosis of tumors. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *2*, 3666-70.

25. Pennica, D.; Nedwin, G.; Hayflick, J.; Seeburg, P.; Derynck, R.; Palladino, M.; Kohr, W.; Aggarwal, B.; Goeddel, D. Human tumor necrosis factor: precursor, structure, expression and homology to lymphotoxin. *Nature*, **1984**, *312*, 724-29.

26. Newton, R.C.; Decicco, C.P. Therapeutic potential and strategies for inhibiting tumor necrosis factor-α. *J. Med. Chem.* **1999**, *42*, 2295-314.

27. Amin, A.R. Regulation of TNF and TACE in human osteoarthritis. *Osteo. & Cartil.* **1999**, *7*, 392-94.

28. Baugh, J.A.; Bucala, R. Mechanisms for modulating TNF-α in immune and inflammatory disease. *Curr. Opin. Drug Disco. Devel.* **2001**, *4*, 635-50.

29. Tracey, K.J.; Cerami, A. Tumor necrosis factor: a pleiotropic cytokine and therapeutic target. *Ann. Rev. Med.* **1994**, *45*, 491-03.

30. Goldfeld, A.E.; Strominger, J.L.; Doyle, C. Human tumor-necrosis-factor-alpha gene-regulation in phorbol ester stimulated T-cell and B-cell lines. *J. Exp. Med.* **1991**, *174*, 73-81.

31. Evans, T. Protective effect of 55 but not 75-kD soluble tumor necrosis factor receptor-immunoglobulin G fusion proteins in an animal model of gram-negative sepsis. *J. Exp. Med.* **1994**, *180*, 2173-79.

32. Tartaglia, L.A.; Pennica, D.; Goeddel, D.V. Ligand passing: the 75-kDa tumor necrosis factor (TNF) receptor recruits TNF for signaling by the 55-kDa TNF receptor. *J. Biol. Chem.* **1993**, *268*, 18542-8.

33. Kulkarni, S.K.; Varghese, N.P. COX-2, TNF-α and apoptosis: newer strategies in inflammatory disorders. *Ind. Drugs* **1998**, *35*, 245-60.

34. Bertolini, D.R.; Nedwin, G.E.; Bringman, T.S.; Smith, D.D.; Mundy, G.R. Stimulation of bone resorption and inhibition of bone formation *in vitro* by human tumor necrosis factor- α. *Nature*, **1986**, *319*, 516-18.

35. Sakalatvala, J. Tumor necrosis factor-α stimulates resorption and inhibits synthesis of proteoglycan in cartilage. *Nature*, 1986, *319*, 547-49.

36. Ahmadzadeh, N.; Shingu, M.; Nobunago, M. The effect of recombinant tumor necrosis factor-alpha on superoxide and metalloproteinase production by synovial cells and chondrocytes. *Clin. Exp.. Rheumatol.* **1990**, *8*, 387-91.

37. Klebanoff, S.J.; Vada, M.A.; Harlan, J.M. Stimulation of neutrophils by tumor necrosis factor. *J. Immunol.* **1986**, *136*, 4220-25.

38. Taylor, P.C. Anti-TNF-α therapy for rheumatoid arthritis: An update. *Intern. Med.* **2003**, *42*, 15-20.

39. Palladino, M.A.; Bahjat, F.R.; Theodorakis, E.A.; Moldawer, L.L. Anti-TNF-α therapies: The next generation. *Nature Rev. Drug Disc.* **2003**, *2*, 736-48.

40. Furst, D.E.; Keystone, E.C.; Breedveld, F.C.; Kalden, J.R.; Smolen, J.S.; Antoni, C.E.; Burmester, G.R.; Crofford, L.J.; kavanaugh, A. Updated consensus statement on tumor necrosis factor blocking agents for the treatment of rheumatoid arthritis and other rheumatic diseases. *Ann. Rheum. Dis.* **2001**, *60*, 2-5.

41. Newton, R.C.; Solomon, K.A.; Covington, M.B.; Deccico, C.P.; Haley, P.J.; Friedeman, S.M.; Vaddi, K. Biology of TACE inhibition. *Ann. Rheum. Dis.* **2001**, *60*, 25-32.

42. Hasegawa, A.; Takasaki, W.; Greene, M. I.; Murali, R. Modifying TNF-α for therapeutic use: A perspective on the TNF receptor system. *Mini. Rev. Med. Chem.* **2001**, *1*, 5-16.

43. Skotnicki, J. S.; DiGrandi, M. J.; Levin J. I. Design strategies for the identification of MMP-13 and TACE inhibitors. *Curr. Opin. Drug Disco. Devel.* **2003**, 6, 742-59.

44. Nelson F.C.; Zask A. The therapeutic potential of small molecule TACE inhibitors. *Exp. Opin. Invest. Drugs* **1999**, *8*, 383-92.

45. Le, G.T.; Abbenante, G. Inhibitors of TACE and Caspase-1 as anti-inflammatory drugs. *Curr. Med. Chem.* **2005**, *12*, 2963-77.

46. Black, R.A.; Rauch, C.T.; Kozlosky, C.J.; peschon, J.J.; Slack, J.L.; Wolfson, M.F.; Castner, B.J.; Stocking, K.L.; Reddy, P.; Srinivasan, S.; Nelson, N.; Boiani, N.; Schooley, K.A.; gerhart, M.; Davis, R.; Fitzner, J.N.; Johnson, R.S.; Paxton,. R.J.; March, C.J.; Cerretti, D.P. A metalloproteinase disintegrin that releases tumor-necrosis factor-alpha from cells. *Nature* **1997**, *385*, 729-33.

47. Moss, M.L.; Jin, S.L.; Milla, M.E.; Bickett, D.M.; Burkhart, W.; Carter, H.L.; Chen, W.J.; Clay, W.C.; Didsbury, J.R.; Hassler, D.; Hoffman, C.R.; Kost, T.A.; Lambert, M.H.; Lessnitzer, M.A.; McCauley, P.; McGeehan, G.; Mitchell, J.; Moyer, M.; Pahel, G.; Rocque, W.; Overton, L.K.; Schoenen, F.; Seaton, T.; Su, J.L.; Becherer, J.D. Cloning of a disintegrin metalloproteinase that processes precursor tumor-necrosis factor-alpha. *Nature* **1997**, *385*, 733-36.

48. Moss, M.L.; Bartsch, J.W. Therapeutic benefits from targeting of ADAM family members. *Biochem.* **2004**, *43*, 7227-35.

49. Milla, M.E.; Leesnitzer, M.A.; Moss, M.L.; Clay, W.C.; Carter, H.L.; Miller, A.B.; Su, J.L. Lambert, M.H.; Willard, D.H.; Sheeley. D.M.; Kost, T.A.; Burkhart, W.; Moyer, M.; Blackburn, R.K.; Pahel, G.L.; Mitchell, J.L.; Hoffman, C.R.; Becherer, J.D. Specific sequence elements are required for the expression of functional tumor necrosis factor-alpha-converting enzyme (TACE). *J. Biol. Chem* 1999, *274*, 30563-70.

50. Maskos, K.; Catalan, C.F.; Huber, R.; Bourenkov, G.P.; Bartunik, H.; Ellestad, G.A.; Reddy, P.; Wolfson, M.F.; Rauch, C.T.; Castner, B.J.; Davis, R.; Clarke, H.R.G.; Petersen, M.; Fitzner, J.N.; Cerreti, D.P.; March, C.J.; Paxton, R.J.; Black, R.A.; Bode, W. Crystal structure of the catalytic domain of human tumor necrosis factor-α-converting enzyme. *Proc. Natl. Acad. Sci. USA* 1998, *95*, 3408-12.

51. Peiretti, F.; canault, M.; Beauclair, P.D.; Berthet, V.; Bonardo, B.; Vague, I.J.; Nalbone, G. Intracellelar maturation and transport of tumor necrosis factor alpha converting enzyme. *Expt. Cell Res.* 2003, *285*, 278-85.

52. Reddy, P.; Slack, J.L.; Davis, R.; Cerretti, D.P.; Kozlosky, C.J.; Blanton, R.A.; Shows, D.; Peschon, J.J.; Black, R.A. Functional analysis of the domain structure of tumor necrosis factor-alpha converting enzyme. *J. Biol. Chem* 2000, *275*, 14608-14.

53. Diaz-Rodriguez, E.; Montero, J.C.; Esparis-Ogando, A.; Yuste, L.; Pandiella, A. Extracellular signal regulated kinase phosphorylates TACE at threonine 735: A potential role in regulated shedding. *Mol. Biol. Cell*, 2002, *13*, 2031-44.

54. Peschon, J.J.; Slack, J.L.; Reddy, P.; Stocking, K.L.; Sunnarborg, S.W.; Lee, D.C.; Russel, W.L.; Castner, B.J.; Johnson, R.S.; Fitzner, J.N.; Boyce, R.W.; Nelson, N.; Kozlosky, C.J.; Wolfson,M.W.; Rauch, C.T.; Cerretti, D.P.; Paxton, R.J.; March, C.J.; Balck, R.A. An essential role in ectodomain shedding in mammalian development. *Science*, 1998, *282*, 1281-84.

55. Black, R.A. Molecules in Focus: Tumor necrosis factor converting enzyme. *Int. J. Biochem. Cell Biol.* 2002, *34*, 1-5.

56. Fan, H.; Derynck, R. Ectodomain shedding of TGF- α and other transmembrane proteins is induced by receptor tyrosine kinase and MAP kinase signaling cascades. *EMBO J.* 1999, *18*, 6962-72.

57. Amour, A.; Slocombe, P.M.; Webster, A.; Butler, M.; Knight, C.G.; Smith, B.J.; Stephens, P.E.; Shelley, C.; Hutton, M.; Knauper, V.; Docherty, A.J.P.; Murphy, G. TACE is inhibited by TIMP-3. *FEBS Lett.* 1998, *435*, 39-44.

58. Solomon, A; Rosenblum, G.; Gonzales, P.E.; Leonards, J.D.; Mobashery, S.; Milla, M.E.; Sagi, I. Pronounced diversity in electronic and chemical properties between the catalytic zinc sites of tumor necrosis factor-α converting enzyme and matrix metalloproteinases despite their high structural similarity. *J. Biol. Chem* 2004, *279*, 31646-54.

59. Lukacova, V.; Zhang, Y.; Kroll, D.M.; Raha, S.; Comez, D.; Balaz, S. A comparison of the binding sites of matrix metalloproteinases and tumor necrosis factor-α converting enzyme: implications for selectivity. *J. Med. Chem* 2005, *48*, 2361-70.

60. Brinckerhoff, C.E. Joint destruction in arthritis: Metalloproteinase in the spotlight. *Arthritis Rheum* 1991, *34*, 1073-75.

61. Close, D.R. Matrix metalloproteinase inhibitors in rheumatic diseases. *Ann. Rheum. Dis.* 2001, *60*, 62-67.

62. Brown, P.D. Ongoing trials with matrix metalloproteinases inhibitors. *Expert Opin. Investig. Drugs* 2000, *9*, 2167-77.

63. Shaw, T.; Nixon, J.S.; Bottomley, K.M. Metalloproteinase inhibitors: new opportunities for the treatment of rheumatoid arthritis and osteoarthritis. *Expert Opin. Investig. Drugs* 2000, *9*, 1469-78.

64. Elliot, S.; Cawston, T. The clinical potential of matrix metalloproteinase inhibitors in the rheumatic disease. *Drugs Aging* 2001, *18*, 87-99.

65. Wasserman, Z.R.; Duan, J.J.W.; Voss, M.E.; Xue, C.B.; Cherney, R.J.; Nelson, D.J.; Hardman, K.D.; Decicco, C.P. Identification of a selective determinant for inhibition of tumor necrosis factor-α converting enzyme by comparative modeling. *Chem & Biol.* 2003, *10*, 215-23.

66. Aranapakam, V.; Davis, J.M.; Grosu, G.T.; Baker, J.; Ellingboe, J.; Zask, A; Levin, J.I.; Sandanayaka, V.P.; Du, M.; Skotnicki, J.S.; DiJoseph, J.F.; Sung, A; Sharr, M.A.; Killar, L.M.; Walter, T.; Jin, G.; Cowling, R.; Tillett, J.; Zhao, W.; McDevitt, J.; Xu, Z.B. Synthesis and structure activity relationship of N-substitued 4-arylsulfonylpiperidine-4-hydroxamic acids as novel orally active matrix metalloproteinase inhibitors for the treatment of osteoarthritis. *J. Med. Chem.* 2003, *46*, 2376-96.

67. Levin, J.I.; Du, M.T.; DiJoseph, J.F.; Killar, L.M.; Walter, T.; Sharr, M.A.; Roth, C.E.; Moy, F.J.; powers, R.; Jin, G.; Cowling, R.; Skotnicki, J.S. The discovery of anthranilic acid based MMP inhibitors. Part 1: SAR of the 3-position. *Bioorg. Med. Chem. Lett.* 2001, *11*, 235-39.

68. Zask, A.; Kaplan, J.; Du, X.M.; macEwan, G.; Sandanayaka, V.; Eudy, N.; Levin, J.; Jin, G.; Xu, J.; Cummons, T.; Barone, D.; Kaloustian, S.A.; Skotnicki, J. Synthesis and SAR of diazepine and thiazepine TACE and MMP inhibitors. *Bioorg. Med. Chem. Lett.* 2005, *15*, 1641-45.

69. Yocum, S.A.; Lopresti-Monow,L.L.; Reeves, L.M.; Mitchell, P.G. In Inhibition of Matrix Metalloproteinnases: Therapeutic Applications; Greenwald, R.A.; Zucker, S.; Golub,L.M. (Eds.) The New York Academy of Sciences:NY,1999, pp. 583-86.

70. Holmbeck, K.; Binaco, P.; Caterina, J.; Yamada, S.; Kromer, M.; Kuznetsov, S.A.; Mankani, M.; Robey, P.G.; Poole, A.R.; Pidoux, I.; Ward, J.M.; Birkedal-Hansen, H. MT-1-MMP-deficient mice develop dwarfism, osteopenia, arthritis, and connective tissue diseases due to inadequate collagen turnover. *Cell*, 1999, 99, 81-92.

71. Conway, J.G.; Andrews, R.C.; Beaudet, B.; Bickett, D.M.; Bonecek, V.; Brodie, T.A.; Clark, R.L.; Crumrine, R.C.; Leenitzer, M.A.; McDougald, D.L.; Han, B.; Hedeen, K.; Lin, P.; Milla, M.; Moss, M.; Pink, H.; Rabinowitz, M.H.; Tippin, T.; Scates, P.W.; Selph, J.; Stimpson, S.A.; Warner, J.; Becherer, J.D. Inhibition of Tumor Necrosis Factor-α (TNF-α) production and arthritis in the rat by GW3333, a dual Inhibitor of TNF-α-converting enzyme and matrix metalloproteinases. *J. Pharm Exp. Ther.* 2001, *298*, 900-05.

72. Robinson, R.P.; Laird, E.R.; Blake, J.F.; Bordner, J.; Donahue, K.M.; Lopresti-Morrow, L.L.; Mitchell, P.G.; Reese, M.R.; Reeves, L.M.; Stam, E.J.; Yocum, S.A.

Structure-based design and synthesis of a potent matrix metalloproteinase-13 inhibitor based on a pyrrolidinone scaffold. *J. Med. Chem.* 2000, *43*, 2293-301.

73. Venkatesan, A.M.; Davis, J.M.; Grosu, G.T.; Baker, J.; Zask, A.; Levin, J.I.; Ellingboe, J.; Skotnicki, J.S.; DiJoseph, J.F.; Sung, A.; Jin, G.; Xu, W.; McCarthy, D.J.; Barone, D. Synthesis and structure-activity relationships of 4-alkynyloxy phenyl sulfanyl, sufinyl and sulfonyl alkyl hydroxamates as tumor necrosis factor-α converting enzyme and matrix metalloproteinase inhibitors. *J. Med. Chem.* 2004, *47*, 6255-69.

74. Zhang, Y.; Xu, J.; Levin. J; Hegen, M.; Li, G.; Robertshaw, H.; brennan, F.; Cummons, T.; Clarke, D.; Vansell, N.; Nickerson-Nutter, C.; Barone, D.; Mohler, K.; Black, R.; Skotnicki, J.; Gibbons, J.; Feldmann, M.; Frost, P.; Larsen, G.; Lin, L.L. Identification and characterization of TMI-1, a novel dual TACE/MMP inhibitor for the treatment of RA. *J. Pharmacol. Expt. Ther.* 2004, *309*, 348-55.

75. Duan, J.J.W.; Chen, L.; Wasserman, Z.R.; Lu, Z.; Liu, R.Q.; Covington, M.B.; Qian, M.; Hardman, K.D.; Magolda, R.L.; Newton, R.C.; Christ, D.D.; Wexler, R.R.; Decicco, C.P. Discovery of γ-lactam hydroxamic acids as selective inhibitors of tumor necrosis factor-α converting enzyme: design, synthesis and structure-activity relationships. *J. Med. Chem.* 2002, *45*, 4954-57.

76. Cherney, R.J.; King, B.W.; Gilmore, J.L., Liu, R.Q.; Covington, M.B.; Duan, J.J.W.; Decicco, C.P. Conversion of potent MMP inhibitors into selective TACE inhibitors. *Bioorg. Med. Chem. Lett.* 2006, *16*, 1028-31.

77. Cherney, R.J.; Mo, R.; Meyer, D.T.; Hardman, K.D.; Liu, R.Q.; Covington, M.B.; Qian, M.; Wasserman, Z.R.; Christ, D.D.; Trzaskos, J.M.; Newton, R.C.; Deccico, C.P. Sultam hydroxamates as matrix metalloproteinase inhibitors. *J. Med. Chem.* 2004, *47*, 2981-90.

78. Levin, J.I. The design and synthesis of aryl hydroxamic acid inhibitors of MMPs and TACE. *Curr. Topic Med. Chem.* 2004, *4*, 1289-310.

79. Zhao, Y.; Feng, W.; Yang, Y.; Ling, L.; Chen, R. Comparison of properties of tumor necrosis factor-alpha converting enzyme (TACE) and some matrix metalloproteases (MMPs) in catalytic domains. J. *Huazhong. Univ. Sci. Technolog. Med. Sci.* 2006, *26*, 637-39.

80. Butler, D.M.; Maini, R.N.; Feldmann, M.; Brennan, F.M. Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures. Comparison of monoclonal anti TNF-alpha antibody with the interleukin-1 receptor antagonist. *Eur. Cytine Netw.* 1995, *6*, 225-30.

81. Kriegler, M.; Perez, C.; DeFay, K.; Albert, I.; Lu, S.D. A novel form of TNF/cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF. *Cell*, 1988, *53*, 45-53.

82. Althoff, k.; Reddy, P.; Voltz, N.; Rose-John, S.; Mullberg, J. Shedding of interleukin-6 receptor and tumor necrosis factor alpha. Contribution of the stalk sequence to the cleavage pattern of transmembrane proteins. *Eur. J. Biochem.* 2000, *267*, 2624-31.

83. Gearing, A.J.H.; beckett, P.; Christodoulou, M.; Churchill, M.; Clements, J.; Davidson, A.H.; Drummond, A.H.; Galloway, W.A.; Gilbert, R.; Gordon, J.L.; Leber, T.M.; mangan, M.; Miller, K.; Nayee, P.; Owen, K.; Patel, S.; Thomas, W.; Wells, G.; Wood, L.M.; Woolley, K. *Nature*, 194, *370*, 555-57.

84. Solomon, K.A.; Covington, M.B.; Deccico, C.P.; Newton, R.C. The fate of pro-TNF-α following inhibition of metalloprotease dependent processing of soluble-TNF-α in human monocytes. *J. Immunol.* **1997**, *159*, 4524-31.

85. Mohan, M.J.; Seaton, T.; Mitchell, J.; Howe, A.; Blackburn, K.; Burkhart, W.; Moyer, M.; Patel, I.; Waitt, G.M.; Becherer, D.; Moss, M.L.; Milla, M.E. The tumor necrosis factor-α converting enzyme (TACE): A unique metalloproteinase with high defined substrate selectivity. *Biochem.* **2002**, *41*, 9462-69.

86. Barlaam, B.; Bird, T.G.; Brempt, L.vanDer; Campbell, D.; Foster, S.J.; Maciewicz, R. New α-substituted succinate-based hydroxamic acids as TNF- α convervatse inhibitors. *J. Med. Chem.* **1999**, *42*, 4890-908.

87. Fujisawa, T.; Igeta, K.; Odake, S; Morita, Y.; Yasuda, J.; Morikawa, T. Highly water soluble matrix metalloproteinases inhibitors and their effects in a rat adjuvant-induced arthritis model. *Bioorg. Med Chem.* **2002**, *10*, 2569-81.

88. Trifilieff, A.; Walker, C; Keller, T.; Kottirsch, G.; Neumann, U. Pharmacological profile of PKF 242-484 and PKF 241-466, novel dual inhibitors of TNF- α converting enzyme and matrix metalloproteinases, in models of airway inflammation. *Br. J. Pharmacol.* **2002**, 135, 1655-64.

89. Watson, B. TNF inhibitors: A review of recent patent literature. *IDrugs*. **2002**, *5*, 1151-61.

90. Rabinowitz, M.H.; Andrews, R.C.; Becherer, J.D. Bickett, D.M.; Bubacz, D.G.; Conway, J.G.; Cowan. D.J.; Gaul, M.; Glennon, K.; Lambert, M.H.; Leesnitzer, M.A. Design of selective and water soluble inhibitors of tumor necrosis factor- α converting enzyme. *J. Med. Chem.* **2001**, *44*, 4252-67.

91. Conway, J.G.; Andrews, R.C.; Beaudet, B.; Bickett, D.M.; Boncek, V.; Brodie, T.A.; Clark, R.L.; Crumrine, R.C.; Leenitzer, M.A.; Mcdougold, D.L.; Han, B.; Hedeen, K.; Lin, P.; Milla, M.; Moss, M.; Pink, H.; Robinwitz, M.H.; Tippin, T.; Scates, P.W.; Selph, J.; Stimpson, S.; Warner, J.; becherer, J.D. Inhibition of TNF-α production and arthritis in the rat by GW-3333, a dual inhibitor of TACE and MMPs. *J. Pharmacol. Expt. Biol.* **2001**, *298*, 900-08.

92. Kottirsch, G.; Koch, G.; Feifel, R.; Neumann, U. β-aryl succinic acid hydroxamate as dual inhibitors of MMPs and TACE. *J. Med. Chem.* **2002**, *45*, 2289-93.

93. Holms, J.; Mast, K.; marcotte, P.; Elmore, I.; Li, J.; Pease, L.; Glaser, K.; Morgan, D.; Michaelides, M.; Davidson, S. Discovery of selective hydroxamic acid inhibitors of TACE. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2907-10.

94. Xue, C.B.; He, X.; Corbett, R.L.; Roderick, R.; Wassermann, Z.R.; Liu, R.Q.; Jaffee, B.D.; Covington, M.B.; Qian, M.; Trzaskos, J.M.; Newton, R.C. Discovery of macrocyclic hydroxamic acids containing biphenyl methyl derivatives at P1', a series of selective TACE inhibitors with potent cellular activity in the inhibition of TNF- α release. *J. Med. Chem.* **2001**, *44*, 3351-54.

95. Skotnicki, J. S.; Levin J. I. "Chapter 16. TNF- α converting enzyme", in Hagemann (Ed.) 'Inflammatory, pulmonary, gastrointestinal diseases', In Dohearty. A.M. (Ed.) *Ann. Reports Med. Chem.* 38, Academic Press, London, **2003**, pp. 153-62.

96. Chen, J.M.; Jin, G.; Sung, A.; Levin J.I. Anthranilate sulphonamide hydroxamate TACE inhibitors. Part 1: Structure based design of novel acetylenic P1' groups. *Bioorg. Med Chem Lett.* 2002, *12*, 1195-98.

97. Levin J.I.; Chen, J.M.; Du, M.T.; Nelson, F.C.; Killar, L.M.; Skala, S. Sung, A.; Jin, G.; Cowling, R.; Barone, D.; March, J.; Mohler, K.M.; Black, R.A.; Skotnicki, J.S. Anthranilate sulphonamide hydroxamate TACE inhibitors. Part II: SAR of acetylenic P1' group. *Bioorg. Med Chem. Lett.* 2002, *12*, 1199-202.

98. Levin, J.I.; Chen, J.M.; Cole, D.C.; Preparation of α-amino acid based sulphonamide hydroxamic acid TACE inhibitors. WO 00/44709, 2000. *Chem Abstr.* 2000, *133*, 150908.

99. Levin, J.I.; Chen, J.M.; Laakso, L.M.; Du, M.; Schmid, J.; Xu, W.; Cummons, T.; Xu, J.; Jin, G.; Barone, D.; Skotnicki, J.S. Acetylenic TACE inhibitors. Part 3: Thiomorpholine sulphonamide hydroxamate. *Bioorg. Med. Chem. Lett.* 2006, *16*, 1605-09.

100. Zhang, Y.; Hegen, M.; Xu, J.; Keith, J.C.; Jin, G.; Du, X.; Cummons, T.; Sheppard, B.J.; Sun, L.H.; Zhu, Y.; Rao, V.R.; Wang, Q.; Xu, W.; Cowling, R.; Nickerson-Nutter, C.L.; Gibbons, J.; Skotnicki, J.; Lin, L.L., Levin, J. Characterization of (2R,3S)-2-({[4-(2-butynyloxy)phenyl]sulphonyl}amino)-N, 3-dihydroxybutanamide, a potent and selective inhibitor of TACE. *Int. Immunopharmacol.* 2004, *4*, 1845-57.

101. Zhou, H.; Afsharvand, M.; Kotake, A.; Duan, L.; Zhang, H.; Noveck, R.; Raible, D. *In vitro, ex vivo, in vivo* inhibition of TNF-α, a potent TACE inhibitor for rheumatoid arthritis. *Ann. Rheum. Dis.* 2005, *64 (Suppl 3)*, 171-75.

102. Thabet, M.M.; Huizinga, T.W.J. Drug evaluation: Apratastat, a novel TACE/MMP inhibitor for rheumatoid arthritis. *Curr. Opin. Invest. Drugs*, 2006, *7*, 1014-19.

103. Zask, A.; Gu, Y.; Albright, J.D.; Du, X.; Hogan, M.; Levin, J.I.; Chen, J.M.; Lillar, L.M.; Sung, A.; Dijoseph, J.F.; Sharr, M.A.; Roth, C.E.; Skala, S.; Jin, G.; Cowling, R.; Mohler, K.M.; Barone, D.; Black, R.; March, C.; Skotnicki, J.S. Synthesis and SAR of bicyclic heteroaryl hydroxamic acid MMP and TACE inhibitors. *Bioorg. Med. Chem. Lett.* 2003, *13*, 1487-90.

104. Nelson, F.C.; Santos, E.D.; Levin, J.I.; Chen, J.M.; Skotnicki, J.S.; DiJoseph, J.F.; Sharr, M.A.; Sung, A.; Killar, L.M.; Cowling, R.; Jin, G.; Roth, C.E.; Albright, J.D. Benzodiazepine Inhibitors of the MMPs and TACE. *Bioorg. Med. Chem. Lett.* 2002, *12*, 2867-70.

105. Levin, J.I.; Nelson, F.C.; Santos, E.D.; Du, M.T.; MacEwan, G.; Chen, J.M.; Ayral-Kaloustian, S.; Xu, J.; Jin, G.; Cummons, T.; Barone, D. Benzodiazepine inhibitors of the MMPs and TACE. Part 2. *Bioorg. Med. Chem. Lett.* 2004, *14*, 4147-51.

106. Letavic, M.A.; Axt, M.Z.; Barberia, J.T.; Carty, T.J.; Danley, D.E.; Geoghegan, K.F.; Halom, N.S.; Hoth, L.R.; Kamath, A.V.; Laird, E.R., Lopresti-Morrow, L.L.; McClure, K.F.; Mitchell, P.G.; Natarajan, V.; Noe, M.C.; Pandit, J.; Reeves, L.; Schulte, G.K.; Snow. S.L.; Sweeney, F.J.; Tan, D.H.; Yu, C.H. Synthesis and biological activity of selective pipecolic acid based TACE inhibitors. *Bioorg. Med. Chem. Lett.* 2002, *12*, 1387-90.

107. Letavic, M.A.; Barberia, J.T.; Carty, T.J.; Hardink, J.R.; Liras, J.; Lopresti-Morrow, L.L.; Mitchell, P.G.; Noe, M.C.; Reeves, L.M.; Snow, S.L.; Stam, E.J.; Sweeney, F.J.; Maughn, M.L.; Yu, C.H. Synthesis and biological activity of piperazine based dual MMP-13 and TACE inhibitor. *Bioorg. Med. Chem. Lett.* 2003, *13*, 3243-46.

108. Park, K.; Aplasca, A.; Du, M.T.; Sun, L.H.; Zhu, Y.; Zhang, Y.; Levin, J.I. Design and synthesis of butynyloxyphenyl β-sulfone piperidine hydroxamates as TACE inhibitors. *Bioorg. Med. Chem. Lett.* 2006, *16*, 3927-31.

109. Condon, J.S.; Joseph-McCarthy, D.; Levin, J.I.; Lombart, H.G.; Lovering, F.E.; Sun, L.; Wang, W.; Xu, W.; Zhang, Y. Identification of potent and selective TACE inhibitor via the S1' pocket. *Bioorg. Med. Chem. Lett.* 2007, *17*, 34-39.

110. Huan, A.; McCarthy, D.J.; Lovering, F.; Sun, L.; Wang, W.; Zhu, Y.; Cui, J.; Zhang, Y.; Levin, J.I. Structure based design of TACE selective inhibitors: Manipulations in the S1'–S3' pocket. *Bioorg. Med. Chem.* 2007, *15*, 6170-81.

111. Duan, J.J.W.; Lu, Z.; Xue, C.B.; He, X.; Seng, J.L.; Roderick, J.J.; Wasserman, Z.R.; Liu, R.Q.; Covington, M.B.; Magolda, R.L.; Newton, R.C.; Trzaskos, J.M.; Decicco, C.P. Discovery of N-hydroxy-2-(2-oxo-3-pyrrolidinyl)acetamides as potent and selective inhibitors of TACE. *Bioorg. Med. Chem. Lett.* 2003, *13*, 2035-40.

112. Grootveld, M.; McDermott, M.F. BMS-561392. *Curr. Opin. Investig. Drugs*, 2003, *4*, 598-602.

113. Duan, J.; Decicco, C.P.; Wasserman, Z.R.; Maduskuie, T.P. Novel lactam metalloproteinase inhibitors. US Patent 000624183.

114. Qian, M.; Bai, S.A.; Brogdon, B.; Wu, J.T.; Liu, R.Q.; Covington, M.B.; Vaddi, K.; Newton, R.C.; Fossler, M.J.; Garner, E.; Deng, Y.; Maduskuies, T.; Trzaskos, J.; Duan, J.J.W.; Decicco, C.P., Christ, D.D. Pharmacokinetics and pharmacodynamics of DPC-333, a potent and selective inhibitor of TACE in rodents, dogs, chimpanzees and humans. *Drug Metab. Dispos.* 2007, *35*, 1916-25.

115. Xue, C.B.; He, X.; Roderick, J.; Corbett, R.L.; Duan, J.J.W.; Liu, R.Q.; Covington, M.B.; Newton, R.C.; Trzaskos, J.M.; Magolda, R.L.; Wexler, R.R.; Decicco, C.P. Rational design, synthesis and structure-activity relationships of a cyclic succinate series of TACE inhibitors. Part 1: Lead identification. *Bioorg. Med. Chem. Lett.* 2003, *13*, 4293-97.

116. Xue, C.B.; He, X.; Roderick, J.; Corbett, R.L.; Duan, J.J.W.; Liu, R.Q.; Covington, M.B.; Quian, M.; Ribadeneira, M.D.; Vaddi, K.; Christ, D.D.; Newton, R.C.; Trzaskos, J.M.; Magolda, R.L.; Wexler, R.R.; Decicco, C.P. Rational design, synthesis and structure-activity relationships of a cyclic succinate series of TACE inhibitors. Part 2: Lead optimization. *Bioorg. Med. Chem. Lett.* 2003, *13*, 4299-304.

117. Duan, J.J.W.; Chen, L.; Lu, Z.; Xue, C.B.; Liu, R.Q.; Covington, M.B.; Qian, M.; Wasserman, Z. R.; Vaddi, K.; Christ, D.D.; Trzaskos, J.M.; Newton, R.C.; Decicco, C.P. Discovery of β-benzamido hydroxamic acids as potent, selective, and orally bioavailable TACE inhibitors. *Bioorg. Med. Chem. Lett.* 2008, *18*, 241-46.

118. Ott, G.R.; Asakawa, N.; Lu, Z.; Liu, R.Q.; Covgington, M.B.; Vaddi, K.; Qian, M.; Newton, R.C.; Christ, D.D.; Trazkos, J.M.; Decicco, C.P.; Duan, J.J.W. α, β-cyclic- β-benzamido hydroxamic acids: Novel templates for the design, synthesis,

and evaluation of selective inhibitors of TACE. *Bioorg. Med. Chem. Lett.* 2008, *18*, 694-99.

119. Ott, G.R.; Asakawa, N.; Liu, R.Q.; Covington, M.B.; Qian, M.; Vaddi, K.; Newton, R.C.; Trzaskos, J.M.; Christ, D.D.; Galya, L.; Scholz, T.; Marshall, W.; Duan, J.J.W. α,β-cyclic-β-benzamido hydroxamic acids: Novel oxaspiro[4.4]nonane templates for the discovery of potent, selective, orally bioavailable inhibitors of TACE. *Bioorg. Med. Chem. Lett.* 2008, *18*, 1288-92.

120. Ott, G.R.; Asakawa, N.; Lu, Z.; Anand, R.; Liu, R.Q.; Covington, M.B.; Vaddi, K.; Qian, M.; Newton, R.C.; Christ, D.D.; Trzaskos, J.M.; Duan, J.J.W. Potent, exceptionally selective, orally bioavailable inhibitors of TACE: Novel 2-substituted-1*H*-benzo[*d*]imidazol-1-yl)methyl) benzamide P1' substituents. *Bioorg. Med. Chem. Lett.* 2008, *18*, 1577-82.

121. Lu, Z.; Ott, G.R.; Anand, R.; Liu, R.Q.; Covington, M.B.; Vaddi, K.; Qian, M.; Newton, R.C.; Christ, D.D.; Trzaskos, J.; Duan, J.J.W. Potent, selective, orally bioavailable inhibitors of TACE: Discovery of indole, benzofuran, imidazopyridine and pyrazolopyridine P1' substituent. *Bioorg. Med. Chem. Lett.* 2008, *18*, 1958-62.

122. Cherney, R.J.; Duan, J.J.W.; Voss, M.E.; Chen, L.; Wang, L.; Meyer, D.T.; Wasserman, Z.R.; Hardman, K.D.; Liu, R.Q.; Covington, M.B.; Qian, M.; Mandlekar, S.; Christ, D.D.; Trzasokos, J.M.; Newton, R.C.; Magolda, R.L.; Wexler, R.R.; Decicco, C.P. Design, synthesis, and evaluation of benzothiadiazepine hydroxamates as selective TACE inhibitors. *J. Med. Chem.* 2003, *46*, 1811-23.

123. Murumkar, P.R.; Giridhar, R.; Yadav, M.R. 3D-Quantitative structure activity relationship studies on benzothiadiazepine hydroxamates as inhibitors of TACE. *Chem. Biol. Drug Des.* 2008, *71*, 363-73.

124. Cross, J.B.; Duca, J.S.; Kaminski, J.J.; Madison, V.S. The active site of a zinc-dependent metalloproteinase influences the computed Pk_a of ligands coordinated to the catalytic zinc atom. *J. Am. Chem. Soc.* 2002, *124*, 11004-07.

125. Gilmore, J.L.; King, B.W.; Asakawa, N.; Harrison, K.; Tebben, A.; Sheppeck, J.E.II; Liu, R.Q.; Covington, M.; Duan, J.J.W. Synthesis and structure activity relationship of a novel, non-hydroxamate series of TACE inhibitors. *Bioorg. Med. Chem. Lett.* 2007, *17*, 4678-82.

126. Duan, J.J.W.; Lu, Z.; Wasserman, Z.R.; Liu, R.Q.; Covington, M.B.; Decicco, C.P. Non-hydroxamate 5-phenylpyrimidine-2,4,6-trione derivatives as selective inhibitors of TACE. *Bioorg. Med. Chem. Lett.* 2005, *15*, 2970-73.

127. Duan, J.J.W.; Chen, L.; Lu, Z.; Jiang, B.; Asakawa, N.; Sheppeck, J.E.II; Liu, R.Q.; Covington, M.B.; Pitts, W.; Kim, S.H.; Decicco, C.P. Discovery of low nanomolar non-hydroxamate inhibitors of TACE. *Bioorg. Med. Chem. Lett.* 2007, *17*, 266-71.

128. Sheppeck, J.E.II; Tebben, A.; Gilmore, J.L.; Yang, A.; Wasserman, Z.R.; Decicco, C.P.; Duan, J.J.W. A molecular modeling analysis of novel non-hydroxamate inhibitors of TACE. *Bioorg. Med. Chem. Lett.* 2007, *17*, 1408-12.

129. Sheppeck, J.E.II, Gilmore, J.L.; Yang, A.; Chen, X.T.; Xue, C.B.; Roderick, J.; Liu, R.Q.; Covington, M.B.; Decicco, C.P.; Duan, J.J.W. Discovery of novel

hydantoins as selective non-hydroxamate inhibitors of TACE. *Bioorg. Med. Chem Lett.* 2007, *17*, 1413-17.

130. Sheppeck, J.E.II, Gilmore, J.L.; Tebben, A.; Xue, C.B.; Liu, R.Q.; Decicco, C.P.; Duan, J.J.W. Hydantoins, triazolones and imidazolones as selective non-hydroxamate inhibitors of TACE. *Bioorg. Med. Chem Lett.* 2007, *17*, 2769-74.

131. Gilmore, J.L.; King, B.W.; Asakawa, N.; Harrison, K.; Tebben, A.; Sheppeck, J.E.II; Liu, R.Q.; Covongton, M.B.; Duan, J.J.W. Synthesis and structure activity relationship of a novel, non-hydroxamate series of TACE. *Bioorg. Med. Chem. Lett.* 2007, *17*, 4678-82.

132. Sawa, M.; Kurokawa, K.; Inoue, Y.; Kondo, H.; Yoshino, K. Discovery of selective phosphonamide based inhibitors of TACE. *Bioorg. Med. Chem. Lett.* 2003, *13*, 2021-24.

133. Moriyama, H.; Tsukida, T.; Inoue, Y.; Kondo, H.; Yoshino, K.; Nishimura, S.I. Structure activity relationship of azasugar based MMP-ADAM inhibitors. *Bioorg. Med. Chem Lett.* 2003, *13*, 2737-40.

134. Moriyama, H.; Tsukida, T.; Inoue, Y.; Kondo, H.; Yoshino, K.; Nishimura, S.I. Design, synthesis and evaluation of novel azasugar based MMP/ADAM inhibitors. *Bioorg. Med. Chem Lett.* 2003, *13*, 2741-44.

135. Park, S.K.; Han, S.B.; Lee, K.; Lee, H.J.; kho, Y.H.; Chun, H.; Choi, Y.; Yang, J.Y.; Yoon, Y.D.; Lee, C.W.; Kim, H.M.; Choi, H.M.; Tae, H.S.; Lee, H.Y.; Nam, K.Y.; Han, G. Gelastatins and their hydroxamates as dual functional inhibitors for TNF-*a* converting enzyme and matrix metalloproteinases: Synthesis, biological evaluation, and mechanism studies. *Biochem. Biophys. Res. Comm.* 2006, *341*, 627-34.

136. Chun, K.; Park, S.K.; Kim, H.M.; Choi, Y.; Kim, M.H.; Park, C.H.; Joe, B.Y.;Chun, T.G.; Choi, H.M.; Lee, H.Y.; Hong, S.H.; Kim, M.S.; Nam, K.Y.; Han, G. Chromen-based TACE inhibitors: Design, synthesis, and biological evaluation. *Bioorg. Med. Chem* 2008, *16*, 530-35.

137. Freskos, J.N.; Mischke, B.V.; Decrescenzo, G.A.; Heintz, R.; Getman, D.P.; Howard, S.C.; Kishore, N.N.; McDonald, J.J.; Munie, G.E.; Rangwala, S. *Bioorg. Med. Chem Lett.* 1999, *9*, 943-48.

138. Govind Rao, B.; Bandarage, U.K.; Wang, T.; Come, J.H.; Perola, E.; Wei, Y.; Tian, S.K.; Saunders, J.O. Novel thiol based TACE inhibitors: rational design, synthesis, and SAR of thiol-containing aryl sulphonamides. *Bioorg. Med. Chem Lett.* 2007, *17*, 2250-53.

139. Bandarage, U.K.; Wang, T.; Come, J.H.; Perola, E.; Wei, Y.; Govind Rao, B. Novel thiol based TACE inhibitors. Part 2: Rational design, synthesis, and SAR of thiol containing aryl sulphons. *Bioorg. Med. Chem Lett.* 2008, *18*, 44-48.

140. Niu, X.; Umland, S.; Ingram, R.; Beyer, B.M.; Liu, Y.H.; Sun, J.; Lundell, D.; Orth, P. IK-682, a tight binding inhibitor of TACE. *Arch. Biochem Biophys.* 451, *2006*, 43-50.

141. Kenny, P.A. Tackling EGFR signaling with TACE antagonists: a rational target for metalloprotease inhibitors in cancer. *Expert Opin. Ther. Targets*, 2007, *11*, 1287-98.

142. Aldrich Research Chemicals Catalogue, 2000; pp. 188.

143. Hayashi, H.; Miwa, Y.; Miki, I.; Ichikawa, S.; Yoda, N.; Ishii, A.; Kono, M.; Suzuki, F. 5-HT_3 receptor antagonists. 1. New quinoline derivatives. *J. Med. Chem.* **1992**, *35*, 4893-902.

144. El Ashray, E.S.H.; Ramadan, E.S.; Hamid, H.A.; Hagar, M. Microwave assisted synthesis of quinoline derivatives from isatin. *Syn. Comm.* **2005**, *35*, 2243-50.

145. Aldrich Research Chemicals Catalogue, 2000, pp. 1299.

146. Wasfy, A.A.F.; Nassar, S.A.; Eissa, A.M.F. Heterocycles derived from 2-amino-5-[6-(dibenzothien-4-yl)-4,5-dihydropyridazin-3-yloxymethyl]-1,3,4-thiadiazole. *Ind. J. Chem.* **1996**, *35B*, 1218-20.

147. Tu, G.G.; Li, S.H.; Li, G.; Xiong, F.; Mai, X.; Zhu, H.; Kuang, B.; Xu, W.F. Novel aminopeptidase N inhibitors derived from 1,3,4-thiadiazole scaffold. *Bioorg. Med. Chem.* **2008**, *16*, 6663-68.

148. King, L.C.; Hlavacek, R.J. The reaction of ketones with iodine and thiourea. *J. Am. Chem. Soc.* **1950**, *72*, 3722-24.

9

149. Gorbatenko, V. I.; Samarai, L. I. *Synthesis*, **1980**, *2*, 85-110.

150. Shia, K. S.; Li, W. T.; Chang, C. M.; Hsu, M. C.; Chern, J. H.; Leong, M. K.; Tseng, S. N.; Lee, C. C.; Lee, Y. C.; Chen, S. J.; Peng, K. C.; Tseng, H. Y.; Chang, Y. L.; Tai, C. L.; Shin, S. R. Design, synthesis and structure-activity relationship of pyridyl imidazolidinones: A novel class of potent and selective Human Enterovirus 71 inhibitors. *J. Med. Chem.* **2002**, *45*, 1644-54.

151. Chern, J. H.; Chang, C. S.; Tai, C. L.; Lee, Y. C.; Lee, C. C.; Kang, I. J.; Lee, C. Y.; Shin, S. R. Synthesis and antipicornavirus activity of (*R*)- and (*S*)-1-[5-(4'-chlorobiphenyl-4-yloxy)-3-methylpentyl]-3-pyridin-4-yl-imidazolidin-2-one. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4206-11.

152. Frank, R.L.; Smith, P.V. The preparation of mercaptans from alcohols. *J. Am. Chem. Soc.* **1946**, *68*, 2103-04.

153. Szarek, W.A.; Kong, X. "Direct halogenation of carbohydrate derivatives", In Hanessian, S. (Ed.) Preparative Carbohydrate Chemistry, CRC Press, New York, 1997, pp. 107-108.

154. Kirkegaard, T; Pedersen, G; Saermark, T; Brynskov, J. Tumor necrosis factor-α converting enzyme (TACE) activity in human colonic epithelial cells. *Clin. Exp. Immunol.* **2004**, *135*, 146-53.

155. www.merckbiosciences.com/product/CBA042, User Protocol CBA042 Rev.

156. Crowe, P.D.; Walter, B.N.; Mohler, K.M.; Evans, C.O.; BVlack, R.A.; Ware, C. F. A metalloprotease inhibitor blocks shedding of the 80-kD TNF receptor and TNF processing in T Lymphocytes. *J. Exp. Med.* **1995**, *181*, 1205-10.