
QUALIFICATIONS

JOHN M WETZEL, PHD
PRINCIPAL
WETZEL CHEMISTRY CONSULTING, LLC



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PROFESSIONAL POSITIONS

Ohio University, Athens, OH
2007 – present:
Visiting Assistant Professor, Department of Chemistry and Biochemistry

Wetzel Chemistry Consulting, LLC, Albany, OH
2005 – present:
Principal

How Clients Benefited in Drug Discovery:

- Several chemical series were prioritized according to their potential to yield drug-like leads for an anti-cancer target
- The binding mode, structure-activity relationships and likely sites of off-target binding were elucidated for two leading chemical series
- Predicted off-target binding was experimentally verified for several key cross-reactivity sites
- Testing strategies were designed and implemented for efficient prioritization of new compounds and minimization of off-target interactions
- New analogs with improved selectivity for the desired target were identified
- Patent applications were carefully written, Examiner concerns were addressed and patents were issued

How Clients Benefited in Drug Development:

- Chemistry, Manufacturing and Controls (CMC) documents were provided in support of Investigational New Drug Application (IND), New Drug Application (NDA) and post-approval change filings
- Chemistry concerns raised by regulatory agencies were successfully addressed; one drug received U.S. marketing approval
- Technical challenges were solved in active pharmaceutical ingredient (API) synthesis
- API manufacturing costs were reduced
- Toxic and environmentally hazardous chemistry was eliminated from an API synthetic process

Lundbeck Research USA, Paramus, NJ

2003 – 2005:

Director, Chemistry Support Services

- Led project teams for MCH1 antagonist discovery and Chemistry Technology Platform development.
- Co-led the selection of an automated storage / retrieval strategy for the Lundbeck screening collection worldwide.

Synaptic Pharmaceutical Corporation, Paramus, NJ

1990 – 2003:

Positions of increasing responsibility, culminating in Director, Chemistry

- Managed 40 FTEs, including Medicinal, Computational, Analytical and Bioanalytical Chemists.
- Managed the outsourcing of Chemistry, Manufacturing and Controls (CMC) efforts for preclinical and clinical development of a novel anti-depressant, including chemical process development, GMP-compliant synthesis, GLP-compliant analysis and bioanalysis, and formulation. Contributed CMC section to IND filing and annual update.
- Designed and synthesized alpha-1a adrenoceptor antagonists for treatment of benign prostatic hyperplasia.
- Discovered the first subtype-selective alpha-1a antagonist, SNAP 5089.
- Discovered highly selective alpha-1d adrenoceptor antagonists exemplified by SNAP 8493.
- Designed and implemented a novel strategy for the efficient characterization, purification and formatting of combinatorial libraries culminating in neat solid archive samples.
- Developed a novel LCMS-guided HPLC purification strategy for library purification.
- Conducted numerous HPLC separations, including enantioselective separations and high-throughput library purifications, on milligram and gram scales.
- Procured and maintained NMR, LCMS, HPLC and other instruments.

Suntory Institute for Bioorganic Research, Osaka, Japan

1988 – 1990:

Postdoctoral Fellow

- Explored the chemical relationship between the brown planthopper (*Nilaparvata lugens*) and its intracellular yeast-like symbiote through deuterium labeling and GCMS techniques.
- Advisors: Prof. Koji Nakanishi and Dr. Yoko Naya.

EDUCATION

The Johns Hopkins University, Ph.D., Chemistry, 1988

- Dissertation: Part I: Silicon-promoted ring contractions in the synthesis of carbocyclic spiro compounds. Total synthesis of (-)-solavetivone. Part II: The trimethylsilyl cationic species as a bulky proton. Application to chemoselective dioxolanation.
- Advisor: Prof. Reuben Jih-Ru Hwu.

Ohio University, B.S., Chemistry, 1982

GRANTS

1. Tool Compounds for Alpha Adrenoceptors. SBIR Phase I (1995). #2 R43 NS-33418-02 ZRG7 SSS-Z (15), \$75,000.
 2. Tool Compounds for Alpha Adrenoceptors. SBIR Phase II (1996). #2 R44 NS-33418-02 ZRG7 SSS-Z (15), \$750,000.
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PATENTS

1. Use of α 1C Specific Compounds to Treat Benign Prostatic Hyperplasia. Gluchowski, C.; Furray, C.C.; Chiu, G.; Brancheck, T.A.; Wetzel, J.M.; Hartig, P.R. (1995). U.S. Patent 5,403,847.
2. Use of α -1C Specific Compounds to Treat Benign Prostatic Hyperplasia. Gluchowski, C.; Furray, C.C.; Chiu, G.; Brancheck, T.A.; Wetzel, J.M.; Hartig, P.R. (1996). U.S. Patent 5,578,611.
3. Dihydropyridines and New Uses Thereof. Gluchowski, C.; Wetzel, J.M.; Chiu, G.; Marzabadi, M.R.; Wong, W.C.; Nagarathnam, D. (1998). U.S. Patent 5,767,131.
4. Use of α 1c Specific Compounds to Treat Benign Prostatic Hyperplasia. Gluchowski, C.; Furray, C.C.; Chiu, G.; Brancheck, T.A.; Wetzel, J.M.; Hartig, P.R. (1998). U.S. Patent 5,780,485.
5. α 1C Specific Compounds to Treat Benign Prostatic Hyperplasia. Gluchowski, C.; Furray, C.C.; Chiu, G.; Brancheck, T.A.; Wetzel, J.M.; Hartig, P.R. (1999) U.S. Patent 5,990,128.
6. Use of Alpha-1C Specific Compounds to Treat Benign Prostatic Hyperplasia. Gluchowski, C.; Furray, C.C.; Chiu, G.; Brancheck, T.A.; Wetzel, J.M.; Hartig, P.R. (2000) U.S. Patent 6,015,819.
7. Dihydropyridines and New Uses Thereof. Gluchowski, C.; Wetzel, J.M.; Chiu, G.; Marzabadi, M.R.; Wong, W.C.; Nagarathnam, D. (2001) U.S. Patent 6,211,198.
8. Dihydropyridines and New Uses Thereof. Gluchowski, C.; Wetzel, J.M.; Chiu, G.; Marzabadi, M.R.; Wong, W.C.; Nagarathnam, D. (2001) U.S. Patent 6,310,076.
9. Use of α 1C Specific Compounds to Treat Benign Prostatic Hyperplasia. Gluchowski, C.; Furray, C.C.; Chiu, G.; Brancheck, T.A.; Wetzel, J.M.; Hartig, P.R. (2003). U.S. Patent 6,602,888.
10. Dihydropyridines and New Uses Thereof. Gluchowski, C.; Wetzel, J.M.; Chiu, G.; Marzabadi, M.R.; Wong, W.C.; Nagarathnam, D. (2003). U.S. Patent 6,608,086.
11. Compounds Specific for the Human α 1d Adrenergic Receptor and Uses Thereof. Konkel, M.; Wetzel, J.M.; Noble, S.A.; Gluchowski, C.; Craig, D.A. (2004). U.S. Patent 6,706,716.
12. Selective Melanin Concentrating Hormone-1 (MCH1) Receptor Antagonists and Uses Thereof. Marzabadi, M.R.; Wetzel, J.; DeLeon, J.E.; Lagu, B; Gluchowski, C.; Noble, S.; Nagarathnam, D. (2004). U.S. Patent 6,720,324.
13. Substituted Anilinic Piperidines as MCH Selective Antagonists. Marzabadi, M.R.; Wetzel, J.; DeLeon, J.E.; Jiang, Y.; Chen, C.-A.; Lu, K. (2004). U.S. Patent 6,727,264.
14. Substituted Anilinic Piperidines as MCH Selective Antagonists. Marzabadi, M.R.; Wetzel, J.; DeLeon, J.E.; Jiang, Y.; Chen, C.-A.; Lu, K. (2006). U.S. Patent 7,067,534.
15. Use of GALR3 Receptor Antagonists for the Treatment of Depression and/or Anxiety and Compounds Useful in Such Methods. Konkel, M.; Wetzel, J.M.; Talisman, J. (2006). U.S. Patent 7,081,470.
16. Substituted Alkyl Amido Piperidines. Marzabadi, M.R.; Wetzel, J.; Chen, C.-A.; Jiang, Y.; Lu, K. (2006). U.S. Patent 7,105,544.
17. 3-Imino-2-indolones for the Treatment of Depression and/or Anxiety. Konkel, M.; Wetzel, J.M.; Talisman, J. (2007). U.S. Patent 7,166,635.
18. Substituted Alkyl Amido Piperidines. Marzabadi, M.R.; Wetzel, J.; Chen, C.-A.; Jiang, Y.; Lu, K. (2007). U.S. Patent 7,199,135.
19. Spirocyclic Piperidines as MCH1 Antagonists and Uses Thereof. Marzabadi, M.R.; Jiang, Y.; Lu, K.; Chen, C.-A.; De Leon, J.E.; Wetzel, J.M.; Andersen, K. (2008). U.S. Patent 7,335,665.
20. Use of GALR3 Antagonist for Treatment of Depression and/or Anxiety and Compounds

- Useful in Such Methods. Blackburn, T.P.; Konkel, M.J.; Boteju, L.W.; Talisman, I.J.; Wetzel, J.M.; Packiarajan, M.; Chen, H.; Jimenez, H. (2008). U.S. Patent 7,465,750.
21. Secondary Amino Anilinic Piperidines as MCH1 Antagonists and Uses Thereof. Marzabadi, M.R.; Jiang, Y.; Lu, K.; Chen, C.-A.; De Leon, J.E.; Wetzel, J.M. (2009). U.S. Patent 7,473,698.
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PUBLICATIONS

1. Mechanistic studies in the deoxygenation of pyridine N-oxide: new 1,2 elimination. Hwu, J.R.; Wetzel, J.M. (1985) *Journal of Organic Chemistry* 50(3), 400-2.
2. The trimethylsilyl cationic species as a bulky proton. Application to chemoselective dioxolanation. Hwu, J.R.; Wetzel, J.M. (1985) *Journal of Organic Chemistry* 50(20), 3946-8.
3. Calcium in liquid ammonia for the reduction of benzyl ethers. Mechanistic clues derived from chemoselectivity studies. Hwu, J.R.; Chua, V.; Schroeder, J.E.; Barrans, R.E., Jr.; Khoudary, K.P.; Wang, N.; Wetzel, J.M. (1986) *Journal of Organic Chemistry* 51(24), 4731-3.
4. General scope of 1,3-dioxolanation of α,β -unsaturated aldehydes with 1,2-bis(trimethylsilyloxy)ethane and trimethylsilyl trifluoromethanesulfonate. Hwu, J.R.; Leu, L.C.; Robl, J.A.; Anderson, D.A.; Wetzel, J.M.. (1987) *Journal of Organic Chemistry* 52(2), 188-91.
5. Silicon-promoted ring contractions in the formation of carbocyclic spiro compounds. Total synthesis of (-)-solavetivone. Hwu, J.R.; Wetzel, J.M. (1992) *Journal of Organic Chemistry* 57(3), 922-8.
6. Diversity in steroidogenesis of symbiotic microorganisms from planthoppers. Wetzel, J.M.; Ohnishi, M.; Fujita, T.; Nakanishi, K.; Naya, Y.; Noda, H.; Sugiura, M. (1992) *Journal of Chemical Ecology* 18(11), 2083-94.
7. Comparison of the electronic effect and the steric influence between the 1,1,2,2,2-pentamethyldisilyl and the trimethylsilyl groups. Hwu, J.R.; Wetzel, J.M.; Lee, J.S.; Butcher, R.J. (1993) *Journal of Organometallic Chemistry* 453(1), 21-8.
8. The α 1-adrenergic receptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned human α 1c subtype. Forray, C.; Bard, J.A.; Wetzel, J.M.; Chiu, G.; Shapiro, E.; Tang, R.; Lepor, H.; Hartig, P.R.; Weinshank, R.L.; Branchek, T.A.; Gluchowski, C. (1994) *Molecular Pharmacology* 45(4), 703-8.
9. Discovery of α 1a-adrenergic receptor antagonists based on the L-type Ca^{2+} channel antagonist nifedipine. Wetzel, J. M.; Miao, S.W.; Forray, C.; Borden, L.A.; Branchek, T.A.; Gluchowski, C. (1995) *Journal of Medicinal Chemistry* 38(10), 1579-81.
10. Fragmentation studies of ergosterol. The formation of the fragment ion at m/z 337. Kenney, P.T.M.; Wetzel, J.M. (1995) *European Mass Spectrometry* 1(4), 411-13.
11. Modeling and mutagenesis of the human α 1a-adrenoceptor: orientation and function of transmembrane helix V sidechains. Wetzel, J.M.; Salon, J.A.; Tamm, J.A.; Forray, C.; Craig, D.; Nakanishi, H.; Cui, W.; Vaysse, P.J.-J.; Chiu, G.; Weinshank, R.L.; Hartig, P.R.; Branchek, T.A.; Gluchowski, C. (1996) *Receptors and Channels* 4(3), 165-177.
12. Localization of mRNA and receptor binding sites for the α 1a-adrenoceptor subtype in the rat, monkey and human urinary bladder and prostate. Walden, P.D.; Durkin, M.M.; Lepor, H.; Wetzel, J.M.; Gluchowski, C.; Gustafson, E.L. (1997) *Journal of Urology* (Baltimore) 157(3), 1032-1038.
13. Characterization of specific binding of [^{125}I]L-762,459, a selective α 1A-adrenoceptor radioligand to rat and human tissues. O'Malley, S.S.; Chen, T.B.; Francis, B.E.; Gibson, R.E.; Burns, H.D.; DiSalvo, J.; Bayne, M.L.; Wetzel, J.M.; Nagarathnam, D.; Marzabadi, M.; Gluchowski, C.; Chang, R.S.L. (1998) *European Journal of Pharmacology* 348(2/3), 287-295.
14. Identification of a dihydropyridine as a potent α 1a adrenoceptor-selective antagonist that inhibits phenylephrine-induced contraction of the human prostate. Wong, W.C.; Chiu, G.; Wetzel, J.M.; Marzabadi, M.R.; Nagarathnam, D.; Wang, D.; Fang, J.; Miao, S.W.; Hong, X.; Forray, C.; Vaysse, P.J.J.; Branchek, T.A.; Gluchowski, C.; Tang, R.; Lepor, H. (1998) *Journal of Medicinal Chemistry* 41(14), 2643-2650.
15. Design and synthesis of novel α 1a adrenoceptor-selective dihydropyridine antagonists for the treatment of benign prostatic hyperplasia. Nagarathnam, D.; Wetzel, J.M.; Miao, S.W.; Marzabadi, M.R.; Chiu, G.; Wong, W.C.; Hong, X.; Fang, J.; Forray, C.; Branchek, T.A.;

- Heydorn, W.E.; Chang, R.S.L.; Broten, T.; Schorn, T.W.; Gluchowski, C. (1998) *Journal of Medicinal Chemistry* 41(26), 5320-5333.
16. Design and synthesis of novel dihydropyridine α -1A antagonists. Marzabadi, M.R.; Hong, X.; Nagarathnam, D.; Miao, S.; Chiu, G.; Wong, W.C.; Wetzel, J.M.; Fang, J.; Forray, C.; Chen, T.B.; O'Malley, S.S.; Chang, R.S.L.; Gluchowski, C. (1999) *Bioorganic & Medicinal Chemistry Letters* 9(19), 2843-2848.
 17. Design and synthesis of novel α 1a adrenoceptor-selective antagonists. 4. Structure-activity relationship in the dihydropyrimidine series. Wong, W.C.; Sun, W.; Lagu, B.; Tian, D.; Marzabadi, M.R.; Zhang, F.; Nagarathnam, D.; Miao, S.W.; Wetzel, J.M.; Peng, J.; Forray, C.; Chang, R.S.L.; Chen, T.B.; Ransom, R.; O'Malley, S.; Broten, T.P.; Kling, P.; Vyas, K.P.; Zhang, K.; Gluchowski, C. (1999) *Journal of Medicinal Chemistry* 42(23), 4804-4813.
 18. Design and synthesis of novel α 1a adrenoceptor-selective antagonists. 1. Structure-activity relationship in dihydropyrimidinones. Nagarathnam, D.; Miao, S.W.; Lagu, B.; Chiu, G.; Fang, J.; Dhar, T.G.M.; Zhang, J.; Tyagarajan, S.; Marzabadi, M.R.; Zhang, F.; Wong, W.C.; Sun, W.; Tian, D.; Wetzel, J.M.; Forray, C.; Chang, R.S.L.; Broten, T.P.; Ransom, R.W.; Schorn, T.W.; Chen, T.B.; O'Malley, S.; Kling, P.; Schneck, K.; Bendesky, R.; Harrell, C.M.; Vyas, K.P.; Gluchowski, C. (1999) *Journal of Medicinal Chemistry* 42(23), 4764-4777.
 19. Design and synthesis of novel α 1a adrenoceptor-selective antagonists. 2. Approaches to eliminate opioid agonist metabolites via modification of linker and 4-methoxycarbonyl-4-phenylpiperidine moiety. Dhar, T.G.M.; Nagarathnam, D.; Marzabadi, M.R.; Lagu, B.; Wong, W.C.; Chiu, G.; Tyagarajan, S.; Miao, S.W.; Zhang, F.; Sun, W.; Tian, D.; Shen, Q.; Zhang, J.; Wetzel, J.M.; Forray, C.; Chang, R.S.L.; Broten, T.P.; Schorn, T.W.; Chen, T.B.; O'Malley, S.; Ransom, R.; Schneck, K.; Bendesky, R.; Harrell, C.M.; Vyas, K.P.; Zhang, K.; Gilbert, J.; Pettibone, D.J.; Patane, M.A.; Bock, M.G.; Freidinger, R.M.; Gluchowski, C. (1999) *Journal of Medicinal Chemistry* 42 (23), 4778-4793.
 20. De novo design of a novel oxazolidinone analogue as a potent and selective α 1A adrenergic receptor antagonist with high oral bioavailability. Lagu, B.; Tian, D.; Jeon, Y.; Li, C.; Wetzel, J.M.; Nagarathnam, D.; Shen, Q.; Forray, C.; Chang, R.S.L.; Broten, T.P.; Ransom, R.W.; Chan, T.-B.; O'Malley, S.S.; Schorn, T.W.; Rodrigues, A.D.; Kassahun, K.; Pettibone, D.J.; Freidinger, R.; Gluchowski, C. (2000) *Journal of Medicinal Chemistry* 43(15), 2775-2778.
 21. Determination of the relative and absolute stereochemistry of a potent and α 1A-selective adrenoceptor antagonist. Lagu, B.; Wetzel, J.M.; Forray, C.; Patane, M.A.; Bock, M.G. (2000) *Bioorganic & Medicinal Chemistry Letters* 10(24), 2705-2707.
 22. Identification and characterization of two G protein-coupled receptors for neuropeptide FF. Bonini, J.A.; Jones, K.A.; Adham, N.; Forray, C.; Artymyshyn, R.; Durkin, M.M.; Smith, K.E.; Tamm, J.A.; Boteju, L.W.; Lakhiani, P.P.; Raddatz, R.; Yao, W.-J.; Ogozalek, K.L.; Boyle, N.; Kouranova, E.V.; Quan, Y.; Vaysse, P.J.; Wetzel, J.M.; Brancheck, T.A.; Gerald, C.; Borowsky, B. (2000) *Journal of Biological Chemistry* 275(50), 39324-39331.
 23. Synthesis and structure-activity relationship of fluoro analogues of 8-{2-[4-(4-methoxyphenyl)piperazin-1-yl]ethyl}-8-azaspiro[4.5]decane-7,9-dione as selective α (1d)-adrenergic receptor antagonists. Konkel, M.J.; Wetzel, J.M.; Cahir, M.; Craig, D.A.; Noble, S.A.; Gluchowski, C. (2005) *Journal of Medicinal Chemistry* 48(8), 3076-3079.
 24. Synthesis and SAR Investigations for Novel Melanin-Concentrating Hormone 1 Receptor (MCH1) Antagonists Part 1. The Discovery of Arylacetamides as Viable Replacements for the Dihydropyrimidinone Moiety of an HTS Hit. Jiang, Y.; Chen, C.-A.; Lu, K.; Daniewska, I.; De Leon, J.; Kong, R.; Forray, C.; Li, B.; Hegde, L.G.; Wolinsky, T.D.; Craig, D.A.; Wetzel, J.M.; Andersen, K.; Marzabadi, M. (2007) *Journal of Medicinal Chemistry* 50(16), 3870-3882.
 25. Synthesis and SAR Investigations for Novel Melanin-Concentrating Hormone 1 Receptor (MCH1) Antagonists Part 2: A Hybrid Strategy Combining Key Fragments of HTS Hits. Chen, C.-A.; Jiang, Y.; Lu, K.; Daniewska, I.; Mazza, C.G.; Negron, L.; Forray, C.; Parola, T.; Li, B.; Hegde, L.G.; Wolinsky, T.D.; Craig, D.A.; Kong, R.; Wetzel, J.M.; Andersen, K.; Marzabadi, M. (2007) *Journal of Medicinal Chemistry* 50(16), 3883-3890.

SELECTED PRESENTATIONS

1. Binding and intrinsic activity profiles of 4-aminoquinazolines and 4-aminoquinolines at cloned human α adrenergic receptors. Wetzel, J.M., Miao, S.W., Gluchowski, C., Forray,

- C., Vaysse, P.J.-J., Borden, L.A., Brancheck, T.A., Bard, J.A., Weinshank, R.L. and Hartig, P.H. (1993). Presented at the 206th American Chemical Society National Meeting, Chicago, IL, Aug. 22-27, MEDI 53.
2. Use of recombinant human alpha adrenergic receptors for the pharmacological evaluation of alpha adrenergic ocular hypotensive agents. Gluchowski, C., Jeon, Y.T., Wetzel, J.M., Vaysse, P.J.-J., Brancheck, T.A., Weinshank, R.L., Borden, L.A., Bard, J.A., Hartig, P.R. and Forray, C. (1994). *Invest. Ophthalmol. Vis. Sci.* 35, 1399, 669.
 3. Distribution of the α 1A adrenoceptor in rat CNS - Comparison of in situ hybridization and receptor autoradiography studies. Durkin, M.M., Gustafson, E.L., Forray, C., Smith, K.E., Wetzel, J.M., Gluchowski, C., Brancheck, T.A. (1995). Society for Neuroscience Annual Meeting, San Diego, CA.
 4. Hypotensive potency of α -1 adrenergic receptor antagonists in spontaneously hypertensive rats (SHR) correlates with binding affinity for the α -1d receptor subtype. Scott, A., Broten, T., Siegl, P., Bock, M., DiPardo, R., Payne, L., Chiu, G., Wetzel, J., Marzibadi, M.R., Gluchowski, C., Forray, C. (1999). *FASEB J.* 13, 150.6.
 5. Autoradiographic distribution of the α 1D-AR in the rat CNS. Cahir, M., Konkell, M.J., Durkin, M.M., Wetzel, J.M., Brancheck, T.A., Craig, D.A. (1998). Joint Meeting British Pharmacological Society and The Physiological Society, Southampton, U.K.
 6. A Genomic Approach to Drug Discovery: MCH-1 Antagonists for the Treatment of Obesity and Affective Disorders. Wetzel, J.M. (2003) Case Western Reserve University Department of Chemistry.
 7. 3-Phenyl-2-indolylcarbohydrazide and their azo analogues as potent antagonists for the GalR3 receptor. Topiwala, U.P.; Chen, H.; Jimenez, H.; Reitman, M.; Wetzel, J.M.; Walker, M.; Han, K.; Boyle, N.; Caputo, G.; Muske, G.; Konkell, M.J. (2004) Abstracts of Papers, 228th ACS National Meeting, Philadelphia, PA, MEDI-030.
 8. Discovery of 3-phenyl-2-indolylcarbohydrazides as antagonists of the GalR3 receptor. Chen, H.; Topiwala, U.P.; Boteju, L.W.; Eldemenky, E.; Jimenez, H.; Reitman, M.; Walker, M.W.; Han, K.; Boyle, N.; Caputo, G.; Muske, G.; Yang, J.; Konkell, M.J.; Wetzel, J.M. (2004) Abstracts of Papers, 228th ACS National Meeting, Philadelphia, PA, MEDI-031.
 9. Enhancement of Flexibility, Efficiency and Data Quality through Logistics Optimization. Wetzel, J.M. (2005) Drug Discovery Technology 2005, Boston, MA.
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