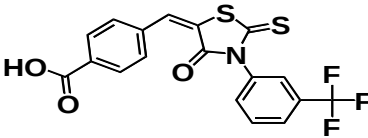
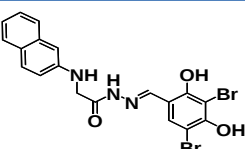
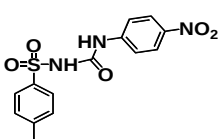
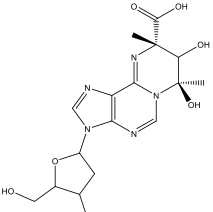
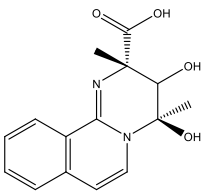
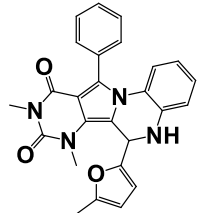
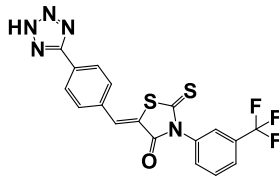
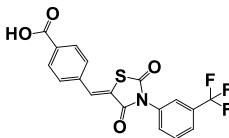
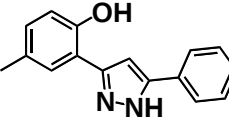
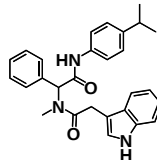
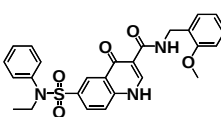
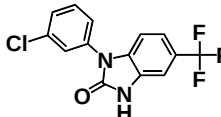
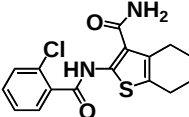
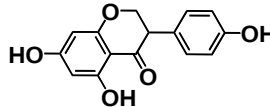
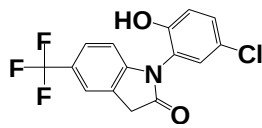
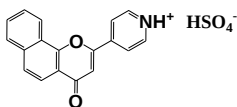


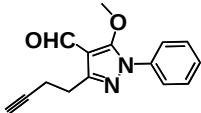
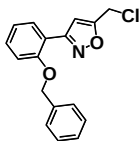
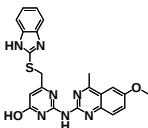
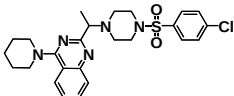
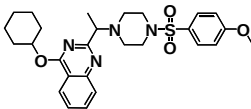
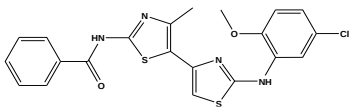
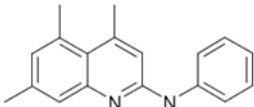
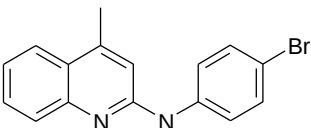
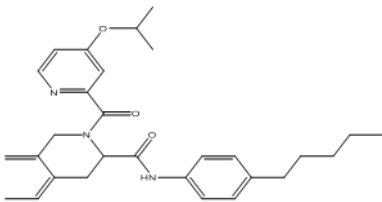
CHEMICAL COMPOUND INVENTORY LISTING

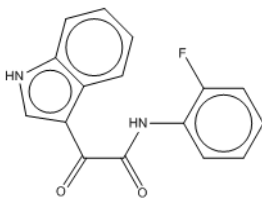
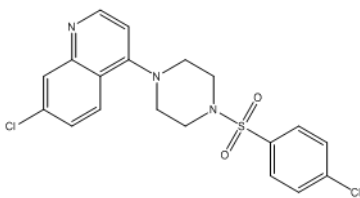
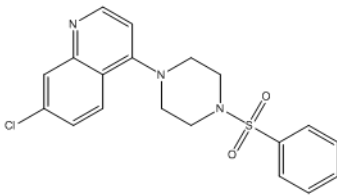
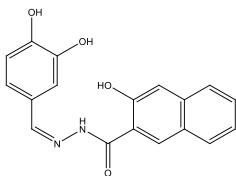
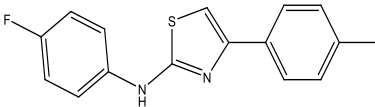
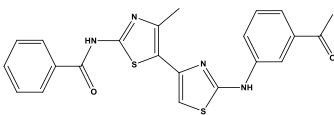
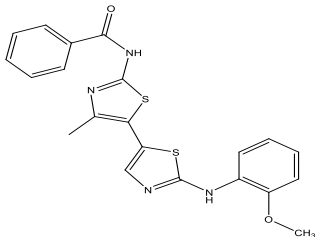
ID	Chemical Name	Chemical Structure	Comments
Blocker (B); Potentiator (P); Corrector (C); NMD-Inhibitor (N)			
B1	4-[4-Oxo-2-thioxo-3-(3-trifluoromethyl-phenyl)-thiazolidin-5-ylidenemethyl]-benzoic acid		Reference *** 1 Name: CFinh-172 Potency: Ki= 300 nM Solvent: DMSO Hints For Use: Slow onset of inhibition in some cell types (e.g. T84 cells) requiring prolonged incubation. M.W.: 409
B2	(Naphthalen-2-ylamino)-acetic acid (3,5-dibromo-2,4,-dihydroxy-benzylidene)-hydrazide		Reference *** 2 Name: GlyH-101 Potency: Ki= 5 microM Solvent: DMSO Hints For Use: M.W.: 493
B3	Diarylsulfonylurea		Reference *** 3 Name: DASU-01 Potency: Ki > 100 microM Solvent: Water or buffer Hints For Use: Useful for CFTR noise analysis M.W. 335.3
B4	(7R,9S)-7,8-dihydroxy-3-(4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7,9-dimethyl-3,7,8,9-tetrahydropyrimido[1,2-i]purine-9-carboxylic acid		Reference ***16 Name: Blocker 5ab Potency: Ki < 100 pM but see Ref.#17 Solvent: Water or buffer Hints For Use: M.W.395.37
B5	(2S,4R)-3,4-dihydroxy-2,4-dimethyl-3,4-dihydro-2H-pyrimido[2,1-a]isoquinoline-2-carboxylic acid		Reference *** 16 Name: Blocker 8ab Potency: Ki < 20 nM but see Ref.# 17 Solvent: Water or buffer Hints For Use: M.W. 288.3
B6	7,9-dimethyl-11-phenyl-6-(5-methylfuran-2-yl)-5,6-dihydro-pyrimido-[4',5'-3,4]pyrrolo[1,2-a]quinoxaline-8,10-(7H,9H)-dione		Reference # 22 Name: PPQ-102. Potency Ki=90 nM Solvent: DMSO Hints for use: M.W. 438.48
B7	5-[[4-(2h-tetrazol-5-yl)phenyl]methylene]-2-thioxo-3-(trifluoromethyl)phenyl]-4-thiazolidinone		Reference # 23 Name: Tetrazolo-Inh.-172. Potency: Ki~1 microM Solvent: DMSO Hints for use: Reported to be more water soluble than Inh.-172 M.W. 433.43

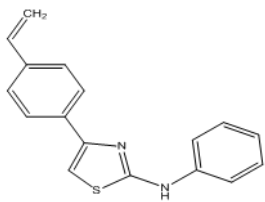
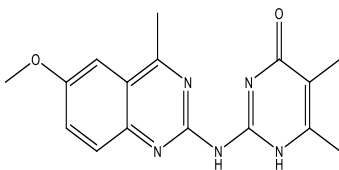
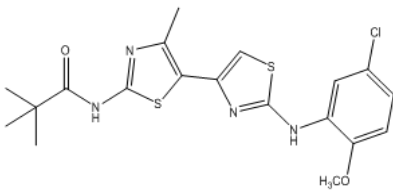
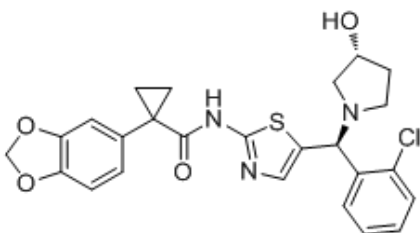
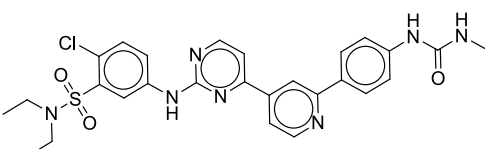
CFTR Compound Program

B8	4-[[3-[3-(trifluoromethyl)phenyl]-2,4-dioxo-5-thiazolidinylidene]methyl]benzoic acid		Reference # 23 Name: Oxo-Inh.-172. Potency: Ki~1 microM Solvent: DMSO Hints for use: Reported to be more water soluble than Inh.-172 M.W. 393.34
P1	4-Methyl-2-(5-phenyl-1H-pyrazol-3-yl)-phenol		Reference ***12 & 15 Name: VRT-532 Potency: Ks 3 to 5 microM Solvent: DMSO Hints For Use: M.W.: 250
P2	2-[(2-1H-Indol-3-yl-acetyl)-methyl-amino]-N-(4-isopropyl-phenyl)-2-phenyl-acetamide		Reference *** 4 Name: PG-01 Potency: Ks= 300 nM Solvent: DMSO Hints For Use: M.W.: 439.5
P3	6-(Ethyl-phenyl-sulfonyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid 2-methoxy-benzylamide		Reference *** 4 Name: SF-03 Potency: Ks= 30 nM Solvent: DMSO Hints For Use: M.W.: 491.6
P4	1-(3-chlorophenyl)-5-trifluoromethyl-3-hydrobenzimidazol-2-one		Reference *** 5 Name: UCCF-853 Potency: Ks= 3 microM Solvent: DMSO Hints For Use: M.W.: 312.7
P5	2-(2-Chloro-benzoylamino)-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid amide		Reference *** 6 Name: dF508^{act}-02 Potency: Ks= 70 nM Solvent: DMSO Hints For Use: M.W.: 334.8
P6	5,7-Dihydroxy-3-(4-hydroxy-phenyl)-chroman-4-one		Reference *** 8 Name: Genistein (discontinued - available from Sigma #G6649) Potency: Ks= 10 to 30 microM Solvent: DMSO Hints For Use: M.W.: 272.3
P7	1-(5-Chloro-2-hydroxy-phenyl)-5-trifluoromethyl-1,3-dihydro-indol-2-one		Reference *** 8 Name: NS004 Potency: EC50 3 microM Solvent: DMSO Hints For Use: Does not work in excised patches. M.W.: 327.7
P8	4-(4-Oxo-4H-benzo[h]chromen-2-yl)-pyridinium; bisulfate		Reference *** 9 and 10 Potency: Ks= 2 microM Solvent: DMSO Hints For Use: M.W.: 371.4

CFTR Compound Program

P9	3-But-3-ynyl-5-methoxy-1-phenyl-1H-pyrazole-4-carbaldehyde		Reference *** 10 Potency: Ks = 10 microM Solvent: DMSO Hints For Use: M.W.: 254.3
P10	3-(2-Benzyloxy-phenyl)-5-chloromethyl-isoxazole		Reference *** 10 Potency: Ks > 50 microM Solvent: DMSO Hints For Use: M.W.: 299.8
C1	6-(1H-Benzoimidazol-2-ylsulfanylmethyl)-2-(6-methoxy-4-methyl-quinazolin-2-ylamino)-pyrimidin-4-ol		Reference *** 11 Potency: Ks = 3 microM Solvent: DMSO Hints For Use: M.W.: 445.5
C2	2-[1-[4-(4-Chloro-benzensulfonyl)-piperazin-1-yl]-ethyl]-4-piperidin-1-yl-quinazoline		Reference. Vertex Presentation Name: VRT-640 Potency: unknown Solvent: DMSO Hints For Use: Likely binds to serum proteins. M.W.: 500.1
C3	4-Cyclohexyloxy-2-[1-[4-(4-methoxy-benzensulfonyl)-piperazin-1-yl]-ethyl]-quinazoline		Reference *** 12,13, 15 Name: VRT-325 Potency: EC50 2 microM Solvent: dry DMSO Hints For Use: Binds to serum proteins M.W.: 510.65
C4	N-[2-(5-Chloro-2-methoxy-phenylamino)-4'-methyl-[4,5']bithiazolyl-2'-yl]-benzamide		Reference *** 11 Name: cmpd 4a Potency: EC50 2 microM Solvent: DMSO Hints For Use: M.W.: 440.9
C5	4,5,7-trimethyl-N-phenylquinolin-2-amine		Reference *** 11: Name: cmpd 5a Potency: EC50 13 microM Solvent: DMSO Hints For Use: M.W.: 262.35
C6	N-(4-bromophenyl)-4-methylquinolin-2-amine		Reference *** 11: Name: cmpd 5c Potency: EC50 8 microM Solvent: DMSO Hints For Use: M.W.: 313.19
C7	2-(4-isopropoxypicolinoyl)-N-(4-pentylphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide		Reference *** 21: Name: Genzyme cmpd 48 only 10mg will be provided Potency: EC50 300 nM Solvent: DMSO Hints For Use: M.W.: 472.6

C8	N-(2-fluorophenyl)-2-(1H-indol-3-yl)-2-oxoacetamide		Reference #** Vertex patent Potency:EC50 Solvent:DMSO Hints For Use: M.W.:282.27
C9	7-chloro-4-(4-(4-chlorophenylsulfonyl)piperazin-1-yl)quinoline		Reference #**18 Name: KM11060 Potency:EC50 < 1 microM Solvent:DMSO Hints For Use: M.W.:422.33
C10	7-chloro-4-(4-(phenylsulfonyl)piperazin-1-yl)quinoline		Reference # 18 Name: KM11057 Potency:EC50 > 100 microM Solvent:DMSO Hints For Use: Inactive derivative of C9 (KM11060) M.W.:387.88
C11	(Z)-N'-(3,4-dihydroxybenzylidene)-3-hydroxy-2-naphthohydrazide		Reference #: 19 Name: Dynasore Potency:EC50 10-20 microM Solvent: DMSO Hints For Use: An inhibitor of dynamin, blocks CFTR endocytosis M.W.:322.31
C12	N-(4-fluorophenyl)-4-p-tolylthiazol-2-amine		Reference #: 11 Name: 2i Potency:EC50 5 microM Solvent: DMSO Hints For M.W.:284.35
C13	N-(2-(3-acetylphenylamino)-4'-methyl-4,5'-bithiazol-2'-yl)benzamide		Reference #: 11 Name: 4c Potency:EC50 2 microM Solvent: DMSO Hints For M.W.:434.53
C14	N-(2'-(2-methoxyphenylamino)-4-methyl-5,5'-bithiazol-2'-yl)benzamide		Reference #: 11 Name: 4d Potency:EC50 7 microM Solvent: DMSO Hints For Use: M.W.:422.52

C15	N-phenyl-4-(4-vinylphenyl)thiazol-2-amine		Reference #: 11 Name: 2b Potency: EC50 16 microM Solvent: DMSO Hints M.W.: 278.37
C16	2-(6-methoxy-4-methylquinazolin-2-ylamino)-5,6-dimethylpyrimidin-4(1H)-one		Reference #: 11 Name: 3d Potency: EC50 15 microM Solvent: DMSO Hints M.W.: 311.34
C17	N-(2-(5-chloro-2-methoxyphenylamino)-4'-methyl-4,5'-bithiazol-2'-yl)pivalamide		Reference #: 20 Name: 15Jf Potency: EC50 1-2 microM Solvent: DMSO Hints For Use: M.W.: 436.98
C18	1-(benzo[d][1,3]dioxol-5-yl)-N-(5-((S)-(2-chlorophenyl)((R)-3-hydroxypyrrolidin-1-yl)methyl)thiazol-2-yl)cyclopropanecarboxamide		Reference # 24 Name: VRT-534 (also known as CF-106951) only 10 mg will be provided Potency Ks ~ 0.6 microM Solvent: DMSO Hints for use: Use at 3 to 6 microM for maximum effect. M.W.: 497.99
6 compounds from the EPIX Pharmaceuticals Dual Corrector/Potentiator series are available through a specific MTA.		Please contact Kathryn Fox (kfox@cff.org) to receive the MTA template.	
N1	2-chloro-N,N-diethyl-5-((4-(2-(4-(3-methylureido)phenyl)pyridin-4-yl)pyrimidin-2-yl)amino)benzenesulfonamide		Reference # 25 Named SMG1i by CFFT Lab Potency: IC50 110 picoM for purified enzyme Solvent: DMSO Hints For Use: 0.1–1 microM in cell-based assays M.W.: 566.07

The order form is an open and working listing of available compounds. It is subject to change. All compounds are at least 95% pure; NMR and melting point data are available upon request.

APPENDIX C: REFERENCES

- 1 **Ma, T., J. R. Thiagarajah, H. Yang, N. D. Sonawane, C. Folli, L. J. V. Galletta and A. S. Verkman.** 2002. Thiazolidinone CFTR inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion. *J. Clin. Invest.* 110(11):1651-1658.
- 2 **Muanprasat, C., N. D. Sonawane, D. Salinas, A. Taddei, L. J. V. Galletta and A. S. Verkman.** 2004. Discovery of glycine hydrazide pore-occluding CFTR inhibitors: Mechanism, structure-activity analysis, and in vivo efficacy. *J. Gen. Physiol.* 124:125-137.
- 3 **Singh, A. K., B. D. Schultz, W. van Driessche and R. J. Bridges.** 2004. Transepithelial fluctuation analysis of chloride secretion. *J. Cyst. Fibros.* 3 Suppl 2:127-132.
- 4 **Pedemonte, N., N. D. Sonawane, A. Taddei, J. Hu, O. Zegarra-Moran, Y. F. Suen, L. I. Robins, C. W. Dicus, D. Willenbring, M. H. Nantz, M. J. Kurth, L. J. Galletta and A. S. Verkman.** 2005. Phenylglycine and sulfonamide correctors of defective delta F508 and G551D cystic fibrosis transmembrane conductance regulator chloride-channel gating. *Mol. Pharmacol.* **67**(5):1797-1807.
- 5 **Caci, E., C. Folli, O. Zegarra-Moran, T. Ma, M. F. Springsteel, R. E. Sammelson, M. H. Nantz, M. J. Kurth, A. S. Verkman and L. J. V. Galletta.** 2003. CFTR activation in human bronchial epithelial cells by novel benzoflavone and benzimidazolone compounds. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 285:L180-L188.
- 6 **Yang, H., A. A. Shelat, R. K. Guy, V. S. Gopinath, T. Ma, K. Du, G. L. Lukacs, A. Taddei, C. Folli, N. Pedemonte Y, L. J. V. Galletta and A. S. Verkman.** 2003. Nanomolar affinity small molecule correctors of defective DF508-CFTR chloride channel gating. *J. Biol. Chem.* 278(37):35079-35085.
- 7 **Ma, T., L. Vetrivel, H. Yang, N. Pedemonte, O. Zegarra-Moran, L. J. V. Galletta and A. S. Verkman.** 2002. High-affinity activators of cystic fibrosis transmembrane conductance regulator (CFTR) chloride conductance identified by high-throughput screening. *J. Biol. Chem.* 277(40):37235-37241.
- 8 **Devor, D. C., R. J. Bridges and J. M. Pilewski.** 2000. Pharmacological modulation of ion transport across wild-type and DeltaF508 CFTR-expressing human bronchial epithelia. *Am. J. Physiol. Cell Physiol.* 279(2):C461-C479
- 9 **Springsteel, M. F., L. J. V. Galletta, T. Ma, K. By, G. O. Berger, H. Yang, C. W. Dicus, W. Choung, C. Quan, A. Shelat, R. K. Guy, A. S. Verkman, M. J. Kurth and M. H. Nantz.** 2003. Benzoflavone activators of the cystic fibrosis transmembrane conductance regulator: Towards a pharmacophore model for the nucleotide-binding domain. *Bioorg. Med. Chem.* 11:4113-4120.
- 10 **Sammelson, R. E., T. Ma, L. J. V. Galletta, A. S. Verkman and M. J. Kurth.** 2003. 3-(2-Benzyloxyphenyl)isoxazoles and isoxazolines: Synthesis and evaluation as CFTR activators. *Bioorg. Med. Chem. Lett.* 13:2509-2512

-
- 11 **Pedemonte, N., G. L. Lukacs, K. Du, E. Caci, O. Zegarra-Moran, L. J. V. Galletta and A. S. Verkman.** 2005. Small-molecule correctors of defective DF508-CFTR cellular processing identified by high-throughput screening. *J. Clin. Invest.* 115(9):2564-2571.
- 12 **Van Goor, F., K. S. Straley, D. Cao, J. Gonzalez, S. Hadida, A. Hazlewood, J. Joubran, T. Knapp, L. R. V Makings, M. Miller, T. Neuberger, E. Olson, V. Panchenko, J. Rader, A. Singh, J. H. Stack, R. Tung, P. D. Grootenhuis and P. Negulescu.** 2006. Rescue of Δ F508 CFTR trafficking and gating in human cystic fibrosis airway primary cultures by small molecules. *Am. J. Physiol. Lung Cell Mol. Physiol.* Epub
- 13 **Loo, T. W., M. C. Bartlett, Y. Wang and D.M. Clarke.** 2006. The chemical chaperone CFcor-325 repairs folding defects in the transmembrane domains of CFTR processing mutants. *Biochem. J.* Epub.
- 14 **Makings, Lewis R.; Singh, Ashvani K.; Miller, Mark T.; Hadida Ruah, Sarah S.; Grootenhuis, Peter; Hamilton, Matthew; Hazelwood, Anna R.; Huang, Liming.** Preparation of pyrimidine derivatives as modulators of ATP-binding cassette transporters. PCT Int. Appl. (2004), WO 20041111014 A1
- 15 **Vangoor, Frederick F.; Hadida Ruah, Sarah S.; Singh, Ashvani K.; Olson, Eric R.; Makings, Lewis R.; Gonzalez, Jesus E., III; Rader, James A.; Chambers, Fred, III; Miller, Mark T.; Grootenhuis, Peter;** Liu, Yahua. Preparation of substituted pyrazoles as modulators of ATP-binding cassette transporters. PCT Int. Appl. (2004) WO 2004080972 A1
- 16 **Routaboul, Christel; Norez, Caroline; Melin, Patricia; Molina, Marie-Carmen; Boucherle, Benjamin; Bossard, Florian; Noel, Sabrina; Robert, Renaud; Gauthier, Chantal; Becq, Frédéric; Décout, Jean-Luc.** 2007. Discovery of α -Aminoazaheterocycle-Methylglyoxal adducts as a new class of high-affinity inhibitors of Cystic Fibrosis transmembrane conductance regulator chloride channels. *J. Pharmacol. Exp. Ther.* 322(3):1023-1035.
- 17 **Sonawane, N.D., Zegarra-Moran, O., Namkung, W., Galletta, L., and Verkman, A.S.** 2008. α -Aminoazaheterocyclic- methylglyoxal adducts do not inhibit CFTR chloride channel activity. *J. Pharmacol. Exp. Ther.* Epub.
- 18 **Robert, R., Carlile, G.W., Pavel, C., Liu, N., Anjos, S.M., Liao, J., Luo, Y., Zhang, D., Thomas, D.Y., and Hanrahan, J.W.** 2008. Structural analog of sildenafil identified as a novel corrector of the F508del-CFTR trafficking defect. *Mol. Pharmacol.* 73(2):478-489.
- 19 **Macia, E., Ehrlich, M., Massol, R., Boucrot, E., Brunner, C., and Kirchhausen, T.** 2006. Dynasore, a cell-permeable inhibitor of dynamin. *Dev. Cell.* 10(6):839-850.
- 20 **Yoo, C.L., Yu, G.J., Yang, B., Robins, L.I., Verkman, A.S., and Kurth, M.J.** 2008. 4'-Methyl-4,5'-bithiazole-based correctors of defective Δ F508-CFTR cellular processing. *Bioorg. Med. Chem. Lett.* 18(8):2610-2614.
- 21 **Hirth, B.H., Qiao, S., Cuff, L.M., Cochran, B.M., Pregel, M.J., Gregory, J.S., Sneddon, S.F., and Kane, J.L. Jr.** 2005. Discovery of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid diamides that increase CFTR mediated chloride transport. *Bioorg. Med. Chem. Lett.* 15(8):2087-2091.
-

- 22 Tradtrantip, L., N.D. Sonawane, W. Namkung, A.S.,Verkman 2009.**
Nanomolar potency Pyrimido-pyrrolo-quinoxalinedione CFTR inhibitor reduces cyst size in a polycystic kidney disease model.
J. Med. Chem. 52(20):6447-55.
- 23 Sonawane, N.D., A.S.,Verkman 2008.**
Thiazolidinone CFTR inhibitors reduces with improved water solubility identified by structure-activity analysis. Bioorg. Med. Chem.
16(17):8175-95
- 24 Vertex Patent WO 2007/021982 A2; paragraph [182]**
- 25 Ariamala Gopalsamya, Eric M. Bennettb, Mengxiao Shia, Wei-Guo Zhangc, Joel Bardb, Ker Yuc 2012**
Identification of pyrimidine derivatives as hSMG-1 inhibitors. Bioorganic & Medicinal Chemistry Letters Volume 22, Issue 21, 1
November 2012, Pages 6636–6641