



(43) International Publication Date

23 August 2012 (23.08.2012)

## (51) International Patent Classification:

C07D 217/24 (2006.01)	A61K 31/472 (2006.01)
C07D 401/06 (2006.01)	A61K 31/4725 (2006.01)
C07D 403/06 (2006.01)	A61P 3/00 (2006.01)
C07D 405/06 (2006.01)	A61P 25/00 (2006.01)
C07D 491/06 (2006.01)	

**CHAUVIGNAC, Cedric** [FR/FR]; 1 Avenue de la Source, Bat. A, F-94130 Nogent sur Marne (FR). **TAVERNE, Thierry** [FR/FR]; 21 rue Michel Ange, Residence Le Vallon, F-62280 St Martin lez Boulogne sur Mer (FR).

(74) Agents: **BANERJEE, Krishna** et al.; Allergan, Inc., 2525 Dupont Drive, Irvine, California 92612 (US).

## (21) International Application Number:

PCT/US2012/025731

## (22) International Filing Date:

17 February 2012 (17.02.2012)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

61/444,566 18 February 2011 (18.02.2011) US

(71) Applicant (for all designated States except US): **ALLERGAN, INC.** [US/US]; 2525 Dupont Drive, Irvine, California 92886 (US).

## (72) Inventors; and

(75) Inventors/Applicants (for US only): **DONELLO, John E.** [US/US]; 34041 Pequito Drive, Dana Point, California 92629 (US). **YANG, Rong** [US/US]; 23732 Via Potes, Mission Viejo, California 92691 (US). **LEBLOND, Bertrand** [FR/FR]; 62, rue de Montreuil, F-75011 Paris (FR). **BEAUSOLEIL, Eric** [CA/FR]; 5 bis rue Chauvelot, F-75015 Paris (FR). **CASAGRANDE, Anne-Sophie** [FR/FR]; 62 Allee de la Cite Nouvelle, F-91210 Darvill (FR). **DESIRE, Laurent J.R.** [FR/FR]; 102 Boulevard Kellermann, F-75013 Paris (FR). **PANDO, Matthew P.** [FR/FR]; 44 Rue Ginoux, F-75015 Paris (FR).

## (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

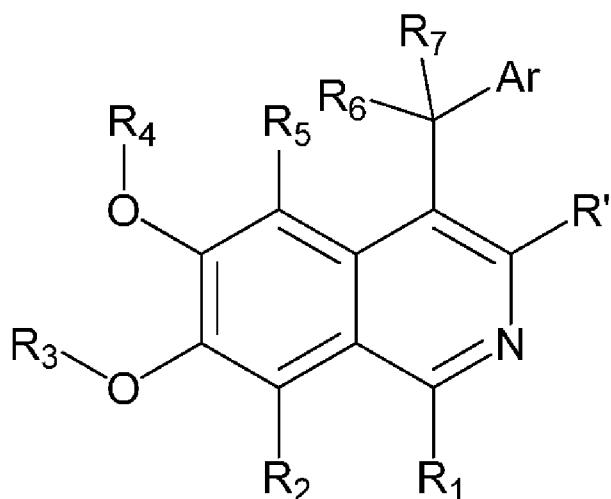
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

[Continued on next page]

(54) Title: SUBSTITUTED 6,7-DIALKOXY-3-ISOQUINOLINOL DERIVATIVES AS INHIBITORS OF PHOSPHODIESTERASE 10 (PDE10A)



(57) Abstract: The invention relates to compounds of the formula wherein R', R<sub>1</sub> through R<sub>7</sub> and Ar are as defined herein. These compounds are useful as inhibitors of phosphodiesterase 10 (PDE10A) which are useful in treating central nervous system diseases such as psychosis and also in treating, for example, obesity, type II diabetes, metabolic syndrome, glucose intolerance, pain and ophthalmic diseases.



— as to the applicant's entitlement to claim the priority of  
the earlier application (Rule 4.17(iii))

**Published:**

— with international search report (Art. 21(3))

**SUBSTITUTED 6,7-DIALKOXY-3-ISOQUINOLINOL DERIVATIVES AS  
INHIBITORS OF PHOSPHODIESTERASE 10 (PDE10A)**

5

**CROSS REFERENCE TO RELATED APPLICATION**

10 This Application claims the benefit of U.S. Provisional Application Serial No. 61/444,566 filed February 18, 2011, which is incorporated by reference herein in its entirety.

**BACKGROUND OF THE INVENTION**

15 Phosphodiesterases (PDEs) are a class of intracellular enzymes involved in the hydrolysis of the nucleotides cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphates (cGMP) into their respective nucleotide monophosphates. The cyclic nucleotides cAMP and cGMP are synthesized by adenylyl and guanylyl cyclases, respectively.

20 The cAMP and cGMP function as intracellular second messengers regulating a vast array of intracellular processes particularly in neurons of the central nervous system. In neurons, this includes the activation of cAMP and cGMP-dependent kinases and subsequent phosphorylation of proteins involved in acute regulation of synaptic transmission as well as in neuronal differentiation and survival. The complexity of cyclic nucleotide signaling is indicated by the molecular diversity of the 25 enzymes involved in the synthesis and degradation of cAMP and cGMP.

30 There are at least ten families of adenylyl cyclases, two of guanylyl cyclases, and eleven of phosphodiesterases. Furthermore, different types of neurons are known to express multiple isozymes of each of these classes, and there is good evidence for compartmentalization and specificity of function for different isozymes within a given neuron.

A principal mechanism for regulating cyclic nucleotide signaling is by phosphodiesterase-catalyzed cyclic nucleotide catabolism. There are 11 known families of PDEs encoded by 21 different genes. Each gene typically yields multiple

splice variants that further contribute to the isozyme diversity. The PDE families are distinguished functionally based on cyclic nucleotide substrate specificity, mechanism(s) of regulation, and sensitivity to inhibitors. Furthermore, PDEs are differentially expressed throughout the organism, including in the central nervous system. As a result of these distinct enzymatic activities and localization, different PDEs' isozymes can serve distinct physiological functions. Furthermore, compounds that can selectively inhibit distinct PDE families or isozymes may offer particular therapeutic effects, fewer side effects, or both.

PDE10 is identified as a unique family based on primary amino acid sequence and distinct enzymatic activity. Homology screening of EST databases revealed human PDE10A as the first member of the PDE10 family of PDEs (Fujishige et al., *J. Biol. Chem.*, 274, 18438- 18445, 1999; Loughney, K. et al., *Gene*, 234, 109-117, 1999). The murine homologue has also been cloned (Soderling, S. et al., *Proc. Natl. Acad. Sci. USA*, 96, 7071-7076, 1999) and N-terminal splice variants of both the rat and human genes have been identified (Kotera, J. et al., *Biochem. Biophys. Res. Comm.*, 261, 551-557, 1999; Fujishige, K. et al., *Eur. J. Biochem.*, 266, 1118-1127, 1999). There is a high degree of homology across species. The mouse PDE10A1 is a 779 amino acid protein that hydrolyzes both cAMP and cGMP to AMP and GMP, respectively. The affinity of PDE10 for cAMP ( $K_m = 0.05 \mu M$ ) is higher than for cGMP ( $K_m = 3 \mu M$ ). However, the approximately 5-fold greater  $V_{max}$  for cGMP over cAMP has lead to the suggestion that PDE10 is a unique cAMP-inhibited cGMPase (Fujishige et al., *J. Biol. Chem.*, 274, 18438-18445, 1999).

PDE10A also is uniquely localized in mammals relative to other PDE families. mRNA for PDE10 is highly expressed only in testis and brain (Fujishige, K. et al., *Eur J Biochem.*, 266, 1118-1127, 1999; Soderling, S. et al., *Proc. Natl. Acad. Sci.*, 96, 7071-7076, 1999; Loughney, K. et al., *Gene*, 234, 109-117, 1999).

These initial studies indicated that within the brain PDE10A expression is highest in the striatum (caudate and putamen), n. accumbens, and olfactory tubercle. More recently, a detailed analysis has been made of the expression pattern in rodent brain of PDE10 mRNA (Seeger, T.F. et al., *Abst. Soc. Neurosci.*, 26, 345.10, 2000) and PDE10 protein (Menniti, F.S., Stick, CA<sub>1</sub> Seeger, T.F., and Ryan, A.M., Immunohistochemical localization of PDE10 in the rat brain, William Harvey

Research Conference 'Phosphodiesterase in Health and Disease', Porto, Portugal, Dec. 5-7, 2001).

PDE10A was shown to be highly expressed in retinal neurons including photoreceptors. The levels of PDE10A transcript and protein display daily rhythms which could be seen in preparations of the whole retina (Wolloscheck T. et al, *Brain Res.*, 2011,1376, 42-50. Epub 2010 Dec 29). These findings place PDE10A in the context of the visual system and suggest an important role of PDE10A in the adaptation of cyclic nucleotide signalling to daily changes in light intensity in retinal neurons including photoreceptors.

10 The tissue distribution of PDE10A indicates that PDE10A inhibitors can be used to raise levels of cAMP and/or cGMP within cells that express the PDE10 enzyme, especially neurons that comprise the basal ganglia, and the PDE10A inhibitors of the present invention would therefore be useful in treating a variety of associated neuropsychiatric conditions involving the basal ganglia such as 15 neurological and psychiatric disorders, schizophrenia, bipolar disorder, obsessive compulsive disorder, and the like, and may have the benefit of not possessing unwanted side effects, which are associated with the current therapies on the market.

20 US 2003/0032579 discloses a method for treating certain neurologic and psychiatric disorders with the PDE10A inhibitor papaverine. In particular, the method relates to psychotic disorders such as schizophrenia, delusional disorders and drug-induced psychosis; to anxiety disorders such as panic and obsessive-compulsive disorder; and to movement disorders including Parkinson's disease and Huntington's disease. Other indications which may be treated using a PDE10A inhibitor are 25 described in WO 20055120514.

30 A variety of therapeutic uses for PDE inhibitors has been reported including obtrusive lung disease, allergies, hypertension, angina, congestive heart failure, depression and erectile dysfunction (WO 2001041807, incorporated herein by reference). Furthermore, publications (WO 2005120514, WO 2005012485, Cantin et al., *Bioorg. & Med. Chem. Lett.*, 17, 2869-2873, 2007) suggest that PDE10A inhibitors may be useful for treatment of obesity and non-insulin dependent diabetes.

WO 2011110545, WO 2011051342 (Janssen Pharmaceutica NV) disclose respectively imidazo[1,2-a]pyrazine derivatives, imidazo[1,2-b]pyridazine derivatives

PDE10A inhibitors useful for the treatment or prevention of neurological, psychiatric and metabolic disorders in which the PDE10 enzyme is involved.

WO 2012007006, WO 2012000519, WO 2011072695, WO 2011072697, WO 2011072694, WO 2011072696, WO 2010145668 (H. Lundbeck A/S) disclose respectively triazolo- and pyrazoloquinazoline derivatives, aryl- and heteroarylamid derivatives, phenylimidazole derivatives comprising an ethynylene linker, heteroaromatic aryl triazole derivatives, heteroaromatic phenylimidazole derivatives, 2-arylimidazole derivatives, novel phenylimidazole derivatives as PDE10A inhibitors reported to be useful for the treatment of psychiatric and neurodegenerative disorders including schizophrenia as well as bipolar disorders, anxiety, stress disorders and Alzheimer's, Parkinson's and Huntington's disease, dementia and attention deficit/hyperactivity disorder.

WO 2011150156 (Sunovion Pharmaceuticals Inc.) discloses heteroaryl compounds as PDE10A inhibitors useful for the treatment, prevention, and/or management of various disorders, such as CNS disorders and metabolic disorders, including, but not limited to, e.g., neurological disorders, psychosis, schizophrenia, obesity, and diabetes.

WO 2010138833 (Biotie Therapies GmbH – Wyeth) discloses substituted imidazo[1,5-a]quinoxalines as PDE10A inhibitors useful in treating central nervous system diseases such as psychosis and also in treating, for example, obesity, type 2 diabetes, metabolic syndrome, glucose intolerance, and pain.

WO 2011053559 or WO 2011022213 or WO 2010138430 and WO 2010138585 or WO 2010138430 (Merck & Co., Inc.) disclose respectively aryl or amino or alkoxy tetrahydro-pyridopyrimidine derivatives or pyrimidinones as PDE10A inhibitors useful for the treatment of neurological and psychiatric disorders including schizophrenia, delusional disorders, drug induced psychosis, anxiety, movement, mood and neurodegenerative disorders.

WO 2010138577 (Merck & Co., Inc.) discloses radiolabeled pyrimidinone compounds which are useful as radiotracers for quantitative imaging of PDE10A in mammals.

WO 2011138657, WO 2011132051, and WO 2011132048 (Glenmark Pharmaceuticals SA) disclose respectively aryl substituted olefinic compounds,

tricyclic compounds, and heteroaryl compounds as PDE10A inhibitors reported to be useful for the treatment of schizophrenia.

WO 2011163355 & WO 2010090737 (Takeda Pharmaceutical Co., Ltd.) disclose respectively fused heterocyclic compounds and pyridazinone compounds as 5 PDE10A inhibitors useful for the treatment of schizophrenia.

WO 2010128995 (EnVivo Pharmaceuticals, Inc.) discloses phenoxyethyl heterocyclic compounds as PDE10A inhibitors useful for the treatment of schizophrenia, bipolar disorder, Huntington's disease, obesity and metabolic syndrome, among other disorders.

10 WO 2010117926 (Schering Corp.) discloses substituted triazolopyridines and analogs thereof as PDE10A inhibitors reported to be useful for the treatment of schizophrenia, psychosis, Alzheimer's disease, bipolar disorder, depression, obesity, diabetes and metabolic syndrome.

15 WO 2011051324 and WO 2010097367 (Janssen Pharmaceutica NV) disclose radiolabeled fluorinated azole PDE10A ligands reported to be useful in positron emission tomography imaging and quantification of PDE10A enzymes.

20 WO 2011117264, WO 2011089132 & WO 2011154327, WO 2011036127, and WO 2010094762 & WO 2010063610 (F. Hoffmann-La Roche AG) disclose respectively *N*-(imidazopyrimidin-7-yl)-heteroaryl amide derivatives, nitrogen-containing heteroaryl derivatives, novel imidazopyridines, and heteroaryl substituted pyridazinone derivatives as PDE10A inhibitors reported to be useful for the treatment of schizophrenia, cognitive disorders, anxiety, substance abuse and dependence, Parkinson's disease, mood disorders, neurodegenerative disorders, stroke, diabetes and cancer, among other disorders.

25 WO 2011143366, WO 2011143365, WO 2011143495, WO 2010077992, and WO 2010057126 (Amgen Inc.) disclose respectively heteroaryloxycarbocyclyl compounds, nitrogen heterocyclic compounds, heteroaryloxyheterocyclyl compounds, aminopyridine and carboxypyridine compounds, and pyridine and pyrimidine derivatives as PDE10A inhibitors that are considered to have potential in 30 the treatment of psychiatric disorders such as schizophrenia, bipolar disorder, obsessive-compulsive disorder, obesity, non-insulin dependent diabetes.

WO 2010062559 (Schering Corp.) discloses substituted pyrazoloquinolines and derivatives thereof as PDE10A inhibitors for the treatment of PDE10-modulated disorders.

WO 2010138833, WO 2010054253 & WO 2010054260 (Biotie Therapies 5 GmbH – Wyeth) disclose respectively substituted imidazo[1,5-a]quinoxalines and triazine derivatives as inhibitors of phosphodiesterases, particularly PDE10A and PDE2A, described as useful for the treatment of pain, cognitive disorders, diabetes, obesity, extrapyramidal disorders, epilepsy and psychiatric disorders such as depression, anxiety, schizophrenia and attention deficit/hyperactivity disorders.

JP 2011201873, WO 2011105628, and WO 2010027097 (Mitsubishi Tanabe 10 Pharma Corp.) disclose respectively trisubstituted pyrimidine compounds, pyrazolopyrimidine compounds, and tri-substituted pyrimidine compounds and their use as PDE10A inhibitors reported to be useful for the treatment of schizophrenia, anxiety, drug addiction, cognitive and mood disorders.

WO 2011112828 and WO 2010017236 (Omeros Corp.) disclose PDE10A 15 inhibitors described as useful for the treatment of neurological and psychiatric disorders such as schizophrenia and post-traumatic stress disorder as well as Parkinson's disease, Huntington's disease, Alzheimer's disease, encephalitis, phobias, epilepsy, pain, sleep disorders, bipolar disorder and multiple sclerosis.

US 2010016303 & WO 2009152825 (H. Lundbeck A/S) disclose novel 20 phenylimidazole derivatives as PDE10A enzyme inhibitors to be useful in the treatment of psychiatric and neurological disorders such as schizophrenia, cognition deficits, Parkinson's disease, Alzheimer's disease, Huntington's disease and substance abuse, among others.

WO 2010006130 (EnVivo Pharmaceuticals, Inc.) discloses vicinal substituted 25 cyclopropyl compounds as PDE10A inhibitors.

WO 2009158473, WO 2009158467 & WO 2009158393 (EnVivo Pharmaceuticals, Inc.) disclose respectively 5- and 6 membered heterocyclic 30 compounds, disubstituted phenyls compounds and 1,2-disubstituted heterocyclic compounds as PDE10A inhibitors described as useful for the treatment of schizophrenia, Huntington's disease, obesity and metabolic syndrome.

WO 2009070583 (Wyeth) discloses pyrido(3,2-e)pyrazines as inhibitors of PDE10A that are considered to have potential in the treatment of psychosis, mood

diseases, anxiety, neurodegenerative disorders, obesity, diabetes, metabolic diseases, pain.

WO 2009068320 & WO 2009070584 (Biotie Therapies GmbH) disclose aryl and heteroaryl fused imidazo(1,5-a)pyrazines as inhibitors of PDE10A that are active 5 compounds for treating central nervous system diseases of mammals, including humans.

WO 2009152825 & WO 2009036766 (H. Lundbeck A/S) disclose respectively novel phenylimidazole derivatives and cyanoisoquinoline derivatives as PDE10A inhibitors.

WO 2009143178, WO 2008064342 & US 2008300240 (Omeros Corp.) disclose quinoline derivatives as PDE10A inhibitors active in psychotic, anxiety, movement disorders and/or neurological disorders such as Parkinson's disease, Huntington's disease, Alzheimer's disease, encephalitis, phobias, epilepsy, aphasia, Bell's palsy, cerebral palsy, sleep disorders, pain, Tourette syndrome, schizophrenia, 15 delusional disorders, drug-induced psychosis and panic and obsessive-compulsive disorders.

WO 2009025839 & WO 2009025823 (Amgen Inc.) disclose cinnoline derivatives as PDE10A inhibitors that are considered to have potential in the treatment of psychiatric disorders such as schizophrenia, bipolar disorder and 20 obsessive-compulsive disorder.

WO 2009029214 (Amgen Inc. – Memory Pharmaceuticals Corp.) discloses isoquinolone derivatives as PDE10A inhibitors that are considered to have potential in the treatment of schizophrenia, bipolar disorder, obsessive-compulsive disorder, obesity and diabetes.

WO 2008032171 (Matrix Laboratories Ltd.) discloses dibenzofuran as 25 inhibitors of PDE4 and PDE10A with potential utility in the treatment of asthma, chronic obstructive pulmonary disease, allergic rhinitis, atopic dermatitis, multiple sclerosis, Huntington disease, Alzheimer's disease, Parkinson's disease, schizophrenia and depression, among other disorders.

WO 2008020302 (Pfizer Products Inc.) discloses heteroaromatic quinoline-based compounds as selective PDE10A inhibitors.

WO 2008006372 (H. Lundbeck A/S) discloses 6,7-dialkoxyquinazoline and 6,7-dialkoxyisoquinoline derivatives as PDE10A inhibitors that are considered to

have potential in the treatment of psychiatric and neurological disorders such as schizophrenia, cognition deficits, Parkinson's disease, Alzheimer's disease, dementia, epilepsy, multiple sclerosis and Huntington's diseases.

WO 2008004117 & WO 2006072828 (Pfizer Products Inc.) disclose 5 respectively selective azole compounds and heteroaromatic quinoline compounds as PDE10A inhibitors that are considered to have potential in the treatment of psychotic, anxiety, movement, mood and neurodegenerative disorders and obesity.

WO 2007137819 & WO 2007137820 (Biotie Therapies GmbH) disclose 10 respectively 4-amino-pyrido(3,2-e)pyrazines and pyrido(3,2-e)pyrazines as PDE10A inhibitors. More particularly, the inventions relate to the treatment of neurologic and psychiatric disorders, for example psychosis and disorders comprising cognitive deficits as symptoms.

WO 2007103370, WO 2007103260, WO 2007100880 & WO 2007022280 15 (Amgen Inc. – Memory Pharmaceuticals Corp.) disclose quinazoline derivatives as PDE10A inhibitors that are considered to have potential in the treatment of schizophrenia, bipolar disorder and obsessive-compulsive disorder. Further applications include obesity and non-insulin diabetes.

WO 2007103554, WO 2007098214 & WO 2007098169 (Amgen Inc. – 20 Memory Pharmaceuticals Corp.) disclose cinnoline derivatives as PDE10A inhibitors that are considered to have potential in the treatment psychiatric disorders such as schizophrenia, bipolar disorders and obsessive-compulsive disorder.

WO 2007096743 & WO 2007085954 (Pfizer Products Inc.) disclose 25 respectively substituted quinazolines and aminophthalazine compounds as PDE10A inhibitors that are considered to have potential in the treatment of psychotic disorders, anxiety disorders, movement disorders such as Parkinson and Huntington diseases, mood disorders, obesity and drug addiction.

WO 2006089815 & WO 2006075012 (Nycomed GmbH) disclose novel 30 pyrrolodihydroisoquinolines as PDE10A inhibitors with potential utility in the treatment of neurological and psychiatric disorders, in diabetes therapy and in the regulation of fertility.

WO 2006071988 & WO 2006028957 (Memory Pharmaceuticals Corp.) disclose respectively thienopyrimidine derivatives and 4-substituted-4,6-dialkoxy-cinnoline derivatives as PDE10A inhibitors that are considered to have potential in

the treatment of psychosis, including schizophrenia, bipolar disorder and obsessive-compulsive disorder, Alzheimer's disease and movement disorders such as Parkinson's disease. Other conditions include epilepsy, multiple sclerosis, Huntington's disease, disorders relating to the basal ganglia, diabetes and obesity.

5 WO 2006070284 & WO 2006011040 (Pfizer Products Inc.) disclose respectively pyrrolidyl derivatives of heteroaromatic compounds, and quinazolin-4-yl-piperidine and cinnolin-4-yl derivatives as PDE10A inhibitors that are considered to have potential in the treatment of CNS disorders, including schizophrenia, delusional disorders, drug-induced psychosis, anxiety, mood and movement disorders, 10 neurodegenerative disorders and drug addiction.

WO 2005082883 (Pfizer Products Inc.) discloses tetrahydroisoquinoliny derivatives of quinazoline and isoquinoline as PDE10A inhibitors that are claimed for use in the treatment of psychotic disorders, anxiety and movement disorders including Parkinson's disease and Huntington's disease, among other conditions.

15 WO 2006034512 & WO 2006034491 (Bayer Pharmaceuticals Corp.) disclose PDE10A inhibitors described as useful for the treatment of diabetes and related disorders. Pyrrolodihydroisoquinolines and variants thereof are disclosed as inhibitors of PDE10A in WO 2005003129 and WO 2005002579 (Nycomed GmbH).

20 WO 2004005291 & WO 2004005290 (Bayer Healthcare AG) disclose heterocyclically substituted imidazotriazines as PDE10A inhibitors described as useful for the treatment of neurodegenerative conditions, particularly Parkinson's disease and schizophrenia, and cancer.

25 WO 2004002484 (Kyowa Hakko Kirin Co., Ltd.) discloses quinoline derivatives as PDE10A inhibitors with potential in the treatment of Parkinson's disease, dyskinesia, anxiety, stress, mood and cognitive disorders, drug abuse, schizophrenia, cerebrovascular disorders, erectile dysfunction, diabetes, ischemic cardiopathies, renal disorders, peripheral vascular disease, hypertension, urinary incontinence, autoimmune diseases, respiratory disorders, allergies, pain, osteoporosis, cancer.

30 WO 2003014116 (Bayer Healthcare AG) discloses pyrrolo[2.1-a]isoquinoline derivatives as PDE10A inhibitors with potential in the treatment of cancer. WO 2003000693 (Bayer Healthcare AG) discloses imidazotriazines for use as PDE10A inhibitors considered to have potential in the treatment of Parkinson's disease.

All the above-mentioned publications are incorporated herein by reference.

However, these disclosures do not pertain to the compounds of the invention, which are structurally unrelated to any of the known PDE10A inhibitors (Kehler, J. et al., *Expert Opin. Ther. Patents*, 17, 147-158, 2007 and above cited patent literature), 5 and which have now been found by the inventors to be highly active and selective PDE10A enzyme inhibitors.

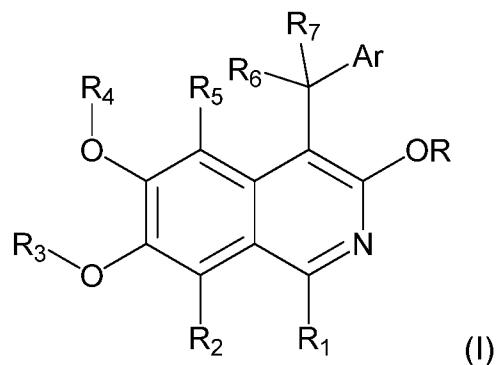
The compounds of the invention offer alternatives to current marketed treatments for neurodegenerative and/or psychiatric disorders, which are not efficacious in all patients.

10

## SUMMARY OF THE INVENTION

The present invention provides compounds that are PDE10A enzyme 15 inhibitors, in particular selective PDE10A enzyme inhibitors. The present invention further provides compounds which have such activity. The invention also provides an effective treatment, in particular long-term treatment, of a human patient, without causing the side effects typically associated with current therapies for neurological and psychiatric disorders. Further aspects of the invention will become apparent 20 upon reading the present specification.

In one aspect the present invention relates to compounds of formula (I):



25 wherein

R<sub>1</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl group which can optionally be substituted with a R<sub>a</sub>NH group, R<sub>a</sub> being selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl-CO and (C<sub>1</sub>-C<sub>4</sub>)alkyl-SO<sub>2</sub>;

R<sub>2</sub> is a hydrogen atom;

R<sub>3</sub> and R<sub>4</sub> independently represent a (C<sub>1</sub>-C<sub>3</sub>)alkyl group;

R<sub>5</sub> is a hydrogen atom;

R<sub>6</sub> and R<sub>7</sub> independently represent a hydrogen atom or a halogen atom, in particular fluorine, or R<sub>6</sub> and R<sub>7</sub> form together a =O group;

5 Ar is an aryl or heteroaryl group which can optionally be substituted with one to four substituents independently selected from the group consisting of hydroxy, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, aryl, (C<sub>1</sub>-C<sub>4</sub>)alkyl-aryl, amino-substituted aryl, aryloxy, heteroaryl, (C<sub>1</sub>-C<sub>4</sub>)alkyl-heteroaryl and R<sub>b</sub>R<sub>c</sub>N, or wherein two substituents at adjacent positions of the aryl or heteroaryl are bound together to form a heterocyclic

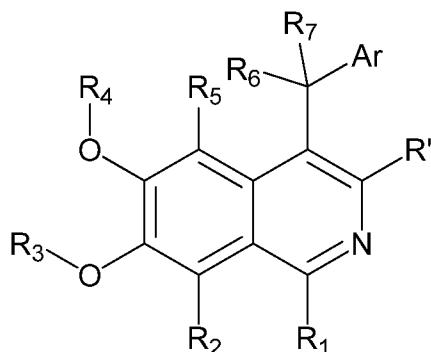
10 ring;

R<sub>b</sub> and R<sub>c</sub> being independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, halogeno(C<sub>1</sub>-C<sub>4</sub>)alkyl, aryl(C<sub>1</sub>-C<sub>4</sub>)alkyl and acetylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl; and

R is a hydrogen atom, a (C<sub>1</sub>-C<sub>3</sub>)alkyl group or a (C<sub>1</sub>-C<sub>3</sub>)alkyl-CO group;

and pharmaceutically acceptable salts, tautomer forms, solvates and esters thereof.

15 In another aspect the present invention relates to compounds of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt, tautomer form, solvate or ester thereof; wherein:

20 R<sub>1</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl group which can optionally be substituted with a -(C<sub>1</sub>-C<sub>4</sub>)alkoxy or a R<sub>a</sub>NH group, R<sub>a</sub> being selected from the group consisting of, (C<sub>1</sub>-C<sub>4</sub>)alkyl-C(=O)- and (C<sub>1</sub>-C<sub>4</sub>)alkyl-S(=O)<sub>2</sub>;

R<sub>2</sub> is a hydrogen atom;

R<sub>3</sub> and R<sub>4</sub> independently represent a (C<sub>1</sub>-C<sub>3</sub>)alkyl group;

25 R<sub>5</sub> is a hydrogen atom;

R<sub>6</sub> and R<sub>7</sub> independently represent a hydrogen atom, a halogen atom, or R<sub>6</sub> and R<sub>7</sub> together with the carbon atom to which they are shown attached form a -C(=O)- group;

R' is  $-\text{NH}_2$  or  $-\text{OR}$ , wherein R is a hydrogen atom, a (C<sub>1</sub>-C<sub>3</sub>)alkyl group or a (C<sub>1</sub>-C<sub>3</sub>)alkyl-C(=O)- group

Ar is an aryl or heteroaryl group which can optionally be substituted with one to four substituents independently selected from the group consisting of halogen, azido,

5 hydroxy, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy,  $-\text{O}(\text{C}_1\text{-}\text{C}_4)\text{alkyl}$ -(C<sub>1</sub>-C<sub>6</sub>)cycloalkyl, aryl, (C<sub>1</sub>-C<sub>4</sub>)alkyl-aryl-, (C<sub>1</sub>-C<sub>4</sub>)alkoxy-aryl-, amino-substituted aryl, N((C<sub>1</sub>-C<sub>4</sub>)alkyl)<sub>2</sub>-substituted aryl, aryloxy, heteroaryl, (C<sub>1</sub>-C<sub>4</sub>)alkyl-heteroaryl-, and R<sub>b</sub>R<sub>c</sub>N, or wherein two substituents at adjacent positions of the aryl or heteroaryl together with the atoms to which they are attached form a heterocyclic ring ; and

10 R<sub>b</sub> and R<sub>c</sub> are independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, halogeno(C<sub>1</sub>-C<sub>4</sub>)alkyl-, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkyl-, aryl(C<sub>1</sub>-C<sub>4</sub>)alkyl- and acetylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl-.

## DETAILED DESCRIPTION OF THE INVENTION

Within the context of the present application, the term "alkyl", alone or in combination with other groups, denotes linear or branched saturated hydrocarbon radical containing preferably from 1 to 10 carbon atoms, in particular from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms, unless otherwise indicated. Examples of alkyl groups having from 1 to 6 carbon atoms inclusive are methyl, ethyl, propyl (e.g., *n*-propyl, iso-propyl), butyl (e.g., *tert*-butyl, *sec*-butyl, *n*-butyl), pentyl (e.g., *neo*-pentyl), hexyl (e.g., *n*-hexyl), 2-methylbutyl, 2-methylpentyl and the other isomeric forms thereof. In the present invention, the alkyl groups can 5 be halogenated or not. The term "halogenoalkyl" denotes such alkyl group substituted by one or more halogens up to the maximum valency of the alkyl group. Representative halogenoalkyl groups include trifluoromethyl (CF<sub>3</sub>), difluoromethyl 10 (CF<sub>2</sub>H) and CF<sub>3</sub>CH<sub>2</sub>.

The term "halogen" denotes a chlorine, bromine, iodine or fluorine atom.

15 The term "acetylaminoalkyl" denotes a CH<sub>3</sub>CONH-alkyl group.

The term "alkoxy" denotes an alkyl-O- group, with alkyl as defined above. Examples of alkoxy groups are methoxy, ethoxy, *n*-propyloxy, isopropyloxy and *sec*-butyloxy.

20 The term "aryl" refers to monocyclic or polycyclic (e.g. having 2, 3 or 4 fused rings) aromatic hydrocarbons such as, for example, phenyl, naphthyl, antracenyl, phenanthrenyl and the like. In some embodiments, an aryl group has from 5 to 20 carbons, in particular from 6 to 14 carbon atoms. Most preferred aryl groups are mono- or bi-cyclic and comprises from 6 to 14 carbon atoms, such as phenyl,  $\alpha$ -naphthyl,  $\beta$ -naphthyl, antracenyl.

25 The term "aryloxy" denotes an aryl-O- group, with aryl as defined above.

The term "heteroaryl" denotes an aryl group interrupted by one or several heteroatoms selected from N, O, S or P. Heteroaryl groups include mono- or polycyclic groups (e.g. having 2, 3 or 4 fused rings). Representative heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl and dibenzofuran groups.

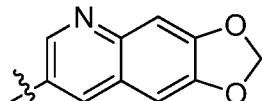
30 It will be understood that aryl and heteroaryl groups as substituents on the compound according to the invention can be branched to the remainder of the compound via any of the carbon atoms contained in said aryl and heteroaryl group.

In particular embodiments, compounds of the invention have one or more of the following features:

- R<sub>1</sub> is a substituted or unsubstituted (C<sub>1</sub>-C<sub>4</sub>)alkyl group preferably selected in the group consisting of methyl, ethyl, n-propyl, isopropyl, CH<sub>3</sub>CONHCH<sub>2</sub> and CH<sub>3</sub>SO<sub>2</sub>NHCH<sub>2</sub>; and/or
- 5 - R<sub>2</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> are hydrogen; and/or
- R<sub>3</sub> and R<sub>4</sub> both represent a methyl group; and/or
- R' is selected from the group consisting of -NH<sub>2</sub>, -OH, -OCH<sub>3</sub>, and -OC(=O)CH<sub>3</sub>; and/or
- 10 - Ar represents a pyridinyl, phenyl, naphthyl, quinolinyl, isoquinolinyl, [1,3]dioxolo[4,5-g]quinolyn, or dibenzofuran group, said Ar group being optionally substituted with one or more (e.g. two or three) substituents independently selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, aryl, (C<sub>1</sub>-C<sub>4</sub>)alkylaryl, heteroaryl, (C<sub>1</sub>-C<sub>4</sub>)heteroaryl, (C<sub>1</sub>-C<sub>4</sub>)alkyloxy, aryloxy, (C<sub>1</sub>-C<sub>4</sub>)alkoxy-aryl-, aminoaryl (i.e, H<sub>2</sub>N-aryl), and R<sub>b</sub>R<sub>c</sub>N.
- 15

In a particular embodiment, Ar represents:

- a pyridinyl group optionally substituted with one or two substituents independently selected from the group consisting of aryl, (C<sub>1</sub>-C<sub>4</sub>)alkylaryl, heteroaryl, (C<sub>1</sub>-C<sub>4</sub>)heteroaryl and (C<sub>1</sub>-C<sub>4</sub>)alkoxy-aryl-;
- 20 - a phenyl group optionally substituted with one or two substituents selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyloxy, aryloxy, (C<sub>1</sub>-C<sub>4</sub>)alkoxy-aryl-, and aminoaryl;
- a naphthyl group optionally substituted with one or two substituents selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyloxy, aryloxy, (C<sub>1</sub>-C<sub>4</sub>)alkoxy-aryl and aminoaryl;
- 25 - a quinolinyl group optionally substituted with one or more substituents, in particular one or two substituents, selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkyloxy and R<sub>b</sub>R<sub>c</sub>N;
- a [1,3]dioxolo[4,5-g]quinolyn group, optionally substituted with a R<sub>b</sub>R<sub>c</sub>N-substituent (i.e., a compound of the structure:
- 30



which is optionally substituted with a  $R_bR_cN$ - substituent);

- an isoquinolinyl group; or
- a dibenzofuran group.

5 Specific representative, and non-limiting, substituents of the Ar group include fluoro, azido, hydroxyl, methyl, ethyl, hydroxy, methoxy, ethoxy, cyclopropylmethoxy (i.e., -O-CH<sub>2</sub>-cyclopropyl), phenyl, methoxyphenyl, aminophenyl, phenoxy, pyridinyl, methylamino, ethylamino, N,N-dimethylamino, ethylamino, n-propylamino, n-butylamino, isopropylamino, trifluoromethyl, 2,2,2-trifluoroethylamino, benzylamino, 10 and acetyl-2-aminoethylamino groups.

In a particular embodiment, the compound of the invention is a compound of formula (I) wherein:

- $R_1$  is an unsubstituted (C<sub>1</sub>-C<sub>3</sub>)alkyl group, preferably selected in the group consisting of methyl, ethyl and n-propyl

15 -  $R_2$ ,  $R_5$ ,  $R_6$ ,  $R_7$  are hydrogen;

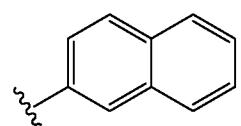
- $R_3$  and  $R_4$  both represent a methyl group;

- R is hydrogen; and

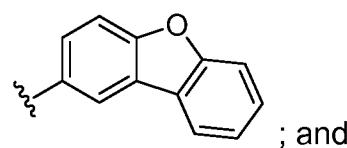
- Ar is selected in the group consisting of:

20 a phenyl group optionally substituted with one or two substituents selected from the group consisting of (C<sub>1</sub>-C<sub>4</sub>)alkyloxy, aryloxy, (C<sub>1</sub>-C<sub>4</sub>)alkoxy-aryl-, and aminoaryl;

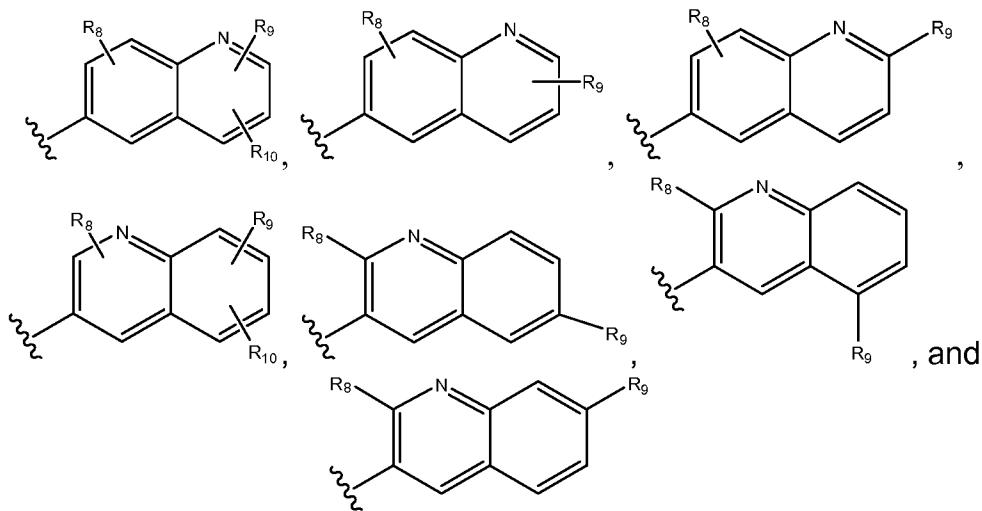
an unsubstituted naphthyl group, in particular the following naphthyl group



25 a dibenzoburan group of the formula



and a quinolinyl group selected from the group consisting of:



5 wherein :

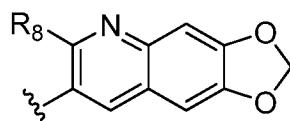
R<sub>8</sub> is selected in the group consisting of hydrogen, halogenoalkyl, azido, (C<sub>1</sub>-C<sub>4</sub>)alkyl, and R<sub>b</sub>R<sub>c</sub>N (such as (C<sub>1</sub>-C<sub>4</sub>)alkylNH, (C<sub>1</sub>-C<sub>4</sub>)halogenoalkylNH or benzylNH, more specifically from methylamino, dimethylamino, ethylamino, n-propylamino, isopropylamino, 2,2,2-trifluoroethylamino, benzylamino, 2-methoxyethylamino, and

10 acetyl-2-aminoethylamino groups;

R<sub>9</sub> and R<sub>10</sub> are independently selected from the group consisting of hydrogen, halogen, hydroxyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy, and -O-(C<sub>1</sub>-C<sub>4</sub>)alkyl-(C<sub>1</sub>-C<sub>6</sub>)cycloalkyl;

or R<sub>9</sub> and R<sub>10</sub>, together with the carbon atoms to which they are attached on the quinolinyl group, form 5- or 6-membered heterocyclic ring, for example as in the

15 following structure:



In one embodiment, R<sub>9</sub> is a methyl group or a (C<sub>1</sub>-C<sub>3</sub>)alkoxy group, in particular methoxy or ethoxy, and R<sub>10</sub> is a hydrogen.

In another embodiment, both R<sub>9</sub> and R<sub>10</sub> are hydroxyl groups.

20 Specific compounds of formula (I) which fall within the scope of the present invention include each of compounds 1 to 88 presented in the following "Examples" part. The invention thus relates to a compound of formula (I), selected in the group consisting of compounds 1 to 88 or a pharmaceutically acceptable salt thereof:

4-benzyl-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride **1**,

25 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride **2**,

4-(3,4-dimethoxybenzyl)-3,6,7-trimethoxy-1-methylisoquinoline hydrochloride **3**,  
6,7-dimethoxy-1-methyl-4-(3-phenoxybenzyl)isoquinolin-3-ol hydrochloride **4**,  
6,7-dimethoxy-1-methyl-4-(4-phenoxybenzyl)isoquinolin-3-ol hydrochloride **5**,  
4-(dibenzo[*b,d*]furan-2-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride  
5 **6**,  
4-(dibenzo[*b,d*]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol hydrochloride  
7,  
4-([1,1'-biphenyl]-3-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride **8**,  
1-ethyl-6,7-dimethoxy-4-((4'-methoxy-[1,1'-biphenyl]-3-yl)methyl)isoquinolin-3-ol  
10 hydrochloride **9**,  
4-((3'-amino-[1,1'-biphenyl]-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol  
dihydrochloride **10**,  
6,7-dimethoxy-1-methyl-4-(pyridin-4-ylmethyl)isoquinolin-3-ol hydrochloride **11**,  
6,7-dimethoxy-1-methyl-4-((6-phenylpyridin-2-yl)methyl)isoquinolin-3-ol  
15 dihydrochloride **12**,  
6,7-dimethoxy-4-((6-(4-methoxyphenyl)pyridin-2-yl)methyl)-1-methylisoquinolin-3-ol  
dihydrochloride **13**,  
4-([2,4'-bipyridin]-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol trihydrochloride  
14,  
20 6,7-dimethoxy-1-methyl-4-((5-phenylpyridin-3-yl)methyl)isoquinolin-3-ol  
dihydrochloride **15**,  
6,7-dimethoxy-4-((5-(4-methoxyphenyl)pyridin-3-yl)methyl)-1-methylisoquinolin-3-ol  
dihydrochloride **16**,  
6,7-dimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride **17**,  
25 3,6,7-trimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinoline hydrochloride **18**,  
1-ethyl-6,7-dimethoxy-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride **19**,  
6,7-dimethoxy-4-(naphthalen-2-ylmethyl)-1-propylisoquinolin-3-ol hydrochloride **20**,  
4-(isoquinolin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **21**,  
4-(isoquinolin-5-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **22**,  
30 6,7-dimethoxy-1-methyl-4-(quinolin-2-ylmethyl)isoquinolin-3-ol dihydrochloride **23**,  
6,7-dimethoxy-1-methyl-4-(quinolin-6-ylmethyl)isoquinolin-3-ol dihydrochloride **24**,  
6,7-dimethoxy-1-methyl-4-(quinolin-4-ylmethyl)isoquinolin-3-ol dihydrochloride **25**,  
6,7-dimethoxy-1-methyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **26**,

6,7-dimethoxy-4-((5-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **27**,

4-((5-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **28**,

5 6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **29**,

4-((7-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **30**,

10 1-ethyl-6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **31**,

6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **32**,

6,7-dimethoxy-1-methyl-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **33**,

15 6,7-dimethoxy-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **34**,

4-((2-(ethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **35**,

4-((2-(dimethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-  
20 propylisoquinolin-3-ol dihydrochloride **36**,

6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **37**,

6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-  
25 propylisoquinolin-3-ol dihydrochloride **38**,

1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-  
30 propylisoquinolin-3-ol dihydrochloride **39**,

1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(ethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **40**,

1-ethyl-6,7-dimethoxy-4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)isoquinolin-3-  
35 ol dihydrochloride **41**,

1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **42**,

1-ethyl-4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **43**,

4-((2-(benzylamino)-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **44**,

5 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **45**,

4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **46**,

4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **47**,

10 6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **48**,

4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **49**,

15 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **50**,

1-isopropyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **51**,

6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-

20 propylisoquinolin-3-ol dihydrochloride **52**,

4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **53**,

6,7-dimethoxy-4-((6-methoxy-2-((2,2,2-trifluoroethyl)amino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **54**,

25 *N*-(2-((3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride **55**,

1-(acetamidomethyl)-4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-yl acetate **56**,

*N*-((4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-

30 dimethoxyisoquinolin-1-yl)methyl)acetamide dihydrochloride **57**,

*N*-((4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)methanesulfonamide dihydrochloride **58**,

3-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-2-(methylamino)quinoline-6,7-diol dihydrochloride **59**,

6,7-dimethoxy-1-methyl-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride **60**,

5 1-ethyl-6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride **61**,

6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **62**,

4-((6-(dimethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **63**,

10 4-((6-(ethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **64**,

4-(dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-amine hydrochloride **65**,

15 4-((2-ethyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **66**,

4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-(methoxymethyl)isoquinolin-3-ol dihydrochloride **67**,

20 4-((2-azido-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **68**,

*N*-(2-((3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride **69**,

4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **70**,

25 4-((2-butyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **71**,

6,7-dimethoxy-4-((6-methoxy-2-(trifluoromethyl)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol hydrochloride **72**,

*N*-(2-((3-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride **73**,

30 6,7-dimethoxy-1-propyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **74**,

(2-(ethylamino)-6-methoxyquinolin-3-yl)(3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methanone dihydrochloride **75**,

6,7-dimethoxy-4-((6-methoxy-2-((2-methoxyethyl)amino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **76**,

1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-((2-methoxyethyl)amino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **77**,

5 1-ethyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **78**,

1-isopropyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **79**,

6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **80**,

1-ethyl-6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)isoquinolin-3-ol dihydrochloride **81**,

1-ethyl-4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **82**,

*N*-(2-((6-(cyclopropylmethoxy)-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride **83**,

15 6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **84**,

1-ethyl-6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **85**,

4-((6-ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **86**,

20 *N*-(2-((6-(cyclopropylmethoxy)-3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride **87**, and

*N*-(2-((6-ethoxy-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride **88**.

25 Included within the scope of the invention are all stereoisomers, tautomeric forms, salts and solvates of the compound of formula (I).

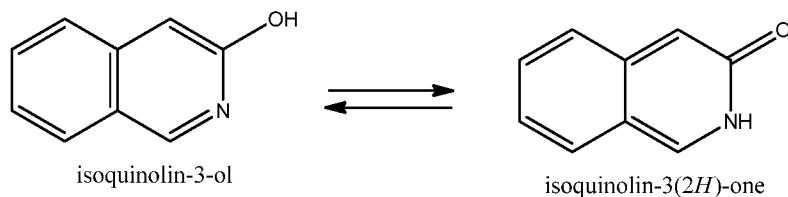
The compounds according to the invention can be in the form of salts, particularly acid or base salts, preferably compatible with pharmaceutical use (i.e. pharmaceutically acceptable salts of the compounds of the invention). It will be 30 appreciated by those skilled in the art that non-pharmaceutically acceptable salts of compounds of formula (I) are also part of the present invention, since such non-pharmaceutically acceptable salts can be useful as intermediates in the preparation of pharmaceutycally acceptables salts.

Salts of compounds of the invention include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in *J. Pharm. Sci.*, 66, 2, 1977 which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Other examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like.

The pharmaceutically acceptable salts can in particular be prepared by reacting the compound of formula (I) with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, fonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane, etc. Mixture of solvents may also be used.

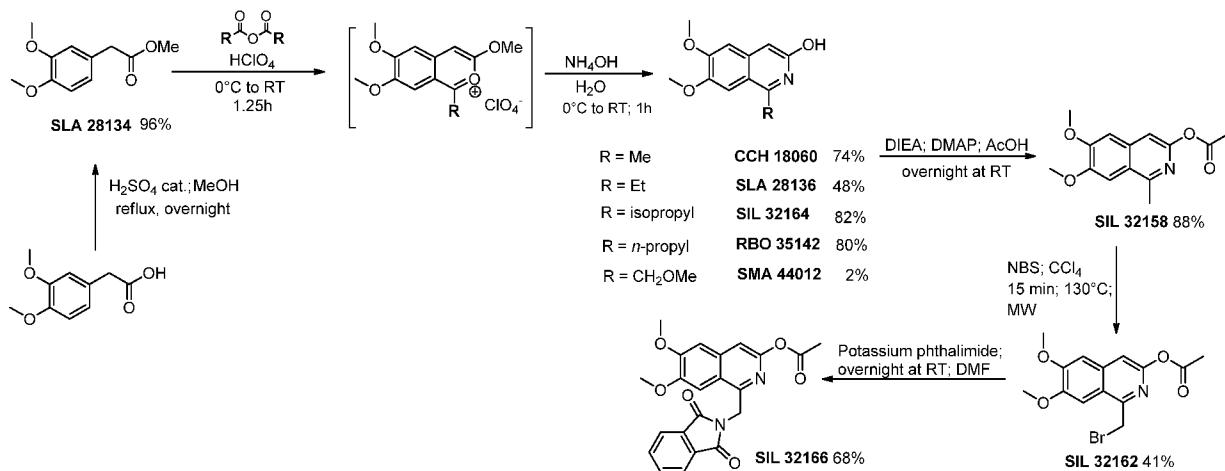
Compounds of Formula (I) may have optical centers and therefore may occur in different enantiomeric and diastereomeric configurations. The present invention includes all enantiomers, diastereomers, and other stereoisomers of such compounds of Formula (I), as well as racemic compounds and racemic mixtures and 5 other mixtures of stereoisomers thereof.

Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism can occur. The compounds having structures that correspond to the formula (I) are also capable of existing as the corresponding 3-keto tautomeric forms. It follows that a single compound may exhibit more than one type of 10 isomerism.



The compounds according to the present invention may be prepared by various methods known to those skilled in the art. General and specific methods for 15 the preparation of compounds of formula (I) are described herein below.

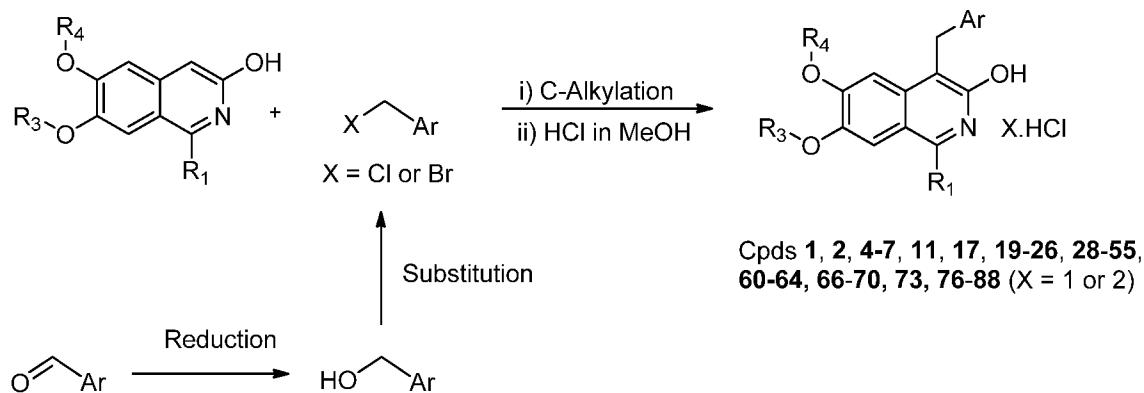
The intermediary 6,7-dimethoxy-1-alkylisoquinolin-3-ols **CCH 18060**, **SLA 28136**, **SIL 32164**, **RBO 35142** and **SMA 44012** were prepared in 2-82% yields (Reaction scheme 1) following a method described by Kanojia, RM et al. starting from the methyl ester **SLA 28134** (Kanojia, RM et al., *J. Med. Chem.*, 1988, 31, 7, 20 1363). The phthalimide derivative **SIL 32166** was prepared in three steps from 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060**: O-acylation of **CCH 18060** with acetic anhydride in presence of diisopropylethylamine and DMAP overnight at RT led to the acetate **SIL 32158** in 88% yield. Bromination of acetate **SIL 32158** with *N*-bromosuccinimide in carbon tetrachloride for 15 min at 130°C under microwave 25 irradiation afforded to the bromomethyl derivative **SIL 32162** in 41% yield. Finally **SIL 32162** was treated with potassium phthalimide in DMF overnight at room temperature to give the phthalimide derivative **SIL 32162** in 68% yield (Reaction scheme 1).



**Reaction Scheme 1:** Synthetic routes used for the preparation of intermediary compounds **CCH 18060**, **SLA 28136**, **SIL 32164**, **RBO 35142**, **SMA 44012** and **SIL 32166**

5

The compounds **1, 2, 4-7, 11, 17, 19-26, 28-55, 60-64, 66-70, 73, 76-88** of the invention (Reaction Scheme 2) were prepared by C-alkylation of 6,7-dimethoxy-1-alkylisoquinolin-3-ols **CCH 18060**, **SLA 28136**, **SIL 32164**, **RBO 35142** or **SMA 10 44012** preferably in toluene or THF at  $110$ - $160^\circ\text{C}$  under microwave irradiation for 15-120 min by a halogenomethyl-aryl or a halogenomethyl-heteroaryl derivative in presence of a 2 N aqueous KOH or LiOH solution as base.



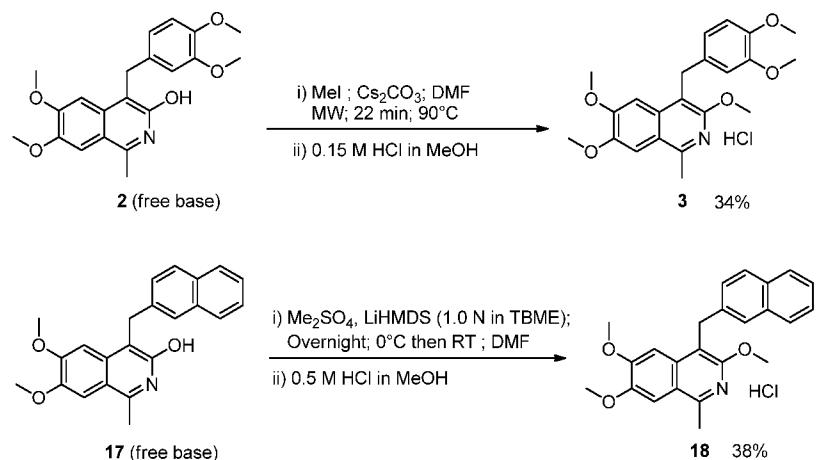
15 **Reaction Scheme 2:** Synthetic routes followed to prepare final compounds

Compound **52** was prepared with the same type of microwave-assisted C-alkylation at  $150^\circ\text{C}$  for 90 min using THF as solvent and a 1.6 M solution of *n*-BuLi in hexane as base. The chloro or bromo-alkylating reagents (halogenomethyl-aryl or halogenomethyl-heteroaryl derivatives) were commercially available or prepared

from the corresponding primary alcohols by substitution of the hydroxyl function by a chlorine or a bromine atom using respectively thionyl chloride or triphenylphosphine and bromine in dichloromethane. The primary alcohols were prepared by reduction of the corresponding aldehydes using sodium borohydride (Reaction scheme 2).

5 In some cases the products obtained by following the reaction Scheme 2 may  
be further modified, for example, by manipulation of substituents.

For example compound **3** was obtained from compound **2** free base by microwave-assisted O-methylation using methyl iodide in presence of cesium carbonate in dimethylformamide (reaction scheme 3).



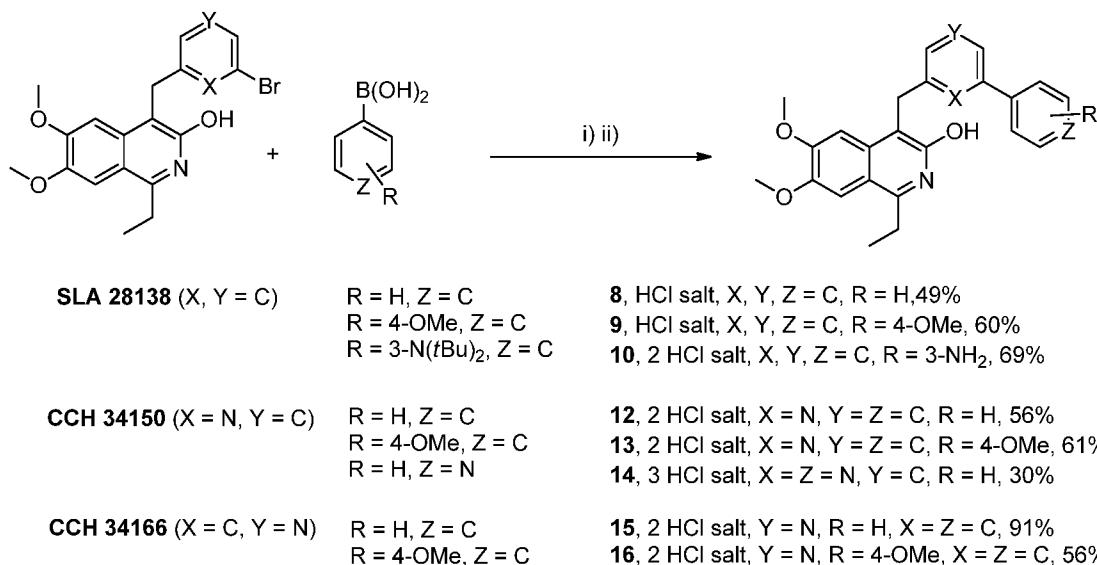
10

### Reaction Scheme 3: Preparation of compounds 3 and 18

Compound **18** was obtained from compound **17** by O-methylation using dimethylsulfate with lithium hexamethyldisilazide (LiHMDS) as base and in dimethylformamide (Reaction scheme 3)

15

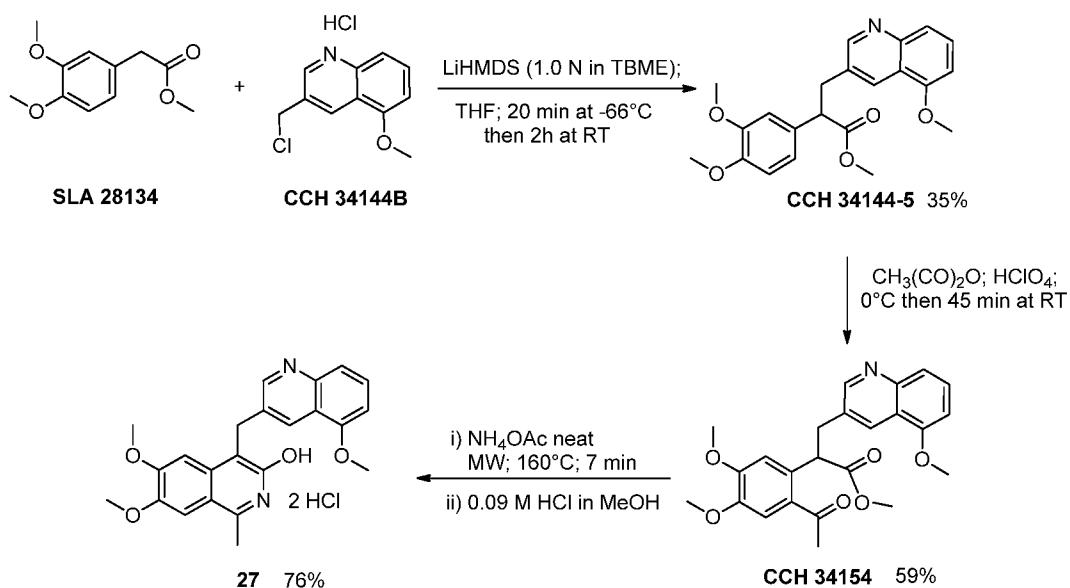
For example microwave-assisted Suzuki cross coupling reaction between the bromo derivatives **SLA 28138**, **CCH 34150** and **CCH 34166** and different substituted phenylboronic acids afforded direct access to compounds **8-10** and **12-14** in 30-91% yields (Reaction Scheme 4).



i)  $\text{Pd}(\text{PPh}_3)_4\text{Cl}_2$ ;  $\text{Na}_2\text{CO}_3$ ; DME; MW;  $140^\circ\text{C}$ . ii) 0.49 M HCl in MeOH

#### Reaction Scheme 4: Synthetic routes followed to prepare compounds 8-10 & 12-14

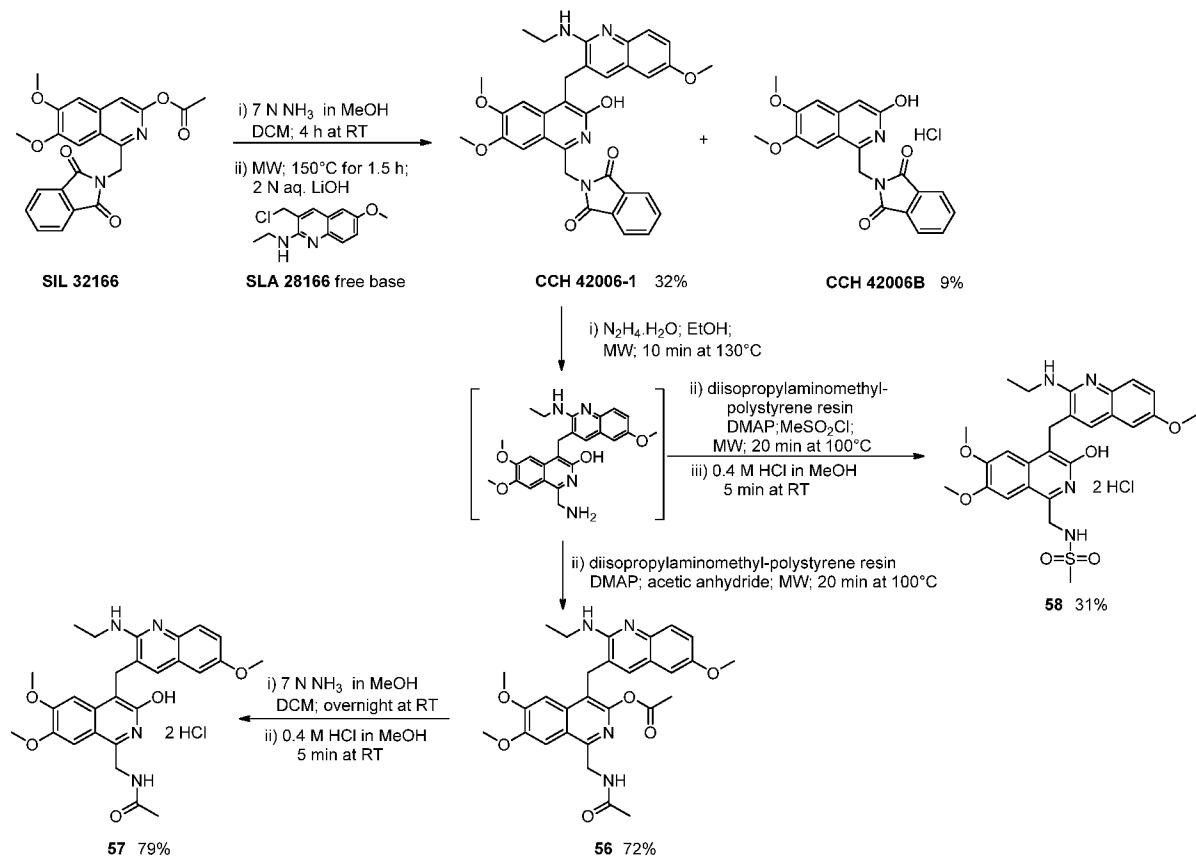
The compound **27** was obtained from a different synthetic route (Reaction scheme 5). The methyl ester **SLA 28134** was deprotonated by LiHMDS followed by treatment with the chloro derivative **CCH 34144B** to obtain the methyl ester **CCH 34144-5** in 35% yield. The methyl ester **CCH 34144-5** was treated with acetic anhydride in presence of perchloric acid to give the corresponding acetyl derivative **CCH 34154** in 59% yield. Finally microwave-assisted treatment of **CCH 34154** by ammonium acetate at  $160^\circ\text{C}$  for 7 minutes followed by a subsequent treatment at room temperature by a 0.09 M HCl solution in methanol afforded compound **27** as a dihydrochloride salt in 76% yield (scheme 5).



**Reaction Scheme 5:** Synthetic route followed to prepare the compound **27**

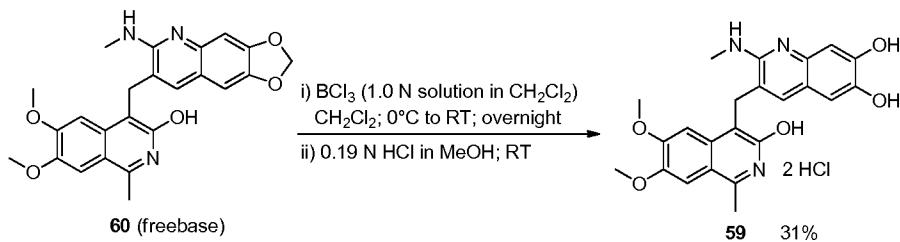
The compounds **56-58** were prepared following the synthetic routes described in scheme 6. The acetate **SIL 32166** was first deprotected to its corresponding hydroxy derivative by a 7N NH<sub>3</sub> solution in methanol for 4 hours at room 5 temperature.

The intermediary hydroxy compound was then C-alkylated in THF with **SLA 28166** free base at 150°C for 1.5 hours in presence of a 2 N aqueous LiOH solution as base and under microwave irradiation. The obtained phthalimide **CCH 42006-1** was then deprotected to its corresponding amino derivative by treatment with hydrazine 10 hydrate in ethanol for 10 min at 130°C under microwave irradiation. The amino derivative was treated by acetic anhydride in presence of diisopropylaminomethyl-polystyrene resin and DMAP for 20 min at 100°C under microwave irradiation to obtain the bis-acetylated derivative **56** in 72% yield. Compound **56** was deprotected 15 to its corresponding hydroxy derivative by a 7 N NH<sub>3</sub> solution in methanol overnight at room temperature to obtain, after treatment at RT with a 0.4 M HCl solution in MeOH, compound **57** as a dihydrochloride salt in 79% yield. The intermediary amino derivative was also treated by methanesulfonyl chloride, in presence of diisopropylaminomethyl-polystyrene resin, and DMAP for 20 min at 100°C under microwave irradiation to obtain, after purification and treatment for 5 min at RT with a 20 0.4 M HCl solution in MeOH, compound **58** as a hydrochloride salt in 31% yield (reaction scheme 6).



**Reaction Scheme 6:** Synthetic routes used to prepare compounds **56-58**

The compound **59** was prepared from compound **60** following the reaction described in scheme 7. Compound **60** freebase in dichloromethane was treated at 0°C by a 1.0 N solution of  $\text{BCl}_3$  in dichloromethane and the reaction mixture was stirred overnight at RT. After purification and treatment with a 0.19 N HCl solution in methanol at RT, compound **59** was obtained as a dihydrochloride salt in 31% yield.

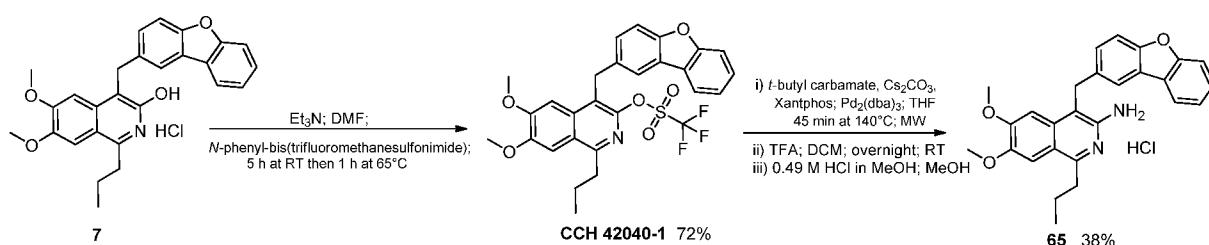


**10 Reaction Scheme 7:** Synthetic route followed to prepare the compound **59**

The compound **65** was prepared from compound **7** following the reaction described in scheme 8. The compound **7** was treated, for 5 hours at room temperature then for 1 hour at 65°C, by *N*-phenyl-bis(trifluoromethanesulfonimide) in

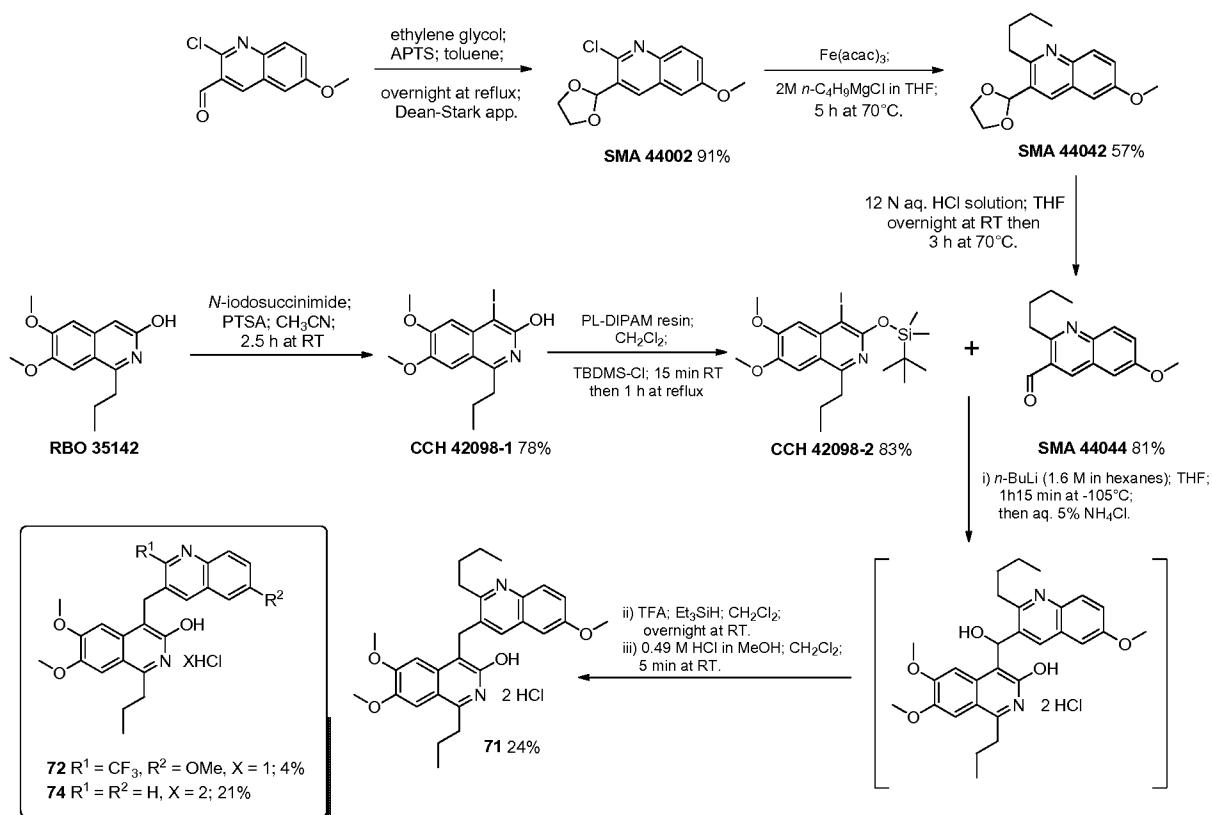
dimethylformamide in presence of triethylamine as a base to obtain the triflate **CCH 42040-1** in 72% yield. Buchwald-Hartwig cross coupling reaction, preferentially for 45 minutes in THF and at 140°C under microwave irradiation, between triflate **CCH 42040-1** and *t*-butylcarbamate using tris(dibenzylideneacetone)dipalladium(0) as catalyst, xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) as ligand and cesium carbonate as a base led, after subsequent trifluoroacetic acid treatment overnight at room temperature followed by a final treatment of the obtained free base in methanol for 5 min at RT with a 0.49 M HCl solution in MeOH, to the compound **59** as a dihydrochloride salt in 31% overall yield (reaction scheme 8).

10



**Reaction Scheme 8:** Synthetic route to prepare the compound **65**

Another method to prepare the compounds of the invention is the route followed to synthesize the compounds **71**, **72** & **74** that is described in scheme 9. The key step is a halogen-metal exchange reaction, preferentially performed at -105°C in presence of anhydrous THF as solvent, between the iodo derivative **CCH 42098-2** and a 1.6 M solution of *n*-butyl lithium in hexanes followed by a subsequent quench with the aldehyde **SMA 44044** to obtain an intermediary secondary alcohol derivative that can be purified by column chromatography. The secondary alcohol derivative can then be reduced, preferentially by using triethylsilane in presence of TFA in dichloromethane overnight at RT. After neutralization of the obtained residue by a NaHCO<sub>3</sub> aqueous solution, the free base of the reduced compound was obtained after purification by column chromatography. The subsequent treatment of the obtained free base in dichloromethane for 5 min at RT with a 0.49 M HCl solution in MeOH led to the compound **71** as a dihydrochloride salt in 24% overall yield. The compounds **72** and **74** were obtained by this method using respectively 6-methoxy-2-(trifluoromethyl)quinoline-3-carbaldehyde **SLA 47010** and 3-quinolinecarboxaldehyde instead of 2-butyl-6-methoxyquinoline-3-carbaldehyde **SMA 44044** (reaction scheme 9).

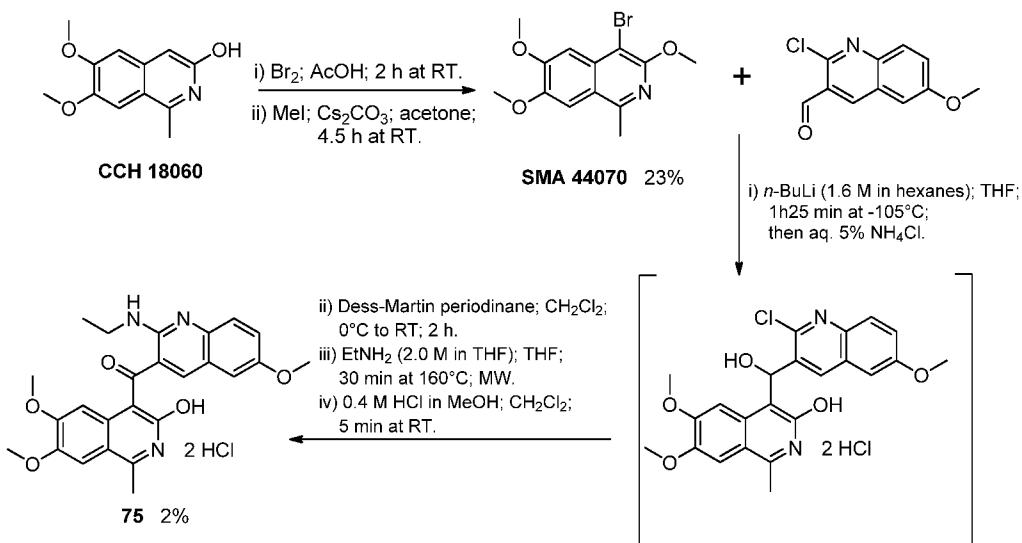


**Reaction Scheme 9:** Synthetic route followed to prepare compounds 71, 72 & 74

5 The compound **75** was prepared from compound **CCH 18060** following the reaction described in scheme 10. The key step is a halogen-metal exchange reaction, performed preferentially at -105°C in presence of anhydrous THF as solvent, between the bromo derivative **SMA 44070** and a 1.6 M solution of *n*-butyl lithium in hexanes followed by a subsequent quench with 2-chloro-6-methoxyquinoline-3-carbaldehyde to obtain an intermediary secondary alcohol derivative that can be purified by column chromatography. The secondary alcohol derivative can then be oxidized in ketone preferentially using Dess-Martin periodinane in dichloromethane from 0°C to RT for 2 hours. The oxidized chloro compound was purified by column chromatography and then the chloro aromatic substituent was substituted in tetrahydrofuran by ethylamine preferentially by using a 2.0 M ethylamine solution in THF for 30 min at 160°C under microwave irradiation. The subsequent treatment of the obtained ethylamine free base derivative in dichloromethane for 5 min at RT with a 0.49 M HCl solution in MeOH led to the compound **75** as a dihydrochloride salt in 2% overall yield (reaction scheme 10).

10

15



**Reaction Scheme 10:** Synthetic route used to prepare the compound **75**

It should be understood that other ways of producing these compounds may be designed by the skilled person, based on common general knowledge and following guidance contained in this application.

Another object of the present invention is the intermediate compounds used for the preparation of compounds of formula (I). In particular, the present invention relates to the intermediate compounds herein below mentioned in the examples.

The compounds of the invention can be administered alone, but are generally administered with a pharmaceutical carrier, with respect to standard pharmaceutical practice (such as described in Remington's Pharmaceutical Sciences, Mack Publishing), in either single or multiple doses. The invention thus also includes a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula (I).

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed thereby can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, liquid preparations, syrups, injectable solutions and the like. These pharmaceutical compositions can optionally contain additional ingredients such as flavorings, binders, excipients and the like. Thus, the compound of the invention may be formulated for oral, ocular, buccal, intranasal, parenteral (e.g. intravenous, intramuscular or subcutaneous), transdermal (e.g. patch) or rectal administration, or in a form suitable for administration by inhalation or insufflation.

The pharmaceutical compositions of the invention can be formulated either as solid or liquid compositions.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycolate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampoules or in multi-dose containers, with an added preservative. They may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. When a product solution is required, it can be made by dissolving the isolated inclusion complex in water (or other aqueous medium) in an amount sufficient to generate a solution of the required strength for oral or parenteral administration to patients. The compounds may be formulated for fast dispersing dosage forms, which are designed to release the active ingredient in the oral cavity. These have often been formulated using rapidly soluble gelatin-based matrices. These dosage forms are well known

and can be used to deliver a wide range of drugs. Most fast dispersing dosage forms utilize gelatin as a carrier or structure-forming agent. Typically, gelatin is used to give sufficient strength to the dosage form to prevent breakage during removal from packaging, but once placed in the mouth, the gelatin allows immediate dissolution of  
5 the dosage form. Alternatively, various starches are used to the same effect. The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The dosages and dosage regimen in which the compounds of formula (I) are  
10 administered will vary according to the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. Accordingly, optimal therapeutic concentrations will be best determined at the time and place through  
15 routine experimentation.

The compounds according to the invention can be used enterally or parenterally. Orally, the compounds according to the invention are suitably administered in the amount from about 0.1 mg per day to 1,000 mg per day. For parenteral, sublingual, intranasal, or intrathecal administration, the compounds  
20 according to the invention are suitably used in the amount from about 0.5 to about 100 mg/day; for depo administration and implants from about 0.5 mg/day to about 50 mg/day; for topical administration from about 0.5 mg/day to about 200 mg/day; for rectal administration from about 0.5 mg to about 500 mg. In a preferred aspect, the therapeutically effective amounts for oral administration is from about 1 mg/day to  
25 about 100 mg/day; and for parenteral administration from about 5 to about 50 mg daily. In a more preferred aspect, the therapeutically effective amounts for oral administration are from about 5 mg/day to about 50 mg/day.

The daily dose may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

30 The present invention also relates to a compound of formula (I), or a composition comprising a compound of formula (I), for use as a medicament. Indeed, the compounds according to the invention have been found to have pharmacologically important properties which can be used therapeutically. The

compounds of the invention can be used alone, in combination with each other or in combination with other active compounds.

The compounds of the invention are inhibitors selective for PDE10A. The invention thus also relates to a compound of formula (I) or a pharmaceutical composition comprising the same, for use in a method for the treatment of a disease selected in the group consisting of the diseases or groups of diseases described below, where inhibition of PDE10 would be efficient in the treatment of said diseases.

The present invention also pertains to a pharmaceutical composition for use in the treatment of certain psychotic disorders and conditions such as schizophrenia, delusional disorders and drug induced psychosis; to anxiety disorders such as panic and obsessive-compulsive disorder; and to movement disorders including Parkinson's disease and Huntington's disease, comprising an amount of a compound of formula (I) effective in inhibiting PDE10A.

In another embodiment, the invention relates to a pharmaceutical composition for treating psychotic disorders and condition such as schizophrenia, delusional disorders and drug induced psychosis; anxiety disorders such as panic and obsessive-compulsive disorder; and movement disorders including Parkinson's disease and Huntington's disease, comprising an amount of a compound of formula (I) effective in treating said disorder or condition.

The invention also relates to a compound of formula (I), for use in the treatment of certain psychotic disorders and conditions such as schizophrenia, delusional disorders and drug induced psychosis; to anxiety disorders such as panic and obsessive-compulsive disorder; and to movement disorders including Parkinson's disease and Huntington's disease.

Examples of psychotic disorders that can be treated according to the present invention include, but are not limited to, schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type. Examples of movement disorders that can be treated

according to the present invention include but are not limited to Huntington's disease and dyskinesia associated with dopamine agonist therapy, Parkinson's disease, restless leg syndrome, and essential tremor.

5 Other disorders that can be treated according to the present invention are obsessive/compulsive disorders, Tourette's syndrome and other tic disorders.

In another embodiment, the invention relates to a method for treating an anxiety disorder or condition in a mammal which method comprises administering to said mammal an amount of a compound of formula (I) effective in inhibiting PDE10A.

10 The invention also provides a method for treating an anxiety disorder or condition in a mammal which method comprises administering to said mammal an amount of a compound of formula (I) effective in treating said disorder or condition.

The invention also relates to a compound of formula (I), for use in the treatment of an anxiety disorder or condition in a mammal.

15 Examples of anxiety disorders that can be treated according to the present invention include, but are not limited to, panic disorder; agoraphobia; a specific phobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; acute stress disorder; and generalized anxiety disorder.

20 The invention further provides a method of treating a drug addiction, for example an alcohol, amphetamine, cocaine, or opiate addiction, in a mammal, including a human, which method comprises administering to said mammal an amount of a compound of formula (I) effective in treating drug addiction. The invention also provides a method of treating a drug addiction, for example an alcohol, amphetamine, cocaine, or opiate addiction, in a mammal, including a human, which method comprises administering to said mammal an amount of a 25 compound of formula (I) effective in inhibiting PDE10A.

The invention also relates to a compound of formula (I), for use in the treatment of a drug addiction, for example an alcohol, amphetamine, cocaine, or opiate addiction, in a mammal, including a human.

30 A "drug addiction", as used herein, means an abnormal desire for a drug and is generally characterized by motivational disturbances such a compulsion to take the desired drug and episodes of intense drug craving.

The invention further provides a method of treating a disorder comprising as a symptom a deficiency in attention and/or cognition in a mammal, including a human,

which method comprises administering to said mammal an amount of a compound of formula (I) effective in treating said disorder. The invention also provides a method of treating a disorder or condition comprising as a symptom a deficiency in attention and/or cognition in a mammal, including a human, which method comprises

5 administering to said mammal an amount of a compound of formula (I) effective in inhibiting PDE10A.

The invention also provides a method of treating a disorder or condition comprising as a symptom a deficiency in attention and/or cognition in a mammal, including a human, which method comprises administering to said mammal an

10 amount of a compound of formula (I) effective in treating said disorder or condition.

The invention also relates to a compound of formula (I), for use in the treatment of a disorder or condition comprising as a symptom a deficiency in attention and/or cognition in a mammal, including a human.

The phrase "deficiency in attention and/or cognition" as used herein in

15 "disorder comprising as a symptom a deficiency in attention and/or cognition" refers to a subnormal functioning in one or more cognitive aspects such as memory, intellect, or learning and logic ability, in a particular individual relative to other individuals within the same general age population. "Deficiency in attention and/or cognition" also refers to a reduction in any particular individual's functioning in one or

20 more cognitive aspects, for example as it occurs in age-related cognitive decline. Examples of disorders that comprise as a symptom a deficiency in attention and/or cognition that can be treated according to the present invention are dementia, for example Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral

25 trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline.

30 The invention also provides a method of treating a mood disorder or mood episode in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula (I) effective in treating said disorder or episode.

The invention also provides a method of treating a mood disorder or mood episode in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula (I) effective in inhibiting PDE10A.

5 The invention also relates to a compound of formula (I), for use in the treatment of a mood disorder or mood episode in a mammal, including a human

Examples of mood disorders and mood episodes that can be treated according to the present invention include, but are not limited to, major depressive episode of the mild, moderate or severe type, a manic or mixed mood episode, a hypomanic mood episode; a depressive episode with atypical features; a depressive 10 episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post- stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder such as delusional disorder or 15 schizophrenia; a bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder.

The invention further provides a method of treating a neurodegenerative disorder or condition in a mammal, including a human, which method comprises administering to said mammal an amount of a compound of formula (I) effective in 20 treating said disorder or condition. The invention further provides a method of treating a neurodegenerative disorder or condition in a mammal, including a human, which method comprises administering to said mammal an amount of a compound of formula (I) effective in inhibiting PDE10A. The invention also provides to a compound of formula (I), for use in the treatment of a neurodegenerative disorder or condition in 25 a mammal, including a human.

As used herein, and unless otherwise indicated, a "neurodegenerative disorder or condition" refers to a disorder or condition that is caused by the dysfunction and/or death of neurons in the central nervous system. The treatment of these disorders and conditions can be facilitated by administration of an agent which 30 prevents the dysfunction or death of neurons at risk in these disorders or conditions and/or enhances the function of damaged or healthy neurons in such a way as to compensate for the loss of function caused by the dysfunction or death of at-risk

neurons. The term "neurotrophic agent" as used herein refers to a substance or agent that has some or all of these properties.

Examples of neurodegenerative disorders and conditions that can be treated according to the present invention include, but are not limited to, Parkinson's disease; Huntington's disease; dementia, for example Alzheimer's disease, multi-infarct dementia, AIDS-related dementia, and Fronto temporal Dementia; neurodegeneration associated with cerebral trauma; neurodegeneration associated with stroke, neurodegeneration associated with cerebral infarct; hypoglycemia-induced neurodegeneration; neurodegeneration associated with epileptic seizure; neurodegeneration associated with neurotoxin poisoning; and multi-system atrophy.

In one embodiment of the invention, the neurodegenerative disorder is Parkinson's disease or Alzheimer's disease.

In one embodiment of the present invention, the neurodegenerative disorder or condition comprises neurodegeneration of striatal medium spiny neurons in a mammal, including a human.

In a further embodiment of the present invention, the neurodegenerative disorder or condition is Huntington's disease.

The invention also provides a pharmaceutical composition for treating psychotic disorders, delusional disorders and drug induced psychosis; anxiety disorders, movement disorders, mood disorders, neurodegenerative disorders, obesity, and drug addiction, comprising an amount of a compound of formula (I) effective in treating said disorder or condition.

The invention also provides a method of treating a disorder selected from psychotic disorders, delusional disorders and drug induced psychosis; anxiety disorders, movement disorders, obesity, mood disorders, and neurodegenerative disorders, which method comprises administering an amount of a compound of formula (I) effective in treating said disorder.

The invention also provides to a compound of formula (I), for use in the treatment of a disorder selected from psychotic disorders, delusional disorders and drug induced psychosis; anxiety disorders, movement disorders, obesity, mood disorders, and neurodegenerative disorders.

The invention also provides a method of treating disorders selected from the group consisting of: dementia, Alzheimer's disease, multi-infarct dementia, alcoholic

dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example 5 reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; age-related cognitive decline, major depressive episode of the mild, moderate or severe type; a manic or mixed mood episode; a hypomanic mood episode; a depressive episode with atypical features; a depressive episode with melancholic features; a depressive episode with catatonic 10 features; a mood episode with postpartum onset; post-stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder comprising a delusional disorder or schizophrenia; a bipolar disorder comprising bipolar I disorder, bipolar II 15 disorder, cyclothymic disorder, Parkinson's disease; Huntington's disease; Fronto temporal Dementia; neurodegeneration associated with cerebral trauma; neurodegeneration associated with stroke; neurodegeneration associated with cerebral infarct; hypoglycemia- induced neurodegeneration; neurodegeneration associated with epileptic seizure; neurodegeneration associated with neurotoxin 20 poisoning; multi-system atrophy, paranoid, disorganized, catatonic, undifferentiated or residual type; schizophreniform disorder; schizoaffective disorder of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, obesity, inhalants, opioids, or phencyclidine; personality disorder of 25 the paranoid type; and personality disorder of the schizoid type, which method comprises administering an amount of a compound of Formula (I) effective in treating said disorders. The invention thus also provides a compound of formula (I), for use in the treatment of the diseases mentioned in the previous sentence.

The invention also provides a method for the treatment of psychotic disorders, 30 delusional disorders and drug induced psychosis; anxiety disorders, movement disorders, mood disorders, neurodegenerative disorders, obesity, and drug addiction which method comprises administering an amount of a compound of formula (I) effective in inhibiting PDE10A.

The invention also provides a method for the treatment of diseases of the retina, which method comprises administering an amount of a compound of formula (I) effective in inhibiting PDE10A. By "diseases of the retina," the applicants mean any condition of the retina which impairs the normal functioning of the retina, its surrounding tissues, or the eye. These include macular degeneration, myopic retinal degeneration, diabetic retinopathy, choroidal neovascularization, macular edema (also referred to as cystoid macular edema and macular swelling), epiretinal membrane (macular pucker), macular hole, retinitis (such as retinitis pigmentosa), macular dystrophies (such as Stargardt's juvenile macular degeneration, Best's vitelliform dystrophy, cone dystrophies, and pattern dystrophy of the retinal pigmented epithelium), retinal detachment, retinal trauma, retinal tumors and retinal diseases associated with them, congenital hypertrophy of the retinal pigmented epithelium, acute posterior multifocal placoid pigment epitheliopathy, acute retinal pigment epithelitis, and uveitis (including iritis, pars planitis, choroiditis, retinitis, and 15 chorioretinitis).

According to a particular aspect, the invention relates to a compound of formula (I) or a composition comprising a compound of formula (I), for use in a method for the treatment of type I or type II diabetes, impaired glucose tolerance, impaired fasting glucose, metabolic syndrome, metabolism related disorders including excess of body weight or excess of body fat in obese patients, psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, 20 Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention- deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, 25 stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma and breast cancer, pain, ophthalmic diseases such as macular degeneration/retinal degeneration, including wet Age Related Macular Degeneration (ARMD), dry ARMD, retinitis pigmentosa, choroidal neovascularization, vascular

diseases/exudative diseases, retinopathy, including diabetic retinopathy, uveitis/retinitis/choroiditis, Stargard's disease, macular edema, retinal detachment, trauma, systemic disorders with associated retinal dystrophies, cone dystrophies, dystrophy of the retinal pigmented epithelium, myopic retinal degeneration, acute 5 retinal pigment epithelitis, retinal tumors, retinal disease associated with tumors.

The invention further relates to a method for the treatment of type I or type II diabetes, impaired glucose tolerance, impaired fasting glucose, metabolic syndrome, metabolism related disorders including excess of body weight or excess of body fat in obese patients, psychotic disorders, schizophrenia, positive, negative and/or 10 cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, 15 depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma and breast cancer, pain, ophthalmic diseases such as macular 20 degeneration/retinal degeneration, including wet Age Related Macular Degeneration, dry ARMD, retinitis pigmentosa, choroidal neovascularization, vascular diseases/exudative diseases, retinopathy, including diabetic retinopathy, uveitis/retinitis/choroiditis, Stargard's disease, macular edema, retinal detachment, trauma, systemic disorders with associated retinal dystrophies, cone dystrophies, 25 dystrophy of the retinal pigmented epithelium, myopic retinal degeneration, acute retinal pigment epithelitis, retinal tumors, retinal disease associated with tumors, which method comprises administering an amount of a compound of formula (I) effective in inhibiting PDE10A.

The invention further relates to a method for the treatment of type I or type II 30 diabetes, impaired glucose tolerance, impaired fasting glucose, metabolic syndrome, metabolism related disorders including excess of body weight or excess of body fat in obese patients, psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-

induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, 5 depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma and breast cancer, pain, ophthalmic diseases such as macular 10 degeneration/retinal degeneration, including wet Age Related Macular Degeneration, dry ARMD, retinitis pigmentosa, choroidal neovascularization, vascular diseases/exudative diseases, retinopathy, including diabetic retinopathy, uveitis/retinitis/choroiditis, Stargardt's disease, macular edema, retinal detachment, trauma, systemic disorders with associated retinal dystrophies, cone dystrophies, 15 dystrophy of the retinal pigmented epithelium, myopic retinal degeneration, acute retinal pigment epithelitis, retinal tumors, retinal disease associated with tumors, which method comprises administering an amount of a compound of Formula (I) effective in treating said disorders.

The term "treating", as in "a method of treating a disorder", refers to reversing, 20 alleviating, or inhibiting the progress of the disorder to which such term applies, or one or more symptoms of the disorder. As used herein, the term also encompasses, depending on the condition of the patient, preventing the disorder, including preventing onset of the disorder or of any symptoms associated therewith, as well as reducing the severity of the disorder or any of its symptoms prior to onset. "Treating" 25 as used herein refers also to preventing a recurrence of a disorder.

The following examples illustrate the invention. However, it is to be understood that the invention is not limited to the details provided in these examples.

## EXAMPLES

30 **Example 1: preparation of compounds according to the invention**

**General**

<sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded at ambient temperature with an Advance 300 (Bruker) spectrometer.

The compounds were analyzed by reverse phase high performance liquid chromatography (HPLC) using a Waters Autopurification System equipped with a 5 Waters 2525 Pump, a Waters 2696 photodiode array detector. The Method A (10 min) was performed with an XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482) and the Method B was performed with an XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113). Solvent A was H<sub>2</sub>O with 0.05% TFA and solvent B was CH<sub>3</sub>CN with 0.05% TFA. The 10 min gradient run was realized using 10 1.0 mL min<sup>-1</sup> with 5% B in A (0.0–1.0 min), 5% to 100% B in A (1.0–7.0 min), 100% to 5% B in A (7.0–7.5 min), 5 B in A (7.5–10.0 min). The 5 min gradient run was realized using 1.0 mL min<sup>-1</sup> with 5% B in A (0.0–0.25 min), 5% to 100% B in A (0.25–3.0 min), 100% to 5% B in A (3.0–4.0 min), 5% B in A (4.0–5.0 min).

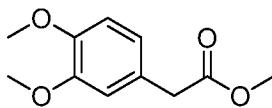
15 Melting points were measured with a Büchi B-545 melting point apparatus and were uncorrected. Microwave reactions were performed in a Biotage Initiator 60 EXP microwave reactor.

To isolate reaction products the solvent were removed by evaporation using a 20 vacuum rotatory evaporator, unless otherwise indicated, the water bath temperature did not exceed 40°C.

### Preparation of 4-benzyl-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride 1

#### 25 Methyl 2-(3,4-dimethoxyphenyl)acetate **SLA 28134**

To a solution of 2-(3,4-dimethoxyphenyl)acetic acid (25.0 g, 127.4 mmol) in MeOH (100 mL) in a 500 mL round-bottomed flask equipped with a magnetic stirrer was added a catalytic amount of sulfuric acid (around 10 drops) and the mixture was stirred overnight under reflux. After cooling to RT, MeOH was removed at 40°C 30 under vacuum and the product was taken up in CH<sub>2</sub>Cl<sub>2</sub> (250 mL), washed with water (5x20 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to give methyl 2-(3,4-dimethoxyphenyl)acetate **SLA 28134** as an orange oil (25.77 g, 96% yield).

**SLA 28134**

**MW:** 210.23; **Yield:** 96%; Orange oil.

**R<sub>f</sub>:** 0.25 (cyclohexane:EtOAc = 3:1).

5 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.56 (s, 2H, CH<sub>2</sub>), 3.70 (s, 3H, CH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 6.82-6.83 (m, 3H, 3xArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 40.6, 51.9, 55.8 (2xC), 111.2, 112.4, 121.4, 126.4, 148.2, 148.9, 172.2.

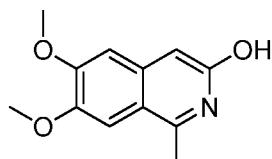
**MS-ESI** m/z (% rel. Int.): 233.2 ([M+Na]<sup>+</sup>, 3), 151.1 (100).

10 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.78 min.

#### 6,7-Dimethoxy-1-methylisoquinolin-3-ol CCH 18060

To a solution of methyl 2-(3,4-dimethoxyphenyl)acetate **SLA 28134** (23.82 g, 113.30 mmol) in acetic anhydride (57 mL) at 0°C in a 1 L round-bottomed flask equipped with a magnetic stirrer under N<sub>2</sub> was added perchloric acid (70% solution in water, 11.3 mL) over a period of 30 min. The reaction mixture was then allowed to warm up to RT, stirred for a further 45 min and diluted with Et<sub>2</sub>O (450 mL). The solid was then filtered and washed several times with Et<sub>2</sub>O (6x15 mL) to give after drying under vacuum a dark yellow solid (27.97 g, 74% yield).

To a suspension of the above solid (11.09 g, 34.58 mmol) in H<sub>2</sub>O (60 mL) in a 500 mL 3-neck round-bottomed flask equipped with a dropping funnel and a magnetic stirrer in an ice bath was added dropwise conc. NH<sub>4</sub>OH (90 mL) and the reaction mixture was stirred at RT for 1 h, after which the solid was filtered and washed with cold water (4x15 mL). After drying under high vacuum, 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** was isolated as a yellow solid (7.53 g, 99% yield).



**MW:** 219.24; **Yield:** 74%; Yellow solid; **Mp** (°C): 283 (dec.).

30 **R<sub>f</sub>:** 0.2 (cyclohexane:EtOAc = 2:1).

**<sup>1</sup>H-NMR** (DMSO d<sub>6</sub>, δ): 2.68 (s, 3H, CH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 6.51 (s, 1H, ArH), 6.97 (s, 1H, ArH), 7.12 (s, 1H, ArH), 10.69 (broad s, 1H, OH).

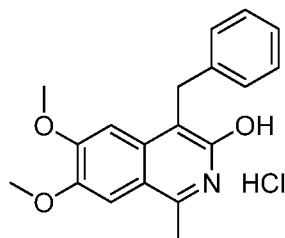
**<sup>13</sup>C-NMR** (DMSO d<sub>6</sub>, δ): 20.3, 55.6, 55.7, 99.5, 103.6, 103.8, 116.2, 138.0, 147.1, 152.0, 153.3, 159.0.

5 **MS-ESI** m/z (rel. int.): 220 ([M+H]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 3.83 min.

**4-Benzyl-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride 1**

10 To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (51 mg, 233 μmol) in toluene (1 mL) in a 2 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.12 mL, 0.24 mmol) at RT followed by benzyl bromide (30 mg, 251 μmol) and the mixture was stirred at 110°C for 15 min under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (5 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The organic phase was isolated and the aqueous phase was acidified with AcOH (5 drops) and then further extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was combined, washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) gave, after evaporation and drying, 4-benzyl-6,7-dimethoxy-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.2 M HCl solution in MeOH (1 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 4-benzyl-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride **1** as a pale brown solid (31 mg, 38% yield).



1

**MW:** 345.82; **Yield:** 38%; Pale brown solid; **Mp (°C):** 189.1 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.02 (s, 3H, CH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.46 (s, 2H, CH<sub>2</sub>), 7.13-7.30 (m, 6H, 6xArH), 7.42 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 15.7, 29.7, 56.8, 56.9, 103.7, 105.8, 114.9, 120.0, 127.7, 129.3 (2xC), 129.8 (2xC), 139.8, 140.5, 150.4, 151.2, 151.8, 158.9.

5 **MS-ESI** m/z (rel.int.): 310 ([MH]<sup>+</sup>, 100).

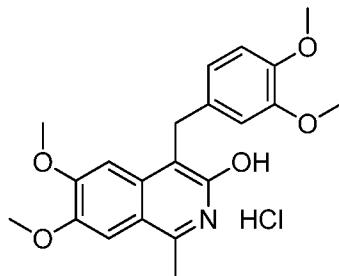
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.74 min, peak area 98.9%.

10 Preparation of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol

hydrochloride 2

To a solution of triphenylphosphine (950 mg, 3.62 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0°C in a 50 mL round-bottomed flask equipped with a magnetic stirrer is added bromine (150  $\mu$ L, 2.93 mmol) and the solution is stirred at 0°C for 15 min, after which 3,4-dimethoxybenzyl alcohol (0.50 mL, 3.42 mmol) is added. The reaction mixture is stirred at RT for 2.5 h then concentrated under vacuum.

To a solution of the freshly prepared bromide in toluene (8 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (495 mg, 2.26 mmol) at RT followed by a 2 N aq. KOH solution (1.70 mL, 3.40 mmol) and the mixture was stirred at 110°C for 15 min under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic phase was isolated and washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:4.5) gave 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol as a yellow solid (286 mg, 34% yield). A portion of the free base (43 mg) was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.15 M HCl solution in MeOH (2 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum. The solid was then washed with cold MeOH to afford, after drying, 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride **2** as a yellow solid (22 mg, 47% yield).



2

**MW:** 405.87; **Yield:** 16%; **Yellow solid;** **Mp** (°C): 211.9 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:4.5).

5 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.01 (s, 3H, CH<sub>3</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.27 (s, 2H, CH<sub>2</sub>), 6.74-6.81 (m, 3H, 3xArH), 7.08 (s, 1H, ArH), 7.13 (s, 1H, ArH).

10 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.2, 30.6, 56.2, 56.3, 56.6, 56.8, 102.9, 104.6, 112.1, 112.3, 114.8, 119.1, 120.7, 131.4, 140.1, 148.4, 149.8, 150.8, 150.9, 157.9, (1xC not observed).

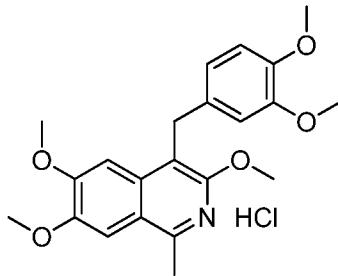
**MS-ESI** m/z (rel.int.): 370 ([MH]<sup>+</sup>, 100).

**HPLC** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.41 min, peak area 97.0%.

15 Preparation of 4-(3,4-dimethoxybenzyl)-3,6,7-trimethoxy-1-methylisoquinoline hydrochloride 3

A mixture of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol (compound **2** free base, 60 mg, 162 μmol), cesium carbonate (70 mg, 215 μmol) and iodomethane (13 μL, 208 μmol) in dry DMF (2 mL) in a 5 mL microwave vial 20 equipped with a magnetic stirrer was stirred at 90°C for 22 min under microwave irradiation. After cooling to RT, the mixture was diluted with Et<sub>2</sub>O (50 mL) before washing with water (10 mL) then with brine (10 mL), drying over Na<sub>2</sub>SO<sub>4</sub>, filtration and concentration at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave 4-(3,4-dimethoxybenzyl)- 25 3,6,7-trimethoxy-1-methylisoquinoline as a colorless oil (33 mg). This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.15 M HCl solution in MeOH (1.5 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum. The solid was then washed with Et<sub>2</sub>O to afford, after drying, 4-(3,4-

dimethoxybenzyl)-3,6,7-trimethoxy-1-methylisoquinoline hydrochloride **3** as a pale brown solid (23 mg, 34% yield).



**3**

5 **MW:** 419.90; **Yield:** 34%; **Yellow solid; Mp (°C):** 182.2 (dec.).

**R<sub>f</sub>**(free base): 0.2 (cyclohexane:EtOAc = 75:25).

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 2.94 (s, 3H, CH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.10 (s, 3H, OCH<sub>3</sub>), 4.32 (s, 2H, CH<sub>2</sub>), 6.69 (d, 1H, J = 8.0 Hz, ArH), 6.80 (d, 1H, J = 8.0 Hz, ArH), 6.87 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.39 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.6, 30.9, 56.5, 56.6, 57.0, 57.2, 63.8, 104.6, 106.4, 113.2, 113.5, 120.9, 121.6, 121.7, 132.7, 140.0, 149.4, 150.8, 151.9, 152.5, 152.8, 159.1.

**MS-ESI** m/z (rel.int.): 384 ([MH]<sup>+</sup>, 100).

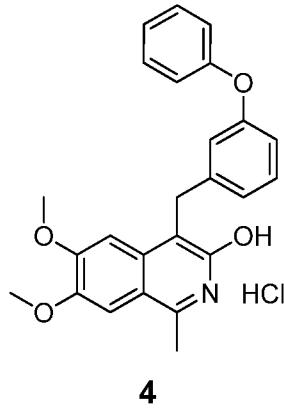
15 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 5.23 min, peak area 96.2%.

Preparation of 6,7-dimethoxy-1-methyl-4-(3-phenoxybenzyl)isoquinolin-3-ol hydrochloride **4**

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (152 mg, 20 693 μmol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.38 mL, 0.76 mmol) at RT followed by 1-(bromomethyl)-3-phenoxybenzene (191 mg, 726 μmol) and the mixture was stirred at 130°C for 45 min under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with EtOAc (50 mL). The organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic phases were washed with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:3) gave 28 mg of 6,7-dimethoxy-1-methyl-4-(3-phenoxybenzyl)isoquinolin-3-ol. This free base was

dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (2 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-(3-phenoxybenzyl)isoquinolin-3-ol hydrochloride

5 **4** as a brown solid (31 mg, 10% yield).



**MW:** 437.92; **Yield:** 10%; **Brown solid;** **Mp** (°C): 95.1 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:3).

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.00 (s, 3H, CH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.44 (s, 2H, CH<sub>2</sub>), 6.81-6.87 (m, 4H, 4xArH), 6.99-7.12 (m, 3H, 3xArH), 7.23-7.29 (m, 3H, 3xArH), 7.43 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.3, 31.1, 56.9, 57.0, 103.6, 105.9, 114.6, 118.0, 119.5, 119.9 (2xC), 120.0, 124.2, 124.5, 130.8 (2xC), 131.2, 140.5, 142.0, 150.6, 151.2,

15 151.9, 158.4, 159.0, 159.2.

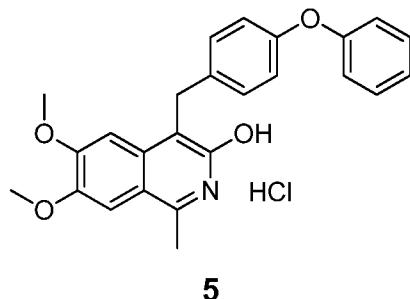
**MS-ESI** m/z (rel.int.): 402 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 5.78 min, peak area 97.7%.

20 Preparation of 6,7-dimethoxy-1-methyl-4-(4-phenoxybenzyl)isoquinolin-3-ol hydrochloride 5

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (152 mg, 693 μmol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.38 mL, 0.76 mmol) at RT followed by 1-(bromomethyl)-4-phenoxybenzene (191 mg, 726 μmol) and the mixture was stirred at 140°C for 50 min under microwave irradiation then at 160°C for 50 min under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with EtOAc (50 mL). The organic phase was isolated and the

aqueous phase was further extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL). Both organic phases were washed with brine (10 mL), combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 100:0$  to 95:3) gave 43 mg of 6,7-dimethoxy-1-methyl-4-(4-phenoxybenzyl)isoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (3 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-(4-phenoxybenzyl)isoquinolin-3-ol hydrochloride **5** as a brown solid (47 mg, 15% yield).



10

**MW:** 437.92; **Yield:** 15%; **Brown solid;** **Mp (°C):** 98.0 (dec.).

**R<sub>f</sub>**(free base): 0.2 ( $\text{CH}_2\text{Cl}_2:\text{MeOH} = 95:3$ ).

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 3.02 (s, 3H,  $\text{CH}_3$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 4.00 (s, 3H,  $\text{OCH}_3$ ), 4.44 (s, 2H,  $\text{CH}_2$ ), 6.87-6.90 (m, 4H, 4xArH), 7.03-7.08 (m, 1H, ArH), 7.18-7.28 (m, 5H, 5xArH), 7.43-7.45 (m, 1H, ArH).

**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 17.3, 30.6, 56.8, 57.1, 103.7, 105.9, 115.0, 119.7 (2xC), 120.1 (2xC), 120.1, 124.4, 130.7 (2xC), 130.9 (2xC), 134.7, 140.5, 150.5, 151.1, 151.9, 157.5, 158.6, 159.0.

**MS-ESI** m/z (rel.int.): 402 ( $[\text{MH}]^+$ , 100).

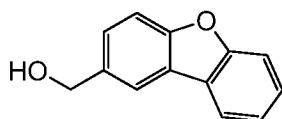
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 5.89 min, peak area 97.8%.

Preparation of 4-(dibenzo[*b,d*]furan-2-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride **6**

#### Dibenzo[*b,d*]furan-2-ylmethanol CCH 34116

To a solution of dibenzo[*b,d*]furan-2-carbaldehyde (191 mg, 973  $\mu\text{mol}$ ) in THF (10 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer was

added NaBH<sub>4</sub> (37 mg, 0.978 mmol) and the mixture was stirred for 2 h at RT and quenched by adding 10 mL of a 1 N aq. HCl solution. The reaction mixture was stirred at RT for 20 min and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and 5 concentrated at 40°C under vacuum to afford dibenzo[*b,d*]furan-2-ylmethanol **CCH 34116** as an off-white solid (192 mg, 100% yield).

**CCH 34116**

**MW:** 198.22; **Yield:** 100%; Off-white solid.

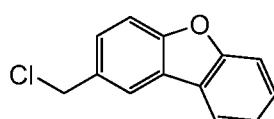
10 **R<sub>f</sub>:** 0.45 (cyclohexane:EtOAc = 1:1).

**MS-ESI** m/z (% rel. Int.): 181.1 ([M-OH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 5.74 min.

15 **2-(Chloromethyl)dibenzo[*b,d*]furan CCH 34116-2**

Dibenzo[*b,d*]furan-2-ylmethanol **CCH 34116** (174 mg, 878  $\mu$ mol) was immediately dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer before slow addition of SOCl<sub>2</sub> (1.0 mL, 13.78 mmol) and the reaction mixture was stirred for 20 min at 80°C under microwave irradiation. After 20 cooling to RT, the volatiles were removed at 40°C under vacuum. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 2-(chloromethyl)dibenzo[*b,d*]furan **CCH 34116-2** as a grey solid (189 mg, 99% yield).

**CCH 34116-2**

**MW:** 216.66; **Yield:** 99%; Grey solid.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 4.76 (s, 2H, CH<sub>2</sub>), 7.32-7.37 (m, 1H, ArH), 7.44-7.58 (m, 4H, 4xArH), 7.92-7.97 (m, 2H, 2xArH).

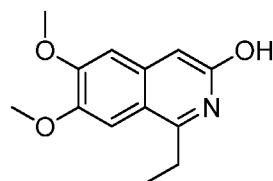
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 46.6, 111.8, 111.9, 120.8, 121.0, 122.9, 123.8, 124.6, 127.5, 30 127.9, 132.2, 156.0, 156.7.

**MS-ESI** m/z (% rel. Int.): 181.1 ([M-Cl]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 6.61 min.

5 **1-Ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136****

To a solution of methyl 2-(3,4-dimethoxyphenyl)acetate **SLA 28134** (10.01 g, 47.6 mmol) in propionic anhydride (24.0 mL, 187.2 mmol) at 0°C in a 500 mL round-bottomed flask equipped with a magnetic stirrer was added HClO<sub>4</sub> (ca. 70% solution in water, 4.89 mL, 56.6 mmol) over a period of 30 min. The reaction mixture was 10 then allowed to warm up to RT, stirred for 45 min and diluted with Et<sub>2</sub>O (450 mL). The solid was filtered and washed several times with Et<sub>2</sub>O giving 10.5 g of a brown solid. To a suspension of this solid (9.98 g, 29.8 mmol) in H<sub>2</sub>O (54 mL) in a 500 mL round-bottomed flask equipped with a magnetic stirrer and cooled in an ice bath was 15 added dropwise concentrated NH<sub>4</sub>OH (81 mL). After complete addition, the ice bath was removed and the reaction mixture was stirred at RT for 1 h, after which the solid was filtered and washed with plenty of water until neutral pH of the filtrate. The solid was dried under vacuum in presence of P<sub>2</sub>O<sub>5</sub> to give 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** as a yellow solid (5.30 g, 48% yield).



20

**SLA 28136**

**MW:** 233.26; **Yield:** 48%; **Yellow solid;** **Mp** (°C): 219.7

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>:CD<sub>3</sub>OD = 1:1,  $\delta$ ): 1.42 (t, 3H,  $J$  = 7.6 Hz, CH<sub>3</sub>), 3.11 (q, 2H,  $J$  = 7.6 Hz, CH<sub>2</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 6.56 (s, 1H, ArH), 6.74 (s, 1H, ArH), 6.92 (s, 1H, ArH).

25 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>:CD<sub>3</sub>OD = 1:1,  $\delta$ ): 17.6, 28.0, 59.5, 59.7, 105.6, 106.6, 108.8, 116.4, 146.7, 152.0, 154.7, 159.3, 165.0.

**MS-ESI** m/z (% rel. Int.): 234.1 ([MH]<sup>+</sup>, 100).

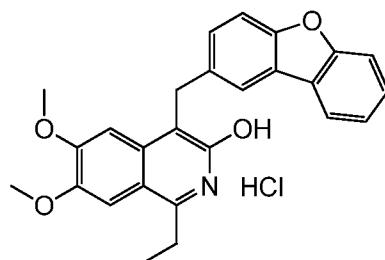
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 3.47 min.

30

4-(Dibenzo[*b,d*]furan-2-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride**6**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (50 mg, 214 µmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.11 mL, 0.22 mmol) at RT followed by 2-(chloromethyl)dibenzo[*b,d*]furan **CCH 34116-2** (47 mg, 217 µmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with a mixture CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum.

Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 96:4) gave 4-(dibenzo[*b,d*]furan-2-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol (10 mg, 11%). This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.2 M HCl solution in MeOH (0.25 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 4-(dibenzo[*b,d*]furan-2-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride **6** as a pale brown solid (11 mg, 11% yield).

**6**

**MW:** 449.93; **Yield:** 11%; Pale brown solid; **Mp** (°C): 225.6 (dec.).

**20 R<sub>f</sub>**(free base): 0.3 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.49 (t, 3H, *J* = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.33-3.43 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.61 (s, 2H, CH<sub>2</sub>), 7.23-7.53 (m, 7H, 7xArH), 7.90-7.92 (m, 2H, 2xArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.7, 25.3, 31.3, 56.8, 56.9, 103.8, 105.3, 112.6, 112.7, 115.2, 119.0, 121.2, 121.7, 124.0, 125.0, 125.8, 128.5, 128.6, 134.6, 141.3, 151.7, 152.0, 155.2, 156.3, 157.9, 159.0.

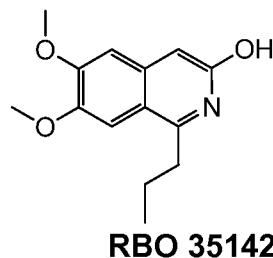
**MS-ESI** *m/z* (rel. int.): 414.3 ([M+H]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 µm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 6.14 min, peak area 95.0%.

Preparation of 4-(dibenzo[*b,d*]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol hydrochloride 7

5 6,7-Dimethoxy-1-propylisoquinolin-3-ol RBO 35142

To a solution of 3,4-dimethoxy-phenyl)-acetic acid methyl ester **SLA 28134** (15.0 g, 71 mmol) in butyric anhydride (150 mL) in a round-bottomed flask equipped with a magnetic stirrer was added perchloric acid (10 mL) dropwise at 0°C. The mixture was stirred overnight at RT to obtain a black and viscous mixture that was 10 diluted in Et<sub>2</sub>O (600 mL). The precipitate formed was filtered, washed with Et<sub>2</sub>O (3x150 mL) and dried under high vacuum to give a yellow solid (23.34 g). The solid was suspended in 300 mL of water and ammonia (25% aq. solution, 90 mL) was added dropwise at 0°C. The mixture was stirred at RT for 2 h, filtered and dried under high vacuum to obtain 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** as 15 yellow solid (14.12 g, 80% yield).



**MW:** 247.30; **Yield:** 80%; **Yellow solid;** **Mp** (°C): 227.2°C.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.01 (t, 3H *J* = 9Hz, CH<sub>3</sub>), 1.89 (m, 2H, CH<sub>2</sub>), 3.13 (t, 2H *J* = 6Hz, CH<sub>2</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 6.58 (s, 1H, ArH), 6.62 (s, 1H, ArH), 6.87 (s, 1H, ArH), OH not seen.

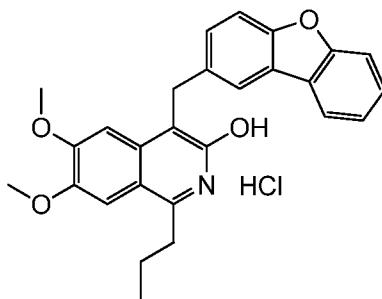
**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 13.8, 22.9, 32.7, 55.8, 56.2, 102.3, 102.7, 104.7, 112.7, 141.9, 148.3, 150.5, 154.7, 162.0.

**MS-ESI** m/z (rel.int.): 248 ([MH]<sup>+</sup>, 100).

25 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 3.56 min, peak area 99.9%.

4-(Dibenzo[*b,d*]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol hydrochloride 7

To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (75 mg, 303  $\mu$ mol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.15 mL, 0.30 mmol) at RT followed by 2-(chloromethyl)dibenzo[*b,d*]furan **CCH 34116-2** (70 mg, 323  $\mu$ mol) and the mixture 5 was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1 (50 mL), washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2$ :MeOH = 100:0 to 96:4) gave, after evaporation and drying, 4-(dibenzo[*b,d*]furan-2-ylmethyl)-6,7-dimethoxy-1-10 propylisoquinolin-3-ol (11 mg, 8% yield). This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.20 M HCl solution in MeOH (0.25 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 4-(dibenzo[*b,d*]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol hydrochloride 15 **7** as a pale brown solid (11 mg, 8% yield).



7

**MW:** 463.95; **Yield:** 8%; Pale brown solid; **Mp** (°C): 212.7 (dec.)

**R<sub>f</sub>**(free base): 0.32 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 95.5:4.5).

20 **<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.11 (t, 3H,  $J$  = 7.4 Hz,  $\text{CH}_2\text{CH}_3$ ), 1.93 (sextuplet, 2H,  $J$  = 7.4 Hz,  $\text{CH}_2\text{CH}_3$ ), 3.32-3.37 (m, 2H,  $\text{CH}_2\text{CH}_2$ ), 3.83 (s, 3H,  $\text{OCH}_3$ ), 3.96 (s, 3H,  $\text{OCH}_3$ ), 4.60 (s, 2H,  $\text{CH}_2$ ), 7.21 (s, 1H, ArH), 7.26-7.49 (m, 6H, 6xArH), 7.89-7.91 (m, 2H, 2xArH).

25 **<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 14.2, 24.7, 31.3, 33.4, 56.8, 57.0, 103.8, 105.6, 112.5, 112.8, 115.4, 119.5, 121.2, 121.7, 124.0, 125.0, 125.8, 128.6 (2xC), 134.7, 141.1, 151.5, 151.9, 153.9, 156.3, 157.9, 159.0.

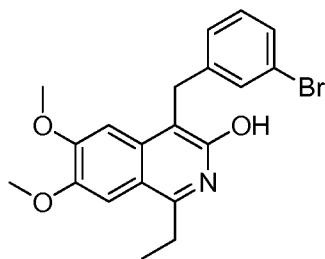
**MS-ESI** *m/z* (rel. int.): 428.3 ([M+H]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 6.38 min, peak area 96.9%.

Preparation of 4-([1,1'-biphenyl]-3-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride 8

5 4-(3-Bromobenzyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28138**

To a stirred solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (1.00 g, 4.29 mmol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 1-bromo-3-(bromomethyl)benzene (1.07 g, 4.29 mmol) at RT followed by a 2 N aq. LiOH solution (1.07 mL, 2.14 mmol) and the mixture was 10 stirred at 150°C for 1.5 h. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL) and washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) gave, after evaporation and drying, 4-(3-bromobenzyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28138** as a 15 brown solid (0.403 mg, 23% yield).



**SLA 28138**

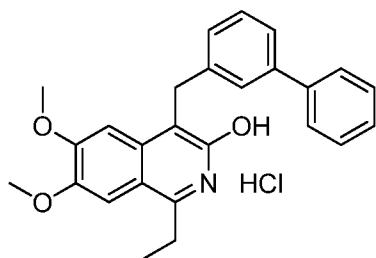
**MW:** 402.28; **Yield:** 23%; Brown solid; **Mp (°C):** 251.4

<sup>1</sup>**H-NMR** (CDCl<sub>3</sub>, δ): 1.41 (t, 3H, J = 7.6 Hz, CH<sub>3</sub>), 3.12 (q, 2H, J = 7.6 Hz, CH<sub>2</sub>), 3.90 20 (s, 3H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.28 (s, 2H, CH<sub>2</sub>), 6.74 (s, 1H, ArH), 6.89 (s, 1H, ArH), 7.07-7.13 (m, 1H, ArH), 7.26-7.29 (m, 2H, 2xArH), 7.53-7.54 (m, 1H, ArH).  
<sup>13</sup>**C-NMR** (CDCl<sub>3</sub>, δ): 14.2, 24.6, 31.1, 55.8, 55.8, 100.2, 102.8, 112.4, 113.4, 122.4, 127.1, 128.9, 129.8, 131.6, 139.0, 144.0, 146.9, 150.0, 154.6, 160.9.

25 4-([1,1'-Biphenyl]-3-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride 8

To a stirred solution of 4-(3-bromobenzyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28138** (79 mg, 0.196 mmol) in EtOH (0.9 mL) in a 20 mL microwave vial equipped with a magnetic stirrer were added phenylboronic acid (48 mg, 0.393 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10.0 mg), a 2 N aq. Na<sub>2</sub>CO<sub>3</sub> solution (0.30 mL, 0.60 mmol),

$\text{H}_2\text{O}$  (2.7 mL), dimethoxyethane (3.5 mL) and the resulting mixture was stirred at 140°C for 25 min. After cooling to RT, the mixture was diluted with EtOAc (30 mL) and the organic solution was passed through a celite plug and washed with brine (10 mL). The celite plug was then further washed with  $\text{CH}_2\text{Cl}_2$  (50 mL) and the organic layer was washed with brine (20 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 100:0$  to 98:2) gave, after evaporation and drying, 4-([1,1'-biphenyl]-3-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol. This free base was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) in a 10 mL round-bottomed flask before addition of a 0.49 M HCl solution in MeOH (3 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to give 4-([1,1'-biphenyl]-3-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride **8** as a yellow solid (42 mg, 49% yield).



15

**8**

**MW:** 435.94; **Yield:** 49%; **Yellow solid;** **Mp** (°C): 159.5

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.47 (t, 3H,  $J = 7.6$  Hz,  $\text{CH}_3$ ), 3.39 (q, 2H,  $J = 7.6$  Hz,  $\text{CH}_2$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 3.99 (s, 3H,  $\text{OCH}_3$ ), 4.53 (s, 2H,  $\text{CH}_2$ ), 7.166 (d, 1H,  $J = 7.5$  Hz, ArH), 7.23 (s, 1H, ArH), 7.30-7.54 (m, 9H, 9xArH).

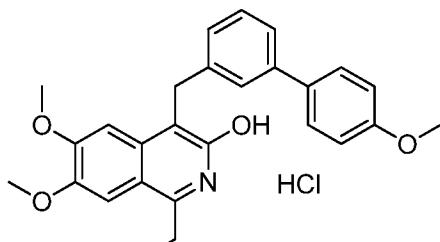
**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 13.1, 23.8, 29.9, 55.3, 55.4, 102.4, 103.9, 113.5, 117.5, 124.9, 126.4, 126.5, 126.6, 126.6, 127.0, 128.4, 128.4, 128.8, 138.9, 139.7, 140.6, 141.6, 150.0, 150.5, 153.8, 157.5.

**MS-ESI** m/z (% rel. Int.): 400 ( $[\text{MH}]^+$ , 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 5.45 min, peak area 98.2%.

Preparation of 1-ethyl-6,7-dimethoxy-4-((4'-methoxy-[1,1'-biphenyl]-3-yl)methyl)isoquinolin-3-ol hydrochloride **9**

To a stirred solution of 4-(3-bromobenzyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28138** (79 mg, 0.196 mmol) in EtOH (0.9 mL) in a 20 mL microwave vial equipped with a magnetic stirrer were added 4-methoxyphenylboronic acid (60 mg, 0.393 mmol),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (10.0 mg), a 2 N aq.  $\text{Na}_2\text{CO}_3$  solution (0.3 mL),  $\text{H}_2\text{O}$  (2.7 mL) and dimethoxyethane (3.5 mL) and the resulting mixture was stirred at 140°C for 25 min. After cooling to RT, the mixture was diluted with EtOAc (30 mL) and the organic solution was passed through a celite plug, then washed with brine (10 mL). The celite plug was then further washed with  $\text{CH}_2\text{Cl}_2$  (50 mL) and the organic layer was washed with brine (20 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 100:0$  to 98:2) gave 1-ethyl-6,7-dimethoxy-4-((4'-methoxy-[1,1'-biphenyl]-3-yl)methyl)isoquinolin-3-ol. This free base was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (3 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 1-ethyl-6,7-dimethoxy-4-((4'-methoxy-[1,1'-biphenyl]-3-yl)methyl)isoquinolin-3-ol hydrochloride **9** as a yellow solid (55 mg, 60% yield).

**9**

**20 MW:** 465.17; **Yield:** 60%; **Yellow solid;** **Mp** (°C): 130.7

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.44-1.47 (m, 3H,  $\text{CH}_3$ ), 3.34-3.39 (m, 2H,  $\text{CH}_2$ ), 3.78 (s, 3H,  $\text{OCH}_3$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ), 3.98 (s, 3H,  $\text{OCH}_3$ ), 4.50 (s, 2H,  $\text{CH}_2$ ), 6.90-6.94 (m, 2H 2xArH), 7.10-7.45 (m, 8H, 8xArH).

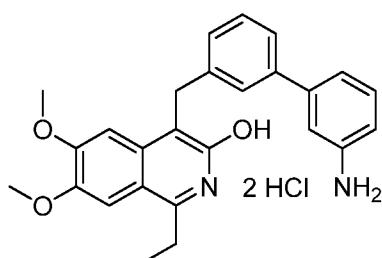
**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 13.1, 23.8, 30.0, 54.2, 55.3, 55.5, 102.4, 103.9, 113.8 (2xC), 117.5, 124.4, 125.9, 126.1, 127.4, 128.8, 132.9, 138.9, 139.7, 141.2, 150.5, 159.3 (5xC not observed).

**MS-ESI** m/z (% rel. Int.): 430 ( $[\text{MH}]^+$ , 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 5.52 min, peak area 95.2 %.

Preparation of 4-((3'-amino-[1,1'-biphenyl]-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride 10

To a stirred solution of 4-(3-bromobenzyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28138** (79 mg, 0.196 mmol) in EtOH (0.9 mL) in a 20 mL microwave vial equipped with a magnetic stirrer were added di-*tert*-butyl 3-aminophenylboronate (49 mg, 0.393 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10.0 mg), a 2 N aq. Na<sub>2</sub>CO<sub>3</sub> solution (0.3 mL), H<sub>2</sub>O (2.7 mL) and dimethoxyethane (3.5 mL) and the resulting mixture was stirred at 140°C for 25 min. After cooling to RT, the mixture was diluted with EtOAc (30 mL) and the organic solution was passed through a celite plug, then washed with brine (10 mL). The celite plug was then further washed with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic layer was washed with brine (20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 98:2) gave 4-((3'-amino-[1,1'-biphenyl]-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (3 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 4-((3'-amino-[1,1'-biphenyl]-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **10** as a yellow solid (43 mg, 69% yield).



**10**

**MW:** 450.96; **Yield:** 49%; **Yellow solid;** **Mp** (°C): 225.1

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.46 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 3.40 (q, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 4.57 (s, 2H, CH<sub>2</sub>), 7.21-7.27 (m, 2H, 2xArH), 7.37-7.44 (m, 2H, 2xArH), 7.49-7.53 (m, 2H, 2xArH), 7.57-7.62 (m, 3H, 3xArH), 7.66 (d, 1H, *J* = 7.0 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 14.6, 25.3, 31.4, 56.9, 57.1, 103.9, 105.5, 114.9, 119.1, 122.6, 123.0, 126.5, 128.1, 128.7, 129.2, 130.7, 131.8, 132.6, 141.0, 141.1, 141.2, 144.4, 151.5, 152.1, 155.4, 159.1.

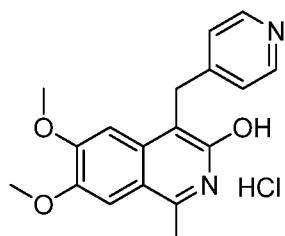
**MS-ESI** m/z (% rel. Int.): 415 ([MH]<sup>+</sup>, 100).

5 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 3.97 min, peak area 97.3%.

Preparation of 6,7-dimethoxy-1-methyl-4-(pyridin-4-ylmethyl)isoquinolin-3-ol hydrochloride 11

10 To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (197 mg, 899  $\mu$ mol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (1.20 mL, 2.40 mmol) at RT followed by 4-(bromomethyl)pyridine hydrobromide (250 mg, 988  $\mu$ mol) and the mixture was stirred at 110°C for 15 min under microwave irradiation. After cooling to RT, the mixture was 15 diluted with H<sub>2</sub>O (5 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 90:10) gave 70 mg of 6,7-dimethoxy-1-methyl-4-(pyridin-4-ylmethyl)isoquinolin-3-ol as a yellow solid. This free base was dissolved in MeOH (5 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer before 20 addition of a 0.15 M HCl solution in MeOH (7 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-(pyridin-4-ylmethyl)isoquinolin-3-ol hydrochloride **11** as a yellow solid (78 mg, 25% yield).

25



**11**

**MW:** 346.81; **Yield:** 25%; **Yellow solid;** **Mp** (°C): 158.2 (dec.).

**R<sub>f</sub>**(free base): 0.2 (cyclohexane:EtOAc = 75:25).

**<sup>1</sup>H-NMR** (DMSO d<sub>6</sub>, δ): 2.88 (s, 3H, CH<sub>3</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 4.75 (s, 2H, CH<sub>2</sub>), 7.03 (s, 1H, ArH), 7.32 (s, 1H, ArH), 7.90 (d, 2H, J = 6.4 Hz, 2xArH), 8.77 (d, 2H, J = 6.4 Hz, 2xArH).

**<sup>13</sup>C-NMR** (DMSO d<sub>6</sub>, δ): 17.8, 30.5, 55.8, 56.2, 100.9, 105.0, 109.0, 116.2, 126.6

5 (2xC), 137.5, 140.9 (2xC), 148.0, 149.7, 154.1, 155.8, 161.2.

**MS-ESI** m/z (rel.int.): 311 ([MH]<sup>+</sup>, 100).

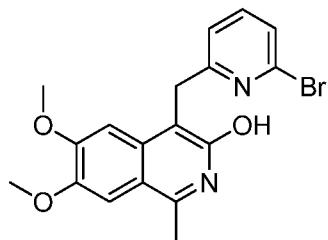
**HPLC** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 3.60 min, peak area 99.3%.

10 Preparation of 6,7-dimethoxy-1-methyl-4-((6-phenylpyridin-2-yl)methyl)isoquinolin-3-ol dihydrochloride 12

4-((6-Bromopyridin-2-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol CCH 34150

To a solution of 2-bromo-6-(hydroxymethyl)pyridine (0.54 g, 2.87 mmol) in dry 15 CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C under N<sub>2</sub> in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (4.2 mL, 57.90 mmol) and the mixture was stirred for 2 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in CHCl<sub>3</sub> (20 mL) before concentration back to dryness 20 at 40°C under vacuum (done twice) to give 2-bromo-6-(chloromethyl)pyridine hydrochloride **CCH 34150-1** as a brown solid (0.65 g, 93% yield ).

The solid **CCH 34150-1** (300 mg, 1.23 mmol) was added to a mixture of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (318 mg, 1.45 mmol) with a 2 N aq. KOH solution (0.72 mL, 1.44 mmol) and toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer. This resulting mixture was stirred at 150°C for 20 25 min under microwave irradiation. After cooling to RT, another portion of a 2 N aq. KOH solution (0.30 mL, 0.60 mmol) was added and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>: MeOH=9:1 (90 mL) and the resulting organic solution was washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. 30 Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>: MeOH = 100:0 to 94:6) gave 4-((6-bromopyridin-2-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 34150** as a yellow solid (234 mg, 42% yield).

**CCH 34150**

**MW:** 389.24; **Yield:** 42%; Yellow solid.

**R<sub>f</sub>:** 0.25 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 94:6).

5 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.79 (s, 3H, CH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.47 (s, 2H, CH<sub>2</sub>), 5.32 (broad s, 1H, OH), 6.81 (s, 1H, ArH), 7.17 (s, 1H, ArH), 7.26-7.41 (m, 3H, 3xArH).

10 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 17.1, 33.9, 55.8, 56.4, 101.1, 102.6, 112.8, 113.4, 122.1, 125.4, 139.2, 139.6, 140.5, 143.8, 147.3, 155.1, 160.1, 163.2.

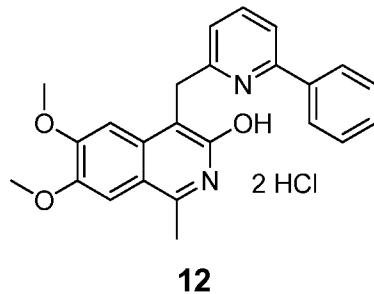
10 **MS-ESI** m/z (rel.int.): 389 ([MH]<sup>+</sup>, <sup>79</sup>Br, 94), 391 ([MH]<sup>+</sup>, <sup>81</sup>Br, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.34 min.

15 6,7-Dimethoxy-1-methyl-4-((6-phenylpyridin-2-yl)methyl)isoquinolin-3-ol dihydrochloride 12

To a stirred solution of 4-((6-bromopyridin-2-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 34150** (59 mg, 152 μmol) in absolute EtOH (0.9 mL) in a 20 mL microwave vial equipped with a magnetic stirrer were added phenylboronic acid (18 mg, 148 μmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10 mg, 14 μmol), a 2 N aq. Na<sub>2</sub>CO<sub>3</sub> solution (0.30 mL, 0.60 mmol), H<sub>2</sub>O (2.7 mL) and dimethoxyethane (3.5 mL) and the resulting mixture was stirred at 140°C for 25 min. After cooling to RT, the mixture was diluted with EtOAc (30 mL) and the organic solution was filtered through a celite plug, then washed with brine (10 mL). The organic layer was isolated and the celite plug was 20 then further washed with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the resulting organic layer was washed with brine (20 mL). The organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) provided 32 mg of 6,7-dimethoxy-1-methyl-4-((6-phenylpyridin-2-yl)methyl)isoquinolin-3-ol. This free base was dissolved 25

in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.5 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-((6-phenylpyridin-2-yl)methyl)isoquinolin-3-ol dihydrochloride 5 **12** as a pale brown solid (38 mg, 56% yield).



**MW:** 459.36; **Yield:** 56%; Pale brown solid; **Mp** (°C): 208.4 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5).

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.11 (s, 3H, CH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.07 (s, 3H, OCH<sub>3</sub>), 5.12 (s, 2H, CH<sub>2</sub>), 7.33 (s, 1H, ArH), 7.41 (d, 1H, *J* = 7.8 Hz, ArH), 7.57 (s, 1H, ArH), 7.72-7.76 (m, 3H, 3xArH), 8.09-8.12 (m, 2H, 2xArH), 8.22 (d, 1H, *J* = 8.0 Hz, ArH), 8.45 (dd, 1H, *J* = 8.0 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.7, 30.1, 57.0, 57.8, 102.7, 106.4, 109.3, 120.0, 125.2,

15 125.6, 129.9 (2xC), 130.8 (2xC), 132.6, 133.5, 140.7, 148.3, 152.1, 152.2, 152.3, 155.0, 155.8, 160.2.

**MS-ESI** m/z (rel.int.): 387 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.97 min, peak area 98.7%.

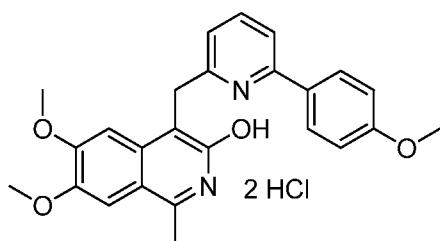
20

Preparation of 6,7-dimethoxy-4-((6-(4-methoxyphenyl)pyridin-2-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride 13

To a stirred solution of 4-((6-bromopyridin-2-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 34150** (59 mg, 152 μmol) in EtOH (0.9 mL) in a 20 mL microwave vial equipped with a magnetic stirrer were added 4-methoxyphenylboronic acid (23 mg, 151 μmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10 mg, 14 μmol), a 2 N aq. Na<sub>2</sub>CO<sub>3</sub> solution (0.30 mL, 0.60 mmol), H<sub>2</sub>O (2.7 mL) and dimethoxyethane (3.5 mL) and the resulting mixture was stirred at 140°C for 25 min. After cooling to RT, the mixture was diluted with EtOAc (30 mL) and the solution was filtered through

a celite plug, then washed with brine (10 mL). The organic phase was isolated and the celite plug was then further washed with  $\text{CH}_2\text{Cl}_2$  (50 mL) and the resulting organic layer was washed with brine (20 mL). The organic layers were then combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at 40°C under vacuum.

5 Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 100:0$  to 94:6) provided 39 mg of 6,7-dimethoxy-4-((6-(4-methoxyphenyl)pyridin-2-yl)methyl)-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (1.0 mL). The reaction mixture was stirred for 5 min at RT then 10 concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((6-(4-methoxyphenyl)pyridin-2-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **13** as a brown solid (45 mg, 61% yield).



**13**

15 **MW:** 489.39; **Yield:** 61%; Brown solid; **Mp (°C):** 190.3 (dec.).

**R<sub>f</sub>**(free base): 0.2 ( $\text{CH}_2\text{Cl}_2:\text{MeOH} = 94:6$ ).

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 3.07 (s, 3H,  $\text{CH}_3$ ), 3.96 (s, 3H,  $\text{OCH}_3$ ), 4.05 (s, 6H, 2x $\text{OCH}_3$ ), 5.02 (s, 2H,  $\text{CH}_2$ ), 7.23-7.36 (m, 4H, 4xArH), 7.52 (s, 1H, ArH), 8.06-8.17 (m, 3H, 3xArH), 8.33-8.39 (m, 1H, ArH).

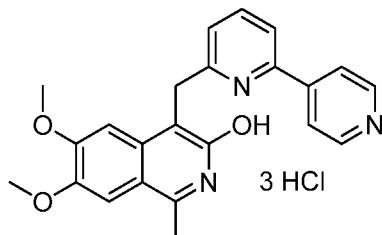
20 **<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 17.5, 30.1, 56.3, 56.9, 57.6, 102.4, 106.2, 109.5, 116.3 (2xC), 119.5, 124.0, 124.4, 124.7, 131.5 (2xC), 140.7, 147.8, 151.6, 151.9, 154.8, 155.5, 160.0, 164.9 (1xC not observed).

**MS-ESI** m/z (rel.int.): 417 ( $[\text{MH}]^+$ , 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 25 186003113), detection UV 254 nm, RT = 4.06 min, peak area 98.7%.

Preparation of 4-([2,4'-bipyridin]-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol trihydrochloride **14**

To a stirred solution of 4-((6-bromopyridin-2-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 34150** (53 mg, 136  $\mu$ mol) in EtOH (0.9 mL) in a 20 mL microwave vial equipped with a magnetic stirrer were added 4-pyridinylboronic acid (17 mg, 138  $\mu$ mol),  $Pd(PPh_3)_2Cl_2$  (10 mg, 14  $\mu$ mol), a 2 N aq.  $Na_2CO_3$  solution (0.30 5 mL, 0.60 mmol),  $H_2O$  (2.7 mL) and dimethoxyethane (3.5 mL) and the resulting mixture was stirred at 140°C for 25 min. After cooling to RT, the mixture was diluted with EtOAc (30 mL) and the solution was filtered through a celite plug, then washed with brine (10 mL). The organic layer was isolated and the celite plug was then further washed with  $CH_2Cl_2$  (50 mL) and the organic layer was washed with brine (20 10 mL). The organic layers were then combined, dried over  $Na_2SO_4$ , filtered, and concentrated at 40°C under vacuum. Purification by column chromatography ( $SiO_2$ , eluent  $CH_2Cl_2:MeOH$  = 100:0 to 92:8) provided 16 mg of 4-(2,4'-bipyridin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before 15 addition of a 0.49 M HCl solution in MeOH (0.5 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-(2,4'-bipyridin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol trihydrochloride trihydrochloride **14** as a pale brown solid (20 mg, 30% yield).



20

**14**

**MW:** 496.81; **Yield:** 30%; Pale brown solid; **Mp** (°C) > 250 (dec.).

**R<sub>f</sub>**(free base): 0.25 ( $CH_2Cl_2:MeOH$  = 92:8).

**<sup>1</sup>H-NMR** ( $CD_3OD$ ,  $\delta$ ): 3.05 (s, 3H,  $CH_3$ ), 3.92 (s, 3H,  $OCH_3$ ), 4.00 (s, 3H,  $OCH_3$ ), 4.80 (s, 2H,  $CH_2$ ), 7.38 (s, 1H, ArH), 7.47 (s, 1H, ArH), 7.71 (d, 1H,  $J$  = 7.8 Hz, ArH), 8.05 25 (dd, 1H,  $J$  = 7.8 Hz, ArH), 8.23 (d, 1H,  $J$  = 7.8 Hz, ArH), 8.68 (d, 2H,  $J$  = 5.4 Hz, 2xArH), 8.94 (d, 2H,  $J$  = 5.4 Hz, 2xArH).

**<sup>13</sup>C-NMR** ( $CD_3OD$ ,  $\delta$ ): 17.4, 34.1, 56.9, 57.2, 103.4, 106.0, 113.7, 120.1, 122.7, 125.3 (2xC), 127.2, 140.6, 140.7, 143.3 (2xC), 150.8, 151.3, 151.6, 152.0, 156.6, 159.3, 161.3.

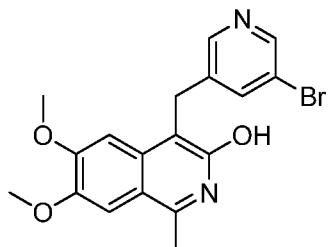
**MS-ESI** m/z (rel.int.): 388 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.31 min, peak area 98.1%.

5 Preparation of 6,7-dimethoxy-1-methyl-4-((5-phenylpyridin-3-yl)methyl)isoquinolin-3-ol dihydrochloride 15

4-((5-Bromopyridin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol CCH 34166

To a mixture of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (318 mg, 10 1.45 mmol) and 3-bromo-5-(chloromethyl)pyridine hydrochloride (352 mg, 1.45 mmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 2 N aq. KOH (1.42 mL, 2.84 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (90 mL) and the organic solution was washed with brine (15 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>: 7N NH<sub>3</sub> in MeOH = 100:0 to 95:5) gave, after evaporation and drying, 4-((5-bromopyridin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 34166** as a yellow solid (189 mg, 33% yield).



20 **CCH 34166**

**MW:** 389.24; **Yield:** 33%; Yellow solid.

**R<sub>f</sub>:** 0.2 (CH<sub>2</sub>Cl<sub>2</sub>: 7N NH<sub>3</sub> in MeOH = 95:5).

25 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 2.80 (s, 3H, CH<sub>3</sub>), 3.94 (s, 6H, 2xOCH<sub>3</sub>), 4.27 (s, 2H, CH<sub>2</sub>), 6.72 (s, 1H, ArH), 6.86 (s, 1H, ArH), 7.82 (s, 1H, ArH), 8.46 (s, 1H, ArH), 8.59 (s, 1H, ArH), OH not seen.

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 17.2, 28.3, 55.9, 55.9, 99.4, 103.3, 112.0, 113.4, 120.8, 138.6, 138.7, 138.8, 144.9, 147.0, 148.0, 148.4, 155.2, 160.8.

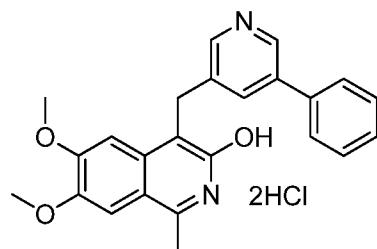
**MS-ESI** m/z (rel.int.): 389 ([MH]<sup>+</sup>, <sup>79</sup>Br, 94), 391 ([MH]<sup>+</sup>, <sup>81</sup>Br, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.77 min.

6,7-Dimethoxy-1-methyl-4-((5-phenylpyridin-3-yl)methyl)isoquinolin-3-ol

5 dihydrochloride 15

To a stirred solution of 4-((5-bromopyridin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 34166** (66 mg, 170  $\mu$ mol) in absolute EtOH (0.9 mL) in a 20 mL microwave vial equipped with a magnetic stirrer were added phenylboronic acid (20 mg, 164  $\mu$ mol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10 mg, 14  $\mu$ mol), a 2 N aq. Na<sub>2</sub>CO<sub>3</sub> solution (0.30 mL, 0.60 mmol), H<sub>2</sub>O (2.7 mL) and dimethoxyethane (3.5 mL) and the resulting mixture was stirred at 140°C for 25 min. After cooling to RT, the mixture was diluted with EtOAc (30 mL) and the solution was filtered through a celite plug, then washed with brine (10 mL). The organic layer was isolated and the celite plug was then further washed with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic layer was washed with brine (20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) provided 60 mg of 6,7-dimethoxy-1-methyl-4-((5-phenylpyridin-3-yl)methyl)isoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before 20 addition of a 0.49 M HCl solution in MeOH (1.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to give 6,7-dimethoxy-1-methyl-4-((5-phenylpyridin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **15** as a pale brown solid (71 mg, 91% yield).



25

**15**

**MW:** 459.36; **Yield:** 91%; Pale brown solid; **Mp (°C):** 89.0

**R<sub>f</sub>**(free base): 0.15 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 93:7).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.08 (s, 3H, CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.86 (s, 2H, CH<sub>2</sub>), 7.24 (s, 1H, ArH), 7.53-7.58 (m, 4H, 4xArH), 7.80-7.82 (m, 2H, 2xArH), 8.64 (s, 1H, ArH), 8.87 (s, 1H, ArH), 9.08 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 17.6, 28.6, 56.9, 57.4, 102.4, 106.2, 111.6, 119.3, 128.5 (2xC), 130.7 (2xC), 131.4, 134.6, 139.0, 139.9, 140.1, 141.4, 141.5, 145.0, 151.1, 151.4, 152.7, 159.3.

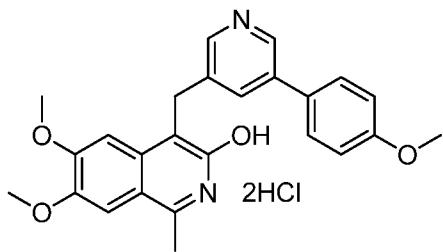
**MS-ESI** m/z (rel.int.): 387 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.68 min, peak area 98.5%.

10

Preparation of 6,7-dimethoxy-4-((5-(4-methoxyphenyl)pyridin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **16**

To a stirred solution of 4-((5-bromopyridin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 34166** (53 mg, 136  $\mu$ mol) in absolute EtOH (0.9 mL) in a 15 20 mL microwave vial equipped with a magnetic stirrer were added 4-methoxyphenylboronic acid (41 mg, 270  $\mu$ mol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10 mg, 14  $\mu$ mol), a 2 N aq. Na<sub>2</sub>CO<sub>3</sub> solution (0.30 mL, 0.60 mmol), H<sub>2</sub>O (2.7 mL) and dimethoxyethane (3.5 mL) and the resulting mixture was stirred at 140°C for 25 min. After cooling to RT, the mixture was diluted with EtOAc (30 mL) and this solution was filtered through 20 a celite plug, then washed with brine (10 mL). The organic phase was isolated and the celite plug was then further washed with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic layer was washed with brine (20 mL). The organic layers were then combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column 25 chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) provided 32 mg of 6,7-dimethoxy-4-((5-(4-methoxyphenyl)pyridin-3-yl)methyl)-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.5 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under 30 vacuum to give 6,7-dimethoxy-4-((5-(4-methoxyphenyl)pyridin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **16** as a pale brown solid (37 mg, 56% yield).



16

**MW:** 489.39; **Yield:** 56%; Pale brown solid; **Mp** (°C): 195.0 (dec.)

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 94:6).

5 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.04 (s, 3H, CH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 4.79 (s, 2H, CH<sub>2</sub>), 7.13-7.19 (m, 3H, 3xArH), 7.48 (s, 1H, ArH), 7.75 (d, 2H, J = 7.3 Hz, 2xArH), 8.55 (s, 1H, ArH), 8.80 (s, 1H, ArH), 9.01 (s, 1H, ArH).  
 10 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.5, 28.5, 56.0, 56.8, 57.4, 102.2, 106.0, 111.8, 116.1 (2xC), 119.3, 126.4, 129.7 (2xC), 138.2, 138.8, 140.2, 141.3, 141.5, 144.0, 150.8, 151.5, 152.8, 159.4, 162.9.

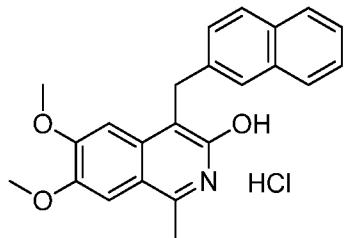
**MS-ESI** m/z (rel.int.): 417 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.73 min, peak area 97.7%.

15 Preparation of 6,7-dimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride 17

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (232 mg, 1.06 mmol) in toluene (4.5 mL) in a 10 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.55 mL, 1.10 mmol) at RT followed by 2-(bromomethyl)naphthalene (252 mg, 1.14 mmol) and the mixture was stirred at 20 110°C for 15 min under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (5 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 25 100:0 to 95:5) gave 210 mg of 6,7-dimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol as a yellow solid. The free base was dissolved in MeOH (10 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.15 M HCl solution in MeOH (8 mL). The reaction mixture was stirred 25 for 5 min at RT and concentrated at 40°C under vacuum to afford after drying 6,7-

dimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride **17** as a yellow solid (230 mg, 55% yield).

**17**

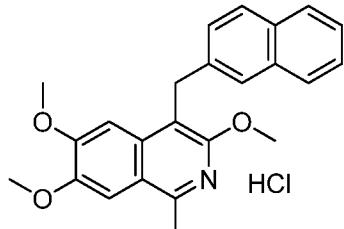
5 **MW:** 395.88; **Yield:** 55%; **Yellow solid;** **Mp (°C):** 171.6 (dec.).  
**R<sub>f</sub>**(free base): 0.3 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5).  
**<sup>1</sup>H-NMR** (DMSO d<sub>6</sub>, exchang. with CD<sub>3</sub>OD, δ): 2.99 (s, 3H, CH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.66 (s, 2H, CH<sub>2</sub>), 7.28 (s, 1H, ArH), 7.41-7.47 (m, 4H, 4xArH), 7.76-7.83 (m, 4H, 4xArH).

10 **<sup>13</sup>C-NMR** (DMSO d<sub>6</sub>, δ): 17.2, 30.0, 56.0, 56.2, 102.1, 105.1, 113.3, 117.6, 125.4, 126.1, 126.2, 127.1, 127.2, 127.4, 127.9, 131.6, 132.9, 137.2, 137.9, 148.9, 149.3, 151.0, 156.0.  
**MS-ESI** m/z (rel.int.): 360 ([MH]<sup>+</sup>, 100).  
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 15 186000482), detection UV 254 nm, RT = 5.30 min, peak area 99.6%.

Preparation of 3,6,7-trimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinoline hydrochloride **18**

To a solution of 6,7-dimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol **CCH 29038** free base (58 mg, 161 μmol) in dry DMF (6 mL) at 0°C in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added LiHMDS (1.0 N in TBME, 175 μL, 175 μmol) and the mixture was stirred for 20 min at RT. Dimethyl sulphate (18 μL, 192 μmol) was then added at 0°C and the mixture was stirred overnight at RT. The mixture was then concentrated to dryness at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (40 mL). The organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 86:14) provided 23 mg of 3,6,7-trimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinoline. This free base was dissolved in MeOH (2 mL) 25 in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of 30

a 0.50 M HCl solution in MeOH (0.4 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 3,6,7-trimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinoline hydrochloride **18** as a brown solid (25 mg, 38% yield).



5

**18**

**MW:** 409.91; **Yield:** 38%; Brown solid; **Mp (°C):** 129.7 (dec.)

**R<sub>f</sub>**(free base): 0.2 (cyclohexane:EtOAc = 86:14).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.11 (s, 3H, CH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 4.23 (s, 3H, OCH<sub>3</sub>), 4.62 (s, 2H, CH<sub>2</sub>), 7.34-7.42 (m, 4H, 4xArH), 7.52 (s, 1H, ArH), 7.64-7.78 (m, 4H, 4xArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.8, 31.6, 56.9, 57.1, 63.4, 104.4, 106.3, 120.2, 121.7, 126.8, 127.4, 127.7 (2xC), 128.4, 128.6, 129.6, 133.7, 135.0, 137.6, 139.9, 152.2, 152.6, 152.7, 159.1.

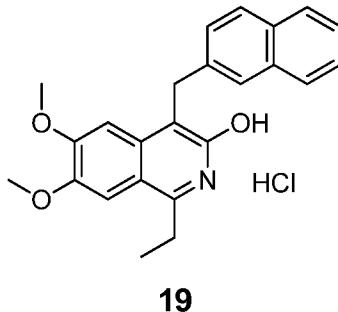
**15 MS-ESI** m/z (rel.int.): 374 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 6.25 min, peak area 97.8%.

Preparation of 1-ethyl-6,7-dimethoxy-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride **19**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (125 mg, 536 μmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.30 mL, 0.60 mmol) at RT followed by 2-(bromomethyl)naphthalene (123 mg, 556 μmol) and the mixture was stirred at 150°C 25 for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (80 mL). The organic phase was isolated and washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) gave 41 mg of 1-ethyl-6,7-dimethoxy-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol. This free base was dissolved in MeOH (2

5 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.42 M HCl solution in MeOH (4.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 1-ethyl-6,7-dimethoxy-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride **19** as a yellow solid (44 mg, 20% yield).



**MW:** 409.91; **Yield:** 20%; Brown solid; **Mp** (°C): 166.0

**R<sub>f</sub>**(free base): 0.2 (cyclohexane:EtOAc = 97:3).

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.50 (t, 3H, *J* = 7.6 Hz, CH<sub>3</sub>), 3.42 (q, 2H, *J* = 7.6 Hz, CH<sub>2</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 4.63 (s, 2H, CH<sub>2</sub>), 7.23 (s, 1H, ArH), 7.39-7.43 (m, 3H, 3xArH), 7.48 (s, 1H, ArH), 7.63 (s, 1H, ArH), 7.70-7.73 (m, 1H, ArH), 7.78-7.81 (m, 2H, 2xArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.6, 25.3, 31.6, 56.8, 56.9, 103.9, 105.4, 114.8, 119.1, 126.8,

15 127.4, 127.5, 127.6, 128.5, 128.6, 129.6, 133.8, 135.0, 137.2, 141.4, 151.5, 152.1, 155.3, 159.1.

**MS-ESI** m/z (rel.int.): 374 ([MH]<sup>+</sup>, 100).

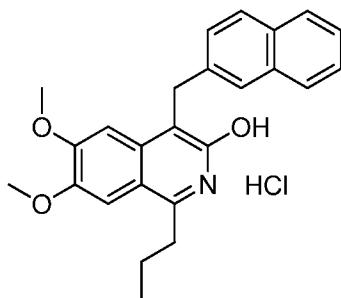
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 5.64 min, peak area 95.0%.

20

Preparation of 6,7-dimethoxy-4-(naphthalen-2-ylmethyl)-1-propylisoquinolin-3-ol hydrochloride **20**

To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (125 mg, 505 μmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.30 mL, 0.60 mmol) at RT followed by 2-(bromomethyl)naphthalene (123 mg, 556 μmol) and the mixture was stirred at 150°C for 45 min under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (80 mL). The organic phase was isolated and washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and

concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) gave 57 mg of 6,7-dimethoxy-4-(naphthalen-2-ylmethyl)-1-propylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 5 0.42 M HCl solution in MeOH (4.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-(naphthalen-2-ylmethyl)-1-propylisoquinolin-3-ol hydrochloride **20** as a yellow solid (62 mg, 29% yield).



10

**20**

**MW:** 423.93; **Yield:** 29%; Brown solid; **Mp** (°C): 135.0

**R<sub>f</sub>**(free base): 0.2 (cyclohexane:EtOAc = 97:3).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.12 (t, 3H, *J* = 7.3 Hz, CH<sub>3</sub>), 1.89-1.97 (m, 2H, CH<sub>2</sub>), 3.38 (t, 2H, *J* = 7.6 Hz, CH<sub>2</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.63 (s, 2H, CH<sub>2</sub>), 7.28 (s, 1H, ArH), 7.39-7.46 (m, 4H, 4xArH), 7.63 (s, 1H, ArH), 7.69-7.81 (m, 3H, 3xArH).  
15 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.1, 24.6, 31.6, 33.4, 56.8, 56.9, 103.8, 105.6, 114.9, 119.5, 126.8, 127.4, 127.5, 127.6, 128.5, 128.6, 129.6, 133.7, 135.0, 137.3, 141.3, 151.5, 152.0, 154.0, 159.1.

**MS-ESI** m/z (rel.int.): 388 ([MH]<sup>+</sup>, 100).

20 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 5.80 min, peak area 96.0%.

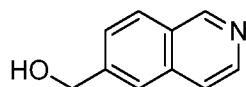
Preparation of 4-(isoquinolin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **21**

25

Isoquinolin-6-ylmethanol MDE 32046

To a solution of methyl isoquinoline-6-carboxylate (0.50 g, 2.67 mmol) in absolute EtOH (25 mL) at 0°C in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (404 mg, 10.68 mmol) and the mixture was

stirred 4 h under reflux. The solution was then cooled down to 0°C before quenching with 2.0 mL of a 6N aq. HCl solution. The reaction mixture was stirred at RT for 20 min, then basified with 5.3 mL of 2 N aq. NaOH solution. EtOH was removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL). The organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave, after evaporation and drying, isoquinolin-6-ylmethanol **MDE 32046** as an off-white solid (263 mg, 62% yield).



10

**MDE 32046**

**MW:** 159.19; **Yield:** 62%; **Off-white solid;** **Mp (°C):** 78.2

**R<sub>f</sub>:** 0.25 (cyclohexane:EtOAc = 75:25).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 4.02 (broad s, 1H, OH), 4.93 (s, 2H, OCH<sub>2</sub>), 7.61-7.65 (m, 1H, ArH), 7.70-7.76 (m, 2H, 2xArH), 7.80 (d, 1H, J = 8.2 Hz, ArH), 7.95 (d, 1H, J = 8.2 Hz, ArH), 9.20 (s, 1H, ArH).

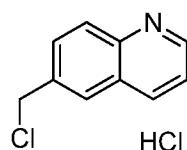
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 65.0, 116.8, 126.5, 127.0, 127.6, 127.9, 130.7, 136.4, 152.0, 153.1.

**MS-ESI** m/z (% rel. Int.): 160 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 3.53 min.

**6-(Chloromethyl)isoquinoline hydrochloride MDE 32048**

To a solution of quinolin-4-ylmethanol **MDE 32046** (0.24 g, 1.51 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C under N<sub>2</sub> in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (2.3 mL, 31.2 mmol) and the mixture was stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 6-(chloromethyl)quinoline hydrochloride **MDE 32048** as an off-white solid (301 mg, 93% yield).



30

**MDE 32048**

**MW:** 214.09; **Yield:** 93%; Off-white solid; **Mp** (°C): 202.4

<sup>1</sup>**H-NMR** (CD<sub>3</sub>OD, δ): 3.55 (s, 2H, CH<sub>2</sub>), 6.48 (dd, 1H, *J* = 7.0 Hz, ArH), 6.65-6.73 (m, 2H, 2xArH), 6.95-6.97 (m, 2H, 2xArH), 8.28 (s, 1H, ArH).

5 <sup>13</sup>**C-NMR** (CD<sub>3</sub>OD, δ): 41.7, 126.3, 128.3, 129.0, 131.9, 132.7, 138.7, 140.5, 142.0, 150.0.

**MS-ESI** m/z (% rel. Int.): 178 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 180 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 32).

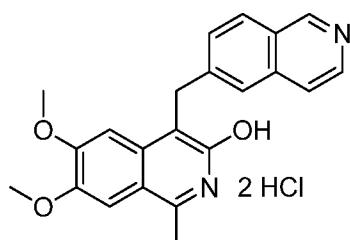
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.30 min.

10

4-(Isoquinolin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride 21

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (158 mg, 721 μmol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.70 mL, 1.40 mmol) at RT followed by

15 **MDE 32048** (185 mg, 864 μmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with EtOAc (50 mL). The organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic phases were washed with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and 20 concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) gave 56 mg of 4-(isoquinolin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (3 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (5.0 mL). The reaction mixture was stirred for 5 min at 25 RT and concentrated at 40°C under vacuum to afford 4-(isoquinolin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **21** as a brown solid (67 mg, 21% yield).

**21**

30 **MW:** 433.33; **Yield:** 21%; Brown solid; **Mp** (°C) > 250 (dec.).

*R*<sub>f</sub>(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 94:6).

<sup>1</sup>**H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.05 (s, 3H, CH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.96 (s, 2H, CH<sub>2</sub>), 7.21 (s, 1H, ArH), 7.49 (s, 1H, ArH), 7.97-8.13 (m, 4H, 4xArH), 8.48 (d, 1H, *J* = 8.2 Hz, ArH), 9.79 (s, 1H, ArH).

5 <sup>13</sup>**C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 16.2, 28.0, 56.9, 57.5, 102.2, 106.0, 119.4, 124.2, 127.6, 128.3, 131.4, 131.7, 138.1, 140.6, 140.7, 114.6, 148.6, 151.1, 151.6, 159.6 (2xC not observed).

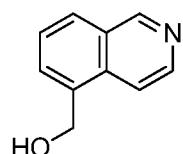
**MS-ESI** m/z (rel.int.): 361 ([MH]<sup>+</sup>, 100).

10 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.38 min, peak area 96.7%.

Preparation of 4-(isoquinolin-5-ylmethyl)-6,7-dimethoxy-1-methyliisoquinolin-3-ol **22**

Isoquinolin-5-ylmethanol **MDE 32040**

15 To a solution of isoquinoline-5-carboxaldehyde (0.65 g, 4.14 mmol) in absolute EtOH (20 mL) at 0°C in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (156 mg, 4.14 mmol) and the mixture was stirred overnight at RT. The solution was then cooled down to 0°C before quenching with 2.8 mL of a 6 N aq. HCl solution. The reaction mixture was stirred at RT for 15 min 20 then basified with a 2 N aq. NaOH solution (8.3 mL). EtOH was removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL). The organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave, after evaporation and drying, 25 isoquinolin-5-ylmethanol **MDE 32040** as an off-white solid (536 mg, 81% yield).



**MDE 32040**

**MW:** 159.19; **Yield:** 81%; Off-white solid; **Mp** (°C): 101.2

*R*<sub>f</sub>: 0.25 (cyclohexane:EtOAc = 75:25).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 3.23 (broad s, 1H, OH), 5.13 (s, 2H, OCH<sub>2</sub>), 7.55 (dd, 1H,  $J$  = 7.7 Hz, ArH), 7.76 (d, 1H,  $J$  = 7.0 Hz, ArH), 7.86-7.88 (m, 2H, 2xArH), 8.48 (d, 1H,  $J$  = 6.0 Hz, ArH), 9.17 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 62.5, 116.8, 126.9, 127.7, 128.8, 129.2, 134.0, 136.0, 143.1,

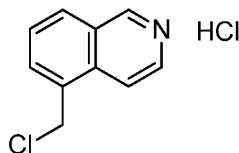
5 152.9.

**MS-ESI** m/z (% rel. Int.): 160 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 3.41 min.

10 **5-(Chloromethyl)isoquinoline hydrochloride MDE 32044**

To a solution of isoquinolin-5-ylmethanol **MDE 32040** (0.53 g, 3.33 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C under N<sub>2</sub> in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (4.9 mL, 67.4 mmol) and the mixture was stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 5-(chloromethyl)quinoline hydrochloride **MDE 32044** as an off-white solid (301 mg, 42% yield).



**MDE 32044**

20 **MW:** 214.09; **Yield:** 42%; Off-white solid; **Mp** (°C): 207.3

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.71 (s, 2H, CH<sub>2</sub>), 6.45 (dd, 1H,  $J$  = 7.7 Hz, ArH), 6.76 (d, 1H,  $J$  = 7.1 Hz, ArH), 6.97 (d, 1H,  $J$  = 8.3 Hz, ArH), 7.12-7.19 (m, 2H, 2xArH), 8.29 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 42.9, 123.6, 129.7, 132.2, 132.8, 132.9, 136.3, 138.7, 139.1,

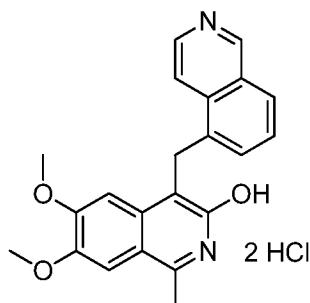
25 149.1.

**MS-ESI** m/z (% rel. Int.): 178 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 180 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 32).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 3.96 min, peak area %.

30 **4-(Isoquinolin-5-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride 22**

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (158 mg, 721  $\mu$ mol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.86 mL, 1.72 mmol) at RT followed by **MDE 32016** (185 mg, 864  $\mu$ mol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with EtOAc (50 mL). The organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic phases were washed with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, 10 eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) gave 48 mg of 4-(isoquinolin-5-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol. The free base was dissolved in MeOH (3 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (4.5 mL). The reaction mixture solution was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 4-(isoquinolin-5-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **22** as a brown solid (58 mg, 19% yield).

**22**

**MW:** 433.33; **Yield:** 19%; Brown solid; **Mp** (°C) > 250 (dec.).

**20 R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 94:6).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.09 (s, 3H, CH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 5.06 (s, 2H, CH<sub>2</sub>), 7.02 (s, 1H, ArH), 7.50-7.54 (m, 2H, 2xArH), 7.84 (dd, 1H, *J* = 7.3 Hz, ArH), 8.42 (d, 1H, *J* = 8.0 Hz, ArH), 8.78 (d, 1H, *J* = 4.5 Hz, ArH), 9.00-9.02 (m, 1H, ArH), 9.87 (s, 1H, ArH).

**25 <sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 17.5, 28.2, 56.9, 57.1, 103.0, 106.3, 112.0, 120.0, 123.6, 129.7, 130.7, 132.2, 132.7, 136.2, 136.7, 139.5, 141.0, 148.8, 151.4, 152.1, 159.6 (1xC not observed).

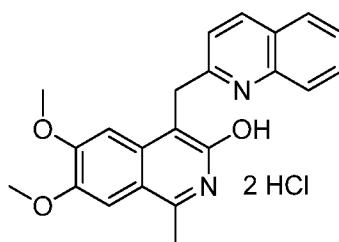
**MS-ESI** m/z (rel.int.): 361 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.11 min, peak area 99.5%.

Preparation of 6,7-dimethoxy-1-methyl-4-(quinolin-2-ylmethyl)isoquinolin-3-ol

5 dihydrochloride 23

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (147 mg, 0.67 mmol) in toluene (3 mL) in a 10 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.70 mL, 1.40 mmol) at RT followed by 2-(chloromethyl)quinoline hydrochloride (158 mg, 0.74 mmol) and the mixture was 10 stirred at 115°C for 25 min under microwave irradiation. Another portion of a 2 N aq. KOH solution (0.30 mL, 0.60 mmol) was then added at RT followed by 2-(chloromethyl)quinoline hydrochloride (70 mg, 0.33 mmol) and the mixture was stirred at 115°C for 10 min under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (5 mL) and neutralised with a 10% aqueous citric acid 15 solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 20 100:7) gave 49 mg of 6,7-dimethoxy-1-methyl-4-(quinolin-2-ylmethyl)isoquinolin-3-ol as a yellow solid. The free base (45 mg) was dissolved in MeOH (10 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (5.5 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-(quinolin-2-ylmethyl)isoquinolin-3-ol hydrochloride **23** as a yellow solid (54 mg, 19% yield).



25

**23**

**MW:** 433.33; **Yield:** 19%; Brown solid; **Mp** (°C): 196.7 (dec.).

**R<sub>f</sub>**(free base): 0.25 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:7).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.07 (s, 3H, CH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 5.17 (s, 2H, CH<sub>2</sub>), 7.29 (s, 1H, ArH), 7.52 (s, 1H, ArH), 7.65 (d, 1H, *J* = 8.6 Hz, ArH),

7.97 (dd, 1H, *J* = 7.6 Hz, ArH), 8.18-8.23 (m, 1H, ArH), 8.30 (d, 1H, *J* = 8.3 Hz, ArH), 8.41 (d, 1H, *J* = 8.6 Hz, ArH), 9.00 (d, 1H, *J* = 8.6 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 17.6, 31.1, 56.9, 57.7, 102.3, 106.3, 109.4, 119.6, 121.2, 122.8, 129.2, 130.4, 131.0, 136.5, 139.5, 140.8, 148.5, 151.8, 151.9, 153.2, 159.4,

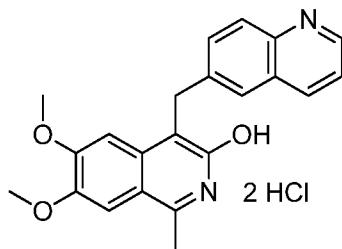
5 160.1.

**MS-ESI** m/z (rel.int.): 361 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.09 min, peak area 99.6%.

10 Preparation of 6,7-dimethoxy-1-methyl-4-(quinolin-6-ylmethyl)isoquinolin-3-ol dihydrochloride 24

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (200 mg, 0.912 mmol) in DME (5 mL) in a 10 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.95 mL, 1.90 mmol) at RT followed by 6-15 (chloromethyl)quinoline hydrochloride (234 mg, 1.093 mmol, prepared by stirring quinolin-6-yl methanol (330 mg) in SOCl<sub>2</sub> (1 mL) for 1 h at RT, then concentration under vacuum and repeated coevaporation with CH<sub>2</sub>Cl<sub>2</sub> and the mixture was stirred at 115°C for 25 min under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (5 mL) before extraction with EtOAc (50 mL). The organic phase 20 was washed with brine (10 mL) and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The dichloromethane phase was washed with brine (10 mL), combined with the first organic phase, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) gave 37 mg of 6,7-dimethoxy-1-methyl-4-(quinolin-6-25 ylmethyl)isoquinolin-3-ol as a yellow solid. This free base was dissolved in MeOH (10 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (4.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-(quinolin-6-ylmethyl)isoquinolin-3-ol dihydrochloride **24** as a brown solid (44 30 mg, 11% yield).

**24**

**MW:** 433.33; **Yield:** 11%; Brown solid; **Mp** (°C): 269.9 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 92:8).

5 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.10 (s, 3H, CH<sub>3</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 4.85 (s, 2H, CH<sub>2</sub>), 7.20 (s, 1H, ArH), 7.53 (d, 1H, J = 1.6 Hz, ArH), 8.06-8.10 (m, 1H, ArH), 8.11 (s, 1H, ArH), 8.22 (dd, 1H, J = 1.6 and 8.9 Hz, ArH), 8.30 (d, 1H, J = 8.9 Hz, ArH), 9.12 (d, 1H, J = 8.4 Hz, ArH), 9.20 (dd, 1H, J = 1.3 and 5.4 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.5, 31.2, 56.9, 57.2, 103.1, 106.2, 113.1, 120.2, 121.9,

10 123.4, 128.6, 130.8, 137.6, 138.1, 140.5, 143.1, 145.4, 148.4, 151.4, 151.6, 152.0, 159.5.

**MS-ESI** m/z (rel.int.): 361 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.18 min, peak area 99.8%.

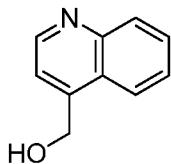
15

Preparation of 6,7-dimethoxy-1-methyl-4-(quinolin-4-ylmethyl)isoquinolin-3-ol dihydrochloride 25

Quinolin-3-ylmethanol MDE 32014

20 To a solution of 4-quinolinecarboxaldehyde (0.47 g, 3.00 mmol) in a mixture of EtOH:THF = 1:1 (40 mL) at 0°C in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (0.11 g, 3.01 mmol) and the mixture was stirred overnight at RT. The solution was then cooled down to 0°C before quenching a 6 N aq. HCl solution (2 mL). The reaction mixture was stirred at RT for 15 min then 25 basified with a 2 N aq. NaOH solution (6 mL). EtOH was removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL). The organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent

cyclohexane:EtOAc = 100:0 to 0:100) gave, after evaporation and drying, quinolin-4-ylmethanol **MDE 32014** as an off-white solid (311 mg, 65% yield).



### MDE 32014

5 **MW:** 159.19; **Yield:** 65%; Off-white solid; **Mp** (°C): 109.3

**R<sub>f</sub>:** 0.25 (EtOAc = 100%).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.86 (broad s, 1H, OH), 5.23 (s, 2H, OCH<sub>2</sub>), 7.51-7.56 (m, 2H, 2xArH), 7.69 (dd, 1H, J = 7.6 Hz, ArH), 7.94 (d, 1H, J = 8.4 Hz, ArH), 8.09 (d, 1H, J = 8.4 Hz, ArH), 8.67-8.77 (m, 1H, ArH).

10 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 61.3, 118.1, 122.9, 125.8, 126.7, 129.3, 129.7, 146.8, 147.6, 150.2.

**MS-ESI** m/z (% rel. Int.): 160 ([MH]<sup>+</sup>, 100).

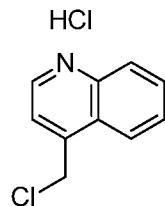
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.20 min.

15

### 4-(Chloromethyl)quinoline hydrochloride MDE 32016

To a solution of quinolin-4-ylmethanol **MDE 32014** (0.28 g, 1.76 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (18 mL) at 0°C under N<sub>2</sub> in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (2.6 mL, 36.0 mmol) and the mixture

20 was stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 4-(chloromethyl)quinoline hydrochloride **MDE 32016** as an off-white solid (246 mg, 65% yield).



### MDE 32016

25 **MW:** 214.09; **Yield:** 65%; Off-white solid; **Mp** (°C): 40.1

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 4.91 (s, 2H, CH<sub>2</sub>), 8.07 (dd, 1H, J = 7.7 Hz, ArH), 8.21-8.35 (m, 3H, 3xArH), 8.59 (d, 1H, J = 8.6 Hz, ArH), 9.26 (d, 1H, J = 5.6 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 42.0, 122.3, 122.9, 126.4, 128.3, 131.7, 136.3, 139.1, 146.0, 156.9.

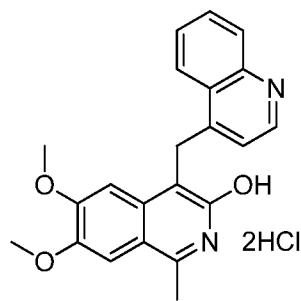
**MS-ESI** m/z (% rel. Int.): 178 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 180 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 32).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model #

5 186000482), detection UV 254 nm, RT = 4.43 min.

**6,7-Dimethoxy-1-methyl-4-(quinolin-4-ylmethyl)isoquinolin-3-ol dihydrochloride 25**

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (120 mg, 547  $\mu$ mol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.58 mL, 1.16 mmol) at RT followed by **MDE 32016** (130 mg, 607  $\mu$ mol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with EtOAc (50 mL). The organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic phases 10 were washed with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) gave 37 mg of 6,7-dimethoxy-1-methyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in 15 a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (4 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-(quinolin-4-ylmethyl)isoquinolin-3-ol dihydrochloride **25** as a brown solid (44 mg, 20 19% yield).



25

**25**

**MW:** 433.33; **Yield:** 19%; Brown solid; **Mp** (°C): 236.6 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.10 (s, 3H, CH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 5.31 (s, 2H, CH<sub>2</sub>), 7.03 (s, 1H, ArH), 7.38-7.40 (m, 1H, ArH), 7.55 (s, 1H, ArH), 8.17-8.36 (m, 3H, 3xArH), 8.90-8.98 (m, 2H, 2xArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 17.5, 29.7, 56.9, 57.1, 102.6, 106.3, 110.3, 119.7, 121.2, 5 122.3, 126.8, 129.6, 131.6, 136.3, 138.7, 140.9, 145.4, 151.7, 151.9, 159.8, 160.3 (1xC not observed).

**MS-ESI** m/z (rel.int.): 361 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.13 min, peak area 99.4%.

10

15

Preparation of 6,7-dimethoxy-1-methyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **26**

Quinolin-3-ylmethanol **MDE 32002**

20 To a solution of 3-quinolinecarboxaldehyde (0.39 g, 2.48 mmol) in absolute EtOH (25 mL) at 0°C in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (48 mg, 1.26 mmol) and the mixture was stirred overnight at RT. Then a second portion of NaBH<sub>4</sub> (48 mg, 1.26 mmol) was added at RT and stirring was continued for 1 h at RT. The solution was then cooled down to 0°C 25 before quenching with a 6 N aq. HCl solution (2 mL). The reaction mixture was stirred at RT for 15 min and then basified with a 2 N aq. NaOH solution (8 mL). EtOH was removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL). The organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column 30 chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) gave, after evaporation and drying, quinolin-3-ylmethanol **MDE 32002** as an off-white solid (280 mg, 71% yield).

**MDE 32002**

**MW:** 159.19; **Yield:** 71%; Off-white solid; **Mp** (°C): 87.6

**R<sub>f</sub>:** 0.25 (EtOAc = 100%).

5 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.80 (broad s, 1H, OH), 4.90 (s, 2H, OCH<sub>2</sub>), 7.49-7.54 (m, 1H, ArH), 7.64-7.70 (m, 1H, ArH), 7.76 (d, 1H, *J* = 8.1 Hz, ArH), 8.50 (d, 1H, *J* = 8.5 Hz, ArH), 8.15 (s, 1H, ArH), 8.80 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 62.6, 126.9, 127.7, 127.9, 128.9, 129.4, 133.8, 147.3, 150.1 (1xC not observed).

10 **MS-ESI** m/z (% rel. Int.): 160 ([MH]<sup>+</sup>, 100).

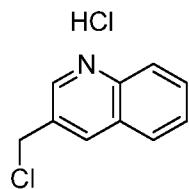
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.62 min.

**3-(Chloromethyl)quinoline hydrochloride MDE 32004**

15

To a solution of quinolin-3-ylmethanol **MDE 32002** (0.26 g, 1.63 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C under N<sub>2</sub> in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (2.4 mL, 33.1 mmol) and the mixture was stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum

20 and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)quinoline hydrochloride **MDE 32004** as an off-white solid (301 mg, 85% yield).

**MDE 32004**

25 **MW:** 214.09; **Yield:** 85%; Off-white solid; **Mp** (°C): 192.1

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 5.10 (s, 2H, CH<sub>2</sub>), 8.01-8.06 (m, 1H, ArH), 8.24-8.26 (m, 1H, ArH), 8.31 (d, 1H, *J* = 8.4 Hz, ArH), 8.39 (d, 1H, *J* = 8.4 Hz, ArH), 9.32 (s, 1H, ArH), 9.41-9.42 (m, 1H, ArH).

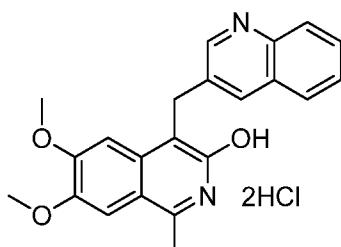
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 42.3, 121.5, 130.3, 130.7, 131.9, 134.5, 136.8, 138.6, 146.5, 147.8.

**MS-ESI** m/z (% rel. Int.): 178 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 180 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 32).

**HPLC:** Method A (10 min), Xterra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 5 186000482), detection UV 254 nm, RT = 4.55 min.

**6,7-Dimethoxy-1-methyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride 26**

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (120 mg, 10 547  $\mu$ mol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.58 mL, 1.16 mmol) at RT followed by **MDE 32004** (130 mg, 607  $\mu$ mol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic phase was washed with brine (10 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) gave 67 mg of 6,7-dimethoxy-1-methyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol. The free base was dissolved in MeOH (2 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (6 mL). The 20 reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **26** as a brown solid (80 mg, 31% yield).



**26**

25 **MW:** 433.33; **Yield:** 31%; Brown solid; **Mp** (°C): 229.7 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.06 (s, 3H, CH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.88 (s, 2H, CH<sub>2</sub>), 7.22 (s, 1H, ArH), 7.52 (s, 1H, ArH), 7.93 (dd, 1H, *J* = 7.6 Hz, ArH), 8.11-8.26 (m, 3H, 3xArH), 8.88 (s, 1H, ArH), 9.25 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 17.6, 28.6, 56.9, 57.5, 102.8, 106.4, 111.7, 120.2, 121.3, 130.2, 130.4, 131.6, 135.1, 136.0, 137.9, 140.5, 146.5, 146.5, 151.8, 152.1, 159.9 (1xC not observed).

**MS-ESI** m/z (rel.int.): 361 ([MH]<sup>+</sup>, 100).

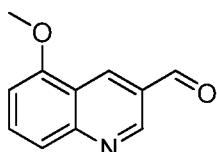
5 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.24 min, peak area 98.9%.

Preparation of 6,7-dimethoxy-4-((5-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride 27

10

5-Methoxyquinoline-3-carbaldehyde RBO 35110

Two 20 mL microwave vials were equipped with a magnetic stirrer and charged with a solution of 3-methoxyaniline (0.625 mL, 5.6 mmol) in absolute EtOH (10 mL) before addition of vinamidinium bis-tetrafluoroborate **RW/EXH 001-AB** (6.0 g, 16.8 mmol) and each vial was heated with stirring at 150°C for 15 min under microwave irradiation. After cooling to RT, AcOH (10 mL) was then added in each vial before stirring at 150°C for 15 min under microwave irradiation. The mixture was then cooled down to RT and combined into a 250 mL round-bottomed flask before addition of a mixture of THF:1 N aq. HCl=1:1 (40 mL) and stirring was continued at 15 20 RT for 2 h. The mixture was then neutralised with saturated aqueous NaHCO<sub>3</sub> solution. THF and EtOH were then removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 75:25) gave, after 25 evaporation and drying, 5-methoxyquinoline-3-carbaldehyde **RBO 35110A** as a yellow solid (90 mg, 4% yield).



**RBO 35110A**

**MW:** 187.20; **Yield:** 4%; Yellow solid.

30 **R<sub>f</sub>:** 0.18 (cyclohexane:EtOAc = 75:25).

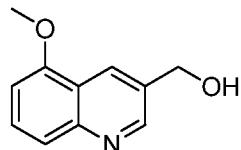
**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 4.02 (s, 3H, OCH<sub>3</sub>), 6.92-6.98 (m, 1H, ArH), 7.75-7.83 (m, 2H, 2xArH), 9.00 (s, 1H, ArH), 9.32 (s, 1H, ArH), 10.21 (s, 1H, HC=O).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 56.0, 105.5, 119.7, 121.6, 127.8, 133.1, 135.7, 149.3, 151.2, 156.3, 190.9.

5

**(5-Methoxyquinolin-3-yl)methanol CCH 34144-3**

To a stirred solution of 5-methoxyquinoline-3-carbaldehyde **RBO 35110A** (98 mg, 524 μmol) in THF (20 mL) at 0°C in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (20 mg, 529 μmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (10 mL). After stirring for 20 min at that temperature, the mixture was basified with a 2 N aq. NaOH solution (8 mL). THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (60 mL), and the organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) provided, after evaporation and drying, (5-methoxyquinolin-3-yl)methanol **CCH 34144-3** as a pale brown solid (80 mg, 81% yield ).



20

**CCH 34144-3**

**MW:** 189.21; **Yield:** 81%; Pale brown solid.

**R<sub>f</sub>:** 0.20 (EtOAc 100%).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.25 (broad s, 1H, OH), 4.01 (s, 3H, OCH<sub>3</sub>), 4.90 (s, 2H, OCH<sub>2</sub>), 6.86 (dd, 1H, J = 0.7 & 7.6 Hz, ArH), 7.57-7.70 (m, 2H, 2xArH), 8.54-8.55 (m, 1H, ArH), 8.88 (d, 1H, J = 2.2 Hz, ArH).

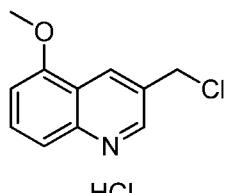
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 55.8, 63.2, 104.5, 120.3, 121.2, 128.8, 129.4, 132.6, 148.4, 150.4, 155.2.

**MS-ESI** m/z (% rel. Int.): 190 (MH)<sup>+</sup>, 100).

**HPLC:** Method A (10 min), Xterra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 30 186000482), detection UV 254 nm, RT = 3.57 min.

**3-(Chloromethyl)-5-methoxyquinoline hydrochloride CCH 34144B**

To a solution of (5-methoxyquinolin-3-yl)methanol **CCH 34144-3** (80 mg, 423 µmol) in dry  $\text{CH}_2\text{Cl}_2$  (12 mL) at 0°C under  $\text{N}_2$  in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (0.60 mL, 8.27 mmol) 5 and the mixture was stirred for 2 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-5-methoxyquinoline hydrochloride **CCH 34144B** as an off-white solid (87 mg, 84% yield).



10

**CCH 34144B**

**MW:** 244.12; **Yield:** 84%; Off-white solid; **Mp** (°C): 50.3

**<sup>1</sup>H-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 4.19 (s, 3H,  $\text{OCH}_3$ ), 4.80 (broad s, 1H, NH), 5.04 (s, 2H,  $\text{CH}_2$ ), 7.36 (d, 1H,  $J$  = 8.0 Hz, ArH), 7.87 (d, 1H,  $J$  = 8.6 Hz, ArH), 8.13 (dd, 1H,  $J$  = 8.3 Hz, 15 ArH), 9.31 (s, 1H, ArH), 9.44 (s, 1H, ArH).

**<sup>13</sup>C-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 42.8, 58.2, 110.1, 113.3, 123.5, 133.4, 138.7, 139.7, 143.2, 146.3, 157.8.

**MS-ESI** m/z (% rel. Int.): 208 ( $[\text{MH}]^+$ ,  $^{35}\text{Cl}$ , 100), 210 ( $[\text{MH}]^+$ ,  $^{37}\text{Cl}$ , 35).

**HPLC:** : Method A (10 min), XTerra<sup>TM</sup> column (5 µm, C18, 4.5 × 50 mm, Model # 20 186000482), detection UV 254 nm, RT = 3.61 min.

**Methyl 2-(3,4-dimethoxyphenyl)-3-(5-methoxyquinolin-3-yl)propanoate CCH 34144-5**

To a solution of methyl 2-(3,4-dimethoxyphenyl)acetate **SLA 28134** (73 mg, 347 µmol) in dry THF (10 mL) at -66°C in a 25 mL round-bottomed flask equipped 25 with a magnetic stirrer was added LiHMDS (1.0 N in TBME, 0.70 mL, 700 µmol) and the mixture was stirred for 20 min at that temperature. 3-(Chloromethyl)-5-methoxyquinoline hydrochloride **CCH 34144B** (84 mg, 344 µmol) was then added and the mixture was stirred for 2 h allowing the temperature to reach RT. The mixture was then quenched by carefully adding  $\text{H}_2\text{O}$  (4 mL) and diluted with EtOAc 30 (30 mL). The organic phase was isolated and the aqueous phase was further

extracted with  $\text{CH}_2\text{Cl}_2$  (40 mL). Both organic phases were washed with brine (10 mL), then combined, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent cyclohexane:EtOAc = 100:0 to 50:50) provided methyl 2-(3,4-dimethoxyphenyl)-3-(5-methoxyquinolin-3-yl)propanoate **34144-5** as a pale yellow oil (46 mg, 35% yield).



**CCH 34144-5**

**MW:** 381.42; **Yield:** 35%; Pale yellow oil.

**<sup>1</sup>H-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 3.20 (dd, 1H,  $J$  = 7.1 & 13.9 Hz,  $\text{CHH}$ ), 3.56 (dd, 1H,  $J$  = 8.5 & 13.9 Hz,  $\text{CHH}$ ), 3.62 (s, 3H,  $\text{OCH}_3$ ), 3.85 (s, 6H, 2x $\text{OCH}_3$ ), 3.85-3.91 (m, 1H,  $\text{CH}$ ), 3.99 (s, 3H,  $\text{OCH}_3$ ), 6.81-6.87 (m, 4H, 4xArH), 7.52-7.65 (m, 2H, 2xArH), 8.33 (s, 1H, ArH), 8.66 (d, 1H,  $J$  = 2.2 Hz, ArH).

**<sup>13</sup>C-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 37.3, 52.2, 52.8, 55.7, 55.9, 55.9, 104.3, 110.9, 111.3, 120.2, 120.4, 121.3, 128.8, 130.1, 130.4, 130.9, 147.8, 148.5, 149.1, 152.1, 154.9, 173.6.

**15 MS-ESI** m/z (% rel. Int.): 382 ( $[\text{MH}]^+$ , 100).

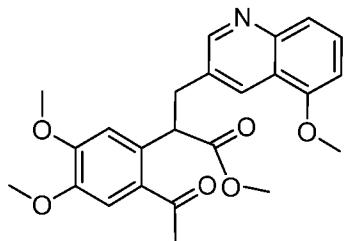
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 3.99 min.

Methyl 2-(2-acetyl-4,5-dimethoxyphenyl)-3-(5-methoxyquinolin-3-yl)propanoate CCH

**20 34154**

To a solution of methyl 2-(3,4-dimethoxyphenyl)-3-(5-methoxyquinolin-3-yl)propanoate **CCH 34144-5** (46 mg, 121  $\mu\text{mol}$ ) in acetic anhydride (2.0 mL, 21.2 mmol) at 0°C in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added  $\text{HClO}_4$  (ca. 70% solution in water, 0.1 mL, 1.2 mmol). The reaction mixture was then allowed to warm up to RT, stirred for 45 min and diluted with  $\text{Et}_2\text{O}$  (40 mL). The solid was filtered and washed several times with  $\text{Et}_2\text{O}$  giving a brown residue. The residue was then suspended in  $\text{CH}_2\text{Cl}_2$  (40 mL) before neutralisation with saturated aqueous  $\text{NaHCO}_3$  solution. The organic phase was isolated, washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent cyclohexane:EtOAc = 100:0 to

0:100) gave methyl 2-(2-acetyl-4,5-dimethoxyphenyl)-3-(5-methoxyquinolin-3-yl)propanoate **CCH 34154** as a yellow solid (30 mg, 59% yield).



**CCH 34154**

5 **MW:** 423.46; **Yield:** 59%; Yellow solid.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.46 (s, 3H, CH<sub>3</sub>), 3.23 (d, 1H, *J* = 13.8 Hz, CHH), 3.52 (d, 1H, *J* = 13.8 Hz, CHH), 3.61 (s, 3H, OCH<sub>3</sub>), 3.85-3.89 (m, 1H, CH), 3.86 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 6.82 (d, 1H, *J* = 7.5 Hz, ArH), 6.89-6.91 (m, 1H, ArH), 7.18 (s, 1H, ArH), 7.51-7.64 (m, 2H, 2xArH), 8.41 (s, 1H, ArH), 8.70 (d, 1H, *J* = 2.0 Hz, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 29.3, 37.1, 48.3, 52.1, 55.7, 56.0, 56.1, 104.2, 111.7, 113.0, 120.4, 121.2, 128.7, 129.6, 130.4, 131.2, 132.3, 147.3, 147.7, 151.8, 152.4, 154.9, 173.8, 199.9.

**MS-ESI** m/z (% rel. Int.): 424 ([MH]<sup>+</sup>, 100).

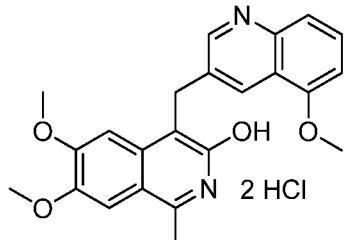
15 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 214 nm, RT = 3.90 min.

6,7-Dimethoxy-4-((5-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol

dihydrochloride 27

20 A mixture of methyl 2-(2-acetyl-4,5-dimethoxyphenyl)-3-(5-methoxyquinolin-3-yl)propanoate **CCH 34154** (30 mg, 71 μmol) and NH<sub>4</sub>OAc (0.50 g, 6.49 mmol) in a 2 mL microwave vial equipped with a magnetic stirrer was stirred at 160°C for 7 min under microwave irradiation. After cooling to RT, the mixture was taken up in CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (50 mL) and H<sub>2</sub>O (10 mL). The organic layer was isolated and 25 the aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (25 mL). The organics were combined, washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 93:7) gave 21 mg of 6,7-dimethoxy-4-((5-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) 30 in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of

a 0.09 M HCl solution in MeOH (2 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((5-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **27** as a brown solid (25 mg, 76% yield).



5

**27**

**MW:** 463.35; **Yield:** 76%; Brown solid; **Mp** (°C) > 250 (dec.).

**R<sub>f</sub>:** 0.20 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 93:7).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.08 (s, 3H, CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.10 (s, 3H, OCH<sub>3</sub>), CH<sub>2</sub> hidden by H<sub>2</sub>O peak, 7.29 (s, 1H, ArH), 7.38 (d, 1H, J = 7.7 Hz, ArH), 7.53 (s, 1H, ArH), 7.77 (d, 1H, J = 8.2 Hz, ArH), 8.06-8.11(m, 1H, ArH), 9.16-9.19 (m, 2H, 2xArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.5, 28.6, 56.9, 57.4, 57.4, 102.6, 106.3, 109.4, 112.5, 119.9, 123.1, 134.1, 137.1, 138.8, 140.3, 141.4, 146.1, 151.6, 152.0, 152.2, 157.0, 159.8, (1xC not observed).

**MS-ESI** m/z (rel.int.): 391 ([MH]<sup>+</sup>, 100), 413 ([M+Na]<sup>+</sup>, 8).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 214 nm, RT = 3.49 min, peak area 98.4%.

20 Preparation of 4-((5-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **28**

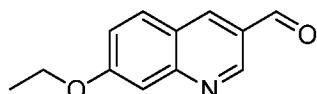
7-Ethoxyquinoline-3-carbaldehyde CCH 29158A & 5-ethoxyquinoline-3-carbaldehyde CCH 29158B

25 To a solution of 3-aminophenol (0.78 g, 7.15 mmol) in absolute EtOH (60 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added vinamidinium bis-tetrafluoroborate (prepared according the method of Tom, N.; Ruel, E., *Synthesis*, 2001, 9, 135) (18.00 g, 21.45 mmol) and the reaction mixture was stirred overnight under reflux, then concentrated at 40°C under vacuum. The residue

was taken up in a mixture of THF:1 N aq. HCl = 1:1 (80 mL) and stirred for 1 h at 50°C before neutralisation with saturated NaHCO<sub>3</sub> aqueous solution. THF was then removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, 5 and concentrated under vacuum. The residue was purified by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 96:4) to give a mixture of two regioisomers **MDE 32056-2** (300 mg, 24% yield).

To a suspension of **MDE 32056-2** (300 mg, 1.73 mmol) in DMF (10 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added Cs<sub>2</sub>CO<sub>3</sub> 10 (1.13 g, 3.47 mmol) followed by bromoethane (0.273 mL, 3.66 mmol). The reaction mixture was stirred overnight at RT and then DMF was removed at 60°C under vacuum. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C 15 under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) provided, after evaporation and drying, 7-ethoxyquinoline-3-carbaldehyde **CCH 29158A** as a pale yellow solid (195 mg, 56% yield, 14% yield over 2 steps) and of 5-ethoxyquinoline-3-carbaldehyde **CCH 29158B** as a pale yellow solid (106 mg, 30% yield, 7% yield over 2 steps).

20 7-ethoxyquinoline-3-carbaldehyde CCH 29158A :



**CCH 29158A**

**MW:** 201.22; **Yield:** 14% over 2 steps; **Pale yellow solid;** **Mp (°C):** 152.6

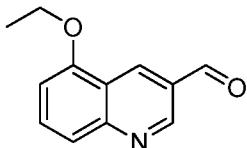
**R<sub>f</sub>:** 0.25 (cyclohexane:EtOAc = 75:25).

25 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.52 (t, 3H, J = 7.5 Hz, CH<sub>3</sub>), 4.23 (q, 2H, J = 7.5 Hz, CH<sub>2</sub>), 7.26-7.30 (m, 1H, ArH), 7.44-7.47 (m, 1H, ArH), 7.84 (dd, 1H, J = 1.6 & 9.0 Hz, ArH), 8.51 (s, 1H, ArH), 9.26 (s, 1H, ArH), 10.17 (s, 1H, HC=O).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.5, 64.1, 108.3, 121.5, 122.1, 127.0, 130.5, 139.0, 150.0, 152.8, 162.7, 190.5.

30 **MS-ESI** m/z (% rel. Int.): 202 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 5.04 min.

5-ethoxyquinoline-3-carbaldehyde CCH 29158B :**CCH 29158B**

5 **MW:** 201.22; **Yield:** 7% over 2 steps; Pale yellow solid; **Mp (°C):** 78.9  
**R<sub>f</sub>:** 0.18 (cyclohexane:EtOAc = 75:25).

10 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.59 (t, 3H, J = 8.4 Hz, CH<sub>3</sub>), 4.25 (q, 2H, J = 8.4 Hz, CH<sub>2</sub>), 6.91 (d, 1H, J = 7.0 Hz, ArH), 7.70-7.79 (m, 2H, 2xArH), 9.02-9.07 (m, 1H, ArH), 9.32 (d, 1H, J = 2.0 Hz, ArH), 10.22 (s, 1H, HC=O).

15 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.7, 64.4, 106.1, 119.7, 121.3, 127.7, 133.2, 135.7, 149.3, 151.2, 155.7, 190.9.

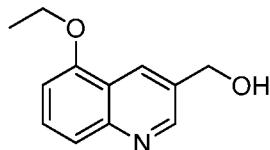
**MS-ESI** m/z (% rel. Int.): 202 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 5.04 min.

15

(5-Ethoxyquinolin-3-yl)methanol MDE 32076

To a stirred solution of 5-ethoxyquinoline-3-carbaldehyde **CCH 29158B** (98 mg, 487 μmol) in THF (10 mL) at 0°C in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (18 mg, 476 μmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 6 N aq. HCl solution (0.33 mL). After stirring for 15 min at that temperature, the mixture was basified by a 2 N aq. NaOH solution (1.0 mL). THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) provided 41 mg (5-ethoxyquinolin-3-yl)methanol **MDE 32076** as a colorless oil (41 mg, 41% yield).

**MDE 32076**

**MW:** 203.24; **Yield:** 41%; Colorless oil.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.50 (t, 3H, J = 8.3 Hz, CH<sub>3</sub>), 3.82-4.52 (broad, s, 1H, OH), 4.14 (q, 2H, J = 8.3 Hz, CH<sub>2</sub>), 4.84 (s, 2H, OCH<sub>2</sub>), 6.75-6.79 (m, 1H, ArH), 7.47-7.60 (m, 2H, 2xArH), 8.52 (s, 1H, ArH), 8.74 (s, 1H, ArH).

5 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.7, 62.8, 64.0, 105.2, 120.5, 120.7, 129.0, 129.3, 132.9, 148.1, 150.2, 154.4.

**MS-ESI** m/z (% rel. Int.): 204 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 3.65 min.

10

3-(chloromethyl)-5-ethoxyquinoline hydrochloride CCH 29192

To a solution of (5-ethoxyquinolin-3-yl)methanol **MDE 32076** (40 mg, 197 μmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C under N<sub>2</sub> in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (0.30 mL, 4.13 mmol)

15 and the mixture was stirred for 30 min at 0°C then for 2 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-5-ethoxyquinoline hydrochloride **CCH 29192** as a yellow solid (51 mg, 100% yield).



20

**CCH 29192**

**MW:** 258.14; **Yield:** 100%; Yellow solid; **Mp** (°C): 218.5

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.62 (t, 3H, J = 6.8 Hz, CH<sub>3</sub>), 4.41 (q, 2H, J = 6.8 Hz, CH<sub>2</sub>), 5.09 (s, 2H, CH<sub>2</sub>), 7.41 (d, 1H, J = 8.1 Hz, ArH), 7.78 (d, 1H, J = 8.6 Hz, ArH), 8.09-8.15 (m, 1H, ArH), 9.34 (d, 1H, J = 1.5 Hz, ArH), 9.47 (s, 1H, ArH).

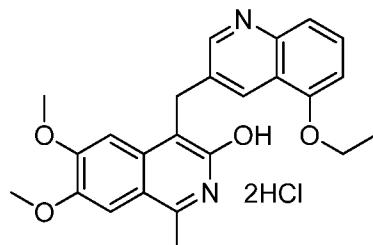
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.8, 42.4, 66.8, 110.3, 112.4, 123.2, 133.2, 138.3, 139.4, 142.7, 146.3, 156.8.

**MS-ESI** m/z (% rel. Int.): 222 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 224 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 35).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.52 min.

4-((5-Ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride 28

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (51 mg, 233  $\mu$ mol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.22 mL, 0.44 mmol) at RT followed by **CCH 29192** (50 mg, 194  $\mu$ mol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with EtOAc (50 mL). The organic layer was isolated and the aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic layers were washed with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) gave 4-((5-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (2 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 4-((5-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **28** as a yellow solid (11 mg, 12% yield).

**28**

**MW:** 477.38; **Yield:** 12%; **Yellow solid;** **Mp (°C):** 220.2 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 94:6).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.52 (t, 3H,  $J$  = 7.0 Hz, CH<sub>3</sub>), 3.05 (s, 3H, CH<sub>3</sub>), 4.02 (s, 6H, 2xOCH<sub>3</sub>), 4.36 (q, 2H,  $J$  = 7.06 Hz, CH<sub>2</sub>), 4.87 (s, 2H, CH<sub>2</sub>), 7.32-7.36 (m, 2H, 2xArH), 7.50 (s, 1H, ArH), 7.73 (d, 1H,  $J$  = 8.6 Hz, ArH), 8.01-8.07 (m, 1H, ArH), 9.05 (s, 1H, ArH), 9.31 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.7, 17.5, 28.6, 56.9, 57.4, 66.6, 102.6, 106.3, 110.0, 112.3, 112.6, 119.8, 123.2, 134.0, 137.5, 138.9, 140.3, 141.8, 145.8, 151.4, 151.9, 152.3, 156.3, 159.8.

**MS-ESI** m/z (rel.int.): 405 [M+H]<sup>+</sup> (100).

5 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), RT = 3.80 min, peak area 98.4 %.

Preparation of 6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride 29

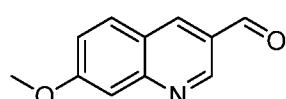
10

7-Methoxyquinoline-3-carbaldehyde MDE 32006

To a solution of 3-methoxyaniline (0.40 mL, 3.56 mmol) in absolute EtOH (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added

15 vinamidinium bis-tetrafluoroborate (prepared according the method of Tom, N.; Ruel, E., *Synthesis*, 2001, 9, 135) (4.12 g, 11.05 mmol) and the reaction mixture was stirred at 150°C for 8 min under microwave irradiation. After cooling to RT, AcOH (5 mL) was added and the reaction mixture was stirred at 150°C for 8 min under microwave irradiation. The mixture was then cooled down to RT and transferred into a 250 mL round-bottomed flask before adding a mixture of THF:1 N aq. HCl = 1:1 (40 mL) and stirring was continued at RT for 2 h. The mixture was then neutralised with a saturated NaHCO<sub>3</sub> aqueous solution. THF and EtOH were then removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent

20 cyclohexane:EtOAc = 70:30) gave, after evaporation and drying, 7-methoxyquinoline-3-carbaldehyde **MDE 32006** as a yellow solid (352 mg, 53% yield).



**MDE 32006**

**MW:** 187.20; **Yield:** 53%; **Yellow solid;** **Mp (°C):** 126.5

30 **R<sub>f</sub>:** 0.20 (cyclohexane:EtOAc = 70:30).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 4.00 (s, 3H, OCH<sub>3</sub>), 7.29 (dd, 1H,  $J$  = 2.5 & 9.0 Hz, ArH), 7.49 (d, 1H,  $J$  = 2.5 Hz, ArH), 7.85 (d, 1H,  $J$  = 9.0 Hz, ArH), 8.53 (d, 1H,  $J$  = 1.9 Hz, ArH), 9.27 (d, 1H,  $J$  = 1.9 Hz, ArH), 10.18 (s, 1H, HC=O).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 55.8, 107.7, 121.2, 122.2, 127.1, 130.5, 139.1, 150.0, 152.8,

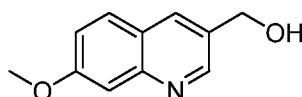
5 163.4, 190.5.

**MS-ESI** m/z (% rel. Int.): 188 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.42 min.

10 **(7-Methoxyquinolin-3-yl)methanol MDE 32010**

To a stirred solution of 7-methoxyquinoline-3-carbaldehyde **MDE 32006** (0.328 g, 1.75 mmol) in a mixture of EtOH:THF = 18:6 mL at 0°C in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added sodium borohydride NaBH<sub>4</sub> (66 mg, 1.75 mmol) and the mixture was stirred overnight at RT then cooled 15 in an ice bath before quenching by addition of a 6 N aq. HCl solution (1.20 mL). After stirring for 15 min at that temperature, the mixture was basified with 2 N aq. NaOH solution (3.60 mL). THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography 20 (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) provided, after evaporation and drying, (7-methoxyquinolin-3-yl)methanol **MDE 32010** as an off-white solid (246 mg, 74% yield).



**MDE 32010**

25 **MW:** 189.21; **Yield:** 74%; Off-white solid; **Mp** (°C): 223.0

**R<sub>f</sub>:** 0.20 (EtOAc 100%).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 3.63 (broad s, 1H, OH), 3.89 (s, 3H, OCH<sub>3</sub>), 4.83 (s, 2H, OCH<sub>2</sub>), 7.17 (dd, 1H,  $J$  = 2.5 & 9.0 Hz, ArH), 7.35 (d, 1H,  $J$  = 2.5 Hz, ArH), 7.63 (d, 1H,  $J$  = 9.0 Hz, ArH), 8.02 (s, 1H, ArH), 8.74 (s, 1H, ArH).

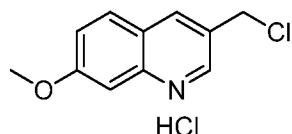
30 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 55.5, 62.7, 106.9, 120.1, 123.1, 128.7, 131.6, 133.9, 149.1, 150.2, 160.7.

**MS-ESI** m/z (% rel. Int.): 190 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.32 min.

**3-(Chloromethyl)-7-methoxyquinoline hydrochloride MDE 32012**

5 To a solution of (7-methoxyquinolin-3-yl)methanol **MDE 32006** (219 mg, 1.16 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (12 mL) at 0°C under  $\text{N}_2$  in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (1.68 mL, 23.16 mmol) and the mixture was stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) before concentration 10 back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-7-methoxyquinoline hydrochloride **MDE 32012** as an off-white solid (246 mg, 87% yield).



**MDE 32012**

15 **MW:** 244.12; **Yield:** 87%; Off-white solid; **Mp (°C):** 50.3

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 4.12 (s, 3H,  $\text{OCH}_3$ ), 5.04 (s, 2H,  $\text{CH}_2$ ), 7.60-7.65 (m, 2H, 2xArH), 8.28 (d, 1H,  $J$  = 8.9 Hz, ArH), 9.18 (s, 1H, ArH), 9.23 (s, 1H, ArH).

**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 42.7, 57.7, 100.1, 125.3, 126.5, 132.0, 132.5, 141.8, 145.2, 147.6, 167.5.

20 **MS-ESI** m/z (% rel. Int.): 208 ( $[\text{MH}]^+$ ,  $^{35}\text{Cl}$ , 100), 210 ( $[\text{MH}]^+$ ,  $^{37}\text{Cl}$ , 35).

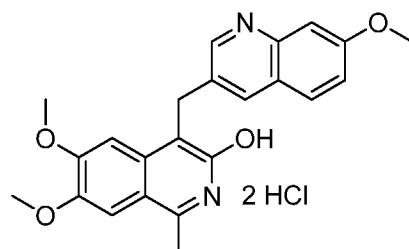
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.50 min.

**6,7-Dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol**

25 **dihydrochloride 29**

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (200 mg, 912  $\mu$ mol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.95 mL, 1.90 mmol) at RT followed by 3-(chloromethyl)-7-methoxyquinoline hydrochloride **MDE 32012** (245 mg, 1.00 mmol) and the mixture was stirred at 150°C for 20 min under microwave irradiation. After 30 cooling to RT, another portion of a 2 N aq. KOH solution (0.30 mL, 0.60 mmol) was

added and the mixture was stirred at 150°C for 20 min under microwave irradiation. After cooling to RT, the mixture was diluted with EtOAc (50 mL) and acidified by a 10% aqueous citric acid solution (5 mL) before neutralisation with a saturated aqueous NaHCO<sub>3</sub> solution. The organic phase was isolated and the aqueous phase 5 was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic phases were washed with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:7N NH<sub>3</sub> in MeOH = 100:0 to 94:6) gave 23 mg of 6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in 10 a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (4 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **29** as a brown solid (27 mg, 6% yield).



15

**29**

**MW:** 463.35; **Yield:** 6%; Brown solid; **Mp** (°C) > 250 (dec.).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.06 (s, 3H, CH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 7.21 (s, 1H, ArH), 7.50-7.53 (m, 3H, 3xArH), 8.09-8.12 (m, 1H, ArH), 20 8.80 (s, 1H, ArH), 9.04 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.5, 28.2, 56.9, 57.2, 57.4, 99.5, 102.6, 106.3, 112.1, 119.9, 124.8, 126.3, 131.7, 132.4, 140.4, 140.7, 144.5, 146.2, 151.4, 151.9, 152.4, 159.7, 166.5.

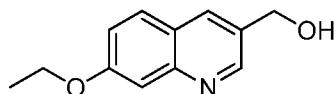
**MS-ESI** m/z (rel.int.): 391 ([MH]<sup>+</sup>, 100), 413 ([M+Na]<sup>+</sup>, 8).

**HPLC:** Method A (10 min), Xterra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.41 min, peak area 98.2%.

Preparation of 4-((7-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **30**

**(7-Ethoxyquinolin-3-yl)methanol MDE 32072**

To a stirred solution of 7-ethoxyquinoline-3-carbaldehyde **CCH 29158A** (184 mg, 0.91 mmol) in THF (10 mL) at 0°C in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added sodium borohydride NaBH<sub>4</sub> (34 mg, 0.90 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 6 N aq. HCl solution (0.60 mL). After stirring for 15 min at that temperature, the mixture was basified with 2 N aq. NaOH solution (1.80 mL). THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 25:75) provided, after evaporation and drying, (7-ethoxyquinolin-3-yl)methanol **MDE 32072** as an off-white solid (94 mg, 51% yield).



15 **MDE 32072**

**MW:** 203.24; **Yield:** 51%; Off-white solid; **Mp** (°C): 99.5

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.43 (t, 3H, J = 7.0 Hz, CH<sub>3</sub>), 4.04 (q, 2H, J = 7.0 Hz, CH<sub>2</sub>), 4.25 (broad s, 1H, OH), 4.79 (s, 2H, OCH<sub>2</sub>), 7.12 (dd, 1H, J = 2.5 and 9.0 Hz, ArH), 7.26 (d, 1H, J = 2.5 Hz, ArH), 7.57 (d, 1H, J = 9.0 Hz, ArH), 7.97 (s, 1H, ArH), 8.67 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.6, 62.4, 63.7, 107.2, 119.9, 123.0, 128.6, 131.8, 133.9, 148.9, 150.0, 160.0.

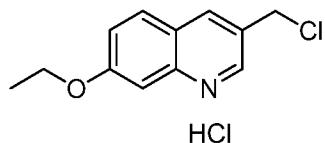
**MS-ESI** m/z (% rel. Int.): 204 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 25 186000482), detection UV 254 nm, RT = 3.62 min.

**3-(Chloromethyl)-7-ethoxyquinoline hydrochloride CCH 29190**

To a solution of (7-ethoxyquinolin-3-yl)methanol **MDE 32072** (88 mg, 433 μmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C under N<sub>2</sub> in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (0.64 mL, 8.82 mmol) and the mixture was stirred for 30 min at 0°C then for 2 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20

5 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-7-ethoxyquinoline hydrochloride **CCH 29190** as a brown solid (113 mg, > 100% yield).



5 **CCH 29190**

**MW:** 258.14; **Yield:** quant.; **Brown solid;** **Mp (°C):** 235.6

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.53 (t, 3H, J = 7.0 Hz, CH<sub>3</sub>), 4.35 (q, 2H, J = 7.0 Hz, CH<sub>2</sub>), 5.03 (s, 2H, CH<sub>2</sub>), 7.55-7.61 (m, 2H, 2xArH), 8.25 (d, 1H, J = 9.1 Hz, ArH), 9.15 (s, 1H, ArH), 9.20 (s, 1H, ArH).

10 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.7, 42.4, 66.7, 100.3, 125.3, 126.1, 131.6, 132.2, 141.4, 144.7, 147.3, 166.4.

**MS-ESI** m/z (% rel. Int.): 222 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 224 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 35).

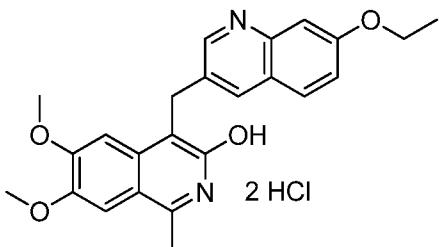
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.15 min.

15

4-((7-Ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **30**

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (112 mg, 511 μmol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.48 mL, 0.96 mmol) at RT followed by **CCH 29190** (110 mg, 426 μmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with EtOAc (50 mL). The organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic phases were washed with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) gave 47 mg of 4-((7-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol. The free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of 0.09 M HCl in MeOH (4 mL) and the solution was stirred for 5 min at RT, and concentrated at 40°C under vacuum to afford 4-((7-ethoxyquinolin-3-

yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **30** as a yellow solid (56 mg, 28% yield).

**30**

5 **MW:** 477.38; **Yield:** 28%; **Yellow solid;** **Mp** (°C): 242.6 (dec.).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.51 (t, 3H, *J* = 6.6 Hz, CH<sub>3</sub>), 3.01 (s, 3H, CH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 4.30 (q, 2H, *J* = 6.6 Hz, CH<sub>2</sub>), 4.76 (s, 2H, CH<sub>2</sub>), 7.17 (s, 1H, ArH), 7.46-7.53 (m, 3H, 3xArH), 8.09 (d, 1H, *J* = 8.4 Hz, ArH), 8.78 (s, 1H, ArH), 9.00 (s, 1H, ArH).

10 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.6, 17.4, 28.2, 56.8, 57.3, 66.5, 99.9, 102.4, 106.2, 112.2, 119.5, 125.0, 126.3, 131.7, 132.4, 140.4, 140.8, 144.5, 146.1, 151.1, 151.7, 159.6, 165.7.

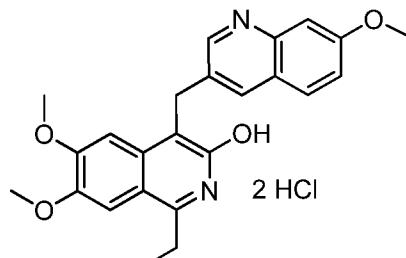
**MS-ESI** m/z (rel.int.): 405 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 3.81 min, peak area 98.0%.

Preparation of 1-ethyl-6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **31**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (121 mg, 20 519 μmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.57 mL, 1.14 mmol) at RT followed by 3-(chloromethyl)-7-methoxyquinoline hydrochloride **MDE 32012** (136 mg, 557 μmol) and the mixture was stirred at 150°C for 2 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and H<sub>2</sub>O (10 mL). The 25 organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The combined organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) gave 34 mg of 1-ethyl-6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol. This free

base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (3.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 1-ethyl-6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **31** as a brown solid (40 mg, 16% yield).

**31**

**MW:** 477.38; **Yield:** 16%; **Brown solid;** **Mp (°C):** 247.9 (dec.).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.49 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 3.40 (q, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 10 3.95 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 4.76 (s, 2H, CH<sub>2</sub>), 7.20 (s, 1H, ArH), 7.50-7.55 (m, 3H, 3xArH), 8.11 (d, 1H, *J* = 9.1 Hz, ArH), 8.81 (s, 1H, ArH), 9.04 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.6, 25.3, 28.1, 56.9, 57.1, 57.4, 99.4, 102.5, 105.5, 112.3, 118.6, 124.8, 126.2, 131.5, 132.2, 140.6, 140.8, 144.2, 146.1, 151.9, 155.6, 159.5, 15 166.4, (1xC not observed).

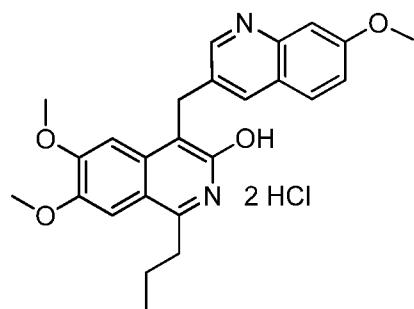
**MS-ESI** m/z (rel.int.): 405 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.47 min, peak area 95.2%.

20 Preparation of 6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **32**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **RBO 35142** (117 mg, 473 μmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.52 mL, 1.04 mmol) at RT followed by 3-25 (chloromethyl)-7-methoxyquinoline hydrochloride **MDE 32012** (124 mg, 508 μmol) and the mixture was stirred at 150°C for 2 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and H<sub>2</sub>O (10 mL). The organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The combined organic phase was washed with brine (10 mL), dried

over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 100:0$  to  $95:5$ ) gave 26 mg of 6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol. This free base was dissolved in  $\text{MeOH}$  (2 mL) in a 10 mL round-bottomed flask equipped with 5 a magnetic stirrer before addition of a 0.09 M  $\text{HCl}$  solution in  $\text{MeOH}$  (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **32** as a brown solid (30 mg, 13% yield).



10

**32**

**MW:** 491.41; **Yield:** 13%; **Brown solid;** **Mp (°C):** 253.5 (dec.).

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.13 (t, 3H,  $J = 6.7$  Hz,  $\text{CH}_3$ ), 1.90-1.96 (m, 2H,  $\text{CH}_2$ ), 3.36-3.40 (m, 2H,  $\text{CH}_2$ ), 3.96 (s, 3H,  $\text{OCH}_3$ ), 4.02 (s, 3H,  $\text{OCH}_3$ ), 4.07 (s, 3H,  $\text{OCH}_3$ ), 4.80 (s, 2H,  $\text{CH}_2$ ), 7.22 (s, 1H, ArH), 7.52-7.54 (m, 3H, 3xArH), 8.12 (d, 1H,  $J = 8.8$  Hz, 15 ArH), 8.81 (s, 1H, ArH), 9.05 (s, 1H, ArH).

**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 14.2, 24.5, 28.1, 33.5, 56.9, 57.1, 57.4, 99.3, 102.6, 105.8, 112.3, 119.3, 124.8, 126.2, 131.5, 132.0, 140.6, 140.8, 144.3, 146.1, 151.9, 152.0, 154.6, 159.6, 166.4.

**MS-ESI** m/z (rel.int.): 419 ( $[\text{MH}]^+$ , 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.82 min, peak area 95.1%.

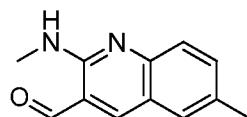
Preparation of 6,7-dimethoxy-1-methyl-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **33**

25

6-Methyl-2-(methylamino)quinoline-3-carbaldehyde **MDE 32036**

To a solution of 2-chloro-6-methylquinoline-3-carboxaldehyde (400 mg, 1.95 mmol) in 1,4-dioxan (10 mL) in a 20 mL microwave vial equipped with a magnetic

stirrer was added methylamine (40 wt% in H<sub>2</sub>O, 1.68 mL, 19.5 mmol) and the reaction mixture was stirred for 10 min at 120°C under microwave irradiation then for an additional 45 min at 160°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl=1:1 (50 mL) and stirred for 1 h at RT. The volatiles were removed at 40°C under vacuum and the residue was neutralised with saturated NaHCO<sub>3</sub> aqueous solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 91:9) to give, after evaporation and drying, 6-methyl-2-(methylamino)quinoline-3-carbaldehyde **MDE 32036** as a yellow solid (330 mg, 85% yield).



**MDE 32036**

15 **MW:** 200.24; **Yield:** 85%; **Yellow solid;** **Mp** (°C): 96.9

**R<sub>f</sub>:** 0.25 (cyclohexane:EtOAc = 91:9).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.43 (s, 3H, CH<sub>3</sub>), 3.16 (d, 3H, J = 4.9 Hz, NCH<sub>3</sub>), 7.40-7.43 (m, 1H, ArH), 7.48 (dd, 1H, J = 4.9 & 8.6 Hz, ArH), 7.61 (d, 1H, J = 8.6 Hz, ArH), 7.95-7.99 (broad m, 1H, NH), 8.12 (s, 1H, ArH), 9.95 (s, 1H, HC=O).

20 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 21.0, 27.6, 117.4, 121.7, 126.3, 128.0, 131.9, 135.8, 147.9, 149.7, 155.1, 193.1.

**MS-ESI** m/z (% rel. Int.): 201 ([MH]<sup>+</sup>, 100).

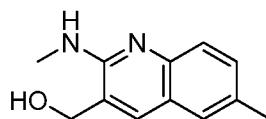
**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.09 min.

25

(6-Methyl-2-(methylamino)quinolin-3-yl)methanol **MDE 32060**

To a stirred solution of 6-methyl-2-(methylamino)quinoline-3-carbaldehyde **MDE 32036** (134 mg, 0.67 mmol) in THF (10 mL) at 0°C in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (25 mg, 0.66 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 6 N aq. HCl solution (0.45 mL). After stirring for 15 min at +4°C, the mixture was basified with a 2 N aq. NaOH solution (1.35 mL). THF was then

removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 50:50) provided, after evaporation and drying, 6-methyl-2-(methylamino)quinolin-3-yl)methanol **MDE32060** as a white solid (73 mg, 55% yield).

**MDE 32060**

**MW:** 202.25; **Yield:** 55%; **White solid;** **Mp (°C):** 169.8

10 **<sup>1</sup>H-NMR** (DMSO d<sub>6</sub>, δ): 2.38 (s, 3H, CH<sub>3</sub>), 2.94 (d, 3H, J = 4.7 Hz, NCH<sub>3</sub>), 4.47-4.49 (m, 2H, CH<sub>2</sub>OH), 5.37 (t, 1H, J = 5.4 Hz, CH<sub>2</sub>OH), 6.22-6.24 (broad m, 1H, NHCH<sub>3</sub>), 7.28 (dd, 1H, J = 2.0 and 8.4 Hz, ArH), 7.40-7.42 (m, 1H, ArH), 7.46 (d, 1H, J = 8.4 Hz, ArH), 7.74 (s, 1H, ArH).

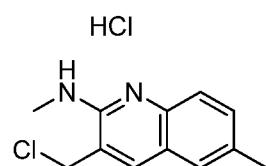
15 **<sup>13</sup>C-NMR** (DMSO d<sub>6</sub>, δ): 20.7, 28.0, 59.9, 122.6, 124.4, 125.2, 126.3, 129.9, 130.2, 131.9, 145.2, 155.0.

**MS-ESI** m/z (% rel. Int.): 203 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.21 min.

20 3-(Chloromethyl)-N,6-dimethylquinolin-2-amine hydrochloride **MDE 32062**

To a solution of 6-methyl-2-(methylamino)quinolin-3-yl)methanol **MDE32060** (56 mg, 0.28 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C under N<sub>2</sub> in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (0.40 mL, 5.51 mmol) and the mixture was stirred for 2 days at RT. The volatiles were then 25 removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-N,6-dimethylquinolin-2-amine hydrochloride **MDE 32062** as an off-white solid (56 mg, 78% yield).



**MDE 32062**

**MW:** 257.16; **Yield:** 78%; Off-white solid; **Mp** (°C): 92.4

**<sup>1</sup>H-NMR** (DMSO d<sub>6</sub>, δ): 2.44 (s, 3H, CH<sub>3</sub>), 3.23 (d, 3H, J = 4.7 Hz, NCH<sub>3</sub>), 3.45-3.56 (broad m, NH), 4.98 (s, 2H, CH<sub>2</sub>), 7.63 (dd, 1H, J = 1.5 & 8.5 Hz, ArH), 7.67-7.71 (m,

5 1H, ArH), 8.11 (d, 1H, J = 8.5 Hz, ArH), 8.45 (s, 1H, ArH), 9.09-9.32 (broad s, 1H, NH).

**<sup>13</sup>C-NMR** (DMSO d<sub>6</sub>, δ): 20.5, 30.1, 41.3, 117.9, 120.5, 122.1, 127.8, 134.1, 134.7, 141.8, 151.0, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 221 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 223 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 32).

10 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 5.51 min.

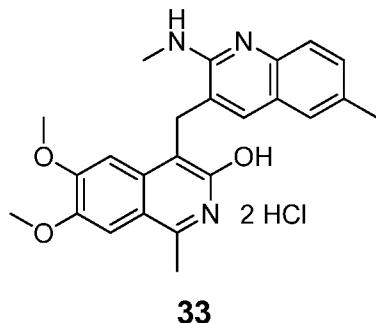
6,7-Dimethoxy-1-methyl-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride 33

15 To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (40 mg, 182 μmol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 2 N aq. KOH solution (0.17 mL, 0.34 mmol) at RT followed by 3-(chloromethyl)-N,6-dimethylquinolin-2-amine hydrochloride **MDE 32062** (39 mg, 152 μmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation.

20 After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before to be extracted with EtOAc (50 mL). The organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic phases were washed with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0

25 to 94:6 to 90:10) gave 12 mg of 6,7-dimethoxy-1-methyl-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (1.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-

30 dimethoxy-1-methyl-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **33** as a brown solid (14 mg, 19% yield).



**MW:** 476.40; **Yield:** 19%; Brown solid; **Mp** (°C) > 250 (dec.).

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 90:10).

5 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 2.39 (s, 3H, CH<sub>3</sub>), 3.06 (s, 3H, CH<sub>3</sub>), 3.39 (s, 3H, CH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 4.33 (s, 2H, CH<sub>2</sub>), 7.08 (s, 1H, ArH), 7.43-7.58 (m, 4H, 4xArH), 7.87 (d, 1H, J = 8.5 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.5, 20.9, 27.0, 30.0, 56.9, 57.3, 102.3, 106.2, 118.1, 119.4, 122.6, 124.1, 128.8, 134.7, 134.8, 137.1, 139.3, 141.1, 151.1, 151.7, 154.2, 159.7

10 (2xC not observed).

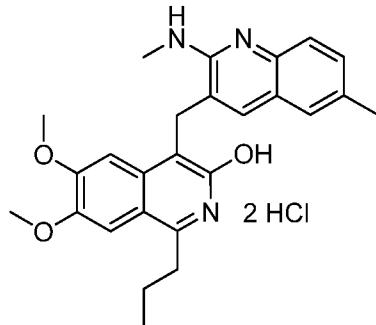
**MS-ESI** m/z (rel.int.): 404 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 4.01 min, peak area 96.6%.

15 Preparation of 6,7-dimethoxy-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride 34

To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (250 mg, 1 mmol) in toluene (15 mL) in a 20 mL microwave vial was added a 2 N KOH solution (1 mL, 2 mmol) following by 3-(chloromethyl)-N,6-dimethylquinolin-2-amine hydrochloride **MDE 32062** (352 mg, 1.2 mmol). The reaction mixture was stirred at 160°C for 1.5 h under microwave irradiation then cooled to RT. The volatiles were removed under vacuum and the residue was taken back in a mixture of CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (50 mL). The organic layer was washed with water (3x20mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to give yellow solid that was purified by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 90:10) to give, after evaporation and drying, 6,7-dimethoxy-4-(6-methyl-2-methylamino-quinolin-3-ylmethyl)-1-propyl-isoquinolin-3-ol (26 mg). This free base was dissolved in MeOH (5 mL) and a 0.19 N HCl solution in MeOH (600 μL, 0.11 mmol) was slowly added. The reaction mixture was stirred at 4°C for 15 min. After evaporation of the solvent and

drying under vacuum pump over  $P_2O_5$ , 6,7-dimethoxy-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol hydrochloride **34** was obtained as a yellow solid (28.7 mg, 5% yield).

**34**

**MW:** 504.45; **Yield:** 5%; **Yellow Solid;** **Mp (°C):** 264.2°C

**R<sub>f</sub>:** 0.20 ( $CH_2Cl_2:MeOH = 9:1$ , free base).

**<sup>1</sup>H-NMR** ( $CD_3OD$ ,  $\delta$ ): 1.15 (t, 3H,  $J = 6$  Hz,  $CH_3$ ), 2.00 (m, 2H,  $CH_2$ ), 2.40 (s, 3H,  $CH_3$ ), 3.30 (s, 2H,  $CH_2$ ), 3.40 (s, 3H,  $NCH_3$ ), 3.93 (s, 6H,  $O-CH_3$ ), 4.04 (s, 3H,  $O-CH_3$ ), 4.36 (s, 2H,  $CH_2$ ), 7.10 (s, 1H, ArH), 7.33-7.78 (m, 2H, ArH), 7.53-7.59 (m, 2H, ArH), 7.92 (d, 1H,  $J = 9$  Hz, ArH), 8.04 (s, 1H, ArH).

**<sup>13</sup>H-NMR** ( $CD_3OD$ ,  $\delta$ ): 14.3, 21.0, 24.7, 27.1, 30.2, 33.7, 57.0, 57.5, 102.7, 106.0, 109.9, 118.1, 119.3, 122.6, 123.8, 128.8, 134.7, 134.8, 137.1, 139.1, 141.6, 152.1, 152.6, 154.2, 155.0, 159.9.

**MS-ESI m/z (% rel. Int.):** 432 ( $[MH]^+$ , 100).

**HPLC:** Method A, XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 4.14 min, peak area 99.0%.

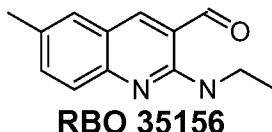
Preparation of 4-((2-(ethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-

20 propylisoquinolin-3-ol dihydrochloride 35

2-(Ethylamino)-6-methylquinoline-3-carbaldehyde RBO 35156

To a solution of 2-chloro-6-methylquinoline-3-carbaldehyde (1.0 g, 4.86 mmol) in dioxane (10 mL) in a 20 mL microwave vial was added ethylamine (4 mL, 70% in water) and the resulting mixture was heated at 160°C under microwave irradiation for 25 min. After cooling to RT, the mixture was poured into a solution  $THF:1\text{ N HCl} = 1:1$  (25 mL) and stirred for 25 min at RT. The mixture was neutralized until pH = 7 with a saturated solution of  $NaHCO_3$  and extracted with  $CH_2Cl_2$  (50 mL). The organic

layer was washed with  $H_2O$  (3x30mL), brine (30 mL), dried over  $Na_2SO_4$ , filtered and evaporated to give 2-(ethylamino)-6-methylquinoline-3-carbaldehyde **RBO 35156** as a yellow solid (566 mg, 54% yield).



**MW:** 214.27; **Yield:** 54%; Yellow Solid.

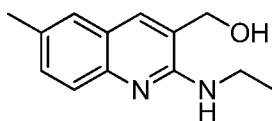
**$^1H$ -NMR** ( $CDCl_3$ ,  $\delta$ ): 1.33 (t, 3H,  $J$  = 7.5 Hz,  $CH_3$ ), 2.45 (s, 3H,  $CH_3$ ), 3.67 (m, 2H,  $CH_2CH_3$ ), 6.93 (s, 1H, ArH), 7.43 (s, 1H, ArH), 7.48 (d, 1H,  $J$  = 9.0 Hz, ArH), 7.58 (d, 1H,  $J$  = 9.0 Hz, ArH), 8.13 (s, 1H, ArH), 9.95 (s, 1H,  $HC=O$ ).

10

(2-(Ethylamino)-6-methylquinolin-3-yl)methanol RBO 35160

To a solution of 2-(ethylamino)-6-methylquinoline-3-carbaldehyde **RBO 35156** (500 mg, 2.33 mmol) in a mixture  $EtOH:THF$  = 7:3 (35 mL) at 0°C was added  $NaBH_4$  (88 mg, 2.33 mmol) by small portions. The reaction mixture was stirred overnight at 15 RT, cooled at 0°C and treated by a 6 N HCl solution (6 mL). The solution was then neutralized with 2 N NaOH solution until pH = 7 and concentrated under vacuum at 45°C. The crude residue was diluted in  $CH_2Cl_2$  (50 mL), washed with brine (3×50 mL), dried over  $Na_2SO_4$ , filtered to give, after evaporation, (2-(ethylamino)-6-methylquinolin-3-yl)methanol **RBO 35160** as a yellow solid (460 mg, 91% yield).

20



**RBO 35160**

**MW:** 216.29; **Yield:** 91%; Yellow Solid.

**$^1H$ -NMR** ( $CDCl_3$ ,  $\delta$ ): 1.29 (t, 3H,  $J$  = 7.5 Hz,  $CH_3$ ), 2.45 (s, 3H,  $CH_3$ ), 3.57 (m, 2H,  $CH_2CH_3$ ), 4.46 (s, 2H,  $CH_2OH$ ), 6.86 (s, 1H, ArH), 7.13 (s, 1H, ArH), 7.35 (d, 1H,  $J$  = 6.0 Hz, ArH), 7.57 (d, 1H,  $J$  = 6.0 Hz, ArH).

**MS-ESI** m/z (rel.int.) : 217 ( $[MH]^+$ , 100).

**HPLC:** Method A, XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254nm, RT = 3.28 min, peak area 99.9%.

30 3-(Chloromethyl)-N-ethyl-6-methylquinolin-2-amine hydrochloride RBO 35162

To a solution of (2-(ethylamino)-6-methylquinolin-3-yl)methanol **RBO 35160** (460 mg, 2.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) in a round-bottomed flask equipped with a magnetic stirrer was added thionyl chloride (1.55 mL, 21.3 mmol). The mixture was stirred for 2 h at RT, evaporated under vacuum at 45°C, coevaporated twice with 5 CH<sub>2</sub>Cl<sub>2</sub> to remove SOCl<sub>2</sub> to afford 3-(chloromethyl)-N-ethyl-6-methylquinolin-2-amine hydrochloride **RBO 35162** as a yellow solid (520 mg, 90% yield).

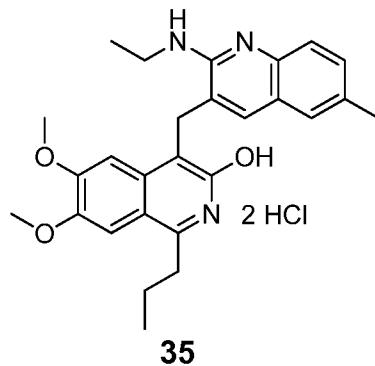


**MW:** 301.17; **Yield:** 90%; **Mp (°C):** 253.5

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.43 (t, 3H,  $J$  = 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>), 2.50 (s, 3H, CH<sub>3</sub>), 3.73 (q, 2H,  $J$  = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>), 4.89 (s, 2H, CH<sub>2</sub>), 7.67 (m, 2H, 2xArH), 7.86 (d, 1H  $J$  = 6 Hz, ArH), 8.39 (s, 1H, ArH).

4-((2-(Ethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 35

15 To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 34142** (250 mg, 1.0 mmol) in toluene (15 mL) in a 20 mL microwave vial with magnetic stirrer was added a 2 N LiOH solution (1mL, 2.0 mmol) followed with 3-(chloromethyl)-N-ethyl-6-methylquinolin-2-amine hydrochloride **RBO 35162** (271.2 mg, 1.0 mmol). The mixture was heated for 1.5 h at 150°C under microwave irradiation. The vial was 20 cooled to RT and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The organic layer was washed with H<sub>2</sub>O (3x30mL), brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered to give, after evaporation under reduced pressure, a yellow solid. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:7 N NH<sub>3</sub> solution in MeOH = 95:5) gave, after evaporation, 4-(6-ethylamino-[1,3]dioxolo[4,5-g]quinolin-7-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol. This free base was treated by a 0.49 N HCl solution in MeOH (5 mL) for 5 min at RT to give, after evaporation and drying, 4-((2-(ethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride as yellow solid **35** (21.5 mg, 4% yield).



**MW:** 518.48; **Yield:** 4%; **Yellow Solid;** **Mp (°C):** 252.6°C

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.13 (t, 3H, *J* = 9 Hz, CH<sub>3</sub>), 1.53 (t, 3H *J* = 7.5 Hz, CH<sub>3</sub>), 1.93

5 (m, 2H, CH<sub>2</sub>), 2.41 (s, 3H, CH<sub>3</sub>), 3.33 (shoulder behind MeOD, CH<sub>2</sub>N), 3.78 (q, 2H, *J* = 9 Hz, CH<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.35 (s, 2H, OCH<sub>2</sub>O), 7.10 (s, 1H, ArH), 7.47 (s, 2H, 2xArH), 7.57 (d, 1H, *J* = 9Hz, ArH), 7.70 (broad s, 1H, ArH), 7.85 (d, 1H, *J* = 9 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 13.8, 14.1, 20.9, 24.6, 27.5, 33.5, 39.1, 56.7, 57.2, 102.0,

10 105.7, 110.0, 118.0 (2xC), 122.5, 124.6, 128.7, 134.7 (2xC), 137.1, 140.0, 141.7, 151.3, 153.2, 159.4, (2xC not observed).

MS-ESI m/z (rel.int.) : 446 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model #

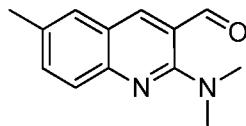
186003113), detection UV 254 nm, RT = 4.58 min, peak area 95.0%.

15

Preparation of 4-((2-(dimethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 36

**2-(Dimethylamino)-6-methylquinoline-3-carbaldehyde RBO 35148**

20 To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.0 g, 4.86 mmol) in dioxane (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added dimethylamine (40% in water, 6.1 mL, 48.6 mmol) and the reaction mixture was stirred for 45 min at 160°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil 25 was taken back in CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The organic layer was washed with water (3x20mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give 2-(dimethylamino)-6-methylquinoline-3-carbaldehyde **RBO 35148** as a yellow oil (988 mg, 95% yield).

**RBO 35148**

**MW:** 214.26; **Yield:** 95%; Yellow oil.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.5 (s, 3H, CH<sub>3</sub>), 3.20 (s, 6H, 2xNCH<sub>3</sub>), 7.50 (m, 1H, 2xArH),

5 7.69 (d, 1H, J = 10 Hz, ArH), 8.35 (s, 1H, ArH), 10.15 (s, 1H, HC=O).

**MS-ESI** m/z (% rel. Int.): 215 ([MH]<sup>+</sup>, 100).

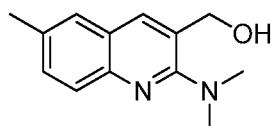
**HPLC:** Method A, XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 3.33 min, peak area 98 %.

10 **(2-(Dimethylamino)-6-methylquinolin-3-yl)methanol RBO 40152**

To a stirred solution of 2-(dimethylamino)-6-methylquinoline-3-carbaldehyde

**RBO 35148** (988 mg, 4.61 mmol) in a mixture EtOH:THF = 50 mL:20 mL in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (174 mg, 4.61 mmol) and the mixture was stirred overnight at RT, cooled in an ice bath

15 and treated by a 6 N aq. HCl solution (2 mL). After stirring for 1 h at 4°C, the mixture was brought to pH = 9 with a 2N aq. NaOH solution (6 mL). Volatiles were removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic layer was washed with water (3x20mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to give (2-(dimethylamino)-6-20 methylquinolin-3-yl)methanol **RBO 40152** as yellow oil (900 mg, 90% yield).

**RBO 40152**

**MW:** 216.29; **Yield:** 90%; Yellow oil.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.48 (s, 3H, CH<sub>3</sub>), 2.94 (s, 6H, 2xNCH<sub>3</sub>), 4.85 (s, 2H, CH<sub>2</sub>), 7.44

25 (m, 2H, 2xArH), 7.76 (d, 1H, J = 9 Hz, ArH), 7.88 (s, 1H, ArH), OH not observed.

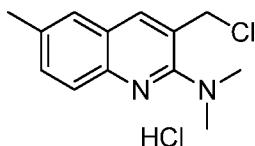
**MS-ESI** m/z (% rel. Int.): 217.0 ([MH]<sup>+</sup>, 100).

**HPLC:** Method A, XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, RT = 3.18 min, peak area 98 %.

**3-(chloromethyl)-N,N,6-trimethylquinolin-2-amine hydrochloride RBO 35154**

To a stirred solution of 2-(dimethylamino)-6-methylquinolin-3-yl)methanol **RBO 40152** (900 mg, 4.16 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (30 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (3 mL, 42 mmol).

5 The mixture was stirred for 3 h at RT then concentrated to dryness at 40°C under vacuum. The residue was coevaporated twice with  $\text{CH}_2\text{Cl}_2$  (20 mL) at 40°C under vacuum to give of 3-(chloromethyl)-N,N,6-trimethylquinolin-2-amine hydrochloride **RBO 35154** as a yellow solid (558 mg, 50% yield).



10

**RBO 35154**

**MW:** 271.19; **Yield:** 50 %; **Yellow solid.**

**$^1\text{H-NMR}$  (MeOD,  $\delta$ ):** 2.52 (s, 3H,  $\text{CH}_3$ ), 3.53 (s, 6H, 2x $\text{OCH}_3$ ), 5.00 (s, 2H,  $\text{CH}_2$ ), 7.73 (m, 2H, 2xArH), 7.90 (d, 1H,  $J$  = 9 Hz, ArH), 8.58 (s, 1H, ArH).

**MS-ESI m/z (%) rel. Int.):** 231.1 ( $[\text{MH}]^+$ , 100).

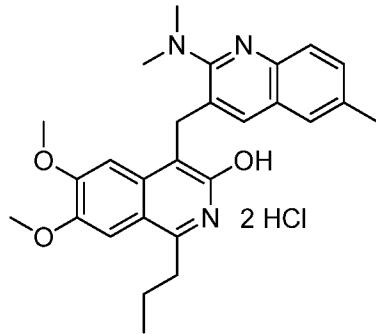
15 **HPLC:** Method A, XTerra<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 3.43 min, peak area 65%. [RT = 3.11 min, peak area 35% (m/z = 217.1)]

**4-((2-(Dimethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-**

20 **propylisoquinolin-3-ol dihydrochloride 36**

To a stirred solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (173 mg, 0.638 mmol) in toluene (10 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added 3-(chloromethyl)-N,N,6-trimethylquinolin-2-amine hydrochloride **RBO 35154** (158 mg, 0.638 mmol) and the mixture was stirred at 150°C for 1.5 h. After cooling to RT, the volatiles were removed and the residue was taken back in  $\text{CH}_2\text{Cl}_2$  (20mL). This solution was washed with water (3x10mL), brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2$ :7 N  $\text{NH}_3$  solution in  $\text{MeOH}$  = 100:0 to 95:5) gave after evaporation 20.2 mg of 4-((2-(dimethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol

as a yellow solid. The free base was dissolved in MeOH (2mL) and converted into salt by addition of a 0.19 M HCl solution in MeOH (0.525 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-(2-dimethylamino-6-methyl-quinolin-3-ylmethyl)-6,7-dimethoxy-1-propyl-soquinolin-3-ol dihydrochloride **36** as a yellow solid (22.2 mg, 6.7% yield).

**36**

**MW:** 504.45; **Yield:** 6.7%; **Yellow solid;** **Mp** (°C): 68.5

**1H-NMR** (CD<sub>3</sub>OD, δ): 1.10 (t, 3H, *J* = 9 Hz, CH<sub>3</sub>), 1.91 (q, 2H *J* = 9 Hz, CH<sub>2</sub>), 2.35 (s, 3H, CH<sub>3</sub>), 3.35 (m, 2H, CH<sub>2</sub>), 3.59 (s, 6H, 2xNCH<sub>3</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 4.60 (s, 2H, CH<sub>2</sub>), 6.99 (s, 1H, ArH), 7.40 (s, 1H, ArH), 7.52 (s, 1H, ArH), 7.61 (m, 2H, 2xArH), 7.90 (d, 1H, *J* = 9 Hz, ArH).

**13C-NMR** (CD<sub>3</sub>OD, δ): 14.2, 21.0, 24.7, 29.5, 33.6, 43.4 (2xC), 56.9, 57.2, 102.7, 106.0, 112.3, 118.5 (2xC), 119.6, 123.8, 126.9, 128.5, 131.5, 135.8, 138.2, 141.2, 143.8, 152.2, 155.2, 157.4, 159.9, (2xC not observed).

**MS-ESI** m/z (% rel. Int.): 446.3 ([MH]<sup>+</sup>, 100).

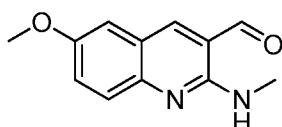
**HPLC:** Method A, XTerra<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186000482), detection UV 254 nm, detection UV 254 nm, RT = 4.27 min, peak area 97%.

**20** Preparation of 6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methyl-isouquinolin-3-ol dihydrochloride **37**

6-Methoxy-2-(methylamino)quinoline-3-carbaldehyde **SLA 28150**

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.50 g, 6.77 mmol) in 1,4-dioxan (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added methylamine (40 wt% solution in water, 2.10 mL, 24.3 mmol) and the reaction mixture was stirred for 6 h at 160°C under microwave

irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl=1:1 (50 mL) and stirred for 1 h at RT. THF was removed at 40°C under vacuum and the residue was then neutralised with a saturated NaHCO<sub>3</sub> aqueous solution before to be extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum, to give 6-methoxy-2-(methylamino)quinoline-3-carbaldehyde **SLA 28150** as an orange oil (1.44 g, 98% yield).



10

**SLA 28150**

**MW:** 216.24; **Yield:** 98%; Orange oil.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.15 (d, 3H, J = 4.9 Hz, NCH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 6.97 (d, 1H, J = 2.9 Hz, ArH), 7.33 (dd, 1H, J = 2.9 & 9.2 Hz, ArH), 7.64 (d, 1H, J = 9.2 Hz, ArH), 7.84 (broad s, 1H, NH), 8.14 (s, 1H, ArH), 9.97 (s, 1H, HC=O).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 27.6, 55.5, 106.8, 117.4, 121.9, 125.9, 127.9, 147.1, 147.2, 154.5, 154.8, 193.1.

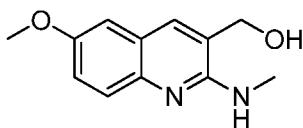
**MS-ESI** m/z (% rel. Int.): 217.1 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.99 min.

20

((6-Methoxy-2-(methylamino)quinolin-3-yl)methanol **SLA 28152**)

To a stirred solution of 6-methoxy-2-(methylamino) quinoline-3-carbaldehyde **SLA 28150** (1.006 g, 4.65 mmol) in THF (80 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added sodium borohydride NaBH<sub>4</sub> (0.176 g, 4.65 mmol) and the mixture was stirred for 4 h at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 min at RT, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to give (6-methoxy-2-(methylamino)quinolin-3-yl)methanol **SLA 28152** as an orange oil (0.907 g, 89% yield).

**SLA 28152**

**MW:** 218.25; **Yield:** 89%; Orange oil.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.09 (s, 3H, NCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 4.64 (s, 2H, CH<sub>2</sub>), 6.97

5 (d, 1H, J = 2.9 Hz, ArH), 7.19 (dd, 1H, J = 2.9 Hz & 9.1 Hz, ArH), 7.62 (s, 1H, ArH), 7.69 (d, 1H, J = 9.1 Hz, ArH), OH & NH not seen.

**<sup>13</sup>C-NMR** (DMSO, δ): 28.1, 55.2, 59.9, 106.8, 119.2, 123.1, 124.7, 126.7, 131.7, 142.2, 153.8, 154.2.

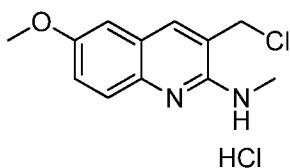
**MS-ESI** m/z (% rel. Int.): 219.1 ([MH]<sup>+</sup>, 100).

10 **HPLC:** Method A (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 5.01 min.

**3-(Chloromethyl)-6-methoxy-N-methylquinolin-2-amine hydrochloride SLA 28154**

To a stirred solution of (6-methoxy-2-(methylamino)quinolin-3-yl)methanol

15 **SLA 28152** (0.906 g, 4.15 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (100 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (6.03 mL, 83.1 mmol). The mixture was stirred for 1 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-6-methoxy-N-methylquinolin-2-amine hydrochloride **SLA 28154** (1.20 g, >100%) as a yellow solid.

**SLA 28154**

**MW:** 273.16; **Yield:** Quantitative; Yellow solid.

25 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, exchange with CD<sub>3</sub>OD, δ): 3.37 (s, 3H, NCH<sub>3</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 4.80 (s, 2H, CH<sub>2</sub>), 7.09 (d, 1H, J = 2.7 Hz, ArH), 7.35 (dd, 1H, J = 2.7 & 9.2 Hz, ArH), 8.10 (s, 1H, ArH), 8.32 (d, 1H, J = 9.2 Hz, ArH).

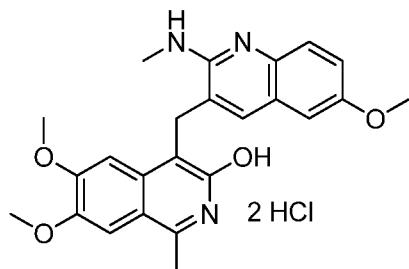
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, exchange with CD<sub>3</sub>OD, δ): 30.3, 40.9, 55.7, 108.4, 119.6, 121.6, 122.0, 123.2, 131.1, 141.3, 150.5, 157.2.

**MS-ESI** m/z (% rel. Int.): 237.3 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 239.3 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 33).

**HPLC:** Method A (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 4.65 min.

5 **6,7-Dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride 37**

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (77 mg, 351  $\mu$ mol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.35 mL, 0.70 mmol) at RT followed by 3-10 (chloromethyl)-6-methoxy-N-methylquinolin-2-amine hydrochloride **SLA 28154** (90 mg, 350  $\mu$ mol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with H<sub>2</sub>O (10 mL) before extraction with EtOAc (50 mL). The organic phase was isolated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Both organic phases were washed 15 with brine (10 mL), combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6 to 90:10) gave 19 mg of 6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a 20 magnetic stirrer before addition of a 0.09 M HCl solution in MeOH (2 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **37** as a brown solid (22 mg, 13% yield).



25

**37**

**MW:** 492.39; **Yield:** 13%; Brown solid; **Mp** (°C) > 250(dec.).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.09 (s, 3H, CH<sub>3</sub>), 3.39 (s, 3H, CH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.07 (s, 3H, OCH<sub>3</sub>), 4.39 (s, 2H, CH<sub>2</sub>), 7.03 (s, 2H, 2xArH), 7.32 (d, 1H, *J* = 9.1 Hz, ArH), 7.40-7.44 (m, 2H, 2xArH), 7.98 (d, 1H, *J* = 9.1 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 17.5, 26.6, 30.0, 56.1, 56.8, 57.3, 101.7, 105.3, 109.0, 109.6, 118.7, 119.3, 122.8, 123.0, 123.7, 130.7, 138.7, 140.4, 149.8, 151.0, 152.6, 158.0, 159.0, (1xC not observed).

**MS-ESI** m/z (rel.int.): 420 ([MH]<sup>+</sup>, 100).

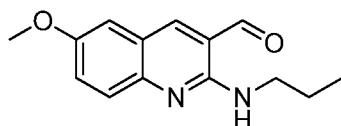
5 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.30 min, peak area 96.4%.

Preparation of 6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride 38

10

6-Methoxy-2-(propylamino)quinoline-3-carbaldehyde SLA 28172

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.50 g, 6.77 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added propan-1-amine (5.6 mL, 67.7 mmol) and the reaction mixture was 15 stirred for 1.5 h at 160°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl = 1:1 (50 mL) and stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with a saturated NaHCO<sub>3</sub> aqueous solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> 20 (100 mL). The organic phase was washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum to give 6-methoxy-2-(propylamino)quinoline-3-carbaldehyde **SLA 28172** as an orange solid (1.68 g, 99% yield).



25

**SLA 28172**

**MW:** 244.29; **Yield:** 99%; **Orange solid;** **Mp** (°C): 110.0

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 1.04 (t, 3H,  $J$  = 7.4 Hz, CH<sub>3</sub>), 1.66-1.77 (m, 2H, CH<sub>2</sub>), 3.56-3.62 (m, 2H, NHCH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 6.97 (d, 1H,  $J$  = 2.8 Hz, ArH), 7.33 (dd, 1H,  $J$  = 2.8 & 9.2 Hz, ArH), 7.60 (d, 1H,  $J$  = 9.2 Hz, ArH), 7.89 (broad s, 1H, NH), 8.12 (s, 30 1H, ArH), 9.97 (s, 1H, HC=O).

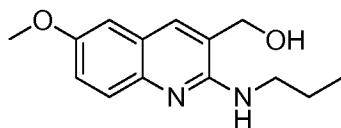
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 11.7, 22.6, 42.5, 55.5, 106.7, 117.2, 121.9, 125.9, 128.0, 147.2, 147.3, 154.0, 154.8, 193.2.

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.68 min.

5

(6-Methoxy-2-(propylamino)quinolin-3-yl)methanol **SLA 28174**

To a stirred solution of 6-methoxy-2-(propylamino)quinoline-3-carbaldehyde **SLA 28172** (1.565 g, 6.41 mmol) in THF (120 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added sodium borohydride NaBH<sub>4</sub> (0.242 g, 6.41 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 min at that temperature, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to give (6-methoxy-2-(propylamino)quinolin-3-yl)methanol **SLA 28174** as an orange solid (1.55 g, 98% yield).



**SLA 28174**

**MW:** 246.30; **Yield:** 98%; Orange solid; **Mp** (°C): 113.5

20 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 1.02 (t, 3H,  $J$  = 7.4 Hz, CH<sub>3</sub>), 1.21 (s, 1H, OH), 1.62-1.75 (m, 2H, CH<sub>2</sub>), 3.45-3.55 (m, 2H, NCH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 4.44 (s, 2H, OCH<sub>2</sub>), 5.74 (broad s, 1H, NH), 6.74 (d, 1H,  $J$  = 2.9 Hz, ArH), 6.80 (s, 1H, ArH), 7.19 (dd, 1H,  $J$  = 2.9 Hz & 9.1 Hz, ArH), 7.59 (d, 1H,  $J$  = 9.1 Hz, ArH).

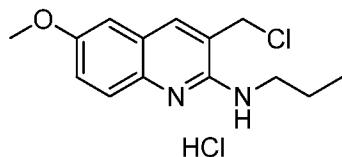
25 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 11.8, 22.8, 42.9, 55.5, 63.9, 106.7, 120.3, 122.1, 123.3, 126.7, 134.1, 142.9, 154.5, 155.3.

**MS-ESI** m/z (% rel. Int.): 245 ([MH]<sup>+</sup>, 100),

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 2.22 min.

30 3-(Chloromethyl)-6-methoxy-N-propylquinolin-2-amine hydrochloride **SLA 28178**

To a stirred solution of (6-methoxy-2-(propylamino)quinolin-3-yl)methanol **SLA 28174** (1.45 g, 5.88 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (115 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (8.53 mL, 118 mmol). The mixture was stirred for 2 h at RT then concentrated to dryness at 40°C under 5 vacuum. The residue was then taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times), to give 3-(chloromethyl)-6-methoxy-N-propylquinolin-2-amine hydrochloride **SLA 28178** (1.28 g, 82% yield) as a yellow solid.



10

**SLA 28178**

**MW:** 301.21; **Yield:** 82%; **Yellow solid;** **Mp (°C):** 118.8

**$^1\text{H-NMR}$  (CDCl<sub>3</sub>,  $\delta$ ):** 1.02 (t, 3H,  $J$  = 6.5Hz, CH<sub>3</sub>), 1.82-1.90 (m, 2H, CH<sub>2</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 4.04-4.08 (m, 2H, CH<sub>2</sub>), 5.02 (s, 2H, CH<sub>2</sub>), 6.98 (s, 1H, ArH), 7.24-7.28 (m, 1H, ArH), 8.02 (s, 1H, ArH), 8.17 (broad s, 1H, NH), 8.82 (d, 1H,  $J$  = 9.0Hz, ArH), 15 13.6 (broad s, 1H, NH).

**$^{13}\text{C-NMR}$  (CDCl<sub>3</sub>,  $\delta$ ):** 11.2, 21.9, 42.2, 45.7, 55.8, 108.0, 120.7, 121.6, 122.0, 123.1, 131.6, 141.4, 149.7, 157.1.

**MS-ESI m/z (% rel. Int.):** 265.0 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 267.0 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 34).

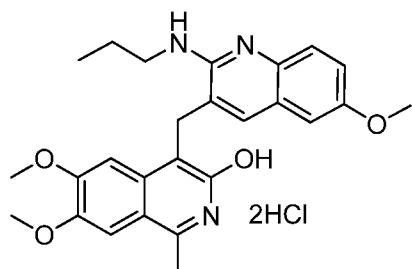
**HPLC:** **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, 20 Model # 186003113), detection UV 214 nm, RT = 4.10 min.

6,7-Dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-

25 propylisoquinolin-3-ol dihydrochloride 38

To a stirred solution of 3-(chloromethyl)-6-methoxy-N-propylquinolin-2-amine hydrochloride **SLA 28178** (308 mg, 1.16 mmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (255 mg, 1.16 mmol) followed by a 2.0 N aq. 30 LiOH solution (1.17 mL, 2.34 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with

CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL) and washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 92:8) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) 5 provided 37.6 mg of a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.70 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **38** as a 10 yellow solid (36.7 mg, 6% yield).

**38**

**MW:** 520.45; **Yield:** 6%; **Yellow solid;** **Mp (°C):** 148.3

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.14 (t, 3H, *J* = 7.2 Hz, CH<sub>3</sub>), 1.90-1.95 (m, 2H, CH<sub>2</sub>), 2.97 (s, 15 3H, CH<sub>3</sub>), 3.62-3.71 (m, 2H, CH<sub>2</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 6H, 2xOCH<sub>3</sub>), 4.36 (s, 2H, CH<sub>2</sub>), 7.08 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.34-7.38 (m, 2H, 2xArH), 7.87 (d, 1H, *J* = 9.0 Hz, ArH), 7.91 (s, 1H, ArH).

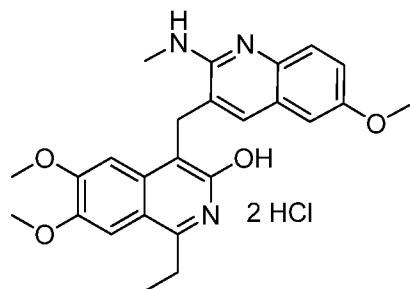
**MS-ESI** m/z (% rel. Int.): 448 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), X Bridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 20 186003113), detection UV 254 nm, RT = 4.26 min, peak area 96.2%.

Preparation of 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-ol **39**

To a stirred solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (200 25 mg, 0.86 mmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-methoxy-N-methylquinolin-2-amine hydrochloride **SLA 28154** (234 mg, 0.86 mmol) at RT followed by a 2 N aq. LiOH solution (0.86 mL, 1.72 mmol) and the mixture was stirred at 150°C for 1.5 h under

microwave irradiation. After cooling to RT, the mixture was diluted with a mixture CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) provided 21 mg of 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.40 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **39** as a yellow solid (20.0 mg, 5% yield).

**39**

**MW:** 506.42; **Yield:** 5%; **Yellow solid;** **Mp** (°C): 198.0

15 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.54 (t, 3H, *J* = 7.4 Hz, CH<sub>3</sub>), 3.38 (s, 3H, NCH<sub>3</sub>), 3.43 (q, 2H, *J* = 7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 4.34 (s, 2H, CH<sub>2</sub>), 7.08 (s, 1H, ArH), 7.13 (s, 1H, ArH), 7.32 (dd, 1H, *J* = 1.6 & 9.2 Hz, ArH), 7.53 (s, 1H, ArH), 7.56 (s, 1H, ArH), 7.92 (d, 1H, *J* = 9.2 Hz, ArH).

20 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.7, 25.5, 27.0, 30.0, 56.3, 56.9, 57.4, 102.6, 105.8, 109.5, 109.8, 118.7, 119.6, 123.3, 123.7, 124.3, 131.2, 138.9, 141.7, 152.1, 152.9, 153.5, 156.1, 158.7, 159.9.

**MS-ESI** m/z (% rel. Int.): 434 ([MH]<sup>+</sup>, 100).

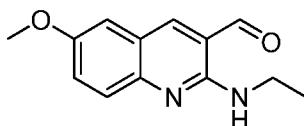
**HPLC:** Method B (10 min), X Bridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.11 min, peak area 95.8%.

25

Preparation of 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(ethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **40**

2-(Ethylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 28162**

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.51 g, 6.80 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added ethylamine (2 M in THF, 33.8 mL, 67.6 mmol) and the mixture was stirred at 160°C for 6 h under microwave irradiation. After cooling to RT, the volatiles 5 were removed under vacuum at 40°C and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl=1:1 (50 mL) and stirred for 15 min at RT. THF was removed at 40°C under vacuum and the residue was then neutralised with a saturated NaHCO<sub>3</sub> aqueous solution before to be extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and 10 concentrated at 40°C under vacuum to give 2-(ethylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 28162** as an orange oil (1.19 g, 76% yield).



**SLA 28162**

**MW:** 230.26; **Yield:** 76%; Orange oil.

15 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.33 (t, 3H, J = 7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.60-3.70 (m, 2H, CH<sub>2</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 6.96 (d, 1H, J = 2.9 Hz, ArH), 7.33 (dd, 1H, J = 2.9 & 9.2 Hz, ArH), 7.60 (d, 1H, J = 9.2 Hz, ArH), 7.82 (broad s, 1H, NH), 8.13 (s, 1H, ArH), 9.97 (s, 1H, HC=O).

20 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.8, 35.4, 55.5, 106.4, 117.2, 121.9, 125.8, 128.0, 147.1, 147.3, 153.8, 154.8, 193.1.

**MS-ESI** m/z (% rel. Int.): 231 ([MH]<sup>+</sup>, 100)

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.47 min.

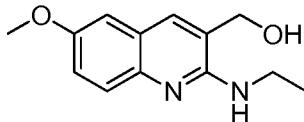
25

(2-(Ethylamino)-6-methoxyquinolin-3-yl)methanol **SLA 28164**

To a stirred solution of **SLA 28162** (1.495 g, 6.49 mmol) in THF (120 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added sodium 30 borohydride NaBH<sub>4</sub> (0.246 g, 6.50 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 min at RT, the mixture was basified to pH = 9 with a 2 N aq.

NaOH solution. THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under at 40°C under vacuum to give (2-(ethylamino)-6-methoxyquinolin-3-yl)methanol **SLA 28164** as an orange oil (1.17 g, 78% yield).

5

**SLA 28164**

**MW:** 232.28; **Yield:** 78%; Orange oil.

10 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.29 (t, 3H, J = 7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.30 (broad s, 1H, OH), 3.52-3.61 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 4.46 (s, 2H, CH<sub>2</sub>OH), 5.64 (broad s, 1H, NH), 6.74 (d, 1H, J = 2.8 Hz, ArH), 6.86 (s, 1H, ArH), 7.19 (dd, 1H, J = 2.8 & 9.1 Hz, ArH), 7.60 (d, 1H, J = 9.1 Hz, ArH).

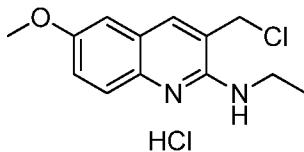
15 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.9, 35.9, 55.5, 63.9, 106.7, 120.4, 122.1, 123.0, 126.8, 134.2, 143.0, 154.6, 155.2.

**MS-ESI** m/z (% rel. Int.): 233.2 ([MH]<sup>+</sup>, 100).

15 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.33 min.

### 3-(Chloromethyl)-N-ethyl-6-methoxyquinolin-2-amine **SLA 28166**

To a stirred solution of (2-(ethylamino)-6-methoxyquinolin-3-yl)methanol **SLA 28164** (1.150 g, 4.95 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (127 mL) a 250 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (7.18 mL, 99.0 mmol). The mixture was stirred for 2 h at RT then concentrated to dryness at 40°C under vacuum. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-N-ethyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28166** as a yellow solid (1.43 g, 100% yield) that was used immediately in the next step.

**SLA 28166**

**MW:** 287.18; **Yield:** 100 %; Yellow solid; **Mp** (°C): 168.7

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.44 (t, 3H, J = 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 4.10-4.17 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 5.05 (s, 2H, CH<sub>2</sub>Cl), 7.00 (d, 1H, J = 2.2 Hz, ArH), 7.25-7.29 (m, 1H, ArH), 8.05 (s, 1H, ArH), 8.42-8.50 (broad m, 1H, NH), 8.83 (d, 1H, J = 9.2 Hz, ArH), 13.51 (broad s, 1H, NH).

5 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.0, 39.2, 42.0, 55.8, 108.1, 120.3, 121.6, 122.4, 122.9, 131.5, 141.3, 149.5, 157.0.

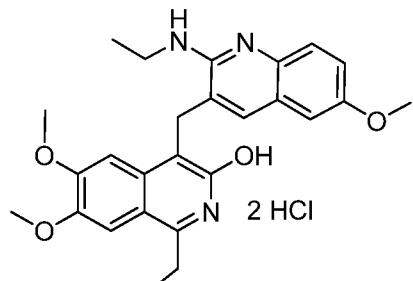
**MS-ESI** m/z (rel.int.): 251 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 253 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 35).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.92 min.

10

1-Ethyl-6,7-dimethoxy-4-((6-methoxy-2-(ethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride 40

To a stirred solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (250 mg, 1.07 mmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-N-ethyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28166** (308 mg, 1.07 mmol) followed by 2N aq. LiOH solution (1.07 ml, 2.14 mmol) and the mixture was stirred for 1.5 h at 150°C under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL) and washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) provided 29 mg of 1-ethyl-4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol as a brown solid. This product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.55 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 1-ethyl-4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **40** as a yellow solid (20 mg, 4% yield).



40

**MW:** 520.45; **Yield:** 4 %; **Yellow solid;** **Mp (°C):** 218.4 (dec.)

**<sup>1</sup>H NMR** (CD<sub>3</sub>OD, δ): 1.40-1.44 (m, 6H, 2xCH<sub>3</sub>), 3.30 (q, 2H, *J* = 6.9 Hz, CH<sub>2</sub>CH<sub>3</sub>),

5 3.67 (q, 2H, *J* = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 4.26 (s, 2H, CH<sub>2</sub>), 6.99 (s, 1H, ArH), 7.08 (s, 1H, ArH), 7.25 (d, 1H, *J* = 9.1 Hz, ArH), 7.39 (s, 1H, ArH), 7.63 (s, 1H, ArH), 7.80 (d, 1H, *J* = 9.1 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 13.8, 14.7, 25.4, 27.4, 39.0, 56.3, 56.8, 57.3, 102.2, 105.5,

10 109.5, 110.0, 117.8, 119.6, 123.3, 123.6, 124.9, 131.2, 139.8, 141.7, 151.6, 152.5,

15 155.3, 158.8, 159.5.

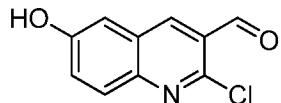
**MS-ESI** m/z (% rel. Int.): 462 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), X Bridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.46 min, peak area 99.4%.

15 Preparation of 1-ethyl-6,7-dimethoxy-4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride 41

#### 2-Chloro-6-hydroxyquinoline-3-carbaldehyde SLA 41026

To a solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.01 g, 4.54 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (36 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer at 0°C under N<sub>2</sub> was added dropwise BBr<sub>3</sub> (1.0 N solution in CH<sub>2</sub>Cl<sub>2</sub>, 13.60 mL, 13.60 mmol). After complete addition, the bath was removed and stirring was continued overnight at RT. The reaction mixture was then added dropwise to a mixture of water and ice (50 mL) under stirring. After complete addition, the mixture was stirred for 30 min at RT and then filtered to give, after drying, 2-chloro-6-hydroxyquinoline-3-carbaldehyde as a yellow solid (0.77 g, 82% yield).



**SLA 41026**

**MW:** 207.61; **Yield:** 82%; **Yellow solid; Mp (°C):** 205.0

**<sup>1</sup>H-NMR** (DMSO,  $\delta$ ): 7.43 (d, 1H,  $J$  = 2.7 Hz, ArH), 7.52 (dd, 1H,  $J$  = 2.7 & 9.1 Hz, ArH), 7.90 (d, 1H,  $J$  = 9.1 Hz, ArH), 8.77 (s, 1H, ArH), 10.35 (s, 1H, HC=O), 10.46 (broad s, 1H, OH).

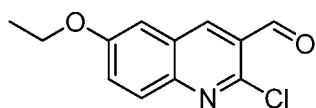
**<sup>13</sup>C-NMR** (DMSO,  $\delta$ ): 110.2, 126.1, 126.2, 127.8, 129.3, 139.5, 143.7, 145.4, 156.7, 189.6.

**MS-ESI** m/z (% rel. Int.): 208 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 210 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 36).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 10 186003113), detection UV 254 nm, RT = 2.55 min.

**2-Chloro-6-ethoxyquinoline-3-carbaldehyde SLA 41028**

To a solution of 2-chloro-6-hydroxyquinoline-3-carbaldehyde **SLA 41026** (0.70 g, 3.37 mmol) in dry DMF (15 mL) in a 50 mL round-bottomed flask equipped with a 15 magnetic stirrer was added Cs<sub>2</sub>CO<sub>3</sub> (1.21 g, 3.71 mmol) and the reaction mixture was stirred at RT for 10 min before adding bromoethane (0.30 mL, 4.05 mmol). The reaction mixture was stirred overnight at RT, then diluted with Et<sub>2</sub>O (100 mL) and H<sub>2</sub>O (10 mL). The organic phase was isolated and further washed with H<sub>2</sub>O (2x10 mL), brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under 20 vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc:= 100:0 to 75:25) provided, after evaporation and drying, 2-chloro-6-ethoxyquinoline-3-carbaldehyde **SLA 41028** as a yellow solid (544 mg, 68% yield).

**SLA 41028**

**25 MW:** 235.67; **Yield:** 68%; **Yellow solid; Mp (°C):** 165.7

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 1.53 (t, 3H,  $J$  = 7.0 Hz, CH<sub>3</sub>), 4.17 (q, 2H,  $J$  = 7.0 Hz, CH<sub>2</sub>), 7.17 (d, 1H,  $J$  = 2.7 Hz, ArH), 7.51 (dd, 1H,  $J$  = 2.7 & 9.2 Hz, ArH), 7.95 (d, 1H,  $J$  = 9.2 Hz, ArH), 8.62 (s, 1H, ArH), 10.55 (s, 1H, HC=O).

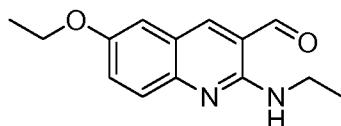
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 14.6, 64.2, 107.1, 126.4, 126.8, 127.8, 129.9, 138.6, 145.8, 147.6, 158.2, 189.5.

**MS-ESI** m/z (% rel. Int.): 236 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.32 min.

**6-Ethoxy-2-(ethylamino)quinoline-3-carbaldehyde SLA 41034**

5 To a stirred solution of 2-chloro-6-ethoxyquinoline-3-carbaldehyde (298 mg, 1.26 mmol) in a 20 mL microwave vial equipped with a magnetic stirrer was added ethylamine (2.0 N in THF, 13.0 mL, 26.0 mmol) and the reaction mixture was stirred for 10 h at 140°C under microwave irradiation then for 13 h at 130°C still under microwave irradiation. After cooling to RT, the reaction mixture was concentrated to 10 dryness at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl=1:1 (50 mL) and stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with saturated NaHCO<sub>3</sub> aqueous solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated 15 under vacuum, which gave 6-ethoxy-2-(ethylamino)quinoline-3-carbaldehyde **SLA 41034** as an orange solid (313 mg, >100% yield).



**SLA 41034**

**MW:** 244.29; **Yield:** quantitative; Orange solid.

20 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 1.33 (t, 3H,  $J$  = 7.2 Hz, CH<sub>3</sub>), 1.47 (t, 3H,  $J$  = 7.0 Hz, CH<sub>3</sub>), 3.61-3.70 (m, 2H, NCH<sub>2</sub>), 4.09 (q, 2H,  $J$  = 7.0 Hz, OCH<sub>2</sub>), 6.95 (d, 1H,  $J$  = 2.6 Hz, ArH), 7.33 (dd, 1H,  $J$  = 2.6 & 9.1 Hz, ArH), 7.60 (d, 1H,  $J$  = 9.1 Hz, ArH), 7.81 (broad s, 1H, NH), 8.12 (s, 1H, ArH), 9.96 (s, 1H, HC=O).

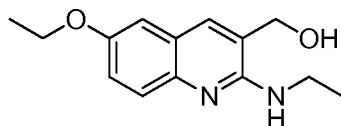
25 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 14.8, 14.8, 35.4, 63.8, 107.5, 117.2, 121.9, 126.2, 127.9, 147.2, 153.8, 154.1, 193.1, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 245 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), X Bridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 2.13 min.

30 **(6-Ethoxy-2-(ethylamino)quinolin-3-yl)methanol SLA 41040**

To a stirred solution of 6-ethoxy-2-(ethylamino)quinoline-3-carbaldehyde **SLA 41034** (0.605 g, 2.48 mmol) in THF (50 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (0.094 g, 2.48 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by 5 addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 min at that temperature, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to give (6-ethoxy-2-(ethylamino)quinolin-3-yl)methanol 10 **SLA 41040** as an orange solid (481 mg, 79% yield).



**SLA 41040**

**MW:** 246.30; **Yield:** 79%; Orange solid, **Mp (°C):** 133.8

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.32 (t, 3H, J = 9.0 Hz, CH<sub>3</sub>), 1.43-1.51 (m, 3H, CH<sub>3</sub>), 3.52-3.58 15 (m, 2H, CH<sub>2</sub>), 4.07 (q, 2H, J = 6.9 Hz, CH<sub>2</sub>), 4.48 (s, 2H, CH<sub>2</sub>), 5.64 (broad s, 1H, NH), 6.75 (d, 1H, J = 2.6 Hz, ArH), 6.92 (s, 1H, ArH), 7.17-7.23 (m, 1H, ArH), 7.61 (d, 1H, J = 9.0 Hz, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.9, 14.9, 36.0, 63.8, 63.9, 107.7, 120.8, 122.1, 123.3, 126.8, 134.2, 142.9, 153.9, 155.1.

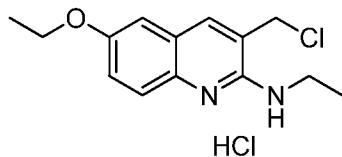
**20 MS-ESI** m/z (% rel. Int.): 247 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.17 min.

3-(Chloromethyl)-6-ethoxy-N-ethylquinolin-2-amine hydrochloride **SLA 41042**

25 To a stirred solution of (6-ethoxy-2-(ethylamino)quinolin-3-yl)methanol **SLA 41040** (0.457 g, 1.86 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (40 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (2.63 mL, 37.1 mmol). The mixture was stirred for 4 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration 30 back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-6-

ethoxy-*N*-ethylquinolin-2-amine hydrochloride **SLA 41042** as a yellow solid (552 mg, 99% yield).



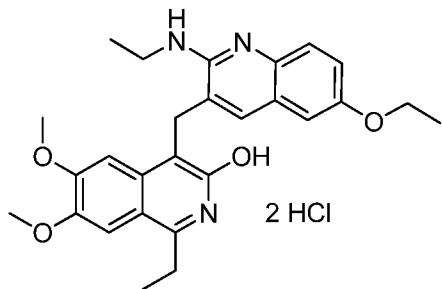
**SLA 41042**

5 **MW:** 301.21; **Yield:** 99%; **Yellow solid;** **Mp** (°C): 118.7  
<sup>1</sup>**H-NMR** (CD<sub>3</sub>OD, δ): 1.38-1.50 (m, 6H, 2xCH<sub>3</sub>), 3.73 (q, 2H, *J* = 8.4 Hz, CH<sub>2</sub>), 4.16 (q, 2H, *J* = 7.0 Hz, CH<sub>2</sub>), 4.91 (s, 2H, CH<sub>2</sub>), 7.36 (s, 1H, ArH), 7.43-7.47 (m, 1H, ArH), 7.92 (d, 1H, *J* = 9.3 Hz, ArH), 8.41 (s, 1H, ArH).  
<sup>13</sup>**C-NMR** (CD<sub>3</sub>OD, δ): 13.7, 15.0, 38.8, 42.0, 65.4, 110.7, 119.8, 123.5, 123.8, 124.9, 10 132.0, 143.7, 151.2, 158.2.  
**MS-ESI** m/z (% rel. Int.): 265 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 267 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38).  
**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.44 min.

15 4-((6-Ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride 41

To a stirred solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (140 mg, 0.60 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-ethoxy-*N*-ethylquinolin-2-amine hydrochloride 20 **SLA 41042** (181 mg, 0.60 mmol) at RT followed by a 2 N aq. LiOH solution (0.60 mL, 1.20 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 25 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) provided after evaporation 33 mg of 4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before 30 addition of a 0.49 M HCl solution in MeOH (1.05 mL). The reaction mixture was

stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **41** as a yellow solid (31.4 mg, 10% yield).

**41**

**MW:** 534.47; **Yield:** 10%; **Yellow solid;** **Mp** (°C): 242.2

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.28 (t, 3H, *J* = 6.7 Hz, CH<sub>3</sub>), 1.35-1.45 (s, 6H, 2xCH<sub>3</sub>), 3.28 (q, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 3.65 (q, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 3.88-3.99 (m, 2H, CH<sub>2</sub>), 4.25 (s, 2H, CH<sub>2</sub>), 6.99 (s, 1H, ArH), 7.07 (s, 1H, ArH), 7.26 (d, 1H, *J* = 9.2 Hz, ArH), 7.36 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.77 (d, 1H, *J* = 9.2 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.0, 14.7, 15.0, 25.6, 27.2, 39.2, 57.1, 57.5, 65.3, 102.7, 105.8, 110.2, 118.7, 119.6, 123.7, 124.4, 131.1, 139.5, 141.7, 152.0, 152.5, 153.1, 156.0, 158.0, 159.8, (2xC not observed).

**15 MS-ESI** m/z (% rel. Int.): 462 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.57 min, peak area 96.2%

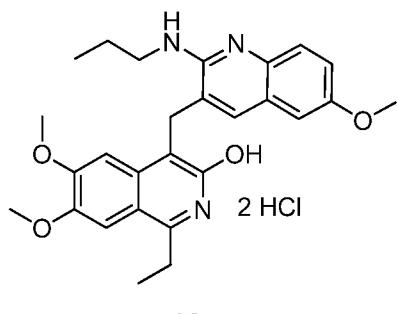
Preparation of 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-

yl)methyl)isoquinolin-3-ol dihydrochloride **42**

To a stirred solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (250 mg, 1.07 mmol) in *p*-cymene (11 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added 3-(chloromethyl)-6-methoxy-*N*-propylquinolin-2-amine hydrochloride **SLA 28178** (323 mg, 1.07 mmol) at RT followed by a 2 N aq.

**25 LiOH** solution (1.07 mL, 2.14 mmol) and the mixture was stirred at 150°C for 1 h before addition of a new portion of **SLA 28178** (323 mg, 1.07 mmol, done 3 times). After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL) and washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C

under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 92:8) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) provided, after evaporation, 14.8 mg of 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)isoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.26 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum, to afford 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **42** as a yellow solid (6 mg, 10% yield).

**42**

**MW:** 534.47; **Yield:** 10%; **Yellow solid;** **Mp** (°C): 160.0

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.05 (t, 3H, *J* = 9.0 Hz, CH<sub>3</sub>), 1.42 (t, 3H, *J* = 9.0 Hz, CH<sub>3</sub>), 1.80-1.89 (m, 2H, CH<sub>2</sub>), 3.30-3.33 (m, 2H, CH<sub>2</sub>), 3.58-3.63 (m, 2H, CH<sub>2</sub>), 3.69 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 4.27 (s, 2H, CH<sub>2</sub>), 6.98 (s, 1H, ArH), 7.07 (s, 1H, ArH), 7.23 (d, 1H, *J* = 9.2 Hz, ArH), 7.41 (s, 1H, ArH), 7.60 (s, 1H, ArH), 7.80 (d, 1H, *J* = 9.2 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 11.7, 14.7, 22.6, 25.4, 27.3, 45.7, 56.3, 56.9, 57.3, 102.3, 105.6, 109.5, 109.9, 118.1, 119.6, 123.4, 123.6, 124.7, 131.2, 139.7, 141.7, 151.7, 152.6, 155.7, 158.8, 159.6, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 462 ([MH]<sup>+</sup>, 100).

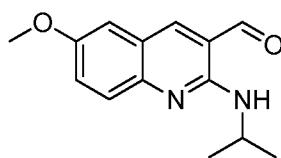
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 4.51 min.

25

Preparation of 1-ethyl-4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **43**

**2-(Isopropylamino)-6-methoxyquinoline-3-carbaldehyde SLA 28186**

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.50 g, 6.77 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added propan-2-amine (5.76 mL, 67.7 mmol) and the reaction mixture 5 was stirred for 12.5 h at 160°C and finally 45 min at 180°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl = 1:1 (50 mL) and stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with saturated NaHCO<sub>3</sub> aqueous 10 solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum to give 2-(isopropylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 28186** as an orange solid (1.64 g, 99% yield).



15 **SLA 28186**

**MW:** 244.29; **Yield:** 99%; Orange solid; **Mp** (°C): 160.0

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.32 (d, 6H, J = 6.0 Hz, 2xCH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 4.44-4.57 (m, 1H, CH), 6.96 (d, 1H, J = 2.8 Hz, ArH), 7.32 (dd, 1H, J = 2.8 & 9.2 Hz, ArH), 7.58 (d, 1H, J = 9.2 Hz, ArH), 7.75 (broad d, 1H, J = 9.0 Hz, CHNH), 8.12 (s, 1H, ArH), 20 9.96 (s, 1H, HC=O).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 22.9, 41.8, 55.5, 106.6, 117.1, 121.8, 125.8, 128.1, 147.2, 147.4, 153.2, 154.7, 193.2, (1xC not observed).

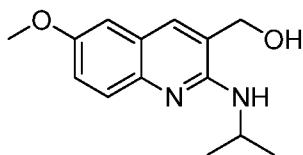
**MS-ESI** m/z (% rel. Int.): 245 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 25 186003113), detection UV 254 nm, RT = 2.76 min.

**(2-(Isopropylamino)-6-methoxyquinolin-3-yl)methanol SLA 28188**

To a stirred solution of 2-(isopropylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 28186** (1.55 g, 6.35 mmol) in THF (100 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added sodium borohydride 30

NaBH<sub>4</sub> (0.24 g, 6.35 mmol) and the mixture was stirred for overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 min at that temperature, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and the 5 solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give (2-(isopropylamino)-6-methoxyquinolin-3-yl)methanol **SLA 28188** as an orange solid (1.45 g, 93% yield).

**SLA 28188**

10 **MW:** 246.30; **Yield:** 93%; orange solid; **Mp (°C):** 150.0

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.28 (d, 6H, J = 6.0 Hz, 2xCH<sub>3</sub>), 2.46 (broad, s, 1H, OH), 3.87 (s, 3H, OCH<sub>3</sub>), 4.36-4.45 (m, 1H, CH), 4.56 (s, 2H, OCH<sub>2</sub>), 5.37 (broad d, 1H, J = 6.0 Hz, CHNH), 6.82 (d, 1H, J = 2.8 Hz, ArH), 7.18 (dd, 1H, J = 2.8 & 9.1 Hz, ArH), 7.26 (s, 1H, ArH), 7.60 (d, 1H, J = 9.1 Hz, ArH).

15 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 23.0 (2xC), 42.2, 55.4, 63.8, 106.6, 120.3, 122.2, 122.9, 127.1, 134.3, 143.1, 154.2, 154.5.

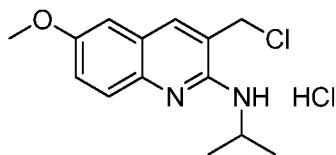
**MS-ESI** m/z (% rel. Int.): 247 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.13 min.

20

### 3-(Chloromethyl)-N-isopropyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28190**

To a stirred solution of (2-(isopropylamino)-6-methoxyquinolin-3-yl)methanol **SLA 28188** (1.41 g, 5.72 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (115 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (8.30 mL, 114 mmol). The mixture was stirred for 1 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-N-isopropyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28190** as a yellow solid (1.79 g, >100% yield).

**SLA 28190**

**MW:** 301.21; **Yield:** Quantitative; **yellow solid;** **Mp** (°C): 145.0

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.49 (d, 6H, J = 6.3 Hz, 2xCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 5.01 (s, 2H,

5 CH<sub>2</sub>), 5.28-5.38 (m, 1H, CH), 7.02 (d, 1H, J = 2.7 Hz, ArH), 7.20 (broad d, 1H, J = 8.6 Hz, NH), 7.29 (dd, 1H, J = 2.7 & 9.2 Hz, ArH), 8.07 (s, 1H, ArH), 9.00 (d, 1H, J = 9.2 Hz, ArH), 14.11 (s, 1H, NH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 22.0, 42.2, 46.7, 56.4, 109.9, 120.0, 123.4, 123.9, 124.5, 132.2, 143.9, 150.3, 158.9, (1xC not observed).

10 **MS-ESI** m/z (% rel. Int.): 265 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 267 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38)

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.40 min.

1-Ethyl-4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-

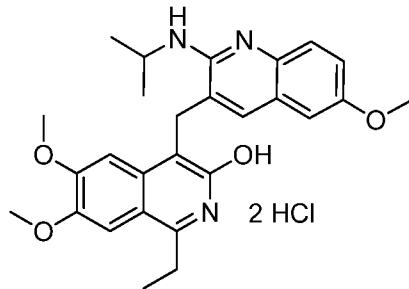
15 dimethoxyisoquinolin-3-ol dihydrochloride 43

To a stirred solution of 3-(chloromethyl)-N-isopropyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28190** (323 mg, 1.07 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (250 mg, 1.07 mmol) followed by a 2 N aq.

20 LiOH solution (1.07 mL, 2.14 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 94:6) followed by a second 25 purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 93:7) provided, after evaporation, 60 mg of 1-ethyl-4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (1.04 mL).

30 The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under

vacuum to afford 1-ethyl-4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **43** as a yellow solid (69 mg, 12% yield).

**43**

5 **MW:** 534.47; **Yield:** 12%; **Yellow solid; Mp** (°C): 257.6

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.52-1.59 (m, 9H, 3xCH<sub>3</sub>), 3.48 (q, 2H, *J* = 9.0 Hz, CH<sub>2</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 4.44 (s, 2H, CH<sub>2</sub>), 4.50-4.59 (m, 1H, CH), 7.15-7.16 (m, 2H, 2xArH), 7.33 (d, 1H, *J* = 9.0 Hz, ArH), 7.58 (s, 1H, ArH), 7.62 (s, 1H, ArH), 8.00 (d, 1H, *J* = 9.0 Hz, ArH).

15 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.7, 22.3, 25.5, 27.3, 46.6, 56.3, 57.0, 57.4, 102.6, 105.8, 109.4, 110.0, 118.7, 119.7, 123.4, 123.6, 124.4, 131.2, 139.6, 141.7, 151.6, 152.0, 152.9, 156.1, 158.7, 159.9, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 462 ([MH]<sup>+</sup>, 100).

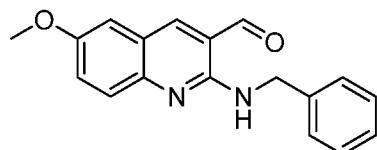
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.50 min, peak area 97.2%.

Preparation of 4-((2-(benzylamino)-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **44**

20 2-(Benzylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 41002**

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (2.00 g, 9.02 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added benzylamine (4.88 mL, 90.20 mmol) and the reaction mixture was stirred for 1.5 h at 160°C then 45 min at 180°C under microwave irradiation. After 25 cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl = 1:1 (50 mL) and stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with a saturated NaHCO<sub>3</sub> aqueous solution before extraction

with  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic phase was washed with brine (20 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent cyclohexane:EtOAc = 100:0 to 75:25) provided a mixture of the desired product and its benzyl imine derivative. This mixture was 5 taken up in a mixture of THF:1 N aq. HCl = 1:1 (20 mL) and stirred for 2 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with a saturated  $\text{NaHCO}_3$  aqueous solution before extraction with  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic phase was washed with brine (20 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column 10 chromatography ( $\text{SiO}_2$ , eluent cyclohexane:EtOAc = 100:0 to 75:25) gave, after evaporation and drying, 2-(benzylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 41002** as a yellow solid (0.431 g, 16% yield).



**SLA 41002**

15 **MW:** 292.33; **Yield:** 16%; **Yellow solid;** **Mp** (°C): 131.7

**<sup>1</sup>H-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 3.88 (s, 3H,  $\text{OCH}_3$ ), 4.86 (d, 2H,  $J$  = 6.0 Hz,  $\text{CH}_2$ ), 6.99-7.00 (m, 1H, ArH), 7.23-7.44 (m, 6H, 6xArH), 7.62 (d, 1H,  $J$  = 7.9 Hz, ArH), 8.17 (s, 1H, ArH), 8.20 (broad s, 1H, NH), 9.99 (s, 1H,  $\text{HC=O}$ ).

**<sup>13</sup>C-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 44.5, 55.6, 106.7, 117.3, 122.2, 125.9, 127.1, 127.8 (2xC),

20 128.1, 128.4, 128.5 (2xC), 139.5, 147.1, 153.6, 155.0, 193.0.

**MS-ESI** m/z (% rel. Int.): 293 ( $[\text{MH}]^+$ , 100).

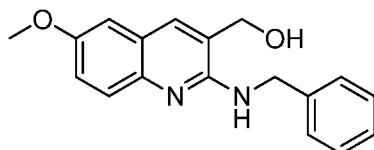
**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model #

186003113), detection UV 254 nm, RT = 2.51min.

25 (2-(Benzylamino)-6-methoxyquinolin-3-yl)methanol **SLA 41006**

To a stirred solution of 2-(benzylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 41002** (0.40 g, 1.37 mmol) in THF (50 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added sodium borohydride  $\text{NaBH}_4$  (0.24 g, 6.35 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before 30 quenching by addition of a 1 N aq. HCl solution (15 mL). After stirring for 15 min at

that temperature, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to give (2-(benzylamino)-6-methoxyquinolin-3-yl)methanol **SLA 41006** as a yellow solid (0.395 g, 98% yield).

**SLA 41006**

**MW:** 294.35; **Yield:** 98%; **Yellow solid;** **Mp** (°C): 132.2

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.88 (s, 3H, OCH<sub>3</sub>), 4.61 (s, 2H, OCH<sub>2</sub>), 4.76 (d, 2H, *J* = 5.3 Hz, 10 NCH<sub>2</sub>), 5.90-5.92 (broad m, NH or OH), 6.86 (d, 1H, *J* = 2.8 Hz, ArH), 7.20 (dd, 1H, *J* = 2.8 Hz & 9.0 Hz, ArH), 7.26-7.36 (m, 5H, 4xArH and NH or OH), 7.39-7.42 (m, 2H, 2xArH), 7.62 (d, 1H, *J* = 9.0 Hz, ArH).

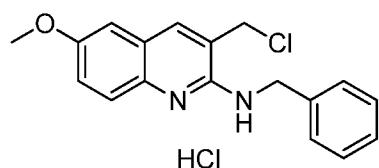
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 45.4, 55.6, 63.9, 106.6, 120.6, 122.1, 123.5, 127.1, 127.4, 128.0 (2xC), 128.5 (2xC), 134.5, 139.9, 143.1, 154.7, 154.9.

**15 MS-ESI** m/z (% rel. Int.): 295 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.34 min.

#### N-Benzyl-3-(chloromethyl)-6-methoxyquinolin-2-amine hydrochloride **SLA 41008**

20 To a stirred solution of (2-(benzylamino)-6-methoxyquinolin-3-yl)methanol **SLA 41006** (0.101 g, 0.343 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (0.50 mL, 6.86 mmol). The mixture was stirred for 1 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before 25 concentration back to dryness at 40°C under vacuum (done 3 times) to give *N*-benzyl-3-(chloromethyl)-6-methoxyquinolin-2-amine hydrochloride **SLA 41008** (120 mg, 100% yield) as a yellow solid.



**SLA 41008**

**MW:** 349.25; **Yield:** 100%; **Yellow solid;** **Mp (°C):** 233.2

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.93 (s, 3H, OCH<sub>3</sub>), 4.97-4.98 (m, 4H, 2xCH<sub>2</sub>), 7.33-7.46 (m, 7H, 7xArH), 7.83 (d, 1H, J = 9.0 Hz, ArH), 8.49 (s, 1H, ArH).

5 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 42.1, 46.9, 56.4, 110.0, 119.8, 123.7, 123.9, 124.9, 128.2 (2xC), 129.2, 130.1 (2xC), 132.0, 136.3, 144.2, 151.6, 159.1.

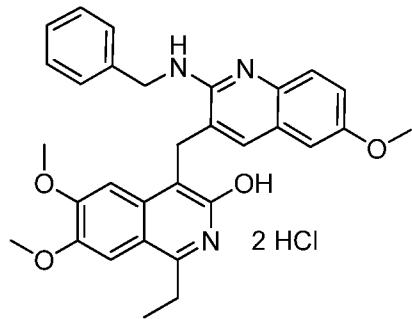
**MS-ESI** m/z (% rel. Int.): 313 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 315 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38),

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.59 min.

10

4-((2-(Benzylamino)-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride 44

To a stirred solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (70 mg, 0.30 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic 15 stirrer was added *N*-benzyl-3-(chloromethyl)-6-methoxyquinolin-2-amine hydrochloride **SLA 41008** (105 mg, 0.30 mmol) followed by a 2 N aq. LiOH (0.30 mL, 0.60 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave 20 irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 25 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) provided, after evaporation, 17.3 mg of 4-((2-(benzylamino)-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.28 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((2-(benzylamino)-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride 44 as a yellow solid (16 mg, 9% yield).

**44**

**MW:** 582.52; **Yield:** 9%; **Yellow solid;** **Mp** (°C): 250.0

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.46 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 3.23-3.30 (m, 2H, CH<sub>2</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.41 (s, 2H, CH<sub>2</sub>), 4.98 (s, 2H, CH<sub>2</sub>), 7.08 (s, 1H, ArH), 7.27 (d, 1H, *J* = 2.6 Hz, ArH), 7.34-7.41 (m, 7H, 7xArH), 7.79 (d, 1H, *J* = 9.1 Hz, ArH), 8.08 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.7, 25.4, 27.4, 47.1, 56.3, 56.8, 57.2, 102.1, 105.6, 109.4, 109.9, 119.6, 123.6, 123.9, 128.4 (2xC), 129.2, 130.1 (2xC), 131.1, 136.6, 140.4, 141.7, 152.7, 155.6, 158.9, 159.5, (4xC not observed).

**MS-ESI** m/z (% rel. Int.): 510 ([MH]<sup>+</sup>, 100).

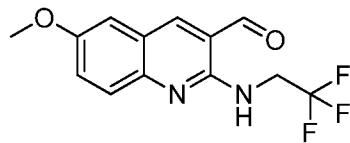
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.62 min, peak area 95.3%.

15 Preparation of 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride 45

#### 6-Methoxy-2-(2,2,2-trifluoroethylamino)quinoline-3-carbaldehyde SLA 41066

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.50 g, 6.77 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 2,2,2-trifluoroethanamine (10.06 mL, 102.0 mmol) and the reaction mixture was stirred for 10 h at 160°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl = 1:1 (50 mL) and stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with saturated NaHCO<sub>3</sub> aqueous solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over MgSO<sub>4</sub>,

filtered and concentrated under vacuum to give 6-methoxy-2-(2,2,2-trifluoroethylamino)quinoline-3-carbaldehyde **SLA 41066** as an orange solid (2.22 g, >100% yield).



5

**SLA 41066**

**MW:** 284.23; **Yield:** >100%; **Orange solid;** **Mp (°C):** 129.2

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.92 (s, 3H, CH<sub>3</sub>), 4.37-4.48 (m, 2H, CH<sub>2</sub>), 7.02 (d, 1H, J = 2.8 Hz, ArH), 7.38 (dd, 1H, J = 2.8 Hz & 9.1 Hz, ArH), 7.65 (d, 1H, J = 9.1 Hz, ArH), 8.24 (s, 1H, ArH), 10.01 (s, 1H, HC=O).

10 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 41.0 (q, J = 34.2 Hz), 55.2, 106.1, 116.8, 122.5, 125.8, 127.9, 145.9, 146.6, 152.3, 155.2, 192.7, (CF<sub>3</sub> not seen).

**MS-ESI** m/z (% rel. Int.): 285 ([MH]<sup>+</sup>, 100).

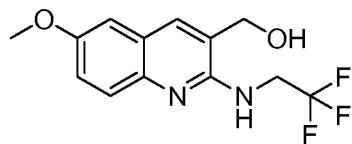
**HPLC:** Method B (5 min), X Bridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.11 min.

15

(6-Methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methanol **SLA 41068**

To a stirred solution of 6-methoxy-2-(2,2,2-trifluoroethylamino)quinoline-3-carbaldehyde **SLA 41066** (1.98 g, 6.97 mmol) in THF (150 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added sodium borohydride

20 NaBH<sub>4</sub> (0.264 g, 6.98 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 min at that temperature, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (500 mL), washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, 25 filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) provided, after evaporation and drying, (6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methanol **SLA 41068** as an orange solid (1.47 g, 74% yield).

**SLA 41068**

**MW:** 286.25; **Yield:** 74%; Orange solid; **Mp (°C):** 171.9

5 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.85 (s, 3H, OCH<sub>3</sub>), 4.34 (q, 2H, *J* = 9.4 Hz, CH<sub>2</sub>), 4.70 (s, 2H, CH<sub>2</sub>), 7.02 (d, 1H, *J* = 2.7 Hz, ArH), 7.21 (dd, 1H, *J* = 2.7 & 9.1 Hz, ArH), 7.65 (d, 1H, *J* = 9.1 Hz, ArH), 7.72 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 43.2 (q, *J* = 33.5 Hz), 56.7, 63.8, 107.8, 122.1, 124.3, 125.5, 128.5, 136.2, 143.6, 155.2, 156.7, (CF<sub>3</sub> not seen).

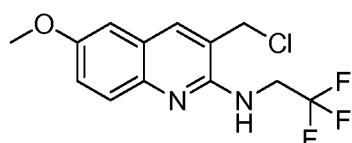
**MS-ESI** m/z (% rel. Int.): 287 ([MH]<sup>+</sup>, 100).

10 **HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.15 min.

3-(Chloromethyl)-6-methoxy-N-(2,2,2-trifluoroethyl)quinolin-2-amine hydrochloride

**SLA 41070**

15 To a stirred solution of (6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methanol **SLA 41068** (1.45 g, 5.07 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (7.35 mL, 101.3 mmol). The mixture was stirred for 2 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) 20 before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-6-methoxy-N-(2,2,2-trifluoroethyl)quinolin-2-amine hydrochloride **SLA 41070** as a yellow solid (1.74 g, >100% yield).

**SLA 41070**

25 **MW:** 341.16; **Yield:** >100%; Yellow solid; **Mp (°C):** 231.2

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 3.94 (s, 3H, OCH<sub>3</sub>), 4.65 (q, *J* = 8.7 Hz, 2H, CH<sub>2</sub>), 4.95 (s, 2H, CH<sub>2</sub>), 7.45 (d, 1H, *J* = 2.4 Hz, ArH), 7.52 (dd, 1H, *J* = 2.4 Hz & 9.2 Hz, ArH), 8.01 (d, 1H, *J* = 9.2 Hz, ArH), 8.60 (s, 1H, ArH).

<sup>13</sup>C-NMR (CD<sub>3</sub>OD,  $\delta$ ): 41.8, 44.1 (q,  $J$  = 34.7 Hz), 56.5, 109.7, 120.1, 123.8, 124.3, 125.6 (q,  $J$  = 279.4 Hz), 125.6, 131.9, 145.3, 151.9, 159.5.

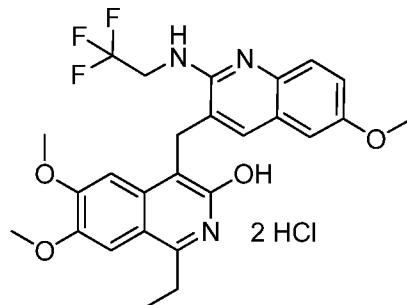
MS-ESI m/z (% rel. Int.): 305 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 307 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38).

HPLC: Method B, XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113),

5 detection UV 254 nm, RT = 4.50 min.

1-Ethyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride 45

To a stirred solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (342 mg, 1.47 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-methoxy-N-(2,2,2-trifluoroethyl)quinolin-2-amine hydrochloride **SLA 41070** (500 mg, 1.47 mmol) at RT followed by a 2 N aq. LiOH solution (1.47 mL, 2.94 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 97:3) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) provided, after evaporation and drying, 233 mg of 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (3.05 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **45** as a yellow solid (200 mg, 24% yield).



**45**

**MW:** 574.42; **Yield:** 24%; **Yellow solid; Mp (°C):** 118.6

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.46-1.58 (m, 3H, CH<sub>3</sub>), 3.45-3.54 (m, 2H, CH<sub>2</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.47 (s, 2H, CH<sub>2</sub>), 4.81 (q, 2H, J = 8.0 Hz, CH<sub>2</sub>), 7.11 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.40 (d, 1H, J = 9.1 Hz, ArH), 7.59

5 (s, 1H, ArH), 7.77 (s, 1H, ArH), 8.05 (d, 1H, J = 9.1 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.7, 25.5, 27.3, 44.5 (q, J = 34.9 Hz), 56.4, 57.0, 57.4, 102.6, 105.9, 109.2, 109.6, 118.9, 119.9, 124.2, 124.5, 124.5, 125.8 (q, J = 279.3 Hz), 131.0, 141.0, 141.6, 152.1, 152.7, 153.0, 156.4, 159.3, 160.0.

**MS-ESI** m/z (% rel. Int.): 502 ([MH]<sup>+</sup>, 100).

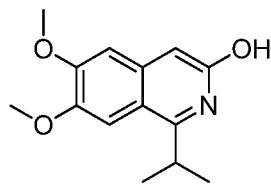
10 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.41 min, peak area 99.0%.

Preparation 4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **46**

15

1-Isopropyl-6,7-dimethoxyisoquinolin-3-ol **SIL 32164**

To a solution of methyl 2-(3,4-dimethoxyphenyl)acetate **SLA 28134** (10.09 g, 48.0 mmol) in isobutyric anhydride (60.5 mL, 364.8 mmol) at 0°C in a 500 mL round-bottomed flask equipped with a magnetic stirrer was added HClO<sub>4</sub> (ca. 70% solution 20 in water, 4.91 mL, 56.8 mmol) over a period of 10 min. The reaction mixture was then allowed to warm up to RT, stirred for 2 h and diluted with Et<sub>2</sub>O (400 mL). The solid was filtered and washed several times with Et<sub>2</sub>O to give 16.88 g of a brown solid. The solid was then suspended in H<sub>2</sub>O (70 mL) in a 500 mL round-bottomed flask equipped with a magnetic stirrer and cooled in an ice bath before dropwise 25 addition of concentrated NH<sub>4</sub>OH (180 mL). After complete addition, the ice bath was removed and the reaction mixture was stirred overnight at RT. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL, the organic layer was isolated and the aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x100 mL). The organic layers were combined, washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under 30 vacuum to give 1-isopropyl-6,7-dimethoxyisoquinolin-3-ol **SIL 32164** as a yellow solid (9.69 g, 82% yield).

**SIL 32164**

**MW:** 247.29; **Yield:** 82%; **Yellow solid;** **Mp (°C):** 175.0

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.52 (d, 6H, J = 6.9 Hz, 2xCH<sub>3</sub>), 3.63-3.70 (m, 1H, CH), 3.93 (s,

5 3H, OCH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 6.57 (s, 1H, ArH), 6.60 (s, 1H, ArH), 6.94 (s, 1H, ArH), OH not seen.

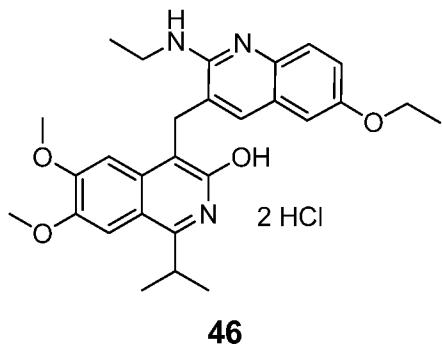
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 21.1 (2xC), 29.4, 55.8, 56.0, 101.8, 102.8, 104.8, 111.8, 142.0, 147.5, 154.5, 154.8, 161.2.

**MS-ESI** m/z (% rel. Int.): 248 ([MH]<sup>+</sup>, 100).

10 **HPLC:** Method B (5 min), X Bridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.13 min.

4-((6-Ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride 46

15 To a stirred solution of 1-isopropyl-6,7-dimethoxyisoquinolin-3-ol **SIL 32164** (149 mg, 0.60 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-ethoxy-N-ethylquinolin-2-amine hydrochloride **SLA 41042** (181 mg, 0.68 mmol) at RT followed by a 2 N aq. LiOH solution (0.60 mL, 1.20 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) 20 provided 16 mg of 4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (1.05 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **46** as a yellow solid (12 mg, 4% yield).

**46**

**MW:** 548.50; **Yield:** 4%; **Yellow solid;** **Mp** (°C): 222.2

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.42 (t, 3H, *J* = 6.8 Hz, CH<sub>3</sub>), 1.46-1.55 (m, 9H, 3xCH<sub>3</sub>), 3.69

5 (q, 2H, *J* = 6.8 Hz, CH<sub>2</sub>), 3.97-4.05 (m, 1H, CH), 3.93 (s, 3H, OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.10 (q, 2H, *J* = 6.8 Hz, CH<sub>2</sub>), 4.35 (s, 2H, CH<sub>2</sub>), 7.07 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.33 (d, 1H, *J* = 9.1 Hz, ArH), 7.40 (s, 1H, ArH), 7.83 (d, 1H, *J* = 9.1 Hz, ArH), 8.11 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 13.7, 15.0, 21.3, 28.0, 30.3, 39.0, 56.6, 57.1, 65.3, 103.3,

10 104.8, 110.2, 114.7, 115.2, 119.5, 123.4, 123.6, 125.9, 131.1, 140.7, 141.9, 150.3, 152.5, 156.7, 158.0, 158.5, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 476 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.78 min, peak area 98.3%.

15

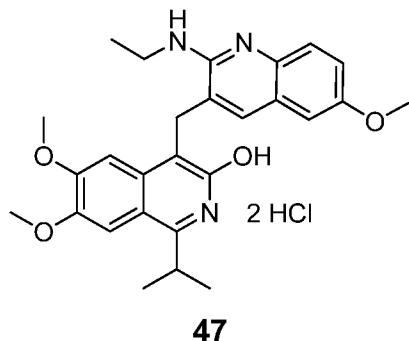
Preparation 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride 47

To a stirred solution of 3-(chloromethyl)-*N*-ethyl-6-methoxyquinolin-2-amine hydrochloride (250 mg, 0.87 mmol) in THF (10 mL) in a 20 mL microwave vial

20 equipped with a magnetic stirrer was added 1-isopropyl-6,7-dimethoxyisoquinolin-3-ol **SIL 32164** (215 mg, 0.87 mmol) followed by a 2 N aq. LiOH solution (0.87 mL, 1.74 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at

25 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) provided, after evaporation and drying, 38 mg of 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol as a brown solid. This free base was

dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.70 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **47** as a yellow solid (24 mg, 5% yield).



**MW:** 534.47; **Yield:** 5%; Yellow solid.

**$^1\text{H-NMR}$  (CD<sub>3</sub>OD,  $\delta$ ):** 1.51-1.65 (m, 9H, 3xCH<sub>3</sub>), 3.72-3.88 (m, 2H, CH<sub>2</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.12-4.30 (m, 1H, CH), 4.38 (s, 2H, CH<sub>2</sub>), 6.98 (s, 1H, ArH), 7.18 (s, 1H, ArH), 7.34 (d, 1H,  $J$  = 8.6 Hz, ArH), 7.61 (s, 1H, ArH), 7.73 (s, 1H, ArH), 7.91 (d, 1H,  $J$  = 8.6 Hz, ArH).

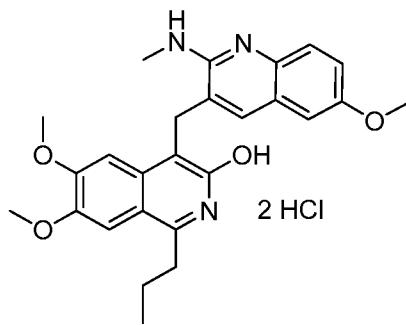
**MS-ESI m/z (% rel. Int.):** 462 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), X Bridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.50 min, peak area 98.4%.

Preparation of 6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **48**

To a stirred solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (250 mg, 1.01 mmol) in toluene (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-methoxy-N-methylquinolin-2-amine hydrochloride **SLA 28154** (276 mg, 1.01 mmol) followed by a 2 N aq. LiOH solution (1.01 mL, 2.02 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with a  $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1 mixture (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) provided, after evaporation and drying, 39 mg of 6,7-dimethoxy-4-((6-methoxy-2-

(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.40 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under 5 vacuum to give 6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **48** as a yellow solid (31 mg, 6% yield).

**48**

**MW:** 520.45; **Yield:** 6%; **Yellow solid, Mp (°C):** 216.9 (dec.)

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.13 (t, 3H, *J* = 7.2 Hz, CH<sub>3</sub>), 1.93 (t, 2H, *J* = 7.2 Hz, CH<sub>2</sub>), 3.28 (s, 3H, CH<sub>3</sub>), 3.35 (s, 2H, CH<sub>2</sub>), 3.76 (s, 3H, CH<sub>3</sub>), 3.91 (s, 3H, CH<sub>3</sub>), 4.01 (s, 3H, CH<sub>3</sub>), 4.30 (s, 2H, CH<sub>2</sub>), 7.06 (s, 1H, ArH), 7.11 (s, 1H, ArH), 7.31 (dd, 1H, *J* = 9.1 Hz, *J* = 2.2 Hz, ArH), 7.52 (s, 1H, ArH), 7.88 (d, 1H, *J* = 9.2 Hz, ArH).

15 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.2, 24.7, 27.1, 29.9, 33.6, 56.3, 56.9, 57.3, 102.4, 105.9, 109.5, 109.9, 119.0, 119.6, 123.3, 123.7, 124.3, 131.2, 139.0, 141.7, 152.0, 153.2, 153.5, 154.7, 158.8, 159.9.

**MS-ESI** m/z (% rel. Int.): 448.3 ([MH]<sup>+</sup>, 100).

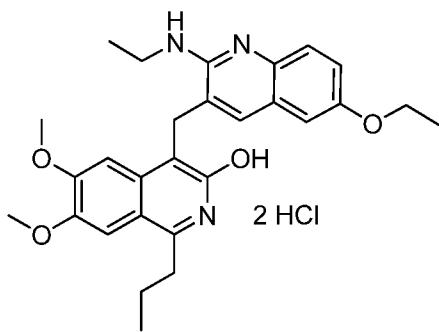
**HPLC:** Method B (10 min), X Bridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.34 min, peak area 99.6 %.

20

Preparation of 4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **49**

To a stirred solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (149 mg, 0.60 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a 25 magnetic stirrer was added 3-(chloromethyl)-6-ethoxy-*N*-ethylquinolin-2-amine hydrochloride **SLA 41042** (181 mg, 0.68 mmol) at RT followed by a 2 N aq. LiOH solution (0.60 mL, 1.20 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with

CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL) and washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) 5 provided 35 mg of 4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (1.0 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((6-ethoxy-2- 10 (ethylamino)quinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **49** as a yellow solid (14 mg, 4% yield).

**49**

**MW:** 548.50; **Yield:** 4%; **Yellow solid;** **Mp (°C):** 132.2

15 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.17 (t, 3H, *J* = 7.1 Hz, CH<sub>3</sub>), 1.49 (t, 3H, *J* = 7.1 Hz, CH<sub>3</sub>), 1.57 (t, 3H, *J* = 6.8 Hz, CH<sub>3</sub>), 1.91-2.00 (m, 2H, CH<sub>2</sub>), 3.30-3.38 (m, 2H, CH<sub>2</sub>), 3.72-3.78 (m, 2H, CH<sub>2</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 4.09-4.20 (m, 2H, CH<sub>2</sub>), 4.40 (s, 2H, CH<sub>2</sub>), 7.13-7.20 (m, 1H, ArH), 7.27 (s, 1H, ArH), 7.39-7.43 (m, 2H, 2xArH), 7.90 (d, 1H, *J* = 9.0 Hz, ArH), 8.06 (s, 1H, ArH).

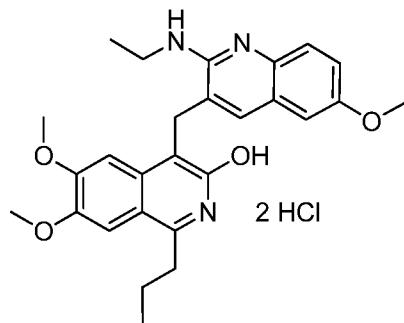
20 **MS-ESI** m/z (% rel. Int.): 476 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.77 min, peak area 97.8%.

25 Preparation of 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **50**

To a stirred solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (250 mg, 1.01 mmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-*N*-ethyl-6-methoxyquinolin-2-amine

hydrochloride **SLA 28166** (290 mg, 1.01 mmol) followed by a 2 N aq. LiOH solution (1.01 mL, 2.02 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, 5 filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 92:8) provided, after evaporation and drying, 25 mg of 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol as a brown 10 solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.45 mL). The reaction mixture was stirred for 5 min at RT, concentrated at 40°C under vacuum, to afford 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **50** as a yellow solid (30 mg, 6% 15 yield).

**50**

**MW:** 534.47; **Yield:** 6%; **Yellow solid;** **Mp** (°C): 218.4 (dec.)

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.02 (t, 3H, *J* = 6.8 Hz, CH<sub>3</sub>), 1.42 (t, 3H, *J* = 6.6 Hz, CH<sub>3</sub>), 20 1.79-1.90 (m, 2H, CH<sub>2</sub>), 3.18-3.28 (m, 2H, CH<sub>2</sub>), 3.65 (q, 2H, *J* = 6.8 Hz, CH<sub>2</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 4.26 (s, 2H, CH<sub>2</sub>), 6.98 (s, 1H, ArH), 7.08 (s, 1H, ArH), 7.23 (d, 1H, *J* = 9.1 Hz, ArH), 7.34 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.79 (d, 1H, *J* = 9.1 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 13.8, 14.2, 24.6, 30.8, 33.5, 39.1, 56.3, 56.8, 57.3, 102.1, 25 105.7, 109.5, 119.6, 123.3, 123.6, 123.6, 131.2, 139.9, 141.7, 151.3, 152.5, 153.9, 158.8, 159.4, (3xC not observed).

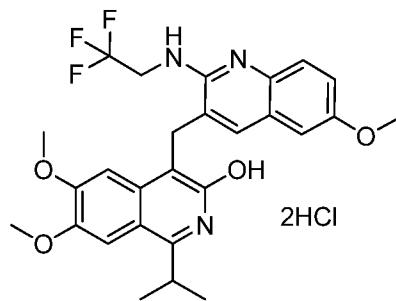
**MS-ESI** m/z (% rel. Int.): 462.3 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.50 min, peak area 99.4 %.

Preparation of 1-isopropyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-

trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride 51

To a stirred solution of 1-isopropyl-6,7-dimethoxyisoquinolin-3-ol **SIL 32164** (362 mg, 1.46 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-methoxy-N-(2,2,2-trifluoroethyl)quinolin-2-amine hydrochloride **SLA 41070** (500 mg, 1.47 mmol) at RT followed by a 2 N aq. solution of LiOH (1.47 mL, 2.94 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) provided, after evaporation, 161 mg of 1-isopropyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (1.5 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 1-isopropyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **51** as a yellow solid (130 mg, 15% yield).



25

**51**

**MW:** 588.45; **Yield:** 15%; **Yellow solid;** **Mp** (°C): 210.0

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.62 (d, 6H,  $J$  = 6.9 Hz, 2xCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.18-4.25 (m, 1H, CH), 4.44 (s, 2H, CH<sub>2</sub>), 4.73 (q,

2H,  $J$  = 8.7 Hz,  $\text{CH}_2$ ), 7.10 (s, 1H, ArH), 7.27 (d, 1H,  $J$  = 2.6 Hz, ArH), 7.43 (dd, 1H,  $J$  = 2.6 Hz &  $J$  = 9.2 Hz, ArH), 7.63 (s, 1H, ArH), 7.93 (s, 1H, ArH), 7.99 (d, 1H,  $J$  = 9.2 Hz, ArH).

**$^{13}\text{C-NMR}$**  ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 21.3 (2xC), 27.4, 30.6, 44.3 (q,  $J$  = 35.2 Hz), 56.4, 56.9, 57.3,

5 102.1, 105.5, 109.2, 109.6, 117.6, 119.8, 124.5, 124.5, 125.6 (q,  $J$  = 281.9 Hz), 131.0, 141.4, 141.9, 151.7, 153.0, 154.5, 158.6, 159.3, 159.8, (1xC not observed).

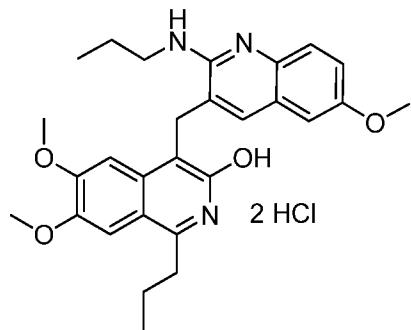
**MS-ESI** m/z (% rel. Int.): 516 ( $[\text{MH}]^+$ , 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.64 min, peak area 99.1%

10

Preparation of 6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride 52

To a stirred solution of 6,7-dimethoxy-1-propyl-isoquinolin-3-ol **RBO 35134** (250 mg, 1.01 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-methoxy-N-propylquinolin-2-amine free base **SLA 28178** (269 mg, 1.01 mmol) followed by a dropwise addition of *n*-Buli (1.6 M in hexane, 0.65 mL, 1.04 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1 (150 mL) and washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent EtOAc:MeOH = 100:0 to 92:8) followed by a second purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2$ :MeOH = 100:0 to 95:5) provided, after evaporation, 70 mg of 6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol as a brown solid. This free base was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.40 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **52** as a yellow solid (26.6 mg, 5% yield).

**52**

**MW:** 548.50; **Yield:** 5%; **Yellow solid;** **Mp** (°C): 148.3

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.02-1.18 (m, 6H, 2xCH<sub>3</sub>), 1.80-1.85 (m, 4H, 2xCH<sub>2</sub>), 3.20-3.25 (m, 2H, CH<sub>2</sub>), 3.57-3.87 (m, 2H, CH<sub>2</sub>), 3.70 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 4.27 (s, 2H, CH<sub>2</sub>), 6.98 (s, 1H, ArH), 7.08 (s, 1H, ArH), 7.23 (d, 1H, *J* = 9.2 Hz, ArH), 7.36 (s, 1H, ArH), 7.66 (s, 1H, ArH), 7.80 (d, 1H, *J* = 9.2 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 11.8, 14.2, 22.6, 24.6, 27.5, 33.5, 45.7, 56.3, 56.8, 57.3, 102.4, 105.7, 109.5, 109.5, 119.6, 119.6, 123.3, 123.3, 123.6, 124.8, 131.2, 139.9, 141.7, 151.4, 152.6, 154.1, 158.8, 159.9.

**MS-ESI** m/z (% rel. Int.): 476 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 4.72 min, peak area 95.1%.

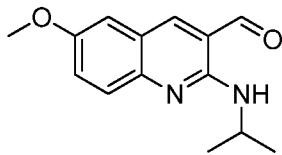
15

Preparation of 4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 53

2-(Isopropylamino)-6-methoxyquinoline-3-carbaldehyde SLA 28186

20 To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.50 g, 6.77 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added propan-2-amine (5.76 mL, 67.7 mmol) and the reaction mixture was stirred for 12.5 h at 160°C and finally 45 min at 180°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl = 1:1 (50 mL) and stirred for 1 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with a saturated NaHCO<sub>3</sub> aqueous solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic layer was washed with

brine (20 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated under vacuum to give 2-(isopropylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 28186** as an orange solid (1.64 g, 99% yield).



5

**SLA 28186**

**MW:** 244.29; **Yield:** 99%; **Orange solid;** **Mp** (°C): 160.0

**<sup>1</sup>H-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 1.32 (d, 6H,  $J$  = 6.0 Hz,  $2\times\text{CH}_3$ ), 3.77 (s, 3H,  $\text{OCH}_3$ ), 4.44-4.57 (m, 1H, CH), 6.96 (d, 1H,  $J$  = 2.8 Hz, ArH), 7.32 (dd, 1H,  $J$  = 2.8 & 9.2 Hz, ArH), 7.58 (d, 1H,  $J$  = 9.2 Hz, ArH), 7.75 (broad d, 1H,  $J$  = 9.0 Hz,  $\text{CHNH}$ ), 8.12 (s, 1H, ArH), 9.96 (s, 1H,  $\text{HC=O}$ ).

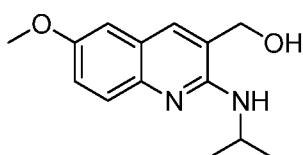
**<sup>13</sup>C-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 22.9, 41.8, 55.5, 106.6, 117.1, 121.8, 125.8, 128.1, 147.2, 147.4, 153.2, 154.7, 193.2, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 245 ( $[\text{M}+\text{H}]^+$ , 100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 2.76 min.

(2-(Isopropylamino)-6-methoxyquinolin-3-yl)methanol **SLA 28188**

To a stirred solution of 2-(isopropylamino)-6-methoxyquinoline-3-carbaldehyde **SLA 28186** (1.55 g, 6.35 mmol) in THF (100 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added  $\text{NaBH}_4$  (0.24 g, 6.35 mmol) and the mixture was stirred for overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 min at that temperature, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was removed at 40°C under vacuum and the solution was extracted with  $\text{CH}_2\text{Cl}_2$  (200 mL). The organic layer was washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under vacuum to give (2-(isopropylamino)-6-methoxyquinolin-3-yl)methanol **SLA 28188** as an orange solid (1.45 g, 93% yield).



**SLA 28188**

**MW:** 246.30; **Yield:** 93%; Orange solid; **Mp (°C):** 150.0

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.28 (d, 6H, J = 6.0 Hz, 2xCH<sub>3</sub>), 2.46 (broad s, 1H, OH), 3.87 (s, 3H, OCH<sub>3</sub>), 4.36-4.45 (m, 1H, CH), 4.56 (s, 2H, OCH<sub>2</sub>), 5.37 (broad d, 1H, J = 6.0 Hz, NH), 6.82 (d, 1H, J = 2.8 Hz, ArH), 7.18 (dd, 1H, J = 2.8 & 9.1 Hz, ArH), 7.26 (s, 1H, ArH), 7.60 (d, 1H, J = 9.1 Hz, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 23.0, 42.2, 55.4, 63.8, 106.6, 120.3, 122.2, 122.9, 127.1, 134.3 143.1, 154.2, 154.5, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 247 ([M+H]<sup>+</sup>, 100).

**10 HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.13 min.

3-(Chloromethyl)-N-isopropyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28190**

To a stirred solution of (6-methoxy-2-(propylamino)quinolin-3-yl)methanol **SLA 28188** (1.41 g, 5.72 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (115 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (8.30 mL, 114 mmol). The mixture was stirred for 1 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give of 3-(chloromethyl)-N-isopropyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28190** as a yellow solid (1.79 g, >100% yield).

**SLA 28190**

**MW:** 301.21; **Yield:** Quantitative; Yellow solid; **Mp (°C):** 145.0

**25 <sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.49 (d, 6H, J = 6.3 Hz, 2xCH<sub>3</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 5.01 (s, 2H, CH<sub>2</sub>), 5.28-5.38 (m, 1H, CH), 7.02 (d, 1H, J = 2.7 Hz, ArH), 7.20 (broad d, 1H, J = 8.6 Hz, NH), 7.29 (dd, 1H, J = 2.7 & 9.2 Hz, ArH), 8.07 (s, 1H, ArH), 9.00 (d, 1H, J = 9.2 Hz, ArH).

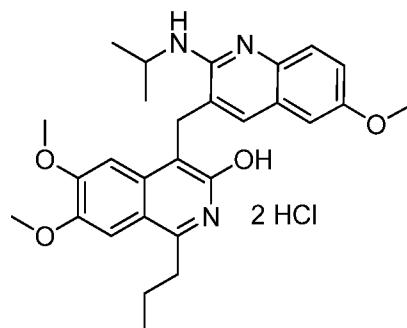
**30 <sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 22.0, 42.2, 46.7, 56.4, 109.9, 120.0, 123.4, 123.9, 124.5, 132.2, 143.9, 150.3, 158.9, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 265 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 267 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38)

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 2.40 min.

5 **4-((2-(Isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 53**

To a stirred solution of 3-(chloromethyl)-N-isopropyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28190** (305 mg, 1.01 mmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (250 mg, 1.01 mmol) followed by a 2 N aq. LiOH solution (1.01 mL, 2.02 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 94:6) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) provided 61 mg of 4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer 20 before addition of a 0.49 M HCl solution in MeOH (1.05 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **53** as a yellow solid (68 mg, 12% yield).



25

**53**

**MW:** 548.50; **Yield:** 12%; **Yellow solid;** **Mp (°C):** 148.3

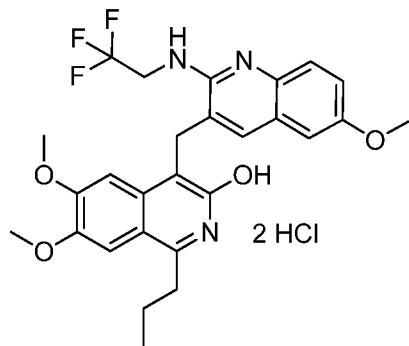
<sup>1</sup>H-NMR (CD<sub>3</sub>OD,  $\delta$ ): 1.10 (t, 3H,  $J$  = 6.5 Hz, CH<sub>3</sub>), 1.47 (d, 6H,  $J$  = 5.4 Hz, 2xCH<sub>3</sub>), 1.85-1.90 (m, 2H, CH<sub>2</sub>), 3.22-3.31 (m, 2H, CH<sub>2</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.29-4.40 (m, 3H, CH & CH<sub>2</sub>), 7.06 (s, 1H, 1xArH), 7.24 (s, 1H, 1xArH), 7.32-7.36 (m, 2H, 2xArH), 7.84 (d, 1H,  $J$  = 9.1 Hz, 1xArH), 8.08 (s, 1H, 1xArH).

MS-ESI m/z (% rel. Int.): 476 ([MH]<sup>+</sup>, 100).

HPLC: method B (10 min) XBridge<sup>TM</sup> column( 5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.57 min, peak area 95.2%.

10 Preparation of 6,7-dimethoxy-4-((6-methoxy-2-((2,2,2-trifluoroethyl)amino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride 54

To a stirred solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (116 mg, 0.47 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-methoxy-N-(2,2,2-trifluoroethyl)quinolin-2-amine hydrochloride **SLA 41062** (160 mg, 0.47 mmol) at RT followed by a 2 N aq. solution of LiOH (0.47 mL, 0.94 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 97:3) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) provided, after evaporation, 30 mg of 6,7-dimethoxy-4-((6-methoxy-2-((2,2,2-trifluoroethyl)amino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (1.05 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to give 6,7-dimethoxy-4-((6-methoxy-2-((2,2,2-trifluoroethyl)amino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **SLA 41064** as a yellow solid (31 mg, 11% yield).

**54**

**MW:** 588.45; **Yield:** 11%; **Yellow solid;** **Mp** (°C): 245.5

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.13 (t, 3H, *J* = 7.0 Hz, CH<sub>3</sub>), 1.90-1.97 (m, 2H, CH<sub>2</sub>), 3.31-3.35 (m, 2H, CH<sub>2</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 6H, 2xOCH<sub>3</sub>), 4.43 (s, 2H, CH<sub>2</sub>), 4.65 (q, 2H, *J* = 8.7 Hz, CH<sub>2</sub>), 7.08 (s, 1H, ArH), 7.31 (s, 1H, ArH), 7.42-7.45 (m, 2H, 2xArH), 7.95 (d, 1H, *J* = 9.2 Hz, ArH), 8.09 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.1, 24.6, 27.8, 33.5, 44.3 (q, *J* = 34.4 Hz), 56.4, 56.8, 57.3, 101.8, 105.6, 109.2, 117.7, 119.8, 124.3, 124.4, 125.2, 127.5, 131.0, 141.6, 141.8, 151.1, 153.1, 153.7, 155.8, 159.3, 159.3, CF<sub>3</sub> not seen.

**MS-ESI** m/z (% rel. Int.): 516 ([MH]<sup>+</sup>, 100).

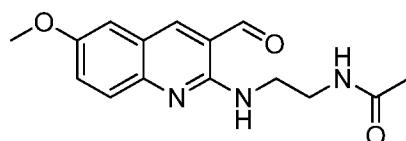
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.70 min, peak area 95.1%.

15 Preparation of *N*-(2-((3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride 55

*N*-(2-((3-Formyl-6-methoxyquinolin-2-yl)amino)ethyl)acetamide **SLA 41086**

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.00 g, 4.51 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added ethylenediamine (2.71 g, 45.09 mmol) and the reaction mixture was stirred for 2 h at 160°C under microwave irradiation then for 45 min at 180°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the residue was taken up in a mixture of THF:1 N aq. HCl = 1:1 (50 mL) and stirred for 1 h at RT. THF was then removed at 40°C under vacuum and the residue was neutralised with a saturated NaHCO<sub>3</sub> aqueous solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> (200 mL). The organic layer was isolated, washed with brine

(20 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under vacuum to give 1.22 g of a brown solid. This solid (600 mg, 2.45 mmol) was then dissolved in dry  $\text{CH}_2\text{Cl}_2$  (100 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer before addition of triethylamine (0.481 mL, 3.46 mmol) and acetic anhydride (0.28 mL, 2.96 mmol) and the reaction mixture was stirred overnight at RT. The organic solution was then washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent cyclohexane:EtOAc = 100:0 to 50:50) gave *N*-(2-((3-formyl-6-methoxyquinolin-2-yl)amino)ethyl)acetamide **SLA 41086** as a brown solid (150 mg, 21% yield).



10

**SLA 41086**

**MW:** 287.31; **Yield:** 21%; Brown solid; **Mp** (°C): 147.2

**<sup>1</sup>H-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 1.93 (s, 3H,  $\text{CH}_3\text{CO}$ ), 3.51-3.56 (m, 2H,  $\text{CH}_2\text{N}$ ), 3.77-3.83 (m, 2H,  $\text{CH}_2\text{N}$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 7.02 (d, 1H,  $J$  = 2.8 Hz, ArH), 7.38 (dd, 1H,  $J$  = 2.8 Hz and 9.2 Hz, ArH), 7.46 (broad s, 1H, NH), 7.58 (d, 1H,  $J$  = 9.2 Hz, ArH), 8.17-8.22 (broad m, 1H, NH), 8.21 (s, 1H, ArH), 9.99 (s, 1H,  $\text{HC=O}$ ).

**<sup>13</sup>C-NMR** ( $\text{CDCl}_3$ ,  $\delta$ ): 23.3, 40.1, 42.2, 55.6, 106.9, 117.4, 122.4, 126.3, 127.3, 146.2, 147.4, 154.5, 155.3, 170.3, 192.9.

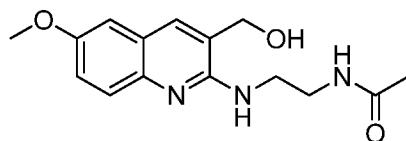
**MS-ESI** m/z (% rel. Int.): 288 ( $[\text{MH}]^+$ , 100).

20 **HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 1.98 min.

#### *N*-(2-(3-(Hydroxymethyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide **SLA 41088**

To a stirred solution of *N*-(2-((3-formyl-6-methoxyquinolin-2-yl)amino)ethyl)acetamide **SLA 41086** (147 mg, 512  $\mu\text{mol}$ ) in THF (20 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added sodium borohydride  $\text{NaBH}_4$  (19 mg, 502  $\mu\text{mol}$ ) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 min at that temperature, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and

the solution was extracted with  $\text{CH}_2\text{Cl}_2$  (100 mL). The organic layer was washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum to give *N*-(2-((3-hydroxymethyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide **SLA 41088** as an orange solid (113 mg, 76% yield).

**SLA 41088**

**MW:** 289.33; **Yield:** 76%; **Orange solid;** **Mp** ( $^{\circ}\text{C}$ ): 168.5

**$^1\text{H-NMR}$**  ( $\text{CDCl}_3$ ,  $\delta$ ): 1.84 (s, 3H,  $\text{CH}_3\text{CO}$ ), 3.39-3.44 (m, 2H,  $\text{CH}_2$ ), 3.64-3.68 (m, 2H,  $\text{CH}_2$ ), 3.85 (s, 3H,  $\text{OCH}_3$ ), 4.62 (s, 2H,  $\text{CH}_2$ ), 6.88 (d, 1H,  $J$  = 2.6 Hz, ArH), 7.18 (dd, 10

1H,  $J$  = 2.6 & 9.1 Hz, ArH), 7.46 (s, 1H, ArH), 7.55 (d, 1H,  $J$  = 9.1 Hz, ArH), OH not seen.

**$^{13}\text{C-NMR}$**  ( $\text{CDCl}_3$ ,  $\delta$ ): 23.1, 40.7, 42.4, 55.5, 63.2, 106.7, 120.8, 122.8, 123.5, 126.6, 134.8, 142.4, 154.9, 155.5, 171.1.

**MS-ESI** m/z (% rel. Int.): 290 ( $[\text{MH}]^+$ , 100).

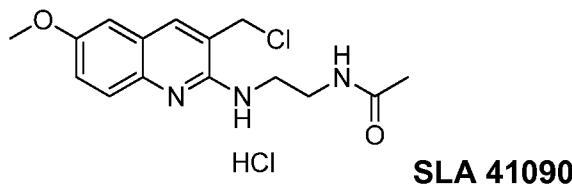
15 **HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu\text{m}$ , C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 2.03 min.

*N*-(2-((3-Chloromethyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide hydrochloride

**SLA 41090**

20 To a stirred solution of *N*-(2-((3-hydroxymethyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide **SLA 41088** (113 mg, 391  $\mu\text{mol}$ ) in dry  $\text{CH}_2\text{Cl}_2$  (20 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (0.28 mL, 3.86 mmol). The mixture was stirred for 1.5 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in

25  $\text{CH}_2\text{Cl}_2$  (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give *N*-(2-((3-chloromethyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide hydrochloride **SLA 41090** as a yellow solid (135 mg, 100% yield).

**SLA 41090**

**MW:** 344.24; **Yield:** 100%; **Yellow solid; Mp (°C):** 197.5

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 2.10 (s, 3H, CH<sub>3</sub>CO), 3.50-3.60 (m, 2H, CH<sub>2</sub>), 3.72-3.83 (m, 2H, CH<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.90-4.91 (m, 2H, CH<sub>2</sub>), 7.42 (s, 1H, ArH), 7.48 (d, 1H, J = 8.8 Hz, ArH), 8.05 (d, 1H, J = 8.8 Hz, ArH), 8.47 (s, 1H, ArH).

5 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 22.4, 38.7, 41.9, 42.9, 56.5, 109.8, 120.3, 123.7, 123.8, 124.8, 132.3, 143.8, 151.7, 159.1, 175.8.

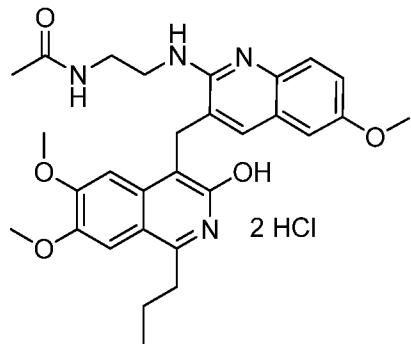
**MS-ESI** m/z (% rel. Int.): 308 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 310 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.18 min.

10

N-(2-((3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide 55

To a stirred solution of *N*-(2-((3-(chloromethyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide hydrochloride **SLA 41090** (128 mg, 0.372 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (103 mg, 0.417 mmol) followed by a 2 N aq. LiOH solution (0.21 mL, 0.42 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL) and washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 92:8) provided 19.4 mg of *N*-(2-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (1.0 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afforded *N*-(2-((3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride **55** as a yellow solid (20 mg, 9% yield).

**55**

**MW:** 591.53; **Yield:** 9%; **Yellow solid;** **Mp** (°C): 165.8

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.21-1.29 (m, 3H, CH<sub>3</sub>), 1.92-1.98 (m, 2H, CH<sub>2</sub>), 2.06 (s, 3H, CH<sub>3</sub>CO), 3.34-3.55 (m, 4H, 2xCH<sub>2</sub>), 3.70-3.98 (m, 8H, 2xOCH<sub>3</sub> and CH<sub>2</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 4.34 (s, 2H, CH<sub>2</sub>), 7.07-7.18 (m, 2H, 2xArH), 7.33 (d, 1H, *J* = 8.3 Hz, ArH), 7.45-7.61 (m, 2H, 2xArH), 8.01 (d, 1H, *J* = 8.3 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.3, 22.5, 24.8, 27.2, 33.7, 37.9, 39.0, 43.5, 56.5, 57.1, 57.6, 102.9, 106.0, 109.4, 119.3, 120.0, 123.6, 123.9, 124.4, 131.3, 139.5, 141.7, 152.2, 152.9, 154.9, 158.8, 160.0, 175.7, (1xC not observed).

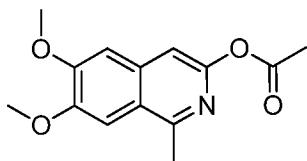
**MS-ESI** m/z (% rel. Int.): 519 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.28 min, peak area 98.2%.

15 Preparation of 4-((2-((2-acetamidoethyl)amino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-yl acetate 56

#### 6,7-Dimethoxy-1-methylisoquinolin-3-yl acetate SIL 32158

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (3.11 g, 20 14.19 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (230 mL) in a 500 mL round-bottomed flask equipped with a magnetic stirrer was added DIEA (2.46 mL, 14.88 mmol), DMAP (173 mg, 1.42 mmol) and acetic anhydride (1.39 mL, 14.80 mmol) and the reaction mixture was stirred overnight at RT. The organic solution was then washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. The residue was finally 25 purified by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 50:50) to give 6,7-dimethoxy-1-methylisoquinolin-3-yl acetate **SIL 32158** as an off-white solid (3.26 g, 88% yield).

**SIL 32158**

**MW:** 261.27; **Yield:** 88%; Off-white solid; **Mp** (°C): 139.4

**R<sub>f</sub>**(free base): 0.2 (cyclohexane:EtOAc = 50:50).

5 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.38 (s, 3H, CH<sub>3</sub>), 2.86 (s, 3H, CH<sub>3</sub>CO), 4.01 (s, 3H, OCH<sub>3</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 7.03 (s, 1H, ArH), 7.18 (s, 1H, ArH), 7.23 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 21.4, 22.1, 56.0 (2xC), 103.7, 105.2, 108.2, 122.2, 135.4, 149.7, 151.9, 153.2, 155.9, 169.7.

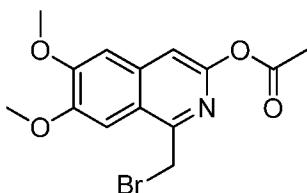
**MS-ESI** m/z (% rel. Int.): 262 ([MH]<sup>+</sup>, 100).

10 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.04 min.

**1-(Bromomethyl)-6,7-dimethoxyisoquinolin-3-yl acetate SIL 32162**

To a solution of 6,7-dimethoxy-1-methyliisoquinolin-3-yl acetate **SIL 32158**

15 (261 mg, 1.00 mmol) in dry CCl<sub>4</sub> (5 mL) in a 10 mL microwave vial equipped with a magnetic stirrer was added benzoyl peroxide (12 mg, 0.05 mmol) followed by NBS (178 mg, 1.00 mmol) and the mixture was stirred for 15 min at 130 °C under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under 20 vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave 1-(bromomethyl)-6,7-dimethoxyisoquinolin-3-yl acetate **SIL 32162** as a yellow solid (140 mg, 41% yield ).

**SIL 32162**

25 **MW:** 340.17; **Yield:** 41%; Yellow solid; **Mp** (°C): 164.9

**R<sub>f</sub>**: 0.2 (cyclohexane:EtOAc = 75:25).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.39 (s, 3H, CH<sub>3</sub>), 4.03 (s, 3H, CH<sub>3</sub>O), 4.07 (s, 3H, CH<sub>3</sub>O), 4.92 (s, 2H, CH<sub>2</sub>Br), 7.07 (s, 1H, ArH), 7.32 (s, 1H, ArH), 7.38 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 21.4, 31.2, 56.2 (2xC), 103.2, 105.2, 111.0, 121.5, 136.6, 150.3, 151.6, 152.4, 153.7, 169.5.

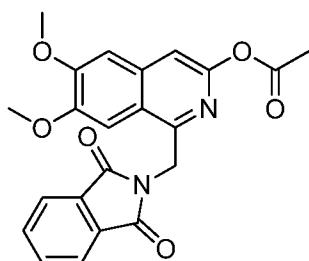
**MS-ESI** *m/z* (rel. int.): 340 ([MH]<sup>+</sup>, <sup>79</sup>Br, 63), 342 ([MH]<sup>+</sup>, <sup>81</sup>Br, 68).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model #

5 186003113), detection UV 254 nm, RT = 2.77 min.

**1-((1,3-Dioxoisindolin-2-yl)methyl)-6,7-dimethoxyisoquinolin-3-yl acetate SIL 32166**

To a stirred solution of 1-(bromomethyl)-6,7-dimethoxyisoquinolin-3-yl acetate **SIL 32162** (2.57 g, 7.56 mmol) in dry DMF (60 mL) in a 250 mL round-bottomed 10 flask equipped with a magnetic stirrer was added potassium phthalimide (2.43 g, 13.12 mmol) and the mixture was stirred overnight at RT and then diluted with Et<sub>2</sub>O (150 mL) and H<sub>2</sub>O (40 mL). A solid appeared and was isolated by filtration. The aqueous phase was isolated and diluted with Et<sub>2</sub>O (100 mL) before vigorous stirring 15 for 15 min, which gave a new amount of solid that was isolated by filtration (done 3 times). The solids were then combined, further washed with Et<sub>2</sub>O (100 mL) and dried overnight under vacuum in presence of P<sub>2</sub>O<sub>5</sub>, which gave 2.10 g of 1-((1,3-dioxoisindolin-2-yl)methyl)-6,7-dimethoxyisoquinolin-3-yl acetate **SIL 32166** as an off-white solid (68%).



20

**SIL 32166**

**MW:** 406.39; **Yield:** 68%; Off-white solid; **Mp** (°C): 247.0 (dec.).

**R<sub>f</sub>:** 0.25 (cyclohexane:EtOAc = 50:50).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 2.26 (s, 3H, CH<sub>3</sub>), 4.00 (s, 3H, CH<sub>3</sub>O), 4.05 (s, 3H, CH<sub>3</sub>O), 5.39 (s, 2H, CH<sub>2</sub>), 7.04 (s, 1H, ArH), 7.25 (s, 1H, ArH), 7.49 (s, 1H, ArH), 7.69-7.75 (m, 2H, 2xArH), 7.85-7.91 (m, 2H, 2xArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 21.4, 41.2, 56.1, 56.2, 102.4, 105.1, 109.8, 120.9, 123.4 (2xC), 132.3, 134.0 (2xC), 136.1, 150.2, 150.8, 151.9, 153.3, 168.2 (2xC), 169.3, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 407 ([MH]<sup>+</sup>, 100).

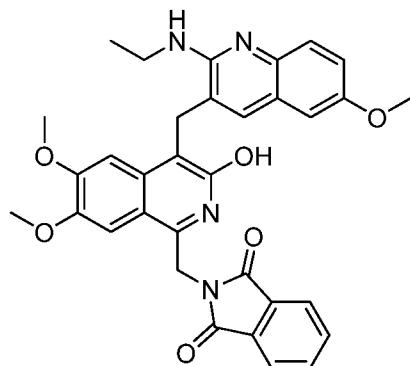
**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.92 min.

5 **2-((4-((2-(Ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)isoindoline-1,3-dione CCH 42006-1 and 2-((3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)isoindoline-1,3-dione hydrochloride CCH 42006B**

10 To a solution of 1-((1,3-dioxoisooindolin-2-yl)methyl)-6,7-dimethoxyisoquinolin-3-yl acetate **SIL 32166** (297 mg, 0.73 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (9 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added a 7 N NH<sub>3</sub> solution in MeOH (1 mL) and the reaction mixture was stirred for 4 h at RT then concentrated to dryness at 40°C under vacuum. The solid was taken up in THF (7 mL) and 15 transferred in a 20 mL microwave vial equipped with a magnetic stirrer before addition of a 2 N aq. LiOH solution (0.37 mL, 0.74 mmol) and 3-(chloromethyl)-N-ethyl-6-methoxyquinolin-2-amine **SLA 28166** free base (240 mg, 0.96 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (80 mL) and the organic 20 solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 97:3) followed by a second purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) gave 2-((4-((2-ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)isoindoline-1,3-dione **CCH 42006-1** as a yellow oil (75 mg, 32%).

25 During the purification, 2-((3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)isoindoline-1,3-dione was also isolated. The free base (23 mg) was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.5 mL). The 30 reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 2-((3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)isoindoline-1,3-dione hydrochloride **CCH 42006B** as a yellow solid (25 mg, 9% yield).

2-((4-((2-(Ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)isoindoline-1,3-dione CCH 42006-1 :



**CCH 42006-1**

5 **MW:** 578.61; **Yield:** 32%; Yellow oil.

**R<sub>f</sub>**(free base): 0.2 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 97:3).

10 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.23 (t, 3H, J = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.51 (q, 2H, J = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.08 (s, 2H, CH<sub>2</sub>), 5.26 (s, 2H, CH<sub>2</sub>), 6.76 (d, 1H, J = 2.5 Hz, ArH), 6.88 (s, 1H, ArH), 7.07 (dd, 1H, J = 2.5 and 9.0 Hz, ArH), 7.24-7.28 (m, 1H, ArH), 7.46 (s, 1H, ArH), 7.55-7.63 (m, 3H, 3xArH), 7.72-7.76 (m, 2H, 2xArH).

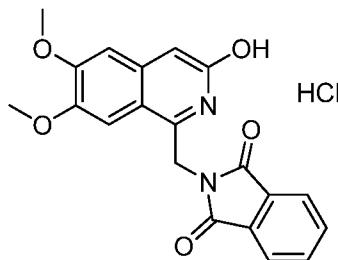
15 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.6, 28.2, 36.6, 38.4, 55.5, 56.0, 56.1, 62.1, 100.6, 102.3, 106.3, 112.4, 115.2, 119.5, 122.5, 123.2, 123.5 (2xC), 127.0, 131.8 (2xC), 134.2 (2xC), 134.8, 138.9, 141.5, 148.0, 154.4, 158.6, 168.0 (2xC), (3xC not observed).

20 **MS-ESI** m/z (% rel. Int.): 579 ([MH]<sup>+</sup>, 100).

**HPLC:** method B (5 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.53 min.

2-((3-Hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)isoindoline-1,3-dione

25 hydrochloride CCH 42006B :



**CCH 42006B**

**MW:** 400.81; **Yield:** 9%; Yellow solid; **Mp** (°C): 274.1

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>:CD<sub>3</sub>OD = 1:1,  $\delta$ ): 4.01 (s, 3H, OCH<sub>3</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 5.41 (s, 2H, CH<sub>2</sub>), 7.16-7.20 (m, 2H, 2xArH), 7.58 (s, 1H, ArH), 7.81-7.91 (m, 4H, 4xArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>:CD<sub>3</sub>OD = 1:1,  $\delta$ ): 38.6, 57.2, 57.4, 103.7, 105.2, 105.4, 118.7, 124.9 (2xC), 133.0 (2xC), 136.1 (2xC), 143.4, 145.7, 152.3, 155.5, 158.8, 169.3

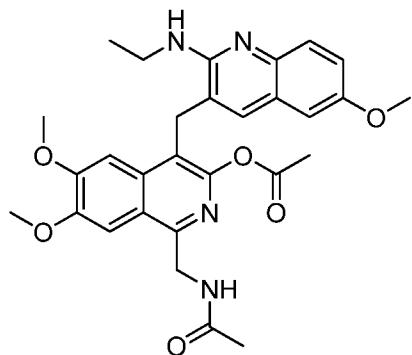
5 (2xC).

**MS-ESI** m/z (% rel. Int.): 365 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.02 min, peak area 98.9%.

10 **1-(Acetamidomethyl)-4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-yl acetate 56**

To a solution of 2-((4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)isoindoline-1,3-dione **CCH 42006-1** (75 mg, 130  $\mu$ mol) in EtOH (5 mL) in a 10 mL microwave vial equipped with a 15 magnetic stirrer was added hydrazine monohydrate (26  $\mu$ L, 536  $\mu$ mol) and the mixture was stirred for 10 min at 130°C under microwave irradiation. After cooling to RT, the reaction mixture was concentrated to dryness at 40°C under vacuum. The residue **CCH 42006-2** was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and half of the solution (around 65  $\mu$ mol) was transferred in a 5 mL microwave vial equipped with a 20 magnetic stirrer before addition of diisopropylaminomethyl-polystyrene resin (3 mmol/g, 86 mg, 258  $\mu$ mol), DMAP (2 mg, 16  $\mu$ mol) and acetic anhydride (34.5  $\mu$ L, 365  $\mu$ mol) and the reaction mixture was stirred for 20 min at 100°C under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL), filtered through cotton wool, then washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and 25 concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) gave 1-(acetamidomethyl)-4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-yl acetate **56** as an off-white solid (25 mg, 72% yield).

**56**

**MW:** 532.59; **Yield:** 72%; Off-white solid; **Mp** (°C): 262.5

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.36 (t, 3H, J = 7.1 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.15 (s, 3H, CH<sub>3</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 3.67-3.76 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 4.03-4.04 (m, 5H, OCH<sub>3</sub> & CH<sub>2</sub>), 4.58-4.62 (broad m, 1H, NH), 5.01-5.02 (m, 2H, CH<sub>2</sub>), 6.67 (d, 1H, J = 2.6 Hz, ArH), 6.94 (s, 1H, ArH), 7.08-7.16 (m, 3H, 2xArH & NH), 7.38 (s, 1H, ArH), 7.64 (d, 1H, J = 9.1 Hz, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 15.1, 21.1, 23.3, 27.1, 36.7, 42.1, 55.4, 56.0, 56.4, 102.6, 102.9, 106.0, 115.7, 120.2, 120.5, 121.3, 123.6, 127.4, 134.2, 134.9, 142.3, 150.2, 150.6, 151.4, 153.6, 153.7, 154.8, 169.6, 170.1.

**MS-ESI** m/z (% rel. Int.): 533 ([MH]<sup>+</sup>, 100), 555 ([M+Na]<sup>+</sup>, 16).

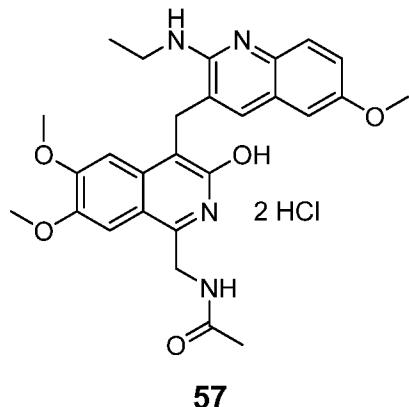
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.85 min, peak area 96.2%.

15

Preparation of N-(2-((3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride 57

To a solution of 1-(acetamidomethyl)-4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-yl acetate **56** (20 mg, 38 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (9 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added a 7 N NH<sub>3</sub> solution in MeOH (1 mL) and the reaction mixture was stirred overnight at RT then diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (50 mL) and the organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 90:10) gave *N*-(4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)acetamide. The free base was dissolved in MeOH (3 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before

addition of a 0.4 M HCl solution in MeOH (1 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford *N*-(4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)acetamide dihydrochloride **57** as a pale yellow solid (17 mg, 79% yield).



**MW:** 563.47; **Yield:** 79%; Pale yellow solid; **Mp (°C):** 210.3

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.51-1.56 (m, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.13 (s, 3H, CH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.83-3.88 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 4.41-4.43 (m, 2H, CH<sub>2</sub>), 5.12 (s, 2H, CH<sub>2</sub>), 7.12-7.19 (m, 2H, 2xArH), 7.28-7.38 (m, 1H, ArH), 7.50 (s, 1H, ArH), 7.66-7.72 (m, 1H, ArH), 7.93-8.01 (m, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 14.0, 22.7, 27.0, 39.2, 40.2, 56.3, 57.2, 57.5, 102.5, 105.5, 109.5, 111.6, 119.0, 119.7, 123.4, 123.7, 124.1, 131.2, 139.2, 142.0, 149.1, 152.3, 152.4, 158.7, 160.1, 174.3, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 533 ( $[\text{MH}]^+$ , 100), 555 ( $[\text{M}+\text{Na}]^+$ , 16).

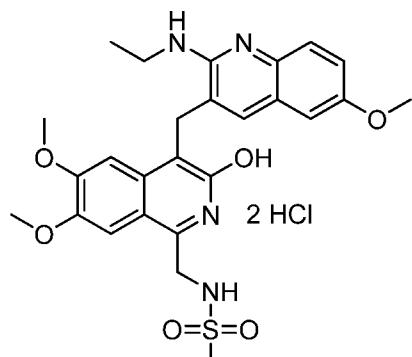
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.85 min, peak area 96.2%.

Preparation of *N*-(4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)methanesulfonamide dihydrochloride 58

The other portion of the residue **CCH 42006-2** (see preparation of compound **56**) was transferred in a 5 mL microwave vial equipped with a magnetic stirrer before addition of diisopropylaminomethyl-polystyrene resin (3 mmol/g, 86 mg, 258  $\mu$ mol), DMAP (2 mg, 16  $\mu$ mol) and methanesulfonyl chloride (25  $\mu$ L, 323  $\mu$ mol) and the reaction mixture was stirred for 20 min at 100°C under microwave irradiation. After cooling to RT, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL), filtered through cotton wool, then washed with brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated.

under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) gave 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-(methylsulfonamidomethyl)isoquinolin-3-yl methanesulfonate as a pale yellow solid.

5 This solid (21 mg, 35 µmol) was then dissolved in dry THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer before addition of phenylmagnesium bromide (1.0 N in THF, 0.25 mL, 0.25 mmol) and the reaction mixture was stirred for 20 min at 140°C under microwave irradiation. After cooling to RT, another portion of phenylmagnesium bromide (1.0 N in THF, 0.10 mL, 0.10 mmol) was added and the 10 reaction mixture was stirred for 20 min at 150°C under microwave irradiation. After cooling to RT, the mixture was carefully quenched with H<sub>2</sub>O (5 mL), then THF was removed at 40°C under vacuum and the residue was acidified with 1 mL of a 1 N aqueous HCl solution then neutralised with a saturated aqueous NaHCO<sub>3</sub> solution before to be extracted by a mixture CH<sub>2</sub>Cl<sub>2</sub>:MeOH=9:1 (30 mL). The organic layer 15 was isolated, washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 90:10) gave N-((4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)methanesulfonamide. This free base was dissolved in MeOH (3 mL) in a 10 mL round-bottomed flask equipped with a 20 magnetic stirrer before addition of a 0.4 M HCl solution in MeOH (1 mL). The reaction mixture was stirred for 5 min at RT, and concentrated at 40°C under vacuum to afford N-((4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)methanesulfonamide dihydrochloride **58** as a pale yellow solid (12 mg, 31% yield over 2 steps).



25

**58**

**MW:** 599.53; **Yield:** 31%; Pale yellow solid; **Mp (°C):** 205.7 (dec.)

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.55 (t, 3H,  $J$  = 6.5 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.22 (s, 3H, CH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.83-3.88 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 4.42 (s, 2H, CH<sub>2</sub>), 5.07 (s, 2H, CH<sub>2</sub>), 7.08-7.22 (m, 2H, 2xArH), 7.34 (d, 1H,  $J$  = 8.9 Hz, ArH), 7.52-7.65 (m, 1H, ArH), 7.72 (s, 1H, ArH), 7.94 (d, 1H,  $J$  = 8.9 Hz, ArH).

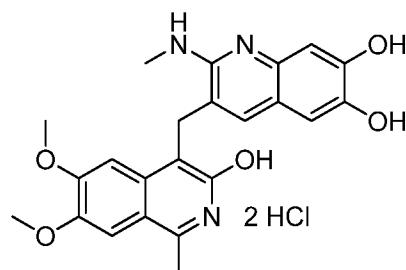
5 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 13.9, 27.1, 39.1, 40.0, 43.3, 56.4, 57.2, 57.5, 102.3, 105.4, 109.5, 111.8, 118.7, 119.6, 123.4, 123.6, 124.3, 131.2, 139.6, 142.0, 148.1, 152.1, 152.5, 158.7, 159.9, (1xC not observed).

**MS-ESI** m/z (% rel. Int.): 527 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 10 186003113), detection UV 254 nm, RT = 4.00 min, peak area 99.4%.

Preparation of 3-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-2-(methylamino)quinoline-6,7-diol dihydrochloride 59

To a solution of 6,7-dimethoxy-1-methyl-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)isoquinolin-3-ol **60** free base (28 mg, 65  $\mu$ mol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0°C in a 25 mL round-bottomed flask equipped with a magnetic stirrer under N<sub>2</sub> was added dropwise BCl<sub>3</sub> (1.0 N solution in CH<sub>2</sub>Cl<sub>2</sub>, 0.30 mL, 0.30 mmol). After complete addition, the bath was immediately removed and stirring was continued overnight at RT. The reaction mixture was then carefully quenched with MeOH (3 mL) and the mixture was concentrated to dryness at 40°C under vacuum before purification by prep. HPLC (eluent H<sub>2</sub>O:CH<sub>3</sub>CN:TFA = 100:0:0.05 to 60:40:0.05 in 10 min) and lyophilisation. The residue was then dissolved in a 0.19 N HCl solution in MeOH (5 mL) before concentration at 40°C under vacuum. Ion exchange on Amberlite IRA-400 (chloride form, 50 eq.) finally afforded 3-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-2-(methylamino)quinoline-6,7-diol dihydrochloride **59** as a brown solid (10 mg, 31% yield).



**59**

**MW:** 494.37; **Yield:** 31%; Brown solid; **Mp** (°C) > 295.0 (dec.)

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.04 (s, 3H, CH<sub>3</sub>), 3.35 (s, 3H, CH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.25 (s, 2H, CH<sub>2</sub>), 6.90 (s, 1H, ArH), 7.03 (s, 1H, ArH), 7.37-7.38 (m, 2H, 2xArH), 7.48 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 17.4, 26.6, 29.7, 56.8, 57.2, 102.2, 102.8, 106.1, 110.0, 111.9, 116.7, 119.4, 119.5, 132.2, 138.8, 141.0, 146.4, 151.0, 151.6, 153.0, 153.1, 159.6, (1xC not observed).

**MS-ESI** m/z (rel.int.): 422 ([MH]<sup>+</sup>, 100).

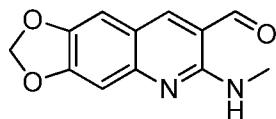
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.38 min, peak area 98.7%.

10

Preparation of 6,7-dimethoxy-1-methyl-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride **60**

6-(Methylamino)-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde **CCH 34158-1**

15 To a stirred solution of 6-chloro[1,3]dioxolo[4,5-g]quinoline-7-carboxaldehyde (1.14 g, 4.84 mmol) in 1,4-dioxane (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added methylamine (40 wt.%, 4.0 mL, 46.2 mmol) and the reaction mixture was stirred for 25 min at 160°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting 20 yellow oil was taken up in a mixture of THF:2 N aq. HCl = 1:1 (10 mL) and stirred for 20 min at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with a 10 N aqueous NaOH solution before extraction with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum to give 6-(methylamino)-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde **CCH 34158-1** as a yellow solid (1.10 g, 99% yield).



**CCH 34158-1**

**MW:** 230.22; **Yield:** 99%; Orange solid; **Mp** (°C): 177.6

30 **R<sub>f</sub>**(free base) = 0.2 (cyclohexane:EtOAc = 84:16).

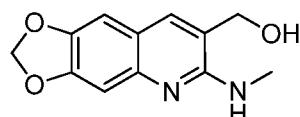
**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 3.14 (d, 3H,  $J$  = 4.8 Hz, NHCH<sub>3</sub>), 6.09 (s, 2H, OCH<sub>2</sub>O), 6.94 (s, 1H, ArH), 7.06 (s, 1H, ArH), 7.92-8.00 (broad m, 1H, NH), 8.01 (s, 1H, ArH), 9.90 (s, 1H, HC=O).

**MS-ESI** m/z (% rel. Int.): 231 ([MH]<sup>+</sup>, 100).

5 **HPLC:** Method A (10 min), XTerra<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186000482), detection UV 254 nm, RT = 3.10 min.

**(6-(Methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methanol CCH 34158-2**

To a stirred solution of 6-(methylamino)-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde **CCH 34158-1** (1.10 g, 4.78 mmol) in THF (50 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (184 mg, 4.86 mmol) and the mixture was stirred for 2 h at RT then quenched by addition of a 2 N aq. HCl solution (10 mL). After stirring for 10 min at RT, THF was removed at 40°C under vacuum and the mixture was then neutralised with a 2 N aq. NaOH solution, extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic layer was washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 33:67) gave, after evaporation, (6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methanol **CCH 34158-2** as an off-white solid (1.03 g, 93% yield).



20

**CCH 34158-2**

**MW:** 232.24; **Yield:** 93%; Off-white solid; **Mp** (°C): 191.6 (dec.).

**R<sub>f</sub>**(free base) = 0.2 (cyclohexane:EtOAc = 33:67).

25 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub> exchang. with CD<sub>3</sub>OD,  $\delta$ ): 3.05 (s, 3H, CH<sub>3</sub>), 4.59 (s, 2H, CH<sub>2</sub>O), 6.01 (s, 2H, OCH<sub>2</sub>O), 6.87 (s, 1H, ArH), 7.15 (s, 1H, ArH), 7.48 (s, 1H, ArH).

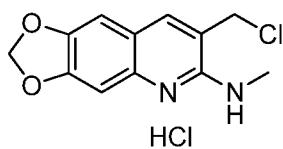
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub> exchang. with CD<sub>3</sub>OD,  $\delta$ ): 29.8, 64.5, 102.9, 105.0, 105.3, 119.8, 122.0, 136.4, 146.0, 146.8, 152.1, 158.0.

**MS-ESI** m/z (% rel. Int.): 233 ([MH]<sup>+</sup>, 100).

30 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.08 min.

7-(Chloromethyl)-N-methyl-[1,3]dioxolo[4,5-g]quinolin-6-amine hydrochloride CCH  
34158B

To a stirred solution of (6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methanol **CCH 34158-2** (1.00 g, 4.31 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (5.0 mL, 68.9 mmol). The mixture was stirred for 2 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in  $\text{CH}_2\text{Cl}_2$  (15 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 7-(chloromethyl)-N-methyl-[1,3]dioxolo[4,5-g]quinolin-6-amine hydrochloride **CCH 34158B** as a yellow solid (1.24 g, 100% yield).



**CCH 34158B**

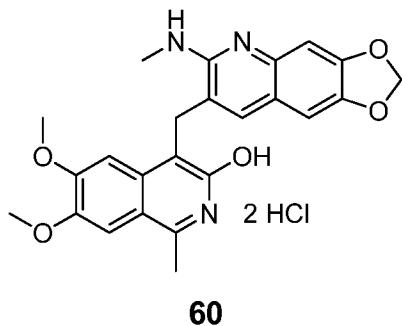
**MW:** 287.14; **Yield:** 100%; Yellow solid.

<sup>1</sup>**H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 3.26 (s, 3H,  $\text{CH}_3$ ), 4.81 (s, 2H,  $\text{CH}_2$ ), 6.19 (s, 2H,  $\text{OCH}_2\text{O}$ ), 7.23 (s, 1H, ArH), 7.45 (s, 1H, ArH), 8.27 (s, 1H, ArH).  
<sup>13</sup>**C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 29.8, 42.0, 97.9, 104.6, 106.2, 118.0, 120.5, 135.5, 143.4, 148.4, 152.4, 154.8.

6,7-Dimethoxy-1-methyl-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride 60

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (147 mg, 670  $\mu\text{mol}$ ) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. KOH solution (0.70 mL, 1.40 mmol) at RT followed by 7-(chloromethyl)-N-methyl-[1,3]dioxolo[4,5-g]quinolin-6-amine hydrochloride **CCH 34158B** (200 mg, 697  $\mu\text{mol}$ ) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 9:1$  (80 mL) and the organic solution was washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2:7\text{ N NH}_3$  solution in  $\text{MeOH} = 100:0$  to 95:5) gave 6,7-dimethoxy-1-methyl-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)isoquinolin-3-ol. This free base was dissolved

in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.19 M HCl solution in MeOH (1 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-1-methyl-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride **60** as a brown solid (30 mg, 6% yield).



**MW:** 506.38; **Yield:** 6%; Brown solid; **Mp** (°C) > 295 (dec.)

**R<sub>f</sub>**(free base) = 0.3 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5).

10 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.09 (s, 3H, CH<sub>3</sub>), 3.37 (s, 3H, NCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.29 (s, 2H, CH<sub>2</sub>), 6.11 (s, 2H, OCH<sub>2</sub>O), 6.99 (s, 1H, ArH), 7.06 (s, 1H, ArH), 7.38 (s, 1H, ArH), 7.47 (s, 1H, ArH), 7.55 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 17.6, 26.6, 30.0, 57.0, 57.4, 97.7, 102.5, 104.3, 105.9, 106.3, 109.8, 118.3, 120.0, 120.9, 134.1, 139.0, 141.0, 148.1, 151.6, 152.0, 153.5, 153.8,

15 159.9, (1xC not observed)..

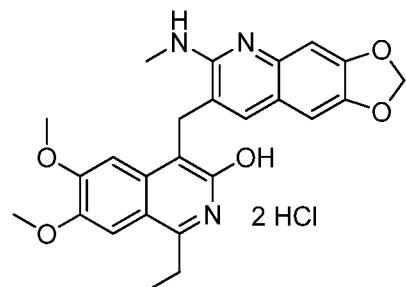
**MS-ESI** m/z (% rel. Int.): 434 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.83 min, peak area 97.9%.

20 Preparation of 1-ethyl-6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride **61**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (284 mg, 1.22 mmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. LiOH solution (1.20 mL, 2.40 mmol) at RT followed by 7-25 (chloromethyl)-N-methyl-[1,3]dioxolo[4,5-g]quinolin-6-amine hydrochloride **CCH 34158B** (350 mg, 1.22 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (80 mL) and the organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum.

Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:7 N NH<sub>3</sub> solution in MeOH = 100:0 to 95:5) gave 1-ethyl-6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)isoquinolin-3-ol. This free base was dissolved in MeOH (6 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer 5 before addition of a 0.19 M HCl solution in MeOH (5 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum. Recrystallization from a mixture of MeOH:Et<sub>2</sub>O afforded 1-ethyl-6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride **61** as a pale brown solid (104 mg, 16% yield).



10

**61**

**MW:** 520.40; **Yield:** 16%; Pale brown solid; **Mp** (°C): 263.4

**R<sub>f</sub>**(free base): 0.25 (CH<sub>2</sub>Cl<sub>2</sub>:7 N NH<sub>3</sub> in MeOH = 95:5).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD:CDCl<sub>3</sub> = 1:1, δ): 1.41 (t, 3H, *J* = 7.6 Hz, CH<sub>3</sub>), 3.14 (q, 2H, *J* = 7.6 Hz, CH<sub>2</sub>), 3.20 (s, 3H, NCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.09 (s, 3H, OCH<sub>3</sub>), 4.26 (s, 2H, CH<sub>2</sub>), 6.16 (s, 2H, OCH<sub>2</sub>O), 7.00 (s, 1H, ArH), 7.06 (s, 1H, ArH), 7.17 (s, 1H, ArH), 7.38 (s, 1H, ArH), 8.30 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD:CDCl<sub>3</sub> = 1:1, δ): 17.5, 27.9, 31.2, 32.5, 59.4, 59.8, 100.5, 103.4, 106.7, 107.1, 108.4, 113.3, 116.9, 120.5, 126.1, 136.6, 144.1, 144.5, 150.7, 151.8, 20 156.2, 156.3, 160.2 (2xC not observed).

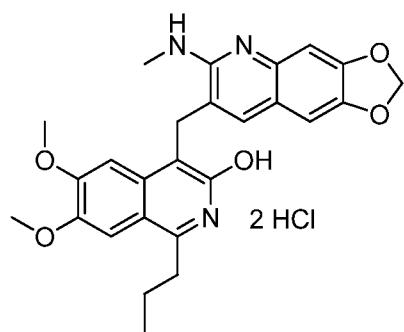
**MS-ESI** m/z (% rel. Int.): 448 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.99 min, peak area 98.7%.

25 Preparation of 6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **62**

To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (245 mg, 0.99 mmol) in toluene (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 2 N aq. LiOH solution (1.00 mL, 2.00 mmol) at RT followed by 7-

(chloromethyl)-*N*-methyl-[1,3]dioxolo[4,5-*g*]quinolin-6-amine hydrochloride **CCH 34158B** (284 mg, 0.99 mmol) and the mixture was stirred at 150°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (80 mL) and the organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:7 N NH<sub>3</sub> solution in MeOH = 100:0 to 95:5) gave, after evaporation, 6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)-1-propylisoquinolin-3-ol. This free base was dissolved in MeOH (3 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.19 M HCl solution in MeOH (2 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **62** as a beige solid (46 mg, 9% yield).



15

**62**

**MW:** 534.43; **Yield:** 9%; Beige solid; **Mp (°C)** > 295 (dec.)

**R<sub>f</sub>**(free base) = 0.3 (CH<sub>2</sub>Cl<sub>2</sub>:7N NH<sub>3</sub> in MeOH = 95:5).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.13 (t, 3H, *J* = 7.1 Hz, CH<sub>3</sub>), 1.90-1.97 (m, 2H, CH<sub>2</sub>), 3.25-3.38 (m, 5H, NCH<sub>3</sub> & CH<sub>2</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.27 (s, 2H, CH<sub>2</sub>), 6.12 (s, 2H, OCH<sub>2</sub>O), 7.03-7.05 (m, 2H, 2xArH), 7.42-7.52 (m, 3H, 3xArH).  
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.2, 24.7, 26.8, 29.9, 33.5, 56.8, 57.3, 97.6, 102.3, 104.3, 105.8, 110.1, 118.2, 118.8, 121.2, 134.1, 139.2, 141.6, 148.1, 151.8, 153.5, 153.8, 154.5, 159.7 (2xC not observed).

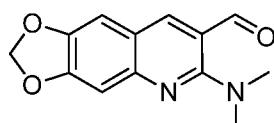
**MS-ESI** m/z (% rel. Int.): 462 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.21 min, peak area 97.6%.

Preparation of 4-((6-(dimethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 63

6-(Dimethylamino)-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde RBO 35166

5 To a stirred solution of 6-chloro-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (1.0 g, 4.07 mmol) in dioxane (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added dimethylamine (40% in water, 5.1 mL, 40.7 mmol) and the reaction mixture was stirred for 45 min at 160°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the 10 resulting yellow oil was taken back in water (30 mL). The precipitate formed was filtered through a fritted glass filter (porosity 3) to give after evaporation 6-(dimethylamino)-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde **RBO 35166** (960 mg, 97%).



15

**RBO 35166**

**MW:** 244.25; **Yield:** 97%; Green solid.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 3.12 (s, 6H, 2xNCH<sub>3</sub>), 6.10 (s, 2H, CH<sub>2</sub>), 7.00 (s, 1H, ArH), 7.15 (s, 1H, ArH), 8.26 (s, 1H, ArH), 10.10 (s, 1H, HC=O).

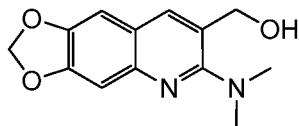
**MS-ESI** m/z (% rel. Int.): 245.2 ([MH]<sup>+</sup>, 100).

20 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 μm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.30 min, peak area 98.0%.

(6-(Dimethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methanol RBO 35168

To a stirred solution of 6-dimethylamino-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde **RBO 35166** (960 mg, 3.93 mmol) in a mixture EtOH:THF = 50 mL:20 mL in a 250 mL round-bottomed flask equipped with a magnetic stirrer at 0°C was added NaBH<sub>4</sub> (149 mg, 3.93 mmol) and the mixture was stirred overnight at RT. After cooling with an ice bath, a 6 N aq. HCl solution (2 mL) was added. After stirring for 1 h at 0°C, the mixture was brought to pH = 9 with a 2 N aq. NaOH solution (6 mL). The volatiles were removed at 40°C under vacuum until precipitation of a solid. This solid was filtered, washed with water (315 mL) to give after drying (6-

(dimethylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methanol **RBO 35168** as a green solid (775 mg, 80% yield).



**RBO 35168**

5 **MW:** 246.27; **Yield:** 80%; Green solid.

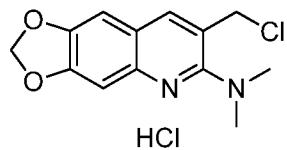
**<sup>1</sup>H-NMR** (MeOD,  $\delta$ ): 2.85 (s, 6H, 2xNCH<sub>3</sub>), 4.62 (s, 2H, CH<sub>2</sub>), 5.93 (s, 2H, CH<sub>2</sub>), 6.95 (s, 1H, ArH), 7.05 (s, 1H, ArH), 7.90 (s, 1H, ArH).

**MS-ESI** m/z (% rel. Int.): 247.0 ([MH]<sup>+</sup>, 100).

10 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.17 min, peak area 90 %.

7-(Chloromethyl)-*N,N*-dimethyl-[1,3]dioxolo[4,5-*g*]quinolin-6-amine hydrochloride  
**RBO 35172**

To a stirred solution of (6-(dimethylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methanol **RBO 35168** (775 mg, 3.15 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (2.3 mL, 31.5 mmol). The mixture was stirred for 1.5 h at RT then concentrated to dryness at 40°C under vacuum. The residue was coevaporated twice with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 40°C under vacuum to give after further drying 7-(chloromethyl)-*N,N*-dimethyl-[1,3]dioxolo[4,5-*g*]quinolin-6-amine hydrochloride **RBO 35172** as a green solid (850 mg, 90% yield).



**RBO 35172**

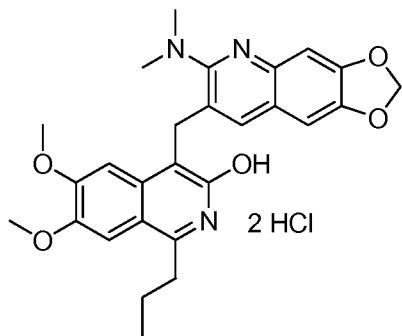
**MW:** 301.19; **Yield:** 90%; green solid; **Mp (°C)** > 360.0

25 **<sup>1</sup>H-NMR** (MeOD,  $\delta$ ): 3.29 (s, 6H, 2xNCH<sub>3</sub>), 4.80 (s, 2H, CH<sub>2</sub>), 6.05 (s, 2H, CH<sub>2</sub>), 7.10 (s, 1H, ArH), 7.22 (s, 1H, ArH), 8.30 (s, 1H, ArH).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.22 min, peak area 92%.

4-((6-(Dimethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 63

To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (250 mg, 1.0 mmol) in toluene in a 20 mL microwave vial was added LiOH.H<sub>2</sub>O (84 mg, 2.0 mmol) and 7-(chloromethyl)-N,N-dimethyl-[1,3]dioxolo[4,5-g]quinolin-6-amine hydrochloride **RBO 35172** (301 mg, 1.0 mmol). The mixture was stirred at 150°C for 1.5 h under microwave irradiation then cooled to RT. The volatiles were removed under vacuum and the residue was taken back in dichloromethane (30 mL), washed with water (3x10 mL), brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to give an orange solid. This solid was purified by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:7 N NH<sub>3</sub> solution in MeOH = 100:0 to 95:5) to give after evaporation and drying 4-((6-(dimethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol (142 mg). This free base was dissolved in MeOH (5 mL) and a HCl 0.19 N solution in MeOH (1.35 mL, 0.26 mmol) was slowly added. The reaction mixture was stirred at 4°C for 15 min. After evaporation and drying under vacuum pump under P<sub>2</sub>O<sub>5</sub>, 4-((6-(dimethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **63** was obtained as a yellow solid (148 mg, 55% yield).



20

**63**

**MW:** 548.46; **Yield:** 13%; **Yellow Solid;** **Mp** (°C): 169.6

**R<sub>f</sub>**(free base) = 0.10 (CH<sub>2</sub>Cl<sub>2</sub>: 7 N NH<sub>3</sub> solution in MeOH = 95:5).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.15 (t, 3H, *J* = 9 Hz, CH<sub>3</sub>), 1.95 (q, 2H, *J* = 9 Hz, CH<sub>2</sub>), 3.39 (2H, CH<sub>2</sub>, peak under solvent signal), 3.55 (s, 6H, 2xCH<sub>3</sub>N), 3.95 (s, 3H, CH<sub>3</sub>O), 4.03 (s, 3H, CH<sub>3</sub>O), 4.55 (s, 2H, CH<sub>2</sub>), 6.13 (s, 2H, CH<sub>2</sub>), 6.96 (s, 1H, ArH), 7.04 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.50 (s, 1H, ArH), 7.72 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 14.2, 24.7, 28.8, 33.6, 43.4, 56.9, 57.3, 98.0, 102.6, 104.6 (2xC), 105.1, 106.0, 112.8, 119.2, 121.0, 124.6, 135.6, 141.1, 143.5, 149.3, 152.0, 152.7, 154.7, 156.4, 159.7.

**MS-ESI** m/z (% rel. Int.): 476 ([MH]<sup>+</sup>, 100).

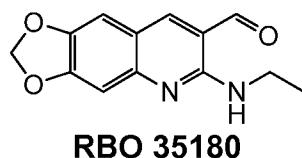
5 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.23 min, peak area 99.0 %.

Preparation of 4-((6-(ethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 64

10

6-(Ethylamino)-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde RBO 35180

To a solution of 6-chloro-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde (1.0 g, 4.24 mmol) in dioxane (10 mL) was added ethylamine (3.58 mL, 70% in water) and the mixture was heated at 160°C under microwave irradiation for 45 min. After 15 cooling to RT, the mixture was poured into a mixture of THF:1 N HCl aq. solution = 1:1 (25 mL) and stirred for 25 min at RT. The mixture was brought to pH = 7 with a saturated aq. solution of NaHCO<sub>3</sub> and extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic layer was washed with H<sub>2</sub>O (3x30mL), brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to give 6-(ethylamino)-[1,3]dioxolo[4,5-g]quinoline-7-carbaldehyde RBO 20 35180 as a yellow solid (941 mg, 91% yield).



**MW:** 244.25; **Yield:** 91%; Yellow solid.

25 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 1.32 (t, 3H,  $J$  = 7.5 Hz, CH<sub>3</sub>), 3.59-3.69 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 6.06 (s, 2H, OCH<sub>2</sub>O), 6.93 (s, 1H, ArH), 7.03 (s, 1H, ArH), 7.95 (broad s, 1H, NH), 8.00 (s, 1H, ArH), 9.89 (s, 1H, HC=O).

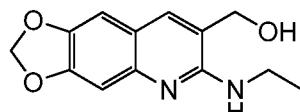
**MS-ESI** m/z (rel.int.): 245 ([M+H]<sup>+</sup>, 100).

**HPLC:** Method (5 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 30 186003113), detection UV 254 nm, RT = 2.08 min, peak area 98%.

(6-(Ethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methanol RBO 40002

To a solution of 6-(ethylamino)-[1,3]dioxolo[4,5-*g*]quinoline-7-carbaldehyde **RBO 35180** (941 mg, 3.85 mmol) in a mixture EtOH:THF = 5:2 (70 mL) at 0°C was added NaBH<sub>4</sub> (146 mg, 3.85 mmol) by small portions. The mixture was stirred for 2 h at RT, cooled at 0°C and treated with a 1 N HCl solution (6 mL). The solution was 5 neutralized with a concentrated NaHCO<sub>3</sub> aq. solution and evaporated under vacuum at 45°C. The crude residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (3x50 mL) and the separated organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered to give, after evaporation and drying, (6-(ethylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methanol **RBO 40002** as a brown solid (901 mg, 95% yield).

10

**RBO 40002**

**MW:** 246.26; **Yield:** 95%; Brown Solid.

**MS-ESI** m/z (rel.int.): 247 ([M+H]<sup>+</sup>, (100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 15 186003113), detection UV 254 nm, RT = 2.03 min, peak area 98%.

**7-(Chloromethyl)-N-ethyl-[1,3]dioxolo[4,5-*g*]quinolin-6-amine hydrochloride RBO 40004**

20 To a solution of (6-(ethylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methanol **RBO 40002** (901 mg, 3.66 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) in a round-bottomed flask equipped with a magnetic stirrer was added thionyl chloride (2.65 mL, 36.6 mmol). The mixture was stirring for 3 h at RT, evaporated under vacuum at 45°C and coevaporated twice with CH<sub>2</sub>Cl<sub>2</sub> (to remove SOCl<sub>2</sub>) to afford 7-(chloromethyl)-N-ethyl-[1,3]dioxolo[4,5-*g*]quinolin-6-amine hydrochloride **RBO 40004** as a yellow solid (1.01 g, 92% yield).

25

**RBO 40004**

30 **MW:** 301.17; **Yield:** 92%; Yellow Solid; **Mp** (°C): 71.4

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.43 (t, 3H,  $J$  = 7.5 Hz, CH<sub>3</sub>), 3.71 (q, 2H,  $J$  = 6.9 Hz, CH<sub>2</sub>CH<sub>3</sub>), 4.85 (s, 2H, OCH<sub>2</sub>O), 6.20 (2H, s, CH<sub>2</sub>Cl), 7.25 (s, 1H, ArH), 7.45 (s, 1H, ArH), 8.30 (s, 1H, ArH).

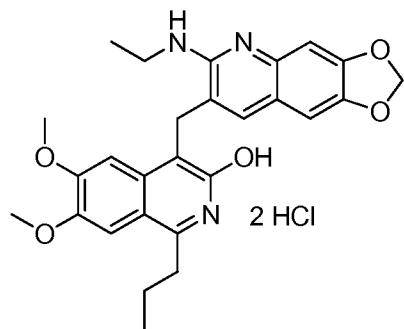
**MS-ESI** m/z (rel.int.): 265 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100), 267 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 36).

5 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.77 min, peak area%.

**4-((6-(Ethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 64**

10 To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (305 mg, 1.0 mmol) in toluene (12 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added LiOH.H<sub>2</sub>O (56% LiOH solution) (84 mg, 2.0 mmol) followed by 7-(chloromethyl)-N-ethyl-[1,3]dioxolo[4,5-g]quinolin-6-amine hydrochloride **RBO 40004** (250 mg, 1.0 mmol). The mixture was heated for 1.5 h at 150°C under microwave 15 irradiation. The vial was cooled to RT and the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The organic layer was washed with H<sub>2</sub>O (3x30 mL), brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered to give, after evaporation, a yellow solid. This crude solid was purified by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:7 N NH<sub>3</sub> solution in MeOH = 100:0 to 95:5) to give after evaporation 4-((6-(ethylamino)- 20 [1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol. This free base was treated for 5 min by a 0.49 N HCl solution in MeOH (5 mL). The reaction mixture was evaporated to give, after further drying, 4-((6-(ethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride as a yellow solid **64** (20 mg, 3.6% yield).

25



**64**

30 **MW:** 548.46; **Yield:** 3.6%; Yellow Solid.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.11 (t, 3H,  $J$  = 7.5 Hz, CH<sub>3</sub>), 1.50 (t, 3H  $J$  = 6 Hz, CH<sub>3</sub>), 1.90 (m, 2H, CH<sub>2</sub>), 3.28 (shoulder behind CD<sub>3</sub>OD, 2H, CH<sub>2</sub>N), 3.70 (q, 2H,  $J$  = 6 Hz, CH<sub>2</sub>), 4.00 (s, 6H, 2OCH<sub>3</sub>), 4.30 (s, 2H, OCH<sub>2</sub>O), 6.13 (s, 2H, CH<sub>2</sub>), 7.04 (s, 1H, ArH), 7.09 (s, 1H, ArH), 7.39 (s, 2H, 2xArH), 7.81 (s, 1H, ArH).

5 **MS-ESI** m/z (rel.int.) : 476 ([M+H]<sup>+</sup>, 100).

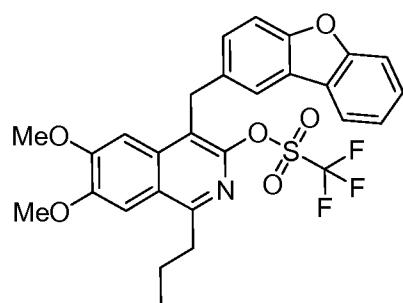
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5  $\mu$ m, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.47 min, peak area 94.0%.

Preparation of 4-(dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-amine hydrochloride 65

10

4-(Dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-yl trifluoromethanesulfonate CCH 42040-1

To a solution of 4-(dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol hydrochloride **7** (15 mg, 32  $\mu$ mol) in DMF (2 mL) in a 5 mL round-bottomed flask equipped with a magnetic stirrer were added triethylamine (16  $\mu$ L, 114  $\mu$ mol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (30 mg, 84  $\mu$ mol). The mixture was stirred for 5 h at RT, then for 1 h at 65°C. After cooling to RT, the mixture was diluted with Et<sub>2</sub>O (30 mL) and washed with brine (10 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave 4-(dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-yl trifluoromethanesulfonate **CCH 42040-1** as a pale yellow oil (13 mg, 72% yield).



**CCH 42040-1**

25 **MW:** 559.55; **Yield:** 72%; Pale Yellow Oil.

**R<sub>f</sub>:** 0.2 (cyclohexane:EtOAc = 75:25).

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 1.09 (t, 3H,  $J$  = 7.4 Hz, CH<sub>3</sub>), 1.94-2.05 (m, 2H, CH<sub>2</sub>), 3.17 (t, 2H,  $J$  = 7.5 Hz, CH<sub>2</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.55 (s, 2H, CH<sub>2</sub>), 7.18

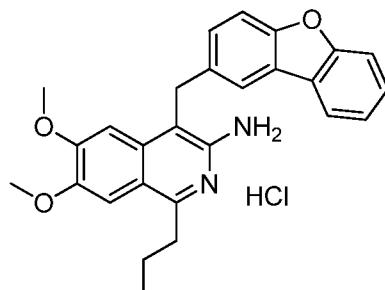
(s, 1H, ArH), 7.28-7.34 (m, 2H, 2xArH), 7.39-7.54 (m, 4H, 4xArH), 7.71-7.73 (m, 1H, ArH), 7.80-7.86 (m, 1H, ArH).

<sup>13</sup>C-NMR (CD<sub>3</sub>OD, δ): 14.1, 21.0, 31.7, 36.3, 55.9, 56.0, 103.5, 104.0, 111.7 (2xC), 116.3, 120.0, 120.7, 122.7, 123.4, 123.9, 124.7, 127.2, 127.3, 133.2, 134.8, 149.9,

5 150.1, 153.2, 155.0, 156.5, 158.2, CF<sub>3</sub> not seen.

4-(Dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-amine hydrochloride 65

A 2 mL microwave vial equipped with a magnetic stirrer was charged under N<sub>2</sub> with 4-(dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-yl trifluoromethanesulfonate **CCH 42040-1** (13 mg, 23 μmol), *t*-butyl carbamate (5 mg, 43 μmol), dry powdered cesium carbonate (15 mg, 46 μmol), 9,9-dimethyl-4,5-bis (diphenylphosphino)xanthene (4 mg, 7 μmol) and tris(dibenzylideneacetone) dipalladium(0) (4 mg, 4 μmol). Dry THF (1.5 mL) was then added and the mixture was stirred for 45 min at 140°C under microwave irradiation. After cooling to RT, the mixture was diluted with EtOAc (30 mL), then filtered through celite. The solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. The residue was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of TFA (1 mL) and the mixture was stirred overnight at RT then concentrated to dryness under vacuum. The residue was basified with a saturated NaHCO<sub>3</sub> solution (10 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (40 mL). The organic phase was isolated, washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 25 50:50) gave 4 mg of 4-(dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-amine. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.5 mL) and the solution was stirred for 5 min at RT, and concentrated at 40°C under vacuum to afford 4-(dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-amine hydrochloride **65** as a pale brown solid (4 mg, 38% yield).



65

**MW:** 462.97; **Yield:** 38%; Pale Brown Solid.

**R<sub>f</sub>:** 0.2 (cyclohexane:EtOAc = 50:50, free base).

5 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.13 (t, 3H, *J* = 7.3 Hz, CH<sub>3</sub>), 1.94 (sextuplet, 2H, *J* = 7.3 Hz, CH<sub>2</sub>), 3.25-3.35 (m, 2H, CH<sub>2</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.52 (s, 2H, CH<sub>2</sub>), 7.15 (s, 1H, ArH), 7.30-7.36 (m, 3H, 3xArH), 7.44-7.56 (m, 3H, 3xArH), 7.88-7.94 (m, 2H, 2xArH).

10 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.2, 24.3, 31.6, 33.7, 56.6, 56.8, 102.3, 104.9, 112.2, 112.6, 112.8, 117.7, 121.0, 121.6, 124.0, 125.1, 125.9, 128.4, 128.6, 134.2, 140.9, 147.1, 151.2, 151.5, 156.4, 158.0, 159.1.

**MS-ESI** *m/z* (rel. int.): 427 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 5.57 min, peak area 95.8%.

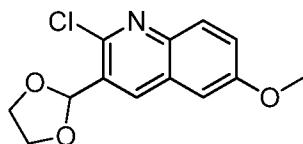
15

Preparation of 4-((2-ethyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 66

2-Chloro-3-(1,3-dioxolan-2-yl)-6-methoxyquinoline SMA 44002

20 To a solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (4.01 g, 18.10 mmol) in toluene (200 mL) in a 500 mL round-bottomed flask equipped with a magnetic stirrer under N<sub>2</sub> was added ethylene glycol (1.20 mL, 21.52 mmol) followed by *p*-toluenesulfonic acid monohydrate (348 mg, 1.83 mmol). The mixture was stirred overnight under reflux using a Dean-Stark apparatus. After cooling to RT, the mixture  
25 was concentrated at 40°C under vacuum, then the residue was diluted with saturated aqueous NaHCO<sub>3</sub> solution (40 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was isolated, washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography

(SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 92:8 to 75:25) gave 2-chloro-3-(1,3-dioxolan-2-yl)-6-methoxyquinoline **SMA 44002** as a white solid (4.39 g, 91% yield).



5

**SMA 44002**

**MW:** 265.69; **Yield:** 91%; **White Solid;** **Mp (°C):** 93.6

**R<sub>f</sub>:** 0.2 (cyclohexane:EtOAc = 75:25).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 3.93 (s, 3H, OCH<sub>3</sub>), 4.11-4.23 (m, 4H, 2xCH<sub>2</sub>), 6.22 (s, 1H, CH), 10 7.11 (d, 1H, J = 2.7 Hz, ArH), 7.40 (dd, 1H, J = 2.7 & 9.2 Hz, ArH), 7.92 (d, 1H, J = 9.2 Hz, ArH), 8.31 (s, 1H, ArH).

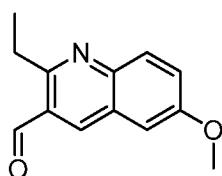
**MS-ESI** m/z (% rel. Int.): 268 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38), 266 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100).

**HPLC:** Method B (5 min), XBridgeTM column(5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 3.01 min.

15

#### 2-Ethyl-6-methoxyquinoline-3-carbaldehyde SMA 44004

To a solution of 3-[1,3]dioxolan-2-yl-2-ethyl-6-methoxyquinoline **SMA 44002** (400 mg, 1.54 mmol) in THF (10 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added a 1 N aqueous HCl solution (5 mL) and the mixture 20 was stirred overnight at RT, then for 1 h at 70°C. A 6 N aqueous HCl solution (2.5 mL) was then added and the mixture was stirred for 26 h at 70°C. THF was removed at 40°C under vacuum before addition of a conc. NH<sub>4</sub>OH solution (5 mL). The solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic phase was isolated, washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C 25 under vacuum to give 2-ethyl-6-methoxyquinoline-3-carbaldehyde **SMA 44004** as a brown oil (269 mg, 81% yield).

**SMA 44004**

**MW:** 215.25; **Yield:** 81%; **Brown Oil.**

30 **R<sub>f</sub>:** 0.25 (cyclohexane:EtOAc = 75:25, free base).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.38 (t, 3H, J = 7.5 Hz, CH<sub>3</sub>), 3.35 (q, 2H, J = 7.5 Hz, CH<sub>2</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 7.16 (d, 1H, J = 2.7 Hz, ArH), 7.48 (dd, 1H, J = 2.7 & 9.2 Hz, ArH), 7.99 (d, 1H, J = 9.2 Hz, ArH), 8.50 (s, 1H, ArH), 10.38 (s, 1H, CHO).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.3, 29.3, 55.6, 106.0, 125.4, 127.1, 127.4, 130.1, 140.6,

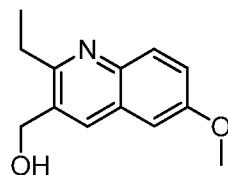
5 145.7, 157.9, 160.8, 191.4.

**MS-ESI** m/z (% rel. Int.): 216 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.05 min.

10 **(2-Ethyl-6-methoxyquinolin-3-yl)-methanol SMA 44008**

To a solution of 2-ethyl-6-methoxyquinoline-3-carbaldehyde **SMA 44004** (256 mg, 1.19 mmol) in THF (12 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (48 mg, 1.25 mmol) and the mixture was stirred for 2 h at RT, then quenched by careful addition of 2 N aqueous HCl (2.6 mL). After 15 stirring for 30 min at RT, the mixture was basified with 2 N aqueous NaOH (2.6 mL) and THF was removed at 40°C under vacuum. The residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic phase was isolated, washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 50:50) gave (2-ethyl-6-methoxyquinolin-3-yl)-methanol **SMA 44008** as a white solid (173 mg, 67% yield).



**SMA 44008**

**MW:** 217.26; **Yield:** 67%; White Solid.

**Rf:** 0.25 (cyclohexane:EtOAc = 50:50, free base).

25 **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.31 (t, 3H, J = 7.5 Hz, CH<sub>3</sub>), 2.90 (q, 2H, J = 7.5 Hz, CH<sub>2</sub>), 3.46 (br, s, 1H, OH), 3.88 (s, 3H, OCH<sub>3</sub>), 4.86 (s, 2H, CH<sub>2</sub>), 6.96 (d, 1H, J = 2.5 Hz, ArH), 7.28 (dd, 1H, J = 2.5 & 9.1 Hz, ArH), 7.90 (d, 1H, J = 9.1 Hz, ArH), 8.00 (s, 1H, ArH).

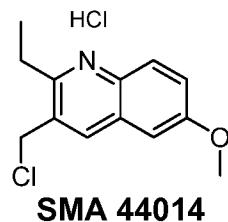
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 13.5, 28.3, 55.5, 61.9, 105.2, 121.6, 127.8, 129.6, 132.5, 133.1, 143.0, 157.3, 159.3.

30 **MS-ESI** m/z (% rel. Int.): 218 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 1.93 min.

**3-Chloromethyl-2-ethyl-6-methoxyquinoline hydrochloride SMA 44014**

5 To a solution of (2-ethyl-6-methoxyquinolin-3-yl)-methanol **SMA 44008** (150 mg, 0.69 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20 mL) at 0°C under  $\text{N}_2$  in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (1.0 mL, 13.8 mmol) and the mixture was stirred for 2 h at RT. The volatiles were then removed at 40°C under vacuum and the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) before 10 concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-chloromethyl-2-ethyl-6-methoxyquinoline hydrochloride **SMA 44014** as a brown solid (197 mg, >100% yield).



15

**MW:** 272.17; **Yield:** >100%; Brown Solid.

**$^1\text{H NMR}$**  ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.44 (t, 3H,  $J$  = 7.6 Hz,  $\text{CH}_3$ ), 3.27 (q, 2H,  $J$  = 7.6 Hz,  $\text{CH}_2$ ), 3.94 (s, 3H,  $\text{OCH}_3$ ), 4.99 (s, 2H,  $\text{CH}_2$ ), 7.58 (d, 1H,  $J$  = 1.7 Hz, 1xArH), 7.67 (dd, 1H,  $J$  = 1.7 and 9.3 Hz, 1xArH), 8.10 (d, 1H,  $J$  = 9.3 Hz, 1xArH), 8.99 (s, 1H, 1xArH).

20  **$^{13}\text{C-NMR}$**  ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 14.3, 26.1, 42.0, 56.9, 107.6, 122.3, 129.4, 130.9, 133.2, 134.9, 147.0, 159.5, 161.7.

**MS-ESI** m/z (% rel. Int.): 238 ( $[\text{MH}]^+$ ,  $^{37}\text{Cl}$ , 38), 236 ( $[\text{MH}]^+$ ,  $^{35}\text{Cl}$ , 100).

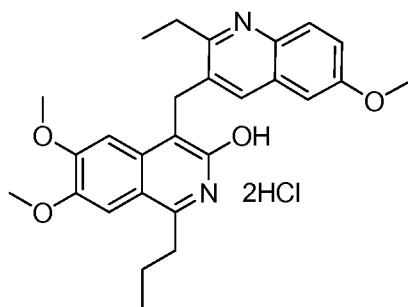
**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.26 min.

25

**4-((2-Ethyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride SLA 41122**

To a stirred solution of 3-(chloromethyl)-2-ethyl-6-methoxyquinoline hydrochloride **SMA 44014** (183 mg, 0.67 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (166 mg, 0.67 mmol) followed by a 2 N aq. LiOH solution (0.67 mL, 1.34 mmol) and the mixture was stirred at 160°C for 1.5 h under

microwave irradiation. After cooling to room temperature, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent EtOAc:MeOH = 100:0 to 95:5) followed by a new 5 purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2$ :MeOH = 100:0 to 95:5) provided after evaporation 4-((2-ethyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol. This free base was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.32 mL) and the mixture was stirred for 5 min at RT then 10 concentrated at 40°C under vacuum to afford 4-((2-ethyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **66** as a yellow solid (17 mg, 5% yield).

**66**

15 **MW:** 519.46; **Yield:** 5%; **Yellow Solid;** **Mp (°C):** 200.9.

**<sup>1</sup>H NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.14 (t, 3H,  $J$  = 9.0 Hz,  $\text{CH}_3$ ), 1.61 (t, 3H,  $J$  = 9.0 Hz,  $\text{CH}_3$ ), 1.94-1.97 (m, 2H,  $\text{CH}_2$ ), 3.39-3.44 (m, 2H,  $\text{CH}_2$ ), 3.48-3.55 (m, 2H,  $\text{CH}_2$ ), 3.84 (s, 3H,  $\text{OCH}_3$ ), 3.86 (s, 3H,  $\text{OCH}_3$ ), 4.02 (s, 3H,  $\text{OCH}_3$ ), 4.75 (s, 2H,  $\text{CH}_2$ ), 7.04 (s, 1H, ArH), 7.39 (s, 1H, ArH), 7.57 (s, 1H, ArH), 7.64 (d, 1H,  $J$  = 9.2 Hz, ArH), 8.13-8.17 (m, 2H, 20 2xArH).

**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 13.3, 14.2, 24.7, 26.7, 27.7, 33.6, 56.7, 56.9, 57.3, 102.8, 106.1, 107.2, 111.2, 119.6, 122.1, 128.3, 130.9, 133.5, 133.9, 141.4, 143.3, 152.2, 152.4, 155.2, 159.6, 159.9, 161.5.

**MS-ESI m/z (% rel. Int.):** 447 ( $[\text{MH}]^+$ , 100).

25 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.07min, peak area 99.1%.

Preparation of 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-(methoxymethyl)isoquinolin-3-ol dihydrochloride 67

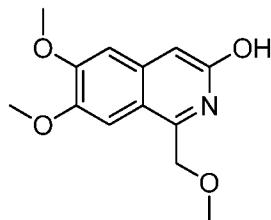
6,7-Dimethoxy-1-methoxymethyl-isoquinolin-3-ol SMA 44012

5 A mixture of methoxyacetic acid (21.9 g, 242.67 mmol) and acetic anhydride (24.80 g, 242.67 mmol) in a 250 mL round-bottomed flask equipped with a magnetic stirrer and a distillation assembly was heated with stirring for 2 h at 100°C and then distilled under reduced pressure. Methoxyacetic anhydride (13.5 g, 34% yield) was collected at 108°C at around 20 mb.

10 To a solution of methyl 2-(3,4-dimethoxy-phenyl)acetate **SLA 28134** (3.36 g, 15.98 mmol) in methoxyacetic anhydride **SMA 44010** (10.19 g, 62.85 mmol) at 0°C in a 250 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{HClO}_4$  (ca. 70% solution in water, 1.64 mL, 18.98 mmol). The mixture was then stirred for 45 min at RT then diluted with  $\text{Et}_2\text{O}$  (151 mL). The organic solution

15 was removed to give a viscous residue that was suspended in  $\text{H}_2\text{O}$  (30 mL) at 5°C before dropwise addition of a conc.  $\text{NH}_4\text{OH}$  solution (38 mL). After complete addition, the mixture was stirred overnight at RT and extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL) then with  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 95:5$  (100 mL). The organic phase was combined, washed with brine (30 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under

20 vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 100:0$  to 93:7) gave 6,7-dimethoxy-1-methoxymethyl-isoquinolin-3-ol **SMA 44012** as a yellow solid (96 mg, 2% yield).



**SMA 44012**

25 **MW:** 249.27; **Yield:** 2%; Yellow Solid. **Mp** (°C): 214.1 (dec.)

**Rf** (free base) = 0.2 ( $\text{CH}_2\text{Cl}_2:\text{MeOH} = 95:5$ ).

**$^1\text{H NMR}$**  ( $\text{CDCl}_3:\text{CD}_3\text{OD} = 2:1$ ,  $\delta$ ): 3.57 (s, 3H,  $\text{OCH}_3$ ), 3.95 (s, 3H,  $\text{OCH}_3$ ), 4.00 (s, 3H,  $\text{OCH}_3$ ), 4.88 (s, 2H,  $\text{CH}_2$ ), 6.65 (s, 1H, ArH), 6.74 (s, 1H, ArH), 6.87 (s, 1H, ArH).

**$^{13}\text{C-NMR}$**  ( $\text{CDCl}_3:\text{CD}_3\text{OD} = 2:1$ ,  $\delta$ ): 57.4, 57.6, 60.5, 70.3, 102.3, 104.2, 107.9, 114.5,

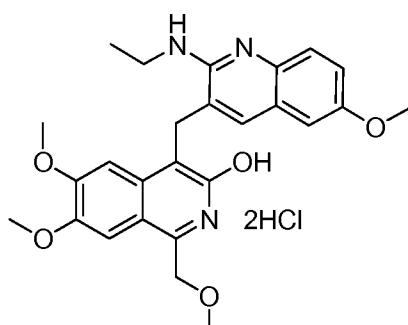
30 143.9, 145.2, 150.0, 156.9, 161.8.

**MS-ESI** m/z (% rel. Int.): 250 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.00 min.

5 4-((2-(Ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-(methoxymethyl)isoquinolin-3-ol dihydrochloride 67

To a stirred solution of 3-(chloromethyl)-N-ethyl-6-methoxyquinolin-2-amine hydrochloride **SLA 28166** (84 mg, 0.29 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 6,7-dimethoxy-1-(methoxymethyl)isoquinolin-3-ol **SMA 44012** (73 mg, 0.29 mmol) followed by a 2 N aq. LiOH solution (0.29 mL, 0.58 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) provided 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-(methoxymethyl)isoquinolin-3-ol. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 20 0.49 M HCl solution in MeOH (0.28 mL) and the mixture was stirred for 5 min at room temperature and concentrated at 40°C under vacuum to afford 4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-(methoxymethyl)isoquinolin-3-ol dihydrochloride **67** as a yellow solid (9 mg, 6% yield).



25

**67**

**MW:** 536.45; **Yield:** 6%; **Yellow Solid;** **Mp (°C):** 199.9.

**<sup>1</sup>H NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.51 (t, 3H,  $J$  = 7.0 Hz, CH<sub>3</sub>), 3.63 (s, 3H, OCH<sub>3</sub>), 3.68 (s, 3H, OCH<sub>3</sub>), 3.68-3.76 (m, 2H, NCH<sub>2</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 4.37 (s, 2H, CH<sub>2</sub>), 5.24 (s, 2H, CH<sub>2</sub>), 7.11 (s, 2H, 2xArH), 7.32 (d, 1H,  $J$  = 9.1 Hz, ArH), 7.43 (s, 1H, ArH), 7.57 (s, 1H, ArH), 7.89 (d, 1H,  $J$  = 9.1 Hz, ArH).

5    **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 13.9, 27.0, 39.1, 56.3, 56.9, 57.4, 60.0, 69.0, 102.2, 104.6, 109.5, 111.4, 117.8, 119.6, 123.4, 123.7, 124.4, 131.2, 139.5, 141.7, 148.6, 152.0, 152.5, 153.4, 158.7, 160.0.

**MS-ESI** m/z (% rel. Int.): 464 ([MH]<sup>+</sup>, 100).

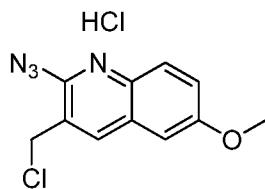
10    **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.08 min, peak area 99.5%.

Preparation of 4-((2-azido-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride 68

15    2-Azido-3-(chloromethyl)-6-methoxyquinoline hydrochloride SLA 41152

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (0.94 g, 4.24 mmol) in DMF (10 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added sodium azide (303 mg, 4.66 mmol) and the mixture was stirred overnight at 80°C. After cooling to RT, the mixture was diluted with Et<sub>2</sub>O (50 mL) and the solid was filtered, washed with more Et<sub>2</sub>O (50 mL) then with H<sub>2</sub>O (10 mL) and dried under vacuum to give 0.88 g of a beige solid (91%). This solid (446 mg, 1.95 mmol) was then dissolved in MeOH (30 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer before addition of NaBH<sub>4</sub> (150 mg, 3.97 mmol) and the reaction mixture was stirred for 1.5 h at RT. MeOH was then removed at 20 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 7:1 (40 mL) and the solution was washed with H<sub>2</sub>O (10 mL), brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum to give 435 mg of an off-white solid (97% yield). This solid (200 mg, 0.87 mmol) was then dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer before 25 dropwise addition of SOCl<sub>2</sub> (1.26 mL, 17.37 mmol). The mixture was stirred for 2 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum 30

(done 3 times) to give 2-azido-3-(chloromethyl)-6-methoxyquinoline hydrochloride **SLA 41152** as a yellow solid (200 mg, 92% yield).



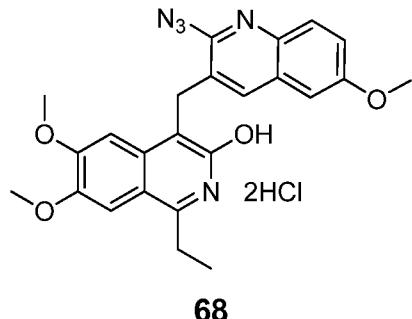
**SLA 41152**

5 **MW:** 285.13; **Yield:** 81% (3 steps); **Yellow Solid;** **Mp** (°C): 145.1.  
<sup>1</sup>**H NMR** ((CD<sub>3</sub>)<sub>2</sub>SO, δ): 3.95 (s, 3H, CH<sub>3</sub>), 5.22 (s, 2H, CH<sub>2</sub>), 7.59 (dd, 1H, *J* = 2.7 & 9.2 Hz, ArH), 7.76 (d, 1H, *J* = 2.7 Hz, ArH), 8.33 (s, 1H, ArH), 8.53 (d, 1H, *J* = 9.2 Hz, ArH).  
<sup>13</sup>**C-NMR** ((CD<sub>3</sub>)<sub>2</sub>SO, δ): 41.0, 55.9, 110.7, 117.7, 120.9, 122.8, 124.3, 125.1, 132.6, 145.7, 158.6.  
**MS-ESI** m/z (% rel. Int.): 251 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 14), 249 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 45), 221 (100).  
**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column( 5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.89 min.

15 4-((2-Azido-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride 68

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (161 mg, 0.69 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 2-azido-3-(chloromethyl)-6-methoxyquinoline hydrochloride **SLA 41152** (197 mg, 0.69 mmol) followed by a 2 N aq. LiOH solution (0.69 mL, 1.38 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, THF was removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) gave 4-((2-azido-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol (10 mg). This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.149 M HCl solution in MeOH (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under

vacuum to afford 4-((2-azido-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **68** as a yellow solid (11 mg, 3% yield).



5 **MW:** 518.39; **Yield:** 3%; **Yellow Solid;** **Mp (°C):** 168.4.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.55 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 3.28-3.44 (m, 2H, CH<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 6H, 2xOCH<sub>3</sub>), 4.89 (s, 2H, CH<sub>2</sub>), 7.38-7.51 (m, 4H, 4xArH), 7.95 (s, 1H, ArH), 8.52 (d, 1H, *J* = 9.0 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 13.8, 24.3, 25.9, 55.6, 56.0, 56.6, 102.1, 104.1, 109.7, 112.0,

10 117.7, 120.7, 123.4, 124.2, 125.9, 131.8, 139.9, 147.0, 150.7, 150.9, 154.2, 158.3, 159.6, 1xC not observed.

**MS-ESI** m/z (rel.int.): 446 ([MH]<sup>+</sup>, 100).

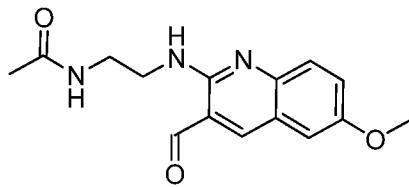
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.68 min, peak area 96.6%.

15

Preparation of *N*-(2-(3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide dihydrochloride **69**

*N*-(2-(3-Formyl-6-methoxyquinolin-2-ylamino)ethyl)acetamide **SLA 41168**

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (2.00 g, 9.0 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added *N*-(2-aminoethyl)acetamide (2.76 g, 27.1 mmol) and the reaction mixture was stirred for 1 h at 160°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). This organic solution was washed with brine (2x10 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was finally purified by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) to give *N*-(2-(3-formyl-6-methoxyquinolin-2-ylamino)ethyl)acetamide **SLA 41168** as an orange solid (601 mg, 23% yield).

**SLA 41168**

**MW:** 287.31; **Yield:** 23%; **Brown Solid;** **Mp** (°C): 150.0.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.93 (s, 3H, CH<sub>3</sub>C=O), 3.53 (q, 2H, J = 5.7 Hz, CH<sub>2</sub>N), 3.80 (q,

5 2H, J = 5.7 Hz, CH<sub>2</sub>N), 3.90 (s, 3H, OCH<sub>3</sub>), 7.02 (d, 1H, J = 2.8 Hz, ArH), 7.38 (dd, 1H, J = 2.8 & 9.2 Hz, ArH), 7.46 (broad s, 1H, NH), 7.58 (d, 1H, J = 9.2 Hz, ArH), 8.18 (broad s, 1H, NH), 8.21 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 23.3, 40.1, 42.2, 55.6, 106.9, 117.4, 122.4, 126.3, 127.3, 146.2, 147.4, 154.5, 155.3, 170.3, 192.9.

10 **MS-ESI** m/z (% rel. Int.): 288 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 1.98 min.

**N-(2-(3-(Hydroxymethyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide SLA 41174**

15 To a stirred solution of *N*-(2-(3-formyl-6-methoxyquinolin-2-ylamino)ethyl)acetamide **SLA 41168** (0.70 g, 2.43 mmol) in THF (30 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (0.09 g, 2.43 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (40 mL). After stirring for 15 20 min, the mixture was basified to pH = 9 using a 2 N aq. NaOH solution. THF was removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give *N*-(2-(3-(hydroxymethyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide **SLA 41174** as an orange solid (0.65 g, 93% yield).



25

**SLA 41174**

**MW:** 289.33; **Yield:** 93 %; **Orange Solid;** **Mp** (°C): 168.5.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.84 (s, 3H, CH<sub>3</sub>C=O), 3.39-3.44 (m, 2H, CH<sub>2</sub>), 3.64-3.68 (m, 2H, CH<sub>2</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 4.62 (s, 2H, CH<sub>2</sub>), 6.88 (d, 1H, J = 2.6 Hz, ArH), 7.18 (dd, 1H, J = 2.6 & 9.1 Hz, ArH), 7.46 (s, 1H, ArH), 7.55 (d, 1H, J = 9.1 Hz, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 23.1, 40.7, 42.4, 55.5, 63.2, 106.7, 120.8, 122.8, 123.5, 126.6,

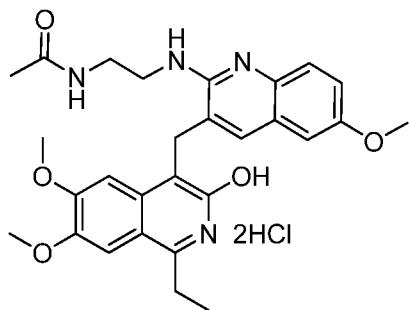
5 134.8, 142.4, 154.9, 155.5, 171.1.

**MS-ESI** m/z (% rel. Int.): 290 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.03 min.

10 N-(2-((1-Ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide dihydrochloride 69

To a stirred solution of *N*-(2-(3-(chloromethyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide hydrochloride **SLA 41174** (350 mg, 1.02 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (237 mg, 1.02 mmol) followed by a 2 N aq. LiOH solution (1.02 mL, 2.0 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 90:10) provided *N*-(2-(3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide. The product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (2 mL) and the solution was stirred for 5 min at RT then concentrated at 40°C under vacuum to give *N*-(2-(3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide dihydrochloride **69** as a yellow solid (83.5 mg, 17% yield).



**MW:** 577.50; **Yield:** 17%; **Yellow Solid;** **Mp** (°C): 244.8.

**<sup>1</sup>H NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.50-1.65 (m, 3H, CH<sub>3</sub>), 2.10 (s, 3H, CH<sub>3</sub>O), 3.40-3.50 (m, 2H, CH<sub>2</sub>), 3.52-3.65 (m, 2H, CH<sub>2</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.82-3.90 (m, 2H, CH<sub>2</sub>), 3.96 (s, 5 3H, OCH<sub>3</sub>), 4.07 (s, 3H, OCH<sub>3</sub>), 4.35 (s, 2H, CH<sub>2</sub>), 7.15 (s, 2H, 2xArH), 7.39 (d, 1H,  $J$  = 9.0 Hz, ArH), 7.54 (s, 1H, ArH), 7.61 (s, 1H, ArH), 8.02 (d, 1H,  $J$  = 9.0 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 14.7, 22.5, 25.6, 27.1, 39.0, 43.6, 56.4, 57.1, 57.6, 102.2, 103.0, 105.8, 109.4, 112.3, 119.9, 123.7, 123.9, 126.8, 131.3, 139.5, 141.8, 144.7, 145.7, 152.2, 152.9, 158.1, 158.9, 175.8.

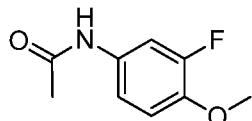
10 MS-ESI m/z (% rel. Int.): 505 ( $[\text{MH}]^+$ , 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.77 min, peak area 96.2%.

Preparation of 4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 70

## ***N*-(3-Fluoro-4-methoxyphenyl)acetamide **SMA 44032****

To a solution of 3-fluoro-4-methoxyaniline (1.15 g, 8.15 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (81 mL) in a 250 mL round-bottomed flask equipped with a magnetic stirrer were added DIEA (5.4 mL, 32.7 mmol), DMAP (221 mg, 1.81 mmol) and acetic anhydride (4.4 mL, 46.5 mmol) and the mixture was stirred overnight at RT. The solution was washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent cyclohexane:EtOAc = 100:0 to 50:50) gave *N*-(3-fluoro-4-methoxyphenyl)acetamide **SMA 44032** as a brown solid (1.08 g, 72% yield).



**SMA 44032**

**MW:** 183.18; **Yield:** 72%; Brown solid; **Mp** (°C): 112.4.

**R<sub>f</sub>:** 0.25 (cyclohexane:EtOAc = 50:50).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 2.15 (s, 3H, CH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 6.88 (dd, 1H, J = 9.0 Hz & 9.0 Hz, ArH), 7.08-7.16 (m, 1H, ArH), 7.40 (dd, J = 2.4 Hz & 12.8 Hz, 1H, ArH),

5 7.51 (broad s, 1H, NH).

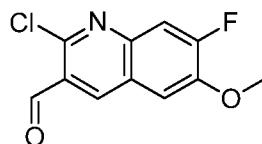
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 24.3, 56.6, 109.4 (d, J = 22.6 Hz), 113.7 (d, J = 2.4 Hz), 115.7 (d, J = 3.5 Hz), 131.4 (d, J = 9.3 Hz), 144.4 (d, J = 10.9 Hz), 152.1 (d, J = 245.3 Hz), 168.3.

**MS-ESI** m/z (% rel. Int.): 184 ([MH]<sup>+</sup>, 100).

10 **HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.32 min.

**2-Chloro-7-fluoro-6-methoxyquinoline-3-carbaldehyde SMA 44034**

POCl<sub>3</sub> (3.6 mL, 39.3 mmol) was added dropwise under N<sub>2</sub> to DMF (0.7 mL, 15 9.04 mmol) at 0°C in a 2 mL microwave vial equipped with a magnetic stirrer. The mixture was then stirred for 15 min at 0°C before addition of *N*-(3-fluoro-4-methoxyphenyl)acetamide **SMA 44032** (1.00 g, 5.46 mmol) and the mixture was stirred overnight at RT then for 30 min at 160°C under microwave irradiation. After cooling to RT, the mixture was poured on a mixture of ice-water (20 mL) then neutralized with a 10 N aqueous NaOH solution (to pH = 7) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (80 mL). The separated organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 83:17) gave 2-chloro-7-fluoro-6-methoxyquinoline-3-carbaldehyde **SMA 44034** as a yellow solid (20 233 mg, 18% yield).



**SMA 44034**

**MW:** 239.64; **Yield:** 18%; Yellow Solid; **Mp** (°C): 290.0.

**R<sub>f</sub>:** 0.30 (cyclohexane:EtOAc = 83:17).

30 **<sup>1</sup>H NMR** (DMSO d<sub>6</sub>, δ): 4.01 (s, 3H, OCH<sub>3</sub>), 7.89-7.95 (m, 2H, 2xArH), 8.86 (s, 1H, ArH), 10.36 (s, 1H, CHO).

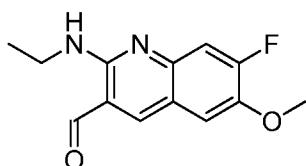
**<sup>13</sup>C-NMR** (DMSO d<sub>6</sub>, δ): 56.4, 110.0 (d, J = 3.0 Hz), 112.8 (d, J = 18.9 Hz), 124.5, 125.9 (d, J = 3.0 Hz), 139.3, 144.8 (d, J = 12.8 Hz), 147.6, 148.4 (d, J = 13.6 Hz), 156.3 (d, J = 258.0 Hz), 189.2.

**MS-ESI** m/z (% rel. Int.): 242 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38), 240 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100).

5 **HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 5.43 min.

**2-(Ethylamino)-7-fluoro-6-methoxyquinoline-3-carbaldehyde CCH 42068**

To a stirred solution of 2-chloro-7-fluoro-6-methoxyquinoline-3-carbaldehyde **SMA 44034** (219 mg, 0.91 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added ethylamine (2 M in THF, 4.50 mL, 9.00 mmol) and the mixture was stirred at 150°C for 2 h under microwave irradiation. After cooling to RT, the volatiles were removed under vacuum at 40°C and the resulting yellow oil was taken up in a 2 N aq. HCl solution (15 mL) and stirred for 15 min at RT then neutralised with a 2 N aq. NaOH solution (15 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (50 mL) and the organic phase was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave 2-(ethylamino)-7-fluoro-6-methoxyquinoline-3-carbaldehyde **CCH 42068** 20 as a yellow oil (105 mg, 46% yield).



**CCH 42068**

**MW:** 248.25; **Yield:** 46%; Yellow Oil.

**Rf:** 0.45 (cyclohexane:EtOAc = 75:25).

25 **<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.29 (t, 3H, J = 7.2 Hz, CH<sub>3</sub>), 3.59-3.68 (m, 2H, CH<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 7.04 (d, J = 9.2 Hz, 1H, ArH), 7.34 (d, J = 12.8 Hz, 1H, ArH), 7.93 (broad s, 1H, NH), 8.10 (s, 1H, ArH), 9.94 (s, 1H, CHO).

30 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.7, 35.5, 56.2, 108.9 (d, J = 3.8 Hz), 111.9 (d, J = 18.2 Hz), 116.5 (d, J = 2.3 Hz), 118.4, 145.2 (d, J = 3.8 Hz), 146.5, 147.9 (d, J = 13.1 Hz), 154.3, 157.8 (d, J = 257.6 Hz), 192.7.

**MS-ESI** m/z (% rel. Int.): 249 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.17 min.

5 **(2-Ethylamino-7-fluoro-6-methoxyquinolin-3-yl)methanol SMA 44090**

To a solution of 2-(ethylamino)-7-fluoro-6-methoxyquinoline-3-carbaldehyde **CCH 42068** (500 mg, 2.01 mmol) in THF (50 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (80 mg, 2.11 mmol) and the reaction mixture was stirred overnight at RT, then cooled in an ice bath and 10 quenched by addition of a 6 N aqueous HCl solution (10 mL). The mixture was then basified with a 10 N aqueous NaOH solution (to pH = 12). THF was then removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic phase was isolated, washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, 15 eluent cyclohexane:EtOAc = 100:0 to 50:50) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 100:0 to 90:10) gave (2-ethylamino-7-fluoro-6-methoxyquinolin-3-yl)methanol **SMA 44090** as a white solid (290 mg, 58% yield).



20 **SMA 44090**

**MW:** 250.27; **Yield:** 58%; **White Solid;** **Mp (°C):** 154.6.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.29 (t, 3H, J = 7.2 Hz, CH<sub>3</sub>), 2.78 (br, 1H, OH), 3.51-3.60 (m, 2H, CH<sub>2</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.55 (s, 2H, CH<sub>2</sub>), 5.61-5.65 (br, m, 1H, NH), 6.83 (d, 1H, J = 9.2 Hz, ArH), 7.09 (s, 1H, ArH), 7.30 (d, 1H, J = 12.9 Hz, ArH).

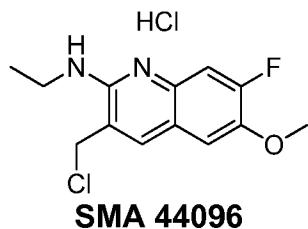
25 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.8, 35.9, 56.3, 63.8, 108.4, 111.3 (d, J = 18.1 Hz), 119.3 (d, J = 1.5 Hz), 121.1 (d, J = 2.2 Hz), 133.7, 143.3 (d, J = 12.1 Hz), 144.3 (d, J = 12.8 Hz), 154.7 (d, J = 249.8 Hz), 155.5.

**MS-ESI** m/z (% rel. Int.): 251 [MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 30 186003113), detection UV 214 nm, RT = 3.25 min.

3-(Chloromethyl)-N-ethyl-7-fluoro-6-methoxyquinolin-2-amine hydrochloride **SMA 44096**

To a solution of (2-ethylamino-7-fluoro-6-methoxyquinolin-3-yl)methanol **SMA 44090** (278 mg, 1.11 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (30 mL) at 0°C under  $\text{N}_2$  in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (1.60 mL, 22.1 mmol) and the mixture was stirred for 3 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then diluted with  $\text{CH}_2\text{Cl}_2$  (30 mL) and concentrated back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-N-ethyl-7-fluoro-6-methoxyquinolin-2-amine hydrochloride **SMA 44096** as a yellow solid (348 mg, quantitative yield).



**MW:** 305.22; **Yield:** quantitative; **Yellow Solid;** **Mp (°C):** 226.6 (dec.).

**1H NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.45 (t, 3H,  $J$  = 7.2 Hz,  $\text{CH}_3$ ), 3.75 (q, 2H,  $J$  = 7.2 Hz,  $\text{CH}_3$ ), 4.01 (s, 3H,  $\text{OCH}_3$ ), 4.91 (s, 2H,  $\text{CH}_2$ ), 7.58 (d, 1H,  $J$  = 8.7 Hz, ArH), 7.82 (d, 1H,  $J$  = 11.6 Hz, ArH), 8.43 (s, 1H, ArH).

**13C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 13.7, 39.0, 41.9, 57.2, 105.9 (d,  $J$  = 24.9 Hz), 112.1 (d,  $J$  = 3.0 Hz), 119.5 (d,  $J$  = 2.2 Hz), 123.0 (d,  $J$  = 3.0 Hz), 132.4 (d,  $J$  = 11.3 Hz), 143.3, 148.3 (d,  $J$  = 12.0 Hz), 151.67, 157.2 (d,  $J$  = 257.3 Hz).

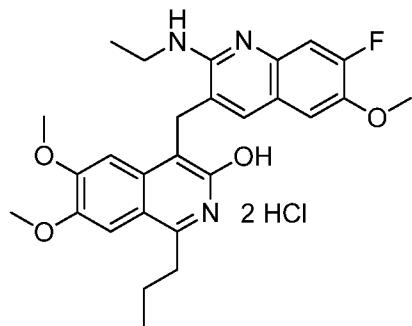
**MS-ESI** m/z (% rel. Int.): 271 ( $[\text{MH}]^+$ ,  $^{37}\text{Cl}$ , 38), 269 ( $[\text{MH}]^+$ ,  $^{35}\text{Cl}$ , 100).

**HPLC:** XBridge<sup>TM</sup> column(5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.19 min.

25 4-((2-(Ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **70**

To a stirred solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (184 mg, 0.744 mmol) in THF (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-N-ethyl-7-fluoro-6-methoxyquinolin-2-amine hydrochloride **SMA 44096** (227 mg, 0.744 mmol) at RT followed by a 2 N aq. LiOH solution (0.75 mL, 1.50 mmol) and the mixture was stirred at 155°C for 1.5 h

under microwave irradiation. The microwave vial was then cooled in an ice bath and the solid was filtered, washed with cold THF (20 mL) and taken up in  $\text{CH}_2\text{Cl}_2$ :MeOH = 9:1 (50 mL). The organic solution was washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2$ :MeOH = 100:0 to 95:5) followed by a second purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{EtOAc}$ :MeOH = 100:0 to 95:5) gave 83 mg of 4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol as a brown solid. This free base was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (1.0 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **70** as a yellow solid (96 mg, 23% yield).



15

**70**

**MW:** 552.47; **Yield:** 23%; **Yellow Solid;** **Mp** (°C): 215.8 (dec.).

**R<sub>f</sub>:** 0.25 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 95:5, free base).

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.15 (t, 3H,  $J$  = 7.2 Hz,  $\text{CH}_3$ ), 1.54 (t, 3H,  $J$  = 7.1 Hz,  $\text{CH}_3$ ), 1.91-1.98 (m, 2H,  $\text{CH}_2$ ), 3.30-3.36 (m, 2H,  $\text{CH}_2$ ), 3.78 (q, 2H,  $J$  = 6.9 Hz,  $\text{CH}_2$ ), 3.88 (s, 3H,  $\text{OCH}_3$ ), 3.99 (s, 3H,  $\text{OCH}_3$ ), 4.02 (s, 3H,  $\text{OCH}_3$ ), 4.37 (s, 2H,  $\text{CH}_2$ ), 7.09 (s, 1H, ArH), 7.40 (d, 1H,  $J$  = 8.1 Hz, ArH), 7.47 (s, 1H, ArH), 7.75-7.80 (m, 2H, 2xArH).

**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 13.9, 14.2, 24.7, 27.0, 33.6, 39.2, 56.9, 57.0, 57.4, 102.6, 105.6 (d,  $J$  = 24.2 Hz), 106.0, 109.9, 111.6 (d,  $J$  = 3.1 Hz), 119.3, 119.7, 123.4, 131.3 (d,  $J$  = 11.3 Hz), 138.8, 141.6, 148.0 (d,  $J$  = 12.0 Hz), 152.18, 152.5, 152.9, 155.0, 156.4 (d,  $J$  = 255.5 Hz), 160.04.

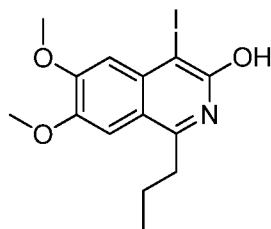
**MS-ESI** m/z (rel. int.): 480 ( $[\text{MH}]^+$ , 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.47 min, peak area 99.6%.

Preparation of 4-((2-butyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride 71

5 4-ido-6,7-dimethoxy-1-propylisoquinolin-3-ol CCH 42098-1

A mixture of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (2.00 g, 8.09 mmol) and *p*-toluenesulfonic acid monohydrate (1.50 g, 7.89 mmol) in dry CH<sub>3</sub>CN (20 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was stirred for 10 min at RT before portionwise addition of *N*-iodosuccinimide (1.82 g, 10 8.09 mmol) under vigorous stirring. After 2.5 h, the mixture was slowly poured into a cold solution of NaHCO<sub>3</sub> (2.0 g) in 50 mL of water and the solid was filtered, washed with water (50 mL) and dried overnight under vacuum to yield 4-ido-6,7-dimethoxy-1-propylisoquinolin-3-ol **CCH 42098-1** as a brown solid (2.35 g, 78% yield).



15 **CCH 42098-1**

**MW:** 373.19; **Yield:** 78%; Brown Solid.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.10 (t, 3H, *J* = 7.3 Hz, CH<sub>3</sub>), 1.84-1.92 (m, 2H, CH<sub>2</sub>), 3.14 (t, 2H, *J* = 7.6 Hz, CH<sub>2</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 6.90 (s, 1H, ArH), 7.07 (s, 1H, ArH), OH not seen.

20 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.0, 23.2, 32.7, 56.0, 56.2, 103.0, 108.4, 112.5, 143.1, 147.6, 150.5, 156.6, 159.4, 1xC not observed.

**MS-ESI** *m/z* (rel. int.): 374 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.29 min.

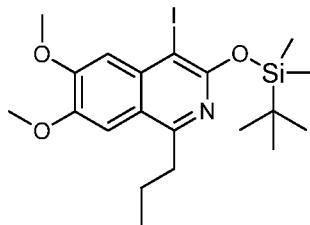
25

3-(*tert*-Butyldimethylsilyloxy)-4-ido-6,7-dimethoxy-1-propylisoquinoline CCH 42098-2

To a mixture of 4-ido-6,7-dimethoxy-1-propylisoquinolin-3-ol **CCH 42098-1** (0.60 g, 1.61 mmol) and diisopropylaminomethyl-polystyrene resin (3 mmol/g, 0.80 g, 30 2.40 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (16 mL) in a 50 mL round-bottomed flask equipped with a

magnetic stirrer was added *tert*-butylchlorodimethylsilane (267 mg, 1.77 mmol) and the reaction mixture was stirred for 15 min at RT then for 1 h under reflux. After cooling to RT, the reaction mixture was filtered and the filtrate was washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum.

5 Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 95:5) gave 3-(*tert*-butyldimethylsilyloxy)-4-iodo-6,7-dimethoxy-1-propylisoquinoline **CCH 42098-2** as an off-white solid (0.65 g, 83% yield).

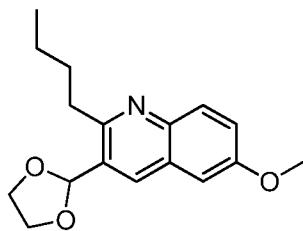
**CCH 42098-2**

10 **MW:** 487.45; **Yield:** 83%; Off-White Solid; **Mp** (°C): 193.1 (dec.).  
**R<sub>f</sub>:** 0.3 (cyclohexane:EtOAc = 95:5).  
**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 0.38 (s, 6H, 2xCH<sub>3</sub>), 1.08 (s, 9H, 3xCH<sub>3</sub>), 1.02-1.09 (m, 3H, CH<sub>3</sub>), 1.89-1.91 (m, 2H, CH<sub>2</sub>), 3.02-3.09 (m, 2H, CH<sub>2</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 7.20 (s, 1H, ArH), 7.30 (s, 1H, ArH).

15 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): -4.1 (2xC), 14.2, 18.2, 21.5, 25.9 (3xC), 36.1, 56.0 (2xC), 103.7, 109.7, 119.1, 138.0, 148.1, 153.8, 157.0, 157.7, 1xC not observed.

### 2-Butyl-3-(1,3-dioxolan-2-yl)-6-methoxyquinoline **SMA 44042**

To a solution of 2-chloro-3-(1,3-dioxolan-2-yl)-6-methoxyquinoline **SMA 44002** (1.41 g, 5.31 mmol) in dry THF (27 mL) at 0°C under N<sub>2</sub> in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added Fe(acac)<sub>3</sub> (197 mg, 0.547 mmol) followed by dropwise addition of *n*-butylmagnesium chloride (2.0 M in THF, 12.4 mL, 24.8 mmol). After complete addition, the mixture was stirred for 5 h at 70°C then cooled to RT and quenched with water (10 mL). THF was then removed at 40°C under vacuum and the resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic phase was isolated, washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 100:0 to 95:5) gave 2-butyl-3-(1,3-dioxolan-2-yl)-6-methoxyquinoline **SMA 44042** as an orange oil (867 mg, 57% yield).

**SMA 44042**

**MW:** 287.35; **Yield:** 57%; Orange Oil.

**R<sub>f</sub>** = 0.3 (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 95:5).

5 **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 0.94-0.96 (m, 3H, CH<sub>3</sub>), 1.45-1.52 (m, 2H, CH<sub>2</sub>), 1.78-1.81 (m, 2H, CH<sub>2</sub>), 3.00-3.06 (m, 2H, CH<sub>2</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 4.11-4.19 (m, 4H, 2xOCH<sub>2</sub>), 6.13 (s, 1H, CH), 7.07 (s, 1H, ArH), 7.33-7.36 (m, 1H, ArH), 7.91-7.95 (m, 1H, ArH), 8.21-8.22 (m, 1H, ArH).

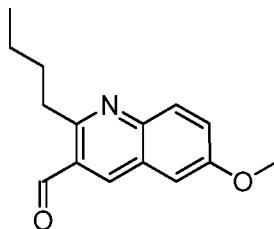
10 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.0, 23.0, 31.9, 35.3, 55.4, 65.3 (2xC), 101.2, 105.5, 122.3, 127.2, 129.4, 130.0, 132.7, 144.0, 157.3, 158.7.

**MS-ESI** m/z (% rel. Int.): 288 [MH]<sup>+</sup> (100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 4.11 min.

15 **2-Butyl-6-methoxyquinoline-3-carbaldehyde SMA 44044**

To a solution of 2-butyl-3-(1,3-dioxolan-2-yl)-6-methoxyquinoline **SMA 44042** (847 mg, 2.95 mmol) in THF (20 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added a 12 N aqueous HCl solution (5.0 mL, 60.0 mmol) and the mixture was stirred overnight at RT then for 3 h at 70°C. After cooling to RT, 20 THF was removed at 40°C under vacuum before addition of a 10 N aqueous NaOH solution until neutral pH. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic layer was isolated, washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 100:0 to 98:2) gave 2-butyl-6-methoxyquinoline-3-carbaldehyde **SMA 44044** as an orange solid (583 mg, 81% yield).



**SMA 44044**

**MW:** 243.30; **Yield:** 81%; **Orange Solid;** **Mp** (°C): 86.5.

**R<sub>f</sub>:** 0.35 (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc = 98:2).

5      **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 0.96-1.01 (m, 3H, CH<sub>3</sub>), 1.45-1.51 (m, 2H, CH<sub>2</sub>), 1.72-1.80 (m, 2H, CH<sub>2</sub>), 3.30-3.34 (m, 2H, CH<sub>2</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 7.16-7.17 (m, 1H, ArH), 7.46 (d, 1H, *J* = 9.3 Hz, ArH), 7.98 (d, 1H, *J* = 9.3 Hz, ArH), 8.51 (s, 1H, ArH), 10.39 (s, 1H, CHO).

10     **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 13.9, 22.8, 32.6, 35.7, 55.6, 106.0, 125.3, 127.0, 127.7, 130.3, 140.1, 145.7, 157.9, 160.0, 191.2.

15     **MS-ESI** m/z (% rel. Int.): 244 [MH]<sup>+</sup> (100).

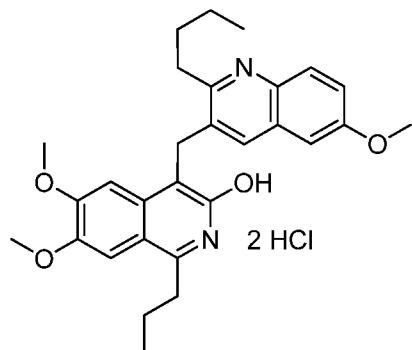
**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.49 min.

4-((2-Butyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol

15     dihydrochloride 71

To a stirred solution of 3-(*tert*-butyldimethylsilyloxy)-4-iodo-6,7-dimethoxy-1-propylisoquinoline **CCH 42098-2** (200 mg, 0.41 mmol) in freshly distilled dry THF (4 mL) at -105°C in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise *n*-BuLi (1.6 M in hexanes, 0.40 mL, 0.64 mmol) and the reaction mixture was stirred for 15 min at -105°C before quick addition of a solution of 2-butyl-6-methoxyquinoline-3-carbaldehyde **SMA 44044** (100 mg, 0.41 mmol) in dry THF (1 mL). The reaction mixture was stirred for 1 h at -105°C then quenched by addition of a 5% aqueous NH<sub>4</sub>Cl solution (5 mL), allowing the medium to warm up to RT. THF was then removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 66:34) gave 120 mg of a yellow solid. This solid (120 mg, 245 µmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of TFA (0.6 mL) and triethylsilane (60 µL, 372 µmol). The mixture was stirred overnight at RT, concentrated to dryness at 40°C under vacuum. The residue was neutralised with a saturated aqueous NaHCO<sub>3</sub> solution (5 mL) before to be extracted with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The organic phase was isolated, washed with brine (5 mL), dried

over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{EtOAc:MeOH} = 100:0$  to  $95:5$ ) gave 4-((2-butyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol as a yellow solid. This free base was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.5 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((2-butyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **71** as a pale brown solid (54 mg, 24% yield).



10

**71**

**MW:** 547.51; **Yield:** 24%; Pale Brown Solid; **Mp (°C):** 227.4 (dec.)

**R<sub>f</sub>:** 0.2 ( $\text{EtOAc:MeOH} = 95:5$ , free base).

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.08 (t, 3H,  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.19 (t, 3H,  $J = 7.3$  Hz,  $\text{CH}_3$ ), 1.69 (sextuplet, 2H,  $J = 7.3$  Hz,  $\text{CH}_2$ ), 1.95-2.05 (m, 4H, 2x $\text{CH}_2$ ), 3.32-3.33 (m, 2H,  $\text{CH}_2$ ), 3.46-3.58 (m, 2H,  $\text{CH}_2$ ), 3.88 (s, 3H,  $\text{OCH}_3$ ), 3.92 (s, 3H,  $\text{OCH}_3$ ), 4.06 (s, 3H,  $\text{OCH}_3$ ), 4.83 (s, 2H,  $\text{CH}_2$ ), 7.13 (s, 1H, ArH), 7.47 (d, 1H,  $J = 1.8$  Hz, ArH), 7.62-7.67 (m, 2H, 2xArH), 7.75 (d, 1H,  $J = 9.6$  Hz, ArH), 8.26 (s, 1H, ArH).

**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 14.1, 14.3, 24.0, 24.7, 27.9, 32.2, 33.0, 33.6, 56.8, 57.0, 57.4, 103.0, 106.2, 107.2, 111.6, 119.8, 122.0, 128.2, 130.9, 133.6, 133.8, 141.3, 143.5, 151.9, 152.3, 155.3, 158.6, 159.9, 161.4.

**MS-ESI**  $m/z$  (rel. int.): 475 ( $[\text{MH}]^+$ , 100).

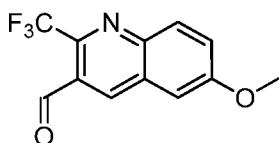
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18,  $4.5 \times 50$  mm, Model # 186003113), detection UV 254 nm, RT = 4.68 min, peak area 99.5%.

25

Preparation of 6,7-dimethoxy-4-((6-methoxy-2-(trifluoromethyl)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol hydrochloride **72**

**6-Methoxy-2-(trifluoromethyl)quinoline-3-carbaldehyde SLA 47010**

To a solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.50 g, 6.77 mmol) in *N,N*-dimethylacetamide (13.6 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer were added dibromodifluoromethane (1.30 mL, 14.23 mmol) and Cu (2.58 g, 40.60 mmol) and the mixture was stirred for 1 h at 100°C then overnight at 150°C. After cooling to RT, the mixture was stirred through celite and the celite plug was washed with EtOAc (50 mL). The organic solution was washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave 6-methoxy-2-(trifluoromethyl)quinoline-3-carbaldehyde **SLA 47010** as a brown solid (536 mg, 31% yield).



**SLA 47010**

**MW:** 255.19; **Yield:** 31%; Brown Solid; **Mp** (°C): 114.9

**Rf:** 0.2 (cyclohexane:EtOAc = 75:25).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 3.99 (s, 3H, OCH<sub>3</sub>), 7.25 (d, 1H, *J* = 2.7 Hz, ArH), 7.59 (dd, *J* = 9.3 & 2.7 Hz, ArH), 8.16 (d, 1H, *J* = 9.3 Hz, ArH), 8.82 (s, 1H, ArH), 10.50-10.52 (m, 1H, CHO).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 53.8, 106.0, 121.8 (q, *J* = 273.3 Hz), 126.4, 126.7, 129.5, 131.5, 137.8, 143.8 (q, *J* = 273.3 Hz), 144.0, 160.16, 187.9-188.0 (m).

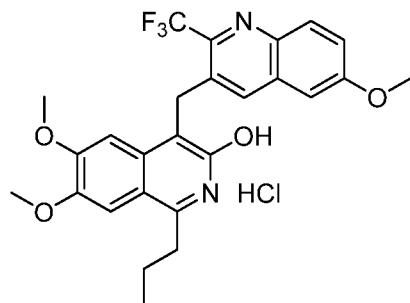
**MS-ESI** m/z (% rel. Int.): 256 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridgeTM column(5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 5.76 min.

**25 6,7-Dimethoxy-4-((6-methoxy-2-(trifluoromethyl)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol hydrochloride 72**

To a stirred solution of 3-(*tert*-butyldimethylsilyloxy)-4-iodo-6,7-dimethoxy-1-propylisoquinoline **CCH 42098-2** (200 mg, 0.41 mmol) in freshly distilled dry THF (4 mL) at -105°C in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise *n*-BuLi (1.6 M in hexanes, 0.30 mL, 0.48 mmol) and the reaction mixture was stirred for 15 min at -105°C before quick addition of a solution of 6-

methoxy-2-(trifluoromethyl)quinoline-3-carbaldehyde **SLA 47010** (105 mg, 0.41 mmol) in dry THF (1 mL). The reaction mixture was stirred for 1 h at -105°C then quenched by addition of a 5% aqueous NH<sub>4</sub>Cl solution (5 mL), allowing the medium to warm up to RT. THF was then removed at 40°C under vacuum and the residue 5 was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 10 66:34) gave 187 mg of a yellow solid. This solid (120 mg, around 200 µmol) was then dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of TFA (0.6 mL) and triethylsilane (60 µL, 372 µmol). The mixture was stirred overnight at RT, then concentrated to dryness at 40°C under 15 vacuum. The residue was neutralised with saturated aqueous NaHCO<sub>3</sub> solution (5 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The organic phase was isolated, washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 15 95:5) gave 6,7-dimethoxy-4-((6-methoxy-2-(trifluoromethyl)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.5 mL). The reaction mixture was stirred for 5 min at RT then 20 concentrated at 40°C under vacuum to afford a pale brown solid. This solid was purified by column chromatography (RP18, eluent H<sub>2</sub>O:CH<sub>3</sub>CN = 100:0 to 40:60), then concentrated to dryness at 40°C under vacuum. The residue was dissolved in 0.5 M HCl in MeOH (2 mL) and concentrated back to dryness. Finally, 25 recrystallization from MeOH/Et<sub>2</sub>O gave 6,7-dimethoxy-4-((6-methoxy-2-(trifluoromethyl)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol hydrochloride **72** as a pale brown solid (9 mg, 4% yield).



72

**MW:** 522.94; **Yield:** 4%; Pale Brown Solid; **Mp** (°C): 258.7 (dec.).

**R<sub>f</sub>:** 0.2 (EtOAc:MeOH = 95:5, free base).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD:CDCl<sub>3</sub> = 1:1, δ): 1.17 (t, 3H, J = 7.2 Hz, CH<sub>3</sub>), 1.96-2.04 (m, 2H, CH<sub>2</sub>), 3.43 (t, 2H, J = 7.4 Hz, CH<sub>2</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.70 (s, 2H, CH<sub>2</sub>), 6.84 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.40-7.44 (m, 2H, 2xArH), 7.60 (s, 1H, ArH), 8.05 (d, 1H, J = 9.2 Hz, ArH).

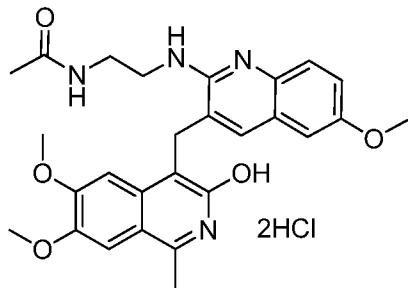
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD:CDCl<sub>3</sub> = 1:1, δ): 13.8, 22.6, 25.8, 33.0, 55.5, 55.7, 55.8, 100.4, 104.7, 105.1, 108.2, 122.5 (q, J = 251.1 Hz), 123.3, 130.2, 130.5, 135.2, 137.7, 140.2, 142.0, 142.4, 147.8, 153.1, 155.1, 155.4, 159.1, 1xC not seen.

10 **MS-ESI** *m/z* (rel. int.): 475 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 5.60 min, peak area 95.1%.

Preparation of *N*-(2-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide dihydrochloride **73**

To a stirred solution of *N*-(2-(3-(chloromethyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide hydrochloride **SLA 41176** (115 mg, 0.33 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH18060** (73 mg, 0.33 mmol) followed by a 2 N 20 aq. LiOH solution (0.33 mL, 0.66 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 90:10) provided *N*-(2-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of 0.49 M HCl in MeOH (2 mL) and the solution was stirred for 5 min at RT then concentrated at 25 40°C under vacuum to afforded *N*-(2-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-ylamino)ethyl)acetamide dihydrochloride **73** as a yellow solid (19.5 mg, 10% yield).



73

**MW:** 563.47; **Yield:** 10%; **Yellow Solid;** **Mp** (°C): 160.4.

**<sup>1</sup>H NMR** (CD<sub>3</sub>OD, δ): 2.09 (s, 3H, CH<sub>3</sub>), 3.08 (s, 3H, CH<sub>3</sub>), 3.59-3.64 (m, 2H, CH<sub>2</sub>),

5 3.80 (s, 3H, OCH<sub>3</sub>), 3.83-3.88 (m, 2H, CH<sub>2</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 4.33 (s, 2H, CH<sub>2</sub>), 7.14 (s, 1H, ArH), 7.15 (d, 1H, J = 2.7 Hz, ArH), 7.39 (dd, 1H, J = 2.7 & 9.2 Hz, ArH), 7.53 (s, 1H, ArH), 7.61 (s, 1H, ArH), 8.00 (d, 1H, J = 9.2 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 17.4, 22.4, 27.0, 39.0, 43.5, 56.3, 56.9, 57.4, 102.4, 106.2,

10 109.4, 109.4, 119.9, 123.6, 123.9, 124.4, 131.3, 139.4, 141.2, 152.0, 152.9, 158.9, 159.9, 175.8, 3xC not observed.

**MS-ESI** m/z (% rel. Int.): 491 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.63 min, peak area 98.6%.

15

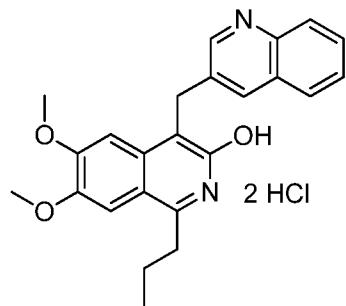
Preparation of 6,7-dimethoxy-1-propyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride 74

To a stirred solution of 3-(*tert*-butyldimethylsilyloxy)-4-iodo-6,7-dimethoxy-1-propylisoquinoline **CCH 42098-2** (497 mg, 1.02 mmol) in freshly distilled dry THF (4

20 mL) at -105°C in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise *n*-BuLi (1.6 M in hexanes, 0.79 mL, 1.26 mmol) and the reaction mixture was stirred for 10 min at -105°C then another portion of *n*-BuLi (1.6 M in hexanes, 0.79 mL, 1.26 mmol) was added dropwise and stirring was continued for 5 min at -105°C before quick addition of a solution of 3-quinolinecarboxaldehyde (165

25 mg, 1.05 mmol) in dry THF (1 mL). The reaction mixture was stirred for 1 h at -105°C then quenched by addition of a 5% aqueous NH<sub>4</sub>Cl solution (5 mL), allowing the medium to warm up to RT. THF was then removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum.

Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave 45 mg of a yellow solid. This solid (45 mg, 111 µmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of TFA (0.29 mL) and triethylsilane (21 µL, 130 µmol). The mixture 5 was stirred for 2 h at RT, then another portion of triethylsilane (160 µL, 0.99 mmol) was added and stirring was continued for 1 h at RT, then for 1.5 h under reflux. After concentration to dryness at 40°C under vacuum, the residue was neutralised with a saturated aqueous NaHCO<sub>3</sub> solution (5 mL) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The organic phase was isolated, washed with brine (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, 10 filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) gave 6,7-dimethoxy-1-propyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a 15 magnetic stirrer before addition of a 0.4 M HCl solution in MeOH (0.5 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to give 6,7-dimethoxy-1-propyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol hydrochloride **74** as a pale yellow solid (10 mg, 21% yield).



20

**74**

**MW:** 461.38; **Yield:** 21%; **Pale Yellow Solid;** **Mp (°C):** 239.8 (dec.).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD:CDCl<sub>3</sub> = 1:1, δ): 1.14 (t, 3H, *J* = 7.3 Hz, CH<sub>3</sub>), 1.92-2.00 (m, 2H, CH<sub>2</sub>), 3.38 (t, 2H, *J* = 7.7 Hz, CH<sub>2</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.90 (s, 2H, CH<sub>2</sub>), 7.27 (s, 1H, ArH), 7.43 (s, 1H, ArH), 7.92-7.97 (m, 1H, ArH), 8.10-8.15 (m, 1H, ArH), 8.24 (d, 1H, *J* = 8.2 Hz, ArH), 8.32 (d, 1H, *J* = 8.5 Hz, ArH), 8.95 (s, 1H, ArH), 9.27 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD:CDCl<sub>3</sub> = 1:1,  $\delta$ ): 14.6, 24.7, 28.9, 33.8, 57.3, 58.0, 102.7, 105.9, 119.1, 121.6, 130.3, 130.4, 131.8, 135.3, 136.2, 138.0, 141.0, 146.2, 146.7, 152.0, 154.3, 159.9, 2xC not observed.

**MS-ESI** *m/z* (rel. int.): 389 ([MH]<sup>+</sup>, 100).

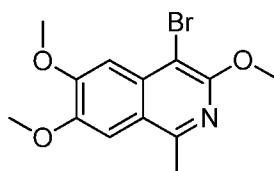
5 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.85 min, peak area 96.8%.

Preparation of (2-(ethylamino)-6-methoxyquinolin-3-yl)(3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methanone dihydrochloride 75

10

4-Bromo-3,6,7-trimethoxy-1-methylisoquinoline SMA 44070

To a solution of 6,7-dimethoxy-1-methylisoquinolin-3-ol **CCH 18060** (603 mg, 2.75 mmol) in acetic acid (27 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise bromine (0.15 mL, 2.92 mmol) and the mixture 15 was stirred for 2 h at RT. The solid was then filtered and washed with acetic acid (20 mL), EtOAc (30 mL), Et<sub>2</sub>O (4x7 mL), CH<sub>2</sub>Cl<sub>2</sub> (55 mL), saturated NaHCO<sub>3</sub> (15 mL) and finally with H<sub>2</sub>O (10 mL). After drying under vacuum, a yellow solid was obtained (718 mg). This solid (500 mg, 1.68 mmol) was dissolved in acetone (20 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer before addition of Cs<sub>2</sub>CO<sub>3</sub> (550 mg, 1.69 mmol). The mixture was stirred for 20 min at RT, MeI (1.0 mL, 16.06 mmol) was added and the mixture was stirred for 4.5 h at RT. After addition of SiO<sub>2</sub> (3.0 g), the residue was filtered and washed several times with a mixture of cyclohexane:EtOAc = 90:10 (until all the desired product was eluted). The filtrate 20 was then concentrated to dryness at 40°C under vacuum to give 4-bromo-3,6,7-trimethoxy-1-methylisoquinoline **SMA 44070** as a yellow solid (139 mg, 23% yield).



**SMA 44070**

**MW:** 312.16; **Yield:** 23%; **Yellow Solid;** **Mp** (°C): 202.3.

1 **<sup>1</sup>H NMR** (CDCl<sub>3</sub>,  $\delta$ ): 2.79 (s, 3H, CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 4.09 (s, 3H, OCH<sub>3</sub>), 7.13 (s, 1H, ArH), 7.33 (s, 1H, ArH).

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, δ): 21.9, 54.4, 56.0, 56.1, 98.0, 103.8, 104.0, 120.1, 134.8, 148.2, 152.7, 153.8, 155.0.

MS-ESI m/z (% rel. Int.): 314 ([MH]<sup>+</sup>, <sup>81</sup>Br, 50), 312 ([MH]<sup>+</sup>, <sup>79</sup>Br, 50).

HPLC: Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 5 186003113), detection UV 214 nm, RT = 3.54 min.

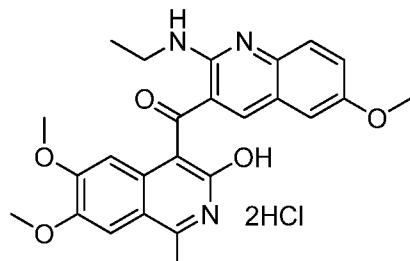
(2-(Ethylamino)-6-methoxyquinolin-3-yl)(3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methanone 75

To a stirred solution of 4-bromo-3,6,7-trimethoxy-1-methylisoquinoline **SMA 10 44070** (242 mg, 775 μmol) in freshly distilled dry THF (10 mL) at -105°C in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise *n*-BuLi (1.6 M in hexanes, 0.56 mL, 0.90 mmol) and the reaction mixture was stirred for 15 min at -105°C then another portion of *n*-BuLi (1.6 M in hexanes, 0.60 mL, 0.96 mmol) was added dropwise and stirring was continued for 10 min at -105°C before quick 15 addition of 2-chloro-6-methoxyquinoline-3-carbaldehyde (172 mg, 776 μmol). The reaction mixture was stirred for 1 h at -105°C then quenched by addition of 5% aqueous NH<sub>4</sub>Cl solution (5 mL), allowing the medium to warm up to RT. THF was removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and 20 concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 50:50) gave 51 mg of a yellow solid (14%).

This solid (51 mg, 112 μmol) was then dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0°C in a 25 mL round-bottomed flask equipped with a magnetic stirrer before addition of Dess Martin periodinane (57 mg, 134 μmol). After addition, the reaction mixture was 25 stirred for 2 h, allowing the medium to reach RT. The mixture was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), filtered through celite and the organic solution was washed with a saturated aq. NaHCO<sub>3</sub> solution (10 mL), brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 75:25) gave 32 mg of a pale yellow 30 solid (63%).

This solid (32 mg, 71 μmol) was then dissolved in THF (3 mL) in a 10 mL microwave vial equipped with a magnetic stirrer before adding ethylamine (2.0 M in THF, 1.0 mL, 2.0 mmol) and the mixture was stirred for 30 min at 160°C under

microwave irradiation. After cooling to RT, the volatiles were removed under vacuum at 40°C and the residue was then taken up in 6N aq. HCl solution and the solution was stirred for 1 h at 110°C, then cooled to RT and neutralised with a saturated aq. NaHCO<sub>3</sub> solution before extraction with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5 (30 mL). The organic phase was washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) gave (2-(ethylamino)-6-methoxyquinolin-3-yl)(3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methanone. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a 5 magnetic stirrer before addition of a 0.4 M HCl solution in MeOH (0.5 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to give (2-(ethylamino)-6-methoxyquinolin-3-yl)(3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methanone dihydrochloride **75** as a pale orange solid (10 mg, 10 2% overall yield).



15

**75**

**MW:** 520.40; **Yield:** 2%; Pale Orange Solid; **Mp (°C):** 240.9 (dec.).

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.51 (t, 3H, J = 7.2 Hz, CH<sub>3</sub>), 2.96 (s, 3H, CH<sub>3</sub>), 3.80 (q, 2H, J = 7.2 Hz, CH<sub>2</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 7.22 (s, 1H, ArH), 7.34 (s, 1H, ArH), 7.43 (d, 1H, J = 2.5 Hz, ArH), 7.55 (dd, 1H, J = 2.5 & 9.2 Hz, ArH), 7.99 (d, 1H, J = 9.2 Hz, ArH), 8.80 (s, 1H, ArH).

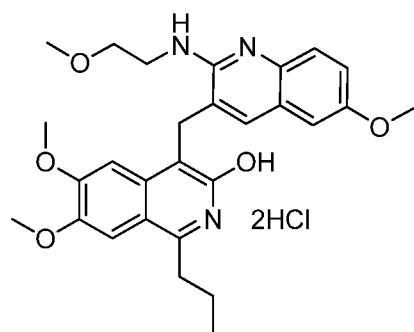
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 13.9, 17.8, 38.8, 56.5, 56.7, 56.9, 102.3, 105.9, 111.4, 112.3, 116.4, 119.9, 122.3, 123.1, 127.5, 133.9, 141.0, 149.5, 150.2, 152.1, 155.0, 158.9, 159.8, 195.8, 1xC not observed.

**25 MS-ESI** *m/z* (rel. int.): 448 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.86 min, peak area 98.1%.

Preparation of 6,7-dimethoxy-4-((6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride 76

To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (312 mg, 1.3 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer were added 3-(chloromethyl)-6-methoxy-*N*-(2-methoxyethyl)quinolin-2-amine hydrochloride **SLA 47064B** (400 mg, 1.3 mmol) and a 2 N aq. LiOH solution (1.26 mL, 2.52 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to room temperature, THF was removed at 40°C under vacuum and the residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>3</sub>CN:H<sub>2</sub>O:TFA= 100:0:0.05 to 50:50:0.05) gave 6,7-dimethoxy-4-((6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.149 M HCl solution in MeOH (2.0 mL). The reaction mixture was stirred for 5 min at room temperature and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **76** as a brown solid (39.5 mg, 5% yield).



20

**76**

**MW:** 564.50; **Yield:** 5%; **Brown Solid;** **Mp** (°C): 204.1.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.17 (t, 3H, *J* = 7.2 Hz, CH<sub>3</sub>), 1.95-2.03 (m, 2H, CH<sub>2</sub>), 3.41-3.46 (m, 2H, CH<sub>2</sub>), 3.50 (s, 3H, OCH<sub>3</sub>), 3.80 (s, 3H, OCH<sub>3</sub>), 3.86-3.90 (m, 2H, CH<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.02-4.04 (m, 2H, CH<sub>2</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 4.36 (s, 2H, CH<sub>2</sub>), 7.03 (s, 1H, ArH), 7.20 (s, 1H, ArH), 7.32 (s, 1H, ArH), 7.36 (d, 1H, *J* = 9.3 Hz, ArH), 7.75 (d, 1H, *J* = 9.3 Hz, ArH), 8.34 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 14.2, 24.7, 27.4, 33.6, 44.2, 56.4, 56.9, 57.3, 59.5, 72.3, 102.3, 105.8, 109.5, 119.7, 123.6, 123.8, 124.6, 130.9, 140.0, 141.6, 151.7, 153.2, 154.5, 158.9, 159.6, 3xC not observed.

**MS-ESI** m/z (rel.int.): 492 ([MH]<sup>+</sup>,100).

5 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 4.47 min, peak area 99.9%.

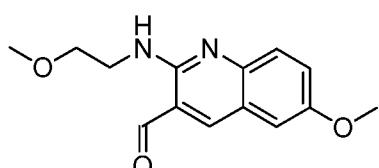
Preparation of 1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride 77

10

6-Methoxy-2-(2-methoxyethylamino)quinoline-3-carbaldehyde SLA 47060

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (1.5 g, 6.8 mmol) in THF (8 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 2-methoxyethylamine (11.82 mL, 135.0 mmol) and the mixture was 15 stirred at 160°C for 1.5h under microwave irradiation. After cooling to room temperature, THF was removed at 40°C under vacuum and the residue was taken up in THF (8 mL) before addition of a 6 N aq. HCl solution until pH = 2. After stirring for 3 h at RT, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution and further stirred for 1 h at RT. THF was then removed at 40°C under vacuum and the 20 solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 50:50) gave, after evaporation and drying, 6-methoxy-2-(2-methoxyethylamino)quinoline-3-carbaldehyde SLA 47060 as a yellow solid (1.30 g, 73% yield).

25



**SLA 47060**

**MW:** 260.29; **Yield:** 73 %; **Yellow Solid;** **Mp** (°C): 88.0.

**<sup>1</sup>H NMR** (CD<sub>3</sub>OD,  $\delta$ ): 3.43 (s, 3H, OCH<sub>3</sub>), 3.64-3.69 (m, 2H, CH<sub>2</sub>), 3.75-3.79 (m, 2H, CH<sub>2</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 7.16 (d, 1H,  $J$  = 3.0 Hz, ArH), 7.33 (dd, 1H,  $J$  = 3.0 & 9.3

30 Hz, ArH), 7.55 (d, 1H,  $J$  = 9.3 Hz, ArH), 8.40 (s, 1H, ArH), 9.97 (s, 1H, CHO).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 41.3, 56.1, 59.0, 72.2, 108.2, 119.0, 123.8, 126.8, 128.2, 147.7, 149.1, 155.0, 156.6, 194.9.

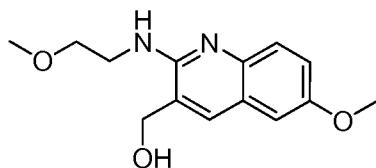
**MS-ESI** m/z (% rel. Int.): 261 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5  $\times$  50 mm, Model #

5 186003113), detection UV 254 nm, RT = 3.43min.

**(6-Methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methanol SLA 47064A**

To a stirred solution of 6-methoxy-2-(2-methoxyethylamino)quinoline-3-carbaldehyde **SLA 47060** (0.895 g, 3.4 mmol) in THF (34 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (0.13 g, 3.4 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (10 mL). After stirring for 15 min at that temperature, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to give (6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methanol **SLA 47064A** as a yellow oil (0.90 g, 100% yield).



**SLA 47064A**

20 **MW:** 262.30; **Yield:** 100 %; Yellow Oil.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>,  $\delta$ ): 2.05 (broad s, 1H, NH or OH), 3.41 (s, 3H, OCH<sub>3</sub>), 3.65-3.69 (m, 2H, CH<sub>2</sub>), 3.76-3.82 (m, 2H, CH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 4.69 (s, 2H, CH<sub>2</sub>), 5.82 (broad s, 1H, NH or OH), 6.90 (d, 1H,  $J$  = 2.7 Hz, ArH), 7.20 (dd, 1H,  $J$  = 2.7 & 9.1 Hz, ArH), 7.46 (s, 1H, ArH), 7.63 (d, 1H,  $J$  = 9.1 Hz, ArH).

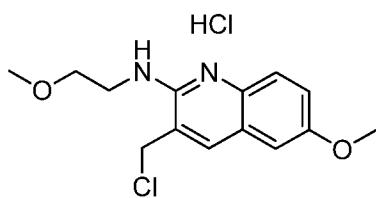
25 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 40.9, 55.5, 58.8, 63.8, 71.6, 106.6, 120.6, 122.3, 123.3, 127.5, 134.4, 143.0, 154.7, 154.8.

**MS-ESI** m/z (% rel. Int.): 263 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 3.33 min.

3-(Chloromethyl)-6-methoxy-N-(2-methoxyethyl)quinolin-2-amine hydrochloride **SLA 47064B**

To a stirred solution of (6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methanol **SLA 47064A** (0.90 g, 3.43 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (30 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (4.98 mL, 68.6 mmol). The mixture was stirred for 1.5 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-6-methoxy-N-(2-methoxyethyl)quinolin-2-amine hydrochloride **SLA 47064** as a yellow solid (1.13 g, 100%).



**SLA 47064B**

**MW:** 317.21; **Yield:** 100%; **Yellow Solid;** **Mp (°C):** 170.6.

**$^1\text{H NMR}$  (CD<sub>3</sub>OD,  $\delta$ ):** 3.42 (s, 3H, OCH<sub>3</sub>), 3.66-3.76 (m, 4H, 2XCH<sub>2</sub>), 3.87 (s, 3H, OCH<sub>3</sub>), 4.65 (s, 2H, CH<sub>2</sub>), 7.09 (d, 1H,  $J$  = 3.0 Hz, ArH), 7.17 (dd, 1H,  $J$  = 3.0 & 9.0 Hz, ArH), 7.60 (d, 1H,  $J$  = 9.0 Hz, ArH), 7.77 (s, 1H, ArH).

**$^{13}\text{C-NMR}$  (CD<sub>3</sub>OD,  $\delta$ ):** 41.9, 56.0, 59.0, 63.1, 72.4, 107.9, 121.4, 125.0, 125.1, 127.4, 135.4, 143.8, 156.3, 156.4.

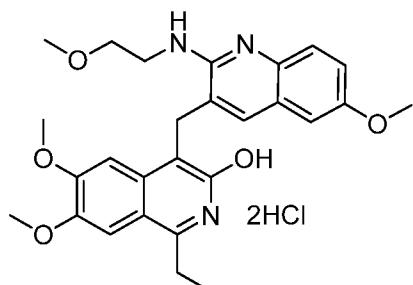
**MS-ESI m/z (% rel. Int.):** 283 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38), 281 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 3.38 min.

1-Ethyl-6,7-dimethoxy-4-((6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **77**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 47022** (215 mg, 0.92 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 3-(chloromethyl)-6-methoxy-N-(2-methoxyethyl)quinolin-2-amine hydrochloride **SLA 47064B** (292 mg, 0.92 mmol) and a 2 N aq. LiOH solution (0.92 mL, 1.84 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to room temperature, THF was then removed at 40°C under

vacuum and the solution was extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL), washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under vacuum. Purification by column chromatography (RP 18, eluent  $\text{CH}_3\text{CN}:\text{H}_2\text{O}:\text{TFA} = 100:0:0.05$  to  $50:50:0.05$ ) followed by a new purification by column chromatography (RP 18, eluent  $\text{CH}_3\text{CN}:\text{H}_2\text{O}:\text{TFA} = 100:0:0.05$  to  $66:34:0.05$ ) gave 6,7-dimethoxy-4-((6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol (mg). This free base was dissolved in  $\text{MeOH}$  (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.149 M  $\text{HCl}$  solution in  $\text{MeOH}$  (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at  $40^\circ\text{C}$  under vacuum to afford 6,7-dimethoxy-4-((6-methoxy-2-(2-methoxyethylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **77** as a brown solid (61 mg, 12% yield).

**77**

**MW:** 550.47; **Yield:** 12%; **Brown Solid;** **Mp** ( $^\circ\text{C}$ ): 212.3.

**1H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.53 (t, 3H,  $J = 7.5$  Hz,  $\text{CH}_3$ ), 3.39-3.45 (m, 2H,  $\text{CH}_2$ ), 3.46 (s, 3H,  $\text{OCH}_3$ ), 3.82 (s, 3H,  $\text{OCH}_3$ ), 3.83-3.88 (m, 2H,  $\text{CH}_2$ ), 3.92 (s, 3H,  $\text{OCH}_3$ ), 3.93-3.98 (m, 2H,  $\text{CH}_2$ ), 4.03 (s, 3H,  $\text{OCH}_3$ ), 4.40 (s, 2H,  $\text{CH}_2$ ), 7.10 (s, 1H, ArH), 7.20-7.22 (m, 1H, ArH), 7.37 (dd, 1H,  $J = 2.5$  &  $9.2$  Hz, ArH), 7.51 (s, 1H, ArH), 7.76 (s, 1H, ArH), 7.85 (d, 1H,  $J = 9.2$  Hz, ArH).

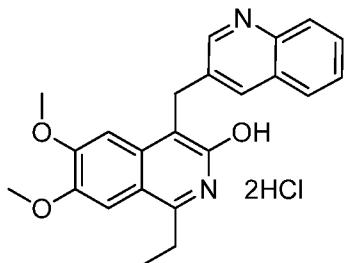
**20 13C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 14.6, 25.4, 27.4, 44.3, 56.4, 56.9, 57.3, 59.5, 72.0, 102.3, 105.7, 109.5, 117.9, 119.7, 123.6, 123.8, 124.8, 130.9, 140.0, 141.7, 151.6, 153.2, 154.4, 155.5, 158.9, 159.6, 1xC not observed.

**MS-ESI** m/z (rel.int.): 478 ( $[\text{MH}]^+$ , 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18,  $4.5 \times 50$  mm, Model # 186003113), detection UV 254 nm, RT = 4.16 min, peak area 99.0%.

Preparation of 1-ethyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **78**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 47022** (436 mg, 1.9 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)quinoline hydrochloride **SLA 47064B** (400 mg, 1.9 mmol) and a 2 N aq. LiOH solution (1.90 mL, 3.80 mmol) and the mixture was stirred 5 at 160°C for 1.5 h under microwave irradiation. After cooling to RT, THF was removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) provided 1-ethyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol. This 10 free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of 0.149 M HCl solution in MeOH (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 1-ethyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **78** as a yellow solid (87.5 mg, 10% yield).



15

**78**

**MW:** 447.35; **Yield:** 10%; **Yellow Solid;** **Mp** (°C): 268.2.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.52 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 3.31-3.34 (m, 2H, CH<sub>2</sub>), 3.40-3.48 (m, 2H, CH<sub>2</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.88 (s, 2H, CH<sub>2</sub>), 7.23 (s, 1H, ArH), 7.54 (s, 1H, ArH), 7.95 (dd, 1H, *J* = 7.5 & 7.5 Hz, ArH), 8.16 (dd, 1H, *J* = 8.2 & 8.2 Hz, ArH), 8.23-8.27 (m, 2H, 2xArH), 8.93 (s, 1H, ArH), 9.28 (s, 1H, ArH). **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.6, 25.5, 28.5, 56.9, 57.3, 102.8, 105.7, 118.1, 121.4, 130.2, 130.5, 131.5, 133.2, 135.9, 138.1, 140.9, 146.4, 146.6, 152.0, 159.9, (3xC not observed).

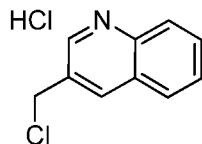
**25 MS-ESI** m/z (rel.int.): 375 ([MH]<sup>+</sup>,100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.53 min, peak area 99.9%.

Preparation of 1-isopropyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride 79

3-(Chloromethyl)quinoline hydrochloride SLA 47074B

5 To a stirred solution of quinoline-3-carbaldehyde (1.00 g, 6.36 mmol) in THF (60 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (0.24 g, 6.36 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution. After stirring for 15 min at RT, the mixture was basified to pH = 9 with a 2 N aq. NaOH 10 solution. THF was removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum to give quinolin-3-ylmethanol **SLA 47074A** as a yellow oil (1.06 g, >100%). This oil (1.056 g, 6.6 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (40 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer before dropwise 15 addition of SOCl<sub>2</sub> (9.62 mL, 133.3 mmol). The mixture was stirred for 2 h at RT and concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)quinoline hydrochloride **SLA 47074B** as a yellow solid (1.20 g, 85% yield).



**SLA 47074B**

**MW:** 214.09; **Yield:** 85%; **Yellow Solid;** **Mp** (°C): 155.2.

25 **<sup>1</sup>H NMR** (CD<sub>3</sub>OD, δ): 5.08 (s, 2H, CH<sub>2</sub>), 7.99-8.05 (m, 1H, ArH), 8.18-8.24 (m, 1H, ArH), 8.28 (d, 1H, *J* = 8.3 Hz, ArH), 8.37 (d, 1H, *J* = 8.3 Hz, ArH), 9.30 (d, 1H, *J* = 1.5 Hz, ArH), 9.39 (d, 1H, *J* = 1.5 Hz, ArH).

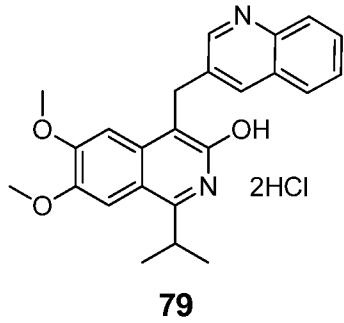
**MS-ESI** m/z (% rel. Int.): 180 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 32), 178 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 3.38 min.

30 1-Isopropyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride 79

To a solution of 1-isopropyl-6,7-dimethoxyisoquinolin-3-ol **SIL 32164** (462 mg, 1.87 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 3-(chloromethyl)quinoline hydrochloride **SLA 47064B** (400 mg, 1.87 mmol) and a 2 N aq. LiOH solution (1.87 mL, 3.74 mmol) and the mixture was 5 stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, THF was removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) provided 1-isopropyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol.

10 This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of 0.149 M HCl solution in MeOH (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 1-isopropyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **79** as a yellow solid (76 mg, 9% yield).



**MW:** 461.38; **Yield:** 9%; **Yellow Solid;** **Mp (°C):** 200.2.

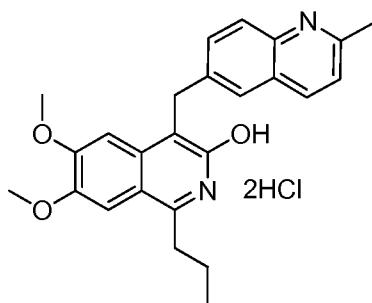
**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.63 (d, 6H, *J* = 6.9 Hz, 2xCH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 4.24-4.29 (m, 1H, CH), 4.92-4.99 (m, 2H, CH<sub>2</sub>), 7.32 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.95 (dd, 1H, *J* = 7.5 & 7.0 Hz, ArH), 8.15 (dd, 1H, *J* = 7.5 & 8.1 Hz, ArH), 8.28 (dd, 2H, *J* = 7.0 & 8.1 Hz, 2xArH), 9.00 (s, 1H, ArH), 9.30 (s, 1H, ArH).  
**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 21.4 (2xC), 28.6, 30.8, 57.0, 57.6, 102.9, 105.6, 105.8, 111.9, 118.6, 121.3, 130.3, 130.5, 131.6, 135.1, 136.0, 137.9, 141.4, 146.5, 146.7, 152.3, 158.9, 160.1.

25 **MS-ESI** m/z (rel.int.): 389 ([MH]<sup>+</sup>,100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.70 min, peak area 99.9%.

Preparation of 6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride 80

To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (434 mg, 1.75 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 6-(chloromethyl)-2-methylquinolinehydrochloride **SLA 47080B** (400 mg, 1.75 mmol) and a 2 N aq. LiOH solution (1.75 mL, 3.50 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, THF was removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and 10 concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) provided 6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)-1-propylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a 15 magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **80** as a yellow solid (28 mg, 3% yield).



20

**80**

**MW:** 475.41; **Yield:** 3%; **Yellow Solid;** **Mp (°C):** 201.0.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.14 (t, 3H, *J* = 7.3 Hz, CH<sub>3</sub>), 1.92-2.00 (m, 2H, CH<sub>2</sub>), 3.01 (s, 3H, CH<sub>3</sub>), 3.39 (t, 2H, *J* = 7.3 Hz, CH<sub>2</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.80 (s, 2H, CH<sub>2</sub>), 7.18 (s, 1H, ArH), 7.52 (s, 1H, ArH), 7.90(d, 1H, *J* = 8.8 Hz, ArH), 8.07 (s, 1H, ArH), 8.12 (d, 1H, *J* = 8.8 Hz, ArH), 8.20 (d, 1H, *J* = 8.7 Hz, ArH), 8.92 (d, 1H, *J* = 8.7 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 14.2, 20.8, 24.6, 31.3, 33.5, 56.9, 57.2, 103.3, 105.9, 113.9, 119.4, 121.4, 125.1, 128.5, 128.9, 136.9, 138.0, 141.1, 142.3, 147.3, 152.0, 152.2, 154.5, 158.9, 159.5.

**MS-ESI** m/z (rel.int.): 403 ([MH]<sup>+</sup>, 82), 202 (100).

5 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 254 nm, RT = 3.78 min, peak area 97.2%.

Preparation of 1-ethyl-6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)isoquinolin-3-ol dihydrochloride 81

10

(2-Methylquinolin-6-yl)methanol SLA 47080A

To a stirred solution of 2-methylquinoline-6-carbaldehyde (1.00 g, 5.8 mmol) in THF (60 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (0.221 g, 5.8 mmol) and the mixture was stirred overnight 15 at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (10 mL). After stirring for 15 min at RT, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to give (2-methylquinolin-6-yl)methanol **SLA 47080A** as a yellow oil (1.056 g, quant.).



**SLA 47080A**

**MW:** 173.21; **Yield:** 100%; Yellow Oil.

25 **<sup>1</sup>H NMR** (CDCl<sub>3</sub>,  $\delta$ ): 2.60 (broad s, 1H, OH), 2.70 (s, 3H, CH<sub>3</sub>), 4.87 (s, 2H, CH<sub>2</sub>), 7.27 (d, 1H,  $J$  = 8.5 Hz, ArH), 7.63 (dd, 1H,  $J$  = 2.1 & 8.7 Hz, ArH), 7.72-7.74 (m, 1H, ArH), 7.96-8.02 (m, 2H, 2xArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>,  $\delta$ ): 25.2, 64.9, 122.2, 124.8, 126.3, 128.7, 128.8, 136.1, 138.4, 147.4, 158.9.

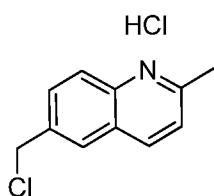
**MS-ESI** m/z (% rel. Int.): 174 ([MH]<sup>+</sup>, 100).

30 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5  $\times$  50 mm, Model # 186003113), detection UV 214 nm, RT = 2.39 min.

**6-(Chloromethyl)-2-methylquinoline hydrochloride SLA 47080B**

To a stirred solution of (2-methylquinolin-6-yl)methanol **SLA 47080A** (0.973 g, 5.62 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (40 mL) in a 100 mL round-bottomed flask equipped with a 5 magnetic stirrer was added dropwise  $\text{SOCl}_2$  (8.15 mL, 112 mmol). The mixture was stirred for 2 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 6-(chloromethyl)-2-methylquinoline hydrochloride **SLA 47080B** as a yellow solid (1.30 g, quant).

10



**SLA 47080B**

**MW:** 228.12; **Yield:** 100%; **Yellow Solid;** **Mp (°C):** 134.0.

**MS-ESI m/z (% rel. Int.):** 194 ( $[\text{MH}]^+$ ,  $^{37}\text{Cl}$ , 34), 192 ( $[\text{MH}]^+$ ,  $^{35}\text{Cl}$ , 100).

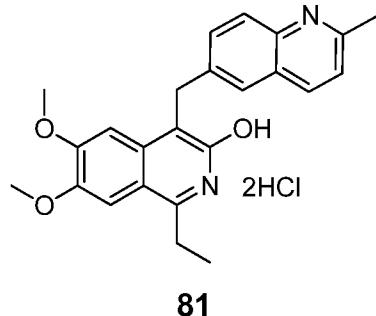
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 15 186003113), detection UV 214 nm, RT = 3.30 min.

**1-Ethyl-6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)isoquinolin-3-ol**

**dihydrochloride 81**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 47022** (409 mg, 20 1.7 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 6-(chloromethyl)-2-methylquinolinehydrochloride **SLA 47080B** (400 mg, 1.7 mmol) and a 2 N aq. LiOH solution (1.75 mL, 3.5 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to 25 RT, THF was removed at 40°C under vacuum and the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (50 mL), washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{EtOAc:MeOH} = 100:0$  to  $93:7$ ) followed by a new purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2:\text{MeOH} = 100:0$  to  $93:7$ ) provided 1-ethyl-6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)isoquinolin-3-ol. This free base was 30 dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a

magnetic stirrer before addition of a 0.149 M HCl solution in MeOH (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 1-ethyl-6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)isoquinolin-3-ol dihydrochloride **81** as a yellow solid (66 mg, 8% yield).



**MW:** 461.38; **Yield:** 8%; **Yellow Solid;** **Mp (°C):** 198.1.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.53 (t, 3H, *J* = 7.6 Hz, CH<sub>3</sub>), 3.01 (s, 3H, CH<sub>3</sub>), 3.46 (q, 2H, *J* = 7.6 Hz, CH<sub>2</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 4.03 (s, 3H, OCH<sub>3</sub>), 4.81 (s, 2H, CH<sub>2</sub>), 7.19 (s, 1H, ArH), 7.55 (s, 1H, ArH), 7.90 (d, 1H, *J* = 8.4 Hz, ArH), 8.05 (s, 1H, ArH), 8.13 (s, 1H, *J* = 8.4 Hz, ArH), 8.19 (d, 1H, *J* = 8.7 Hz, ArH), 8.92 (d, 1H, *J* = 8.7 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.6, 20.8, 25.4, 31.2, 56.9, 57.2, 103.4, 105.8, 113.6, 119.2, 121.4, 125.1, 128.5, 128.9, 136.9, 138.0, 141.2, 142.2, 147.3, 151.9, 152.2, 155.9, 159.0, 159.6.

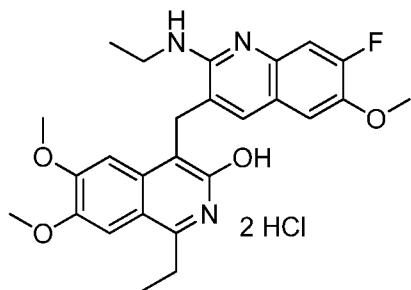
**15 MS-ESI** m/z (rel.int.): 389 ([MH]<sup>+</sup>, 56), 195 (100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.43 min, peak area 97.3%.

1-Ethyl-4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **82**

20 To a stirred solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (114 mg, 0.49 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-*N*-ethyl-7-fluoro-6-methoxyquinolin-2-amine hydrochloride **SMA 44096** (149 mg, 0.49 mmol) at RT followed by a 2 N aq. LiOH solution (0.49 mL, 0.98 mmol) and the mixture was stirred at 155°C for 1.5 h under microwave irradiation. After cooling to RT, THF was removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0

to 95:5) gave 16 mg of 1-ethyl-4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol as a brown solid. This free base was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.5 mL). The 5 reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 1-ethyl-4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **82** as a yellow solid (19 mg, 7% yield).

**82**

10 **MW:** 538.44; **Yield:** 7%; **Yellow Solid;** **Mp** (°C): 178.1 (dec.)

**R<sub>f</sub>:** 0.2 ( $\text{CH}_2\text{Cl}_2$ :MeOH = 95:5, free base).

**<sup>1</sup>H-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 1.51-1.56 (m, 6H, 2x $\text{CH}_3$ ), 3.33-3.40 (m, 2H,  $\text{CH}_2$ ), 3.76 (q, 2H,  $J$  = 6.8 Hz,  $\text{CH}_2$ ), 3.89 (s, 3H,  $\text{OCH}_3$ ), 3.99 (s, 3H,  $\text{OCH}_3$ ), 4.02 (s, 3H,  $\text{OCH}_3$ ), 4.36 (s, 2H,  $\text{CH}_2$ ), 7.08 (s, 1H, ArH), 7.40 (d, 1H,  $J$  = 7.2 Hz, ArH), 7.47 (s, 1H, ArH), 7.75 (d, 1H,  $J$  = 11.6 Hz, ArH), 7.73-7.84 (m, 1H, ArH).

**<sup>13</sup>C-NMR** ( $\text{CD}_3\text{OD}$ ,  $\delta$ ): 13.9, 14.7, 25.5, 27.1, 39.3, 57.0, 57.1, 57.5, 102.7, 105.5, 105.8, 110.1, 111.7, 118.7, 119.7, 123.6, 131.3 (d,  $J$  = 11.4 Hz), 139.2, 141.7, 148.0 (d,  $J$  = 12.0 Hz), 152.0, 152.9, 156.0, 156.4 (d,  $J$  = 255.3 Hz), 159.9, 1xC not seen.

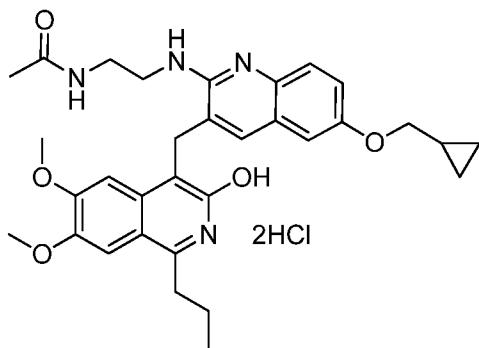
**MS-ESI** *m/z* (rel. int.): 466 ([ $\text{MH}$ ]<sup>+</sup>, 100).

20 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.26 min, peak area 96.1%.

Preparation of *N*-(2-(6-(cyclopropylmethoxy)-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide dihydrochloride **83**

25 To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (151 mg, 0.6 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added *N*-(2-(3-(chloromethyl)-6-(cyclopropylmethoxy)quinolin-2-ylamino)ethyl)-acetamide hydrochloride **SLA 47096B** (235 mg, 0.6 mmol) followed by a 2 N aq. LiOH solution (0.612 mL, 1.2 mmol) and the mixture was stirred at

160°C for 1.5 h under microwave irradiation. After cooling to RT, THF was removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) provided *N*-(2-(6-(cyclopropylmethoxy)-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide. The free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.149 M HCl solution in MeOH (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford *N*-(2-(6-(cyclopropylmethoxy)-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide dihydrochloride **83** as a brown solid (41 mg, 11% yield).

**83**

**15 MW:** 631.59; **Yield:** 11%; Brown Solid; **Mp (°C):** 210.6.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 0.29-0.34 (m, 2H, CH<sub>2</sub>), 0.56-0.63 (m, 2H, CH<sub>2</sub>), 1.18 (t, 3H, J = 6.7 Hz, CH<sub>3</sub>), 1.28-1.35 (m, 1H, CH), 1.96-2.03 (m, 2H, CH<sub>2</sub>), 2.09 (s, 3H, CH<sub>3</sub>), 3.41-3.46 (m, 2H, CH<sub>2</sub>), 3.60-3.66 (m, 2H, CH<sub>2</sub>), 3.81 (t, 2H, J = 6.7 Hz, CH<sub>2</sub>), 3.86-3.91 (m, 2H, CH<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.26 (s, 2H, CH<sub>2</sub>), 7.11-7.15 (m, 2H, 2xArH), 7.38 (d, 1H, J = 9.1 Hz, ArH), 7.52 (s, 1H, ArH), 7.58 (s, 1H, ArH), 8.02 (d, 1H, J = 9.1 Hz, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 3.5, 3.5, 10.9, 14.2, 22.5, 24.7, 27.1, 33.6, 39.0, 43.5, 56.9, 57.5, 74.4, 102.7, 106.0, 109.9, 110.2, 119.2, 119.9, 123.9, 124.0, 124.3, 124.5, 131.2, 139.4, 141.7, 152.1, 152.9, 154.9, 158.3, 160.0, 175.7.

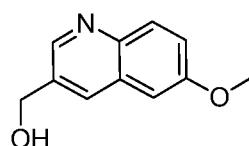
**25 MS-ESI** m/z (rel.int.): 559 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.68 min, peak area 95.5%.

Preparation of 6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride 84

(6-Methoxyquinolin-3-yl)methanol SLA 47088A

5 To a stirred solution of 6-methoxyquinoline-3-carbaldehyde (1.00 g, 5.3 mmol) in THF (50 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (0.20 g, 5.3 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath before quenching by addition of a 1 N aq. HCl solution (12 mL). After stirring for 15 min at RT, the mixture was basified to pH = 9 with a 2 N  
10 aq. NaOH solution. THF was removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 0:100) gave (6-methoxyquinolin-3-yl)methanol **SLA 47088A** as a yellow solid (0.49 g, 49% yield).



**SLA 47088A**

**MW:** 189.21; **Yield:** 49 %; **Yellow Solid;** **Mp** (°C): 169.1.

19 **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 3.48 (broad s, 1H, OH), 3.90 (s, 3H, OCH<sub>3</sub>), 4.85 (s, 2H, CH<sub>2</sub>), 6.99 (d, 1H, J = 2.7 Hz, ArH), 7.30 (dd, 1H, J = 2.7 & 9.0 Hz, ArH), 7.93 (d, 1H, J = 9.0 Hz, ArH), 7.98 (d, 1H, J = 1.5 Hz, ArH), 8.64 (d, 1H, J = 1.5 Hz, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 55.5, 62.8, 105.2, 122.1, 129.0, 130.3, 132.6, 134.1, 143.6, 147.5, 158.0.

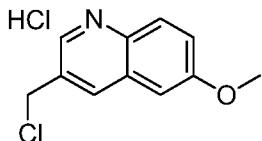
**MS-ESI** m/z (% rel. Int.): 190 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 25 186003113), detection UV 214 nm, RT = 2.83 min.

3-(Chloromethyl)-6-methoxyquinoline hydrochloride SLA 47088B

To a stirred solution of (6-methoxyquinolin-3-yl)methanol **SLA 47088A** (0.476 g, 2.5 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise SOCl<sub>2</sub> (3.65 mL, 50.4 mmol). The mixture  
30

was stirred for 2 h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give 3-(chloromethyl)-6-methoxyquinoline hydrochloride **SLA 47088B** as a yellow solid (0.60 g, 98% yield).



**SLA 47088B**

**MW:** 244.12; **Yield:** 98%; **Yellow Solid;** **Mp** (°C): 178.5.

**<sup>1</sup>H NMR** (CD<sub>3</sub>OD, δ): 4.07 (s, 3H, OCH<sub>3</sub>), 5.08 (s, 2H, CH<sub>2</sub>), 7.75 (d, 1H, *J* = 2.7 Hz, ArH), 7.83 (dd, 1H, *J* = 2.7 & 9.3 Hz, ArH), 8.22 (d, 1H, *J* = 9.3 Hz, ArH), 9.17 (s, 1H, ArH), 9.19 (s, 1H, ArH).

**<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 42.4, 57.0, 107.7, 122.9, 130.0, 132.5, 134.5, 134.7, 142.9, 145.8, 162.3.

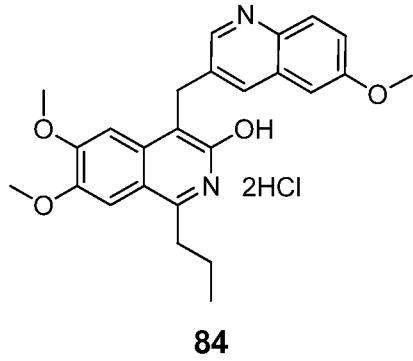
**MS-ESI** m/z (% rel. Int.): 210 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 34), 208 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 3.55 min.

6,7-Dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **84**

To a solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (316 mg, 20 1.3 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added a 3-(chloromethyl)-6-methoxyquinoline hydrochloride **SLA 47088B** (265 mg, 1.1 mmol) and a 2 N aq. LiOH solution (1.3 mL, 2.6 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, THF was then removed at 40°C under vacuum and the residue was then taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) gave 89 mg of 6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of 30 a 0.149 M HCl solution in MeOH (3.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to afford 6,7-dimethoxy-4-((6-

methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **84** as a brown solid (93 mg, 17% yield).

**84**

5 **MW:** 491.41; **Yield:** 17%; **Brown Solid;** **Mp** (°C): 220.0.

**<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.13 (t, 3H, *J* = 6.7 Hz, CH<sub>3</sub>), 1.90-1.96 (m, 2H, CH<sub>2</sub>), 3.36-3.40 (m, 2H, CH<sub>2</sub>), 3.97 (s, 6H, 2xOCH<sub>3</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 4.89 (s, 2H, CH<sub>2</sub>), 7.23 (s, 1H, ArH), 7.54 (s, 1H, ArH), 7.61 (s, 1H, ArH), 7.75 (d, 1H, *J* = 9.7 Hz, ArH), 8.15 (d, 1H, *J* = 9.7 Hz, ArH), 8.75 (s, 1H, ArH), 9.07 (s, 1H, ArH).

10 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.0, 24.6, 28.8, 33.3, 56.9, 56.9, 57.3, 102.4, 105.9, 107.2, 112.4, 118.8, 122.7, 129.1, 132.6, 133.9, 135.8, 141.1, 142.9, 144.5, 149.9, 151.6, 154.2, 159.2, 162.1.

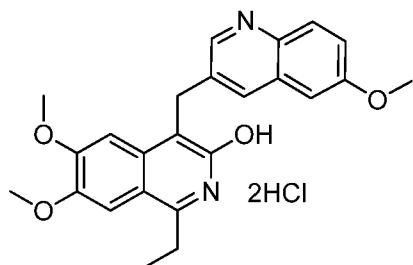
**MS-ESI** m/z (rel.int.): 419 ([MH]<sup>+</sup>,100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.85 min, peak area 96.2%.

Preparation of 1-ethyl-6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **85**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 28136** (288 mg, 20 1.18 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 3-(chloromethyl)-6-methoxyquinoline hydrochloride **SLA 47088B** (275 mg, 1.18 mmol) and a 2 N aq. LiOH solution (1.20 mL, 2.40 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, THF was then removed at 40°C under vacuum and the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 94:6) followed by a new purification by column chromatography (RP 18, eluent CH<sub>3</sub>CN:H<sub>2</sub>O= 100:0 to 34:66) gave 1-ethyl-6,7-

dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.149 M HCl solution in MeOH (3.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum 5 to afford 1-ethyl-6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **85** as a brown solid (46.5 mg, 8% yield).

**85**

**MW:** 477.38; **Yield:** 8%; Brown Solid; **Mp (°C):** 220.2 (dec.).

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.53 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>), 3.46 (q, 2H, *J* = 7.5 Hz, CH<sub>2</sub>), 3.98 (s, 6H, 2xOCH<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 4.76 (s, 2H, CH<sub>2</sub>), 7.24 (s, 1H, ArH), 7.55 (s, 1H, ArH), 7.61 (s, 1H, ArH), 7.77 (d, 1H, *J* = 9.4 Hz, ArH), 8.16 (d, 1H, *J* = 9.4 Hz, ArH), 8.75 (s, 1H, ArH), 9.08 (s, 1H, ArH).

15 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 14.6, 25.5, 28.6, 56.9, 56.9, 57.4, 102.8, 105.8, 107.2, 118.9, 122.7, 129.2, 132.1, 132.6, 133.9, 135.5, 140.2, 141.1, 143.0, 152.2, 152.7, 156.1, 159.9, 162.1.

**MS-ESI** m/z (rel.int.): 405 ([MH]<sup>+</sup>,100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 3.58 min, peak area 99.6%.

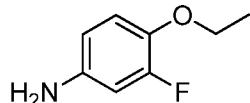
20

Preparation of 4-((6-Ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **86**

4-Ethoxy-3-fluoroaniline SMA 44094

25 To a solution of 4-amino-2-fluorophenol (2.15 g, 16.9 mmol) in dry DMF (60 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer was added Cs<sub>2</sub>CO<sub>3</sub> (10.6 g, 25.4 mmol) and the mixture was stirred for 10 min at RT before addition of bromoethane (1.5 mL, 20.3 mmol). The reaction mixture was then stirred for 7 h at RT, concentrated to dryness, and the residue was partitioned between

CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and water (20 mL). The organic layer was washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 88:12) gave 4-ethoxy-3-fluoroaniline **SMA 44094** as a brown oil (480 mg, 18% yield).



5

### SMA 44094

**MW:** 155.17; **Yield:** 18%; Brown Oil.

**<sup>1</sup>H-NMR** (CDCl<sub>3</sub>, δ): 1.38 (t, 3H, J = 7.0 Hz, CH<sub>3</sub>), 3.45 (broad s, 2H, NH<sub>2</sub>), 4.01 (q, 2H, J = 7.0 Hz, CH<sub>2</sub>), 6.33-6.37 (m, 1H, ArH), 6.46 (dd, 1H, J = 2.7 & 12.7 Hz, ArH), 10 6.79 (dd, 1H, J = 8.9 & 8.9 Hz, ArH).

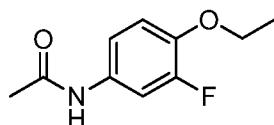
**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 15.0, 66.5, 104.1 (d, J = 21.8 Hz), 110.4 (d, J = 3.0 Hz), 118.0 (d, J = 3.8 Hz), 139.2 (d, J = 11.3 Hz), 141.3 (d, J = 9.8 Hz), 153.9 (d, J = 244.5 Hz).

**MS-ESI** m/z (% rel. Int.): 156 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 15 186003113), detection UV 214 nm, RT = 1.83 min.

### N-(4-ethoxy-3-fluorophenyl)acetamide SMA 44098

To a solution of 4-ethoxy-3-fluoroaniline **SMA 44094** (464 mg, 2.99 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer 20 were added DIEA (2.0 mL, 12 mmol), DMAP (87 mg, 0.7 mmol) and acetic anhydride (1.7 mL, 18 mmol) and the mixture was stirred for 5 h at RT. The solution was then diluted with more CH<sub>2</sub>Cl<sub>2</sub> (30 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 50:50) gave *N*-(4-ethoxy-3-fluorophenyl)acetamide **SMA 44098** as a beige solid (242 mg, 41% yield).



### SMA 44098

**MW:** 197.21; **Yield:** 41%; Beige Solid; **Mp (°C):** 127.4.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.42 (t, 3H, J = 7.0 Hz, CH<sub>3</sub>), 2.15 (s, 3H, CH<sub>3</sub>), 4.08 (q, 2H, J = 7.0 Hz, CH<sub>2</sub>), 6.88 (dd, 1H, J = 8.9 & 8.9 Hz, ArH), 7.07-7.10 (m, 1H, ArH), 7.29 (broad s, 1H, NH), 7.40 (dd, 1H, J = 2.5 & 12.8 Hz, ArH).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.0, 23.5, 64.6, 108.5 (d, J = 22.6 Hz), 114.6, 114.8 (d, J = 3.8

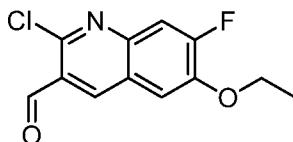
5 Hz), 130.6 (d, J = 9.1 Hz), 142.8 (d, J = 10.6 Hz), 151.7 (d, J = 245.3 Hz), 167.3.

**MS-ESI** m/z (% rel. Int.): 198 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.37 min.

10 **2-Chloro-6-ethoxy-7-fluoroquinoline-3-carbaldehyde SMA 44100**

POCl<sub>3</sub> (0.77 mL, 8.32 mmol) was added dropwise under N<sub>2</sub> to DMF (0.23 mL, 2.95 mmol) at 0°C in a 2 mL microwave vial equipped with a magnetic stirrer. The mixture was stirred for 15 min at 0°C before addition of *N*-(4-ethoxy-3-fluorophenyl)acetamide **SMA 44098** (232 mg, 1.18 mmol) and the mixture was stirred for 45 min at 120°C under microwave irradiation. After cooling to RT, the mixture was poured on a mixture of ice-water (10 mL) and basified with a 10 N aqueous NaOH solution (pH = 12) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (80 mL). The separated organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent cyclohexane:EtOAc = 100:0 to 90:10) gave 2-chloro-6-ethoxy-7-fluoro-quinoline-3-carbaldehyde **SMA 44100** as a yellow solid (119 mg, 40% yield).



**SMA 44100**

**MW:** 253.66; **Yield:** 40%; **Yellow Solid.**

25 **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.56 (t, 3H, J = 7.0 Hz, CH<sub>3</sub>), 4.25 (q, 2H, J = 7.0 Hz, CH<sub>2</sub>), 7.28 (d, 1H, J = 8.7 Hz, ArH), 7.70 (d, 1H, J = 11.4 Hz, ArH), 8.61 (s, 1H, ArH), 10.53 (s, 1H, CHO).

**<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.4, 65.2, 109.1 (d, J = 3.8 Hz), 113.6 (d, J = 18.9 Hz), 124.5, 125.9 (d, J = 2.2 Hz), 138.1, 145.9 (d, J = 12.8 Hz), 148.9 (d, J = 13.6 Hz), 157.4 (d,

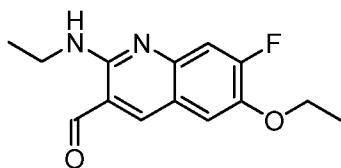
30 J = 261.9 Hz), 189.1, 1xC not observed.

**MS-ESI** m/z (% rel. Int.): 256 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38), 254 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 3.22 min.

**6-Ethoxy-2-(ethylamino)-7-fluoroquinoline-3-carbaldehyde SMA 44102**

5 A solution of 2-chloro-6-ethoxy-7-fluoroquinoline-3-carbaldehyde **SMA 44100** (110 mg, 0.43 mmol) in ethylamine (2.0 M in THF, 2.20 mL, 4.40 mmol) in a 10 mL microwave vial equipped with a magnetic stirrer was stirred for 3.5 h at 150°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl = 10 50:50 (10 mL) and the mixture was stirred for 30 min at RT. THF was then removed at 40°C under vacuum and the residue was basified with a 10 N aq. NaOH solution (pH = 8) before extraction with CH<sub>2</sub>Cl<sub>2</sub> (40 mL). The separated organic layer was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent 15 cyclohexane:EtOAc = 100:0 to 90:10) gave 6-ethoxy-2-(ethylamino)-7-fluoroquinoline-3-carbaldehyde **SMA 44102** as a yellow solid (63 mg, 56% yield).



**SMA 44102**

**MW:** 262.28; **Yield:** 56%; **Yellow Solid.**

20 **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 1.31 (t, 3H, J = 7.2 Hz, CH<sub>3</sub>), 1.53 (t, 3H, J = 7.0 Hz, CH<sub>3</sub>), 3.58-3.67 (m, 2H, CH<sub>2</sub>), 4.14 (q, 2H, J = 7.0 Hz, CH<sub>2</sub>), 7.01 (d, 1H, J = 9.1 Hz, ArH), 7.32 (d, 1H, J = 12.7 Hz, ArH), 7.91 (br, s, 1H, NH), 8.05 (s, 1H, ArH), 9.92 (s, 1H, CHO).  
25 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 14.6, 14.7, 35.4, 64.9, 110.2 (d, J = 4.5 Hz), 111.8 (d, J = 18.9 Hz), 116.4 (d, J = 2.2 Hz), 118.4, 144.4 (d, J = 13.6 Hz), 146.5, 147.8 (d, J = 12.8 Hz), 154.3, 158.0 (d, J = 258.1 Hz), 192.7.

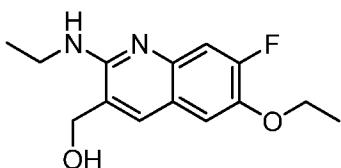
**MS-ESI** m/z (% rel. Int.): 263 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.22 min.

30 **((6-Ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methanol SMA 44104**

To a solution of 6-ethoxy-2-(ethylamino)-7-fluoroquinoline-3-carbaldehyde **SMA 44102** (63 mg, 0.24 mmol) in THF (10 mL) in a 25 mL round-bottomed flask

equipped with a magnetic stirrer was added  $\text{NaBH}_4$  (11 mg, 0.29 mmol) and the reaction mixture was stirred for 3 h at RT, then cooled down to 0°C and quenched with a 6 N aq. HCl solution (5 mL). The mixture was stirred for 10 min at RT before basification to pH = 12 with a 10 N aq. NaOH. THF was then removed at 40°C and the residue was extracted with  $\text{CH}_2\text{Cl}_2$  (30 mL). The organic phase was isolated, washed with brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated at 40°C under vacuum to give (6-ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methanol **SMA 44104** as a pink solid (61 mg, 96% yield).



10

**SMA 44104**

**MW:** 264.30; **Yield:** 96%; Pink Solid.

**$^1\text{H NMR}$**  ( $\text{CDCl}_3$ ,  $\delta$ ): 1.27 (t, 3H,  $J$  = 7.2 Hz,  $\text{CH}_3$ ), 1.49 (t, 3H,  $J$  = 7.0 Hz,  $\text{CH}_3$ ), 3.49-3.53 (m, 3H, OH &  $\text{CH}_2$ ), 4.08 (q, 2H,  $J$  = 7.0 Hz,  $\text{CH}_2$ ), 4.42 (s, 2H,  $\text{CH}_2$ ), 5.71 (broad s, 1H, NH), 6.69 (d, 1H,  $J$  = 9.1 Hz, ArH), 6.77 (s, 1H, ArH), 7.31 (d, 1H,  $J$  = 12.8 Hz, ArH).

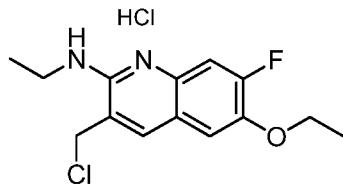
**$^{13}\text{C-NMR}$**  ( $\text{CDCl}_3$ ,  $\delta$ ): 14.7, 14.8, 35.9, 63.7, 65.1, 109.8 (d,  $J$  = 2.2 Hz), 111.1 (d,  $J$  = 18.9 Hz), 119.3 (d,  $J$  = 1.5 Hz), 121.2 (d,  $J$  = 3.0 Hz), 133.7, 143.1 (d,  $J$  = 12.1 Hz), 143.4 (d,  $J$  = 12.8 Hz), 154.9 (d,  $J$  = 250.5 Hz), 155.6.

**MS-ESI** m/z (% rel. Int.): 265 [ $\text{MH}^+$ ] (100).  
**20 HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.09 min.

3-(Chloromethyl)-6-ethoxy-N-ethyl-7-fluoroquinolin-2-amine hydrochloride **SMA 44106**

To a solution of (6-ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methanol **SMA 44104** (61 mg, 0.23 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0°C under  $\text{N}_2$  in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (0.33 mL, 4.56 mmol) and the mixture was stirred for 3 h at RT. The mixture was then concentrated to dryness at 40°C under vacuum and the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) before concentration back to dryness (done 3 times) to give 3-

(chloromethyl)-6-ethoxy-N-ethyl-7-fluoroquinolin-2-amine hydrochloride **SMA 44106** as a brown solid (88 mg, >100% yield).



**SMA 44106**

5

**MW:** 319.20; **Yield:** >100%; Brown solid.

**<sup>1</sup>H NMR** (CD<sub>3</sub>OD,  $\delta$ ): 1.45 (t, 3H,  $J$  = 7.2 Hz, CH<sub>3</sub>), 1.50 (t, 3H,  $J$  = 7.0 Hz, CH<sub>3</sub>), 3.74 (q, 2H,  $J$  = 7.2 Hz, CH<sub>2</sub>), 4.25 (q, 2H,  $J$  = 7.0 Hz, CH<sub>2</sub>), 4.90 (s, 2H, CH<sub>2</sub>), 7.57 (d, 1H,  $J$  = 8.6 Hz, ArH), 7.77 (d, 1H,  $J$  = 11.6 Hz, ArH), 8.40 (s, 1H, ArH).

10 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD,  $\delta$ ): 13.7, 14.8, 38.9, 41.9, 66.5, 105.9 (d,  $J$  = 24.9 Hz), 112.9 (d,  $J$  = 3.8 Hz), 119.5 (d,  $J$  = 2.2 Hz), 123.0 (d,  $J$  = 3.0 Hz), 132.4 (d,  $J$  = 12.1 Hz), 143.3, 147.6 (d,  $J$  = 12.8 Hz), 151.7, 157.4 (d,  $J$  = 256.6 Hz).

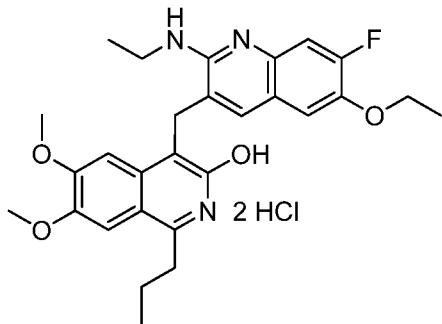
**MS-ESI** m/z (% rel. Int.): 285 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 38), 283 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100).

15 **HPLC:** Method B (5 min), XBridgeTM column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 2.35 min.

4-((6-Ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol **86**

To a stirred solution of 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35142** (55 mg, 222  $\mu$ mol) in THF (5 mL) in a 10 mL microwave vial equipped with a magnetic stirrer was added a solution of 3-(chloromethyl)-6-ethoxy-N-ethyl-7-fluoroquinolin-2-amine hydrochloride **SMA 44106** (76 mg, 238  $\mu$ mol) in MeOH (0.5 mL) at RT followed by a 2 N aq. LiOH solution (240  $\mu$ L, 480  $\mu$ mol) and the mixture was stirred at 155°C for 1.5 h under microwave irradiation. After cooling to RT, THF and MeOH were removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic solution was washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent EtOAc:MeOH = 100:0 to 95:5) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 96:4) gave 4-((6-ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol as a brown solid. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2

5 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.49 M HCl solution in MeOH (0.5 mL). The reaction mixture was stirred for 5 min at RT then concentrated at 40°C under vacuum to afford 4-((6-ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol **86** as a brown solid (15 mg, 12% yield).

**86**

**MW:** 566.49; **Yield:** 12%; **Brown Solid;** **Mp** (°C): 180.3 (dec.)

**R<sub>f</sub>:** 0.35 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 95:5, free base).

10 **<sup>1</sup>H-NMR** (CD<sub>3</sub>OD, δ): 1.15 (t, 3H, *J* = 7.1 Hz, CH<sub>3</sub>), 1.41 (t, 3H, *J* = 6.3 Hz, CH<sub>3</sub>), 1.54 (t, 3H, *J* = 7.1 Hz, CH<sub>3</sub>), 1.91-2.00 (m, 2H, CH<sub>2</sub>), 3.36 (t, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 3.79 (q, 2H, *J* = 7.1 Hz, CH<sub>2</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.05-4.11 (m, 2H, CH<sub>2</sub>), 4.38 (s, 2H, CH<sub>2</sub>), 7.09 (s, 1H, ArH), 7.38 (d, 1H, *J* = 8.0 Hz, ArH), 7.47 (s, 1H, ArH), 7.74 (s, 1H, ArH), 7.79 (d, 1H, *J* = 11.6 Hz, ArH).

15 **<sup>13</sup>C-NMR** (CD<sub>3</sub>OD, δ): 13.8, 14.2, 14.8, 24.6, 27.4, 33.5, 39.2, 56.8, 57.3, 66.4, 102.1, 105.6 (d, *J* = 24.3 Hz), 105.8, 110.1, 112.5, 118.1, 119.7 (d, *J* = 12.2 Hz), 124.0, 131.2 (d, *J* = 11.2 Hz), 139.4, 141.7, 147.2 (d, *J* = 12.2 Hz), 151.4, 152.9, 154.0, 154.7, 156.6 (d, *J* = 254.7 Hz), 159.5.

**MS-ESI** *m/z* (rel. int.): 494 ([MH]<sup>+</sup>, 100).

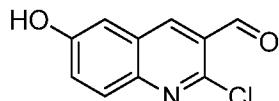
20 **HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.75 min, peak area 97.6%.

Preparation of *N*-(2-(cyclopropylmethoxy)-3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide dihydrochloride

25 **87**

2-Chloro-6-hydroxyquinoline-3-carbaldehyde SLA 47016

To a stirred solution of 2-chloro-6-methoxyquinoline-3-carbaldehyde (5.27 g, 23.8 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (180 mL) in a 500 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{BBr}_3$  (71.3 mL, 71.3 mmol) at 0°C and the mixture was stirred at RT overnight. The mixture was then added 5 dropwise to a water/ice mixture, and the solid was filtered and dried under vacuum to give 2-chloro-6-hydroxyquinoline-3-carbaldehyde **SLA 47016** as a yellow solid (3.14 g, 64% yield).

**SLA 47016**

10 **MW:** 207.61; **Yield:** 64 %; **Yellow Solid;** **Mp** (°C): 170.0.

**$^1\text{H NMR}$**  (( $\text{CD}_3$ )<sub>2</sub>SO,  $\delta$ ): 4.50 (br s, 1H, OH), 7.43 (s, 1H, ArH), 7.51 (d, 1H,  $J$  = 8.2 Hz, ArH), 7.89 (d, 1H,  $J$  = 8.2 Hz, ArH), 8.77 (s, 1H, ArH), 10.34 (s, 1H, CHO).

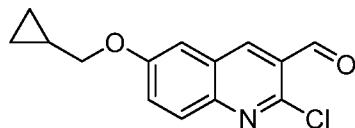
**$^{13}\text{C-NMR}$**  (( $\text{CD}_3$ )<sub>2</sub>SO,  $\delta$ ): 110.3, 126.2, 128.0, 128.6, 139.5, 143.7, 145.4, 156.8, 189.6, 1xC not observed.

15 **MS-ESI** m/z (% rel. Int.): 208 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.28 min.

#### 2-Chloro-6-(cyclopropylmethoxy)quinoline-3-carbaldehyde **SLA 47086**

20 A mixture of 2-chloro-6-hydroxyquinoline-3-carbaldehyde **SLA 47016** (1.00 g, 4.8 mmol), cesium carbonate (3.14 g, 9.6 mmol) and (bromomethyl)cyclopropane (0.94 mL, 9.6 mmol) in dry DMF (30 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer was stirred overnight at RT. DMF was removed at 40°C under vacuum and the residue was taken up in  $\text{CH}_2\text{Cl}_2$  (50 mL), washed with brine (10 mL), 25 dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under vacuum. Purification by column chromatography ( $\text{SiO}_2$ , eluent cyclohexane:EtOAc = 100:0 to 95:5) followed by a new purification by column chromatography ( $\text{SiO}_2$ , eluent  $\text{CH}_2\text{Cl}_2$ :MeOH = 100:0 to 95:5) gave 2-chloro-6-(cyclopropylmethoxy)quinoline-3-carbaldehyde **SLA 47086** as a pale brown solid (513 mg, 41% yield).



30

**SLA 47086**

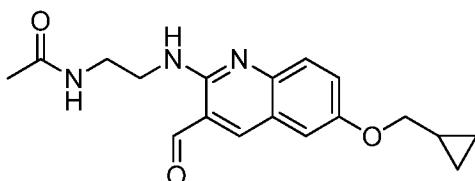
**MW:** 261.70; **Yield:** 41%; Brown Solid; **Mp (°C):** 182.1.

**MS-ESI** m/z (rel.int.): 262 ([MH]<sup>+</sup>,100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 5 186003113), detection UV 254 nm, RT = 3.39 min, peak area 99.9%.

*N*-(2-(6-(Cyclopropylmethoxy)-3-formylquinolin-2-ylamino)ethyl)acetamide **SLA 47092**

To a stirred solution of 2-chloro-6-(cyclopropylmethoxy)quinoline-3-carbaldehyde **SLA 47086** (770 mg, 2.94 mmol) in THF (15 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added *N*-(2-aminoethyl)acetamide (1.202 g, 11.8 mmol) and the reaction mixture was stirred for 6 h at 160°C under microwave irradiation. After cooling to RT, the volatiles were removed at 40°C under vacuum and the resulting yellow oil was taken up in a mixture of THF:1 N aq. HCl = 1:1 (50 mL) and stirred for 20 min at RT. The volatiles were then removed at 40°C under vacuum and the residue was then neutralised with a 10 N aqueous NaOH solution. THF was then evaporated before extraction with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The separated organic layer was washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum to give *N*-(2-(6-(cyclopropylmethoxy)-3-formylquinolin-2-ylamino)ethyl)acetamide **SLA 47092** as a yellow solid (365 mg, 38% yield).

**SLA 47092**

**MW:** 327.38; **Yield:** 38 %; Yellow Solid; **Mp (°C):** 185.4.

**25 <sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 0.39-0.43 (m, 2H, CH<sub>2</sub>), 0.66-0.73 (m, 2H, CH<sub>2</sub>), 1.25-1.36 (m, 1H, CH), 1.92 (s, 3H, CH<sub>3</sub>), 3.50-3.56 (m, 2H, CH<sub>2</sub>), 3.76-3.82 (m, 2H, CH<sub>2</sub>), 3.88 (d, 2H, J = 6.9 Hz, OCH<sub>2</sub>), 7.00 (d, 1H, J = 2.8 Hz, ArH), 7.41 (dd, 1H, J = 2.8 & 9.2 Hz, ArH), 7.45 (s, 1H, NH), 7.57 (d, 1H, J = 9.2 Hz, ArH), 8.15(s, 1H, NH), 8.17 (s, 1H, ArH), 9.97 (s, 1H, CHO).

**30 MS-ESI** m/z (% rel. Int.): 328 ([MH]<sup>+</sup>,100).

**HPLC:** Method B (5 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 2.18 min.

N-(2-(6-(Cyclopropylmethoxy)-3-(hydroxymethyl)quinolin-2-ylamino)ethyl)acetamide

5 **SLA 47096A**

To a stirred solution of *N*-(2-(6-(cyclopropylmethoxy)-3-formylquinolin-2-ylamino)ethyl)acetamide **SLA 47092** (0.35 g, 1.1 mmol) in THF (10 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer was added NaBH<sub>4</sub> (0.04 g, 1.1 mmol) and the mixture was stirred overnight at RT then cooled in an ice bath 10 before quenching by addition of a 1 N aq. HCl solution. After stirring for 15 min at RT, the mixture was basified to pH = 9 with a 2 N aq. NaOH solution. THF was removed at 40°C under vacuum and the residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum, to give *N*-(2-(6-(cyclopropylmethoxy)-3-(hydroxymethyl)quinolin-2-ylamino)ethyl)acetamide **SLA 47096A** as a yellow oil (0.39 g, quant. yield).



SLA 47096A

**MW:** 329.39; **Yield:** 100%; **Yellow Oil.**

20 **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, δ): 0.34-0.40 (m, 2H, CH<sub>2</sub>), 0.63-0.69 (m, 2H, CH<sub>2</sub>), 1.25-1.43 (m, 1H, CH), 1.84 (s, 3H, CH<sub>3</sub>), 3.41-3.44 (m, 2H, CH<sub>2</sub>), 3.65-3.67 (m, 2H, CH<sub>2</sub>), 3.83 (d, 2H, J = 6.9 Hz, OCH<sub>2</sub>), 4.63 (s, 2H, CH<sub>2</sub>), 6.87 (d, 1H, J = 2.7 Hz, ArH), 7.21 (dd, 1H, J = 2.7 & 9.1 Hz, ArH), 7.45 (s, 1H, ArH), 7.55 (d, 1H, J = 9.1 Hz, ArH) (NH & OH not seen).

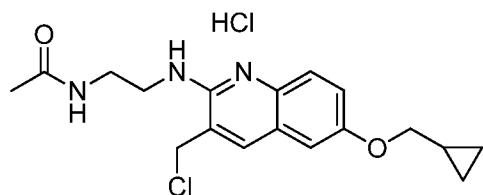
25 **<sup>13</sup>C-NMR** (CDCl<sub>3</sub>, δ): 3.2, 3.2, 10.1, 23.1, 40.8, 42.4, 63.3, 73.2, 107.9, 121.3, 122.6, 123.6, 126.6, 134.8, 142.5, 154.4, 155.5, 170.9.

**MS-ESI** m/z (% rel. Int.): 330 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 214 nm, RT = 3.79 min.

*N*-(2-(3-(Chloromethyl)-6-(cyclopropylmethoxy)quinolin-2-ylamino)ethyl)acetamide hydrochloride **SLA 47096B**

To a stirred solution of *N*-(2-(6-(cyclopropylmethoxy)-3-(hydroxymethyl)quinolin-2-ylamino)ethyl)acetamide **SLA 47096A** (0.374 g, 1.1 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (11 mL) in a 25 mL round-bottomed flask equipped with a magnetic stirrer was added dropwise  $\text{SOCl}_2$  (1.65 mL, 22.7 mmol). The mixture was stirred for 2h at RT then concentrated to dryness at 40°C under vacuum. The residue was then taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) before concentration back to dryness at 40°C under vacuum (done 3 times) to give *N*-(2-(3-(chloromethyl)-6-(cyclopropylmethoxy)quinolin-2-ylamino)ethyl)acetamide hydrochloride **SLA 47096B** as a yellow solid (0.475 g, 100% yield).



**SLA 47096B**

15 **MW:** 384.30; **Yield:** 100%; **Yellow Solid;** **Mp (°C):** 162.5.

**$^1\text{H NMR}$  (CD<sub>3</sub>OD,  $\delta$ ):** 0.40-0.44 (m, 2H, CH<sub>2</sub>), 0.64-0.71 (m, 2H, CH<sub>2</sub>), 1.30-1.33 (m, 1H, CH), 2.08 (s, 3H, CH<sub>3</sub>), 3.53 (t, 2H,  $J$  = 6.8 Hz, CH<sub>2</sub>), 3.77 (t, 2H,  $J$  = 6.8 Hz, CH<sub>2</sub>), 3.96 (d, 2H,  $J$  = 6.7 Hz, OCH<sub>2</sub>), 4.86 (s, 2H, CH<sub>2</sub>), 7.37 (d, 1H,  $J$  = 2.7 Hz, ArH), 7.47 (dd, 1H,  $J$  = 2.7 & 9.0 Hz, ArH), 8.04 (d, 1H,  $J$  = 9.0 Hz, ArH), 8.43 (s, 1H, ArH).

**$^{13}\text{C-NMR}$  (CD<sub>3</sub>OD,  $\delta$ ):** 3.6, 3.6, 11.0, 22.4, 38.7, 41.8, 43.0, 74.5, 110.7, 120.3, 123.7, 123.7, 125.2, 132.2, 143.8, 151.7, 158.5, 175.8.

**MS-ESI m/z (% rel. Int.):** 350 ([MH]<sup>+</sup>, <sup>37</sup>Cl, 36), 348 ([MH]<sup>+</sup>, <sup>35</sup>Cl, 100).

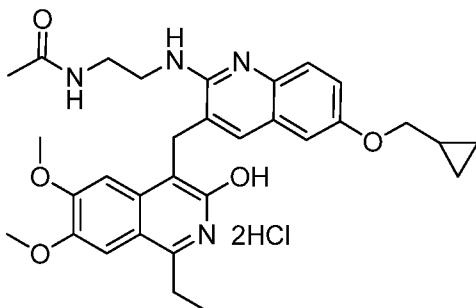
**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model #

25 186003113), detection UV 214 nm, RT = 4.25 min.

*N*-(2-(6-(Cyclopropylmethoxy)-3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide dihydrochloride **87**

To a solution of 1-ethyl-6,7-dimethoxyisoquinolin-3-ol **SLA 47022** (128 mg, 0.55 mmol) in THF (13 mL) in a 20 mL microwave vial equipped with a magnetic

stirrer was added *N*-(2-(3-(chloromethyl)-6-(cyclopropylmethoxy)quinolin-2-ylamino)ethyl)acetamide hydrochloride **SLA 47096B** (211 mg, 0.55 mmol) and 2 N aq. LiOH solution (0.55 mL, 1.10 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, THF was then removed at 40°C under vacuum and the residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 93:7) followed by a new purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 95:5) gave 27 mg of *N*-(2-(6-(cyclopropylmethoxy)-3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide. This free base was dissolved in MeOH (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of a 0.149 M HCl solution in MeOH (2.0 mL). The reaction mixture was stirred for 5 min at RT and concentrated at 40°C under vacuum to give *N*-(2-(6-(cyclopropylmethoxy)-3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide dihydrochloride **87** as a brown solid (28.9 mg, 8% yield).

**87**

**MW:** 617.56; **Yield:** 8%; **Brown Solid;** **Mp** (°C): 201.2.

**1H-NMR** (CD<sub>3</sub>OD, δ): 0.29-0.34 (m, 2H, CH<sub>2</sub>), 0.56-0.63 (m, 2H, CH<sub>2</sub>), 1.20-1.25 (m, 1H, CH), 1.56 (t, 3H, *J* = 6.9 Hz, CH<sub>3</sub>), 2.09 (s, 3H, CH<sub>3</sub>), 3.44-3.49 (m, 2H, CH<sub>2</sub>), 3.60-3.66 (m, 2H, CH<sub>2</sub>), 3.80 (d, 2H, *J* = 7.0 Hz, OCH<sub>2</sub>), 3.86-3.91 (m, 2H, CH<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 4.35 (s, 2H, CH<sub>2</sub>), 7.12 (s, 1H, ArH), 7.15 (s, 1H, ArH), 7.38 (d, 1H, *J* = 9.2 Hz, ArH), 7.53 (s, 1H, ArH), 7.60 (s, 1H, ArH), 8.03 (d, 1H, *J* = 9.2 Hz, ArH).

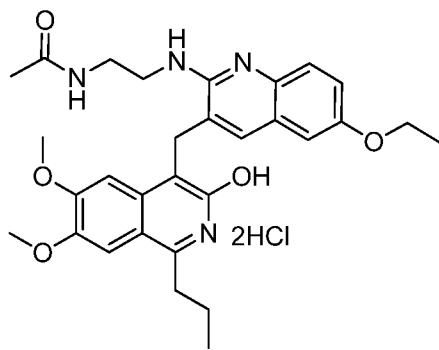
**13C-NMR** (CD<sub>3</sub>OD, δ): 3.5, 3.5, 10.9, 14.6, 22.5, 25.5, 27.1, 39.0, 43.5, 57.0, 57.5, 74.4, 102.7, 105.8, 110.0, 110.6, 117.5, 119.9, 123.9, 124.0, 124.3, 131.2, 139.4, 141.8, 152.2, 152.9, 156.1, 158.3, 160.0, 175.7, 1xC not observed.

**MS-ESI** m/z (rel.int.): 545 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.61 min, peak area 97.4%.

5 Preparation of *N*-(2-(6-ethoxy-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide dihydrochloride 88

To a stirred solution of *N*-(2-(3-chloromethyl)-6-ethoxyquinolin-2-ylamino)ethylacetamide hydrochloride **SMA 44092** (231 mg, 0.65 mmol) in THF (10 mL) in a 20 mL microwave vial equipped with a magnetic stirrer was added 6,7-dimethoxy-1-propylisoquinolin-3-ol **RBO 35134** (159 mg, 0.65 mmol) followed by a 2 N aq. LiOH solution (0.65 mL, 1.29 mmol) and the mixture was stirred at 160°C for 1.5 h under microwave irradiation. After cooling to RT, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 9:1 (150 mL) and washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated at 40°C under vacuum. Purification by column chromatography (SiO<sub>2</sub>, eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH = 100:0 to 93:7) provided *N*-(2-(6-ethoxy-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide. This free base was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) in a 10 mL round-bottomed flask equipped with a magnetic stirrer before addition of 0.49 M HCl in MeOH (2 mL) and the solution was stirred for 5 min at RT then concentrated at 20 40°C under vacuum to afford *N*-(2-(6-ethoxy-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-ylamino)ethyl)acetamide dihydrochloride **88** as a yellow solid (25 mg, 6% yield).



88

25 **MW:** 605.55; **Yield:** 6%; **Yellow Solid;** **Mp (°C):** 164.7.

**<sup>1</sup>H NMR** (CD<sub>3</sub>OD, δ): 1.18 (t, 3H, *J* = 7.3 Hz, CH<sub>3</sub>), 1.36 (t, 3H, *J* = 6.5 Hz, CH<sub>3</sub>), 1.96-2.04 (m, 2H, CH<sub>2</sub>), 2.10 (s, 3H, CH<sub>3</sub>), 3.43-3.49 (m, 2H, CH<sub>2</sub>), 3.61-3.67 (m, 2H,

CH<sub>2</sub>), 3.89-3.92 (m, 2H, CH<sub>2</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 3.94-3.97 (m, 2H, CH<sub>2</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 4.38 (s, 2H, CH<sub>2</sub>), 7.13 (s, 1H, ArH), 7.17 (s, 1H, ArH), 7.35 (d, 1H, J = 9.2 Hz, ArH), 7.49 (s, 1H, ArH), 7.61 (s, 1H, ArH), 8.05 (d, 1H, J = 9.2 Hz, ArH).

<sup>13</sup>C-NMR (CD<sub>3</sub>OD, δ): 14.2, 14.9, 22.5, 24.7, 27.10, 33.7, 39.1, 43.5, 57.0, 57.6,

5 65.2, 102.9, 106.1, 109.9, 110.1, 119.5, 119.9, 123.9, 123.9, 124.1, 131.2, 139.2, 141.7, 152.2, 152.3, 152.8, 155.2, 158.14, 160.2, 175.8.

**MS-ESI** m/z (% rel. Int.): 533 ([MH]<sup>+</sup>, 100).

**HPLC:** Method B (10 min), XBridge<sup>TM</sup> column (5 mm, C18, 4.5 × 50 mm, Model # 186003113), detection UV 254 nm, RT = 4.43 min, peak area 95.8%.

10

**Example 2: PDE10A inhibitory activity of compounds according to the invention**

**Phosphodiesterase Assay**

15 The PDE assay is based on the homogenous time-resolved fluorescence resonance energy transfer (TR-FRET) technology (LANCE® from Perkin Elmer). This competition based assay is formatted using a cAMP specific antibody labeled with the dye, Alexa Fluor® 647, biotin-cAMP and streptavidin labeled with Europium (Eu-SA). As the complex of Eu-SA / biotin-cAMP / Alexa Fluor 647 labeled antibody 20 is formed, an increase in signal is generated. When there is PDE activity, resulting in the degradation of the cyclic nucleotide, the complex is not formed and a decrease in signal is observed.

25 The phosphodiesterase assay was developed using the LANCE® cAMP kit (PerkinElmer). The assay buffer contained HBSS with 5 mM HEPES, 0.1 % BSA, and 1.5 mM MgCl<sub>2</sub>, pH 7.4. PDE10A (BPS Bioscience) was used at 200 pg/well (with a specific activity of 3200 pmole/min/μg with assay conditions: 10 mM Tris-HCl, pH7.4, 10 mM MgCl<sub>2</sub>, 1 mM MnCl<sub>2</sub>, 200 μM cAMP, 2.5 kU 5' nucleotidase, 37°C, 20 min). The Biotin-cAMP tracer, supplied in 10 mmol/L Tris-HCl buffered (pH 8.0) salt solution with 1 mmol/L ethylenediaminetetraacetic acid (EDTA), 0.1% bovine serum 30 albumin (BSA), and 0.05% sodium azide, is used at a dilution of 1/375. The assay detection mixture contained the LANCE Eu-W8044 labeled streptavidin 1/2250 (supplied in 50 mmol/L Tris-HCl buffered (pH 7.8) salt solution with 0.9% sodium chloride (NaCl), 0.1% BSA, and 0.05% sodium azide) and the Alexa Fluor® 647-anti

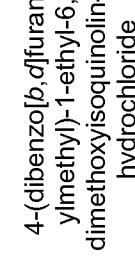
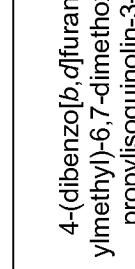
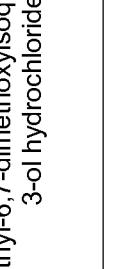
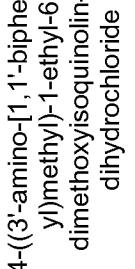
cAMP antibody 1/200 (supplied in 50 mmol/L Tris-HCl buffered (pH 7.8) salt solution with 0.9% NaCl, 0.1% BSA, and 0.05% sodium azide). Chemical compounds were dissolved in DMSO (final concentration 2% (v/v)).

5 In a 384-well plate, 2  $\mu$ L inhibitor and 3  $\mu$ L PDE were added to the well, followed by the addition of 5  $\mu$ L substrate biotinylated cAMP (1:5). After 60 min incubation at room temperature, 10  $\mu$ L of assay detection mixture was added to the assay plate. After 1 h at room temperature, the signal was measured on EnVision™ (PerkinElmer).

The results are summarized in table 1.

Table 1: PDE10A inhibitory activity for compounds of the invention

Compd No.	Structure	Name	PDE10A IC <sub>50</sub>	Compd No. (cont.)	Structure	Name	PDE10A IC <sub>50</sub>
1		4-benzyl-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride	-	33		6,7-dimethoxy-1-methyl-4-((6-methyl-3-yl)methyl)isoquinolin-3-ol dihydrochloride	13 nM
2		4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride	-	34		6,7-dimethoxy-4-((6-methyl-3-yl)methyl)-1-propylisoquinolin-3-ol hydrochloride	1.9 nM
3		4-(3,4-dimethoxybenzyl)-3,6,7-trimethoxy-1-methylisoquinoline hydrochloride	-	35		4-((2-(ethylamino)-6-methoxy-1-propylisoquinolin-3-ol dihydrochloride	1.5 nM
4		6,7-dimethoxy-1-methyl-4-(3-phenoxobenzyl)isoquinolin-3-ol hydrochloride	140 nM	36		4-(2-dimethylamino-6-methyl-quinolin-3-ylmethyl)-6,7-dimethoxy-1-propyl-soquinolin-3-ol dihydrochloride	698 nM

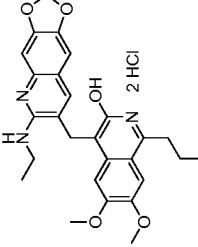
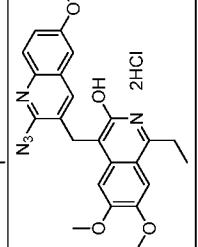
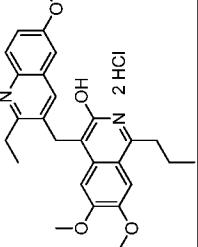
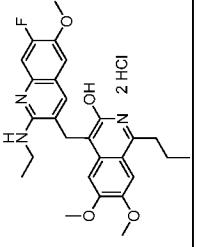
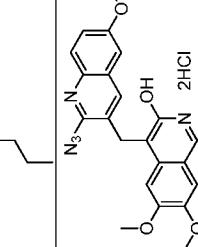
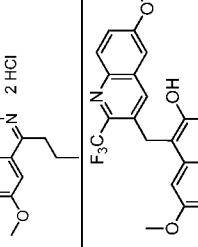
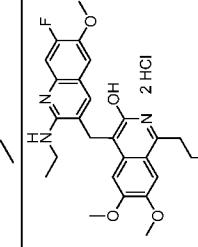
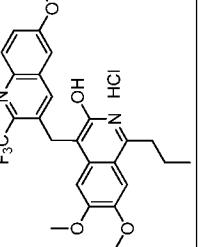
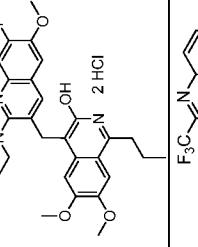
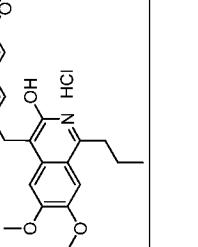
5		6,7-dimethoxy-1-methyl-4-(4-phenoxybenzyl)isoquinolin-3-ol hydrochloride	-	37	0.12 nM	6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methoxyisoquinolin-3-ol dihydrochloride	6 nM
6		4-(dibenzofuran-2-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride		38	0.5 nM	1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methoxyisoquinolin-3-ol dihydrochloride	2.7 nM
7		4-(dibenzofuran-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol hydrochloride		39	0.5 nM	1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methoxyisoquinolin-3-ol dihydrochloride	1.6 nM
8		4-([1,1'-biphenyl]-3-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride		40	6710 nM	1-ethyl-4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride	0.4 nM
9		1-ethyl-6,7-dimethoxy-4-((4'-methoxy-1,1'-biphenyl)-3-yl)methyl)-1-ethoxyisoquinolin-3-ol hydrochloride		41	10600 nM	4-((6-ethylamino)-2-(ethylamino)quinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride	5 nM
10		4-((3'-amino-[1,1'-biphenyl]-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride		42	52 nM	1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methoxyisoquinolin-3-ol dihydrochloride	0.5 nM

11	6,7-dimethoxy-1-methyl-4-(pyridin-4-ylmethyl)isoquinolin-3-ol hydrochloride	223 nM	43		1-ethyl-4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride	3.5 nM
12	6,7-dimethoxy-1-methyl-4-((6-phenylpyridin-2-yl)methyl)isoquinolin-3-ol dihydrochloride	94 nM	44		4-(2-(benzylamino)-6-methoxyquinolin-3-yl)methyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride	8 nM
13	6,7-dimethoxy-4-((6-(4-methoxyphenyl)pyridin-2-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride	50 nM	45		1-ethyl-6,7-dimethoxy-4-((6-methoxyethoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride	30 nM
14	4-(2,4'-bipyridin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol trihydrochloride	100 nM	46		4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride	29 nM
15	6,7-dimethoxy-1-methyl-4-((5-phenylpyridin-3-yl)methyl)isoquinolin-3-ol dihydrochloride	97 nM	47		4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride	11 nM
16	6,7-dimethoxy-4-((5-(4-methoxyphenyl)pyridin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride	69 nM	48		6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride	0.34 nM

17		6,7-dimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride	14 nM	49		4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride	4.6 nM
18		3,6,7-trimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinoline hydrochloride	1410 nM	50		4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride	0.28 nM
19		1-ethyl-6,7-dimethoxy-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride	11 nM	51		1-isopropyl-6,7-dimethoxy-4-((6-methoxyethoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride	55 nM
20		6,7-dimethoxy-4-(naphthalen-2-ylmethyl)-1-propylisoquinolin-3-ol hydrochloride	34 nM	52		6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride	1.5 nM
21		4-(isquinolin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride	333 nM	53		4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride	0.8 nM

22		333 nM	54		23 nM
23		130 nM	55		4.4 nM
24		86 nM	56		175 nM
25		265 nM	57		47 nM
26		24 nM	58		221 nM

27		6,7-dimethoxy-4-((5-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride	17 nM	59		3-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-2-(methylamino)quinoline-6,7-diol dihydrochloride	27 nM
28		4-((5-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride	6 nM	60		6,7-dimethoxy-4-((6-methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride	2.7 nM
29		6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride	29 nM	61		1-ethyl-6,7-dimethoxy-4-((6-methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride	2.2 nM
30		4-((7-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride	21 nM	62		6,7-dimethoxy-4-((6-methylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride	1.1 nM
31		1-ethyl-6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride	13 nM	63		4-((6-dimethylamino)-[1,3]dioxolo[4,5-g]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride	560 nM

32		64	4 nM		1.2 nM
65		66	967 nM		16 nM
67		68	1.8 nM		200 nM
69		70	1.5 nM		2.4 nM
71		72	93 nM		445 nM

73		2.7 nM	74		6.1 nM
75		>1000 nM	76		2.3 nM
77		2.0 nM	78		27 nM
79		88 nM	80		3.2 nM
81		7.5 nM	82		1.4 nM

83	<chem>CC(C)N[C@@H](C)C(=O)N1C[C@H]2[C@H]1Cc3cc(Oc4ccccc4)cc(Oc4ccccc4)cc3N2Cc4ccccc4</chem>	<i>N</i> -(2-((6-(cyclopropylmethoxy)-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride	10 nM	84	<chem>CC(C)N[C@@H](C)C(=O)N1C[C@H]2[C@H]1Cc3cc(Oc4ccccc4)cc(Oc4ccccc4)cc3N2Cc4ccccc4</chem>	<i>N</i> -(2-((6-(cyclopropylmethoxy-4-((6-methoxyquinolin-3-yl)methyl)methoxy)-1-propylisoquinolin-3-ol-2HCl)-1-propylisoquinolin-3-ol dihydrochloride	1.6 nM
85	<chem>CC(C)N[C@@H](C)C(=O)N1C[C@H]2[C@H]1Cc3cc(Oc4ccccc4)cc(Oc4ccccc4)cc3N2Cc4ccccc4</chem>	1-ethyl-6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride	0.4 nM	86	<chem>CC(C)N[C@@H](C)C(=O)N1C[C@H]2[C@H]1Cc3cc(Oc4ccccc4)cc(Oc4ccccc4)cc3N2Cc4ccccc4</chem>	4-((6-ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride	0.3 nM
87	<chem>CC(C)N[C@@H](C)C(=O)N1C[C@H]2[C@H]1Cc3cc(Oc4ccccc4)cc(Oc4ccccc4)cc3N2Cc4ccccc4</chem>	<i>N</i> -(2-((6-(cyclopropylmethoxy)-3-((1-ethyl-3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride	3.9 nM	88	<chem>CC(C)N[C@@H](C)C(=O)N1C[C@H]2[C@H]1Cc3cc(Oc4ccccc4)cc(Oc4ccccc4)cc3N2Cc4ccccc4</chem>	<i>N</i> -(2-((6-ethoxy-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride	1.8 nM

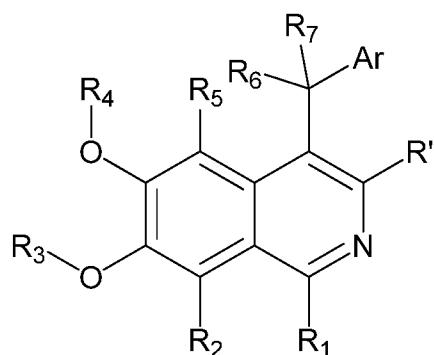
The compounds have also been tested for their activities on PDEs1-9 and PDE11. The most active PDE10A inhibitors are all selective (at least 100 to 10000-fold) vs PDEs1-3, PDEs5-9 and PDE11. They are also selective (at least 15-fold) for PDE10A vs PDE4D3 (excepted the compound **6** that inhibits PDE4D3 with an IC<sub>50</sub> of 0.9 nM, compound **31** that inhibits PDE4D3 with an IC<sub>50</sub> of 82 nM, and compound **51** that inhibits PDE4D3 with an IC<sub>50</sub> of 280 nM).

Each and every reference (whether patent publication or a scientific/journal publication) disclosed herein is incorporated by reference herein for all purposes.

The details of specific embodiments described in this invention are not to be construed as limitations. Various equivalents and modifications may be made without departure from the essence and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

What is claimed is:

1. A compound of Formula (I)



Formula (I)

or a pharmaceutically acceptable salt thereof; wherein:

R<sub>1</sub> is a (C<sub>1</sub>-C<sub>4</sub>)alkyl group which can optionally be substituted with a -(C<sub>1</sub>-C<sub>4</sub>)alkoxy or a R<sub>a</sub>NH group, R<sub>a</sub> being selected from the group consisting of, (C<sub>1</sub>-C<sub>4</sub>)alkyl-C(=O)- and (C<sub>1</sub>-C<sub>4</sub>)alkyl-S(=O)<sub>2</sub>-;

R<sub>2</sub> is a hydrogen atom;

R<sub>3</sub> and R<sub>4</sub> independently represent a (C<sub>1</sub>-C<sub>3</sub>)alkyl group;

R<sub>5</sub> is a hydrogen atom;

R<sub>6</sub> and R<sub>7</sub> independently represent a hydrogen atom, a halogen atom, or R<sub>6</sub> and R<sub>7</sub> together with the carbon atom to which they are shown attached form a -C(=O)- group;

R' is -NH<sub>2</sub> or -OR, wherein R is a hydrogen atom, a (C<sub>1</sub>-C<sub>3</sub>)alkyl group or a (C<sub>1</sub>-C<sub>3</sub>)alkyl-C(=O)- group

Ar is an aryl or heteroaryl group which can optionally be substituted with one to four substituents independently selected from the group consisting of halogen, azido, hydroxy, (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>1</sub>-C<sub>4</sub>)alkoxy, -O-(C<sub>1</sub>-C<sub>4</sub>)alkyl-(C<sub>1</sub>-C<sub>6</sub>)cycloalkyl, aryl, (C<sub>1</sub>-C<sub>4</sub>)alkyl-aryl-, (C<sub>1</sub>-C<sub>4</sub>)alkoxy-aryl-, amino-substituted aryl, N((C<sub>1</sub>-C<sub>4</sub>)alkyl)<sub>2</sub>-substituted aryl, aryloxy, heteroaryl, (C<sub>1</sub>-C<sub>4</sub>)alkyl-heteroaryl-, and R<sub>b</sub>R<sub>c</sub>N, or wherein two substituents at adjacent positions of the aryl or heteroaryl together with the atoms to which they are attached form a heterocyclic ring ; and

R<sub>b</sub> and R<sub>c</sub> are independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>4</sub>)alkyl, halogeno(C<sub>1</sub>-C<sub>4</sub>)alkyl-, (C<sub>1</sub>-C<sub>4</sub>)alkoxy(C<sub>1</sub>-C<sub>4</sub>)alkyl-, aryl(C<sub>1</sub>-C<sub>4</sub>)alkyl- and acetylamino(C<sub>1</sub>-C<sub>4</sub>)alkyl-.

2. The compound according to claim 1, wherein  $R_3$  and  $R_4$  both represent a methyl group.
3. The compound according to claim 1, wherein  $R_1$  is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl,  $CH_3C(=O)NHCH_2-$ ,  $CH_3S(=O)_2NHCH_2-$ , and  $CH_3OCH_2-$ .
4. The compound according to claim 1, wherein  $R'$  is selected from the group consisting of  $-NH_2$ ,  $-OH$ ,  $-OCH_3$ , and  $-OC(=O)CH_3$ .
5. The compound according to claim 1, wherein Ar represents
  - a pyridinyl group optionally substituted with one or two substituents independently selected from the group consisting of aryl,  $(C_1-C_4)alkylaryl$ , heteroaryl,  $(C_1-C_4)heteroaryl$  and  $(C_1-C_4)alkoxy-aryl$ ;
  - a phenyl group optionally substituted with one or two substituents selected from the group consisting of  $(C_1-C_4)alkyloxy$ , aryloxy,  $(C_1-C_4)alkoxy-aryl$ -, and aminoaryl;
  - a naphthyl group optionally substituted with one or two substituents selected from the group consisting of  $(C_1-C_4)alkyloxy$ , aryloxy,  $(C_1-C_4)alkoxy-aryl$  and aminoaryl;
  - a quinolinyl group optionally substituted with one or more substituents, in particular one or two substituents, selected from the group consisting of  $(C_1-C_4)alkyl$ ,  $(C_1-C_4)alkyloxy$  and  $R_bR_cN$ ;
  - [1,3]dioxolo[4,5-*g*]quinolyn group, optionally substituted with a  $R_bR_cN$ - substituent;
  - an isoquinolinyl group; or
  - a dibenzofuran group.
6. The compound of claim 1, wherein Ar is an aryl or heteroaryl group which can optionally be substituted with one to four substituents independently selected from the group consisting of fluoro, azido, hydroxyl, methyl, ethyl, hydroxy, methoxy, ethoxy,  $-O-CH_2$ -cyclopropyl, phenyl, methoxyphenyl, aminophenyl, phenoxy, pyridinyl, methylamino, ethylamino, N,N-dimethylamino, ethylamino, n-propylamino, n-butylamino,

isopropylamino, trifluoromethyl, 2,2,2-trifluoroethylamino, benzylamino, and acetyl-2-aminoethylamino.

7. The compound according to claim 1, selected from the group consisting of:

4-benzyl-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride **1**,  
4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol hydrochloride **2**,  
4-(3,4-dimethoxybenzyl)-3,6,7-trimethoxy-1-methylisoquinoline hydrochloride **3**,  
6,7-dimethoxy-1-methyl-4-(3-phenoxybenzyl)isoquinolin-3-ol hydrochloride **4**,  
6,7-dimethoxy-1-methyl-4-(4-phenoxybenzyl)isoquinolin-3-ol hydrochloride **5**,  
4-(dibenzo[*b,d*]furan-2-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride **6**,  
4-(dibenzo[*b,d*]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol hydrochloride **7**,  
4-([1,1'-biphenyl]-3-ylmethyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol hydrochloride **8**,  
1-ethyl-6,7-dimethoxy-4-((4'-methoxy-[1,1'-biphenyl]-3-yl)methyl)isoquinolin-3-ol hydrochloride **9**,  
4-((3'-amino-[1,1'-biphenyl]-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **10**,  
6,7-dimethoxy-1-methyl-4-(pyridin-4-ylmethyl)isoquinolin-3-ol hydrochloride **11**,  
6,7-dimethoxy-1-methyl-4-((6-phenylpyridin-2-yl)methyl)isoquinolin-3-ol dihydrochloride **12**,  
6,7-dimethoxy-4-((6-(4-methoxyphenyl)pyridin-2-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **13**,  
4-([2,4'-bipyridin]-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol trihydrochloride **14**,  
6,7-dimethoxy-1-methyl-4-((5-phenylpyridin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **15**,  
6,7-dimethoxy-4-((5-(4-methoxyphenyl)pyridin-3-yl)methyl)-1-methylisoquinolin-3-ol dihydrochloride **16**,  
6,7-dimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride **17**,  
3,6,7-trimethoxy-1-methyl-4-(naphthalen-2-ylmethyl)isoquinoline hydrochloride **18**,  
1-ethyl-6,7-dimethoxy-4-(naphthalen-2-ylmethyl)isoquinolin-3-ol hydrochloride **19**,  
6,7-dimethoxy-4-(naphthalen-2-ylmethyl)-1-propylisoquinolin-3-ol hydrochloride **20**,  
4-(isoquinolin-6-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride **21**,  
4-(isoquinolin-5-ylmethyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol **22**,  
6,7-dimethoxy-1-methyl-4-(quinolin-2-ylmethyl)isoquinolin-3-ol dihydrochloride **23**,  
6,7-dimethoxy-1-methyl-4-(quinolin-6-ylmethyl)isoquinolin-3-ol dihydrochloride **24**,

6,7-dimethoxy-1-methyl-4-(quinolin-4-ylmethyl)isoquinolin-3-ol dihydrochloride **25**,  
6,7-dimethoxy-1-methyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **26**,  
6,7-dimethoxy-4-((5-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol  
dihydrochloride **27**,  
4-((5-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride  
**28**,  
6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-methylisoquinolin-3-ol  
dihydrochloride **29**,  
4-((7-ethoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-methylisoquinolin-3-ol dihydrochloride  
**30**,  
1-ethyl-6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride  
**31**,  
6,7-dimethoxy-4-((7-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol  
dihydrochloride **32**,  
6,7-dimethoxy-1-methyl-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-  
ol dihydrochloride **33**,  
6,7-dimethoxy-4-((6-methyl-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-  
ol dihydrochloride **34**,  
4-((2-(ethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol  
dihydrochloride **35**,  
4-((2-(dimethylamino)-6-methylquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-  
ol dihydrochloride **36**,  
6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-methyl-isoquinolin-  
3-ol dihydrochloride **37**,  
6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-  
ol dihydrochloride **38**,  
1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)isoquinolin-3-  
ol **39**,  
1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(ethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol  
dihydrochloride **40**,  
1-ethyl-6,7-dimethoxy-4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol  
dihydrochloride **41**,  
1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)isoquinolin-3-  
ol dihydrochloride **42**,

1-ethyl-4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **43**,

4-((2-(benzylamino)-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **44**,

1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **45**,

4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **46**,

4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-1-isopropyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **47**,

6,7-dimethoxy-4-((6-methoxy-2-(methylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **48**,

4-((6-ethoxy-2-(ethylamino)quinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **49**,

4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **50**,

1-isopropyl-6,7-dimethoxy-4-((6-methoxy-2-(2,2,2-trifluoroethylamino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **51**,

6,7-dimethoxy-4-((6-methoxy-2-(propylamino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **52**,

4-((2-(isopropylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **53**,

6,7-dimethoxy-4-((6-methoxy-2-((2,2,2-trifluoroethyl)amino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **54**,

*N*-(2-((3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride **55**,

1-(acetamidomethyl)-4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-yl acetate **56**,

*N*-((4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)acetamide dihydrochloride **57**,

*N*-((4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-3-hydroxy-6,7-dimethoxyisoquinolin-1-yl)methyl)methanesulfonamide dihydrochloride **58**,

3-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-2-(methylamino)quinoline-6,7-diol dihydrochloride **59**,

6,7-dimethoxy-1-methyl-4-((6-(methylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride **60**,

1-ethyl-6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)isoquinolin-3-ol dihydrochloride **61**,

6,7-dimethoxy-4-((6-(methylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **62**,

4-((6-(dimethylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **63**,

4-((6-(ethylamino)-[1,3]dioxolo[4,5-*g*]quinolin-7-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **64**,

4-(dibenzo[b,d]furan-2-ylmethyl)-6,7-dimethoxy-1-propylisoquinolin-3-amine hydrochloride **65**,

4-((2-ethyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **66**,

4-((2-(ethylamino)-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-(methoxymethyl)isoquinolin-3-ol dihydrochloride **67**,

4-((2-azido-6-methoxyquinolin-3-yl)methyl)-1-ethyl-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **68**,

*N*-(2-((3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride **69**,

4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **70**,

4-((2-butyl-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **71**,

6,7-dimethoxy-4-((6-methoxy-2-(trifluoromethyl)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol hydrochloride **72**,

*N*-(2-((3-((3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methyl)-6-methoxyquinolin-2-yl)amino)ethyl)acetamide dihydrochloride **73**,

6,7-dimethoxy-1-propyl-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **74**,

(2-(ethylamino)-6-methoxyquinolin-3-yl)(3-hydroxy-6,7-dimethoxy-1-methylisoquinolin-4-yl)methanone dihydrochloride **75**,

6,7-dimethoxy-4-((6-methoxy-2-((2-methoxyethyl)amino)quinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **76**,

1-ethyl-6,7-dimethoxy-4-((6-methoxy-2-((2-methoxyethyl)amino)quinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **77**,  
1-ethyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **78**,  
1-isopropyl-6,7-dimethoxy-4-(quinolin-3-ylmethyl)isoquinolin-3-ol dihydrochloride **79**,  
6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **80**,  
1-ethyl-6,7-dimethoxy-4-((2-methylquinolin-6-yl)methyl)isoquinolin-3-ol dihydrochloride **81**,  
1-ethyl-4-((2-(ethylamino)-7-fluoro-6-methoxyquinolin-3-yl)methyl)-6,7-dimethoxyisoquinolin-3-ol dihydrochloride **82**,  
*N*-(2-((6-(cyclopropylmethoxy)-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride **83**,  
6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)-1-propylisoquinolin-3-ol dihydrochloride **84**,  
1-ethyl-6,7-dimethoxy-4-((6-methoxyquinolin-3-yl)methyl)isoquinolin-3-ol dihydrochloride **85**,  
4-((6-ethoxy-2-(ethylamino)-7-fluoroquinolin-3-yl)methyl)-6,7-dimethoxy-1-propylisoquinolin-3-ol dihydrochloride **86**,  
*N*-(2-((6-(cyclopropylmethoxy)-3-((1-ethyl-3-hydroxy-6,7-dimethoxyisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride **87**, and  
*N*-(2-((6-ethoxy-3-((3-hydroxy-6,7-dimethoxy-1-propylisoquinolin-4-yl)methyl)quinolin-2-yl)amino)ethyl)acetamide dihydrochloride **88**; or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising at least one compound of claim 1, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

9. A method for inhibiting PDE10A in a mammal, comprising administering to said mammal in need thereof, a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof.

10. A method for treating a disease in a mammal modulated by PDE10A, comprising administering to said mammal in need thereof, a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof.

11. The method of claim 10, wherein said disease is selected from the group consisting of: type I or type II diabetes, impaired glucose tolerance, impaired fasting glucose, metabolic syndrome, metabolism related disorders, psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention- deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma and breast cancer, pain, macular degeneration/retinal degeneration, wet Age Related Macular Degeneration (ARMD), dry ARMD, retinitis pigmentosa, choroidal neovascularization, vascular diseases/exudative diseases, retinopathy, diabetic retinopathy, uveitis/retinitis/choroiditis, Stargard's disease, macular edema, retinal detachment, trauma, systemic disorders with associated retinal dystrophies, cone dystrophies, dystrophy of the retinal pigmented epithelium, myopic retinal degeneration, acute retinal pigment epithelitis, retinal tumors, and retinal disease associated with tumors.

12. The method of claim 10, wherein said disease is selected from the group consisting of: dementia, Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; age-related cognitive decline, major depressive episode of the mild, moderate or severe type; a manic or mixed mood episode; a hypomanic mood episode; a depressive episode with

atypical features; a depressive episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post-stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder comprising a delusional disorder or schizophrenia; a bipolar disorder comprising bipolar I disorder, bipolar II disorder, cyclothymic disorder, Parkinson's disease; Huntington's disease; Fronto temporal Dementia; neurodegeneration associated with cerebral trauma; neurodegeneration associated with stroke; neurodegeneration associated with cerebral infarct; hypoglycemia- induced neurodegeneration; neurodegeneration associated with epileptic seizure; neurodegeneration associated with neurotoxin poisoning; multi-system atrophy, paranoid, disorganized, catatonic, undifferentiated or residual type; schizophreniform disorder; schizoaffective disorder of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, obesity, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type.

13. A method of treating a disorder in a mammal, said disorder being selected from the group consisting of: dementia, Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; age-related cognitive decline, major depressive episode of the mild, moderate or severe type; a manic or mixed mood episode; a hypomanic mood episode; a depressive episode with atypical features; a depressive episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post-stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder comprising a delusional disorder or schizophrenia; a bipolar disorder comprising bipolar I disorder, bipolar II disorder, cyclothymic disorder, Parkinson's

disease; Huntington's disease; Fronto temporal Dementia; neurodegeneration associated with cerebral trauma; neurodegeneration associated with stroke; neurodegeneration associated with cerebral infarct; hypoglycemia-induced neurodegeneration; neurodegeneration associated with epileptic seizure; neurodegeneration associated with neurotoxin poisoning; multi-system atrophy, paranoid, disorganized, catatonic, undifferentiated or residual type; schizophreniform disorder; schizoaffective disorder of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, obesity, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type, said method comprising administering to said mammal in need thereof, a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof.

14. A method of treating a disorder in a mammal, said disorder being selected from the group consisting of: dementia, Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; age-related cognitive decline, major depressive episode of the mild, moderate or severe type; a manic or mixed mood episode; a hypomanic mood episode; a depressive episode with atypical features; a depressive episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post-stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder comprising a delusional disorder or schizophrenia; a bipolar disorder comprising bipolar I disorder, bipolar II disorder, cyclothymic disorder, Parkinson's disease; Huntington's disease; Fronto temporal Dementia; neurodegeneration associated with cerebral trauma; neurodegeneration associated with stroke; neurodegeneration associated with cerebral infarct; hypoglycemia-induced neurodegeneration; neurodegeneration associated with epileptic seizure;

neurodegeneration associated with neurotoxin poisoning; multi-system atrophy, paranoid, disorganized, catatonic, undifferentiated or residual type; schizophreniform disorder; schizoaffective disorder of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, obesity, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type, said method comprising administering to said mammal in need thereof, a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2012/025731

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>	<b>INV.</b>	<b>C07D217/24</b>	<b>C07D401/06</b>	<b>C07D403/06</b>	<b>C07D405/06</b>	<b>C07D491/056</b>
		A61K31/472	A61K31/4725	A61P3/00	A61P25/00	

**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

**C07D**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/006372 A1 (LUNDBECK & CO AS H [DK]; KEHLER JAN [DK]) 17 January 2008 (2008-01-17) cited in the application Claims, pages 1 and 6 and examples -----	1-14
A	WO 2009/036766 A1 (LUNDBECK & CO AS H [DK]; KEHLER JAN [DK]; NIELSEN JACOB [DK]; LANGGAAR) 26 March 2009 (2009-03-26) cited in the application Claims, pages 1 and 7 and examples -----	1-14
A	WO 2007/103554 A1 (AMGEN INC [US]; MEMORY PHARM CORP [US]; LIU RUIPING [US]; ARRINGTON MA) 13 September 2007 (2007-09-13) cited in the application Claims, pages 1 and 3 and examples -----	1-14
		-/-



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 April 2012	08/05/2012

Name and mailing address of the ISA/  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Lécaillon, Jennifer

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2012/025731

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KEHLER J ET AL: "The potential therapeutic use of phosphodiesterase 10 inhibitors", EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 17, no. 2, 1 February 2007 (2007-02-01), pages 147-158, XP002529529, ISSN: 1354-3776, DOI: 10.1517/13543776.17.12.147 cited in the application the whole document -----	1-14
1		

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/025731

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 2008006372	A1	17-01-2008	CN	101495476 A	29-07-2009
			EP	2057153 A1	13-05-2009
			JP	2009542732 A	03-12-2009
			US	2011098286 A1	28-04-2011
			WO	2008006372 A1	17-01-2008
<hr style="border-top: 1px dashed black;"/>					
WO 2009036766	A1	26-03-2009	AR	068466 A1	18-11-2009
			CA	2691474 A1	26-03-2009
			CN	101743239 A	16-06-2010
			EP	2203438 A1	07-07-2010
			JP	2010539195 A	16-12-2010
			TW	200918519 A	01-05-2009
			WO	2009036766 A1	26-03-2009
<hr style="border-top: 1px dashed black;"/>					
WO 2007103554	A1	13-09-2007	AU	2007223801 A1	13-09-2007
			CA	2644850 A1	13-09-2007
			EP	1996574 A1	03-12-2008
			JP	2009529060 A	13-08-2009
			US	2007299067 A1	27-12-2007
			WO	2007103554 A1	13-09-2007
<hr style="border-top: 1px dashed black;"/>					