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(54) Benævnelse: **MELLEMPRODUKTER TIL FREMSTILLING AF C-TERMINALE HSP90-INHIBITORER**

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US-A1- 2010 105 630
JOSEPH A. BURLISON ET AL: "Novobiocin: Redesigning a DNA Gyrase Inhibitor for Selective Inhibition of Hsp90", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 128, no. 48, 1 December 2006 (2006-12-01), pages 15529-15536, XP055057623, ISSN: 0002-7863, DOI: 10.1021/ja065793p
BHASKAR REDDY KUSUMA ET AL: "Synthesis and Evaluation of Novologues as C-Terminal Hsp90 Inhibitors with Cytoprotective Activity against Sensory Neuron Glucotoxicity", JOURNAL OF MEDICINAL CHEMISTRY, vol. 55, no. 12, 28 June 2012 (2012-06-28) , pages 5797-5812, XP55195980, ISSN: 0022-2623, DOI: 10.1021/jm300544c

DESCRIPTION

Description

[0001] This invention was made with government support under Grant Nos. CA120458, CA109265, NS054847 and DK073594, awarded by the National Institutes of Health. The government has certain rights in the invention.

DESCRIPTION OF RELATED ART

[0002] Approximately 26 million Americans are afflicted with either Type 1 or Type 2 diabetes. Despite the use of insulin and oral anti-diabetic medications to help maintain euglycemia, about 60-70% of these individuals develop diabetic peripheral neuropathy (DPN). Veves, A.; Backonja, M.; Malik, R. A., Painful diabetic neuropathy: Epidemiology, natural history, early diagnosis, and treatment options. Pain Med. 2008, 9, 660-674.

[0003] To date, approaches toward the treatment of DPN have centered on pathways/targets directly limited to hyperglycemia (i.e., polyol & hexosamine pathways, advanced glycation end products (AGEs), enhanced oxidative stress, PKC activation). Tomlinson, D. R.; Gardiner, N. J., Glucose neurotoxicity. Nat Rev Neurosci 2008, 9 (1), 36-45.

[0004] Unfortunately, the contribution of these targets/pathways to the progression of DPN differs between individuals and does not occur with biochemical uniformity, and consequently, these approaches have resulted in little success for the management of DPN. As an alternative approach, we have explored the pharmacologic modulation of molecular chaperones to promote a broad cytoprotective response that may enhance a patient's ability to tolerate hyperglycemic insults and improve the symptoms of DPN.

[0005] Molecular chaperones, such as heat shock proteins 90 and 70 (Hsp90, Hsp70), are essential for folding nascent polypeptides into their biologically active structures and for the refolding of aggregated and denatured proteins that occur upon cellular stress. Mayer, M. P.; Bukau, B., Hsp70 chaperones: cellular functions and molecular mechanism. Cell Mol Life Sci 2005, 62 (6), 670-84; Peterson, L. B.; Blagg, B. S., To fold or not to fold: modulation and consequences of Hsp90 inhibition. Future Med Chem 2009, 1 (2), 267-283.

[0006] Numerous conditions that cause cell stress can also induce the "heat shock response" (HSR); the transcriptional upregulation of antioxidant genes and chaperones such as Hsp70. Importantly, small molecule inhibition of Hsp90 is sufficient to induce the HSR. KU-32 (FIG.1) is a small molecule Hsp90 C-terminal inhibitor that is based on novobiocin, a naturally occurring antimicrobial agent that inhibits DNA gyrase. KU-32 is disclosed in U.S. Pat. No. 7,622,451 to

Blagg et al. and U.S. Pat. No. 7,960,353 to Blagg. Although the etiology of DPN is unrelated to the accumulation of one specific mis-folded or aggregated protein, hyperglycemia can increase oxidative stress and the oxidative modification of amino acids (Obrosova, I. G., Diabetes and the peripheral nerve. Biochim Biophys Acta 2009, 10, 931-940; Akude, E.; Zherebitskaya, E.; Roy Chowdhury, S. K.; Girling, K.; Fernyhough, P., 4-Hydroxy-2-Nonenal Induces Mitochondrial Dysfunction and Aberrant Axonal Outgrowth in Adult Sensory Neurons that Mimics Features of Diabetic Neuropathy. Neurotox Res 2009, 1, 28-38) that impair protein folding, (Muchowski, P. J.; Wacker, J. L., Modulation of neurodegeneration by molecular chaperones. Nat Rev Neurosci 2005, 6 (1), 11-22) decrease mitochondrial protein import (Baseler, W. A.; Dabkowski, E. R.; Williamson, C. L.; Croston, T. L.; Thapa, D.; Powell, M. J.; Razunguzwa, T. T.; Hollander, J. M., Proteomic alterations of distinct mitochondrial subpopulations in the type 1 diabetic heart: contribution of protein import dysfunction. Am J Physiol Regul Integr Comp Physiol 2011, 300 (2), R186-200) and promote mitochondrial dysfunction. Tomlinson et al., 2008 Id.; Obrosova et al., 2009 Id.

[0007] Even in the absence of a single, disease-specific protein aggregate, it has been shown that pharmacologic induction of cytoprotective molecular chaperones can improve myelinated and unmyelinated fiber function in cellular models of glucotoxic stress and animal models of DPN. Urban, M. J.; Li, C.; Yu, C.; Lu, Y.; Krise, J. M.; McIntosh, M. P.; Rajewski, R. A.; Blagg, B. S. J.; Dobrowsky, R. T., Inhibiting Heat Shock Protein 90 Reverses Sensory Hypoalgesia in Diabetic Mice. ASN Neuro 2010, 2, e00040 DOI :189-199.

[0008] Mechanistically, KU-32 was ineffective at preventing neuregulin-induced demyelination of myelinated cultures of sensory neurons prepared from Hsp70.1 and 70.3 double knockout mice, indicating that Hsp70 is necessary for the neuroprotective activity manifested by KU-32. Similarly, weekly treatment with KU-32 restored normal sensory and motor nerve function in diabetic wild type mice, but was unable to reverse multiple clinical indices of DPN in the diabetic Hsp70 knockout mice. Urban et al., 2010 Id. Collectively, these studies provide the biological and clinical rationale to support the modulation of molecular chaperones as a viable approach toward the treatment of DPN.

[0009] An enviable aspect of KU-32 is that it induces Hsp70 at concentrations well below those needed to inhibit Hsp90's protein folding ability. Urban et al., 2010 Id. Thus, KU-32 possesses a rather broad therapeutic window that dissociates cytoprotective properties from potentially cytotoxic effects resulting from the degradation of Hsp90-dependent client proteins. Peterson et al., 2009 Id. This lab previously demonstrated that molecules containing a benzamide, as found in novobiocin, exhibit anti-proliferative activities, whereas molecules containing an acetamide (e.g., KU-32) manifest neuroprotective properties. However, these prior studies sought to evaluate structure-activity relationships for novobiocin analogues as anti-cancer agents, (Burlison, J. A.; Avila, C.; Vielhauer, G.; Lubbers, D. J.; Holzbeierlein, J.; Blagg, B. S., Development of novobiocin analogues that manifest anti-proliferative activity against several cancer cell lines. J Org Chem 2008, 73 (6), 2130-7; Donnelly, A. C.; Mays, J. R.; Burlison, J. A.; Nelson, J. T.; Vielhauer, G.; Holzbeierlein, J.; Blagg, B. S. J., The Design, Synthesis, and Evaluation of Coumarin Ring Derivatives of the Novobiocin Scaffold that Exhibit Antiproliferative

Activity. J. Org. Chem. 2008, 73 (22), 8901-8920) rather than exploring chemical attributes that enhance the neuroprotective properties of novobiocin-based analogs. Therefore, diversification of the KU-32 scaffold was explored to identify novel compounds which lack the coumarin ring system yet surprisingly enhance the neuroprotective properties manifested by Hsp90 C-tenninal inhibitors.

[0010] The present invention is directed to the compounds defined in the annexed claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011]

FIG. 1 shows chemical structures of novobiocin and KU-32.

FIG. 2A shows a molecular model of KU-32 docked to Hsp90 C-terminal binding site.

FIG. 2B shows a molecular model of a novologue (structure shown in FIG. 2D) docked to Hsp90 C-terminal binding site.

FIG. 2C shows an overlay of KU-32 and a novologue (structure shown in FIG. 2D) docked to Hsp90 C-terminal binding site.

FIG. 2D shows the chemical structure of a novologue and its attributes.

FIG. 3 shows the determination of EC_{50} of select novologues KU-32, 11f, 111, 11b, 11n, 11h, and 11o. DRG sensory neurons were incubated in the absence or presence of 0.1-1000 nM of the indicated novologue overnight and then subjected to 4 hrs of hyperglycemia. Cell viability was measured as described in Example 2 and the data expressed as percent of normoglycemic controls. Under hyperglycemic conditions and in the absence of any novologues, cell viability was 20% ± 7.

FIG. 4 shows determination of EC_{50} of select novologues KU-32, 1 lf, 111, 11b, 11n, 11h, and 11o from FIG 3. The EC_{50} was determined using the $EC_{anything}$ function of GraphPad Prism 5.0 and the mean ± SEM (n=3-8) is shown. #, $p< 0.05$ versus KU-32.

FIG. 5 shows immunoblot analysis of induction of Hsp70 by select novologues KU-32, 11n and 11b. DRG sensory neurons were incubated in the presence of DMSO (Cntrl) or 10-1000 nM of the indicated novologue overnight and then subjected to 4 hrs of hyperglycemia. The neurons were harvested and Hsp70 and β-actin levels were determined by immunoblot analysis. Band intensity was quantified using Image J, Hsp70 expression was normalized to the level of β-actin.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENT

[0012] Molecular terms, when used in this application, have their common meaning unless otherwise specified. It should be noted that the alphabetical letters used in the formulas of the present invention should be interpreted as the functional groups, moieties, or substituents as defined herein. Unless otherwise defined, the symbols will have their ordinary and customary meaning to those skilled in the art.

[0013] The compounds of the present invention can exist in tautomeric, geometric, or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S- enantiomers, diastereomers, D-isomers, L-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention.

[0014] Also included in the family of compounds of the present invention are the pharmaceutically acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the present invention be prepared from inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucoronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethyleneldiamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compounds by reacting, for example, the appropriate acid or base with the compounds of the present invention.

[0015] The term "neuroprotection" embraces inhibition of progressive deterioration of neurons that leads to cell death.

[0016] The term "neurodegenerative disorder" embraces a disorder in which progressive loss of neurons occurs either in the peripheral nervous system or in the central nervous system. In one embodiment, the condition treated and/or prevented by the compounds, compositions and methods of the disclosure is a neurodegenerative disorder. Without being bound by theory, it is believed that the compounds and compositions of the present disclosure provide neuroprotective effects of the Hsp90 inhibitor(s) during the treatment of the neurodegenerative

disorder by inhibiting the progressive deterioration of neurons that leads to cell death.

[0017] In one aspect, the neurodegenerative disorder is sensory neuron glucotoxicity resultant from, e.g., hyperglycemia associated with a diabetic condition, and resultant in, e.g., diabetic peripheral neuropathy.

[0018] Examples of neurodegenerative disorders include, but are not limited to chronic neurodegenerative diseases such as diabetic peripheral neuropathy (including third nerve palsy, mononeuropathy, mononeuropathy multiplex, diabetic amyotrophy, autonomic neuropathy and thoracoabdominal neuropathy), Alzheimer's disease, age-related memory loss, senility, age-related dementia, Pick's disease, diffuse Lewy body disease, progressive supranuclear palsy (Steel-Richardson syndrome), multisystem degeneration (Shy-Drager syndrome), motor neuron diseases including amyotrophic lateral sclerosis ("ALS"), degenerative ataxias, cortical basal degeneration, ALS-Parkinson's-Dementia complex of Guam, subacute sclerosing panencephalitis, Huntington's disease, Parkinson's disease, multiple sclerosis ("MS"), synucleinopathies, primary progressive aphasia, striatonigral degeneration, Machado-Joseph disease/spinocerebellar ataxia type 3 and olivopontocerebellar degenerations, Gilles De La Tourette's disease, bulbar and pseudobulbar palsy, spinal and spinobulbar muscular atrophy (Kennedy's disease), primary lateral sclerosis, familial spastic paraplegia, Wernicke-Korsakoff s related dementia (alcohol induced dementia), Werdnig-Hoffmann disease, Kugelberg-Welander disease, Tay-Sach's disease, Sandhoff disease, familial spastic disease, Wohifart-Kugelberg-Welander disease, spastic paraparesis, progressive multifocal leukoencephalopathy, and prion diseases (including Creutzfeldt-Jakob, Gerstmann-Straussler-Scheinker disease, Kuru and fatal familial insomnia). Other conditions also included within the methods of the present invention include age-related dementia and other dementias, and conditions with memory loss including vascular dementia, diffuse white matter disease (Binswanger's disease), dementia of endocrine or metabolic origin, dementia of head trauma and diffuse brain damage, dementia pugilistica, and frontal lobe dementia. Also, other neurodegenerative disorders resulting from cerebral ischemia or infarction include embolic occlusion and thrombotic occlusion as well as intracranial hemorrhage of any type (including, but not limited to, epidural, subdural, subarachnoid, and intracerebral), and intracranial and intravertebral lesions (including, but not limited to, contusion, penetration, shear, compression, and laceration). Thus, the term also encompasses acute neurodegenerative disorders such as those involving stroke, traumatic brain injury, schizophrenia, peripheral nerve damage, hypoglycemia, spinal cord injury, epilepsy, and anoxia and hypoxia.

[0019] In some embodiments, the neurodegenerative disorder is amyloidosis. Amyloidosis is observed in Alzheimer's Disease, hereditary cerebral angiopathy, nonneuropathic hereditary amyloid, Down's syndrome, macroglobulinemia, secondary familial Mediterranean fever, Muckle-Wells syndrome, multiple myeloma, pancreatic- and cardiac-related amyloidosis, chronic hemodialysis arthropathy, and Finnish and Iowa amyloidosis. In preferred embodiments, the neurodegenerative disorder treated and/or prevented using the methods and compositions of the disclosure is diabetic peripheral neuropathy.

[0020] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

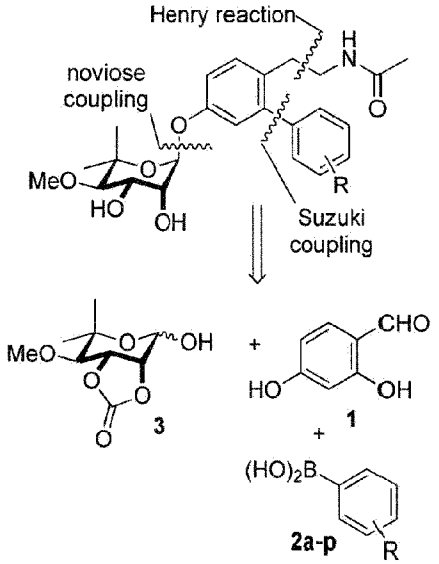
[0021] KU-32 is a first-generation novologue (a novobiocin-based, C-terminal, heat shock protein 90 (Hsp90) inhibitor) that decreases glucose-induced death of primary sensory neurons and reverses numerous clinical indices of diabetic peripheral neuropathy in mice. The structures of KU-32 and Novobiocin are shown in FIG. 1. The disclosure provides a new series of C-terminal Hsp90 inhibitors designed to optimize hydrogen bonding and hydrophobic interactions in an attempt to enhance neuroprotective activity. A series of substituted phenylboronic acids was used in a synthetic route to replace the coumarin lactone of KU-32 with an aryl moiety, such as a biphenyl moiety. Electronegative atoms placed at the meta-position of the B-ring were identified that exhibit improved cytoprotective activity, which while not wishing to be bound by theory, is believed to result from favorable interactions with Lys539 in the Hsp90 C-terminal binding pocket. Consistent with these results, a *meta*-3-fluorophenyl substituted novologue (**11b)** surprisingly exhibited a 14-fold lower ED_{50} compared to KU-32 for protection against glucose-induced toxicity of primary sensory neurons.

[0022] Recently, molecular modeling studies were performed by this lab and azide-containing novobiocin derivatives as photoaffinity probes were used to elucidate, for the first time, the Hsp90 C-terminal binding site. Matts, R. L.; Dixit, A.; Peterson, L. B.; Sun, L.; Voruganti, S.; Kalyanaraman, P.; Hartson, S. D.; Verkhivker, G. M.; Blagg, B. S., Elucidation of the Hsp90 C-Terminal Inhibitor Binding Site. ACS Chem Biol 2011**.** As shown in FIG. 2 (A-C), KU-32 docks to this region and appears to exhibit binding interactions with both the protein backbone and the amino acid side chains similar to those manifested by novobiocin. Interestingly, the coumarin lactone of KU-32 appears too distant from Lys539 to provide complementary interactions with this residue. In addition, the 3-amido side chain appears to project into a large hydrophobic pocket that could accommodate more flexible linkers. As a consequence of these observations, the novologue scaffold (FIG. 2D) was designed to project the B-ring into the pocket where Lys539 resides and to serve as a lead compound for further diversification. Without being bound to theory, it is possible that the flexible ethyl amide projecting from the A-ring could accommodate a number of orientations that could better occupy the large hydrophobic pocket that remains vacant in the presence of KU-32.

[0023] Based on the novologue design, construction of a parallel library was designed to validate this scaffold for use as a neuroprotective agent. The library was designed so that the 3'-carbamate on noviose was omitted; based upon prior studies that showed this group to be detrimental to Hsp90 inhibitory activity. Burlison, J. A.; Neckers, L.; Smith, A. B.; Maxwell, A.; Blagg, B. S. J., Novobiocin: Redesigning a DNA Gyrase Inhibitor for Selective Inhibition of Hsp90. Journal of the American Chemical Society 2006, 128 (48), 15529-15536.

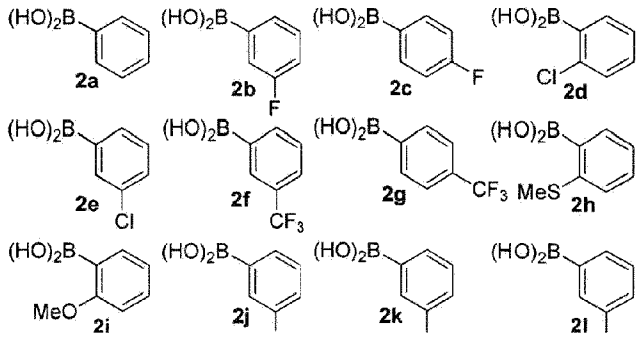
[0024] In contrast, additional hydrophobic and hydrogen bonding interactions are provided by the incorporation of functionalities onto the 3-aryl substituent (B-ring), which was designed to provide complementary interactions with Lys539. The 4-ethyl acetamide is included to occupy the binding pocket about the coumarin ring system. In one aspect, consistent with data obtained from prior studies, the 7-noviosyl linkage is maintained as well the requisite 2',3'-diol. The disclosure provides the parallel synthesis of rationally designed novologues as Hsp90 C-terminal inhibitors and assessment of their neuroprotective activities.

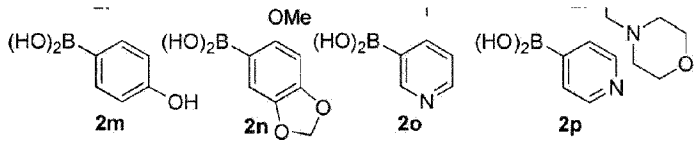
[0025] Retrosynthetically, a library of novologues was designed for construction via four components (Scheme 1); a resorcinolic benzaldehyde **(1),** a variety of commercially available boronic acids **(2a-p),** noviose **(3),** and the acetamide side chain (Scheme 1). Prior work from this laboratory demonstrated that the trichloroacetimidate of noviose carbonate undergoes rapid coupling with phenols to give the desired α-anomer in high yield.



Scheme 1. Retrosynthetic analysis for the construction of novologue.

[0026] The boronic acids chosen for this study contain both electronic and steric moieties that could aid in elucidation of structure-activity relationships and provide crucial interactions with Lys539 and the surrounding pocket. Towards this goal, phenylboronic acids (Scheme 2) containing electronegative atoms at the *meta*- and *para*-positions were explored. In addition, hydrogen bond acceptors were included at these locations to provide potential hydrogen bonding interactions with the protonated form of Lys539. To serve as controls, hydrophobic groups **(2j, 2k)** and a tertiary amine **(2l)** were included in this series.





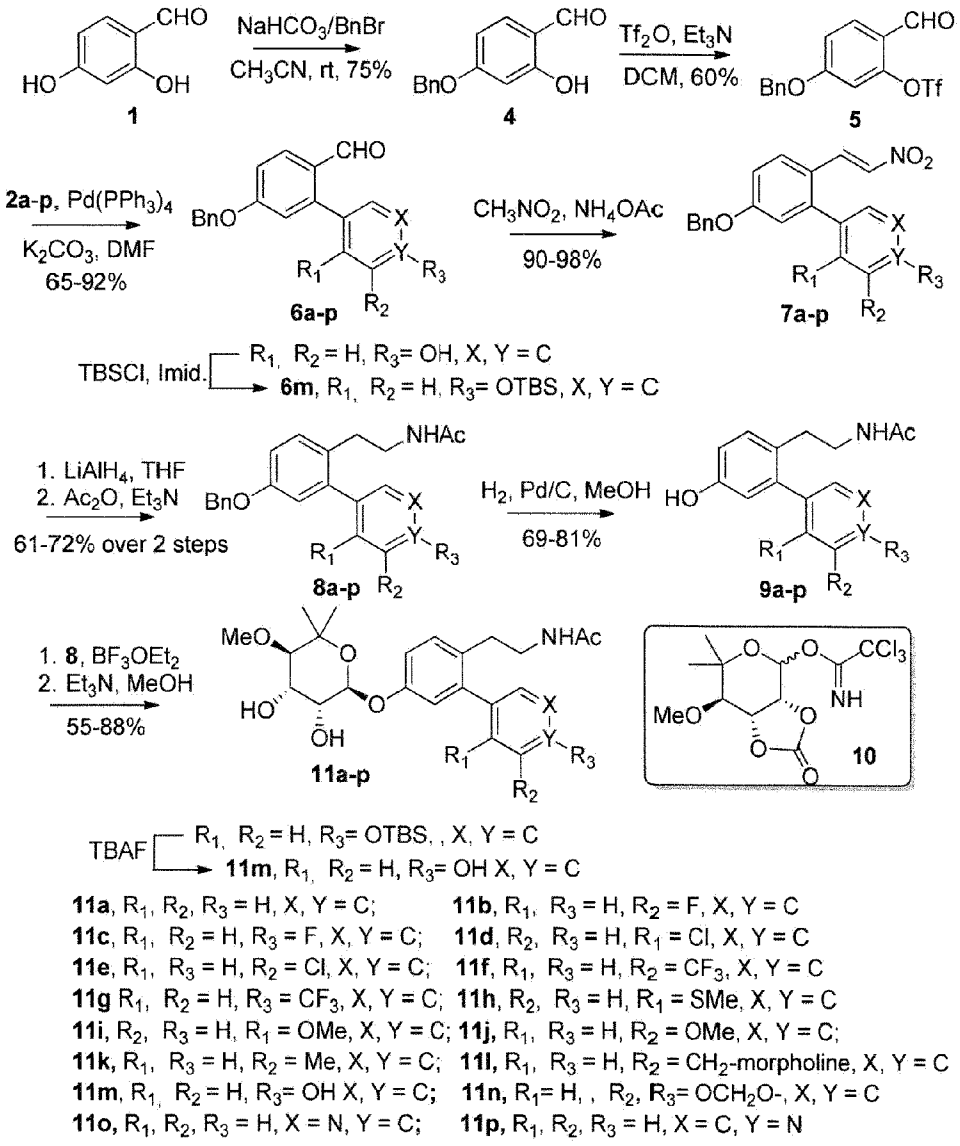
Scheme 2. Boronic acids selected for incorporation into novologue X scaffold.

[0027] The synthesis of ethyl acetamide side chain containing novologues **11a-p,** began with commercially available 2,4-dihydroxybenzaldehyde, **1.** The 4-phenol of resorcinolic benzaldehyde **1** was protected as the corresponding benzyl ether **4,** (Lee, M.; Gubernator, N. G.; Sulzer, D.; Sames, D., Development of pH-Responsive Fluorescent False Neurotransmitters. Journal of the American Chemical Society 2010, 132 (26), 8828-8830) and the 2-phenol converted to triflate **5** using trifluoromethanesulfonic anhydride and triethylamine (Scheme 3). Compound **5** was subsequently coupled with commercially available aryl boronic acids **(2a-p)** under standard Suzuki conditions to give biaryl ring systems **6a-p** in good yields. Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P., Suzuki-Miyaura Cross-Coupling Reactions Mediated by Palladium/Imidazolium Salt Systems. Organometallics 2002, 21 (14), 2866-2873; Olson, J. P.; Gichinga, M. G.; Butala, E.; Navarro, H. A.; Gilmour, B. P.; Carroll, F. I., Synthesis and evaluation of 1,2,4-methyltriazines as mGluR5 antagonists. Organic & Biomolecular Chemistry 2011, 9 (11), 4276-4286.

[0028] Benzaldehydes **6a-p** were converted to the corresponding nitrostyrenes **(7a-p),** following a Henry reaction with nitromethane and ammonium acetate. Fuganti, C.; Sacchetti, A., Biocatalytic enantioselective approach to 3-aryl-2-nitropropanols: Synthesis of enantioenriched (R)-5-methoxy-3-aminochroman, a key precursor to the antidepressant drug Robalzotan. Journal of Molecular Catalysis B: Enzymatic 2010, 66 (3-4), 276-284; Wood, K.; Black, D. S.; Kumar, N., Ring closing metathesis strategies towards functionalised 1,7-annulated 4,6-dimethoxyindoles. Tetrahedron 2011, 67 (22), 4093-4102.

[0029] Reduction of the nitro and olefin functionalities with lithium aluminum hydride was followed by acylation of the resulting amines to afford acetamides **8a-p** in good yields. The benzyl ether of compounds **8a-p** was cleaved under hydrogenolysis conditions to afford phenols **9a-p,** which were coupled with the tricloroacetimidate of noviose carbonate **10**[14] in the presence of a catalytic amount of boron trifluoride etherate. Burlison, J. A.; Neckers, L.; Smith, A. B.; Maxwell, A.; Blagg, B. S. J., Novobiocin: Redesigning a DNA Gyrase Inhibitor for Selective Inhibition of Hsp90. Journal of the American Chemical Society 2006, 128 (48), 15529-15536; Kusuma, B. R.; Peterson, L. B.; Zhao, H.; Vielhauer, G.; Holzbeierlein, J.; Blagg, B. S. J., Targeting the Heat Shock Protein 90 Dimer with Dimeric Inhibitors. Journal of Medicinal Chemistry 2011, 54 (18), 6234-6253.

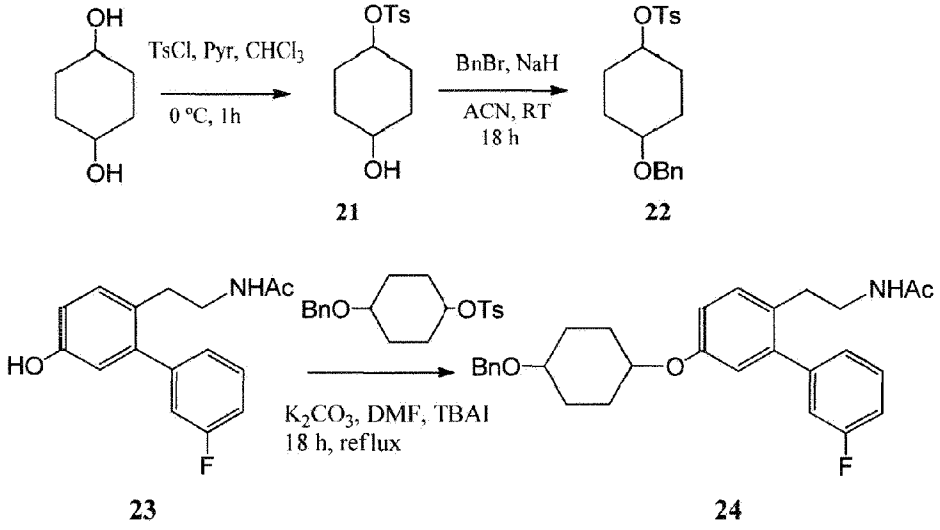
[0030] The resulting noviosylated biaryl systems were exposed to methanolic ammonia to solvolyze the cyclic carbonate and give the desired novologues (**11a-p**) in good to moderate yields.



11a, R_1, R_2, R_3 = H, X, Y = C; **11b**, R_1, R_3 = H, R_2 = F, X, Y = C
11c, R_1, R_2 = H, R_3 = F, X, Y = C; **11d**, R_2, R_3 = H, R_1 = Cl, X, Y = C
11e, R_1, R_3 = H, R_2 = Cl, X, Y = C; **11f**, R_1, R_3 = H, R_2 = CF_3, X, Y = C
11g R_1, R_2 = H, R_3 = CF_3, X, Y = C; **11h**, R_2, R_3 = H, R_1 = SMe, X, Y = C
11i, R_2, R_3 = H, R_1 = OMe, X, Y = C; **11j**, R_1, R_3 = H, R_2 = OMe, X, Y = C;
11k, R_1, R_3 = H, R_2 = Me, X, Y = C; **11l**, R_1, R_3 = H, R_2 = CH_2-morpholine, X, Y = C
11m, R_1, R_2 = H, R_3= OH X, Y = C; **11n**, R_1= H, , R_2, R_3= OCH_2O-, X, Y = C
11o, R_1, R_2, R_3 = H, X = N, Y = C; **11p**, R_1, R_2, R_3 = H, X = C, Y = N

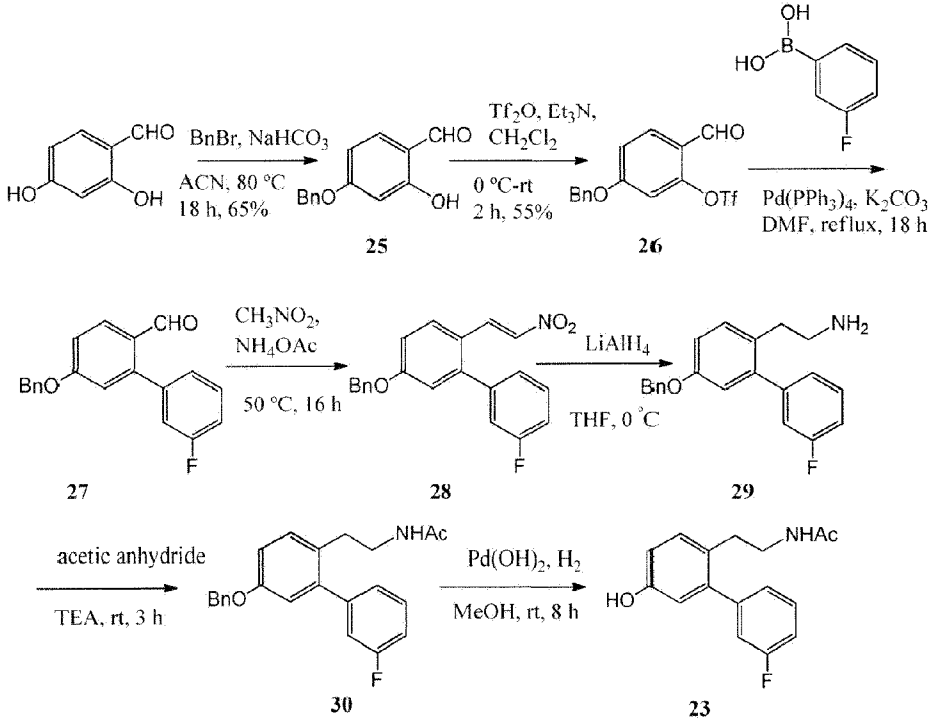
Scheme 3. Synthesis of ethyl acetamide side chain containing novologues.

[0031] Certain compounds are prepared by the synthetic route shown in Scheme 5.



Scheme 5. Synthesis of carbocyclic sugar analogue compound **24**.

[0032] The phenol core compound **23** in **Scheme** 5 can be prepared by the synthetic route shown in Scheme **6.**



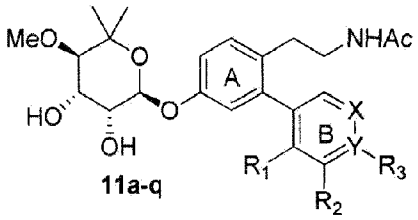
Scheme 6. Synthesis of phenol core compound **23**.

Evaluation of Neuroprotective Efficacy

[0033] Upon synthesis of ethyl acetamide side chain novologues **11a-p** that contain various substitutions on the B-ring (hydrogen bond acceptors, hydrogen bond donors, hydrophobic groups, and a tertiary amine), their neuroprotective efficacy against glucose-induced toxicity of embryonic dorsal root ganglion (DRG) sensory neuron cultures was evaluated. As shown in Table 1, *meta*-substituted acetamide novologues **(11b**, **11e** and **11f)** showed significant protection against glucotoxicity and were comparable to that observed with KU-32. Although the corresponding *ortho*- and *para*- substituted **(11c, 11d** and **11g)** derivatives showed significant protection against glucose-induced cell death, they were modestly less effective than novologues **11b, 11e** and **11f**. However, in the case of analogues **11i** (*ortho*-OMe) and **11j** (*meta*-OMe) the opposite trend was observed. Electronegative atoms at the *meta*-position (F, Cl, CF_3) exhibited greater cytoprotective activity, which is believed to result from favorable interactions with Lys539 in the Hsp90 C-terminal binding pocket. Consistent with this hypothesis, increasing the size of the electronegative atom at the *meta*-position (F to Cl to CF_3) resulted in a decrease in neuroprotective activity. Similarly, steric bulk was disfavored as well. Analogue **11b** (*meta*-F) was the most cytoprotective (95%±14) compound evaluated.

[0034] Electronegative atoms at the *ortho*- or para-position on ring B **(11c, 11d** and **11g)** manifested activities comparable to the unsubstituted analogue **(11a)** and were less active than the corresponding *meta*-substituted analogues (**11b**, **11e** and **11f).** Although novologues **11d** and **11g** manifested protection against neuronal glucotoxicity, they were less effective than KU-32 and **11b.** Compound **(11m)** (*para*-OH), with hydrogen-bond donor characteristics at the para position of the B-ring, was also somewhat, but not significantly less protective than the unsubstituted analogue **(11a)**.

Table 1. Cell viability data of ethyl acetamide side chain novologues.



11a-q

Entry	R_1	R_2	R_3	X	Y	% of cell viability [a]	
11a	H	H	H	C	C		76%±11#
11b	H	F	H	C	C		95%±14#
11c	H	H	F	C	C		75%±27#
11d	Cl	H	H	C	C		71%±21#,*
11e	H	Cl	H	C	C		90%±23#
11f	H	CF_3	H	C	C		83%±16#
11g	H	H	CF_3	C	C		74%±19#,*
11h	SMe	H	H	C	C		83%±40#
11i	OMe	H	H	C	C		92%±10#
11j	H	OMe	H	C	C		78%±34#
11k	H	Me	H	C	C		82%±30#
11l	H	CH_2-N-morpholine	H	C	C		83%±26#
11m	H	H	OH	C	C		67%±10*
11n	H	-OCH_2O-		C	C		83%±18#
11o	H	H	H	N	C		61%±7*
11p	H	H	H	C	N		81%± 12#

[a]In the presence of 1 μM of each novologue + 20 mM excess glucose. Viability in the presence of 20mM excess glucose + DMSO was 54% ± 2 and 86% ± 2 in the presence of glucose + 1 μM KU-32. #, $p<0.05$ versus glucose + DMSO; * $p<0.05$ versus glucose + KU-32 (n=6-24) per novologue.

[0035] On the other hand, hydrogen bond acceptors at the *para*-position **(11c** and **11g**) protected against glucose-induced neuronal death but did not display significantly increased protection compared to the novologue containing a *para*-position hydrogen bond donor **(11m).**

[0036] Pyridine-containing analogues (**11o-p**) were also synthesized and evaluated for neuroprotective activity. The 3-pyridine analogue (**11o**) was unable to protect against glucose-induced oxicity and was also significantly less protective than the corresponding 4-pyridine analogue, **11p,** KU-32, and the unsubstituted phenyl analogue, **11a.** Although the 4-pyridine-containing analogue **(11p)** demonstrated a modestly improved neuroprotective activity when compared to the simple phenyl analogue **11a**, this difference in efficacy was not significant.

[0037] The data in Table 1 clearly supports that the majority of novologues synthesized decrease neuronal toxicity induced by hyperglycemic stress. Although some of these compounds appear more effective than KU-32 at I μM, the differences were relatively minor. Therefore, to further scrutinize their efficacy, compounds exhibiting high neuroprotective activity were further evaluated for determination of EC_{50} values. Since the difference in efficacy for novologues with *meta*-F and *meta*-CF_3 substitutions on **11b** and **11f** was not significantly different from KU-32 or each other at 1μM, the EC_{50} values for these compounds were determined alongside **11h, 11l, 11n**, and **11o**. As shown in FIG. 4, EC_{50} values were significantly improved upon closer inspection and clear distinctions were obtained. Novologue **11b** exhibited an EC_{50} value (13.0 ± 3.6 nM) that was approximately 14-fold lower than KU-32 (240.2 ± 42.5 nM) or **11f** (187.7 ± 43.5 nM). Similar results were also observed for novologue **11n**, which exhibited an EC_{50} value of 18.4 ± 3.2 nM. In contrast, novologue **11h** which manifested similar efficacy to KU-32 at 1 μM, exhibited an EC_{50} of 384 ± 108 nM, approximately 1.6-fold greater than KU-32.

[0038] The data in FIG. 4 demonstrate that novologues **11b** and **11n** are surprisingly more cytoprotective than the initial lead compound, KU-32. Since it was previously shown that the cytoprotective activity manifested by KU-32 requires Hsp70, the ability of **11b** and **11n** to induce Hsp70 was determined relative to KU-32. Increasing concentrations of KU-32, **11n**, and **11b** were incubated with DRG sensory neurons for 24 hours before the cells were subjected to 4 hours of glucotoxic stress. Hsp70 levels were examined by performing immunoblot analysis with the cellular lysates (FIG. 5). **11n** and **11b** induced Hsp70 levels at similar concentrations (10 nM) as those needed for neuroprotection. Although correlative, these data provide a clear link between neuroprotection and the ability of **11**b and **11 in** to induce the heat shock response as exemplified by Hsp70 levels.

[0039] Through systematic replacement of substituents on the novologue B-ring (see Table 2), compound **11b** was identified as a neuroprotective agent that surprisingly exhibited ~14-fold greater efficacy against glucose-induced toxicity than the lead compound, KU-32. The concentration of **11b** needed to manifest neuroprotective activity correlated well with its ability to induce Hsp70 levels, and therefore linking cytoprotection to Hsp70 induction. When

combined, these data demonstrate that the rationally designed novologue scaffold provides a promising platform on which diversification of the B-ring can lead to compounds that exhibit better neuroprotective activities.

[0040] The active compounds have been shown to inhibit Hsp90 *in vitro.* As such, it is contemplated that therapeutically effective amounts of the active compounds will be useful as neuroprotective agents that result in at least a 10% enhancement of cell viability compared to the control over a given time period and under certain conditions, for example, such as glucose-induced toxicity in vitro or under a diabetic condition in vivo.

[0041] In the context of neuroprotection, it is contemplated that some of the active compounds may be used with other Hsp90 inhibitors and/or neuroprotective agents.

[0042] The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

[0043] Therapeutically effective amounts of one or more of the active compounds disclosed herein can be used to treat and/or prevent a neurodegenerative disorder such as diabetic peripheral neuropathy and/or to provide neuroprotection.

Compositions of the Present Invention

[0044] The compounds of the invention can be used to provide a pharmaceutical composition, which comprises a therapeutically effective amount of one or more active compounds as described herein or a pharmaceutically acceptable salt, ester or prodrug thereof, together with a pharmaceutically acceptable diluent or carrier. The pharmaceutical compositions provide neuroprotection and may be used to treat and/or prevent neurodegenerative disorders.

[0045] The compositions may be formulated for any route of administration, in particular for oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal administration. The compositions may be formulated in any conventional form, for example, as tablets, capsules, caplets, solutions, suspensions, dispersions, syrups, sprays, gels, suppositories, patches, and emulsions.

[0046] Accordingly, the active compounds described herein are useful in the treatment or alleviation of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Lou Gehrig's disease, or multiple sclerosis, to name a few, not to mention central or peripheral nervous system damage, dysfunction, or complications involving same stemming from edema, injury, or trauma. Such damage, dysfunction, or complications may be characterized by an apparent neurological, neurodegenerative, physiological, psychological, or behavioral aberrations, the symptoms of which can be reduced by the administration of a therapeutically

effective amount of the active compounds.

[0047] The following examples are provided for further illustration of the present invention, and do not limit the invention.

EXAMPLES

Example 1. Preparation of Embryonic Dorsal Root Ganglion (DRG) Neuron Cultures.

[0048] DRG from embryonic day 15-18 Sprague Dawley rat pups were harvested into Leibovitz's L15 medium (L15) and dissociated with 0.25% trypsin for 30 min at 37°C. The ganglia were sedimented at 1,000 x g for 5 min, resuspended in growth media [phenol red free Neurobasal medium (Gibco, Grand Island, NY) containing 25 mM glucose, 1X B-27 additive, 50 ng/ml NGF (Harlan Bioscience, Indianapolis, IN), 4 mM glutamine, 100 U/mL penicillin and 100 µg/mL streptomycin] and triturated with a fire-polished glass pipette. The cells were cultured on collagen-coated (0.1 mg/mL collagen followed by overnight air drying in a laminar flow hood) black-walled 96-well plates (Coming Incorporated Corning, NY) at a seeding density of 2-3 x 10^4 cells per well. DRG neurons were re-fed the next day with fresh growth media containing 40 µM fluorodeoxyuridine and 10 µM cytosine β-D-arabinoside (both from Sigma Aldrich, St. Louis, MO) for 2 days to remove proliferating cells. Experiments were performed on DRG neurons on the third day in culture after placing the cells in fresh growth medium.

Example 2. Glucotoxicity Assay.

[0049] Immature DRG are susceptible to hyperglycemia-induced death. Vincent, A. M.; Kato, K.; McLean, L. L.; Soules, M. E.; Feldman, E. L., Sensory Neurons and Schwann Cells Respond to Oxidative Stress by Increasing Antioxidant Defense Mechanisms. Antioxid Redox Signal 2009, 11, 425-438. Therefore, an additional 20 mM glucose was added to the growth medium of Example 1 (yielding a total of 45mM glucose) for 4 hours. Preliminary experiments found that 20 mM excess glucose for 4 hrs was sufficient to induce a reproducible 40-50% loss in neuronal viability. As a result, the toxicity induced by the acute change in glucose concentration makes it a useful model for drug screening. Urban, M. J.; Li, C.; Yu, C.; Lu, Y.; Krise, J. M.; McIntosh, M. P.; Rajewski, R. A.; Blagg, B. S. J.; Dobrowsky, R. T., Inhibiting Heat Shock Protein 90 Reverses Sensory Hypoalgesia in Diabetic Mice. ASN Neuro 2010, 2, e00040 DOI :189-199; Vincent, A. M.; Stevens, M. J.; Backus, C.; McLean, L. L.; Feldman, E. L., Cell culture modeling to test therapies against hyperglycemia-mediated oxidative stress and injury. Antioxid Redox Signal 2005, 7 (11-12), 1494-506.

[0050] Given the short time frame that the neurons are grown in vitro, they are not pure neuronal cultures but instead, highly enriched. Importantly, the contaminating SCs that remain

in the culture are resistant to glucose-induced death as we and others have reported previously. Vincent, A. M.; Kato, K.; McLean, L. L.; Soules, M. E.; Feldman, E. L., Sensory Neurons and Schwann Cells Respond to Oxidative Stress by Increasing Antioxidant Defense Mechanisms. Antioxid Redox Signal 2009, 11, 425-438; Zhang, L.; Yu, C.; Vasquez, F. E.; Galeva, N.; Onyango, I.; Swerdlow, R. H.; Dobrowsky, R. T., Hyperglycemia alters the schwann cell mitochondrial proteome and decreases coupled respiration in the absence of superoxide production. J Proteome Res 2010, 9 (1), 458-71.

[0051] Unfortunately, the use of highly purified cultures is problematic since the cells extend neurites and establish connections with each other, thus becoming resistant to hyperglycemia-induced death. Yu, C.; Rouen, S.; Dobrowsky, R. T., Hyperglycemia and downregulation of caveolin-1 enhance neuregulin-induced demyelination. Glia 2008, 56, 877-887.

[0052] DRG neurons were incubated overnight with the test compounds in the presence of Neurobasal medium, 50 ng/ml NGF and antibiotics only. In order to monitor the efficiency of the compounds in protecting DRG neurons against glucotoxicity, Calcein AM (Invitrogen, Carlsbad, CA) was utilized to measure cell viability. Hydrolysis of calcein AM to a fluorescent product can only occur in live cells. Excess glucose was added to the cultures for 4 hrs and cell viability was measured by incubating the cells with 2 μM calcein AM for 30 min in the dark at 37°C. Fluorescence was then measured using a plate reader with excitation and emission wavelengths set to 485nm and 520nm, respectively. The arbitrary fluorescence readings were normalized to the total amount of protein from each respective well of the neuronal cultures. The protein concentrations in each well were determined using the DC protein assay (Bio-Rad). Significant differences in the efficacy of the novologues for increasing cell viability were determined using a Kruskal-Wallis non-parametric ANOVA and Dunn's post-test.

Example 3. Chemistry General-NMR.

[0053] ^{1}H NMR were recorded at 400 or 500 MHz (Bruker DRX-400 Bruker with a H/C/P/F QNP gradient probe) spectrometer and ^{13}C NMR spectra were recorded at 125 MHz (Bruker DRX 500 with broadband, inverse triple resonance, and high resolution magic angle spinning HR-MA probe spectrometer); chemical shifts are reported in δ (ppm) relative to the internal reference chloroform-d ($CDCl_3$, 7.27 ppm).

Example 4. Chemistry General-Mass Spectroscopy and HPLC.

[0054] FAB (HRMS) spectra were recorded with a LCT Premier (Waters Corp., Milford, MA).

[0055] The purity of all compounds was determined to be >95%, as determined by ^{1}H NMR and ^{13}C NMR spectra, unless otherwise noted. The most active 5 compounds were verified for

>95% purity by HPLC analyses. TLC was performed on glass backed silica gel plates (Uniplate) with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure.

Example 5. Synthesis of 5-(benzyloxy)-2-formylphenyl

[0056] trifluoromethanesulfonate (3): A solution of phenol **2** (11.2 g, mmol) in anhydrous DCM (245mL) was stirred at 0 °C and triethylamine (10.2 mL, 73.5mmol) was added followed by triflic anhydride (13.8 mL, 63.5 mmol) over 5 minutes. Upon completion, the reaction was quenched by addition of water (50 mL), washed with saturated aqueous NaCl solution, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2, 4:1, Hex:EtOAc) to afford triflate **3** as a yellow oil (8.4g, 23.6 mmol, 48%) which was immediately used in Suzuki coupling reactions.

Example 6. General procedure for Suzuki coupling reaction of triflate 3 and boronic acids 2a-p:

[0057] 5-(benzyloxy)-[1,1'-biphenyl]-2-carbaldehyde (6a): Triflate **5** (0.246 g, 0.68 mmol), phenylboronic acid 2**a** (92 mg, 0.75 mmol), tetrakis(triphenylphosphine)palladium(0) (70.4 mg, 0.068 mmol) and K_2CO_3 (0.169 g, 1.2 mmol) was dissolved in DMF (6.8 mL) under argon atmosphere in a sealed tube. The resulting reaction mixture was sealed and heated to reflux for 16 h. The reaction was cooled to RT, quenched with saturated sodium bicarbonate, extracted with EtOAc (3 x 5 mL), washed with saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 3:1, Hex:EtOAc) to afford **6a** (0.16 g, 0.56 mmol, 82%) as an amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.55 - 7.34 (m, 10H), 7.11 (d, *J* = 8.7 Hz, 1H), 7.0 3 (d, *J* = 2.4 Hz, 1H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 162.8, 148.6, 137.8, 136.0, 130.0, 128.8, 128.4, 127.6, 116.3, 114.7, 70.4; HRMS (FAB) m/z: [M + Na^+] for $C_{20}H_{16}O_2Na$, calcd, 311.1042; found, 311.1046.

[0058] 5-(benzyloxy)-3'-fluoro-[1,1'-biphenyl]-2-carbaldehyde (6b): Using 3-fluorophenylboronic acid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (d, *J* = 0.7 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.49 - 7.33 (m, 6H), 7.20 - 7.13 (m, 2H), 7.13 - 7.08 (m, 2H), 7.03 (d, *J* = 2.5 Hz, 1H), 5.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 162.9, 161.7, 147.2, 140.1, 36.0, 130.5, 129.0, 128.6, 127.8, 126.0, 117.1, 116.9, 116.4, 115.5, 115.1, 70.6; HRMS *m/z:* [M + Na^+] for $C_{20}H_{15}FO_2Na$, calcd, 329.0948; found, 329.0952.

[0059] 5-(benzyloxy)-4'-fluoro-[1,1'-biphenyl]-2-carbaldehyde (6c): Using 4-fluorophenylboronic: acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.06 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.49 - 7.40 (m, 4H), 7.40 - 7.32 (m, 3H), 7.21 - 7.13 (m, 2H), 7.12 - 7.06 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 162.8, 147.4, 136.0, 131.7, 131.6, 130.5, 128.8, 128.5, 127.7, 127.6, 116.5, 115.6, 115.4, 114.7, 70.4; HRMS *m/z*: [M + Na^+] for $C_{20}H_{15}FO_2Na$, calcd, 329.0948; found, 329.0944.

[0060] 5-(benzyloxy)-2'-chloro-[1,1'-biphenyl]-2-carbaldehyde (6d): Using 2-Chlorophenylboronic acid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.55 - 7.49 (m, 1H), 7.49 - 7.32 (m, 8H), 7.17-7.12 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.99 (d, *J* = 2.6 Hz, 1H), 5.16 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 162.9, 145.1, 136.8, 135.9, 133.5, 131.6, 130.0, 129.8, 129.6, 128.8, 128.4, 127.6, 127.6, 126.9, 116.7, 115.1, 70.4; HRMS *m/z*: [M + Na^+] for $C_{20}H_{15}ClO_2Na$, calcd, 345.0658; found, 345.0653.

[0061] 5-(benzyloxy)-3'-chloro-[1,1'-biphenyl]-2-carbaldehyde (6e): Using 3-Chlorophenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.49 - 7.33 (m, 8H), 7.26 (m, 1H), 7.13 - 7.07 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 162.8, 146.8, 139.7, 135.9, 134.5, 130.5, 129.8, 129.7, 128.8, 128.5, 128.4, 128.3, 127.6, 127.5, 116.3, 115.0, 70.4; HRMS *m/z:* [M + Cl^-] for $C_{2O}H_{15}Cl_2O_2$, calcd, 341.0505; found, 341.0508.

[0062] 5-(benzyloxy)-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (6f): Using 3-(Trifluoromethyl)phenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.05 (m, 1H), 7.72 (m, 1H), 7.67 - 7.64 (td, *J* = 1.6, 0.8 Hz, 1H), 7.64 - 7.53 (m, 2H), 7.50 - 7.35 (m, 5H), 7.15 - 7.11 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 163.0, 146.8, 138.8, 135.9, 133.4, 131.0, 130.9, 129.0, 129.0, 128.6, 127.8, 127.6, 126.6, 126.5, 125.2, 116.7, 115.2, 70.6; HRMS *m/z:* [M + Na^+] for $C_{21}H_{15}F_3O_2Na$, calcd, 379.0922; found, 379.0926.

[0063] 5-(benzyloxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (6g): Using 4-(Trifluoromethyl)phenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.55 - 7.49 (m, 2H), 7.49 - 7.34 (m, 6H), 7.17 - 7.12 (dd, *J* = 9.1, 2.2 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 162.9, 146.7, 141.7, 135.9, 130.8, 130.3, 128.9, 128.6, 127.7, 127.5, 125.5, 125.4, 122.8, 116.6, 115.1, 70.5; HRMS *m/z*: [M + H^+] for $C_{21}H_{16}F_3O_2$, calcd, 357.1097; found, 357.1096.

[0064] 5-(benzyloxy)-2'-(methylthio)-[1,1'-biphenyl]-2-carbaldehyde (6h): Using 2-(Methylthio)phenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.05 (d, *J* = 8.7 Hz,

1H), 7.47 - 7.32 (m, 6H), 7.30 - 7.23 (m, 2H), 7.24 - 7.20 (m, 1H), 7.13 - 7.09 (m, 1H), 6.93 - 6.90 (m, 1H), 5.17 (s, 2H), 2.36 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 163., 146.3, 138.4, 136.2, 136.1, 130.4, 129.5, 129.1, 128.8, 128.4, 127.8, 127.7, 124.7, 124.6, 116.4, 115.3, 70.4, 15.6; HRMS *m/z*: [M + H^+] for $C_{21}H_{18}O_2SNa$, calcd, 357.0920; found, 357.0923.

[0065] 5-(benzyloxy)-2'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (6i): Using 2-Methoxyphenylboronic acid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.07 (d, *J*= 8.7 Hz, 1H), 7.48 - 7.39 (m, 5H), 7.37 (d, *J*= 6.5 Hz, 1H), 7.32 - 7.27 (m, 1H), 7.13 - 7.07 (m, 2H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.98 - 6.95 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.15 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 163.1, 156.6, 144.5, 136.2, 131.4, 130.1, 129.2, 128.8, 128.4, 127.9, 127.7, 126.8, 121.0, 116.9, 114.5, 110.8, 70.3, 55.5; HRMS *m/z:* [M + H^+] for $C_{21}H_{19}O_3$, calcd, 319.1329; found, 319.1333.

[0066] 5-(benzyloxy)-3'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (6j): Using 3-Methoxyphenylboronic acid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.06 (d, *J*= 9.0 Hz, 1H), 7.52 - 7.35 (m, 6H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.05 - 6.93 (m, 4H), 5.20 (s, 2H), 3.89 (s, 3H); HRMS *m/z:* [M + Na^+] for $C_{21}H_{18}O_3Na$, calcd, 341.1154; found, 341.1150.

[0067] 5-(benzyloxy)-3'-methyl-[1,1'-biphenyl]-2-carbaldehyde (6k): Using 3-Methylphenylboronic acid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (d, *J* = 0.9 Hz, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.49 - 7.39 (m, 3H), 7.39 - 7.32 (m, 2H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.22 - 7.16 (m, 2H), 7.09 - 7.05 (ddd, *J* = 8.8, 2.6, 0.9 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 5.15 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 162.8, 148.9, 138.3, 137.9, 136.2, 130.9, 130.1, 129.2, 128.9, 128.5, 128.5, 127.8, 127.3, 116.3, 114.8, 70.5, 21.7; HRMS *m/z:* [M + H^+] for $C_{21}H_{18}O_2Na$, calcd, 325.1205; found, 325.1217.

[0068] 5-(benzyloxy)-3'-(morpholinomethyl)-[1,1'-biphenyl]-2-carbaldehyde (6l): Using 3-(4-Morpholinomethyl)phenylboronic acid pinacol ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.83 (d, *J* = 8.7 Hz, 1H), 7.47 - 7.31 (m, 7H), 7.32 - 7.24 (m, 1H), 7.12 - 7.04 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.05 (d, *J* = 2.5 Hz, 1H), 5.17 (s, 2H), 3.79 - 3.68 (t, *J* = 4.6 Hz, 4H), 3.56 (s, 3H), 2.49 (d, *J* = 6.5 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 162.7, 148.5, 138.3, 137.8, 136.0, 130.7, 130.2, 129.1, 128.8, 128.4, 127.6, 127.6, 116.4, 114.5, 70.4, 67.1, 63.2, 53.7; HRMS m/z: [M + Na^+] for $C_{25}H_{25}NO_3Na$, calcd, 410.1726; found, 410.1730.

[0069] 5-(benzyloxy)-4'-hydroxy-[1,1'-biphenyl]-2-carbaldehyde (6m): Used 4-Hydroxyphenylboronic acid.

[0070] Partially purified biaryl phenol was treated with TBSCl (1.2 eq.) and imidazole (3 eq.) in

DCM and stirred for 2 h at RT. After reaction was completed by TLC, the resulting reaction mixture was concentrated. The crude product was purified by column chromatography (SiO_2, 4:1, Hex:EtOAc) to afford **6m** (94%) as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.52 - 7.33 (m, 5H), 7.26 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.05 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.02 - 6.93 (m, 3H), 5.17 (s, 2H), 1.05 (s, 9H), 0.29 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 162.7, 156.0, 148.4, 136.1, 131.2, 130.6, 130.0, 128.7, 128.3, 127.6, 127.5, 120.0, 116.1, 114.3, 70.3, 25.7, 18.3, 4.3; ESI-HRMS *m/z* : $[M + Na]^+$ for $C_{26}H_{30}NaO_3Si$, calcd, 441.5899, found 441.5896.

[0071] 2-(benzo[d][1,3]dioxol-5-yl)-4-(benzyloxy)benzaldehyde (6n): Using 3,4-(Methylenedioxy)phenylboronic acid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.48 - 7.39 (m, 4H), 7.39 - 7.35 (m, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.91 - 6.86 (m, 2H), 6.83 - 6.79 (m, 1H), 6.03 (s, 2H), 5.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 162.8, 148.2, 147.9, 147.9, 136.1, 131.6, 130.2, 128.8, 128.4, 127.7, 127.6, 124.0, 116.2, 114.5, 110.3, 108.3, 101.5, 70.4; HRMS (FAB) m/z: $[M + Na^+]$ for $C_{21}H_{16}O_4Na$, calcd, 355.0941; found, 355.0935.

[0072] 4-(benzyloxy)-2-(pyridin-3-yl)benzaldehyde (6o): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.65 (dd, 2H, *J* = 5.1, 8.3 Hz), 8.01 (d, 1H, *J* = 8.8 Hz), 7.67 (m, 1H), 7.48-7.26 (m, 6H), 7.09 (dd, 1H, *J* = 2.4, 8.7 Hz), 6.93 (d, 1H, *J* = 2.4 Hz), 5.14 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8, 165.3, 160.5, 135.8, 131.2, 129.0, 128.7, 127.8, 120.0, 109.5, 102.1, 91.0, 70.8; HRMS (FAB) *m/z:* $[M + H^+]$ for $C_{19}H_{16}NO_2$, calcd, 290.1181; found, 290.1177.

[0073] 4-(benzyloxy)-2-(pyridin-4-yl)benzaldehyde (6p): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.67 (d, *J* = 5.9 Hz, 2H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.49-7.33 (m, 6H), 7.30 (d, *J* = 6.0 Hz, 1H), 7.15-7.10 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.95 (d, *J* = 2.6 Hz, 1H), 5.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.7, 162.9, 149.8, 145.8, 145.2, 135.7, 131.0, 128.8, 128.5, 127.6, 127.1, 124.6, 116.3, 115.4, 70.5; HRMS (FAB) *m/z:* $[M + H^+]$ for $C_{19}H_{16}NO_2$, calcd, 290.1181; found, 290.1183.

Example 7. General procedure for Henry Reaction of compounds 6a-p:

[0074] (E)-5-(benzyloxy)-2-(2-nitrovinyl)-1,1'-biphenyl (7a): Nitromethane (1.4 mL) was added to a mixture of aldehyde **6a** (0.16g, 0.56 mmol) and ammonium acetate (77mg, 1.0mmol) and heated to 50 °C. Upon completion (~15-30 min), the reaction mixture was cooled to RT and purified without work-up by column chromatography (SiO_2, 3:1, Hex:EtOAc) to afford nitrostyrene **7a** as a yellow oil (182 mg, 0.55 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.02 (d, *J* = 13.6 Hz, 1H), 7.64 (d, *J* = 9.5 Hz, 1H), 7.50 - 7.35 (m, 10H), 7.31(d, *J* = 2.1 Hz, 2H), 7.04 (d, *J* = 2.5 Hz, 1H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 146.1, 138.1, 136.4, 136.3, 135.5, 131.8 131.7, 129.9, 129.2, 128.8, 128.0, 121.3, 117.3, 116.3, 116.0, 115.6, 70.7; HRMS (FAB) m/z: [M+Na$^+$] for $C_{21}H_{18}NO_3$, calcd, 332.1281; found, 332.1290.

[0075] (E)-5-(benzyloxy)-3'-fluoro-2-(2-nitrovinyl)-1,1'-biphenyl(7b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 13.5 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.49-7.35 (m, 7H), 7.20 - 7.13 (ddd, *J* = 9.3, 7.9, 2.6 Hz, 1H), 7.09 - 7.03 (m, 2H), 7.02 (d, *J* = 2.8 Hz, 2H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.5, 145.4, 141.4, 137.6, 136.1, 136.0, 130.5, 130.4, 129.6, 128.6, 127.7, 125.7, 121.0, 116.9, 116.6, 115.6, 115.4, 70.5; HRMS *m/z*: [M + H$^+$] for $C_{21}H_{17}FNO_3$, calcd, 350.1187; found, 350.1185.

[0076] (E)-5-(benzyloxy)-4'-fluoro-2-(2-nitrovinyl)-1,1'-biphenyl (7c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 13.6 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.50 - 7.34 (m, 6H), 7.32 - 7.24 (m, 2H), 7.23 - 7.14 (t, *J* = 8.3 Hz, 2H), 7.10 - 7.00 (m, 2H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 145.7, 137.8, 136.1, 136.0, 131.5, 131.4, 129.6, 128.9, 128.5, 127.7, 121.0, 117.0, 115.9, 115.7, 115.3, 70.4; HRMS m/z: [M + Na$^+$] for $C_{21}H_{16}FNO_3Na$, calcd, 372.1006; found, 372.1011.

[0077] (E)-5-(benzyloxy)-2'-chloro-2-(2-nitrovinyl)-1,1'-biphenyl (7d): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 - 7.75 (m, 1H), 7.74 - 7.66 (m, 1H), 7.55 (m, 1H), 7.53 - 7.34 (m, 8H), 7.31 (d, *J* = 5.3 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.01 (t, *J* = 2.0 Hz, 1H), 5.20- 5.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 143.8, 137.7, 137.0, 135.9, 133.2, 131.4, 130.0, 130.0, 129.3, 128.7, 128.3, 127.6, 127.1, 123.4, 121.5, 117.1, 115.6, 70.3; HRMS *m/z*: [M + H$^+$] for $C_{21}H_{17}ClNO_3$, calcd, 366.0892; found, 366.0895.

[0078] 5-(benzyloxy)-3'-chloro-2-(2-nitrovinyl)-1,1'-biphenyl (7e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 13.5 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.50 - 7.36 (m, 8H), 7.33 (s, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 7.09 - 7.04 (m, 1H), 7.00 (d, *J* = 2.6 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 141.1, 140.9, 137.4, 136.1, 134.7, 129.9, 129.6, 129.6, 129.5, 129.0, 128.8, 128.5, 128.4, 128,0, 127.6, 120.9, 116.9, 115.5, 109.9, 70.4; HRMS *m/z*: [M + Cl$^-$] for $C_{21}H_{16}Cl_2NO_3$, calcd, 400.0513; found, 400.0505.

[0079] (E)-5-(benzyloxy)-2-(2-nitrovinyl)-3'-(trifluoromethyl)-1,1'-biphenyl (7f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 13.5 Hz, 1H), 7.78 - 7.70 (m, 1H), 7.69 - 7.55 (m, 3H), 7.51 - 7.34 (m, 7H), 7.13 - 7.05 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.02 (d, *J* = 2.6 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 155.7, 152.1, 145.1, 140.6, 140.0, 137.2, 136.4, 136.0, 133.2, 129.7, 129.3, 129.0, 128.6, 127.7, 121.0, 117.1, 115.8, 70.6; HRMS *m/z*: [M + H$^+$] for

$C_{22}H_{17}F_3NO_3$, calcd, 400.1161; found, 400.1157.

[0080] (E)-5-(benzyloxy)-2-(2-nitrovinyl)-4'-(trifluoromethyl)-1,1'-biphenyl (7g): Pushed through plug of SiO_2. TSI-189: ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 - 7.90 (m, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.52 - 7.37 (m, 8H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4, 147.8, 144.9, 144.3, 139.8, 138.6, 137.1, 136.4, 135.8, 133.5, 131.2, 129.5, 129.1, 128.8, 128.5, 127.6, 124.2, 120.8, 120.4, 117.0, 115.6, 70.4; HRMS m/z: [M + H^+] for $C_{22}H_{17}F_3NO_3$, calcd, 400.1155; found, 400.1151.

[0081] (E)-(5'-(benzyloxy)-2'-(2-nitrovinyl)-[1,1'-biphenyl]-2-yl)(methyl)sulfane (7h): ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 13.6 Hz, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.45 - 7.31 (m, 7H), 7.31 - 7.29 (m, 1H), 7.25 - 7.19 (t, *J* = 7.2 Hz, 1H), 7.13 - 6.99 (m, 2H), 6.95 (d, *J* = 2.8 Hz, 1H), 5.09 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 144.9, 138.0, 137.5, 137.2, 136.1, 135.7, 130.0, 129.4, 129.3, 128.8, 128.4, 127.7, 125.0, 124.9, 121.6, 117.0, 115.8, 70.3, 15.6; HRMS m/z: [M + K^+] for $C_{22}H_{19}NO_3SK$, calcd, 416.0718; found, 416.0756.

[0082] (E)-5-(benzyloxy)-2'-methoxy-2-(2-nitrovinyl)-1,1'-biphenyl (7i): ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 13.8 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.57 - 7.34 (m, 7H), 7.24 - 7.17 (m, 1H), 7.16 - 6.99 (m, 4H), 5.15 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 156.4, 143.7, 138.8, 136.3, 135.3, 131.4, 130.4, 128.9, 128.4, 127.7, 122.0, 121.1, 117.5, 115.1, 111.4, 70.4, 55.6; HRMS m/z: [M + H^+] for $C_{22}H_{19}NO_4$, calcd, 362.1387; found, 362.1389.

[0083] (E)-5-(benzyloxy)-3'-methoxy-2-(2-nitrovinyl)-1,1'-biphenyl (7j): ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 13.6 Hz, 1H), 7.62 (d, *J* = 9.5 Hz, 1H), 7.46 - 7.37 (m, 6H), 7.07 - 7.02 (m, 3H), 7.02 - 6.97 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.88 - 6.84 (m, 1H), 6.84 - 6.80 (dd, *J* = 2.6, 1.6 Hz, 1H), 5.15 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 159.8, 146.8, 140.6, 138.2, 136.2, 135.9, 129.9, 129.5, 129.0, 128.6, 127.7, 122.3, 121.1, 116.8, 115.4, 115.4, 114.1, 70.5, 55.6; HRMS *m/z*: [M + Na^+] for $C_{22}H_{19}NO_4Na$, 384.1212; found, 384.1218.

[0084] (E)-5-(benzyloxy)-3'-methyl-2-(2-nitrovinyl)-1,1'-biphenyl(7k): ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 13.6 Hz, 1H), 7.62 (m, 1H), 7.48 - 7.39 (m, 7H), 7.39 - 7.33 (t, *J* = 7.7 Hz, 1H), 7.14 - 7.07 (m, 2H), 7.05 - 6.99 (m, 2H), 5.15 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 135.8, 130.4, 129.5, 129.3, 128.9, 128.7, 128.5, 127.8, 127.8, 126.9, 121.1, 116.8, 115.3, 77.5, 77.4, 77.2, 77.0, 70.5 21.7; HRMS *m/z*: [M + Na^+] for $C_{22}H_{19}NO_3Na$lcd, 368.1263; found, 368.1257.

[0085] (E)-4-((5'-(benzyloxy)-2'-(2-nitrovinyl)-[1,1'-biphenyl]-3-yl)methyl)morpholine (7l):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 13.6 Hz, 1H), 7.63 (d, *J* = 9.5 Hz, 1H), 7.48 - 7.33 (m, 8H), 7.33 (d, *J* = 1.7 Hz, 1H), 7.23 - 7.20 (dd, *J* = 6.7, 1.8 Hz, 1H), 7.08 - 6.99 (m, 2H), 5.15 (d, *J* = 1.6 Hz, 2H), 3.79 - 3.67 (t, *J* = 4.1 Hz, 4H), 3.56 (s, 2H), 2.55 - 2.40 (dd, *J* = 5.7, 3.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 146.9, 139.2, 138.5, 138.1, 136.1, 135.8, 130.6, 129.5, 129.3, 128.9, 128.8, 128.5, 128.4, 127.7, 121.0, 116.9, 115.1, 70.4, 67.1, 63.3, 53.8; HRMS *m/z*: [M + H$^+$] for $C_{26}H_{27}N_2O_4$, calcd, 431.1971; found, 431.1974.

[0086] (E)-((5'-(benzyloxy)-2'-(2-nitrovinyl)-11,1'-biphenyl]-4-yl)oxy)(tert-butyl)dimethylsilane (7m): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 13.7 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.49 - 7.33 (m, 6H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.02 (s, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 5.15 (s, 2H), 1.04 (s, 9H), 0.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 156.2, 146.8, 138.5, 136.2, 135.8, 132.2, 131.0, 129.6, 128.9, 128.5, 127.7, 121.1, 120.4, 116.8, 115.0, 70.4, 25.9, 18.4, -4.1; HRMS (FAB) *m/z:* [M + Na$^+$] for $C_{27}H_{31}NO_4SiNa$, calcd, 484.1914; found, 484.1936.

[0087] (E)-5-(5-(benzyloxy)-2-(2-nitrovinyl)phenyl)benzo[d][1,3]dioxole (7n): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 13.6 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.50 - 7.33 (m, 6H), 7.05 - 6.98 (m, 2H), 6.92 - 6.85 (m, 1H), 6.79 (s, 1H), 6.71(d, *J* = 7.9 Hz, 1H), 6.03 (s, 2H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 148.0, 147.9, 146.5, 138.1, 136.1, 135.7, 132.9, 129.5, 128.8, 128.4, 127.6, 123.6, 121.0, 116.7, 115.0, 109.9, 108.5, 101.5, 70.3; HRMS (FAB) *m/z*: [M + H$^+$] for $C_{22}H_{18}NO_5$, calcd, 376.1185; found, 376.1160.

[0088] (E)-3-(5-(benzyloxy)-2-(2-nitrovinyl)phenyl)pyridine (7o): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.59 (d, *J* = 1.6 Hz, 1H), 7.89 (d, *J* = 13.5 Hz, 1H), 7.68 - 7.60 (m, 2H), 7.47 - 7.32 (m, 8H), 7.12 - 7.06 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.00 (d, *J* = 2.6 Hz, 1H), 5.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 149.9, 149.6, 142.8, 136.9, 136.8, 136.3, 135.8, 134.8, 129.7, 128.8, 128.5, 127.6, 123.4, 121.1, 1 17.1, 115.8, 70.4; HRMS (FAB) *m/z*: [M +Na$^+$] for $C_{20}H_{17}N_2O_3$, 333.1239; found, 333.1234.

[0089] (E)-4-(5-(benzyloxy)-2-(2-nitrovinyl)phenyl)pyridine (7p): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (dd, 2H, *J* = 1.6, 4.4 Hz), 7.91 (d, 1H, *J* = 13.6 Hz), 7.67 (d, 1H, *J* = 8.8 Hz), 7.48 (d, 1H, *J* = 13.4 Hz), 7.41 (m, 5H), 7.25 (dd, 2H, *J* = 1.6, 4.4 Hz), 7.11 (dd, 1H, *J* =2.6, 8.7 Hz), 7.01 (d, 1H, *J* = 2.5 Hz), 5.17 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 150.2, 147.0, 143.7, 136.7, 136.6, 135.8, 128.9, 127.6, 124.5, 120.7, 116.8, 116.1, 70.6; ESI-HRMS *m/z* calculated for $C_{20}H_{17}N_2O_3$ [M + H]$^+$ 333.1239, found 333.1249.

Example 8. General procedure for preparation of 8a-p from 7a-p:

[0090] N-(2-(5-(benzyloxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8a): Nitrostyrene **7a** (182 mg, 0.55 mmol) in THF (0.7 mL) was added dropwise to a solution of Lithiumaluminium hydride (42 mg, 1.12 mmol) in THF (2 mL) under argon atmosphere at RT. Upon completion (nearly immediately) the reaction was quenched by the addition of water (42 µL), 3M NaOH (42 µL), and water (84 µL). The resulted mixture was filtered through a plug of celite, washed with DCM, and dried over K_2CO_3. Upon filtration the mixture was concentrated to oil and used without further purification. Acetic anhydride (58 µL, 0.62 mmol) and triethylamine (93 µL, 0.67 mmol) were added to a solution of the crude amine in DCM (5.6 mL) under an argon atmosphere at RT. After 3 h the reaction was quenched with saturated aqueous ammonium chloride and extracted with DCM (3 x 10 mL); combined organic fractions were washed with saturated aqueous sodium chloride, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2; 3:1, Hex:EtOAc) to afford acetamide **8a** (0.12 g, 0.35 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 - 7.38 (m, 8H), 7.38 - 7.30 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.01 - 6.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.93 (d, *J* = 2.7 Hz, 1H), 5.71 (br s, NH), 5.08 (s, 2H), 3.42 - 3.16 (q, *J* = 7.0 Hz, 2H), 2.89 - 2.64 (t, *J* = 7.2 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 157.2, 143.4, 141.4, 137.0, 130.8, 129.1, 128.7, 128.6, 128.4, 128.0, 127.6, 127.2, 116.6, 114.2, 70.1, 40.7, 31.9, 23.2; HRMS *m/z*: [M + K^+] for $C_{23}H_{23}NO_2K$ calcd, 384.1361; found, 384.1359.

[0091] N-(2-(5-(benzyloxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.30 (m, 6H), 7.24 - 7.18 (d, *J* = 8.4 Hz, 1H), 7.12 - 7.04 (m, 2H), 7.04 - 6.92 (ddd, *J* = 18.6, 8.2, 2.5 Hz, 2H), 6.85 (d, *J* = 2.7 Hz, 1H), 5.34 (br s, NH), 5.05 (s, 2H), 3.32 - 3.21 (q, *J* = 6.4, 5.9 Hz, 2H), 2.79 - 2.68 (t, *J* = 7.1 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 157.3, 143.7, 142.2, 136.9, 131.0, 130.1, 123.0, 128.8, 128.6, 128.2, 127.7, 125.0, 116.5, 116.4, 114.6, 114.4, 70.2, 40.8, 32.0, 23.3; HRMS *m/z*: [M + H^+] for $C_{23}H_{23}FNO_2$, calcd, 364.1713; found, 364.1705.

[0092] N-(2-(5-(benzyloxy)-4'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.31 (m, 6H), 7.27 - 7.22 (dd, *J* = 8.4, 5.5 Hz, 1H), 7.21 - 7.17 (d, *J* = 8.4 Hz, 1H), 7.12 - 7.05 (m, 3H), 6.96 - 6.91 (dd, *J* = 8.3, 3.0 Hz, 1H), 5.83 (br s, NH), 5.05 (s, 2H), 3.33 - 3.15 (q, *J* = 6.7 Hz, 2H), 2.78 - 2.66 (t, *J* = 7.2 Hz, 2H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 157.3, 142.4, 137.0, 130.9, 130.8, 130.7, 128.7, 128.7, 128.2, 127.7, 116.8, 115.5, 115.3, 114.3, 70.2, 40.8, 32.0, 23.1; HRMS *m/z*: [M + Na^+] for $C_{23}H_{22}FNO_2Na$, calcd, 386.1527; found, 386.1529.

[0093] N-(2-(5-(benzyloxy)-2'-chloro-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8d): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 - 7.45 (m, 1H), 7.45 - 7.40 (m, 2H), 7.40 - 7.35 (m, 3H), 7.35 - 7.29 (m, 3H), 7.25 - 7.21 (m, 1H), 7.05 - 6.95 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 5.93 (d, *J* = 5.4 Hz, 1H), 5.05 (s, 2H), 3.36 - 3.19 (ddq, *J* = 19.3, 13.0, 6.1 Hz, 2H), 2.67 - 2.49

(m, 2H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 171.0, 157.1, 140.4, 139.8, 136.9, 133.1, 131.3, 130.4, 129.6, 129.0, 128.6, 128.0, 127.6, 126.8, 116.4, 114.9, 70.1, 40.3, 31.8, 22.9; HRMS *m/z*: [M + H$^+$] for $C_{23}H_{23}ClNO_2$, calcd, 380.1417; found, 380.1415.

[0094] N-(2-(5-(benzyloxy)-3'-chloro-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8e): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 - 7.28 (m, 8H), 7.25 - 7.17 (m, 2H), 6.99 - 6.92 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.84 (d, *J* = 2.8 Hz, 1H), 5.46 (br s, NH), 5.06 (s, 2H), 3.34 - 3.25 (m, 2H), 2.83 - 2.68 (t, *J* = 7.3 Hz, 2H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 157.5, 143.2, 142.1, 136.9, 134.3, 131.1, 129.9 129.3, 128.8, 128.3, 127.7, 127.6, 127.5, 116.7, 114.8, 70.3,46.1, 41.3, 31.7, 22.5, 8.8; HRMS *m/z*: [M + H$^+$] for $C_{23}H_{23}ClNO_2$, calcd, 380.1412; found, 380.1414.

[0095] N-(2-(5-(benzyloxy)-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.59 - 7.54 (m, 2H), 7.55 - 7.49 (t, *J* = 7.3 Hz, 1H), 7.47 - 7.32 (m, 5H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.01 - 6.96 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.87 (d, *J* = 2.7 Hz, 1H), 5.90 (br s, NH), 5.06 (s, 2H), 3.34 - 3.23 (q, *J* = 6.9 Hz, 2H), 2.79 - 2.68 (t, *J* = 7.3 Hz, 2H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 157.4, 142.2, 141.9, 136.9, 132.6, 131.1, 129.0, 128.8, 128.5, 128.2, 127.7, 124.2, 116.7, 114.8, 70.3, 40.8,31.9, 23.0; HRMS *m/z:* [M + H$^+$] for $C_{24}H_{23}F_3NO_2$, calcd, 414.1676; found, 414.1681.

[0096] N-(2-(5-(benzyloxy)-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.46 - 7.23 (m, 8H), 6.99 - 6.94 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.03 (t, *J* = 5.5 Hz, 1H), 5.06 (s, 2H), 3.33 - 3.19 (dd, *J* = 14.3, 6.4 Hz, 2H), 2.76 - 2.68 (dd, *J* = 8.3, 6.6 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 157.1, 145.1, 141.8, 136.8, 130.9, 129.5, 129.1, 128.6, 128.6, 127.5, 125.6, 125.2, 125.2, 122.9, 116.4, 114.6, 70.1, 40.6, 31.9; HRMS *m/z*: [M + Na$^+$] for $C_{24}H_{22}F_3NO_2Na$, calcd, 436.1495; found, 436.1489.

[0097] N-(2-(5-(benzyloxy)-2'-(methylthio)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8h): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.30 (m, 7H), 7.28 - 7.18 (m, 2H), 7.14 (s, 1H), 7.03 - 6.98 (ddd, *J* = 8.5, 2.8, 1.0 Hz, 1H), 6.87 - 6.83 (m, 1H), 5.63 (br s, NH), 5.05 (s, 2H), 3.43 - 3.16 (ddt, *J* = 42.5, 13.3, 6.6 Hz, 2H), 2.66 - 2.52 (t, *J* = 6.7 Hz, 2H), 2.39 (d, *J* = 1.0 Hz, 3H), 1.84 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 157.3, 141.1, 139.1, 137.6, 137.0, 130.6, 129.8, 129.4, 128.7, 128.4, 128.1, 127.7, 124.5, 124.0, 116.5, 115.2, 70.2, 40.1, 31.7, 23.3, 15.2; HRMS *m/z:* [M + Na$^+$] for $C_{24}H_{25}NO_2SNa$, calcd, 414.1504; found, 414.1509.

[0098] N-(2-(5-(benzyloxy)-2'-methoxy-[1,1'-biphenyl] -2-yl)ethyl)acetamide (8i): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.30 (m, 5H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.17 - 7.13 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.07 - 6.95 (m, 4H), 6.85 (d, *J* = 2.7 Hz, 1H), 5.51 (br s, NH), 5.07 (s, 2H), 3.77 (s,

3H), 3.44 - 3.18 (m, 2H), 2.68 - 2.56 (td, *J* = 6.8, 3.7 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 157.2, 156.4, 139.9, 137.1, 131.2, 130.1, 129.2, 128.7, 128.1, 127.8, 120.9, 116.8, 114.4, 111.2, 70.1, 55.8, 40.4, 31.9, 23.5; HRMS *m/z*: [M + H$^+$] for $C_{24}H_{26}NO_3$, calcd, 376.1913; found, 376.1902.

[0099] N-(2-(5-(benzyloxy)-3'-methoxy-[1,1'-biphenyl] -2-yl)ethyl)acetamide (8j): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.36 (m, 4H), 7.36 - 7.30 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.98 - 6.92 (m, 1H), 6.92 - 6.82 (m, 3H), 5.49 (br s, NH), 5.06 (s, 2H), 3.85 (s, 3H), 3.34 - 3.22 (q, *J* = 6.6, 6.2 Hz, 2H), 2.85 - 2.68 (t, *J* = 7.2 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 159.5, 157.2, 143.3, 142.9, 137.0, 130.8, 129.5, 128.7, 128.1, 128.1, 127.7, 121.6, 116.5, 114.9, 114.3, 112.7, 70.17, 55.4, 40.8, 32.0, 23.3; HRMS *m/z*: [M + H$^+$] for $C_{24}H_{25}NO_3Na$, calcd, 398.1732; found, 398.1725.

[0100] N-(2-(5-(benzyloxy)-3'-methyl-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8k): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 3H), 7.40 (m, 3H), 7.37 - 7.30 (q, *J* = 7.7, 7.1 Hz, 1H), 7.21 (d, *J* = 1.4 Hz, 1H), 7.15 -7.10 (m, 2H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.90 (s, 1H), 5.51 (br s, NH), 5.08 (s, 2H), 3.34 - 3.24 (q, *J* = 6.5 Hz, 2H), 2.83 - 2.71 (t, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 157.2, 143.5, 141.4, 138.0, 137.0, 130.7, 129.9, 128.7, 128.7, 128.3, 128.1, 128.0, 127.6, 126.2, 116.5, 114.2, 70.1, 40.8, 31.9, 23.3, 21.6; ESI-HRMS *m/z* calculated for $C_{24}H_{25}NO_2Na$ [M + Na]$^+$ 382.1777, found 382.1770.

[0101] N-(2-(5-(benzyloxy)-3'-(morpholinomethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8l): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.30 (m, 7H), 7.28 (s, 1H), 7.24 - 7.18 (m, 2H), 6.98 - 6.93 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.89 (d, *J* = 2.7 Hz, 1H), 5.40 (s, 1H), 5.05 (s, 2H), 3.75 - 3.69 (t, *J* = 4.7 Hz, 4H), 3.55 (s, 2H), 3.36 - 3.22 (q, *J* = 6.9 Hz, 2H), 2.80 - 2.68 (t, *J* = 7.1 Hz, 2H), 2.47 (m, 4H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 157.3, 143.4, 141.5, 138.0, 137.1, 130.9, 123.0, 128.7, 128.7, 128.4, 128.2, 128.2, 128.0, 127.7, 116.8, 114.1, 70.2, 67.1, 63.5, 53.8, 40.6, 32.1, 23.4; HRMS *m/z*: [M + H$^+$] for $C_{28}H_{33}N_2O_3$, calcd, 445.2491; found, 445.2494.

[0102] N-(2-(5-(benzyloxy)-4'-((tert-butyldimethylsilyl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (8m): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 3H), 7.42 - 7.36 (dt, *J* = 10.5, 5.7 Hz, 3H), 7.36 - 7.31 (m, 1H), 7.21 - 7.14 (m, 3H), 6.94 - 6.86 (m, 2H), 5.08 (s, 2H), 3.34 - 3.23 (q, *J* = 6.7 Hz, 2H), 2.75 (t, *J* = 7.1 Hz, 2H), 1.74 (s, 3H), 1.97 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 157.3, 155.0, 143.3, 137.2, 134.5, 130.8, 130.2, 128.7, 128.1, 127.7, 120.0, 116.8, 114.0, 70.2, 53.6, 40.7, 32.1, 25.8, 23.4, 18.4, -4.2; HRMS (FAB) *m/z*: [M + Na$^+$] for $C_{29}H_{37}NO_3SiNa$, calcd, 498.2440; found, 498.2447.

[0103] N-(2-(benzo[d][1,3]dioxol-5-yl)-4-(benzyloxy)phenethyl)acetamide (8n): ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.49 - 7.36 (m, 5H), 7.34 (d, *J* = 4.4 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 6.96 - 6.89 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.90- 6.84 (m, 2H), 6.81 - 6.73 (m, 1H), 6.00 (s, 2H), 5.69 - 5.60 (t, *J* = 5.8 Hz, 1H), 5.06 (s, 2H), 3.42 - 3.16 (m, 2H), 2.93 - 2.68 (t, *J* = 7.3 Hz, 2H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 157.2, 147.5, 146.8, 143.0, 137.0, 135.2, 130.8, 129.3, 128.8, 128.1, 127.6, 123.2, 122.4, 116.7, 114.1, 109.7, 108.3, 101.2, 70.1, 40.7, 31.9, 23.2; HRMS (FAB) *m/z*: [M + Na^+] for $C_{24}H_{23}NO_4Na$, 412.1519; found, 412.1524.

[0104] N-(4-(benzyloxy)-2-(pyridin-3-yl)phenethyl)acetamide (8o): ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 - 8.52 (dd, *J* = 18.2, 4.0 Hz, 2H), 7.71 - 7.63 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.49 - 7.31 (m, 7H), 7.06 - 6.97 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.84 (d, *J* = 2.8 Hz, 1H), 5.06 (s, 2H), 3.36 - 3.20 (q, *J* = 6.5 Hz, 2H), 2.78 - 2.67 (dd, *J* = 8.1, 6.6 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 157.5, 149.6, 148.5, 139.5, 136.9, 131.2, 129.0, 128.8, 128.3, 127.7, 123.5, 116.9, 115.0, 70.3, 40.7, 32.2, 23.5; HRMS (FAB) *m/z*: [M + H^+] for $C_{22}H_{23}N_2O_2$, calcd, 347.1759; found, 347.1754.

[0105] N-(4-(benzyloxy)-2-(pyridin-4-yl)phenethyl)acetamide (8p): ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 5.1 Hz, 2H), 7.46 - 7.39 (m, 5H), 7.36 (s, 1H), 7.30 (s, 2H), 7.06 - 7.01 (m, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 5.94 (d, *J* = 4.8 Hz, 1H), 5.09 (s, 2H), 3.35 - 3.23 (dd, *J* = 14.5, 6.4 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 158.1, 156.3, 137.2, 132.3, 132.2, 130.8, 128.7, 128.5, 129.7, 127.5, 117.9, 106.2, 103.0, 69.9, 41.1, 29.7, 29.6, 23.1; HRMS (FAB) *m/z:* [M + Na^+] for $C_{22}H_{22}N_2O_2Na$, calcd, 369.1579; found, 369.1573.

Example 9. General hydrogenolysis procedure for compounds 8a-p.

[0106] N-(2-(5-hydroxy-[1,1'-biphenyl]-Z-yl)ethyl)acetamide (9a): Palladium on carbon (10%, 5 mg) was added to **8a** (120 mg, 0.35 mmol) in degassed MeOH (3.5 mL) and the solution was placed under an atmosphere of H_2. After 12 h, the solution was diluted with DCM and filtered through Celite. The eluent was concentrated to afford a yellow solid, which was purified by column chromatography (SiO_2, 100:5, DCM:MeOH) to afford phenol **9a** (64 mg, 0.25mmol, 79%) as a pale yellow amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 - 7.14 (m, 5H), 7.11 - 7.05 (m, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 5.61 (t, *J* = 5.5 Hz, 1H), 3.12 - 3.02 (m, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 155.2, 143.4, 141.6, 130.8, 129.1, 128.4, 127.2, 127.2, 117.4, 115.0, 41.1, 31.8, 23.2; HRMS *m/z*: [M + Na^+] for $C_{16}H_{17}NO_2Na$, calcd, 278.1151; found, 278.1155.

[0107] N-(2-(3'-fluoro-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9b): ^1H NMR (500

MHz, MeOD) δ 7.88 (s, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.16 - 6.99 (m, 4H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 3.15 (t, *J* = 6.6 Hz, 2H), 2.66 (t, *J* = 7.4 Hz, 2H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, MeOD) δ 173.1, 164.8, 162.9, 156.7, 145.5, 143.3, 132.0, 131.0, 128.3, 126.1, 117.6, 115.9, 114.7, 41.8, 32.8, 22.5; HRMS *m/z*: [M + Na$^+$] for $C_{16}H_{16}FNO_2Na$, calcd, 296.1063; found, 296.1059.

[0108] N-(2-(4'-fluoro-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9e): ^{1}H NMR (400 MHz, MeOD) δ 7.26 - 7.20 (m, 2H), 7.11 - 7.03 (m, 3H), 6.71 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.56 (d, *J* = 2.5 Hz, 1H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 173.0, 156.7, 143.5, 139.2, 131.9, 131.9, 131.8, 128.5, 117.8, 116.0, 115.8, 115.7, 41.8, 32.9, 22.5; HRMS *m/z*: [M +Na$^+$] for $C_{16}H_{16}FNO_2Na$, calcd, 296.1063; found, 296.1065.

[0109] N-(2-(2'-chloro-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br s, OH), 7.45 - 7.39 (m, 1H), 7.32 - 7.24 (m, 2H), 7.21 - 7.15 (m, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.68 (d, *J* = 2.6 Hz, 1H), 5.62 (s, 1H), 3.40 - 3.14 (m, 2H), 2.63 - 2.44 (dd, *J* = 7.1, 5.1 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 155.1, 140.5, 140.0, 133.2, 131.4, 130.5, 129.7, 129.0, 127.7, 126.9, 117.3, 115.7, 40.5, 31.8, 23.3; HRMS *m/z*: [M + H$^+$] for $C_{16}H_{17}ClNO_2$, 290.0948; found, 290.0941.

[0110] N-(2-(3'-chloro-5-hydroxy-[1,1'-biphenyl)-2-yl)ethyl)acetamide (9e): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.09 (m, 5H), 6.83 - 6.76 (dq, *J* = 8.1, 4.9, 3.8 Hz, 1H), 6.76 - 6.67 (dd, *J* = 18.3, 2.7 Hz, 1H), 3.34 - 3.23 (p, *J* = 6.6 Hz, 2H), 2.77 - 2.64 (dt, *J* = 14.3, 7.2 Hz, 2H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 154.9, 143.6, 141.6, 131.0, 130.9, 129.7, 129.2, 128.5, 127.5, 117.4, 115.5, 115.0, 41.0, 32.0, 23.4; HRMS *m/z*: [M + Na$^+$] for $C_{16}H_{16}ClNO_2Na$, calcd, 312.0762; found, 312.0788.

[0111] N-(2-(5-hydroxy-3'-(trifluoromethyl)-(1,1'-biphenyl]-2-yl)ethyl)acetamide (9f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.39 (m, 4H), 7.07 (s, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 6.00 (s, 1H), 3.34 - 3.18 (q, *J* = 6.8 Hz, 2H), 2.66 (t, *J* = 7.0 Hz, 2H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 155.4, 142.4, 141.8, 132.6, 131.0, 130.8, 128.9, 126.9, 125.8, 125.8, 124.0, 117.3, 115.6, 60.7, 41.0, 21.2; HRMS *m/z*: [M + Na$^+$] for $C_{17}H_{16}F_3NO_2Na$, calcd, 346.1031; found, 346.1040.

[0112] N-(2-(5-hydroxy-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 1H, *J* = 8.3 Hz), 6.72 (dd, 1H, *J* = 2.5, 8.3 Hz), 6.59 (d, 1H, *J* = 2.5 Hz), 4.09 (br s, 2H), 3.10 (t, *J* = 7.5 Hz, 2H), 2.56 (t, 2H, *J* = 7.5 Hz), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.1, 146.3,

141.7, 130.8, 129.5, 127.1, 125.1 (q, *J* = 4.2 Hz), 116.9, 116.5, 115.3, 45.6, 40.6, 23.0; HRMS *m/z*: [M + H^+] for $C_{17}H_{16}F_3NO_2Na$, calcd, 346.1031; found, 346.1025.

[0113] N-(2-(5-hydroxy-2'-(methylthio)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9h): ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 - 7.34 (m, 1H), 7.25 - 7.14 (m, 3H), 7.12 - 7.07 (m, 1H), 6.86- 6.82 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.68 (d, *J* = 2.7 Hz, 1H), 5.51 (br s, NH), 3.42 - 3.16 (m, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.37 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 154.5, 141.2, 139.1, 137.6, 130.7, 123.0, 128.8, 128.5, 124.6, 124.0, 117.3, 115.6, 40.2, 31.6, 23.4, 15.2; HRMS *m/z*: [M + Na^+] for $C_{17}H_{19}NO_2SNa$, calcd, 324.1034; found, 324.1035.

[0114] N-(2-(5-hydroxy-2'-methoxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9i): ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (br s, OH), 7.41 - 7.31 (m, 1H), 7.14 - 7.07 (dd, *J* = 8.4, 6.4 Hz, 1H), 7.05 - 6.94 (m, 3H), 6.83 - 6.76 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 5.55 (s, 1H), 3.76 (s, 3H), 3.41 - 3.17 (ddt, *J* = 34.4, 13.1, 6.5 Hz, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.4, 155.1, 139.9, 131.3, 130.5, 130.1, 129.1, 128.5, 121.0, 117.7, 115.2, 111.4,55.9, 40.7, 31.7, 23.3; HRMS *m/z*: [M + Na^+] for $C_{17}H_{19}NO_3Na$, calcd, 308.1263; found, 308.1264.

[0115] N-(2-(5-hydroxy-3'-methoxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9j): ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, OH), 7.30 - 7.24 (m, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.90 - 6.70 (m, 5H), 5.59 (t, *J* = 5.7 Hz, 1H), 3.79 (s, 3H), 3.33 - 3.19 (q, *J* = 6.9 Hz, 2H), 2.69 (t, *J* = 7.1 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 159.4, 155.1, 143.3, 143.0, 130.9, 129.5, 127.3, 121.7, 117.2, 115.1, 115.0, 112.6, 55.4, 41.1, 31.8, 23.3; HRMS m/z: [M + H^+] for $C_{17}H_{20}NO_3$, calcd, 286.1443; found, 286.1436.

[0116] N-(2-(5-hydroxy-3'-methyl-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9k): ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (br s, OH), 7.30 - 7.24 (m, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.09 - 7.03 (m, 3H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.73 (s, 1H), 5.53 (br s, NH), 3.31 - 3.21 (q, *J* = 6.7 Hz, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (1001 MHz, $CDCl_3$) δ 170.9, 155.0, 143.6, 141.6, 138.1, 130.8, 1230.0, 128.3, 128.0, 127.4, 126.3, 117.4, 114.9, 41.1, 31.8, 23.3, 21.7; HRMS m/z: [M + Na^+] for $C_{17}H_{19}NO_2Na$, calcd, 292.1308; found, 292.1314.

[0117] N-(2-(5-hydroxy-3'-(morpholinomethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9l): ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 - 7.23 (m, 4H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.74 - 6.69 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 5.50 (br s, NH), 3.74 (m, 4H), 3.53 (s, 3H), 3.29 - 3.20 (q, *J* = 6.7 Hz, 2H), 2.69 (t, *J* = 7.0 Hz, 2H), 2.49 (t, *J* = 4.8 Hz, 4H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 155.0, 143.4, 141.7, 130.9, 130.2, 128.4, 128.2, 117.5, 115.0, 66.9, 63.4, 53.8, 40.8, 32.0, 23.4; HRMS *m/z*: [M + H^+] for

$C_{21}H_{27}N_2O_3$, calcd, 355.2022; found, 355.2024.

[0118] N-(2-(4'-((tert-butyidimethylsilyl)oxy)-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (9m): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 - 7.10 (d, *J* = 6.7 Hz, 2H), 7.10 - 7.06 (d, *J* = 8.2 Hz, 1H), 7.00 (br s, OH), 6.91 - 6.84 (d, *J* = 8.4 Hz, 2H), 6.79 - 6.72 (m, 2H), 5.38 (s, 1H), 3.34 - 3.21 (q, *J* = 6.6 Hz, 2H), 2.78 - 2.64 (t, *J*= 6.9 Hz, 2H), 1.93 - 1.81 (s, 3H), 1.00 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 155.0, 154.9, 143.3, 134.6, 130.9, 130.3, 127.8, 120.0, 117.5, 114.7, 41.0, 32.0, 26.0, 23.4, 18.4, -4.1; HRMS (FAB) *m/z*: [M + Na^+] for $C_{22}H_{31}NO_3SiNa$, calcd, 408.1965; found, 408.1960.

[0119] N-(2-(benzo[d][1,3]dioxol-5-yl)-4-hydroxyphenethyl)acetamide (9n): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (br s, OH), 7.08 - 6.98 (d, *J* = 8.3 Hz, 1H), 6.81 - 6.73 (m, 2H), 6.73 - 6.68 (m, 2H), 6.68 - 6.64 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.97 - 5.92 (s, 2H), 5.70 - 5.63 (t, *J* = 5.7 Hz, 1H), 3.29 - 3.21 (td, *J* = 7.1, 5.6 Hz, 2H), 2.75 - 2.63 (t, *J* = 7.2 Hz, 2H), 1.89 - 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 155.1, 147.5, 146.8, 143.0, 135.4, 130.8, 127.4, 122.4, 117.5, 114.9, 109.8, 108.3, 101.2, 41.1, 31.9, 23.3; HRMS (FAB) m/z: [M + Na^+] for $C_{17}H_{17}NO_4Na$, calcd, 322.1050; found, 322.1022.

[0120] N-(4-hydroxy-2-(pyridin-3-yl)phenethyl)acetamide (9o): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 2H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.42 - 7.34 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.14 (d, *J*= 8.4 Hz, 1H), 6.90 - 6.84 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.82 (t, *J* = 5.9 Hz, 2H), 3.33 - 3.19 (q, *J* = 6.8 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 156.1, 149.1, 147.7, 138.8, 138.0, 131.4, 127.3, 123.7, 117.5, 116.4, 100.2, 40.9, 32.0, 23.4; HRMS (FAB) *m/z:* [M + H^+] for $C_{15}H_{17}N_2O_2$, calcd, 257.1290; found, 257.1297.

[0121] N-(4-hydroxy-2-(pyridin-4-yl)phenethyl)acetamide (9p): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 - 8.60 (m, 2H), 7.25 (d, *J*= 1.5 Hz, 2H), 7.17 (d, *J*= 8.4 Hz, 1H), 6.90 - 6.83 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 6.02 (br s, OH), 5.47 (s, 1H), 3.33 - 3.24 (q, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 7.4 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 157.1, 152.8, 149.7, 149.6, 141.3, 132.4, 128.0, 126.2, 117.2, 117.1, 116.9, 41.8, 32.8, 22.5; HRMS (FAB) *m/z:* [M + Na^+] for $C_{15}H_{16}N_2O_2Na$, calcd, 279.1104; found, 279.1109.

Example 10. General procedure for activated Noviose carbamate coupling and followed by methanolysis of compounds 9a-p:

[0122] Borontrifluoride etherate (6.2 µL, 0.05 mmol) was added to **9a-p** (0.25 mmol) and activated noviose (0.2 mmol) in 2.5 mL anhydrous DCM. After stirring at RT for 2 h, triethylamine (150 µL) was added and the solvent was concentrated. The residue was partially

purified via column chromatography (SiO_2, 100:8 DCM:acetone) to give noviose coupled product as a colorless foam, which was used directly for next step. Triethylamine (0.22 mL, 10%) was added to the cyclic carbonate (100 mg, 0.22 mmol) in MeOH (2.2 mL). After 12 h, the solvent was concentrated and the residue was purified via column chromatography (SiO_2, 10:1, DCM:Acetone) to afford inseparable diastereomers **11a-p** (see following experimental section for diastereoselectivities) as a colorless amorphous solids.

[0123] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11a): Colorless amorphous solid (63% yield over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, 3H), 7.28 - 7.18 (dt, *J*= 5.9, 3.2 Hz, 2H), 7.13 (m, 1H), 6.97 (m, 1H), 6.92 - 6.78 (dd, *J* = 7.6, 2.7 Hz, 1H), 5.55 - 5.47 (dd, *J* = 7.7, 2.7 Hz, 1H), 5.39 (m, 1H), 4.14 (m, 2H), 3.58 - 3.46 (m, 3H), 3.34 - 3.15 (m, 4H), 3.03 (d, *J* = 5.5 Hz, 1H), 2.77 - 2.65 (m, 2H), 1.84 - 1.76 (m, 3H), 1.31 (d, *J* = 4.9 Hz, 3H), 1.21 - 1.10 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 155.4, 143.5, 141.4, 130.8, 129.5, 129.2, 128.5, 127.4, 118.2, 115.2, 98.1, 84.5, 78.4, 71.5, 68.8, 62.0, 40.8, 32.1, 29.2, 23.4, 23.1; HRMS *m/z*: [M + H$^+$] for $C_{24}H_{32}NO_6$, calcd, 430.2224; found, 430.2227.

[0124] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11b): Colorless amorphous solid (51% yield over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, 1H, *J* = 7.9, 13.9 Hz), 7.22 (d, 1H, *J* = 8.5 Hz), 7.07 (dd, 2H, *J* = 7.5, 10.5 Hz), 7.02 (dd, 1H, *J* = 2.8, 8.4 Hz), 6.99 (m, 1H), 6.91 (d, 1H, *J* = 2.7 Hz), 5.34 (d, 1H, *J* = 1.3 Hz), 5.28 (s, 1H), 4.20 (d, 1H, *J* = 2.2 Hz), 3.80 (m, 1H), 3.63 (s, 3H), 3.30 (d, 1H), 3.28 (m, 2H), 2.75 (t, 2H, *J* = 7.2 Hz), 2.63 (m, 2H, *J* = 15.9 Hz), 1.87 (s, 3H), 1.41 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 163.5-161.6 (d, *J* = 251 Hz) 155.0, 143.2 (d, *J* = 7.8 Hz), 142.1 (d, *J* = 1.8 Hz), 130.9, 130.1, 130.0 (d, *J* = 8.8 Hz), 124.8 (d, *J* = 2.8 Hz), 118.0, 116.0 (d, *J* = 8.8 Hz), 115.4, 114.3 (d, *J* = 21.6 Hz), 93.8, 84.2, 76.0, 71.3, 71.1, 62.0, 40.4, 32.0, 28.6, 23.3, 18.5; HRMS *m/z*: [M + H$^+$] for $C_{24}H_{31}FNO_6$, calcd, 448.2180; found, 448.2174. This material was determined to be 95.6% pure (retention time = 6.401) by HPLC (Phenomenex Luna C-18, 5 µm, 10 x 250 mm column eluting with 30% CH_3CN, 70% H_2O, flow rate 5.0 mL/min).

[0125] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-4'-fluoro-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11c): Colorless amorphous solid (57% yield over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, 2H, *J* = 5.4, 8.6 Hz), 7.18 (d, 1H, *J* = 8.5 Hz), 7.10 (t, 2H, *J* = 8.7 Hz), 7.01 (dd, 1H, *J* = 2.7, 8.5 Hz), 6.87 (d, 1H, J = 2.7 Hz), 5.54 (d, 1H, *J* = 2.2 Hz), 5.37 (t, 1H, *J* = 5.2 Hz), 4.20 (dd, 1H, *J* = 3.3, 9.1 Hz), 4.15 (m, 1H), 3.59 (s, 3H), 3.33 (d, 1H, *J* = 9.1 Hz), 3.26 (q, 2H, J = 6.9 Hz), 2.97 (s, 1H), 2.81 (s, 1H), 2.72 (t, 2H, J = 7.3), 1.87 (s, 3H), 1.36 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 163.2-161.3 (d, *J* = 250 Hz), 155.3, 142.3, 137.2 (d, *J* = 3.2 Hz), 130.8, 130.8, 130.7, 129.5, 118.1, 115.4, 115.3, 115.3, 97.9, 84.4, 78.3, 71.4, 68.7, 62.0, 40.6, 32.1, 29.1, 23.4, 23.1;

HRMS *m/z:* [M + Na^+] for $C_{24}H_{30}FN0_6$, calcd, 470.1955; found, 470.1958.

[0126] N-(2-(2'-chloro-5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11d): Colorless amorphous solid (62% yield over 2 steps); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (m, 1H), 7.31 (m, 2H), 7.21 (m, 2H), 7.03 (m, 1H), 6.86 (dd, 1H, *J* = 2.7, 13.2 Hz), 5.55 (m, 1H), 5.42 (s, 1H), 4.20 (dt, 1H, *J* = 3.0, 9.1 Hz), 4.14 (m, 1H), 3.59 (s, 3H), 3.33 (dd, 1H, *J* = 2.5, 9.1 Hz), 3.26 (ddt, 2H, *J* = 4.8, 6.8, 9.3 Hz), 3.11 (s, 1H), 2.93 (s, 1H), 2.58 (tq, 2H, *J* = 7.1, 14.2 Hz), 1.86 (s, 3H), 1.35 (d, 3H, *J*= 2.4 Hz), 1.20 (t, 3H, *J* = 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 155.2, 140.6, 140.5, 139.8, 133.4, 131.4, 130.5, 129.8, 126.9, 118.1, 117.9, 116.05, 97.9, 84.5, 78.4, 71.5, 71.4, 68.7, 62.1, 62.0, 40.2, 40.2, 32.1, 32.1, 29.3, 29.2, 23.5, 23.1, 23.0; HRMS m/z: [M + Na^+] for $C_{24}H_{30}ClNO_6Na$, 486.1659; found, 486.1652.

[0127] N-(2-(3'-chloro-5-(((3R,4S,SR)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11e): Colorless amorphous solid (55% yield over 2 steps); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.28 (m, 1H), 7.18 (m, 2H), 7.03 (dd, 1H, *J* = 2.7, 8.5 Hz), 6.87 (d, lH, *J* = 2.7 Hz), 5.55 (t, 1H, *J* = 2.5 Hz), 5.34 (m, 1H), 4.21 (dd, 1H, *J* = 3.1, 9.1 Hz), 4.16 (m, 1H), 3.60 (s, 3H), 3.34 (dd, 1H, *J* = 1.9, 9.1 Hz), 3.28 (m, 2H), 2.75 (dt, 4H, *J* = 7.3, 14.5 Hz), 1.88 (s, 3H), 1.37 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 155.4, 143.5, 142.0, 134.3, 131.0, 130.9, 129.8, 129.4, 128.5, 127.6, 127.4, 118.2, 115.7, 97.9, 84.6, 78.4, 71.5, 68.7, 62.1, 40.8, 32.1, 29.2, 23.6, 23.1; HRMS *m/z*: [M + Na^+] for $C_{24}H_{30}ClNO_6Na$, calcd, 486.1659; found, 486.1642.

[0128] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11f): Colorless amorphous solid (52% yield over 2 steps); ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, 1H, *J* = 7.7 Hz), 7.55 (t, 2H, *J* = 7.6 Hz), 7.49 (m, 1H), 7.23 (d, 1H, *J* = 8.5 Hz), 7.06 (dd, 1H, *J* = 2.7, 8.4 Hz), 6.89 (d, 1H, J = 2.7 Hz), 5.56 (d, 1H, *J* = 2.2 Hz), 5.31 (s, 1H), 4.19 (m, 2H), 3.60 (s, 3H), 3.34 (d, 1H, *J* = 9.1 Hz), 3.29 (dd, 2H, *J* = 7.0, 13.3 Hz), 2.72 (t, 2H, *J* = 7.3 Hz), 2.69 (s, lH), 2.64 (s, 1H), 1.87 (s, 3H), 1.37 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 155.4, 142.1, 141.9, 132.6, 131.0, 130.7 *(q, J = 31.5* Hz), 129.4, 129.0, 125.9 (q, *J* = 3.6, 7.2 Hz), 125.3, 124.2 (q, *J* = 3.6, 7.2 Hz), 123.1, 118.0, 115.8, 97.9, 84.4, 77.4, 71.4, 68.7, 62.0, 40.6, 32.1, 29.8, 29.2, 23.4, 23.0; HRMS *m/z:* [M + Na^+] for $C_{25}H_{30}F_3NO_6Na$, 520.1923; found, 520.1932. This material was determined to be 97.2% pure (retention time = 7.631) by HPLC (Phenomenex Luna C-18, 5 µm, 10 x 250 mm column eluting with 30% CH_3CN, 70% H_2O, flow rate 5.0 mL/min).

[0129] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-4'-(trifluoromethyl)-[1,1'-biphenyl)-2-yl)ethyl)acetamide (11g): Colorless amorphous solid (49% yield over 2 steps); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz,

2H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.09 - 7.03 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.90 (d, *J* = 2.7 Hz, 1H), 5.55 (d, *J* = 2.3 Hz, 1H), 5.33 (m, 1H), 4.26 -4.11 (m, 2H), 3.60 (s, 3H), 3.36 - 3.25 (m, 3H), 2.74 (t, *J*= 7.4 Hz, 2H), 2.56 (br s, 2OH), 1.88 (s, 3H), 1.37 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, MeOD) δ 173.1, 156.8, 146.9, 143.2, 132.1, 130.9, 130.7, 130.5, 130.2, 126.3, 126.2, 124.7, 118.5, 116.8, 100.1, 85.3, 79.5, 72.8, 69.5, 62.1, 41.7, 32.9, 29.2, 23.6, 22.5; HRMS m/z: [M + Na^+] for $C_{25}H_{30}F_3NO_6Na$, 520.1923; found, 520.1934.

[0130] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-2'-(methylthio)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11h): Colorless amorphous solid (63% yield over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, IH, *J* = 7.0 Hz), 7.27 (m, 3H), 7.09 (m, 1H), 7.01 (m, 1H), 6.87 (s, 1H), 5.64 (s, 1H), 5.54 (m, 1H), 4.16 (m, 2H), 3.32 (d, 2H, *J* = 8.8 Hz), 3.27 (m, 2H), 3.06 (s, 1H), 2.56 (t, 2H, *J* = 6.2 Hz), 2.36 (d, 3H, *J* = 7.6 Hz), 1.83 (s, 3H), 1.33 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 155.1, 155.0, 141.0, 138.9, 130.5, 130.1, 129.8, 128.4, 124.6, 124.2, 118.3, 116.2, 115.9, 97.9, 84.5, 78.3, 71.5, 68.7, 62.0, 53.6, 40.1, 31.7, 29.3, 23.3, 15.3, 15.2; HRMS *m/z*: [M + Na^+] for $C_{25}H_{33}NO_6SNa$, calcd, 498.1926; found, 498.1925. This material was determined to be 95% pure (retention time = 7.465) by HPLC (Phenomenex Luna C-18, 5 µm, 10 x 250 mm column eluting with 30% CH_3CN, 70% H_2O, flow rate 5.0 mL/min).

[0131] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-2'-methoxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11i): Colorless amorphous solid (41% yield over 2 steps); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (ddd, 1H, *J* = 1.8, 7.6, 8.2 Hz), 7.18 (d, 1H, J = 8.3 Hz), 7.12 (t, 1H, *J* = 5.8 Hz), 7.02 (m, 3H), 6.87 (dd, 1H, *J* = 2.3, 11.3 Hz), 5.54 (s, 1H), 5.39 (s, 1H), 4.21 (dt, 1H, *J* = 3.3, 9.0 Hz), 4.15 (m, 1H), 3.77 (d, 3H, *J* = 6.9 Hz), 3.60 (s, 3H), 3.33 (d, 1H, *J* = 8.7 Hz), 3.29 (m, 2H), 2.73 (s, 1H), 2.66 (s, 1H), 2.60 (dd, 2H, *J* = 6.5, 12.8 Hz), 1.84 (s, 3H), 1.37 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 156.4, 155.2, 139.9, 131.2, 130.8, 130.2, 130.0, 129.2, 120.9, 118.6, 118.3, 115.7, 115.2, 111.4, 111.2, 98.0, 97.9, 84.5, 78.2, 71.4, 68.7, 62.0, 55.9, 55.9, 40.3, 31.9, 30.2, 29.3, 29.2, 23.4, 23.1; HRMS *m/z:* [M + H^+] for $C_{25}H_{34}NO_7$, calcd, 460.2335; found, 460.2336. This material was determined to be 96.1% pure (retention time = 5.057) by HPLC (Phenomenex Luna C-18, 5 µm, 10 x 250 mm column eluting with 30% CH_3CN, 70% H_2O, flow rate 5.0 mL/min).

[0132] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3'-methoxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11j): Colorless amorphous solid (53% yield over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.02-6.96 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.92 - 6.83 (m, 4H), 6.81 (d, *J* = 1.5 Hz, 2H), 5.54 (d, *J* = 2.2 Hz, 1H), 5.45 (s, 1H), 4.25 - 4.16 (dd, *J* = 9.1, 3.2 Hz, 1H), 4.17 - 4.10 (dd, *J* = 3.3, 2.2 Hz, 1H), 3.82 (s, 3H), 3.58 (s, 3H), 3.39 - 3.20 (m, 3H), 3.24 (br s, OH), 2.97 (br s, OH), 2.75 (t, *J* = 7.1 Hz, 2H), 1.85 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

170.4, 159.5, 155.3, 143.3, 142.8, 130.8, 129.5, 129.5, 121.7, 118.0, 115.3, 115.1, 112.7, 98.1, 84.5, 78.4, 71.5, 68.7, 62.0, 55.4, 40.9, 32.0, 29.1, 23.4, 23.1; HRMS *m/z:* [M + H^+] for $C_{25}H_{34}NO_7$, calcd, 460.2335; found, 460.2322.

[0133] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3'-methyl-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11k): Colorless amorphous solid (44% yield over 2 steps); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.27 (m, 1H), 7.16 (d, *J* = 6.6 Hz, 2H), 7.10 - 7.04 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.88 (s, 1H), 5.55 (s, 1H), 5.41 (s, 1H), 4.25 - 4.08 (m, 2H), 3.57 (s, 3H), 3.37 - 3.20 (m, 5H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.39 (s, 3H), 1.83 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.3, 143.6, 141.3, 138.1, 130.8, 130.0, 129.5, 128.3, 128.1, 126.3, 118.1, 115.1, 98.1, 84.5, 78.4, 71.5, 68.7, 62.0, 40.9, 32.0, 29.2, 23.4, 23.1, 21.7; HRMS *m/z*: [M + H^+] for $C_{25}H_{33}NO_6Na$, calcd, 466.2206; found, 466.2203.

[0134] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-3'-(morpholinomethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11l): Colorless amorphous solid (47% yield over 2 steps); ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 - 7.29 (m, 2H), 7.27 (m, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.04 - 6.99 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.91 (d, *J* = 2.7 Hz, 1H), 5.55 (d, *J* = *2.4* Hz, 1H), 5.35 (s, 1H), 4.26 - 4.18 (dd, *J* = 9.0, 3.3 Hz, 1H), 4.15 (t, J = 2.8 Hz, 1H), 3.72 (t, J = 4.7 Hz, 4H), 3.59 (s, 3H), 3.56 (s, 2H), 3.34 (d, *J* = 9.0 Hz, 1H), 3.30 - 3.21 (q, *J* = 6.7 Hz, 2H), 2.75 (t, *J* = 7.1 Hz, 2H), 2.58- 2.41 (m, 6H), 1.85 (s, 3H), 1.36 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 143.4, 141.5, 137.8, 130.9, 130.1, 129.6, 128.5, 128.3, 128.2, 118.2, 115.3, 98.1, 84.6, 78.4, 71.5, 68.8, 67.1, 63.5, 62.0, 53.8, 40.7, 32.2, 29.2, 23.5, 23.2; HRMS (FAB) *m/z:* [M + Na^+] for $C_{29}H_{40}N_2O_7Na$, calcd, 551.2728; found, 551.2734.

[0135] N-(2-(5-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-4'-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamide (11m):

[0136] After cyclic carbonate hydrolysis following the same procedure as compound **11a-p,** the crude TBS protected compound was dissolved in THF (2 mL) and tertrabutylammonium fluoride (1.5 eq.) was added dropwise at 0 °C under argon atmosphere. After 1 h the reaction was quenched with water and extracted with EtOAc (3 x 10 mL); combined organic fractions were washed with saturated aqueous sodium chloride, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2; 10:1, DCM:acetone) to afford acetamide **11m** as a amorphous solid (40% yield over 3 steps). ^1H NMR (500 MHz, MeOD) δ 7.20 (d, *J* = 8.4 Hz, 1H), 7.15 - 7.08 (d, *J* = 8.4 Hz, 2H), 6.96 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.85 - 6.79 (m, 3H), 5.45 (d, *J* = 2.4 Hz, 1H), 4.12 (dd, *J* = 9.3, 3.3 Hz, 1H), 3.96 (t, *J* = 2.8 Hz, 1H), 3.59 (s, 3H), 3.21 (d, *J* = 9.3, Hz, 1H), 3.16 (dd, *J* = 8.5, 6.5 Hz, 2H), 2.70 (dd, *J* = 8.5, 6.5 Hz, 2H), 1.84 (s, 3H), 1.32 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, MeOD) δ 173.1, 157.7, 156.6, 144.7, 134.0, 131.7, 131.2, 131.1, 118.9, 116.0, 115.7, 100.1,

85.4, 79.4, 72.8, 69.5, 62.1, 41.8, 33.0, 29.2, 23.6, 22.5; HRMS (FAB) *m/z:* [M + Na^+] for $C_{24}H_{31}NO_7Na$, calcd, 468.1998; found, 468.1999.

[0137] N-(2-(benzo[d][1,3]dioxol-5-yl)-4-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)phenethyl)acetamide (11n): Colorless amorphous solid (51% yield over 2 steps); ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 7.00 - 6.96 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.88 (d, *J* = 2.6 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.76 (d, *J* = 1.6 Hz, 1H), 6.74 - 6.69 (m, 1H), 6.01 (s, 2H), 5.54 (d, *J* = 2.4 Hz, 1H), 5.40 (s, 1H), 4.21 (dd, *J* = 9.1, 3.3 Hz, 1H), 4.14 (t, *J* = 2.7 Hz, 2H), 3.58 (s, 3H), 3.33 (d, *J* = 9.1 Hz, 1H), 3.30 - 3.23 (q, *J* = 6.9 Hz, 2H), 3.11 (br s, OH), 2.92 (br s, OH), 2.74 (t, *J* = 7.2 Hz, 2H), 1.86 (s, 3H), 1.34 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 155.4, 147.7, 147.0, 143.1, 135.3, 130.8, 129.7, 122.6, 118.3, 115.2, 109.9, 108.4, 101.3, 98.1, 84.6, 78.4, 71.5, 68.8, 62.0, 40.8, 32.1, 29.2, 23.4, 23.2; HRMS (FAB) *m/z:* [M + Na^+] for $C_{25}H_{31}NO_8Na$, calcd, 496.1947; found, 496.1940. This material was determined to be 98.4% pure (retention time = 4.384) by HPLC (Phenomenex Luna C-18, 5 µm, 10 x 250 mm column eluting with 40% CH_3CN, 60% H_2O, flow rate 5.0 mL/min).

[0138] N-(4-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-2-(pyridin-3-yl)phenethyl)acetamide (11o): Colorless amorphous solid (37% yield over 2 steps); ^1H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 3.9 Hz, 1H), 8.49 (s, 1H), 7.60 (m, 1H), 7.35 (dd, *J* = 7.8, 4.5 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.05 - 6.99 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.85 (d, *J* = 2.6 Hz, 1H), 5.52 (d, *J* = 2.4 Hz, 1H), 5.36 (s, 1H), 4.14 (dd, *J* = 3.4, 9.1 Hz, 1H), 4.10 (t, *J* = 2.7 Hz, 1H), 3.59 (s, 3H), 3.31 (d, *J* = 9.0 Hz, 1H), 3.27 - 3.20 (m, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 1.86 (s, 3H), 1.33 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 155.5, 149.8, 148.7, 139.5, 136.8, 131.1, 131.0, 130.6, 129.8, 123.4, 118.3, 118.2, 116.1, 98.0, 84.5, 78.5, 71.4, 68.7, 62.1, 40.7, 32.2, 29.2, 23.5, 23.1; HRMS (FAB) *m/z:* [M + Na^+] for $C_{23}H_{31}N_2O_6$, calcd, 431.2182; found, 431.2194.

[0139] N-(4-(((3R,4S,5R)-3,4-dihydroxy-5-methoxy-6,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-2-(pyridin-4-yl)phenethyl)acetamide (11p): Colorless amorphous solid (42% yield over 2 steps); ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 - 8.63 (dd, *J* = 5.7, 3.9 Hz, 2H), 7.27 - 7.23 (m, 3H), 7.11 - 7.03 (m, 1H), 6.86 (t, *J* = 2.8 Hz, 1H), 5.55 (d, *J* = 2.3 Hz, 1H), 5.41 - 5.31 (m, 2H), 4.26 - 4.13 (m, 2H), 4.05 (d, *J* = 6.9 Hz, 1H), 3.61 (s, 3H), 3.36 - 3.25 (m, 2H), 2.78 - 2.71 (dd, *J* = 8.3, 6.8 Hz, 2H), 1.90 (s, 3H), 1.39 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 155.5, 149.8, 140.5, 131.4, 129.1, 124.4, 117.9, 116.3, 98.0, 94.1, 84.5, 71.5, 71.4, 68.7, 62.1, 40.7, 32.2, 29.2, 28.8, 23.5, 23.1, 18.7; HRMS (FAB) m/z: [M + Na^+] for $C_{23}H_{30}N_2O_6Na$, calcd, 453.2001; found, 453.1972.

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Patentkrav

1. Forbindelse, der er valgt blandt:

N-(2-(5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9a)

N-(2-(3'-fluor-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9b)

N-(2-(4'-fluor-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9c)

N-(2-(2'-chlor-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9d)

N-(2-(3'-chlor-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9e)

N-(2-(5-hydroxy-3'-(trifluormethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9f)

N-(2-(5-hydroxy-4'-(trifluormethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9g)

N-(2-(5-hydroxy-2'-(methylthio)-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9h)

N-(2-(5-hydroxy-2'-methoxy-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9i)

N-(2-(5-hydroxy-3'-methoxy-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9j)

N-(2-(5-hydroxy-3'-methyl-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9k)

N-(2-(5-hydroxy-3'-(morpholinomethyl)-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9l)

N-(2-(4'-((tert-butyldimethylsilyl)oxy)-5-hydroxy-[1,1'-biphenyl]-2-yl)ethyl)acetamid (9m)

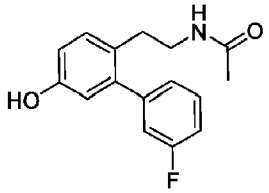
N-(2-(benzo[d][1,3]dioxol-5-yl)-4-hydroxyphenethyl)acetamid (9n)

N-(4-hydroxy-2-(pyridin-3-yl)phenethyl)acetamid (9o)

N-(4-hydroxy-2-(pyridin-4-yl)phenethyl)acetamid (9p)

eller et farmaceutisk acceptabelt salt deraf.

2. Forbindelse ifølge krav 1, der yderligere er defineret som:



eller et farmaceutisk acceptabelt salt deraf.

DRAWINGS

Drawing

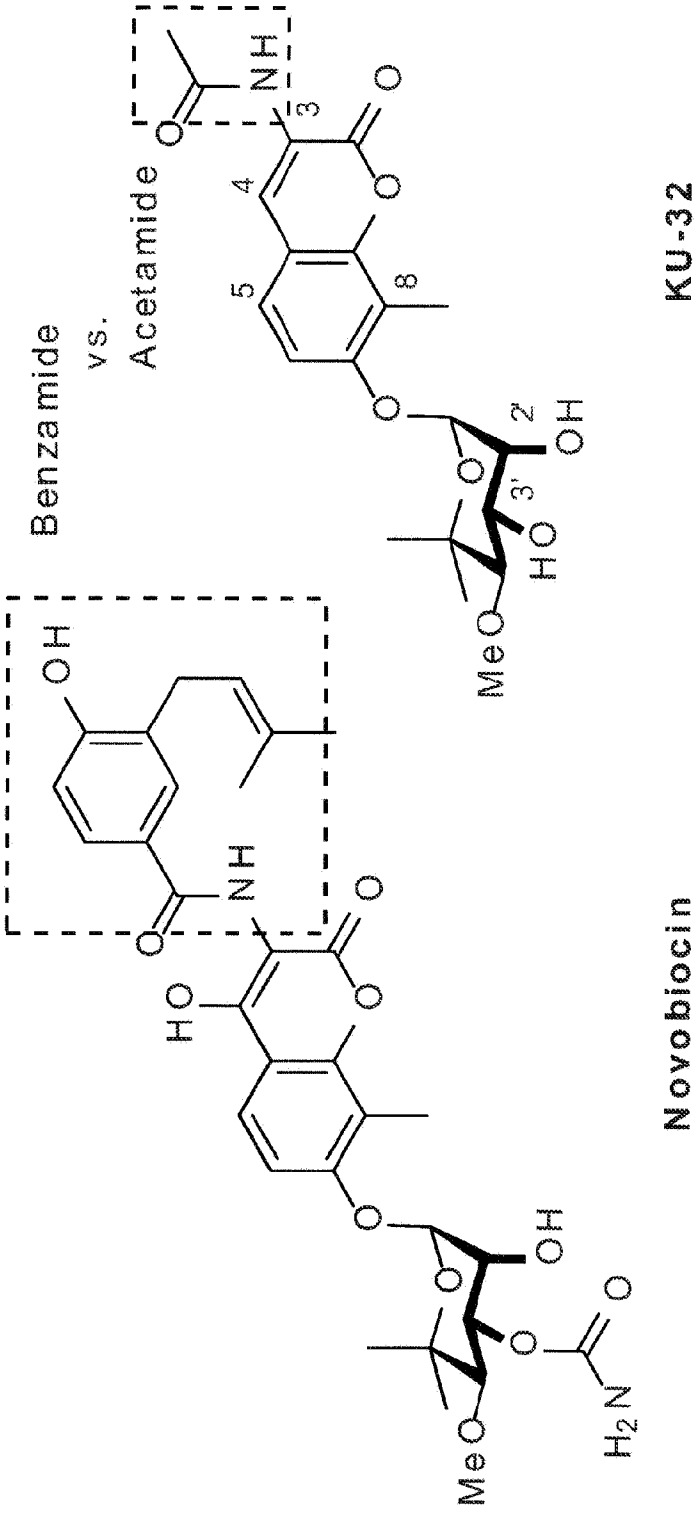


FIG. 1

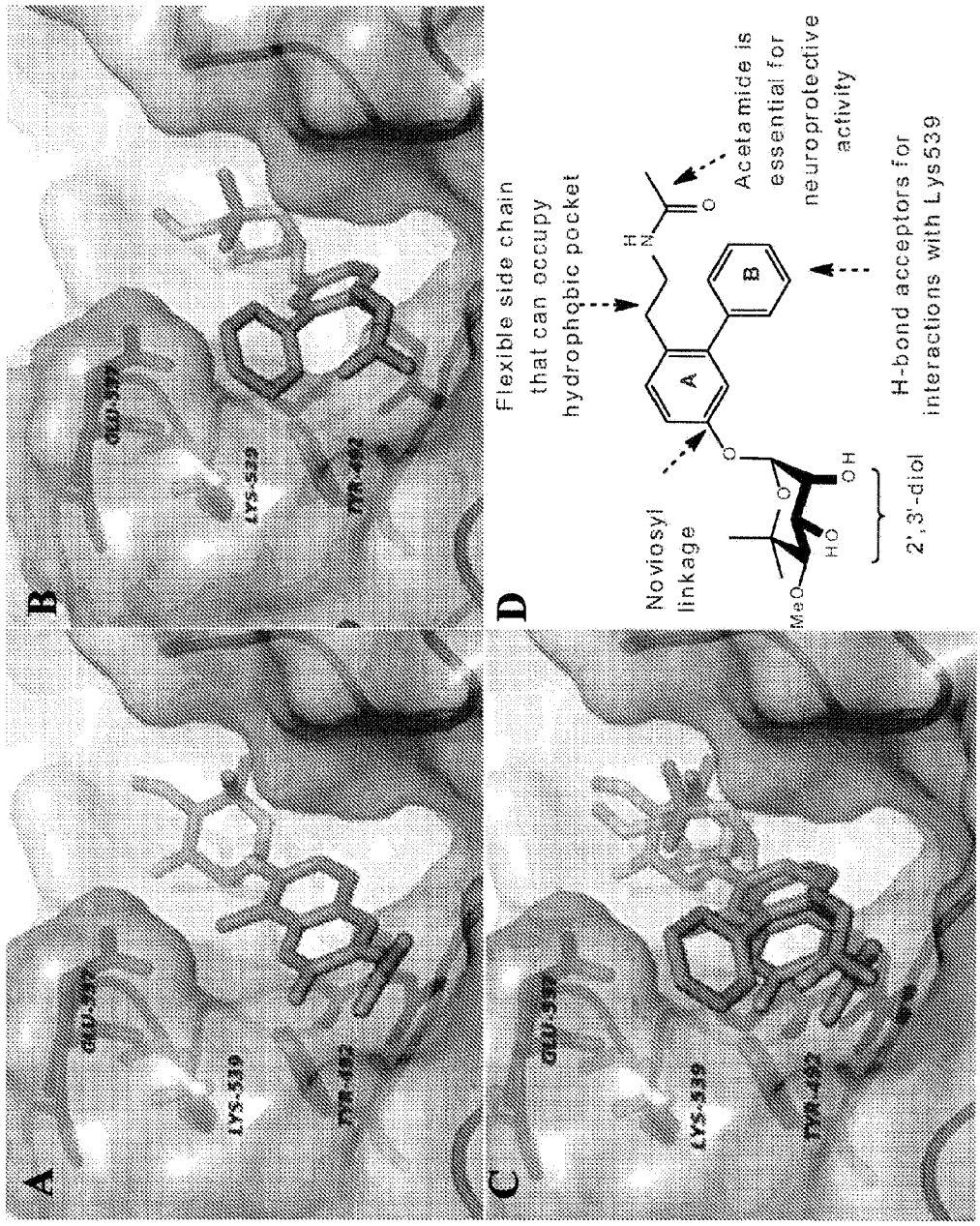

A
GLU-337
LYS-339
TYR-462
B
GLU-337
LYS-339
TYR-462
C
GLU-337
LYS-339
TYR-462
D
Flexible side chain
that can occupy
hydrophobic pocket
Noviosyl
linkage
Acetamide is
essential for
neuroprotective
activity
H-bond acceptors for
interactions with Lys539
2',3'-diol
A
B
MeO
HO
OH

FIG. 2

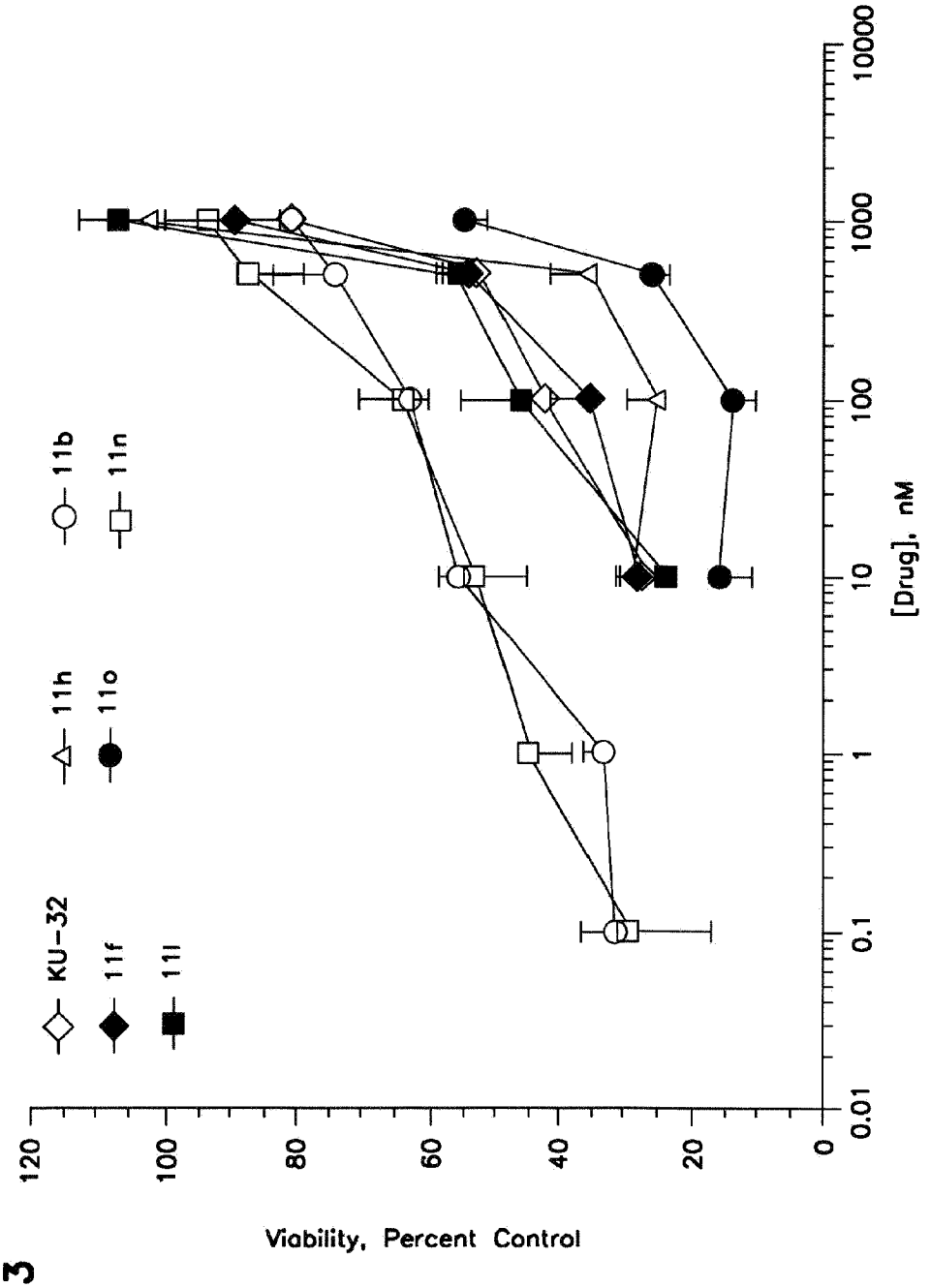

KU-32
11b
11f
11h
11l
11n
11o
120
100
80
60
40
20
0
0.01
0.1
1
10
100
1000
10000
[Drug], nM
Viability, Percent Control

FIG. 3

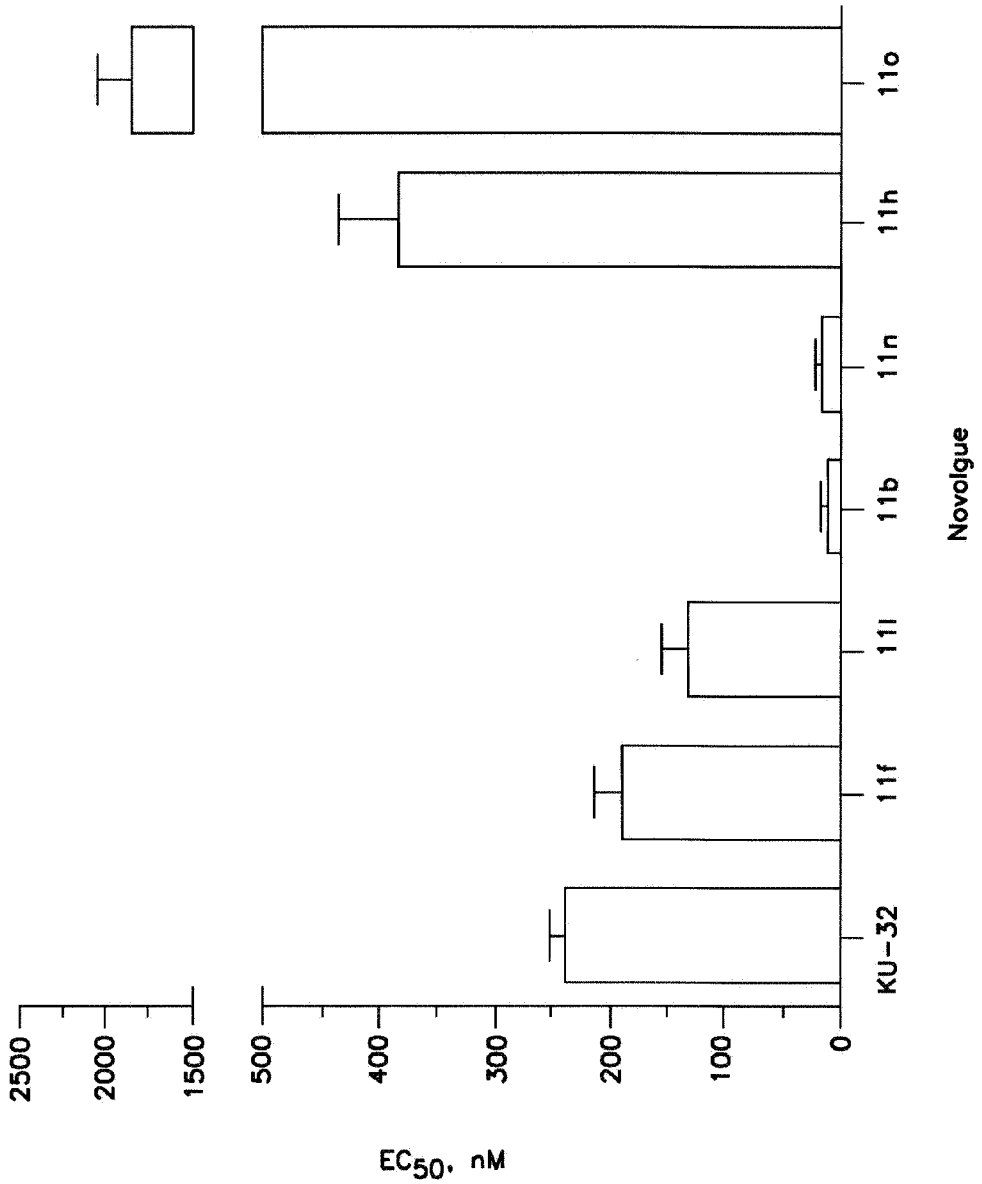
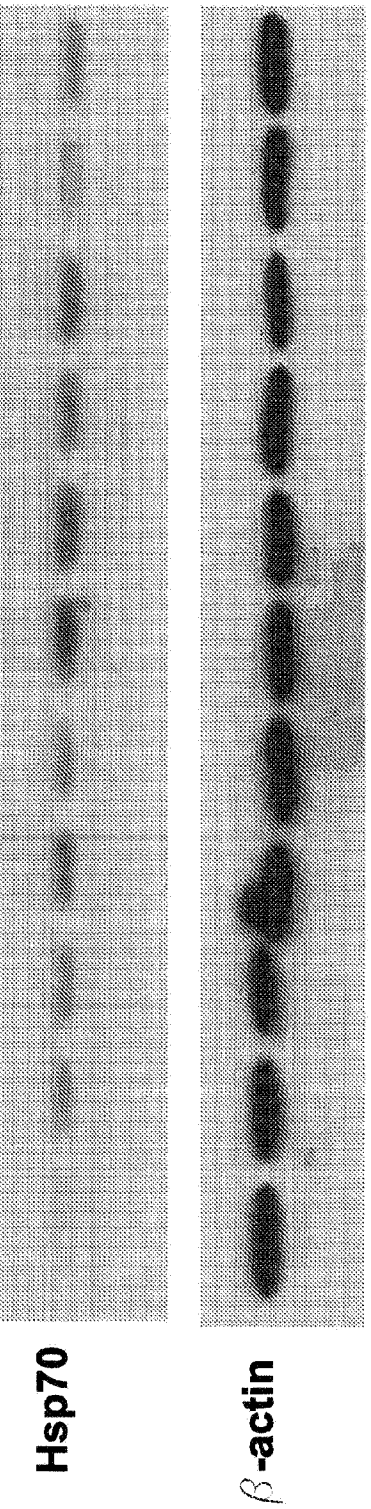

2500
2000
1500
500
400
300
200
100
0
EC50, nM
KU-32
11f
11l
11b
11n
11h
11o
Novolgue

FIG. 4

FIG. 5


10 nM
100 nM
1000 nM
KU-32 11n 11b
KU-32 11n 11b
KU-32 11n 11b
Cntrl
Cntrl
Hsp70
β-actin