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Discovery of a novel 2,3,11,11a-tetrahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4(6*H*)-dione series promoting neurogenesis of human neural progenitor cells

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ABSTRACT

A novel neurogenic compound (**1**), discovered from a mouse neural progenitor cell (NPC) screen, showed profound neurogenic effect on human NPCs. Synthesis and SAR of this novel 2,3,11,11a-tetrahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-1,4(6*H*)-dione series are described. Compound **20** is brain penetrable in rodents, and promotes neurogenesis in wild type mice, therefore it is a good tool molecule to study neurogenesis induction as a potential treatment for conditions associated with neurogenesis impairment diseases.

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The stimulation of neuronal formation through the process of neurogenesis has been considered as a potential therapeutic approach for devastating genetic disorders such as Down Syndrome[1] and Huntington's Disease,[2] neurodegenerative diseases such as Alzheimer's Disease[3] and Parkinson's Disease,[4] depression,[5] and central nervous system injuries such as traumatic brain injury, stroke, and spinal cord injury.[6] This approach has been endorsed by the strong evidence of neurogenesis in the adult human brain throughout life[7] and successful identification of many small molecules in vitro and in vivo to promote neurogenesis.[8] In addition, small molecules have been progressed to clinical trials for some of above mentioned diseases.[9]

Neurogenesis screens have been developed with both rodent NPCs and human NPCs to identify small molecules that can promote either proliferation, or differentiation, or both.[10] At GSK, we have developed a 384-well high throughput screen based on mouse NPCs (mNPCs) as previously described.[11] We have also developed a 96-well medium throughput screen using human H9-derived NPCs (H9 NPCs) to potentially improve human translation for any hit molecule or target identified.[12,13] This assay was validated by numerous hits reported previously, such as GSK3β inhibitors and Gamma Secretase inhibitors (GSI).[14] Isx-9,[10] a neurogenic compound identified from a screen using rat hippocampal NPCs, also promotes neurogenesis in H9 NPC assay (data not shown).

Compound **1** (Fig. 1) was originally a weak hit from mNPC screen. Compared to DMSO control, it induced about 1.2 fold increase in the percentages of cells expressing the neuronal marker βIII tubulin (Tuj1), as stained by a Tuj1 antibody (Fig. 2). However, it showed more profound neurogenic effect on human H9 NPCs, inducing about 1.8 fold increase in % Tuj1+ cells. This neurogenic effect was confirmed by a dose-dependent increase in Tuj1 protein by Western blotting[15] as shown in Figure 3.

Although compound **1** was originated from a legacy Apo B100 inhibition program,[16] the molecular target, microsomal triglyceride transfer protein (MTP) appears irrelevant to the neurogenic effect because MTP inhibitory potency does not correlate with neurogenic effect on H9 NPCs (data not shown).

In an attempt to identify its molecular target, compound **1** was profiled against a panel of 340 kinases (Reaction Biology Company, data not shown) but had no inhibitory activity at 10 μM. It also

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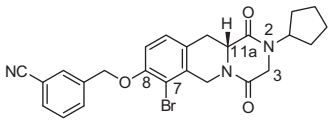

Figure 1. Novel neurogenic compound **1**.

showed no significant activity in a panel of about 160 G protein-coupled receptor (GPCR) targets (Millpore GPCR panel, data not shown) in either agonism or antagonism assays. Although the identity of the target remains unknown, compound **1** is brain penetrable in a mouse pharmacokinetics studies with a brain/blood plasma ratio of 1:2, therefore, a good lead molecule for further optimization. Herein, we report the synthesis and structure–activity relationship (SAR) of this novel neurogenic chemical series.

Taking compound **1** as a lead molecule, we explored SAR at various positions of the molecule. Modifications around *N*-2position were accomplished by the similar chemistry described previously.[16]

Modifications at *C*-8 position also used similar chemistry for ethers, but different when *C*-8 is linked with an N or a C atom. As shown in Scheme 1, methylation of commercially available acid **2** catalyzed by thionyl chloride in methanol at reflux afforded methyl ester **3**, which was converted to chloroacetamide **4** with chloroacetyl chloride in the presence of sodium carbonate in chloroform at 55 °C. Intermediate **4** was treated with cyclohexanamine under basic conditions in ethanol at reflux to close the ring. Nitro group of pyrazinone was reduced to aniline **6** with hydrazine catalyzed by Raney Ni in a mixture of methylene chloride and methanol at room temperature. Reductive amination of aniline **6** and 3-formylbenzinitrile with sodium cyanoborohydride afforded compound **7**. Under the same conditions, methyl or ethyl was introduced to give compound **8** or **9**.

C-8 position carbon linked analog **13** was prepared as depicted in Scheme 2. Intermediate **4** was treated with cyclopentanamine under basic condition in ethanol at reflux to close the ring. The nitro group of compound **10** was reduced with hydrogen gas catalyzed by 10% Pd/C in methanol to an aniline, which was oxidized

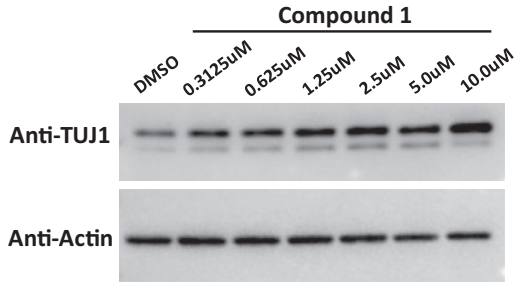

Figure 3. Compound **1** increased Tuj1 protein expression in H9 NPCs dose-dependently after 5 days in culture.

by *t*-BuONO in the presence of copper bromide in acetonitrile to afford bromide **11**. One carbon homologation was achieved by first a Pd(0) mediated coupling reaction of bromide **11** with methyl acrylate using palladium acetate and tri-*o*-tolylphosphine in the presence of triethylamine in DMF at 130 °C. Then an oxidative cleavage of the double bound with OsO_4, $NaIO_4$ in a mixture of acetone and water afforded an aldehyde, which was reduced to a hydroxyl group. Chlorination of this hydroxyl group with thionyl chloride in methylene chloride at reflux afforded chloride **12**, which was replaced with 3-hydroxylbenzonitrile in the presence of potassium carbonate in acetonitrile at 80 °C to provide final compound **13**.

Small groups such as methyl, methoxy and hydroxymethyl were introduced to *C*-3 position as depicted in Scheme 3. Similar to previously described in Scheme 1, acetylation of compound **3** with α-substituted acetylchlorides **14** provided various α-substituted acetamides **15**, followed by the ring closure with cyclopentanamine to give pyrazinones **16**. Reduction of nitro group afforded the anilines, which were oxidized to the phenol with sodium nitrite in the presence of sulfuric acid and urea in water at 0 °C followed by heating the reaction mixture to 60 °C for 5 h. The phenols were treated with 3-(bromomethyl)benzonitrile in the presence of potassium carbonate in acetone at 60 °C provided 3-substituted analogs **17** and **18**, while one extra step to remove

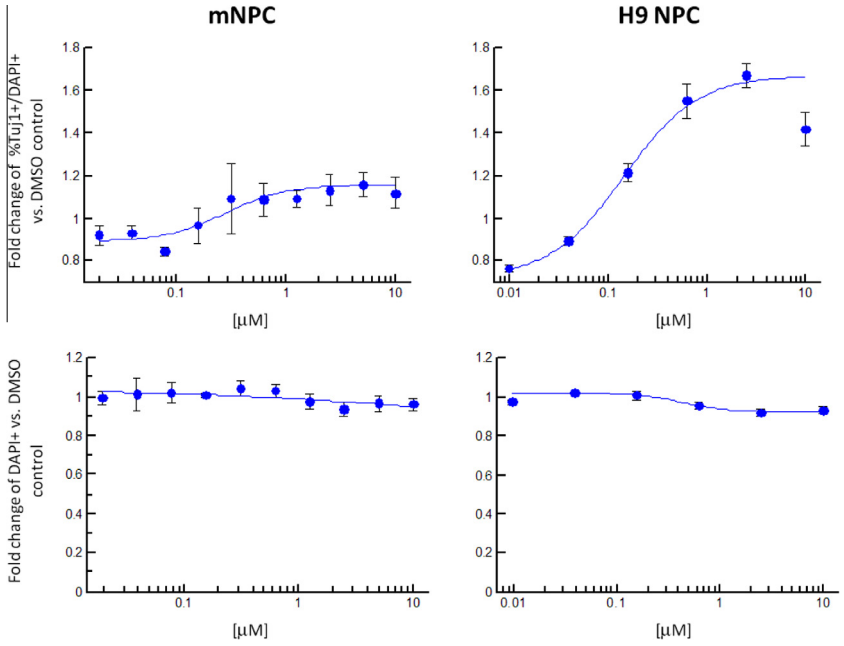

Figure 2. Neurogenic effects of compound **1** in mouse NPC (left column) and human NPC (H9 NPC; right column) as measured by increases in Tuj1+ cells in a high content imaging assay (upper row). All doses of the compound were devoid of cellular toxicity (lower row).

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