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Design and Synthesis of Novel Small-molecule Inhibitors of the Hypoxia Inducible Factor Pathway

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Abstract

Hypoxia, a reduction in partial oxygen pressure, is a salient property of solid tumors. Hypoxia drives malignant progression and metastasis in tumors and participates in tumor resistance to radio- and chemotherapies. Hypoxia activates the hypoxia-inducible factor (HIF) family of transcription factors, which induce target genes that regulate adaptive biological processes such as anaerobic metabolism, cell motility and angiogenesis. Clinical evidence has demonstrated that expression of HIF-1 is strongly associated with poor patient prognosis and activation of HIF-1 contributes to malignant behavior and therapeutic resistance. Consequently, HIF-1 has become an important therapeutic target for inhibition by small molecules. Herein, we describe the design and synthesis of small molecules that inhibit the HIF-1 signaling pathway. Many of these compounds exhibit inhibitory activity in the nanomolar range. Separate mechanistic studies indicate that these inhibitors do not alter HIF-1 levels, but interfere with the HIF-1α/HIF-1β/p300/CBP complex formation by interacting with p300 and CBP.

Keywords

drug development; cancer; hypoxia; hypoxia-inducible factor; transcription factor

Introduction

Hypoxia is a hallmark of solid tumors, largely due to inadequate vascularization, and is characterized by a reduction in the partial oxygen pressure in cells or tissue.[1-3] Tumor hypoxia has been shown to reduce the effectiveness of radiation and chemotherapy.[4, 5] The Hypoxia Inducible Factor (HIF) family are the primary transcription factors activated by hypoxia and are responsible for orchestrating a number of cellular responses such as angiogenesis and glycolysis that help tumor cells adapt to hypoxic conditions.[6] HIFs are a basic helix-loop-helix heterodimers composed of – an oxygen sensitive HIF-α subunit and a constitutively expressed HIF-1β.[7] The levels of HIF-1α are determined by intracellular oxygen concentration. Under normoxic conditions, HIF-α is continually degraded by

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ubiquitination and proteosomal degradation. Degradation occurs when HIF-1α is hydroxylated at Pro 564 and Pro 402 located at its oxygen-dependent degradation domain (ODDD). This process is facilitated by a family of prolyl hydroxylases (PHDs) that require oxygen, iron and 2-oxoglutarate as the co-substrate to hydroxylate the specific amino acid residues.[8-10] After hydroxylation, HIF-1α binds to the von Hippel-Lindau protein (pVHL) which is part of an E3-ubiquitin ligase complex that marks HIF-1 for proteasomal degradation through ubiquitination.[11, 12] Oxygen is required for the function of PHDs, therefore, under hypoxic conditions, HIF-1α is stabilized, accumulates and translocates to the nucleus where it interacts with HIF-1β to form the active transcription factor, HIF-1.[11, 12] HIF-1 then specifically activates the transcription of over 100 selected genes by binding to a hypoxia-responsive element (HRE) on the gene regulatory DNA sequence.[13, 14] The genes targeted for activation include those that encode enzymes that carry out anaerobic glycolysis, erythropoietin, a hormone that triggers red blood cell production, and vascular endothelial cell growth factor (VEGF), a powerful activator of new capillary formation, and major driver of tumor angiogenesis.[15, 16] Elevated levels of HIF-1α have been found in many human cancers [17-19] and this is associated with poor response to treatment and patient mortality.[17, 20-23] As a result, the HIF pathway has been exploited for the development of new cancer therapies; [24-27] including the development of small molecule inhibitors targeting HIF-1.[28-30]

To identify novel compounds for HIF-1 pathway inhibition, some 10,000 compounds from a 2,2-dimethylbenzopyran combinatorial library were screened.[31] The benzopyran moiety was chosen because it appears in more than 4,000 natural products and is considered to be lipophilic enough to cross the blood-brain barrier.[32] The library was screened using a human glioma cell line containing an HRE-alkaline phosphatase reporter gene.[33, 34] **1** (KCN-1) was identified as a potent inhibitor.[35] Further tests in animal models for cancer have shown its ability to inhibit cancer growth.[36, 37] Separate mechanistic studies indicate that **1** does not alter HIF-1 levels, but interferes with the ability of the HIF-1α/HIF-1β complex to associate with transcriptional co-factors p300/(CREB-binding protein) CBP by interacting directly with the CH1 domain of p300 and CBP.[36] p300/CBP are transcription co-activating proteins. They interact with various transcription factors such as HIF-1 and increase the expression of their target genes. Such a mechanism is different from all known HIF-1 inhibitors, and may lead to significant insight into novel approaches to control solid tumor. We desire to improve potency. Our goal was to build an SAR profile around the lead compound **1** in search of more potent and soluble small-molecule inhibitors of HIF-1-mediated transcription. This will help our effort in addressing the poor solubility of **1** and its need for cremophor:ethanol in formulation, which is associated with toxicity.[38]

Results and Discussion

Design

The modification of compound **1** was approached in a systematic manner, in which the molecule was divided into four regions as shown in Figure 1. In all, seven classes of compounds were designed and synthesized (Figure 2). The sulfonamide group of Region I was either eliminated (Class 1) or replaced by an amide group (Class 7). Regions II and III were modified with several alkyl and aryl substitutions; using known synthetic procedures (Class 2). Namely, the aldehyde derivative of the core structure underwent reductive amination with a variety of alkyl and aryl primary amines to provide modifications to region II. Then, sulfonylation of the resulting secondary amines with various sulfonyl chlorides allowed modifications to region III. The benzopyran ring of region IV was probed to determine the influence of subtle and major modifications of this region on activity. The first modification was the replacement of the *gem*-dimethyl group of region IV with the 2-ethyl-2-methyl group (class 3). The benzopyran ring of region IV was also replaced with a

quinoline ring (class 4) and benzofuran ring (class 5). Finally, the benzopyran ring of region IV was replaced with a pyranopyridine fused ring to give classes **6a, 6b** and **6c**.

Chemistry

Class 1: Benzopyran analogues A—For the synthesis of the class 1 analogues, the benzopyran moiety was retained, while the sulfonyl and 3,4-dimethoxyphenyl groups were eliminated. To afford these analogues, the aldehyde derivative of the benzopyran moiety was synthesized followed by reductive amination and methylation of the resulting secondary amine (in some cases).

The synthesis of class I analogues began with 2,2-dimethyl-2H-chromene-6-carbaldehyde that was synthesized according to literature procedures.[39] Reductive amination of 2,2-dimethyl-2H-chromene-6-carbaldehydewith several primary amines gave analogues **2**. Methylation of secondary amine **2** with MeI and NaH generated analogues **3** (Scheme 1)

Next, modifications were separately made to region II (**5a – 5i**) and then to region III (**5j – 5m**) of compound **1** with various alkyl and aryl substituents, in order to probe their effect on activity. Reductive amination of 2,2-dimethyl-2H-chromene-6-carbaldehyde with various aryl or alkyl amines afforded compound **4** that was subsequently converted to sulfonamides with various sulfonylchlorides to give analogues **5** (Scheme 2).

Class 3: 2-Ethyl-2-methyl benzopyran analogues—Next, class 3 analogues were generated that involved a slight modification to the benzopyran portion (Region IV) of **1**. The ethyl group replaced one of the gem-dimethyl groups on the benzopyran ring (Scheme 3). For the synthesis of these analogues, *O*-alkylation of 4-hydroxybenzophenone **6** with 3-methylpentyn-3-ol afforded compound **7**. Claisen rearrangement and re-aromatization of **7** by microwave irradiation yielded compound **8**. Reductive amination of aldehyde **8** gave the secondary amine **9** that was converted to the corresponding sulfonamide **10** with 3, 4-dimethoxybenzenesulfonyl chloride.

Class 4: Quinoline analogues—The next modification to region IV was the replacement of the benzopyran ring with another fused ring system - quinoline (Scheme 4). Commercially available quinoline aldehyde **11** was subjected to reductive amination, followed by sulfonylation to afford compound **13** in 45% yield.

Class 5: Benzofuran analogues—Additionally, the 2,2-dimethylbenzopyran ring (Region IV) of **1** was replaced with a 2,2-dimethylbenzofuran ring (Scheme 5). Commercially available 2,2-dimethyl-2,3-dihydrobenzofuran-5-carbaldehyde **14** was subjected to reductive amination with various primary amines to give compound **15** and then sulfonylation with 3,4-dimethoxybenzenesulfonyl chloride to give analogues **16**.

Class 6: Pyranopyridines—We also replaced one of the carbons on the aromatic portion of the benzopyran ring with nitrogen to afford pyranopyridine analogues. The pyridine nitrogen was separately placed in each of the three available positions on the benzopyran ring. It was envisioned that these compounds would provide increased water solubility and additional interaction points and therefore increased activity. The incorporation of a nitrogen atom may also decrease the electron density and make it more stable toward oxidative metabolism.

The first of these compounds was the pyrano(2,3b)pyridines **20**. The 2H-pyrano-[2,3b]-pyridine core **17** was synthesized as previously described.[40] Formylation of **17** with BuLi and DMF gave compound **18**. Reductive amination with aniline (**19a**) or cyclohexylamine

(**19b**) followed by sulfonylation with 3,4-dimethoxybenzesulfonyl chloride afforded compounds **20a** and **20b** (Scheme 6).

The second set of analogues in this class was the pyrano(3,2b)pyridines that were prepared using the following procedure: *O*-alkylation of commercially available 2-bromo-5-hydroxypyridine **22** followed by Claisen rearrangement and formylation gave compound **24** with a 23% overall yield for the two steps. Subsequent reductive amination of **24** and then reaction of secondary amine **25** with various sulfonyl chlorides afforded analogues **26** (Scheme 7).

The final pyranopyridine derivative was the pyrano(2,3c)pyridines (class 6c). To synthesize these analogues, 2-hydroxy-5-methyl pyridine **27** was brominated to afford compound **28**.[41] *N*-oxidation of **28** with m-CPBA gave product **29** in 70% yield. Rearrangement of **29**, facilitated by TFAA afforded compound **30**. *O*-alkylation of **30** with 3-chloro-3-methyl-1-butene followed by Claisen rearrangement gave compound **32**. Nucelophilic substitution of the primary alcohol **32** with bromine gave compound**33**. Subsequent nucleophilic substitution of **33** with various primary amines followed by removal of the bromine with BuLi afforded compound **35**. Next sulfonylation of **35** with aryl sulfonylchlorides resulted in analogues **36** (Scheme 8).

Class 7: Amide analogue—Finally, we replaced the sulfonamide of compound **26a** with an amide group. The amide group is a common bioisostere for sulfonamide and may enhance activity. In this case, the previously synthesized **25a** was reacted with 3,4-dimethoxybenzoylchloride in the presence of triethylamine to give the product **37** with a 98% yield (Scheme 9).

Biology

The synthesized analogues of **1** were evaluated for their potential to inhibit HIF-1-mediated transcription under hypoxia (1% O_2) using a human glioma cell line LN229-HRE-Lux, which stably expresses a hypoxia-responsive luciferase reporter gene (Table 1 - 9). The IC_{50} values of all compounds were calculated based on a concentration curve testing of compounds at 0, 1, 5, 10 and 25 μM. The compounds were tested in single (n=1) or multiple (n>1) independent experiments each carried out in quadruplicate. Compound **1** was always tested along with the new analogues and had an IC_{50} of 0.7 ± 0.4 μM (n = 26) using this cell-based reporter assay (Figure 1).

Class I (benzopyran A) analogues were designed to probe the importance of the sulfonyl group. In general, removal of the sulfonyl group in compound **2a - 2f** and **3a - 3c** resulted in a marked decrease in activity (Table 1). For secondary amine compounds **2a - 2f**, only **2a** and **2b** had IC_{50} values below 10 μM, the others were higher than 25 μM. The best compound in that series was the 3,4-dimethoxyphenyl derivative **2a** with an IC_{50} of 3.0 μM. Analogues **3a - 3c** showed similar IC_{50} values as their secondary amine counterparts **2a - 2c**, with the exception of the 2,4-dimethoxyphenyl derivative **3c** that had an IC_{50} of 2.6 μM. Therefore, methylation of the secondary amine had no effect. As a result, it was concluded that the sulfonyl group was essential to the activity of these compounds and was retained in future modifications of compound **1**.

Next, Region II of the molecule was probed with various alkyl and aryl substituent (**5a – 5k**). All the compounds were active to some extent (Table 2). The best of this group was the propargyl derivative **5b**, *iso*-butyl derivative **5g** and the cyclopropyl derivative **5i** with IC_{50} values of 1.3, 1.6 and 1.5 μM respectively. In general, longer branched alkyl chains such as the *iso*-butyl group of **5g** (1.6 μM) tended to do better than long unbranched chains such as

the butyl group of **5c** (3.3 μM) or shorter branched chains as the *tert*-butyl group of **5d** (3.5 μM). Also, alkyl rings smaller than 6 carbons were better tolerated.

Compound **5j – 5m**, were modified at region III of **1** with various aryl substitutions (Table 3). The best compound in this group was the 4-methoxyphenyl substituted **5j** and 3,5-dimethylphenylsubstituted **5k** with IC_{50} values of 0.6 and 0.5 μM respectively. The 2-trifluoromethoxy-4-bromo phenyl substitution (**5m**) resulted in a significant decrease in activity

Compound **10** represented a subtle change to region IV of **1**. In this case, simply substituting one of the gem-dimethyls of the benzopyran ring system of **1** with an ethyl group resulted in a decrease in activity with an IC_{50} of 3.1μM (Table 4). In the case of compound **13**, replacement of the benzopyran ring of **1** with a quinoline ring led to a reduction in HIF-1 inhibitory activity with an IC_{50} of 3.5 μM (Table 4).

The benzofuran derivatives **16** afforded some potent compounds (Table 5). A comparison of compound **16a** (IC_{50} = 0.5 μM) to **1** shows that the substitution of the benzopyran ring with benzofuran did not necessarily result in a more potent compound than**1**, but the benzofuran analogue was comparable to that of **1**. The foreseeable benefit of the benzofuran structure of **16** is that it eliminates the double bond on the pyran ring of **1**. Since that double bond may be susceptible to epoxidation *in vivo* and thereby introduce toxicity, the benzofuran ring may be a better alternative. The ring size of the cycloalkyl derivatives seems to have an effect on activity. A comparison of the cycloheptyl ring of **16b** (9.1 μM), the cyclohexyl ring of **16e** (8.2 μM) and the cyclopentyl ring of **16f** (0.4 μM) seems to suggest that smaller rings (ring size 5 or smaller), tend to be more favorable than large rings (6 carbons or more). This is similar to the trend seen with the benzopyran analogues B (class 2).

The first of the pyranopyridine analogues was Class 6a, the pyrano(2,3b)pyridines. Two compounds were synthesized in this class. Compound **20a** had the same substitutions as compound **1** with the exception of the pyranopyridine core. This compound showed modest activity with an IC_{50} of 2.5 μM. However, it was not as potent as **1**. Replacing the phenyl ring by the cyclohexyl ring (**20b**) resulted in a loss of activity, that is, the IC_{50} was higher than 25 μM (Table 6).

The next group of compounds in this class was the pyrano(3,2b)pyridine (class 6b). Compounds **26a – 26j** were modified at region I with various alkyl and aryl amines. This class of compounds was among the best in the pyranopyridine class (Table 7). All of these compounds inhibited HIF-mediated transcription with the exception of the 2,4-dimethoxy derivative **26c**. Phenyl derivative **26a** is similar in structure to **1** with the exception of the pyrano(3,2b)pyridine core. This compound had an IC_{50} of 1.3 μM, which is within the range of activity observed for **1**. Replacement of the phenyl group of **26a** with cyclopentyl group (**26d**) and cyclohexyl group (**26e**) was effective. The best compound in this group (**26a – 26t**) was the cyclobutyl derivative **26i** with an IC_{50} of 0.25 μM. It should also be noted that **26i** was tested many times in independent experiments (n=15) side by side with **1** and consistently showed ~3-fold higher potency than **1**. Comparing all the cylcoalkyl analogues, the general trend remained about the same as that of other series, in that smaller rings (< 6 carbons) tend to have better activity than larger ring derivatives (> 6 carbons). The tetrahydronaphthalene derivatives **26f** and the 4-flurophenyl derivative **26k** had the lowest activity in this series with IC_{50} of 6.15 and 7.7 μM respectively.

Additionally, these pyrano(3,2b)pyridines **26k – 26t** were also modified at region III with alkyl and aryl sulphonyl derivatives. Generally, this group did not produce very active compounds (Table 8). The cyclohexyl group was well tolerated in this position leading to derivative **26k**, with an IC_{50} of 0.4 μM. In this case, the cyclopropyl derivative (**26m**)

showed almost no activity within the experimental conditions. Compound **26r** and **26t** was an attempt to fix the conformation of the 2,4-dimethoxybenzyl group to see if this modification would enhance activity. Compound **26r** that separated the oxygen atoms by one carbon showed a decrease in activity (IC_{50} = 6.5 μM) compared to the 3,4 dimethoxy substituted compound **26a** (1.3 μM). However **26t**, in which 2 carbons separate the oxygen atoms, showed an IC_{50} of 0.85 μM. Also noted is the quinoline derivative **26s** that showed relatively good activity with an IC_{50} of 0.9 μM.

The third group of compounds in class 6 was the pyrano(2,3c)pyridinyl derivatives (class 6c). These compounds also showed good activities, which were comparable to**1** (Table 9). Derivatives **36a, 36b** and **36c** all showed similar IC_{50} values of 1.42, 1.80 and 1.08 μM respectively. The cylcohexyl derivative **36d** was similar to other series of compounds with a much higher IC_{50} of 5.8 μM. Comparing **36c** to **36d**, the isopropylphenyl derivative (**36c**) allowed for improvement in activity compared to the 3,4-dimethoxy substitution of **36d**.

Since the pyranopyridine analogues were among the most potent compounds, we decided to replace the sulfonamide group with an amide group to see what effect this modification would have on activity. An amide is a commonly used bioisostere for sulfonamide. The amide derivative showed a 2-fold increase in activity over the sulfonamide derivative (Figure 3). This amide group can be incorporated in future modifications of the compound.

Following chemical optimization, the best compounds were subsequently re-tested in the luciferase reporter assay in a dose-response fashion to establish an IC_{50} value of inhibitory activity on HIF transcription (Fig. 4 and data not shown). Four-parameter logistic function was used to describe the dose response relationship and the data was fitted into the nonlinear mixed effects[42]model by **nlme** library in R.[43] Each compound was tested a minimum of 6 times on different days. To address variations from experiment to experiment we used the nonlinear mixed effects model in which IC_{50} was set to have an associated random effect. The results indicate that 5 compounds displayed IC_{50} values in the sub-micromolar range (Table 10), with **16a** and **26i** being the most promising as they both showed more than two-fold improvement over **1**.

We further confirmed inhibitory activity of these compounds on the HIF pathway by conducting additional experiments with the hypoxia-responsive promoter of the endogenous HIF transcriptional target gene *vascular endothelial growth factor (VEGF)*. Using LN229 glioma cells stably transfected with a *VEGF* promoter-luciferase reporter (LN229-VEGF-Luc) we found that the tested compounds at 10 μM all significantly inhibited hypoxia-induced transcription from the *VEGF* promoter (Figure 5).

For further mechanistic studies, we picked the representative compounds and previously characterized HIF pathway inhibitors (**1, 38** (Figure 6)[35] and bortezomib) as controls to evaluate their molecular basis of action using biochemical techniques. As HIF regulation typically occurs at the protein level, we probed by Western blotting whether the selected compounds had a direct effect on HIF-1α protein accumulation under hypoxia. HIF-1α levels were examined in cell extracts from cells grown under hypoxia in the presence or absence of inhibitor (20 μM). As expected, the results show that bortezomib, a proteasome inhibitor, leads to the accumulation of HIF-1α in an inactive form;[44] whereas 38, a HIF-1α translation inhibitor, leads to a blockage of HIF-1α accumulation under hypoxia.[45] It was found that some of the compounds **5g** and **16a** reduced the level of expression of HIF-1α at 20 μM, whereas the remaining compounds did not (Figure 7). These data suggest that inhibition of HIF-1α expression is not a general cause of the strong inhibition seen against HIF-mediated transcription in the reporter assay. Such results suggest that at least for some of the compounds, **16d, 16f** and **26a**, the main biological activity is not mediated by

inhibiting HIF-1α gene expression, or affecting HIF-1α turnover through a blockage in translation of HIF-1α mRNA, or accelerated protein degradation. Instead, these findings imply that these inhibitors render the HIF transcriptional complex functionally inactive. Potential mechanisms may involve protein misfolding, incomplete protein modifications and/or lack of HIF complex assembly. To dissect the precise mechanism of action of this class of HIF pathway inhibitors, additional work is needed. Ongoing mechanistic studies indicate that **1** does not alter HIF-1 levels, but interferes with the ability to the HIF-1α/HIF-1β complex to associate with transcriptional co-factors p300/CBP and we anticipate that this will be similar for the new analogs identified here.[35]

Conclusion

Several potent analogues of the lead compound **1** were synthesized. These analogues were able to yield information on the important functional groups at each of the four regions identified in Figure 1. General conclusions about the SAR of this molecule were determined (Figure 4). Analogues **2** demonstrated that the sulfonyl group was required for the activity of these compounds. Also, alkyl rings 5 carbons or shorter, as well as longer branched chains were well tolerated at region II of **1**. At region III, aryl substitutions seem to be better than alkyl substitutions. The benzofuran analogues (**16**) were also successful, in that, the analogues in this series showed activity comparable to that of **1**. These benzofuran analogues may be a good future alternative to the benzopyran derivatives, since it does not contain an electron-rich double bond. To date, the pyrano(3,2b)pyridine analogues (**26**) provided the most improvement in activity as compared to **1**. The best overall compound came from this group – the cyclobutyl derivative **26i**, which had an IC_{50} value of 280 nM. The improvement in activity of these analogues over **1** may be a result of increased hydrophilicity and/or hydrogen bond interactions as a result of the addition of the pyridine ring. Overall, these small molecules show potential as effective HIF-1 inhibitors for anti-tumor therapy. These compounds can be especially useful in tumors that exhibit hypoxic resistance to chemotherapy and radiotherapy.

Experimental

Biology

LN229-HRE-luciferase glioblastoma cells were used to perform the assay. These cells contain stably integrated reporter construct (V6R) made of six copies of the HIF responsive element derived from the VEGF gene as previously described.[26] 48-well plates were seeded with 3.10^4 cells per well and incubated under normoxic conditions for 24 h. Cells were then pre-treated with different concentrations of **1** or its analogues for 1 h and then transferred to hypoxic conditions. After 24 h, media was aspirated, cells were lysed and reporter activity was measured in the lysate using Luciferase Assay System (Promega, Madison, WI) with $20/20^n$ Luminometer (Promega).

Chemistry

General—All commercial chemicals and solvents were reagent grade and were used without further purification unless otherwise indicated. Microwave heating was performed in a single-mode microwave cavity of a Discover Synthesis System (CEM corp.) and all microwave-irradiated reactions were conducted in a heavy walled glass vials sealed with Teflon septa. ^{1}H NMR and ^{13}C NMR were recorded at 400 MHz and 100 MHz respectively on a Bruker 400 NMR spectrometer with TMS or deuterated solvent as the internal standard. Coupling constants are in Hz. Mass Spectral analysis was performed by the Mass Spectrometry Facilities at Georgia State University. The purities of tested compounds were assessed as being at least 95% with analytical HPLC, which was performed using a C18 5

μm (250 × 4.6mm) column at 254 nm and eluted with a gradient of 70 - 80 % solvent B (methanol) in solvent A (water) at 0.8 mL/min.

General procedure for reductive amination for synthesis of 2a - 2f

To a solution of 2,2-dimethyl-2H-chromene-6-carbaldehyde (1 equiv.) in methanol was added the amine (2 equiv.), sodium cyanoborohydride (2 equiv.) and zinc chloride (anhydrous) (2 equiv.). The reaction was stirred overnight, then the solvent removed by rotary evaporation and 1M NaOH added to the residue. The organic layer was extracted with ethyl acetate or DCM (× 2), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel).

(3,4-Dimethoxy-phenyl)-(2,2-dimethyl-2H-chromen-6-ylmethyl)-amine (2a)— Yield: 60%. ^{1}H NMR ($CDCl_3$): δ 7.09 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.30 (s, 1H), 6.30 – 6.24 (m, 1H), 6.17 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.61 (d, *J* = 9.8 Hz, 1H), 4.15 (s, 2H), 3.81 (t, *J* = 6.2 Hz, 6H), 1.43 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 152.2, 150.0, 143.3, 141.6, 131.6, 131.1, 128.4, 125.7, 122.2, 121.4, 116.4, 113.3, 103.6, 99.0, 76.2, 56.7, 55.7, 48.8, 28.1 ppm. HRMS (ESI) *m/z* calcd for $C_{20}H_{23}NO_3$ [(M + H)$^+$]; 326.1756, found: 326.1750, calc:. HPLC, ret. time = 9.41 min, 99.5%

(2,2-Dimethyl-2H-chromen-6-ylmethyl)-methyl-pyridin-2-yl-amine (2b)—Yield: 60 %. ^{1}H NMR ($CDCl_3$): δ 8.10 - 8.08 (m, 1H), 7.77- 7.35 (m, 1H), 7.08 – 7.07 (m, 1H), 7.00 – 6.96 (m, 1H), 6.77 – 6.72 (m, 1H), 6.50 – 6.58 (m, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 6.28 (d, *J* = 9.6 Hz, 1H), 4.80 (s, br, 1H), 4.40 (s, 2H), 1.41 ppm (s, 6H). HRMS (ESI) *m/z* calcd for $C_{17}H_{18}N_2O$ [(M + H)$^+$] 267.149, found: 267.1505. HPLC: ret. time = 12.8 min, 99.6%.

(2,2-Dimethyl-2H-chromen-6-ylmethyl)-(2,4-dimethyl-phenyl)-amine (2c)— Yield: 69%. ^{1}H NMR ($CDCl_3$): δ 7.10 (dd, J = 6.0 Hz, 2.4 Hz, 1H), 6.99 (d, J = 8.0 Hz), 6.92 – 6.90 (m, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 6.30 (d, J = 9.6 Hz, 1H) 4.21 (s, 2H), 2.23 (s, 3H), 2.12 (s, 3H), 1.43 ppm (s, 6H). MS (ESI) *m/z* 292 [(M + H)$^+$]. HPLC, ret. time = 20.84 min, 97.9%

4-[(2,2-Dimethyl-2H-chromen-6-ylmethyl)-amino]-benzoic acid (2d)—White powder, Yield: 58%; mp 148 °C.^{1}H NMR ($(CD_3)_2SO$): δ7.71 ppm (s, 2H), 7.08 (s, 1H), 7.03 (s, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.54 (d, J = 7.7 Hz, 2H), 6.37 (d, J = 9.8 Hz, 1H),5.72 (d, J = 9.8 Hz, 1H),4.17 (d, J = 5.5 Hz, 2H), 1.35 (s, 6H), HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NO_3$ [(M − H)$^+$] 308.1287, found: 308.1276. HPLC

(2-Bromo-phenyl)-(2,2-dimethyl-2H-chromen-6-ylmethyl)-amine (2e)—Yield: 11%. ^{1}H NMR ($CDCl_3$): δ 7.43 (d, *J* = 7.8 Hz, 1H), 7.20 – 7.04 (m, 2H), 6.97 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 7.1 Hz, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.61 (d, *J* = 9.8 Hz, 1H), 4.63 (s, 1H), 4.26 (d, *J* = 5.3 Hz, 2H), 1.43 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 152.3, 144.9, 132.3, 131.1, 130.7, 128.5 128.1, 125.4, 122.2, 121.4, 117.9, 116.5, 111.6, 109.6, 76.3, 47.6, 28.0 ppm. HRMS (ESI) m/z calcd for $C_{18}H_{18}NOBr$ [(M + H)$^+$] 344.0650, found: 344.0663. HPLC, ret. time = 19.71 min, 97.9%

(2,2-Dimethyl-2H-chromen-6-ylmethyl)-(2-fluoro-phenyl)-amine (2f)—Yield: 71%. ^{1}H NMR ($CDCl_3$): δ 7.10 (dd, *J* = 6.0, 2.0 Hz, 1H), 6.99 – 6.94 (m, 3H), 6.76 – 6.56 (m, 3H), 6.29 (d, *J* = 9.6 Hz, 1H), 5.61 (d, *J* = 9.6Hz, 1H), 4.23 (s, 3H), 1.43 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 152.4, 143.9, 138.1, 136., 130.9, 128.3, 128.2, 127.5, 127.1, 124.7, 123.5, 122.3, 121.2, 116.2, 77.4, 28.1, 21.5 ppm. HRMS 0(ESI) *m/z* calcd for $C_{18}H_{18}NOF$ [(M + H)$^+$] 284.1451, found: 284.1442. HPLC: ret. time = 16.55 min, 97.3%

General Procedure for synthesis of 3a - 3c by methylation of secondary amines 2a, 2b and 2c respectively—A solution of secondary amine **2** (1 equiv.) in THF was added to a flask containing NaH (2 equiv) in THF. After 5 min, MeI (2 equiv) was added and the reaction stirred overnight. The reaction mixture was quenched with water and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel).

(3,4-Dimethoxy-phenyl)-(2,2-dimethyl-2H-chromen-6-ylmethyl)-methylamine (3a)—Yield: 60 %. ^{1}H NMR ($CDCl_3$): δ 6.98 (dt, *J* = 7.2, 3.6 Hz, 1H), 6.87 (s, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.73 (s, 1H), 6.43 (s, 1H), 6.27 (d, *J* = 10.1 Hz, 2H), 5.59 (d, *J* = 9.8 Hz, 1H), 4.31 (s, 2H), 3.82 (d, *J* = 2.2 Hz, 6H), 2.89 (s, 3H), 1.42 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 149.7, 145.6, 131.2, 130.9, 127.9, 125.1, 122.3, 121.3, 116.3, 113.0, 104.8, 99.5, 77.4, 77.0, 76.7, 76.2, 57.6, 56.7, 55.8, 38.9, 28.0 ppm. HRMS (ESI) *m/z* calcd for $C_{21}H_{25}NO_3$ [(M + H)$^+$] 340.1913, found: 340.1900.HPLC, ret. time = 21.7, 98.7%.

(2,2-Dimethyl-2H-chromen-6-ylmethyl)-methyl-pyridin-2-yl-amine (3b)—Yield: 81%. ^{1}H NMR ($CDCl_3$): δ 8.21 (m, 1H), 7.45 (m, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.86 (s, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.52-6.59 (m, 2H), 6.28 (d, *J* = 10Hz, 1H), 5.60 (d, *J* = 10 Hz, 1H), 4.70 (s, 2H), 3.06 (s, 3H), 1.44 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.9, 148.0, 137.3, 130.9, 130.8, 127.8, 125.0, 122.4, 121.3, 116.3, 11.7, 105.8, 76.1, 52.6, 36.0, 28.0 ppm. HRMS (ESI) *m/z* calcd for: $C_{18}H_{20}N_2O$ [M + H)+] 281.1654, found: 281.1659. HPLC, ret. time = 16.55, 97.3%.

(2,2-Dimethyl-2H-chromen-6-ylmethyl)-(2,4-dimethyl-phenyl)-methyl-amine (3c)—Yield: 48%. ^{1}H NMR ($CDCl_3$): d 7.13 (dd, *J* = 2.0, 6.0 Hz, 1H), 7.05 – 7.00 (m, 4H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.34 (d, *J* = 9.6 Hz, 1H), 5.63 (d, *J* = 9.2 Hz, 1H), 3.88 (s, 2H), 2.55 (s, 3H), 2,40 (s, 3H), 2.31 (s, 3H), 1.45 ppm (s, 6H). MS (ESI) *m/z* 308 [(M + H)$^+$].HPLC, ret. time = 12.17, 96.8%.

General Procedure for synthesis of 5a –5m by alkyl sulfonylation

To a solution of 2,2-dimethyl-2H-chromene-6-carbaldehyde (1 eq) in methanol was added the primary amine (1 equiv.), $ZnCl_2$ (2 equiv.) and the reaction was stirred at room temperature for 2 h. Then $NaCNBH_3$ (2 equiv.) was added and the reaction was stirred at room temperature overnight. The solvent was removed by rotary evaporation and EtOAc was added to the residue. The solid was filtered through Celite and the filtrate washed with 1M NaOH, water and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude secondary amine product **4** was used without further purification.

To a solution of the secondary amine **4** (1 equiv.) in DCM was added triethylamine (3 equiv.) and the sulfonylchloride (1.5 equiv.). The reaction was stirred for 24 to 48 h. Then water was added and the organic layer extracted with DCM, dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography.

***N*-(2,2-Dimethyl-2H-chromen-6-ylmethyl)-N-isopropyl-3,4-dimethoxy-benzenesulfonamide (5a)—**Yield: 58%; mp 132 -134 °C^{1}H NMR ($CDCl_3$): δ 7.39 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.07 (dd, J = 6.0, 2.0 Hz, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.90 (t, *J* = 8.6 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.28 (d, *J* = 9.8 Hz, 1H), 5.60 (d, *J* = 9.8 Hz, 1H), 4.39 – 4.19 (m, 2H), 4.23 – 4.02 (m, 1H), 4.04 – 3.73 (m, 6H), 1.41 (s, 6H), 1.05 ppm (d, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 152.2, 152.2, 149.0, 133.2, 131.0, 130.8, 128.6, 126.0, 122.3, 121.2, 120.8, 116.1, 110.5, 109.6, 76.3, 56.2, 56.1, 50.0, 46.0,

27.9, 21.3 ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{29}NO_5S$ [(M + Na)$^+$] 451.1664, found: 451.1651. HPLC: ret. time = 11.76 min, 97.2%.

***N*-(2,2-Dimethyl-2H-chromen-6-ylmethyl)-3,4-dimethoxy-*N*-prop-2-ynyl-benzenesulfonamide (5b)—**Yield: 95% ^{1}H NMR ($CDCl_3$): δ 7.53 (dd, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.09 – 7.07 (m, 1H), 7.00 – 6.96 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 9.6 Hz, 1H), 5.64 (d, *J* = 9.6 Hz, 1H), 4.24 (s, 1H), 4.01 – 3.96 (m, 7 H), 1.59 (s, 2H), 1.43 ppm (s, 6H). HRMS (ESI) *m/z* calcd for $C_{23}H_{25}NO_5S$ [(M + Na)$^+$] 450.1351, found: 450.1352. HPLC, ret. time = 10.65 min, 96.61%

(*N*-Butyl-*N*-(2,2-dimethyl-2H-chromen-6-ylmethyl)-3,4-dimethoxy-benzenesulfonamide(5c)—Yield: 55%; 82 C^{1}H NMR ($CDCl_3$): δ 7.46 (dd, *J* = 6.4, 2.1 Hz, 1H), 7.28 (m, 1H), 7.00 – 6.89 (m, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.27 (d, *J* = 10.0 Hz, 1H), 5.63 (d, *J* = 9.6 Hz, 1H), 4.23 (s, 1H), 3.97 – 3.92 (m, 6H), 3.10 (t, *J* = 7.6 Hz, 2H), 1.43(s, 6H), 1.38 – 1.16 (m, 6H), 0.79 ppm (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 152.3, 149.0, 132.2, 131.1, 129.1, 128.5, 126.4, 122.1, 121.3, 121.0, 116.2, 110.6, 109.8, 76.3, 56.2, 56.2, 51.1, 47.4, 30.0, 27.9, 19.9, 13.6 ppm. HRMS (ESI) *m/z* calcd for $C_{24}H_{31}NO_5S$ + Na 468.1821, found: 468.1815. HPLC, ret. time = 14.0 min, 96.3%

***N-tert*-Butyl-*N*-(2,2-dimethyl-2H-chromen-6-ylmethyl)-3,4-dimethoxy-benzenesulfonamide (5d)—**Yield: 49%. ^{1}H NMR ($CDCl_3$): δ 7.41 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.22 – 7.12 (m, 2H), 7.06 (d, *J* = 2.1 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.74 (t, *J* = 9.7 Hz, 1H), 6.30 (t, *J* = 8.9 Hz, 1H), 5.62 (t, *J* = 9.5 Hz, 1H), 4.56 (s, 2H), 3.94 (d, *J* = 13.4 Hz, 3H), 3.85 (d, *J* = 14.6 Hz, 3H), 1.48 – 1.39 (m, 6H), 1.33 ppm (s, 9H). MS (ESI) *m/z* 468 [(M + Na)$^+$]. HPLC: ret. time = 13.2 min, 96.3%.

***N*-Allyl-*N*-(2,2-dimethyl-2H-chromen-6-ylmethyl)-3,4-dimethoxy-benzenesulfonamide (5e)—**Yield: 53%; mp 94 -98 C.^{1}H NMR ($CDCl_3$): δ 7.48 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.29 (t, *J* = 2.3 Hz, 1H), 7.01 – 6.91 (m, 2H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.72 (t, *J* = 9.7 Hz, 1H), 6.29 (d, *J* = 6.4 Hz, 1H), 5.64 (t, *J* = 10.6 Hz, 1H), 5.53 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H), 5.09 (ddd, *J* = 18.4, 13.6, 1.3 Hz, 2H), 4.28 (d, *J* = 25.4 Hz, 2H), 4.03 – 3.95 (m, 3H), 3.95 – 3.88 (m, 3H), 3.84 – 3.72 (m, 2H), 1.44 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 152.6, 152.4, 149.1, 132.4, 132.4, 131.9, 129.4, 127.9, 126.6, 122.1, 121.3, 121.1, 199.2, 116.2, 110.6, 109.8, 76.4, 56.2, 56.18, 49.6, 49.2, 28.0 ppm. EI probe: M$^+$ 429. HPLC: ret. time = 11.9 min, 97.0%

***N*-(2,2-Dimethyl-2H-chromen-6-ylmethyl)-3,4-dimethoxy-*N*-(3-methyl-butyl)-benzenesulfonamide (5f)—**Yield: 31%; mp 103 -105.^{1}H NMR ($CDCl_3$): δ 7.44 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.29 – 7.28 (m, 1H), 6.96 – 6.94 (m, 2H), 6.83 (s, 1H), 6.24 (d, *J* = 10.0 Hz, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 4.23 (s, 2H), 3.97(s, 3H), 3.92 (s, 3H), 2.90 (d, *J* = 7.6 Hz, 2H), 1.75 (sep, *J* = 6.8 Hz, 1H), 1.43 (s, 6H),1.28 (s, 2H), 0.792 – 0.779 ppm (m, 6H). ^{13}C NMR ($CDCl_3$): δ 152.5, 152.3, 149.0, 132.1, 131.1, 129.2, 128.5, 126.5, 122.1, 121.3 121.1, 116.2, 110.5, 109.9, 76.3, 56.2, 56.2, 55.8, 52.1, 27.9, 26.9, 20.0 ppm. HRMS (ESI) *m/z* calcd for $C_{24}H_{31}NO_5S$ 468.1821 [(M + Na)+] found: 468.1801. HPLC: ret. time = 13.92 min, 97.5%.

***N*-Cyclopentyl-N-(2,2-dimethyl-2H-chromen-6-ylmethyl)-3,4-dimethoxy-benzenesulfonamide (5g)—**Yield: 58%, mp 110 -112 °C.^{1}H NMR ($CDCl_3$): δ 7.39 (d, *J* = 6.4 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 7.10 – 6.82 (m, 3H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.26 (d, *J* = 9.8 Hz, 1H), 5.57 (d, *J* = 9.8 Hz, 1H), 4.22 (s, 2H), 3.88 (d, *J* = 20.2 Hz, 6H), 1.70 – 1.18 ppm (m, 15H). ^{13}C NMR ($CDCl_3$): δ 152.2, 152.1, 150.0, 132.7, 131.0, 130.9, 127.9, 152.3, 122.3, 121.2, 121.0, 116.1, 110.5, 109.8, 76.2, 59.5, 56.2, 56.1, 46.8, 29.3, 28.0, 23.5

ppm. HRMS (ESI) *m/z* calcd for $C_{25}H_{31}NO_5S$ 480.1842 [(M + Na)+] found: 480.1822. HPLC: ret. time = 14.11 min, 98.1%

N-Cyclopropyl-*N*-(2,2-dimethyl-2H-chromen-6-ylmethyl)-3,4-dimethoxy-benzenesulfonamide(5h)—off-white semi-solid. Yield: 47%; mp 94 °C ^{1}H NMR ($CDCl_3$): δ 7.46 (dd, *J* = 2.0, 6.4 Hz, 1H), 7.27 (d, *J* = 2.0Hz, 1H), 7.06 (dd, *J* = 2.0, 6.4 Hz, 1H), 6.97- 6.93 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.29 (d, *J* = 9.6 Hz, 1H), 4.27 (s, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 5.62 (d, *J* = 9.6 Hz, 1H), 2.01 (quin, *J* = 4.0 Hz, 1H), 1.44(s, 6H), 0.72 (q, *J* = 3.2 Hz, 2H), 0.59 ppm (q, *J* = 3.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 152.5, 148.9, 131.0, 130.5, 129.7, 129.0, 126.9, 122.2, 121.6, 121.1, 116.0, 110.4, 110.2, 76.3, 56.2, 56.2, 54.2, 30.6, 28.0, 27.3 ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_5S$ 452.1508 [(M + Na)+] found: 452.1489. HPLC: ret. time = 7.48 min, 99.5%.

***N*-Cyclohexyl-*N*-(2,2-dimethyl-2H-chromen-6-ylmethyl)-3,4-dimethoxy-benzenesulfonamide (5i)—**Yield: 79%. ^{1}H NMR ($CDCl_3$): δ 7.42 (dd, *J* = 2.0 Hz, 6.4 Hz, 1H), 7.30 – 7.15 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.10 – 7.08 (m, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 9.6 Hz, 1H), 5.63 (d, *J* = 9.6 Hz, 1H), 4.31 (s, 2H), 3.95 (s, 3H), 3.90 (s, 3H), 1.70 – 1.54 (m, 4H), 1.43 (s, 6H), 1.27 – 1.20 ppm (m, 6H). Yield: 79%. HPLC: ret. time = 14.4 min, 99.5%.

General Procedure for the synthesis of 5j – 5m—To a solution of secondary amine **4** (1 equiv) in DCM was added triethylamine (3 equiv.) and then the appropriate sulfonylchloride (2 equiv.). The reaction was stirred at room temperature for 24 h. Then sat. NH_4Cl was added to the reaction mixture, which was extracted with DCM (× 2). After drying over $MgSO_4$ the DCM solution was concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel).

***N*-((2,2-Dimethyl-2H-chromen-6-yl)methyl)-4-methoxy-N-phenylbenzenesulfonamide (5j)—**Yield:26.4 mg (30 %). ^{1}H NMR ($CDCl_3$): δ 7.60 (d, *J* = 9.2 Hz, 2H), 7.28-7.22 (m, 3H), 7.00 – 6.93 (m, 4H), 6.91-6.88 (m, 2H),6.62 (s, 1H), 6.24(d, *J* = 10.0 Hz, 1H), 5.58 (d, *J* = 10 Hz, 1H), 4.62 (s, 2H), 3.90 (s, 3H), 1.40 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 162.9, 139.1, 130.9, 129.8, 129.3, 129.1, 128.8, 128.1, 127.8, 126.6, 122.3, 116.0, 114.0, 76.3, 55.6, 54.3, 28.0 ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NO_5S$: 452.1508 [(M + H)$^+$] found: 452.1489. HPLC, ret. time = 14.03 min, 96.1%

***N*-((2,2-Dimethyl-2H-chromen-6-yl)methyl)-3,5-dimethyl-*N*-phenylbenzenesulfonamide (5k)—**Yield: 65 mg, (40%) ^{1}HNMR: δ 7.54 (s, 2H), 7.30 – 7.23 (m, 3H), 7.00 – 6.97 (m, 1H), 6.90 – 6.88 (m, 2H), 6.60 (d, *J* = 8.8 Hz, 1H), 6.24 (d, *J* = 10 Hz, 1H), 5.58 (d, *J* = 9.6 Hz, 1H), 4.63 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 1.42(s, 6H). MS (ESI) m/z 458 [(M + Na)$^+$]. HPLC, ret. Time = 23.7 min, 96.8%

2,5-Dichloro-*N*-((2,2-dimethyl-2H-chromen-6-yl)methyl)-*N*-phenylbenzenesulfonamide (5l)—Yield: 69 mg (32%)^{1}H NMR ($CDCl_3$): δ 7.84 (d, J = 2.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.23 – 7.21 (m, 3H), 7.06 – 7.04 (m, 2H), 6.92 – 6.90 (m, 2H), 6.64 (d, J = 7.6 Hz, 1H), 6.27 (d, J = 10.0 Hz, 1H), 5.60 (d, J = 9.6 Hz, 1H), 4.92 (s, 2H), 1.42 ppm (s, 6H). MS (ESI) m/z 471 [(M + Na)$^+$].

4,4-Bromo-*N*-((2,2-dimethyl-2H-chromen-6-yl)methyl)-*N*-phenyl-2-(trifluoromethoxy)benzenesulfonamide (5m)—Yield: 23%.^{1}HNMR ($CDCl_3$): δ 1.45 (s, 6H), 4.95 (s, 2H), 5.60 (d, 1H, *J* = 9.6), 6.27 (d, 1H, *J* = 10), 6.64 (s, 1H, *J* = 7.6), 6.91 (m, 2H), 7.05 (m, 2H), 7.21 (m, 3H,) 7.43 (m, 1H) 7.48 (m, 1H), 7.84 ppm (d, 1H, 2.4). HPLC: ret. time = 19.6 min, 96.7%.

4-(3-Methylpent-1-yn-3-yloxy)benzaldehyde (7)—To a solution of 3-methyl-1-pentyn-3-ol **6** (0.319 mL, 2.83 mmol) in acetonitrile (3 mL) at 0 °C was added DBU (0.55 mL, 3.69 mmol). Then TFAA (0.34 mL, 2.46 mmol) was added drop wise and the solution was stirred at 0 °C for 30 min. To a solution of 4-hydroxybenzaldehyde (300 mg, 2.46 mmol) in acetonitrile at 0 °C was added DBU (0.55 mL 3.69 mmol) and $CuCl_2.2H_2O$ (0.42 mg, 0.0025 mmol). The first mixture was added to the second mixture over a period of five min. The reaction was stirred overnight. The solvent was removed by rotary evaporation and the residue diluted with DCM. Then the organic layer washed with 1M HCl, 1M NaOH, sat $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuum to give 170 mg (30%) of product. ^{1}H NMR ($CDCl_3$): δ 9.91(s, 1H), 7.83 – 7.81 (m, 2H), 7.36 -7.34 (m, 2H), 2.69 (s, 1H), 2.06 – 1.92 (m, 2H), 1.66 (s, 3H), 1.12 ppm (t, *J* = 7.2 Hz, 3H).

2-Ethyl-2-methyl-2H-chromene-6-carbaldehyde (8)—A solution of 7 (170 mg) in xylene (3 mL) was subjected to microwave irradiation for 100 min at 220 W, 200 torr, 120 °C. The solvent was removed in vacuum to give a quantitative yield of the product (170 mg). ^{1}H NMR ($CDCl_3$): δ 9.81 (s, 1H), 7.63 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.42 (d, *J* = 10.0 Hz, 1H), 5.62 (d, *J* = 10.0 Hz, 1H), 1.81 – 1.66 (m, 3H), 1.43 (s, 3H), 0.97 ppm (t, *J* = 7.6 Hz, 3H).

***N*-((2-Ethyl-2-methyl-2H-chromen-6-yl)methyl)benzenamine (9)—**Reaction was carried out following the same procedure as for **2a - 2f** using 170 mg of **8** to give 90.9 mg (41%) of product. ^{1}H NMR ($CDCl_3$): δ 7.22- 7.18 (m, 5H), 7.11(dd, *J* = 6.0 Hz, 2.4 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 2H), 6.77 - 6.74 (m, 3H), 6.68 – 6.66 (m, 2H), 6.36 (d, *J* = 10.0 Hz, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 4.21 (s, 2H), 1.76 – 1.71 (m, 3H), 1.33(s, 3H), 0.96 ppm (t, *J* = 7.6 Hz, 3H).

***N*-((2-Ethyl-2-methyl-2H-chromen-6-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (10)—**To a solution of **9** (80 mg, 0.29 mmol) in DCM (3 mL) was added Et_3N (0.12 mL, 0.85 mmol) and 3,4-dimethoxybenzenesulfonyl chloride (135 mg, 0.573 mmol). After 24 h, sat. NH4Cl was added to the reaction mixture and the aqueous layer was extracted with DCM (5 × 2 mL). The organic layers was combined, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column (silica gel, 5: 1 Hx/EtOAc) to give a white solid (42.6 mg). Yield: 32%; mp 129 -130^{1}H NMR($CDCl_3$): δ 7.35 (dd, *J* = 6.4 Hz, 2.0 Hz, 1H), 7.25 – 7.23 (m, 3H), 7.02 – 6.98 (m, 3H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.91 – 6.88 (m, 2H), 4.62 (s, 2H), 3.98 (s, 3H), 3.77 (s, 3H), 1.71 – 1.65 (m, 2H), 1.43 (s, 3H), 0.94 ppm (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 152.8, 152.5, 148.7, 139.2, 130.5, 129.8, 129.3, 129.2, 128.8, 127.9, 127.8, 126.6, 122.8, 121.4, 121.1, 115.8, 110.4, 79.0, 56.2, 56.1, 54.3, 34.0, 26.0 ppm. MS (ESI) m/z 502 [$(M + Na)^+$]. HPLC: ret. time = 5.9 min, 98.9%.

***N*-Phenylquinolin-3-amine (12)—**To a solution of quinoline-3-carbaldehyde **11** (79 mg, 0.5 mmol) in MeOH (5 mL) was added aniline (0.05 mL, 0.55 mmol) and $ZnCl_2$ (136 mg, 2.0 mmol) and the reaction was stirredat room temperature for 15 min. Then $NaCNBH_3$ (62.8 mg, 2.0 mmol) was added and to the reaction was stirred overnight at room temperature. The solvent was removed by rotary evaporation and the residue suspended in EtOAc. The organic layers were combined and washed with $NaHCO_3$, water, and brine and then dried over MgSO. Concentration *in vacuo* gave the crude product, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): 9.05 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.54 – 7.51 (m, 1H), 7.21 – 7.16 (m, 2H), 6.76 – 6.72 (m, 1H), 6.68 – 6.60 (m, 2H), 4.54 (s, 2H), 4.16 (s, br, 1H).

3,4-Dimethoxy-*N*-phenyl-*N*-(quinolin-3-ylmethyl)benzenesulfonamide (13)—To a solution of **12** (75 mg, 0.320 mmol) in DCM was added 3,4 dimethoxybenzylsulfonyl chloride (83 mg, 0.35 mmol) and triethylamine (0.09 mL, 0.640 mmol). The reaction was stirred overnight at room temperature and the reaction mixture was washed with water and brine. The organic layer was dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography (silica gel, 2:1 Hexane/EtOAc) to give a white powder. Yield: 45%; mp 173. ^{1}H NMR ($CDCl_3$): 8.86 (s, 1H), 8.14(d, *J* = 8.0 Hz, 2H), 7.84 (dd, *J* =7.2 Hz, 1.2 Hz, 1H), 7.80 – 7.76 (m, 1H), 7.64 -7.60 (m, 1H), 7.49 (dd, *J* = 6.0 Hz, 2.4 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.17 – 7.14 (m, 2H), 7.08 – 7.05 (m, 2H), 5.03 (s, 2H), 4.08 (s, 3H), 3.85 ppm (s, 3H). ^{13}C NMR ($CDCl_3$): 152.8, 150.8, 148.8, 147.6, 138.0 135.7, 129.6, 129.2, 129.1, 129.0, 128.2, 127.7, 127.7, 126.9, 121.6, 110.5, 110.4, 56.2, 56.1, 52.4 ppm. MS (ESI) *m/z* 435 [(M + H)$^+$]. HPLC: ret. time = 14.6 min, 95.2%.

***N*-((2,2-Dimethyl-2H-chromen-6-yl)methyl)benzenamine (15a)—**To a solution of 2,3-dihydro-2,2-dimethylbenzofuran-5-carboxaldehyde **14** (250 mg, 1.42 mmol) in MeOH (10 mL) was added aniline (0.14 mL, 1.022 mmol), $NaCNBH_3$ (178 mg, 2.84 mmol) and $ZnCl_2$ (dried in oven) (387 mg, 2.84 mmol). The reaction was stirred at room temperature overnight, and then the solvent was removed by rotary evaporation. 0.1M NaOH was added to the resulting residue, which was extracted with EtOAc (× 2). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuum to give 301 mg of the product (84 %). ^{1}H NMR ($CDCl_3$): d 7.29 – 7.22 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.95 – 6.70 (m, 4H), 4.28 (s, 2H), 3.06 (s, 2H), 1.55 ppm (s, 6H).

***N*-((2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzenesulfonamide (16a)—**To a solution of **15a** (100 mg, 0.395 mmol) in DCM (5 mL) was added triethylamine (0.17 mL, 0.790 mmol) and 3,4-dimethoxybenzenesulfonylchloride (187 mg, 0.790 mmol) dissolved in 1mL of DCM and the reaction was stirred for 72 h. Ammonium chloride was added to the reaction mixture, which was then extracted with DCM (× 2). After drying the combined organic layers over $MgSO_4$ and concentration in vacuum, the crude reaction mixture was purified by column (silica gel, 3:1 Hx/EtOAc) to give a white solid (76 mg, 42 %), mp 136 °C^{1}H NMR ($CDCl_3$): δ 7.33 (dd, *J* = 2.13, 8.44, 1H), 7.26 - 7.21 (m, 3H), 7.09 (s, 1H) 7.00 - 6.96 (m, 3H), 6.92 (d, *J* = 8.5, 1H), 6.83 (d, *J* = 8.1,1H), 6.52 (d, *J* = 8.1, 1H), 4.62 (s, 2H), 3.95 (s, 1H), 3.75 (s, 1H), 2.92 (s, 2H), 1.42 ppm (s, 1H). ^{13}C NMR ($CDCl_3$): δ 158.4, 152.5, 148.7, 139.3, 129.2, 127.5, 125.6, 121.4, 110.4, 108.9, 86.9, 56.2, 56.1, 54.6, 42.7, 28.2 ppm. MS (ESI) *m/z* 435 [(M + H)]. HPLC: ret. time = 10.5 min, 96.1%.

General Procedure for the Synthesis of compound 16b – 16f—To a solution of **14** in methanol was added amine (1 .1 equiv.), zinc chloride (2 equiv.) and the reaction mixture was stirred for 2 h before $NaCNBH_3$ (2 equiv.) was added. The reaction was then stirred at room temperature overnight. The solvent was removed by rotary evaporation and the residue diluted with EtOAc and washed with Na_2CO_3 (sat) and brine. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The product was used without further purification in the next step. To the resulting secondary amine **15** (1 equiv.) in DCM was added Et_3N (2 equiv.) and the appropriate aryl or alkyl sulfonyl chloride (1.1 equiv.) and the reaction stirred at room temperature overnight. The reaction mixture was diluted with DCM and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel).

***N*-Cycloheptyl-*N*-((2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)methyl)-3,4dimethoxybenzenesulfonamide (16b)—**Yield: 14%; mp 90 °C^{1}H NMR ($CDCl_3$): δ 7.43 (dd, J = 2.14, 8.44, 1H), 7.25 – 7.24 (m, 2H), 7.05 (d, *J* = 8.13, 1H),

6.92 (d, *J* = 8.5, 1H), 6.65 (d, *J* = 8.1, 1H), 4.28 (s, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 3.00 (s, 2H), 1.63 -1.51 (m, 8H), 1.48 (s, 6H), 1.45 -1.27 ppm (m, 7H). HRMS (ESI) calcd for $C_{26}H_{35}NO_5S$ *m/z* [(M + Na)$^+$] 496.2134, found: 496.2122. HPLC: ret. time = 18.6 min, 99.4%.

***N*-((2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)methyl)-N-isopropyl-3,4-dimethoxybenzenesulfonamide(16c)—**Yield: 18%.^{1}H NMR ($CDCl_3$): δ 7.45 (d, *J* = 8.2 Hz, 1H), 7.27 (s, 1H), 7.10 (d, *J* = 15.6 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 2H), 6.63 (d, *J* = 7.6 Hz, 1H), 4.24 (s, 2H), 3.94 (d, *J* = 19.3 Hz, 6H), 3.05 – 2.93 (m, 2H), 2.91 (d, *J* = 6.9 Hz, 2H), 1.82 – 1.66 (m, 1H), 1.48 (s, 6H), 0.77 ppm (d, *J* = 5.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 158.5, 152.3, 149.0, 132.1, 128.4, 127.9, 127.7, 125.6, 121.1, 110.5, 109.9, 109.0, 87.1, 77.4, 77.1, 76.7, 56.2, 56.1, 55.8, 52.4, 42.7, 28.1, 26.9, 20.0 ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{31}NO_5S$ [(M + Na)$^+$] 456.1821, found: 456.1833. HPLC: ret. time = 11.5 min, 97.6 %.

***N*-Butyl-*N*-((2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)methyl)-3,4-dimethoxybenzenesulfonamide(16d)—**Yield: 21%. ^{1}H NMR ($CDCl_3$): δ 7.47 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.34 – 7.22 (m, 2H), 7.13 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 1H), 4.25 (s, 2H), 3.95 (d, *J* = 16.7 Hz, 6H), 3.22 – 3.03 (m, 2H), 2.99 (s, 2H), 1.57 (d, *J* = 21.8 Hz, 1H), 1.49 (s, 6H), 1.41 – 1.24 (m, 3H), 1.23 – 1.08 (m, 2H), 0.79 ppm (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 158.6, 152.2, 149.2, 143.0, 132.3, 128.3, 127.4, 125.5, 120.9, 110.5, 109.8, 109.0, 87.1, 77.4, 77.0, 76.7, 56.2, 56.1, 51.3, 47.3, 42.7, 29.9, 28.1, 19.9, 13.7 ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{31}NO_5S$ [(M + Na)$^+$] 456.1821, found: 456.1812. HPLC: ret. time = 11.2 min, 98.0%

***N*-Cyclohexyl-N-((2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)methyl)-3,4-dimethoxybenzenesulfonamide (16e)—**Yield: 36%; mp 102 °C.^{1}H NMR ($CDCl_3$) δ 7.41 (d, *J* = 8.4, 1H), 7.22 (s, 2H), 7.03 (d, *J* = 7.9, 1H), 6.90 (d, *J* = 8.3, 1H), 6.63 (d, *J* = 7.9, 1H), 4.31 (s, 2H), 3.70 (1H) 3.94 (s, 3H) 3.88 (s, 3H), 2.98 (s, 1H), 1.69 – 1.52 (m, 7H), 1.47(s, 6H), 1.27- 1.22 ppm (m, 4H). HRMS (ESI) *m/z* calcd for $C_{25}H_{33}$ NO_5S [(M + Na)$^+$] 482.1977, found: 482.1981. HPLC: ret. time = 16.4 min, 95.6%.

***N*-Cyclopentyl-*N*-((2,2-dimethyl-2,3-dihydrobenzofuran-5-yl)methyl)-3,4-dimethoxybenzenesulfonamide (16f)—**Yield: 31%. ^{1}H NMR ($CDCl_3$): δ 7.44 (d, *J* = 8.5, 1H), 7.27 (s, 2H), 7.04 (d, *J* = 8.10, 1H), 6.92 (d, *J* = 8.4, 1H), 6.65 (d, *J* = 8.1, 1H), 4.29 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 2.99 (s, 2H), 1.85 -1.58 (m, 3H), 1.60 – 1.22 ppm (m, 12 H). HRMS (ESI) *m/z* calcd for $C_{24}H_{31}NO_5S$ [(M + Na)+] 468.1821; found: 468.1817. HPLC: ret. time = 14.4 min, 95.0%

2,2-Dimethyl-2H-pyrano[2,3-b]pyridine-6-carbaldehyde (18)—To a solution of **17** (100 mg, 0.390 mmol) in dry ether (2 mL) was added BuLi (0.25 mL, 2.5 M solution in THF) drop wise at -65 °C and the reaction stirred for 15 min. Then DMF (anhydrous) was added drop wise and the reaction was stirred at -65 °C for 1.5 h. Water was added to quench the reaction, which was extracted with EtOAc (× 2). The organic layers were washed with water (× 1), brine (× 1), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography (silica gel) 6:1 Hx/EtOAc gave a white solid 23 mg (31 %).^{1}H NMR ($CDCl_3$): δ 1.58 (s, 1H); 5.79 (d, 1H, *J* = 8.0 Hz), 6.36 (d, 1H, *J* = 9.6 Hz), 7.76 (s, 1H), 8.50 (s, 1H), 9.92 ppm (s, 1H).

***N*-((2,2-Dimethyl-2H-pyrano[2,3-b]pyridin-6-yl)methyl)benzenamine (19a)—**To a solution of 2,2-dimethyl-2H-pyrano[2,3-b]pyridine-6-carbaldehyde **18** (20 mg, 0.106 mg) in methanol (1ml) was added aniline (0.01 mL, 0.12 mmol), $NaCNBH_3$ (13 mg, 0.212 mmol)

and $ZnCl_2$ (29 mg, 0.212 mmol). The reaction was stirred for 30 minutes after which the solvent was removed by rotary evaporation and the 1M NaOH added to the residue, extracted with DCM, dried over MgSO4 and concentrated in vacuo. Purified by column chromatography (3:1 Hx/EtOAc) to give a white solid 20 mg (72%). ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.29 (s, 1H), 7.26 – 7.16 (m, 2H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J*= 8.0 Hz, 1H), 6.26 (d, *J* = 9.6 Hz, 1H), 5.67 (d, *J* = 9.6 Hz, 1H), 4.21 (s, 2H), 1.51 ppm (s, 6H). ^{13}C NMR ($CDCl_3$) δ 159.6, 147.8, 146.4, 133.8, 132.2, 129.3, 128.4, 120.9, 118.0, 115.4, 113.0, 79.2, 45.4, 28.8 ppm. HRMS (ESI) *m/z* calcd for $C_{11}H_{11}NO_2$ [(M + H)$^+$] 190.0868, found: 190.0870.

N-((2,2-dimethyl-2H-pyrano[2,3-b]pyridin-6-yl)methyl)cyclohexanamine (19b)— To a solution of 2,2-dimethyl-2H-pyrano[2,3-b]pyridine-6-carbaldehyde **18** (23 mg, 0.121 mmol) in MeOH (1mL) was added cyclohexylamine (0.014 mL, 0.121 mmol), $NaCNBH_3$ (15 mg, 0.242 mmol) and Zinc chloride (33 mg, 0.242 mmol) and stirred overnight. The solvent was removed by rotary evaporation and the residue dissolved in EtOAc and washed with 1M NaOH, water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was used in the next step without further purification.

N-((2,2-Dimethyl-2H-pyrano[2,3-b]pyridin-6-yl)methyl)-3,4-dimethoxy-N-phenylbenzenesulfonamide (20a)—To a solution of **19a** (20 mg, 0.075 mmol) in DCM (1 mL) was added 3,4-dimethoxybenzenesulfonyl chloride (36 mg, 0.150 mmol) and triethylamine (0.021 mL, 0.150 mmol). The reaction was stirred for 24 hours at room temperature. The reaction mixture was washed with water (× 2) and the organic layer dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (2:1 hexane/EtOAc) gave a white solid (15mg). Yield: 43%.^{1}H NMR ($CDCl_3$): δ 1.47(s, 6H), 3.76 (s, 3H), 3.97 (s, 3H), 4.60 (s, 2H), 5.66 (d,1H, J = 9.6), 6.26 (d, 1H, J = 10), 6.93 – 6.99 (m, 4H), 7.23 – 7.25 (m, 3H), 7.32 – 7.36 (m, 2H), 7.63 ppm (d, 1H, J = 2.4). HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_2O_5S$ [M + H)$^+$] 467.1641, found: 467.1636. HPLC: ret. time = 7.5 min, 99.0%

***N*-Cyclohexyl-*N*-((2,2-dimethyl-2H-pyrano[2,3-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (20b)—**Yield: 60%. ^{1}H NMR ($CDCl_3$): δ 7.89 (s, 1H), 7.49 (s, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.28 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.31 (d, *J* = 10 Hz, 1H), 5.69 (d, *J* =10 Hz, 1H), 4.30 (s, 2H), 3.95 (s, 3H), 3.91 (s, 3H), 1.71 – 1.52 (m, 10 H), 1.29 – 1.21 ppm (m, 6H). HRMS (ESI) *m/z* calcd for $C_{25}H_{32}N_2O_5S$ [(M + H)$^+$] 473.2110, found: 473.2127. HPLC: ret. time = 11.4 min, 95.0%.

6-bromo-2,2-dimethyl-2H-pyrano[3,2-b]pyridine(23)—To a solution 2-methyl-3-butyn-2-ol (**21**) in acetonitrile (6 mL) was added DBU (0.80 mL, 6.61 mmol) at 0 °C, then TFAA was added dropwise, also at 0 °C. The reaction was stirred for 30 min. In another round bottom flask, DBU (0.80 mL, 6.61 mmol) was added to a solution of 2-bromo-5-hydroxy pyridine (1g, 5.75 mmol) in 6 mL of acetonitrile at 0 °C. Then 2-methyl-3-butyn-2-ol was added dropwise into this reaction, which was stirred for 30 additional min. The solvent was removed by rotary evaporation, and the residue was diluted with DCM. After separation, the organic layer was washed with 1M HCl, 1M NaOH, sat $NaHCO_3$ and brine, was dried over $MgSO_4$ and concentrated in vacuum. The crude product was dissolved in 2 ml of xylene and subjected to microwave irradiation (130 °C, 220 W) for 30 min. The solvent was removed by rotary evaporation and the product concentrated in vacuum. The crude product was purified by column chromatography (silica gel) (10:1 Hx/EtOAc) to give 300 mg of a yellow solid (23 % over the two steps).^{1}H NMR ($CDCl_3$): 1.45 (s, 6H), 5.86 (d, 1H, *J* = 10.4), 6.44 (d, 1H, *J* = 10), 6.90 (d, 1H, *J* = 8.8), 7.14 ppm (s, 1H, *J* = 8.4). HRMS (ESI) *m/z* calcd for $C_{10}H_{11}NOBr$ [(M + H)$^+$] 240.0024, found: 240.0026.

2,2-Dimethyl-2H-pyrano[3,2-b]pyridine-6-carbaldehyde (24)—To a solution of **23** (200 mg, 0.83 mmol) in anhydrous THF (5 mL) at -78 °C was added BuLi (2.5M, 0.35 mL) and stirred for 35 minutes, then DMF (0.08 mL, 0.1 mmol) was added dropwise. The reaction was stirred at -78°C for 30 additional minutes. Water (3 mL) was added to quench the reaction and was extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography; 20:1 Hx/EtOAc. To give the product as a yellowish solid (23% yield).^{1}H NMR δ 1.53 (s, 6H), 6.01 (d 1H, *J* = 10.4), 6.58 (d, 1H, *J* = 10.4), 7.13 (d, 1H, *J* = 8.4), 7.77 (d, 1H, *J* = 8.4), 9.93 ppm (s, 1H).^{13}C NMR δ 28.8, 78.7, 123.0, 123.3, 123.4, 136.3, 145.8, 153.7, 191.9 ppm

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)aniline (25a)—**To a solution of 2,2-dimethyl-2H-pyrano[3,2-b]pyridine-6-carbaldehyde (434 mg, 2.28 mmol) in methanol (3 mL) was added aniline (0.3 mL, 2.52 mmol) and zinc chloride (621 mg, 4.56 mmol) and stirred at room temperature for 2 hours. Then $NaCNBH_3$ (287 mg, 4.56 mmol) was added and stirred overnight. Purification by column: 4: 1 Hx/ EtOAc to give an off-white solid. Yield: 48%.^{1}H NMR ($CDCl_3$) δ 1.49 (s, 6H), 4.361 (s, 2H), 5.91 (d, 1H, *J* = 10), 6.55 (d, 1H, *J* = 10), 6.68 – 6.71 (m, 3H), 7.01 (d, 1H, *J* = 8.4), 7.08 (d, 1H, *J* = 8.4), 7.18 – 7.38 ppm (m, 2H).

***N*-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxy-N-phenylbenzenesulfonamide (26a)—**To a solution of the **25a** (60 mg, 0.237 mmol) in dichloromethane (2.5 mL) was added triethylamine (0.07 mL, 0.474 mmol) and the 3,4-dimethoxybenzenesulfonyl chloride (84 mg, 0.355 mmol), the reaction was stirred for 24 hours. The reaction mixture diluted with DCM and the organic layer washed with then water and brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, 3:1 hexane/EtOAc to 1:1 hexane/EtOAc) to give an off-white solid (56 mg). Yield: 50 %, mp 143 C.^{1}H NMR ($CDCl_3$): δ 7.29 (dd, *J* = 8.4, 2.1 Hz, 2H), 7.25 – 7.17 (m, 3H), 7.14 – 7.09 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.92 – 6.86 (m, 2H), 6.32 (d, *J* = 10.1 Hz, 1H), 5.80 (d, *J* = 10.1 Hz, 1H), 4.78 (s, 2H), 3.94 (s, 3H), 3.72 (s, 3H), 1.40 ppm (s, 6H). HRMS (ESI) m/z calcd for $C_{25}H_{26}N_2O_5S$ [$(M + H)^+$] 467.1641, found 467.1641. HPLC: ret. time = 9.7 min, 98.1%

General Procedure for the synthesis of 26b – 26j by reaction with alkylsulfonyl chloride

To a solution of **25** (1 eq) in methanol was added the primary amine (1 equiv.), $ZnCl_2$ (2 equiv.) and the reaction was stirred at room temperature for 2 h. Then $NaCNBH_3$ (2 equiv.) was added and the reaction was stirred at room temperature overnight. The solvent was removed by rotary evaporation and EtOAc was added to the residue. The solid was filtered through Celite and the filtrate washed with 1M NaOH, water and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude secondary amine product was used without further purification.

To a solution of the secondary amine (1 equiv.) in DCM was added triethylamine (3 equiv.) and the sulfonylchloride (1.5 equiv.). The reaction was stirred for 24 to 48 h. Then water was added and the organic layer extracted with DCM, dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography.

***N*-Butyl-*N*-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (26b)—**Yield: 42%. ^{1}H NMR ($CDCl_3$): δ 7.45 (d, *J* = 2.4 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.04 (d, *J* = 8.4, 1H), 6.94 (d, *J* = 8.8, 1H), 6.40 (d, *J* = 8.0, 1H), 5.88 (d, *J* = 10, 1H), 4.37 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.18 (t, *J* = 7.6, 2H), 1.48 (s, 6H), 1.38 (m, 2H), 1.18 (sx, *J* = 7.2, 2H), 0.79 ppm (t, *J* = 7.2, 3H). ^{13}C NMR

($CDCl_3$): δ 152.4, 149.0, 148.8, 148.7, 135.4, 131.6, 123.7, 123.7, 122.7, 121.0, 110.5, 109.8, 56.2, 56.2, 53.3, 48.8, 30.2, 28.2, 19.9, 13.6 ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{31}N_2O_5S$ [$(M + H)^+$] 447.1954, observed: 447.1937. HPLC, ret. time = 11.4 min, 95.4%

***N*-(3,4-Dimethoxyphenyl)-N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (26c)—**Yield: 51%; mp 117 °C.^{1}H NMR δ ($CDCl_3$): δ 7.32 – 7.38 (m, 2H), 7.01 – 6.98 (m, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J*= 8.4 Hz. 1H), 6.68 – 6.62 (m, 2H), 6.34 (dd, *J* = 12.0, 0.4 Hz, 1H), 5.82 (d, *J* = 10.0 Hz, 1H), 4.76 (s, 2H), 3.96 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 1.43 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 152.6, 148.7, 148.7, 148.6, 148.5, 147.8, 140.2, 135.3, 132.2, 129.6, 123.6, 123.6, 122.6, 121.8, 121.0, 112.5, 110.5, 110.3, 56.2, 56.2, 56.1, 55.9, 28.2 ppm. HRMS (ESI) m/z calcd for $C_{27}H_{31}N_2O_7S$ [$(M + H)^+$] 527.1852 found: 527.1866, HPLC: ret. time = 7.6 min, 98.4%

***N*-Cyclopentyl-*N*-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (26d)—**Yield: 31%.^{1}H NMR ($CDCl_3$): δ 7.55 – 7.35 (m, 2H), 7.35 – 7.22 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.98 – 6.86 (m, 1H), 6.46 (dd, *J* = 14.7, 10.2 Hz, 1H), 5.89 (d, *J* = 10.1 Hz, 1H), 4.44 – 4.24 (m, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 1.76 – 1.15 ppm (m, 15H). ^{13}C NMR ($CDCl_3$): δ 152.4, 150.7, 149.0 148.5,140.0 135.4, 132.2, 123.8, 123.7, 121.9, 121.2, 110.5, 109.8, 59.4, 56.3, 56.2, 48.6, 29.1, 28.2, 23.4 ppm. HRMS (ESI) *m/z* calcd for $C_{24}H_{31}N_2O_5$ [$(M + H)^+$] 459.1954, found: 459.1938. HPLC: ret. time = 11.3 min, 96.9%.

***N*-Cyclohexyl-*N*-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (26e)—**Yield: 46%.^{1}H NMR ($CDCl_3$): 7.47 (dd, *J* = 2.4, 6.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.06 (d, *J* = 8.4, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.45 (d, *J* = 10 Hz, 1H), 5.88 (d, *J* = 10 Hz, 1H), 4.34 (s, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 3.80 (m, 1H), 1.64 (m, 3H), 1.48 (m, 9H), 1.25 -1.20 ppm (m, 4H). ^{13}C NMR ($CDCl_3$): δ 152.2, 150.7, 149.1, 148.5, 140.0, 135.2, 133.2, 123.7, 123.7, 122.5, 120.7, 110.6, 109.5, 58.4, 56.2, 56.1, 48.5, 31.3, 28.2, 26.1, 25.2 ppm. HRMS (ESI) *m/z* calcd for $C_{25}H_{33}N_2O_5S$ [$(M + H)^+$] 473.2110, found: 473.2118. HPLC: ret. time = 13.1 min, 96.8%

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxy-N-(5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide (26f)—**^{1}H NMR ($CDCl_3$): δ 7.39 – 7.31 (m, 2H), 6.99 (dd, *J* = 13.4, 5.2 Hz, 2H), 6.92 (dd, *J* = 8.1, 2.8 Hz, 2H), 6.81 (d, *J* = 7.6 Hz, 2H), 6.35 (d, *J* = 10.1 Hz, 1H), 5.94 – 5.71 (m, 1H), 4.78 (d, *J* = 25.5 Hz, 2H), 3.97 (s, 3H), 3.79 (d, J = 5.3 Hz, 3H), 2.65 (dd, *J* = 25.6, 13.3 Hz, 4H), 1.83 – 1.66 (m, 4H), 1.41 ppm (d, *J* = 16.1 Hz, 6H). MS (ESI) [$(M + H)^+$] 521. HPLC: ret. time = 15.6 min, 96.9%

***N*-Cycloheptyl-N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (26g)—**Yield: 18%; mp 73 °C^{1}H NMR ($CDCl_3$): δ 7.47 (dt, *J* = 4.4, 2.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.94 (dd, J = 8.5, 4.9 Hz, 1H), 6.45 (dd, *J* = 10.1, 0.5 Hz, 1H), 5.88 (d, *J* = 10.1 Hz, 1H), 4.44 – 4.29 (m, 2H), 3.96 (s, 3H), 3.94 (s, 1H), 3.93 (s, 3H), 1.62 – 1.29 ppm (m, 18H). HPLC: ret. time = 15.2 min, 98.8%

***N*-Cyclooctyl-N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (26h)—**Yield: 45%; mp 117° C^{1}H NMR ($CDCl_3$): δ 7.49 (d, *J* = 6.4, 1H), 7.46 (d, *J* = 10, 1H), 7.32 – 7.29 (m, 1H), 7.07 (d, *J* = 8.0, 1H), 6.94 (d, *J* = 8.4, 1H), 6.45 (d, *J* = 10, 1H), 5.89 (d, *J* = 10, 1H), 4.38 (s, 2H), 3.97 – 3.93 (m, 7H),

1.61 – 1.42 ppm (m, 20H). MS (ESI) *m/z* [(M + H)$^+$] 501. HPLC, ret. time = 16.5 min, 99.0%

***N*-Cyclobutyl-N-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (26i)—**Yield: 40%.^{1}H NMR ($CDCl_3$): δ 7.44 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.21 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.94 (t, *J* = 6.9 Hz, 1H), 6.40 (dd, *J* = 32.8, 10.0 Hz, 1H), 5.88 (t, *J* = 10.6 Hz, 1H), 4.49 – 4.28 (m, 3H), 3.96 (s, 3H), 3.93 (d, J = 3.0 Hz, 3H), 2.08 – 1.83 (m, 4H), 1.60 – 1.40 ppm (m, 8H). ^{13}C NMR ($CDCl_3$): δ 152.5, 150.3, 149.0, 148.6, 140.1, 135.4, 131.7, 123.8, 123.7, 121.8, 121.0, 110.5, 109.6, 77.4, 77.0, 76.7, 56.2, 56.2, 52.7, 49.3, 28.9, 28.2, 15.0 ppm. MS (ESI +) *m/z* [(M + H)$^+$] 445. HPLC: ret. time = 8.7 min, 97%

***N*-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-(4-fluorophenyl)-3,4-dimethoxybenzenesulfonamide (26j)—**Yield: 12%.^{1}H NMR ($CDCl_3$): δ 7.55 – 7.40 (m, 1H), 7.38 – 7.23 (m, 3H), 7.16 – 7.01 (m, 4H), 7.00 – 6.87 (m, 5H), 6.40 (t, *J* = 11.7 Hz, 1H), 5.88 (t, *J* = 13.4 Hz, 1H), 4.83 (d, *J* = 14.0 Hz, 2H), 3.97 (s, 3H), 3.86 – 3.73 (m, 3H), 1.44 ppm (s, 6H). HRMS (ESI) *m/z* calcd for $C_{25}H_{25}FN_2O_5S$ [(M + H)$^+$] 485.1546, found: 485.1531. HPLC: ret. time = 10.2 min, 97.6%.

General Procedure for 26k – 26t—To a solution of **25a** (1 equiv.) in pyridine at 0 °C was added the appropriate sulfonyl chloride dropwise. The reaction was allowed to warm up to room temperature overnight. The reaction mixture was then diluted with EtOAc and the organic layer was washed with 10% citric acid, sat. $NaHCO_3$, water and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel).

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-phenylcyclohexanesulfonamide (26k)—**Yield: 60%. ^{1}H NMR ($CDCl_3$): δ 7.30 – 7.22 (m, 4H), 7.07 – 7.01 (m, 2H), 6.90 (dd, *J* = 24.2, 1.8 Hz, 1H), 6.46 (dd, *J* = 29.3, 2.1 Hz, 1H), 5.86 (d, *J* = 29.3 Hz, 1H), 5.05 (d, *J* = 48.2 Hz, 1H), 4.90 (d, *J* = 48.2 Hz, 1H), 2.13 – 1.96 (m, 4H), 1.78- 1.70 (m, 5H), 1.44 (d, *J* = 6.3 Hz, 6H), 1.27 ppm (m, 2H). ^{13}C NMR ($CDCl_3$): δ 148.5, 148.3, 143.6, 140.4, 135.2, 129.1, 123.9, 123.8, 123.6, 122.0, 121.8, 92.4, 34.5, 31.8, 28.3, 28.2, 24.7, 21.7, 21.3 ppm. MS (ESI +) *m/z* [(M + Na)$^+$] 435. HPLC: ret. time = 10.16 min, 97.6%

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-phenylpropane-2-sulfonamide (26l)—**Yield: 58%.^{1}H NMR ($CDCl_3$): δ 7.37 – 7.19 (m, 4H), 7.16 – 6.99 (m, 2H), 6.93 (t, *J* = 9.4 Hz, 1H), 6.46 (dd, *J* = 10.1, 0.5 Hz, 1H), 5.87 (d, *J* = 10.1 Hz, 1H), 4.92 (dd, *J* = 36.5, 16.5 Hz, 2H), 1.81 (s, 3H), 1.75 (d, *J* = 11.8 Hz, 4H), 1.45 ppm (t, *J* = 5.8 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 148.5, 148.2, 143.1, 140.5, 135.3, 129.1, 124.2, 123.7, 123.6, 122.2, 122.1, 86.0, 28.3, 28.2, 27.4, 25.4 ppm. MS (ESI +) *m/z* [(M + H)$^+$] 373. HPLC: ret. time = 10.0 min, 97.8%.

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-phenylcyclopropanesulfonamide (26m)—**Yield: 46%. ^{1}H NMR ($CDCl_3$): δ 7.44 – 7.42 (m, 2H), 7.34 – 7.23 (m, 4H), 6.99 (d, *J* = 8 Hz, 1H), 6.40 (d, *J* = 10, 1H), 5.85 (dd, *J* = 10, 1H), 4.98 (s, 2H), 2.55 (m, 1H), 1.44 (d, *J* = 16.1 Hz, 6H), 1.13 - 1.11 (m, 2H), 0.98 - 0.95ppm (m, 2H). ^{13}C NMR ($CDCl_3$): δ 148.7, 148.1, 140.4, 139.7, 135.3, 129.1, 128.8, 127.7, 123.7, 123.6, 122.4, 56.2, 28.6, 28.2, 5.16 ppm. HPLC, ret. time = 8.31 min, 95.8%. HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_2O_3S$ [(M + Na)$^+$] 393.1212, found: 393.1231. HPLC: ret. time = 10.1 min, 98.3%

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-phenylbutane-1-sulfonamide (26n)—**Yield: 48%.^{1}HNMR ($CDCl_3$): δ 7.41 – 7.29 (m, 4H), 7.27 – 7.22 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.00 (dd, *J* = 12.4, 5.5 Hz, 1H), 6.41 (d, *J* = 10.1 Hz, 1H), 5.86 (d, *J* = 10.1 Hz, 1H), 4.94 (s, 2H), 3.38 – 2.79 (m, 2H), 1.96 – 1.77 (m, 2H), 1.54 – 1.38 (m, 8H), 1.12 – 0.77 ppm (m, 3H). ^{13}C NMR ($CDCl_3$): δ 170.85, 148.78, 148.19, 139.60, 135.37, 129.28, 128.34, 127.62, 123.68, 123.62, 122.54, 56.25, 51.28, 28.22, 25.29, 21.68, 13.61 ppm. MS (ESI) *m/z* [(M + H)$^+$] 387. HPLC, ret. time = 8.3 min, 95.8%.

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-phenylpropane-1-sulfonamide (26o)—**Yield: 20%; mp 120 °C^{1}H NMR ($CDCl_3$): δ 7.40 – 7.21 (m, 6H), 7.17 (d, *J* = 8.3 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.40 (d, *J* = 10.1 Hz, 1H), 5.85 (d, *J* = 10.1 Hz, 1H), 4.93 (s, 2H), 3.20 – 2.99 (m, 2H), 1.98 – 1.79 (m, 2H), 1.43 (s, 6H), 1.03 ppm (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 148.78, 148.18, 139.59, 135.38, 129.28, 128.35, 127.62, 123.67, 123.63, 122.53, 77.34, 77.02, 76.70, 56.19, 53.17, 28.21, 17.08, 13.09 ppm. MS (ESI) *m/z* [(M + H)$^+$] 373. HPLC: ret. time = 9.23 min, 97.4%.

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-2-methyl-*N*-phenylpropane-1-sulfonamide (26p)—**Yield: 28%. ^{1}H NMR ($CDCl_3$): δ 7.40 – 7.30 (m, 4H), 7.27 – 7.21 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.42 (d, *J* = 10.1 Hz, 1H), 5.89 (dd, *J* = 21.3, 10.0 Hz, 1H), 4.93 (s, 2H), 3.01 (dd, *J* = 14.1, 6.5 Hz, 2H), 2.34 (dd *J* = 13.3, 6.7 Hz, 1H), 1.47 (d, *J* = 14.5 Hz, 6H), 1.10 ppm (d, *J* = 6.7 Hz, 6H). MS (ESI) *m/z* [(M + H)$^+$] 387. HPLC, ret. time = 10.4 min, 96.3%.

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-N-phenylbiphenyl-4-sulfonamide(26q)—**Yield: 17%; mp 170 °C^{1}H NMR ($CDCl_3$): δ 7.69 (s, 4H), 7.67 – 7.60 (m, 2H), 7.57 – 7.41 (m, 3H), 7.36 – 7.22 (m, 5H), 7.21 – 7.13 (m, 2H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.34 (d, *J* = 10.1 Hz, 1H), 5.83 (t, *J* = 9.5 Hz, 1H), 4.86 (d, *J* = 5.9 Hz, 2H), 1.43 ppm (s, 6H). HRMS (ESI) *m/z* calcd for $C_{29}H_{27}N_2O_3S$ [(M + H)$^+$] 483.1742, found: 483.1723. HPLC, ret. time = 16.6 min, 96.1%.

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-phenylbenzo[d][1,3]dioxole-4-sulfonamide(26r)—**Yield: 65%; mp 187 °C^{1}H NMR ($CDCl_3$): δ 7.35 – 7.21 (m, 4H), 7.21 – 7.12 (m, 3H), 7.08 (t, J = 3.9 Hz, 1H), 7.02 – 6.93 (m, 1H), 6.88 – 6.78 (m, 1H), 6.36 (dd, J = 10.1, 0.5 Hz, 1H), 6.09 (s, 2H), 5.84 (dd, J = 14.0, 9.0 Hz, 1H), 4.82 (s, 2H), 1.68 (s, 2H), 1.43 ppm (s, 6H). HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_2O_5S$ [(M + H)$^+$] 451.1328, found: 451.1316. HPLC, ret. time = 10.7 min, 99.7%.

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-phenylquinoline-8-sulfonamide (26s)—**Yield: 65%; mp 149 °C^{1}H NMR ($CDCl_3$): δ 9.19 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.43 – 8.16 (m, 2H), 8.00 (dt, *J* = 10.5, 5.3 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.54 – 7.47 (m, 1H), 7.14 – 6.94 (m, 6H), 6.40 (d, *J* = 10.1 Hz, 1H), 5.85 (t, *J* = 15.1 Hz, 1H), 5.58 (d, *J* = 35.1 Hz, 2H), 1.45 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.3, 150,0, 148.5, 144.2, 140.1, 139.6, 137.1, 136.5, 135.1, 133.7, 133.5, 128.8, 128.8, 128.2, 127.2, 125.4, 123.9, 123.8, 122.4, 122.1, 77.4, 77.1, 76.9, 76.7, 58.8, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{26}H_{24}N_3O_3S$ [(M + H)$^+$] 485.1538, found: 485.1543. HPLC: ret. time = 10.0 min, 96.9%.

***N*-((2,2-dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-*N*-phenyl-2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamide(26t)—**Yield: 57%; mp 131 °C^{1}H NMR ($CDCl_3$); δ 1.419 (s, 6H), 4.33 - 4.28 (m, 2H), 4.81 (s, 2H), 5.82 (d, 1H, *J* = 10), 6.35 (d, 1H, *J* = 10), 6.89 (d, 1H, *J* = 8.4), 6.97 (d, 1H, *J* = 8.4), 7.06 (dd, 1H), 7.12 -7.15 (m, 2H), 7.20 – 7.30 ppm (m, 5H). ^{13}C NMR ($CDCl_3$): δ 148.6, 147.7, 147.5, 143.4, 140.2, 139.4, 135.2, 130.4, 128.8, 128.5, 127.6, 123.7, 123.6, 122.4, 121.6, 117.4, 117.4, 77.4, 77.1, 77.0, 76.7,

64.6, 64.1, 60.4, 55.7, 28.2, 21.1, 14.2 ppm. HRMS (ESI) *m/z* calcd for $C_{15}H_{15}N_2O_5S$ [(M + H)$^+$] 465.1484, found: 465.1489. HPLC: ret. time = 10.9 min, 98.2%.

***N*-((2,2-Dimethyl-2H-pyrano[3,2-b]pyridin-6-yl)methyl)-3,4-dimethoxy-*N*-phenylbenzamide (27)—**To a solution of **25a** (60 mg, 0.226 mmol) in DCM (3 mL) was added triethylamine (0.06 mL, 0.452 mmol) and 3,4-dimethoxybenzoyl chloride (54 mg, 0.271 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was washed with dH2O (×2) and sat. $NaHCO_3$ (× 2), dried over MgSO4 and concentrated in vacuo. Purification by column: silica gel: 3:1 DCM/EtOAc gave a quantitative yield of a light yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.26 – 7.17 (m, 3H), 7.17 – 7.08 (m, 3H), 7.06 – 6.97 (m, 2H), 6.95 (t, *J* = 5.0 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.53 – 6.40 (m, 1H), 5.92 – 5.79 (m, 1H), 5.16 (s, 2H), 3.83 (s, 3H), 3.66 (s, 3H), 1.46 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 169.9, 150.3, 149.0, 148.6, 147.9, 144.7, 140.6, 135.1, 129.0, 127.8, 127.2, 126.3, 124.0, 123.6, 123.0, 122.3, 112.6, 109.9, 77.4, 77.0, 77.0, 76.7, 55.8, 55.7, 55.6, 28.2 ppm. HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_2O_4$ [(M + H)$^+$] 431.1971, found: 431.1951.

2-Bromo-6-(hydroxymethyl)pyridin-3-ol (30)—A solution of 2-bromo-3-hydroxy-6-methylpyridine 1-oxide **29** (15g, 0.075 mol) in TFAA (50 mL, 0.375 mol) and was stirred at 40 °C for 24 h. The solvent was removed under vacuum. The residue was purified by column chromatography (silica gel: EA:Hex, 2:1). Yield: 4.5g, 30%. ^{1}H NMR ($CDCl_3$): δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 4.56 (s, 2H).

(6-Bromo-5-(2-methylbut-3-yn-2-yloxy)pyridin-2-yl)methanol (31)—Compound **30**(1.02g, 5 mmol) was dissolved in acetone (20 mL) and then K_2CO_3 (166 mg, 7mmol), KI (33.2 mg, 0.2 mmol), and $CuCl_2.2H_2O$ (33.2 mg, 0.02 mmol) were added. The suspension was stirred at 60 °C for 10 min. The solution of 3-chloro-3-methyl-2-butyne (1.02g, 5 mmol) in acetone (5 mL) was added dropwise to the solution of **30**. The reaction mixture was cooled to room temperature and the suspension filtered. The solid residue was washed with MeOH. The filtrate was concentrated under vacuum and purified with column chromatography (silica gel, EA: hexane, 1:1). Yield: 700 mg, 57%. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 4.72 (s, 2H), 1.73 ppm (s, 6H). ^{13}C NMR ($CDCl_3$): δ 154.7, 149.6, 137.03, 129.5, 120.4, 85.7, 75.8, 75.7, 64.6, 30.1 ppm.

(8-Bromo-2,2-dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methanol (32)—A solution of **31** (700 mg, 2.5 mmol) in toluene (10 mL) was subjected to microwave irradiation (200 W, 120 °C) for 1 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under vacuum and the residue purified by column chromatography (silica gel, EA:Hex 1:3 – 1:2). Yield: 500 mg,70%. ^{1}H NMR ($CDCl_3$):δ 6.88 (s, 1H), 6.28 (d, *J* = 10 Hz, 1H), 5.90 (d, *J* = 9.6 Hz, 1H), 4.63 (s, 2H), 1.51 ppm (s, 6H).

8-Bromo-6-(bromomethyl)-2,2-dimethyl-2H-pyrano[2,3-c]pyridine (33)—To a solution of **32** in DCM (2 mL) was added CBr_4 (66 mg, 0.2 mmol) and PPh_3 (264 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum and the residue purified by column chromatography (silica gel, EA:Hex, 1:4). Yield: 260 mg, 40%. ^{1}H NMR ($CDCl_3$): δ 6.28 (d, *J* = 10 Hz, 1H), 5.91 (d, *J* = 10 Hz, 1H), 4.47 (s, 2H), 1.53 ppm (s, 6H).

General Procedure for the synthesis of 34—To a degassed flask with **33** (1 eq) was added DMF, aniline (1.5 eq) and DIEA (1.5 eq). The mixture was stirred at room temperature overnight. Water (50 mL) was added to the reaction mixture and the resulting solution was extracted with ethyl acetate (3 × 25ml). The combined organic layers was washed with 0.5 N HCl (50 mL), 40 % $NaHCO_3$ (50 mL), water (50 mL) and brine, dried

over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (silica gel).

***N*-((8-bromo-2,2-dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methyl)benzenamine 34a—**Yield: 78%. ^{1}H NMR ($CDCl_3$): δ 7.26 - 7.21 (m, 3H), 6.97 - 6.95 (m, 3H), 6.23 (d, *J* = 9.6 Hz, 1H), 5.85 (d, *J* = 9.6 Hz, 1H), 4.40 (s, 2H), 1.48 ppm (s, 6 H).

***N*-((8-Bromo-2,2-dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methyl)cyclohexanamine (34b)—**Yield: 60%.^{13}C NMR (CD_3OD): δ 152.0, 145.2, 136.9, 129.7, 129.1, 119.8, 118.7, 78.5, 56.0, 49.8, 32.4, 26.8, 25.8, 24.7 ppm.

General Procedure for the synthesis of compound 35—A flask of secondary amine **34** (1 equiv.) was degassed and THF (anhydrous) was added under nitrogen. The solution was cooled to -78°C and stirred for 1 h. BuLi (2.5 equiv.) was the added to the solution dropwise at -78°C. The resulting solution was stirred for 1 h. Water (10 mL) was added to the solution, which was diluted with ethyl acetate (25 mL). After separation, the aqueous layer was extracted with ethyl acetate and washed with water (25 ml × 3) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (silica gel, EA: Hex, 1:4)

***N*-((2,2-Dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methyl)benzenamine (35a)—**Yield: 70%.^{1}H NMR (CD_3OD): δ 7.91 (s, 1H), 7.08 -7.04 (m, 3H), 6.59 – 6.57 (m, 3H), 6.28 (d, *J* = 9.6 Hz, 1H), 5.92 (s, *J* = 10 Hz, 1H), 4.88 (s, 2H), 1.41 ppm (s, 6H). ^{13}C NMR (CD_3OD): δ 152.3, 148.3, 148.2, 136.7, 135.2, 128.9, 128.7, 119.9, 117.8, 116.8, 112.6, 76.9, 26.8 ppm.

***N*-((2,2-Dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methyl)cyclohexanamine (35b)—**Yield: 50%.^{1}H NMR (CD_3OD): δ 7.95 (s, 1H), 7.08 (s, 1H), 6.44 (d, *J* = 9.6 Hz, 1H), 6.03 (d, *J* = 10 Hz, 1H), 3.78 (s, 2H), 2.46 (m, 1H), 1.97 – 1.75 (m, 5 H), 1.46 (s, 6H, 1.27 -1.16 ppm (m, 5H). ^{13}C NMR (CD_3OD): δ 151.5, 148.3, 136.7, 136.5, 128.7, 119.9, 119.0, 77.00, 56.0, 50.3, 32.4, 26.8, 25.8, 24.7 ppm.

General procedure for Synthesis of 36—A mixture of compound **35** (1 equiv.) and the appropriate sulfonyl chloride (2 equiv.) in pyridine was stirred overnight at room temperature. 1 M HCl was added to the reaction mixture and the solution extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with water (3 × 20 mL), brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue purified by column chromatography: silica gel (EA: Hex; 1:4).

***N*-((2,2-Dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methyl)-4-methoxy-*N*-phenylbenzenesulfonamide (36a)—**Yield: 50%. ^{1}H NMR (CD_3OD): δ 7.76 (s, 1H), 7.59 – 7.56 (m, 2H), 7.25 – 7.18 (m, 3H), 7.09 – 7.04 (m, 4H), 6.37 (d, *J* = 10 Hz, 1H) 5.97 (d, *J* = 10 Hz, 1H), 4.88 (s, 3H), 4.78 (s, 2H), 3.084 (s, 3H), 1.40 ppm (s, 6H). ^{13}C NMR (CD_3OD): 163.5, 148.6, 139.3, 136.7, 136.1, 129.7, 129.3, 128.8, 128.5, 128.5, 127.6, 119.7, 119.4, 113.9, 77.1, 55.0, 54.9, 26.8 ppm. MS (ESI) m/z [$(M + H)^+$] 437. HPLC: ret. time = 9.6 min, 97.8%.

***N*-((2,2-Dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methyl)-4-nitro-*N*-phenylbenzenesulfonamide (36b)—**Yield: 59%. ^{1}H NMR (CD_3OD): δ 8.41 (dd, *J* = 2.0 Hz, 4.8 Hz, 2H), 7.89 (dd, *J* = 2.0 Hz, 4.8 Hz), 7.78 (s, 1H), 7.29 – 7.28 (m, 4H), 7.10 – 7.08 (m, 2H), 6.39 (d, *J* = 10 Hz, 1H), 6.00 (d, *J* = 10 Hz, 1H), 1.42 ppm (s, 6H). MS (ESI) *m/z* [$(M + H)^+$] 452. HPLC: ret. time = 9.03 min, 95.2%.

***N*-Cyclohexyl-*N*-((2,2-dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methyl)-4-isopropylbenzenesulfonamide (36c)—**Yield: 28%. ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 1H), 7.77 – 7.75 (m, 2H), 7.37 – 7.34 (m, 1H), 7.28 (d, J = 8.8 Hz, 1H), 6.34 (d, *J* = 9.6 Hz, 1H), 5.84 (d, *J* = 10 Hz, 1H), 4.42 (s, 2H), 3.80 (m, 1H), 2.99 (m, 1H), 1.75 – 1.59 (m, 3H), 1.55 – 1.39 (m, 9 H), 1.29 – 1.27 (m, 6H), 1.23 -1.19 ppm (m, 4H). ^{13}C NMR ($CDCl_3$): δ 153.8, 151.8, 148.1, 138.7, 136.7, 135.8, 128.1, 127.1, 127.3, 120.9, 118.9, 58.5, 48.7, 34.1, 28.0, 26.1, 25.1, 23.7 ppm. MS (ESI) *m/z* [$(M + H)^+$] 455. HPLC: ret. time = 18.6 min, 98.2%.

***N*-Cyclohexyl-*N*-((2,2-dimethyl-2H-pyrano[2,3-c]pyridin-6-yl)methyl)-3,4-dimethoxybenzenesulfonamide (36d)—**Yield: 28%. ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.50 – 7.47 (m, 1H), 7.33 – 7.29 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.36 (d, *J* = 9.6 Hz, 1H), 5.86 (d, *J* = 9.6 Hz, 1H), 5.32 (s, 2H), 3.967 (s, 3H), 3.94 (s, 3H), 3.97 (m, 1H), 1.68 -1.52 (m, 4H), 1,48 (s, 6H), 1.28 -1.20 ppm (m, 4H). ^{13}C NMR ($CDCl_3$): δ 151.7, 149.1, 136.7, 135.9, 133.2, 128.1, 120.8, 120.7, 118.9, 110.6, 109.5, 83.1, 58.5, 56.2, 56.2, 48.6, 31.4, 28.0, 26.1, 25.1 ppm. MS (ESI) *m/z* [$(M + H)^+$] 473. HPLC: ret. time = 10.3 min, 97.3%.

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Abbreviations

AP	alkaline phosphatase
CBP	CREB-binding protein
HIF	hypoxia inducible factor
HRE	hypoxia-responsive element

ODDD	oxygen –dependent degradation domain
PHD	prolyl hdroylase
VEGF	vascular endothelial growth factor
pVHL	von Hippel-Lindau protein

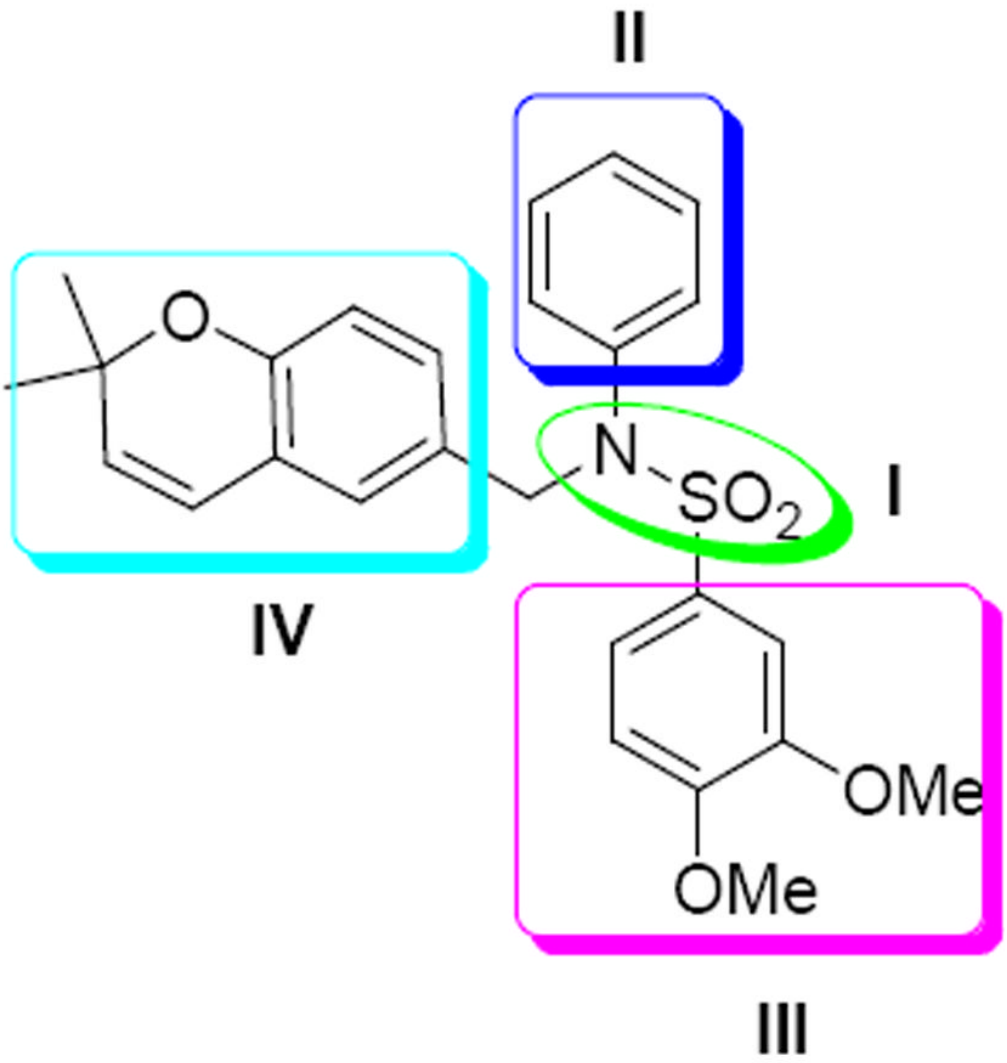


Figure 1.
Four regions for modification of **1**

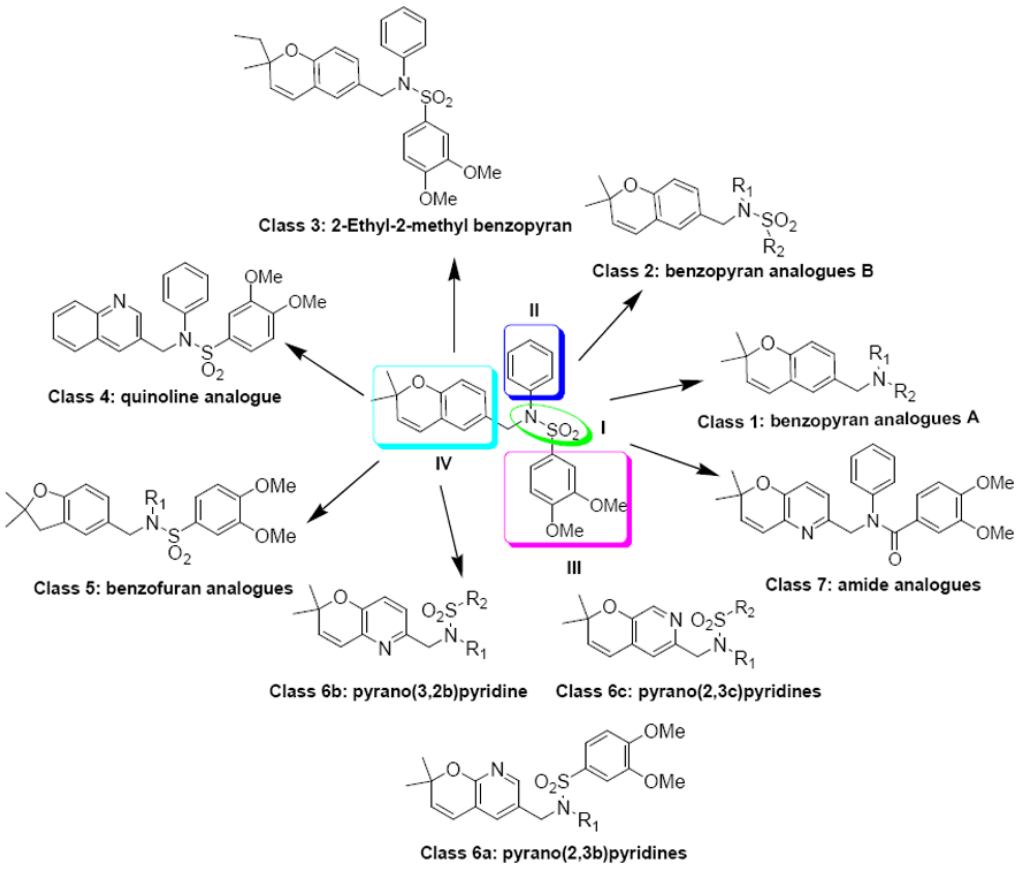
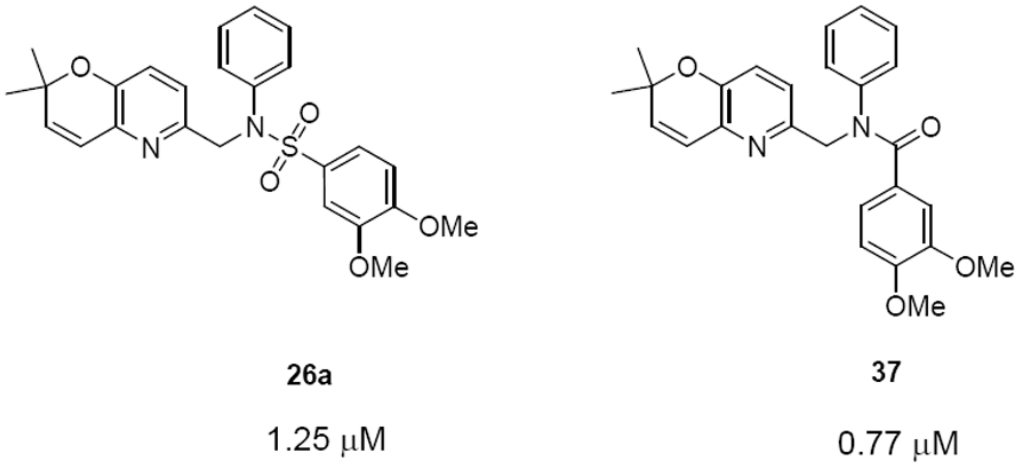


Figure 2.
Analogues designed and synthesized



26a

1.25 μM

37

0.77 μM

Figure 3.
Comparison of structures and activities of **26a** and **37**

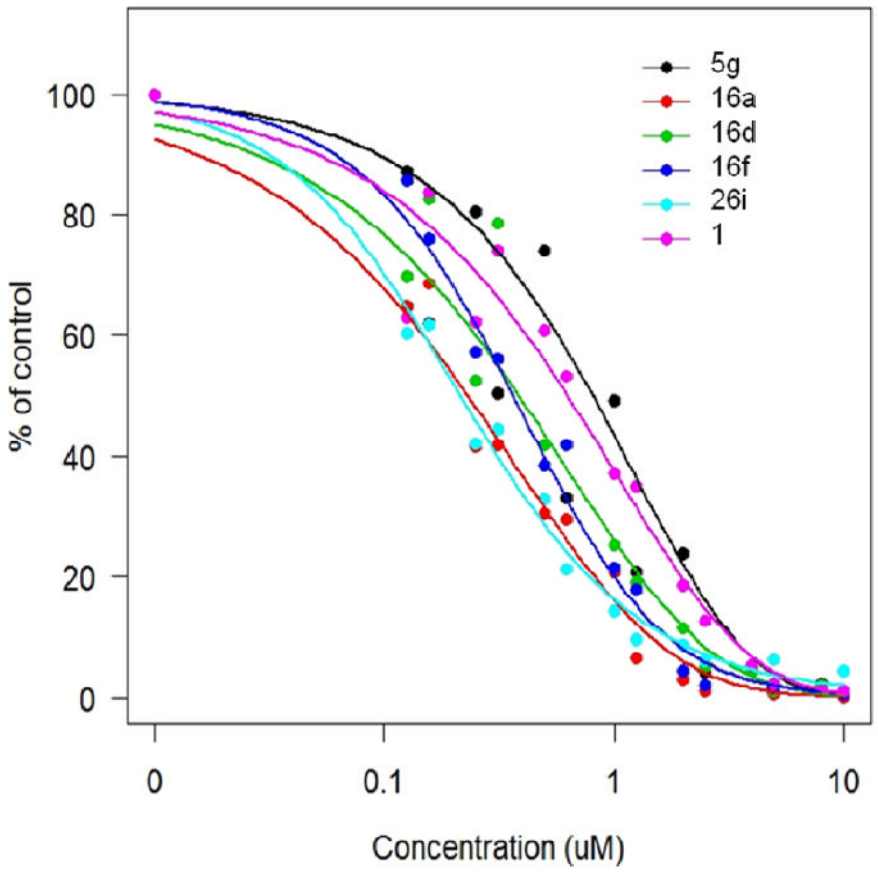


Figure 4.

Dose-response of a selected set of compounds using the HRE-luciferase reporter system. Cells were pre-treated with various concentrations of inhibitors (control 1% DMSO) for 1 h in normoxia, followed by 24 hrs incubation in hypoxia with inhibitors present. Luciferase activity was measured in cell extracts using a 20/20^{n} Luminometer (Turner Biosystems). Data, expressed as percent of control, are averages from at least 4 independent experiments carried out in triplicates.

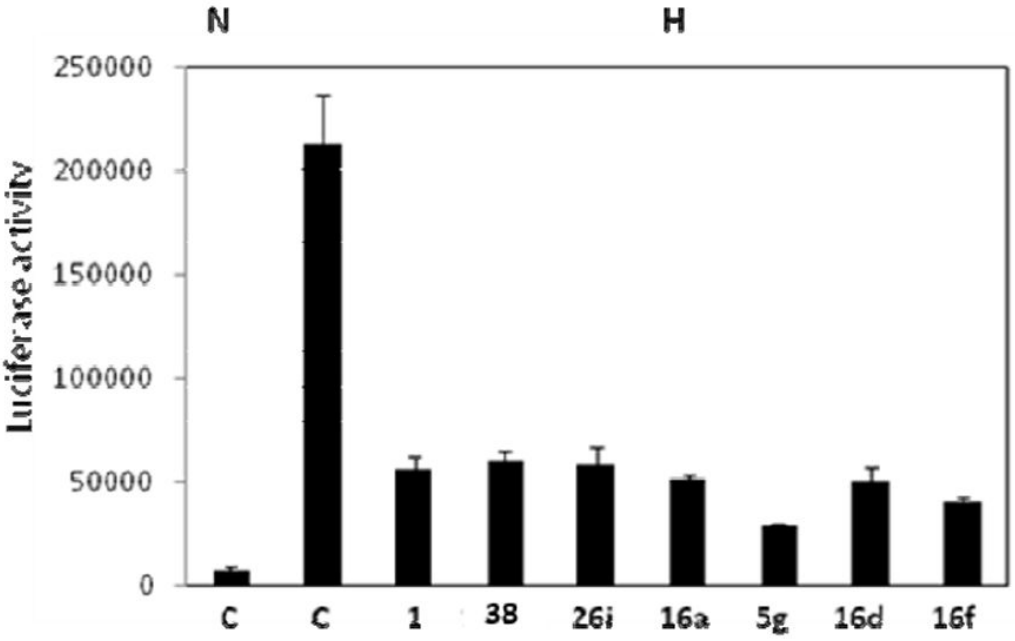


Figure 5.

Luciferase reporter assays showing the effect of the selected set of compounds in LN229-VEGF-luc cells. Cells were pre-treated with inhibitors (10 μM final concentration) for 1 h in normoxia, followed by 24 hrs incubation in normoxia (N) or hypoxia (H) and luciferase measured as indicated in Figure 4. Each value represents an average from triplicates +/- standard deviation.

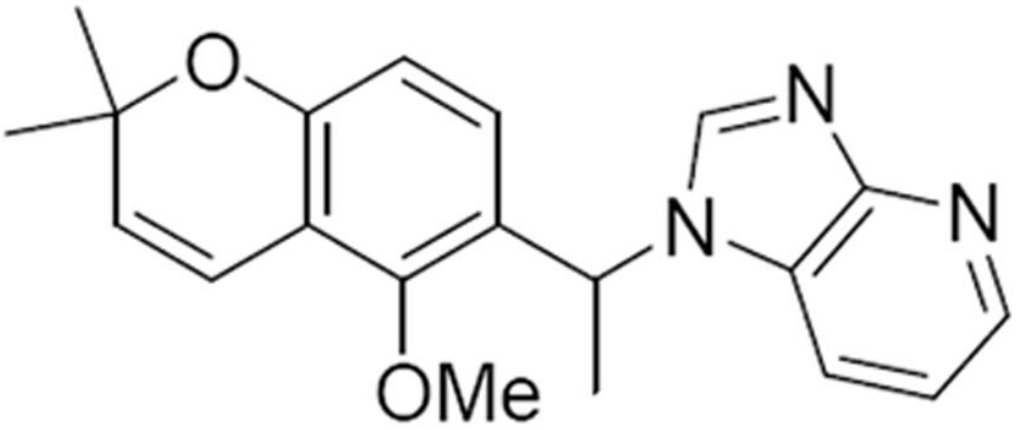


Figure 6.
Structure of **38** (103D5)[33]

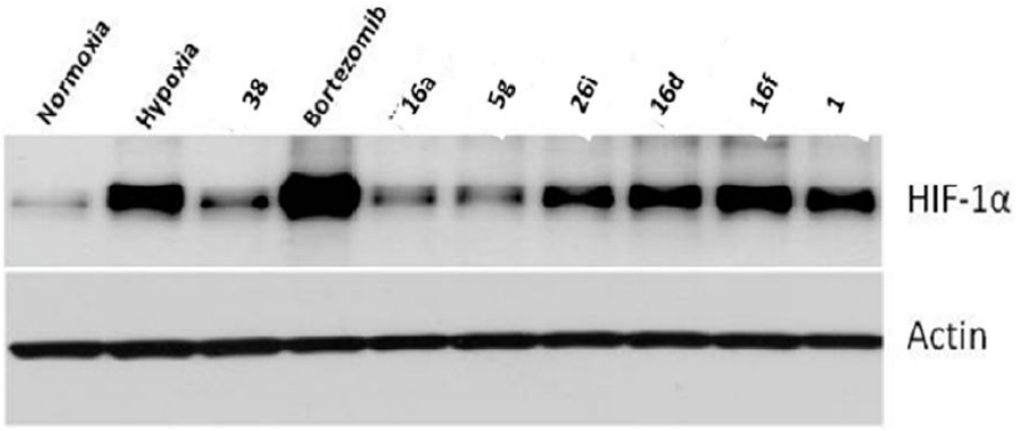


Figure 7.

Western blots showing the effect of the selected set of compounds on hypoxic accumulation of HIF-1α in LN229 cells. Cells were pre-treated with indicated inhibitors at 20 μM final concentration (bortezomib 100 nM) for 1 h before incubation in normoxia or hypoxia for 24 hrs. Immunoblotting of HIF-1α and actin was as described earlier.

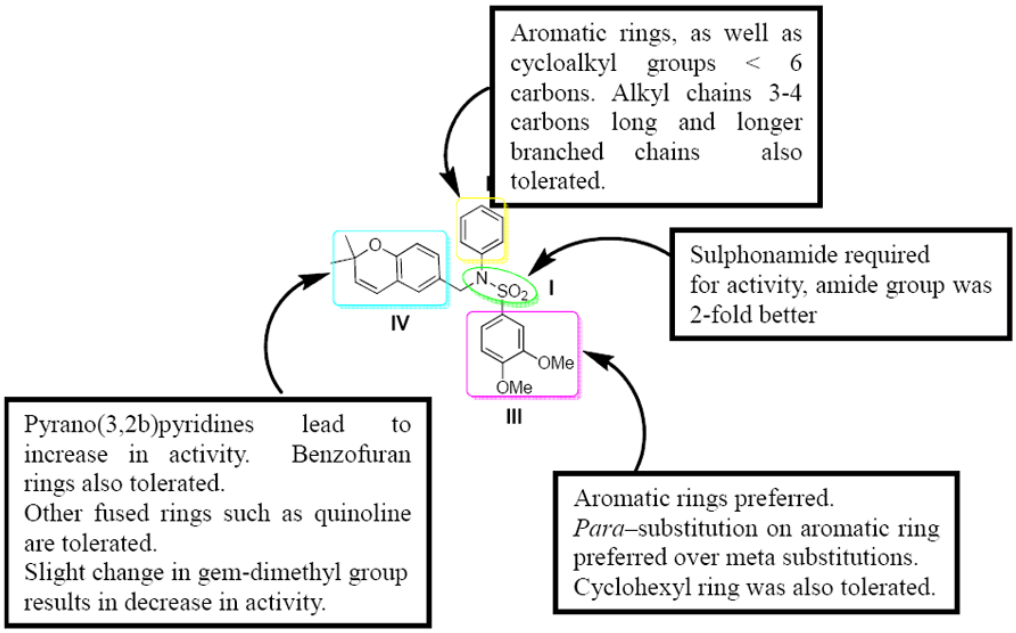
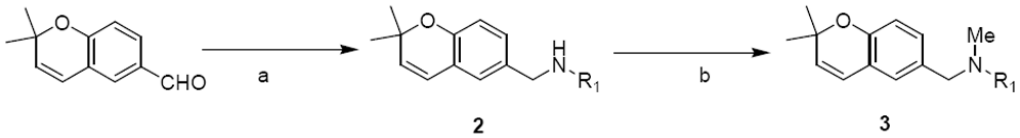


Figure 8.
Structure-activity relationship of **1**

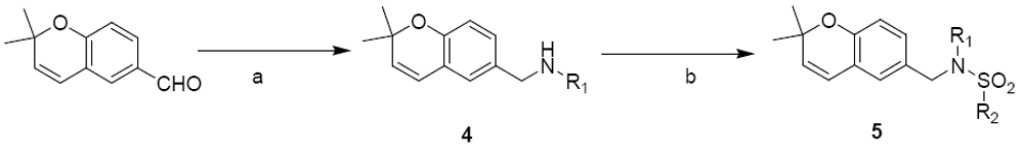


Scheme 1.

Synthesis of benzopyran analogues A[a]

R_1 = 3,4-dimethoxyphenyl (**2a, 3a**), 2-pyridinyl (**2b, 3b**), 2,4-dimethylphenyl (**2c, 3c**), 4-carboxyphenyl (**2d**), 2-bromophenyl (**2e**), 2-fluorophenyl (**2f**)

[a]Reagents and Conditions: (a) R_1NH_2, $ZnCl_2$, $NaCNBH_3$, r.t., 11 – 70%; (b) MeI, NaH, THF, r.t., 50 – 81%.Class 2: Benzopyran analogues B



Scheme 2.

Synthesis of benzopyran analogues B[a]

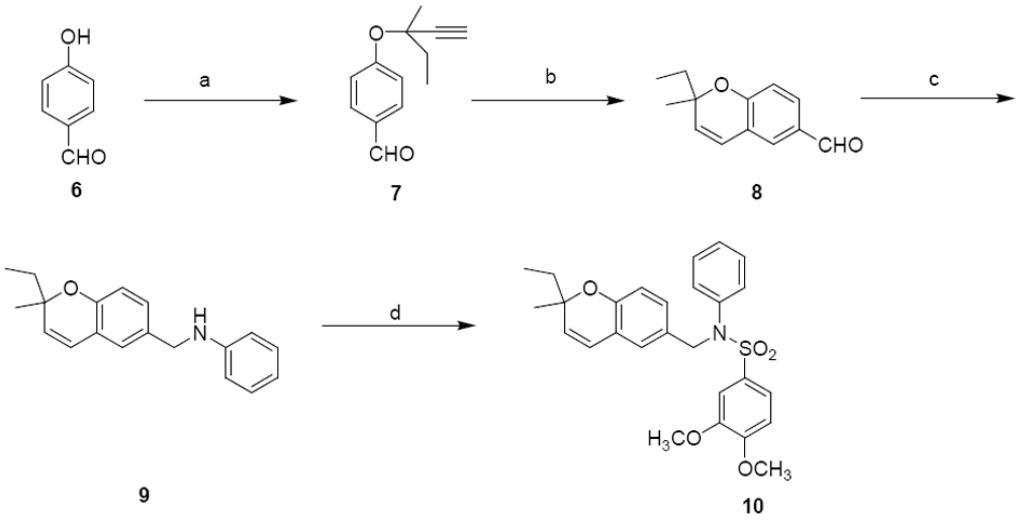
R_2 = 3,4-dimethoxyphenyl and

R_1 = phenyl (**1**), isopropyl (**5a**), propargyl (**5b**), butyl (**5c**), *t*-butyl (**5d**), allyl (**5e**), isobutyl (**5f**), cyclopentyl (**5g**), cyclopropyl (**5h**), cyclohexyl (**5i**)

R_1 = phenyl and

R_2 = 4-methoxyphenyl (**5j**), 3,5-dimethylphenyl (**5k**), 2,5-dichlorophenyl (**5l**), 2-trifluoromethoxy-4-bromophenyl (**5m**)

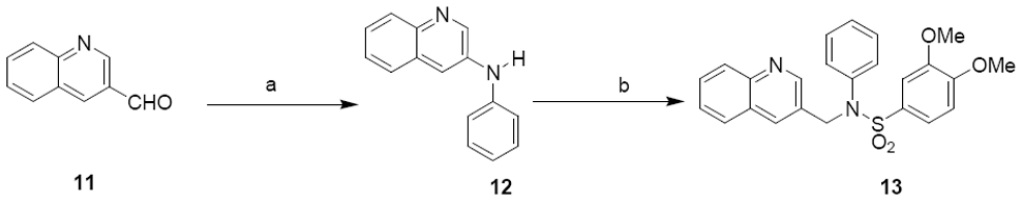
[a]Reagents and Conditions: (a) R_1NH_2, $ZnCl_2$, $NaCNBH_3$, r.t., 60 – 70%; (b) R_2SO_2Cl, Et_3N, DCM, r.t., 30 – 95%.



Scheme 3.

Synthesis of 2-ethyl-2-methylbenzopyran analogue[a]

[a]Reagents and Conditions: (a) 3-Methyl-pent-1-yn-3-ol DBU, TFAA, CuCl, CH_3CN, 0 °C to r.t., 30%; (b) xylene, microwave (220 W, 200 torr, 120 °C, 100 min; (c) aniline, $ZnCl_2$, $NaCNBH_3$, r.t., overnight, 41%; d) 3,4-dimethoxybenzylsulfonyl chloride, Et_3N, DCM, r.t., 24 h, 32%.

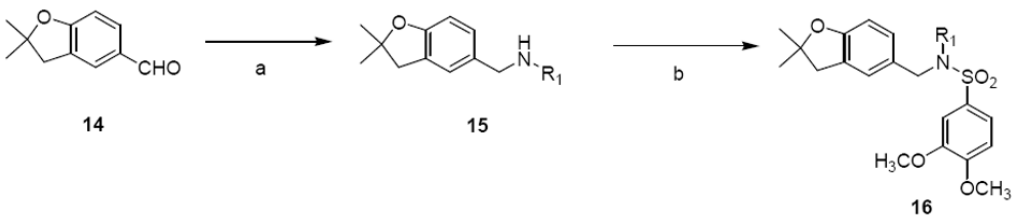


11 12 13

Scheme 4.

Synthesis of quinoline analogue[a]

[a]Reagents and Conditions: (a) aniline, $ZnCl_2$, $NaCNBH_3$, r.t., 64%; (b) 3,4-dimethoxybenzylsulfonyl chloride, pyridine. r.t., 45%.

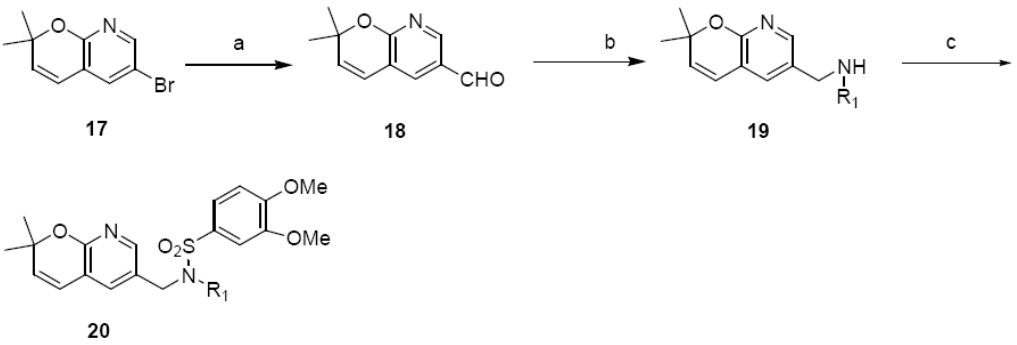


Scheme 5.

Synthesis of benzofuran analogues[a]

R_1 = phenyl (**16a**), cycloheptyl (**16b**), isopropyl (**16c**), butyl (**16d**), cyclohexyl (**16e**), cyclopentyl (**16f**)

[a]Reagents and Conditions: (a) R_1NH_2, $ZnCl_2$, $NaCNBH_3$, r.t., 2 h; (b) 3,4-dimethoxybenzenesulfonyl chloride, Et_3N, DCM, r.t., 14 – 42%.

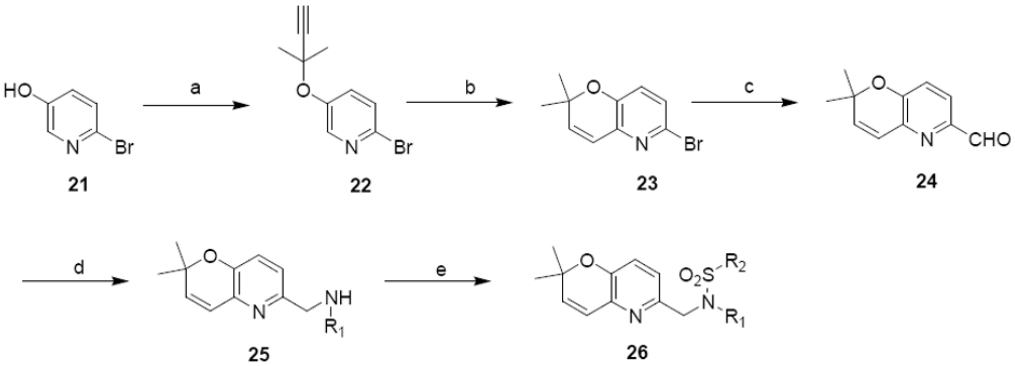


Scheme 6.

Synthesis of pyrano(2,3b)pyridine analogues[a]

R_1 = phenyl (**20a**), cyclohexyl (**20b**)

[a] Reagents and Conditions: (a) (i) BuLi, -78 °C (ii). DMF, anh.ether, 31%; (b) R_1NH_2, $ZnCl_2$, $NaCNBH_3$, MeOH, 49%; (c) 3,4-diethoxybenzenesulfonyl chloride, Et_3N, DCM, r.t., 43 – 60%.



Scheme 7.

Synthesis of pyrano(3,2b)pyridine analogues[a]

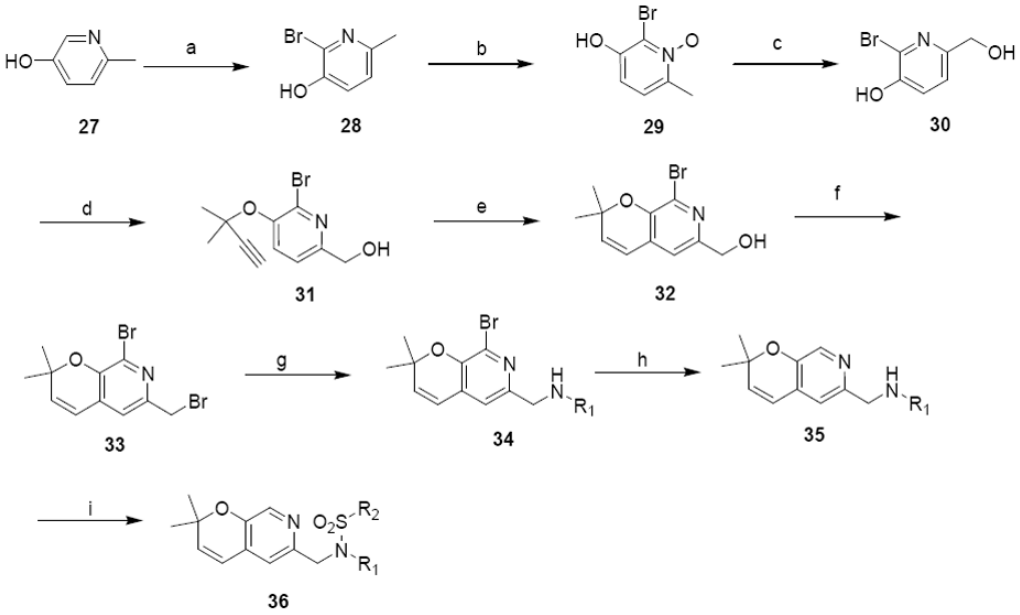
R_2 = 3,4-dimethoxyphenyl and

R_1 = phenyl (**26a**), butyl (**26b**), 3,4-dimethoxyphenyl (**26c**), cyclopentyl (**26d**), cyclohexyl (**26e**), tetrahydranapthyl (**26f**), cycloheptyl (**26g**), cyclooctyl (**26h**), cyclobutyl (**26i**), p-fluorophenyl (**26j**)

R_1 = phenyl and

R_2 = cyclohexyl (**26k**), isopropyl (**26l**), cyclopropyl (**26m**), butyl (**26n**), propyl (**26o**), isobutyl (**26p**), 4-biphenyl (**26q**), benzodioxolyl (**26r**), quinolin (**26s**), 2,3-dihydrobenzo(1,4)dioxinyl (**26t**)

[a] Reagents and Conditions: (a) 2-methylbut-3-yn-2-ol, TFAA, DBU, CH_3CN; (b) xylene, microwave heating 120 °C, 30 min, 23% for 2 steps; (c) 1. BuLi, 2. DMF, anhydrous THF, 23%; (d) R_1NH_2, $ZnCl_2$, $NaCNBH_3$, MeOH; (d) R_2SO_2Cl, Et_3N, DCM, 40 – 65% for 2 steps.



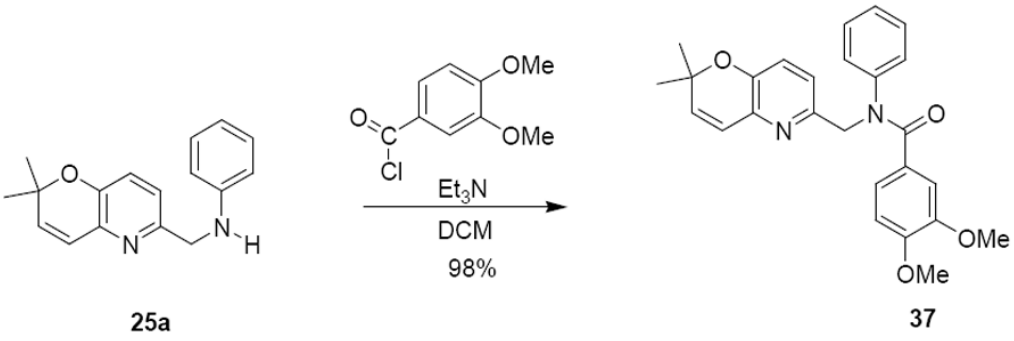
Scheme 8.

Synthesis of pyrano(2,3c) pyridine analogues[a]

R_1 = phenyl and R_2 = 4-methoxyphenyl (**36a**), 4-nitrophenyl (**36b**)

R_1 = cyclohexyl and R_2 =4-isopropylphenyl (**36c**), 3,4-dimethoxyphenyl (**36d**)

[a] Reagents and Conditions: (a) Br_2, pyridine, 0°C, 74%; (b) m-CPBA, THF, 70%; (c) 1. TFAA, 2. MeOH, 30%; (d) 3-chloro-3-methyl -1-butene, K_2CO_3, KI, $CuCl_2$, acetone, 57%; (e) CuCl, toluene, microwave heating (200 W, 120 °C, 1 hour), 70%; (f) CBr_4, PPh_3, DCM, 40%; (g) DIEA, DMF, 60 - 78%; (h) BuLi, THF, -78°C, 50 – 70% (i) R_2SO_2Cl, pyridine, r.t., 70 – 89%.

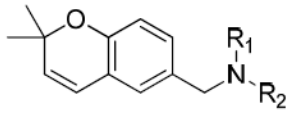


25a 37

Scheme 9.
Synthesis of compound **37**

Table 1

Structures and activities of analogues **2a** to **3c**



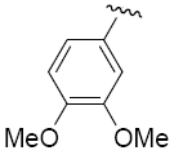
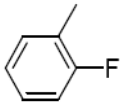
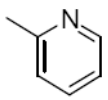
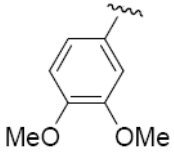
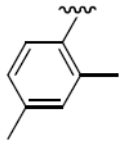
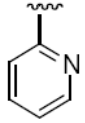
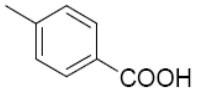
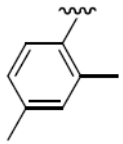
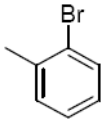
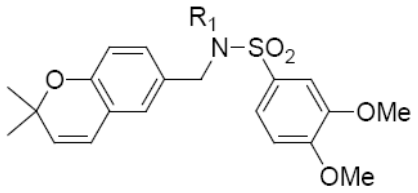
Compound	R_1	R_2	IC_{50} (μM)	Compound	R_1	R_2	IC_{50} (μM)
2a	H		3.0	**2f**	H		>25
2b	H		8.5	**3a**	Me		5.0
2c	H		>25.	**3b**	Me		8.4
2d	H		>25	**3c**	Me		2.6
2e	H		>25				

Table 2

Structures and activities of analogues **5a – 5i**



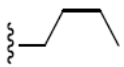
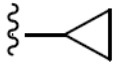
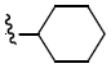
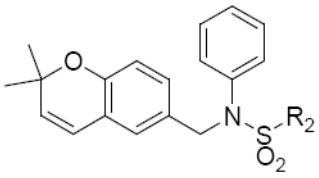
Compound	R_1	IC_{50} (μM)	Compound	R_1	IC_{50} (μM)
5a		3.1	**5e**		3.4
5b		1.3	**5f**		1.6
5c		3.3	**5g**		0.5
5d		3.5	**5h**		1.5
			5i		4.0

Table 3

Structures and activities of analogues **5j – 5m**[a]



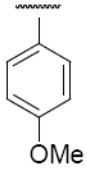
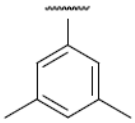
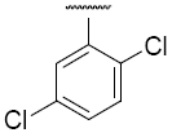
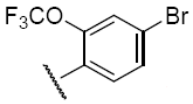
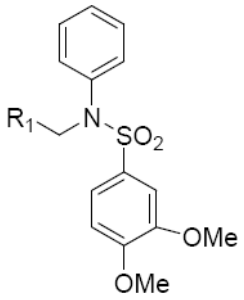
Compound	R_2	IC_{50} (μM)
5j		0.6
5k		0.5
5l		2.1
5m		>25

Table 4

Structures and activities of analogues **10** and **13** [a]



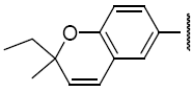
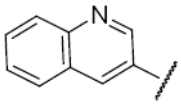
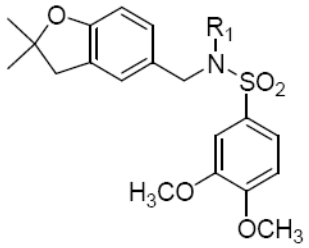
Compound	R_1	IC_{50} (μM)
10		3.1
13		1.3

Table 5

Structures and activities of analogues **16a-f**[a]



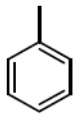
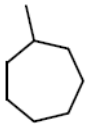
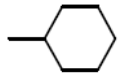
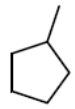
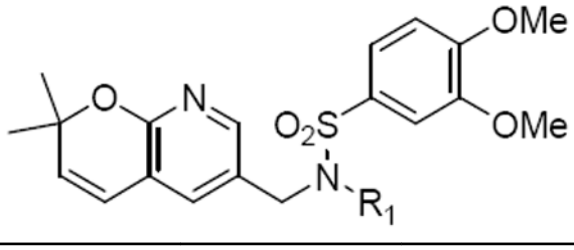
Compound	R_1	IC_{50}	Compound	R_1	IC_{50}
16a		0.5	**16d**		0.6
16b		9.1	**16e**		8.2
16c		1.5	**16f**		0.4

Table 6

Structures and activities analogues **20a** and **20b**



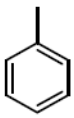
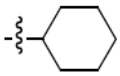
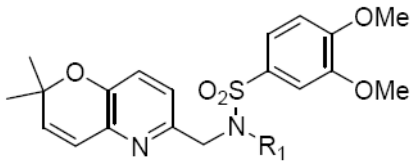
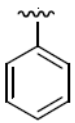
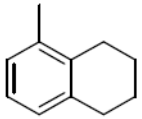
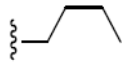
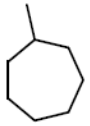
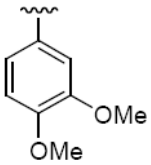
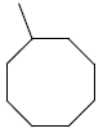
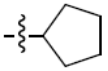
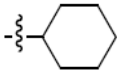
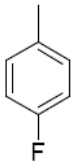
Compound	R_1	IC50 (μM)
20a		2.5
20b		>25

Table 7

Structures and activities of analogues **26a – 26j**[a]

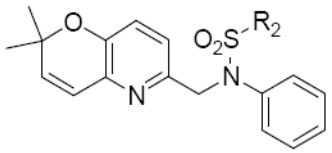


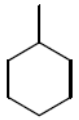
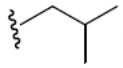
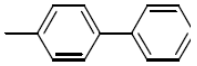
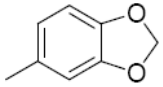
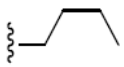
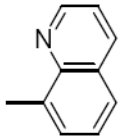
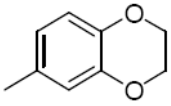
Compound	R_1	IC_{50} (μM)	Compound	R_1	IC_{50} (μM)
26a		1.3	**26f**		6.2
26b		0.9	**26g**		6.6
26c		>25	**26h**		0.7
26d		0.6	**26i**		0.25
26e		0.8	**26j**		5.7

[a]Results were from single runs

Table 8

Structure and activities of analogues **26k – 26t**[a]

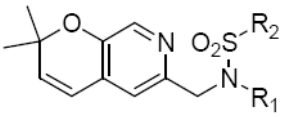


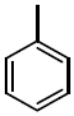
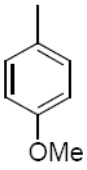
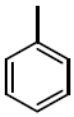
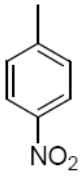
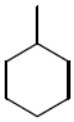
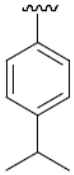
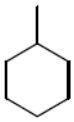
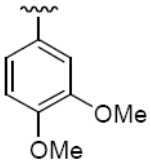
Compound	R_2	IC_{50} (μM)	Compound	R_2	IC_{50} (μM)
26k		0.4	**26p**		0.9
26l		13.4	**26q**		3.4
26m		>25	**26r**		6.5
26n		5.0	**26s**		0.9
26o		6.4	**26t**		0.9

[a]Results were from single runs

Table 9

Structures and activities analogues **36**[a]



Compound	R_1	R_2	IC_{50} (μM)
36a			1.4
36b			1.8
36c			1.1
36d			5.8

[a]Results were from single runs

Table 10

Average IC_{50} (from n independent experiments in μM) of selected arylsulfonamide HIF-1 pathway inhibitors as established in the HRE-luciferase assay.

Name	# of repeats	IC_{50}	Std. Error	95% CI
1	42	0. 648	0.044	(0.562, 0.734)
16a	6	0.306	0.06	(0.187, 0.425)
5g	6	0.813	0.141	(0.533, 1.093)
16d	6	0.478	0.105	(0.270, 0.686)
16f	6	0.378	0.062	(0.255, 0.501)
26i	30	0.280	0.022	(0.237, 0.323)

CI - Confidence Interval.