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Dehydrative formation and biological evaluation of allylic sulfonamides from allylic alcohols using recyclable silica-supported acid catalysts

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A reusable transition-metal-free catalytic system has been developed to facilitate the dehydrative sulfonamidation of primary and secondary allylic alcohols under mild reaction conditions. The method employs *p*-toluenesulfonic acid as an immobilized Brønsted acid on a silica gel solid-support, and the catalytic system has been shown to be recyclable without significant loss of activity for 3–5 uses. A wide range of sulfonamide and allylic alcohol substrates are tolerated in this transformation, and products have been isolated from reactions employing known pharmaceuticals such as celecoxib and methocarbamol as nucleophilic substrates. The antibacterial, antifungal, and cytotoxic properties of the isolated products was investigated along with their activity as metabolic inhibitors of ATP production.

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Introduction

Allylamines are important structural units in the production of fine chemicals and biologically active compounds,[1] making the development of new methods to synthesize them a valuable synthetic goal. The allylamine unit is an important feature in natural products and pharmacological agents, but they are also valuable intermediates that can be further modified by either functionalizing the double bond or using reductive or oxidative processes to produce a variety of other compounds.[2] Allylic sulfonamides are a particularly important subset of *N*-allylamines due to their prevalence as structural features in a variety of biologically active compounds and medicinal agents (Fig. 1).[3] Construction of the *N*-allyl sulfonamide moiety is most directly accomplished by *N*-allylation methods, but this approach can be challenging due to the relatively low nucleophilicity of sulfonamides as compared to electron-rich amines.

In a general sense, common approaches toward the incorporation of a nucleophile to an allyl unit involves the activation of an allyl moiety with a good leaving group such as tosylate, phosphate, or acetate (Scheme 1A),[1] and/or the use of a transition-metal (such as Pd,[4] Pt,[5] Ir,[6] Au,[7] Ru,[8] Ni,[9] Re,[10] and Hg[11]) to form a reactive *p*-allyl complex to serve as an electrophilic unit (Scheme 1B).[12] Using allylic alcohol as a reactive substrate is synthetically attractive, but it is largely underdeveloped because the hydroxyl group has poor leaving group ability and metal catalysts have low tolerance to water.[1,13] The most direct means of *N*-allylation involves a dehydrative coupling of an *N*-nucleophile (such as an amine, amide, or sulfonamide) with an allylic alcohol which results in water as the only by-product (Scheme 1C).[1,13] Brønsted acid-promoted reactions can provide

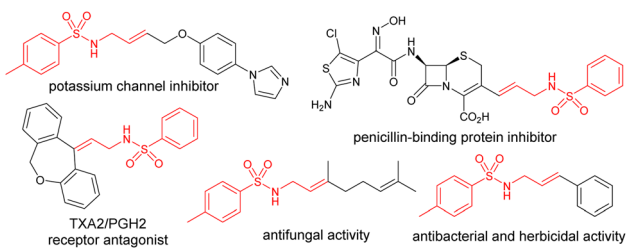
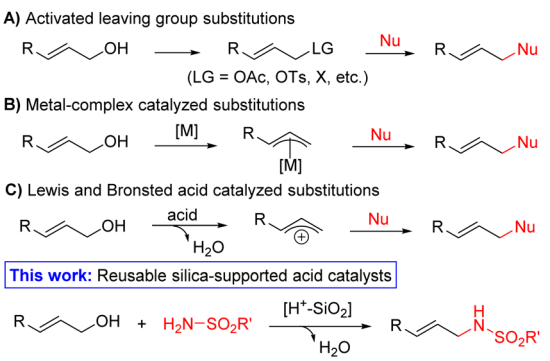


Fig. 1 Examples of biologically active allylic sulfonamides (*N*-allyl sulfonamide unit shown in red).



Scheme 1 General approaches toward substitution of the hydroxyl group of an allylic alcohol.

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a metal-free approach for direct substitution of 3° and 2° allylic alcohols, and a variety of nucleophiles have been described using either stoichiometric or catalytic loadings of Brønsted or Lewis acids (montmorillonite,[14] Al,[15] Fe,[16] Bi,[17] Mg,[18] Ca,[19] and others[20]). However, limitations associated with substitutions of 1° allylic alcohols and the inability to recover and reuse the acid leaves room for a more atom-economical transformation to be developed.

In recent years, catalyst immobilization in a solid-supported system has been an effective approach to minimize the amount of catalyst used in a reaction and to make it reusable, which are both important aspects of the "green chemistry" initiative. Numerous examples of immobilized catalysts on solid carriers have been reported but may suffer from a time-consuming and/or difficult preparation of the heterogeneous catalyst.[21] In contrast, the immobilization of a homogeneous catalyst to a solid support such as commercial grade silica gel *via* a co-condensation method is operationally simple and cost-effective.[21] Silica-supported Brønsted acid catalysts have received a great deal of attention over the past two decades for a wide variety of synthetic transformations due to their attractive features offered in the areas of "green chemistry", atom-economy, and catalyst reusability.[21,22] A direct condensation of benzylic alcohols with sulfonamides and amides has been reported along with a condensation of secondary allylic alcohols and amides.[22d] However, to our knowledge, the activation of allylic alcohols using silica-supported acid catalysis for reaction with a sulfonamide nucleophile has not been reported.

Allylic alcohols are a structural motif found in a variety of natural products and medicinal agents and are often widely available as bulk feedstock chemicals.[23] In terms of the allylic alcohols typically employed in methods that involve installation of a nucleophile, the majority of reports tend to utilize 3° and 2° allylic alcohol substrates, which are more reactive than 1° allylic alcohols. Cinnamyl alcohol, a 1° allylic alcohol, is a large volume feedstock but is rarely used in allylic amination under transition-metal-free conditions. Considering the prevalence of the *N*-cinnamyl functional motif in FDA-approved drugs and bioactive compounds, it stands to reason that a dehydrative condensation reaction that utilizes cinnamyl alcohol as reactive partner under mild conditions would provide a valuable tool for the synthetic and medicinal chemistry communities. For this reason, our aim is to develop a method that can effectively activate a less reactive 1° allylic alcohol such as cinnamyl alcohol under mild reaction conditions. Herein, we describe the screening of several silica-supported acid catalysts for the direct dehydrative condensation of unactivated primary and secondary allylic alcohols with sulfonamides and subsequent investigation of the catalyst reusability.

Results and discussion

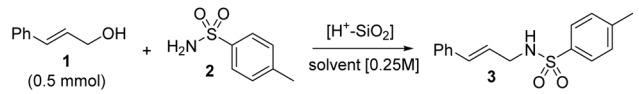
Reaction development, synthesis of library compounds, and mechanistic investigation

To begin our investigation, a series of solid-supported acid catalysts were prepared in a co-condensation method based upon literature precedent using four different Brønsted acids (sulfuric acid, triflic acid, perchloric acid, and *p*-toluenesulfonic acid) in 3 mol% and 6 mol% acid loadings.[22] Initial reaction conditions for solid-support catalyst screening were selected to offer operationally convenient and practical settings (Table 1). It was observed that the reaction is more efficient at 65 °C than at 20 °C using all catalysts (see SI for full details of optimization), so reactions were performed at 65 °C in a sealed screwcap reaction vessel for all subsequent reactions.

As shown in Table 1, PTSA-SiO_2 (3 mol%) was observed as the most efficient solid-support acid catalyst (entries 1–4). Deuterated chloroform was initially used as solvent in order to directly monitor the formation of product **3** and the yield was determined by ^{1}H NMR integration using 1,3-dinitrobenzene as internal standard. Additional solvents were tested (entries 5–7), and chloroform was observed as the best solvent. Next, variation of the stoichiometry of cinnamyl alcohol and sulfonamide substrates (entries 8–11) indicate that an excess of sulfonamide leads to the highest yield of product **3** (entry 9, 63% yield). The use of PTSA-SiO_2 (6 mol%) resulted in a 68% yield of **3** when using a lower stoichiometric excess of sulfonamide (entry 11). Lastly, variation of the amount of solid-support silica catalyst (entries 13 and 14) indicate that a similar yield of **3** is obtained when decreasing from 55 mg to 30 mg of PTSA-SiO_2, but a more noticeable decrease in yield of **3** was observed when a larger loading of 80 mg of silica-gel was used (decreasing from 58% to 48%). The resulting optimized reaction conditions are as follows: 1.0 equiv. (0.5 mmol) of allylic alcohol 1, 2.0 equiv. of sulfonamide 2, 55 mg of PTSA-SiO_2 (6 mol%), chloroform (0.25 M) in a sealed screwcap vessel heated with stirring at 65 °C for 6 hours.

With optimized reaction conditions, we set out to explore the substrate scope (Fig. 2). Upon attempting to isolate the allylic

Table 1 Optimization of reaction conditions



Entry[a]	Equiv. **2**	Acid catalyst (mol%)	Solvent	Yield **3**[b] (%)
1	1.1	SA (3%)	$CDCl_3$	15
2	1.1	TfOH (3%)	$CDCl_3$	24
3	1.1	$HClO_4$ (3%)	$CDCl_3$	32
4	1.1	PTSA (3%)	$CDCl_3$	43
5	1.1	PTSA (3%)	THF	0
6	1.1	PTSA (3%)	DCE	32
7	1.1	PTSA (3%)	DCM	38
8	0.5	PTSA (3%)	$CDCl_3$	32
9	3.0	PTSA (3%)	$CDCl_3$	63
10	2.0	PTSA (3%)	$CDCl_3$	58
11	**2.0**	**PTSA (6%)**	**$CDCl_3$**	**68**
12	1.1	PTSA (6%)	$CDCl_3$	49
13	2.0	PTSA (3%)[c]	$CDCl_3$	64
14	2.0	PTSA (3%)[d]	$CDCl_3$	48

[a] Entries 1–14: 6-hour reaction time, 65 °C, 55 mg silica gel. SA = sulfuric acid; TfOH = triflic acid; $HClO_4$ = perchloric acid; PTSA = *p*-toluenesulfonic acid. [b] Yield of **3** determined by ^{1}H NMR integration using 1,3-dinitrobenzene as internal standard. [c] 30 mg silica gel. [d] 80 mg silica gel.

sulfonamide products, we found that the 2 : 1 excess of sulfonamide from the optimized conditions can lead to difficult separation (due to overlap of product with unreacted sulfonamide), and isolation was cleaner when using 1.1 equivalents of sulfonamide substrate. We first sought to investigate the more reactive (*E*)-1,3-diphenyl-2-propen-1-ol as a 2° allyl alcohol substrate using the reaction conditions. At 65 °C, a complex mixture was observed by crude ^{1}H NMR after 6 hours. However, when the reaction was performed at room temperature (20 °C) for 6 hours, product **4** was cleanly produced and isolated in 79% yield. Thus, this method provides a rare example of non-metal catalyzed allylic sulfonamidation of an unactivated 2° allylic alcohol at ambient (20 °C) temperature.[7c,10,15,17,20h,24] The reaction was also shown to be scalable, with a 87% yield of **4** obtained in a gram-scale reaction. For all subsequent reactions utilizing the 2° diphenyl allylic alcohol substrate, the lower temperature (20 °C) reaction conditions were employed. Isolated yields from reactions employing aryl sulfonamides with electron-withdrawing (aryl halides and nitro) or donating groups (alkyl and alkoxy) on the benzene unit were tested, and the functionalities were tolerated under the reaction conditions (products **4–13**).

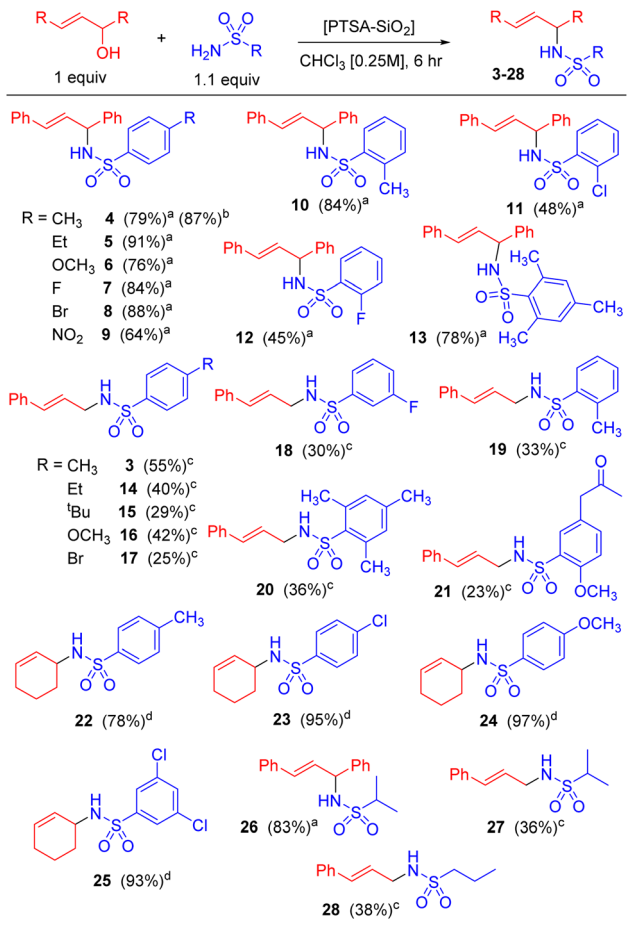


Fig. 2 Substrate scope: sulfonamidation of allylic alcohols. All products are isolated. (a) Reaction performed at 20 °C. (b) Gram-scale reaction (1.1 grams isolated). (c) Reaction performed at 65 °C. (d) Reaction performed at 45 °C.

In addition to diphenyl allyl substrate, we turned our attention to the sulfonamidation of the less commonly employed cinnamyl alcohol. Isolated yields from sulfonamidation of cinnamyl alcohol are noticeably lower (23–72% for products **3** and **14–21**) of the 1° allylic alcohol than for the more reactive secondary/benzylic diphenyl allyl alcohol (yields of **4–13** ranging from 45–91%). Additionally, 2-cyclohexen-1-ol was explored as an allylic alcohol substrate and it was determined that the reaction is best performed at 45 °C for 6 hours (see SI). Sulfonamidated products **22–25** were isolated from 2-cyclohexen-1-ol in excellent yields ranging from 78–97%. Lastly, the use of alkyl sulfonamides was demonstrated resulting in products **26–28**.

To further demonstrate the applicability of the silica-supported acid catalyst approach, the pharmaceutical celecoxib was employed as sulfonamide substrate and was cleanly added to (*E*)-1,3-diphenyl-2-propen-1-ol to form **29** in a 83% isolated yield (Fig. 3). In addition to sulfonamide, the approach also tolerates an amine as nucleophile, as demonstrated by the formation of product **30** in excellent yield from cinnamyl alcohol. As shown in Fig. 3, allylic substitution occurs exclusively *via* the primary amine N-atom, which is more nucleophilic than the sulfonamide N-atom. Finally, the pharmaceutical methocarbamol was employed using the carbamate functionality as nucleophile (Fig. 3, product **31**), indicating that the dehydrative formation *via* silica-supported acid catalyst approach has potential to create a library of products from carbamate substrates in addition to sulfonamide and amine. The product of *O*-allylation, potentially from the alcohol group on methocarbamol, was not observed.

To demonstrate the catalyst reuse at the two extremes of the reaction conditions (20 °C and 65 °C), two separate substrates were selected for catalyst recycling experiments. The sulfonamidation of cinnamyl alcohol (**1**) with *p*-toluenesulfonamide (**2**) was carried out according to the optimized reaction conditions for a primary allylic alcohol (Fig. 4, Box A). The use of PTSA-SiO_2 (3 mol%) and PTSA-SiO_2 (6 mol%) were tested separately. In the catalyst reuse experiments, the reaction was performed at 65 °C for 6 hours and then the silica gel was filtered and washed with chloroform. The filtrate was analyzed by ^{1}H NMR using an internal standard to determine the yield of **3**. The silica gel was

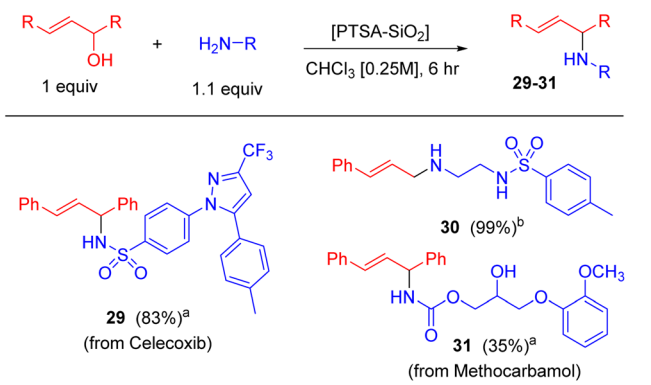
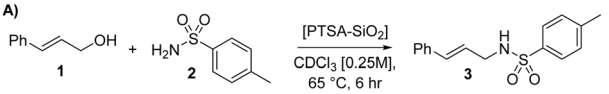


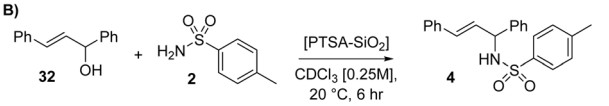
Fig. 3 Substrate scope: additional representative *N*-nucleophiles. All products are isolated. (a) Reaction performed at 20 °C. (b) Reaction performed at 65 °C.

A)



Entry	Catalyst	Catalyst use	^{1}H NMR %Yield of **3**
1	PTSA-SiO_2 (3 mol%)	**Fresh**	61
2	PTSA-SiO_2 (3 mol%)	1st recycle	57
3	PTSA-SiO_2 (3 mol%)	2nd recycle	40
4	PTSA-SiO_2 (3 mol%)	3rd recycle	31
5	PTSA-SiO_2 (3 mol%)	4th recycle	11
6	PTSA-SiO_2 (3 mol%)	5th recycle	0
7	PTSA-SiO_2 (6 mol%)	**Fresh**	65
8	PTSA-SiO_2 (6 mol%)	1st recycle	59
9	PTSA-SiO_2 (6 mol%)	2nd recycle	59
10	PTSA-SiO_2 (6 mol%)	3rd recycle	67
11	PTSA-SiO_2 (6 mol%)	4th recycle	57
12	PTSA-SiO_2 (6 mol%)	5th recycle	33
13	PTSA-SiO_2 (6 mol%)	6th recycle	1

B)



Entry	Catalyst	Catalyst use	^{1}H NMR %Yield of **4**
1	PTSA-SiO_2 (6 mol%)	**Fresh**	98
2	PTSA-SiO_2 (6 mol%)	1st recycle	92
3	PTSA-SiO_2 (6 mol%)	2nd recycle	74
4	PTSA-SiO_2 (6 mol%)	3rd recycle	28
5	PTSA-SiO_2 (6 mol%)	4th recycle	12
6	PTSA-SiO_2 (6 mol%)	5th recycle	1

Fig. 4 Reusability of PTSA-SiO_2 catalyst: Box A = recyclability at 65 °C; Box B = recyclability at 20 °C.

allowed to air dry, then dried under vacuum for 5–10 minutes, and weighed. The next reaction was then performed with the stoichiometry adjusted to the amount of silica gel. As shown in Fig. 4, the use of PTSA-SiO_2 (3 mol%) displayed a significant decrease in activity after two recycles. The PTSA-SiO_2 (6 mol%) proved to be more robust, with a yield >50% of **3** being obtained in the fourth recycle of silica gel catalyst. The ability to recycle the PTSA-SiO_2 (6 mol%) catalyst four times without significant loss of activity is in line with other reported applications of solid-supported acid catalysts in reactions that generate water as a byproduct.[22b]

To test the PTSA-SiO_2 (6 mol%) catalyst reuse for reactions performed at 20 °C, diphenyl allyl alcohol **32** was used as substrate with *p*-toluenesulfonamide (**2**). After 6 hours, the catalyst was removed by filtration, air-dried, dried under vacuum for 5–10 minutes, and weighed prior to being reused. The filtrate was analyzed by ^{1}H NMR to determine yield of **4** using an internal standard. As seen in Fig. 4 Box B, reuse of PTSA-SiO_2 (6 mol%) is not as effective at 20 °C, with significant loss of activity being observed during the third recycle step.

It is plausible that the higher reaction temperature (65 °C) plays a role in removing the water formed in the reaction to the walls of the reaction vessel as an azeotrope. In the lower temperature conditions, the water would be completely sequestered by the silica gel, which may inactivate the catalyst by blocking or coordination with the Brønsted acid sites of the catalyst system.

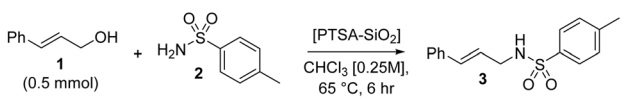
In an attempt to further understand the mechanistic role and limitations of the catalyst system, a series of control experiments was performed (Fig. 5). The use of silica gel without embedded catalytic acid to promote sulfonamidation of cinnamyl alcohol **1** did not result in any observable formation of product **3**, which indicates the embedded acid is an essential component of the catalyst system. The use of an equimolar amount of PTSA without silica gel resulted in a reduced yield of **3**. We hypothesized that this positive effect of the PTSA-SiO_2 catalytic system might be due to the hygroscopic nature of the silica gel.

The inactivation of the PTSA-SiO_2 catalyst in the reuse experiments may be due to: (1) leaching of the acid from the silica gel during the reaction; or (2) saturation of the silica gel with water generated during the reaction, which can block or coordinate the Brønsted acidic sites of the catalyst.

The absorption of a stoichiometric equivalent of water by the silica gel each time the reaction is performed may be the cause for the inactivation of the catalyst in the reuse experiments. To test the effect of water on the activity of the PTSA-SiO_2 catalyst, an experiment was conducted in which 3 stoichiometric equivalents of H_2O was added to the reaction mixture at the beginning of the reaction period. The use of 3 equivalents was meant to simulate the PTSA-SiO_2 after 3 successive reactions of use, recovery, and reuse. The observed yield of **3** was 50%, which is reduced from the yield observed in the absence of water (66%). An additional experiment was conducted in which 6 stoichiometric equivalents of water was added at the beginning of the reaction period, and the yield of **3** was reduced to 35%. This result indicates that the absorption of H_2O by the PTSA-SiO_2 catalyst is responsible for decrease in activity.

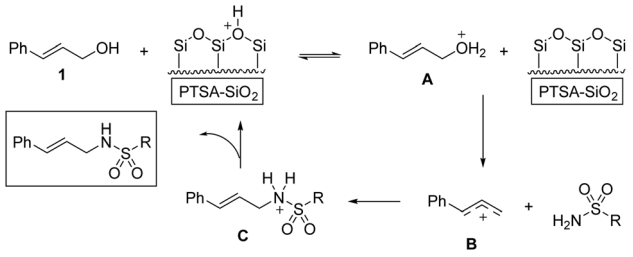
To test for the possibility of acid leaching from the silica gel, we tested the solvent on the top of the vessel wall with pH paper following a reaction and it was observed to be slightly acidic. Therefore, we believe that it is most likely a combination of catalyst inactivation by absorption of water and acid leaching out of the silica gel, with the water saturation of active sites likely playing a larger role.

The exact nature of the reaction mechanism with regard to the interaction of the substrate with the PTSA-SiO_2 catalyst is unclear at this time. However, a plausible mechanism that is based upon observations of product formation and preliminary mechanistic experiments is displayed in Scheme 2. In the mechanism, the catalytic PTSA-SiO_2 protonates the allylic alcohol substrate (**A**) which can then dehydrate to the allylic cation (**B**). The sulfonamide nucleophile then attacks **B** at the more accessible C atom to form protonated species **C**, which



Variation from optimized conditions	% Yield of **3**
1) None	66%
2) Silica gel instead of [PTSA-SiO_2]	0%
3) PTSA instead of [PTSA-SiO_2]	58%
4) Addition of 3 equiv H_2O at start of reaction	50%
5) Addition of 6 equiv H_2O at start of reaction	35%

Fig. 5 Mechanistic control reactions with yields determined by ^{1}H NMR using internal standard.



Scheme 2 Plausible reaction mechanism.

regenerates the acidic PTSA-SiO_2 and forms the allylic sulfonamide product.

In vitro antibacterial and antifungal screening of 3–31

To test the bactericidal effects of the library compounds, a cell viability screening of **3–31** (50 μM; 18-hour compound exposure) against *E. coli* (DH5α strain), a representative Gram-negative bacteria, was conducted using CellTiter-Glo (CTG) Cell Viability (Promega) assay. The negative control used for the screening is a blank well that contains cells and DMSO solvent. Activity values are displayed as percent of the negative DMSO control (POC). To determine the maximum inhibition, known antibacterials ampicillin, kanamycin, and carbenicillin were used as positive controls (**+C**). A "strong hit" is defined within this investigation as a compound with a POC value within 25% of the maximum inhibition observed by **+C**, indicating a high increase in the number of dead cells. A graphical depiction of the activity of compounds **3–31** is shown in Fig. 6. The compounds display little to no effect on *E. coli* at 50 μM when compared to known antibacterials ampicillin, kanamycin, and carbenicillin.

In addition, the antifungal properties of **3–31** were investigated in a cell viability screening (50 μM; 18-hour compound exposure) against *Saccharomyces cerevisiae*. None of the compounds showed strong activity at 50 μM when compared with clove essential oil, a positive control in the screening (Fig. 7).

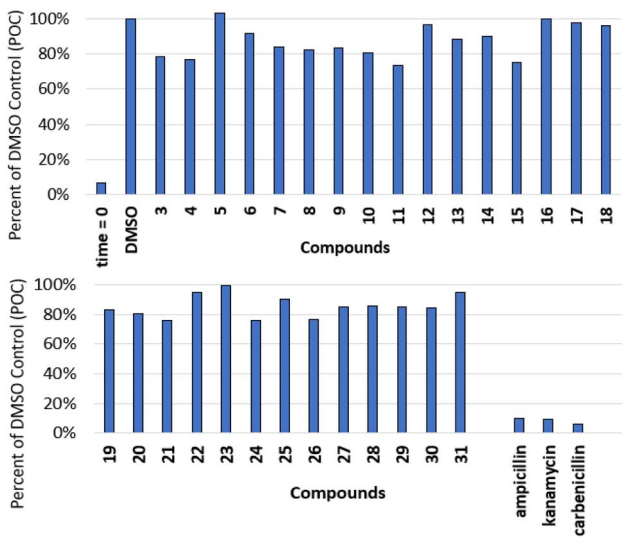


Fig. 6 Bacterial cell viability assay (*E. coli*) using compounds **3–31** at 50 μM (CellTiter-Glo kit, Promega) and 18-hour exposure. Values are shown as percent of DMSO control (POC).

In vitro cytotoxicity screening of 3–31

In order to determine the general cytotoxicity of **3–31**, the synthesized compounds were evaluated at a single concentration (50 μM; 24-hour compound exposure) in DMEM cell media using CellTiter-Blue (CTB assay (Promega)). The compounds were screened against cancerous cell lines H293 (human embryonic kidney) and A549 (lung adenocarcinoma), and a noncancerous, immortalized cell line (HDF; human diploid fibroblast). All cell cultures were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). The complete results of the screening are displayed in Table S2 in the SI, and a graphical representation is shown in Fig. 8. Compounds **7**, **8**, **13**, and **23** displayed cytotoxicity within 25% of the positive control (**+C**; a combination of 10 mM 2-deoxy-D-glucose and 1.5 μM rotenone, which are known inhibitors of glycolysis and mitochondrial OXPHOS, respectively) against all three of the cell lines. In addition, compounds **9**, **12**, **15**, and **20** displayed cytotoxicity within 25% of the **+C** against two of the three cell lines (see Table S2).

From a structural standpoint, five of the eight cytotoxic compounds have *S*-aryl units that contain an electron-withdrawing substituent (*i.e.*, **7–9**, **12**, and **23**). In addition, both analogs with *S*-mesitylene aromatic units (**13** and **20**) display cytotoxicity. None of the *S*-alkyl analogs (**26–28**) or analogs synthesized from known pharmaceuticals (**29** and **31**) display significant cytotoxicity at 50 μM.

In vitro metabolic inhibition assays

Following the traditional 24-hour cytotoxicity screening of compounds **3–31**, we turned our attention to screening the

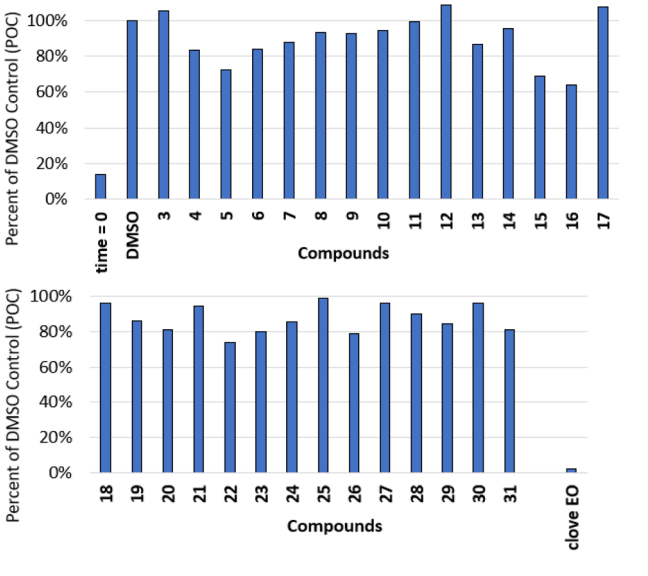


Fig. 7 Fungal cell viability assay (*Saccharomyces cerevisiae*) using compounds **3–31** at 50 μM (CellTiter-Glo kit, Promega) and 18-hour exposure. Values are shown as percent of DMSO control (POC). Clove EO = clove essential oil (positive control).

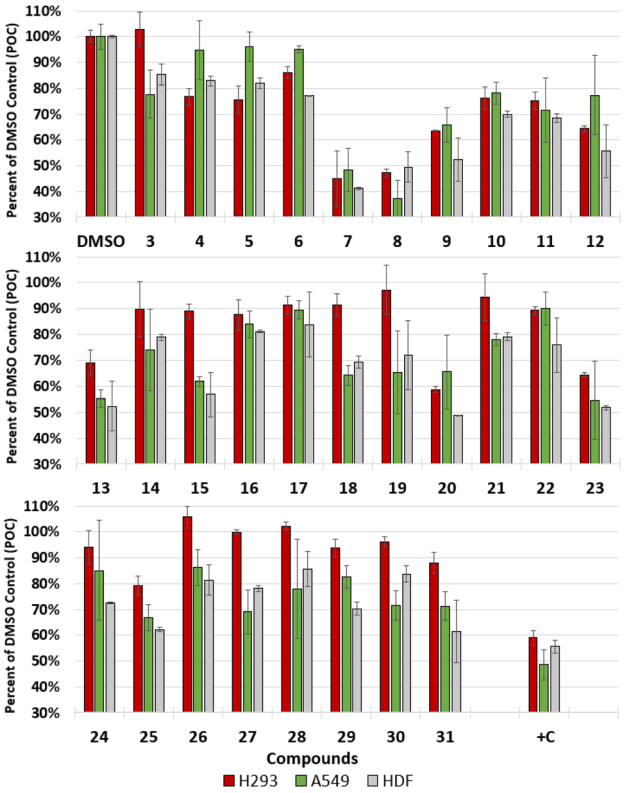


Fig. 8 Cytotoxicity screening of library compounds **3–31** (50 μM) with 24-hour compound exposure against cancerous H293 (red bars), A549 (green bars), and non-cancerous HDF (gray bars) cell lines using CellTiter-Blue assay. All values are shown as POC (percent of DMSO control) and error bars represent standard deviation calculated by Microsoft Excel with 85% CI from duplicate experiments. Lower POC values indicate stronger hits. Maximum inhibition, or positive control (**+C**), is determined from a mixture of 10 mM 2-DG and 1.5 μM rotenone.

compounds to detect activity as OXPHOS inhibitors of mitochondrial ATP production.[25] In several recent reports, we have described the synthesis and identification of novel sulfonamide-containing compounds with activity as oxidative phosphorylation (OXPHOS) inhibitors of mitochondrial ATP production toward pancreatic cancer and glioblastoma cell lines.[26] In our reports, a rapid assay was developed to identify compounds that possess biological activity that may not have been detected as hits during an initial traditional (24–72 hour compound exposure) cytotoxicity screening. A compound targeting OXPHOS ATP production may not be detectable in a 24–72 hour cell viability assay, as cells can redirect resources to glycolysis to meet their energy needs for survival.

We have described two different protocols for rapid screening of OXPHOS inhibition activity based upon the cell growth media employed: (1) addition of glycolysis inhibitor 2-deoxy-D-glucose (2-DG) to cell media (DMEM) to effectively block glycolysis, and (2) use of L-15 cell media which contains galactose instead of glucose.[26] Two ATP are required for the multi-step conversion of galactose to glucose-6-phosphate (G6P) in the Leloir pathway, which enters glycolysis to produce two ATP, thus resulting in a net production of 0 ATP. Compounds targeting OXPHOS are easily identified when results are compared in the presence and absence of glucose (L-15 *versus* L-15 plus 10 mM glucose). A noticeable decline in ATP levels is observable within 1–2 hours of compound exposure. This assay provides an early indication of eventual cell death, as the cells are unable to produce ATP due to the blockage of both glycolytic and OXPHOS pathways when a library compound has OXPHOS inhibiting activity.

As a comparable assay to the "L-15 *versus* L-15 plus glucose", our lab has developed a minimal media for cell growth that does not contain glucose, galactose, or amino acids. This minimal media allows for more control over the carbon-source nutrients available to the cells. In the assay, ATP levels are measured using CellTiter-Glo from cells cultured in "minimal media plus glucose" and compared to ATP levels from cells in "minimal media plus glutamine". Cells grown in "media plus glutamine" cannot enter glycolysis and can only produce ATP *via* the TCA cycle. Thus, compounds that inhibit ATP production in "media plus glutamine" but do not inhibit ATP production in "media plus glucose" are targeting mitochondrial OXPHOS in the TCA cycle.

Compounds **3–31** were screened at 25 μM against H293 cells using CellTiter-Glo assay in "media plus glucose" and "media plus glutamine" conditions and the graphical results against H293 are displayed as percent of DMSO control (POC) in Fig. 9 (full results in Table S3 of SI). Rotenone, a known OXPHOS inhibitor, is used as the positive control (**+C**). Several compounds display the characteristic activity of an OXPHOS inhibitor at 25 μM with inhibition of ATP production similar to rotenone against cancerous H293 cells.

CellTiter-Glo (CTG) is an assay that measures cell viability by lysing cell membranes and releasing intracellular ATP. The ATP then reacts with luciferin (a reagent in CTG), catalyzed by luciferase (also present in CTG), to generate a quantifiable light output. Thus, the intensity of the light is directly proportional to the amount of ATP present. In a separate control reaction performed (based upon literature precedent)[26g] in which exogenous ATP was added to media in the absence of cells, it was confirmed that compounds **3–31** (50 μM, 10 min exposure) do not inhibit the CellTiter-Glo luciferase assay itself (see Fig. S32 in SI).

Regarding structural variations of **3–31**, a few trends are apparent. None of the *S*-alkyl sulfonamides (compounds **26–28**) are active as OXPHOS inhibitors at 25 μM, indicating that an *S*-aryl unit is an important component. Allylic sulfonamides formed from 2-cyclohexen-1-ol (**22–25**) were also largely inactive as OXPHOS inhibitors except for compound **25**. All 10 of the allylic sulfonamides formed from (*E*)-1,3-diphenyl-2-propen-1-ol with *S*-aryl sulfonamides (compounds **4–13**) displayed OXPHOS inhibition activity, indicating that the *N*-allylic unit is also an important component. Seven of the nine allylic *S*-aryl sulfonamides derived from cinnamyl alcohol were also active (**3**, **14–17**, **19**, and **20**). Lastly, the allylic sulfonamides synthesized from known pharmaceuticals (**29** and **31**) were not active as OXPHOS inhibitors at 25 μM. It is particularly noteworthy that several compounds (**3–6**, **10**, **11**, **14**, **16**, **17**, and **19**) were

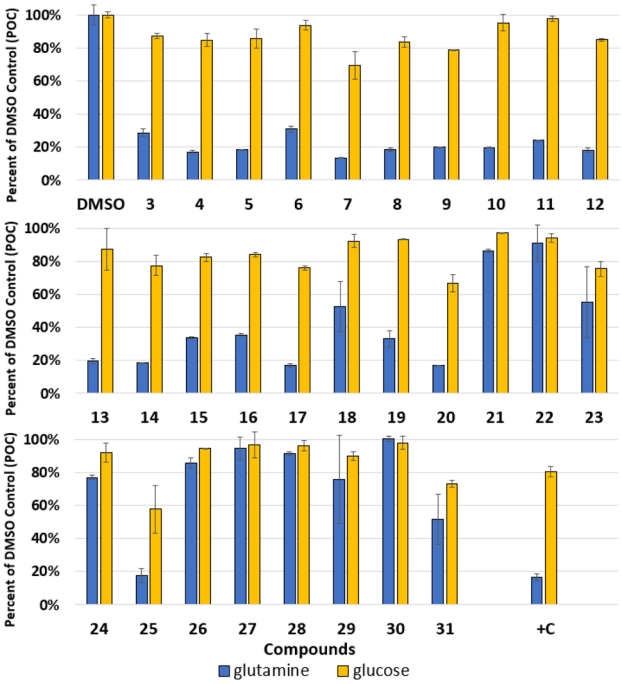


Fig. 9 Cell viability screening results against kidney (H293) cancer cell line in the presence (minimal media plus 10 mM glucose; yellow bars) and absence (minimal media plus 4 mM glutamine; blue bars) of glucose. Library compounds were screened at 25 μM with 2-hour compound exposure. All values are shown as POC (percent of DMSO control) and error bars represent standard deviation calculated by Microsoft Excel with 85% CI from duplicate experiments. Lower POC values indicate stronger hits. Rotenone (1.5 μM) is a known OXPHOS inhibitor used as a positive control (+C) for comparison to library compounds.

observed as OXPHOS inhibitors at 25 μM but did not display significant cytotoxicity against the three cell lines (Fig. 8) at 50 μM. The unexpected observation of the synthesized allylic sulfonamides as OXPHOS inhibitors warrants further structural exploration, which is currently underway in our laboratories.

Conclusions

In conclusion, a dehydrative sulfonamidation of 1° and 2° allylic alcohols that operates under mild reaction conditions has been achieved using PTSA-SiO_2 as a solid-support acid catalyst. The silica gel catalyst has been shown to be reusable up to 5 times in reactions conducted at 65 °C and 3 times in reactions at room temperature. A variety of functionalities are tolerated in the reaction conditions as shown by the sulfonamide substrate scope investigation, which includes known pharmaceutical celecoxib. Isolated yields of sulfonamidated products derived from 2° allylic alcohols range from 45–91% and yields from the less reactive 1° allylic alcohols range from 23–72%. The PTSA-SiO_2 approach extends beyond sulfonamide substrates with isolated yields obtained from a 1° amine and methocarbamol, a carbamate-containing substrate. Mechanistic investigations indicate that the loss of activity in PTSA-SiO_2 after several uses is largely due to the absorption of water, which may block the Brønsted acidic sites.

Biological activity of synthesized products **3–31** was evaluated in a series of experimental assays. None of the compounds (50 μM) displayed significant antibacterial activity against *E. coli* (F5B strain), antifungal activity against *Saccharomyces cerevisiae*, or activity as luciferase inhibitors. In a traditional (24-hour compound exposure) cytotoxicity assay using CellTiter-Blue, compounds **7–9**, **12**, **13**, **15**, **20**, and **23** displayed cytotoxicity towards two or more of the three cell lines (H293, A549, and HDF) at 50 μM. Lastly, several compounds (**3–17**, **19**, **20**, and **25**) were identified as inhibitors of OXPHOS ATP production at 25 μM against H293 cells *via* a protocol for rapid detection of cellular ATP levels using a minimal media with either glucose or glutamine added as carbon-source nutrient. Compounds **3–6**, **10**, **11**, **14**, **16**, **17**, and **19** are of particular significance as compounds with OXPHOS activity at 25 μM that were not observed as cytotoxic at 50 μM in a traditional assay. Additional synthetic variation to structurally optimize the allylic sulfonamide core using *N*-nucleophiles is currently underway in our laboratory in the effort to produce novel OXPHOS inhibitors.

Experimental

General information

All reagents and solvents were purchased from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400/100 (400 MHz) spectrometer in deuterated chloroform ($CDCl_3$) with the solvent residual peak as internal reference unless otherwise stated ($CDCl_3$: $^{1}H = 7.26$ ppm, $^{13}C = 77.16$ ppm). Data are reported in the following order: chemical shifts (δ) are reported in ppm, and spin–spin coupling constants (J) are reported in Hz, while multiplicities are abbreviated by s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (double of triplets), td (triplet of doublets), m (multiplet), q (quartet). Infrared spectra were recorded on a Nicolet iS50 FT-IR spectrometer, and peaks are reported in reciprocal centimeters (cm^{-1}). Melting points (m.p.) were recorded on a Mel-Temp II (Laboratory Devices, USA) and were uncorrected.

General procedure for preparation of Brønsted acid immobilized on silica gel

Four separate acid-loaded silica gel catalysts were prepared following literature precedent[22c] using either sulfuric acid, triflic acid, perchloric acid, or *p*-toluenesulfonic acid. In a representative procedure, 2.5 mmol of the respective acid was added to 5 g of silica gel and stirred in 17.5 mL of diethyl ether for 1 hour at room temperature. The slurry was then placed on a rotary evaporator to remove solvent and dried under high vacuum at 110 °C for 4 hours to afford the [H^+–SiO_2] (3 mol%) catalyst. To prepare the 6 mol% catalyst, 5.0 mmol of acid was used in place of 2.5 mmol and the procedure was carried out in the same manner.

General procedure for sulfonamidation of allylic alcohols using PTSA-SiO_2 (isolation)

Allylic alcohol (0.5 mmol), sulfonamide reagent (0.55 mmol), a stir bar, 55 mg of PTSA-SiO_2 (6 mol%) and 2 mL of $CDCl_3$ was

added to a reaction vessel and sealed. For cinnamyl alcohol, the vessel was heated at 65 °C with stirring for 6 hours. For 2-cyclohexen-1-ol, the reaction was heated to 45 °C for 6 hours. For (*E*)-1,3-diphenyl-2-propen-1-ol, the reaction was stirred at room temperature for 6 hours. Upon completion, the silica gel was filtered and rinsed with EtOAc, and the filtrate was evaporated prior to performing column chromatography. Products were purified using the eluent reported in the compound characterization.

Note – a 1 to 1.1 stoichiometric ratio of allylic alcohol to sulfonamide (respectively) was used despite the optimization experiments indicating that a 1 : 2 ratio produces the highest yield by ^{1}H NMR integration. During the isolation of many of these compounds, we found that an excess of sulfonamide can lead to difficult separation (due to overlap of product with unreacted sulfonamide), and isolation was cleaner when using a 1 : 1.1 stoichiometric ratio.

General procedure for experiments to determine reusability of PTSA-SiO_2

Following the general procedure for sulfonamidation using [PTSA-SiO_2] as described above, the reaction mixture was filtered *via* vacuum filtration. The filtrate was collected and analyzed by ^{1}H NMR using 1,3-dinitrobenzene as internal standard. The filtered silica gel was rinsed with 5 mL of chloroform, then air-dried on vacuum for 3–5 minutes. The silica gel was collected from the filter paper, weighed, and reused in the next reaction after adjusting the stoichiometry to be the same ratio as the initial conditions based upon the amount of silica gel that was recovered.

Experimental procedure for gram-scale production of compound 4

To a round-bottom flask was added (*E*)-1,3-diphenyl-2-propen-1-ol (0.736 g, 3.5 mmol), *p*-toluenesulfonamide (0.659 g, 3.85 mmol), a stir bar, 0.385 g of PTSA-SiO_2 (6 mol%), and 14 mL of chloroform. The reaction was stirred at room temperature for 6 hours. Upon completion, the silica gel was filtered and rinsed with EtOAc, and the filtrate was evaporated prior to performing column chromatography. Product **4** (1.104 g, 87%) was isolated *via* column chromatography using a 70 : 30 (hexanes/EtOAc) eluent and deemed pure by ^{1}H NMR.

Experimental procedure for antibacterial assay

CellTiter-Glo was obtained from Promega (Madison, WI, USA). All other materials and supplies were purchased from commercial sources and used without additional purification. *E. coli* (DH5α strain) was grown overnight in LB media at 37 °C with shaking to reach stationary phase. The overnight culture was diluted (1 : 50) into fresh LB media. Then 500 μL was transferred to 1.5 mL centrifuge tubes. A time zero was taken by pelleting the *E coli* by centrifugation (2 min, 13 K, room temperature). Supernatant was removed and the pellet frozen at −20 °C. For screening the library compounds **3–31**, 5 μL DMSO solvent (negative) control or 5 μL of 5 mM library compound in DMSO was added to the *E. coli*. The final drug concentration was 50 μM. The antibiotics ampicillin, kanamycin, and carbenicillin were each used at a final concentration of 100 micrograms mL^{-1} as a positive control (**+C**) to inhibit *E. coli* growth. Samples were shaken overnight at 37 °C for 18 hours. The next day, *E. coli* were pelleted as described above and supernatant discarded. Then 200 μL of 3% TCA (trichloroacetic acid) was added and vortexed to resuspend. Samples were then stored at room temperature for 10 minutes. Samples were then sonicated for 30 seconds at power level 5 using a probe sonicator. Then 100 μL of 0.5 M Hepes pH 9 was added to neutralize pH. Samples were vortexed and centrifuged (2 min, 13 K, room temperature) to pellet debris. To measure ATP in a 96 well plate, 10 μL of the supernatant (containing ATP) was added to 75 μL distilled H_2O, followed by addition of 25 μL of a 1 : 7 dilution in distilled H_2O of CellTiterGlo (Promega). Samples were shaken for 5 minutes at 500 rpm (room temperature) on a plate shaker, and light emission (luminescence) was quantized using a Cytation Biotek 5 plate reader.

Experimental procedure for antifungal assay

CellTiter-Glo was obtained from Promega (Madison, WI, USA). All other materials and supplies were purchased from commercial sources and used without additional purification. To 20 mL of sterilized YPD yeast growth media was added 2 mg of instant dried baker's yeast (*Saccharomyces cerevisiae*) and the sample was stirred for 10 minutes at ambient room temperature (~20 °C). Aliquots of 500 μL of the yeast and media was then transferred to small glass test tubes. A time zero was immediately taken by removing 400 μL, pelleting the yeast by centrifugation (2 min, 13 K, room temperature), removing the supernatant, and freezing the yeast pellet at −20 °C. For screening, 5 μL of DMSO solvent control or 5 μL of 5 mM library compounds (**3–31** in DMSO) was added to the 500 μL yeast aliquot. Final drug concentration was 50 μL. The test tubes were then incubated in a shaker overnight at 30 °C for 18 hours. As a positive control (**+C**), 0.2 μL of clove essential oil was used to demonstrate inhibition of yeast growth. To analyze drug effects on yeast growth, 400 μL of the sample was pelleted as described above and supernatant discarded. Then 200 μL of 3% TCA (trichloroacetic acid) was added and vortexed to resuspend the yeast pellet. The sample was then incubated for 10 minutes at room temperature followed by sonication using a probe sonicator (30 seconds, power level 5) to ensure yeast lysis. 100 μL of 0.5 M Hepes pH 9 was then added to neutralize pH and samples were vortexed to mix thoroughly. Samples were then spun 5 minutes at 13 K (room temperature) to pellet debris. To measure ATP in a 96 well plate, 10 μL of the supernatant (containing ATP) was added to 75 μL of distilled H_2O, followed by addition of 25 μL of a 1 : 7 dilution of CellTiterGlo (in distilled H_2O). Samples were shaken for 5 minutes at 500 rpm (room temperature) on a plate shaker, and light emission was quantized using a Cytation Biotek 5 plate reader.

Experimental procedure for cytotoxicity assay

CellTiter-Blue was obtained from Promega (Madison, WI, USA). All cell cultures were obtained from the American Type Culture

Collection (ATCC, Manassas, VA, USA). All other materials and supplies were purchased from commercial sources and used without additional purification. Cell cultures were removed from p100 culture dishes using PBS containing 2.5 mM EDTA. Cells were pelleted by centrifugation and resuspended in DMEM media containing 10% FBS. Approximately 25 000 cells per well were distributed in a black tissue culture treated 96 well plate. The plate was incubated overnight (~18 hours) at 37 °C in a CO_2 incubator to allow cells to attach to the plate. To screen library compounds **3–31**, 1% DMSO solvent control (final concentration) or 50 μL compound (final concentration) was added to the wells. All experiments were performed in duplicate. Maximum inhibition, or positive control (**+C**), is determined from a mixture of 10 mM 2-DG and 1.5 μM rotenone. The plate was incubated for 24 hours at 37 °C in the CO_2 incubator. The next day, media was aspirated and wells were gently washed with 100 μL of PBS to remove dead cells. Then 100 μL of DMEM containing 10 μL of CellTiterBlue (Promega) was added. The conversion of resazurin to fluorescent resorufin (indicative of living cells) was quantified using a Cytation Biotek 5 plate reader at 560 nm excitation and 590 nm emission.

Experimental procedure for OXPHOS inhibition assay in minimal media supplemented with different carbon sources (nutrients)

All cell cultures were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). All other materials and supplies were purchased from commercial sources and used without additional purification. Cell cultures were maintained in DMEM (Fisher Scientific, 11965 – high glucose) supplemented with 10% fetal bovine serum (Atlas Biologicals) and Penn/Strep. Cultures were kept in a 37 °C water-jacketed incubator with 5% CO_2. For experiments in 96-well plates, proliferating H293 cells were removed from the stock plate using PBS plus 2.5 mM EDTA. Cells were pelleted by brief centrifugation and supernatant discarded. The cell pellet was resuspended in DMEM minimal media (see below for components), which does not contain glucose, any amino acids, or pyruvate. It therefore lacks a carbon source that can be used to synthesize ATP. A defined carbon source (in this case either glucose or glutamine) was added back to the media in order to activate a specific metabolic pathway resulting in ATP formation. Our version also lacks the buffering component sodium bicarbonate and so was buffered to pH 7.5 with 20 mM Hepes. The desired number of cells (~20 000) were distributed in a white 96-well plate containing 100 μL DMEM minimal media plus or minus 10 mM glucose or 4 mM glutamine (final concentrations). Glucose will be metabolized by glycolysis to generate ATP (non-mitochondrial pathway) while glutamine must be metabolized by the TCA cycle and Electron Transport Chain (ETC) in order to produce ATP (mitochondrial pathway). The plate was incubated at 37 °C (no CO_2) for 30 minutes to allow cells to acclimate to the new media conditions. To screen library compounds **3–31** for inhibition of ATP production *via* these two pathways, 25 μM of the drug (final concentration) was added to the cells after the preincubation for 30 minutes. All experiments were performed in duplicate. To serve as the solvent control, 1% DMSO (final concentration) was used. Plates were shaken for 30 seconds (700 rpm) and then incubated for 1–2 hours at 37 °C in the absence of exogenous CO_2. ATP levels were determined by adding 10 μL of the CellTiter-Glo reagent (Promega) to the cells and shaking for 5 minutes. Luminescence was measured on a BioTek Cytation 5 plate reader. As a positive control, a combination of 1.25 μM rotenone and 10 mM 2-deoxy glucose was used to inhibit OXPHOS and glycolysis, respectively.

Our minimal media is created using the following components (all values in mg L^{-1}): 4 mg choline chloride, 4 mg D-calcium pantothenate, 4 mg folic acid, 4 mg niacinamide, 4 mg pyridoxine hydrochloride, 0.4 mg riboflavin, 4 mg thiamine hydrochloride, 7.2 mg i-inositol, 200 mg calcium chloride (anhyd.), 0.1 mg ferric nitrate, 97.67 mg magnesium sulfate (anhyd.), 400 mg potassium chloride, 6400 mg sodium chloride, 125 mg sodium phosphate monobasic, and 15 mg phenol red. The composition is equivalent to commercially available (Fisher) DMEM high glucose media but without any amino acids, glucose, pyruvate, and sodium bicarbonate. After addition of either glutamine (4 mM final concentration) or glucose (10 mM final concentration), the solution is buffered to pH 7.5 with 20 mM Hepes and sterile filtered through a 0.2 micron polyethersulfone (PES) membrane filter.

Product characterization

All products were isolated according to general procedure unless otherwise noted and display the characterizational data shown below.

***N*-Cinnamyl-4-methylbenzenesulfonamide (3).** The title compound was prepared according to the general procedure and the data matches those previously reported.[27] White solid (81 mg, 55%). m.p. 86–88 °C. Purification (hexanes/EtOAc, 70 : 30). $R_f = 0.47$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.78 (d, $J = 8.4$ Hz, 2H), 7.34–7.16 (m, 7H), 6.43 (d, $J = 15.8$ Hz, 1H), 6.00 (dt, $J = 15.8$, 6.4 Hz, 1H), 4.67 (t, $J = 6.4$ Hz, 1H), 3.75 (td, $J = 6.4$, 1.5 Hz, 2H), 2.41 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 143.7, 137.2, 136.2, 133.2, 129.9, 128.7, 128.1, 127.3, 126.5, 124.2, 45.6, 21.6 ppm. IR (neat): ν = 3281, 3067, 1597, 1493, 1449, 1419, 1321, 1305, 1292, 1185, 1165, 1154, 1119 cm^{-1}.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-4-methylbenzenesulfonamide (4). The title compound was prepared according to the general procedure and the data matches those previously reported.[20c] White solid (148 mg, 79%). m.p. 128–130 °C. Purification (hexanes/EtOAc, 70 : 30). $R_f = 0.43$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.65 (d, $J = 8.3$ Hz, 2H), 7.29–7.07 (m, 12H), 6.32 (dd, $J = 15.8$, 1.2 Hz, 1H), 6.06 (dd, $J = 15.8$, 6.8 Hz, 1H), 5.38 (d, $J = 7.5$ Hz, 1H), 5.11–5.07 (m, 1H), 2.29 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 143.3, 139.7, 137.8, 136.1, 132.1, 129.5, 128.8, 128.5, 128.2, 127.94, 127.87, 127.4, 127.1, 126.6, 59.9, 21.5 ppm. IR (neat): ν = 3290, 3027, 2925, 1744, 1597, 1493, 1452, 1425, 1388, 1339, 1324, 1304, 1292, 1213, 1184, 1160, 1150 cm^{-1}.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-4-ethylbenzenesulfonamide (5). The title compound was prepared following the general procedure. White solid (170 mg, 91%).

m.p. 135–138 °C. Purification (hexanes/EtOAc, 80 : 20). R_f = 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): 7.67 (d, J = 8.4 Hz, 2H), 7.28–7.07 (m, 12H), 6.32 (dd, J = 15.8, 1.3 Hz, 1H), 6.06 (dd, J = 15.8, 6.8 Hz, 1H), 5.52 (d, J = 7.7 Hz, 1H), 5.11 (ddd, J = 7.7, 6.8, 1.3 Hz, 1H), 2.57 (q, J = 7.6 Hz, 2H), 1.14 (t, J = 7.6 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 149.4, 139.7, 137.9, 136.1, 132.0, 128.7, 128.5, 128.3, 128.2, 127.9, 127.8, 127.5, 127.1, 126.6, 59.8, 28.8, 15.3 ppm. IR (neat): ν = 3264, 3027, 2970, 2929, 1735, 1600, 1495, 1455, 1431, 1366, 1348, 1315, 1229, 1218, 1163 cm^{-1}. HRMS (ESI): calculated for $C_{23}H_{24}NO_2S$ $[M + H]^+$ requires 378.1528 m/z, found 378.1530 m/z.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-4-methoxybenzenesulfonamide (6). The title compound was prepared according to the general procedure and the data matches those previously reported.[20c] White solid (146 mg, 76%). m.p. 135–138 °C. Purification (hexanes/EtOAc, 40 : 60). R_f = 0.74. ^{1}H NMR (400 MHz, $CDCl_3$): 7.69 (d, J = 8.9 Hz, 2H), 7.29–7.12 (m, 10H), 6.76 (d, J = 8.9 Hz, 2H), 6.34 (dd, J = 15.8, 1.3 Hz, 1H), 6.07 (dd, J = 15.8, 7.1 Hz, 1H), 5.37 (d, J = 7.1 Hz, 1H), 5.09 (td, J = 7.1, 1.3 Hz, 1H), 3.72 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 162.7, 139.7, 136.2, 132.3, 132.1, 129.5, 128.8, 128.5, 128.3, 127.95, 127.89, 127.1, 126.6, 114.0, 59.9, 55.6 ppm. IR (neat): ν = 3251, 3026, 2927, 2855, 1743, 1685, 1597, 1577, 1495, 1453, 1440, 1370, 1303, 1259 cm^{-1}.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-4-fluorobenzenesulfonamide (7). The title compound was prepared according to the general procedure. White solid (159 mg, 84%). m.p. 92–95 °C. Purification (hexanes/EtOAc, 70 : 30). R_f = 0.60. ^{1}H NMR (400 MHz, $CDCl_3$): 7.77–7.67 (m, 2H), 7.32–7.12 (m, 10H), 6.95 (t, J = 8.6 Hz, 2H), 6.37 (dd, J = 15.8, 1.3 Hz, 1H), 6.10 (dd, J = 15.8, 6.7 Hz, 1H), 5.51 (d, J = 7.1 Hz, 1H), 5.14 (td, J = 7.1, 1.3 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 164.9 (C–F, $^1J_{CF}$ = 254.5 Hz), 139.3, 136.9 (C–F, $^4J_{CF}$ = 3.3 Hz), 135.9, 132.4, 130.0 (C–F, $^3J_{CF}$ = 9.3 Hz), 128.8, 128.7, 128.2, 128.10, 128.06, 127.2, 126.6, 116.0 (C–F, $^2J_{CF}$ = 22.5 Hz), 60.0 ppm. IR (neat): ν = 3271, 3066, 3004, 2927, 1740, 1591, 1494, 1456, 1448, 1418, 1347, 1324, 1292, 1235, 1167, 1155 cm^{-1}. HRMS (ESI): calculated for $C_{21}H_{19}FNO_2S$ $[M + H]^+$ requires 368.1121 m/z, found 368.1123 m/z.

(*E*)-4-Bromo-*N*-(1,3-diphenyl-prop-2-en-1-yl) benzenesulfonamide (8). The title compound was prepared according to the general procedure and the data matches those previously reported.[28] Yellowish white solid (188 mg, 88%). m.p. 106–108 °C. Purification (hexanes/EtOAc, 80 : 20). R_f = 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): 7.56 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.27–7.13 (m, 10H), 6.34 (dd, J = 15.8, 1.3 Hz, 1H), 6.06 (dd, J = 15.8, 6.8 Hz, 1H), 5.61 (d, J = 7.6 Hz, 1H), 5.17–5.08 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 139.8, 139.2, 135.9, 132.4, 132.1, 128.85, 128.83, 128.7, 128.2, 128.0, 127.9, 127.4, 127.2, 126.6, 60.1 ppm. IR (neat): ν = 3260, 3064, 3032, 2930, 1739, 1575, 1470, 1456, 1413, 1389, 1361, 1328, 1296, 1271, 1234, 1179, 1152 cm^{-1}.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-4-nitrobenzenesulfonamide (9). The title compound was prepared according to the general procedure and the data matches those previously reported.[28] White solid (129 mg, 64%). m.p. 146–149 °C. Purification (hexanes/EtOAc, 60 : 40). R_f = 0.61. ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (d, J = 8.9 Hz, 1H), 7.85 (d, J = 8.9 Hz, 1H), 7.33–7.12 (m, 10H), 6.40 (dd, J = 15.8, 1.2 Hz, 1H), 6.08 (dd, J = 15.8, 6.7 Hz, 1H), 5.29 (d, J = 7.9 Hz, 1H), 5.26–5.19 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 149.7, 146.7, 138.7, 135.5, 133.1, 129.0, 128.8, 128.6, 128.4, 127.4, 127.2, 126.6, 124.1, 60.4 ppm. IR (neat): ν = 3283, 3028, 1606, 1528, 1498, 1457, 1417, 1365, 1343, 1335, 1312, 1267, 1176, 1158 cm^{-1}.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-2-methylbenzenesulfonamide (10). The title compound was prepared according to the general procedure. Yellow solid (155 mg, 84%). m.p. 106–109 °C. Purification (hexanes/EtOAc, 80 : 20). R_f = 0.38. ^{1}H NMR (400 MHz, $CDCl_3$): 7.88 (d, J = 7.9 Hz, 1H), 7.33 (td, J = 7.5, 1.4 Hz, 1H), 7.27–7.11 (m, 12H), 6.35 (dd, J = 15.8, 1.3 Hz, 1H), 6.10 (dd, J = 15.8, 7.0 Hz, 1H), 5.26 (d, J = 7.0 Hz, 1H), 5.04 (td, J = 7.0, 1.3 Hz, 1H), 2.52 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 139.6, 138.4, 137.0, 136.1, 132.7, 132.4, 132.2, 129.8, 128.8, 128.6, 128.03, 128.01, 127.1, 126.6, 126.1, 59.8, 20.3 ppm. IR (neat): ν = 3276, 3061, 3028, 2928, 1734, 1599, 1494, 1471, 1454, 1383, 1322, 1290, 1157, 1133 cm^{-1}. HRMS (ESI): calculated for $C_{22}H_{22}NO_2S$ $[M + H]^+$ requires 364.1371 m/z, found 364.1371 m/z.

(*E*)-2-Chloro-*N*-(1,3-diphenyl-prop-2-en-1-yl) benzenesulfonamide (11). The title compound was prepared according to the general procedure. White solid (94 mg, 48%). m.p. 93–96 °C. Purification (hexanes/EtOAc, 70 : 30). R_f = 0.49. ^{1}H NMR (400 MHz, $CDCl_3$): 7.96 (dd, J = 7.7, 1.1 Hz, 1H), 7.32–7.14 (m, 13H), 6.33 (dd, J = 15.9, 1.2 Hz, 1H), 6.10 (dd, J = 15.9, 6.9 Hz, 1H), 5.48 (d, J = 8.3 Hz, 1H), 5.10 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 139.0, 138.1, 135.9, 133.5, 132.7, 131.38, 131.35, 131.2, 128.8, 128.6, 128.2, 127.2, 127.1, 127.0, 126.6, 60.3 ppm. IR (neat): ν = 3292, 3096, 3056, 2023, 2925, 1740, 1577, 1491, 1453, 1448, 1420, 1332, 1268, 1254, 1217, 1168, 1127, 1114 cm^{-1}. HRMS (ESI): calculated for $C_{21}H_{19}ClNO_2S$ $[M + H]^+$ requires 384.0825 m/z, found 384.0820 m/z.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-2-fluorobenzenesulfonamide (12). The title compound was prepared according to the general procedure. White solid (83 mg, 45%). m.p. 81–84 °C. Purification (hexanes/EtOAc, 70 : 30). R_f = 0.47. ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (td, J = 7.6, 1.8 Hz, 1H), 7.37 (dddd, J = 8.2, 7.0, 5.1, 1.8 Hz, 1H), 7.28–7.16 (m, 10H), 7.10 (td, J = 7.6, 1.1 Hz, 1H), 6.96 (ddd, J = 10.3, 8.3, 1.1 Hz, 1H), 6.37 (dd, J = 15.8, 1.3 Hz, 1H), 6.12 (dd, J = 15.8, 6.6 Hz, 1H), 5.32 (d, J = 8.2 Hz, 1H), 5.14 (ddd, J = 8.2, 6.6, 1.3 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 158.7 (C–F, $^1J_{CF}$ = 253.7 Hz), 139.1, 136.0, 134.8 (C–F, $^3J_{CF}$ = 8.7 Hz), 132.5, 130.2, 128.9, 128.7 (C–F, $^2J_{CF}$ = 20.2 Hz), 128.1 (C–F, $^3J_{CF}$ = 4.4 Hz), 127.5, 127.0, 126.6, 124.4 (C–F, $^4J_{CF}$ = 3.7 Hz), 116.7 (C–F, $^2J_{CF}$ = 21.1 Hz), 60.0 ppm. IR (neat): ν = 3270, 3026, 2926, 2855, 1744, 1600, 1578, 1494, 1475, 1454, 1434, 1370, 1333, 1300, 1219, 1169, 1154, 1128 cm^{-1}. HRMS (ESI): calculated for $C_{21}H_{19}FNO_2S$ $[M + H]^+$ requires 368.1121 m/z, found 368.1125 m/z.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-2,4,6-trimethylbenzenesulfonamide (13). The title compound was prepared according to the general procedure. White solid

(157 mg, 78%). m.p. 86–89 °C. Purification (hexanes/EtOAc, 80 : 20). $R_f = 0.49$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.21 (m, 8H), 7.12 (dd, $J = 8.0$, 1.7 Hz, 2H), 6.79 (s, 2H), 6.32 (dd, $J = 15.8$, 1.1 Hz, 1H), 6.02 (dd, $J = 15.8$, 7.1 Hz, 1H), 5.06–5.01 (m, 1H), 4.98 (d, $J =$ 6.1 Hz, 1H), 2.55 (s, 6H), 2.19 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 142.2, 139.7, 139.0, 136.1, 134.7, 132.1, 131.9, 128.8, 128.5, 128.03, 128.00, 127.96, 127.0, 126.6, 60.1, 23.0, 20.9 ppm. IR (neat): ν = 3259, 3055, 3030, 2939, 1744, 1603, 1494, 1453, 1378, 1349, 1301, 1226, 1188, 1147 cm^{-1}. HRMS (ESI): calculated for $C_{24}H_{26}NO_2S$ $[M + H]^+$ requires 392.1684 *m*/*z*, found 392.1689 *m*/*z*.

***N*-Cinnamyl-4-ethylbenzenesulfonamide (14).** The title compound was prepared according to the general procedure. Yellow solid (62 mg, 40%). m.p. 73–76 °C. Purification (hexanes/EtOAc, 80 : 20). $R_f = 0.21$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.81 (d, $J =$ 8.4 Hz, 2H), 7.35–7.17 (m, 7H), 6.43 (dt, $J = 15.8$, 1.5 Hz, 1H), 5.99 (dt, $J = 15.8$, 6.3 Hz, 1H), 4.76 (t, $J = 6.3$ Hz, 1H), 3.76 (td, $J =$ 6.3, 1.5 Hz, 2H), 2.70 (q, $J = 7.6$ Hz, 2H), 1.24 (t, $J = 7.6$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 149.8, 137.4, 136.2, 133.2, 128.74, 128.68, 128.0, 127.4, 126.5, 124.2, 45.6, 28.9, 15.3 ppm. IR (neat): ν = 3265, 3026, 2963, 2932, 2856, 1743, 1599, 1453, 1435, 1408, 1315, 1224, 1189, 1155 cm^{-1}. HRMS (ESI): calculated for $C_{17}H_{20}NO_2S$ $[M + H]^+$ requires 302.1215 *m*/*z*, found 302.1217 *m*/*z*.

4-(*tert*-Butyl)-*N*-cinnamylbenzenesulfonamide (15). The title compound was prepared from celecoxib according to the general procedure. Beige solid (48 mg, 29%). m.p. 120–122 °C. Purification (hexanes/EtOAc, 80 : 20). $R_f = 0.29$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (d, $J = 8.6$ Hz, 2H), 7.50 (d, $J = 8.6$ Hz, 2H), 7.32–7.17 (m, 5H), 6.43 (dt, $J = 15.8$, 1.6 Hz, 1H), 5.97 (dt, $J =$ 15.8, 6.3 Hz, 1H), 4.78 (t, $J = 6.3$ Hz, 1H), 3.78 (td, $J = 6.3$, 1.6 Hz, 2H), 1.32 (s, 9H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 156.6, 137.2, 136.2, 133.1, 128.7, 128.0, 127.2, 126.5, 126.3, 124.3, 45.6, 35.2, 31.2 ppm. IR (neat): $\nu = 3273$, 2959, 1597, 1493, 1449, 1432, 1401, 1362, 1319, 1292, 1270, 1201, 1160, 1114 cm^{-1}. HRMS (ESI): calculated for $C_{19}H_{24}NO_2S$ $[M + H]^+$ requires 330.1528 *m*/*z*, found 330.1530 *m*/*z*.

***N*-Cinnamyl-4-methoxybenzenesulfonamide (16).** The title compound was prepared according to the general procedure and the data matches those previously reported.[29] White solid (66 mg, 42%). m.p. 94–96 °C. Purification (hexanes/EtOAc, 50 : 50). $R_f = 0.74$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.82 (d, $J = 9.0$ Hz, 1H), 7.33–7.16 (m, 5H), 6.92 (d, $J = 9.0$ Hz, 1H), 6.41 (d, $J =$ 15.8 Hz, 1H), 5.99 (dt, $J = 15.8$, 6.3 Hz, 1H), 5.01 (t, $J = 6.3$ Hz, 1H), 3.80 (s, 3H), 3.75–3.67 (m, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 162.9, 136.2, 133.0, 131.6, 129.4, 128.6, 127.9, 126.5, 124.3, 114.3, 55.7, 45.5 ppm. IR (neat): ν = 3270, 2925, 1740, 1596, 1496, 1448, 1318, 1300, 1255, 1178, 1154 cm^{-1}.

4-Bromo-*N*-cinnamylbenzenesulfonamide (17). The title compound was prepared according to the general procedure and the data matches those previously reported.[30] Yellow solid (44 mg, 25%). m.p. 106–109 °C. Purification (hexanes/EtOAc, 70 : 30). $R_f = 0.53$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.75 (d, $J =$ 8.3 Hz, 2H), 7.63 (d, $J = 8.3$ Hz, 2H), 7.40–7.18 (m, 5H), 6.44 (d, J = 15.8 Hz, 1H), 5.99 (dt, $J = 15.8$, 6.3 Hz, 1H), 4.81 (t, $J = 6.3$ Hz, 1H), 3.77 (t, $J = 6.3$ Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 139.3, 136.0, 133.6, 132.6, 128.9, 128.8, 128.2, 127.9, 126.6, 123.8, 45.6 ppm. IR (neat): $\nu = 3280$, 3091, 1575, 1493, 1471, 1449, 1421, 1388, 1325, 1276, 1165, cm^{-1}.

***N*-Cinnamyl-4-fluorobenzenesulfonamide (18).** The title compound was prepared from antipyrine according to the general procedure. Yellow solid (44 mg, 30%). m.p. 60–62 °C. Purification (hexanes/EtOAc, 70 : 30). $R_f = 0.43$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.69 (dt, $J = 7.8$, 1.3 Hz, 1H), 7.61 (ddd, $J = 8.2$, 2.6, 1.7 Hz, 1H), 7.49 (td, $J = 8.2$, 5.3 Hz, 1H), 7.32–7.21 (m, 6H), 6.47 (d, $J = 15.8$ Hz, 1H), 6.02 (dt, $J = 15.8$, 6.3 Hz, 1H), 4.83–4.75 (m, 1H), 3.79 (td, $J = 6.3$, 1.5 Hz, 2H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 162.6 (C–F, $^1J_{CF} = 251.8$ Hz), 142.3 (C–F, $^3J_{CF} = 6.6$ Hz), 136.0, 133.6, 131.1 (C–F, $^3J_{CF} = 7.7$ Hz), 128.7, 128.2, 126.5, 123.7, 123.0 (C–F, $^4J_{CF} = 3.3$ Hz), 120.1 (C–F, $^2J_{CF} = 21.2$ Hz), 114.7 (C–F, $^2J_{CF} = 24.4$ Hz), 45.7 ppm. IR (neat): $\nu = 3288$, 2927, 2855, 1741, 1519, 1495, 1473, 1449, 1435, 1335, 1306, 1271, 1224, 1151 cm^{-1}. HRMS (ESI): calculated for $C_{15}H_{15}FNO_2S$ $[M + H]^+$ requires 292.0808 *m*/*z*, found 292.0808 *m*/*z*.

***N*-Cinnamyl-2-methylbenzenesulfonamide (19).** The title compound was prepared according to the general procedure and the data matches those previously reported.[31] Yellow solid (49 mg, 33%). m.p. 69–72 °C. Purification (hexanes/EtOAc, 80 : 20). $R_f = 0.33$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.99 (d, $J = 7.6$ Hz, 1H), 7.45 (td, $J = 7.6$, 1.4 Hz, 1H), 7.34–7.19 (m, 7H), 6.43 (dd, $J =$ 15.8, 1.8 Hz, 1H), 5.99 (dt, $J = 15.8$, 6.3 Hz, 1H), 4.79 (t, $J =$ 6.3 Hz, 1H), 3.73 (td, $J = 6.3$, 1.8 Hz, 2H), 2.66 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 138.1, 137.1, 136.1, 133.3, 133.0, 132.7, 129.7, 128.7, 128.1, 126.5, 126.3, 124.2, 45.4, 20.5 ppm. IR (neat): $\nu = 3276$, 3027, 2926, 2854, 1741, 1598, 1495, 1449, 1420, 1369, 1312, 1223, 1157, 1135 cm^{-1}.

***N*-Cinnamyl-2,4,6-trimethylbenzenesulfonamide (20).** The title compound was prepared according to the general procedure. Beige solid (48 mg, 29%). m.p. 120–122 °C. Purification (hexanes/EtOAc, 80 : 20). $R_f = 0.29$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.35–7.16 (m, 5H), 6.94 (s, 2H), 6.41 (dt, $J = 15.8$, 1.5 Hz, 1H), 5.96 (dt, $J = 15.8$, 6.5 Hz, 1H), 4.75–4.64 (m, 1H), 3.70 (td, $J = 6.5$, 1.5 Hz, 2H), 2.65 (s, 6H), 2.27 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 142.4, 139.2, 136.2, 134.0, 133.1, 132.1, 128.6, 128.0, 126.5, 124.3, 45.2, 23.1, 21.0 ppm. IR (neat): ν = 3273, 2959, 1597, 1493, 1449, 1432, 1401, 1362, 1319, 1292, 1270, 1201, 1160, 1114 cm^{-1}. HRMS (ESI): calculated for $C_{19}H_{24}NO_2S$ $[M + H]^+$ requires 330.1528 *m*/*z*, found 330.1528 *m*/*z*.

***N*-Cinnamyl-2-methoxy-5-(2-oxopropyl)benzenesulfonamide (21).** The title compound was prepared according to the general procedure. Yellow oil (44 mg, 23%). Purification (hexanes/EtOAc, 40 : 60). $R_f = 0.44$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.73 (d, $J = 2.3$ Hz, 1H), 7.35 (dd, $J = 8.5$, 2.3 Hz, 1H), 7.30–7.18 (m, 5H), 6.98 (d, $J = 8.5$ Hz, 1H), 6.42 (d, $J = 15.8$ Hz, 1H), 6.00 (dt, $J =$ 15.8, 6.4 Hz, 1H), 5.11 (t, $J = 6.4$ Hz, 1H), 3.94 (s, 3H), 3.71 (td, J = 6.4, 1.5 Hz, 2H), 3.68 (s, 2H), 2.17 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 205.6, 155.3, 136.2, 135.6, 133.1, 131.2, 128.7, 128.0, 127.8, 126.9, 126.4, 124.0, 112.5, 56.6, 49.2, 45.8, 29.7 ppm. IR (neat): ν = 3299, 2972, 2855, 1714, 1607, 1576, 1494, 1440, 1414, 1358, 1325, 1282, 1254, 1224, 1152 cm^{-1}. HRMS (ESI): calculated for $C_{19}H_{22}NO_4S$ $[M + H]^+$ requires 360.1270 *m*/*z*, found 360.1268 *m*/*z*.

***N*-(Cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide (22).** The title compound was prepared according to the general

procedure and the data matches those previously reported.[32] White solid (106 mg, 78%). m.p. 97–99 °C. Purification (hexanes/EtOAc, 70 : 30). $R_f = 0.46$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (d, $J = 8.1$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 5.76–5.71 (m, 1H), 5.36–5.30 (m, 1H), 4.81 (d, $J = 8.5$ Hz, 1H), 3.83–3.74 (m, 1H), 2.41 (s, 3H), 2.00–1.80 (m, 2H), 1.80–1.67 (m, 1H), 1.65–1.42 (m, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 143.4, 138.4, 131.7, 129.8, 127.1, 127.1, 49.1, 30.3, 24.6, 21.7, 19.4 ppm. IR (neat): $\nu = 3270$, 2927, 2855, 1740, 1700, 1653, 1559, 1539, 1507, 1495, 1457, 1446, 1419, 1369, 1320, 1221, 1183, 1156, 1119 cm^{-1}. HRMS (ESI): calculated for $C_{13}H_{18}NO_2S$ $[M + H]^+$ requires 252.1058 *m*/*z*, found 252.1057 *m*/*z*.

4-Chloro-*N*-(cyclohex-2-en-1-yl)benzenesulfonamide (23). The title compound was prepared according to the general procedure and the data matches those previously reported.[33] White solid (126 mg, 95%). m.p. 66–69 °C. Purification (hexanes/EtOAc, 70 : 30). $R_f = 0.88$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.83 (d, $J = 8.6$ Hz, 2H), 7.46 (d, $J = 8.6$ Hz, 2H), 5.80–5.70 (m, 1H), 5.38–5.29 (m, 1H), 5.10 (d, $J = 8.5$ Hz, 1H), 3.86–3.73 (m, 1H), 2.00–1.81 (m, 2H), 1.80–1.66 (m, 1H), 1.64–1.45 (m, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 140.0, 139.1, 132.0, 129.5, 128.5, 126.8, 49.2, 30.3, 24.5, 19.3 ppm. IR (neat): $\nu =$ 3267, 2936, 1479, 1415, 1396, 1295, 1280, 1182, 1167, 1156 cm^{-1}. HRMS (ESI): calculated for $C_{12}H_{15}ClNO_2S$ $[M + H]^+$ requires 272.0512 *m*/*z*, found 272.0515 *m*/*z*.

***N*-(Cyclohex-2-en-1-yl)-4-methoxybenzenesulfonamide (24).** The title compound was prepared according to the general procedure and the data matches those previously reported.[34] White solid (126 mg, 97%). m.p. 93–95 °C. Purification (hexanes/EtOAc, 50 : 50). $R_f = 0.57$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.81 (d, $J = 8.9$ Hz, 2H), 6.95 (d, $J = 8.9$ Hz, 2H), 5.72 (dtd, $J = 9.8$, 3.8, 1.8 Hz, 1H), 5.32 (ddt, $J = 9.8$, 3.8, 2.2 Hz, 1H), 4.90 (d, $J =$ 8.5 Hz, 1H), 3.85 (s, 3H), 3.81–3.69 (m, 1H), 1.99–1.79 (m, 2H), 1.76–1.66 (m, 1H), 1.63–1.45 (m, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 162.8, 133.0, 131.6, 129.2, 127.2, 114.3, 55.7, 49.0, 30.3, 24.6, 19.4 ppm. IR (neat): $\nu = 3278$, 2927, 1595, 1500, 1440, 1324, 1261, 1149 cm^{-1}. HRMS (ESI): calculated for $C_{13}H_{18}NO_3S$ $[M + H]^+$ requires 268.1007 *m*/*z*, found 268.1009 *m*/*z*.

3,5-Dichloro-*N*-(cyclohex-2-en-1-yl)benzenesulfonamide (25). The title compound was prepared according to the general procedure. Tan solid (138 mg, 93%). m.p. 85–87 °C. Purification (hexanes/EtOAc, 80 : 20). $R_f = 0.64$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.76 (d, $J = 1.9$ Hz, 2H), 7.54 (t, $J = 1.9$ Hz, 1H), 5.81 (dtd, $J = 9.8$, 3.7, 1.8 Hz, 1H), 5.38 (ddt, $J = 9.8$, 3.7, 2.5 Hz, 1H), 4.98 (d, $J =$ 8.6 Hz, 1H), 3.90–3.81 (m, 1H), 2.01–1.87 (m, 2H), 1.84–1.75 (m, 1H), 1.67–1.52 (m, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 144.4, 136.1, 132.6, 132.4, 126.4, 125.4, 49.5, 30.4, 24.5, 19.3 ppm. IR (neat): $\nu =$ 3275, 3079, 3032, 2926, 2855, 1740, 1567, 1417, 1389, 1382, 1328, 1289, 1226, 1169, 1158, 1133 cm^{-1}. HRMS (ESI): calculated for $C_{12}H_{14}Cl_2NO_2S$ $[M + H]^+$ requires 306.0122 *m*/*z*, found 306.0123 *m*/*z*.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)propane-2-sulfonamide (26). The title compound was prepared according to the general procedure. White solid (133 mg, 83%). m.p. 112–115 °C. Purification (hexanes/EtOAc, 70 : 30). $R_f = 0.48$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.19 (m, 10H), 6.58 (dd, $J = 15.8$, 1.3 Hz, 1H), 6.34 (dd, $J = 15.8$, 6.6 Hz, 1H), 5.25 (ddd, $J = 7.9$, 6.6, 1.3 Hz, 1H), 5.10 (d, $J = 7.9$ Hz, 1H), 2.93 (*p*, $J = 6.8$ Hz, 1H), 1.29 (d, $J = 6.8$ Hz, 3H), 1.22 (d, $J = 6.8$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 140.6, 136.1, 132.0, 129.2, 129.0, 128.7, 128.1, 127.2, 126.7, 59.7, 54.3, 16.5 ppm. IR (neat): $\nu = 3264$, 2982, 2937, 1744, 1598, 1494, 1466, 1452, 1434, 1369, 1311, 1268, 1223, 1168, 1142, 1128 cm^{-1}. HRMS (ESI): calculated for $C_{18}H_{22}NO_2S$ $[M + H]^+$ requires 316.1371 *m*/*z*, found 316.1373 *m*/*z*.

***N*-Cinnamylpropane-2-sulfonamide (27).** The title compound was prepared according to the general procedure. Orange solid (45 mg, 36%). m.p. 76–78 °C. Purification (hexanes/EtOAc, 70 : 30). $R_f = 0.35$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.21 (m, 5H), 6.57 (dt, $J = 15.8$, 1.5 Hz, 1H), 6.20 (dt, $J =$ 15.8, 6.3 Hz, 1H), 4.55 (t, $J = 6.3$ Hz, 1H), 3.91 (td, $J = 6.3$, 1.5 Hz, 2H), 3.18 (*p*, $J = 6.8$ Hz, 1H), 1.38 (d, $J = 6.8$ Hz, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 136.2, 132.9, 128.7, 128.1, 126.6, 125.2, 53.9, 45.8, 16.7 ppm. IR (neat): $\nu = 3277$, 3024, 2982, 2930, 1739, 1588, 1494, 1448, 1425, 1386, 1313, 1269, 1223, 1145, 1131 cm^{-1}. HRMS (ESI): calculated for $C_{12}H_{18}NO_2S$ $[M + H]^+$ requires 240.1058 *m*/*z*, found 240.1059 *m*/*z*.

***N*-Cinnamylpropane-1-sulfonamide (28).** The title compound was prepared according to the general procedure. Yellow solid (46 mg, 38%). m.p. 65–68 °C. Purification (hexanes/EtOAc, 60 : 40). $R_f = 0.46$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.39–7.23 (m, 5H), 6.59 (dt, $J = 15.8$, 1.5 Hz, 1H), 6.19 (dt, $J = 15.8$, 6.4 Hz, 1H), 4.65 (t, $J = 6.4$ Hz, 1H), 3.90 (td, $J = 6.4$, 1.5 Hz, 2H), 3.05–2.99 (m, 2H), 1.93–1.79 (m, 2H), 1.04 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 136.2, 133.2, 128.8, 128.2, 126.6, 124.9, 55.1, 45.5, 17.5, 13.1 ppm. IR (neat): $\nu = 3281$, 3027, 2928, 2855, 1741, 1599, 1494, 1448, 1428, 1369, 1314, 1290, 1221 cm^{-1}. HRMS (ESI): calculated for $C_{12}H_{18}NO_2S$ $[M + H]^+$ requires 240.1058 *m*/*z*, found 240.1062 *m*/*z*.

(*E*)-*N*-(1,3-Diphenyl-prop-2-en-1-yl)-4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzenesulfonamide (29). The title compound was prepared from celecoxib according to the general procedure and the data matches those previously reported.[35] White solid (244 mg, 86%): m.p. 155–158 °C; purification (hexanes/EtOAc = 70 : 30) $R_f = 0.33$. ^{1}H NMR (400 MHz, $CDCl_3$): 7.73 (d, $J = 8.7$ Hz, 1H), 7.31 (d, $J = 8.7$ Hz, 2H), 7.28–7.19 (m, 10H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 8.0$ Hz, 2H), 6.73 (s, 1H), 6.40 (dd, $J = 15.8$, 1.4 Hz, 1H), 6.13 (dd, $J = 15.8$, 6.7 Hz, 1H), 5.33 (d, $J = 6.7$ Hz, 1H), 5.16 (td, $J = 6.7$, 1.4 Hz, 1H), 2.37 (s, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): 145.2, 144.0 (C–F, $^2J = 38.5$ Hz), 142.4, 140.2, 139.8, 139.4, 135.9, 132.5, 129.8, 128.9, 128.8, 128.7, 128.27, 128.24, 128.21, 128.0, 127.2, 126.7, 125.8, 125.2, 121.2 (C–F, $^1J_{CF} = 269.2$ Hz), 106.4, 60.1, 21.4 ppm. IR (neat): $\nu =$ 3300, 3031, 2924, 1746, 1596, 1496, 1472, 1456, 1449, 1420, 1377, 1353, 1327, 1289, 1274, 1231, 1204, 1160, 1127 cm^{-1}. HRMS (ESI): calculated for $C_{32}H_{27}N_3O_2S_1F_3$ $[M + H]^+$ requires 574.1776 *m*/*z*, found 574.1783 *m*/*z*.

***N*-(2-(Cinnamylamino)ethyl)-4-methylbenzenesulfonamide (30).** The title compound was prepared according to the general procedure. Yellow solid (164 mg, 99%). m.p. 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.71 (d, $J = 8.3$ Hz, 2H), 7.37–7.17 (m, 7H), 6.56 (dt, $J = 15.9$, 1.6 Hz, 1H), 6.32 (dt, $J = 15.9$, 5.7 Hz, 1H), 4.26 (dd, $J = 5.7$, 1.6 Hz, 2H), 4.05 (bs, 2H), 2.93 (dd, $J = 6.6$, 4.5 Hz, 2H), 2.80 (dd, $J = 6.6$, 4.5 Hz, 2H), 2.36 (s, 3H) ppm. ^{13}C

$\{^1H\}$ NMR (101 MHz, $CDCl_3$): 143.3, 136.79, 136.76, 130.6, 129.7, 128.9, 128.6, 127.6, 127.0, 126.4, 63.2, 44.6, 40.7, 21.5 ppm. IR (neat): $\nu = 3027$, 2860, 1597, 1494, 1449, 1318, 1305, 1151 cm^{-1}. HRMS (ESI): calculated for $C_{18}H_{23}N_2O_2S$ $[M + H]^+$ requires 331.1480 *m*/*z*, found 331.1484 *m*/*z*.

2-Hydroxy-3-(2-methoxyphenoxy)propyl(*E*)-(1,3-diphenylprop-2-en-1-yl)carbamate (31). The title compound was prepared from methocarbamol according to the general procedure. White solid (77 mg, 35%): m.p. 75–78 °C; purification (hexanes/EtOAc = 40 : 60) $R_f = 0.50$. ^1H NMR (400 MHz, $CDCl_3$): 7.41–7.16 (m, 10H), 7.01–6.85 (m, 4H), 6.55 (d, $J = 15.9$ Hz, 1H), 6.31 (dd, $J = 15.9$, 6.1 Hz, 1H), 5.50 (bs, 1H), 5.34 (bd, $J = 8.4$ Hz, 1H), 4.38–4.19 (m, 3H), 4.13–3.96 (m, 2H), 3.83 (s, 3H), 3.50 (bs, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): 155.9, 150.0, 148.0, 140.8, 136.4, 131.4, 129.0, 128.7, 128.6, 128.0, 127.9, 127.1, 126.7, 122.5, 121.1, 115.5, 112.0, 71.3, 68.9, 66.2, 57.0, 55.9 ppm. IR (neat): ν = 3309, 2930, 1685, 1594, 1534, 1506, 1453, 1329, 1300, 1250, 1220, 1178, 1154, 1124 cm^{-1}. HRMS (ESI): calculated for $C_{26}H_{28}N_1O_5$ $[M + H]^+$ requires 434.1967 *m*/*z*, found 434.1972 *m*/*z*.

Author contributions

ZCB, KLK, BK, BYY, and HZ carried out the synthesis of compounds, mechanistic experiments, and characterization of all compounds. Preparation of acid-immobilized silica gel catalysts and initial reaction discovery and optimization of conditions was carried out by JTS and PMK. Biological assays were designed and carried out by RJS. AAL conceptualized the overall project and prepared the manuscript, which was reviewed and edited by all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: ^1H and ^{13}C NMR and additional experimental data. See DOI: https://doi.org/10.1039/d6ra01478j.

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