Practical synthesis and biological screening of sulfonyl hydrazides†

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A methodology for the synthesis of sulfonyl hydrazides mediated by hypervalent iodine is described. Taking advantage of the umpolung properties of hypervalent iodine reagents, the polarity of sodium sulfinate salts is reversed, and a key intermediate is generated and reacted with mono- and disubstituted hydrazines. To highlight the practical utility of this protocol, a diverse range of sulfonyl hydrazides were synthesized in yields up to 62%. Furthermore, a gram-scale reaction was performed, showing the robustness of the procedure. Mechanistic studies, including DFT calculations, were performed and the bioactivity of the generated compounds was evaluated.

Introduction

Sulfonyl-containing compounds, such as sulfonamides and sulfonyl hydrazides, are important functional groups in both organic and medicinal chemistry (Fig. 1).[1,2] In particular, sulfonyl hydrazides, being a sulfonyl source, are of special interest in synthetic chemistry.[1,2] Consequently, sulfonyl hydrazides are important building blocks in many total syntheses.[3,4] Traditional methods for the incorporation of sulfonyl groups rely on the use of gaseous sulphur dioxide, whose manipulation is difficult and hazardous.

Sulfonyl chlorides have also been used as electrophilic sources of SO_2.[5] Despite being very effective in the sulfonylation of organic compounds, sulfonyl chlorides show poor functional group tolerance.[6] SO_2 surrogates have emerged as safe alternatives for the delivery of SO_2 moieties. An important example of SO_2 surrogates is DABSO.[7] This surrogate has been used in the synthesis of sulfonyl hydrazides, in the presence of a palladium catalyst[8] (Scheme 1A), in a radical metal-free methodology[9] (Scheme 1B), and in a radical methodology using diaryliodonium salts[10] (Scheme 1C) or alkyl halides.[7] Although these methods are versatile, they either depend on metal catalysts and/or pre-functionalized substrates.

Hypervalent iodine reagents have gained much attention not only due to their oxidative properties but also due to their umpolung reactivity.[11] In this context, iodine(III) compounds exhibit chemical properties and reactivities similar to those of transition metal complexes, constituting electrophilic synthons of inherently nucleophilic groups.

Among the various hypervalent iodine compounds, cyclic benziodoxolones have attracted great interest due to their

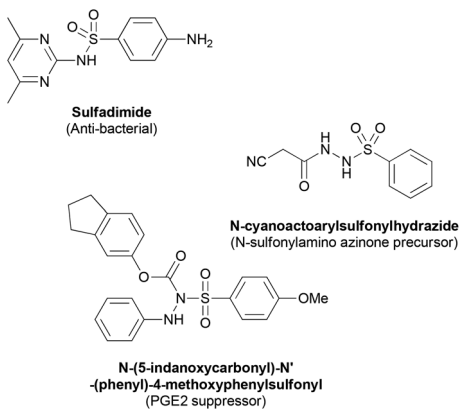

Fig. 1 Examples of relevant sulfonamides and sulfonyl hydrazides.

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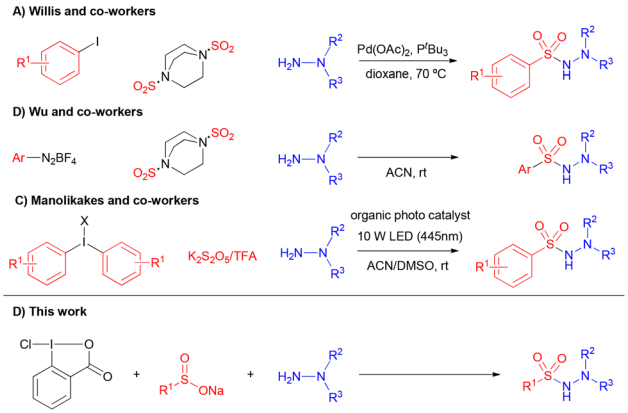


Scheme 1 Reported methods for the synthesis of sulfonyl hydrazide and this work.

increased stability. Thus, these reagents have been widely explored in various chemical transformations involving electrophilic or oxidative atom-transfer reactions. Representative examples are the Togni's reagent, EBX and ABZ, reagents that are able to transfer CF_3, alkynyl, and azide groups, respectively.[12,13]

In 2019, our research group reported the synthesis of sulfonamides mediated by a hypervalent iodine reagent.[14,15] The umpolung reactivity of chlorobenziodoxolone allowed the *in situ* generation of a sulfonyl-transfer reagent, not isolated, that was nucleophilically attacked by amines, generating the corresponding sulfonamides.

As a continuation of our work, and given our interest in sulfonyl hydrazides, we envisaged that hypervalent iodine reagents could also promote the synthesis of the challenging sulfonyl hydrazides, acting as SO_2 surrogates. Thus, we investigated the reactivity of the generated electrophilic hypervalent iodine reagent with several hydrazines.

Results and discussion

Chlorobenziodoxolone (**1**) was prepared according to a reported procedure and used in combination with the sodium phenyl sulfinate salt (**2a**) and 4-aminomorpholine (**3a**) as the model substrates. The study was initiated by applying our previously described conditions for sulfonamide synthesis[14] (Table 1, entry 1). Accordingly, chlorobenziodoxolone (**1**) was used as the limiting reagent and mixed with the sodium phenyl sulfinate salt (**2a**) and tetrabutylammonium iodide, in dichloromethane, under a nitrogen atmosphere, leading to *N*-morpholino-benzenesulfonamide (**4aa**) and the dimorpholinodiazene (**5a**) in 29% and 24% yields, respectively.

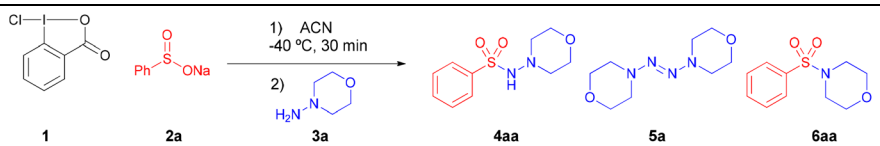
Due to the inherent higher nucleophilicity of hydrazines when compared to amines, hydrazine was used as the limiting reagent, which resulted in slightly lower yields (Table 1, entry 2).

Next, the influence of temperature was investigated. Performing the reaction at −78 °C resulted in lower yields of **4aa** and **5a** (Table 1, entry 3). When equivalent amounts of **1**, **2a** and **3a** were used, **4aa** was obtained in 21% yield, along with **5a** in 35% yield (Table 1, entry 4).

When the reaction was quenched after 1 h, **4aa** was obtained in 46% yield, and the side-product **5a** was obtained only in trace amounts (3% yield) (Table 1, entry 5). Under these new conditions (1 h), the use of excess amounts of hydrazine **3a** was considered, and **4a** was obtained in 27% yield along with trace amounts of **5a** (Table 1, entry 6). Thus, the use of excess amounts of hydrazine did not favour the formation of **4aa**. We hypothesized that TBAI could promote the formation of the oxidized hydrazine **5a**. Thus, conducting the reaction without TBAI afforded product **4aa** in 48% yield, and **5a** was not detected (Table 1, entry 7).

Next we investigated the influence of the solvent. When the reaction was carried out in acetonitrile, **4aa** was isolated in

Table 1 Optimization of the reaction conditions with 4-aminomorpholine (**3a**)



1 **2a** **3a** **4aa** **5a** **6aa**

Entry[a]	(**1**) (equiv.)	(**2a**) (equiv.)	(**3a**) (equiv.)	TBAI (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (**4aa**)[b] (%)	Yield (**5a**)[b] (%)	Yield (**6aa**)[b] (%)
1	1	1.5	1.5	0.2	DCM	−40	4	29	24	NO
2	1.5	1.5	1	0.2	DCM	−40	4	20	28	NO
3	1.5	1.5	1	0.2	DCM	−78	4	11	9	NO
4	1	1	1	0.2	DCM	−40	4	21	35	NO
5	1.5	1.5	1	0.2	DCM	−40	1	46	3	NO
6	1	1	2	0.2	DCM	−40	1	27	7	NO
7	1.5	1.5	1	0	DCM	−40	1	48	NO	NO
8	1.5	1.5	1	0	ACN	−40	1	41	NO	41
9	**1**	**1**	**1**	**0**	**ACN**	**−40**	**1**	**56**	NO	NO

[a] All experiments were carried out under the following conditions: (1) 0.19 mmol of chlorobenziodoxolone (**1**) with sodium benzenesulfinate (**2a**) in 1 mL of solvent for 30 min at −40 °C and (2) hydrazine (**3**) was added to the reaction mixture. [b] Isolated yields. NO – not observed.

41% yield (Table 1, entry 8). Although no **5a** was observed, a new side product was isolated, sulfonamide **6aa**, in 41% yield.

Lastly, upon carrying out the reaction in acetonitrile for 1 h and with stoichiometric amounts of the reagents, **4aa** was isolated in 56% yield (Table 1, entry 9). These results suggest that smaller amounts of **3a** and shorter reaction times promote the formation of the sulfonyl hydrazide, while avoiding the oxidation of the starting hydrazine to **5a** and subsequently the formation of **6aa**.

Product **4a** is poorly soluble in acetonitrile, and in all experiments, it is precipitated from the crude mixture along with the remaining sodium sulfinate salt. Thus, *N*,*N*-methylphenyl hydrazine (**3b**) was also investigated during the optimization studies (Table 2). Similarly, acetonitrile and dichloromethane were tested, both in the presence and absence of TBAI (Table 2, entries 1–4). The optimal conditions found for the formation of **4ab** were the same as those for compound **4aa** (Table 2, entry 5). The desired *N*′,*N*′-methylphenylbenzenesulfonohydrazide (**4ab**) was obtained in 52% yield.

The results obtained suggest that the formation of **5a** is favoured by the presence of TBAI and longer reaction times. Parallelly, the formation of **6aa** was observed when acetonitrile was used and potentiated by longer reaction times. Additionally, the use of 1 or 1.5 equivalents of reagents **1** and **2** led to similar results in the formation of **4aa**/**4ab**. Lastly, better results were observed when using acetonitrile for both products **4aa** and **4ab**. The best conditions involved the use of 1 equivalent of **1**, **2a**, and **3a** in acetonitrile at −40 °C (Table 1, entry 9 and Table 2, entry 5 for **3a** and **3b**, respectively).

To study the versatility of the reaction, different hydrazines and sulfinate salts were tested (Table 3). Regarding the sulfinate salts, when *N*,*N*-methylphenyl hydrazine (**3b**) was reacted with sodium phenylsulfinate (**2a**) or sodium 4-methylphenylsulfinate (**2b**), moderate to good yields of the corresponding sulfonyl hydrazides **4ab** (52%) and **4bb** (47%) were obtained. However, the use of sodium methylsulfinate (**2c**) and sodium naphthalenesulfinate (**2d**) resulted in the corresponding products being obtained in lower yields (**4cb** in 40% and **4db** in 36% yields). When sodium 2-pyridinesulfinate (**2e**) was used with amino morpholine (**3a**), sulfonamide **6ea** was obtained instead of the expected sulfonyl hydrazide. Indeed, the oxidation of this hydrazine has been observed during the optimization studies. When sodium i-propylsulfinate (**2f**) was used, no product was observed, possibly due to steric hindrance.

Table 3 Synthesis of sulfonyl hydrazides from hydrazines and sulfinate salts

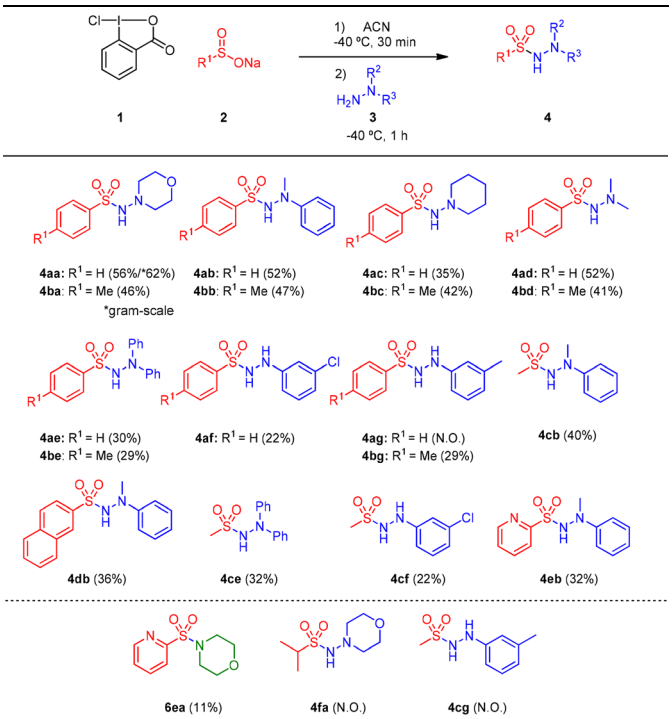
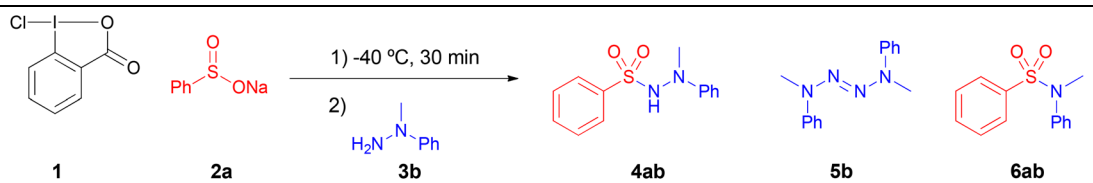


Table 2 Optimization of the reaction conditions with *N*′,*N*′-methylphenylbenzenesulfonohydrazide (**4b**)



Entry[a]	(**1**) (equiv.)	(**2**) (equiv.)	(**3b**) (equiv.)	TBAI (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (**4ab**)[b] (%)	Yield (**5a**)[b] (%)	Yield (**6ab**)[b] (%)
1	1.5	1.5	1	0.2	DCM	−40	1	35	NO	NO
2	1.5	1.5	1	0.2	ACN	−40	1	22	NO	NO
3	1.5	1.5	1	0	DCM	−40	1	26	NO	NO
4	1.5	1.5	1	0	ACN	−40	1	49	NO	18
5	**1**	**1**	**1**	**0**	**ACN**	**−40**	**1**	**52**	NO	NO

[a] All experiments were carried out under the following conditions: (1) 0.19 mmol of chlorobenziodoxolone (**1**) with sodium benzenesulfinate (**2a**) in 1 mL of solvent for 30 min at −40 °C and (2) hydrazine (**3**) was added to the reaction mixture. [b] Isolated yields. NO – not observed.

Regarding the different hydrazines, both *N*,*N*-disubstituted and *N*-monosubstituted hydrazines were considered, and similar reactivity was found, for example for **4ae** (30%) and **4af** (22%), with the *N*,*N*-disubstituted hydrazines affording slightly higher yields.

Different substituents were investigated, and hydrazines bearing alkyl-substituents (**3a**, **3c** and **3d**) and aryl-substituents (**3b**) were tested. When combined with a reactive sulfinic salt, such as **2a**, hydrazines bearing two alkyl substituents (**3a**, **3c** or **3d**) or an aryl and an alkyl substituent (**3b**) gave sulfonyl hydrazides in good yields (**4aa**, **4ab**, **4ac** and **4ad** in up to 56% yields). Lower yields were observed when using *N*,*N*-diphenylhydrazine (**3e**), with **4ae** being isolated in 30% yield.

The use of *m*-chlorophenylhydrazine (**3f**) as the nucleophile afforded the desired product **4cf** in 22% yield, probably due to its lower nucleophilicity. When *m*-methylphenylhydrazine (**3g**) was reacted with **2b**, product **4bg** was afforded in 29% yield. The lower yields of **4bg** and **4af** might be due to be the presence of a second nucleophilic position, and, consequently, more complex reaction mixtures were observed.

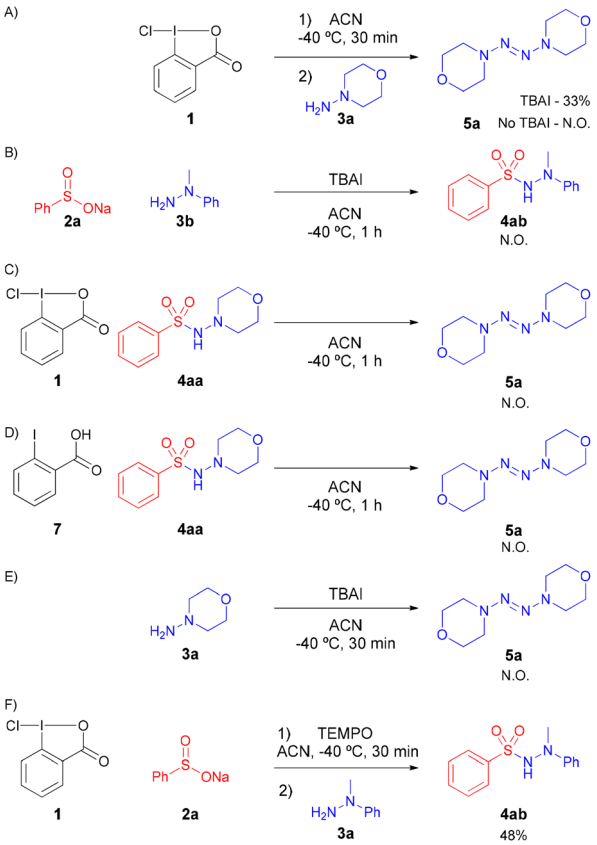
The synthesis of **4aa** was performed at the gram-scale and the product was obtained in 62% yield.

Intrigued by the formation of dimorpholinodiazene **5a**, control experiments were carried out (Scheme 2). During the optimization studies, the formation of **5a** had been observed when TBAI was used. In order to understand if **3a** was being oxidized by **1** and promoted by TBAI, **1** was reacted with **3a** in the presence and absence of TBAI (Scheme 2A). Indeed, the formation of **5a** was observed in 33% yield when TBAI was present, while in the absence of TBAI, no **5a** was observed. In the absence of chlorobenziodozolone (**1**), no reaction occurred, even when TBAI was mixed with hydrazine (Scheme 2B).

We wondered if compound **5a** could be formed from the oxidation of the sulfonyl hydrazide **4aa**. However, when **4aa** was reacted with **1** (Scheme 2C) or 2-iodo benzoic acid (**7**) (Scheme 2D) in the presence and absence of TBAI, **5a** was not observed. Lastly, **3a** was mixed with TBAI to understand if **5a** was obtained from the oxidation of the starting hydrazine, but no **5a** was observed (Scheme 2E). Therefore, **5a** is obtained directly from the oxidation of compound **3a** in the presence of the hypervalent iodine reagent **1** and TBAI.

Next, the mechanism of the reaction was investigated. To understand if a radical mechanism could be involved, an experiment was carried out using the best conditions in the presence of TEMPO. The sulfonyl hydrazide **4ab** was obtained in 48% yield instead of 52% (Scheme 2F). Little difference is observed with or without the addition of TEMPO, suggesting that the reaction does not take place *via* a radical pathway.

Computational studies were performed to understand the mechanism of the reaction. Similar to our previous report,[14] the lowest energy transition state that was found has the synthesized sulfonyl hydrazide linked to the benziodoxolone through an I–O bond (Fig. 2A). Comparing the energy of the transition state obtained for the sulfonyl hydrazide synthesis



Scheme 2 Proposed reaction mechanism.

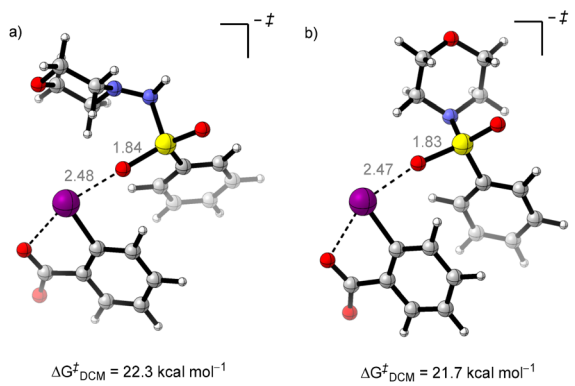
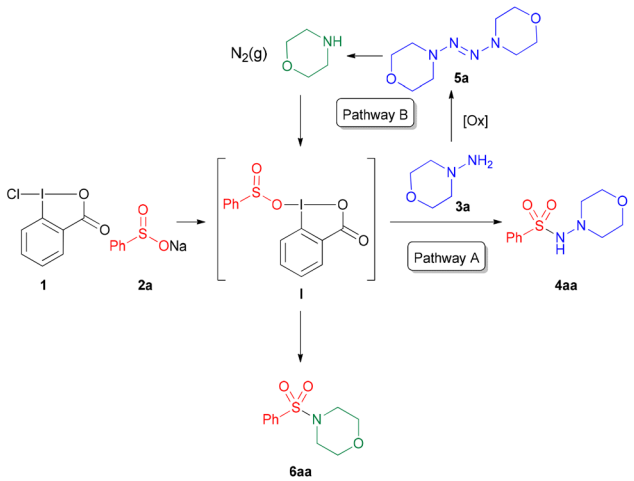


Fig. 2 DFT calculations – comparison between the transition state using: (a) hydrazine and (b) amine.

with that of the previously reported sulfonamide synthesis (Fig. 2B), a slightly lower energy is observed in the transition state of the latter. This observation corroborates with the overall reduced yields in sulfonyl hydrazide synthesis.

Considering the results obtained, and the DFT calculations performed, a reaction pathway was envisioned (Scheme 3). We propose that, similar to our previous approach, sulfonyl benziodoxolone (intermediate **I**) is formed *in situ*, followed by the



Scheme 3 Control experiments.

addition of the amine to the sulfur center. DFT calculations suggested an energy barrier of 22.3 kcal mol $^{-1}$ (*via* a calculated proposed TS structure) for the resultant concerted sulfur oxidation/iodine reduction which yields the corresponding sulfonyl hydrazide **4aa** and 2-iodobenzoic acid (pathway A). When an amine is used instead of the hydrazine, a transition state energy barrier of 21.7 kcal mol $^{-1}$ was found.[14] Both transition states are very close in energy, suggesting a similar mechanism.

In this reaction, a parallel reaction can occur (pathway B). Due to the oxidative conditions generated by the hypervalent iodine reagent, hydrazine **3a** might undergo an oxidative coupling, affording compound **5a** which is always formed along with the sulfonyl hydrazide product. In the absence of TBAI, compound **5a** generates morpholine *in situ*, which then reacts with intermediate **I**, affording sulfonamide **6aa**. Pathway B is circumvented at lower temperatures, shorter reaction times and without excess amounts of reagents (**1a** and **2a**).

As a first step towards the biological characterization of the compounds, their cytotoxicity towards HeLa cells was examined using the MTT assay. As can be seen from the data (see the ESI†), none of the tested compounds had a major impact on the HeLa cell viability within the investigated range of 0.5 μM to 100 μM. However, a decrease in viability – between 10% to 30% – was observed for some compounds (**4aa**, **4ab**, **4bb**, **4db**, and **4cb**). Consequently, the IC_{50} values could not be determined experimentally but they lie in any case above a compound concentration of 100 μM. Owing to the high compound concentrations used in the MTT assay, it cannot be ruled out that in the case of **4aa**, **4ab**, **4bb**, **4db** and **4cb**, the decreasing viability is caused, for example, by an increased metabolic activity required for the depletion of the compounds. Thus, all the tested compounds seem promising with regard to their applications in medicinal chemistry and will be examined in subsequent studies for their antimicrobial properties and activities as inhibitors of indoleamine-2,3-dioxygenase.[16]

Conclusions

A practical and simple synthesis of sulfonyl hydrazides is described, taking advantage of the umpolung reactivity of hypervalent iodine reagents. The easily prepared chlorobenziodoxolone was used in combination with commercially available sulfinate salts and hydrazines. The practical utility of this protocol was demonstrated by the synthesis of various sulfonyl hydrazides in up to 62% yields. Both alky and aryl-substituted hydrazines and sulfinate salts were used.

Mechanistic studies were performed which suggested the formation of a key intermediate bearing an electrophilic sulfonyl source that is transferred to the hydrazines.

Preliminary biological studies on HeLa cells did not indicate any general toxicity originating from the synthesized sulfonyl hydrazides.

Experimental procedures

All reagents and solvents were obtained from commercial sources and used without further purification, unless otherwise mentioned. All the mentioned solvents were, when necessary, dried using typical methods. Molecular sieves were activated by heating in a microwave for 10 minutes and placing in a vacuum.

Analytical TLC was performed on Merck Kieselgel GF 254 0.2 mm plates supported on aluminium. Preparative TLC was performed using Merck Kieselgel 60GS254 silica gel for TLC supported on a glass surface with the described eluent for each case. Flash chromatography was performed using Merck Kieselgel 60A silica gel (70–200 mesh) with the described eluent for each case.

IR spectra were acquired using a PerkinElmer Spectrum Two FT-IR spectrophotometer equipped with a UATR module. The transmittance of the sample was acquired between 4000 and 600 cm $^{-1}$. The IR bands are classified as weak (w), medium (m) or strong (s).

NMR spectra were acquired with Bruker Avance NEO 500 or Bruker ARX 400 spectrometers. ^{1}H NMR and ^{13}C NMR spectra were measured either at 400 and 101 MHz or at 500 and 126 MHz, respectively. Samples were prepared on 5 mm NMR tubes using $CDCl_3$, D_2O or DMSO-d_6 as solvents and NMR data were recorded as follows: chemical shift (δ, in ppm), source of signal (R–H) and relative intensity of signals; multiplicity (*n*H or *n*C, with *n* being the number of protons or carbons) of NMR signals are described as singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), doublet of quartets (dq), triplet (t), quartet (q) and multiplet (m), with the coupling constant (J) being given in Hz.

Low resolution ESI mass spectra were recorded on an ion trap mass analyser (Thermo Scientific LCQ Fleet Ion Trap LC/MS) equipped with an electrospray interface.

Synthesis of 1-chloro-1,2-benziodoxol-3-(1*H*)-one (1)

A round-bottom flask was charged with 2-iodobenzoic acid (500 mg, 2 mmol) and dissolved in 4 mL of acetonitrile. The

mixture was stirred at 82 °C until full dissolution was observed. A solution of TCICA (155 mg, 0.67 mmol) in 1 ml of hot acetonitrile was then added to the mixture. The resulting mixture was stirred at 82 °C for 10 min and, while still hot, filtered through a hot Hirsch funnel and washed with hot acetonitrile. The resulting solution was concentrated under vacuum, affording 1-chloro-1,2-benziodoxol-3-(1*H*)-one (**1**) as a white solid in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δH = 8.26 (d, J = 7.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.99 (t, J = 7.2 Hz, 1H), 7.80 (t, J = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δC = 167.3, 136.8, 133.6, 132.0, 128.8, 127.0, 117.2. **1** is a known compound and the spectral data are in accordance with those reported previously.[14]

General procedure for sulfonyl hydrazide synthesis

A round-bottom flask was charged with chlorobenziodoxolone (55.20 mg, 0.19 mmol) and sulfinate salt (0.19 mmol) in 1 mL of acetonitrile. The reaction was stirred for 30 min at −40 °C. Hydrazine (0.19 mmol) was added to the reaction. The flask was stirred for 1 h at −40 °C. When completed, the reaction mixture was allowed to warm up to room temperature, washed with a saturated solution of sodium hydrogencarbonate, and the resulting aqueous phase was extracted with ethyl acetate. The organic phase was dried with sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified using flash chromatography with ethyl acetate/hexane.

N-Morpholinobenzenesulfonamide (4aa)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a white solid in 56% yield. IR (ATR) = 3135, 2918, 2858, 1451, 1366, 1335 (SO_2), 1264, 1156 (SO_2), 1103. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.00 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.7 Hz, 2H), 5.64 (s, 1H), 3.62 (t, J = 4.4 Hz, 4H), 2.64 (t, J = 4.4 Hz, 4H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 138.8, 133.3, 129.0, 128.3, 66.8, 56.9. M.p. = 100–107 °C. **4aa** is a known compound and the spectral data are in accordance with those reported previously.[10]

N′-Methyl-*N*′-phenylbenzenesulfonohydrazide (4ab)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a yellow solid in 52% yield. IR (ATR) = 3198, 1599, 1501, 1446, 1339 (SO_2), 1157 (SO_2), 1087. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.96 (d, J = 7.7 Hz, 2H), 7.59 (s, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.15 (t, J = 7.6 Hz, 2H), 6.83 (m, 3H), 6.22 (s, 1H), 2.98 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 149.7, 138.7, 133.5, 129.2, 129.1, 128.3, 121.2, 114.5, 43.0. M.p. = 124–132 °C. **4ab** is a known compound and the spectral data are in accordance with those reported previously.[10]

1,2-Dimorpholinodiazene (5a)

IR (ATR) = 2959, 2871, 2842, 1452, 1268, 1108, 1090, 985, 860. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 3.81 (t, J = 5 Hz, 4H), 3.19 (t, J = 5 Hz, 4H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 66.5, 50.4. M.p. = 100–114 °C. **5** is a known compound and the spectral data are in accordance with those reported previously.[17]

4-Methyl-*N*-morpholinobenzenesulfonamide (4ba)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a white solid in 46% yield. IR (ATR) = 3182, 2971, 1456, 1356, 1327 (SO_2), 1261, 1156 (SO_2), 1105. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.84 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.35 (s, 1H), 3.61 (t, J = 4.7 Hz, 4H), 2.62 (t, J = 4.6 Hz, 4H), 2.44 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 144.2, 135.8, 129.6, 128.3, 66.8, 56.9, 21.8. M.p. = 136–142 °C. **4ba** is a known compound and the spectral data are in accordance with those reported previously.[10]

N-Methyl-*N*-phenyl-*N*′-*p*-toluolsulfonyl-hydrazine (4bb)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a yellow solid in 47% yield. IR (ATR) = 3195, 2921, 1499, 1333 (SO_2), 1156 (SO_2), 1089. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.84 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.17 (t, J = 7.8 Hz, 2H), 6.89–6.82 (m, 3H), 6.12 (s, 1H), 2.97 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 149.7, 144.3, 135.6, 129.7, 128.9, 128.2, 120.9, 114.3, 42.8, 21.6. M.p. = 128–132 °C. **4bb** is a known compound and the spectral data are in accordance with those reported previously.[8]

N′-Methyl-*N*′-phenylmethanesulfonohydrazide (4cb)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a pale-yellow oil in 40% yield. IR (ATR) = 3226, 1597, 1322 (SO_2), 1161 (SO_2), 1149. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.31 (t, J = 8.2 Hz, 2H), 7.04 (d, J = 8.4, 2H), 6.96 (t, J = 6.8, 1H), 6.06 (s, 1H), 3.29 (s, 3H), 2.99 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 149.7, 129.5, 121.4, 114.4, 44.0, 39.0. HRMS (ESI+) calculated = 201.0692; found = 201.0688. M.p. = 99–106 °C.

N′-Methyl-*N*′-phenylnaphthalene-2-sulfonohydrazide (4db)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a bright yellow solid in 36% yield. IR (ATR) = 3255, 1600, 1497, 1335 (SO_2), 1160 (SO_2), 1083. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.79 (d, J = 8.6 Hz, 1H), 8.36 (dd, J = 7.4, 1.3 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.98–7.91 (m, 1H), 7.70 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H), 7.65–7.59 (m, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.08–7.00 (m, 2H), 6.82–6.75 (m, 3H), 6.42 (s, 1H), 2.82 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 149.7, 135.2, 134.3, 133.7, 131.8, 129.2, 128.9, 128.8, 128.7, 127.1, 124.9, 124.5, 121.0, 114.5, 42.8. HRMS (ESI+) calculated = 313.1005; found = 313.0998. M.p. = 87–93 °C.

N′-Methyl-*N*′-phenylpyridin-2-sulfonohydrazide (4eb)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a bright orange solid in 32% yield. IR (ATR) = 3055,

2840, 1601, 1349 (SO_2), 1176 (SO_2), 1082. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.79 (d, J = 4.4 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.88 (dt, J = 7.8, 1.6 Hz, 1H), 7.52 (dd, J = 7.6, 4.8 Hz, 1H), 7.40–7.30 (m, 1H), 7.18 (t, J = 8.1 Hz, 2H), 6.94 (d, J = 7.8 Hz, 2H), 6.86 (t, J = 7.3 Hz, 1H), 2.98 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 149.7, 135.2, 134.3, 131.8, 129.2, 128.9, 124.5, 121.0, 114.5, 42.8. HRMS (ESI+) calculated = 264.0801; found = 264.0791. M.p. = 75–79 °C.

N-(Piperidin-1-yl)benzenesulfonamide (4ac)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a pale-yellow solid in 35% yield. IR (ATR) = 3206, 2935, 1325 (SO_2), 1158 (SO_2), 1094. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.97 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 5.32 (s, 1H), 2.52 (t, J = 4.6 Hz, 4H), 1.50 (q, J = 5.7 Hz, 4H), 1.37–1.22 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 138.9, 133.0, 128.8, 128.3, 58.0, 25.8, 23.2. M.p. = 92–94 °C. **4ac** is a known compound and the spectral data are in accordance with those reported previously.[10]

4-Methyl-*N*-(piperidin-1-yl)benzenesulfonamide (4bc)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a pale-yellow solid in 42% yield. IR (ATR) = 3200, 2926, 1330 (SO_2), 1161 (SO_2), 1095. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.84 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 5.23 (s, 1H), 2.52 (t, J = 5.1 Hz, 4H), 2.43 (s, 3H), 1.50 (q, J = 5.1 Hz, 4H), 1.34–1.23 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 143.8, 136.0, 129.5, 128.3, 57.9, 25.8, 23.2, 21.8. M.p. = 118–124 °C. **4bc** is a known compound and the spectral data are in accordance with those reported previously.[18]

2-Benzolsulfonyl-1,1-dimethyl-hydrazin (4ad)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a colourless solid in 52% yield. IR (ATR) = 3236, 2919, 1323 (SO_2), 1148 (SO_2), 1087, 1018. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.96 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 7.4 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 5.27 (s, 1H), 2.39 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 138.9, 133.1, 129.0, 128.3, 48.7. HRMS (ESI+) calculated = 201.0692; found = 201.0686. M.p. = 88–91 °C.

N,*N*-Dimethyl-4-toluenesulfonylhydrazide (4bd)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a colourless solid in 41% yield. IR (ATR) = 3258, 2918, 1326 (SO_2), 1156 (SO_2), 1092, 1020. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.83 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.14 (s, 1H), 2.44 (s, 3H), 2.40 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 144.0, 135.9, 129.6, 128.3, 48.7, 21.7. M.p. = 80–82 °C. **4bd** is a known compound and the spectral data are in accordance with those reported previously.[19]

N′,*N*′-Diphenylbenzenesulfonohydrazide (4ae)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a dark brown solid in 30% yield. IR (ATR) = 3064, 1590, 1493, 1329, 1160 (SO_2), 750. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.77 (d, J = 8.3 Hz, 2H), 7.48–7.43 (m, 1H), 7.31 (t, J = 7.9 Hz, 2H), 7.20–7.13 (m, 4H), 7.04–6.93 (m, 6H), 6.86 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 146.8, 138.6, 133.0, 129.1, 128.8, 128.2, 124.0, 120.7. M.p. = 151 °C. **4ae** is a known compound and the spectral data are in accordance with those reported previously.[10]

4-Methyl-*N*′,*N*′-diphenylbenzenesulfonylhydrazide (4be)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a dark brown solid in 29% yield. IR (ATR) = 3234, 1591, 1494, 1335, 1160 (SO_2), 562. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.63 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 7.8 Hz, 4H), 7.09 (d, J = 8.0, 2H), 7.03–6.92 (m, 7H), 2.34 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 147.0, 144.1, 135.7, 129.5, 129.1, 128.4, 124.0, 120.9, 21.6. M.p. = 128–131 °C. HRMS (ESI+) calculated = 339.1162; found = 339.1150.

N′,*N*′-Diphenylmethanesulfonohydrazide (4ce)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a dark brown solid in 36% yield. IR (ATR) = 3244, 1590, 1493, 1322, 1152 (SO_2), 752, 697. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.34 (t, J = 7.9 Hz, 4H), 7.22 (d, J = 7.7 Hz, 4H), 7.13 (t, J = 7.1 Hz, 2H), 6.64 (s, 1H), 2.83 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 147.1, 129.6, 124.5, 121.0, 40.5. M. p. = 161–162 °C. HRMS (ESI+) calculated = 263.0849; found = 263.0841.

N′-(3-Chlorophenyl)benzenesulfonohydrazide (4af)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a yellow oil in 22% yield. IR (ATR) = 3246, 1599, 1327, 1158 (SO_2), 1090, 583. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.91–7.85 (m, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.00 (t, J = 8.1 Hz, 1H), 6.76–6.55 (m, 2H), 6.37 (s, 1H), 5.78 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 147.3, 137.7, 134.9, 133.7, 130.1, 129.2, 128.2, 121.2, 113.4, 111.5. M.p. = 111–112 °C. HRMS (ESI+) calculated = 283.0303; found = 283.0293.

N′-(3-Chlorophenyl)methanesulfonohydrazide (4cf)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a yellow oil in 22% yield. IR (ATR) = 3248, 1598, 1314, 1145 (SO_2), 770, 493. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.17 (t, J = 8.0 Hz, 1H), 6.96 (t, J = 2.1 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.80 (dd, J = 8.2, 1.3 Hz, 1H), 6.38 (s, 1H), 6.16 (s, 1H), 2.96 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 147.8, 135.4,

130.7, 121.6, 113.5, 111.7, 39.4. HRMS (ESI+) calculated = 221.0146; found = 221.0139.

4-Methyl-*N*′-(*m*-tolyl)benzenesulfonohydrazide (4bg)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as a yellow solid in 29% yield. IR (ATR) = 3248, 1596, 1158 (SO_2), 1091, 552. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 7.78 (d, J = 8.3 Hz, 2H), 7.30–7.24 (m, 2H), 6.99 (dd, J = 7.5, 1.4 Hz, 1H), 6.64 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 7.0 Hz, 2H), 6.34 (s, 1H), 5.64 (s, 1H), 2.42 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ = 144.3, 138.9, 135.0, 129.6, 128.8, 128.2, 121.9, 114.1, 110.6, 30.9. M.p. = 154 °C. **4bg** is a known compound and the spectral data are in accordance with those reported previously.[20]

4-(Pyridin-2-ylsulfonyl)morpholine (6ea)

Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane gave the title product as an oil in 11% yield. IR (ATR) = 2857, 1 452 1340, 1261, 1179 (SO_2), 1114, 1070, 950. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ = 8.74 (d, J = 4.4 Hz, 1H), 7.94 (m, 2H), 7.52 (m, 1H), 3.75 (t, J = 4.8 Hz, 4H), 3.34 (t, J = 4.8 Hz, 4H). HRMS (ESI+) calculated = 229.0641, found = 229.0635. **6ea** is a known compound and the spectral data are in accordance with those reported previously.[21]

Computational details

Density functional theory (DFT) calculations were performed using the Gaussian 16 software package[22] and structural representations were generated with CYLview20.[23] All the geometry optimizations were carried out at the M06 level of theory with the LANL2DZ basis set (Los Alamos National Laboratory 2 double ζ). All of the optimized geometries were verified by frequency computations as minima (zero imaginary frequencies) or transition states (a single imaginary frequency corresponding to the desired reaction coordinate). Single-point energy calculations on the optimized geometries were then evaluated using the Minnesota hybrid *meta*-GGA functional M06-2X and the same basis set, with solvent effects (dichloromethane) calculated by means of the Polarizable Continuum Model (PCM) initially devised by Tomasi and coworkers,[24–27] with radii and non-electrostatic terms of the SMD solvation model developed by Truhlar and co-workers.[28] The free energy values presented in the manuscript and the ESI† were derived from the electronic energy values obtained at the M06-2X/LANL2DZ//M06/LANL2DZ level, including solvent effects, and corrected by using the thermal and entropic corrections based on structural and vibration frequency data calculated at the M06/LANL2DZ level.

Cytotoxicity

The cytotoxicity of compounds was evaluated for HeLa cells. First, 10^4 cells were sowed and incubated for 24 h at 37 °C and 5% CO_2. Subsequently, the cells were treated with different concentrations of the compounds (0.5, 10, 25, 50 and 100 μM). After incubation for three days, MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide] was added. As a positive control, cells were lysed with 20% Triton solution. After 3 h, the reaction was terminated with an aqueous solution containing 10% SDS and 0.3% HCl. The reduced MTT was evaluated after 24 h by measuring the absorbance at 595 nm. All measurements were performed in quintuplicates.

Data availability

Data that refer to the herein described target compounds have been submitted to the Chemotion Repository (**https://www.chemotion-repository.net/**).[29] DOIs created for the data are linked in the ESI.† Samples of the target compounds have been submitted to the Molecule Archive at the Karlsruhe Institute for Technology and are available upon request (**https://compound-platform.eu/home**).

Author contributions

This manuscript was written through contributions from all authors.

Conflicts of interest

There are no conflicts to declare.

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