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Design, synthesis, and biological evaluation of 3-benzenesulfonamide-linked 3-hydrazinoisatin derivatives as carbonic anhydrase inhibitors

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Abstract

A new series of isatin-linked benzenesulfonamide derivatives (**9a–w**) were synthesized using the tail approach and assayed for their inhibitory potency against four different human carbonic anhydrase (hCA) isoforms, hCA I, II, IX, and XII. Most of these synthesized compounds exhibited interesting inhibition potency against isoforms hCA I, IX, and XII in the nanomolar range and by taking the standard drug acetazolamide. The most potent compounds in the case of hCA I were **9c** (435.8 nM) and **9s** (956.4 nM), for hCA IX, **9a** (60.5 nM), **9d** (95.6 nM), **9g** (92.1 nM), and **9k** (75.4 nM), and for hCA XII, **9p** (84.5 nM). However, these compounds showed more selectivity toward hCA IX over hCA I, II, and XII. Thus, these compounds can be further developed as potential lead molecules for the development of isoform-selective hCA IX inhibitors with further structural modifications.

KEYWORDS
cancer, carbonic anhydrase, isatin, isoform selectivity, sulfonamide

1 | INTRODUCTION

Carbonic anhydrases (CAs; EC 4.2.1.1) are metalloenzymes, containing a Zn^{2+} ion at their active center, which is present in all forms of life and responsible for the reversible conversion of CO_2 and H_2O to a weak base bicarbonate (HCO_3-) and a strong acid hydronium ion (H^+).[1–3] They were classified into eight genetically different families (α, β, γ, δ, θ, η, ζ, ι).[4,5] The α-CA was found in mammals consisting of 16 isoforms (hCA I-hCA XV, hCA VA, and VB), from which isoform hCA XV was absent in humans. These isoforms were involved in various catalytic

activities[6,7] and regulate many crucial physiological and pathological processes such as pH and CO_2 homeostasis, electrolyte secretion in various tissues and organs, respiration and transport of carbon dioxide and bicarbonate between metabolizing tissues and lungs, biosynthetic reactions (gluconeogenesis, lipogenesis, and ureagenesis), calcification, bone resorption, and oncogenesis (in mammals). Hence, CA inhibitors (CAIs) have been proposed as diuretics, antiepileptics, antimicrobial, antiglaucoma, or anticancer agents.[8] Classical CAIs like sulfonamides and their bioisosters and nonclassical CAIs like phenols and polyamines, coumarins, and sulfocoumarins were well known for inhibiting the enzymes through different inhibition mechanisms.[9]

Compounds containing isatin moiety have been found to exhibit a wide range of biological activities including anticancer, antibacterial, antifungal, analgesic, anti-inflammatory, anticonvulsant, and anti-HIV.[10] Isatins with aromatic sulphonamides were investigated earlier as potent carbonic anhydrase inhibitors and a limited number of such compounds have been reported. Mohmoud et al. synthesized novel isatin-based benzenesulfonamides, like compounds **A** and **B**, which show K_i values for different isoforms hCA IX = 287 nM; hCA XII = 9.7 nM and K_i; hCA IX = 5.2 nM; hCA XII 6.3 nM, respectively.[11] Hany et al. developed Isatin-pyrazole benzene sulfonamide hybrid **C** which potently inhibits tumor-associated carbonic anhydrase isoforms IX and XII.[12] Melis et al. considered Compound **D** could be a preferential hCA IX inhibitor having a K_i value of 3.0 nM.[13] Akdemer et al. reported that new isatin sulfonamides **E** were moderate–weak hCA XII inhibitors and highly potent hCA IX inhibitors, 18.5 nM and 1.0 nM, respectively (Figure 1i).[14] Aromatic and certain heterocyclic sulphonamides are powerful and specific inhibitors of most α-CAs.[15] Ferraroni et al. reported a series of 4-aryl-benzenesulfonamides with effective inhibitory action against hCA I, II, IX, and XII; among them, compound **F** having K_i for hCA II = 1.2 nM, hCA XII = 14.2 nM and compound **G** K_i for hCA XII = 10.2 nM, hCA XII = 5.6 nM.[16] Daniel et al. reported some aromatic/heterocyclic sulfonamides associated with CA inhibition; among them, compound **H** was found potent toward hCA II having activity (K_i; hCA II = 7.4 nM).[17] Robert et al. investigated compound **I** as a potent hCA VA/VB inhibitor having value K_i hCA VA = 7.2 nM, hCA VA = 7.0 nM (Figure 1i).[18] Our group has reported some triazole-linked 3-benzenesulfonamide derivatives which were found potent and effective against hCA I, II, IV, and IX in the nM range.[19] Supuran et al. described a tail approach in which the attachment of the tail moiety to the Ar-SO_2NH_2 CA anchor has typically been achieved using the formation of covalent links such as amides and imines. It has proven effective in enhancing the physicochemical properties such as lipophilicity, pK_a, solubility, permeability, stability, and cytotoxicity of many CAIs[20] (Figure 1ii).

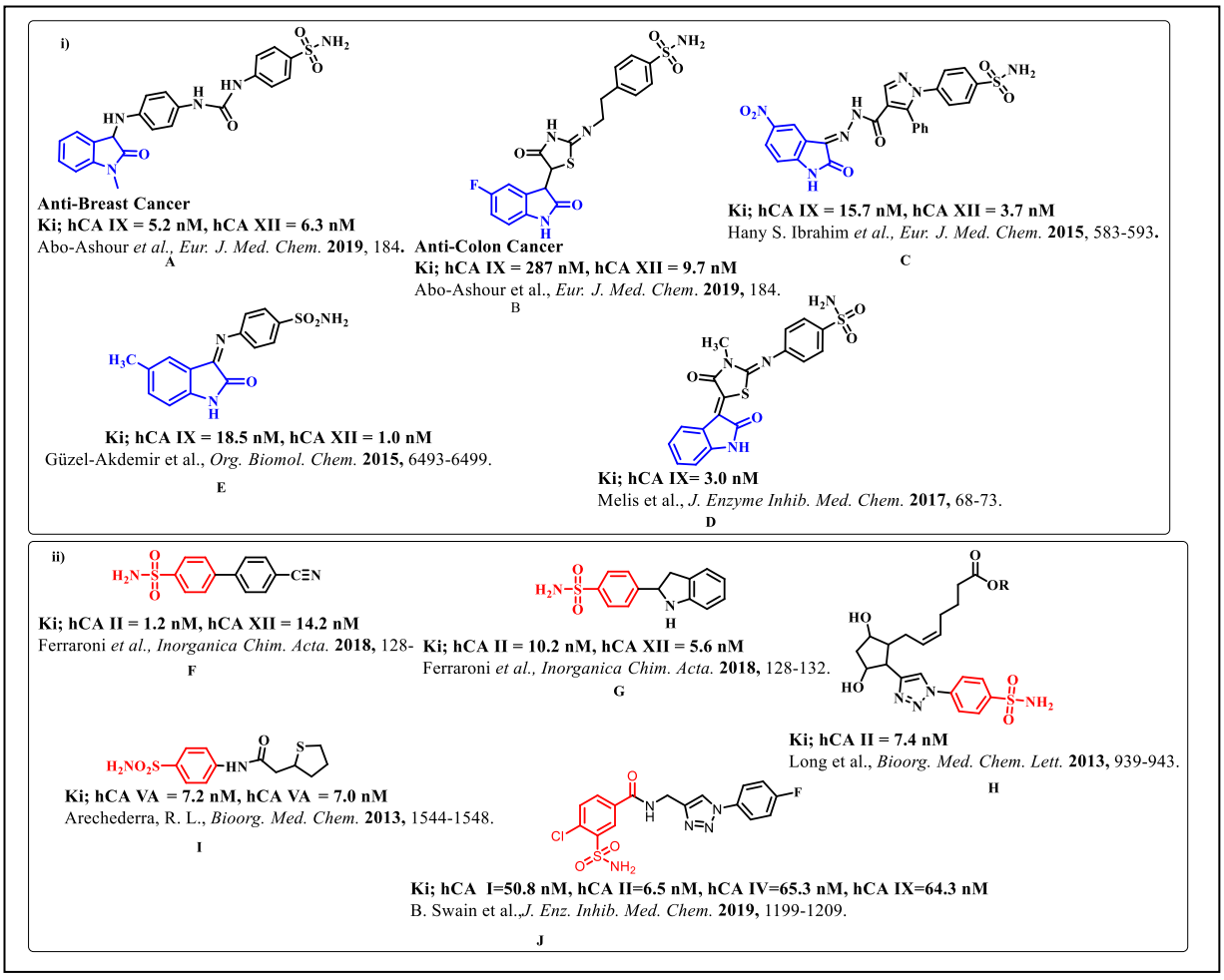


FIGURE 1 Carbonic anhydrase inhibitors containing isatin and benzene sulfonamide moiety.

From these findings, we explored the synthesis of isatins linked with sulfonamides (Figure 2) using the tail approach and evaluated their carbonic anhydrase inhibitory potency by screening against four different CA isoforms, namely, CA I, II, IX, and XII.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The synthesis of the target compounds (shown in Scheme 1) was started with the reaction of commercially available benzoic acids (**1**) with chlorosulfonic acid at 110°C to afford 3-(chlorosulfonyl)benzoic acids (**2**), which were further treated with ammonium hydroxide solution at 0°C to give the corresponding 3-sulfamoylbenzoic acids (**3**). The obtained acids (**3**) were subjected to esterification to give respective 3-sulfamoylbenzoates (**4**) which were further refluxed with hydrazine hydrate to yield substituted 3-(hydrazinecarbonyl) benzenesulfonamide (**5**). On the other hand, different isatins underwent *N*-arylation by reacting with various phenylboronic acids to form *N*-arylated isatins (**8**). Finally, compounds **5** and **8** were refluxed in EtOH using a catalytic amount of acetic acid to produce the imines **9a–w** as the target molecules listed in Table 1. The molecules were confirmed by NMR and mass spectrometry, and the structure conformations were confirmed by XRD analysis (Figure 1) where they showed H-bonding between the C=O of isatin and NH of hydrazine linker and only *E*-isomer was formed in this synthesis.

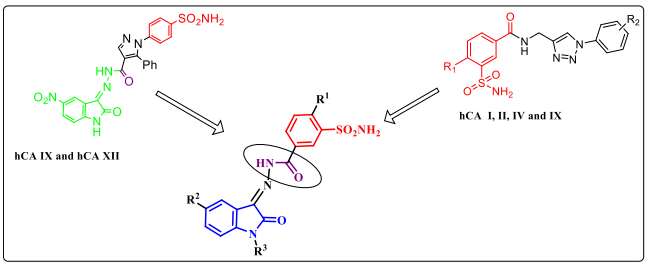
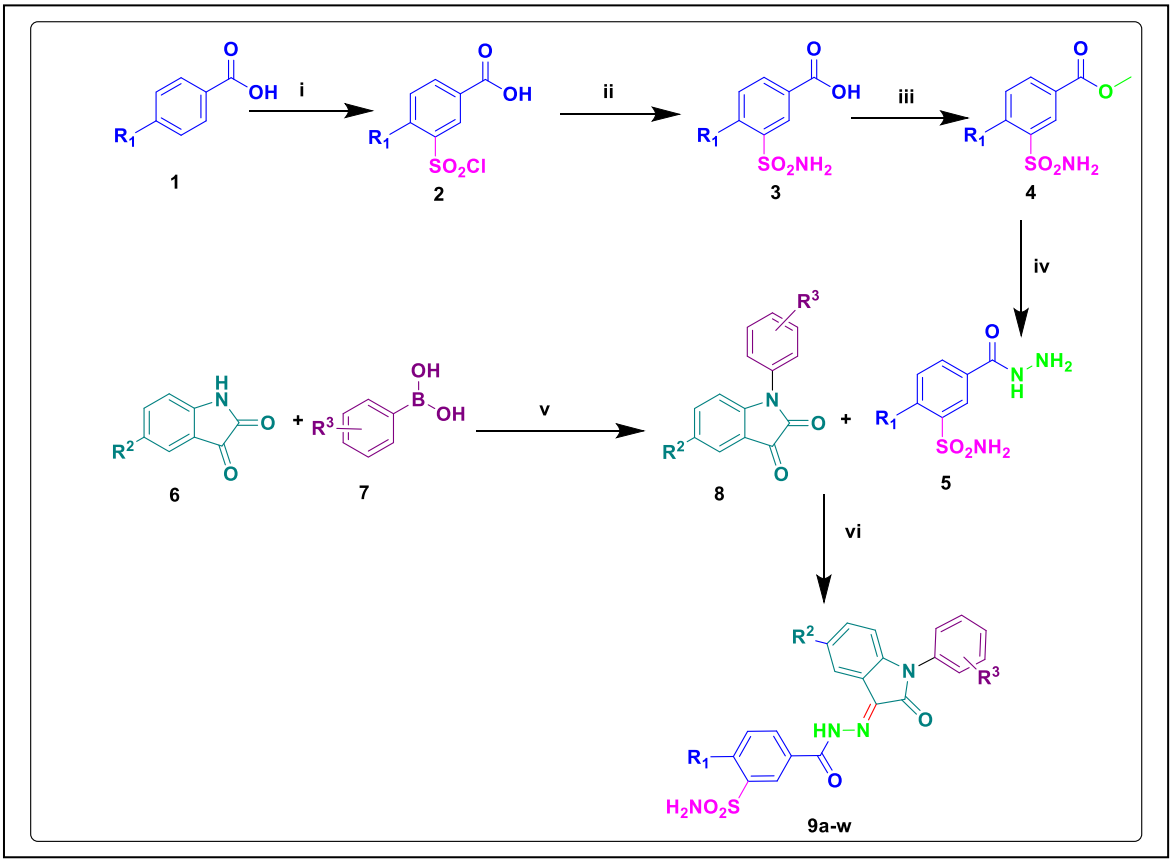


FIGURE 2 Rationale to the designed target molecule.

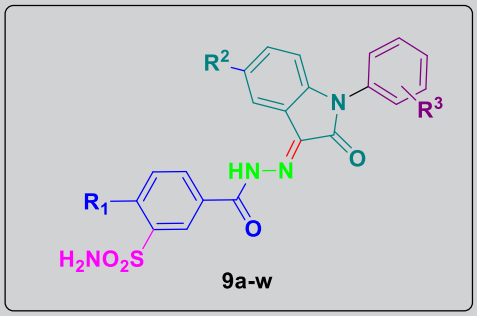
2.2 | Carbonic anhydrase inhibition

The inhibition data for the newly synthesized isatin-linked benzenesulfonamide derivatives were reported against two physiologically relevant cytosolic hCA I and hCA II and two tumor-associated transmembrane hCA IX and hCA XII, taking acetazolamide (AAZ) as



SCHEME 1 Reagent and reaction conditions: (i) HSO_3Cl (5 equiv.), 110°C, 6–8 h, 70%–80%; (ii) NH_4OH sol., 0°C, 2 h; (iii) MeOH, $SOCl_2$, reflux, overnight, 90%–98%; (iv) $NH_2NH_2.H_2O$ (3 equiv.), EtOH, reflux, 4 h, 75%–80%; (v) boronic acid (1.5 equiv.), $Cu(OAc)_2$ (1 equiv.), TEA (2 equiv.), rt, 4 h, 80%–90%; (vi) AcOH (catalytic amount), EtOH, reflux, 4–5 h, 70%–90%.

TABLE 1 List of the synthesized compounds.



9a-w

Comp.	Structure R1	R2	R3
9a	H	H	H
9b	4-Cl	H	H
9c	4-Me	H	H
9d	H	H	4-Me
9e	4-Cl	H	4-Me
9f	4-CH_3	H	3-CH_3
9g	H	H	3-OMe
9h	4-Cl	H	3-OMe
9i	4-Me	H	3-OMe
9j	H	H	OCF_3
9k	H	H	4-Cl
9l	4-Cl	H	4-Cl
9m	4-Me	H	4-Cl
9n	H	5-OMe	H
9o	4-Me	5-OMe	H
9p	4-Cl	5-OMe	4-Cl
9q	4-Me	5-OMe	4-Cl
9r	H	5-Me	H
9s	Cl	5-Me	H
9t	4-Me	5-Me	H
9u	H	5-Me	4-Cl
9v	4-Cl	5-Me	4-Cl
9w	4-Me	5-Me	4-Cl

the standard drug. The results summarized in Table 2 could be interpreted as follows:

- All compounds were screened against cytosolic isoform hCA I and most of them were inactive. Only few of them showed weak inhibition in the nanomolar range and the most potent ones were **9c** (K_i 435.8 nM) and **9s** (K_i 956.4 nM) with –Me and –Cl substitution.

TABLE 2 Inhibition of human carbonic anhydrase (hCA) isoforms I, II, IX, and XII with K_i (nM) data for compounds **9a–w** and acetazolamide (AAZ) as a standard inhibitor, by means of the stopped-flow carbon dioxide assays.[21]

Compound	K_i (nM) hCA I	hCAII	hCA IX	hCA XII
9a	6660	763.2	60.5	398.5
9b	6660	336.1	579.5	464.4
9c	435.8	292.3	898.7	339.0
9d	>10,000	768.3	95.6	372.0
9e	3493	252.5	136.7	569.3
9f	>10,000	5953	2373	503.3
9g	>10,000	6037	92.1	640.6
9h	3176	251.5	322.1	697.2
9i	>10,000	794.5	1333	537.7
9j	>10,000	6015	187.2	385.5
9k	>10,000	6079	75.4	419.1
9l	>10,000	433.5	632.0	416.3
9m	>10,000	2781	1758	509.5
9n	2910	391.4	411.0	490.7
9o	>10,000	4559	3263	939.1
9p	9357	918.9	2140	84.5
9q	>10,000	950.1	>10,000	263.9
9r	>10,000	7068	454.4	526.2
9s	956.4	126.3	140.9	401.4
9t	>10,000	3226	2821	541.0
9u	4168	577.0	960.0	239.2
9v	2871	544.4	2511	152.1
9w	>10,000	415.6	9466	114.8
AAZ	250.0	12.1	25.8	5.7

Note: Mean from three different assays, by a stopped-flow technique (errors were in the range of ±5%–10% of the reported values).

- The physiologically relevant cytosolic isoform hCA II was inhibited very weakly by all the synthesized compounds (**9a–w**) with K_i ranging from 126.3 to 7068 nM compared to the standard AAZ with K_i of 12.1 nM.
- Out of 23 compounds, 14 molecules showed moderate to good inhibition against tumor-associated transmembrane isoform hCA IX with the inhibition constant K_i ranging between 60.5 and 960.0 nM. The four most potent compounds were **9a**, **9d**, **9g**, and **9k** with very low nanomolar K_i values 60.5, 95.6, 92.1, and 75.4 nM, respectively, compared to the standard AAZ with K_i of 25.8 nM. In these four molecules, R_1 and R_2 were unsubstituted and R_3 was H (**9a**), -4-Me (**9d**), 3-OMe (**9g**), 4-Cl (**9k**).

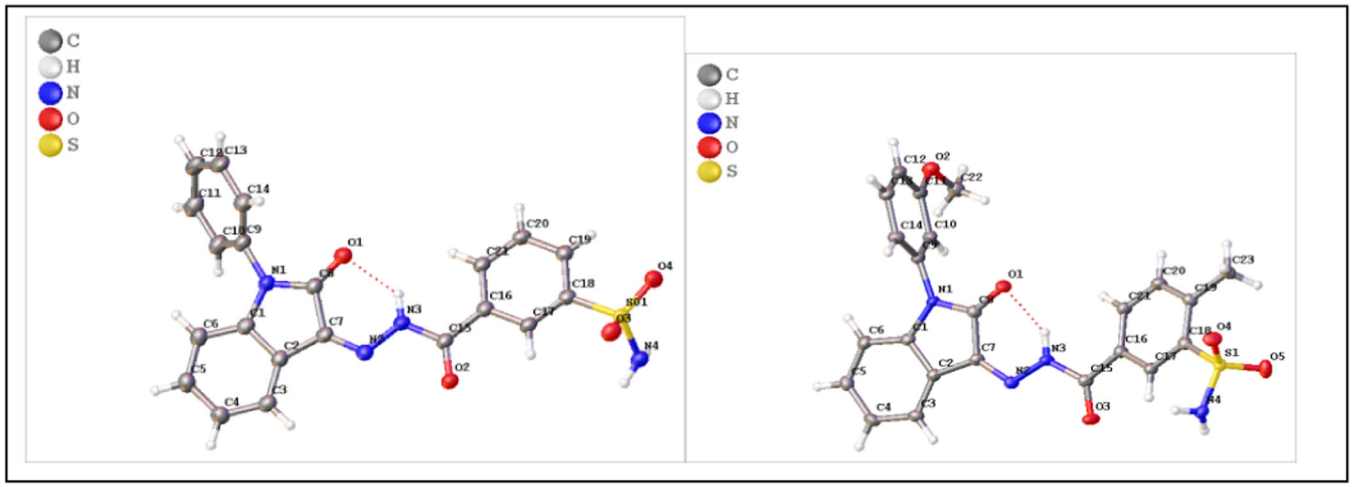


FIGURE 3 X-ray diffraction structures of compounds **9a** and **9i**.

- The transmembrane isoform hCA XII was inhibited very weakly with K_i values in the range of 84.5–939.1 nM by all the synthesized compounds compared to standard AAZ (5.7 nM).
- From the inhibition data, it was also observed that the compounds screened for CA inhibitory activity were more selective toward hCA IX over hCA I, II, and XII.
- It was also observed that the 3-benzenesulfonamide derivatives were less potent than the 4-benzenesulfonamide derivatives reported in the literature. But still, they were showing isoform selectivity toward hCA IX, because of which the active molecules could have been modified further for better potency.

2.3 | Structures of compounds 9a and 9i

Single crystal X-ray analysis for compounds **9a** and **9i** was performed to get the structural insights. Crystals for both compounds were grown in ethanol solvent by a slow evaporation method. A suitable crystal was selected and measured by XtaLAB Pro: Kappa dual home/near diffractometer, keeping at 93(2) K during data collection. In compound **9a**, H-bonding interactions between hydrazine hydrogen and isatin oxygen atoms were found to be $d_{D\cdots A}$ = 2.04 Å and $\theta_{D-H\cdots A}$ = 134.2° (Figure 3). Similarly, **9i** shows H-bonding interactions between hydrazine hydrogen and isatin oxygen atoms ($d_{D\cdots A}$ = 1.98 Å and $\theta_{D-H\cdots A}$ = 138.4°). The present studies provide better structural insight, which confirms that **9a** and **9i** exist in the *E*-isomeric forms.

3 | CONCLUSION

In conclusion, the current research work explained the design and synthesis of new 3-benzenesulfonamide-linked 3-hydrazino-isatin derivatives (**9a–w**) as significant human carbonic anhydrase inhibitors. All the synthesized molecules were screened against CA isoforms (hCA I, II, IX, and XIII) and showed variable degrees of inhibition. These new sulfonamide molecules are selective as most of them showed good selectivity toward hCA IX (K_i ranges 60.5–960.0 nM) over CA I, II, and XII. The inhibition results revealed that singly substituted (R_1/R_2/R_3) molecules were more effective than the multisubstituted ones. Hence it is anticipated that the molecules which are more potent could be taken as the lead for the design and development of selective hCA IX inhibitors with better inhibition potency.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

The compounds reported here were synthesized from commercially available reagents without further purification. Solvents were distilled and dried using standard methods wherever necessary before use. All the air and moisture-sensitive reactions were kept under inert conditions using clean and dried glassware and the syringe technique was used to transfer solutions. Reaction progress was noticed by TLC using Merck silica gel 60F-254 plates. The synthesized molecules were purified by column chromatography on silica gel (100–200 mesh) using a mixture of ethyl acetate and hexane as eluent. Stuart digital melting point apparatus/SMP 30 was used to determine melting points in open capillary tubes and uncorrected. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra (see the Supporting Information) were recorded using a Bruker Avance 500- and 125-MHz spectrometer in DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are represented as δ values in parts per million (ppm) and coupling constants (J) in Hz. Multiplicities were described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). HRMS were determined using Agilent QTOF mass spectrometer 6540 series instrument and were performed in the ESI techniques at 70 eV.

The InChI codes of the investigated compounds, together with some biological activity data, are provided as Supporting Information.

4.1.2 | Compound characterization

(*E*)-3-[2-(2-Oxo-1-phenylindolin-3-ylidene)hydrazine-1-carbonyl] benzenesulfonamide (**9a**): Yellow solid; yield 75%; mp: 264–266°C; ^{1}H NMR (500 MHz, DMSO) δ 13.88 (s, 1H), 8.40 (t, J = 1.6 Hz, 1H), 8.14–8.08 (m, 2H), 7.83 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.64 (tt, J = 4.0, 1.9 Hz, 2H), 7.55 (ddd, J = 9.1, 5.3, 2.6 Hz, 5H), 7.46 (td, J = 7.8, 1.2 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H); ^{13}C NMR (126 MHz, DMSO) δ 161.12, 145.57, 144.35, 133.22, 133.04, 132.47, 130.64, 130.26, 129.27, 127.22, 124.34, 121.65, 119.75, 110.78; HR-MS (ESI): *m/z* calc. for $C_{21}H_{17}N_4O_4S^+$ $[M+H]^+$: 421.0965; found 421.1001.

(*E*)-2-Chloro-5-[2-(2-oxo-1-phenylindolin-3-ylidene)hydrazine-1-carbonyl]benzenesulfonamide (**9b**): Pale yellow solid; yield 78%; mp: 266–268°C; ^{1}H NMR (500 MHz, DMSO) δ 13.89 (s, 1H), 8.55 (s, 1H), 8.07 (dd, J = 8.2, 1.8 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.86 (s, 2H), 7.77 (d, J = 7.3 Hz, 1H), 7.66–7.61 (m, 2H), 7.57–7.52 (m, 3H), 7.45 (td, J = 7.9, 1.1 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 161.05, 145.58, 144.04, 133.59, 132.99, 132.47, 132.13, 130.68, 130.32, 129.13, 124.45, 121.67, 119.79, 110.78; HR-MS (ESI): *m/z* calc. for $C_{21}H_{16}ClN_4O_4S^+$ $[M+H]^+$: 455.0575; found 455.0534.

(*E*)-2-Methyl-5-[2-(2-oxo-1-phenylindolin-3-ylidene)hydrazine-1-carbonyl]benzenesulfonamide (**9c**): Pale yellow solid; yield 70%; mp: 272–274°C; ^{1}H NMR (500 MHz, DMSO) δ 13.91 (s, 1H), 8.47 (s, 1H), 7.98 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 7.4 Hz, 1H), 7.64 (s, 2H), 7.62 (d, J = 3.2 Hz, 3H), 7.56 (d, J = 7.6 Hz, 3H), 7.45 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.14, 144.28, 143.46, 141.78, 133.62, 133.24, 132.35, 130.25, 130.12, 129.25, 127.24, 124.30, 121.60, 119.79, 110.74, 20.45; HR-MS (ESI): *m/z* calc. for $C_{22}H_{19}N_4O_4S^+$ $[M+H]^+$: 435.1122; found 435.1125.

(*E*)-3-{2-[2-Oxo-1-(*p*-tolyl)indolin-3-ylidene]hydrazine-1-carbonyl}benzenesulfonamide (**9d**): Yellow solid; yield 80%; mp: 268–270°C; ^{1}H NMR (500 MHz, DMSO) δ 13.91 (s, 1H), 8.40 (s, 1H), 8.14–8.07 (m, 2H), 7.84 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 7.3 Hz, 1H), 7.59 (s, 2H), 7.52 (t, J = 7.9 Hz, 1H), 7.46 (td, J = 7.9, 1.1 Hz, 1H), 7.37–7.33 (m, 3H), 7.26 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.11, 145.57, 144.38, 139.91, 133.12, 133.03, 132.47, 130.64, 130.23, 130.05, 129.92, 127.56, 124.30, 124.18, 121.63, 119.70, 110.85, 21.36; HR-MS (ESI): *m/z* calc. for $C_{22}H_{19}N_4O_4S^+$ $[M+H]^+$: 435.1122; found 435. 1200.

(*E*)-2-Chloro-5-{2-[2-oxo-1-(*p*-tolyl)indolin-3-ylidene]hydrazine-1-carbonyl}benzenesulfonamide (**9e**): Yellow solid; yield 80%; mp: 272–274°C; ^{1}H NMR (500 MHz, DMSO) δ 13.90 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 7.85 (t, J = 38.3 Hz, 4H), 7.49 (d, J = 32.4 Hz, 2H), 7.31 (d, J = 53.5 Hz, 4H), 6.88 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.08, 143.97, 143.45, 141.82, 133.66, 133.58, 132.36, 132.15, 130.31, 130.05, 129.14, 124.42, 121.62, 119.83, 110.74, 20.45; HR-MS (ESI): *m/z* calc. for $C_{22}H_{17}ClN_4NaO_4S$ $[M+Na]^+$: 491.0557; found 491.0641.

(*E*)-2-Methyl-5-{2-[2-oxo-1-(*p*-tolyl)indolin-3-ylidene]hydrazine-1-carbonyl}benzenesulfonamide (**9f**): Yellow solid; yield 75%; mp: 274–276°C; ^{1}H NMR (500 MHz, DMSO) δ 13.90 (s, 1H), 8.47 (s, 1H), 7.98 (d, J = 6.9 Hz, 1H), 7.77 (d, J = 6.9 Hz, 1H), 7.63 (d, J = 12.4 Hz, 3H), 7.52 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.40–7.32 (m, 3H), 7.26 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 2.69 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.15, 144.33, 143.45, 141.79, 139.91, 133.65, 133.13, 132.38, 130.09, 130.05, 129.92, 127.59, 124.27, 124.22, 121.59, 119.74, 110.82, 21.36, 20.45; HR-MS (ESI): *m/z* calc. for $C_{23}H_{21}N_4O_4S^+$ $[M+H]^+$: 449.1278; found 449.1251.

(*E*)-3-{2-[1-(3-Methoxyphenyl)-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}benzenesulfonamide (**9g**): Yellow solid; yield 73%; mp: 264–266°C; ^{1}H NMR (500 MHz, DMSO) δ 13.89 (s, 1H), 8.40 (s, 1H), 8.15–8.07 (m, 2H), 7.84 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.59 (s, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.16–7.09 (m, 3H), 6.91 (d, J = 8.0 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.06, 160.65, 145.57, 144.37, 134.29, 133.03, 132.50, 131.06, 130.65, 130.23, 124.30, 121.62, 119.69, 119.25, 115.04, 112.99, 110.91, 55.96; HR-MS (ESI): *m/z* calc. for $C_{22}H_{19}N_4O_5S^+$ $[M+H]^+$: 451.1071; found 451.1107.

(*E*)-2-Chloro-5-{2-[1-(3-methoxyphenyl)-2-oxoindolin-3-ylidene] hydrazine-1-carbonyl}benzenesulfonamide (**9h**): Yellow solid; yield 82%; mp: 270–272°C; ^{1}H NMR (500 MHz, DMSO) δ 13.91 (s, 1H), 8.55 (s, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.86 (s, 2H), 7.77 (d, J = 5.9 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 10.6 Hz, 3H), 6.91 (d, J = 7.8 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.03, 160.64, 144.40, 142.23, 136.89, 135.36, 134.27, 133.02, 132.56, 131.32, 131.07, 124.31, 121.65, 119.64, 119.23, 115.03, 112.97, 110.92, 55.95; HR-MS (ESI): *m/z* calc. for $C_{22}H_{18}ClN_4O_5S^+$ $[M+H]^+$: 485.0681; found 485.0629.

(*E*)-2-Chloro-5-{2-[1-(3-methoxyphenyl)-2-oxoindolin-3-ylidene] hydrazine-1-carbonyl}benzenesulfonamide (**9i**): Yellow solid; 83% yield; mp: 284–286°C; ^{1}H NMR (500 MHz, DMSO) δ 13.88 (s, 1H), 8.48 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.3 Hz, 1H), 7.67–7.59 (m, 3H), 7.55 (t, J = 8.0 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 12.2 Hz, 3H), 6.90 (d, J = 7.9 Hz, 1H), 3.83 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.12, 160.64, 145.45, 144.32, 143.45, 141.79, 134.31, 133.64, 132.41, 131.06, 130.10, 124.28, 121.57, 119.73, 119.28, 115.03, 113.01, 110.88, 55.95, 20.45; HR-MS (ESI): *m/z* calc. for $C_{23}H_{21}N_4O_5S^+$ $[M+H]^+$: 465.1227; found 465.1197.

(*E*)-3-{2-[2-Oxo-1-(3-trifluoromethoxyphenyl)indolin-3-ylidene] hydrazine-1-carbonyl}benzenesulfonamide (**9j**): Yellow solid; yield 76%; mp: 282–284°C; ^{1}H NMR (500 MHz, DMSO) δ 13.69 (s, 1H), 8.40 (s, 1H), 8.11 (dd, J = 15.3, 7.9 Hz, 2H), 8.00 (s, 1H), 7.95–7.87 (m, 3H), 7.84 (t, J = 7.8 Hz, 1H), 7.79 (d, J = 7.3 Hz, 1H), 7.60 (s, 2H), 7.48 (t, J = 8.3 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 161.12, 145.56, 143.91, 134.10, 132.95, 132.51, 131.67, 131.51, 131.05, 130.79, 130.69, 130.27, 126.01, 125.25, 124.56, 124.37, 124.34, 121.73, 119.82, 110.71; HR-MS

(ESI): *m/z* calc. for $C_{22}H_{15}F_3N_4NaO_5S$ $[M+Na]^+$: 527.0613; found 527.0389.

(*E*)-3-{2-[1-(4-Chlorophenyl)-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}benzene-sulfonamide (**9k**): Yellow solid; yield 77%; mp: 292–294°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.83 (s, 1H), 8.40 (s, 1H), 8.10 (dd, *J* = 15.6, 7.8 Hz, 2H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.63–7.57 (m, 4H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) δ 161.05, 145.58, 144.04, 133.59, 132.99, 132.47, 132.13, 130.68, 130.32, 130.26, 129.13, 124.45, 121.67, 119.79, 110.78; HR-MS (ESI): *m/z* calc. for $C_{21}H_{16}ClN_4O_5S^+$ $[M+H]^+$: 455.0575; found 455.0576.

(*E*)-2-Chloro-5-{2-[1-(4-chlorophenyl)-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}benzene-sulfonamide (**9l**): Yellow solid; yield 71%; mp: 270–272°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.84 (s, 1H), 8.55 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.86 (s, 2H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO) *δ* 161.00, 144.04, 135.39, 133.59, 133.06, 133.03, 132.52, 132.11, 131.28, 130.32, 129.09, 124.46, 121.71, 119.74, 110.78; HR-MS (ESI): *m/z* calc. for $C_{21}H_{15}Cl_2N_4O_4S^+$ $[M+H]^+$: 489.0186; found 489.0184.

(*E*)-2-Chloro-5-{2-[1-(4-chlorophenyl)-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}benzenesulfonamide (**9m**): Yellow solid; yield 70%; mp: 323–325°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.83 (s, 1H), 8.47 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.62 (dd, *J* = 16.5, 8.4 Hz, 5H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, DMSO) *δ* 161.08, 143.97, 143.45, 141.82, 133.66, 133.58, 132.36, 132.15, 130.31, 130.05, 129.14, 124.42, 121.62, 119.83, 110.74, 20.45; HR-MS (ESI): *m/z* calc. for $C_{22}H_{18}ClN_4O_4S^+$ $[M+H]^+$: 469.0732; found 469.0717.

(*E*)-5-{2-[1-(4-Chlorophenyl)-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}-2-methylbenzene-sulfonamide (**9n**): Orange solid; yield 84%; mp: 262–264°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.96 (s, 1H), 8.41 (s, 1H), 8.14–8.07 (m, 2H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.59 (ddd, *J* = 33.9, 10.9, 4.1 Hz, 7H), 7.31 (s, 1H), 7.03 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, DMSO) *δ* 161.03, 156.74, 145.56, 138.00, 133.37, 132.98, 130.64, 130.21, 129.06, 126.91, 120.56, 118.48, 111.81, 106.50, 56.29; HR-MS (ESI): *m/z* calc. for $C_{22}H_{19}N_4O_5S^+$ $[M+H]^+$: 451.1071; found 451.1056.

(*E*)-5-{2-[1-(3-Methoxyphenyl)-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}-2-methylbenzenesulfonamide (**9o**): Brown solid; yield 73%; mp: 292–294°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.96 (s, 1H), 8.49 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 5H), 7.53 (dd, *J* = 13.2, 7.3 Hz, 3H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, DMSO) *δ* 161.08, 156.72, 143.44, 141.83, 137.96, 133.66, 133.39, 130.22, 130.05, 129.07, 126.96, 120.60, 118.40, 111.78, 106.44, 56.29, 20.45; HR-MS (ESI): *m/z* calc. for $C_{23}H_{21}N_4O_5S^+$ $[M+H]^+$: 465.1227; found 465.1211.

(*E*)-2-Chloro-5-{2-[1-(4-chlorophenyl)-5-methoxy-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}benzenesulfonamide (**9p**): Brick red solid; yield 80%; mp: 288–290°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.86 (s, 1H), 8.57 (s, 1H), 8.10–8.05 (m, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.85 (s, 1H), 7.71–7.67 (m, 2H), 7.59 (t, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 2.2 Hz, 1H), 7.02 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, DMSO) *δ* 160.94, 156.80, 142.21, 137.68, 135.44, 133.32, 133.03, 132.25, 131.17, 130.25, 130.13, 130.10, 128.74, 120.55, 118.47, 111.83, 106.52, 56.29; HR-MS (ESI): *m/z* calc. for $C_{22}H_{17}Cl_2N_4O_5S^+$ $[M+H]^+$: 519.0291; found 519.0269.

(*E*)-5-{2-[1-(4-Chlorophenyl)-5-methoxy-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}-2-methylbenzenesulfonamide (**9q**): Yellow solid; yield 79%; mp: 274–276°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.86 (s, 1H), 8.49 (s, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.72–7.67 (m, 2H), 7.66–7.57 (m, 5H), 7.30 (d, *J* = 2.5 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 3.84 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, DMSO) *δ* 161.03, 156.79, 143.43, 141.86, 137.64, 133.67, 133.32, 132.31, 130.27, 130.00, 128.81, 120.67, 118.37, 111.79, 106.45, 56.30, 20.45; HR-MS (ESI): *m/z* calc. for $C_{23}H_{20}ClN_4O_5S^+$ $[M+H]^+$: 499.0837; found 499.0859.

(*E*)-3-[2-(5-Methyl-2-oxo-1-phenylindolin-3-ylidene)hydrazine-1-carbonyl]benzenesulfonamide (**9r**): Yellow solid; yield 71%; mp: 284–286°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.89 (s, 1H), 8.40 (s, 1H), 8.13–8.07 (m, 2H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.66–7.50 (m, 8H), 7.26 (dd, *J* = 8.1, 0.8 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO) *δ* 161.09, 145.56, 142.12, 133.66, 133.32, 133.04, 132.80, 130.64, 130.21, 129.12, 127.01, 122.00, 119.69, 110.62, 20.94; HR-MS (ESI): *m/z* calc. for $C_{22}H_{19}N_4O_4S^+$ $[M+H]^+$: 435.1122; found 435.1140.

(*E*)-2-Chloro-5-[2-(5-methyl-2-oxo-1-phenylindolin-3-ylidene)hydrazine-1-carbonyl]benzenesulfonamide (**9s**): Yellow solid; yield 77%; mp: 298–300°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.90 (s, 1H), 8.54 (s, 1H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.86 (s, 1H), 7.69–7.44 (m, 7H), 7.25 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, DMSO) *δ* 161.06, 142.15, 135.34, 133.68, 133.30, 133.00, 132.85, 131.32, 130.21, 130.11, 129.12, 127.08, 126.99, 126.87, 122.02, 119.64, 110.62, 20.93; HR-MS (ESI): *m/z* calc. for $C_{22}H_{18}ClN_4O_4S^+$ $[M+H]^+$: 469.0732; found 469.0752.

(*E*)-2-Methyl-5-[2-(5-methyl-2-oxo-1-phenylindolin-3-ylidene)hydrazine-1-carbonyl]benzenesulfonamide (**9t**): Yellow solid; yield 81%; mp: 300–302°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.90 (s, 1H), 8.47 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 9.5 Hz, 6H), 7.56–7.52 (m, 3H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 2.69 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, DMSO) *δ* 161.15, 144.33, 143.45, 141.79, 139.91, 133.65, 133.13, 132.38, 130.09, 130.05, 129.92, 127.59, 124.27, 124.22, 121.59, 119.74, 110.82, 21.36, 20.45; HR-MS (ESI): *m/z* calc. for $C_{23}H_{21}N_4O_4S^+$ $[M+H]^+$: 449.1278; found 449.1213.

(*E*)-3-{2-[1-(4-Chlorophenyl)-5-methyl-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}benzenesulfonamide (**9u**): Yellow solid; yield 76%; mp: 300–302°C; ^{1}H NMR (500 MHz, DMSO) *δ* 13.82 (s, 1H), 8.39 (s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 6.2 Hz, 5H), 7.27

(d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.08, 143.97, 143.45, 141.82, 133.66, 133.58, 132.36, 132.15, 130.31, 130.05, 129.14, 124.42, 121.62, 119.83, 110.74, 20.45; HR-MS (ESI): m/z calc. for $C_{22}H_{18}ClN_4O_4S^+$ $[M+H]^+$: 469.0732; found 469.0715.

(*E*)-2-Chloro-5-{2-[1-(4-chlorophenyl)-5-methyl-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}benzenesulfonamide (**9v**): Yellow solid; yield 71%; mp: 300–302°C; ^{1}H NMR (500 MHz, DMSO) δ 13.82 (s, 1H), 8.54 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.3 Hz, 1H), 7.85 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 3H), 7.54 (t, J = 8.3 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 6.83 (d, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.11, 145.57, 144.38, 139.91, 133.12, 133.03, 132.47, 130.64, 130.23, 130.05, 129.92, 127.56, 124.30, 124.18, 121.63, 119.70, 110.85, 21.36; HR-MS (ESI): m/z calc. for $C_{22}H_{17}Cl_2N_4O_4S^+$ $[M+H]^+$: 503.0342; found 503.0313.

(*E*)-5-{2-[1-(4-Chlorophenyl)-5-methyl-2-oxoindolin-3-ylidene]hydrazine-1-carbonyl}-2-methylbenzenesulfonamide (**9w**): Pale yellow solid; yield 79%; mp: 317–319°C; ^{1}H NMR (500 MHz, DMSO) δ 13.81 (s, 1H), 8.47 (s, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.61 (dt, J = 16.8, 8.4 Hz, 6H), 7.26 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 2.69 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 161.03, 143.43, 141.78, 141.71, 133.76, 133.62, 133.39, 132.66, 132.24, 130.25, 130.04, 128.87, 121.94, 119.76, 110.56, 20.94, 20.45; HR-MS (ESI): m/z calc. for $C_{23}H_{20}ClN_4O_4S^+$ $[M+H]^+$: 483.0894; found 483.0865.

4.2 | Carbonic anhydrase inhibition assay

An SX.18MV-R Applied Photophysics stopped-flow instrument has been used to assay the catalytic/inhibition of various CA isozymes.[22,23] Phenol Red (at a concentration of 0.2 mM) has been used as an indicator, working at the absorbance maximum of 557 nm, with 10 mM Hepes (pH 7.4) as buffer, 0.1 M Na_2SO_4 or $NaClO_4$ (for maintaining constant the ionic strength; these anions are not inhibitory in the used concentration), following the CA-catalyzed CO_2 hydration reaction for a period of 5–10 s. Saturated CO_2 solutions in water at 25°C were used as the substrate. Stock solutions of inhibitors were prepared at a concentration of 10 µM (in DMSO/water 1:1, v/v), and dilutions up to 0.01 nM were done with the assay buffer mentioned above. At least seven different inhibitor concentrations have been used for measuring the inhibition constant. Inhibitor and enzyme solutions were preincubated together for 10 min at room temperature before assay to allow for the formation of the E-I complex. Triplicate experiments were done for each inhibitor concentration, and the values reported throughout the paper are the mean of such results. The inhibition constants were obtained by nonlinear least-squares methods using the Cheng–Prusoff equation, as reported earlier,[24–26] and represent the mean from at least three different determinations. All CA isozymes used here were recombinant proteins obtained as reported earlier by our group.[27–30] Their concentrations in the assay system were in the range of 4.5–12.3 nM.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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