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Synthesis and comparative carbonic anhydrase inhibition of new Schiff's bases incorporating benzenesulfonamide, methanesulfonamide, and methylsulfonylbenzene scaffolds

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ABSTRACT

Herein, we report the synthesis, characterization, and carbonic anhydrase (CA) inhibition of the newly synthesized Schiff's bases **4–18** with benzenesulfonamide, methanesulfonamide, and methylsulfonylbenzene scaffolds. The compound inhibition profiles against human CA (hCA) isoforms I, II, IX, and XII were compared to those of the standard inhibitors, acetazolamide (**AAZ**) and **SLC-0111** (a CA inhibitor in Phase II clinical trials for the treatment of hypoxic tumors). The hCA I was inhibited by compounds **4a–8a** with inhibition constants (K_I) in the range 93.5–428.1 nM (**AAZ** and **SLC-0111**: K_I, 250.0 and 5080.0 nM, respectively). Compounds **4a–8a** proved to be effective hCA II inhibitors, with K_I ranging from 18.2 to 133.3 nM (**AAZ** and **SLC-0111**: K_I, 12.0 and 960.0 nM, respectively). Compounds **4a–8a** effectively inhibited hCA IX, with K_I in the range 8.5–24.9 nM; these values are superior or equivalent to that of AAZ and **SLC-0111** (K_I, 25.0 and 45.0 nM, respectively). Compounds **4a–8a** displayed effective hCA XII inhibitory activity with K_I values ranging from 8.6 to 43.2 nM (**AAZ** and **SLC-0111**: K_I, 5.7 and 4.5 nM, respectively). However, compounds **9b–13b** and **14c–18c** were found to be micromolar CA inhibitors. For molecular docking studies, compounds **5a**, **6a,** and **8a** were selected.

1. Introduction

The zinc enzyme, carbonic anhydrase (CA, EC 4.2.1.1), plays vital physiological roles [1] by catalyzing the simple interconversion between carbon dioxide and bicarbonate. Inhibitors of this enzyme are used to treat many diseases, including glaucoma [2], various neurological disorders [3], gastroduodenal ulcers, and acid-base disequilibria [4]. Although sulfonamides (i.e., CA inhibitors) such as acetazolamide were developed several decades ago for clinical use, only few display high selective human (h) CA isozyme inhibition; to date, 15 hCAs have been described. Isoenzyme selectivity is a crucial factor for inhibitors such as **SLC-0111** (Fig. 1), a new antitumor/anti-metastatic sulfonamide in Phase II clinical trials for the management of advanced metastatic solid tumors [5]. Synthesis of new CA inhibitors with high specificity toward certain hCA isozymes is thus a critical goal [6]. Compounds designed as antitumor treatments should efficiently inhibit isoenzymes CA IX/XII and not the off-targets, CA I and II, to reduce the side effects of the drug. Hence, the design of antiglaucoma compounds with strong and selective CA II/XII inhibition is necessary [7].

Sulfonamides are the most effective compounds as CA inhibitors [6]. However, some sulfonamides such as celecoxib, are cyclooxygenase (COX) inhibitors, while others are antitumor and antibacterial agents [6,8–13]. Sulfonamide-linked chalcone derivatives **I** (Fig. 1) display strong hCA I and CA II inhibitory activities with K_I values of 9.88–24.4 and 20.0–55.43 nM, respectively [14]. Interestingly, phenols containing amines, such as dopamine **II** (Fig. 1), have interesting hCA I and CA II with K_I values of 13.5 and 9.2 μM, respectively [15]. Phenols containing acrylic acid **III** (Fig. 1) showed hCA I, CA II, hCA IX, and CA XII inhibition with K_I values of 1.07–2.89, 0.98–2.40 μM, 5.33–9.87, and 8.01–9.78 μM, respectively [16]. Furthermore, mono, di, or tri-bromo-4-((methylsulfonyl)methyl)benzene-1,2-diol **IV** (Fig. 1) displayed good hCA I and CA II inhibition with K_I values of 58.16–83.04 and 45.04–58.34 nM, respectively, while 3-hydroxybenzoic acid and 3,5-dihydroxybenzoic acid **V** (Fig. 1) inhibited hCA I and CA II with K_I values of 0.55–2.37 and 0.51–0.60 μM, respectively [17]. Recently, hCA I was reported to be selectively inhibited by hydrazinecarbothioamide

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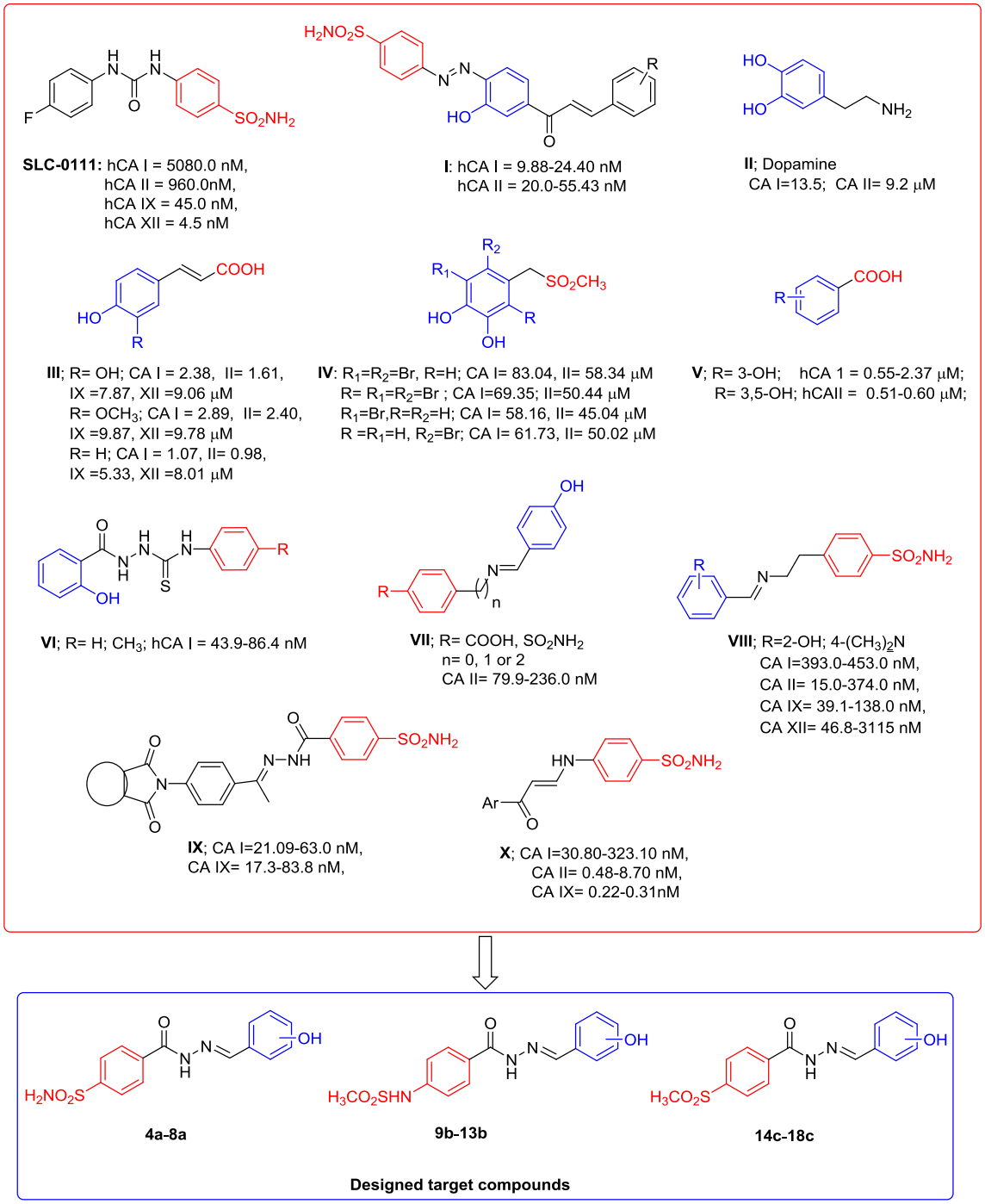
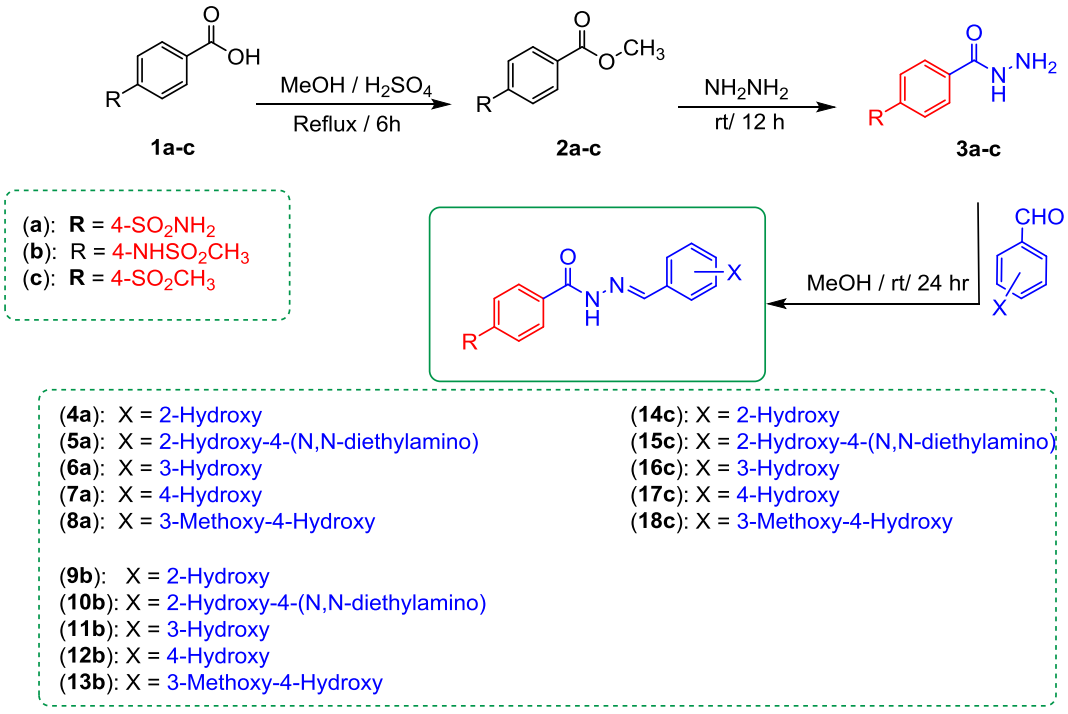


Fig. 1. The reported carbonic anhydrase (CA) inhibitors (**SLC-0111** and **I–X**) and the designed Schiff's bases, **4–18**.

derivatives **VI** (Fig. 1) with K_I values of 43.9–86.4 nM [18]. The hCA II was also selectively inhibited by Schiff's bases containing benzoic acid and benzenesulfonamide moieties **VII** (Fig. 1) and displayed K_I values between 79.9 and 236.0 nM [19]. The Schiff's base derivatives of 4-(2-aminoethyl)- benzenesulfonamide **VIII** (Fig. 1) showed versatile inhibition against CAs I, II, IX, and XII with K_Is of 393.0–453.0, 374.0–474, 39.1–138.0, and 46.8–3115 nM, respectively [7]. Several Schiff's bases of isoindoline-1,3-dione-linked benzenesulfonamide **IX** (Fig. 1) showed selective inhibition of the tumor-associated CA IX with K_Is ranging from 17.3 to 164.3 nM [6a]. Just recently, hCAs I, II, and IX were demonstrated to be inhibited by 4-[(3-oxo-3-arylprop-1-en-1-yl) amino]benzenesulfonamides **X** (Fig. 1) with K_Is of 30.80–323.10 nM, 0.48–8.70 nM, and 0.22–0.31 nM, respectively [20].

Recently, we reported the CA inhibitory activities of isoindoline-1,3-dione bearing benzenesulfonamides [6,8–10,11a]. In the present study, we aimed to report: (i) the synthesis of new derivatives of phenolic Schiff's bases containing benzenesulfonamide, methanesulfonamide, and methylsulfonylbenzene moieties (Fig. 1: **4–18**), (ii) evaluation results for the CA inhibitory activity of these compounds on isoenzymes hCAs I, II, IX, and XII; (iii) the structure-activity relationships of these Schiff's bases with various substituents; (iv) the effectiveness of benzenesulfonamide relative to methanesulfonamide and methylsulfonylbenzene for the inhibition of CA isoforms I, II, IX, and XII, and (v) molecular docking results for the docking of the target molecules into the putative binding site of CA isoforms I, II, IX, and XII.



Scheme 1. Synthesis of new Schiff's bases.

Table 1
Inhibition data of human CA isoforms hCA I, II, IX and XII with compounds reported here and the standard sulfonamide inhibitor acetazolamide (**AAZ**) and **SLC-0111** by a stopped flow CO_2 hydrase assay [23].

Cmpd	K_I (nM)[a]			
	hCA I	hCA II	hCA IX	hCA XII
4a	117.2	26.8	18.9	32.7
5a	428.1	65.5	15.8	8.6
6a	93.5	18.2	23.3	43.2
7a	130.8	58.5	24.9	25.6
8a	234.4	133.3	8.5	9.7
9b[b]	> 100	> 100	> 100	> 100
10b[b]	> 100	> 100	> 100	> 100
11b[b]	55.0	5.6	1.4	6.3
12b[b]	84.0	10.0	1.8	4.7
13b[b]	> 100	28.7	10.0	> 100
14c[b]	> 100	> 100	> 100	> 100
15c[b]	> 100	> 100	> 100	> 100
16c[b]	69.7	4.6	4.6	7.8
17c[b]	47.8	14.0	5.0	5.9
18c[b]	> 100	42.0	45.0	> 100
AAZ	250.0	12.0	25.0	5.7
SLC-0111	5080.0	960.0	45.0	4.5

[a] Mean from three different assays, by a stopped flow technique (errors were in the range of ± 5–10% of the reported values).
[b] Data are in μM.

2. Results and discussion

2.1. Chemistry

The acid hydrazides (**3a-c**) were obtained by reacting esters **2a-c** with hydrazine hydrate according to a reported procedure [6a,21,22]. The 4-[2-(2,3 and 4-hydroxybenzylidene)hydrazine-1-carbonyl]benzenesulfonamides (**4a–8a**), 4-(2-(2,3 and 4-hydroxybenzylidene)hydrazine-1-carbonyl)phenyl)methanesulfonamides (**9b–13b**), and 2,3 and 4-hydroxybenzylidene)-4-(methylsulfonyl)benzohydrazides (**14c–18c**) had yields of 84–95% when the appropriate aldehyde was mixed with the 4-substituted-benzohydrazides (**3a–c**) in methanol containing a catalytic amount of acetic acid at room temperature (Scheme 1). Multiple spectral analyses were performed to confirm the structures of the target compounds. The newly synthesized compounds were confirmed by an amide fragment from the benzylidene benzohydrazide moiety (ArCONH–N=CHAr) by ^{1}H NMR with a peak for the amidic protons at 12.32–11.59 ppm and ^{13}C NMR with characteristic peaks at 162.92–160-23 ppm for the carbonyl groups. Additionally, the imine fragment of the benzylidene benzohydrazide moiety (ArCONH–N=CHAr) was verified by ^{1}H NMR with a peak at 8.69–8.34 ppm and ^{13}C NMR spectra with characteristic peaks at 150.81–147.03 ppm. The phenolic OH group was verified by a singlet peak at 11.37–9.63 ppm in the ^{1}H NMR spectrum while the amino group of the 4-aminosulfonyl moiety (-SO_2NH_2) for compounds **4a-8a** was verified by a peak at 7.57–7.53 ppm in the ^{1}H NMR spectrum. The amino and methyl groups of the 4-methanesulfonamide moiety (-$NHSO_2CH_3$) of compounds **9b-13b** were verified by respective peaks at 11.35–9.58 and 3.12–3.10 ppm in the ^{1}H NMR spectrum, while the methyl group of the 4-methanesulfonamide moiety (-$NHSO_2CH_3$) was validated by peaks at 40.42–40.26 ppm in the ^{13}C NMR spectrum. The methyl group of the 4-methylsulfonyl moiety (-SO_2CH_3) of compounds **14c-18c** was verified by a peak at 3.32–3.29 ppm and 43.77–43.71 ppm in the ^{1}H NMR and ^{13}C NMR spectra, respectively.

2.2. CA inhibitory activity

The CA inhibitory activity of the newly synthesized compounds (**4a-8a**, **9b–13b**, and **14c–18c**) against hCA isoforms I, II, IX, and XII was measured and compared to that of acetazolamide (AAZ) and **SLC-0111**, which are standard sulfonamide inhibitors (Table 1) [23].

For the inhibitory activity of CA toward single hCA isoforms, hCA I was found to be potently inhibited by compounds **4a–8a** with inhibition constant (K_I) values ranging from 93.5 to 428.1 nM (AAZ and **SLC-0111**: K_I, 250.0 and 5080 nM, respectively). Compounds **11b, 12b, 16c**, and **17c** showed weak hCA I inhibitory activity with K_I values of 47.8–84.0 μM. In contrast, **9b**, **10b**, **13b**, **14c**, **15c**, and **18c** had no inhibitory activity with K_Is > 100 μM (Table 1). Compounds **4a–8a** proved to be effective hCA II inhibitors (K_I, 18.2–133.3 nM) as they almost displayed equal potency to AAZ (K_I, 12.0 nM) but had better

values than **SLC-0111** (K_I, 960.0 nM). Compounds **11b–13b** and **16c–18c** showed weak hCA II inhibitory activity with K_I values of 4.6–42.0 μM. In contrast, **9b–10b** and **14c–15c** had no inhibitory activity with K_Is > 100 μM (Table 1). For hCA IX inhibition, compounds **4a–8a** proved to be potent inhibitors (K_I values of 8.5–24.9 nM), with values greater than or equal to those of AAZ and **SLC-0111** (K_I, 25.0 and 45.0 nM, respectively). Compounds **11b–13b and 16c–18c** showed weak inhibitory activity with K_Is from 1.4 to 45.0 μM while **9b–10b** and **14c–15c** had no inhibitory activity with K_Is > 100 μM (Table 1). For hCA XII inhibitory activity, compounds **4a–8a** displayed effective inhibition with K_I values ranging from 8.6 to 43.2 nM; these values were comparable to AAZ and **SLC-0111** (K_I, 5.7 and 4.5 nM, respectively). Compounds **11b–12b and 16c–17c** showed weak inhibitory activity with K_Is from 4.7 to 7.8 μM while compounds **9b**, **10b**, **13b, 14c**, **15c**, and **18c** had no inhibitory activity with K_Is > 100 μM (Table 1).

2.3. Structure-activity relationship analysis

(I) Based on the inhibition results for the hCA isoforms using compounds **4a–8a**, **9b–13b**, and **14c–18c**, the 4-(2-(2-substituted-benzylidene)hydrazine-1-carbonyl)benzenesulfonamides (**4a–8a**) were more active than the corresponding *N*-(4-(2-(substituted-benzylidene)hydrazine-1-carbonyl)phenyl)methanesulfonamides (**9b–13b**) and *N′*-(substituted-benzylidene)-4-(methylsulfonyl) benzohydrazides (**14c–18c**) (Table 1).

(II) For hCA I inhibition, analysis of the structure–activity relationship of the 4-(2-(2-substituted-benzylidene)hydrazine-1-carbonyl)benzenesulfonamide derivatives **4a–8a** indicated that: 1) 4-(2-(3-hydroxybenzylidene)hydrazine-1-carbonyl)benzenesulfonamide (**6a**) with K_I of 93.5 nM, is more active than the corresponding 2-hydroxybenzylidene derivative **4a** (K_I; 117.2 nM) and 4-hydroxybenzylidene derivative **7a** (K_I, 130.8 nM), while the 2-hydroxybenzylidene derivative **4a** (K_I, 117.2 nM) is more potent than the 4-hydroxybenzylidene derivative **7a** (K_I, 130.8 nM); 2) introducing an *N*,*N*-diethylamino or a 3-methoxy group in the hydroxybenzylidene moiety (e.g., **5a** and **8a**) decreases the potency of hCA I inhibition (K_Is, 428.1 and 234.4 nM, respectively); (4-(2-(4-(diethylamino)-2-hydroxybenzylidene)hydrazine-1-carbonyl) benzenesulfonamide (**5a**) (K_I, 428.1 nM) is more active than 4-(2-(4-hydroxy-3-methoxybenzylidene)hydrazine-1-carbonyl)benzenesulfonamide (**8a**) (K_I , 234.4 nM).

(III) For hCA II inhibition, analysis of the structure–activity relationship of the 4-(2-(2-substituted-benzylidene)hydrazine-1-carbonyl) benzenesulfonamide derivatives **4a–8a** indicated that: (1) the 3-hydroxybenzylidene derivative **6a** (K_I, 18.2 nM) is more active than the corresponding 2-hydroxybenzylidene derivative **4a** (K_I, 26.8 nM) and 4-hydroxybenzylidene derivative **7a** (K_I, 58.5 nM), while the 2-hydroxybenzylidene derivative **4a** (K_I, 117.2 nM) is more potent than the 4-hydroxybenzylidene derivative **7a** (K_I, 130.8 nM); **(**2) introducing the *N*,*N*-diethylamino or 3-methoxy group in the hydroxybenzylidene moiety (e.g., **5a** and **8a)** leads to a decrease in the potency of hCA II inhibition (K_I, 65.5 and 133.3 nM, respectively), while (4-(2-(4-(diethylamino)-2-hydroxybenzylidene)hydrazine-1-carbonyl)benzenesulfonamide (**5a**) (K_I value, 65.5 nM) is less active than 4-(2-(4-hydroxy-3-methoxybenzylidene)hydrazine-1-carbonyl)benzenesulfonamide (**8a**) (K_I value, 133.3 nM).

(IV) For hCA IX inhibition, analysis of the structure–activity relationship of the 4-(2-(2-substituted-benzylidene)hydrazine-1-carbonyl) benzenesulfonamide derivatives **4a–8a** indicated that: 1) the 4-hydroxy-3-methoxybenzylidene derivative **8a** (K_I, 8.5 nM) is more active than the substituted-benzylidene derivatives **4a–7a** (K_I, 15.8–24.9 nM); 2) the 4-diethylamino-2-hydroxybenzylidene derivative **5a** is more active than the substituted-benzylidene derivatives **4a, 6a**, and **7a** (K_I, 18.9–24.9 nM); 3) the 2-hydroxybenzylidene derivative **4a** (K_I, 18.9 nM) is more potent than the corresponding 3-hydroxybenzylidene derivative **6a** (K_I, 24.9 nM) and 4-hydroxybenzylidene derivative **7a** (K_I, 130.8 nM), while the 3-hydroxybenzylidene derivative **6a** (K_I, 24.9 nM) is more potent than the 4-hydroxybenzylidene derivative **7a** (K_I, 130.8 nM); and 4) the 4-hydroxy-3-methoxybenzylidene derivative **8a** (K_I, 8.5 nM) is more potent than the 4-diethylamino-2-hydroxybenzylidene derivative **5a** (K_I, 15.8 nM).

(V) For hCA XII inhibition, analysis of the structure-activity relationship of the 4-(2-(2-substituted-benzylidene)hydrazine-1-carbonyl) benzenesulfonamide derivatives **4a–8a** indicated that: 1) the 4-diethylamino-2-hydroxybenzylidene derivative **5a** (K_I, 8.6 nM) is more potent than the substituted-benzylidene derivatives **4a, 6a, 7a** and **8a** (K_I, 9.7–43.2 nM); 2) the 4-hydroxybenzylidene derivative **7a** (K_I, 25.6 nM) is more potent than the corresponding 2-hydroxybenzylidene derivative **4a** and 3-hydroxybenzylidene derivative **6a** (K_I, 32.7 and 43.2 nM, respectively); 3) the 4-diethylamino-2-hydroxybenzylidene derivative **5a** (K_I, 8.6 nM) is more potent than the 4-hydroxy-3-methoxybenzylidene derivative **8a** (K_I, 9.7 nM); and 4) 2-hydroxybenzylidene derivative **4a** (K_I, 32.7 nM) is more potent than the corresponding 3-hydroxybenzylidene derivative **6a** (K_I, 43.2 nM).

2.4. Molecular docking studies

Molecular modeling techniques are important tools for theoretically revealing the biological activities of target molecules and for gaining structural insights for the design of novel therapeutic agents [24–27]. Molecular docking was therefore performed with MOE 2008.10 software (Chemical Computing Group Inc.) according to the standard protocol and the MOE's pose viewer utility [28]. The crystal structures of the CA isozymes with their co-crystallized inhibitors were obtained from protein data bank (PDB).

2.4.1. Molecular docking with hCA I and hCA II

Molecular docking was used to study the interaction between compound **6a** (the most active) and hCA I, and hCA II as well as identify the best binding (Fig. 2). The co-crystallized inhibitors 2,3,5,6-tetrafluoro-4-(propylthio)benzenesulfonamide and 4-{[(4- fluorophenyl) carbamothioyl]amino}benzene-1-sulfonamide with the corresponding hCA I and hCA II isozymes, respectively, were retrieved from Protein Data Bank (pdb entries: 4WR7, and 5ULN, respectively) [29].

The results of the docking of compound **6a** into the catalytic active site of CA I (Fig. 2, upper panel) and CA II (Fig. 2, lower panel) showed that the benzenesulfonamide scaffold traveled deep into the catalytic site and the zinc ion was coordinated by the negatively charged SO_2NH– moiety. Moreover, the sulfonamide group formed two additional hydrogen bonds with Thr199 (2.97 Å and 3.01 Å with CA I and 2.86 Å and 3.06 Å with CA II). The benzenesulfonamide ring had a hydrophobic interaction with Leu198, His200 (CA I), and Val121 (CA II). The extended structure of *N*-benzylidene-3-hydroxybenzohydrazide on the hydrophobic part of CA I interacts with Phe91, Leu131, Ala135, and Ala132 from one side and Tyr204 and Pro202 from the other side. On the other hand, the extended tail structure of compound **6a** was located on the hydrophobic part of CA II in a direction opposite to that of the tail of the co-crystallized ligand that formed contacts with Phe131, Ile91, Thr200, Pro201, and Pro202. The carbonyl group (C═O) of *N*-benzylidene-3-hydroxybenzohydrazide forms a weak hydrogen bond with CH-Aromatic group of Phe91 (3.04 Å) in CA I, while a hydrogen bond with Pro201 mediated by HOH601 was formed for CA II. Finally, the 3-hydroxyl moiety formed a strong H-bond with Tyr204 (2.49 Å) for CA I, while the Gln92 in CA II interacted with the NH group of the *N*-benzylidene-3-hydroxybenzohydrazide fragment by a H-bond (3.12 Å).

2.4.2. Molecular docking with tumor-associated hCA IX and hCA XII

The docking interactions between compound **8a** (the most active

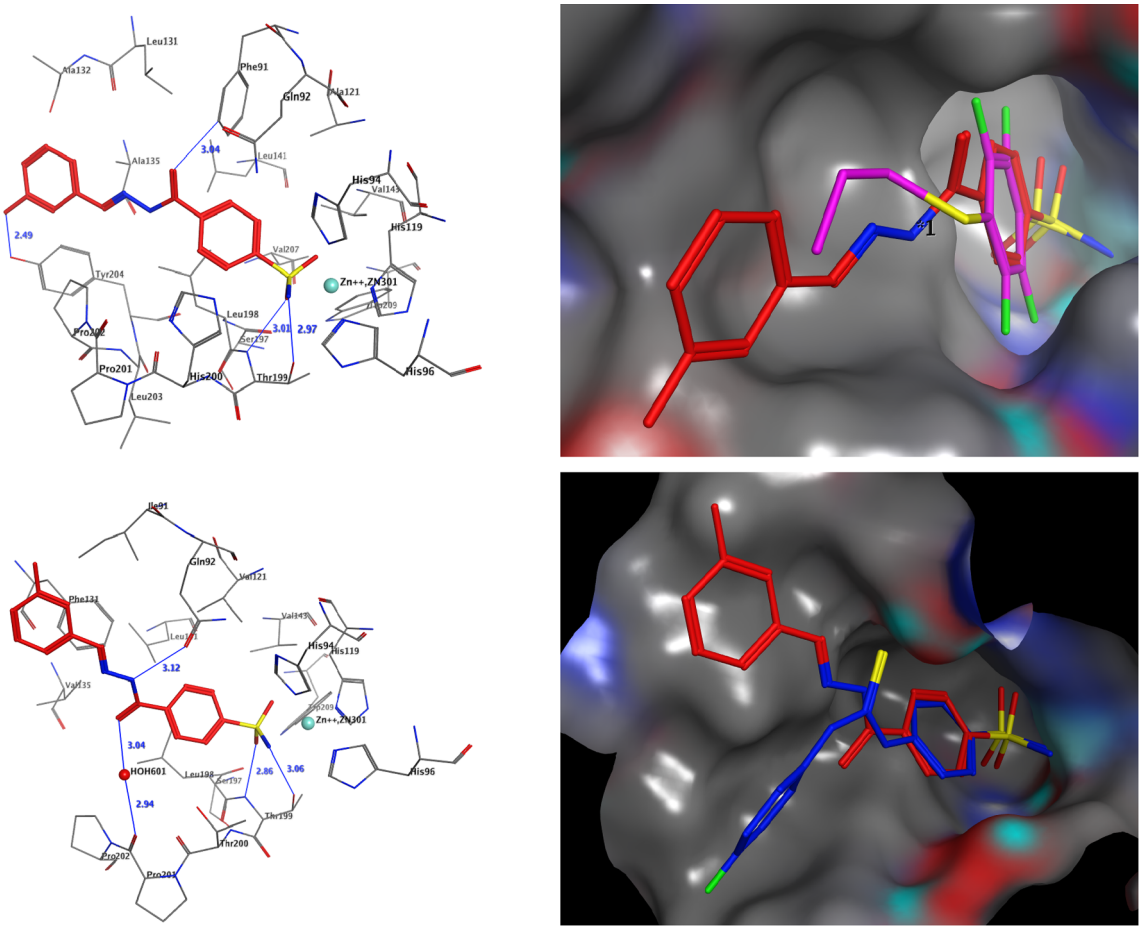


Fig. 2. Left: Three-dimensional binding interactions between compound **6a** (red color) and both hCA I (upper panel) and hCA II (lower panel). Right: Compound **6a** (red color) superimposed on the co-crystallized inhibitors (magenta and blue colors) inside the pockets of the active site. Hydrogen bonds are represented as a blue line.

derivative) and hCA IX, and compound **5a** (the most active derivative) and hCA XII were assessed in silico (Fig. 3). The putative binding sites on hCA IX and hCA XII with the co-crystallized inhibitors 5-(1-naphthalen-1-yl-1,2,3-triazol-4-yl)thiophene-2-sulfonamide and acetazolamide respectively, were retrieved from Protein Data Bank (pdb entries: 5FL4, and 1JD0, respectively) [30].

By molecular docking into the respective catalytic active sites of CA IX (Fig. 3, upper panel) and CA XII (Fig. 3, lower panel), compounds **8a** and **5a** displayed similar binding interactions with their co-crystallized ligands. Furthermore, a binding orientation analogous to that of hCA II was displayed by the benzenesulfonamide scaffold. Its aromatic portion formed hydrophobic contacts with Leu199, Thr200, Pro202, and Pro203 (CA IX) and Leu198, Thr200, and Pro201 (CA XII) on one side, and Val121 and Val142 (CA IX) and Val121 and Val143 (CA XII) on the other side. The *N*-benzylidenebenzohydrazide moiety of compound **8a** was accommodated on the hydrophobic side of CA IX's active site and interacted with Leu134, Val130, and Pro203. The analog portion of compound **5a** was located on the hydrophobic side of CA XII which binds with Asn62, Lys67, Pro201, Ser135, Ser132, and Ala131. The carbonyl (C═O) group of the *N*-benzylidenebenzohydrazide moiety of compound **8a** formed weak H-bonds with the CH_2 group of Pro203 (3.43 Å) and C═O group of Pro202; this was mediated by HOH2199 in CA IX's active site. Through the HOH molecules, the tail of compound **5a** formed three H-bonds with Thr200, Gln92, and Lys67 for CA XII while the NH group of the *N*-benzylidenebenzohydrazide moiety of compound **8a** formed an H-bond with the conserved Gln92 (3.01 Å). Finally, the 3-methoxy-4-hydroxyphenyl fragment of compound **8a** formed two strong H-bonds with Asp131 (2.9 and 3.09 Å) in CA IX, while the 2-hydroxyphenyl fragment of compound **5a** in CA XII formed two additional H-bonds with Ser132 and Ser135 via HOH1646.

3. Conclusion

A new series of substituted Schiff's base **4a–8a**, **9b–13b,** and **14c–18c** was synthesized and evaluated for their *in vitro* hCA inhibitory activity relative to standard compounds, AAZ and **SLC-0111** (Table 1). Compounds **4a–8a** showed strong inhibitory activity against hCA I (K_Is, 93.5–428.1 nM) compared to AAZ and **SLC-0111** (K_Is, 250.0 and 5080 nM, respectively) while compounds **11b, 12b, 16c**, and **17c** showed weak hCA I inhibitory activity (K_Is, 47.8–84.0 µM). Compounds **4a–8a** were also confirmed to be effective hCA II inhibitors (K_I, 18.2–133.3 nM) compared to AAZ and **SLC-0111** (K_I, 12.0 and 960.0 nM, respectively). In contrast, a weak hCA II inhibitory activity was displayed by compounds **11b–13b** and **16c–18c** as they had K_I values ranging from 4.6 to 42.0 µM (Table 1). Against hCA IX, compounds **4a–8a** exhibited effective inhibition (K_I, 8.5–24.9 nM); hence, they were found to be more potent than or equal to AAZ (K_I, 25.0 nM) and more active than **SLC-0111** (K_I, 45.0 nM). Conversely, a weak inhibitory activity was displayed by compounds **11b–13b** and **16c–18c** (K_Is, 1.4–45.0 µM). Compared to AAZ and **SLC-0111** (K_I, 5.7 and 4.5 nM, respectively), compounds **4a–8a** demonstrated efficient hCA XII inhibitory activity with K_I values ranging from 8.6 to 43.2 nM. Interestingly, compound **5a** showed selective tumor-associated isoenzyme CA IX/XII inhibition with K_Is of 15.8 and 8.6, respectively. In contrast, compounds **11b–12b** and **16c–17c** displayed weak inhibitory activity with K_Is in the range, 4.7–7.8 µM. By docking compounds **5a**, **6a**, and

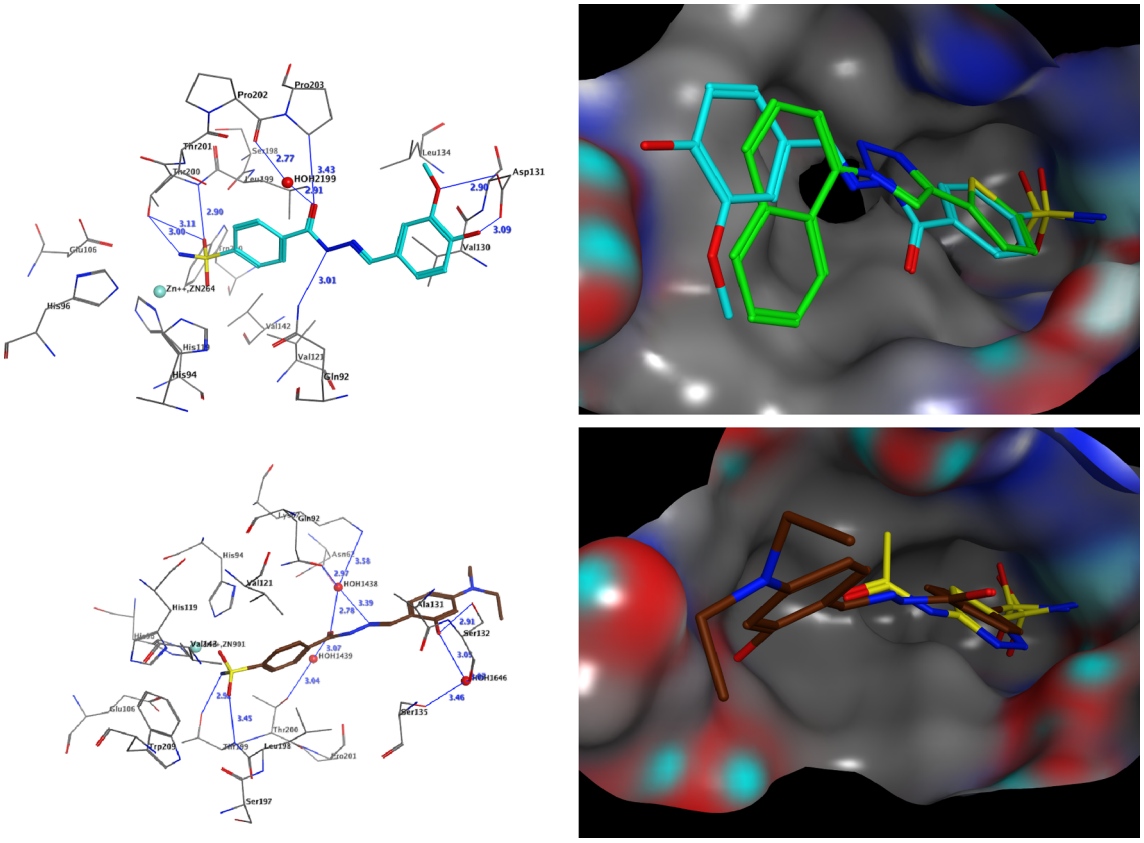


Fig. 3. Left: Three-dimensional binding interactions of compounds **8a** (cyan color) and **5a** (brown color) with hCA IX (upper panel) and hCA XII (lower panel), respectively. Right: compounds **8a** (cyan color) and **5a** (brown color) superimposed on the co-crystallized inhibitors (green and yellow colors) inside the pockets of the active site. Hydrogen bonds are indicated as blue lines.

8a into the binding sites of hCA I, II, IX, and XII, the binding mode could be assessed and insights for further lead optimization could be gained.

4. Experimental

4.1. Chemistry

Melting points (uncorrected) were recorded using a Barnstead 9100 electrothermal melting apparatus (APS Water Services Corporation, Van Nuys, CA, USA). IR spectra were recorded with an FT-IR Perkin-Elmer spectrometer (PerkinElmer Inc., Waltham, MA, USA). The NMR spectra were measured in DMSO-d_6 using Bruker 700 MHz instrument (Bruker, Billerica, MA, USA), with TMS as the internal standard. Chemical shifts were reported in δ ppm. Mass spectra were recorded on a Varian TQ 320 GC/MS/MS mass spectrometer (Varian, Palo Alto, CA). C, H, and N were analyzed at the Research Centre, College of Pharmacy, King Saud University, Saudi Arabia. The results were within ± 0.4% of the theoretical values. Acid hydrazides **3a-c** were synthesized according to the reported procedure [6a,21,22].

4.1.1. General method for the preparation of the Schiff's bases 4–18

An appropriate phenolic aldehyde (10 mmol) was mixed with 4-substituted-benzohydrazides **3a-c** (10 mmol) in methanol (10 ml) containing a catalytic amount of acetic acid (5 drops) at room temperature for 24 h. The solid formed after cooling was filtered, washed with water, and dried (Scheme 1).

4.1.1.1. 4-(2-(2-Hydroxybenzylidene)hydrazine-1-carbonyl) benzenesulfonamide (4a). M.P. 267–268 °C, 93% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3411, 3341, 3255, 3232 (NH, NH_2, and OH), 1654 (C═O), 1610 (C═N), 1354, 1150 (SO_2); ^{1}H NMR (700 MHz, DMSO-d_6): δ 12.28 (s, 1H), 11.20 (s, 1H), 8.69 (s, 1H), 8.12 (d, 2H, J = 8.23 Hz), 8.06 (d, 2H, J = 8.24 Hz), 7.60 (d, 1H, J = 7.46 Hz), 7.57 (s, 2H), 7.32 (t, 1H, J = 7.62 Hz), 6.96 (d, 1H, J = 8.26 Hz), 6.94 (t, 1H, J = 7.45 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.31, 157.94, 149.15, 147.30, 136.23, 132.10, 129.82, 128.88, 126.31, 119.89, 119.14, 116.91;[m/z: 319 & M + 1: 320].

4.1.1.2. 4-(2-(4-(N,N-Diethylamino)-2-hydroxybenzylidene)hydrazine-1-carbonyl)benzenesulfonamide (5a). M.P. 239–241 °C, 89% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3399, 3283, 3198 (NH, NH_2, and OH), 1650 (C═O), 1628 (C═N), 1348, 1162 (SO_2); ^{1}H NMR (700 MHz, DMSO-d_6): δ 11.96 (s, 1H), 11.37 (s, 1H), 8.45 (s, 1H), 8.07 (s, 2H), 7.97 (s, 2H), 7.53 (s, 2H), 7.23 (d, 1H, J = 8.41 Hz), 6.28 (d, 1H, J = 8.13 Hz), 6.14 (s, 1H), 3.36 (s, 4H), 1.11 (s, 6H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 160.23, 150.92, 150.78, 147.03, 136.57, 132.09, 128.66, 126.24, 106.80, 104.21, 97.92, 44.28; [m/z: 390 & M + 1: 391].

4.1.1.3. 4-(2-(3-Hydroxybenzylidene)hydrazine-1-carbonyl) benzenesulfonamide (6a). M.P. 297–299 °C, 86% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3457, 3315, 3175, 3232 (NH, NH_2, and OH), 1630 (C═O), 1605 (C═N), 1381, 1148 (SO_2); ^{1}H NMR (700 MHz, DMSO-d_6): δ 11.97 (s, 1H), 9.67 (s, 1H), 8.38 (s, 1H), 8.09 (d, 2H, J = 8.38 Hz), 7.79 (d, 2H, J = 8.39 Hz), 7.55 (s, 2H), 7.26 (dd, 2H, J = 19.0 & 15.64), 7.13 (d, 1H, J = 7.60 Hz), 6.86 (dd, 1H, J = 8.04 & 1.88 Hz), ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.56, 158.17, 149.05, 147.12, 136.80, 135.87, 130.43, 128.83, 126.24, 119.45, 118.13, 113.12; [m/z: 319 & M + 1: 320].

4.1.1.4. 4-(2-(4-Hydroxybenzylidene)hydrazine-1-carbonyl) benzenesulfonamide (7a). M.P. 340–341 °C, 91% yield (CH_3OH); ^1H NMR (700 MHz, DMSO-d_6): δ 11.82 (s, 1H), 9.99 (s, 1H), 8.36 (s, 1H), 8.06 (d, 2H, J = 8.19 Hz), 7.96 (d, 2H J = 8.26 Hz), 7.59 (d, 2H, J = 8.40 Hz), 7.53 (s, 2H), 6.86 (d, 2H, J = 8.33 Hz), ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.30, 160.07, 149.30, 146.98, 137.01, 129.48, 128.72, 126.20, 125.58, 116.22.

4.1.1.5. 4-(2-(4-Hydroxy-3-methoxybenzylidene)hydrazine-1-carbonyl) benzenesulfonamide (8a). M.P. 264–265 °C, 95% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3451, 3278, 3201 (NH, NH_2, and OH), 1654 (C═O), 1621 (C═N), 1330, 1160 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 11.89 (s, 1H), 9.63 (s, 1H), 8.37 (s, 1H), 8.09 (d, 2H, J = 7.39 Hz), 7.98 (d, 2H, J = 7.35 Hz), 7.56 (s, 2H), 7.35 (s, 1H), 7.12 (d, 1H, J = 7.91 Hz), 6.88 (d, 1H, J = 7.70 Hz), 3.684 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.44, 149.66, 149.61, 148.54, 147.01, 137.00, 128.77, 126.24, 125.97, 122.92, 115.93, 109.37, 56.00; [*m/z*: 349 & M + 1: 350].

4.1.1.6. N-(4-(2-(2-Hydroxybenzylidene)hydrazine-1-carbonyl)phenyl) methanesulfonamide (9b). M.P. 253–255 °C, 90% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3401, 3335, 3181 (NH and OH), 1671 (C═O), 1616 (C═N), 1324, 1154 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 12.07 (s, 1H), 11.35 (s, 1H), 10.27 (s, 1H), 8.64 (s, 1H), 7.95 (d, 2H, J = 8.10 Hz), 7.54 (d, 1H, J = 7.51 Hz), 7.33 (d, 2H, J = 8.19 Hz), 7.30 (t, 1H, J = 7.63 & 8.19 Hz), 6.95 (d, 1H, J = 8.19 Hz), 6.92 (t, 1H, J = 14.98 Hz), 3.12 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.67, 157.92, 148.50, 142.40, 131.80, 130.00, 129.64, 127.69, 119.81, 119.14, 118.36, 116.89, 40.27; [*m/z*: 333 & M + 1: 334].

4.1.1.7. N-(4-(2-(4-(N,N-Diethylamino)-2-hydroxybenzylidene)hydrazine-1-carbonyl)phenyl)methanesulfonamide (10b). M.P. 261–263 °C, 84% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3448, 3398, 3199 (NH and OH), 1647 (C═O), 1610 (C═N), 1334, 1157 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 11.75 (s, 1H), 11.50 (s, 1H), 10.22 (s, 1H), 8.41 (s, 1H), 7.90 (d, 1H, J = 0.85 Hz), 7.89 (s, 1H), 7.31 (d, 2H, J = 8.19 Hz), 7.19 (d, 1H, J = 8.68 Hz), 8.26 (d, 1H, J = 8.68 Hz), 6.13 (s, 1H), 3.35 (q, 4H, J = 6.84 Hz), 3.10 (s, 3H), 1.10 (t, 6H, J = 7.0 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.07, 160.15, 150.56, 150.17, 142.07, 132.06, 129.40, 128.13, 118.41, 106.89, 104.07, 97.93, 44.26, 40.26; [*m/z*: 404 & M + 1: 405].

4.1.1.8. N-(4-(2-(3-Hydroxybenzylidene)hydrazine-1-carbonyl)phenyl) methanesulfonamide (11b). M.P. 255–257 °C, 92% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3410, 3306, 3213 (NH and OH), 1688 (C═O), 1609 (C═N), 1341, 1149 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 11.74 (s, 1H), 10.23 (s, 1H), 9.66 (s, 1H), 8.36 (s, 1H), 7.91 (d, 2H, J = 8.02 Hz), 7.31 (d, 2H, J = 8.22 Hz), 7.26 (t, 1H, J = 7.70 & 7.67 Hz), 7.21 (s, 1H), 7.10 (d, 1H, J = 7.28 Hz), 7.84 (d, 1H, J = 7.70 Hz), 3.11 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.92, 158.13, 148.04, 142.16, 136.09, 130.37, 129.57, 128.38, 119.28, 118.37, 117.87, 113.02, 40.28; [*m/z*: 333 & M + 1: 334].

4.1.1.9. N-(4-(2-(4-Hydroxybenzylidene)hydrazine-1-carbonyl)phenyl) methanesulfonamide (12b). M.P. 317–319 °C, 94% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3490, 3310, 3296 (NH and OH), 1653 (C═O), 1611 (C═N), 1293, 1151 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 11.59 (s, 1H), 10.20 (s, 1H), 9.95 (s, 1H), 8.34 (s, 1H), 7.89 (d, 2H, J = 7.89 Hz), 7.56 (d, 2H, J = 7.82 Hz), 7.30 (d, 2H, J = 7.90 Hz), 6.84 (d, 2H, J = 7.81 Hz), 3.10 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.70, 159.84, 148.30, 141.99, 129.47, 129.30, 128.63, 125.79, 118.40, 116.17, 40.42; [*m/z*: 333 & M + 1: 334].

4.1.1.10. N-(4-(2-(4-Hydroxy-3-methoxybenzylidene)hydrazine-1-carbonyl)phenyl)methanesulfonamide (13b). M.P. 242–244 °C, 91% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3421, 3330, 3123 (NH and OH), 1636 (C═O), 1608 (C═N), 1338, 1151 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 11.63 (s, 1H), 10.21 (s, 1H), 9.58 (s, 1H), 8.34 (s, 1H), 7.90 (d, 2H, J = 8.18 Hz), 7.32 (s, 1H), 7.30 (d, 2H, J = 8.05 Hz), 7.09 (d, 1H, J = 7.91 Hz), 6.85 (d, 2H, 7.92 Hz), 3.83 (s, 3H), 3.10 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.76, 149.41, 148.57, 148.50, 142.01, 129.48, 128.62, 126.21, 122.61, 118.41, 115.88, 109.30, 55.98, 40.41; [*m/z*: 363 & M + 1: 364].

4.1.1.11. N′-(2-Hydroxybenzylidene)-4-(methylsulfonyl)benzohydrazide (14c). M.P. 248–249 °C, 93% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3443, 3348 (NH and OH), 1635 (C═O), 1605 (C═N), 1317, 1135 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 12.32 (s, 1H), 11.14 (s, 1H), 8.69 (s, 1H), 8.18 (d, 2H, J = 7.77 Hz), 8.12 (d, 2H, J = 7.77 Hz), 7.61 (d, 1H, J = 7.63 Hz), 7.33 (t, 1H, J = 7.70), 7.95 (t, 2H, J = 15.75 Hz), 3.31 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.06, 157.92, 149.19, 143.93, 137.83, 132.15, 129.71, 129.16, 127.70, 119.90, 119.17, 116.91, 43.72; [*m/z*: 318 & M + 1: 319].

4.1.1.12. N′-(4-(N,N-Diethylamino)-2-hydroxybenzylidene)-4-(methylsulfonyl)benzohydrazide (15c). M.P. 237–239 °C, 86% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3447, 3295 (NH and OH), 1654 (C═O), 1611 (C═N), 1310, 1151 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 12.04 (s, 1H), 11.36 (s, 1H), 8.45 (s, 1H), 8.15 (d, 2H, J = 8.05 Hz), 8.10 (d, 2H, J = 8.12 Hz), 7.24 (d, 1H, J = 8.68 Hz), 6.28 (d, 1H, J = 8.82 Hz), 6.14 (s, 1H), 3.35 (q, 4H, J = 6.93 & 6.95 Hz), 3.29 (s, 3H), 1.10 (t, 6H, J = 7.03 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ 161.39, 160.24, 151.09, 150.81, 143.63, 138.17, 132.11, 128.98, 127.65, 106.74, 104.21, 97.85, 44.28, 43.74, 12.99; [*m/z*: 398 & M + 1: 399].

4.1.1.13. N′-(3-Hydroxybenzylidene)-4-(methylsulfonyl)benzohydrazide (16c). M.P. 245–246 °C, 91% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3482, 3299 (NH and OH), 1636 (C═O), 1605 (C═N), 1311, 1157 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 12.04 (s, 1H), 9.69 (s, 1H), 8.39 (s, 1H), 8.16 (d, 2H, J = 8.12 Hz), 8.10 (d, 2H, J = 13.16 Hz), 7.28 (t, 1H, J = 7.78 Hz), 7.24 (s, 1H), 7.13 (d, 1H, J = 7.49 Hz), 6.86 (d, 1H, J = 7.94 Hz), 3.30 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.34, 158.17, 149.28, 143.76, 138.39, 135.81, 130.43, 129.13, 127.65, 119.47, 118.18, 113.15, 43.74; [*m/z*: 318 & M + 1: 319].

4.1.1.14. N′-(4-Hydroxybenzylidene)-4-(methylsulfonyl)benzohydrazide (17c). M.P. 287–289 °C, 88% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3482, 3299 (NH and OH), 1647 (C═O), 1612 (C═N), 1313, 1139 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 11.89 (s, 1H), 10.01 (s, 1H), 8.37 (s, 1H), 8.14 (d, 2H, J = 7.63 Hz), 8.09 (d, 2H, J = 7.84 Hz), 7.59 (d, 2H, J = 7.84 Hz), 6.86 (d, 2H, J = 7.77 Hz), 3.30 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.07, 160.12, 149.50, 143.62, 138.61, 130.73, 129.53, 129.05, 127.62, 126.83, 125.52, 116.23, 43.75; [*m/z*: 318 & M + 1: 319].

4.1.1.15. N′-(4-Hydroxy-3-methoxybenzylidene)-4-(methylsulfonyl) benzohydrazide (18c). M.P. 216–217 °C, 92% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3498, 3291 (NH and OH), 1661 (C═O), 1620 (C═N), 1280, 1156 (SO_2); ^1H NMR (700 MHz, DMSO-d_6): δ 11.92 (s, 1H), 9.63 (s, 1H), 8.36 (s, 1H), 8.14 (d, 2H, J = 8.05 Hz), 8.10 (d, 2H, J = 8.05 Hz),7.34 (s, 1H), 7.12 (d, 1H, J = 8.05 Hz), 6.86 (d, 1H, J = 7.98 Hz), 3.84 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (176 MHz, DMSO-d_6): δ 162.12, 149.74, 149.70, 148.53, 143.62, 138.61, 129.05, 127.63, 125.92, 122.89, 115.92, 109.42, 56.00, 43.76; [*m/z*: 348 & M + 1: 349].

4.2. CA inhibition

The inhibition assay for the hCA I, II, IX, and XII isozymes was carried out with the SX.18MV-R stopped-flow instrument (Applied Photophysics, Oxford, UK) according to the method reported previously [23].

4.3. Docking methodology

Molecular docking was conducted with MOE 2008.10 from the Chemical Computing Group Inc. [28] according to the reported methods [24–27].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103225.

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