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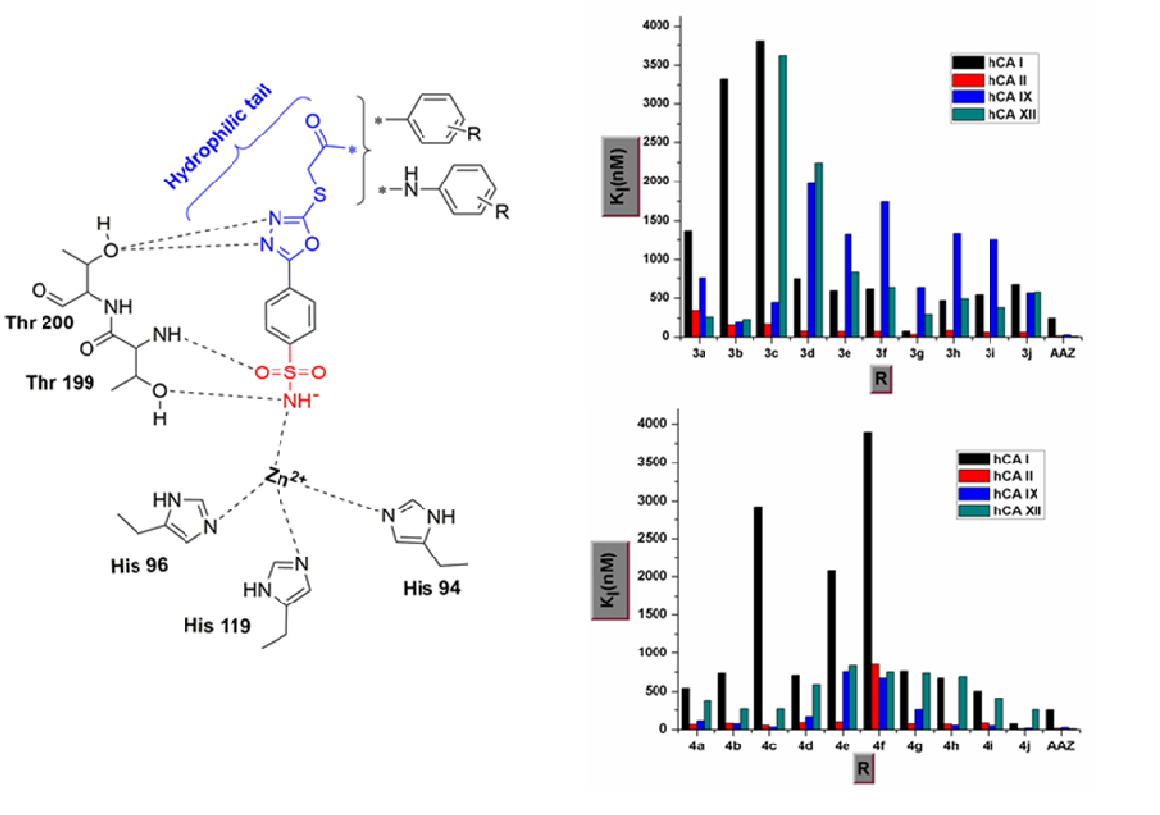
Graphical Abstract



Tail Approach Synthesis of Novel Benzenesulfonamides Incorporating 1,3,4-Oxadiazole Hybrids as Potent Inhibitor of Carbonic Anhydrase I, II, IX, and XII Isoenzymes

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Abstract

Two new series of 1,3,4-oxadiazole benzenesulfonamide hybrids **3** and **4,** having twenty novel compounds, have been designed and synthesized in order to assess their inhibition potential as CAIs against hCA I, II, IX, and XII. 'Tail approach' strategy has been used to design the aromatic sulfonamide scaffolds with carbonyl and amide linker. Excellent inhibitory activity against hCA I has been exhibited by compounds **3g** and **4j**, 3.5 magnitude of order better than reference drug AAZ (K_I = 250 nM). Moreover, compound **4j** (K_I = 7.9 nM) effectively inhibited glaucoma-associated hCA II isoform as well as tumor-associated hCA IX isoform with K_I = 16.3 nM. Further hCA XII was weakly inhibited by all the compounds with K_I values ranging from 0.23 µM–3.62 µM. Interestingly structure-activity relationship (SAR) study indicates that N-(3-nitrophenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4j**) is a potent compound to be investigated further for antiglaucoma and antitumor activity. The chemistry of the nature of different substitutions on the 1,3,4-oxadiazole bearing benzenesulfonamide substituted aromatic ring for potency and selectivity over one hCA isoform versus others is deliberated in the present study. In this context, the 1,3,4-oxadiazole motif can be a valuable tool worth developing for the procurement of novel and potent selective CAIs potentially useful for the management of a variety of diseases as chemotherapeutic agents.

Keywords: 1,3,4-Oxadiazole, Benzenesulfonamide, Carbonic anhydrase, CA isoforms.

Abbreviations: CA: Carbonic anhydrase; hCA: Human carbonic anhydrase; CAIs: Carbonic anhydrase inhibitors; AAZ: Acetazolamide; K_I: Inhibition constant; nM: Nanomolar; µM: Micromolar.

1. Introduction

World Health Organization cited cancer as a major public health problem worldwide with one in six deaths globally attributed to cancer [1]. Cancer is a generic term for an enormous cluster of diseases that matures by the genetic and epigenetic mutations transforming normal healthy cells into malignant phenotypes and the process is referred as metastasizing [1]. Undoubtedly, investigations in the arena of pioneering anti-cancer drug discovery focused on cancer treatment with more effective and less toxic agents are highly desired.

The carbonic anhydrases (CAs, EC 4.2.1.1) are metalloenzymes having the core of Zn^{2+} ion in the active center present all over the phyla of the animal kingdom [2-6]. The CAs catalyze the reversible and fundamental biochemical reaction, hydration of CO_2 into HCO_3^- and H^+ ions as well as other hydrolytic reactions by the metal hydroxide nucleophilic mechanism [7, 8]. This simple reaction is crucial for many physiological mechanisms including electrolyte secretion, respiration, acid-base tuning, bone resorption, tumorigenesis, calcification and biosynthesis of important molecules such as urea, glucose, and lipids, which require HCO_3^- as a substrate [9-11]. CAs have been developed as eight genetically different enzyme families α-, β-, γ-, δ-, ζ-, η-, θ-, and ι-CAs, [12, 13]. Further α-CA isoforms existing in human have been divided into sixteen sub-isoforms that differ by molecular features, oligomeric arrangement, cellular localization, distribution in organs and tissues, expression levels, kinetic properties and response to different classes of inhibitors [14-18]. Various dysfunctions, and/or over-expression of hCAs in different human physiological as well as pathological processes are responsible for many ailments in body such as mental disorders (hCA II, VII, VIII, XIV), obesity (hCA VA, VB), edema (hCA I, II) and glaucoma (hCA II, IV, XII) [19-21]. The eminent transmembrane isoforms hCA IX and XII are overexpressed in hypoxic tumors, with limited expression in most normal cells [14, 19, 22, 23]. These tumor-associated proteins help in pH regulation in tumors, proliferation, angiogenesis, and metastasis of variety of cancer cells, their selective inhibition can lead to the development of new generation anticancer agents [24, 25]. It is noteworthy that ubiquitous hCA I and II are the main off-target isoforms because these are involved in many physiological processes [2].

Traditional primary carbonic anhydrase sulfonamide inhibitors have been used over the last few decades in clinics for the treatment of glaucoma, epilepsy, obesity, and as diuretics [26]. Acetazolamide (AAZ), Methazolamide (MZA) and Ethoxzolamide (EZA) (**Fig. 1**) are the prototypical first and second-generation drugs [19, 27]. The sulfonamide based hCA IX and XII inhibitor SLC-0111 is under clinical investigations [28]. Since most of the CA epitopes are nonspecific, a major challenge in therapeutic antitumor applications of hCA IX and XII sulfonamide-based inhibitors is to the risk of a plethora of undesired side effects [29].

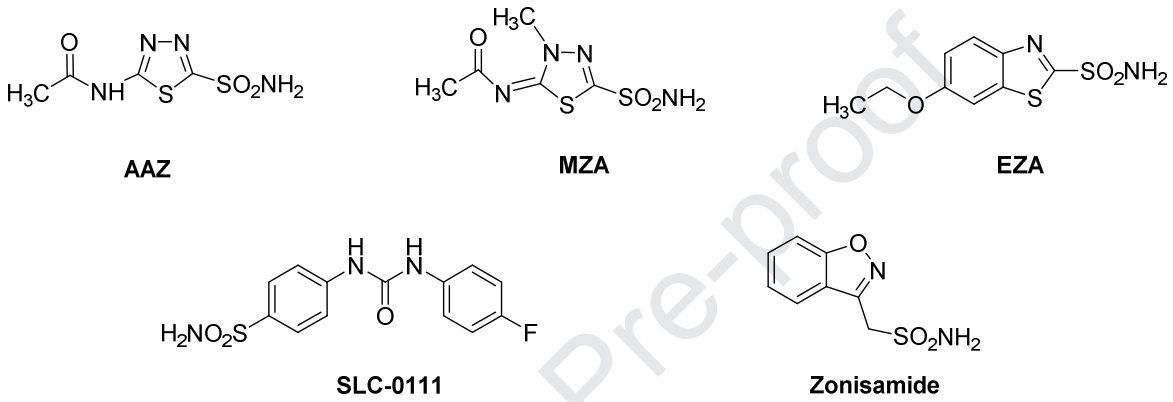


Fig. 1. Some sulfonamide-based drugs in clinical use or in clinical trials as potent CAIs.

The first choice in the field of specific CAI chemotypes is the zinc-binding group (ZBG) primary sulfonamide [23]. The ring and tail approach strategies have been used for the design of isoform-selective sulfonamide based CAIs [23]. The CAIs consisting of modulating moieties with various steric demands were directly attached to the sulfonamide group and appended with different tails to the aromatic/heterocyclic ring in the scaffold of the ZBG in order to target selectively the rim of the active site of CA, a region with significant amino acid difference between isoenzymes [30]. The sulphonamide moiety and the aromatic ring are attached through carbonyl/amide linker (**Fig**. **2**.).

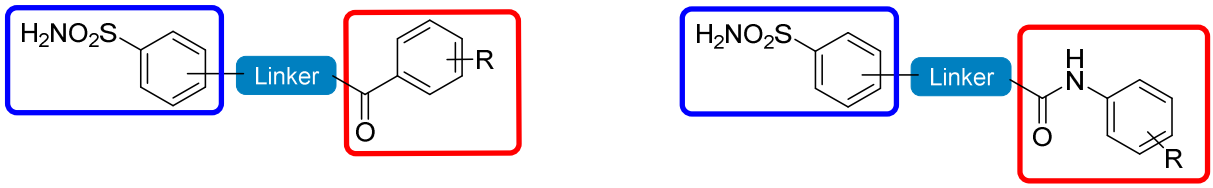


Fig. 2. Tail approach as carbonyl/amide linker bearing benzenesulfonamide.

Several studies have been extensively performed on 1,3,4-oxadiazole moiety, which shows diverse biological activities including antiviral [31], analgesic [32], antitumor [33], and anti-inflammatory [34] activity. The biological potential of these heterocycles against cancer cells has

been reported with different mechanisms of action, such as inhibition of tubulin, mitogenesis, angiogenesis, metastasis in tumors, focal adhesion kinase inhibition, telomerase inhibition, interacting with several receptors involved in proliferation, cell growth, and DNA biosynthesis [32, 35-39]. Azole group present in the 1,3,4-oxadiazole make it more lipophilic and, therefore, more liable to pass through the cell membrane [40].

In previous years, our research group has explored N containing heterocyclic compounds such as 1,2,3-triazoles, 1,2,4 triazoles, pyrazoles and pyrazolines **1** containing benzenesulfonamides as CAIs (**Fig**. **3**) that show moderate to excellent inhibition potential against hCA IX and XII [41-44]. Recently, we reported the synthesis of benzenesulfonamides containing triazole moietiy **2** that showed excellent inhibition against hCA I, II, IV, and IX [45]. In order to explore the heterocyclic scaffolds as CAIs, we report herein the design and synthesis of new sets of twenty novel 1,3,4-oxadiazole containing benzenesulfonamides **3a**–**j** and **4a**–**j** to study the effect of the incorporation of amide and carbonyl linker between the aromatic ring and main 1,3,4-oxadiazole benzenesulfonamide moiety on their inhibition potential against physiologically relevant isoforms hCA I and II as well as tumor-associated isoforms hCA IX and XII (**Fig**. **3**).

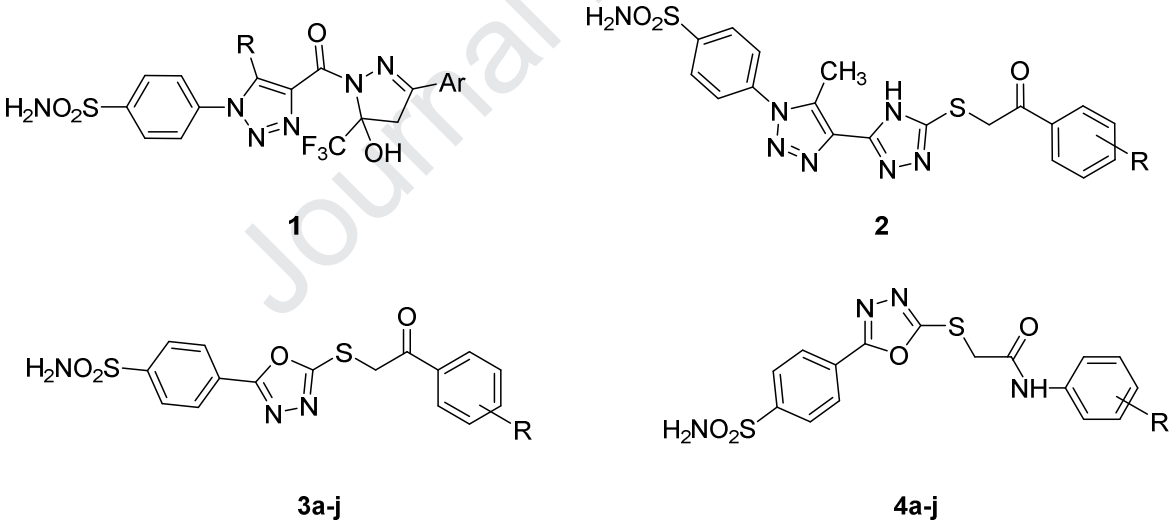


Fig. 3. Chemical structure of the sulfonamide CA inhibitors and derivatives incorporating the pyrazolines and 1,2,3-triazole ring **1-2**, together with the newly designed sulfonamides **3a**–**j** and **4a**–**j**.

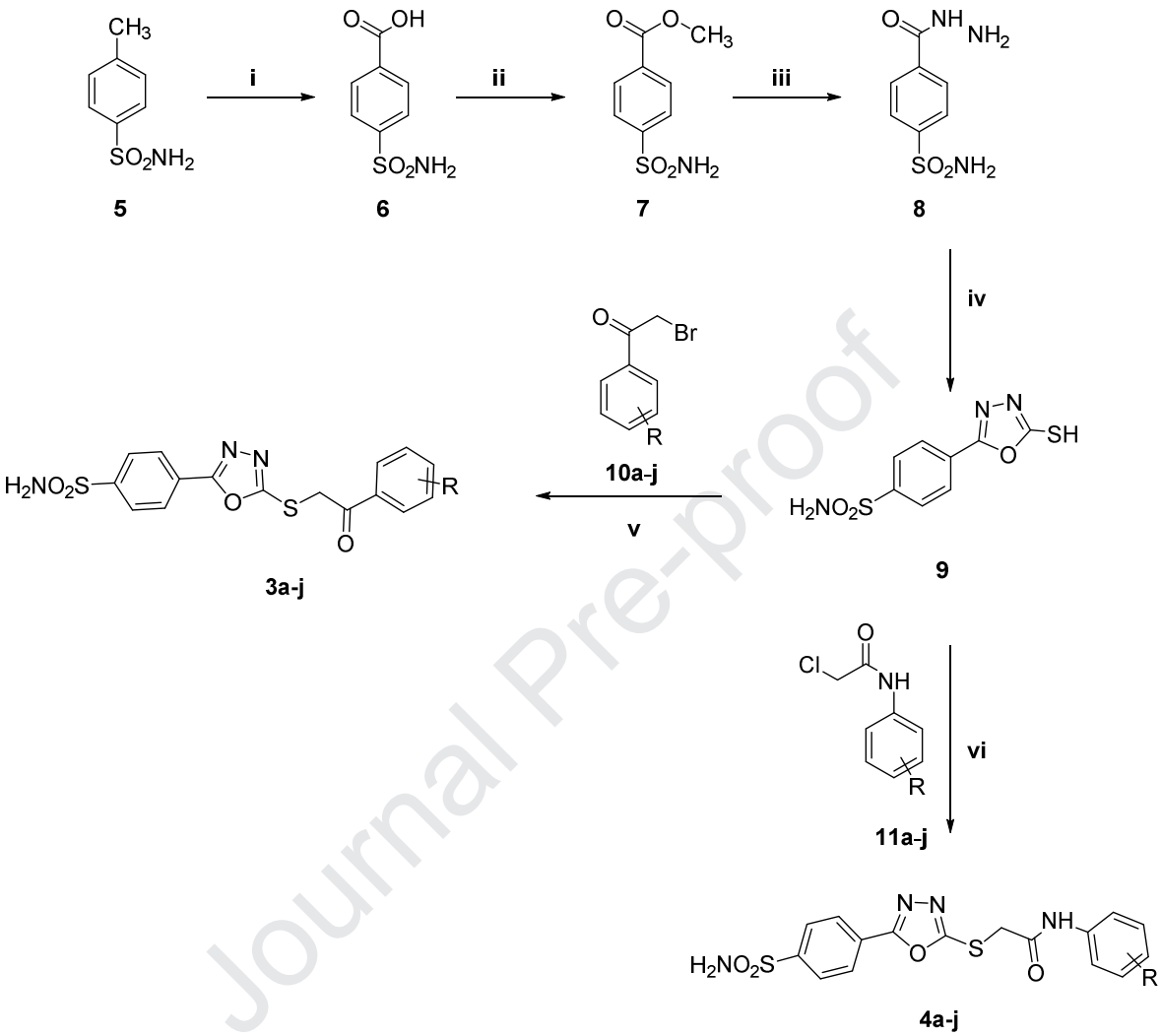
2. Results and discussion

2.1. Chemistry

The synthesis of the novel derivatives of 1,3,4-oxadiazole bearing benzenesulfonamide **3a**–**j** and **4a**–**j** is outlined in Scheme 1. Initially, the 4-sulfamoylbenzoic acid (**6**) was prepared by the oxidation of 4-methylbenzenesulfonamide (**5**) in the presence of $KMnO_4$ that was further converted into methyl 4-sulfamoylbenzoate (**7**) using usual Fischer esterification reaction [46]. Refluxing methyl ester derivatives with hydrazine monohydrate in ethanol afforded corresponding hydrazide **8** [46]. The acid hydrazide **8** was cyclized using carbon disulfide and potassium hydroxide to yield key intermediate 1,3,4-oxadiazole **9**. Which was stirred with differently substituted α-bomoacetophenones **10a**–**j** in acetonitrile solvent in presence of triethylamine resulting in formation of targeted compounds **3a**–**j** while refluxing **9** with differently substituted derivatives of α-chloro-N-phenylacetamide **11a**–**j** in acetone using K_2CO_3 base yielded **4a**–**j**. Differently substituted α-chloro-N-phenylacetamide **11a**–**j** in turn were prepared by the reaction of corresponding anilines with chloroacetyl chloride in DMF by stirring for 8 hrs at room temperature [47].

^{1}H NMR, ^{13}C NMR, IR, and HRMS techniques were used for the characterization of the newly synthesized compounds. According to the IR spectra of the synthesized **3a**–**j** and **4a**–**j** derivatives, the presence of SO_2NH_2 group was confirmed by the absorption at about 3300 cm^{-1} appearing due to NH_2 stretching as well as appearance of characteristic sharp IR absorption bands at ~1333 cm^{-1} and ~1155 cm^{-1} for SO_2 stretching. The presence of SO_2NH_2 group was further confirmed by the appearance of a characteristic singlet of two protons at ~7.58 ppm in ^{1}H NMR spectra. Peaks at ~190 ppm in **3a**–**j** and at ~164 ppm in **4a**–**j** in their ^{13}C NMR were ascribed to the presence of C=O groups. Further, the IR absorption band from 1643 cm^{-1}–1690 cm^{-1} in **3** and **4** confirms the presence of the C=O group in carbonyl and amide functional group. From the ^{1}H NMR spectra of **4a**–**j** the signal for amide N–H protons was identified as singlet which appeared downfield to aromatic protons in the range of 9.74 ppm–11.05 ppm. In addition, the signal for aliphatic protons of methylene was observed as a singlet appearing in the range 4.37 ppm to 5.29 ppm integrating for two protons in ^{1}H NMR spectra of compounds **3a**–**j** and **4a**–**j**. It was speculated from ^{1}H NMR data that compounds **4a**–**j** show some minor peaks which are due to the dynamic equilibrium between imine-enol and keto-amine form [48]. The duplication of each and every proton in NMR revealed the presence of two isomers in the variable ratio in all the compounds but in the compound **4c** the isomer presence was observed in approximately equal amount (**Fig. 4**, supplementary file)[48]. For supporting the fact, ^{1}H NMR

spectrum of representative compound **4c** was taken in DMSO-d_6 in the presence of TFA where only one isomer was observed as duplication of peaks disappeared completely as the compound was supposed to be entirely predisposed in one isomeric form due to restricted rotation about (C=N) linkage (**Fig. 4**, supplementary file). From the data available in TFA it was predicted that the compound **4c** mainly exists in imine-enol from as the methylenec protons in the keto form were supposed to resonate upfield (δ_H = 4.185 ppm) whereas in imine-enol form the same were found to resonate downfield (δ_H = 4.345 ppm). In the ^{1}H NMR spectra in TFA, the upfield (δ_H = 4.185 ppm) value for methylenec protons disappeared whereas the peak at δ_H = 4.3 ppm remains as such confirming the presence of only one isomer in an acidic medium that is in imine-enol form (**Fig**. **4**, supplementary file).



R	H	4-CH_3	4-OCH_3	4-F	4-Cl	4-Br	4-NO_2	3-OCH_3	3-Cl	3-NO_2
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**
	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**

Scheme 1. Synthesis of target compounds. Reagents and conditions: (i) $KMnO_4$, H_2O, reflux; (ii) CH_3OH, H_2SO_4, reflux; (iii) $NH_2NH_2.H_2O$, EtOH, reflux; (iv) CS_2, KOH, EtOH/THF, reflux; (v) CH_3CN, TEA, r.t.; (vi) Acetone, K_2CO_3, reflux.

2.2. CA inhibition studies

All the newly prepared sulfonamides **3a**–**j** and **4a**–**j** were screened for their inhibition efficacy as CAIs against four physiologically relevant isoforms i.e. hCA I, II (cytosolic enzymes), IX, and XII (transmembrane, tumor-associated isoforms) by stopped-flow CO_2 hydrase assay, using standard sulfonamide inhibitor acetazolamide (AAZ) as a reference drug. The following structure-activity relationship (SAR) can be revealed from the data shown in **Table 1**:

i. The ubiquitous isoform hCA I was weakly inhibited by all the newly synthesized sulfonamides with inhibition constants (K_I) specifically spanning between 70.7 nM–3.896 µM. The compounds **3a**–**f**, **3h**–**j**, and **4a**–**i** showed low inhibitory activity while compounds **3g** (K_I = 70.7 nM) and **4j** (K_I = 73.2 nM) displayed inhibitory values better than the reference drug AAZ (K_I = 250 nM). The structure-activity relationship of hCA I indicated that introduction of electron-withdrawing groups, such as fluoro and nitro group, at the para/meta-position enhanced the inhibition potential as compared to electron releasing groups, such as methyl and methoxy group at para position that possess a remarkably diminished inhibitory efficacy towards the hCA I.

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) by a stopped-flow CO_2 hydrase assay [49].

Compounds	R	K_I (nM)[a]			
		hCA I	hCA II	hCA IX	hCA XII
3a	H	1359	346.8	756.5	265.0
3b	4-CH_3	3324	147.8	201.1	230.6
3c	4-OCH_3	3815	157.8	448.6	3618
3d	4-F	744.1	69.4	1977	2239
3e	4-Cl	594.6	67.3	1318	839.9
3f	4-Br	616.9	67.0	1745	635.7

3g	4-NO_2	70.7	29.5	633.3	294.3
3h	3-OCH_3	469.6	79.6	1328	491.5
3i	3-Cl	543.5	59.2	1249	382.7
3j	3-NO_2	669.4	58.5	566.2	576.7
4a	H	542.5	61.1	111.2	366.0
4b	4-CH_3	739.0	78.7	74.1	263.0
4c	4-OCH_3	2924	53.6	29.0	266.3
4d	4-F	710.7	85.7	163.2	587.9
4e	4-Cl	2080	96.0	757.0	837.6
4f	4-Br	3896	847.7	671.2	751.1
4g	4-NO_2	761.9	73.1	256.4	737.1
4h	3-OCH_3	673.1	69.8	53.1	689.9
4i	3-Cl	500.9	81.9	50.8	400.5
4j	3-NO_2	73.2	7.9	16.3	256.7
AAZ	-	250	12.1	25.8	5.7

AAZ = acetazolamide, reference compound, a standard sulfonamide CAI, is also provided for comparison.

[a]Mean from 3 different assays, by a stopped-flow technique (errors were in the range of ±5-10% of the reported values).

ii. The physiologically dominant cytosolic isoform hCA II (associated with glaucoma) was moderately inhibited by all the newly synthesized sulfonamides **3a**–**j** and **4a**–**j** with inhibition constant ranging in between 7.9 nM–0.85 µM. Except for one compound **4j** (K_I = 7.9 nM), which showed better inhibition potency than AAZ, all others were found to be less potent inhibitors as compared to standard drug AAZ (K_I

= 12.5 nM). The introduction of electron-withdrawing groups in phenyl ring in both the series **3a**–**j** and **4a**–**j** in general increases the potency of inhibition against hCA II as compared to electron-donating groups. However, sixteen compounds out of total of twenty compounds were found to inhibit hCA II isoform with K_I < 100 nM. Both the series **3a**–**j** and **4a**–**j**, showed almost similar inhibition potential against hCA II isoform whereas compound **4f** (K_I = 847.7 nM) was found to be exceptionally weak inhibitor.

iii. The transmembrane tumor-associated isoform hCA IX was moderately inhibited by most of the novel compounds herein reported. Only 3-nitro derivative **4j** (K_I = 16.3 nM) showed effective inhibitory efficiency better than the reference drug AAZ, whereas compound **4c** shows inhibition (K_I = 29.0 nM) comparable to the reference drug AAZ. The displacement of the nitro group from meta to para-position in **4g** led to a 16-fold reduction in inhibition activity. The replacement of nitro group in 4-position with electron-donating groups, such as methyl and methoxy in **4a**–**j** compounds leads to an increase in inhibition potential against hCA IX. The novel compounds **3a–j** with carbonyl linker showed weak inhibition efficacy against hCA IX.

iv. The compounds **3a**–**j** and **4a**–**j** have shown variable and diverse inhibition against the transmembrane tumor-associated isoform hCA XII, with K_I spanning between 0.23 µM–3.62 µM. Compound **3b** (K_I = 0.23 µM) with a methyl group was found to be an efficient inhibitor and the 4-methoxy substituted compound **3c** (K_I = 3.62 µM) was the weakest inhibitor against hCA XII. On the other hand, in series **4a**–**j** the 4-methoxy substituted compound **4c** was 13-fold efficient hCA XII inhibitor which shows that 1,3,4-oxadiazole with amide tail/linker having low nanomolar affinity against tumor-associated isoform hCA XII is better than the 1,3,4-oxadiazole with carbonyl tail/linker compounds. The remaining derivatives inhibit hCA XII in a rather narrow range that does not allow to compile further SAR.

v. In terms of structure-activity relationship, the compound **4j** with amide linkage was found to be a better inhibitor against the screened isoforms hCA I, II, and IX as compared to compound **3j** having carbonyl linkage. In **4a**–**j** compounds there is a significant increase in inhibition that may be due to the NH group that can lead to an

increase in polarity and extent of hydrogen bonding. It may indicate that the inhibition potential depends upon the length of the tail and positioning of the linker connecting the two pharmacophores.

Table 2

Selectivity ratios for inhibiting the tumor-associated isoforms hCA IX and XII over cytosolic isoforms hCA I and II, with AAZ and compounds **3a**–**j** and **4a**–**j**.

Compounds	R	Selectivity ratio*			
		I/IX	II/IX	I/XII	II/XII
3a	H	3.812	0.458	5.128	1.354
3b	4-CH_3	16.529	0.734	14.41	0.640
3c	4-OCH_3	8.504	0.351	1.054	0.043
3d	4-F	0.376	0.035	0.332	0.030
3e	4-Cl	0.4511	0.051	0.707	0.080
3f	4-Br	0.353	0.038	0.970	0.105
3g	4-NO_2	0.111	0.046	0.240	0.100
3h	3-OCH_3	0.353	0.059	0.955	0.161
3i	3-Cl	0.435	0.047	1.420	0.154
3j	3-NO_2	1.182	0.103	1.160	0.101
4a	H	4.878	0.549	1.482	0.166
4b	4-CH_3	9.973	1.062	2.809	0.299
4c	4-OCH_3	100.82	1.848	10.981	0.201
4d	4-F	4.354	0.525	1.208	0.145

4e	4-Cl	2.747	0.126	2.483	0.114
4f	4-Br	5.804	1.262	5.187	1.128
4g	4-NO_2	2.971	0.285	1.033	0.099
4h	3-OCH_3	0.126	1.314	0.975	0.101
4i	3-Cl	9.860	1.612	1.250	0.204
4j	3-NO_2	4.490	0.484	0.285	0.030
AAZ	-	9.689	0.468	43.8	2.122

AAZ = acetazolamide, reference compound, a standard sulfonamide CAI, is also provided for comparison.

*The K_I ratios are indicative of isozyme selectivity: a weak selective inhibitor is characterized by a low-value ratio.

vi. The selectivity index (SI) for inhibiting the tumor-associated isoforms hCA IX and XII over the off-targeted cytosolic isoforms hCA I and II have been presented in **Table 2**. It is evident that the compounds didn't show consistent behavior in their potential against all the four tested isoforms (hCA I, II, IX, and XII). It can be observed that some of the investigated derivatives showed promising levels of selective inhibition of the transmembrane associated isoforms over the cytosolic isoforms. It was also observed that compound **4c** and **3b** were exhibiting the best selectivity for hCA IX and XII over hCA I. Indicating that the electron-donating group at para-position having amide tail/linker in 1,3,4-oxadiazole benzenesulfonamide leads to a potent precursor for designing the tumor-selective hCA XI CAIs.

3. Conclusions

As a part of our research aiming to design selective novel carbonic anhydrase inhibitors, we have synthesized two series of twenty compounds **3a**–**j** and **4a**–**j** containing 1,3,4-oxadiazole bearing benzenesulfonamide. These compounds were examined for their inhibition potential against the two dominant cytosolic isoforms hCA I/II and the tumor-associated isoforms hCA IX/XII and

compared with that of reference drug acetazolamide AAZ, a standard inhibitor. The hCA I was relatively weakly inhibited by compounds **3a**–**f**, **3h**–**j**, and **4a**–**i** with K_I ranging from 469.6 nM–3.89 µM except **3g** (K_I = 70.7 nM) and **4j** (K_I = 73.2 nM) which were potent inhibitors of hCA I as compared to that of AAZ (K_I = 250 nM). The compound N-(3-nitrophenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio) (**4j**) exercised strong inhibition potential against hCA II and tumor-associated isoform hCA IX, whereas compounds **3a**–**j** and **4a**–**j** were moderately effective inhibitors of hCA XII. CA inhibition data demonstrated that 1,3,4-oxadiazole bearing benzenesulfonamide with amide tail/linker was an effective inhibitor of hCA IX as per SAR. Compound **4c** was selective inhibitor of tumor-associated isoform hCA IX over off target hCA I (**Table 2**). These results speculated that these molecules can be the choice of future drug candidates targeting hypoxic tumors and can lead to design and optimization of selective hCA inhibitors.

4. Experimental protocols

4.1. Chemistry

4.1.1. General

All the reagents and solvents were purchased from commercial suppliers and were used as received unless otherwise indicated. All the solvents were dried and/or purified according to standard procedures prior to use. All the air or moisture-sensitive reactions were performed under a nitrogen atmosphere using dried glassware and syringes techniques to transfer solutions. Analytical thin-layer chromatography (TLC) was performed on MERCK precoated silica gel on F_{254} aluminium plates using a mixture of chloroform and methanol as eluent while UV lamp was used to visualize the spots. Melting points were determined in open glass capillary tubes by Precision Digital Melting Point apparatus (Popular India) and may be uncorrected values. Infrared (IR) were recorded as KBr disks using an ABB MB 3000 DTGS infrared spectrophotometer. Nuclear magnetic resonance ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Avance III 400 MHz and 100 MHZ respectively, using deuterated dimethyl sulfoxide (DMSO-d_6) and Me_4Si (TMS) as internal standard at room temperature. Chemical shifts are reported as δ values in parts per million (ppm) and the coupling constants (J) are expressed in hertz (Hz). High-resolution mass spectra were obtained from a XEVO G2-S QTof UPLC/MS spectrometer using acetonitrile as solvent. Splitting pattern are designated as follows: singlet (s), doublet (d), doublet of doublet (dd), doublet of triplet (dt), triplet (t), quartet (q),

multiplet (m), exchangeable proton (ex) for NMR assignments and strong (s), medium (m), broad (br) for IR assignments.

4.1.2. Synthesis of 4-(5-mercapto-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**9**)

General procedure: To a mixture of 4-(hydrazinecarbonyl)benzenesulfonamide (**8**) [46] (4.65 mmol) in ethanol/THF (1:1) at room temp. was added a solution of KOH (4.65 mmol) in ethanol (20 ml) followed by the addition of CS_2 (23.25 mmol). Then the reaction mix. was refluxed for 8 hrs. The solvent was evaporated under vacuum and the residue was acidified with dil. HCl and resulting white solid was collected, washed with water, and recrystallized with ethanol to give final product 4-(5-mercapto-1,3,4-oxadiazol-2-yl)benzenesulfonamide.

4.1.2.1. 4-(5-mercapto-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**9**).

Yield 86%; Colour: White; mp: 180–182 ^{o}C; IR (KBr) (ν, cm-1): 3335, 3240 (m, N-H stretch), 2608 (s, S-H stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.08 (d, J = 8.4 Hz, 2H, Ar), 8.00 (d, J = 7.2 Hz, 2H, Ar), 7.59 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 178.11, 159.98, 147.26, 127.26, 127.14, 125.79; HRMS (ESI-MS) m/z 257.9999 $(M+H)^+$, $C_8H_7N_3O_3S_2H^+$, calcd. 257.9928.

4.1.3. Synthesis of 4-(5-((2-aryl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3a**–**j**)

General procedure: To a stirred mixture of 4-(5-mercapto-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**9**) (1.0 mmol) and differently substituted phenacyl bromide **10a**–**j** (1.0 mmol) in acetonitrile, triethylamine (1.5 mmol) was added at room temp. and the immediately formed precipitates were filtered off, washed with water and recrystallized with ethanol to give desired product.

4.1.3.1. 4-(5-((2-oxo-2-phenylethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3a)**.

Yield 76%; Colour: White; mp: 247–249 ^{o}C; IR (KBr) (ν, cm^{-1}): 3348, 3248 (m, N-H stretch), 1651 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.15 (d, J = 8.4 Hz, 2H, Ar), 8.09 (d, J = 7.2 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.73 (t, J = 7.2 Hz, 1H, Ar), 7.63–7.56 (m, 4H, Ar, SO_2NH_2), 5.22 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm):192.56, 164.69, 147.22, 145.13, 133.02, 129.94, 129.10, 127.53, 127.16, 126.19, 41.05, 21.73; HRMS (ESI-MS) m/z 376.0345 $(M+H)^+$, $C_{16}H_{13}N_3O_4S_2H^+$, calcd 376.3548.

4.1.3.2. 4-(5-((2-oxo-2-(p-tolyl)ethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3b)**. Yield 68%; Colour: White; mp: 251–253 ^{o}C; IR (KBr) (ν, cm^{-1}): 3356, 3263 (m, N-H stretch), 1651 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.15 (d, J = 8.0 Hz, 2H, Ar), 8.00 (t, J = 8.0 Hz, 4H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.40 (d, J = 8.0 Hz, 2H, Ar), 5.18 (s, 2H, CH_2), 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 192.56, 164.69, 147.22, 145.12, 133.02, 129.94, 129.10, 127.53, 127.16, 126.19, 41.05, 21.72; HRMS (ESI-MS) m/z 390.0514 $(M+H)^+$, $C_{17}H_{15}N_3O_4S_2H^+$, calcd 390.0582.

4.1.3.3. 4-(5-((2-(4-methoxyphenyl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3c)**.

Yield 73%; Colour: White; mp: 218–220 ^{o}C; IR (KBr) (ν, cm^{-1}): 3348, 3271 (m, N-H stretch), 1651 (s, C=O stretch), 1342, 1173 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.27 (d, J = 2.4 Hz, 1H, Ar), 8.17–8.10 (m, 4H, Ar), 8.01 (d, J = 8.4 Hz, 2H, Ar), 7.58 (s, 2H, SO_2NH_2), 7.31 (d, J = 8.4 Hz, 1H, Ar), 5.17 (s, 2H, CH_2), 3.99 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 190.79, 164.75, 160.23, 147.23, 133.78. 130.84, 129.45, 127.55, 127.16, 126.18, 113.00, 111.50, 57.39; HRMS (ESI-MS) m/z 406.0471 $(M+H)^+$, $C_{17}H_{15}N_3O_5S_2H^+$, calcd 406.0531.

4.1.3.4. 4-(5-((2-(4-fluorophenyl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3d)**.

Yield 82%; Colour: White; mp: 232–234 ^{o}C; IR (KBr) (ν, cm^{-1}): 3371, 3279 (m, N-H stretch), 1666 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.20–8.13 (m, 4H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.44 (t, J = 8.8, 2H, Ar), 5.21 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 191.75, 165.96 (d, $^{1}J_{CF}$ = 251.5 Hz), 164.75, 164.59, 147.23, 132.30 (d, $^{4}J_{CF}$ = 2.7 Hz), 132.11 (d, $^{3}J_{CF}$ = 9.6 Hz), 127.54, 127.16, 126.18, 116.49 (d, $^{2}J_{CF}$ = 22 Hz), 49.97; HRMS (ESI-MS) m/z 394.0257 $(M+H)^+$, $C_{16}H_{12}FN_3O_4S_2H^+$, calcd 394.0331.

4.1.3.5. 4-(5-((2-(4-chlorophenyl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3e)**.

Yield 72%; Colour: White; mp: 228–230 ^{o}C; IR (KBr) (ν, cm^{-1}): 3356, 3263 (m, N-H stretch), 1666 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.14 (d, J = 8.0 Hz, 2H, Ar), 8.10 (d, J = 8.4 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.68 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 5.20 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C

(ppm): 192.23, 164.77, 164.53, 147.24, 139.45, 134.23, 130.91, 129.53, 127.54, 127.16, 126.17, 41.00; HRMS (ESI-MS) m/z 409.9961 $(M+H)^+$, $(M+H+2)^+$ 411.9934, $C_{16}H_{12}ClN_3O_4S_2H^+$, calcd 410.0036.

4.1.3.6. 4-(5-((2-(4-bromophenyl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3f)**.

Yield 72%; Colour: Light yellow ; mp: 233–235 ^oC; IR (KBr) (ν, cm^{-1}): 3356, 3256 (m, N-H stretch), 1659 (s, C=O stretch), 1350, 1165 (s, SO_2 stretch) ; ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.14 (d, J = 8.4 Hz, 2H, Ar), 8.02–8.00 (m, 4H, Ar), 7.82 (d, J = 8.4 Hz, 2H, Ar), 7.56 (s, 2H, SO_2NH_2), 5.19 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 192.44, 164.76, 164.50, 147.24, 134.55, 132.47, 130.94, 128.67, 127.52, 127.15, 126.17, 40.96; HRMS (ESI-MS) m/z 453.9452 $(M+H)^+$, $(M+H+2)^+$ 455.9433, $C_{16}H_{12}BrN_3O_4S_2H^+$, calcd 453.9531.

4.1.3.7. 4-(5-((2-(4-nitrophenyl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3g)**.

Yield 74%; Colour: White; mp: 232–234 ^oC; IR (KBr) (ν, cm^{-1}): 3340, 3271 (m, N-H stretch), 1690 (s, C=O stretch), 1319, 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.41 (d, J = 8.4 Hz, 2H, Ar), 8.31 (d, J = 8.4 Hz, 2H, Ar), 8.15 (d, J = 8.4 Hz, 2H, Ar), 8.01 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 5.28 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 192.54, 164.84, 164.38, 150.82, 147.26, 140.18, 130.43, 127.56, 127.17, 126.16, 124.25, 41.29; HRMS (ESI-MS) m/z 421.0194 $(M+H)^+$, $C_{16}H_{12}N_4O_6S_2H^+$, calcd 421.0276.

4.1.3.8. 4-(5-((2-(3-methoxyphenyl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3h)**.

Yield 70%; Colour: Pale yellow; mp: 212–214 ^oC; IR (KBr) (ν, cm^{-1}): 3612 (br,O-H stretch), 3317, 3240 (m, N-H stretch), 1690 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.18–8.12 (m, 2H, Ar), 8.03–7.98 (m, 2H, Ar), 7.70–7.60 (m, 1H, Ar), 7.60–7.50 (m, 4H, Ar, SO_2NH_2), 7.30 (dd, J = 0.8 Hz, J = 8.4 Hz, 1H, Ar), 5.20 (s, 2H, CH_2), 3.85 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 192.92, 164.74, 164.61, 159.99, 147.23, 136.87, 130.61, 127.57, 127.53, 127.16, 121.48, 120.51, 113.52, 55.95, 41.09; HRMS (ESI-MS) m/z 406.0452 $(M+H)^+$, $C_{17}H_{15}N_3O_5SH^+$, calcd 406.4608.

4.1.3.9. 4-(5-((2-(3-chlorophenyl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3i)**.

Yield 69%; Colour: White; mp: 234–236 ^{o}C; IR (KBr) (ν, cm^{-1}): 3356, 3271 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.15 (d, J = 8.4 Hz, 2H, Ar), 8.11 (s, 1H, Ar), 8.05–7.99 (m, 3H, Ar), 7.80 (d, J = 8.0 Hz, 1H, Ar), 7.64 (t, J = 8.04 Hz, 1H, Ar), 7.57 (s, 2H, SO_2NH_2), 5.21 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 192.26, 164.80, 164.55, 147.25, 137.36, 134.31, 134.16, 131.41, 128.67, 127.62, 127.55, 127.16, 126.17, 40.95; HRMS (ESI-MS) m/z 409.9951 $(M+H)^+$, $(M+H+2)^+$ 411.9924, $C_{16}H_{12}ClN_3O_4S_2H^+$, calcd 410.0036.

4.1.3.10. 4-(5-((2-(3-nitrophenyl)-2-oxoethyl)thio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**3j)**.

Yield 76%; Colour: Off White; mp: 243–245 ^{o}C; IR (KBr) (ν, cm^{-1}): 3333, 3248 (m, N-H stretch), 1682 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.78 (t, J = 2.0 Hz, 1H, Ar), 8.57–8.50 (m, 2H, Ar), 8.16 (dd, J = 6.8, J = 1.6 Hz, 2H, Ar), 8.01 (dd, J = 6.8, J = 2.0 Hz, 2H, Ar), 7.91 (t, J = 8.0 Hz, 1H, Ar), 7.58 (s, 2H, SO_2NH_2), 5.31 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 191.97, 164.83, 164.36, 148.55, 147.22, 136.72, 135.14, 131.25, 128.59, 127.67, 127.15, 126.15, 123.34, 41.04; HRMS (ESI-MS) m/z 421.0194 $(M+H)^+$, $C_{16}H_{12}N_4O_6S_2H^+$, calcd 421.0276.

4.1.4. Synthesis of N-aryl-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4a**–**j**)

A mixture of 4-(5-mercapto-1,3,4-oxadiazol-2-yl)benzenesulfonamide (**9**) (1 mmol), various substituted 2-chloro-N-phenylacetamide **11a**–**j** (1 mmol) and K_2CO_3 (1.5 mmol) was refluxed in acetone (15 ml) for 3–4 h. The reaction was monitored with TLC and after completion of the reaction, excess of solvent was evaporated and diluted with water (about 100 ml). The precipitated was separated out, filtered washed with water and recrystallized with an appropriate solvent.

4.1.4.1. N-phenyl-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4a**).

Yield 71%; Colour: Off White; mp: 243–245 ^{o}C; IR (KBr) (ν, cm^{-1}): 3348, 3248 (m, N-H stretch), 1659 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.46 (s, 1H, NH), 8.16 (d, J = 8.8 Hz, 2H, Ar), 7.99 (d, J = 8.8 Hz, 2H, Ar), 7.61–7.56 (m, 2H, Ar, 2H, SO_2NH_2), 7.33 (t, J = 8.0 Hz, 2H, Ar), 7.09 (t, J = 7.2 Hz, 1H, Ar), 4.38 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 165.31, 164.75, 164.72, 147.19, 139.08,

129.36, 127.52, 127.16, 126.20, 124.22, 119.66, 37.32; HRMS (ESI-MS) m/z 391.0454 $(M+H)^+$, $C_{16}H_{14}N_4O_4S_2H^+$, calcd 391.0529.

4.1.4.2. 2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)-N-(p-tolyl)acetamide (**4b**).

Yield 74%; Colour: White; mp: 259–261 ^oC; IR (KBr) (ν, cm^{-1}): 3340, 3248 (m, N-H stretch), 1659 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.36 (s, 1H, NH), 8.15 (d, J = 8.4 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.47 (d, J = 8.0 Hz, 2H, Ar), 7.13 (d, J = 8.0 Hz, 2H, Ar), 4.36 (s, 2H, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 165.01, 164.74, 147.22, 136.60, 133.18, 129.71, 128.37, 127.51, 127.16, 126.21, 119.67, 37.34, 20.92; HRMS (ESI-MS) m/z 405.0614 $(M+H)^+$, $C_{17}H_{16}N_4O_4S_2H^+$, calcd 405.0686.

4.1.4.3. N-(4-methoxyphenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4c**).

Yield 68%; Colour: Grey; mp: 259–261 ^oC; IR (KBr) (ν, cm^{-1}): 3742 (br, O-H stretch), 3333, 3225 (m, N-H stretch), 1327, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 11.00 & 10.30 (s, 1H, NH/OH), 8.16 (d, J = 8.0 Hz, 1H, Ar), 8.00 (d, J = 8.4 Hz, 1H, Ar), 7.95 (d, J = 8.0 Hz, 1H, Ar), 7.90 (d, J = 8.4 Hz, 1H, Ar), 7.58 (s, 1H, Ar), 7.50 (d, J = 9.2 Hz, 2H, SO_2NH_2), 7.28 (d, J = 8.8 Hz, 1H, Ar), 7.07 (d, J = 8.8 Hz, 1H, Ar), 6.90 (d, J = 8.8 Hz, 1H, Ar), 4.35 & 4.18 (s, 2H, CH_2), 3.82 & 3.73 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 165.12, 160.40, 157.67, 146.38, 140.42, 134.02, 131.32, 127.21, 126.96, 126.66, 122.24, 117.11, 116.29, 37.29.; HRMS (ESI-MS) m/z 421.0561 $(M+H)^+$, $C_{17}H_{16}N_4O_5S_2H^+$, calcd 421.0635.

4.1.4.4. N-(4-fluorophenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4d**).

Yield 68%; Colour: Off White; mp: 279–281 ^oC; IR (KBr) (ν, cm^{-1}): 3394, 3294 (m, N-H stretch), 1636 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.69 & 10.52 (s, 1H, NH/OH), 8.15 (d, J = 8.8 Hz, 2H, Ar), 8.00 (d, J = 8.8 Hz, J = 1.2 Hz, 2H, Ar), 7.95–7.89 (m, 1H, Ar), 7.63–7.57 (m, 3H, 2H, SO_2NH_2), 7.41 (t, J = 8.8 Hz, 1H, Ar), 7.18 (t, J = 8.8 Hz, 1H, Ar), 4.37 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 165.68, 165.24, 164.79, 164.61, 147.20, 127.523, 127.164, 126.194, 121.47 (d, $^3J_{CF}$ = 7.8 Hz), 121.10, 120.08, 115.96 (d, $^2J_{CF}$ = 22.1 Hz), 37.15; HRMS (ESI-MS) m/z 409.0361 $(M+H)^+$, $C_{16}H_{13}FN_4O_4S_2H^+$, calcd 409.0435.

4.1.4.5. N-(4-chlorophenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4e**).

Yield 70%; Colour: White ; mp: 257–259 ^{o}C; IR (KBr) (ν, cm^{-1}): 17, 3232 (m, N-H stretch), 1659 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.60 (s, 1H, NH), 8.15 (d, J = 8.4 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.62 (d, J = 8.8 Hz, 2H, Ar), 7.59 (s, 2H, SO_2NH_2), 7.39 (d, J = 8.8 Hz, 2H, Ar), 4.39 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm):165.49, 164.76, 164.67, 147.21, 138.04, 129.29, 127.77, 127.52, 127.16, 126.20, 121.21, 37.28; HRMS (ESI-MS) m/z 425.0065 $(M+H)^+$, $(M+H+2)^+$ 427.0036, $C_{16}H_{13}ClN_4O_4S_2H^+$, calcd 425.0140.

4.1.4.6. N-(4-bromophenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4f**).

Yield 69%; Colour: Silver; mp: 279–281^{o}C; IR (KBr) (ν, cm^{-1}): 3340, 3263 (m, N-H stretch), 1659 (s, C=O stretch), 1327, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.59 (s, 1H, NH), 8.15 (d, J = 8.4 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.59–7.55 (m, 2H, Ar, 2H, SO_2NH_2), 7.52 (d, J = 8.8 Hz, 2H, Ar), 4.38 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm):165.50, 164.77, 164.66, 147.23, 138.46, 132.19, 127.52, 127.17, 126.20, 121.60, 115.82, 37.32; HRMS (ESI-MS) m/z 468.9561 $(M+H)^+$, $(M+H+2)^+$ 470.9542, $C_{16}H_{13}BrN_4O_4S_2H^+$, calcd 468.9634.

4.1.4.7. N-(4-nitrophenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4g**).

Yield 73%; Colour: Yellow; mp: 234–236 ^{o}C; IR (KBr) (ν, cm^{-1}): 3302, 3254 (m, N-H stretch), 1690 (s, C=O stretch), 1319, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 11.05 (s, 1H, NH), 8.25 (d, J = 9.2 Hz, 2H, Ar), 8.15 (d, J = 8.4 Hz, 2H, Ar), 8.00 (d, J = 8.8 Hz, 2H, Ar), 7.85 (d, J = 9.2 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 4.45 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 166.42, 164.83, 164.57, 147.23, 145.14, 143.05, 127.53, 127.17, 126.18, 125.57, 119.47, 37.38; HRMS (ESI-MS) m/z 436.0310 $(M+H)^+$, $C_{16}H_{13}N_5O_6S_2H^+$, calcd 436.0380.

4.1.4.8. N-(3-methoxyphenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4h**).

Yield 70%; Colour: White; mp: 228–230 ^{o}C; IR (KBr) (ν, cm^{-1}): 3325, 3232 (m, N-H stretch), 1643 (s, C=O stretch), 1327, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.44 (s, 1H, NH), 8.15 (d, J = 8.4 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 2H,

SO_2NH_2), 7.30–7.20 (m, 2H, Ar), 7.12 (d, J = 8.0 Hz, 1H, Ar), 6.68 (d, J = 8.0 Hz, 1H, Ar), 4.37 (s, 2H, CH_2), 3.73 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): δ 165.34, 164.70, 160.06, 147.23, 140.26, 130.18, 127.52, 127.16, 126.21, 111.92, 109.65, 105.48, 55.49, 37.40; HRMS (ESI-MS) m/z 421.0560 $(M+H)^+$, $C_{17}H_{16}N_4O_5S_2H^+$, calcd 421.0635.

4.1.4.9. N-(3-chlorophenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4i**).

Yield 70%; Colour: White; mp: 291–293 ^oC; IR (KBr) (ν, cm^{-1}): 3325, 3248 (m, N-H stretch), 1659 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.65 (s, 1H, NH), 8.15 (d, J = 8.4 Hz, 2H, Ar), 7.80 (t, J = 2.0 Hz, 1H, Ar), 7.58 (s, 2H, SO_2NH_2), 7.47–7.43 (m, 1H, Ar), 7.38 (t, J = 8.0 Hz, 1H, Ar), 7.18–7.14 (m, 1H, Ar), 4.39 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 165.12, 160.40, 157.67, 146.38, 140.42, 134.02, 131.32, 127.21, 126.96, 126.66, 122.24, 117.11, 116.29, 37.29; HRMS (ESI-MS) m/z 425.0061 $(M+H)^+$, $(M+H+2)^+$ 427.0032, $C_{16}H_{13}ClN_4O_4S_2H^+$, calcd 425.0140.

4.1.4.10. N-(3-nitrophenyl)-2-((5-(4-sulfamoylphenyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (**4j**).

Yield 72%; Colour: Pale Yellow; mp: 210–212 ^oC; IR (KBr) (ν, cm^{-1}): 3310, 3248 (m, N-H stretch), 1666 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 10.96 (s, 1H, NH), 8.63 (s, 1H, Ar), 8.16 (d, J = 8.4 Hz, 2H, Ar), 8.01 (d, J = 8.4 Hz, 2H, Ar), 7.96 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H, Ar), 7.92 (d, J = 7.6 Hz, 1H, Ar), 7.65 (t, J = 8.0 Hz, 1H, Ar), 7.57 (s, 2H, SO_2NH_2), 4.43 & 4.21 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm):166.19, 164.82, 164.58, 148.50, 147.25, 140.18, 130.89, 127.53, 127.17, 126.19, 125.65, 118.76, 113.78, 37.24; HRMS (ESI-MS) m/z 436.0314 $(M+H)^+$, $C_{16}H_{13}N_5O_6S_2H^+$, calcd 436.0380.

5. CA inhibition Assay

An SX.18MV-R Applied Photophysics (Oxford, UK) stopped-flow instrument has been used to assay the inhibition of various CA isozymes [50]. 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 a 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 the water at 25 °C were used as substrate. Stock solutions of inhibitors were prepared at a concentration of 10 mM (in DMSO-

water 1:1, v/v) and dilutions up to 0.01 nM done with the assay buffer mentioned above. At least 7 different inhibitor concentrations have been used for measuring the inhibition constant. Inhibitor and enzyme solutions were pre-incubated together for 10 min at room temperature prior to assay, in order 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, and represent the mean from at least three different determinations [50]. All CA isozymes used here were recombinant proteins obtained as reported earlier by our group.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Tail Approach Synthesis of Novel Benzenesulfonamides Incorporating 1,3,4-Oxadiazole Hybrids as Potent Inhibitor of Carbonic Anhydrase I, II, IX, and XII

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Research Highlights

- Two series of 1,3,4-oxadiazole based benzenesulfonamides **3a**–**j** and **4a**–**j** having carbonyl and amide tail/linker were synthesized.
- Inhibitory efficacy of **3a**–**j** and **4a**–**j** was evaluated towards hCA I, II, IX, and XII isoforms.
- Compound **4j** (K_I = 70.7 nM, 7.9 nM, 16.3 nM) emerged as the most potent inhibitor of hCA I, II and IX respectively as compared to AAZ.
- **4c** and **3b** were found to be the most selective hCA IX and XII inhibitors over hCA I.

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Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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