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Design, synthesis, and carbonic anhydrase inhibition activity of benzenesulfonamide-linked novel pyrazoline derivatives

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ABSTRACT

Carbonic anhydrases (CA, EC 4.2.1.1) are Zinc metalloenzymes and are present throughout most living organisms. Among the catalytically active isoforms are the cytosolic CA I and II, and tumor-associated CA IX and CA XII. The carbonic anhydrase (CA) inhibitory activities of newly synthesized pyrazoline-linked benzenesulfonamides **18–33** against human CA (hCA) isoforms I, II, IX, and XII were measured and compared with that of acetazolamide (AAZ), a standard inhibitor. Potent inhibitory activity against hCA I was exerted by compounds **18–25**, with inhibition constant (K_I) values of 87.8–244.1 nM, which were greater than that of AAZ (K_I, 250.0 nM). Compounds **19**, **21**, **22**, **29**, **30**, and **32** were proven to have inhibitory activities against hCA IX with K_I values (5.5–37.0 nM) that were more effective than or nearly equal to that of AAZ (K_I, 25.0 nM). Compounds **20–22**, and **30** exerted potent inhibitory activities (K_Is, 7.1–10.1 nM) against hCA XII, in comparison with AAZ (K_I, 5.7 nM).

1. Introduction

Chalcones [1] are intermediates in the synthesis of numerous heterocyclic compounds such as pyrazolines [2–7], which are five-membered heterocyclic compounds with significant pharmacological actions, such as cytotoxic [4,8], anti-inflammatory [7,9], antimicrobial [5,7], and COX-2 inhibitory activities [9]. Furthermore, several pyrazolines incorporating benzenesulfonamide moieties exhibit potent carbonic anhydrase (CA) inhibition (Fig. 1A–E) [10]. Coxibs such as celecoxib, a pyrazole-linked benzenesulfonamide, are unique and selective COX-2 inhibitors that have anti-inflammatory and anticancer effects [11,12], and have also been reported as potent CA inhibitors (Fig. 1A) [13,14].

It has been reported that benzenesulfonamide-containing compounds have versatile biological actions, such as anticancer, anti-inflammatory, COX-2 inhibition, and antibacterial activities [15–17]. Moreover, sulfonamide derivatives are powerful carbonic anhydrase inhibitors (CAIs) [1,18–20]. Zinc metalloenzymes are a superfamily of CAs that are present in all eukaryotic and many microbial organisms and catalyze the formation of HCO_3^- and H^+ from CO_2 and water [21]. This hydration reaction is involved in variety of biological processes [2]. CA isoforms are present in different tissues, such as the gastrointestinal tract, nervous system, kidneys, lungs, skin, and eyes. CAs are used in several important biochemical pathways, such as acid–base regulation, respiration, carbon dioxide and ion transport, bone resorption, ureagenesis, gluconeogenesis, and lipogenesis [22,23]. The hCA II isoform is usually present in the eye, kidney, and central nervous system; therefore, CAIs are used clinically as antiglaucoma medication, diuretics, and anticonvulsants [24]. CA II, IV, and XII inhibitors are the isoforms targeted by the antiglaucoma agents, CA VA and VB inhibitors are possessed anti-obesity properties, and CA IX and XII inhibitors are useful as antitumor agents or diagnostic tools for imaging hypoxic tumors [2,25–27]. The inhibition and activation of CA isozymes are key therapeutic goals in the treatment of many disorders, such as edema, glaucoma, obesity, cancer, epilepsy, hypertension, and osteoporosis [2,19]. In previous work of these group, we observed that 1-acetyl-3,5-diaryl-4,5-dihydro-1H-pyrazole sulfamates, such as compounds **B**, **C**, and **D** (Fig. 1), showed effective inhibitory potency against CA II and IV

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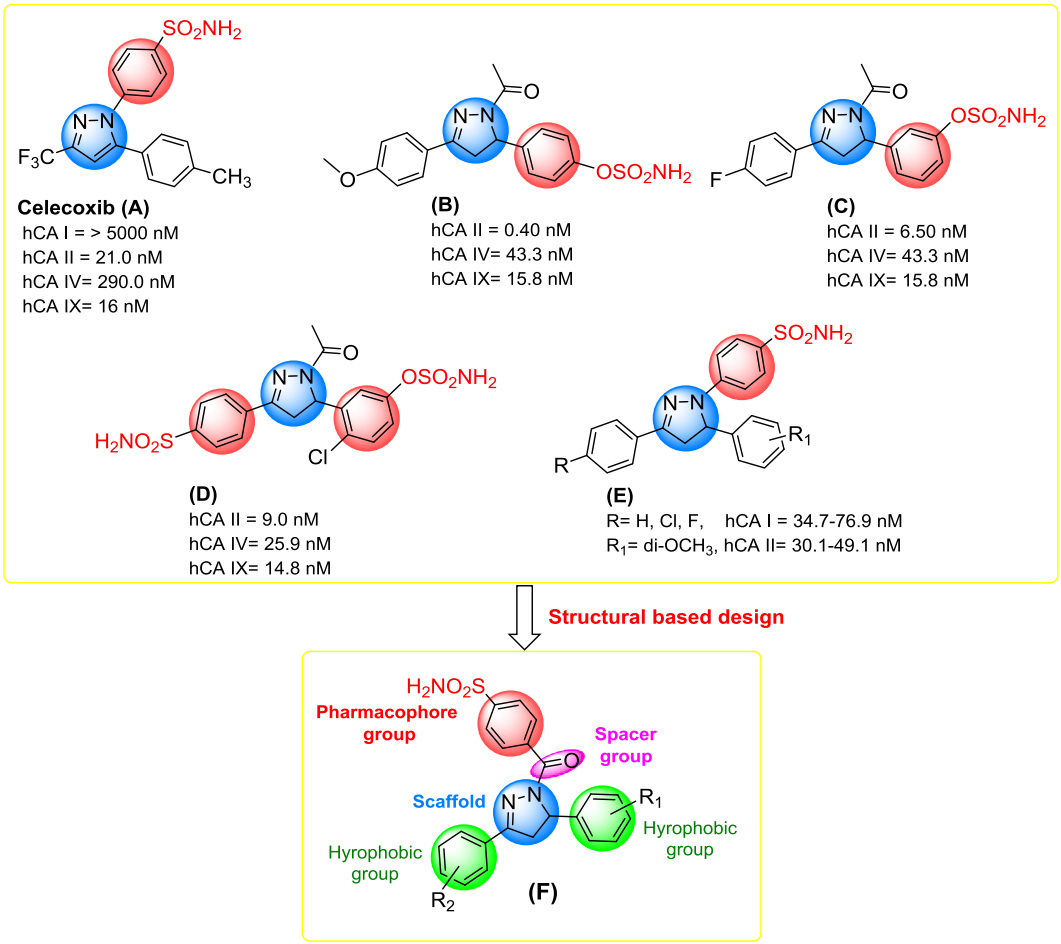


Fig. 1. Reported pyrazole derivatives as carbonic anhydrase inhibitors (A–E), and the designed pyrazoline-linked benzenesulfonamide derivatives (F).

isoforms (K_Is; 0.4–9.0 nM and 25.9–43.3 nM, respectively) comparable with the celecoxib (Fig. 1A) (K_Is; 21.0 and 290.0 nM). Additionally, these compounds inhibited tumor-associated hCA IX (K_Is; 14.8–15.8 nM) with potency similar to celecoxib (K_I; 16.0 nM) [28]. Further, cytosolic hCA I and II isoenzymes were inhibited by 4-(5-(dimethoxyphenyl)-3-(4-substituted phenyl)-4,5-dihydro-1H-pyrazol-1-yl) benzenesulfonamide (**E**) (K_Is; 34.7–76.9 and 30.1–49.1 nM, respectively) (Fig. 1) [29].

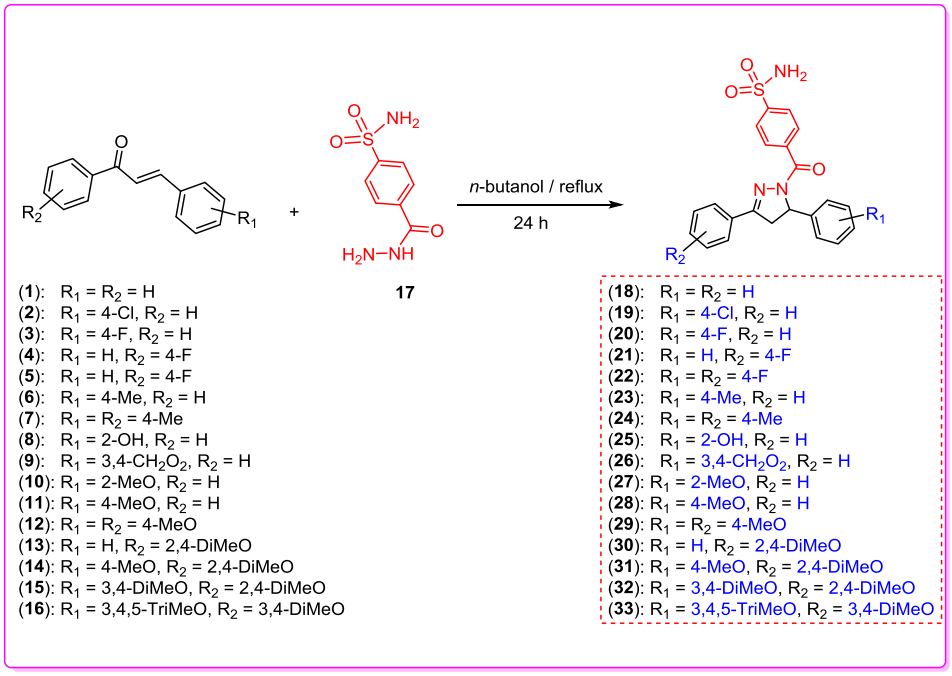
Very recently, we reported the potential carbonic anhydrase activities of several cyclic imides incorporating a benzenesulfonamide fragment [30]; moreover, in continuation of our work, we have herein reported the design and synthesis of novel 4-(4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamides (Fig. 1F) linked with diaryl groups at the 3 and 5 positions to investigate their carbonic anhydrase inhibitory effects on hCAs I, II, IX, and XII isoenzymes.

2. Results and discussion

2.1. Chemistry

The synthesis of 1,3,5-trisubstituted pyrazoline derivatives **18–33** is shown in Scheme 1. In the first step, α,β–unsaturated ketones (chalcones) **1–16** were prepared by methods reported previously using the condensation of acetophenone derivatives and benzaldehyde derivatives in aqueous ethanol (50%; 25 mL) and KOH (50% v/v), at room temperature for 24 h, [31–48]. The pyrazoline derivatives **18–33** were obtained by the reaction of chalcones **1–16** and 4-(hydrazinecarbonyl) benzenesulfonamide (**17**) [30] in *n*-butanol at reflux temperature for 24 h. The newly formed pyrazoline derivatives **18–33** were characterized by ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), and mass spectra (MS). The IR spectra of pyrazoline derivatives contained absorption bands (cm^{-1}) at approximately 3351–3208 (NH_2), 1701–1653 (C=O), and 1355–1333 and 1166–1139 (SO_2). The synthesized pyrazolines possessed characteristic peaks in the ^{1}H NMR spectrum at 3.12–3.26 and 3.88–3.96 ppm, recorded as doublet of doublet (dd) and quartet (q), these were assigned to the protons at the 4-position. Protons at the 5-position of pyrazoline rings are most likely to interact with 4-H protons, which was represented by a doublet of doublet signal peak at 5.73–5.81 ppm. In ^{13}C NMR, two characteristic signals were assigned for C-4 and C-5 of the pyrazoline moiety at values of approximately 42.0 and 61.0 ppm, respectively.

Interestingly, some of the synthesized pyrazolines formed two non-separable rotamers, as shown in ^{1}H NMR spectra at ambient temperatures [49–51] due to a slow rotation of the benzenesulfonamide fragment about the N−C=O bond of pyrazoline ring; compounds **18**, **19**, **21**, and **22** are representative examples. In this case, the ^{1}H NMR spectrum of pyrazoline **18** in DMSO at room temperature revealed a doubling of the benzenesulfonamide signals, indicating the presence of an *s-cis* rotamer and an *s-trans* rotamer [49–51]. The ^{1}H NMR spectrum indicated that the prominence of the *s-trans* rotamer compared with the *s-cis* rotamer, which may be attributable to the stability of the *s-trans* rotamer arising from the four hydrogen bonds between the aromatic hydrogen and carbonyl moiety and the nitrogen of pyrazoline ring as shown in Fig. 2. Moreover, the conformational analysis and energy optimization conducted with semiempirical Austin model 1 (AM1) [52], as implemented in the MOE 10.2008 software package [53], showed the occurrence of two isomeric rotamers (Fig. 2) with an energy



Scheme 1. Synthesis of the designed pyrazolines incorporating benzenesulfonamide.

difference of approximately 2.0 kcal/mol. Owing to this low barrier to rotation, both the *s-cis* and *s-trans* rotamer exist.

2.2. CA inhibitory activity

The CAI activity of the synthesized compounds **18–33** against the hCA I, II, IX, and XII isoforms was measured and compared with that of acetazolamide (AAZ), a standard sulfonamide inhibitor. With regard to the CAI activity for individual hCA isoforms, compounds **18–25** were found to be potent hCA I inhibitors, with inhibition constant (K_I) values of 87.8–244.1 nM, compared with AAZ (K_I, 250.0 nM). Compounds **26–30** showed modest hCA I inhibitory activity, with K_I values of 327.6–875.9 nM. In contrast, compounds **31–33** exhibited weak inhibitory activity, with K_Is of 2674.9–5359.9 nM. Similarly, hCA II was effectively inhibited by compounds **18–30**, with K_I values in the range of 31.7–123.1 nM in comparison with AAZ: (K_I, 12.5.0 nM), whereas compounds **30–33** showed weak inhibitory activity, with K_Is in the range of 352.2–722.8 nM. Compounds **19–24**, **26, 28–30,** and **32** exhibited influential hCA IX inhibitory activity, with K_I values of 5.5–44.5 nM, compared with AAZ (K_I, 25.0 nM). Compounds **18**, **25**, **27**, **31**, and **33** showed moderate hCA IX inhibitory activity, with K_I values of 51.1–72.1 nM. In comparison, against hCA XII, compounds **20–22** and **30** exerted activity similar to that of AAZ (K_I, 5.7 nM), with K_I values of 7.1–10.1 nM, whereas compounds **18**, **19**, **23–29**, and **31–33** had adequate hCA XII inhibitory activities, with K_I values in the range of 18.8–66.1 nM (Table 1).

2.3. Structure-activity relationship analysis

(I) The structure-activity relationship analysis for hCA I inhibition indicated that: 1) the introduction of electron withdrawing groups, such as a fluoro group, at the 3-phenyl/5-phenyl ring of compound **18** (K_I 184.9 nM) produced 4-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**20**), 4-(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl) benzenesulfonamide (**21**), and 4-(3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**22**) with strongly increased CAI activities (K_Is, 87.8, 102.9, and 140.7 nM respectively); additionally, the 4-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**20**) (K_I,

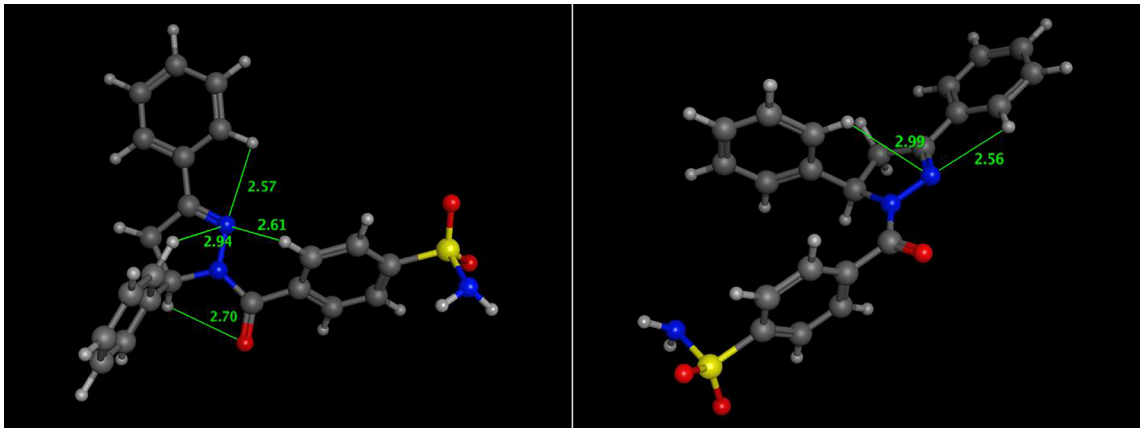


Fig. 2. The left panel shows the most energy stable *s-trans* rotamer and the right panel shows the lowest stable *s-cis* rotamer. Hydrogen bonds are shown as green lines.

Table 1
Inhibition data for human carbonic isoforms (hCA) I, II, IX, and XII with pyrazolines **18–33** and the standard inhibitor acetazolamide (**AAZ**) by a stopped flow CO_2 hydrase assay [54].

Compound	K_I* (nM)			
	CA I	CA II	CA IX	CA XII
18	184.9	81.3	55.6	53.2
19	195.0	52.8	7.9	34.0
20	87.8	57.6	44.5	9.4
21	102.9	31.7	23.1	10.1
22	140.7	41.9	5.5	7.1
23	124.2	69.9	26.8	66.1
24	226.2	85.3	42.3	62.3
25	244.1	57.6	65.5	22.1
26	704.8	70.8	19.6	44.2
27	327.6	69.7	72.1	33.8
28	430.1	65.1	30.2	47.2
29	875.9	94.6	37.0	18.8
30	807.8	123.1	32.9	9.7
31	2674.9	352.2	51.1	35.5
32	2961.3	611.0	36.3	28.9
33	5359.9	722.8	58.7	46.1
AAZ	250	12.5	25	5.7

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

87.8 nM) was more active than the corresponding 4-(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**21**) (K_I, 102.9 nM), whereas the introduction of a chloro group at the 5-phenyl ring produced 4-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**19**) with a neglected decrease the CAI activity (K_I, 195.0 nM); 2) the introduction of electron donating groups, such as the methyl group, on the 5-phenyl ring of compound **18** produced 4-(3-phenyl-5-(4-methylphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**23**), which had significantly improved CAI potency (K_I, 124.2), whereas the introduction of methyl groups on both the 3-phenyl and 5-phenyl rings of compound **18** produced 4-(3,5-bis-(4-methylphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**24**), which showed a minor decrease in CAI activity (K_I, 226.2); 3) the introduction of hydroxy or methoxy groups on the 5-phenyl ring of compound **18** produced 4-(5-(2-hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**25**), 4-(5-(2-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**27**), and 4-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**28**), which showed mild decreases in CAI activities (K_Is, 244.1, 327.6, and 430.1 nM, respectively); 4) the introduction of disubstituted methoxy groups on the 3-phenyl/5-phenyl ring of compound **18** produced 4-(5-(3,4-methylenedioxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**26**), 4-(3,5-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**29**), and 4-(3-(2,4-dimethoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**30**), which showed moderate decreases in CAI activities (K_Is, 704.8, 875.9, and 807.8 nM, respectively), whereas the introduction of polysubstituted methoxy groups on the 3-phenyl/5-phenyl ring of compound **18** produced compounds **31–33**, which had sharply decreased CAI activities (K_Is, 2674.9, 2961.3, and 5359.9 nM, respectively).

(II) The structure-activity relationship analysis for hCA II inhibition indicated that: 1) the introduction of electron withdrawing or donating groups such as chloro, fluoro, methyl, hydroxy, or methoxy groups at the 3-phenyl or 5-phenyl ring of compound **18** (K_I, 81.3 nM) produced compounds **19–28** with significantly improved CAII potency (K_Is, 31.7–85.3 nM); 2) the introduction of dimethoxy and polymethoxy groups at the 3-phenyl or 5-phenyl ring of compound **18** produced compounds **29–33** with significantly decreased CAI potency (K_Is, 94.6–722.8 nM); 3) 4-(3-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**21**) (K_I, 31.7 nM) is more active than 4-(5-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**20**) (K_I, 57.6 nM); 4) 4-(3-(4-fluorophenyl)-5-phenyl derivative **21** (K_Is, 31.7 nM) and 4-(5-(4-methylphenyl)-3-phenyl derivative **23** (K_Is, 69.9 nM) are more active than the corresponding disubstituted derivatives such as compounds **22** (K_Is, 41.9 nM) and **24** (K_Is, 85.3 nM).

(III) The structure-activity relationship analysis for hCA IX inhibition indicated that: 1) substituted 3-phenyl/5-phenyl derivatives **19–33** (K_Is, 5.5–72.1 nM) were almost equivalent or even greater than that of parent compound **18** (K_I, 55.6 nM); 2) 4-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**19**) (K_I, 7.9 nM) was more active than other substituted 3-phenyl/substituted 5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamides **20–33** (K_Is, 19.6–72.1 nM), except 4-(3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**22**) (K_I, 5.5 nM); 3) the 4-(3,5-bis(4-fluorophenyl) derivative **22** (K_I, 5.5 nM) was more active than the 3-(4-fluorophenyl)-5-phenyl/5-(4-fluorophenyl)-3-phenyl derivatives **20** and **21** and the corresponding 4-(3,5-bis(4-methylphenyl)/4-(3,5-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamides **24** and **29** (K_Is, 44.4, 23.1, 42.3, and 37.0 nM, respectively); 5) the 4-(3-(4-fluorophenyl)/4-(3-(4-methoxyphenyl) derivatives **21** and **28** (K_Is, 23.1 and 30.2 nM, respectively) were more active than the corresponding 4-(5-(4-fluorophenyl)/4-(5-(4-methoxyphenyl) derivatives **20** and **27** (K_Is, 44.5 and 72.1 nM, respectively); 6) 3,4-methylenedioxyphenyl derivative **26** (K_I, 19.6 nM), showed more potent CAI activity than the methoxy derivatives, such as compound **25** (K_I, 65.5 nM).

(IV) The structure-activity relationship analysis for hCA XII inhibition indicated that: 1) 4-(3,5-bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (**22**) (K_I, 5.5 nM) was more active than the 4-(5-(4-fluorophenyl)-3-phenyl/4-(3-(4-fluorophenyl)-5-phenyl derivatives **20** and **21** (K_Is, 9.4 and 10.1 nM); 2) the 4-(3,5-bis(4-methylphenyl) derivative **24** (K_I, 62.3 nM) was slightly more potent than the 4-(3-phenyl-5-(4-methylphenyl) derivative **23** (K_I, 66.1 nM); 3) the 4-(5-(2-hydroxyphenyl)-3-phenyl derivative **25** (K_I, 22.1 nM) was stronger than the 3,4-methylenedioxyphenyl derivative **26** (K_I, 44.2 nM) and the 4-(5-(2-methoxyphenyl)-3-phenyl derivative **27** (K_I, 33.8 nM); 4) the 4-(5-(2-methoxyphenyl)-3-phenyl derivative **27** (K_I, 33.8 nM) was more potent than the corresponding 4-(5-(4-methoxyphenyl)-3-phenyl derivative **28** (K_I, 47.2 nM); 5) the 4-(3,5-bis(4-methoxyphenyl) derivative **29** (K_I, 18.8 nM) showed lower CA XII inhibition than the corresponding 4-(3-(2,4-dimethoxyphenyl)-5-phenyl derivative **30** (K_I, 9.7 nM).

3. Conclusion

A series of new substituted pyrazole-conjugated benzenesulfonamides **18–33** were synthesized. They were evaluated for *in vitro* CA inhibition in comparison with acetazolamide (AAZ), a reference inhibitor. Compounds **18–25** showed strong inhibitory activities against hCA I (K_Is, 87.8–244.1 nM) compared to that of AAZ (K_I, 250.0 nM). The hCA I isoform was relatively inhibited by compounds **26–30** (K_Is, 327.6–875.9 nM), whereas compounds **31–33** exhibited mild inhibitory activity (K_Is, 2674.9–5359.9 nM). Compounds **18–30**, showed moderate inhibitory action towards hCA II (K_Is, 31.7–123.1 nM), whereas compounds **31–33** exhibited weaker inhibitory activity (K_Is, 352.2–722.8 nM) that was comparable with AAZ (K_I, 12.5 nM). Compounds **19**, **21–23**, **26**, **28–30**, and **32** exhibited potent hCA IX inhibitory activity with K_I values ranging between 5.5 and 37.0 nM,

which were stronger than or similar to that of AAZ (K_I, 25.0 nM), whereas compounds **18**, **20**, **24**, **25**, **27**, **31**, and **33** were moderately effective inhibitors (K_Is, 42.3–72.1 nM). Similarly, compounds **20–22**, and **30** exercised potent hCA XII inhibitory activities (K_Is, 7.1–10.1 nM) representing similarly analogous CAI activities compared with those of AAZ (K_I, 5.7 nM), whereas compounds **18**, **19**, **23–29**, and **31–33** were effective inhibitors, with K_I values in the range of 18.8–66.1 nM.

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). The IR spectra were recorded using an FT-IR Perkin-Elmer spectrometer (PerkinElmer Inc., Waltham, MA, USA). The NMR spectra were measured in DMSO-d_6 using Bruker 500 and 700 MHz instruments (Bruker, Billerica, MA, USA), with TMS as an internal standard. The 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 of College of Pharmacy, King Saud University, Saudi Arabia. The results were within ± 0.4% of the theoretical values. Chalcones **1–16** were prepared by Claisen-Schmidt condensation in accordance with the reported procedure [31–48]. 4-(Hydrazinecarbonyl)benzenesulfonamide (**17**) was prepared according to our previous report [30].

4.1.1. General procedure for the synthesis of triarylpyrazolines 18–33 (Scheme 1)

To the solution of the appropriate chalcone **1–16** (5 mmol) in 10 mL of *n*-butanol, 4-(hydrazinecarbonyl)benzenesulfonamide (**17**) (5 mmol) was added; the reaction mixture was refluxed for 24 h and the reaction was monitored by TLC. Subsequently, the reaction mixture was cooled, and the obtained precipitate was filtered, dried, and recrystallized from an appropriate solvent to produce the target pyrazoline derivatives **18–33**.

4.1.1.1. 4-(3,5-Diphenyl-4,5-dihydro-1H-pyrazole-1-carbonyl) benzenesulfonamide (18).

M.P. 350–352 °C, 67% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3315, 3213 (NH_2), 1685 (C═O), 1618 (C═N), 1345, 1160 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.23 (1H, dd, J = 18.2 Hz, 4.8 Hz), 3.96 (1H, q, J = 6.2 Hz), 5.80 (1H, dd, J = 16.4 Hz, 6.9 Hz), 7.30 (1H, t, J = 7.1 Hz), 7.35 (2H, d, J = 7.6 Hz), 7.38 (2H, t, J = 7.4 Hz), 7.45–7.49 (3H, m), 7.55, 7.58 (2H, s), 7.73 (2H, d, J = 7.0 Hz), 7.96, 7.99 (2H, d, J = 8.1 Hz, 8.2 Hz), 8.04, 8.10 (2H, d, J = 8.1 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ 42.21, 61.07, 125.64, 126.07, 126.38, 127.34, 127.92, 128.70, 129.30, 130.42, 131.09, 131.26, 138.15, 142.51, 146.17, 156.53, 164.85; $C_{22}H_{19}N_3O_3S$: *m/z* (405.4).

4.1.1.2. 4-(5-(4-Chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (19).

M.P. 346–348 °C, 77% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3315, 3214 (NH_2), 1680 (C═O), 1619 (C═N), 1339, 1155 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.25 (1H, dd, J = 18.0 Hz, 4.9 Hz), 3.96 (1H, q, J = 6.2 Hz), 5.81 (1H, dd, J = 16.5 Hz, 6.7 Hz), 7.38 (2H, d, J = 8.1 Hz), 7.44–7.49 (5H, m), 7.54, 7.57 (2H, s), 7.73 (2H, d, J = 7.1 Hz), 7.95, 7.98 (2H, d, J = 8.0 Hz), 8.03, 8.09 (2H, d, J = 8.0 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ 41.96, 60.53, 125.62, 126.37, 127.37, 128.20, 128.67, 129.24, 129.31, 130.43, 131.14, 131.18, 132.44, 137.97, 141.41, 146.22, 156.57, 164.87; $C_{22}H_{18}ClN_3O_3S$: *m/z* (439.9).

4.1.1.3. 4-(5-(4-Fluorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (20).

M.P. 375–377 °C, 80% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3314, 3210 (NH_2), 1701 (C═O), 1620 (C═N), 1340, 1157 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.24 (1H, dd, J = 17.5 Hz, 4.4 Hz), 3.95 (1H, q, J = 5.7 Hz), 5.81 (1H, t, J = 6.7 Hz), 7.21 (1H, d, J = 7.4 Hz), 7.40 (1H, s), 7.47 (3H, s), 7.53 (1H, s), 7.57 (2H, s), 7.73 (2H, s), 7.95 (1H, s), 7.98 (1H, d, J = 8.0 Hz), 8.02 (2H, d, J = 7.1 Hz), 8.09 (1H, d, J = 7.3 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ 42.08, 60.45, 115.96, 116.08, 125.61, 126.37, 127.35, 128.28, 128.32, 128.69, 129.31, 130.41, 131.13, 131.21, 138.06, 138.65, 146.17, 156.55, 161.18, 162.56, 164.89; $C_{22}H_{18}FN_3O_3S$: *m/z* (423.4).

4.1.1.4. 4-(3-(4-Fluorophenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (21).

M.P. 326–328 °C, 78% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3317, 3211 (NH_2), 1701 (C═O), 1630 (C═N), 1335, 1156 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.24 (1H, dd, J = 18.0 Hz, 4.5 Hz), 3.96 (1H, q, J = 6.1 Hz), 5.80 (1H, dd, J = 15.9 Hz, 7.1 Hz), 7.31 (3H, q, J = 8.6 Hz), 7.34 (2H, d, J = 7.4 Hz), 7.38 (2H, d, J = 7.2 Hz), 7.54, 7.57 (2H, s), 7.79 (2H, d, J = 6.5 Hz), 7.94, 7.98 (2H, d, J = 7.7 Hz, 7.5 Hz), 8.02, 8.09 (2H, d, J = 7.7 Hz, 7.5 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ 42.28, 61.17, 116.35, 116.47, 125.63, 126.08, 126.37, 127.90, 127.93, 128.69, 129.30, 129.73, 129.78, 130.38, 138.12, 142.45, 146.16, 155.64, 163.16, 164.57, 164.86; $C_{22}H_{18}FN_3O_3S$: *m/z* (423.3).

4.1.1.5. 4-(3,5-Bis(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl) benzenesulfonamide (22).

M.P. 313–315 °C, 71% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) ν: 3320, 3219 (NH_2), 1701 (C═O), 1621 (C═N), 1340, 1157 (O═S═O); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.26 (1H, d, J = 18.3 Hz), 3.94 (1H, q, J = 4.9 Hz), 5.81 (1H, d, J = 7.0 Hz), 7.21 (2H, d, J = 9.0 Hz), 7.32 (2H, d, J = 8.9 Hz), 7.40 (2H, d, J = 6.0 Hz), 7.52, 7.55 (2H, s), 7.79 (2H, d, J = 6.7 Hz), 7.93, 7.98 (2H, d, J = 7.2, 6.3 Hz), 8.01, 8.09 (2H, d, J = 8.2, 6.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 42.16, 60.56, 115.96, 116.08, 116.36, 116.48, 125.62, 126.37, 128.28, 128.32, 128.69, 129.75, 129.79, 130.38, 138.04, 138.56, 146.13, 147.33, 155.72, 161.19, 162.57, 163.18, 164.60, 164.94, 165.43; $C_{22}H_{17}F_2N_3O_3S$: *m/z* (441.45).

4.1.1.6. 4-(3-Phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazole-1-carbonyl) benzenesulfonamide (23).

M.P. 298–300 °C, 72% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3312, 3207 (NH_2), 1654 (C═O), 1609 (C═N), 1341, 1161 (O═S═O); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.28 (3H, s), 3.20 (1H, dd, J = 18.0 Hz, 4.8 Hz), 3.94 (1H, q, J = 6.3 Hz), 5.75 (1H, dd, J = 16.4 Hz, 6.9 Hz), 7.17 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.0 Hz), 7.44–7.48 (3H, m), 7.52 (2H, s), 7.72 (2H, dd, J = 9.2 Hz, 5.8 Hz), 7.94 (2H, d, J = 8.3 Hz), 8.01 (2H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.13, 42.15, 60.84, 125.61, 126.04, 127.30, 129.31, 129.79, 130.37, 131.07, 131.29, 137.10, 138.20, 139.56, 146.10, 156.52, 164.78; $C_{23}H_{21}N_3O_3S$: *m/z* (419.5).

4.1.1.7. 4-(3,5-Bis-(p-tolyl)-4,5-dihydro-1H-pyrazole-1-carbonyl) benzenesulfonamide (24).

M.P. 179–181 °C, 72% yield (CH_3OH); IR (KBr, cm^{-1}) ν: 3329, 3230 (NH_2), 1684 (C═O), 1630 (C═N), 1355, 1159 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): δ 2.28 (3H, s), 2.33 (3H, s), 3.16 (1H, dd, J = 18.0 Hz, 4.6 Hz), 3.90 (1H, q, J = 6.2 Hz), 5.73 (1H, dd, J = 16.1 Hz, 7.0 Hz), 7.17 (2H, d, J = 7.8 Hz), 7.20 (2H, d, J = 7.7 Hz), 7.38 (2H, d, J = 7.8 Hz), 7.53 (2H, s), 7.78 (2H, d, J = 7.8 Hz), 7.93 (2H, d, J = 8.0 Hz), 8.00 (2H, d, J = 8.0 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): δ 21.12, 21.56, 42.18, 60.72, 121.42, 125.60, 126.01, 127.29, 129.11, 129.37, 129.83, 130.03, 130.35, 132.46, 135.58, 137.07, 138.27, 139.62, 141.12, 144.01, 144.22, 156.55, 164.66; $C_{24}H_{23}N_3O_3S$: *m/z* (433.5).

4.1.1.8. 4-(5-(2-Hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide (25).

M.P. 306–308 °C, 71% yield (CH_3CH_2OH); ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.12 (1H, dd, J = 17.7 Hz, 3.3 Hz), 3.90 (1H, q, J = 5.5 Hz), 5.89 (1H, dd, J = 14.7 Hz, 7.8 Hz), 6.77 (1H, t, J = 7.1 Hz), 6.88 (1H, d,

J = 7.9 Hz), 7.05 (1H, d, *J* = 7.4 Hz), 7.11 (1H, t, *J* = 7.4 Hz), 7.45 (3H, d, *J* = 6.9 Hz), 7.53 (2H, s), 7.71 (2H, d, *J* = 6.8 Hz), 7.95 (2H, d, *J* = 7.6 Hz), 8.03 (2H, d, *J* = 7.5 Hz), 9.79 (1H, s); ^{13}C NMR (176 MHz, DMSO-d_6): *δ* 40.93, 57.26, 115.98, 119.43, 125.60, 127.22, 127.77, 128.79, 129.27, 130.38, 130.93, 131.50, 138.41, 146.04, 154.68, 156.93, 164.67; $C_{22}H_{19}N_3O_4S$: *m/z* (421.4).

4.1.1.9. 4-(5-(3,4-Methylenedioxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide ***(26)***. M.P. 322–324 °C, 65% yield (CH_3CH_2OH); IR (KBr, cm^{-1}) *ν*: 3321, 3218 (NH_2), 1675 (C═O), 1618 (C═N), 1335, 1161 (O═S═O); ^{1}H NMR (500 MHz, DMSO-d_6): *δ* 3.22 (1H, dd, *J* = 18.1 Hz, 4.9 Hz), 3.91 (1H, q, *J* = 6.3 Hz), 5.72 (1H, dd, *J* = 16.5 Hz, 6.7 Hz), 6.00 (2H, s), 6.83 (1H, d, *J* = 7.9 Hz), 6.89 (2H, d, *J* = 7.8 Hz), 7.44–7.48 (3H, m), 7.53 (2H, s), 7.72 (2H, dd, *J* = 7.5 Hz, 1.7 Hz), 7.94, 7.97 (2H, d, *J* = 8.3 Hz, 8.4 Hz), 8.02, 8.09 (2H, d, *J* = 8.3 Hz, 8.4 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): *δ* 42.18, 60.90, 101.56, 106.71, 108.88, 119.52, 126.37, 127.36, 128.66, 129.33, 130.45, 131.09, 131.34, 136.45, 138.22, 146.16, 147.02, 148.10, 156.53, 164.90; $C_{23}H_{19}N_3O_5S$: *m/z* (449.4).

4.1.1.10. 4-(5-(2-Methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide ***(27)***. M.P. 338–340 °C, 79% yield (CH_3OH); IR (KBr, cm^{-1}) *ν*: 3351, 3261 (NH_2), 1688 (C═O), 1627 (C═N), 1333, 1166 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): *δ* 3.17 (1H, d, *J* = 17.3 Hz), 3.79 (3H, s), 3.96 (1H, q, *J* = 6.0 Hz), 5.77 (1H, d, *J* = 10.1 Hz), 7.00 (2H, d, *J* = 8.1 Hz), 7.27–7.32 (3H, m), 7.38 (2H, d, *J* = 7.5 Hz), 7.52, 7.56 (2H, s), 7.66 (2H, d, *J* = 8.0 Hz), 7.93, 7.97 (2H, d, *J* = 7.5, 7.9 Hz), 8.01, 8.07 (2H, d, *J* = 7.5, 7.8 Hz); $C_{23}H_{21}N_3O_4S$: *m/z* (435.4).

4.1.1.11. 4-(5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide ***(28)***. M.P. 286–288 °C, 87% yield (CH_3OH); IR (KBr, cm^{-1}) *ν*: 3319, 3208 (NH_2), 1670 (C═O), 1621 (C═N), 1339, 1155 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): *δ* 3.17 (1H, d, *J* = 17.3 Hz), 3.79 (3H, s), 3.96 (1H, q, *J* = 6.0 Hz), 5.77 (1H, d, *J* = 10.1 Hz), 7.00 (2H, d, *J* = 8.1 Hz), 7.27–7.32 (3H, m), 7.38 (2H, d, *J* = 7.5 Hz), 7.52, 7.56 (2H, s), 7.66 (2H, d, *J* = 8.0 Hz), 7.93, 7.97 (2H, d, *J* = 7.5, 7.9 Hz), 8.01, 8.07 (2H, d, *J* = 7.5, 7.8 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): *δ* 42.28, 55.83, 60.90, 114.75, 123.69, 125.58, 125.98, 126.37, 127.89, 128.68, 129.05, 129.29, 130.35, 135.77, 138.29, 142.54, 145.99, 147.31, 156.37, 161.63, 164.62, 165.41; $C_{23}H_{21}N_3O_4S$: *m/z* (435.5).

4.1.1.12. 4-(3,5-Bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide ***(29)***. M.P. 290–292 °C, 84% yield (CH_3OH); IR (KBr, cm^{-1}) *ν*: 3323, 3210 (NH_2), 1665 (C═O), 1627 (C═N), 1340, 1156 (O═S ═O); ^{1}H NMR (700 MHz, DMSO-d_6): *δ* 3.18 (1H, d, *J* = 17.7 Hz), 3.74 (3H, s), 3.80 (3H, s), 3.96 (1H, q, *J* = 6.1 Hz), 5.72 (1H, d, *J* = 10.8 Hz), 6.93 (2H, d, *J* = 7.5 Hz), 7.01 (2H, d, *J* = 7.6 Hz), 7.25 (2H, d, *J* = 7.5 Hz), 7.52 (2H, s), 7.67 (2H, d, *J* = 7.7 Hz), 7.93 (2H, d, *J* = 7.5 Hz), 7.99 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): *δ* 42.18, 55.56, 55.83, 60.39, 114.56, 114.73, 123.81, 125.56, 127.42, 129.02, 130.33, 134.61, 138.39, 146.00, 156.30, 158.99, 161.59, 164.49; $C_{24}H_{23}N_3O_5S$: *m/z* (465.5).

4.1.1.13. 4-(3-(2,4-Dimethoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide ***(30)***. M.P. 254–256 °C, 81% yield (CH_3OH); IR (KBr, cm^{-1}) *ν*: 3331, 3209 (NH_2), 1675 (C═O), 1618 (C═N), 1338, 1159 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): *δ* 3.17 (1H, dd, *J* = 18.4 Hz, 4.5 Hz), 3.80 (3H, s), 3.81 (3H, s), 3.95 (1H, q, *J* = 6.7 Hz), 5.70 (1H, dd, *J* = 16.1 Hz, 7.0 Hz), 6.61 (1H, dd, *J* = 8.7 Hz, 2.1 Hz), 6.64 (1H, d, *J* = 2.1 Hz), 7.29 (3H, q, *J* = 7.5 Hz), 7.37 (2H, t, *J* = 7.5 Hz), 7.51, 7.56 (2H, s), 7.65 (1H, d, *J* = 8.6 Hz), 7.92, 7.98 (2H, d, *J* = 8.3 Hz), 8.04, 8.08 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): *δ* 45.29, 55.96, 56.30, 60.52, 99.12, 106.79, 112.70, 125.49, 125.90, 126.37, 127.78, 128.68, 129.27, 130.47, 130.54, 138.29, 142.81, 146.00, 147.37, 155.38, 160.06, 163.06; $C_{24}H_{23}N_3O_5S$: *m/z* (465.5).

4.1.1.14. 4-(3-(2,4-Dimethoxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide ***(31)***. M.P. 271–273 °C, 88% yield (CH_3OH); IR (KBr, cm^{-1}) *ν*: 3328, 3218 (NH_2), 1668 (C═O), 1619 (C═N), 1335, 1161 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): *δ* 3.16 (1H, dd, *J* = 18.4 Hz, 4.4 Hz), 3.73 (3H, s), 3.80 (3H, s), 3.81 (3H, s), 3.90 (1H, q, *J* = 6.7 Hz), 5.64 (1H, dd, *J* = 15.7 Hz, 7.2 Hz), 6.60 (1H, d, *J* = 8.6 Hz), 6.63 (1H, S), 6.91 (2H, d, *J* = 8.4 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 7.50, 7.56 (2H, s), 7.62 (1H, d, *J* = 8.6 Hz), 7.90, 7.96 (2H, d, *J* = 8.1 Hz), 8.00, 8.07 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): *δ* 45.21, 55.55, 55.95, 56.29, 59.99, 99.11, 106.76, 112.78, 114.56, 125.47, 126.36, 127.26, 128.67, 130.41, 130.54, 134.79, 138.40, 145.89, 155.53, 158.93, 160.05, 163.04, 164.30; $C_{25}H_{25}N_3O_6S$: *m/z* (495.5).

4.1.1.15. 4-(3-(2,4-Dimethoxyphenyl)-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide ***(32)***. M.P. 274–276 °C, 85% yield (CH_3OH); IR (KBr, cm^{-1}) *ν*: 3313, 3214 (NH_2), 1685 (C═O), 1625 (C═N), 1340, 1139 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): *δ* 3.19 (1H, d, *J* = 18.3 Hz), 3.73 (3H, s), 3.75 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.90 (1H, q, *J* = 9.8 Hz), 5.65 (1H, d, *J* = 11.0 Hz), 6.60 (1H, d, *J* = 8.0 Hz), 6.65 (1H, s), 6.79 (1H, d, *J* = 7.1 Hz), 6.92 (2H, d, *J* = 11.1 Hz), 7.51, 7.57 (2H, s), 7.63 (1H, d, *J* = 7.9 Hz), 7.92, 7.98 (2H, d, *J* = 6.8 Hz, 7.0 Hz), 8.03, 8.09 (2H, d, *J* = 6.4 Hz, 6.5 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): *δ* 45.28, 55.95, 56.30, 60.28, 60.83, 99.13, 106.75, 110.01, 112.49, 112.85, 117.55, 125.51, 126.37, 128.68, 130.41, 130.52, 135.23, 138.46, 145.95, 148.46, 149.29, 155.47, 160.04, 163.02, 164.37; $C_{26}H_{27}N_3O_7S$: *m/z* (525.5).

4.1.1.16. 4-(3-(3,4-Dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)benzenesulfonamide ***(33)***. M.P. 280–282 °C, 79% yield (CH_3OH); IR (KBr, cm^{-1}) *ν*: 3312, 3208 (NH_2), 1653 (C═O), 1615 (C═N), 1341, 1161 (O═S═O); ^{1}H NMR (700 MHz, DMSO-d_6): *δ* 3.28 (1H, d, *J* = 17.9 Hz, 4.7 Hz), 3.64 (3H, s), 3.75 (6H, s), 3.78 (3H, s), 3.80 (3H, s), 3.88 (1H, q, *J* = 9.8 Hz), 5.73 (1H, d, *J* = 11.4 Hz, 4.8 Hz), 6.60 (2H, s), 7.02 (1H, d, *J* = 8.3 Hz), 7.26 (1H, s), 7.29 (1H, d, *J* = 8.3 Hz), 7.53 (2H, s), 7.95 (2H, d, *J* = 7.8 Hz), 8.07 (2H, d, *J* = 7.8 Hz); ^{13}C NMR (176 MHz, DMSO-d_6): *δ* 42.36, 55.96, 56.08, 56.33, 60.39, 61.17, 102.91, 110.23, 112.02, 121.00, 123.86, 125.61, 130.47, 136.99, 138.26, 138.33, 146.13, 149.14, 151.45, 153.62, 156.56, 164.64; $C_{27}H_{29}N_3O_8S$: *m/z* (555.6).

4.2. Carbonic anhydrase inhibition

The SX.18MV-R stopped-flow instrument (Applied Photophysics, Oxford, UK) was used to assay the inhibition of various CA isozymes, using previously reported methods [30,54].

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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.2019.03.052.

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