Accepted Manuscript

Design and synthesis of novel benzenesulfonamide containing 1,2,3-triazoles as potent human carbonic anhydrase isoforms I, II, IV and IX inhibitors

Rajiv Kumar, Lalit Vats, Silvia Bua, Claudiu T. Supuran, Pawan K. Sharma

PII: S0223-5234(18)30512-9

DOI: 10.1016/j.ejmech.2018.06.021

Reference: EJMECH 10491

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 9 February 2018

Revised Date: 5 June 2018

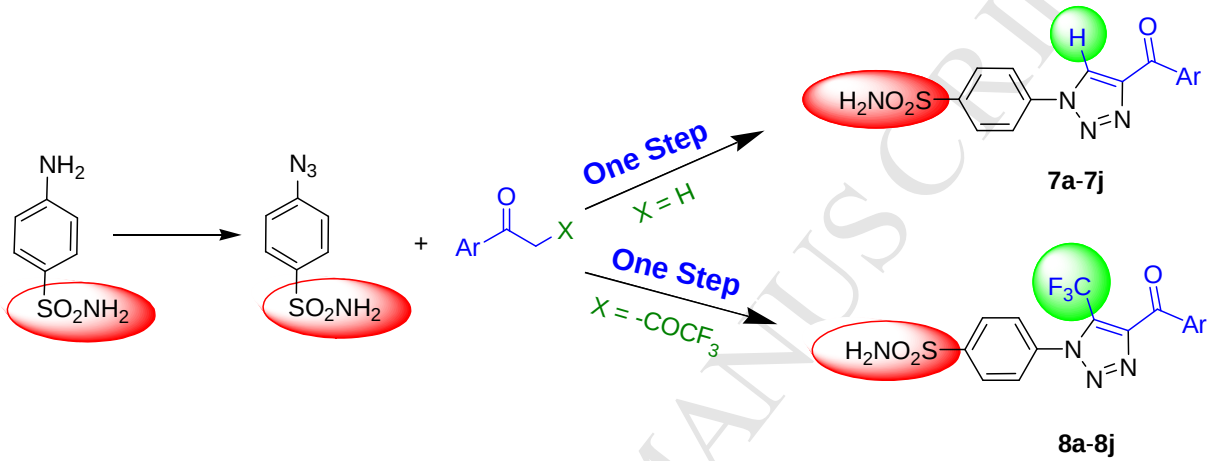
Accepted Date: 7 June 2018

Please cite this article as: R. Kumar, L. Vats, S. Bua, C.T. Supuran, P.K. Sharma, Design and synthesis of novel benzenesulfonamide containing 1,2,3-triazoles as potent human carbonic anhydrase isoforms I, II, IV and IX inhibitors, *European Journal of Medicinal Chemistry* (2018), doi: 10.1016/j.ejmech.2018.06.021.

Design and synthesis of novel benzenesulfonamide containing 1,2,3-triazoles as potent human carbonic anhydrase isoforms I, II, IV and IX inhibitors

Rajiv Kumar, Lalit Vats, Silvia Bua, Claudiu T. Supuran, Pawan K. Sharma

Graphical Abstract



7a-7j, 8a-8j K_i (nM) ≤ 86.8 against hCA I

7b, 7d-7e, 8d-8f, 8j K_i (nM) < 50 against hCA II

7b-7e, 8d-8f K_i (nM) ≤ 95.8 against hCA IV

7d-7f, 8a, 8d-8f, 8i K_i (nM) ≤ 48.2 against hCA IX

Design and synthesis of novel benzenesulfonamide containing 1,2,3-triazoles as potent human carbonic anhydrase isoforms I, II, IV and IX inhibitors

Rajiv Kumar[a], Lalit Vats[a], Silvia Bua[b], Claudiu T. Supuran[b*], Pawan K. Sharma[a*]

[a]Department of Chemistry, Kurukshetra University, Kurukshetra-136119, India.

[b]Università degli Studi di Firenze, Laboratorio di Chimica Bioinorganica, Rm 188, and Neurofarba Department, Sezione di Scienze Farmaceutiche, Via U. Schiff 6, I-50019 Sesto Fiorentino (Firenze), Italy.

*Corresponding authors: Tel.: +91 9416457355; Fax: +91 1744 238277; e-mail: pksharma@kuk.ac.in (PKS); Tel/Fax: +39-055-4573005, e-mail: claudiu.supuran@unifi.it (CTS)

Abstract

In a quest to discover new biologically active compounds, a series of twenty novel heterocyclic derivatives substituted at position 5 with -H (**7a-7j**) or -CF_3 (**8a-8j**), bearing benzenesulfonamide at N-1 position and various aroyl groups at position 4 of the 1,2,3-triazole ring was synthesized and screened for their carbonic anhydrase (CA, EC 4.2.1.1) inhibition potential against four human (h) isoforms hCA I, II, IV and IX. All the compounds (**7a-7j** and **8a-8j)** were synthesized via [3+2] cycloaddition reaction from 4-azidobenzenesulfonamide. Interestingly, compounds **7a-7j** were prepared in one pot manner via enaminone intermediate using novel methodology. All the newly synthesized compounds (**7a-7j** & **8a-8j**) were found to be excellent inhibitors of edema related isoform hCA I with their inhibition constant (K_i) ranging from 30.1-86.8 nM as compared to standard drug acetazolamide (AAZ) with K_i = 250 nM. Further it was found that most of tested compounds were weaker inhibitors of isoform, hCA II although compounds **7b**, **7d**-**7e**, **8a**, **8d**-**8f**, **8i** (mostly with electron withdrawing substituents) have shown better inhibition potential (Ki < 50 nM). Against glaucoma associated hCA IV, compound **7d** was found to be better inhibitor (Ki = 52.4 nM) than AAZ (Ki = 74 nM) while against tumor associated hCA IX, all the compounds have shown moderate inhibition potential. Present study have added one more step in exploring the 1,2,3-triazlole moiety in the medicinal field.

Keywords: 1,2,3-Triazoles, Benzenesulfonamide, Carbonic anhydrase isoforms I, II, IV, IX, Acetazolamide, Enaminones.

1. Introduction

Compounds having 1,2,3-triazole scaffold have received considerable attention due to their association with diverse biological activities including anticancer [1,2], antimicrobial [3], antiproliferative [4], antimalarial [5], antibacterial [6], antitubercular [7] etc. In addition, primary sulfonamides constitute an important pharmacophore in many leading classes of drugs with several types of pharmacological activities [8-12]. Acetazolamide (AAZ), methazolamide (MZA), ethoxzolamide (EZA), celecoxib (CLX) etc. (Fig. 1) are well known clinically used drugs bearing sulfonamide groups cutting across different therapeutic areas [13,14]. These are also established as strong carbonic anhydrase (CA, EC 4.2.1.1) inhibitors, but may have many side effects. Carbonic anhydrases, widespread zinc metalloenzymes, mainly known to catalyze the reversible hydration of carbon dioxide to bicarbonate and protons ($CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$) [15,16], exist in seven unrelated gene families known till date: the α, β, γ, δ, ζ, η and ɵ-CAs [17-19]. Various CA isoforms play vital roles in many physiological processes like respiration, electrolyte secretion in variety of tissues/organs, biosynthetic reactions (i.e. lipogenesis, glucogenesis and ureagenesis), bone resorption, calcification etc. [20,21]. However the overexpression and sluggishness of various CA isoforms are responsible for many diseases in mammals. Out of sixteen human associated α-CA isoforms, hCA I is involved in retinal and cerebral edema while hCA II is associated with glaucoma, edema, epilepsy, and altitude sickness [16,22]. Overactivity of hCA IV is associated with glaucoma, retinitis pigmentosa and stroke while hCA IX, a transmembrane isoform, is over-expressed in many tumors, and known to be associated with cancer progression [16,23,24]. Therefore, selective inhibition of some isoforms over others is highly desired for targeting particular therapeutic areas with minimum side effects.

Recently our group reported some benzenesulfonamide bearing 1,4,5-trisubstituted-1,2,3-triazole scaffolds (**1-5**) as hCA I, II, IV and IX inhibitors (Fig. 1) [25]. Most of these 1,2,3-triazole derivatives have shown excellent inhibitory potency against hCA isoforms II, IV and IX. Furthermore, 1,2,3-triazole ring bearing sulfocoumarin **6** (Fig. 1) and other derivatives have been reported as potent isoform-selective inhibitors of tumor-associated carbonic anhydrases [26]. In the light of these facts and inspired by our previous work in the field of designing various classes of heterocyclic compounds of potential medicinal interest [27-35], we planned to synthesize some novel 5-substituted 4-aroyl-1-aryl-1,2,3-triazoles **7a-7j** and **8a-8j** bearing primary sulfonamide group on the phenyl ring at N-1position and -CF_3/-H group at C-5 position of 1,2,3-

triazole ring for evaluating their CA inhibitory profile against isoforms hCA I, II, IV and IX (Fig. 1).

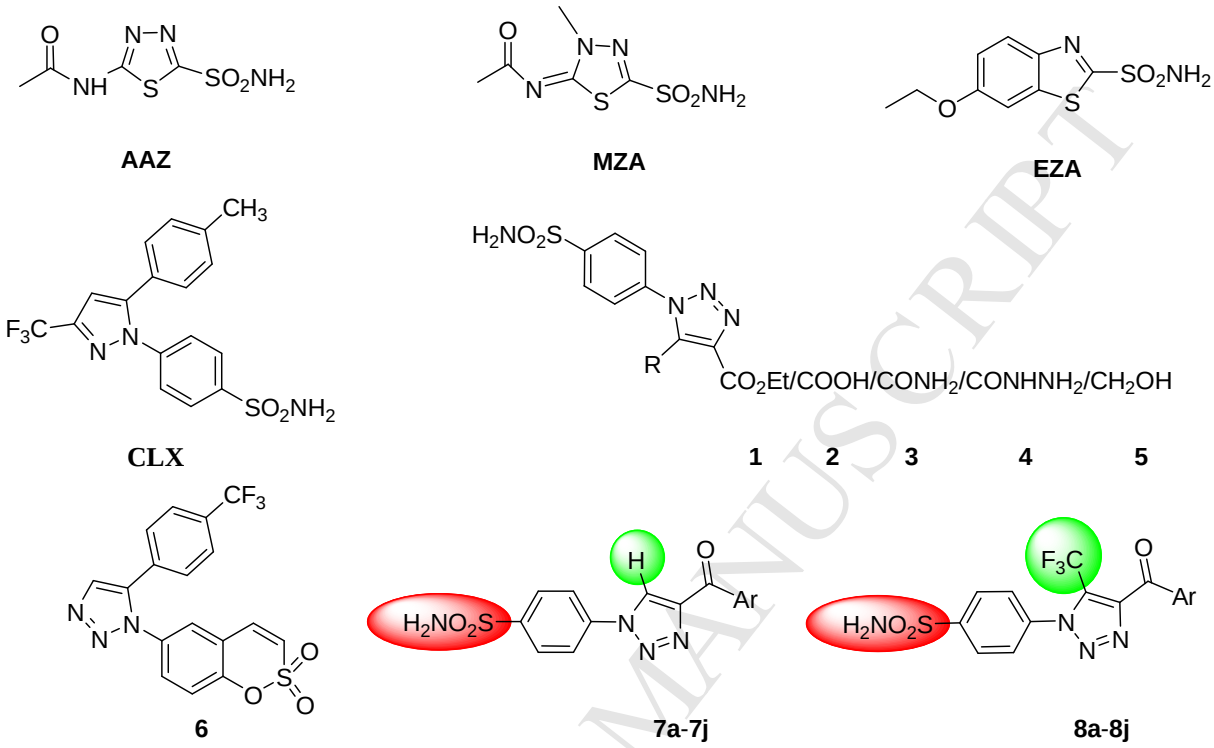


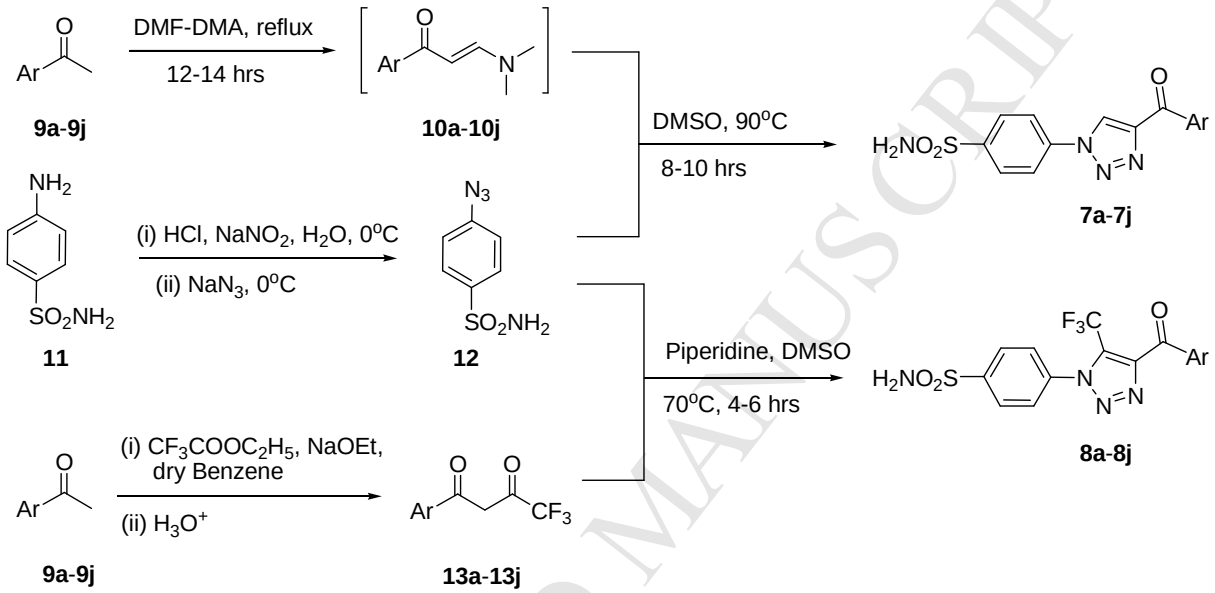
Fig. 1. Some clinically used sulfonamide/sulfocoumarin based drugs and derivatives incorporating the1,2,3-triazole ring (**1**-**6**),together with the designed sulfonamides **7**-**8** acting as CA inhibitors

2. Results and discussion

2.1.Chemistry

All the novel 1,2,3-triazoles were synthesized using 4-azidobenzenesulfonamide (**12**) according to the reaction sequence depicted in Scheme 1. 4-Azidobenzenesulfonamide (**12**) was synthesized from sulfanilamide (**11**) by its diazotization followed by treatment with sodium azide [36]. It is pertinent to mention here that 4-aroyl-1-aryl-1,2,3-triazoles **7a-7j** were synthesized in one pot manner by using a novel variant of the classical click chemistry. First, various methyl ketone derivatives **9a-9j** were refluxed for 12-14 hrs in N,N-dimethylformamide dimethyl acetal (DMF-DMA) reagent/solvent resulting into formation of key intermediates, enaminones **10a-10j**. After evaporating the excess of reagent/solvent, enaminones **10a-10j** (without isolating), were treated with 4-azidobenzenesulfonamide (**12**) in DMSO solvent resulting into formation of the target 1,2,3-triazole derivatives **7a-7j** via [3+2] cycloaddition reaction in high yields. 5-

Trifluoromethyl substituted 1,2,3-triazole derivatives **8a-8j** were synthesized by treatment of 4-azidobenzenesulfonamide (**12**) with variously substituted trifluoro-1,3-diketones **13a-13j** by using organic base piperidine according to earlier reported method [37]. Aryl substituted 1,3-diketones **13a-13j**, in turn, were synthesized by reacting various methyl ketones **9a-9j** with ethyl trifluoroacetate by using sodium ethoxide base [38] as shown in Scheme 1.



7-10, 13	a	b	c	d	e	f	g	h	i	j
Ar	C_6H_5	4-Me C_6H_4	4-MeO C_6H_4	4-F C_6H_4	4-Cl C_6H_4	4-Br C_6H_4	2-naphthyl	2-picolinyl	2-thienyl	2-furyl

Scheme 1. Synthetic pathway of target 1,2,3-triazoles **7a-7j** and **8a-8j**.

The spectral data (IR, ^{1}H NMR, ^{13}C NMR and HRMS) of target compounds **7a-7j** and **8a-8j** were in full agreement with the proposed structures. 1,2,3-Triazoles **7a-7j** showed strong absorption bands at 1620-1659 cm^{-1} corresponding to carbonyl (C=O) stretching in IR spectra while compounds **7a-7j** showed a characteristic singlet around δ ~ 9.70 ppm for triazolic ring proton (C5-H) in ^{1}H NMR spectra. Further, a characteristic signal around δ ~ 184 ppm due to carbonyl carbon was observed in ^{13}C NMR spectra of 1,2,3-triazoles **7a-7j**. In IR-spectra, compounds **8a-8j** showed strong carbonyl (C=O) stretching bands around 1651-1697 cm^{-1} which is slightly higher than band obtained in compounds **7a-7j** definitely due to the presence of –CF_3 group in **8a-8j** in place of –H at C-5 position of triazolic ring. This fact is further supported by

the absence of singnal in compounds **8a-8j** at around δ ~ 9.70 ppm as appeared in **7a-7j** in ^{1}H NMR spectra. In ^{13}C NMR spectra, 1,2,3-triazoles **8a-8j** showed a characteristic signal around δ ~ 184 ppm due to carbonyl carbon along with two other characteristic quartets with $^{1}J_{CF}$ ~ 268 Hz and $^{2}J_{CF}$ ~ 41.3 Hz centering around δ ~ 118 ppm and δ ~ 184 ppm respectively. Further, all the newly synthesized compounds exhibited sharp absorption bands in their FT-IR spectra at ~ 1342 cm^{-1} and ~ 1165 cm^{-1} for SO_2 stretching while SO_2NH_2 group resonated around δ ~ 7.66 ppm as sharp singlet integrating for two protons in ^{1}H NMR spectra.

2.2. CA inhibition studies

All the newly synthesized 1,2,3-triazoles **7a-7j** and **8a-8j** were screened for their CA inhibition potential by stopped-flow, CO_2 hydrase assay method [39] against the physiologically relevant hCA isoforms, cytosolic hCA I (associated with edema), cytosolic hCA II (associated with glaucoma), membrane bound hCA IV (associated with glaucoma and retinitis pigmentosa) and transmembrane hCA IX (associated with tumors). Table 1 presents the results of their CA inhibition profile as compared to the clinically used acetazolamide (AAZ) as reference drug.

(i) The cytosolic isoform, hCA I (edema related) was, in general, strongly inhibited by all the newly synthesized 1,2,3-triazoles **7a-7j** and **8a-8j** with inhibition constant (K_i) in the range 30.1-86.8 nM as compared to standard drug AAZ (K_i = 250 nM). General comparison of the activities of compounds of two series (**7a-7j** and **8a-8j)** revealed that the compounds **8a-8j** with $–CF_3$ group were slightly more effective against CA isoform hCA I than compounds **7a-7j** with –H group at C-5 position of 1,2,3-triazole ring (Table 1).

(ii) The inhibition potential of newly synthesized 1,2,3-triazoles **7a-7j** and **8a-8j** against hCA II (cytosolic isoform) was less satisfactory as all the twenty compounds (**7a-7j** and **8a-8j**) were less effective as hCA II inhibitors with K_i value ≥ 23 nM as compared to AAZ (K_i = 12 nM). Amongst the 4-substituted phenyls with electron donating groups, it was observed that compounds with –H group (**7a-7c)** were found to be better inhibitors than compounds with $–CF_3$ group at C-5 position (**8a-8c**). On the other hand, amongst the haloderivatives, the compounds with $–CF_3$ group (**8d-8f)** were found to be better inhibitors than compounds with –H group at C-5 position (**7d-7f**) of hCA II (Table 1). However, inhibition potential of other compounds against isoform hCA II was inconsistent.

(iii) Against isoform hCA IV (associated with glaucoma) the inhibition potential of some newly synthesized 1,2,3-triazoles **7b-7e**, **8d-8f** with $K_i \leq 95.8$ nM was comparable to standard drug AAZ (K_i = 74 nM) while the compound **7d** was even better inhibitor (K_i = 52.4 nM). However inhibition potential of other compounds was not satisfactory against hCA IV. General comparison of inhibitory potency of series **7a-7j** and **8a-8j**, showed that the compounds **7a-7j** with –H group were slightly more effective than compounds **8a-8j** with –CF_3 group at C-5 position against CA isoform hCA IV with few exceptions (Table 1).

(iv) The tumor associated target isoform hCA IX was moderately inhibited by compounds **7a-7j** and **8a-8j**, with K_i's in the range of 27.3 nM – 0.361 µM as compared to standard drug AAZ (K_i = 25 nM). However, in general, it was observed that some compounds with electron withdrawing substituents i.e. **7d-7f** & **8d-8f** and two others **8a** & **8i** were found to be better inhibitors ($K_i \leq 48.2$ nM) of hCA IX as compared to remaining compounds of both series (Table 1).

(v) Overall comparison of activity, in terms of structure activity relationship (SAR), revealed that compounds with electron withdrawing substituents i.e. **7d-7f** & **8d-8f** were better inhibitors of hCA I, hCA II, hCA IV and hCA IX isoforms in the broader sense. Further, study of inhibitory potency of compounds with heteroaryl substituents (**7h-7j** & **8h-8j**) revealed that these were more potent inhibitors of isoforms hCA I & II over hCA IV & IX as shown in Table 1.

(vi) Selective inhibition is necessary for CA inhibitors to act as potential drugs targeting particular therapeutic area with minimal side effects. Although, the tested compounds did not show strong selectivity against a specific hCA isoform yet the study of recent papers on 1,2,3-triazole moiety from our group [25,40] and the current work, suggests that compounds with haloaroyl substituents at C-5 position along with bulkier groups at C-4 position of 1,2,3-triazole ring could be designed for selective inhibition.

Table 1. Inhibitory potency data for compounds **7a-7j** and **8a-8j** against CA isoforms hCA I, hCA II, hCA IV, and hCA IX

Compounds	R	K_i (nM)[a]			
		hCA I	hCA II	hCA IV	hCA IX
7a	C_6H_5	67.7	67.1	914.4	136.5

7b	4-MeC_6H_4	65.2	40.3	84.9	324
7c	4-$MeOC_6H_4$	36.5	51.3	80.2	145.2
7d	4-FC_6H_4	69.8	48.8	52.4	47.8
7e	4-ClC_6H_4	83.6	40.4	79.4	27.3
7f	4-BrC_6H_4	39.1	80	326.2	44.7
7g	2-naphthyl	61.9	61.4	369.5	127.2
7h	2-picolinyl	57.3	63.9	389.3	182.1
7i	2-thienyl	79.7	180.2	419.2	361.6
7j	2-furyl	66.5	84.5	341.1	217.3
8a	C_6H_5	30.1	94.8	918.5	39.8
8b	4-MeC_6H_4	54.4	55.4	772.5	144.4
8c	4-$MeOC_6H_4$	42.4	61.9	242.3	140.7
8d	4-FC_6H_4	51.2	23	82.3	38.1
8e	4-ClC_6H_4	86.8	31.1	95.8	48.2
8f	4-BrC_6H_4	34.2	48.9	87.7	35.8
8g	2-naphthyl	42.5	55.3	320.9	248.1
8h	2-picolinyl	37.2	67.3	294.7	155.6
8i	2-thienyl	64.5	59	555.7	45.4
8j	2-furyl	42.6	35.8	618.1	189.6
AAZ	-	250	12	74	25

AAZ = acetazolamide (reference compound).

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

3. Conclusion

Two series of twenty novel compounds **7a-7j** and **8a-8j** containing 1,2,3-triazole scaffold have been synthesized, characterized and investigated for their inhibition potential against four of the isoforms of α-class of carbonic anhydrases comprising cytosolic, ubiquitous isoforms hCA I & II

as well as the transmembrane isoforms, hCA IV & IX. The activity profile revealed that all the newly synthesized compounds were moderate inhibitors of hCA II, IV and IX. However, all the newly synthesized compounds **7a-7j** and **8a-8j** showed excellent CAs inhibitory profile ($K_i \leq$ 86.8 nM) against hCA I (edema related) as compared to standard drug acetazolamide (K_i = 250 nM). Although, most of tested compounds have shown weaker inhibition potential as compared to standard drug AAZ against hCA II yet compounds **7b**, **7d-7e**, **8d-8f**, **8j** (mostly with electron withdrawing substituents) were good inhibitors (K_i < 50 nM). Against glaucoma associated hCA IV, compound **7d** was found to be better inhibitor (K_i = 52.4 nM) than AAZ while against tumor associated isoform hCA IX, all the tested compounds have shown weaker inhibition potential. Overall comparison of activity of all the novel 1,2,3-triazoles, **7a-7j** and **8a-8j**, revealed that compounds with electron withdrawing substituents, in broader sense, were more effective as CA inhibitors.

4. Experimental protocols

4.1. General

All the commercially available chemicals were used without further purification. All the solvents were dried and/or purified according to standard procedures prior to use. All the reactions were monitored by thin layer chromatography (TLC) on TLC 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 capillaries in an electrical melting point apparatus and are uncorrected. IR spectra were recorded on ABB MB 3000 DTGS IR instrument using the KBr pellet technique. ^{1}H NMR spectra were recorded on 400 MHz, while ^{13}C NMR spectra were registered at 100 MHz, using deuterated dimethyl sulfoxide (DMSO-d_6) as solvent, and tetramethylsilane (TMS) as internal standard at room temperature. Chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS. High resolution mass spectra were obtained from a MicroMass ESI-TOF MS spectrometer. In NMR data, 'tr' is used for triazolic ring. Multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublet (dd), doublet of triplet (dt), triplet of triplet (tt), exchangeable proton (ex) for NMR assignments and strong (s), medium (m), broad (br) for IR assignments. The coupling constants are expressed in hertz (Hz).

4.2. Synthesis of 4-(4-Aroyl-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7a**-**7j**)

General procedure: A mixture of appropriately substituted aryl methyl ketone (4 mmol) and DMF-DMA (20 mmol) was refluxed for 8-12 hrs and monitored by TLC. After complete consumption of substituted methyl ketone, the mixture was subjected to rotary evaporation under reduced pressure to remove the excess of DMF-DMA and the liberated methanol. After that DMSO (6-8 mL) and 4-azidobenzenesulfonamide (4 mmol) were added to reaction mixture. After addition, reaction mixture was allowed to stir at 90^{o} C for 8-10 hrs in silicon oil bath. After completion, reaction mixture was poured into water to afford required product (**7a**-**7j**). Crude product thus obtained was recrystalized with ethanol.

4.2.1. 4-(4-Benzoyl-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7a**)

Yield 78%; white solid; mp: 224-226 ^{o}C; IR(KBr) (ν, cm^{-1}): 3356, 3263 (m, N-H stretch), 1643 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.71 (s, 1H, tr), 8.29-8.27 (m, 4H, Ar), 8.07 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar), 7.75 (t, J = 7.2 Hz, 1H, Ar), 7.66-7.62 (m, 2H, Ar), 7.59 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 185.51, 147.71, 144.98, 138.58, 136.91, 134.01, 130.46, 129.15, 128.90, 127.92, 121.61; HRMS (ESI-MS) m/z 351.0577 $(M+Na)^+$, $C_{15}H_{12}N_4O_3SNa^+$, calcd 351.0522.

4.2.2. 4-(4-(4-Methylbenzoyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7b**)

Yield 86%; white solid; mp: 242-244 ^{o}C; IR(KBr) (ν, cm^{-1}): 3371, 3248 (m, N-H stretch), 1636 (s, C=O stretch), 1327, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.66 (s, 1H, tr), 8.27 (d, J = 8.4 Hz, 2H, Ar), 8.21 (d, J = 8.0 Hz, 2H, Ar), 8.07 (d, J = 8.4 Hz, 2H, Ar), 7.59 (s, 2H, SO_2NH_2), 7.42 (d, J = 8.0 Hz, 2H, Ar), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 184.90, 147.92, 144.95, 144.95, 138.60, 134.31, 130.64, 129.70, 128.69, 127.92, 121.55, 21.73; HRMS (ESI-MS) m/z 365.0694 $(M+Na)^+$, $C_{16}H_{14}N_4O_3SNa^+$, calcd 365.0679.

4.2.3. 4-(4-(4-Methoxybenzoyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7c**)

Yield 88%; pale yellow solid; mp: 232-234 ^{o}C; IR(KBr) (ν, cm^{-1}): 3294, 3178 (m, N-H stretch), 1643 (s, C=O stretch), 1327, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.64 (s, 1H, tr), 8.36 (d, J = 8.8 Hz, 2H, Ar), 8.27 (d, J = 8.8 Hz, 2H, Ar), 8.08 (d, J = 8.8 Hz, 2H,

Ar), 7.59 (s, 2H, SO_2NH_2), 7.14 (d, J = 8.8 Hz, 2H, Ar), 3.89 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 183.53, 164.04, 148.21, 144.92, 138.62, 133.02, 129.49, 128.50, 127.92, 121.51, 114.46, 56.10; HRMS (ESI-MS) m/z 381.0664 $(M+Na)^+$, $C_{16}H_{14}N_4O_4SNa^+$, calcd 381.0628.

4.2.4. 4-(4-(4-Fluorobenzoyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7d**)

Yield 90%; pale yellow solid; mp: 218-220 ^oC; IR(KBr) (ν, cm^{-1}): 3364, 3263 (m, N-H stretch), 1636 (s, C=O stretch), 1311, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.72 (s, 1H, tr), 8.43-8.40 (m, 2H, Ar), 8.27 (d, J = 8.8 Hz, 2H, Ar), 8.07 (d, J = 8.8 Hz, 2H, Ar), 7.59 (s, 2H, SO_2NH_2), 7.47 (t, J = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 183.85, 165.72 (d, $^1J_{CF}$ = 251.1 Hz), 147.72, 145.03, 138.54, 133.56 (d, $^3J_{CF}$ = 9.6 Hz), 128.98, 127.93, 121.93, 116.26 (d, $^2J_{CF}$ = 21.7 Hz), 111.24; HRMS (ESI-MS) m/z 347.0536 (M+1), $C_{15}H_{11}FN_4O_3S$, calcd 347.0536.

4.2.5. 4-(4-(4-Chlorobenzoyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7e**)

Yield 88%; pale yellow solid; mp: 254-256 ^oC; IR(KBr) (ν, cm^{-1}): 3364, 3240 (m, N-H stretch), 1636 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.73 (s, 1H, tr), 8.33 (d, J = 8.4 Hz, 2H, Ar), 8.27 (d, J = 8.8 Hz, 2H, Ar), 8.07 (d, J = 8.8 Hz, 2H, Ar), 7.72 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm):184.23, 147.58, 145.06, 139.00, 138.52, 135.52, 132.35, 129.30, 129.06, 127.92, 121.62; HRMS (ESI-MS) m/z 363.024/365.0209 (M+1)/(M+3), $C_{15}H_{11}ClN_4O_3S$, calcd 363.024/365.024.

4.2.6. 4-(4-(4-Bromobenzoyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7f**)

Yield 83%; white solid; mp: 256-258 ^oC; IR(KBr) (ν, cm^{-1}): 3333, 3240 (m, N-H stretch), 1636 (s, C=O stretch), 1327, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.73 (s, 1H, tr), 8.27 (d, J = 8.8 Hz, 2H, Ar), 8.24 (d, J = 8.4 Hz, 2H, Ar), 8.07 (d, J = 8.8 Hz, 2H, Ar), 7.86 (d, J = 8.4 Hz, 2H, Ar), 7.58 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm):184.43, 147.56, 145.05, 138.52, 135.85, 132.44, 132.26, 129.08, 128.23, 127.94, 121.61; HRMS (ESI-MS) m/z 406.9735/408.9711 (M+1)/(M+3), $C_{15}H_{11}BrN_4O_3S$, calcd 406.9735/408.9735.

4.2.7. 4-(4-(2-Naphthoyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7g**)

Yield 85%; light brown solid; mp: 228-230 ^{o}C; IR(KBr) (ν, cm^{-1}): 3364, 3263 (m, N-H stretch), 1620 (s, C=O stretch), 1311, 1149 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.76 (s, 1H, tr), 9.04 (s, 1H, Ar), 8.30 (d, J = 8.4 Hz, 2H, Ar), 8.24-8.19 (m, 2H, Ar), 8.14-8.05 (m, 4H, Ar), 7.73 (t, J = 7.2 Hz, 1H, Ar), 7.67 (t, J = 7.6 Hz, 1H, Ar), 7.60 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 185.35, 147.81, 145.00, 138.62, 135.65, 134.22, 132.88, 132.48, 130.37, 129.47, 128.96, 128.83, 128.20, 127.96, 127.55, 125.51, 121.61; HRMS (ESI-MS) m/z 379.0787 (M+1), $C_{19}H_{14}N_4O_3S$, calcd 379.0787.

4.2.8. 4-(4-Picolinoyl-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7h**)

Yield 81%; light brown solid; mp: 238-240 ^{o}C; IR(KBr) (ν, cm^{-1}): 3302, 3202 (m, N-H stretch), 1659 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.87 (s, 1H, tr), 8.84 (d, J = 4.8 Hz, 1H, Ar), 8.28 (d, J = 8.8 Hz, 2H, Ar), 8.18 (d, J = 7.6 Hz, 1H, Ar), 8.12 (dd, J = 7.6 Hz, J = 1.2 Hz, 1H, Ar), 8.08 (d, J = 8.8 Hz, 2H, Ar), 7.76 (dd, J = 7.2 Hz, J = 1.2 Hz, 1H, Ar), 7.60 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 183.50, 153.45, 149.74, 144.91, 144.72, 138.63, 138.31, 130.41, 128.32, 127.95, 123.98, 121.68; HRMS (ESI-MS) m/z 330.0583 (M+1), $C_{14}H_{11}N_5O_3S$, calcd 330.0583.

4.2.9. 4-(4-(2-Thienylcarbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7i**)

Yield 83%; light brown solid; mp: 258-260 ^{o}C; IR(KBr) (ν, cm^{-1}): 3310, 3232 (m, N-H stretch), 1620 (s, C=O stretch), 1327, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.73 (s, 1H, tr), 8.63 (s, 1H, Ar), 8.28 (d, J = 8.8 Hz, 2H, Ar), 8.20 (t, J = 4.0 Hz, 1H, Ar), 8.08 (d, J = 8.8 Hz, 2H, Ar), 7.59 (s, 2H, SO_2NH_2), 7.39 (d, J = 4.0 Hz, 1H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm):176.78, 147.45, 145.03, 142.25, 138.56, 137.08, 136.51, 129.49, 128.27, 127.92, 121.60; HRMS (ESI-MS) m/z 357.0099 $(M+Na)^+$, $C_{13}H_{10}N_4O_3S_2Na^+$, calcd 357.0087.

4.2.10. 4-(4-(2-Furoyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**7j**)

Yield 80%; light brown solid; mp: 198 ^{o}C; IR(KBr) (ν, cm^{-1}): 3310, 3232 (m, N-H stretch), 1620 (s, C=O stretch), 1327, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.72 (s, 1H, tr), 8.27 (d, J = 8.4 Hz, 2H, Ar), 8.19 (s, 1H, Ar), 8.11-8.06 (m, 3H, Ar), 7.59 (s, 2H, SO_2NH_2), 6.87 (d, J = 2.0 Hz, 1H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm):171.15, 150.45,

149.16, 146.31, 144.53, 138.10, 127.68, 127.47, 122.56, 121.12, 113.04; HRMS (ESI-MS) m/z 341.0353 $(M+Na)^+$, $C_{13}H_{10}N_4O_4SNa^+$, calcd 341.0315.

4.3. Synthesis of 4-[4-aroyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8a-8j**)

General procedure: 4-Azidobenzenesulfonamide (4.04 mmol) was dissolved in DMSO (4 mL) in a 50 mL round bottom flask. Thereafter, the appropriate aryl 1,3-diketones (4.04 mmol) and organic base, piperidine (5 mol %) were added to the reaction mixture. After addition, the reaction mixture was stirred at 70^o C in silicon oil bath for 4-6 hrs and progress of reaction was monitored through thin layer chromatography. After completion, reaction mixture was poured into water after cooling to afford desired product (**8a-8j**) which was filtered and recrystalized with ethanol.

4.3.1. 4-[4-Benzoyl-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8a**)

Yield 75%; pale yellow solid; mp: 140-142 ^{o}C; IR(KBr) (ν, cm^{-1}): 3356,3263 (m, N-H stretch), 1651 (s, C=O stretch), 1350, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.16-8.12 (m, 4H, Ar), 8.02 (d, J = 8.4 Hz, 2H, Ar), 7.80 (tt, J = 7.2 Hz, J = 1.2 Hz, 1H, Ar), 7.67-7.63 (m, 4H, Ar, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 185.40, 146.64, 145.07, 137.30, 135.54, 134.60, 130.33, 128.81, 128.74 (q, $^2J_{CF}$ = 41.4 Hz), 127.14, 127.08, 118.83 (q, $^1J_{CF}$ = 268.8 Hz); HRMS (ESI-MS) m/z 419.0377 $(M+Na)^+$, $C_{16}H_{11}F_3N_4O_3SNa^+$, calcd 419.0396.

4.3.2. 4-[4-(4-Methylbenzoyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8b**)

Yield 78%; dirty white solid; mp: 138-140 ^{o}C; IR(KBr) (ν, cm^{-1}): 3380, 3277 (m, N-H stretch), 1659 (s, C=O stretch), 1358, 1149 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.13 (d, J = 8.8 Hz, 2H, Ar), 8.04-8.00 (m, 4H, Ar), 7.67 (s, 2H, SO_2NH_2), 7.45 (d, J = 8.0 Hz, 2H, Ar), 2.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 184.91, 146.64, 145.55, 145.26, 137.33, 133.08, 130.50, 129.43, 128.47 (q, $^2J_{CF}$ = 41.3 Hz), 127.16, 127.08, 118.87 (q, $^1J_{CF}$ = 268.7 Hz), 55.38; HRMS (ESI-MS) m/z 411.0723 $(M+Na)^+$, $C_{17}H_{13}F_3N_4O_3SNa^+$, calcd 411.0733.

4.3.3. 4-[4-(4-Methoxybenzoyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8c**)

Yield 84%; white solid; mp: 142-144 ^{o}C; IR(KBr) (ν, cm^{-1}): 3317, 3240 (m, N-H stretch), 1651 (s, C=O stretch), 1358, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.14-8.11 (m, 4H, Ar), 8.01 (d, J = 8.4 Hz, 2H, Ar), 7.66 (s, 2H, SO_2NH_2), 7.16 (d, J = 8.8 Hz, 2H, Ar), 3.91 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 183.58, 164.44, 146.60, 145.46, 137.34, 132.94, 128.36, 128.23 (q, $^{2}J_{CF}$ = 41.3 Hz), 127.14, 127.07, 118.90 (q, $^{1}J_{CF}$ = 268.6 Hz), 21.31; HRMS (ESI-MS) m/z 449.0488 $(M+Na)^{+}$, $C_{17}H_{13}F_3N_4O_4SNa^{+}$, calcd 449.0502.

4.3.4. 4-[4-(4-Fluorobenzoyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8d**)

Yield 89%; yellow solid; mp: 118-120 ^{o}C; IR(KBr) (ν, cm^{-1}): 3310, 3256 (m, N-H stretch), 1659 (s, C=O stretch), 1358, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.13 (d, J = 8.8 Hz, 2H, Ar), 8.01 (d, J = 8.8 Hz, 2H, Ar), 7.93 (d, J = 9.2 Hz, 2H, Ar), 7.68 (s, 2H, SO_2NH_2), 7.03 (d, J = 9.2 Hz, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 181.96, 154.39, 146.42, 146.12, 137.35, 132.77, 127.43 (q, $^{2}J_{CF}$ = 41.0 Hz), 127.11, 127.00, 123.37, 118.99 (q, $^{1}J_{CF}$ = 266.63 Hz), 112.39; HRMS (ESI-MS) m/z 415.0537 (M+1), $C_{16}H_{10}F_4N_4O_3S$, calcd 415.0410.

4.3.5. 4-[4-(4-Chlorobenzoyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8e**)

Yield 72%; yellow solid; mp: 126-128 ^{o}C; IR(KBr) (ν, cm^{-1}): 3356, 3271 (m, N-H stretch), 1666 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.16 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar), 8.13 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar), 7.99 (d, J = 8.4 Hz, 2H, Ar), 7.88 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar),7.66 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 184.10, 146.62, 144.70, 139.64, 137.25, 134.18, 132.16, 128.99, 129.01 (q, $^{2}J_{CF}$ = 41.3 Hz), 127.10, 127.04, 118.56 (q, $^{1}J_{CF}$ = 269.0 Hz); HRMS (ESI-MS) m/z 452.9987 $(M+Na)^{+}$, $C_{16}H_{10}ClF_3N_4O_3SNa^{+}$, calcd 453.0006.

4.3.6. 4-[4-(4-Bromobenzoyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8f**)

Yield 83%; yellow solid; mp: 126-128 ^{o}C; IR(KBr) (ν, cm^{-1}): 3348, 3256 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1149 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.13 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar), 8.08 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.74 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar),7.66 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 184.35, 146.66, 144.73, 137.29, 134.55, 132.22, 131.98, 129.99, 129.07 (q, $^{2}J_{CF}$ = 41.3 Hz), 127.14, 127.08, 118.76 (q, $^{1}J_{CF}$ = 268.9 Hz); HRMS (ESI-MS) m/z 496.9494 $(M+Na)^{+}$, $C_{16}H_{10}BrF_3N_4O_3Na^{+}$, calcd 496.9501.

4.3.7. 4-[4-(2-naphthoyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8g**)

Yield 77%; pale yellow solid; mp: 168-170 ^{o}C; IR(KBr) (ν, cm^{-1}): 3564, 3250 (m, N-H stretch), 1697 (s, C=O stretch), 1366, 1149 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.82 (s, 1H, Ar), 8.17-8.04 (m, 8H, Ar), 7.78-7.67 (m, 4H, Ar, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 185.27, 146.66, 145.24, 137.33, 135.59, 133.73, 132.94, 131.84, 129.83, 129.578, 128.68, 128.69 (q, $^{2}J_{CF}$ = 41.3 Hz), 127.84, 127.37, 127.16, 127.12, 124.36, 118.88 (q, $^{1}J_{CF}$ = 268.7 Hz); HRMS (ESI-MS) m/z 469.0534 $(M+Na)^{+}$, $C_{20}H_{13}F_3N_4O_3SNa^{+}$, calcd 469.0553.

4.3.8. 4-(4-picolinoyl-5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**8h**)

Yield 85%; brown solid; mp: 182-184 ^{o}C; IR(KBr) (ν, cm^{-1}): 1682 (s, C=O stretch), 1358, 1142 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.79 (d, J = 4.4 Hz, 1H, Ar), 8.23 (d, J = 8.0 Hz, 1H, Ar), 8.17 (dd, J = 7.6 Hz, J = 1.6 Hz, 1H, Ar), 8.13 (d, J = 8.4 Hz, 2H, Ar), 8.03 (d, J = 8.4 Hz, 2H, Ar), 7.82-7.79 (m, 1H, Ar),7.69 (s, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm):186.15, 152.23, 149.58, 146.70, 144.52, 138.07, 137.07, 128.71, 128.41 (q, $^{2}J_{CF}$ = 42.0 Hz), 127.26, 127.16, 123.96, 118.90 (q, $^{1}J_{CF}$ = 268.0 Hz); HRMS (ESI-MS) m/z 420.0390 $(M+Na)^{+}$, $C_{15}H_{10}F_3N_5O_3S\ Na^{+}$, calcd 420.0349.

4.3.9. 4-[4-(2-Thienylcarbonyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8i**)

Yield 87%; pale yellow solid; mp: 206-208 ^{o}C; IR(KBr) (ν, cm^{-1}): 3325, 3225 (m, N-H stretch), 1636 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.33 (dd, J = 4.0 Hz, J = 1.2 Hz, 1H, Ar), 8.28 (dd, J = 5.2 Hz, J = 1.2 Hz, 1H, Ar), 8.12 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar), 8.00 (d, J = 8.4 Hz, 2H, Ar), 7.66 (s, 2H, SO_2NH_2), 7.41-7.39 (m,

1H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 176.24, 146.65, 144.69, 141.41, 138.08, 137.71, 137.41, 129.18, 128.88 (q, $^{2}J_{CF}$ = 41.6 Hz), 127.59, 127.18, 118.75 (q, $^{1}J_{CF}$ = 269.0 Hz); HRMS (ESI-MS) m/z 424.9957 $(M+Na)^+$, $C_{14}H_9F_3N_4O_3S_2Na^+$, calcd 424.9960.

4.3.10. 4-[4-(2-furoyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**8j**)

Yield 77%; brown solid; mp: 184-186 ^{o}C; IR(KBr) (ν, cm^{-1}): 3333, 3209 (m, N-H stretch), 1651 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.26 (d, J = 0.8 Hz, 1H, Ar), 8.12 (dd, J = 6.8 Hz, J = 2.0 Hz, 2H, Ar), 7.98 (d, J = 8.8 Hz, 2H, Ar), 7.90 (d, J = 3.6 Hz, 1H, Ar), 7.65 (s, 2H, SO_2NH_2), 6.89 (dd, J = 3.6 Hz, J = 0.8 Hz, 1H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 170.76, 150.42, 150.35, 146.65, 144.27, 137.35, 128.88 (q, $^{2}J_{CF}$ = 41.6 Hz), 127.16, 127.05, 124.65, 118.74 (q, $^{1}J_{CF}$ = 268.9 Hz), 113.33; HRMS (ESI-MS) m/z 409.0173 $(M+Na)^+$, $C_{14}H_9F_3N_4O_4SNa^+$, calcd 424.1089.

Disclosure statement

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

Acknowledgements

Two of the authors (Rajiv Kumar, Lalit Vats) are grateful to University Grants Commission, New Delhi, India for the award of Senior Research Fellowship and Junior Research Fellowship. Authors are also thankful to Materials Research Centre, MNIT Jaipur for providing HRMS facility.

References

[1] J.F. da Costa, X. García-Mera, O. Caamano, J.M. Brea, M.I. Loza, Synthesis by microwave-assisted 1,3-dipolar cycloaddition of 1,2,3-triazole 1′-homo-3′-isoazanucleosides and evaluation of their anticancer activity, Eur. J. Med. Chem. 98 (2015) 212-220.

[2] C.F. Liu, Q.K. Shen, J.J. Li, Y.S. Tian, Z. Quan, Synthesis and biological evaluation of novel 7-hydroxy-4-phenylchromen-2-one–linked to triazole moieties as potent cytotoxic agents, J. Enzyme Inhib. Med. Chem. 32 (2017) 1111-1119.

[3] R. Kant, D. Kumar, D. Agarwal, R.D. Gupta, R. Tilak, S.K. Awasthi, A. Agarwal, Synthesis of newer 1,2,3-triazole linked chalcone and flavone hybrid compounds and evaluation of their antimicrobial and cytotoxic activities, Eur. J. Med. Chem. 113 (2016) 34-49.

[4] Z.H. Li, D.X. Yang, P.F. Geng, J. Zhang, H.M. Wei, B. Hu, Q. Guo, X.H. Zhang, W.G. Guo, B. Zhao, B. Yu, L.Y. Ma, H.M. Liu, Design, synthesis and biological evaluation of [1,2,3]triazolo[4,5-d]pyrimidine derivatives possessing a hydrazone moiety as antiproliferative agents, Eur. J. Med. Chem. 124 (2016) 967-980.

[5] N. Devender, S. Gunjan, S. Chhabra, K. Singh, V.R. Pasam, S.K. Shukla, A. Sharma, S. Jaiswal, S.K. Singh, Y. Kumar, J. Lal, A.K. Trivedi, R. Tripathi, R.P. Tripathi, Identification of β-Amino alcohol grafted 1,4,5 trisubstituted 1,2,3-triazoles as potent antimalarial agents, Eur. J. Med. Chem. 109 (2016) 187-198.

[6] T.G. Kraljevic, A. Harej, M. Sedic, S.K. Pavelic, V. Stepanic, D. Drenjancevic, J. Talapko, S. Raic-Malic, Synthesis, in vitro anticancer and antibacterial activities and in silico studies of new 4-substituted 1,2,3-triazole-coumarin hybrids, Eur. J. Med. Chem. 124 (2016) 794-808.

[7] A. Anand, R.J. Naik, H.M. Revankar, M.V. Kulkarni, S.R. Dixit, S.D. Joshi, A click chemistry approach for the synthesis of mono and bis aryloxy linked coumarinyl triazoles as anti-tubercular agents, Eur. J. Med. Chem. 105 (2015) 194-207.

[8] M.M. Ghorab, M.S. Alsaid, M.S. El-Gaby, N.A. Safwat, M.M. Elaasser, A.M. Soliman, Biological evaluation of some new N-(2, 6-dimethoxypyrimidinyl) thioureido benzenesulfonamide derivatives as potential antimicrobial and anticancer agents, Eur. J. Med. Chem. 124 (2016) 299-310.

[9] M. Mishra, V.K. Mishra, V. Kashaw, A.K. Iyer, S.K. Kashaw, Comprehensive review on various strategies for antimalarial drug discovery, Eur. J. Med. Chem. 125 (2017) 1300-1320.

[10] J. Sławiński, K. Szafrański, A. Pogorzelska, B. Żołnowska, A. Kawiak, K. Macur, M. Belka, T. Bączek, Novel 2-benzylthio-5-(1, 3, 4-oxadiazol-2-yl) benzenesulfonamides with anticancer activity: Synthesis, QSAR study, and metabolic stability, Eur. J. Med. Chem. 132 (2017) 236-248.

[11] J. Li, J. Lou, Z. Wang, T. Wang, Y. Xiao, X. Hu, P. Liu, X. Hong, Design, synthesis and pharmacological evaluation of novel N-(2-(1, 1-dimethyl-5, 7-dioxo-4, 6-diazaspiro [2.4] heptan-6-yl) ethyl) sulfonamide derivatives as potential anticonvulsant agents, Eur. J. Med. Chem. 92 (2015) 370-376.

[12] M.R. Buemi, L. De Luca, S. Ferro, E. Bruno, M. Ceruso, C.T. Supuran, K. Pospíšilová, J. Brynda, P. Řezáčová, R. Gitto, Carbonic anhydrase inhibitors: Design, synthesis and

structural characterization of new heteroaryl-N-carbonylbenzenesulfonamides targeting druggable human carbonic anhydrase isoforms, Eur. J. Med. Chem. 102 (2015) 223-232.

[13] S. Akocak, N. Lolak, A. Nocentini, G. Karakoc, A. Tufan, C.T. Supuran, Synthesis and biological evaluation of novel aromatic and heterocyclic bis-sulfonamide Schiff bases as carbonic anhydrase I, II, VII and IX inhibitors, Bioorg. Med. Chem. 25 (2017) 3093-3097.

[14] S. Angapelly, P.S. Ramya, A. Angeli, S.M. Monti, M. Buonanno, M. Alvala, M. Arifuddin, Discovery of 4-sulfamoyl-phenyl-β-lactams as a new class of potent carbonic anhydrase isoforms I, II, IV and VII inhibitors: The first example of subnanomolar CA IV inhibitors, Bioorg. Med. Chem. 25 (2017) 539-544.

[15] C.T. Supuran, Carbonic anhydrases: novel therapeutic applications for inhibitors and activators, Nat. Rev. Drug Discov. 7 (2008) 168-181.

[16] V. Alterio, A.D. Fiore, K. D'Ambrosio, C.T. Supuran, G.D. Simone, Multiple Binding Modes of Inhibitors to Carbonic Anhydrases: How to Design Specific Drugs Targeting 15 Different Isoforms?, Chem. Rev. 112 (2012) 4421-4468.

[17] C.T. Supuran, How many carbonic anhydrase inhibition mechanisms exist?, J. Enzyme Inhib. Med. Chem. 31 (2016) 345-360.

[18] C.T. Supuran, C. Capasso, The η-class carbonic anhydrases as drug targets for antimalarial agents, Expert Opin. Ther. Targets 19 (2015) 551-563.

[19] S. Kikutani, K. Nakajima, C. Nagasato, Y. Tsuji, A. Miyatake, Y. Matsuda, Thylakoid luminal θ-carbonic anhydrase critical for growth and photosynthesis in the marine diatom Phaeodactylum tricornutum, Proc. Natl. Acad. Sci. 113 (2016), 9828-9833.

[20] R. Perfetto, S. Del Prete, D. Vullo, G. Sansone, C. Barone, M. Rossi, C.T. Supuran, C. Capasso, Biochemical characterization of the native α-carbonic anhydrase purified from the mantle of the Mediterranean mussel, Mytilus galloprovincialis, J. Enzyme Inhib. Med. Chem. 32 (2017) 632–639.

[21] C.T. Supuran, Carbonic anhydrases: from biomedical applications of the inhibitors and activators to biotechnological use for CO_2 capture, J. Enzyme Inhib. Med. Chem. 28 (2013) 229-230.

[22] C.T. Supuran, Carbonic Anhydrase Inhibition and the Management of Hypoxic Tumors. Metabolites 7 (2017) 48.

[23] M.Y. Mboge, B.P. Mahon, N. Lamas, L. Socorro, F. Carta, C.T. Supuran, R. McKenna, Structure activity study of carbonic anhydrase IX: Selective inhibition with ureido-substituted benzenesulfonamides, Eur. J. Med. Chem. 132 (2017) 184-191.

[24] M. Falsini, L. Squarcialupi, D. Catarzi, F. Varano, M. Betti, L. Di Cesare Mannelli, C.T. Supuran, 3-Hydroxy-1 H-quinazoline-2, 4-dione as a New Scaffold To Develop Potent and Selective Inhibitors of the Tumor-Associated Carbonic Anhydrases IX and XII, J. Med. Chem. 60 (2017) 6428−6439.

[25] R. Kumar, V. Sharma, S. Bua, C.T. Supuran, P.K. Sharma, Synthesis and biological evaluation of benzenesulfonamide-bearing 1,4,5-trisubstituted-1,2,3-triazoles possessing human carbonic anhydrase I, II, IV, and IX inhibitory activity, J. Enzyme Inhib. Med. Chem. 32 (2017) 1887-1894.

[26] K. Tars, D. Vullo, A. Kazaks, J. Leitans, A. Lends, A. Grandane, R. Zalubovskis, A. Scozzafava, C.T. Supuran, Sulfocoumarins (1,2-benzoxathiine-2,2-dioxides): a class of potent and isoform-selective inhibitors of tumor-associated carbonic anhydrases, J. Med. Chem. 56 (2013) 293−300.

[27] S. Ram, G. Celik, P. Khloya, D. Vullo, C.T. Supuran, P.K. Sharma, Benzenesulfonamide bearing 1, 2, 4-triazole scaffolds as potent inhibitors of tumor associated carbonic anhydrase isoforms hCA IX and hCA XII, Bioorg. Med. Chem. 22 (2014) 1873-1882.

[28] S. Ram, M. Ceruso, P. Khloya, C.T. Supuran, P.K. Sharma, 4-Functionalized 1, 3-diarylpyrazoles bearing 6-aminosulfonylbenzothiazole moiety as potent inhibitors of carbonic anhydrase isoforms hCA I, II, IX and XII, Bioorg. Med. Chem. 22 (2014) 6945-6952.

[29] P. Khloya, G. Celik, D. Vullo, C.T. Supuran, P.K. Sharma, 4-Functionalized 1, 3-diarylpyrazoles bearing benzenesulfonamide moiety as selective potent inhibitors of the tumor associated carbonic anhydrase isoforms IX and XII, Eur. J. Med. Chem. 76 (2014) 284-290.

[30] P. Khloya, M. Ceruso, S. Ram, C.T. Supuran, P.K. Sharma, Sulfonamide bearing pyrazolylpyrazolines as potent inhibitors of carbonic anhydrase isoforms I, II, IX and XII, Bioorg. Med. Chem. Lett. 25 (2015) 3208-3212.

[31] N. Chandak, M. Ceruso, C.T. Supuran, P.K. Sharma, Novel sulfonamide bearing coumarin scaffolds as selective inhibitors of tumor associated carbonic anhydrase isoforms IX and XII, Bioorg. Med. Chem. 24 (2016) 2882-2886.

[32] S. Kumar, M. Ceruso, T. Tuccinardi, C.T. Supuran, P.K. Sharma, Pyrazolylbenzo [d] imidazoles as new potent and selective inhibitors of carbonic anhydrase isoforms hCA IX and XII, Bioorg. Med. Chem. 24 (2016) 2907-2913.

[33] R. Kumar, S. Bua, S. Ram, S. Del Prete, C. Capasso, C.T. Supuran, P.K. Sharma, Benzenesulfonamide bearing imidazothiadiazole and thiazolotriazole scaffolds as potent tumor associated human carbonic anhydrase IX and XII inhibitors, Bioorg. Med. Chem. 25 (2017) 1286-1293.

[34] P. Kumar, N. Chandak, P. Kaushik, C. Sharma, D. Kaushik, K.R. Aneja, P.K. Sharma, Synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory–antibacterial agents, Med. Chem. Res. 21 (2012) 3396-3405.

[35] S. Kumar, W. Namkung, A.S. Verkman, P.K. Sharma, Novel 5-substituted benzyloxy-2-arylbenzofuran-3-carboxylic acids as calcium activated chloride channel inhibitors, Bioorg. Med. Chem. 20 (2012) 4237-4344.

[36] B.L. Wilkinson, L.F. Bornaghi, T.A. Houston, A. Innocenti, D. Vullo, C.T. Supuran, S.A. Poulsen, Carbonic Anhydrase Inhibitors: Inhibition of Isozymes I, II, and IX with Triazole-Linked *O*-Glycosides of Benzene Sulfonamides, J. Med. Chem. 50 (2007) 1651-1657.

[37] L.J.T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, Organocatalytic Enamide–Azide Cycloaddition Reactions: Regiospecific Synthesis of 1, 4, 5-Trisubstituted-1, 2, 3-Triazoles, Chem. Eur. J. 17 (2011) 3584-3587.

[38] J.C. Sloop, C.L. Bumgardner, W.D. Loehle, Synthesis of fluorinated heterocycles, J. Fluor. Chem. 118 (2002) 135–147.

[39] R.J. Khalifah, The carbon dioxide hydration activity of carbonic anhydrase I. Stop-flow kinetic studies on the native human isoenzymes B and C, J. Biol. Chem. 246 (1971) 2561-2573.

[40] L. Vats, V. Sharma, A. Angeli, R. Kumar, C.T. Supuran, P.K. Sharma, Synthesis of novel 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide moiety as carbonic anhydrase I, II, IV and IX inhibitors, Eur. J. Med. Chem. 150 (2018) 678-686.

Design and synthesis of novel benzenesulfonamide containing 1,2,3-triazoles as potent human carbonic anhydrase isoforms I, II, IV and IX inhibitors

Rajiv Kumar, Lalit Vats, Silvia Bua, Claudiu T. Supuran, Pawan K. Sharma

Research Highlights

- Twenty novel benzenesulfonamide containing 1,2,3-triazoles were designed and synthesized.
- Newly synthesized compounds were assayed against hCA isoforms I, II, IV and IX.
- Inhibition results were promising as compared to antitumor drug acetazolamide.
- All the tested compounds showed excellent, low nanomolar affinity for hCA I.
- Most of the newly synthesized compounds were moderate inhibitors of hCA II, IV and IX.