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Synthesis of novel 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide moiety as carbonic anhydrase I, II, IV

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Graphical Abstract

Synthesis of novel 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide moiety as carbonic anhydrase I, II, IV and IX inhibitors

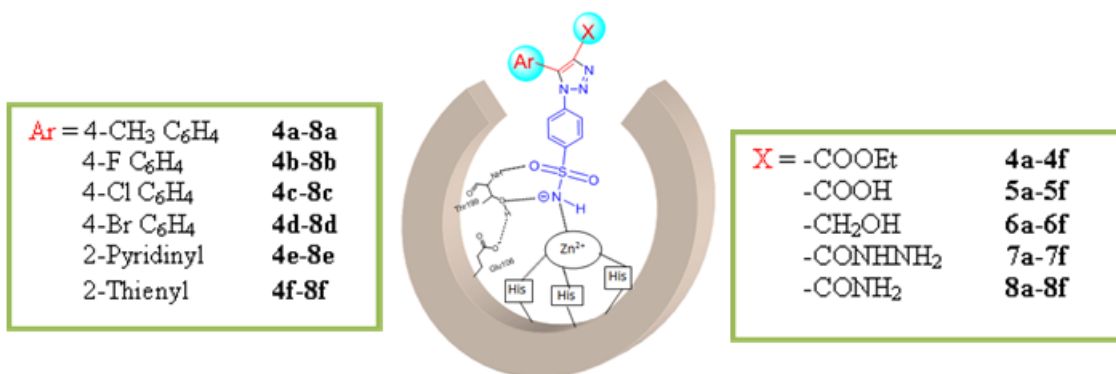
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A series of thirty novel 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide moiety were synthesized and evaluated for their inhibition potential against human carbonic anhydrase isoforms, hCA I, II, IV and IX.



Active site of hCA I, II, IV and IX

Synthesis of novel 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide moiety as carbonic anhydrase I, II, IV and IX inhibitors

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Abstract

Current paper presents design, synthesis and biological evaluation of a library of 1,2,3-triazole carboxylates **4a-4f**, and their derivatives; carboxylic acids **5a-5f**, hydroxymethyls **6a-6f**, carboxylic acid hydrazides **7a-7f**, carboxamides **8a-8f** bearing benzenesulfonamide. All the thirty novel compounds were investigated for their inhibition potential against human carbonic anhydrase (hCA) isoforms hCA I, II, IV and IX choosing acetazolamide (AAZ) as reference drug. Most of the synthesized compounds were found to be weak inhibitors of cytosolic isoform hCA I with K_i 's ranging between 53.2 nM to 7.616 μ M while glaucoma associated cytosolic isoform hCA II was moderately inhibited in the range of K_i 's 21.8 nM to 0.807 μ M. The membrane bound isoform hCA IV was effectively inhibited by some compounds **4a**, **4c**, **4d**, **5c**, **5f**, **7c**, **7d**, **8a**, **8c** with $K_i < 60$ nM out of which compound **8a** was most potent and most selective inhibitor ($K_i = 35.7$ nM) for hCA IV as compared to reference drug AAZ ($K_i = 74$ nM). The compound **6e** was found to be better inhibitor of tumor associated isoform hCA IX ($K_i = 14.3$ nM) as compared to reference drug AAZ ($K_i = 25.8$ nM) while other compounds showed moderate inhibition.

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

Abbreviations: CA: Carbonic anhydrase; hCA: human carbonic anhydrase; CAIs: Carbonic anhydrase inhibitors; AAZ: Acetazolamide; K_i : Inhibition constant; nM: nanomolar; μ M: micromolar; py: pyridinyl; th: thienyl.

1. Introduction: Carbonic anhydrases (CAs, EC 4.2.1.1), also known as carbonate dehydratases, are widely distributed zinc containing metalloenzymes present in all life phyla which maintain pH homeostasis in the body by catalyzing the CO₂ hydration reaction to bicarbonate and proton as well as other hydrolytic reactions [1]. Depending upon their cellular localisation, catalytic activity and susceptibility to different classes of inhibitors, carbonic anhydrases are divided in seven genetically distinct families, α -, β -, γ -, δ -, and θ -CAs [2-4]. Out of these, only α - class is known to be present in humans which can be distinguished into 16 isoforms differing in their subcellular localisation, distribution in tissues and molecular and kinetic properties [5-7]. The CA isoforms are involved in numerous biochemical and physiological processes such as acid base regulation, bone resorption, calcification, gluconeogenesis, gluconeogenesis, tumorigenicity, ureagenesis thus representing valuable biological targets for the design of CA inhibitors (CAIs) with many biomedical applications [8-9]. The ubiquitous isoform hCA I is involved in retinal and cerebral edema, and its inhibition may be a valuable tool for fighting these conditions [10-12]. hCA II is involved in glaucoma, edema and epilepsy [13]. hCA IV is a membrane bound isoform and its overactivity is associated with glaucoma, retinitis pigmentosa and stroke. hCA IX, a transmembrane isoform, is involved in the growth of tumor cell mainly by causing the acidification of extracellular environment and maintaining the neutral intercellular space [14-17]. Thus selective inhibition of some isoforms over others is a challenging approach for obtaining a drug with minimum side effects.

In the last decade, a lot of work has been done on the synthesis of carbonic anhydrase inhibitors (CAIs) like bischalcones, coumarins, benzenesulfonamides, phenols and uracil derivatives [18-30]. Out of these, sulfonamides and their bioisosteres like sulfamates and sulfamides are potent active site coordinating CAIs which, in deprotonated form, binds with the Zn(II) present at active site of enzyme [31-32]. Many sulfonamide based drugs, like acetazolamide (AAZ), methazolamide (MZA), ethoxzolamide (EZA), dorzolamide (DZA), brinzolamide (BRZ), celecoxib (CLX) etc. which are in clinical use as diuretics (target hCA II, IV, XII and XIV), antiepileptics (target hCA VII and XIV), antiglaucoma (target hCA II, IV and XII), antitumor agents (target hCA IX and XII) for the treatment of diseases related to overactivity of carbonic anhydrases [33-34]. Further, the compounds containing 1,2,3-triazole ring system have been studied extensively by medicinal chemists for the synthesis of novel compounds **1-3** of medicinal importance (Fig. 1) [35-37]. Recently, our research group has reported the synthesis and biological evaluation of some benzenesulfonamide bearing 1,2,3-triazoles as hCA I, II, IV and XI inhibitors which showed excellent inhibition profile for

aforesaid CA isoforms [28]. Motivated by the results of our previous work and continuing our interest in designing heterocyclic compounds of potential medicinal interest [20-23,27-29,38-39] we synthesized some novel 4-functionalized 1,5-diaryl-1,2,3-triazoles bearing benzenesulfonamide **4a-4f**, **5a-5f**, **6a-6f**, **7a-7f** and **8a-8f** for evaluation of their carbonic anhydrase inhibition potential against hCA I, II, IV and IX.

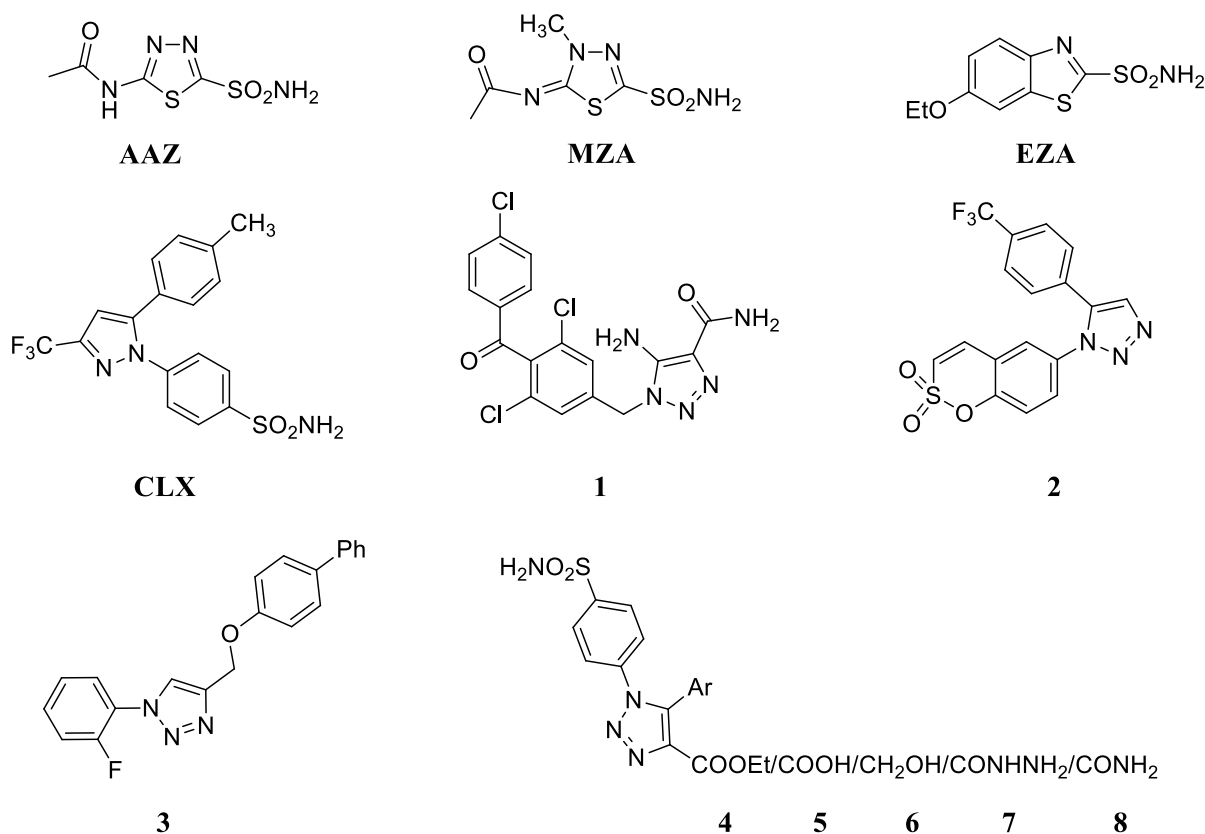
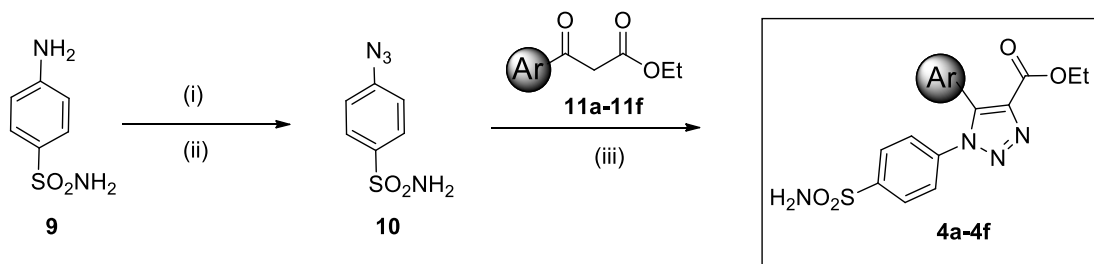


Fig. 1. Some clinically used sulfonamide bearing drugs and 1,2,3-triazole ring containing CA inhibitors.

2. Results and discussion

2.1. Chemistry

The synthesis of 1,2,3-triazole derivatives **4a-4f**, **5a-5f**, **6a-6f**, **7a-7f** and **8a-8f** was performed according to the general synthetic route as outlined in Scheme 1 and 2. The coveted 1,5-diaryl-1,2,3-triazole carboxylates **4a-4f** were synthesized (Scheme 1) starting from commercially available sulfanilamide (**9**) which upon diazotisation and subsequent reaction with sodium azide at 0° C yielded 4-azidobenzenesulfonamide (**10**) [40]. Compound **10** was subsequently treated with differently substituted β -ketoesters **11a-11f**, which were in turn synthesized according to literature procedure [41] to afford 1,5-diaryl-1,2,3-triazole carboxylates **4a-4f**.

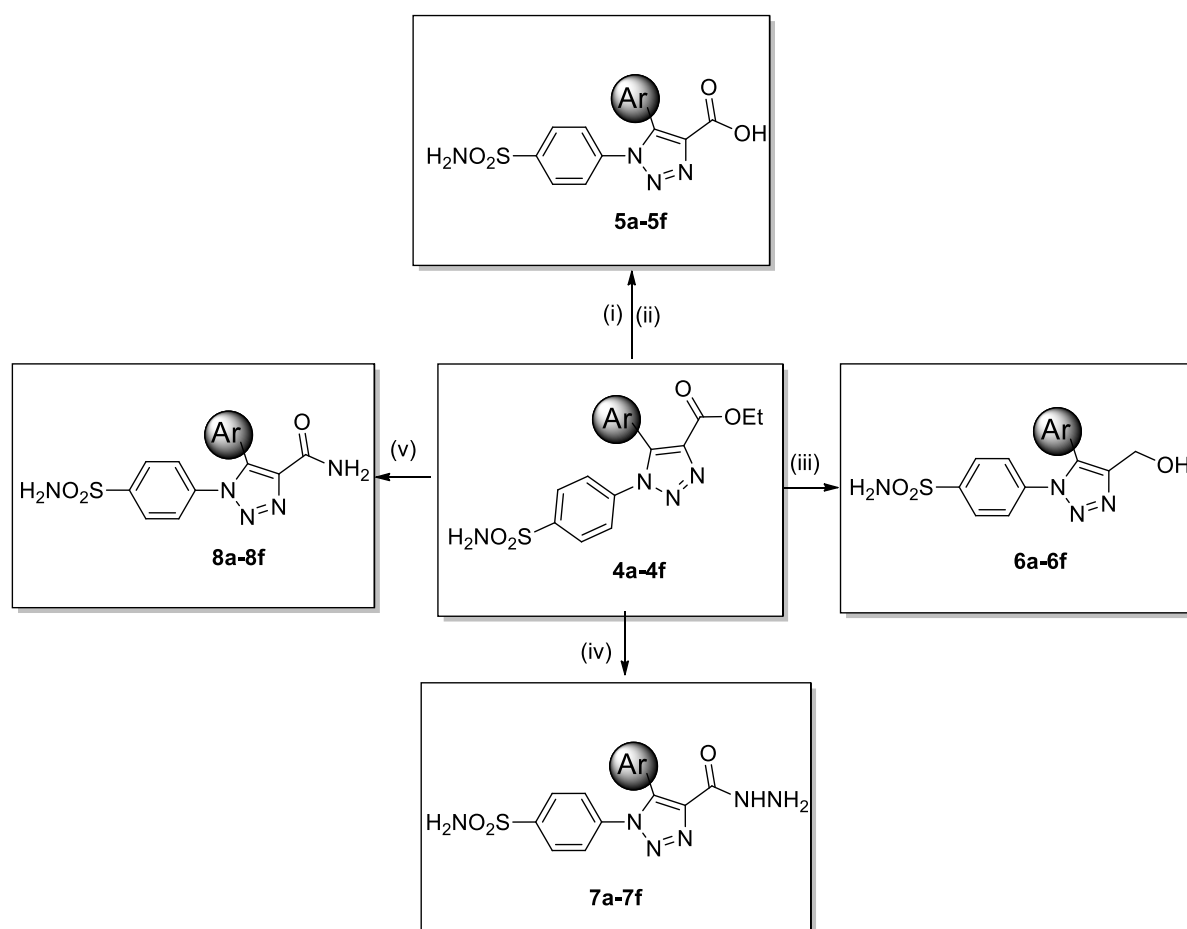


Compounds	a	b	c	d	e	f
Ar	4-CH ₃ C ₆ H ₄	4-F C ₆ H ₄	4-Cl C ₆ H ₄	4-Br C ₆ H ₄	2-Pyridinyl	2-Thienyl

Scheme 1. Synthesis of target compounds **4a-4f**. Reaction conditions: (i) HCl, NaNO₂, H₂O, 0°C; (ii) NaN₃, 0°C; (iii) Piperidine, DMSO, 70°C.

Other derivatives of 1,5-diaryl-1,2,3-triazoles viz carboxylic acids **5a-5f**, methyl alcohols **6a-6f**, carboxylic acid hydrazides **7a-7f** and carboxamides **8a-8f** were synthesized by reacting ethyl carboxylates **4a-4f** with aqueous NaOH, LiAlH₄, hydrazine hydrate, and ammonia solution respectively (Scheme 2) [42-43]. Postulated structures of the synthesized 1,2,3-triazolic benzenesulfonamides were characterized by rigorous analysis of their spectral data (IR, ¹H NMR, ¹³C NMR and HRMS) when their spectral information was found to be in full agreement with the proposed structures. In general, ethyl 1,2,3-triazole carboxylates **4a-4f** were characterized by appearance of a strong characteristic band for C=O in the range 1713-1736 cm⁻¹ in their FT-IR spectra and appearance of a characteristic quartet of two protons and a triplet of three protons in the range 4.23-4.26 ppm and 1.14-1.33 ppm respectively for ethyl protons in their ¹H NMR spectra. The 1,2,3-triazole carboxylic acids **5a-5f** were characterized by a sharp absorption band at 1705-1744 cm⁻¹ corresponding to C=O stretch along with a broad band from 3209 cm⁻¹ to 3265 cm⁻¹ due to O-H stretching of COOH in FT-IR spectra and a broad exchangeable singlet in the range 13.15-13.36 ppm due to acidic proton in ¹H NMR spectra. The methyl alcohols **6a-6f** exhibited a broad band at 3250-3472 cm⁻¹ corresponding to O-H stretch in FT-IR spectra while their ¹H NMR spectra exhibited a triplet in the range 5.17-5.64 ppm along with a doublet in the range 4.50-4.64 ppm corresponding to OH and CH₂ protons respectively. Corresponding hydrazinocarbonyl derivatives **7a-7f** were characterized by a sharp band at 1651-1682 cm⁻¹ for C=O stretching in FT-IR and two exchangeable singlets in the range 9.92-10.01 ppm and 4.49-4.55 ppm for NH and NH₂ protons respectively in ¹H NMR spectra. The 1,2,3-triazole carboxamides **8a-8f** displayed a sharp absorption band at 1643-1675 cm⁻¹ corresponding to C=O stretch in FT-IR and two exchangeable singlets in the range 8.00-8.15 ppm and 7.50-7.65 ppm corresponding

to NH/OH protons in ^1H NMR spectra. Further, all the synthesized compounds exhibited sharp absorption bands in their FT-IR spectra at $\sim 1342\text{ cm}^{-1}$ and $\sim 1165\text{ cm}^{-1}$ for SO_2 stretching, and a sharp singlet at $\sim 7.56\text{ ppm}$ for SO_2NH_2 protons in ^1H NMR spectra.



Compounds	a	b	c	d	e	f
	4-CH ₃ C ₆ H ₄	4-F C ₆ H ₄	4-Cl C ₆ H ₄	4-Br C ₆ H ₄	2-Pyridinyl	2-Thienyl

Scheme 2. Synthesis of target compounds **5a-5f**, **6a-6f**, **7a-7f** and **8a-8f**. Reaction conditions: (i) aq. NaOH, reflux; (ii) H_3O^+ ; (iii) LiAlH_4 , dry THF; (iv) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH, Reflux; (v) NH_3 solution.

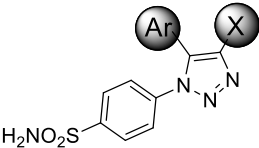
2.2. CA inhibition studies

The target compounds **4a-4f**, **5a-5f**, **6a-6f**, **7a-7f** and **8a-8f** were tested for their efficacy to inhibit 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 isoform hCA IX (associated with tumorigenicity). All the synthesized compounds were screened for their inhibition potential by means of stopped flow carbon dioxide hydration assay and compared with clinically used reference drug acetazolamide (AAZ).

- (a) All the compounds except **5a-5f**, **6a-6d**, **7a**, **7e**, **8d** showed better inhibitory effect ($K_i < 250$ nM) against the cytosolic isoform hCA I as compared to standard drug AAZ. Further, among the synthesized compounds, ethyl carboxylates **4a-4f** were found to be the best hCA I inhibitors while carboxylic acids **5a-5f** were found to be the weakest inhibitors (Table 1).
- (b) All the synthesized compounds moderately inhibited the cytosolic isoforms hCA II ranging between 21.8 nM to 0.807 μ M as compared to reference drug AAZ with K_i 12.1 nM. However most of compounds **4c**, **6a-6f**, **7a-7f**, **8a**, **8d**, **8e**, **8f** inhibited the hCA II with $K_i < 100$ nM (Table 1).
- (c) The membrane bound isoform hCA IV found moderately to strongly inhibited by the synthesized sulfonamides in the range of K_i 35.7 nM to 2.50 μ M. The compounds **4a**, **4c**, **4d**, **5c**, **5d**, **5f**, **5e**, **7c**, **7d**, **8a**, **8c** were most potent inhibitors among the synthesized compounds, K_i ranging from 35.7 nM to 66.2 nM which is even better than reference drug AAZ ($K_i = 74$ nM). In broader sense, derivatives containing 4-chlorophenyl and 4-bromophenyl were found strongest while those having 2-pyridinyl moiety as Ar group were weakest inhibitor of hCA IV in tested compounds (Table 1).
- (d) The membrane bound tumor associated isoform hCA IX is weakly inhibited by all of the reported compounds in the range of K_i 70 nM-2.9 μ M except derivative **6e** which showed better inhibitory property ($K_i = 14.3$ nM) compared to the reference drug AAZ ($K_i = 25.8$ nM) (Table 1).
- (e) Interestingly, in terms of structure activity relationship (SAR), derivatives containing carboxylic acid **5a-5f** have shown weaker inhibition of cytosolic isoform hCA I as compared to standard drug AAZ. In particular, carboxylic acid derivatives **5a** and **5d** were found to be selective inhibitors of glaucoma associated isoforms hCA II and IV at low nanomolar values. During the inhibitory study of tumor associated membrane bound hCA IX isoform, only one compound **6e** was found to be better inhibitor as compared to standard drug AAZ but with poor selectivity over off target isoforms hCA I and II (Table 1).
- (f) A comparative study with our previous work [28] in terms of structure activity relationship (SAR) reveals that compounds containing methyl group at C-5 position of 1,2,3-triazole ring were the best while compounds containing 2-naphthyl were weakest inhibitors of cytosolic isoform hCA I. From this observation it can be concluded that as the bulk at C-5 position of 1,2,3-triazole ring increases their inhibition potency for cytosolic isoform hCA I decreases.

Table 1

Inhibitory potency data for compounds **4a-4f**, **5a-5f**, **6a-6f**, **7a-7f** and **8a-8f** against isozymes hCA I, hCA II, hCA IV, and hCA IX.

Ar = 4-CH ₃ C ₆ H ₄ 4a-8a			K _i (nM)*			
4-F C ₆ H ₄ 4b-8b	CA I		CA II	CA IV	CA IX	
4-Cl C ₆ H ₄ 4c-8c	X = -COOEt	53.2	747.6	36.2	198.3	
4-Br C ₆ H ₄ 4d-8d	-COOH	87.1	356.3	84	633	
2-Pyridinyl 4e-8e	-CH ₂ OH	68	91.5	44.3	1477	
2-Thienyl 4f-8f	-CONHNH ₂	173.8	518.2	53	227.5	
	-CONH ₂	232.1	666.3	836.1	1423	
5a	-COOEt	79.7	376.4	2506.7	237.2	
5b	-COOH	7616.1	553	152.9	1415	
5c	-COOH	613.9	730.7	85.7	1581	
5d	-COOH	377.9	459	44.8	715.5	
5e	-COOH	4715.1	406.3	66.2	1406	
5f	-COOH	881.2	807.5	736.1	2089	
6a	-CH ₂ OH	479.2	707.8	59.8	1307	
6b	-CH ₂ OH	916.1	84.9	648.7	2333	
6c	-CH ₂ OH	322.1	51.8	229.5	2373	
6d	-CH ₂ OH	554.3	29.6	88.3	1213	
6e	-CH ₂ OH	655.7	41	277.9	1730	
6f	-CH ₂ OH	88.4	57.1	1954.2	14.3	
7a	-CONHNH ₂	71.2	21.8	169.2	71.2	
7b	-CONHNH ₂	395	27.2	295.4	737.7	
7c	-CONHNH ₂	95.2	71.3	272.5	2451	
7d	-CONHNH ₂	79.7	48.9	49.5	909	
7e	-CONHNH ₂	203.2	66.2	36.6	1353	
7f	-CONHNH ₂	477.6	92.6	884.9	2905	
8a	-CONH ₂	91	53.3	628.2	2833	
8b	-CONH ₂	194.9	83.7	35.7	73	
8c	-CONH ₂	72.1	637.9	229.4	107.2	
8d	-CONH ₂	90.5	559.5	49.9	116.7	
8e	-CONH ₂	272.9	88.7	79.2	256.4	
8f	-CONH ₂	76	38.3	478.4	730.3	
AAZ	-	87.4	51.6	569.7	225.4	
	-	-	250	12.1	74	25.8

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

(g) Changing the methyl group at C-5 position of 1,2,3-triazole ring with heterocyclic moiety **4e-8e**, **4f-8f** also resulted into overall decrease of inhibition potency for all of the hCA isoforms under study. At the same time it also resulted into better selective inhibition of one isoform over others; e.g. compounds **4f**, **5f**, **6e** and **7e** were found to be selective inhibitors of isoforms hCA I, IV, IX and II respectively.

3. Conclusions

In the present work, we reported a series of thirty novel 1,2,3-triazole derivatives containing primary benzenesulfonamide moiety at N-1 position, different functionalities like ethyl carboxylate **4a-4f**, carboxylic acid **5a-5f**, methyl alcohol **6a-6f**, carboxylic acid hydrazide **7a-7f** and carboxamide **8a-8f** at C-4 position and different/differently substituted aromatic scaffolds at C-5 position of 1,2,3-triazole ring. All the synthesized compounds were assayed as inhibitors of carbonic anhydrase isoforms of pharmacological relevance i.e. cytosolic isoforms (hCA I and hCA II) and membrane bound isoforms (hCA IV and hCA XI). These isoforms were inhibited by the synthesized compounds in low to medium nanomolar range. Most of the compounds showed rather a weak inhibitory potency against hCA I, while some others **4a**, **4c**, **4f**, **6f**, **7c**, **8b** and **8e** showed better inhibition potency in the range of K_i 53 to 80 nM. Against hCA II, nearly all the tested compounds showed moderate inhibition potential in the range of 21.8 nM to 0.807 μ M. For transmembrane isoform hCA IV, in the broader sense, the compounds having 4-chlorophenyl **4c-8c** and 4-bromophenyl **4d-8d** at C-5 position of 1,2,3-triazole ring were found as the most potent inhibitors with low K_i values. Compound **6e** showed better inhibitory effect for tumor associated isoform hCA IX (K_i = 14.3 nM) than reference drug AAZ (K_i = 25.8 nM). In short, it may be concluded that 1,2,3-triazolic benzenesulfonamide scaffold is associated with hCAs inhibition and on further study can prove to be an important pharmacophore for the synthesis of isoform selective CAIs.

4. Experimental protocols

4.1. Chemistry

4.1.1. 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 air- or moisture-sensitive reactions were performed under a nitrogen atmosphere using dried glassware and syringes techniques to transfer solutions. All the reactions were monitored by

thin layer chromatography (TLC) on TLC silica gel on F₂₅₄ 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. ¹H NMR spectra were recorded on 400 MHz, while ¹³C NMR spectra were registered at 100 MHz, using deuterated dimethyl sulfoxide (DMSO-d₆) 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. Multiplicities are described as 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. The coupling constants are expressed in hertz (Hz).

4.1.2. Synthesis of ethyl 1-[4-(aminosulfonyl)phenyl]-5-aryl-1*H*-1,2,3-triazole-4-carboxylates (**4a-4f**)

General procedure: To a solution of appropriate β-diketoester **8a-8f** (16.00 mmol) in DMSO (5 mL) was added piperidine (5 mol%). After 5 min. of stirring at 70° C in silicon oil bath, 4-azidobenzenesulfonamide (15.01 mmol) was added and the mixture was stirred at 70° C for an additional 4-6 hrs and the progress of reaction was monitored by TLC. After the reaction was completed, the reaction mixture was poured into the ice water and the precipitates formed were filtered, washed with water and recrystallized from ethanol.

4.1.2.1. Ethyl 1-[4-(aminosulfonyl)phenyl]-5-(p-tolyl)-1*H*-1,2,3-triazole-4-carboxylate (**4a**)

Yield 80%; mp: 209°C; IR(KBr) (ν, cm⁻¹): 3317, 3225, 3109 (m, N-H stretch), 1713 (s, C=O stretch), 1335, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.94-7.93 (m, 2H, Ar), 7.62-7.57 (m, 4H, Ar, SO₂NH₂), 7.30-7.23 (m, 4H, Ar), 4.23 (q, J = 5.6 Hz, 2H, CH₂), 2.33 (s, 3H, CH₃), 1.17 (t, J = 5.6 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 160.71, 145.50, 141.75, 140.15, 138.33, 136.89, 130.74, 129.31, 127.33, 126.95, 122.78, 61.02, 21.40, 14.38; HRMS (ESI-MS) m/z 387.1121 (M+H)⁺, C₁₈H₁₈N₄O₄SH⁺, calcd 387.1127.

4.1.2.2. Ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1*H*-1,2,3-triazole-4-carboxylate (**4b**)

Yield 75%; mp: 199°C; IR(KBr) (ν , cm^{-1}): 3326, 3077, 2989 (m, N-H stretch), 2989 (m, -CH₃stretch), 1713 (s, C=O stretch), 1327, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.91 (d, J = 8.8 Hz, 2H, Ar), 7.60 (d, J = 8.8 Hz, 2H, Ar), 7.55 (s, 2H, SO₂NH₂), 7.50-7.47 (m, 2H, Ar), 7.29 (t, J = 8.8 Hz, 2H, Ar), 4.24 (q, J = 7.2 Hz, 2H, CH₂), 1.18 (t, J = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 162.88 (d, ¹J_{CF} = 246 Hz), 160.14, 145.09, 140.42, 137.65, 136.66, 132.95 (d, ³J_{CF} = 9 Hz), 126.89, 126.49, 121.85 (d, ⁴J_{CF} = 3 Hz), 115.43 (d, ²J_{CF} = 22 Hz), 56.04, 13.87; HRMS (ESI-MS) m/z 391.0889 (M+H)⁺, C₁₇H₁₅FN₄O₄SH⁺, calcd 391.0876.

4.1.2.3. Ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylate (**4c**)

Yield 76%; mp: 208°C; IR(KBr) (ν , cm^{-1}): 3263, 3186, 3109 (m, N-H stretch), 1713 (s, C=O stretch), 1335, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.92 (d, J = 8.4 Hz, 2H, Ar), 7.60 (d, J = 8.4 Hz, 2H, Ar), 7.53-7.51 (m, 4H, Ar, SO₂NH₂), 7.45 (d, J = 8.4 Hz, 2H, Ar), 4.24 (q, J = 7.2 Hz, 2H, CH₂), 1.17 (t, J = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 160.54, 145.61, 140.65, 138.02, 137.16, 135.40, 132.79, 128.85, 127.38, 126.95, 124.88, 61.13, 14.34; HRMS (ESI-MS) m/z 407.0580 (M+H)⁺, 409.0555 (M+H+2)⁺, C₁₇H₁₅ClN₄O₄SH⁺, calcd 407.0581.

4.1.2.4. Ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-bromophenyl)-1*H*-1,2,3-triazole-4-carboxylate (**4d**)

Yield 81%; ; mp: 227°C; IR(KBr) (ν , cm^{-1}): 3371, 3271, 3103 (m, N-H stretch), 2982 (m, -CH₃stretch), 1713 (s, C=O stretch), 1342, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.92 (d, J = 8.4 Hz, 2H, Ar), 7.65 (d, J = 8.4 Hz, 2H, Ar), 7.61 (d, J = 8.4 Hz, 2H, Ar), 7.55 (s, 2H, SO₂NH₂), 7.38 (d, J = 8.4 Hz, 2H, Ar), 4.24 (q, J = 7.2 Hz, 2H, CH₂), 1.17 (t, J = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 160.09, 145.15, 140.26, 137.56, 136.66, 132.53, 131.32, 126.94, 126.51, 124.79, 123.76, 60.68, 13.89; HRMS (ESI-MS) m/z 451.0075 (M+H)⁺, 453.0057 (M+H+2)⁺, C₁₇H₁₅BrN₄O₄SH⁺, calcd 451.0075.

4.1.2.5. Ethyl 1-[4-(aminosulfonyl)phenyl]-5-(pyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (**4e**)

Yield 70%; mp: 221°C; IR(KBr) (ν , cm^{-1}): 3217, 3086 (m, N-H stretch), 1736 (s, C=O stretch), 1346, 1167 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.55 (dd, J = 4.0 Hz, J = 0.8 Hz, 1H, py), 7.97 (dt, J = 8.0 Hz, J = 1.6 Hz, 1H, py), 7.88 (d, J = 8.8 Hz, 2H,

Ar), 7.85 (d, $J = 6.8$ Hz, 1H, py), 7.58 (d, $J = 8.8$ Hz, 2H, Ar), 7.56 (s, 2H, SO₂NH₂), 7.49 (m, 1H, py), 4.24 (q, $J = 7.2$ Hz, 2H, CH₂), 1.14 (t, $J = 7.2$ Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 159.97, 149.51, 145.19, 144.96, 140.02, 138.00, 137.12, 136.82, 127.24, 126.89, 125.83, 124.83, 56.05, 13.82; HRMS (ESI-MS) m/z 374.0931 (M+H)⁺, C₁₆H₁₅N₅O₄SH⁺, calcd 374.0923.

4.1.2.6. Ethyl 1-[4-(aminosulfonyl)phenyl]-5-(thiophen-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (**4f**)

Yield 75%; mp: 232°C; IR(KBr) (ν , cm⁻¹): 3362, 3194, 3073 (m, N-H stretch), 1728 (s, C=O stretch), 1335, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.97 (dd, $J = 6.8$ Hz, $J = 1.6$ Hz, 2H, Ar), 7.83 (dd, $J = 4.8$ Hz, $J = 1.2$, 1H, th), 7.70 (dd, $J = 6.8$ Hz, $J = 1.6$ Hz, 2H, Ar), 7.59 (s, 2H, SO₂NH₂), 7.36 (dd, $J = 3.6$ Hz, $J = 1.2$ Hz, 1H, th), 7.14 (dd, $J = 4.8$ Hz, $J = 3.6$ Hz, 1H, th), 4.29 (q, $J = 7.2$ Hz, 2H, CH₂), 1.23 (t, $J = 7.2$ Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 160.55, 146.00, 138.19, 137.24, 135.83, 133.23, 131.56, 127.81, 127.38, 127.35, 124.12, 61.30, 14.40; HRMS (ESI-MS) m/z 379.0527 (M+H)⁺, C₁₅H₁₄N₄O₄S₂H⁺, calcd 379.0534.

4.1.3. Synthesis of 1-[4-(aminosulfonyl)phenyl]-5-aryl-1*H*-1,2,3-triazole-4-carboxylic acids (**5a-5f**)

General procedure: An aqueous solution of NaOH (10%, 10 mL) was added into the appropriate 1,2,3-triazolic ester **4a-4f** (1.00 mmol). The mixture was refluxed for 4-5 hrs. Then cooled the solution and the mixture was neutralized with concd HCl in ice bath. The crude white solid was precipitated out which was filtered off, washed with water, dried and recrystallized with appropriate solvent.

4.1.3.1. 1-[4-(Aminosulfonyl)phenyl]-5-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxylic acid (**5a**)

Yield 84%; mp: 177°C; IR(KBr) (ν , cm⁻¹): 3348, 3094 (m, N-H stretch), 3225 (br, O-H stretch), 1713 (s, C=O stretch), 1342, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 13.20 (s, br, 1H, COOH), 7.90 (d, $J = 7.2$ Hz, 2H, Ar), 7.59 (d, $J = 7.6$ Hz, 2H, Ar), 7.55 (s, 2H, SO₂NH₂), 7.27 (d, $J = 7.6$ Hz, 2H, Ar), 7.22 (d, $J = 7.2$ Hz, 2H, Ar), 2.32 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 162.19, 145.38, 141.46, 139.97, 138.44, 137.62, 130.73, 129.32, 127.28, 126.93, 123.09, 21.38; HRMS (ESI-MS) m/z 359.0822 (M+H)⁺, C₁₆H₁₄N₄O₄SH⁺, calcd 359.0814.

4.1.3.2. 1-[4-(Aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (**5b**)

Yield 80%; mp: 187°C; IR(KBr) (ν , cm^{-1}): 3333, 3087 (m, N-H stretch), 3256 (br, O-H stretch), 1706 (s, C=O stretch), 1342, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 13.18 (s, br, 1H, -COOH), 7.90 (dd, $J = 6.8$ Hz, $J = 1.6$ Hz, 2H, Ar), 7.58 (dd, $J = 6.8$ Hz, $J = 1.6$ Hz, 2H, Ar), 7.54 (s, 2H, SO₂NH₂), 7.50–7.45 (m, 2H, Ar), 7.30–7.25 (m, 2H, Ar); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 164.48 (d, ¹J_{CF} = 226 Hz), 162.09, 145.56, 140.58, 138.23, 137.82, 133.24 (d, ³J_{CF} = 8.7 Hz), 127.31, 122.25, (d, ⁴J_{CF} = 3.2 Hz), 115.88 (d, ²J_{CF} = 21.8 Hz); HRMS (ESI-MS) m/z 363.0560 (M+H)⁺, C₁₅H₁₁FN₄O₄SH⁺, calcd 363.0563.

4.1.3.3. 1-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (**5c**)

Yield 88%; mp: 177°C; IR(KBr) (ν , cm^{-1}): 3340 (m, N-H stretch), 3232 (br, O-H stretch), 1735 (s, C=O stretch), 1335, 1080 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 13.25 (s, 1H, OH), 7.93 (d, $J = 8.6$ Hz, 2H, Ar), 7.61 (d, $J = 8.6$ Hz, 2H, Ar), 7.55 (s, 2H, SO₂NH₂), 7.51 (d, $J = 8.4$ Hz, 2H, Ar), 7.45 (d, $J = 8.4$ Hz, 2H, Ar); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 162.06, 145.52, 140.39, 138.17, 137.91, 135.29, 132.81, 128.86, 127.38, 126.95, 125.18; HRMS (ESI-MS) m/z 379.0267 (M+H)⁺, 381.0236 (M+H+2)⁺, C₁₅H₁₁ClN₄O₄SH⁺, calcd 379.0268.

4.1.3.4. 1-[4-(Aminosulfonyl)phenyl]-5-(4-bromophenyl)-1*H*-1,2,3-triazole-4-carboxylic acid (**5d**)

Yield 79%; mp: 180°C; IR(KBr) (ν , cm^{-1}): 3333, 3094 (m, N-H stretch), 3265 (br, O-H stretch), 1744 (s, C=O stretch), 1335, 1111 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 13.25 (s, br, 1H, COOH), 7.92 (d, $J = 8.8$ Hz, 2H, Ar), 7.64 (d, $J = 8.4$ Hz, 2H, Ar), 7.60 (d, $J = 8.4$ Hz, 2H, Ar), 7.54 (s, 2H, SO₂NH₂), 7.37 (d, $J = 8.8$ Hz, 2H, Ar); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 161.62, 145.06, 139.97, 137.70, 137.43, 132.56, 131.32, 126.93, 126.51, 125.11, 123.64; HRMS (ESI-MS) m/z 422.9757 (M+H)⁺, 424.9737 (M+H+2)⁺, C₁₅H₁₁BrN₄O₄SH⁺, calcd 422.9762.

4.1.3.5. 1-[4-(Aminosulfonyl)phenyl]-5-(pyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**5e**)

Yield 94%; mp: 190°C; IR(KBr) (ν , cm^{-1}): 3364, 3094 (m, N-H stretch), 3209 (br, O-H stretch), 1705 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.36 (s, br, 1H, COOH), 8.55-8.54 (m, 1H, py), 7.98-7.93 (m, 4H, py, Ar), 7.58-7.46 (m, 5H, py, Ar, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.91, 149.87, 145.89, 145.31, 140.22, 138.60, 138.31, 137.26, 127.71, 127.30, 126.25, 125.16; HRMS (ESI-MS) m/z 346.0611 ($\text{M}+\text{H}$) $^+$, $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_4\text{SH}^+$, calcd 346.0610.

4.1.3.6. 1-[4-(Aminosulfonyl)phenyl]-5-(thiophen-2-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**5f**)

Yield 89%; mp: 183°C; IR(KBr) (ν , cm^{-1}): 3356, 3101 (m, N-H stretch), 3240 (br, O-H stretch), 1713 (s, C=O stretch), 1358, 1173 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 13.31 (s, br, 1H, COOH), 7.95 (d, $J = 8.4$ Hz, 2H, Ar), 7.80 (d, $J = 4.4$ Hz, 1H, th), 7.68 (d, 2H, $J = 8.4$ Hz, Ar), 7.58 (s, 2H, SO_2NH_2), 7.34 (d, $J = 2.8$ Hz, 1H, th), 7.14-7.12 (m, 1H, th); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.04, 145.90, 138.31, 137.98, 135.48, 133.04, 131.37, 127.80, 127.34, 127.33, 124.47; HRMS (ESI-MS) m/z 351.0222 ($\text{M}+\text{H}$) $^+$, $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_4\text{S}_2\text{H}^+$, calcd 351.0221.

4.1.4. Synthesis of 4-(4-(hydroxymethyl)-5-aryl-1*H*-1,2,3-triazol-1-yl) benzenesulfonamides (**6a-6f**)

General procedure: A solution of 1,2,3-triazolic ester **4a-4f** (1.5 mmol) in dry tetrahydrofuran (30 ml) cooled to 10-15° C was added drop-wise to a cold suspension of LiAlH_4 (3.0 mmol) in dry tetrahydrofuran (5 mL) with stirring under anhydrous condition. After 20 minutes of stirring, the reaction mixture was refluxed for 2 hrs. After completion of reaction, the reaction mixture was neutralized with aqueous solution of 1N HCl and extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized with ethanol.

4.1.4.1. 4-(4-(hydroxymethyl)-5-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)benzenesulfonamide (**6a**)

Yield 65%; mp: 223°C; IR(KBr) (ν , cm^{-1}): 3250 (br, O-H stretch), 3163, 3063, 3032 (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.91 (dd, $J = 6.8$ Hz, $J = 1.6$ Hz, 2H, Ar), 7.57-7.52 (m, 4H, Ar, SO_2NH_2), 7.29-7.22 (m, 4H, Ar), 5.36 (t, $J = 5.6$ Hz, 1H, OH), 4.50 (d, $J = 5.2$ Hz, 2H, CH_2), 2.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 145.79, 144.92, 139.59, 139.12, 136.10, 129.97, 127.45, 126.16, 123.56, 54.37, 21.31; HRMS (ESI-MS) m/z 345.1023 ($\text{M}+\text{H}$) $^+$, $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_3\text{SH}^+$, calcd 345.1021.

4.1.4.2. 4-(4-(hydroxymethyl)-5-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl) benzenesulfonamide (**6b**)

Yield 58%; mp: 215°C; IR(KBr) (ν , cm^{-1}): 3310 (br, O-H stretch), 3225, 3101, 2924 (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.94 (d, $J = 8.4$ Hz, 2H, Ar), 7.57 (d, $J = 8.4$ Hz, 2H, Ar), 7.53 (s, 2H, SO_2NH_2), 7.43 (dd, $J = 8.4$ Hz, $J = 5.6$ Hz, 2H, Ar), 7.34-7.30 (m, 2H, Ar), 5.64-5.17 (br, 1H, OH), 4.52 (s, 2H, CH_2), ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.25 (d, $^1J_{\text{CF}} = 246$ Hz), 146.04, 145.01, 138.91, 135.16, 132.58 (d, $^3J_{\text{CF}} = 8.7$ Hz), 127.49, 126.19, 123.02 (d, $^4J_{\text{CF}} = 3.2$ Hz), 116.52 (d, $^2J_{\text{CF}} = 21.8$ Hz), 54.38; HRMS (ESI-MS) m/z 349.0770 ($\text{M}+\text{H}$) $^+$, $\text{C}_{15}\text{H}_{13}\text{FN}_4\text{O}_3\text{SH}^+$, calcd 349.0770.

4.1.4.3. 4-(4-(hydroxymethyl)-5-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**6c**)

Yield 62%; mp: 130°C; IR(KBr) (ν , cm^{-1}): 3371 (br, O-H stretch), 3232, 3101, (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.93 (d, $J = 8.8$ Hz, 2H, Ar), 7.62-7.50 (m, 6H, Ar, SO_2NH_2) 7.40 (d, $J = 8.8$ Hz, 2H, Ar), 5.40 (t, $J = 5.2$ Hz, 1H, OH), 4.54 (d, $J = 5.2$ Hz, 2H, CH_2), ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 146.51, 145.10, 138.90, 134.94, 134.90, 131.97, 129.49, 127.51, 126.62, 125.51, 54.40; HRMS (ESI-MS) m/z 365.0473 ($\text{M}+\text{H}$) $^+$, 367.0445 ($\text{M}+\text{H}+2$) $^+$, $\text{C}_{15}\text{H}_{13}\text{ClN}_4\text{O}_3\text{SH}^+$, calcd 365.0475.

4.1.4.4. 4-(4-(hydroxymethyl)-5-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**6d**)

Yield 60%; ; mp: 120°C; IR(KBr) (ν , cm^{-1}): 3364 (br, O-H stretch), 3225, 3094, 2947 (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.93 (dd, $J = 6.8$ Hz, $J = 2$ Hz, 2H, Ar), 7.69 (dd, $J = 6.4$ Hz, $J = 2$ Hz, 2H, Ar), 7.58 (dd, $J = 6.8$ Hz, $J = 2$ Hz, 2H, Ar), 7.54 (s, 2H, SO_2NH_2), 7.32 (dd, $J = 6.4$ Hz, $J = 2$ Hz, 2H, Ar), 5.42 (t, $J = 5.6$ Hz, 1H, OH), 4.53 (d, $J = 5.2\text{Hz}$, 2H, CH_2), ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 146.10, 145.06, 138.82, 134.99, 132.41, 132.18, 127.55, 126.23, 125.86, 123.66, 54.38; HRMS (ESI-MS) m/z 408.9988 ($\text{M}+\text{H}$) $^+$, 410.9949 ($\text{M}+\text{H}+2$) $^+$, $\text{C}_{15}\text{H}_{13}\text{BrN}_4\text{O}_3\text{SH}^+$, calcd 408.9970.

4.1.4.5. 4-(4-(hydroxymethyl)-5-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**6e**)

Yield 57%; mp: 220°C; IR(KBr) (ν , cm^{-1}): 3472 (br, O-H stretch), 3178, 3078, 3032 (m, N-H stretch), 1335, 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.56 (d, $J =$

4.4 Hz, 1H, py), 7.99 (dt, $J = 7.6$ Hz, $J = 1.6$ Hz, 1H, py), 7.91 (d, $J = 8.8$ Hz, 2H, Ar), 7.77 (d, $J = 8.4$ Hz, 1H, py), 7.55 (d, $J = 8.8$ Hz, 2H, Ar), 7.53 (s, 2H, SO₂NH₂), 7.47-7.44 (m, 1H, py), 5.43 (t, $J = 5.6$ Hz, 1H, OH), 4.64 (d, $J = 5.2$ Hz, 2H, CH₂), ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 150.32, 146.88, 146.32, 144.81, 139.61, 137.92, 135.07, 127.28, 125.91, 125.76, 124.58, 54.59; HRMS (ESI-MS) m/z 332.0821 (M+H)⁺, C₁₄H₁₃N₅O₃SH⁺, calcd 332.0817.

4.1.4.6. 4-(4-(hydroxymethyl)-5-(thiophen-2-yl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**6f**)

Yield 58%; mp: 222°C; IR(KBr) (ν , cm⁻¹): 3464 (br, O-H stretch), 3240, 3171, 3063 (m, N-H stretch), 1342, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.97 (dd, $J = 6.8$ Hz, $J = 2$ Hz, 2H, Ar), 7.75 (dd, $J = 5.2$ Hz, $J = 1.6$ Hz, 1H, th), 7.67 (dd, $J = 6.8$ Hz, $J = 2$ Hz, 2H, Ar), 7.58 (s, 2H, SO₂NH₂), 7.33 (dd, $J = 3.6$ Hz, $J = 1.2$ Hz, 1H, th), 7.19 (dd, $J = 5.2$ Hz, $J = 3.6$ Hz, 1H, th), 5.44 (t, $J = 5.2$ Hz, 1H, OH), 4.59 (d, $J = 5.2$ Hz, 2H, CH₂), NMR (100 MHz, DMSO-d₆) δ (ppm): 146.08, 145.67, 138.75, 131.09, 130.72, 130.57, 128.37, 127.50, 127.02, 125.82, 54.53; HRMS (ESI-MS) m/z 337.0426 (M+H)⁺, C₁₃H₁₂N₄O₃S₂H⁺, calcd 337.0429.

4.1.5. Synthesis of 4-[4-(hydrazinocarbonyl)-5-aryl-1H-1,2,3-triazol-1-yl]benzenesulfonamides (**7a-7f**)

General procedure: The mixture of a suitable 1,2,3-triazolic ester **4a-4f** (1.0 mmol) and hydrazine hydrate (1.5 mmol) was dissolved in ethanol (12 mL). The reaction mixture was refluxed for 10-12 hrs. Reaction was followed by thin layer chromatography (TLC). After the completion of reaction, some of the solvent was removed under vacuum and allowed to cool at room temperature. The obtained solid was filtered, dried at room temperature and recrystallized from EtOH:THF (1:1) to afford the desired compound in good yield.

4.1.5.1. 4-[4-(hydrazinocarbonyl)-5-(p-tolyl)-1H-1,2,3-triazol-1-yl]benzenesulfonamide (**7a**)
Yield 80%; mp: 187°C; IR(KBr) (ν , cm⁻¹): 3194, 3094 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1157 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 9.84 (s, ex, 1H, NH), 7.90 (d, $J = 8.8$ Hz, 2H, Ar), 7.58 (d, $J = 8.8$ Hz, 2H, Ar), 7.55 (s, 2H, SO₂NH₂), 7.25 (d, $J = 8$ Hz, 2H, Ar), 7.20 (d, $J = 8$ Hz, 2H, Ar), 4.49 (s, br, ex, 2H, NH₂), 2.32 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 159.77, 145.32, 139.80, 139.14, 138.72, 138.54, 130.79, 129.27, 127.35, 126.83, 122.92, 21.37.

4.1.5.2. 4-[4-(hydrazinocarbonyl)-5-(4-fluorophenyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**7b**)

Yield 74%; ; mp: 215°C; IR(KBr) (ν , cm^{-1}): 3078, 3024, 2970 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.92 (s, ex, 1H, NH), 7.91 (d, $J = 6.0$ Hz, 2H, Ar), 7.60-7.26 (m, 8H, SO_2NH_2 , Ar), 4.50 (s, ex, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.70 (d, $^1J_{\text{CF}} = 246$ Hz), 159.11, 144.92, 138.73, 137.87, 137.48, 132.97 (d, $^3J_{\text{CF}} = 8$ Hz), 126.90, 126.38, 121.96 (d, $^4J_{\text{CF}} = 4$ Hz), 115.30 (d, $^2J_{\text{CF}} = 21$ Hz); HRMS (ESI-MS) m/z 377.0829 ($\text{M}+\text{H}$) $^+$, $\text{C}_{15}\text{H}_{13}\text{FN}_6\text{O}_3\text{SH}^+$, calcd 377.0832.

4.1.5.3. 4-[4-(hydrazinocarbonyl)-5-(4-chlorophenyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**7c**)

Yield 81%; mp: 195°C; IR(KBr) (ν , cm^{-1}): 3194, 3124 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1173 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.92 (s, ex, 1H, NH), 7.91 (d, $J = 8.6$ Hz, 2H, Ar), 7.59 (d, $J = 8.6$ Hz, 2H, Ar), 7.54 (s, 2H, SO_2NH_2), 7.49 (d, $J = 8.4$ Hz, 2H, Ar), 7.40 (d, $J = 8.4$ Hz, 2H, Ar), 4.50 (s, ex, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 159.47, 145.45, 139.29, 138.25, 137.74, 135.07, 132.87, 128.75, 127.40, 126.86, 124.99; HRMS (ESI-MS) m/z 393.0540 ($\text{M}+\text{H}$) $^+$, 395.0512 ($\text{M}+\text{H}+2$) $^+$, $\text{C}_{15}\text{H}_{13}\text{ClN}_6\text{O}_3\text{SH}^+$, calcd 393.0536.

4.1.5.4. 4-[4-(hydrazinocarbonyl)-5-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**7d**)

Yield 77%; mp: 215°C; IR(KBr) (ν , cm^{-1}): 3348, 3271, 3225 (m, N-H stretch), 1682 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.93 (s, ex, 1H, NH), 7.91 (d, $J = 8.8$ Hz, 2H, Ar), 7.62-7.58 (m, 4H, Ar), 7.54 (s, 2H, SO_2NH_2), 7.33 (d, $J = 8.8$ Hz, 2H, Ar), 4.49 (s, ex, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 159.03, 145.00, 138.81, 137.80, 137.35, 132.63, 131.23, 126.98, 126.43, 124.92, 123.44; HRMS (ESI-MS) m/z 437.0029 ($\text{M}+\text{H}$) $^+$, 439.0005 ($\text{M}+\text{H}+2$) $^+$, $\text{C}_{15}\text{H}_{13}\text{BrN}_6\text{O}_3\text{SH}^+$, calcd 437.0031.

4.1.5.5. 4-[4-(hydrazinocarbonyl)-5-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**7e**)

Yield 68%; mp: 216°C; IR(KBr) (ν , cm^{-1}): 3248, 3124 (m, N-H stretch), 1682 (s, C=O stretch), 1350, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.01 (s, ex, 1H, NH), 8.49 (d, $J = 4$ Hz, 1H, py), 7.97-7.85 (m, 4H, py, Ar), 7.57-7.54 (m, 4H, Ar,

SO₂NH₂), 7.47-7.44 (m, 1H, py), 4.54 (s, br, ex, 2H, NH₂); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 159.39, 149.83, 145.76, 145.16, 139.90, 138.92, 137.67, 137.15, 127.73, 127.26, 126.23, 124.96; HRMS (ESI-MS) m/z 360.0873 (M+H)⁺, C₁₄H₁₃N₇O₃SH⁺, calcd 360.0879.

4.1.5.6. 4-[4-(hydrazinocarbonyl)-5-(thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**7f**)

Yield 74%; mp: 207°C; IR(KBr) (ν, cm⁻¹): 3310, 3209, 3109 (m, N-H stretch), 1651 (s, C=O stretch), 1391, 1165 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 9.93 (s, ex, 1H, NH), 7.96 (d, J = 8.4 Hz, 2H, Ar), 7.78 (d, J = 5.2 Hz, 1H, th), 7.69 (d, J = 8.4 Hz, 2H, Ar), 7.60 (s, 2H, SO₂NH₂), 7.38 (d, J = 3.2 Hz, 1H, th), 7.11 (t, J = 5.2 Hz, 1H, th), 4.55 (s, br, ex, 2H, NH₂); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 159.11, 145.50, 138.87, 137.95, 132.48, 132.23, 130.64, 127.27, 126.99, 124.26, 56.04 HRMS (ESI-MS) m/z 365.0491 (M+H)⁺, C₁₃H₁₂N₆O₃S₂H⁺, calcd 365.0490.

4.1.6. Synthesis of 1-[4-(Aminosulfonyl)phenyl]-5-aryl-1*H*-1,2,3-triazole-4-carboxamides (**8a-8f**)

General procedure: A mixture of aqueous ammonia solution (5-6 ml) and appropriate 1,2,3-triazolic ester **4a-4f** (1.00 mmol) was stirred at room temperature in a bunged flask for 24-26 hrs. The solid white coloured compound was precipitated out which was filtered off, washed with cold water, dried and recrystallized from ethanol.

4.1.6.1. 1-[4-(Aminosulfonyl)phenyl]-5-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxamide (**8a**)

Yield 75%; mp: 277°C; IR(KBr) (ν, cm⁻¹): 3209, 3086 (m, N-H stretch), 1675 (s, C=O stretch), 1342, 1173 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.00 (s, ex, 1H, NH/OH), 7.91 (d, J = 8 Hz, 2H, Ar), 7.59-7.54 (m, 5H, SO₂NH₂, NH/OH, Ar), 7.26 (d, J = 8 Hz, 2H, Ar), 7.20 (d, J = 8 Hz, 2H, Ar), 3.39 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 162.10, 145.32, 139.70, 139.60, 139.38, 138.58, 130.88, 129.20, 127.30, 126.93, 123.33, 21.38; HRMS (ESI-MS) m/z 358.0979 (M+H)⁺, C₁₆H₁₅N₅O₃SH⁺, calcd 358.0974.

4.1.6.2. 1-[4-(Aminosulfonyl)phenyl]-5-(4-fluorophenyl)-1*H*-1,2,3-triazole-4-carboxamide (**8b**)

Yield 74%; mp: 230°C; IR(KBr) (ν, cm⁻¹): 3209, 3031, 2970 (m, N-H stretch), 1675 (s, C=O stretch), 1342, 1157 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.05 (s, ex, 1H, NH/OH), 7.91 (d, J = 8 Hz, 2H, Ar), 7.59-7.56 (m, 3H, Ar, NH/OH), 7.44-7.41 (m, 2H,

Ar), 7.32 (s, 2H, SO₂NH₂), 7.25 (m, 2H, Ar); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 162.65 (d, ¹J_{CF} = 246 Hz), 161.51, 144.92, 139.25, 138.06, 37.89, 133.04 (d, ³J_{CF} = 8 Hz), 126.84, 126.47, 122.14 (d, ⁴J_{CF} = 3 Hz), 115.23 (d, ²J_{CF} = 22 Hz); HRMS (ESI-MS) m/z 362.0715 (M+H)⁺, C₁₅H₁₂FN₅O₃SH⁺, calcd 362.0723.

4.1.6.3. 1-[4-(Aminosulfonyl)phenyl]-5-(4-chlorophenyl)-1*H*-1,2,3-triazole-4-carboxamide (**8c**)

Yield 74%; mp: 255°C; IR(KBr) (ν, cm⁻¹): 3279, 3225 (m, N-H stretch), 1673 (s, C=O stretch), 1342, 1157 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.06 (s, ex, 1H, OH/NH), 7.92 (d, J = 8.6 Hz, 2H, Ar), 7.59 (d, J = 8.6 Hz, 2H, NH/OH, Ar), 7.53 (s, 2H, SO₂NH₂), 7.48 (d, J = 8.4 Hz, 2H, Ar), 7.41 (d, J = 8.4 Hz, 2H, Ar); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 161.94, 145.46, 139.83, 138.35, 138.29, 135.01, 132.94, 128.69, 127.37, 126.95, 125.20; HRMS (ESI-MS) m/z 378.0428 (M+H)⁺, 380.0401 (M+H+2)⁺, C₁₅H₁₂ClN₅O₃SH⁺, calcd 378.0427.

4.1.6.4. 1-[4-(Aminosulfonyl)phenyl]-5-(4-bromophenyl)-1*H*-1,2,3-triazole-4-carboxamide (**8d**)

Yield 79%; mp: 265°C; IR(KBr) (ν, cm⁻¹): 3279, 3209 (m, N-H stretch), 1672 (s, C=O stretch), 1342, 1173 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.08 (s, ex, 1H, OH/NH), 7.91 (d, J = 8.4 Hz, 2H, Ar), 7.62-7.54 (m, 7H, Ar, SO₂NH₂, OH/NH), 7.33 (d, J = 8.4 Hz, 2H, Ar); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 161.49, 145.01, 139.36, 137.96, 137.84, 132.70, 131.17, 126.94, 126.53, 125.13, 123.37; HRMS (ESI-MS) m/z 421.9910 (M+H)⁺, 423.9889 (M+H+2)⁺, C₁₅H₁₂BrN₅O₃SH⁺, calcd 421.9922.

4.1.6.5. 1-[4-(Aminosulfonyl)phenyl]-5-(pyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxamide (**8e**)

Yield 72%; mp: 220°C; IR(KBr) (ν, cm⁻¹): 3356, 3348 (m, N-H stretch), 1643 (s, C=O stretch), 1335, 1157 (s, SO₂ stretch); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm): 8.49 (d, J = 1.2 Hz, 1H, py), 8.15 (s, ex, 1H, NH/OH), 7.95-7.85 (m, 4H, py, Ar), 7.65 (s, ex, 1H, NH/OH), 7.56-7.44 (m, 5H, py, Ar, SO₂NH₂); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 161.84, 149.63, 145.94, 145.16, 140.43, 138.91, 138.28, 137.07, 127.97, 127.24, 126.27, 124.93; HRMS (ESI-MS) m/z 345.0765 (M+H)⁺, C₁₄H₁₂N₆O₃SH⁺, calcd 345.0770.

4.1.6.6. 1-[4-(Aminosulfonyl)phenyl]-5-(thiophen-2-yl)-1*H*-1,2,3-triazole-4-carboxamide (**8f**)

Yield 70%; mp: 150°C; IR(KBr) (ν , cm^{-1}): 3302, 3225, 3109 (m, N-H stretch), 1659 (s, C=O stretch), 1350, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.08 (s, ex, 1H, NH/OH), 7.96 (d, $J = 8.8$ Hz, 2H, Ar), 7.76 (d, $J = 4.8$ Hz, 1H, th), 7.68 (d, $J = 8.8$ Hz, 2H, Ar), 7.64 (s, ex, 1H, NH/OH), 7.59 (s, 2H, SO_2NH_2), 7.36 (d, $J = 2.8$ Hz, 1H, th), 7.10 (dd, $J = 4.8$ Hz, $J = 4.0$ Hz, 1H, th); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 161.52, 145.48, 139.33, 138.04, 133.07, 132.40, 130.62, 127.16, 127.04, 126.93, 124.41; HRMS (ESI-MS) m/z 350.0381 ($\text{M}+\text{H}$) $^+$, $\text{C}_{13}\text{H}_{11}\text{N}_5\text{O}_3\text{S}_2\text{H}^+$, calcd 350.0381.

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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