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PII: S0223-5234(18)30273-3

DOI: 10.1016/j.ejmech.2018.03.030

Reference: EJMECH 10295

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 17 January 2018

Revised Date: 9 March 2018

Accepted Date: 9 March 2018

Please cite this article as: 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, *European Journal of Medicinal Chemistry* (2018), doi: 10.1016/j.ejmech.2018.03.030.

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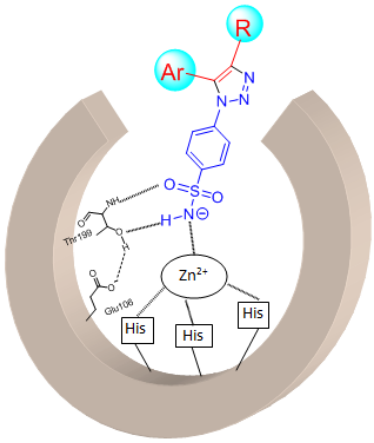
A series of thirty novel 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide moiety were synthesized and evaluated for their inhibition potential against human carbonic anhydrase isoforms, hCA I, II, IV and IX.

Ar =		
	4-CH_3 C_6H_4	**4a-8a**
	4-F C_6H_4	**4b-8b**
	4-Cl C_6H_4	**4c-8c**
	4-Br C_6H_4	**4d-8d**
	2-Pyridyl	**4e-8e**
	2-Thienyl	**4f-8f**



Active site of hCA I, II, IV and IX

R =		
	-COOEt	**4a-4f**
	-COOH	**5a-5f**
	-CH_2OH	**6a-6f**
	-$CONHNH_2$	**7a-7f**
	-$CONH_2$	**8a-8f**

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

The design, synthesis and biological evaluation of a library of 1,2,3-triazole carboxylates incorporating carboxylic acid, hydroxymethyl, carboxylic acid hydrazide, carboxamide and benzenesulfonamide moieties is disclosed. All the novel compounds were investigated for their inhibition potential against carbonic anhydrase (CA, EC 4.2.1.1) human (h) isoforms hCA I, II, IV and IX, well established drug targets. The cytosolic isoform hCA I was inhibited with K_i's ranging between 53.2 nM to 7.616 μM whereas the glaucoma associated cytosolic isoform hCA II was inhibited with K_i's in the range 21.8 nM-0.807 μM. The membrane bound isoform hCA IV, involved in glaucoma and retinitis pigmentosa among others, was effectively inhibited by some of these compounds with K_i < 60 nM, better than the reference drug acetazolamide (AAZ). The tumor associated isoform hCA IX, a recently validated antitumor/antimetastatic drug target, was also effectively inhibited by some of the new sulfonamides, which possess thus the potential to be used as tools for exploring in more details the selective inhibition of hCAs involved in various pathologies.

Keywords: Carbonic anhydrase inhibitors; Isoforms I, II, IV, IX; Benzenesulfonamide; 1,2,3-Triazole.

Abbreviations: CA: Carbonic anhydrase; hCA: human carbonic anhydrase; CAIs: Carbonic anhydrase inhibitors; AAZ: Acetazolamide; K_i: Inhibition constant; nM: nanomolar; μM: micromolar; py: pyridyl; 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 CO_2 hydration reaction to bicarbonate and proton as well as other hydrolytic reactions [1]. Depending upon their localisation in various organisms, 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 the α- class is known to be present in humans, in which 16 isoforms were described which differ 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, ureagenesis, gluconeogenesis, and tumorigenicity, thus representing interesting 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 among others [13]. hCA IV is a membrane bound isoform and its deregulated activity is associated with glaucoma, retinitis pigmentosa and stroke [10]. hCA IX, a transmembrane isoform, being involved in tumor growth, metastases formation and cancer stem cell population dynamics, mainly by causing acidification of extracellular environment and several other process connected to tumorigenesis [14-17]. Thus selective inhibition of some isoforms over others is a challenging approach for obtaining a multitude of different drugs, with minimum side effects.

In the last decade, a lot of work has been done on the synthesis of CA inhibitors (CAIs) belonging to various classes, such as sulfonamides, coumarins, phenols, carboxylic acids, heterocyclic derivatives, dithiocarbamates, etc [18-30]. Out of these, sulfonamides and their bioisosteres like the sulfamates and the sulfamides are potent active site coordinating CAIs which, in deprotonated form, bind to the Zn(II) ion present within the active site of enzyme [31-32]. Many sulfonamide-based drugs, such as acetazolamide (AAZ), methazolamide (MZA), ethoxzolamide (EZA), dorzolamide (DZA), brinzolamide (BRZ), celecoxib (CLX) are known. Some of them are in clinical use as diuretics (targeting hCA II, IV, XII and XIV), antiepileptics (targeting hCA VII and XIV), antiglaucoma (targeting hCA II, IV and XII), or in clinical trials as antitumor/antimetastatic agents (targeting hCA IX and XII) [33-34]. Furthermore, compounds containing 1,2,3-triazole ring system has been studied extensively for the synthesis of novel derivatives, such as **1-3** with pharmacologic applications (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 several CA isoforms [28]. Motivated by the results of our previous work and continuing our interest in designing heterocyclic compounds of potential pharmacologic interest [20-23,27-29,38-39] we report here novel 4-functionalized 1,5-diaryl-1,2,3-triazoles bearing benzenesulfonamide moieties for evaluation of their CA inhibiton potential against hCA I, II, IV and IX.

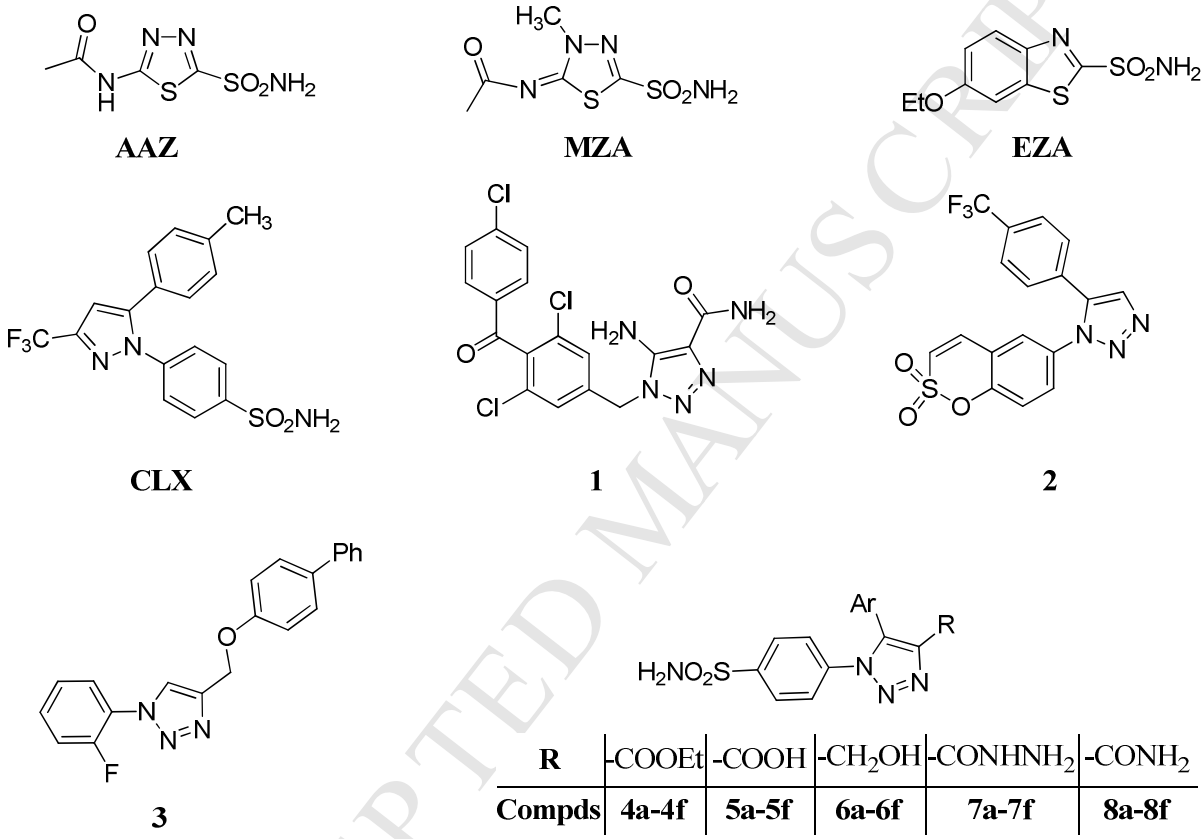


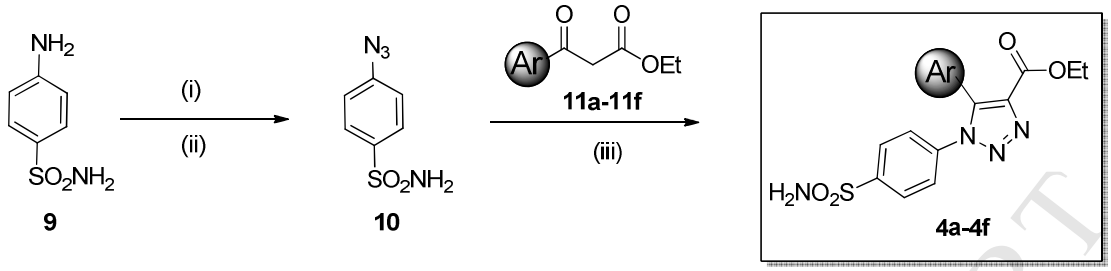
Fig. 1. Clinically used sulfonamide CA inhibitors (**AAZ-CLX)**, and derivatives incorporating the 1,2,3-triazole ring (**1-3**), together with the newly designed sulfonamides **4-8**.

2. Results and discussion

2.1. Chemistry

Synthesis of the 1,2,3-triazole derivatives **4a-4f**, **5a-5f**, **6a-6f**, **7a-7f** and **8a-8f** was performed according to the general synthetic routes as outlined in Schemes 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^{o} 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.**

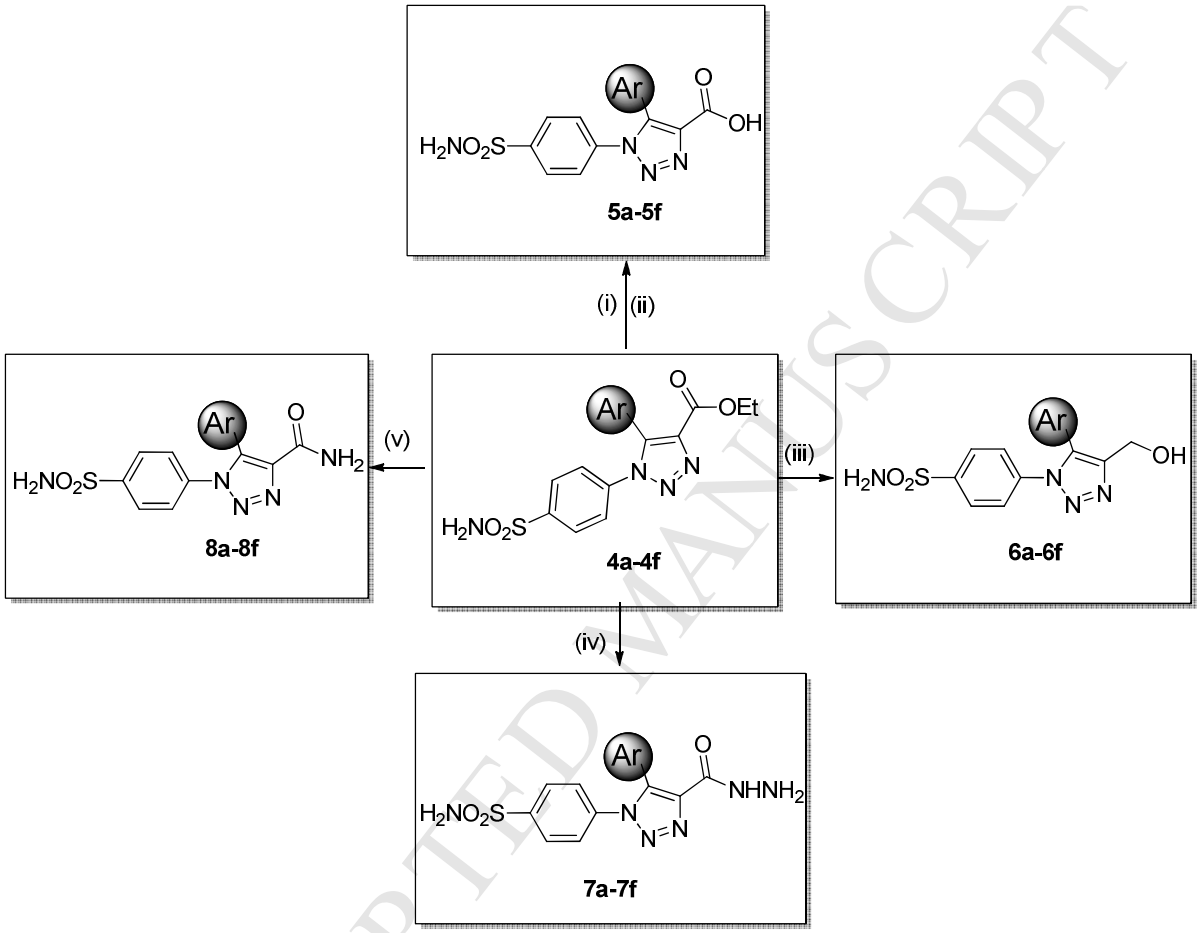


Compounds	a	b	c	d	e	f
Ar	4-CH_3 C_6H_4	4-F C_6H_4	4-Cl C_6H_4	4-Br C_6H_4	2-Pyridyl	2-Thienyl

Scheme 1. Synthesis of target compounds **4a-4f**. Reaction conditions: (i) HCl, $NaNO_2$, H_2O, 0^oC; (ii) NaN_3, 0^oC; (iii) Piperidine, DMSO, 70^oC.

Other derivatives of 1,5-diaryl-1,2,3-triazoles incorporating 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, $LiAlH_4$, hydrazine hydrate, and ammonia solution respectively (Scheme 2) [42-43]. The structures of the synthesized 1,2,3-trizolic benzenesulfonamides were confirmed by rigorous analysis of their spectral data (IR, ^1H NMR, ^{13}C NMR and HRMS). 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 of 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 the C=O stretching vibration along with a broad band at 3209 cm^{-1} - 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 the ^1H NMR spectra. The methyl alcohols **6a-6f** exhibited a broad band at 3250-3472 cm^{-1} corresponding to the O-H stretching in the FT-IR spectra, whereas 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 the OH and CH_2 protons respectively. The corresponding hydrazinocarbonyl derivatives **7a-7f** were characterized by a sharp band at 1651-1682 cm^{-1} for the C=O stretching in the FT-IR spectrum, and two exchangeable singlets in the range 9.92-10.01 ppm and 4.49-4.55 ppm for the NH and NH_2 protons, respectively in the ^1H NMR spectra. The 1,2,3-triazole carboxamides **8a-8f** displayed a sharp absorption

band at 1643-1675 cm^{-1} corresponding to the C=O stretching in FT-IR spectrum and two exchangeable singlets in the range 8.00-8.15 ppm and 7.50-7.65 ppm corresponding to the NH/OH protons in the ^1H NMR spectra. Furthermore, all the synthesized compounds exhibited sharp absorption bands in their FT-IR spectra at ~1342 cm^{-1} and ~1165 cm^{-1} for SO_2 stretching, and a sharp singlet at ~7.56 ppm for SO_2NH_2 protons in the ^1H NMR spectra.



Compounds	a	b	c	d	e	f
Ar	4-CH_3 C_6H_4	4-F C_6H_4	4-Cl C_6H_4	4-Br C_6H_4	2-Pyridyl	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) $NH_2NH_2.H_2O$, 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 hCA IX (associated with tumors). All

the synthesized compounds were screened for their inhibition potential by means of stopped flow carbon dioxide hydration assay and compared with the clinically used reference drug acetazolamide (AAZ).

a) All the synthesized compounds strongly inhibited the cytosolic isoform hCA I with K_i ranging between 53.2 nM to 7.616 μM. Seventeen compounds **4a-4f, 6e-6f**, **7b-7d, 7f, 8a-8c, 8e-8f** showed even better inhibiton potential (with K_i < 250 nM) against the cytosolic isoform hCA I than the standard drug AAZ (K_i = 250 nM). Furthermore, among the synthesized compounds, ethyl carboxylates **4a-4f** were found to be the best hCA I inhibitors (K_i ranging between 53.2-232.1 nM) while carboxylic acids **5a-5f** were found to be the weakest inhibitors (K_i ranging between 377.9-7616.1 nM). It was also found that, amongst the haloderivatives, the compounds with 4-flurorophenyl and 4-chlorophenyl moieties were more effective inhibitors of hCA I as compared to those with 4-bromophenyl moiety (Table 1).
b) All the synthesized compounds moderately inhibited the cytosolic isoform hCA II with K_i ranging between 21.8 nM to 0.807 μM as compared to reference drug AAZ (K_i = 12.1 nM). However, it was found that amongst the synthesized compounds methyl alcohols **6a-6f**, carboxylic acid hydrazides **7a-7f**, and carboxamides **8a-8f**, except **8b** and **8c**, inhibited the cytosolic isoform hCA II with K_i < 100 nM. Furthermore, carboxylic acid hydrazide **7a** was the best inhibitor (K_i = 27.2 nM) whereas carboxylic acid **5e** was the weakest inhibitor (K_i = 807.5 nM) of cytosolic isoform hCA II. Interestingly, the compounds containing 4-chlorophenyl moiety as Ar group were found to be more effective inhibitors of hCA II as compared to those having 4-fluorophenyl moiety (Table 1).
c) The membrane bound isoform hCA IV was strongly inhibited by some of the synthesized sulfonamides, with K_i ranging between 35.7 nM and 2.50 μM. Eleven compounds **4a**, **4c**, **4d**, **5c**, **5d, 5f, 5e**, **7c**, **7d**, **8a** and **8c** were found to be the most potent inhibitors among the synthesized compounds, with K_i ranging from 35.7 nM to 66.2 nM which is even better than the reference drug AAZ (K_i = 74 nM). In a broader sense, derivatives containing 4-chlorophenyl and 4-bromophenyl moieties were found to be more effective inhibitors of hCA IV as compared to those having 2-pyridyl moieties as Ar group (Table 1).
d) The membrane bound tumor associated isoform hCA IX was weakly inhibited by all the synthesized compounds, with K_i's in the range 70 nM-2.9 μM, except for derivative **6e** which showed even better inhibitory potency (K_i = 14.3 nM) as

compared to the reference drug AAZ (K_i = 25.8 nM). Furthermore, the compounds containing 4-fluorophenyl moiety were found to be less effective inhibitors of tumor associated isoform hCA IX as compared to those containing 4-methylphenyl moiety (Table 1).

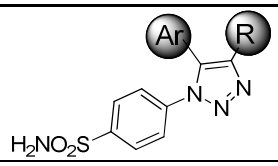
e) Interestingly, in terms of structure activity relationship (SAR), derivatives containing carboxylic acid **5a**-**5f** have shown a weaker inhibiton of cytosolic isoform hCA I as compared to standard drug AAZ. In particular, carboxylic acid derivatives **5a** and **5d** were found to be selective inhibitors of glaucoma associated isoforms hCA II and IV, with efficacies in the low nanomolar range. However, the study of the tumor associated trans-membrane isoform hCA IX, provided only one compound **6e,** as a better inhibitor compared to standard drug AAZ (Table 1).

f) A comparative study with our previous work [28] in terms of structure activity relationship (SAR) revealed that, though a regular trend is not discernible, compounds containing methyl group at C-5 position of the 1,2,3-triazole ring were the most effective CAIs of cytosolic isoform hCA I in their respective class and as bulk of moiety at C-5 position of 1,2,3-triazole ring increases, their inhibition potency for cytosolic isoform hCA I decreases. It is worthy to mention here that 1,2,3-triazole benzenesulfonamide carboxamide having $–CH_3$ group at C-5 position of triazole ring was found to be the best inhibitor of hCA I (K_i = 8.3 nM) whereas 1,2,3-triazole benzenesulfonamide carboxylic acid having 4-methylphenyl moiety at C-5 position of triazole ring was found to be the weakest inhibitor of cytosolic isoform hCA I (K_i = 7616.6 nM).

g) Changing the methyl group at C-5 position of 1,2,3-triazole ring with a heterocyclic moiety, as in **4e**-**8e**, **4f**-**8f**, also resulted into an overall decrease of inhibition potency for all hCA isoforms studied here. At the same time it also led to 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. Furthermore, in a broader sense, compounds containing pyridyl moiety **4e**-**8e** at C-5 position of 1,2,3-triazole ring were found to be less effective inhibitors for all hCA isoforms studied here as compared to those having thienyl moiety **4f**-**8f**.

h) Although it is well demonstrated in literature, on the basis of X-ray crystallography studies, that sulfonamide moiety, in deprotonated form, binds with the Zn (II) ion, the inhibition of CA isoforms by binding of other functionalities like -COOH can't be neglected here. Thus any irregular pattern in the inhibition potential of synthesized

compounds may be due to binding of other functionalities in the molecule via some different mechanism as reported in literature, like –COOH group anchoring to the Zn (II) coordinated water molecule rather than directly binding with Zn (II) ion [31] .

			K_i (nM)*			
Compounds	Ar	R	hCA I	hCA II	hCA IV	hCA IX
4a	4-CH_3 C_6H_4	-COOEt	53.2	747.6	36.2	198.3
4b	4-F C_6H_4	-COOEt	87.1	356.3	84	633
4c	4-Cl C_6H_4	-COOEt	68	91.5	44.3	1477
4d	4-Br C_6H_4	-COOEt	173.8	518.2	53	227.5
4e	2-Pyridyl	-COOEt	232.1	666.3	836.1	1423
4f	2-Thienyl	-COOEt	79.7	376.4	2506.7	237.2
5a	4-CH_3 C_6H_4	-COOH	7616.1	553	152.9	1415
5b	4-F C_6H_4	-COOH	613.9	730.7	85.7	1581
5c	4-Cl C_6H_4	-COOH	377.9	459	44.8	715.5
5d	4-Br C_6H_4	-COOH	4715.1	406.3	66.2	1406
5e	2-Pyridyl	-COOH	881.2	807.5	736.1	2089
5f	2-Thienyl	-COOH	479.2	707.8	59.8	1307
6a	4-CH_3 C_6H_4	-CH_2OH	916.1	84.9	648.7	2333
6b	4-F C_6H_4	-CH_2OH	322.1	51.8	229.5	2373
6c	4-Cl C_6H_4	-CH_2OH	554.3	29.6	88.3	1213
6d	4-Br C_6H_4	-CH_2OH	655.7	41	277.9	1730
6e	2-Pyridyl	-CH_2OH	88.4	57.1	1954.2	14.3
6f	2-Thienyl	-CH_2OH	71.2	21.8	169.2	71.2
7a	4-CH_3 C_6H_4	-$CONHNH_2$	395	27.2	295.4	737.7
7b	4-F C_6H_4	-$CONHNH_2$	95.2	71.3	272.5	2451
7c	4-Cl C_6H_4	-$CONHNH_2$	79.7	48.9	49.5	909
7d	4-Br C_6H_4	-$CONHNH_2$	203.2	66.2	36.6	1353
7e	2-Pyridyl	-$CONHNH_2$	477.6	92.6	884.9	2905
7f	2-Thienyl	-$CONHNH_2$	91	53.3	628.2	2833
8a	4-CH_3 C_6H_4	-$CONH_2$	194.9	83.7	35.7	73
8b	4-F C_6H_4	-$CONH_2$	72.1	637.9	229.4	107.2
8c	4-Cl C_6H_4	-$CONH_2$	90.5	559.5	49.9	116.7
8d	4-Br C_6H_4	-$CONH_2$	272.9	88.7	79.2	256.4
8e	2-Pyridyl	-$CONH_2$	76	38.3	478.4	730.3
8f	2-Thienyl	-$CONH_2$	87.4	51.6	569.7	225.4

AAZ	-	-	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).

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.

3. Conclusions

In the present work, we report a series of thirty novel 1,2,3-triazole derivatives containing primary benzenesulfonamide moiety at N-1 position, and different functionalities such as 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. Furthermore, different/differently substituted aromatic scaffolds are present at C-5 position of 1,2,3-triazole ring. All the synthesized compounds were assayed as inhibitors of CA isoforms of pharmacological relevance i.e. cytosolic isoforms (hCA I and hCA II), membrane bound isoform (hCA IV) and transmembrane isoform (hCA IX). These isoforms were inhibited by the synthesized compounds in the low to medium nanomolar range. Most of the compounds showed rather a weak inhibitory potency against hCA I, whereas some others (**4a**, **4c**, **4f**, **6f**, **7c**, **8b** and **8e)** showed better potency, with K_i in the range 53 to 80 nM. Against hCA II, nearly all the tested compounds showed moderate inhibition potential, with K_i's in the range of 21.8 nM to 0.807 μM. For the transmembrane isoform hCA IV, the compounds having 4-chlorophenyl **4c-8c** and 4-bromophenyl **4d-8d** at the C-5 position of 1,2,3-triazole ring were found to be the most potent inhibitors with low K_i values. Compound **6e** showed the most effective inhibitory action for the tumor associated isoform hCA IX (K_i = 14.3 nM) being a better inhibitor compared to the reference drug AAZ (K_i = 25.8 nM). It may be thus concluded that 1,2,3-triazole benzenesulfonamide scaffold is associated with hCAs inhibitory properties and on further study might be proved 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 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. 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 **11a-11f** (16.00 mmol) in DMSO (5 mL) was added piperidine (5 mol%). After 5 min. of stirring at 70^{o} C in silicon oil bath, 4-azidobenzenesulfonamide (15.01 mmol) was added and the mixture was stirred at 70^{o} 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^{o}C; IR(KBr) (ν, cm^{-1}): 3317, 3225 (m, N-H stretch), 1713 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.94-7.93 (m, 2H, Ar), 7.62-7.57 (m, 4H, Ar, SO_2NH_2), 7.30-7.23 (m, 4H, Ar), 4.23 (q, J = 5.6 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 1.17 (t, J = 5.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^{+}$, $C_{18}H_{18}N_4O_4SH^{+}$, 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}): 3333, 3178 (m, N-H stretch), 1728 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.91 (d, J = 8.8 Hz, 2H, Ar), 7.60 (d, J = 8.8 Hz, 2H, Ar), 7.55 (s, 2H, SO_2NH_2), 7.50-7.47 (m, 2H, Ar), 7.29 (t, J = 8.8 Hz, 2H, Ar), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 1.18 (t, J = 7.2Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{17}H_{15}FN_4O_4SH^+$, 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 (m, N-H stretch), 1713 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.45 (d, J = 8.4 Hz, 2H, Ar), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 1.17 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H+2)^+$, $C_{17}H_{15}ClN_4O_4SH^+$, 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 (m, N-H stretch), 2982 (m, -CH_3stretch), 1713 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.38 (d, J = 8.4 Hz, 2H, Ar), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 1.17 (t, J = 7.2Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H+2)^+$, $C_{17}H_{15}BrN_4O_4SH^+$, 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}): 3248, 3202 (m, N-H stretch), 1736 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.49 (m, 1H, py), 4.24 (q, J = 7.2 Hz, 2H, CH_2), 1.14 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{16}H_{15}N_5O_4SH^+$, 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 (m, N-H stretch), 1728 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 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, CH_2), 1.23 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{15}H_{14}N_4O_4S_2H^+$, 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, 3225 (m, N-H stretch), 2615 (br, O-H stretch), 1713 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.27 (d, J = 7.6 Hz, 2H, Ar), 7.22 (d, J = 7.2 Hz, 2H, Ar), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{16}H_{14}N_4O_4SH^+$, 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, 3256 (m, N-H stretch), 2523 (br, O-H stretch), 1706 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.50–7.45 (m, 2H, Ar,), 7.30-7.25 (m, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{15}H_{11}FN_4O_4SH^+$, 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, 3232 (m, N-H stretch), 2650 (br, O-H stretch), 1735 (s, C=O stretch), 1335, 1080 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.51 (d, J = 8.4 Hz, 2H, Ar), 7.45 (d, J = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H+2)^+$, $C_{15}H_{11}ClN_4O_4SH^+$, 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, 3265 (m, N-H stretch), 2607 (br, O-H stretch), 1744 (s, C=O stretch), 1335, 1111 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.37 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H+2)^+$, $C_{15}H_{11}BrN_4O_4SH^+$, 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, 3209 (m, N-H stretch), 2609 (br, O-H stretch), 1705 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^{1}H 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 $(M+H)^+$, $C_{14}H_{11}N_5O_4SH^+$, 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, 3240 (m, N-H stretch), 2507 (br, O-H stretch), 1713 (s, C=O stretch), 1358, 1173 (s, SO_2 stretch); ^{1}H 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 $(M+H)^+$, $C_{13}H_{10}N_4O_4S_2H^+$, calcd 351.0221.

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

Yield 65%; mp: 223°C; IR(KBr) (ν, cm^{-1}): 3371 (br, O-H stretch), 3232, 3163 (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H 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 $(M+H)^+$, $C_{16}H_{16}N_4O_3SH^+$, 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^{o}C; IR(KBr) (ν, cm^{-1}): 3350 (br, O-H stretch), 3310, 3225 (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H 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, $^{1}J_{CF}$ = 246 Hz), 146.04, 145.01, 138.91, 135.16, 132.58 (d, $^{3}J_{CF}$ = 8.7 Hz), 127.49, 126.19, 123.02 (d, $^{4}J_{CF}$ = 3.2 Hz), 116.52 (d, $^{2}J_{CF}$ = 21.8 Hz), 54.38; HRMS (ESI-MS) m/z 349.0770 $(M+H)^+$, $C_{15}H_{13}FN_4O_3SH^+$, 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^{o}C; IR(KBr) (ν, cm^{-1}): 3394 (br, O-H stretch), 3371, 3232 (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H 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 $(M+H)^+$, 367.0445 $(M+H+2)^+$, $C_{15}H_{13}ClN_4O_3SH^+$, 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^{o}C; IR(KBr) (ν, cm^{-1}): 3375 (br, O-H stretch), 3364, 3225 (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H 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 = 5.2Hz, 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 $(M+H)^+$, 410.9949 $(M+H+2)^+$, $C_{15}H_{13}BrN_4O_3SH^+$, 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^{o}C; IR(KBr) (ν, cm^{-1}): 3464 (br, O-H stretch), 3325, 3171 (m, N-H stretch), 1327, 1149 (s, SO_2 stretch); ^{1}H 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, SO_2NH_2), 7.47-7.44 (m, 1H, py), 5.43 (t, J = 5.6 Hz, 1H, OH), 4.64 (d, J = 5.2Hz, 2H, CH_2), ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{14}H_{13}N_5O_3SH^+$, 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 (m, N-H stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 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, CH_2), NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{13}H_{12}N_4O_3S_2H^+$, calcd 337.0429.

4.1.5. Synthesis of 4-[4-(hydrazinocarbonyl)-5-aryl-1*H*-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)-1*H*-1,2,3-triazol-1-yl]benzenesulfonamide (**7a**)
Yield 80%; mp: 187°C; IR(KBr) (ν, cm^{-1}): 3742, 3394, 3302, 3194 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.25 (d, J =8 Hz, 2H, Ar), 7.20 (d, J = 8 Hz, 2H, Ar), 4.49 (s, br, ex, 2H, NH_2), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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}): 3749, 3410, 3317, 3186 (m, N-H stretch), 1674 (s, C=O stretch), 1327, 1157 (s, SO_2 stretch); ^{1}H 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, $^1J_{CF}$ = 246 Hz), 159.11, 144.92, 138.73, 137.87, 137.48, 132.97 (d, $^3J_{CF}$ = 8 Hz), 126.90, 126.38, 121.96 (d, $^4J_{CF}$ = 4 Hz), 115.30 (d, $^2J_{CF}$ = 21 Hz); HRMS (ESI-MS) m/z 377.0829 $(M+H)^+$, $C_{15}H_{13}FN_6O_3SH^+$, 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}): 3743, 3394, 3263, 3194 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1173 (s, SO_2 stretch); ^{1}H 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 $(M+H)^+$, 395.0512 $(M+H+2)^+$, $C_{15}H_{13}ClN_6O_3SH^+$, 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}): 3734, 3456, 3348, 3271, 3225 (m, N-H stretch), 1682 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H 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 $(M+H)^+$, 439.0005 $(M+H+2)^+$, $C_{15}H_{13}BrN_6O_3SH^+$, 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}): 3730, 3248, 3124 (m, N-H stretch), 1682 (s, C=O stretch), 1350, 1165 (s, SO_2 stretch); ^{1}H 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, SO_2NH_2), 7.47-7.44 (m, 1H, py), 4.54 (s, br, ex, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{14}H_{13}N_7O_3SH^+$, 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}): 3723, 3456, 3310, 3209 (m, N-H stretch), 1651 (s, C=O stretch), 1391, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.38 (d, J = 3.2 Hz, 1H, th), 7.11 (t, J = 5.2 Hz, 1H, th), 4.55 (s, br, ex, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{13}H_{12}N_6O_3S_2H^+$, 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}): 3472, 3371, 3333, 3209 (m, N-H stretch), 1675 (s, C=O stretch), 1342, 1173 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.00 (s, ex, 1H, NH/OH), 7.91 (d, J = 8 Hz, 2H, Ar), 7.59-7.54 (m, 5H, SO_2NH_2, NH/OH, Ar), 7.26 (d, J =8 Hz, 2H, Ar), 7.20 (d, J =8 Hz, 2H, Ar), 3.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{16}H_{15}N_5O_3SH^+$, 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}): 3391, 3209 (m, N-H stretch), 1675 (s, C=O stretch), 1342, 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.25 (m, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{15}H_{12}FN_5O_3SH^+$, 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}): 3394, 3333, 3279, 3225 (m, N-H stretch), 1673 (s, C=O stretch), 1342, 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2), 7.48 (d, J = 8.4 Hz, 2H, Ar), 7.41 (d, J = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H+2)^+$, $C_{15}H_{12}ClN_5O_3SH^+$, 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}): 3456, 3394, 3279 (m, N-H stretch), 1672 (s, C=O stretch), 1342, 1173 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2, OH/NH), 7.33 (d, J = 8.4 Hz, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H+2)^+$, $C_{15}H_{12}BrN_5O_3SH^+$, 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}): 3456, 3356, 3232 (m, N-H stretch), 1643 (s, C=O stretch), 1335, 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) 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, SO_2NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $(M+H)^+$, $C_{14}H_{12}N_6O_3SH^+$, 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^{o}C; IR(KBr) (ν, cm^{-1}): 3456, 3394, 3302, 3225 (m, N-H stretch), 1659 (s, C=O stretch), 1350, 1165 (s, SO_2 stretch); ^{1}H 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 $(M+H)^+$, $C_{13}H_{11}N_5O_3S_2H^+$, 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.

Acknowledgement

The authors, Lalit Vats and Rajiv Kumar, are thankful to University Grants Commission, New Delhi, India for the award of Junior Research Fellowship and for Senior Research Fellowship respectively, and the other, Vikas Sharma, to the Council of Scientific and Industrial Research, New Delhi, India for the award of Junior Research Fellowship.

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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 and IX inhibitors

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Research Highlights

- Synthesis of a library of thirty novel 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide moiety is disclosed.
- All of the synthesized compounds were assayed as inhibitors of carbonic anhydrase isoforms hCA I, II, IV and IX.
- Most of the compounds showed promising inhibition potential for carbonic anhydrase isoforms hCA I, II and IV.
- Heteroaryl derivatives were found to be less effective inhibitors as compared to p-substituted phenyl derivatives.