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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**

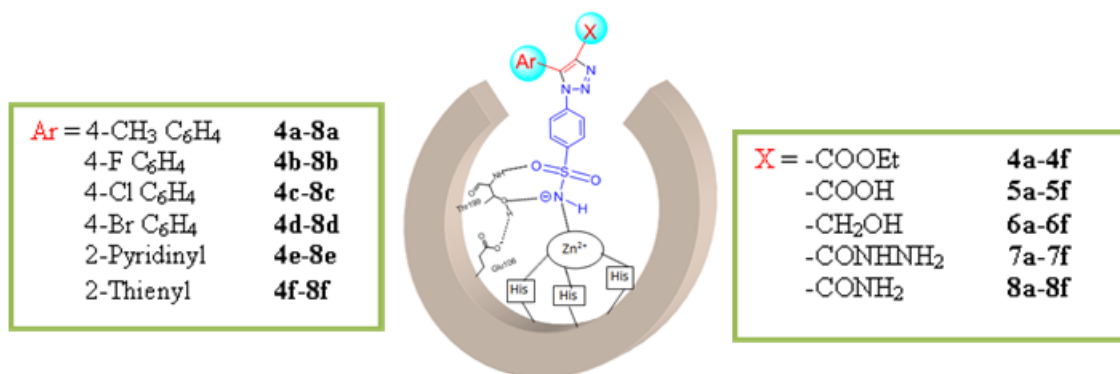
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A series of thirty novel 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide moiety were synthesized and evaluated for their inhibition potential against human carbonic anhydrase isoforms, hCA I, II, IV and IX.



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  $\mu$ M while glaucoma associated cytosolic isoform hCA II was moderately inhibited in the range of  $K_i$ 's 21.8 nM to 0.807  $\mu$ 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.

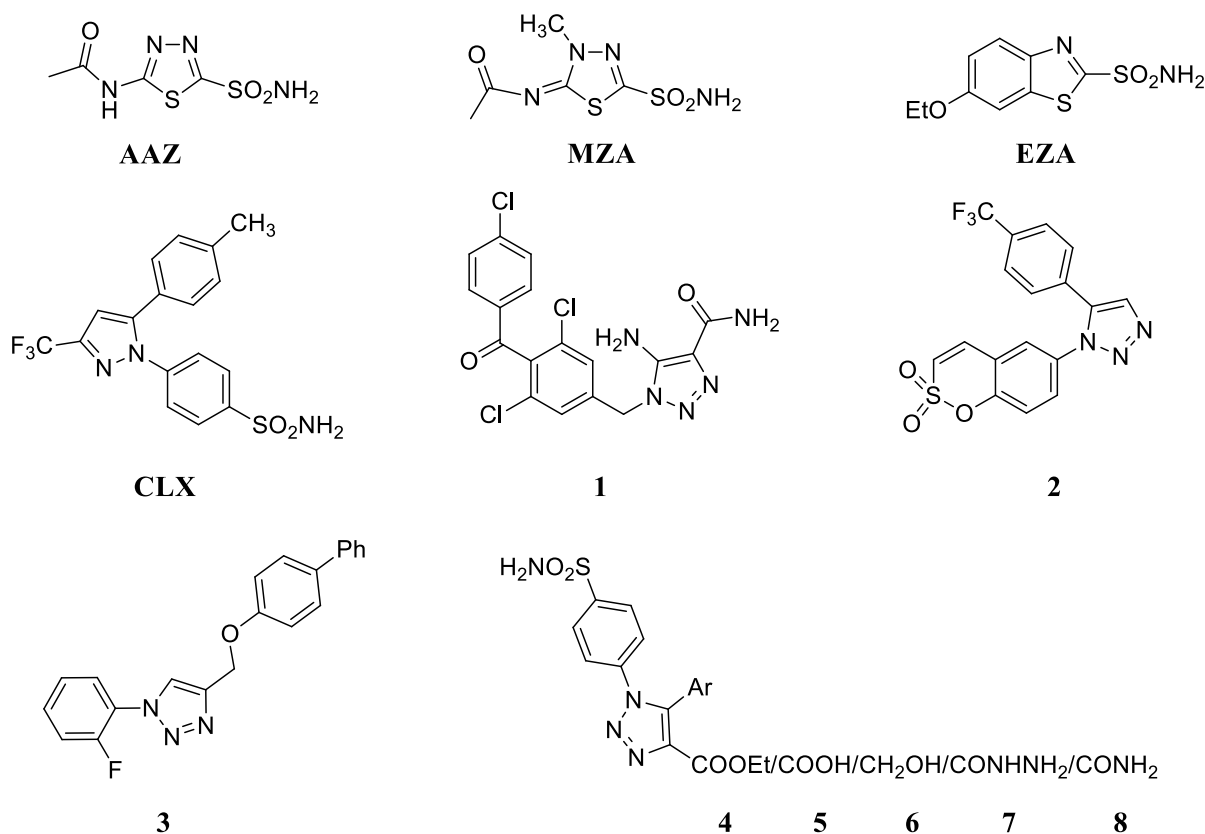
**Keywords:** Carbonic anhydrase inhibitors, Carbonic anhydrase isoforms I, II, IV, IX, Benzenesulfonamide, Acetazolamide, 1,2,3-Triazoles.

**Abbreviations:** CA: Carbonic anhydrase; hCA: human carbonic anhydrase; CAIs: Carbonic anhydrase inhibitors; AAZ: Acetazolamide;  $K_i$ : Inhibition constant; nM: nanomolar;  $\mu$ 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 CO<sub>2</sub> 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,  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ -, and  $\theta$ -CAs [2-4]. Out of these, only  $\alpha$ - 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.

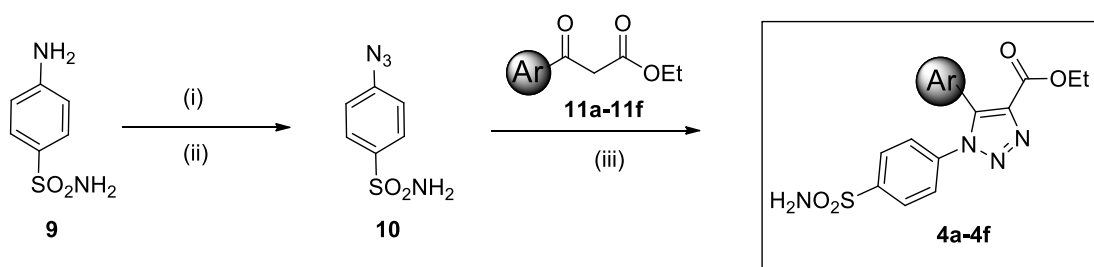


**Fig. 1.** Some clinically used sulfonamide bearing drugs and 1,2,3-triazole ring containing CA inhibitors.

## 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  $\beta$ -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**.

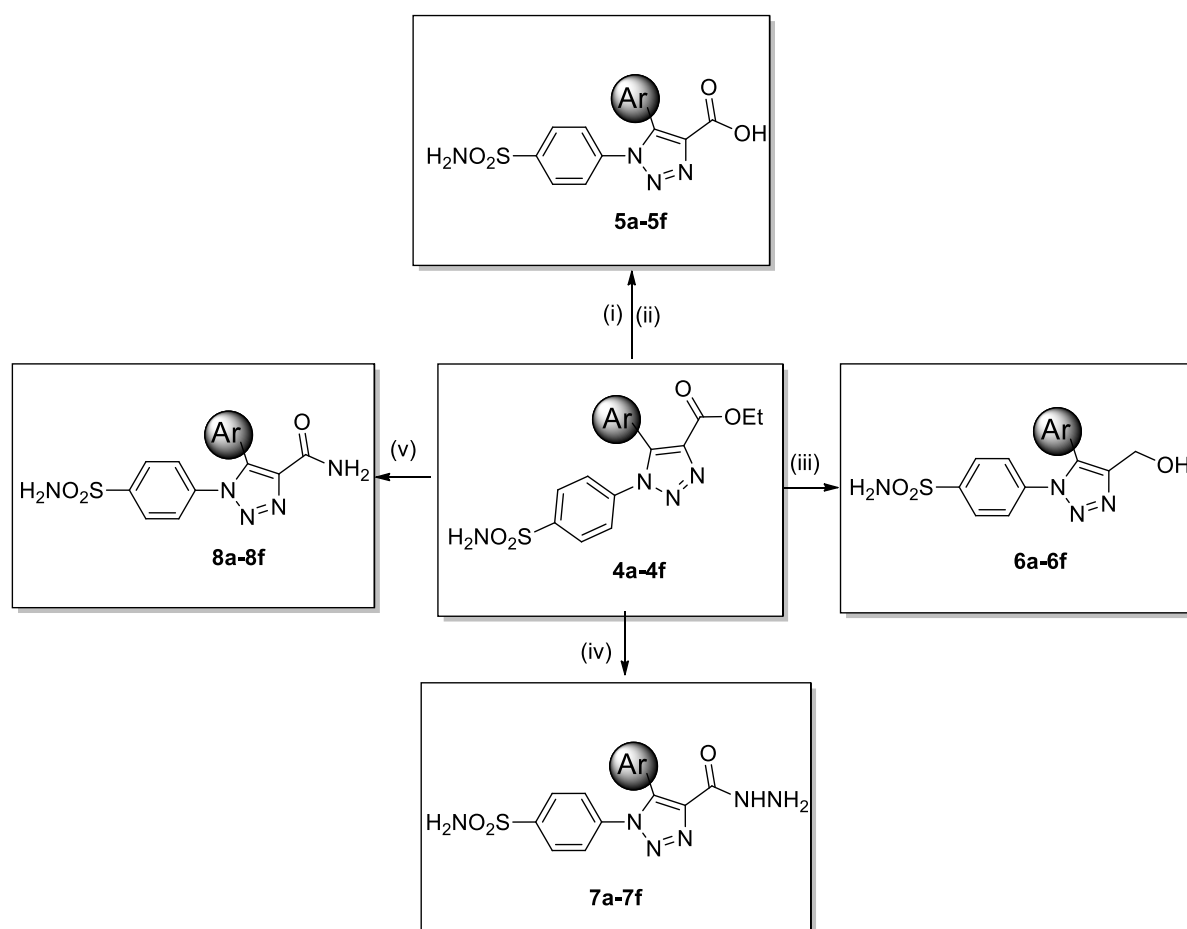


Compounds	a	b	c	d	e	f
Ar	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-F C <sub>6</sub> H <sub>4</sub>	4-Cl C <sub>6</sub> H <sub>4</sub>	4-Br C <sub>6</sub> H <sub>4</sub>	2-Pyridinyl	2-Thienyl

**Scheme 1.** Synthesis of target compounds **4a-4f**. Reaction conditions: (i) HCl, NaNO<sub>2</sub>, H<sub>2</sub>O, 0°C; (ii) NaN<sub>3</sub>, 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, LiAlH<sub>4</sub>, 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, <sup>1</sup>H NMR, <sup>13</sup>C 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<sup>-1</sup> 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 <sup>1</sup>H NMR spectra. The 1,2,3-triazole carboxylic acids **5a-5f** were characterized by a sharp absorption band at 1705-1744 cm<sup>-1</sup> corresponding to C=O stretch along with a broad band from 3209 cm<sup>-1</sup> to 3265 cm<sup>-1</sup> 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 <sup>1</sup>H NMR spectra. The methyl alcohols **6a-6f** exhibited a broad band at 3250-3472 cm<sup>-1</sup> corresponding to O-H stretch in FT-IR spectra while their <sup>1</sup>H 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 CH<sub>2</sub> protons respectively. Corresponding hydrazinocarbonyl derivatives **7a-7f** were characterized by a sharp band at 1651-1682 cm<sup>-1</sup> 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 NH<sub>2</sub> protons respectively in <sup>1</sup>H NMR spectra. The 1,2,3-triazole carboxamides **8a-8f** displayed a sharp absorption band at 1643-1675 cm<sup>-1</sup> 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  $^1\text{H}$  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  $\text{SO}_2$  stretching, and a sharp singlet at  $\sim 7.56\text{ ppm}$  for  $\text{SO}_2\text{NH}_2$  protons in  $^1\text{H}$  NMR spectra.



Compounds	a	b	c	d	e	f
	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4-F C <sub>6</sub> H <sub>4</sub>	4-Cl C <sub>6</sub> H <sub>4</sub>	4-Br C <sub>6</sub> H <sub>4</sub>	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)  $\text{H}_3\text{O}^+$ ; (iii)  $\text{LiAlH}_4$ , dry THF; (iv)  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ , EtOH, Reflux; (v)  $\text{NH}_3$  solution.

## 2.2. CA inhibition studies

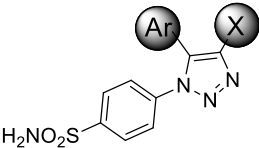
The target compounds **4a-4f**, **5a-5f**, **6a-6f**, **7a-7f** and **8a-8f** were tested for their efficacy to inhibit the physiologically relevant hCA isoforms, cytosolic hCA I (associated with edema), cytosolic hCA II (associated with glaucoma), membrane bound hCA IV (associated with glaucoma and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

\*Mean from 3 different assays, by a stopped flow technique (errors were in the range of  $\pm 5$ -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  $\mu$ 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 F<sub>254</sub> 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. <sup>1</sup>H NMR spectra were recorded on 400 MHz, while <sup>13</sup>C NMR spectra were registered at 100 MHz, using deuterated dimethyl sulfoxide (DMSO-d<sub>6</sub>) as solvent, and tetramethylsilane (TMS) as internal standard at room temperature. Chemical shifts are reported as  $\delta$  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  $\beta$ -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) ( $\nu$ , cm<sup>-1</sup>): 3317, 3225, 3109 (m, N-H stretch), 1713 (s, C=O stretch), 1335, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (ppm): 7.94-7.93 (m, 2H, Ar), 7.62-7.57 (m, 4H, Ar, SO<sub>2</sub>NH<sub>2</sub>), 7.30-7.23 (m, 4H, Ar), 4.23 (q, J = 5.6 Hz, 2H, CH<sub>2</sub>), 2.33 (s, 3H, CH<sub>3</sub>), 1.17 (t, J = 5.6 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3326, 3077, 2989 (m, N-H stretch), 2989 (m, -CH<sub>3</sub>stretch), 1713 (s, C=O stretch), 1327, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (ppm): 7.91 (d,  $J$  = 8.8 Hz, 2H, Ar), 7.60 (d,  $J$  = 8.8 Hz, 2H, Ar), 7.55 (s, 2H, SO<sub>2</sub>NH<sub>2</sub>), 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<sub>2</sub>), 1.18 (t,  $J$  = 7.2 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (ppm): 162.88 (d, <sup>1</sup>J<sub>CF</sub> = 246 Hz), 160.14, 145.09, 140.42, 137.65, 136.66, 132.95 (d, <sup>3</sup>J<sub>CF</sub> = 9 Hz), 126.89, 126.49, 121.85 (d, <sup>4</sup>J<sub>CF</sub> = 3 Hz), 115.43 (d, <sup>2</sup>J<sub>CF</sub> = 22 Hz), 56.04, 13.87; HRMS (ESI-MS)  $m/z$  391.0889 (M+H)<sup>+</sup>, C<sub>17</sub>H<sub>15</sub>FN<sub>4</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3263, 3186, 3109 (m, N-H stretch), 1713 (s, C=O stretch), 1335, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.45 (d,  $J$  = 8.4 Hz, 2H, Ar), 4.24 (q,  $J$  = 7.2 Hz, 2H, CH<sub>2</sub>), 1.17 (t,  $J$  = 7.2 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, 409.0555 (M+H+2)<sup>+</sup>, C<sub>17</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3371, 3271, 3103 (m, N-H stretch), 2982 (m, -CH<sub>3</sub>stretch), 1713 (s, C=O stretch), 1342, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.38 (d,  $J$  = 8.4 Hz, 2H, Ar), 4.24 (q,  $J$  = 7.2 Hz, 2H, CH<sub>2</sub>), 1.17 (t,  $J$  = 7.2 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, 453.0057 (M+H+2)<sup>+</sup>, C<sub>17</sub>H<sub>15</sub>BrN<sub>4</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3217, 3086 (m, N-H stretch), 1736 (s, C=O stretch), 1346, 1167 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.49 (m, 1H, py), 4.24 (q,  $J = 7.2$  Hz, 2H, CH<sub>2</sub>), 1.14 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ , cm<sup>-1</sup>): 3362, 3194, 3073 (m, N-H stretch), 1728 (s, C=O stretch), 1335, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 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<sub>2</sub>), 1.23 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub>H<sup>+</sup>, 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) ( $\nu$ , cm<sup>-1</sup>): 3348, 3094 (m, N-H stretch), 3225 (br, O-H stretch), 1713 (s, C=O stretch), 1342, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.27 (d,  $J = 7.6$  Hz, 2H, Ar), 7.22 (d,  $J = 7.2$  Hz, 2H, Ar), 2.32 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, C<sub>16</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3333, 3087 (m, N-H stretch), 3256 (br, O-H stretch), 1706 (s, C=O stretch), 1342, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.50–7.45 (m, 2H, Ar), 7.30–7.25 (m, 2H, Ar); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm): 164.48 (d, <sup>1</sup>*J*<sub>CF</sub> = 226 Hz), 162.09, 145.56, 140.58, 138.23, 137.82, 133.24 (d, <sup>3</sup>*J*<sub>CF</sub> = 8.7 Hz), 127.31, 122.25, (d, <sup>4</sup>*J*<sub>CF</sub> = 3.2 Hz), 115.88 (d, <sup>2</sup>*J*<sub>CF</sub> = 21.8 Hz); HRMS (ESI-MS) *m/z* 363.0560 (M+H)<sup>+</sup>, C<sub>15</sub>H<sub>11</sub>FN<sub>4</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3340 (m, N-H stretch), 3232 (br, O-H stretch), 1735 (s, C=O stretch), 1335, 1080 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.51 (d, *J* = 8.4 Hz, 2H, Ar), 7.45 (d, *J* = 8.4 Hz, 2H, Ar); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, 381.0236 (M+H+2)<sup>+</sup>, C<sub>15</sub>H<sub>11</sub>ClN<sub>4</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3333, 3094 (m, N-H stretch), 3265 (br, O-H stretch), 1744 (s, C=O stretch), 1335, 1111 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.37 (d, *J* = 8.8 Hz, 2H, Ar); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, 424.9737 (M+H+2)<sup>+</sup>, C<sub>15</sub>H<sub>11</sub>BrN<sub>4</sub>O<sub>4</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3364, 3094 (m, N-H stretch), 3209 (br, O-H stretch), 1705 (s, C=O stretch), 1335, 1157 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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,  $\text{SO}_2\text{NH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3356, 3101 (m, N-H stretch), 3240 (br, O-H stretch), 1713 (s, C=O stretch), 1358, 1173 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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,  $\text{SO}_2\text{NH}_2$ ), 7.34 (d,  $J$  = 2.8 Hz, 1H, th), 7.14-7.12 (m, 1H, th);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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  $\text{LiAlH}_4$  (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  $\text{Na}_2\text{SO}_4$  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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3250 (br, O-H stretch), 3163, 3063, 3032 (m, N-H stretch), 1342, 1165 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 7.91 (dd,  $J$  = 6.8 Hz,  $J$  = 1.6 Hz, 2H, Ar), 7.57-7.52 (m, 4H, Ar,  $\text{SO}_2\text{NH}_2$ ), 7.29-7.22 (m, 4H, Ar), 5.36 (t,  $J$  = 5.6 Hz, 1H, OH), 4.50 (d,  $J$  = 5.2 Hz, 2H,  $\text{CH}_2$ ), 2.33 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3310 (br, O-H stretch), 3225, 3101, 2924 (m, N-H stretch), 1342, 1165 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 7.94 (d,  $J = 8.4$  Hz, 2H, Ar), 7.57 (d,  $J = 8.4$  Hz, 2H, Ar), 7.53 (s, 2H,  $\text{SO}_2\text{NH}_2$ ), 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,  $\text{CH}_2$ ),  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3371 (br, O-H stretch), 3232, 3101, (m, N-H stretch), 1342, 1165 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 7.93 (d,  $J = 8.8$  Hz, 2H, Ar), 7.62-7.50 (m, 6H, Ar,  $\text{SO}_2\text{NH}_2$ ) 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,  $\text{CH}_2$ ),  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3364 (br, O-H stretch), 3225, 3094, 2947 (m, N-H stretch), 1342, 1165 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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,  $\text{SO}_2\text{NH}_2$ ), 7.32 (dd,  $J = 6.4$  Hz,  $J = 2$  Hz, 2H, Ar), 5.42 (t,  $J = 5.6$  Hz, 1H, OH), 4.53 (d,  $J = 5.2$  Hz, 2H,  $\text{CH}_2$ ),  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3472 (br, O-H stretch), 3178, 3078, 3032 (m, N-H stretch), 1335, 1157 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.47-7.44 (m, 1H, py), 5.43 (t,  $J = 5.6$  Hz, 1H, OH), 4.64 (d,  $J = 5.2$  Hz, 2H, CH<sub>2</sub>), <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, C<sub>14</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub>SH<sup>+</sup>, 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) ( $\nu$ , cm<sup>-1</sup>): 3464 (br, O-H stretch), 3240, 3171, 3063 (m, N-H stretch), 1342, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 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<sub>2</sub>), NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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)<sup>+</sup>, C<sub>13</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub>H<sup>+</sup>, 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) ( $\nu$ , cm<sup>-1</sup>): 3194, 3094 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1157 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.25 (d,  $J = 8$  Hz, 2H, Ar), 7.20 (d,  $J = 8$  Hz, 2H, Ar), 4.49 (s, br, ex, 2H, NH<sub>2</sub>), 2.32 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>)  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3078, 3024, 2970 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1157 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (ppm): 9.92 (s, ex, 1H, NH), 7.91 (d,  $J = 6.0$  Hz, 2H, Ar), 7.60-7.26 (m, 8H,  $\text{SO}_2\text{NH}_2$ , Ar), 4.50 (s, ex, 2H,  $\text{NH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3194, 3124 (m, N-H stretch), 1674 (s, C=O stretch), 1335, 1173 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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,  $\text{SO}_2\text{NH}_2$ ), 7.49 (d,  $J = 8.4$  Hz, 2H, Ar), 7.40 (d,  $J = 8.4$  Hz, 2H, Ar), 4.50 (s, ex, 2H,  $\text{NH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3348, 3271, 3225 (m, N-H stretch), 1682 (s, C=O stretch), 1342, 1165 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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,  $\text{SO}_2\text{NH}_2$ ), 7.33 (d,  $J = 8.8$  Hz, 2H, Ar), 4.49 (s, ex, 2H,  $\text{NH}_2$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3248, 3124 (m, N-H stretch), 1682 (s, C=O stretch), 1350, 1165 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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<sub>2</sub>NH<sub>2</sub>), 7.47-7.44 (m, 1H, py), 4.54 (s, br, ex, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) 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)<sup>+</sup>, C<sub>14</sub>H<sub>13</sub>N<sub>7</sub>O<sub>3</sub>SH<sup>+</sup>, 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<sup>-1</sup>): 3310, 3209, 3109 (m, N-H stretch), 1651 (s, C=O stretch), 1391, 1165 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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<sub>2</sub>NH<sub>2</sub>), 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<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) 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)<sup>+</sup>, C<sub>13</sub>H<sub>12</sub>N<sub>6</sub>O<sub>3</sub>S<sub>2</sub>H<sup>+</sup>, 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<sup>-1</sup>): 3209, 3086 (m, N-H stretch), 1675 (s, C=O stretch), 1342, 1173 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ (ppm): 8.00 (s, ex, 1H, NH/OH), 7.91 (d, J = 8 Hz, 2H, Ar), 7.59-7.54 (m, 5H, SO<sub>2</sub>NH<sub>2</sub>, NH/OH, Ar), 7.26 (d, J = 8 Hz, 2H, Ar), 7.20 (d, J = 8 Hz, 2H, Ar), 3.39 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) 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)<sup>+</sup>, C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>SH<sup>+</sup>, 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<sup>-1</sup>): 3209, 3031, 2970 (m, N-H stretch), 1675 (s, C=O stretch), 1342, 1157 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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<sub>2</sub>NH<sub>2</sub>), 7.25 (m, 2H, Ar); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) δ (ppm): 162.65 (d, <sup>1</sup>J<sub>CF</sub> = 246 Hz), 161.51, 144.92, 139.25, 138.06, 37.89, 133.04 (d, <sup>3</sup>J<sub>CF</sub> = 8 Hz), 126.84, 126.47, 122.14 (d, <sup>4</sup>J<sub>CF</sub> = 3 Hz), 115.23 (d, <sup>2</sup>J<sub>CF</sub> = 22 Hz); HRMS (ESI-MS) m/z 362.0715 (M+H)<sup>+</sup>, C<sub>15</sub>H<sub>12</sub>FN<sub>5</sub>O<sub>3</sub>SH<sup>+</sup>, 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<sup>-1</sup>): 3279, 3225 (m, N-H stretch), 1673 (s, C=O stretch), 1342, 1157 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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<sub>2</sub>NH<sub>2</sub>), 7.48 (d, J = 8.4 Hz, 2H, Ar), 7.41 (d, J = 8.4 Hz, 2H, Ar); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) 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)<sup>+</sup>, 380.0401 (M+H+2)<sup>+</sup>, C<sub>15</sub>H<sub>12</sub>ClN<sub>5</sub>O<sub>3</sub>SH<sup>+</sup>, 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<sup>-1</sup>): 3279, 3209 (m, N-H stretch), 1672 (s, C=O stretch), 1342, 1173 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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<sub>2</sub>NH<sub>2</sub>, OH/NH), 7.33 (d, J = 8.4 Hz, 2H, Ar); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) 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)<sup>+</sup>, 423.9889 (M+H+2)<sup>+</sup>, C<sub>15</sub>H<sub>12</sub>BrN<sub>5</sub>O<sub>3</sub>SH<sup>+</sup>, 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<sup>-1</sup>): 3356, 3348 (m, N-H stretch), 1643 (s, C=O stretch), 1335, 1157 (s, SO<sub>2</sub> stretch); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 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<sub>2</sub>NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>) 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)<sup>+</sup>, C<sub>14</sub>H<sub>12</sub>N<sub>6</sub>O<sub>3</sub>SH<sup>+</sup>, 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) ( $\nu$ ,  $\text{cm}^{-1}$ ): 3302, 3225, 3109 (m, N-H stretch), 1659 (s, C=O stretch), 1350, 1165 (s,  $\text{SO}_2$  stretch);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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,  $\text{SO}_2\text{NH}_2$ ), 7.36 (d,  $J = 2.8$  Hz, 1H, th), 7.10 (dd,  $J = 4.8$  Hz,  $J = 4.0$  Hz, 1H, th);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-d}_6$ )  $\delta$  (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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## References

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- [1] B. Żołnowska, J. Sławiński, K. Szafrąński, A. Angeli, C.T. Supuran, A. Kawiak, S. Bartoszewska, Novel 2-(2-arylmethylthio-4-chloro-5-methylbenzenesulfonyl)-1-(1, 3, 5-triazin-2-ylamino) guanidine derivatives: Inhibition of human carbonic anhydrase cytosolic isozymes I and II and the transmembrane tumor-associated isozymes IX and XII, anticancer activity, and molecular modeling studies, *Eur. J. Med. Chem.* (2017) (in press). <https://doi.org/10.1016/j.ejmech.2017.11.005>
- [2] C. Capasso, C.T. Supuran, An overview of the alpha-, beta-and gamma-carbonic anhydrases from Bacteria: can bacterial carbonic anhydrases shed new light on evolution of bacteria?, *J. Enzyme Inhib. Med. Chem.* 30 (2015) 325-332.
- [3] C.T. Supuran, C. Capasso, The  $\eta$ -class carbonic anhydrases as drug targets for antimalarial agents, *Expert Opin. Ther. Targets* 19 (2015) 551-563.
- [4] E. Licsandrua, M. Tancb, I. Kocsisa, M. Barboiua, C.T. Supuran, A class of carbonic anhydrase I-selective activators, *J. Enzyme Inhib. Med. Chem.* 32 (2017) 37-46.
- [5] M. Falsini, L. Squarcialupi, D. Catarzi, F. Varano, M. Betti, L.D.C. 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.
- [6] L. De Luca, F. Mancuso, S. Ferro, M.R. Buemi, A. Angeli, S. Del Prete, C. Capasso, C.T. Supuran, R. Gitto, Inhibitory effects and structural insights for a novel series of coumarin-based compounds that selectively target human CA IX and CA XII carbonic anhydrases, *Eur. J. Med. Chem.* (2017) (in press).  
<http://dx.doi.org/10.1016/j.ejmech.2017.11.061>.
- [7] J. Slawinski, Z. Brzozowski, B. Zolnowska, K. Szafranski, A. Pogorzelska, D. Vullo, C.T. Supuran, Synthesis of a new series of N 4-substituted 4-(2-aminoethyl) benzenesulfonamides and their inhibitory effect on human carbonic anhydrase cytosolic isozymes I and II and transmembrane tumor-associated isozymes IX and XII, *Eur. J. Med. Chem.* 84 (2014) 59-67.
- [8] R. Perfetto, S. Del Prete, D. Vullo, G. Sansone, C. Barone, M. Rossi, C.T. Supuran, C. Capasso, Biochemical characterization of the native  $\alpha$ -carbonic anhydrase purified from the mantle of the Mediterranean mussel, *Mytilus galloprovincialis*, *J. Enzyme Inhib. Med. Chem.* 32 (2017) 632-639.

- 
- [9] C.T. Supuran, Carbonic anhydrases: from biomedical applications of the inhibitors and activators to biotechnological use for CO<sub>2</sub> capture, *J. Enzyme Inhib. Med. Chem.* 28 (2013) 229-230.
- [10] W.M. Eldehna, M.F. Abo-Ashour, A. Nocentini, P. Gratteri, I.H. Eissa, M. Fares, O.E. Ismael, H.A. Ghabbour, M.M. Elaasser, H.A. Abdel-Aziz, C.T. Supuran, Novel 4/3-((4-oxo-5-(2-oxoindolin-3-ylidene) thiazolidin-2-ylidene) amino) benzenesulfonamides: Synthesis, carbonic anhydrase inhibitory activity, anticancer activity and molecular modelling studies, *Eur. J. Med. Chem.* 139 (2017) 250-262.
- [11] B.B. Gao, A. Iermont, S. Rook, S.J. Fonda, V.J. Srinivasan, M. Wojtkowski, J.G. Fujimoto, R.L. Avery, P.G. Arrigg, S.E. Bursell, L.P. Aiello, E.P. Feener, Extracellular carbonic anhydrase mediates hemorrhagic retinal and cerebral vascular permeability through prekallikrein activation, *Nat. Med.* 13 (2007) 181-188.
- [12] M.D. Altıntop, B. Sever, G.A. Çiftçi, K. Kucukoglu, A. Ozdemir, S.S. Soleimani, H. Nadaroglu, Z.A. Kaplancıklı, Synthesis and evaluation of new benzodioxole-based dithiocarbamate derivatives as potential anticancer agents and hCA-I and hCA-II inhibitors, *Eur. J. Med. Chem.* 125 (2017) 190-196.
- [13] N. Hen, M. Bialer, B. Yagen, A. Maresca, M. Aggarwal, A.H. Robbins, R. McKenna, A. Scozzafava, C.T. Supuran, Anticonvulsant 4-aminobenzenesulfonamide derivatives with branched-alkylamide moieties: X-ray crystallography and inhibition studies of human carbonic anhydrase isoforms I, II, VII, and XIV, *J. Med. Chem.* 54 (2011) 3977-3981.
- [14] 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.
- [15] 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.
- [16] D. Fukumura, R.K. Jain, Tumor microenvironment abnormalities: causes, consequences, and strategies to normalize, *J. Cell. Biochem.* 101 (2007) 937-949.
- [17] Z. Hou, B. Lin, Y. Bao, H. Yan, M. Zhang, X. Chang, X. Zhang, Z. Wang, G. Wei, M. Cheng, Y. Liu, C. Guo, Dual-tail approach to discovery of novel carbonic anhydrase IX inhibitors by simultaneously matching the hydrophobic and hydrophilic halves of the active site, *Eur. J. Med. Chem.* 132 (2014) 1-10.

- 
- [18] T. Arslan, G. Celik, H. Celik, M. Senturk, N. Yaylı, D. Ekinçi, Synthesis and Biological Evaluation of Novel Bischalcone Derivatives as Carbonic Anhydrase Inhibitors, *Archiv. Der. Pharmazie* 349 (2016) 741-748.
- [19] M.O. Karatas, B. Alici, U. Cakir, E. Cetinkaya, D. Demir, A. Ergün, O. Arslan, Synthesis and carbonic anhydrase inhibitory properties of novel coumarin derivatives, *J. Enzyme Inhib. Med. Chem.* 28 (2013) 299-304.
- [20] 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.
- [21] 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.
- [22] 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.
- [23] 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.
- [24] S. Işık, D. Vullo, S. Durdagi, D. Ekinçi, M. Şentürk, A. Çetin, C.T. Supuran, Interaction of carbonic anhydrase isozymes I, II, and IX with some pyridine and phenol hydrazinecarbothioamide derivatives, *Bioorg. Med. Chem. Lett.* 25(2015) 5636-5641.
- [25] E.A. Türkoğlu, M. Şentürk, C.T. Supuran, D. Ekinçi, Carbonic anhydrase inhibitory properties of some uracil derivatives, *J. Enzyme Inhib. Med. Chem.* 32 (2017) 74-77.
- [26] 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.
- [27] 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.
- [28] R. Kumar, V. Sharma, S. Bua, C.T. Supuran, P.K. Sharma, Synthesis and biological evaluation of benzenesulphonamide-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.
- [29] 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.
- [30] A. Nocentini, F. Carta, M. Ceruso, G. Bartolucci, C.T. Supuran, Click-tailed coumarins with potent and selective inhibitory action against the tumor-associated carbonic anhydrases IX and XII, *Bioorg. Med. Chem.* 23 (2015) 6955-6966.
- [31] C.T. Supuran, How many carbonic anhydrase inhibition mechanisms exist?, *J. Enzyme Inhib. Med. Chem.* 31 (2016) 345-360.
- [32] W.M. Eldehna, G.H. Al-Ansary, S. Bua, A. Nocentini, P. Gratteri, A. Altoukhy, H. Ghabbour, H.Y. Ahmed, C.T. Supuran, Novel indolin-2-one-based sulfonamides as carbonic anhydrase inhibitors: Synthesis, in vitro biological evaluation against carbonic anhydrases isoforms I, II, IV and VII and molecular docking studies, *Eur. J. Med. Chem.* 127 (2017) 521-530.
- [33] 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.
- [34] S. Angapelly, P.S. Ramya, A. Angeli, S.M. Monti, M. Buonanno, M. Alvala, M. Arifuddin, Discovery of 4-sulfamoyl-phenyl- $\beta$ -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.
- [35] L.Y. Ma, L.P. Pang, B. Wang, M. Zhang, B. Hu, D.Q. Xue, K.P. Shao, B.L. Zhang, Y. Liu, E. Zhang, H.M. Liu, Design and synthesis of novel 1,2,3-triazole-pyrimidine hybrids as potential anticancer agents, *Eur. J. Med. Chem.* 86 (2014) 368-380.
- [ 36 ] A. Grandane, M. Tanc, R. Zalubovskis, C.T. Supuran, 6-Triazolyl-substituted sulfocoumarins are potent, selective inhibitors of the tumor-associated carbonic anhydrases IX and XII, *Bioorg. Med. Chem. Lett.* 24 (2014) 1256-1260.
- [37] A.A. Ali, D. Gogoi, A.K. Chaliha, A.K. Buragohain, P. Trivedi, P.J. Saikia, P.S. Gehlot, A. Kumar, V. Chaturvedi, D. Sarma, Synthesis and biological evaluation of novel

- 
- 1,2,3-triazole derivatives as anti-tubercular agents, *Bioorg. Med. Chem.* 27 (2017) 3698-3703.
- [38] 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.
- [39] 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.
- [40] Y. Morimoto, F. Matsuda, H. Shirahama, Synthetic studies on virantmycin. 1. Total synthesis of (±)-virantmycin and determination of its relative stereochemistry, *Tetrahedron* 52 (1996) 10609-10630.
- [41] J.M. Holub, K.O. Colin, A. Getzel, A. Argenti, M.A. Evans, D.C. Smith, G.A. Dalglish, S. Rifat, D.L. Wilson, B.M. Taylor, U. Miott, J. Glersaye, K.S. Lal, B.J. McCranor, J.D. Berkowitz, R.B. Miller, J.R. Lukens, K. Krumpe, J.T. Gupton, B.S. Burnham, Lipid-Lowering Effects of Ethyl 2-Phenacyl-3-aryl-1H-pyrrole- 4-carboxylates in Rodents, *Molecules* 9 (2004) 134-157.
- [42] T. Rogez-Florent, S. Meignan, C. Foulon, P. Six, A. Gros, C. Bal-Mahieu, P. Depreux, New selective carbonic anhydrase IX inhibitors: synthesis and pharmacological evaluation of diarylpyrazole-benzenesulfonamides, *Bioorg. Med. Chem.* 21 (2013) 1451-1464.
- [43] D. Kumar, V. Judge, R. Narang, S. Sangwan, E. De Clercq, J. Balzarini, B. Narasimhan, Benzylidene/2-chlorobenzylidene hydrazides: Synthesis, antimicrobial activity, QSAR studies and antiviral evaluation, *Eur. J. Med. Chem.* 45 (2010) 2806-2816.