Bioorganic Chemistry 85 (2019) 198–208

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Synthesis of novel benzenesulfonamide bearing 1,2,3-triazole linked hydroxy-trifluoromethylpyrazolines and hydrazones as selective carbonic anhydrase isoforms IX and XII inhibitors

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

[a] Department of Chemistry, Kurukshetra University, Kurukshetra 136119, India
[b] Università degli Studi di Firenze, Laboratorio di Chimica Bioinorganica, Rm 188, and Neurofarba Department, Sezione di Scienze Farmaceutiche, Via U. Schiff 6, I-50019 Sesto Fiorentino, Firenze, Italy

ARTICLE INFO

Keywords:
Pyrazolines
Hydrazones
1,2,3-Triazole
Benzenesulfonamide
Carbonic anhydrase isoforms I, II, IX, XII

ABSTRACT

A series of twenty four hydroxy-trifluoromethylpyrazoline-carbonyl-1,2,3-triazoles and four hydrazones bearing benzenesulfonamide moieties was obtained by condensation of carboxyhydrazides with substituted 1,3-diketones. All the newly synthesized compounds were investigated as inhibitors of physiologically and pharmacologically relevant human (h) carbonic anhydrsae (CA, EC 4.2.1.1) cytosolic isoforms hCA I and II, as well as transmembrane tumor-assosciated isoforms hCA IX and XII. These compounds exhibited excellent CA inhibitory potency against the four CA isoenzymes as compared to clinically used reference drug acetazolamide (AAZ). Some compounds bearing bulkier group at C-5′ position of 1,2,3-triazoles ring were weaker inhibitors of hCA I. Inhibition assay against hCA II indicates, that several derivatives exhibited upto 27-fold more effective inhibitory activity compared to AAZ. Five of the assayed compounds displayed low nanomolar potency ($K_i \leq 10$ nM) against hCA IX, whereas five compounds were found to be endowed with excellent inhibitory potencies ($K_i \leq 5$ nM) against hCA XII. The biological activity profile presented herein will be useful for designing new leads and provide candidates for preclinical investigations.

1. Introduction

Carbonic anhydrases (CA, EC 4.2.1.1) are metalloenzymes using the zinc ion as cofactor in the active site and generates hydrogencarbonate and a proton (or a hydronium cation) by catalyzing the reversible reaction between CO_2 and water with rates approaching diffusion-controlled limits ($k_{cat}/K_M \sim 10^8\ M^{-1}\ s^{-1}$) [1–3]. CAs are ubiquitous enzymes found in all organisms over the tree of life and are engaged in physiological functions including pH regulation, biosynthetic processes (ureagenesis, lipogenesis, gluconeogenesis), CO_2 homeostasis, respiration, production of biological fluids, lung electrolyte secretion, calcification, chemosensing [4], and in metabolic/signaling pathways (e.g., sexual development in fungi) in many pathogens [5–7]. Indeed seven (α, β, γ, δ, ζ, η and θ-CAs) genetic families encoding CAs have involved in organisms all over the tree of life, assuring the homeostasis of CO_2, H^+ and bicarbonate, which differ in their central metal active ion [8–10]. α-CAs is the prominent class in vertebrates, with at least sixteen different hCAs isoforms encoded in their genome [11–13]. Out of the fifteen human isoforms (CA XV is not encoded in the primate genome), hCA I and II, the most abundant isozymes, are primarily involved in important physiologic processes such as respiration and regulation of the acid/base homeostasy, being drug targets in retinal pathologies, cerebral edema, glaucoma and epilepsy [14]. On the other hand, hCA IX and XII are multidomain proteins which contribute for creating the pH regulating system during tumor proliferation, producing an extracellular acidosis, thus helping the growth of tumor cells in hypoxic and acidic microenvironment [15–17]. Therefore, specifically targeting the transmembrane tumor-associated isozymes hCA IX and XII over the off-target hCA I and II is a promising strategy for designing effective and safer agents in the cancer therapy, with one such compound (SLC-0111) in Phase II clinical studies [18].

The tissue dependent expression of CA isozymes regulates variety of biological functions that makes them targets for developing the CA

Abbreviations: CA, carbonic anhydrase; hCA, human carbonic anhydrase; CAIs, carbonic anhydrase inhibitors; AAZ, acetazolamide; K_i, inhibition constant; nM, nanomolar

* Corresponding authors.
E-mail addresses: claudiu.supuran@unifi.it (C.T. Supuran), pksharma@kuk.ac.in (P.K. Sharma).

https://doi.org/10.1016/j.bioorg.2019.01.002
Received 4 November 2018; Received in revised form 30 December 2018; Accepted 1 January 2019
Available online 03 January 2019
0045-2068/

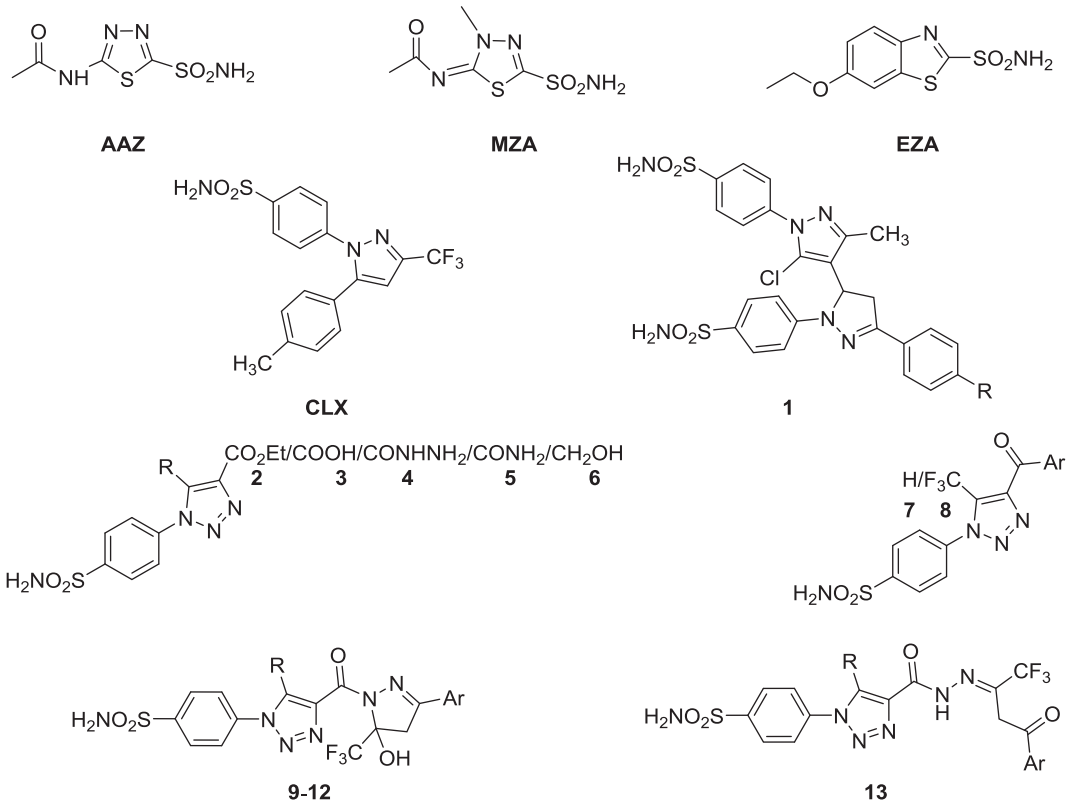


Fig. 1. Chemical structures of the clinically used sulfonamide CA inhibitors and derivatives incorporating the pyrazoles, pyrazolines and 1,2,3-triazole ring **1–8**, together with the newly designed sulfonamides **9–13**.

inhibitor (CAI) based drugs. Primary sulfonamide based CAI drugs such as acetazolamide (AAZ), methazolamide (MZA), ethoxzolamide (EZA), celecoxib (CLX), etc. (Fig. 1) are clinically used for decades to treat several diseases such as glaucoma, edema and also for the management of osteoporosis, idiopathic intracranial hypertension, etc. [19,20]. Sulfonamide inhibits CA activity by swapping water molecule from the zinc coordination sphere. The binding of sulfonamide to metal active site is irreversible and the removal of water molecule from the active site of metal inhibits all the reactions responsible for the activity of CA, which is crucial for catalysis [21,22].

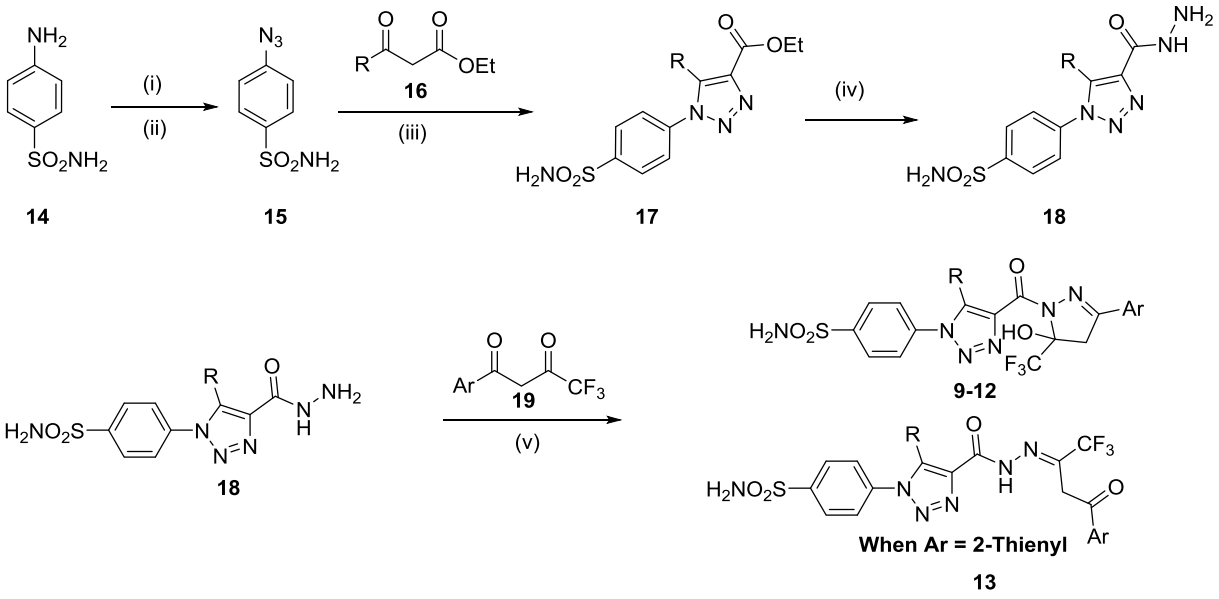
Many contributions in the literature survey revealed that the pyrazolines and 1,2,3-triazoles [23–25] represent an integral biological architecture in medicinal chemistry associated with a diverse array of activities such as anti-inflammatory [26], antimicrobial [27], antitumor [28–30], antifungal [31], antiproliferative [32], anti-tubercular [33] and CAI activities [23–25]. In a previous study from our group, some pyrazolylpyrazolines bearing benzenesulfonamide **1** have been reported to show selective inhibition of hCA IX and XII [34]. Recently, some 4-functionalized 1,5-diaryl-1,2,3-triazoles containing benzenesulfonamide **2–8** have also been reported from our group acting as strong inhibitors of human carbonic anhydrase I, II, IV and IX [35–37]. These results indicate that pyrazoline and 1,2,3-triazole scaffolds are promising entities for exploring molecules of interest as CAIs.

To study the combined effect of these moieties on biological activity and continuing our interest in the field of designing benzenesulfonamide bearing heterocyclic compounds as CAIs, [34–38] we report herein synthesis and biological evaluation of hydroxy-trifluoromethylpyrazoline-carbonyl-1,2,3-triazoles **9–12** and trifluoromethylhydrazone-carbonyl-1,2,3-triazoles **13** bearing benzenesulfonamide as carbonic anhydrase hCA I, II, IX and XII inhibitors (Fig. 1).

2. Results and discussion

2.1. Chemistry

The synthetic pathway employed for the synthesis of targeted sulfonamides is depicted in Scheme 1. Carboxylic acid hydrazides of 1,2,3-triazole bearing benzenesulfonamide **18**, required for the synthesis of target molecules, were prepared by the diazotization of commercially available sulfanilamide (**14**) which upon subsequent reaction with sodium azide at 0 °C yielded 4-azidobenzenesulfonamide (**15**) [39]. Compound **15** was subsequently treated with differently substituted β-ketoesters **16**, to afford 1,5-diaryl-1,2,3-triazole carboxylates **17**, which on further reaction with hydrazinehydrate yielded carboxylic acid hydrazides of 1,2,3-triazole **18** [35]. Variously substituted 1,3-diketones **19** were prepared by the reaction of corresponding acetophenones with ethyl trifluoroacetate by using sodium ethoxide as a base in dry benzene [40]. First of all, it was attempted to synthesize single product by conventional method of refluxing carboxylic acid hydrazides of 1,2,3-triazole bearing benzenesulfonamide **18** and 1,3-diketones **19** in ethanol containing a few drops of conc. HCl for 5–6 hrs but it resulted into a mixture of products. NMR of the isolated solid product confirmed the presence of a mixture of hydroxypyrazolines and pyrazoles. For getting the single desired product, different reaction conditions were unsuccessfully attempted leading to a mixture of products. Finally, reaction in DMF with catalytic amount of conc. HCl, stirring for 5 hrs at 50 °C followed by addition of few drops of conc. H_2SO_4 at 90 °C followed by further stirring for 8–9 hrs, afforded a solid product on workup with water, which was purified by recrystillization. However under the same reaction conditions, carboxylic acid hydrazides of 1,2,3-triazole bearing benzenesulfonamide **18** on reacting with thienyl substituted 1,3-diketones **19** afforded unexpected hydrazone derivatives **13**. Attempts to further cyclize the hydrazones **13** under variety of different conditions did not yield the desired results. Postulated



					Ar						
		16	17	18	C_6H_5	4-$H_3CC_6H_4$	4-ClC_6H_4	4-BrC_6H_4	2-Naphthyl	2-Pyridyl	2-Thienyl
	19	-	-	-	19a	19b	19c	19d	19e	19f	19g
R	CH_3	16a	17a	18a	9a	9b	9c	9d	9e	9f	13a
R	C_6H_5	16b	17b	18b	10a	10b	10c	10d	10e	10f	13b
R	4-$H_3CC_6H_4$	16c	17c	18c	11a	11b	11c	11d	11e	11f	13c
R	4-FC_6H_4	16d	17d	18d	12a	12b	12c	12d	12e	12f	13d

Scheme 1. Synthesis of target compounds **9–13**. Reaction conditions: (i) HCl, $NaNO_2$, H_2O, 0 °C; (ii) NaN_3, 0 °C; (iii) Piperidine, DMSO, 70 °C; (iv) $NH_2NH_2{\cdot}H_2O$, EtOH, Reflux; (v) DMF, H^+.

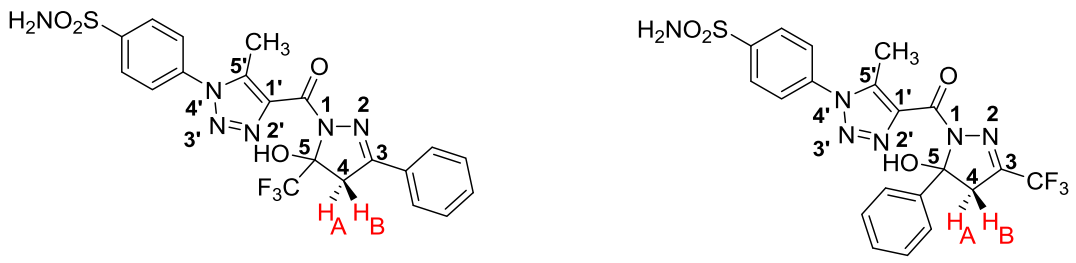
structures of the newly prepared sulfonamides were in full agreement with their spectral data (IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS). In IR spectra of **9–13** the absorption frequencies due to O—H and NH_2 groups appeared in the region 3656–3533 cm^{-1} and 3394–3194 cm^{-1} respectively while absorption band corresponding to C=O and SO_2 appeared in the range of 1690–1643 cm^{-1} and 1358–1142 cm^{-1}respectively. On the other hand hydrazones **13** showed extra peak for C=O absorption at 1720–1705 cm^{-1}. ^{1}H NMR spectra in DMSO-d_6 of compounds **9–13** revealed singlet at δ 8.58–8.34 ppm for O—H, while free SO_2NH_2 group resonated around δ 7.63–7.54 ppm as singlet integrating for two protons. Two characteristic doublets at δ 4.15–3.65 ppm and δ 3.80–3.46 ppm for CH_2 confirm the formation of hydroxypyrazolines **9–12**. At the same time, singlet at δ 4.78–4.72 ppm for the CH_2 group and another singlet at δ 11.90–11.81 ppm for NH confirm the formation of hydrazones **13**.

As there is a possibility of formation of two regioisomers **9a** and **9a′** (Fig. 2.), ^{19}F and ^{13}C NMR spectroscopy had been used to identify the position of CF_3 group. In the ^{13}C NMR spectra, the observed signal from C-5 was a quartet at δ 91.84 ppm ($^2J_{CF}$ = 33.7 Hz) and the C-3 atom gave a singlet at δ 153.3 ppm. This supports **9a** for if the structure was **9a′**, the signal for the sp^2-hybridised C-3 atom would be a quartet with a significant downfield shift around δ 141 ppm rather than the value observed at δ 91.84 ppm, i.e. the CF_3 group is attached to an sp^3-hybridised carbon rather than the C=N carbon atom and also appearance of quartet for CF_3 around δ 123 ppm ($^1J_{CF}$ = 284.0 Hz) confirmed the formation of structure **9a** with position of CF_3 group at C-5 of 5-hydroxypyrazoline [41–45]. Finally, the ^{19}F NMR spectrum gave further evidence to structure **9a** as it displayed a signal at δ −76.8 ppm, which is typical for a C_5–CF_3 of 5-hydroxypyrazoline rather than a C_3–CF_3 which should be at around δ −67 ppm [42–45]. Further hydrazones **13** exhibited a peak at δ 185 ppm in their ^{13}C NMR spectra for carbonyl group which was at around δ 160 ppm in case of pyrazolines.

2.2. CA inhibition studies

The CA inhibitory profile of all the newly synthesized 28 compounds **9–13** was evaluated in vitro for their ability to inhibit physiologically relevant hCA isoforms I and II (cytosolic) as well as hCA IX and XII (transmembrane, tumor-associated isoforms) by means of the stopped-flow CO_2 hydration assay [46] and their activities were compared to the standard reference drug acetazolamide (AAZ). The following structure activity relationship can be compiled from the inhibition data (Table 1).

1. The slow cytosolic isoforms hCA I was inhibited by the compounds **9–13** with K_i's ranging between 41.4 and 947.7 nM. Compounds **9a–9f, 10a–10c, 10f** and **12a** showed excellent inhibition activity ($K_i \leq 100$ nM) as compared to standard drug AAZ (K_i = 250 nM) against hCA I. Among these, compounds **9d, 9e, 10a** and **10f** emerged as the most efficient hCAI inhibitiors with K_i values of 41.4,



9a **9a'**

Fig. 2. Proposed structure for product **9a** and **9a′**.

Table 1
Inhibition data of human CA isoforms hCA I, II, IX and XII with sulfonamides **9–13** reported here and the standard sulfonamide inhibitor acetazolamide (AAZ) by a stopped flow CO_2 hydrase assay [46].

Compounds	R	Ar	K_i (nM)[a]			
			hCA I	hCA II	hCA IX	hCA XII
9a	CH_3	C_6H_5	58.0	0.42	16.3	8.7
9b	CH_3	4-$H_3CC_6H_4$	68.8	0.43	90.5	21.7
9c	CH_3	4-ClC_6H_4	72.9	0.93	20.8	55.9
9d	CH_3	4-BrC_6H_4	41.4	0.46	24.0	8.9
9e	CH_3	2-Naphthyl	55.5	1.7	79.9	64.2
9f	CH_3	2-Pyridyl	86.4	23.5	26.5	88.1
10a	C_6H_5	C_6H_5	53.1	0.57	22.8	42.1
10b	C_6H_5	4-$H_3CC_6H_4$	82.6	6.3	28.2	8.7
10c	C_6H_5	4-ClC_6H_4	70.2	22.8	161.2	9.0
10d	C_6H_5	4-BrC_6H_4	265.5	7.9	24.5	7.6
10e	C_6H_5	2-Naphthyl	172.4	27.8	28.3	10.2
10f	C_6H_5	2-Pyridyl	41.5	1.9	9.9	0.87
11a	4-$H_3CC_6H_4$	C_6H_5	151.5	3.6	31.2	73.9
11b	4-$H_3CC_6H_4$	4-$H_3CC_6H_4$	501.8	24.5	206.9	52.1
11c	4-$H_3CC_6H_4$	4-ClC_6H_4	709.1	53.3	48.9	98.0
11d	4-$H_3CC_6H_4$	4-BrC_6H_4	774.0	30.6	33.2	60.4
11e	4-$H_3CC_6H_4$	2-Naphthyl	947.7	48.3	134.3	4.2
11f	4-$H_3CC_6H_4$	2-Pyridyl	555.9	38.6	6.0	31.8
12a	4-FC_6H_4	C_6H_5	84.8	0.90	6.1	4.2
12b	4-FC_6H_4	4-$H_3CC_6H_4$	240.4	78.2	27.0	6.0
12c	4-FC_6H_4	4-ClC_6H_4	518.0	7.2	14.4	5.1
12d	4-FC_6H_4	4-BrC_6H_4	541.9	8.4	23.6	56.9
12e	4-FC_6H_4	2-Naphthyl	661.2	94.3	25.6	9.0
12f	4-FC_6H_4	2-Pyridyl	692.1	2.5	0.7	24.1
13a	CH_3	2-Thienyl	69.8	0.47	12.5	7.7
13b	C_6H_5	2-Thienyl	69.0	2.4	11.6	1.2
13c	4-$H_3CC_6H_4$	2-Thienyl	91.1	9.5	26.8	34.7
13d	4-FC_6H_4	2-Thienyl	65.2	6.1	1.4	2.4
AAZ	–	–	250	12	25	5.7

AAZ = acetazolamide, reference compound, a standard sulfonamide CAI, is also provided for comparison.

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

55.5, 53.1 and 41.5 nM respectively, with more than 4-fold increased activity than AAZ. Some of the compounds **11b–11f** and **12c–12f** were weak inhibitors of off-targeted hCA I. Trifluoromethylhydrazone-carbonyl-1,2,3-triazole **13** emanate better inhibition potential than hydroxy-trifloromethylpyrazoline-carbonyl-1,2,3-triazole **9–12** against hCA I. In terms of SAR, inhibition potency against hCA I of tested compounds in general decreases as the substituent size increases at C-5′ of 1,2,3-triazole ring.

2. The dominant cytosolic isoform hCA II was effectively inhibited by most of the compounds **9a–9e, 10a, 10b, 10d, 10f, 11a, 12a, 12c, 12d, 12f** and **13a–13d** with K_i in the range of sub-nanomolar to single digit nanomolar 0.42–9.5 nM. Inhibition constant decreases by expanding the substituent on aryl group at C-5′ of 1,2,3-triazole ring. Overall comparison of the hydroxy-trifloromethylpyrazoline-carbonyl-1,2,3-triazoles **9–12** with trifluoromethylhydrazone-carbonyl-1,2,3-triazoles **13** showed that the hydrazones **13** were better inhibitors of hCA II.
3. The inhibition potential against tumor associated hCA IX isoform of all newly synthesized compounds **9–13** investigated here, was in the range of K_i = 0.7–206.9 nM. Furthermore twelve compounds **9a, 9c, 9d, 10a, 10d, 10f, 11f, 12a, 12c, 12d, 13a, 13b** showed better inhibition with $K_i \leq 24.5$ nM for hCA IX as compared to reference drug AAZ (K_i = 25 nM). Indeed, two compounds **12f** and **13d** were found to be respectively 35 and 17-fold more effective than the standard drug AAZ.
4. Tumor associated isoform hCA XII was inhibited by all the synthesized 28 novel compounds **9–13** with K_i values 0.87–98.0 nM. Amongest all the tested compounds, two analogues **10f** (K_i = 0.87 nM), and **13b** (K_i = 1.2 nM) displayed inhibitory potential approximately 5-fold superior than the AAZ (K_i = 5.7 nM). It can be concluded from the table that the trend of CA inhibitory potential against hCA XII was found to be **10f** < **13b** < **13d** < **11e** = **12a** < **12c** with $K_i \leq 5.1$ nM from the most effective to the least effective compound.
5. In general hydrazones **13a-13d** showed excellent inhibiting potential against hCA I, II, IX and XII except, compound **13c** in which tolyl substituent is present at C-5′ position of 1,2,3-triazole ring. It can be concluded that bulkier group at C-5′ position of 1,2,3-triazole ring in general reduces the CAI activity in the newly synthesized compounds.
6. The selectivity ratio for inhibiting the tumor-associated isoforms hCA IX and XII over the off-targeted cytosolic isoforms hCA I and II has been presented in Table 2. It is evident that the compounds didn't show a consistent behavior in their property against all the four tested isoforms (hCA I, II, IX and XII). It can be observed that some of the investigated derivatives showed promising levels of selective inhibition of the transmembrane over the cytosolic isoforms. It was also observed that the compounds which showed excellent inhibition of isoform hCA IX and XII were also shown to be highly selective. Compound **12b** and **12e** showed maximum inhibition selectivity ratio for hCA IX and XII over hCA II and **12c** showed over hCA I. All other compounds of this series that is **12c-12f** were also shown to be excellently selective for hCA IX over hCA I having selectivity ratio more than 10. Thus, the biological activity of these sulfonamides constitute an interesting precursor for exploring in more detail the hydroxy-trifluoromethylpyrazoline-carbonyl-1,2,3-triazoles **9–12** and trifluoromethylhydrazone-carbonyl-1,2,3-triazoles **13** incorporating benzenesulfonamide, for designing isoform-selective metalloenzyme inhibitors.

3. Conclusions

In summary, this study reports the synthesis and unambiguous characterization of twenty four novel hydroxy-trifluoromethylpyrazoline-carbonyl-1,2,3-triazoles and four hydrazones. In light of the CA inhibition profile, it can be concluded that synthesized sulfonamide compounds investigated as inhibitors of four hCA isoforms, the

Table 2
Selectivity ratios for inhibiting the tumor-associated isoforms hCA IX and XII over cytosolic isoforms hCA I and II, with AAZ and compounds **9–13.**

Compounds	R	Ar	Selectivity ratio*			
			I/IX	II/IX	I/XII	II/XII
9a	CH_3	C_6H_5	3.558	0.026	6.667	0.048
9b	CH_3	4-$H_3CC_6H_4$	0.760	0.005	3.171	0.020
9c	CH_3	4-ClC_6H_4	3.505	0.045	1.304	0.017
9d	CH_3	4-BrC_6H_4	1.725	0.019	4.652	0.052
9e	CH_3	2-Naphthyl	0.695	0.021	0.864	0.026
9f	CH_3	2-Pyridyl	3.260	0.887	0.981	0.267
10a	C_6H_5	C_6H_5	2.329	0.025	1.261	0.014
10b	C_6H_5	4-$H_3CC_6H_4$	2.929	0.223	9.494	0.724
10c	C_6H_5	4-ClC_6H_4	0.435	0.141	7.800	2.533
10d	C_6H_5	4-BrC_6H_4	10.837	0.322	34.934	1.039
10e	C_6H_5	2-Naphthyl	6.092	0.982	16.902	2.725
10f	C_6H_5	2-Pyridyl	4.192	0.192	47.701	2.184
11a	4-$H_3CC_6H_4$	C_6H_5	4.856	0.115	2.050	0.049
11b	4-$H_3CC_6H_4$	4-$H_3CC_6H_4$	2.425	0.118	9.631	0.470
11c	4-$H_3CC_6H_4$	4-ClC_6H_4	14.501	1.090	7.236	0.544
11d	4-$H_3CC_6H_4$	4-BrC_6H_4	23.313	0.922	12.815	0.507
11e	4-$H_3CC_6H_4$	2-Naphthyl	7.057	0.360	225.643	11.500
11f	4-$H_3CC_6H_4$	2-Pyridyl	92.650	6.433	17.481	1.214
12a	4-FC_6H_4	C_6H_5	13.902	0.148	20.190	0.214
12b	4-FC_6H_4	4-$H_3CC_6H_4$	8.904	2.896	40.067	13.033
12c	4-FC_6H_4	4-ClC_6H_4	35.972	0.500	101.569	1.412
12d	4-FC_6H_4	4-BrC_6H_4	22.962	0.356	9.524	0.148
12e	4-FC_6H_4	2-Naphthyl	25.828	3.684	73.467	10.478
12f	4-FC_6H_4	2-Pyridyl	988.714	3.571	28.718	0.104
13a	CH_3	2-Thienyl	5.584	0.038	9.065	0.061
13b	C_6H_5	2-Thienyl	5.948	0.207	57.500	2.000
13c	4-$H_3CC_6H_4$	2-Thienyl	3.399	0.354	2.625	0.274
13d	4-FC_6H_4	2-Thienyl	46.571	4.357	27.167	2.542
AAZ	–	–	10.000	0.480	43.860	2.105

AAZ = acetazolamide, reference compound, a standard sulfonamide CAI, is also provided for comparison.

* The K_i ratios are indicative of isozyme selectivity: a weak selective inhibitor is characterized by a low value ratio.

cytosolic CA I and II, as well as the transmembrane, tumor-associated CA IX and XII, interesting inhibitory activities were observed against almost all these isoforms. The most active inhibitors in both the series were found to be the compounds **9d** and **10f**, which had K_i value of around 41.5 nM for hCA I (involved in edema), and compound **9a, 9b, 9d** and **13a** with K_i value of around 0.45 nM for hCA II (an anti-glaucoma drug target). Compound **12f** showed the most effective inhibitory action for the tumor associated isoform hCA IX (an isoform involved in tumors) (K_i = 0.7 nM) being a better inhibitor compared to the reference drug AAZ (K_i = 25 nM). Compound **10f** K_i = 0.87 nM was found to be the most effective inhibitor against hCA XII. Our findings identify the advantage of using compounds with flexible smaller substituents at the C-5 of 1,2,3-triazole ring may provide an avenue to overcome CA isoform specificity, as they may unveil both nanomolar affinity and preferential binding for the tumor associated membrane bound isoforms.

4. Experimental protocols

4.1. General

All the chemicals were purchased from Alfa Aesar, Himedia and used as received without further purification. Melting points were determined in open glass capillaries in an electrical melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel F-254 aluminium plates using a mixture of chloroform and methanol as eluent while UV lamp was used to visualize the spots. Compounds were named following IUPAC rules as applied by ChemDraw Professional 17.0. IR spectra were measured on ABB MB 3000 DTGS IR instrument using the KBr pellet technique. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on Bruker Avance III 400 MHz, 100 MHz and 282.4 MHz respectively, using deuterated dimethyl sulfoxide (DMSO-d_6) as solvent, and tetramethylsilane (TMS) as internal standard at room temperature. Chemical shifts are expressed at δ (ppm) values relative to Me_4Si (TMS). The apparent resonance multiplicity is described as: s (singlet), d (doublet), t (triplet), q (quatret), dd (doublet of doublets), td (triplet of doublets) and m (multiplet) for NMR assignments and strong (s), medium (m) for IR assignments. The coupling constants in NMR are expressed in hertz (Hz). High resolution mass spectra were obtained from Xevo G2-S QTof UPLC/MS spectrometer.

4.2. General procedure for the synthesis of 4-(4-(5-hydroxy-3-aryl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-alkyl/aryl-1H-1,2,3-triazol-1-yl)benzenesulfonamide (9–12) and 4-(5-alkyl/aryl-4-(2-(1,1,1-trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-ylidene)hydrazine-1-carbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (13)

To a solution of Carboxylic acid hydrazides of 1,2,3-triazole bearing benzenesulfonamide **18** (1.1 mmol) and substituted 1,3-diketones **19** (1.1 mmol) in DMF (15 ml), added conc. HCl (1 ml) and then stirred at 50 °C for 5 hrs. Thereafter, few drops of conc. H_2SO_4 were added and the reaction mixture was further stirred at 90 °C in silicon oil bath for 9–12 hrs. The reaction was monitored through TLC and after completion, the reaction mixture was allowed to cool and poured into ice cold water to obtain a solid which was filtered and dried to afford crude solid. Crude product thus obtained was recrystallized in appropriate solvent. It is pertinent to mention here that under the same reaction conditions thienyl substituted 1,3-diketones **19** on reacting with Carboxylic acid hydrazides of 1,2,3-triazole bearing benzenesulfonamide **18** afforded corresponding hydrazone-carbonyl-1,2,3-triazoles **13**.

4.2.1. 4-(4-(5-Hydroxy-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-methyl-1H-1,2,3-triazol-1-yl)benzenesulfonamide (9a)

Recrystallized from ethanol; Yield 68%; Colour: Pale Yellow; mp: 210–212 °C; silica gel F-254 TLC R_f 0.63 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3618 (s, O—H), 3356, 3263 (m, N—H stretch), 1666 (s, C═O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.39 (s, 1H, OH), 8.09 (d, J = 8.4 Hz, 2H, Ar), 7.97 (d, J = 8.4 Hz, 2H, Ar), 7.77 (dd, J = 7.6 Hz, J = 2.0 Hz, 2H, Ar), 7.63 (s, 2H, SO_2NH_2), 7.51–7.46 (m, 3H, Ar), 4.02 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.67 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.83, 152.68, 145.00, 140.03, 137.71, 136.21, 130.73, 129.92, 128.78, 127.08, 126.69, 125.79, 123.20 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 91.84 (q, $^2J_{CF}$ = 33.7 Hz, C-5), 44.20, 9.79; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.05 (C_5–CF_3); HRMS (ESI-MS) *m/z* 495.1057 $(M + H)^+$, $C_{20}H_{17}F_3N_6O_4SH^+$, calcd 495.1062.

4.2.2. 4-(4-(5-Hydroxy-3-(p-tolyl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-methyl-1H-1,2,3-triazol-1-yl)benzenesulfonamide (9b)

Recrystallized from ethanol; Yield 66%; Colour: White; mp: 185–187 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3626 (s, O—H), 3364, 3286 (m, N—H stretch), 1643 (s, C═O stretch), 1327, 1149 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.34 (s, 1H, OH), 8.09 (d, J = 8.8 Hz, 2H, Ar), 7.96 (d, J = 8.8 Hz, 2H, Ar), 7.66 (d, J = 8.0 Hz, 2H, Ar), 7.62 (s, 2H, SO_2NH_2), 7.28 (d, J = 8.0 Hz, 2H, Ar), 3.97 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.64 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.43 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.75, 152.61, 144.98, 140.66, 140.07, 137.70, 136.15, 129.34, 127.18, 127.07, 126.65, 125.77, 123.21 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 91.62 (q, $^2J_{CF}$ = 33.1 Hz, C-5), 44.24, 20.96, 9.78; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.06 (C_5–CF_3); HRMS (ESI-MS) *m/z* 509.1212

$(M + H)^+$, $C_{21}H_{19}F_3N_6O_4SH^+$, calcd 509.1219.

4.2.3. 4-(4-(3-(4-Chlorophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonamide (9c)

Recrystallized from ethanol; Yield 72%; Colour: Brown; mp: 205–207 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3636 (s, O—H), 3340, 3248 (m, N—H stretch), 1690 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.41 (s, 1H, OH), 8.08 (d, J = 8.8 Hz, 2H, Ar), 7.96 (d, J = 8.8 Hz, 2H, Ar), 7.78 (d, J = 8.4 Hz, 2H, Ar), 7.62 (s, 2H, SO_2NH_2), 7.54 (d, J = 8.4 Hz, 2H, Ar), 4.03 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.67 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 160.38, 152.30, 145.58, 140.47, 138.24, 136.95, 135.88, 129.43, 129.02, 127.63, 126.33, 123.69 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 92.60 (q, $^2J_{CF}$ = 33.9 Hz, C-5), 44.66, 10.33; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 75.99 (C_5–CF_3); HRMS (ESI-MS) *m/z* 529.0668 $(M + H)^+$, 531.0638 $(M + H + 2)^+$, $C_{20}H_{16}ClF_3N_6O_4SH^+$, calcd 529.0672

4.2.4. 4-(4-(3-(4-Bromophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonamide (9d)

Recrystallized from ethanol; Yield 64%; Colour: White; mp: 216–218 °C; silica gel F-254 TLC R_f 0.65 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3644 (s, O—H), 3333, 3240 (m, N—H stretch), 1690 (s, C=O stretch), 1350, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.42 (s, 1H, OH), 8.09 (dd, J = 8.8 Hz, J = 2.0 Hz, 2H, Ar), 7.96 (dd, J = 8.8 Hz, J = 2.0 Hz, 2H, Ar), 7.73–7.67 (m, 4H, Ar), 7.62 (s, 2H, SO_2NH_2), 4.03 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.67 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 160.38, 152.40, 145.59, 140.46, 138.24, 136.97, 132.35, 129.77, 129.20, 127.64, 126.33, 124.73, 123.83 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 92.60 (q, $^2J_{CF}$ = 33.4 Hz, C-5), 44.61, 10.34; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 75.98 (C_5–CF_3); HRMS (ESI-MS) *m/z* 573.0159 $(M + H)^+$, 575.0141 $(M + H + 2)^+$, $C_{20}H_{16}BrF_3N_6O_4SH^+$, calcd 573.0167.

4.2.5. 4-(4-(5-Hydroxy-3-(naphthalen-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonamide (9e)

Recrystallized from ethanol; Yield 66%; Colour: Pale Yellow; mp: 237–239 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3618 (s, O—H), 3364, 3271 (m, N—H stretch), 1659 (s, C=O stretch), 1335, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.45 (s, 1H, OH), 8.31 (s, 1H, Ar), 8.11–8.09 (m, 2H, Ar), 8.03–7.91 (m, 6H, Ar), 7.63–7.60 (m, 4H, SO_2NH_2, Ar), 4.15 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.80 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.48 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 160.38, 153.28, 145.57, 140.58, 138.29, 136.96, 134.25, 133.08, 129.03, 128.95, 128.60, 128.09, 127.65, 127.44, 126.39, 123.33 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 123.20, 92.57 (q, $^2J_{CF}$ = 34.4 Hz, C-5), 44.79, 10.39; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 75.97 (C_5–CF_3); HRMS (ESI-MS) *m/z* 545.1212 $(M + H)^+$, $C_{24}H_{19}F_3N_6O_4SH^+$, calcd 545.1219.

4.2.6. 4-(4-(5-Hydroxy-3-(pyridin-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-methyl-1H-1,2,3-triazol-1-yl) benzenesulfonamide (9f)

Recrystallized from ethanol; Yield 62%; Colour: Off White; mp: 204–206 °C; silica gel F-254 TLC R_f 0.63 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3533 (s, O—H), 3348, 3256 (m, N—H stretch), 1674 (s, C=O stretch), 1342, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.69–8.67 (m, 1H, Ar) 8.48 (s, 1H, OH), 8.10–8.07 (m, 2H, Ar), 7.98–7.95 (m, 3H, Ar), 7.91 (td, J = 7.6 Hz, J = 1.6 Hz, 1H, Ar), 7.62 (s, 2H, SO_2NH_2), 7.53–7.50 (m, 1H, Ar), 3.97 (d, $J_{HA\text{-}HB}$ = 19.6 Hz, 1H, pyrazoline), 3.68 (d, $J_{HA\text{-}HB}$ = 19.6 Hz, 1H, pyrazoline), 2.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.89, 153.48, 149.54, 148.92, 145.02, 139.79, 137.67, 137.09, 136.48, 127.06, 125.80, 125.23, 123.12 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 120.81, 91.99 (q, $^2J_{CF}$ = 33.3 Hz, C-5), 44.07, 9.82; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.16 (C_5–CF_3); HRMS (ESI-MS) *m/z* 496.1006 $(M + H)^+$, $C_{19}H_{16}F_3N_7O_4SH^+$, calcd 496.1015.

4.2.7. 4-(4-(5-Hydroxy-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-phenyl-1H-1,2,3-triazol-1-yl)benzenesulfonamide (10a)

Recrystallized from ethanol; Yield 72%; Colour: Yellow; mp: 208–210 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3622 (s, O—H), 3394, 3271 (m, N—H stretch), 1659 (s, C=O stretch), 1327, 1173 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.40 (s, 1H, OH), 7.94 (d, J = 8.4 Hz, 2H, Ar), 7.70 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.45–7.34 (m, 5H, Ar), 7.30–7.26 (m, 5H, Ar), 3.75 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.50 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.46, 152.26, 144.84, 140.44, 137.90, 137.53, 130.61, 129.57, 129.37, 129.15, 128.45, 128.39, 126.82, 126.66, 126.30, 125.58, 123.08 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 91.43 (q, $^2J_{CF}$ = 33.4 Hz, C-5), 44.00; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.28 (C_5–CF_3); HRMS (ESI-MS) *m/z* 557.1212 $(M + H)^+$, $C_{25}H_{19}F_3N_6O_4SH^+$, calcd 557.1219.

4.2.8. 4-(4-(5-Hydroxy-3-(p-tolyl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-phenyl-1H-1,2,3-triazol-1-yl)benzenesulfonamide (10b)

Recrystallized from ethanol; Yield 67%; Colour: Yellow; mp: 190–192 °C; silica gel F-254 TLC R_f 0.65 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3656 (s, O—H), 3356, 3256 (m, N—H stretch), 1674 (s, C=O stretch), 1327, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.35 (s, 1H, OH), 7.93 (d, J = 8.8 Hz, 2H, Ar), 7.68 (d, J = 8.8 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.34 (d, J = 8.0 Hz, 2H, Ar), 7.28 (s, 5H, Ar), 7.16 (d, J = 8.0 Hz, 2H, Ar), 3.71 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.46 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.39, 152.21, 144.83, 140.51, 137.90, 137.48, 129.57, 129.14, 128.96, 128.44, 126.82, 126.68, 126.64, 126.29, 123.10, (q, $^1J_{CF}$ = 283.4 Hz, C_5-CF_3), 91.32 (q, $^2J_{CF}$ = 33.78 Hz, C-5), 44.07, 20.93; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.26 (C_5–CF_3); HRMS (ESI-MS) *m/z* 571.1365 $(M + H)^+$, $C_{26}H_{21}F_3N_6O_4SH^+$, calcd 571.1375.

4.2.9. 4-(4-(3-(4-Chlorophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-phenyl-1H-1,2,3-triazol-1-yl) benzenesulfonamide (10c)

Recrystallized from ethanol; Yield 69%; Colour: Yellow; mp: 212–214 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3618 (s, O—H), 3356, 3263 (m, N—H stretch), 1682 (s, C=O stretch), 1327, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.43 (s, 1H, OH), 7.93 (dd, J = 8.8 Hz, J = 2.0 Hz, 2H, Ar), 7.69 (dd, J = 8.8 Hz, J = 2.0 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.47–7.41 (m, 4H, Ar), 7.28 (s, 5H, Ar), 3.75 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.47 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.41, 151.29, 144.86, 140.31, 137.87, 137.70, 135.21, 129.60, 129.16, 128.49, 128.27, 126.83, 126.28, 125.61, 123.02 (q, $^1J_{CF}$ = 283.2 Hz, C_5-CF_3), 91.61 (q, $^2J_{CF}$ = 34.0 Hz, C-5), 44.89; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.23 (C_5–CF_3); HRMS (ESI-MS) *m/z* 591.0826 $(M + H)^+$, 593.0801 $(M + H + 2)^+$, $C_{25}H_{18}ClF_3N_6O_4SH^+$, calcd 591.0829.

4.2.10. 4-(4-(3-(4-Bromophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-phenyl-1H-1,2,3-triazol-1-yl) benzenesulfonamide (10d)

Recrystallized from ethanol/THF; Yield 68%; Colour: Pale Yellow; mp: 215–217 °C; silica gel F-254 TLC R_f 0.63 ($CHCl_3$:CH_3OH, 90:10, *v/*

v); IR (KBr) (ν, cm^{-1}): 3634 (s, O—H), 3356, 3263 (m, N—H stretch), 1682 (s, C═O stretch), 1327, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.41 (s, 1H, OH), 7.94 (d, J = 8.4 Hz, 2H, Ar), 7.68 (d, J = 8.4 Hz, 2H, Ar), 7.58–7.55 (m, 4H, SO_2NH_2, Ar,), 7.38 (d, J = 8.4 Hz, 2H, Ar), 7.28 (s, 5H, Ar), 3.75 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.48 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.41, 151.40, 144.86, 140.31, 137.86, 137.70, 131.40, 129.60, 129.16, 128.61, 128.48, 126.82, 126.29, 125.60, 124.10, 123.01 (q, $^1J_{CF}$ = 285.0 Hz, C_5-CF_3), 91.61 (q, $^2J_{CF}$ = 33.7 Hz, C-5), 43.84; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.22 (C_5–CF_3); HRMS (ESI-MS) *m/z* 635.0317 $(M + H)^+$, 637.0300 $(M + H + 2)^+$, $C_{25}H_{18}BrF_3N_6O_4SH^+$, calcd 635.0324.

4.2.11. 4-(4-(5-Hydroxy-3-(naphthalen-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-phenyl-1H-1,2,3-triazol-1-yl) benzenesulfonamide (**10e**)

Recrystallized from ethanol; Yield 71%; Colour: Pale Yellow; mp: 229–231 °C; silica gel F-254 TLC R_f 0.65 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3610 (s, O—H), 3317, 3256 (m, N—H stretch), 1659 (s, C═O stretch), 1327, 1173 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.44 (s, 1H, OH), 8.05 (s, 1H, Ar), 7.96–7.90 (m, 4H, Ar), 7.84 (d, J = 8.8 Hz, 1H, Ar), 7.72 (dd, J = 6.8 Hz, J = 1.6 Hz, 2H, Ar), 7.59–7.53 (m, 5H, SO_2NH_2, Ar), 7.34 (dd, J = 8.0 Hz, J = 1.6 Hz, 2H, Ar) 7.29–7.22 (m, 3H, Ar), 3.87 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.64 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.43, 152.25, 144.85, 140.40, 137.94, 137.70, 133.58, 132.26, 129.56. 129.20, 128.46, 128.40, 127.86, 127.73, 127.58, 127.43, 126.96, 126.83, 126.34, 125.66, 124.48 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 122.98, 122.89, 91.54 (q, $^2J_{CF}$ = 34.1 Hz, C-5), 44.04; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.19 (C_5–CF_3); HRMS (ESI-MS) *m/z* 607.1368 $(M + H)^+$, $C_{29}H_{21}F_3N_6O_4SH^+$, calcd 607.1375.

4.2.12. 4-(4-(5-Hydroxy-3-(pyridin-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-phenyl-1H-1,2,3-triazol-1-yl) benzenesulfonamide (**10f**)

Recrystallized from ethanol; Yield 62%; Colour: White; mp: 210–212 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3618 (s, O—H), 3348, 3214 (m, N—H stretch), 1682 (s, C═O stretch), 1335, 1173 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.56–8.54 (m, 1H, Ar) 8.49 (s, 1H, OH), 7.94 (dd, J = 8.4 Hz, J = 1.6 Hz, 2H, Ar), 7.78 (td, J = 8.0 Hz, J = 1.6 Hz, 1H, Ar) 7.70 (dd, J = 8.4 Hz, J = 1.6 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.53 (d, J = 8.0 Hz, 1H, Ar), 7.44–7.41 (m, 1H, Ar), 7.31–7.24 (m, 5H, Ar), 3.65 (d, $J_{HA\text{-}HB}$ = 19.6 Hz, 1H, pyrazoline), 3.47 (d, $J_{HA\text{-}HB}$ = 19.6 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.49, 152.97, 149.23, 148.31, 144.87. 140.19, 137.89, 137.84, 136.58, 129.55, 129.18, 128.45, 126.81, 126.32, 125.62, 125.13, 123.0 (q, $^1J_{CF}$ = 284.3 Hz, C_5-CF_3), 120.93, 91.55 (q, $^2J_{CF}$ = 33.9 Hz, C-5), 43.84; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.41 (C_5–CF_3); HRMS (ESI-MS) *m/z* 558.1162 $(M + H)^+$, $C_{24}H_{18}F_3N_7O_4SH^+$, calcd 558.1171.

4.2.13. 4-(4-(5-Hydroxy-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-(p-tolyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**11a**)

Recrystallized from ethanol; Yield 65%; Colour: White; mp: 220–222 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3600 (s, O—H), 3333, 3256 (m, N—H stretch), 1690 (s, C═O stretch), 1350, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.40 (s, 1H, OH), 7.94 (d, J = 8.4 Hz, 2H, Ar), 7.68 (d, J = 8.4 Hz, 2H, Ar), 7.58 (s, 2H, SO_2NH_2), 7.47–7.36 (m, 5H, Ar), 7.16 (d, J = 8.0 Hz, 2H, Ar), 7.09 (d, J = 8.0 Hz, 2H, Ar), 3.80 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.52 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.16 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 160.14, 152.91, 145.37, 140.89, 139.86, 138.55, 138.07, 131.18, 130.07, 129.64, 128.98, 127.42, 127.20, 126.85, 125.34 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 123.15, 92.04 (q, $^2J_{CF}$ = 34.4 Hz, C-5), 44.59, 21.22; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.30 (C_5–CF_3); HRMS (ESI-MS) *m/z* 571.1369 $(M + H)^+$, $C_{26}H_{21}F_3N_6O_4SH^+$, calcd 571.1375.

4.2.14. 4-(4-(5-Hydroxy-3-(p-tolyl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-(p-tolyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (**11b**)

Recrystallized from ethanol; Yield 67%; Colour: Pale Yellow; mp: 208–210 °C; silica gel F-254 TLC R_f 0.65 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3552 (s, O—H), 3364, 3263 (m, N—H stretch), 1674 (s, C═O stretch), 1327, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.34 (s, 1H, OH), 7.94 (dd, J = 8.4 Hz, J = 2.0 Hz, 2H, Ar), 7.68 (d, J = 8.4 Hz, 2H, Ar), 7.56 (s, 2H, SO_2NH_2), 7.36 (d, J = 8.4 Hz, 2H, Ar), 7.19–7.15 (m, 4H, Ar), 7.10 (d, J = 8.0 Hz, 2H, Ar), 3.77 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.49 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.31 (s, 3H, CH_3), 2.17 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.54, 152.32, 144.80, 140.53, 140.40, 139.30, 138.00, 137.45, 129.07, 129.04, 128.99, 126.86, 126.82, 126.61, 126.27, 123.11 (q, $^1J_{CF}$ = 283.7 Hz, C_5-CF_3), 91.40 (q, $^2J_{CF}$ = 34.0 Hz, C-5), 122.58, 44.09, 20.93, 20.67; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.29 (C_5–CF_3); HRMS (ESI-MS) *m/z* 585.1523 $(M + H)^+$, $C_{27}H_{23}F_3N_6O_4SH^+$, calcd 585.1532.

4.2.15. 4-(4-(3-(4-Chlorophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-(p-tolyl)-1H-1,2,3-triazol-1-yl) benzenesulfonamide (**11c**)

Recrystallized from chloroform/THF; Yield 73%; Colour: White; mp: 206–208 °C; silica gel F-254 TLC R_f 0.63 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3642 (s, O—H), 3371, 3271 (m, N—H stretch), 1674 (s, C═O stretch), 1327, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.41 (s, 1H, OH), 7.94 (d, J = 8.4 Hz, 2H, Ar), 7.67 (d, J = 8.4 Hz, 2H, Ar), 7.56 (s, 2H, SO_2NH_2), 7.48–7.42 (m, 4H, Ar), 7.15 (d, J = 8.0 Hz, 2H, Ar), 7.09 (d, J = 8.0 Hz, 2H, Ar), 3.80 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.50 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.16 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.52, 151.38, 144.82, 140.21, 139.32, 137.96, 135.21, 129.09, 129.07, 128.49, 128.41, 126.85, 126.25, 123.04 (q, $^1J_{CF}$ = 283.7 Hz, C_5-CF_3), 122.61, 91.67 (q, $^2J_{CF}$ = 34.0 Hz, C-5), 43.91, 20.64; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.25 (C_5–CF_3); HRMS (ESI-MS) *m/z* 605.1075 $(M + H)^+$, 607.1047 $(M + H + 2)^+$, $C_{26}H_{20}ClF_3N_6O_4SH^+$, calcd 605.0985.

4.2.16. 4-(4-(3-(4-Bromophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-(p-tolyl)-1H-1,2,3-triazol-1-yl) benzenesulfonamide (**11d**)

Recrystallized from ethanol/THF; Yield 67%; Colour: Pale Yellow; mp: 207–209 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3564 (s, O—H), 3348, 3263 (m, N—H stretch), 1674 (s, C═O stretch), 1342, 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.41 (s, 1H, OH), 7.93 (d, J = 8.8 Hz, 2H, Ar), 7.67 (d, J = 8.8 Hz, 2H, Ar), 7.59–7.56 (m, 4H, SO_2NH_2, Ar), 7.39 (d, J = 8.8 Hz, 2H, Ar), 7.15 (d, J = 8.4 Hz, 2H, Ar), 7.09 (d, J = 8.4 Hz, 2H, Ar), 3.79 (d, $J_{HA\text{-}HB}$ = 19.6 Hz, 1H, pyrazoline), 3.49 (d, $J_{HA\text{-}HB}$ = 19.6 Hz, 1H, pyrazoline), 2.16 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 160.09, 152.06, 145.38, 140.77, 139.89, 138.52, 138.23, 131.99, 129.65, 129.32, 129.15, 127.41, 126.82, 124.64, 123.58 (q, $^1J_{CF}$ = 284.6 Hz, C_5-CF_3), 123.16, 92.25 (q, $^2J_{CF}$ = 33.9 Hz, C-5), 44.42, 21.20; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.25 (C_5–CF_3); HRMS (ESI-MS) *m/z* 649.0472 $(M + H)^+$, 651.4555 $(M + H + 2)^+$,$C_{26}H_{20}BrF_3N_6O_4SH^+$, calcd 649.0498.

4.2.17. 4-(4-(5-Hydroxy-3-(naphthalen-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-(p-tolyl)-1H-1,2,3-triazol-1-yl) benzenesulfonamide (**11e**)

Recrystallized from $CHCl_3$/THF; Yield 68%; Colour: White; mp:

230–232 °C; silica gel F-254 TLC R_f 0.65 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3644 (s, O—H), 3364, 3263 (m, N—H stretch), 1666 (s, C═O stretch), 1327, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.45 (s, 1H, OH), 8.07 (s, 1H, Ar), 7.96–7.91 (m, 4H, Ar), 7.86 (d, J = 8.4 Hz, 1H, Ar), 7.71 (d, J = 8.4 Hz, 2H, Ar), 7.58–7.54 (m, 5H, SO_2NH_2, Ar), 7.20 (d, J = 8.0 Hz, 2H, Ar), 7.08 (d, J = 8.0 Hz, 2H, Ar), 3.92 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.64 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 159.56, 152.37, 144.81, 140.30, 139.28, 138.03, 137.64, 133.59, 132.29, 129.09, 128.38, 127.89, 127.72, 127.60, 127.42, 127.09, 126.86, 126.76, 123.14 (q, $^1J_{CF}$ = 284.7 Hz, C_5-CF_3), 122.83, 122.65, 91.60 (q, $^2J_{CF}$ = 34.0 Hz, C-5),44.06, 20.60; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.22 (C_5–CF_3); HRMS (ESI-MS) *m/z* 621.1526 $(M + H)^+$, $C_{30}H_{23}F_3N_6O_4SH^+$, calcd 621.1532.

4.2.18. 4-(4-(5-Hydroxy-3-(pyridin-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-(p-tolyl)-1H-1,2,3-triazol-1-yl) benzenesulfonamide (11f)

Recrystallized from ethanol; Yield 59%; Colour: Off White; mp: 209–211 °C; silica gel F-254 TLC R_f 0.65 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3604 (s, O—H), 3350, 3286 (m, N—H stretch), 1690 (s, C═O stretch), 1327, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.58 (dd, J = 4.0 Hz, J = 0.8 Hz, 1H, Ar), 8.49 (s, 1H, OH), 7.94 (d, J = 8.4 Hz, 2H, Ar), 7.79 (td, J = 8.0 Hz, J = 1.6 Hz, 1H, Ar) 7.69 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.52 (d, J = 8.0 Hz, 1H, Ar), 7.43 (dd, J = 6.8 Hz, J = 1.6 Hz, 1H, Ar), 7.16 (d, J = 8.0 Hz, 2H, Ar), 7.06 (d, J = 8.0 Hz, 2H, Ar), 3.69 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.50 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.13 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 160.15, 153.62, 149.82, 149.00, 145.40, 140.64, 139.88, 138.50, 138.44, 137.16, 129.63, 127.41, 126.87, 125.69, 123.60 (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 123.19, 121.47, 92.19 (q, $^2J_{CF}$ = 33.7 Hz, C-5), 44.41, 21.18; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.43 (C_5–CF_3); HRMS (ESI-MS) *m/z* 572.1325 $(M + H)^+$, $C_{25}H_{20}F_3N_7O_4SH^+$, calcd 572.1328.

4.2.19. 4-(5-(4-Fluorophenyl)-4-(5-hydroxy-3-phenyl-5-(trifluoromethyl)-4,5-dihydro-1H- pyrazole-1-carbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (12a)

Recrystallized from ethanol; Yield 66%; Colour: Brown; mp: 208–210 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3618 (s, O—H), 3356, 3271 (m, N—H stretch), 1674 (s, C═O stretch), 1327, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.39 (s, 1H, OH), 7.94 (dd, J = 7.2 Hz, J = 1.8 Hz, 2H, Ar), 7.70 (dd, J = 7.2 Hz, J = 1.8 Hz, 2H, Ar), 7.57 (s, 2H, SO_2NH_2), 7.49–7.47 (m, 2H, Ar), 7.44–7.42 (m, 1H, Ar), 7.39–7.34 (m, 4H, Ar), 7.16–7.11 (m, 2H, Ar), 3.80 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.50 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 162.46 (d, $^1J_{CF}$ = 246.4 Hz) 159.31, 152.38, 144.87, 140.47, 137.77, 136.85, 131.70 (d, $^3J_{CF}$ = 8.8 Hz) 130.67, 129.36, 128.42, 126.85, 126.67, 126.31, 123.06 (q, $^1J_{CF}$ = 283.0 Hz, C_5-CF_3), 122.17 (d, $^4J_{CF}$ = 3.2 Hz), 115.63 (d, $^2J_{CF}$ = 21.9 Hz), 91.48 (q, $^2J_{CF}$ = 33.6 Hz, C-5), 43.98; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.28 (C_5–CF_3), 110.93 (F); HRMS (ESI-MS) *m/z* 575.1118 $(M + H)^+$, $C_{25}H_{18}F_4N_6O_4SH^+$, calcd 575.1124.

4.2.20. 4-(5-(4-Fluorophenyl)-4-(5-hydroxy-3-(p-tolyl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (12b)

Recrystallized from ethanol; Yield 64%; Colour: Yellow; mp: 210–212 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3618 (s, O—H), 3350, 3210 (m, N—H stretch), 1674 (s, C═O stretch), 1335, 1173 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.34 (s, 1H, OH), 7.94 (d, J = 8.4 Hz, 2H, Ar), 7.70 (d, J = 8.4 Hz, 2H, Ar), 7.56 (s, 2H, SO_2NH_2), 7.39–7.34 (m, 4H, Ar), 7.19–7.12 (m, 4H, Ar), 3.75 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.47 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 2.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 162.47 (d, $^1J_{CF}$ = 246.7 Hz) 159.25, 152.34, 144.86, 140.57, 140.52, 127.77, 136.80, 131.70 (d, $^3J_{CF}$ = 8.8 Hz) 129.00, 126.85, 126.65, 126.29, 123.11, (q, $^1J_{CF}$ = 284.0 Hz, C_5-CF_3), 122.17 (d, $^4J_{CF}$ = 3.3 Hz), 115.61 (d, $^2J_{CF}$ = 21.9 Hz), 91.36 (q, $^2J_{CF}$ = 33.7 Hz, C-5), 44.04, 20.94; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.27 (C_5–CF_3), 110.92 (F); HRMS (ESI-MS) *m/z* 589.1276 $(M + H)^+$, $C_{26}H_{20}F_4N_6O_4SH^+$, calcd 589.1281.

4.2.21. 4-(4-(3-(4-Chlorophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (12c)

Recrystallized from ethanol; Yield 68%; Colour: White; mp: 215–217 °C; silica gel F-254 TLC R_f 0.66 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3605 (s, O—H), 3356, 3263 (m, N—H stretch), 1674 (s, C═O stretch), 1327, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.43 (s, 1H, OH), 7.95 (d, J = 8.8 Hz, 2H, Ar), 7.70 (d, J = 8.8 Hz, 2H, Ar), 7.58 (s, 2H, SO_2NH_2), 7.50 (d, J = 8.8 Hz, 2H, Ar), 7.44 (d, J = 8.8 Hz, 2H, Ar), 7.38–7.34 (m, 2H, Ar), 7.15 (t, J = 8.8 Hz, 2H, Ar), 3.80 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.49 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 162.49 (d, $^1J_{CF}$ = 246.7 Hz) 159.29, 151.42, 144.89, 140.366, 137.74, 136.99, 135.28, 131.72 (d, $^3J_{CF}$ = 8.8 Hz) 128.54, 128.44, 128.25, 126.87, 126.29, 123.04 (q, $^1J_{CF}$ = 283.5 Hz, C_5-CF_3), 122.18 (d, $^4J_{CF}$ = 3.2 Hz), 115.69 (d, $^2J_{CF}$ = 21.9 Hz), 91.67 (q, $^2J_{CF}$ = 33.8 Hz, C-5), 43.89; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.22 (C_5–CF_3), 110.87 (F); HRMS (ESI-MS) *m/z* 609.0726 $(M + H)^+$, 611.0701 $(M + H + 2)^+$, $C_{25}H_{17}ClF_4N_6O_4SH^+$, calcd 609.0735.

4.2.22. 4-(4-(3-(4-Bromophenyl)-5-hydroxy-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-5-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (12d)

Recrystallized from ethanol; Yield 69%; Colour: Off White; mp: 207–209 °C; silica gel F-254 TLC R_f 0.63 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3610 (s, O—H), 3368, 3256 (m, N—H stretch), 1682 (s, C═O stretch), 1350, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.58 (s, 1H, OH), 7.95 (dd, J = 6.8 Hz, J = 1.6 Hz, 2H, Ar), 7.68 (dd, J = 6.8 Hz, J = 1.6 Hz, 2H, Ar), 7.59–7.57 (m, 2H, SO_2NH_2, 2H, Ar), 7.42 (d, J = 8.8 Hz, 2H, Ar), 7.37–7.33 (m, 2H, Ar), 7.15 (t, J = 8.8 Hz, 2H, Ar), 3.80 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.49 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 162.33 (d, $^1J_{CF}$ = 249.6 Hz), 159.26, 151.54, 144.87, 140.34, 137.73, 137.00, 131.73 (d, $^3J_{CF}$ = 8.8 Hz), 131.45, 129.64, 127.86, 126.29, 123.17 (q, $^1J_{CF}$ = 284.5 Hz, C_5-CF_3), 122.17 (d, $^4J_{CF}$ = 3.3 Hz), 115.66 (d, $^2J_{CF}$ = 21.9 Hz), 91.65 (q, $^2J_{CF}$ = 33.2 Hz, C-5), 43.82; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.22 (C_5–CF_3), 110.88 (F); HRMS (ESI-MS) *m/z* 653.0225 $(M + H)^+$, 655.0208 $(M + H + 2)^+$, $C_{25}H_{17}BrF_4N_6O_4SH^+$, calcd 653.0229.

4.2.23. 4-(5-(4-Fluorophenyl)-4-(5-hydroxy-3-(naphthalen-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (12e)

Recrystallized from ethanol; Yield 67%; Colour: Brown; mp: 233–235 °C; silica gel F-254 TLC R_f 0.65 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3590 (s, O—H), 3387, 3294 (m, N—H stretch), 1666 (s, C═O stretch), 1335, 1173 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.44 (s, 1H, OH), 8.08 (s, 1H, Ar), 7.97–7.85 (m, 5H, Ar), 7.72 (d, J = 8.8 Hz, 2H, Ar), 7.58–7.56 (m, 2H, SO_2NH_2, 3H, Ar), 7.43–7.39 (m, 2H, Ar), 7.13 (t, J = 8.8 Hz, 2H, Ar), 3.92 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline), 3.61 (d, $J_{HA\text{-}HB}$ = 19.2 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 163.03 (d, $^1J_{CF}$ = 245.9 Hz), 159.85, 152.97, 145.44, 141.01, 138.38, 137.55, 134.17, 132.85, 132.32 (d, $^3J_{CF}$ = 8.8 Hz), 128.99, 128.48, 128.35, 128.17, 128.03, 127.50, 127.42, 126.91, 123.42, 123.09 (q, $^1J_{CF}$ = 282.5 Hz, C_5-CF_3), 122.77 (d, $^4J_{CF}$ = 3.2 Hz), 116.19, (d, $^2J_{CF}$ = 22.2 Hz), 92.16 (q, $^2J_{CF}$ = 33.8 Hz, C-5), 44.60; ^{19}F NMR

(DMSO-d_6, 282.4 MHz) –δ 76.18 (C_5–CF_3), 110.94 (F); HRMS (ESI-MS) m/z 625.1275 $(M + H)^+$, $C_{29}H_{20}F_4N_6O_4SH^+$, calcd 625.1281.

4.2.24. 4-(5-(4-Fluorophenyl)-4-(5-hydroxy-3-(pyridin-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazole-1-carbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (12f)

Recrystallized from ethanol; Yield 60%; Colour: Brown; mp: 209–211 °C; silica gel F-254 TLC R_f 0.64 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3618 (s, O—H), 3364, 3263 (m, N—H stretch), 1682 (s, C═O stretch), 1327, 1165 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 8.57 (d, J = 4.8 Hz, 1H, Ar), 8.48 (s, 1H, OH), 7.94 (d, J = 8.4 Hz, 2H, Ar), 7.79 (t, J = 8.0 Hz, 1H, Ar) 7.70 (d, J = 8.4 Hz, 2H, Ar), 7.57 (s, 3H, SO_2NH_2, 1H, Ar), 7.44 (t, J = 6.2 Hz, 1H, Ar), 7.38–7.35 (m, 2H, Ar), 7.11 (t, J = 8.8 Hz, 2H, Ar), 3.70 (d, $J_{HA\text{-}HB}$ = 19.6 Hz, 1H, pyrazoline), 3.50 (d, $J_{HA\text{-}HB}$ = 19.6 Hz, 1H, pyrazoline); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 162.34 (d, $^1J_{CF}$ = 249.4 Hz), 159.35, 153.13, 149.30, 148.33, 144.90, 137.72, 137.17, 136.65, 131.76 (d, $^3J_{CF}$ = 8.7 Hz), 126.84, 126.32, 125.18, 123.34 (q, $^1J_{CF}$ = 283.0 Hz, C_5-CF_3), 122.20, 120.90 (d, $^4J_{CF}$ = 3.2 Hz), 115.62, (d, $^2J_{CF}$ = 22.0 Hz), 91.28 (q, $^2J_{CF}$ = 33.2 Hz, C-5), 43.74; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 76.40 (C_5–CF_3), 110.90 (F); HRMS (ESI-MS) m/z 576.1069 $(M + H)^+$, $C_{24}H_{17}F_4N_7O_4SH^+$, calcd 576.1077.

4.2.25. 4-(5-Methyl-4-(2-(1,1,1-trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-ylidene)hydrazine-1-carbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (13a)

Recrystallized from ethanol; Yield 76%; Colour: Off White; mp: 142–144 °C; silica gel F-254 TLC R_f 0.70 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3333, 3217 (m, N—H stretch), 1720, 1682 (s, C═O stretch), 1327, 1142 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 11.81 (s, 1H, NH), 8.16 (dd, J = 4.8 Hz, J = 0.8 Hz, 1H, Ar), 8.13 (dd, J = 6.0 Hz, J = 6.0 Hz, 1H, Ar), 8.07 (dd, J = 6.8 Hz, J = 1.8 Hz, 2H, Ar), 7.89 (dd, J = 6.8 Hz, J = 1.8 Hz, 2H, Ar), 7.61 (s, 2H, SO_2NH_2), 7.35–7.34(m, 1H, Ar), 4.78 (s, 2H, CH_2), 2.59 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 185.44, 145.25, 145.06, 142.02, 138.53, 137.30, 135.95, 134.96, 128.89, 127.09, 125.85, 125.78 (q, $^1J_{CF}$ = 240.2 Hz), 34.70, 9.42; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 68.57 (CF_3); HRMS (ESI-MS) m/z 501.0616 $(M + H)^+$, $C_{18}H_{15}F_3N_6O_4S_2H^+$, calcd 501.0626.

4.2.26. 4-(5-Phenyl-4-(2-(1,1,1-trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-ylidene)hydrazine-1-carbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (13b)

Recrystallized from ethanol; Yield 71%; Colour: Brown; mp: 149–151 °C; silica gel F-254 TLC R_f 0.69 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3310, 3194 (m, N—H stretch), 1705, 1659 (s, C═O stretch), 1350, 1173 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 11.90 (s, 1H, Ar), 8.13 (m, 2H, Ar), 7.90 (d, J = 8.8 Hz, 2H, Ar), 7.60 (d, J = 8.8 Hz, 2H, Ar), 7.54 (s, 2H, SO_2NH_2), 7.47–7.38 (m, 5H, Ar), 7.34 (t, J = 8.8.4 Hz, J = 4.4 Hz, 1H, Ar), 4.72 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 183.71, 145.03, 141.98, 137.74, 137.60, 134.90, 133.49, 130.08, 129.94, 128.88, 128.35, 126.83, 126.34, 126.12 (q, $^1J_{CF}$ = 240.0 Hz), 124.76, 114.50, 36.71; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 68.66 (CF_3); HRMS (ESI-MS) m/z 563.0776 $(M + H)^+$, $C_{23}H_{17}F_3N_6O_4S_2H^+$, calcd 563.0783.

4.2.27. 4-(5-(p-Tolyl)-4-(2-(1,1,1-trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-ylidene)hydrazine-1-carbonyl)-1H-1,2,3-triazol-1-yl)benzenesulfonamide (13c)

Recrystallized from ethanol; Yield 77%; Colour: Pale Yellow; mp: 145–147 °C; silica gel F-254 TLC R_f 0.71 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3343, 3256 (m, N—H stretch), 1713, 1643 (s, C═O stretch), 1358, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 11.89 (s, 1H, Ar), 8.13 (m, 2H, Ar), 7.91 (d, J = 8.8 Hz, 2H, Ar), 7.59 (d, J = 8.8 Hz, 2H, Ar), 7.55 (s, 2H, SO_2NH_2), 7.34 (t, J = 4.4 Hz, J = 8.8 Hz, 1H, Ar), 7.25–7.22 (m, 4H, Ar), 4.72 (s, 2H, CH_2), 2.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 185.86, 145.55, 142.54, 140.30, 138.23, 136.46, 135.48, 130.54, 129.53, 129.44, 127.42, 126.91, 125.84 (q, $^1J_{CF}$ = 237.8 Hz), 37.28, 21.39; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 68.64 (CF_3); HRMS (ESI-MS) m/z 577.0932 $(M + H)^+$, $C_{24}H_{19}F_3N_6O_4S_2H^+$, calcd 577.0939.

4.2.28. 4-(5-(4-fluorophenyl)-4-(2-(1,1,1-trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-ylidene)hydrazine-1-carbonyl)-1H-1,2,3-triazol-1-yl) benzenesulfonamide (13d)

Recrystallized from ethanol; Yield 74%; Colour: Yellow; mp: 138–140 °C; silica gel F-254 TLC R_f 0.70 ($CHCl_3$:CH_3OH, 90:10, *v/v*); IR (KBr) (ν, cm^{-1}): 3364, 3271 (m, N—H stretch), 1705, 1643 (s, C═O stretch), 1358, 1157 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 11.90 (s, 1H, Ar), 8.13 (m, 2H, Ar), 7.90 (d, J = 8.4 Hz, 2H, Ar), 7.59 (d, J = 8.4 Hz, 2H, Ar), 7.54 (s, 2H, SO_2NH_2), 7.44 (s, 2H, Ar), 7.34–7.25 (m, 3H, Ar), 4.73 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 185.97, 145.62, 142.54, 139.64, 138.02, 136.49, 135.49, 129.45, 127.44, 126.93, 125.40 (q, $^1J_{CF}$ = 240.6 Hz), 116.20, 115.98, 96.73, 37.32; ^{19}F NMR (DMSO-d_6, 282.4 MHz) –δ 68.67 (CF_3), 110.43 (F); HRMS (ESI-MS) m/z 581.0785 $(M + H)^+$, $C_{23}H_{16}F_4N_6O_4S_2H^+$, calcd 581.0689.

5. CA inhibition assay

An SX.18MV-R Applied Photophysics (Oxford, UK) stopped-flow instrument has been used to assay the inhibition of various CA isozymes [47]. Phenol Red (at a concentration of 0.2 mM) has been used as an indicator, working at the absorbance maximum of 557 nm, with 10 mM Hepes (pH 7.4) as a buffer, 0.1 M Na_2SO_4 or $NaClO_4$ (for maintaining constant the ionic strength; these anions are not inhibitory in the used concentration), following the CA-catalyzed CO_2 hydration reaction for a period of 5–10 s. Saturated CO_2 solutions in water at 25 °C were used as substrate. Stock solutions of inhibitors were prepared at a concentration of 10 mM (in DMSO-water 1:1, v/v) and dilutions up to 0.01 nM done with the assay buffer mentioned above. At least 7 different inhibitor concentrations have been used for measuring the inhibition constant. Inhibitor and enzyme solutions were pre-incubated together for 10 min at room temperature prior to assay, in order to allow for the formation of the E-I complex. Triplicate experiments were done for each inhibitor concentration, and the values reported throughout the paper are the mean of such results. The inhibition constants were obtained by non-linear least-squares methods using the Cheng-Prusoff equation, as reported earlier, and represent the mean from at least three different determinations [47–49]. All CA isozymes used here were recombinant proteins obtained as reported earlier by our group.

Disclosure statement

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

Acknowledgement

One of the authors (Vikas Sharma) is grateful to the Council of Scientific and Industrial Research, New Delhi, India for the award of Junior Research Fellowship and the other (Rajiv Kumar), is thankful to University Grants Commission, New Delhi, India for the award of Senior Research Fellowship. Authors are also thankful to Materials Research Centre, MNIT Jaipur for providing HRMS facility.

References

[1] B. Żołnowska, J. Sławiński, K. Szafrański, 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. 143 (2018) 1931–1941, https://doi.org/10.1016/j.ejmech.2017.11.005.
[2] M. Aggarwal, T.K. Chua, M.A. Pinard, D.M. Szebenyi, R. McKenna, Carbon dioxide "Trapped" in a β-carbonic anhydrase, Bioorg. Chem. 54 (2015) 6631–6638, https://doi.org/10.1021/acs.biochem.5b00987.
[3] C.T. Supuran, A. Scozzafava, Carbonic anhydrase inhibitors-Part 94. 1,3,4-Thiadiazole-2-sulfonamide derivatives as antitumor agents, Eur. J. Med. Chem. 35 (2000) 867–874, https://doi.org/10.1016/S0223-5234(00)00169-0.
[4] (a) C.T. Supuran, How many carbonic anhydrase inhibition mechanisms exist ? J. Enzyme Inhib. Med. Chem. 31 (2016) 345–360, https://doi.org/10.3109/14756366.2015.1122001;
(b) C.T. Supuran, Structure and function of carbonic anhydrases, Biochem. J. 473 (2016) 2023–2032, https://doi.org/10.1042/BCJ20160115.
[5] (a) P. Pan, A.B. Vermelho, A. Scozzafava, S. Parkkila, C. Capasso, C.T. Supuran, Anion inhibition studies of the α-carbonic anhydrase from the protozoan pathogen Trypanosoma cruzi, the causative agent of Chagas disease, Bioorg. Med. Chem. 21 (2013) 4472–4476, https://doi.org/10.1016/j.bmc.2013.05.058;
(b) O. Güzel-Akdemir, A. Akdemir, P. Pan, A.B. Vermelho, S. Parkkila, A. Scozzafava, C. Capasso, C.T. Supuran, A class of sulfonamides with strong inhibitory action against the α-carbonic anhydrase from Trypanosoma cruzi, J. Med. Chem. 56 (2013) 5773–5781, https://doi.org/10.1021/jm400418p.
[6] R. Perfetto, S. Del Prete, D. Vullo, G. Sansone, C. Barone, M. Rossi, C.T. Supuran, C. Capasso, Biochemical characterization of the native α-carbonic anhydrase purified from the mantle of the Mediterranean mussel, Mytilusgalloprovincialis, J. Enzyme Inhib. Med. Chem. 32 (2017) 632–639, https://doi.org/10.1080/14756366.2017.1284069.
[7] C.T. Supuran, Carbonic anhydrases: novel therapeutic applications for inhibitors and activators, Nat. Rev. Drug Discov. 7 (2008) 168–181, https://doi.org/10.1038/nrd2467.
[8] 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, https://doi.org/10.3109/14756366.2014.910202.
[9] C.T. Supuran, C. Capasso, The η-class carbonic anhydrases as drug targets for antimalarial agents, Expert Opin. Ther. Targets. 19 (2015) 551–563, https://doi.org/10.1517/14728222.2014.991312.
[10] E. Licsandru, M. Tanc, I. Kocsis, M. Barboiu, C.T. Supuran, A class of carbonic anhydrase I-selective activators, J. Enzyme Inhib. Med. Chem. 32 (2017) 37–46.
[11] 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, https://doi.org/10.1021/acs.jmedchem.7b00766.
[12] 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. 143 (2018) 276–282, https://doi.org/10.1016/j.ejmech.2017.11.061.
[13] 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, https://doi.org/10.1016/j.ejmech.2014.06.074.
[14] C.T. Supuran, Carbonic anhydrases as drug targets-an overview, Curr. Top. Med. Chem. 7 (2007) 825–833, https://doi.org/10.2174/156802607780636690.
[15] M.Y. Mboge, B.P. Mahon, N. Lamas, L. Socorro, F. Carta, C.T. Supuran, S.C. Frost, R. McKenna, Structure activity study of carbonic anhydrase IX: Selective inhibition with ureido-substituted benzenesulfonamides, Eur. J. Med. Chem. 132 (2017) 184–191, https://doi.org/10.1016/j.ejmech.2017.03.026.
[16] D. Neri, C.T. Supuran, Interfering with pH regulation in tumours as a therapeutic strategy, Nat. Rev. Drug Discov. 10 (2011) 767–777, https://doi.org/10.1038/nrd3554.
[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, https://doi.org/10.1016/j.ejmech.2017.03.023.
[18] (a) C.T. Supuran, Carbonic anhydrase inhibitors and activators for novel therapeutic applications, Future Med. Chem. 3 (2011) 1165–1180, https://doi.org/10.4155/fmc.11.69;
(b) E. Masini, F. Carta, A. Scozzafava, C.T. Supuran, Antiglaucoma carbonic anhydrase inhibitors: a patent review, Expert Opin. Ther. Pat. 23 (2013) 705–716, https://doi.org/10.1517/13543776.2013.794788.
[19] D. Vullo, M. Franchi, E. Gallori, J. Pastorek, A. Scozzafava, S. Pastorekova, C.T. Supuran, Carbonic anhydrase inhibitors. Inhibition of the tumor associated isozyme IX with aromatic and heterocyclic sulfonamides, Bioorg. Med. Chem. Lett. 13 (2003) 1005–1009, https://doi.org/10.1016/S0960-894X(03)00091-X.
[20] (a) C.T. Supuran, Carbonic anhydrase inhibitors and their potential in a range of therapeutic areas, Expert Opin. Ther. Pat. 28 (2018) 709–712, https://doi.org/10.1080/13543776.2018.1523897;
(b) C.T. Supuran, Applications of carbonic anhydrases inhibitors in renal and central nervous system diseases, Expert Opin. Ther. Pat. 28 (2018) 713–721, https://doi.org/10.1080/13543776.2018.1519023.
[21] A. Nocentini, C.T. Supuran, Carbonic anhydrase inhibitors as antitumor/antimetastatic agents: a patent review (2008–2018), Expert Opin. Ther. Pat. 28 (2018) 729–740, https://doi.org/10.1080/13543776.2018.1508453.
[22] J.D. Kanamori, Roberts, Nitrogen-15 nuclear magnetic resonance study of benzenesulfonamide and cyanate binding to carbonic anhydrase, Biochemistry 22 (1983) 2658–2664, https://doi.org/10.1021/bi00280a011.
[23] 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, https://doi.org/10.1016/j.ejmech.2014.08.010.
[24] 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, https://doi.org/10.1016/j.bmcl.2014.01.076.
[25] 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, https://doi.org/10.1016/j.bmcl.2017.07.008.
[26] S. Viveka, P. Dinesha, G.K. Shama, S. Nagaraja, S. Ballav, Kerkar, Design and synthesis of some new pyrazolyl-pyrazolines as potential anti-inflammatory, analgesic and antibacterial agents, Eur. J. Med. Chem. 101 (2015) 442–451, https://doi.org/10.1016/j.ejmech.2015.07.002.
[27] R. Kant, D. Kumar, D. Agarwal, R.D. Gupta, R. Tilak, S.K. Awasthi, A. Agarwal, Synthesis of newer 1,2,3-triazole linked chalcone and flavone hybrid compounds and evaluation of their antimicrobial and cytotoxic activities, Eur. J. Med. Chem. 113 (2016) 34–49, https://doi.org/10.1016/j.ejmech.2016.02.041.
[28] M. Allam, A.K.D. Bhavani, A. Mudiraj, N. Ranjan, M. Thippana, P.P. Babu, Synthesis of pyrazolo[3,4-d]pyrimidin-4(5H)-ones tethered to 1,2,3-triazoles and their evaluation as potential anticancer agents, Eur. J. Med. Chem. 156 (2018) 43–52, https://doi.org/10.1016/j.ejmech.2018.06.055.
[29] J.F. da Costa, X. García-Mera, O. Caamano, J.M. Brea, M.I. Loza, Synthesis by microwave assisted 1,3-dipolar cycloaddition of 1,2,3-triazole 1′-homo-3′-isoazanucleosides and evaluation of their anticancer activity, Eur. J. Med. Chem. 98 (2015) 212–220, https://doi.org/10.1016/j.ejmech.2015.05.029.
[30] C.F. Liu, Q.K. Shen, J.J. Li, Y.S. Tian, Z. Quan, Synthesis and biological evaluation of novel 7-hydroxy-4-phenylchromen-2-one–linked to triazole moieties as potent cytotoxic agents, J. Enzyme Inhib. Med. Chem. 32 (2017) 1111–1119, https://doi.org/10.1080/14756366.2017.1344982.
[31] M.D. Altıntop, A. Özdemir, G. Turan-Zitouni, S. Ilgın, Ö. Atlı, R. Demirel, Z.A. Kaplancıklı, A novel series of thiazolyl-pyrazoline derivatives: synthesis and evaluation of antifungal activity, cytotoxicity and genotoxicity, Eur. J. Med. Chem. 92 (2015) 342–352, https://doi.org/10.1016/j.ejmech.2014.12.055.
[32] Z.H. Li, D.X. Yang, P.F. Geng, J. Zhang, H.M. Wei, B. Hu, Q. Guo, X.H. Zhang, W.G. Guo, B. Zhao, B. Yu, L.Y. Ma, H.M. Liu, Design, synthesis and biological evaluation of [1,2,3]triazolo[4,5-d]pyrimidine derivatives possessing a hydrazone moiety as antiproliferative agents, Eur. J. Med. Chem. 124 (2016) 967–980, https://doi.org/10.1016/j.ejmech.2016.10.022.
[33] A. Anand, R.J. Naik, H.M. Revankar, M.V. Kulkarni, S.R. Dixit, S.D. Joshi, A click chemistry approach for the synthesis of mono and bisaryloxy linked coumarinyl triazoles as anti-tubercular agents, Eur. J. Med. Chem. 105 (2015) 194–207, https://doi.org/10.1016/j.ejmech.2015.10.019.
[34] 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. 25 (2015) 3208–3212, https://doi.org/10.1016/j.bmcl.2015.05.096.
[35] 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-triazolescontaining benzenesulfonamide moiety as carbonic anhydrase I, II, IV and IX inhibitors, Eur. J. Med. Chem. 150 (2018) 678–686, https://doi.org/10.1016/j.ejmech.2018.03.030.
[36] R. Kumar, L. Vats, S. Bua, C.T. Supuran, P.K. Sharma, Design and synthesis of novel benzenesulfonamide containing 1, 2, 3-triazoles as potent human carbonic anhydrase isoforms I, II, IV and IX inhibitors, Eur. J. Med. Chem. 155 (2018) 545–551, https://doi.org/10.1016/j.ejmech.2018.06.021.
[37] 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, https://doi.org/10.1080/14756366.2017.1367775.
[38] 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, https://doi.org/10.1016/j.bmc.2014.01.055.
[39] 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, https://doi.org/10.1016/0040-4020(96)00609-6.
[40] J.C. Sloop, C.L. Bumgardner, W.D. Loehle, Synthesis of fluorinated heterocycles, J. Fluor. Chem. 118 (2002) 135–147, https://doi.org/10.1016/S0022-1139(02)00221-X.
[41] L. Song, S. Zhu, Regioselective synthesis of fluorinated pyrazole derivatives from trifluoromethyl-1,3-diketone, J. Fluor. Chem. 111 (2001) 201–205, https://doi.org/10.1016/s0022-1139(01)00454-7.
[42] S.P. Singh, J.K. Kapoor, D. Kumar, M.D. Threadgill, Reaction of hydrazinoquinolines with trifluoromethyl-β-diketones: structural and mechanistic studies, J. Fluor. Chem. 83 (1997) 73–79, https://doi.org/10.1016/S0022-1139(96)03570-1.
[43] S.P. Singh, D. Kumar, B.G. Jones, M.D. Threadgill, Formation and dehydration of a series of 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazoles, J. Fluor. Chem. 94

(1999) 199–203, https://doi.org/10.1016/S0022-1139(99)00011-1.
[44] P.K. Sharma, N. Chandna, S. Kumar, P. Kumar, S. Kumar, P. Kaushik, D. Kaushik, Heteroaromatic analogues of 1,5-diarylpyrazole classas anti-inflammatory agents, Med. Chem. Res. 21 (2012) 3757–3766, https://doi.org/10.1007/s00044-011-9898-4.
[45] Y. Zhao, A. Bacher, B. Illarionov, M. Fischer, G. Georg, Q. Ye, P.E. Fanwick, S.G. Franzblau, B. Wan, M. Cushman, Discovery and development of the covalent hydrates of trifluoromethylated pyrazoles as riboflavin synthase inhibitors with antibiotic activity against mycobacterium tuberculosis, J. Org. Chem. 74 (2009) 5297–5303, https://doi.org/10.1021/jo900768c.
[46] M. Tanc, F. Carta, A. Scozzafavab, C.T. Supuran, 6-Substituted 1,2-benzoxathiine-2,2-dioxides are isoform-selective inhibitors of human carbonic anhydrases IX, XII and VA, Org. Biomol. Chem. 13 (2015) 77–80, https://doi.org/10.1039/C4OB02155J.
[47] H. Küçükbay, N. Buğday, F. Zehra Küçükbay, E. Berrino, G. Bartolucci, S. Del Prete, C. Capasso, C.T. Supuran, Synthesis and carbonic anhydrase inhibitory properties of novel 4-(2- aminoethyl)benzenesulfonamide-dipeptide conjugates, Bioorg. Chem. (2018), https://doi.org/10.1016/ j.bioorg.2018.11.003.
[48] (a) S. Akocak, N. Lolak, D. Vullo, M. Durgun, C.T. Supuran, Synthesis and biological evaluation of histamine Schiff bases as carbonic anhydrase I, II, IV, VII, and IX activators, J. Enzyme Inhib. Med. Chem. 32 (2017) 1305–1312, https://doi.org/10.1080/14756366.2017.1386660;
(b) M. Senturk, I. Gulcin, S. Beydemir, Ö.İ. Küfrevioğlu, C.T. Supuran, In vitro inhibition of human carbonic anhydrase I and II isozymes with natural phenolic compounds, Chem. Biol. Drug. Des. 77 (2011) 494–499, https://doi.org/10.1111/j.1747-0285.2011.01104.x;
(c) N. Krall, F. Pretto, W. Decurtins, G.J. Bernardes, C.T. Supuran, D. Neri, A small molecule drug conjugate for the treatment of carbonic anhydrase IX expressing tumors, Angew. Chem. Int. Ed. Engl. 53 (2014) 4231–4235, https://doi.org/10.1002/anie.201310709;
(d) G. De, E. Simone, D. Langella, C.T. Esposito, S.M. Supuran, J.Y. Monti, V. Alterio Winum, Insights into the binding mode of sulphamates and sulphamides to hCA II: crystallographic studies and binding free energy calculations, J. Enzyme Inhib. Med. Chem. 32 (2017) 1002–1011.
[49] J. Borras, A. Scozzafava, L. Menabuoni, F. Mincione, F. Briganti, G. Mincione, C.T. Supuran, Carbonic anhydrase inhibitors: synthesis of water-soluble, topically effective intraocular pressure lowering aromatic/heterocyclic sulfonamides containing 8-quinoline-sulfonyl moieties: is the tail more important than the ring? Bioorg. Med. Chem. 7 (1999) 2397–2406, https://doi.org/10.1016/S0968-0896(99)00190-X.