Carbonic anhydrases (CAs, also known as carbonate dehydratase, EC 4.2.1.1) are metalloenzymes present in Archaea, prokaryotes and eukaryotes, that catalyse the efficient interconversion of CO₂ to HCO₃⁻ and protons via a ping-pong mechanism under physiological conditions 1–6. This physiologically very simple, but highly relevant reaction plays an important role for the regulation of many physiologic processes in all living organisms. Up to now, seven genetically distinct CA families (α, β, γ, δ, ε, η, and θ-CAs) were described in various taxa, for all of them with numerous isoforms being present in all the investigated organisms 1–6.

In humans, 15 different isoforms have been described, all belonging to the α-CA family, with some of them being cytosolic (hCA I, II, VII, and XIII), others membrane-bound (hCA IV, IX, XII, and XIV), two mitochondrial (hCA VA and VB), as well as the tumour-associated membrane-bound isoform hCA IX. All isoforms investigated here were inhibited by the newly synthesised 1,3-diaryltriazene sulfonamide derivatives from the micromolar to the nanomolar range. The cytosolic isoforms were inhibited with Kᵢ in the range of 92.3–8371.1 nM (hCA I), 4.3–9194.0 nM (hCA II), and 15.6–9477.8 nM (hCA VII), respectively. For the membrane-bound tumour-associated isoform hCA IX, the Kᵢ ranged between 50.8 and 9268.5 nM. The structure–activity relationship (SAR) with these newly synthesised metanilamide derivatives is discussed in detail.

**Introduction**

Triazenes are a diverse group of compounds which are amenable to many synthetic transformations and are also used for different applications, such as natural product synthesis, combinatorial chemistry, and biomedical applications 10. On the other hand, triazene compounds of clinical interest (such as Temozolomide and Dacarbazine), are a group of anticancer alkylating agents, with excellent pharmacokinetic properties and limited toxicity 10 (Figure 1). The X-ray crystal structure of SLC-0111 bound to hCA II as well as of four of its congeners, with various tail moieties was reported 5. As shown in Figure 2, the benzenesulfonamide fragment of molecules is rather superimposable for the four derivatives, whereas the ureido fragment allows a quite flexible orientation of the tail moieties in various parts of the active site, depending on nature and substitution pattern of the R moiety 9. This has as a consequence the fact that some of these compounds show a rather impressive isoform specificity. For example, SLC-0111 is an effective inhibitor of only hCA IX, XII, and XIV, being a weak inhibitor of off-target isoforms such as hCA I, II, or IV 9.

In continuation of our recent interest in CAIs 11, in this work, we report the synthesis and hCA I, II, VII, and IX inhibitory activity of new 1,3-diaryltriazene sulfonamides 4(a–h) obtained from the reaction of the diazonium salt of metanilamide with different substituted aromatic amines (Figure 3).

**Materials and methods**

**General**

All chemicals and anhydrous solvents were purchased from Sigma-Aldrich, Merck, Alfa Aesar and TCI and used without further purification.

Discovery of novel 1,3-diaryltriazene sulfonamides as carbonic anhydrase I, II, VII, and IX inhibitors

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**ABSTRACT**

A series of new 1,3-diaryltriazene sulfonamides was synthesised by reaction of diazonium salt of metanilamide (3-aminobenzene sulfonamide) with substituted aromatic amines. The obtained new compounds were assayed as inhibitors of four physiologically and pharmacologically relevant human (h) isoforms of carbonic anhydrases (CA, EC 4.2.1.1), specifically, hCA I, hCA II, and hCA VII (cytosolic isoforms), as well as the tumour-associated membrane-bound isoform hCA IX. All isoforms investigated here were inhibited by the newly synthesised 1,3-diaryltriazene sulfonamide derivatives from the micromolar to the nanomolar range. The cytosolic isoforms were inhibited with Kᵢ in the range of 92.3–8371.1 nM (hCA I), 4.3–9194.0 nM (hCA II), and 15.6–9477.8 nM (hCA VII), respectively. For the membrane-bound tumour-associated isoform hCA IX, the Kᵢ ranged between 50.8 and 9268.5 nM. The structure–activity relationship (SAR) with these newly synthesised metanilamide derivatives is discussed in detail.
Figure 1. Clinically used triazene substituted compounds (TMZ and DTIC) and efficient CAI SLC-0111 (phase I/II trials for the advanced metastatic solid tumours).

Figure 2. Ribbon diagram (a) and active site detail of the adducts with ureido-substituted benzenesulfonamide CAIs (b); SLC-0111 (cyan, pdb: 3N4B), 4–(3-nitrophenoyleuroideo) benzenesulfonamide (pink, pdb: 3N2P), 4–(3-(2-isopropylphenyl)ureido) benzenesulfonamide (yellow, pdb: 3N3J) and 4–(3-cyclohexylureido) benzenesulfonamide (light orange, pdb: 3MZC) (superimposed). Figure made using PyMol (Delano Scientific).

Figure 3. General CA inhibitor design structure and design strategy of the reported 1,3-diaryltriazen-substituted sulfonamide derivatives starting from SLC-0111.
purification. Melting points (mp) were determined with SMP30 melting point apparatus in open capillaries and are uncorrected. FT-IR spectra were recorded by using Perkin Elmer Spectrum 100 FT-IR spectrometer. Nuclear Magnetic Resonance (1H-NMR and 13C-NMR) spectra of compounds were recorded using a Bruker Advance III 300 MHz spectrometer in DMSO-d$_6$ and TMS as an internal standard operating at 300 MHz for 1H-NMR and 75 MHz for 13C-NMR. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F$_{254}$ plates.

**General procedure for preparation 1,3-diaryltriazene sulfonamide derivatives 4(a-h)**

A solution of metanilamide 1 (5 mmol) in 1.5 ml of conc. hydrochloric acid and 3 ml of water was cooled to 0–5°C, sodium nitrite (7 mmol) in 3 ml of water was added dropwise to this solution during about 15–20 min under continuous stirring. The mixture was stirred about 20 min at 0–5°C, and diazonium solution was added to aniline solution (prepared by 5 mmol anilines in 5 ml of MeOH) by adjusting the pH around 6–7 with simultaneous addition of saturated sodium acetate. Then, the reaction mixture was stirred 3 h at 0–5°C and overnight at room temperature in dark. The obtained colorful mixture was filtered off, washed several times with cold water and the crystallized from ethanol. The final desired products 4(a–h) were dried under vacuum, kept under dark and fully characterised by FT-IR, 1H-NMR, 13C-NMR, and melting points.

3-(3-(4-fluorophenyl)triaz-1-en-1-yl) benzenesulfonamide (4a).
Yield: 85%; Color: light brown; mp: 140–142°C; FT-IR (cm$^{-1}$): 3333, 3251 (NH$_3$), 1599, 1497 (asymmetric), 1314, 1145 (symmetric) (S=O), 1094; 1H-NMR (DMSO-d$_6$ 300 MHz, δ ppm): 12.73 (s, 1H, –NH–), 7.87 (s, 1H, Ar-H), 7.75–7.48 (m, 5H, Ar-H), 7.46 (s, 2H, –SO$_2$NH$_2$), 7.28 (t, 2H, J = 2.2, Ar-H); 13C-NMR (DMSO-d$_6$ 75 MHz, δ ppm): 158.3, 151.5, 145.7, 138.6, 130.6, 124.3, 123.6, 119.8, 116.3, 115.8.

4-(3-(3-sulfamoylphenyl)triaz-2-en-1-yl) benzoic acid (4b).
Yield: 70%; Color: yellow; mp: 161–163°C; FT-IR (cm$^{-1}$): 3373, 3245 (NH$_3$), 1605, 1526, 1405 (asymmetric), 1335, 1161 (symmetric) (S=O), 1097; 1H-NMR (DMSO-d$_6$ 300 MHz, δ ppm): 12.88 (br.s, 1H, –COOH), 12.75 (s, 1H, –NH–), 7.92 (s, 1H, Ar-H), 7.79–7.52 (m, 5H, Ar-H), 7.46 (s, 2H, –SO$_2$NH$_2$), 7.30 (t, 2H, J = 2.3, Ar-H); 13C-NMR (DMSO-d$_6$ 75 MHz, δ ppm): 179.6, 159.5, 151.2, 146.2, 139.5, 130.8, 124.7, 123.3, 119.5, 116.2, 115.1.

3-(3-(4-cyanophenyl)triaz-1-en-1-yl) benzenesulfonamide (4c).
Yield: 75%; Color: light yellow; mp: 170–172°C; FT-IR (cm$^{-1}$): 3369, 3266 (NH$_3$), 2218 (CN), 1606, 1521 (asymmetric), 1326, 1139 (symmetric) (S=O), 1094; 1H-NMR (DMSO-d$_6$ 300 MHz, δ ppm): 13.01 (s, 1H, –NH–), 8.01 (s, 1H, Ar-H), 7.85–7.72 (m, 5H, Ar-H), 7.71–7.61 (m, 2H, Ar-H), 7.50 (s, 2H, –SO$_2$NH$_2$); 13C-NMR (DMSO-d$_6$ 75 MHz, δ ppm): 160.1, 151.8, 146.6, 139.8, 131.0, 125.2, 123.9, 119.8, 118.2, 116.6, 115.3.

3-(3-(4-butoxyphenyl)triaz-1-en-1-yl) benzenesulfonamide (4d).
Yield: 78%; Color: brown; mp: 140–143°C; FT-IR (cm$^{-1}$): 3362, 3267 (NH$_3$), 1596, 1503 (asymmetric), 1333, 1147 (symmetric) (S=O), 1092; 1H-NMR (DMSO-d$_6$ 300 MHz, δ ppm): 12.92 (s, 1H, –NH–), 7.96 (s, 1H, Ar-H), 7.83–7.70 (m, 5H, Ar-H), 7.69–7.62 (m, 2H, Ar-H), 7.49 (s, 2H, –SO$_2$NH$_2$), 3.92 (t, 2H, –OCH$_2$CH$_2$CH$_2$CH$_3$), 2.00–1.95 (m, 2H, –OCH$_2$CH$_2$CH$_2$CH$_3$), 1.68–1.60 (m, 2H, –OCH$_2$CH$_2$CH$_2$CH$_3$), 0.98 (t, 3H, –OCH$_2$CH$_2$CH$_2$CH$_3$); 13C-NMR (DMSO-d$_6$ 75 MHz, δ ppm): 159.8, 151.4, 146.1, 139.5, 131.3, 125.7, 123.2, 119.5, 116.2, 115.5, 64.8, 32.5, 19.9, 15.7.

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using the Cheng–Prusoff equation, as reported earlier, and represent the mean from at least three different determinations. All CA isozymes used here were recombinant proteins obtained as reported earlier by our group.

Results and discussion

Chemistry

The rationale behind the design of these new 1,3-diaryltriazene sulfonamide derivatives presented in this work is based on our recent report, in which we showed that novel 1,3-diraryltriazene-substituted sulfonamide derivatives possess interesting CA inhibitory properties. These compounds showed potent inhibition against the cytosolic hCA II, with great selectivity versus hCA I, hCA VII, and hCA IX inhibition. Thus, we decided to apply the same procedure by changing of position of the sulfonamide moiety from para to meta, in order to investigate whether the potency comes from triazene linker or the position of the sulfonamide zinc-binding group.

A series of structurally diverse 1,3-diaryltriazene sulfonamide derivatives were synthesised according to general synthetic route shown in Scheme 1. Briefly, the diazonium salt derived of metanilamide was reacted with different substituted aromatic amines, leading to the formation of 1,3-diaryltriazene sulfonamides. The chemical structures of these novel 1,3-diaryltriazene sulfonamide derivatives reported here were confirmed by using several analytical and spectral data (see experimental part for details).

CA inhibition studies

The newly synthesised 1,3-diaryltriazene sulfonamides 4(a–h) were evaluated as inhibitors of four physiologically relevant CA isozymes, the cytosolic hCA I, hCA II, and hCA VII, and the transmembrane tumour-associated hCA IX, by a stopped-flow CO2 hydrase assay. The clinically used sulfonamide acetazolamide (AAZ) was used as a positive control.

The following structure-activity relationship (SAR) may be drawn regarding the inhibition data of Table 1, for the series of 1,3-diaryltriazene substituted sulfonamides 4(a–h):

i. The ubiquitous cytosolic isoform hCA I, which is highly abundant among others in the gastrointestinal tract and red blood cells, was moderately inhibited by all compounds investigated here, with inhibition constants in the range of 92.3–8371.1 nM. Compound 4b (possessing a 4-COOH moiety) showed the best inhibition potency against hCA I, with a KI of 92.3 nM. Interestingly, the 3,4-disubstituted compounds 4g (3,4-diMeO) and 4h (3,4-diCl) displayed the lowest hCA I inhibition activity among this series, with KIs of 3853.9 and 8371.1 nM, respectively.

ii. An interesting inhibition profile with the reported 1,3-diaryltriazene-substituted metanilamide derivatives was observed for the physiologically dominant isoform hCA II, for which KIs ranging between 4.3 and 9194.0 nM were obtained. The most effective inhibitor was 4f, which has the 3,5-dimethyl substitution pattern and a KI of 4.3 nM, being almost 3 times more effective compared to the standard inhibitor AAZ (Table 1).

Another cytosolic isoform, hCA VII, mostly present in the brain, was inhibited by most of the new compounds...
investigated here in the micromolar range, except the compound 4f which had a $K_i$ of 15.6 nM.

iv. The inhibition potential of novel 1,3-diallyltriazone-substituted metanimamide derivatives 4(a–h) against hCA IX was not satisfactory since all the compounds reported here were rather inefficient hCA IX inhibitors, with $K_i$s in the range of 50.8–9268.5 nM (compared to AZA which has an inhibition constant of 25 nM).

Conclusions
We investigated a series of 1,3-diallyltriazone-substituted sulfonamide derivatives as CA inhibitors, continuing our most recent research on 1,3-diallyltriazone based compounds. The compounds were synthesised by reaction of diazonium salt of metanimamide with substituted aromatic amines. The new compounds discovered here were assessed as CAIs, against several pharmacologically relevant isoforms, namely hCA I, hCA II, hCA VII (cytosolic isoforms), as well as membrane-bound tumor-associated isoform hCA IX. Only compound 4f showed potent inhibition against hCA II and hCA VII with $K_i$s of 4.3 and 15.6 nM, respectively. Since hCA II is an important drug target for several diseases such as, glaucoma, retinis pigmentosa, and edema, and hCA VII recently validated antineuropathic pain target, some of these compounds might be improved and used potent CAIs and potential drug candidates.

Disclosure statement
No potential conflict of interest was reported by the authors.

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